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Published on Web 10/12/2002

Mechanism of Preferential Enrichment, an Unusual Enantiomeric Resolution Phenomenon Caused by Polymorphic Transition during Crystallization of Mixed Crystals Composed of Two Enantiomers

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Received March 28, 2002

Abstract: The mechanism of Preferential Enrichment, an unusual enantiomeric resolution phenomenon observed upon recrystallization of a series of racemic crystals which are classified as a racemic mixed crystal with fairly ordered arrangement of the two enantiomers, has been studied. On the basis of the existence of polymorphs and the occurrence of the resulting polymorphic transition during crystallization from solution, the mechanism has been accounted for in terms of (1) a preferential homochiral molecular association to form one-dimensional chain structures in the supersaturated solution of the racemate or nonracemic sample with a low ee value, (2) a kinetic formation of a metastable crystalline phase retaining the homochiral chain structures in a process of nucleation, (3) a polymorphic transition from the metastable phase to a stable one followed by enantioselective liberation of the excess *R* (or *S*) enantiomers from the transformed crystal into solution at the beginning of crystal growth to result in *a slight enrichment (up to 10% ee) of the opposite S* (or *R) enantiomer in the deposited crystals*, together with *an enantiomeric enrichment of the R* (or *S*) *enantiomer in the mother liquor*, and (4) a chiral discrimination by the once formed *S* (or *R*)-rich stable crystalline phase in a process of the subsequent crystal growth, leading to *a considerable enantiomeric enrichment of the R* (*or S*) *enantiomer up to 100% ee in the mother liquor*. The processes (3) and (4) are considered to be directly responsible for an enrichment of one enantiomer in the mother liquor. The association mode of the two enantiomers in solution has been investigated by means of (i) the solubility measurement and (ii) the number-averaged molecular weight measurement in solution by vapor pressure osmometry, together with (iii) the molecular dynamics simulation of oligomer models. The polymorphic transition during crystallization has been observed visually and by means of the in situ FTIR technique and DSC measurement. Both metastable and stable crystals have been obtained, and their crystal structures have been elucidated by X-ray crystallographic analysis of their single crystals.

Introduction

Nowadays, in connection with the industrial and pharmaceutical needs of chiral organic substances, exploitation of economically and environmentally acceptable enantiomeric resolution methods along with catalytic asymmetric syntheses has been the subject of considerable recent development.[1−8] In this context, the practical methods for enantiomeric resolution of racemates comprising nonracemizable enantiomers by crystallization are classified into two categories; one is a method using an external chiral element like a diastereomeric salt formation followed by fractional crystallization[4−8] or a diastereoselective host−guest inclusion complexation,[2] and the other is a straightforward method to separate enantiomers by crystallization in the absence of an external chiral element. In the latter category, there seem to be two contrastive cases. One is the well-known "Preferential Crystallization" method using a racemic conglomerate composed of a mixture of homochiral *R* and *S* crystals, in

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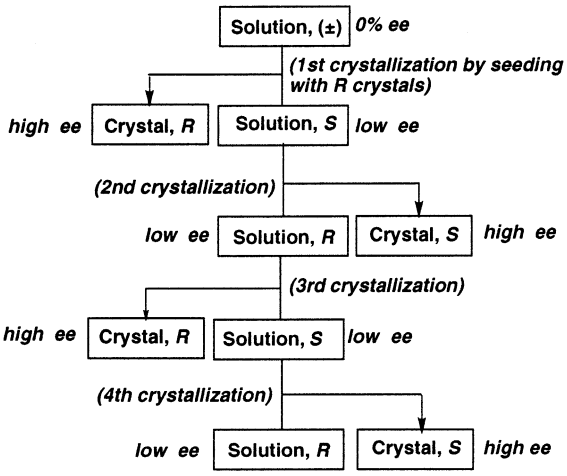

Figure 1. Principle of preferential crystallization of conglomerates.

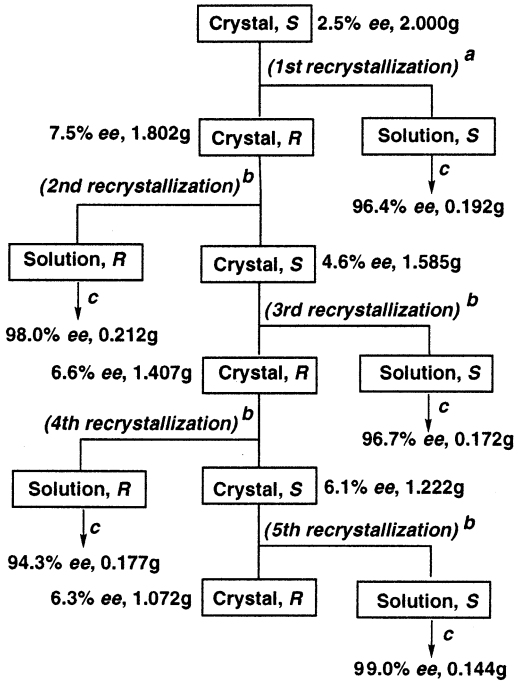

Figure 2. Preferential Enrichment of **1a**. Conditions: (a) EtOH (32 mL) at 25 °C for 4 days. (b) EtOH (32 mL) at 25 °C for 2 days. (c) Removal of the solvent by evaporation.

which by repeating crystallization from the supersaturated solution with the aid of its enantiopure seed crystals the enantiomerically enriched crystals are efficiently deposited in the alternating chirality sense (Figure 1).[9−15] The other is the completely reverse case of Preferential Crystallization, that is, it is in the mother liquor that considerable enantiomeric enrichment occurs by recrystallization (e.g., Figure 2). In principle, since the accomplishment of the manual resolution of a racemic conglomerate by Pasteur[9] and the discovery of the Preferential Crystallization technique by Gernez in the 19th century,[10] this latter ideal case had been believed to be totally unfeasible for more than a century by taking into account the crystalline nature of known homochiral and heterochiral crystals. Contrary to this common recognition, however, we found the first instance where this latter ideal enantiomeric resolution is indeed the case (Figure 2), and this unusual enantiomeric resolution phenomenon was referred to as Preferential Enrichment.[16−21]

Preferential Enrichment has the following four features (Figure 2): (1) Repeated crystallization of the racemate and each crop of resulting deposited crystals from the 4−25-fold supersaturated solution leads to a remarkable alternating enrichment of the two enantiomers up to 100% ee in the mother liquors (*a considerable enantiomeric enrichment in the mother liquor*). (2) At the same time, whenever recrystallization is carried out, the resulting deposited crystals always display the opposite chirality (*a slight enrichment of the opposite enantiomer in the deposited crystals*) with a full reproducibility. (3) Racemates or nonracemates with low ee values (less than 10% ee) are the more suitable starting material for Preferential Enrichment than those with higher ee values, achieving a very efficient resolution; the use of the nonracemic samples of more than 35% ee leads to an enantiomeric enrichment in the mother liquor, but fails to induce the characteristic enrichment of the opposite enantiomer in the deposited crystals. Therefore, only the racemates or nonracemates with low ee values (less than 10% ee) have to be crystalline to carry out the Preferential Enrichment experiment. In contrast to Preferential Crystallization, it is no matter whether the enantiomerically enriched materials with high ee values exist as the solids or the oils. (4) No addition of seed crystals is necessary at all.

These unique features are unusual and quite different from those of Preferential Crystallization of a racemic conglomerate in which a considerable enantiomeric enrichment occurs in the deposited crystals. Therefore, characterization of the crystalline nature of a series of compounds showing Preferential Enrichment and elucidation of the mechanism of this unusual phenomenon are crucial to the utilization of Preferential Enrichment as a potent enantiomeric resolution method for certain racemic substances.

On the basis of the unique polymorphism observed for certain sulfonium and ammonium sulfonates (**1e** and **2c**) showing Preferential Enrichment (Chart 1),[16,28] it has been expected that

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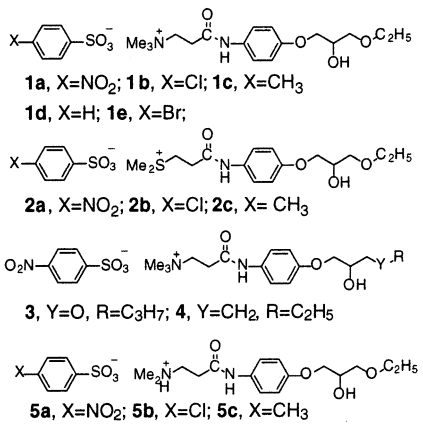
Chart 1. Ammonium and Sulfonium Sulfonates: Compounds **1a**, **1b**, **1d**, **1e**,**2a**, **2b**, **2c**, **5a**, and **5b** Showed Preferential Enrichment, while **1c**, **3**, **4**, and **5c** Failed to Do So



polymorphic transition from a metastable crystalline phase to a thermodynamically stable one at the stage of nucleation or crystal growth might be responsible for Preferential Enrichment.[14,22] To elucidate the mode of this polymorphic transition, it is primarily necessary to clarify the stable crystal structures of a series of compounds showing Preferential Enrichment and compare them with the enantiomeric assembly mode in solution or in the first-formed metastable crystal prior to polymorphic transition.

Evaluation of the enantiomeric association mode in solution has not been an easy task. Enantiomeric discrimination in solution was reported to be observed in the ^{1}H NMR spectra of the nonracemic samples of particular chiral organic compounds such as carboxamides,[23] dicarboxamides,[24] phosphinamides,[25] and phosphinothioic acids[26] which can easily form intermolecular hydrogen bonds. In these cases, it is essential that the diastereomeric signal separations in their ^{1}H NMR spectra should be observed arising from the presence of both homochiral and heterochiral molecular association species in solution. Therefore, this method is not applicable to the case where a solution of the racemic or nonracemic sample contains only either the homochiral or heterochiral molecular association species in equilibrium with the corresponding monomers. In this case, as we indicate in this report, the combined use of the solubility measurement under various conditions and the number-averaged molecular weight measurement in solution by vapor pressure osmometry[27] may become a potent tool to predict which molecular association mode is preponderant in solution, the homochiral one or the heterochiral one.

In this work, we report that (1) a newly found compound (**1a**) showing Preferential Enrichment has a unique melting point phase diagram implying the existence of two polymorphs, and this compound shows a visually observable phase transition at the early stage of crystallization, (2) the compounds (**1a** and **2c**) showing Preferential Enrichment favor a homochiral molecular association over a heterochiral one in solution, (3) another new compound (**1d**) showing Preferential Enrichment, which indeed exhibits the gradual polymorphic transition of the first-formed metastable crystalline form to give the more stable forms during crystallization, has been found, and (4) the crystal structures of the key metastable form as well as the stable one have been determined. On the basis of these findings, we discuss the mechanism of this polymorphic transition during crystallization and correlate it with an unusual key phenomenon, *a slight enrichment of the opposite enantiomer in the deposited crystals*. Finally, we propose the overall mechanism of Preferential Enrichment.

