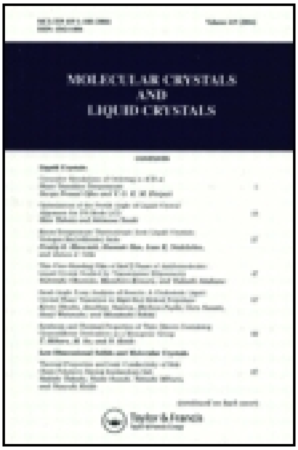

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Preferential Enrichment: Mode of Polymorphic Transformation of a Mixed Crystal into a Racemic Compound Crystal

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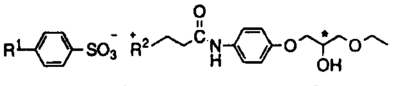
A novel enantiomeric resolution phenomenon observed upon simple recrystallization of the racemates of ST, SC, SN and $NNMe_3$ has been designated as "Preferential Enrichment" in the mother liquor. By the investigation of their crystal properties, it has been suggested that the presence of polymorphism and the resultant polymorphic transformation are responsible for the "Preferential Enrichment." In this context, on the basis of the molecular alignment and intermolecular interactions in the crystals, a mode of the polymorphic transformation of a metastable mixed crystal (solid solution) of enantiomers into a stable racemic compound crystal is discussed.

Keywords: preferential enrichment; enantiomeric resolution; mixed crystal

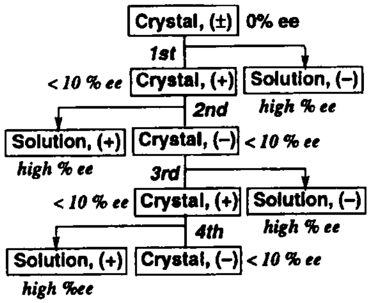
INTRODUCTION

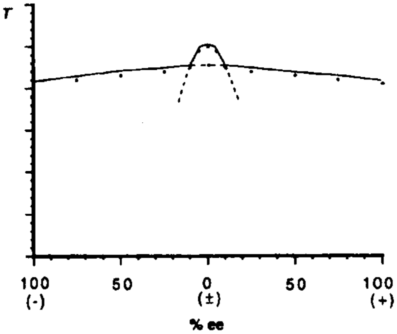
Recently we have reported the first case of accomplishment of an enantiomeric resolution by simple recrystallization of a series of racemic compounds [(±)-ST,[1,2] SC,[3] SN[4] and $NNMe_3$[5]], although in principle this sort of enantiomeric resolution has been believed to be infeasible for more than a century since the discovery of chiral crystals by Pasteur[6] and preferential crystallization by Gernez.[7] We have designated this new enantiomeric resolution phenomenon as "Preferential Enrichment" in the mother liquor. The features of the "Preferential Enrichment" are summarized as follows. (1) Remarkable enantiomeric enrichment up to 100% ee occurs in the mother liquor by recrystallization of the racemate or nonracemate with low enantiomeric purity, (2) repetition of crystallization of the racemate and each crop of the resulting deposited crystals successively results in the alternate enantiomeric enrichment of the two enantiomers in the mother liquors and simultaneously leads to the regular reversal of chirality in the deposited crystals as shown in Scheme 1, and (3) only the racemates or nonracemates with low enantiomeric purity have to be crystalline, since highly enantiomerically enriched materials are obtained from the mother liquor. These unique features are quite different from those of preferential crystallization of conglomerates in which the alternate enantiomeric enrichment occurs in the deposited crystals.[8]

The investigation of the crystal properties of ST[1,2] and NNMe3[5] suggested that (1) the presence of polymorphism between a metastable mixed crystal (solid solution) of enantiomers and a stable racemic compund, (2) the intersection of the two phase curves of a mixed crytal type and a racemic compound one (Figure 1), and thereby (3) the transformation of the metastable polymorph into the stable one are responsible for the phenomenon of "Preferential Enrichment." Here we propose a mode of polymorphic transformation of the mixed crystal into the corresponding racemic compound crystal in the solid state on the basis of their X-ray crystal structures.



ST, R^1=CH_3 R^2=Me_2S SN, R^1=NO_2 R^2=Me_2S
SC, R^1=Cl R^2=Me_2S NNMe₃, R^1= NO_2 R^2=Me_3N





SCHEME 1 Preferential Enrichment.

FIGURE 1 Outline of melting point phase diagrams of ST and NNMe3.