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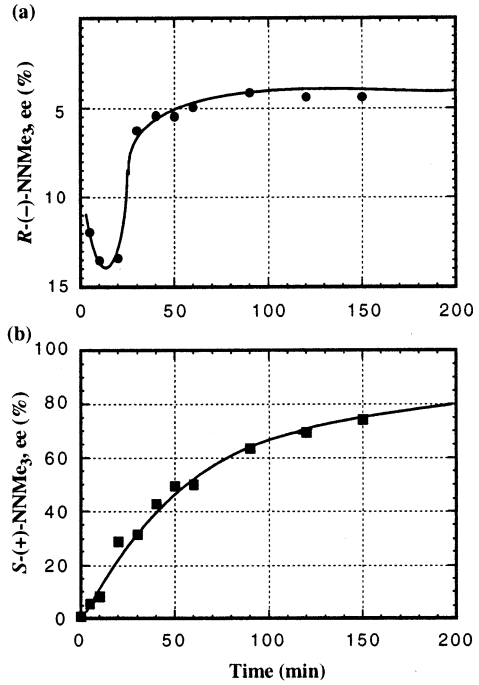


Figure 3. Time profile of the changes in the ee values (a) in the deposited crystals and (b) in the mother liquor during crystallization from the supersaturated EtOH solution of *S*-rich **1a** (0.9% ee, 1.0 g/16 mL) at 25 °C.

Results and Discussion

Preferential Enrichment, Binary Melting Point Phase Diagram and Crystal Structure of 1a. To find out an appropriate compound that (1) shows Preferential Enrichment, (2) can explicitly give the unique melting point phase diagram, and (3) exhibits a behavior of polymorphic transition in response to the occurrence of Preferential Enrichment, we have carried out screening of various ammonium sulfonate analogues which would be more easily crystallized than the corresponding sulfonium sulfonate. Finally we have found a new compound, (±)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]-trimethylammonium *p*-nitrobenzenesulfonate [(±)-**1a**], which satisfies the above requirements.

Very efficient Preferential Enrichment has been achieved when **1a** was recrystallized from ethanol (EtOH) at 25 °C (Figure 2). Although **1a** was synthesized from (±)-epichlorohydrin, the solid powder sample of **1a** obtained after final methylation of the precursor amine with methyl *p*-nitrobenzenesulfonate in acetone was no longer racemic but contained either enantiomer in small excess (less than 5% ee) (eq 1). Repetition of recrystallization of this nonracemic sample of **1a** and each crop of resulting deposited crystals successively from its 20-fold or less supersaturated EtOH solution led to *a slight enrichment of the opposite enantiomer in the deposited crystals* regularly, along with *a considerable enantiomeric enrichment in the mother liquors* in the alternating chirality sense (Figure 2). Thus, by collecting the enantiomerically enriched mother

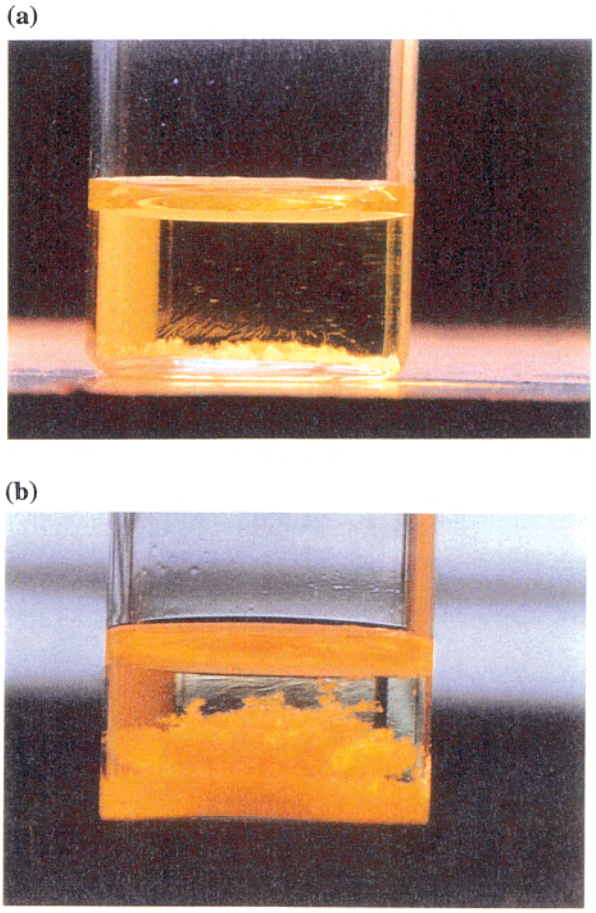
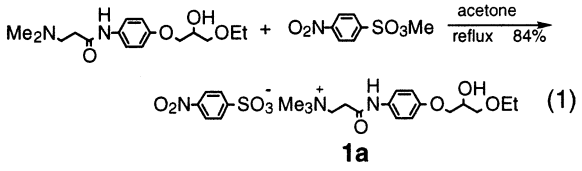


Figure 4. Visual observation of polymorphic transition and redissolution of one enantiomer from the once formed crystals during crystallization from the supersaturated EtOH solution of (±)-**1a** (0.1 mol/L); (a) 15 min and (b) 60 min after crystallization began.

liquors with the same handedness, very efficient separation of the two enantiomers (>96% ee) has been achieved, leading to the 35−40% recovery of both enantiomers after four consecutive recrystallizations.



The time profiles of the changes in the ee values in the deposited crystals as well as in the mother liquor during crystallization are shown in Figure 3. *A slight enrichment of the opposite enantiomer in the deposited crystals* occurred at the incipient stage of crystallization and the ee value in the deposited crystals became constant at around 5% after 40 min, while the ee value in the mother liquor gradually increased. The photographs shown in Figure 4 indicate that during the first 90 min of crystallization, one of the two enantiomers continues to redissolve predominantly from the just-made crystals into solution, as can be seen as a lot of convective streams evolved from the crystal surface. In fact, the ee values in solution in the proximity of the crystals were always higher by about 4−6% than those in the area distant from the crystals. After 90 min, the average ee value in solution reached about 60%. As

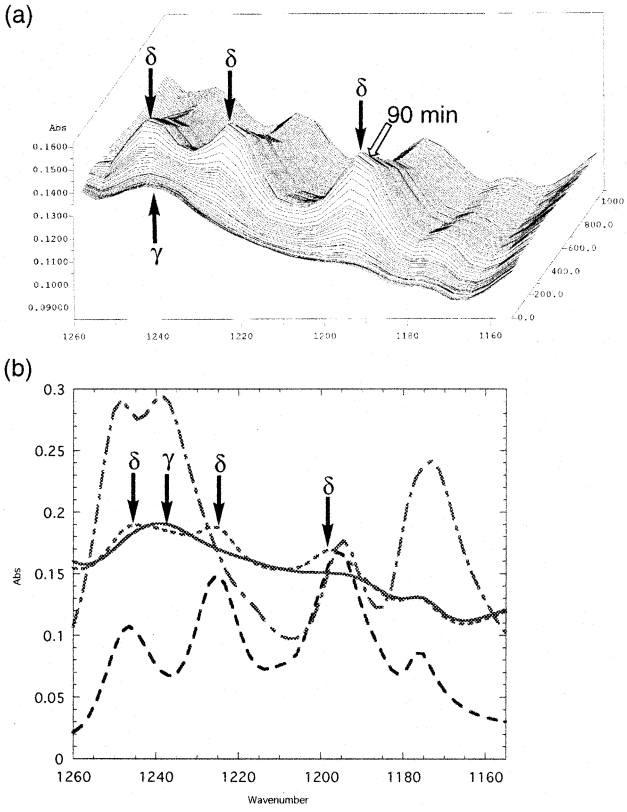


Figure 5. (a) Time development of the in situ FTIR spectra monitered by means of React IR spectroscopy during crystallization from the supersaturated EtOH solution of (±)-**1a** (0.1 mol/L). (b) Comparison of spectra at the beginning (solid line, −) and the end (dotted line, ···) of crystallization, taken from the above spectra, with the spectra in the solid state of (±)-**la** (dashed line, - - -, δ-form crystal structure) and (±)-**3** (dashed and dotted line, -·-·-·, γ-form crystal structure). Black arrows indicate the absorptions corresponding to the δ- or γ-form supramolecular structure. A white arrow points the absorption at 90 min after crystallization began.

described in the following section, this redissolution behavior of one enantiomer seems to correspond to the polymorphic transition of the metastable crystalline phase (γ-form) to the stable one (δ-form). Similarly, by means of the in situ FTIR measurement using ReactIR spectroscopy which can detect absorptions by small particles less than 1 μm as well as both solute and solvent molecules in suspensions, it has been observed that three new absorption bands at 1246, 1225, and 1198 cm^{-1} corresponding to S−O stretching vibrations of the powder sample of the stable δ-form of **1a** appear after crystallization begins and their intensity gradually increases for the first 90 min (Figure 5). Since the crystal structure of the metastable crystalline phase (γ-form) is very similar to the supramolecular structure in solution as described in the following section, it is reasonable that only single-phase change can seemingly be observed by the in situ FTIR measurement.

To characterize the crystalline nature of **1a**, the binary melting point phase diagram was constructed from the temperatures of crystal fusion which were measured by differential scanning calorimetry (DSC). Microcrystals for DSC measurement were produced in a kinetically controlled manner by rapid concentration of each of the EtOH solutions of **1a** (ca. 0.1 mol/L) with various ee values which were prepared by mixing two solutions of **1a** with high and low ee values and then heating this mixture at 70 °C followed by cooling, because slow crystallization always led to the convergent deposition of crystals of less than

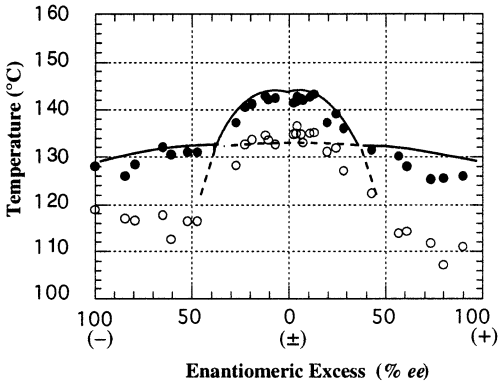


Figure 6. Binary melting-point phase diagram of **1a**. White and black circles represent the temperatures of the beginning and the end of fusion, respectively.

10% ee, a phenomenon typical of Preferential Enrichment, irrespective of the original ee values of **1a** in solutions. The average ee value of microcrystals (ca. 1.0 mg) in each small DSC pan was determined by HPLC analysis immediately after each DSC measurement. The deviation of the ee values of the microcrystals in each flask was ±1, ±2, and ±5% for the microcrystals of 0−8, 10−35, and more than 50% ee, respectively. The rough phase diagram thus obtained clearly suggests that the two phase curves intersect at two points around 35% ee (Figure 6). From the relatively high temperatures of fusion in the range of 0−15% ee in this phase diagram, it is conceivable that the crystals in this range are liable to be deposited during crystallization from the supersaturated solution.

X-ray crystallographic analysis of the single crystal of almost racemic **1a** of less than 0.4% ee which was prepared by very slow crystallization from the 2-fold supersaturated EtOH solution at 25 °C revealed that the crystal structure is characterized by two kinds of centrosymmetric cyclic dimers; one is formed by the hydrogen bonds between the hydroxy groups and the ethoxy oxygen atoms (O···O distance: 2.820(4) Å) in a pair of *R* and *S* molecules resulting in the formation of a head-to-head cyclic dimer (type A), and the other is formed by the hydrogen bond between an oxygen atom of a sulfonate ion and the amide NH (N···O distance: 2.942(4) Å) and the electrostatic interactions between another oxygen atom of the same sulfonate ion and the ammonium nitrogen atom in the neighboring long-chain cation ($N^+\cdots O^-$ distance: 4.098(4) Å), giving a head-to-head cyclic dimer (type B) (Figure 7 and Table 1). By virtue of these intermolecular interactions, a heterochiral one-dimensional (1D)-chain is formed. Furthermore, each 1D-chain interacts with two adjacent chains by another electrostatic

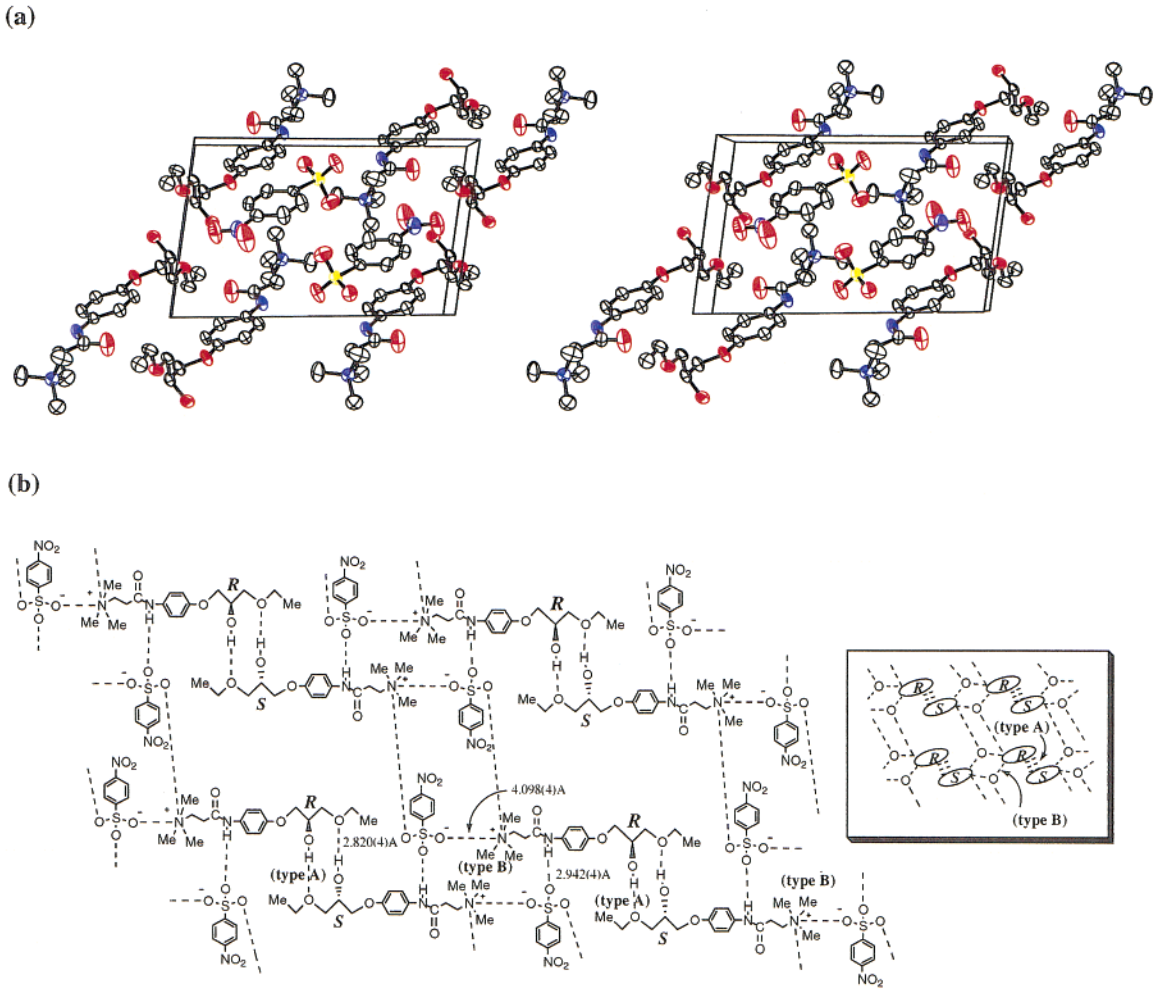


Figure 7. Crystal structure of the δ-form of racemic **1a**. (a) A view down the *a* axis. The carbon, oxygen, nitrogen, and sulfur atoms are representated by black, red, blue, and yellow ellipsoids, respectively. (b) Schematic representation of the intermolecular interactions in the crystal. The ellipsoid and circle in the inset indicated the long-chain cation and sulfonate ion, respectively. The dashed lines show the intermolecular hydrogen bonds and electrostatic interactions.

Table 1. Summary of X-ray Crystallographic Data

	(±)-**1a**	(±)-**3**	(±)-**1d**	(±)-**4**
empirical formula	$C_{23}H_{33}O_9N_3S$	$C_{24}H_{35}N_3O_9S$	$C_{23}H_{34}N_2O_7S$	$C_{24}H_{35}N_3O_8S$
formula weight	527.59	541.62	482.59	525.62
crystal system	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)
a, Å	9.852(2)	9.337(2)	9.4967(13)	13.120(1)
b, Å	15.148(4)	16.2933(7)	14.947(3)	16.299(2)
c, Å	9.040(9)	9.338(3)	9.0688(13)	6.5805(4)
α, deg	96.52(5)	100.57(2)	99.301(7)	96.957(5)
β, deg	92.57(4)	103.63(1)	102.637(10)	99.590(5)
γ, deg	107.19(2)	80.88(1)	89.263(9)	76.310(4)
V, Å	1276(1)	1347.2(4)	1239.3(3)	1343.2(2)
Z	2	2	2	2
F(000)	560.00	576.00	516.00	560.00
D_{calc}, g/cm^3	1.373	1.335	1.293	1.300
T, °C	23	23	23	23
crystal size, nm	0.35 × 0.25 × 0.05	0.32 × 0.07 × 0.07	0.25 × 0.20 × 0.15	0.30 × 0.30 × 0.30
μ (Cu Kα), cm^{-1}	16.18	15.46	–	–
μ (Mo Kα), cm^{-1}	–	–	1.75	1.71
$2\theta_{max}$, deg	120.0	135.9	57.5	56.6
no. of reflns measd	4039	4132	5718	14071
no. of reflns obsd	3242 ($I > 2.00\sigma(I)$)	1476 ($I > 3.00\sigma(I)$)	1834 ($I > 3.00\sigma(I)$)	2853 ($I > 3.00\sigma(I)$)
no. of variables	325	366	331	359
R^a, R_w^b	0.062; 0.120	0.065; 0.089	0.091; 0.157	0.049; 0.077
GOF	1.88	1.14	1.46	0.93

[a] $R = \sum(F_o^2 - F_c^2)/\sum F_o^2$. [b] $R_w = (\sum\omega(F_o^2 - F_c^2)^2/\sum\omega(F_o^2))^{1/2}$; $\omega = 1/\sigma^2(F_o)$.

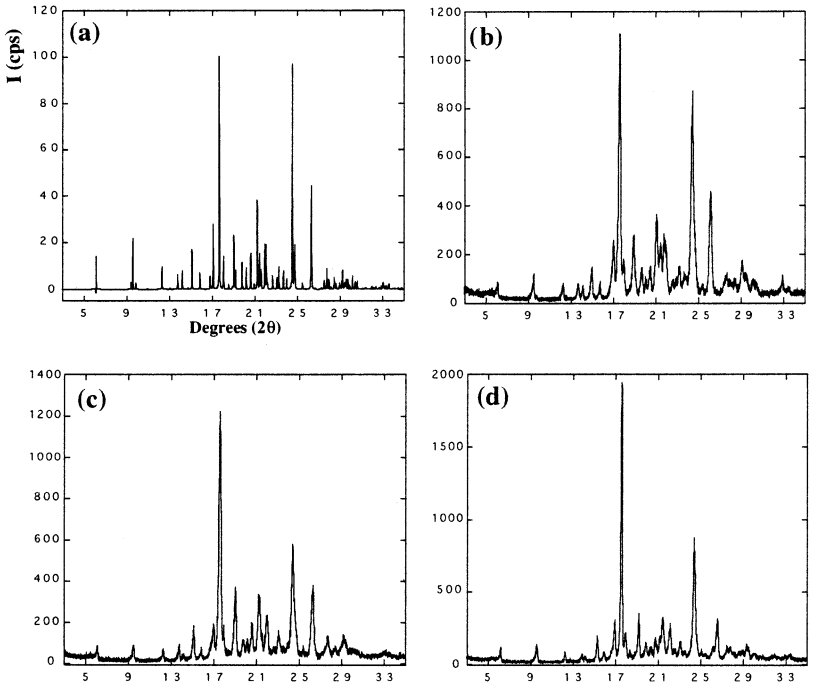


Figure 8. X-ray diffraction patterns of **1a**, simulated from the X-ray crystallographic data of almost racemic single crystal (a) and measured for polycrystalline powder samples; (b) 5% ee, (c) 41% ee, and (d) 94% ee.

interaction between the third oxygen atom of the same sulfonate ion and the ammonium nitrogen atom in the adjacent chains, eventually forming a rigid two-dimensional sheet structure. We call this type of crystal structure a *δ*-form, which is commonly found in most of the compounds showing Preferential Enrichment.[17,19,20,28−30] Thus, the phase curve in the range of 0−15% ee in Figure 6 has proved to correspond to either a racemic compound or a highly ordered racemic mixed crystal.[14] The powder X-ray diffraction pattern simulated from the above X-ray crystallographic data was almost identical to the experimental diffraction pattern of the polycrystalline powder of less than 10% ee obtained by the Preferential Enrichment experiment (Figure 8, a and b).

Although both the pure enantiomers and nonracemates (>40% ee) of **1a** showed a tendency to form polycrystalline powder and gave no single crystal of adequate quality for the X-ray analysis at all, from the shape of the overall flat phase curve in this range and the similarity in the powder X-ray diffraction patterns of the nonracemates with various ee values more than 40% ee (Figure 8, c and d), we concluded that the flat phase curve must correspond to the mixed crystals composed of different amounts of the *R* and *S* enantiomers in a crystal lattice similar to that of the pure enantiomer.

Thus, it can be deduced that during crystallization from the supersaturated solution of **1a** with a low ee value, the metastable mixed crystals are initially formed in a kinetically controlled manner, followed by its polymorphic transition into the stable, highly ordered crystals via either a solid-to-solid type[31,32] or a solvent-mediated type of polymorphic transition according to

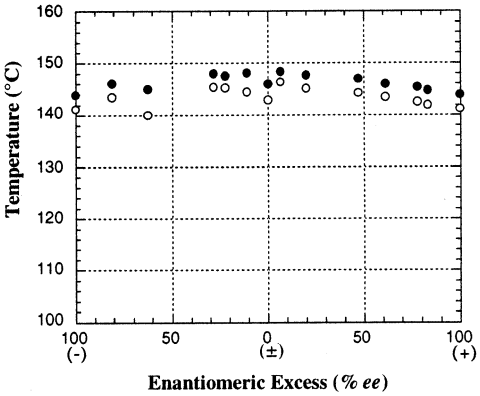


Figure 9. Binary melting-point phase diagram of **1c**. White and black circles represent the temperatures of the beginning and end of fusion, respectively.

the "Ostwald's law of stages".[33−35] The intersection of the two phase curves implies that the energy difference between the two polymorphs is small enough to allow such a polymorphic transition to proceed at a moderate rate during crystallization, in good agreement with the visual observation and the consequence of the in situ FTIR measurement shown in Figures 4 and 5, respectively.