INTERMOLECULAR INTERACTIONS IN THE CRYSTAL

Of four compounds which showed "Preferential Enrichment," X-ray crystallographic analysis of the racemates of ST,[1,2] SC[3] and NNMe$_3$,[5] the mixed crystal of ST,[1,2] and the pure enantiomer of ST[1,2] has been accomplished. Their space groups and lattice parameters are summarized in Table I. In all crystal structures of the three racemates, there are a pair of R and S enantiomers in the unit cell of a centrosymmetric space group P$\bar{1}$. Their hydrogen bonding modes are classified into two types. One is observed in the case of (±)-ST, where there are two intermolecular hydrogen bondings between the hydroxy and carbonyl groups in a pair of R and S enantiomers, forming a centrosymmetric head-to-tail type of cyclic dimer (type A) (Figure 2a). The other hydrogen bonding mode is noted in the cases of (±)-SC and (±)-NNMe$_3$; two intermolecular hydrogen bondings are observed between the hydroxy group and ethoxy oxygen atom in a pair of R and S enantiomers, giving another type of centrosymmetric head-to-tail type of cyclic dimer (type B) (Figure 2b). Additional hydrogen bondings were observed between the amide hydrogen atom and one of the sulfonate oxygen atoms in both cyclic dimers (types A and B).

We have reported that the crystallographic parameters and molecular and crystal structure of the mixed crystals of ST with various enantiomeric purities are almost identical with those of the crystals of the pure enantiomers, except that the C-OH bond is disordered in the mixed crystals.[1,2] Its hydrogen bonding

TABLE I Space group and lattice parameters.

compound	space group	Z	a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)
(±)-ST	$P\bar{1}$	2	14.638	15.681	6.228	100.31	99.78	66.26
(-)-ST	$P1$	2	10.762	15.615	8.223	100.41	108.50	85.73
ST§	$P1$	2	10.764	15.618	8.225	100.44	108.47	85.62
(±)-SC	$P\bar{1}$	2	9.907	15.012	8.922	98.73	90.67	107.97
(±)-NNMe$_3$	$P\bar{1}$	2	9.852	15.148	9.040	96.52	92.57	107.19

§ Mixed crystal of ca. 1% ee. R, Rw, V(Å^3): 0.052, 0.049, 1280 for (±)-ST; 0.043, 0.044, 1289 for (-)-ST; 0.044, 0.042, 1289 for ST (Mixed crystal of ca. 1% ee); 0.111, 0.114, 1245 for (±)-SC; 0.061, 0.119, 1276 for (±)-NNMe$_3$.

mode is illustrated in Figure 3. The two long-chain moieties interact each other indirectly by hydrogen bondings through the intermediacy of two sulfonate groups to give a cyclic dimer structure (type C); one of the sulfonate oxygen atoms interacts with the hydroxy group in one long-chain moiety, while another oxygen atom of the same sulfonate group does with the amide hydrogen atom in the other long-chain moiety. There should be three kinds of cyclic dimers in the crystallographically disordered (C-OH) crystal; heterochiral (R, S) dimer and homochiral (R, R) and (S, S) dimers, with each content depending on the enantiomeric purity of the whole crystal.

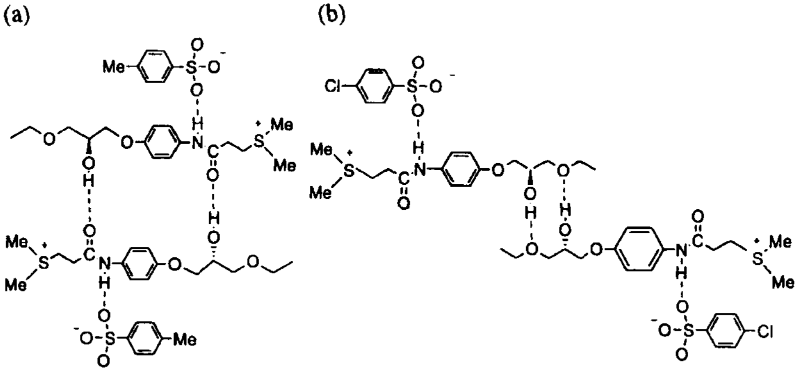


FIGURE 2 Intermolecular hydrogen bonding modes in the racemic compounds of (a) (±)-ST (type A) and (b) (±)-SC (type B).