Besides the melting point phase diagram of **1a**, another compound **1e** showing Preferential Enrichment has been reported to have a different type of binary melting point phase diagram which consists of two somewhat convex curves.[28] In this case, the two curves do not intersect but are located closely to each other; one is a stable polymorph belonging to a fairly ordered racemic mixed crystal, and the other is a metastable one which cannot be characterized. This result also implies the importance of polymorphic transition for the occurrence of Preferential Enrichment.

In contrast, compound **1c**, the *p*-toluenesulfonate derivative of **1a**, has failed to show Preferential Enrichment and has a single convex curve (Figure 9), indicating that this compound exists only as a single type of a mixed crystal composed of the two enantiomers over a wide range of ee values like **5c**.[19] This classification of the crystalline nature has been confirmed by the fact that the powder X-ray diffraction pattern of (±)-**1c** is almost identical to that of the corresponding almost pure enantiomer (Figure 10).

In addition to the presence of polymorphs, structural requirements must be satisfied for the occurrence of Preferential Enrichment. For example, it was reported that there exist two polymorphs for oxime of carvone, both of which are classified as a mixed crystal over a wide range of ee values, and the two melting point phase curves are located closely to each other, but not intersected,[36] similar to the case of **1e**.[28] However,

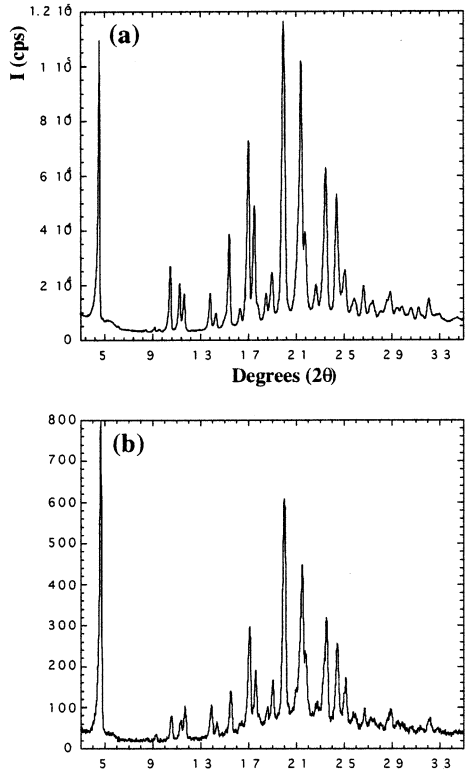


Figure 10. X-ray diffraction patterns of powder samples of **1c**; (a) 0% ee and (b) 99% ee.

Preferential Enrichment did not occur by recrystallization of the racemate. This is because only molecular conformation is different from each other with respect to the two polymorphs of oxime of carvone, and there is no possibility of rearrangement of hydrogen bonds in the crystal lattice.[36]

Assembly Mode of Enantiomers in Solution. Since compounds showing Preferential Enrichment like **1a** and **2c** have failed to exhibit the signal separations in the ^{1}H NMR spectra of the nonracemic samples with various ee values taken in $CDCl_3$, C_2D_5OD, or $(CD_3)_2CDOD$ at −30−25 °C, the ^{1}H NMR technique has proved not to be applicable for deciding which molecular association mode is more stable in solution, the homochiral one or the heterochiral one. Instead, we have measured the solubility of the sulfonium sulfonate **2c** as well as that of the ammonium sulfonate **1a**. Compound **2c** shows much higher solubility in organic solvents due to its sulfonium salt structure than **1a**. The saturated solution of **2c** was prepared by stirring the crystals in 2-PrOH for 48 h at 25 °C. The solubility of the pure *R* enantiomer (11.4 mg/mL) was higher than that of the racemic sample (6.6 mg/mL). Furthermore, under the conditions for supersolubility measurement in which the crystals are dissolved in 2-PrOH by heating at 70 °C followed by cooling and standing for 45 h at 25 °C, the pure *R* enantiomer has exhibited a drastic increase of the supersolubility (more than 150 mg/mL) compared to the racemate (10 mg/mL). In this case, to avoid the complexity arising from the occurrence

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(31) For polymorphic transformation, see: Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193−200.
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(36) (a) Oonk, H. A. J.; Kroon, J. *Acta Crystallogr.* **1976**, *B32*, 500−504. (b) Kroon, J.; van Grup, P. R. E.; Oonk, H. A. J.; Baert, F.; Fouret, R. *Acta Crystallogr.* **1976**, *B32*, 2561−2564. (c) Baert, F.; Fouret, R.; Oonk, H. A. J.; Kroon, J. *Acta Crystallogr.* **1978**, *B34*, 222−226. (d) Oonk, H. A. J.; Tjoa, K. H.; Brants, F. E.; Kroon, J. *Thermochim. Acta* **1997**, *19*, 161−171. (e) Meijer, E. L.; Blok, J. G.; Kroon, J.; Oonk, H. A. J. *Thermochim. Acta* **1977**, *20*, 325−334. (f) Calvet, T.; Oonk, H. A. J. *Calphad* **1995**, *19*, 49−56.

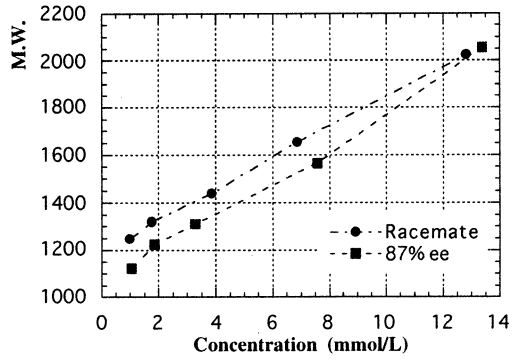

Figure 11. Number-averaged molecular weight measurement of the racemate and nonracemic sample of **2c** in $CHCl_3$ at 30 °C by vapor pressure osmometry.

of Preferential Enrichment, this supersolubility measurement for racemic **2c** was carried out carefully by using a much lower concentration of **2c** in 2-PrOH than the standard experimental conditions (250 mg/mL) used for the Preferential Enrichment experiment. These results indicate that the homochiral supramolecular structure in 2-PrOH is very different from that in the enantiopure crystalline state and is much more stable than any heterochiral molecular association structure in 2-PrOH solution. As expected, the equimolar mixing of the respective enantiopure solutions of the *R* and *S* enantiomers in 2-PrOH (125 mg/mL each) at 25 °C has resulted in gradual deposition of nonracemic crystals with low ee values to induce Preferential Enrichment. These results and the fact that it takes long (sometimes more than 24 h) before crystallization begins from the supersaturated solution of the racemic or nonracemic **2c** suggest that even in a high concentration (0.50 mol/L) of racemic **2c** in 2-PrOH the stable, homochiral *R* and *S* supramolecular structures are preferentially formed, gradually interact with each other probably due to dipole−dipole interactions, and finally undergo phase transition to form new heterochiral supramolecular structures, which show low solubility in 2-PrOH and are deposited as the crystals.

To confirm the preferential homochiral molecular association in a solution of racemic **2c**, we have measured the number-averaged molecular weights of the racemic and nonracemic (87% ee) samples of **2c** in $CHCl_3$ over the range of concentrations of 1.0×10^{-3} to 1.4×10^{-2} mol/L at 30 °C by using a vapor pressure osmometer (Figure 11), because the measurement in $CHCl_3$ is considered to reflect strong solute−solute interactions even in the diluted solutions and the measurements in EtOH or 2-PrOH have indicated that the anion and cation moieties of **2c** are almost separated by solvation in the same measurable concentration range. In $CHCl_3$ the molecular weight increased in proportion to the concentration of **2c** to give the tetramer at the concentration of 1.3×10^{-2} mol/L with respect to both samples, and there was no appreciable difference between the racemate and the nonracemate of 87% ee (with an experimental error of ±10%) (Figure 11). This result suggests that (1) the molecular assembly structure is a 1D-chain and (2) in a diluted solution of racemic **2c**, the preferential molecular association mode is homochiral or random. In combination with the results of solubility measurements, the preferential molecular association mode in a solution of racemic **2c** is probably homochiral.

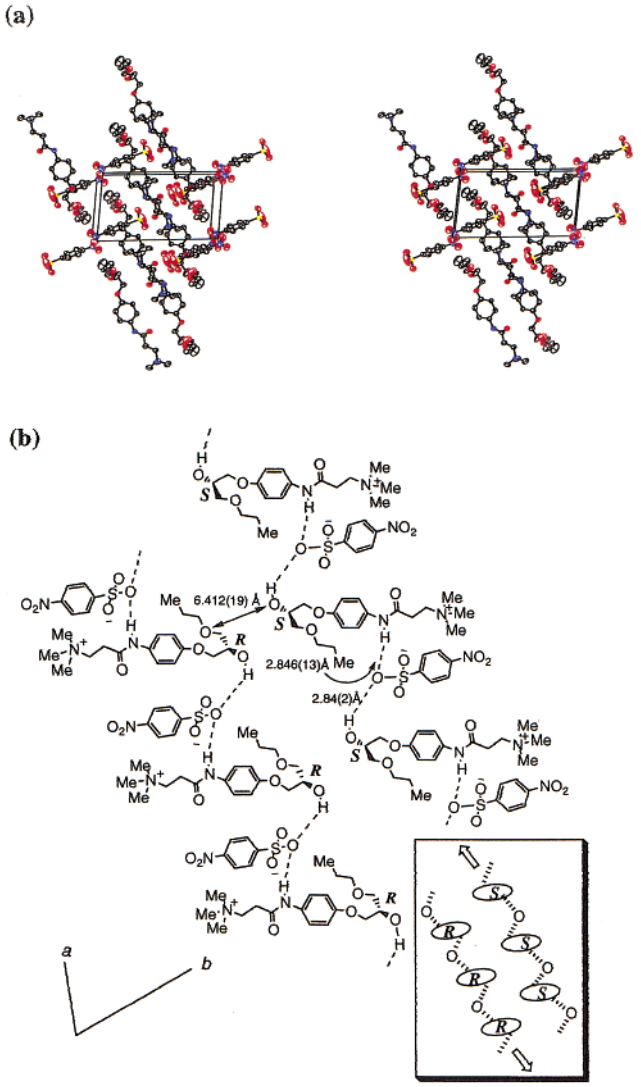

Figure 12. Crytal structure of the γ-form of racemic **3**. (a) A steroview down the *c* axis. The carbon, oxygen, nitrogen, and sulfur atoms are representated by black, red blue, and yellow ellipsoids, respectively. (b) Schematic representation of the intermolecular interactions in the crystal. The ellipsoid and circle in the inset indicate the long-chain cation and sulfonate ion, respectively. The dashed lines show the intermolecular hydrogen bonds.

Likewise, an *S*-rich sample of **1a** of 93% ee showed higher solubility (71.1 mg/mL) than an almost racemic one of less than 0.4% ee (3.1 mg/mL) in EtOH at 25 °C. Furthermore, the number-averaged molecular weight of the *S*-rich sample in $CHCl_3$ was also in proportion to the concentration of **1a** to give a tetramer at the concentration of 1.5×10^{-2} mol/L, although measurement of the racemic sample was unfeasible due to its very low solubility in $CHCl_3$ even at elevated temperatures. In fact, the equimolar mixing of the respective solutions of the *R* and *S* enantiomers in $CHCl_3$ (1.5×10^{-2} mol/L each) resulted in prompt deposition of almost racemic solid. Probably, this insolubility of the racemic sample in $CHCl_3$ stems from stronger dipole−dipole interactions between the homochiral *R* and *S* chains followed by prompt phase transiton to form new heterochiral supramolecular structures. In EtOH, the equimolar mixing of the respective solutions of the *R* and *S* enantiomers of **1a** led to gradual deposition of nonracemic crystals with low ee values to induce Preferential Enrichment; this behavior is

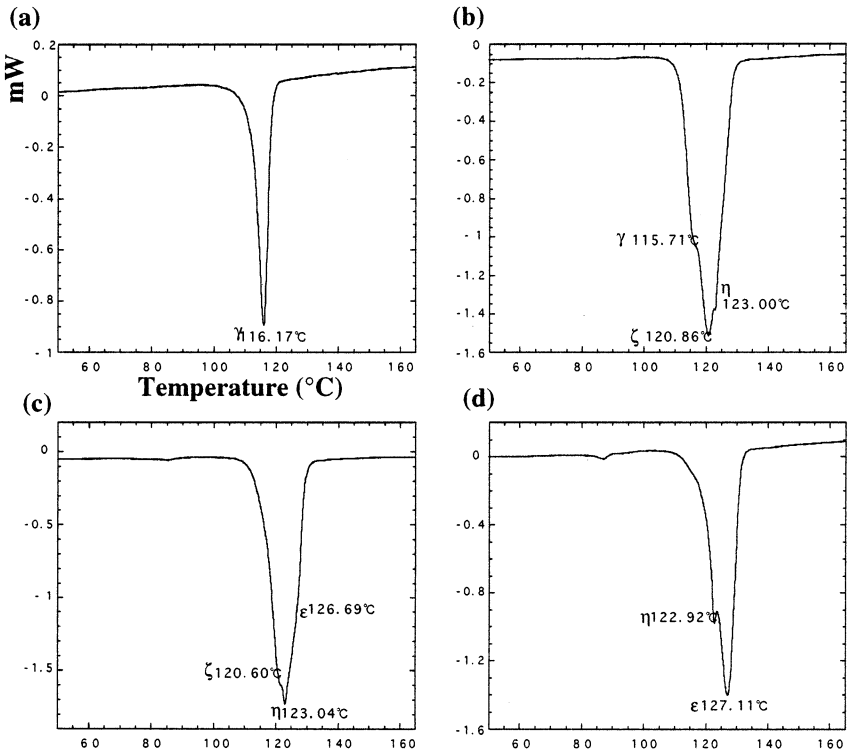

Figure 13. DSC aspects of gradual polymorphic transition of the deposited crystals observed during crystallization of (±)-**1d** from EtOH: (a) γ-form, (b) a mixture of γ, ζ, and η-forms after 8 days, (c) a mixture of ζ, η and ϵ-forms after 13 days, and (d) a mixture of η and ϵ-forms after 19 days. The endothermal peak at ca. 85 °C corresponds to the desorption of EtOH remaining around the crystals.

the same as that in the usual Preferential Enrichment experiment.

These results strongly sugggest that a homochiral molecular assembly is essentially in preference to a heterochiral one in the supersaturated 2-PrOH or EtOH solutions of the racemic samples of **1a** and **2c** as well as in the diluted $CHCl_3$ solutions of racemic **2c** and that the homochiral supramolecular structure must be a 1D-chain.

Assembly Mode of Enantiomers in the Metastable Crystal and Polymorphic Transition. Next, to predict the homochiral supramolecular structure in solution, we have searched a compound which possesses a homochiral 1D-chain structure in the crystal, because it is very possible that a molecular conformation or a molecular assembly structure in solution would be retained in the first-formed crystal by crystallization from the same solvent.[37,38] Consequently, we have found that racemic **3**, the terminal propoxy derivative of **1a**, possesses a crystal structure (γ-form) which is composed of alternating alignment of homochiral *R* and *S* 1D-chains in an antiparallel direction with a space group $P\bar{1}$ (No. 2) ($Z = 2$) (Figure 12 and Table 1). Furthermore, the FTIR absorption spectra of an EtOH solution (0.20 mol/L) of racemic **1a** is very similar to those of the solid racemic **3** rather than the solid racemic **1a** (Figure 5), implying the similarity between the supramolecular structure in the supersaturated EtOH solution of racemic **1a** and that in the solid state of racemic **3**. However, since racemic **3** failed to show Preferential Enrichment, we have sought another compound which can show Preferential Enrichment and possess an analogous homochiral chain structure in the metastable polymorph. Compound **1d**, the phenylsulfonate derivative of **1a**, has turned out to fit this requirement.

When racemic **1d** was initially recrystallized from 2-PrOH, the desired γ-form crystal exhibiting an endothermic peak at 116.2 °C by DSC measurement was obtained as a stable form (Figure 13a). The crystal structure of the γ-form polymorph of racemic **1d** is very similar to that of racemic **3**; each homochiral chain comprises the long-chain cation and the sulfonate anion in alternating alignment by two hydrogen bonds between one oxygen atom of the sulfonate ion and the hydroxy group (O··· ·O distance: 2.797(12) Å) and between the same oxygen atom and the amide NH (O···N distance: 2.869(12) Å) (Figure 14 and Table 1). There is no appreciable interchain interaction.

Although in 2-PrOH the racemate of **1d** failed to show Preferential Enrichment, the phenomenon began to occur slowly when recrystallization was carried out in EtOH (Figure 15). DSC measurements of the deposited crystals successfully showed the occurrence of the successive polymorphic transitions as the enantiomeric enrichment in the mother liquor proceeded; the first-formed γ-form polymorph was gradually transformed into the most stable one (ϵ-form), corresponding to the endothermic peak at 127 °C via two different metastable polymorphs (ζ- and η-forms) in turn during crystallization from EtOH (Figure 13 b, c, and d). Once Preferential Enrichment occurred in EtOH, the pure γ-form crystal was no longer obtained as a stable crystal even by crystallization from 2-PrOH; Preferential Enrichment began to occur very slowly in 2-PrOH, also. These results indicate that the polymorphic transition of the metastable γ-form into the more stable forms should be a key process for the occurrence of Preferential Enrichment.

Molecular Dynamics Simulation of Supramolecular Structures in Solution. As a model for the homochiral supramo-

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(38) (a) Kitamura, M.; Ueno, S.; Sato, K. Molecular Aspects of the Polymorphic Crystallization of Amino Acids and Lipids. In *Crystallization Processes*; Ohtaki, H., Ed.; Wiley: Chichester, 1998; pp 99−129. (b) Kitamura, M. *J. Cryst. Growth* **1989**, *96*, 541−546.

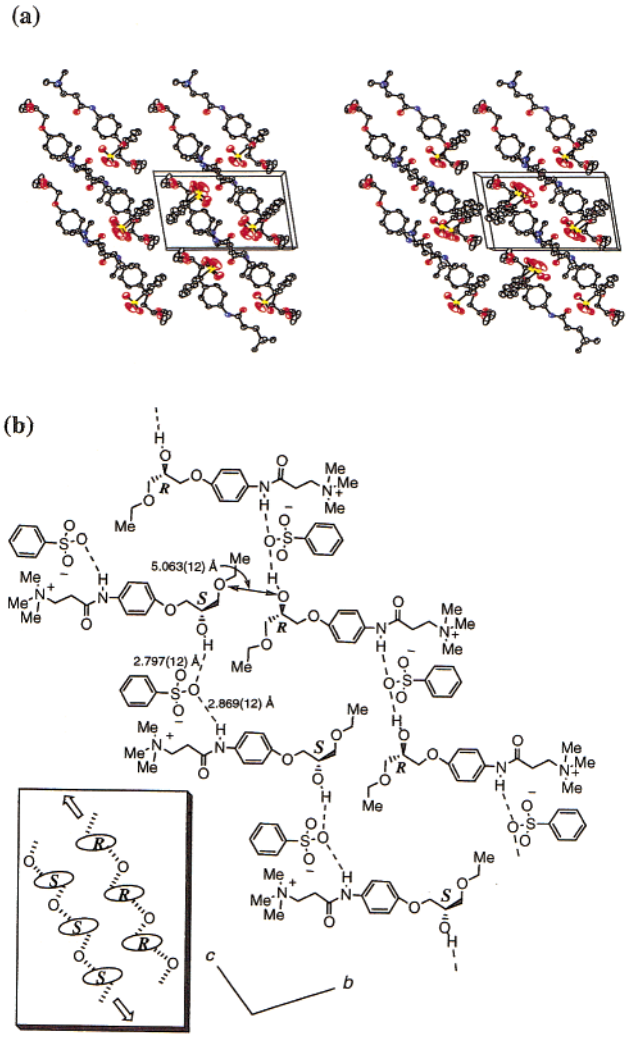


Figure 14. Crystal structure of the γ-form of racemic **1d**. (a) A stereoview down the *a* axis. The carbon, oxygen, nitrogen, and sulfur atoms are represented by black, red, blue, and yellow ellipsoids, respectively. (b) Schematic representation of the intermolecular interactions in the crystal. The ellipsoid and circle in the inset indicate the long-chain cation and sulfonate ion, respectively. The dashed lines show the intermolecular hydrogen bond.

lecular structure in solution, the 1D-chain structure observed in the γ-form crystal of racemic **1d** is supposed to be appropriate, because (1) the homochiral 1D-chain is formed only by intermolecular hydrogen bonds and no appreciable electrostatic interaction is observed, (2) there is no interchain interaction in the crystal, and (3) the γ-form crystal has a space group of $P\bar{1}$ (No. 2) with the second-lowest symmetry, implying the flexible conformation of this chain in solution. To verify the possibility of the presence of this model structure in solution, the molecular dynamics simulation (see the Experimental Section for the detail) of the homochiral and heterochiral trimers (*SSS* vs *SRS*) has been carried out at 300 K for **1a** and **2c**. The used trimer model, consisting of three long-chain cations and two sulfonate ions, was taken from the γ-form crystal structure of racemic **1d**. The reason only two sulfonate ions were used inside the trimer model instead of three ions was that we could save the calculation time without affecting both the energy difference between two trimers and the conformation of each trimer. The hydrogen bonds in each trimer are fixed to prevent the component ionic species from dispersing. Consequently,

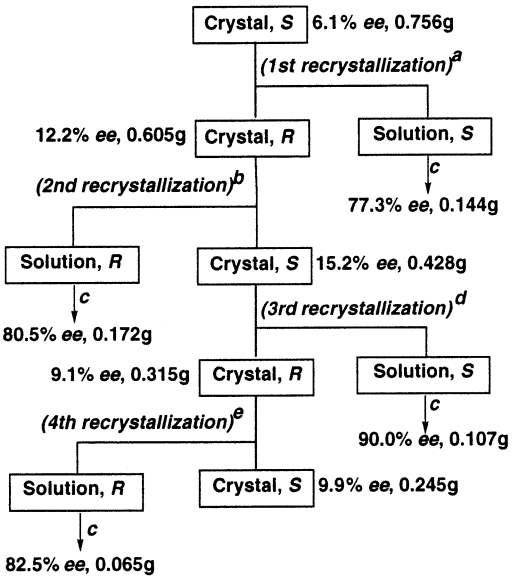


Figure 15. Preferential Enrichment of **1d**. Conditions: (a) EtOH (6.0 mL) at 25 °C for 30 days. (b) EtOH (6.0 mL) at 25 °C for 17 days. (c) Removal of the solvent by evaporation. (d) EtOH (4.0 mL) at 25 °C for 11 days. (e) EtOH (3.0 mL) at 25 °C for 9 days.

there was only a small energy difference between the two structures in the case of **2c** (-132.1 ± 9.9 and -129.8 ± 10.0 kcal/mol for *SSS* and *SRS*, respectively), while in the case of **1a** the homochiral trimer structure was appreciably more stable than the heterochiral one (102.0 ± 9.5 and 117.2 ± 9.5 kcal/mol for *SSS* and *SRS*, respectively). Noteworthy is the fact that the stable homochiral *SSS* trimer structures for both **1a** and **2c** adopt a similar compact conformation so as to allow further elongation of the chain, whereas the stable heterochiral trimer structures of both **1a** and **2c** adopt an analogous U-shaped structure which is not advantageous for elongation of the chain (Figure 16, a and b). In fact, the stable homochiral tetramer (*SSSS* consisting of four cations and three anions) of **1a** and **2c** exhibited the expected homologous chain structure after the same molecular dynamics simulation (Figure 16, c and d). Thus, the calculated homochiral oligomer structure seems to be a good candidate in solution.