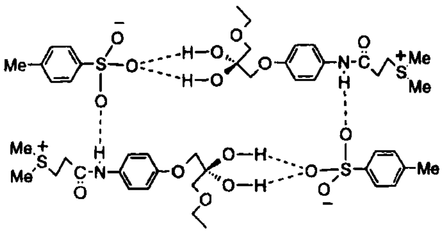


FIGURE 3 Intermolecular hydrogen bonding mode in the mixed crystal of ST of ca. 1% ee (type C).

MODE OF POLYMORPHIC TRANSFORMATION

We have suggested that the polymorphic transformation of the metastable mixed microcrystals into the stable racemic compound microcrystals during crystallization is a crucial process for "Preferential Enrichment" as can be deduced from the phase diagrams depicted in Figure 1.[5] Although the crystal structures of the mixed crystals of ST with various enantiomeric purities were easily determined,[1,2] the nonracemic SC existed as an oily material and the mixed crystals of nonracemic NNMe3 were always obtained as polycrystalline powder giving no single crystal of adequate quality for the X-ray analysis. We presume that the structure of the mixed crystals of NNMe3 is very similar to that of ST, because the pattern of the powder X-ray diffraction of the nonracemic mixed crystals of NNMe3 is similar to that of ST and because the MM2 calculations of homochiral and heterochiral cyclic dimers of NNMe3 indicate that the cyclic dimer structure corresponding to type C is the most stable of the three cyclic dimer structures corresponding to types A, B and C in solution (Figures 2 and 3).

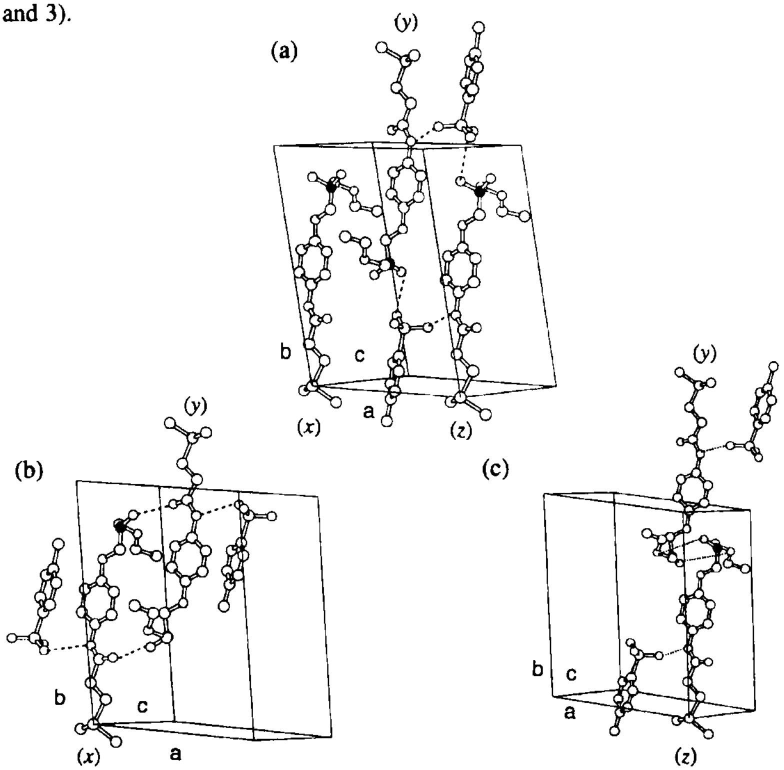


FIGURE 4 Mode of polymorphic transformation of a mixed crystal of (a) type C [(R, S) dimer] into a racemic compound of (b) type A or (c) type B. Black circles represents the asymmetric carbon atoms. The dotted lines indicate hydrogen bondings.

Then, by comparing the molecular alignment of type A with those of types B and C in the crystals, the mode of transformation of the cyclic dimer of type A into either type B or type C has been estimated. The results are shown in Figure 4 by using ST molecule as an example. Figure 4a shows the actual molecular alignment in the mixed crystal corresponding to the cyclic dimer of type C. By sliding the molecule (*y*) in Figure 4a along the b axis by ca. -1/5, the cyclic dimer structure of type A was realized as illustrated in Figure 4b. Furthermore, by sliding the same molecule (*y*) in Figure 4a along the b and c axes by ca. +1/4 and +2/5, respectively, the cyclic dimer structure of type B was obtained as shown in Figure 4c.

Although the mechanism of polymorphic transformation in molecular crystals are largely unknown,[9] the results described here indicate that solid-solid polymorphic transformation can be initiated by the molecular sliding along the crystal axes inside the crystal, followed by the formation of a critical nuclei and its subsequent growth.

Acknowledgments

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