Assembly Mode of Enantiomers in the Stable Crystal. So far we have finished X-ray crystallographic analyses of seven racemates (**1a**, **1b**,[29] **1e**,[28] **2b**,[17,30] **2c**,[16,30] **5a**,[19] and **5b**[20]), two pure enantiomers (**1e**[28] and **2c**[16]), and three nonracemates (**1e**,[28] **2c**,[16] **5b**[20]) among a series of compounds showing Preferential Enrichment. Of these racemates and nonracemates, there are two important stable crystal structures, α- and δ-forms, which are closely associated with the mechanism of Preferential Enrichment. It has been indicated that (1) the formation of the α-form crystal (observed only in the case of **2c**) which is a racemic compound type is not essential to the occurrence of Preferential Enrichment and is considered to be caused by further polymorphic transition of the once-formed δ-form polymorph, because other compounds which have the stable α-form crystal structure due to no structural possibility of giving the δ-form polymorph have failed to show Preferential Enrichment,[16,21,30,39] and (2) the δ-form crystal (Figures 7 and 17) which is commonly

(39) Compound (±)-**4**, in which the ethoxy oxygen atom in (±)-**1a** is replaced by CH_2 group, has been found to fail to show Preferential Enrichment. The crystal structure of (±)-**4** has been determined to be an α-form (Table 1). See also ref 21.

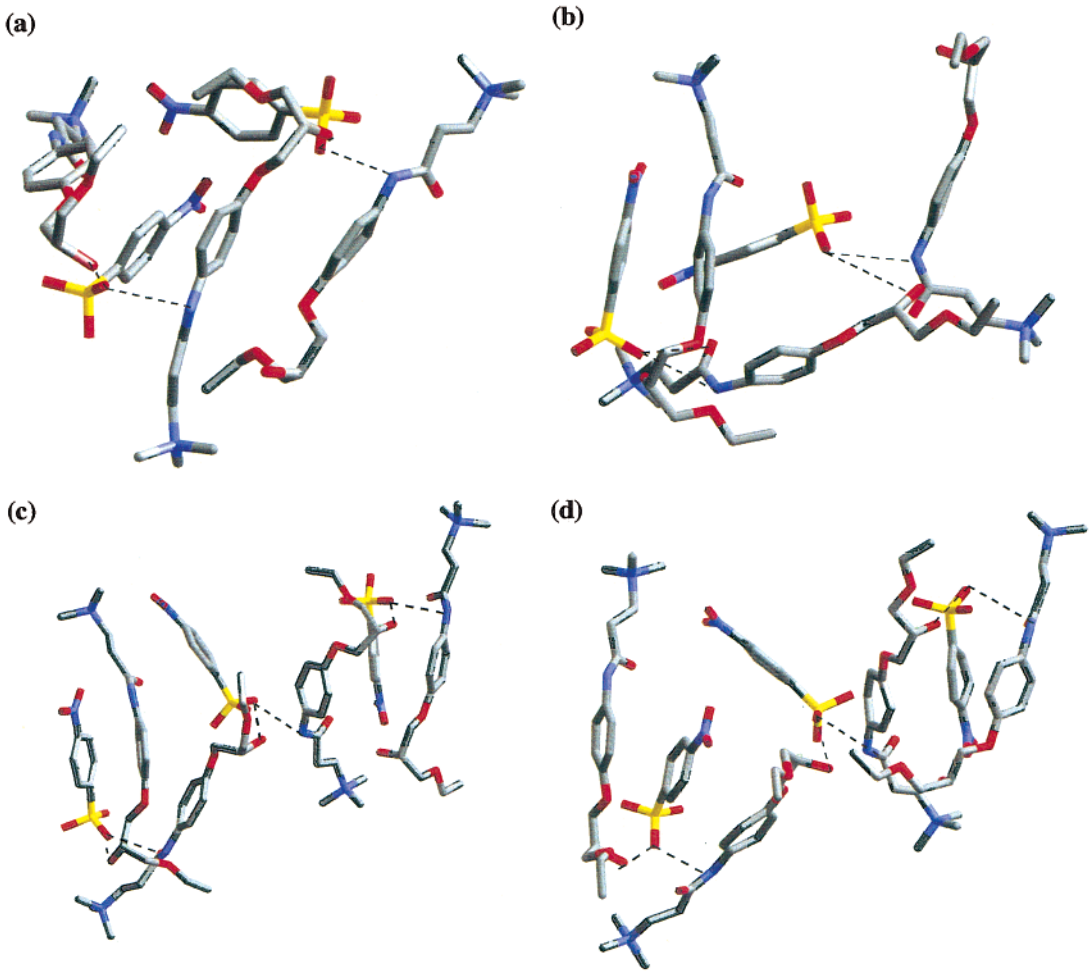


Figure 16. Oligomeric structure of γ-form for **1a** optimized by molecular dynamics simulations; (a) *SSS* trimer, (b) *SRS* trimer, (c) *SSSS* tetramer, and (d) *SRSR* tetramer. The dashed lines indicate the fixed hydrogen bonds. See the Experimental Section for the detail of calculations.

found as the stable form in the other six racemates seems to be crucial to the occurrence of Prefrerential Erichment.

With regard to δ-form crystals, strictly speaking, there are two types: One is a completely ordered mixed crystal very similar to a racemic compound as observed in the racemic crystals of **1a**, **2b**, and **5a** (e.g., Figure 7), and the other is a fairly ordered mixed crystal found in both racemic or nonracemic **1b**, **1e**, and **5b**; the crystal structure of the nonracemate is virtually isomorphous with that of the racemate and similar to that of the pure enantiomer.[20,28] For example, the intermolecular interactions observed in the nonracemic crystal of **1e** of 20% ee are shown in Figure 17 in more detail than in ref 28. Since two δ-form crystal structures of **1a** and **1e** are virtually identical except that the orientational disorder was observed at the position of the hydroxy group on an asymmetric carbon atom in **1e**, it is conceivable that the nonracemic crystal of **1a** with a low ee value which is always produced by the Preferential Enrichment experiment would also adopt such a fairly ordered δ-form structure to accommodate excess enantiomers flexibly in the crystal lattice. Therefore, it is concluded that the crystalline nature of the racemates of the compounds showing Preferential Enrichment should be classified as a racemic mixed crystal composed of the two enantiomers.

Molecular Structure Required for Preferential Enrichment. Thus far compounds which have been found to show Preferential Enrichment are analogous linear asymmetric secondary alcohols containing a glycerol moiety, an amide group, and a sulfonium sulfonate or ammonium sulfonate structure (Chart 1). Their molecular weights are about 500. Scheme 1 summarizes the structural requirements for the occurrence of Preferential Enrichment: (1) The amide, hydroxy, and terminal alkoxy groups are all indispensable for the formation of hydrogen bonds.[21,39] (2) The terminal alkoxy group must be ethoxy or methoxy; larger alkoxy groups fail to show Preferential Enrichment. (3) The onium sulfonate salt structure is advantageous for the polymorphic transition, owing to the mobility of the anion in the crystal lattice. (4) Hence, the selection of para-substituent X on the benzenesulfonate ion is very important; the sulfonate ions with low basicity having an electron-withdrawing group X form weak hydrogen bonds to allow the rearrangement of hydrogen bonds in the crystal lattice and hence polymorphic transition, while highly basic sulfonate ions which make strong hydrogen bonds fail to induce polymorphic transition.[18,19]

Mechanism of Polymorphic Transition. By comparing the crystal structures of γ- and δ-forms, it can be easily deduced that a solvent-assisted solid-to-solid type of polymorphic transition of the metastable γ-form crystal,[31,32] which is considered to retain the supramolecular structure in solution, into the stable polymorph like the δ-form during crystallization would be responsible for Preferential Enrichment. Indeed, we have indicated that in case of racemic **1d** polymorphic transition

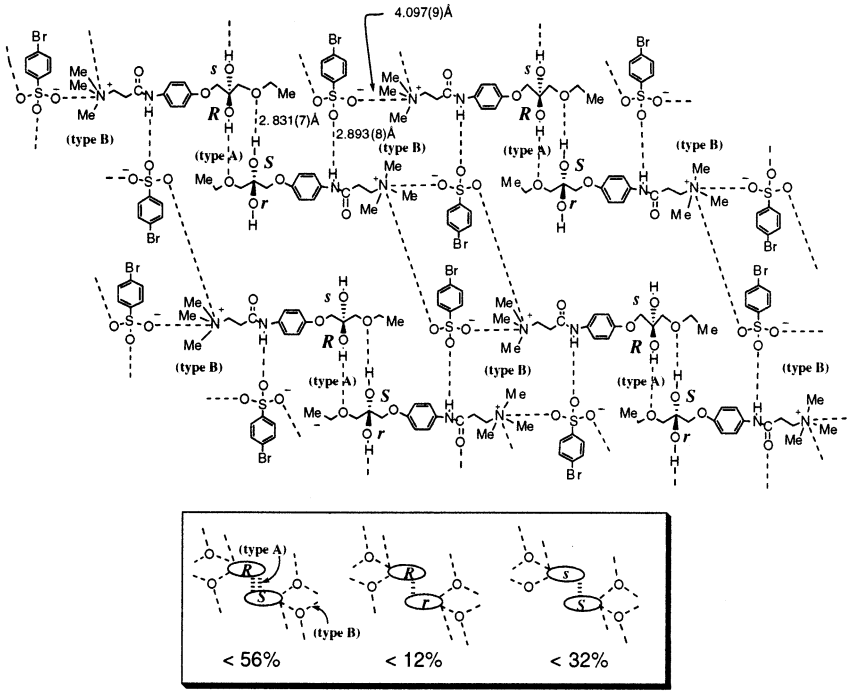
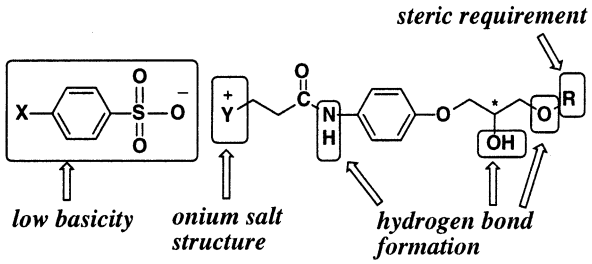


Figure 17. Schematic representation of the intermolecular hydrogen bonds in the δ-form crystal of *S*-rich **1e** (20% ee). The ellipsoid and circle in the inset indicate the long-chain cation and sulfonate ion, respectively. The dotted lines represent the intermolecular hydrogen bonds and electrostatic interactions. The hydroxy group on the asymmetric carbon atom is disordered over two positions. The *R* and *S* enantiomers in the sites with higher ocuppancy factor (0.75) are designated ***R*** and ***S***, and those in sites with lower occupancy factors (0.25) ***r*** and ***s***. The contents of three dimer structures in the inset were estimated from the occupancy factors of the orientationally disordered hydroxy groups and the ee value (20%) of the crystal. See also refs 20 and 28.

Scheme 1. Structural Requirements for the Occurrence of Preferential Enrichment



is closely associated with Preferential Enrichment (Figure 13). In the γ-form crystal of racemic **1d** (Figure 14), the shortest interatomic distances between the hydroxy oxygen atoms in the *R* chain and the ethoxy oxygen atoms in the adjacent *S* chain are only 5.063(12) Å. Therefore, it is very possible for the nearest *R* and *S* enantiomers between the two adjacent chains to form new hydrogen bonds between the hydroxy groups and the ethoxy oxygen atoms by slight movement of the two molecules along the [100] plane in the crystal. This rearrangement of hydrogen bonds accompanied by slight movement of the sulfonate ions so as to form the cyclic dimers of types A and B shown in Figures 7 and 17 occurs one after another in the crystal lattice to lead to the heterochiral 1D-chain structure (Figure 18). Probably the reason racemic **3** takes a stable γ-form crystal structure but fails to show Preferential Enrichment is due to the steric hindrance of the terminal propoxy group, which would prevent the molecular rearrangement in the crystal lattice.

The fashion of alignment of the two homochiral chains in the γ-form metastable crystal must largely define the type of the resulting δ-form crystal structure after phase transition; (1) when equal numbers of two homochiral chains are alternatingly aligned in an antiparallel direction along one axis, a completely

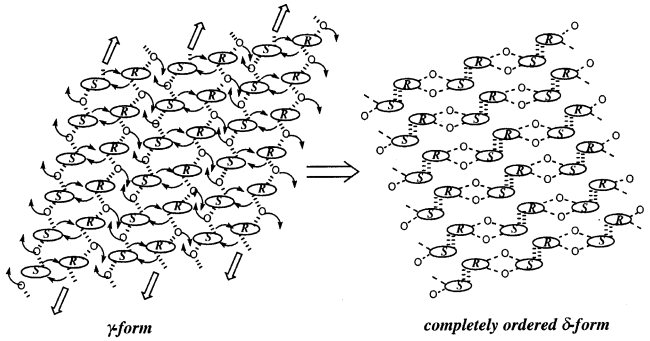


Figure 18. Polymorphic transition in the case where equal numbers of homochiral *R* and *S* chains are alternatingly aligned in the γ-form crystal, leading to the completely ordered δ-form crystal without crystal disintegration. White arrows show the direction of alignment of homochiral chains. Black arrows indicate the formation of new hydrogen bonds and electrostatic interactions. See Figures 7 and 14 for the details of each schematic representation.

ordered δ-form crystal structure will be formed after polymorphic transition (Figure 18), (2) when an odd number of homochiral *R* (or *S*) chains are aligned between two *S* (*R*) chains locally, after polymorphic transition, the fairly ordered δ-form crystal structure will locally be formed without disintegration of the crystal (Figure 19), and (3) when an even number of homochiral *R* (*S*) chains are aligned between two *S* (*R*) chains locally, after polymorphic transition, partial disintegration of the crystal occurs to release the *R* (*S*)-rich area into solution (Figure 20), because the *R* (*S*)-rich area was surrounded by the sites, where hydrogen bonds of type A cannot be formed, as well as the sites with weak electrostatic interactions (Figure 21). This third case can well explain the origin of *a slight enrichment of the opposite enantiomer in the deposited crystals*. If the metastable γ-form crystals contain the *R* enantiomer in a small

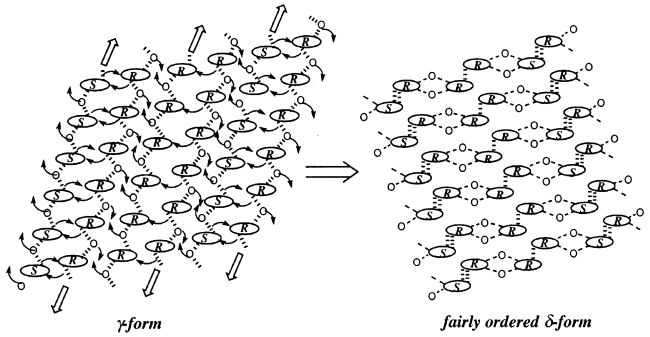


Figure 19. Polymorphic transition in the case where an odd number of homochiral *R* chains are aligned between two *S* chains in the γ-form crystal, leading to the fairly ordered δ-form crystal without crystal disintegration. White arrows show the direction of alignment of homochiral chains. Black arrows indicate the formation of new hydrogen bonds and electrostatic interactions. See Figures 14 and 17 for the details of each schematic representation.

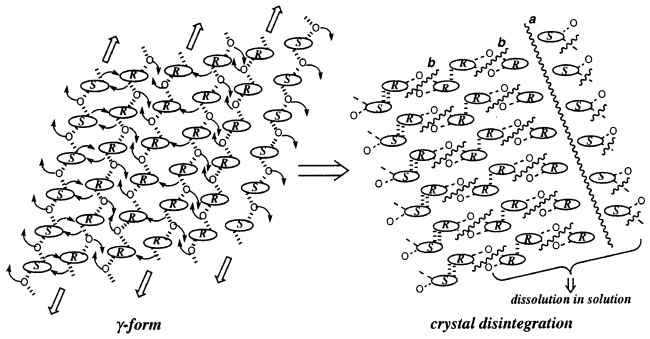


Figure 20. Polymorphic transition in case that an even number of homochiral *R* chains are aligned between two *S* chains in the γ-form crystal, leading to the local crystal disintegration in the δ-form crystal, which occurs between the sites ***a*** and ***b*** (see Figure 21, also). White arrows show the direction of alignment of homochiral chains. Black arrows indicate the formation of new hydrogen bonds and electrostatic interactions.

excess (e.g., ca. 5% ee), probably the sum of the *R* chains is larger than that of the *S* ones in the crystal, and the probability for an even number of *R* chains to be aligned between two *S* chains should be higher than the opposite case. If so, after polymorphic transition, a substantial amount of the *R* enantiomers must be liberated into solution eventually to give slightly *S*-rich crystals.

Mechanism of Preferential Enrichment. The proposed mechanism of Preferential Enrichment in the case of enrichment of the *R* enantiomer in the mother liquor from the slightly *R*-rich (ca. 5% ee) supersaturated solution is illustrated in Figure 22. In solution, homochiral oligomers are formed preferentially and aggregate to form a supramolecular cluster, which undergoes phase transition to give a metastable crystal of γ-form in a process of nucleation. Since the *R* enantiomer is in solution slightly in excess, the resulting metastable crystal becomes slightly *R*-rich, too, and this crystal contains large *R*-chain-rich areas (represented by four consecutive *R* chains in Figure 22) and small *S*-chain-rich areas (represented by three consecutive *S* chains) except alternating *R*- and *S*-chain alignment. The next step is polymorphic transition in a process of crystal growth arising from rearrangement of hydrogen bonds in the crystal lattice as described in the previous section. After polymorphic transtion, the large *R*-rich area can no longer stay inside the transformed crystal due to partial disintegration of the crystal, dissolving into solution (see the photographs shown in Figure 4). However, the small *S*-rich area can be maintained in the crystal lattice by newly formed hydrogen bonds to form an *S*-rich crystal with a fairly ordered δ-form. Eventually, together with *a slight enrichment of the opposite S enantiomer in the deposited crystals, an enrichment of the R enantiomer in the mother liquor* occurs to some extent at this stage. Subsequently, the resulting slightly *S*-rich δ-form crystals induce chiral discrimination to promote the growth of the crystals with the same handedness and ee values. Thus, the enantiomeric purity of the *R* enantiomer in the mother liquor is gradually raised until the crystal growth ceases. In addition, higher solubility of the materials with high ee values than those with low ee ones accelerates the *R* enantiomer to be enriched in the mother liquor.

Such a chiral discrimination process induced by the transformed crystals in a process of crystal growth is proved by the following experiment with five independent runs (Figure 23). By recrystallization of *R*-rich **2c** of 8.2% ee from 2-PrOH at 25 °C, the initially deposited *S*-rich microcrystals of 5.4% ee were separated by decantation. To the *S*-rich microcrystals (ca. 0.5 g) was added immediately an independently prepared supersaturated solution of *S*-rich **2c** (1.0 g) of 7.3% ee in 2-PrOH (4 mL). On standing at 25 °C, *S*-rich crystals of 5−6% ee continue to be deposited during crystallization, and thereby the original *S*-rich solution gradually becomes *R*-rich through the racemic solution during crystallization. After 4 days at 25 °C, the enantiomeric purity of the *R* enantiomer in the mother liquor reaches 64−69% ee. This result was fully reproducible in all five runs. In contrast, without addition of the *S*-enriched

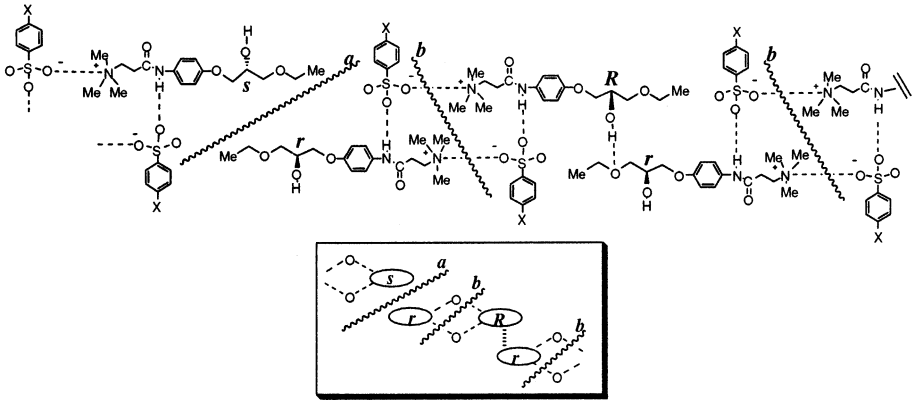


Figure 21. Site of crystal disintegration. There is one hydrogen bond between the ***R*** and ***r*** enantiomers (or the ***s*** and ***S*** enantiomers), but on hydrogen bond at the site ***a*** between the ***r*** and ***s*** enantiomers. Crystal disintegration occurs at this site ***a*** and the site ***b*** with weak electrostatic interactions (see Figure 20, also).

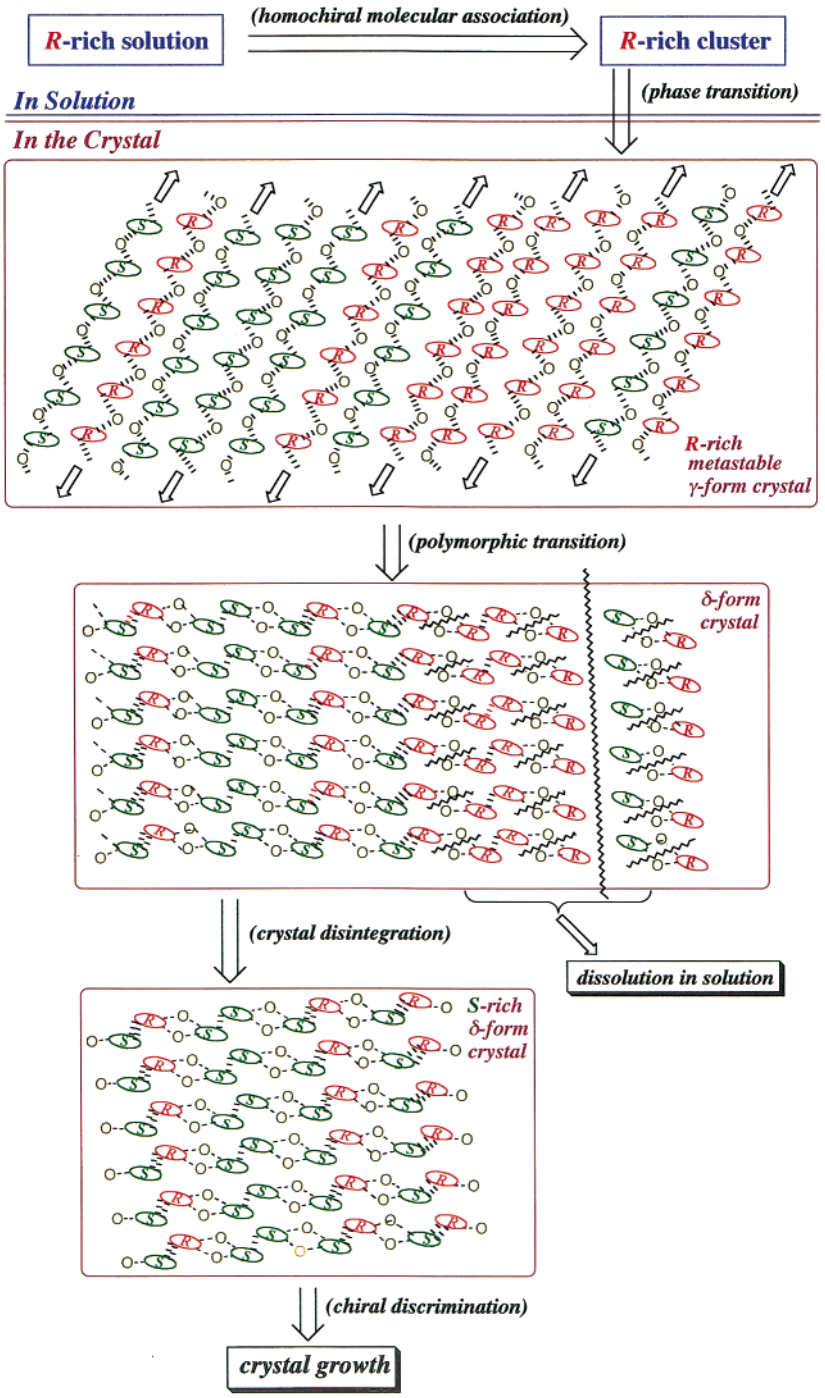


Figure 22. Mechanism of Preferential Enrichment characterized by homochiral molecular association, polymorphic transition, followed by crystal disintegration, and chiral discrimination.

microcrystals, that is, under the standard conditions for the Preferential Enrichment experiment, the *S* enantiomer is enriched in the mother liquor up to 75% ee after 4 days at 25 °C, and enrichment of the opposite enantiomer occurs in the deposited crystals as expected.

In addition, it should be noted that when the original supersaturated solution for crystallization is strictly racemic (0% ee), the probability for either the *R* or the *S* enantiomer to be enriched in solution after crystallization is 0.5; in other words, initial capricious formation of the very first nonracemic metastable crystal nucleus seems to doom which enantiomer is enriched in solution later. In fact, when exactly racemic **2c** was used for recrystallization, the probability of obtaining one particular enantiomer in excess in the mother liquor after a number of independent recrystallizations was 0.5.[16]

Conclusions

We have proposed the mechanism of Preferential Enrichment based on (1) the unique polymorphism of the compounds showing Preferential Enrichment, (2) their metastable and stable crystal structures, (3) the association mode of the two enantiomers in solution, and (4) the aspects of polymorphic transition

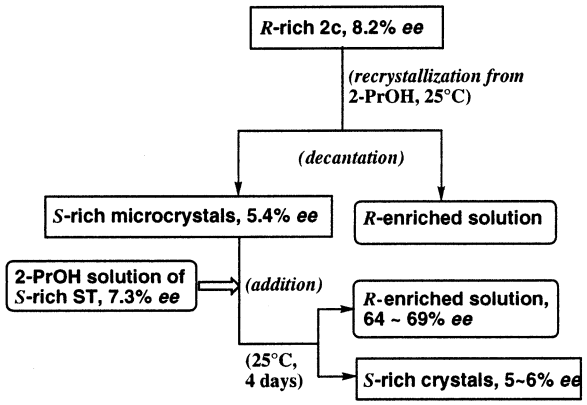


Figure 23. Chiral discrimination by initially formed crystals with a low ee value.

observed during crystallization. *A slight enrichment of the opposite enantiomer in the deposited crystals* observed regularly after each recrystallization could be rationalized in terms of the solvent-assisted solid-to-solid type of polymorphic transition from the kinetically formed metastable crystal to the thermodynamically stable one. *A considerable enantiomeric enrichment in the mother liquor* has been correlated with this polymorphic transition and the subsequent chiral discrimination by the once formed stable crystals with low ee values. We anticipate that such a polymorphism will be ubiquitous in chiral organic compounds, in which the homochiral chain structure is stable in solution while the heterochiral chain structure is stable in the crystal. Probably this type of chiral compound comprises large molecules, which can form homochiral chain structures in solution and in the metastable crystalline phase, and must have at least three hydrogen bond-forming functional groups at the appropriate positions so as to allow the subsequent polymorphic transition. Furthermore, the onium salt structure seems to be advantageous for rearrangement of hydrogen bonds to undergo polymorphic transition. We believe that Preferential Enrichment could be extended to a powerful general method for the enantiomeric resolution of organic racemates which are classified as a fairly ordered mixed crystal composed of the two enantiomers and show a similar polymorphism and thereby polymorphic transition during crystallization.

Experimental Section

Generals. Melting points are measured by DSC. Differential scanning calorimetry (DSC) was performed at the scanning rate of 5 °C/min. FT Infrared spectra were recorded as KBr pellets. The in situ FTIR spectra were recored in solution or suspension by using the attenuated total reflection (ATR) method on ReactIR 4000 (ST Japan). ^{1}H NMR spectrum was recorded at 400 MHz, and ^{13}C NMR was recorded at 100 MHz; $CDCl_3$ or CD_3OD was used as the solvent. HPLC analysis was carried out by using a chiral stationary phase column (Daicel Chiralcel OD-H, 0.46 × 25 cm), a mixture of hexane, ethanol, trifloroacetic acid, and diethylamine (800:200:5:1) as the mobile phase at the flow rate of 0.5 mL/min, and a UV−vis spectrometer (254 nm) as the detector.[40] Powder X-ray diffraction patterns were recorded at a continuous scanning rate of 2° 2θ/min using Cu Kα radiation (40 kV, 20 mA) with the intensity of diffracted X-rays being collected at intervals of 0.02° 2θ. A Ni filter was used to remove Cu K$_\beta$ radiation. The number-averaged molecular weights of the solute in $CHCl_3$ were measured on the basis of the differential vapor pressure technique by using the KNAUER vapor pressure osmometer K-7000 with dry $CHCl_3$ (H_2O content: 5−10 ppm) and benzil as the standard sample for calibration, and the results of the triplicate experiments were reproducible. The initial structure for molecular dynamics simulations was energetically minimized by molecular mechanics calculations, in which the Quasi-Newton (BFGS) method with convergence criterion of 0.001 kcal/mol/Å was used for minimization along with the COMPASS force field.[41,42] Then molecular dynamics simulations were conducted by using Discover[41] as the software with COMPASS force field under the following calculation conditions: cutoff distance, 15.5 Å; spline width, 5.00 Å; buffer width, 2.00 Å; temperature control, 300 K by the Nose method; time step, 1.0 fs; calculation time, 6000 ps (3000 ps each for equilibration and production runs). The average energies were calculated from the last 200 ps of production run.

Typical Crystallization Procedure for Preferential Enrichment. In the case of **1a** (Figure 2): *S*-Rich **1a** (2.000 g) of 2.5% ee was dissolved in EtOH (32 mL) on heating. The resulting ca. 20-fold supersaturated solution was stirred at 25 °C until crystallization began (usually within 2 h) and then allowed to stand for 4 days at the same temperature. The deposited crystals were separated from the mother liquor by filtration (or centrifugation if the amount is small). From the *S*-rich solution, 0.192 g (96.4% ee) of **1a** was obtained as a viscous oil after evaporation of the solvent. The deposited *R*-rich crystals (1.802 g, 7.5% ee) were subsequently recrystallized from EtOH (32 mL) in a similar way, leading to the deposition of antipodal *S*-rich crystals (1.585 g, 4.6% ee) and an enrichment of the *R* enantiomer in the mother liquor, from which *R*-rich **1a** (0.212 g, 98.0% ee) was obtained as a viscous oil. Similar crystallizations were repeated five times in all.

X-ray Crystallographic Analysis. For the X-ray crystallographic analysis, the single crystal was mounted in a sealed capillary. The data collections were performed at 293 K on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation to $2\theta_{max}$ of 120.0° for (±)-**1a**, an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu Kα radiation to $2\theta_{max}$ of 135.9° for (±)-**3**, and an Enraf-Nonius Kapp CCD diffractometer with graphite-monochromated MoKα radiation to $2\theta_{max}$ of 57.5° and 56.6° for (±)-**1d** and (±)-**4**, respectively. All of the crystallographic calculations were performed by using teXan software package of the Molecular Structure Corp. The crystal structure was solved by the direct methods and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. The summary of the fundamental crystal data and experimental parameters for structure determinations is given in Table 1. The experimental details including data collection, data reduction, and structure solution and refinement as well as the atomic coordinates and B_{iso}/B_{eq}, anisotropic displacement parameters, have been deposited in the Supporting Information.

Acknowledgment. The present work was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture, Sports and Technology of Japan. R.T. is grateful for supports from the Asahi Glass Foundation, the Mitsubishi Foundation, and the Takeda Science Foundation. We thank Daiso Co., Ltd. for the generous gifts of *R*- and *S*-epichlorohydrins.

Supporting Information Available: X-ray crystallographic file (CIF) for (±)-**1a** (alternative name, $NNMe_3$), (±)-**1d** ($NPMe_3$), (±)-**3** ($NNMe_3$-OPr), and (±)-**4** ($NNMe_3$-C); the synthetic scheme of (±)-**1a**, and experimental procedures for the synthesis of compounds (±)-**1a**, (±)-**1c**, (±)-**1d**, (±)-**3**, and (±)-**4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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