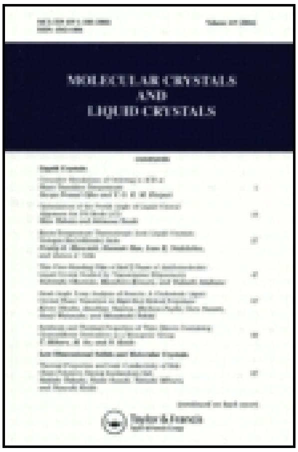

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POLYMORPHISM OF COMPOUND EXISTING AS BOTH RACEMIC COMPOUND CRYSTALS AND MIXED CRYSTALS OF ENANTIOMERS

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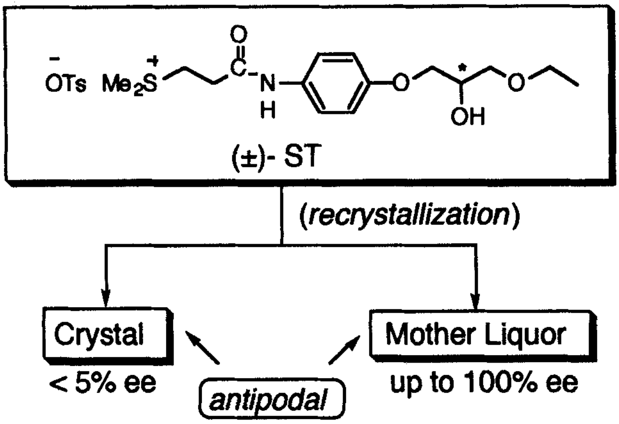
Abstract By recrystallization of certain racemic compound (ST), racemic compound crystals, mixed crystals of two enantiomers, or a mixture of these two types of crystals were obtained, depending on the recrystallization conditions employed. Their crystal forms were determined by X-ray diffraction of the single crystals and powdered materials. The space group and lattice parameters of the mixed crystals were identical with those of the enantiomeric crystals. This polymorphism of ST crystals would be ascribed to the small difference in the thermodynamic stability between the enantiomeric and racemic crystals. The physicochemical properties of ST are described, too.

INTRODUCTION

In connection with the industrial and pharmaceutical needs of chiral organic compounds, exploitation of economically and environmentally acceptable optical resolution methods has been the subject of considerable recent development.[1-5] Although an optical resolution by simple crystallization of enantiomer mixtures provides an easy access to chiral organic compounds, it has been limited to two special cases.[1] One is known as a preferential crystallization of racemic mixtures (conglomerates) consisting of a mixture of two enantiomeric crystals, leading to the substantial optical enrichment of the deposited crystals compared with the mother liquor. The other case is the considerable optical enrichment of the mother liquor often observed upon recrystallization of the non-racemate of racemic compound crystals, resulting from the principal deposition of racemic compound crystals with lower solubility than the corresponding optically active crystals. However, optical resolution of the racemate of racemic compound crystals exactly consisting of pairs of two enantiomers by simple recrystallization has been believed to be totally infeasible. Recently we have found a surprising exception for this protocol. Namely, simple recrystallization of the racemate of certain racemic compound, (±)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]dimethylsulfonium p-toluene-



SCHEME 1 Unusual optical resolution phenomenon of (±)-ST.

sulfonate [(±)-ST],[6, 7] led to remarkable optical enrichment (up to 100% ee) of the mother liquor, along with the deposition of a large amount of the antipodal crystals of low optical purity (Scheme 1).[8]

In order to gain an insight into the mechanism of this unusual optical resolution phenomenon, we have investigated the properties of ST crystals obtained under various recrystallization conditions and found that (±)-ST is usually composed of a racemic compound crystal but ST can also exist as the mixed crystal of the two enantiomers with a wide range of optical purities. This unique polymorphism observed on crystallization of ST has turned out to be responsible for the remarkable optical resolution phenomenon.[8] Here we describe the molecular and crystal structure of the polymorphic forms of ST obtained under various recrystallization conditions and their physicochemical properties.

MOLECULAR AND CRYSTAL STRUCTURE OF ST

Recrystallization of ST was performed under various conditions and each deposited crystal was characterized by the X-ray diffraction method, HPLC analysis[7] and microscopy of the powdered material or the single crystal. The racemic compound crystals were obtained by recrystallization of (±)-ST in 2-PrOH at 25°C in the presence of the crystal seeds of (±)-ST. Its selected crystallographic parameters and molecular and crystal structure are shown in Table I and Figure 1, respectively. The molecules retain a L shape by bending steeply at the position of the carbon atom of C-OH. Both the methylene group adjacent to the carbonyl group and the dimethylsulfonium moiety are disordered. In contrast, addition of the enantiomeric crystal seeds [(+) or (-)] to (±)-ST in 2-PrOH at 25°C resulted in the deposition of the mixed crystals with nearly 0% ee. Similarly, recrystallization of ST with various optical purities (0 to 80% ee) in 2-PrOH at 25°C in the presence of the enantiomeric crystal seeds led to the deposition of the mixed crystals with the same optical purity and chirality as the original solution (0 to 80% ee). The X-ray crystallographic analysis of the mixed crystal (e. g., 0% ee) thus obtained showed that its space group, lattice parameters, and molecular and crystal structure were almost identical with those of the enantiomeric crystal, but the C-OH bond in the mixed crystal is disordered, reflecting random arrangement of two enantiomers in the defined positions in the crystal, as shown in Table I and Figure 2. The molecules assume a L shape structure similarly to (±)-ST.

In the crystal of (±)-ST, there are two types of direct intermolecular interactions between the long-chain moieties in a pair of enantiomers; one is a hydrogen-bonding between hydroxyl group and carbonyl group, and the other is an electrostatic interaction between hydroxyl group and sulfonium group. On the other hand, in the crystal of (-)-enantiomer or the mixed crystal the two long-chain moieties interact each other indirectly through the intermediacy of the two sulfonate groups. These hydrogen-bonding and electrostatic interaction and the corresponding intermolecular distances between heteroatoms are illustrated in Scheme 2.

TABLE I Selected crystallographic parameters for ST crystals.

Parameter	Racemate	(-)-Enantiomer	Mixed Crystal[a]
space group	$P\bar{1}$	$P1$	$P1$
a, Å	14.638 (2)	10.762 (3)	10.748 (7)
b, Å	15.681 (2)	15.615 (2)	15.616 (2)
c, Å	6.2281 (6)	8.223 (2)	8.234 (3)
α, deg	100.32 (1)	100.41 (2)	100.50 (2)
β, deg	99.781 (9)	108.50 (2)	108.47 (3)
γ, deg	66.258 (9)	85.73 (2)	85.51 (2)
V, Å^3	1279.9 (6)	1289 (1)	1288 (2)
Z	2	2	2
R, Rw	0.052, 0.049	0.043, 0.044	0.044, 0.047

[a] 0 % ee determined by the population analysis of the antipodal isomers.

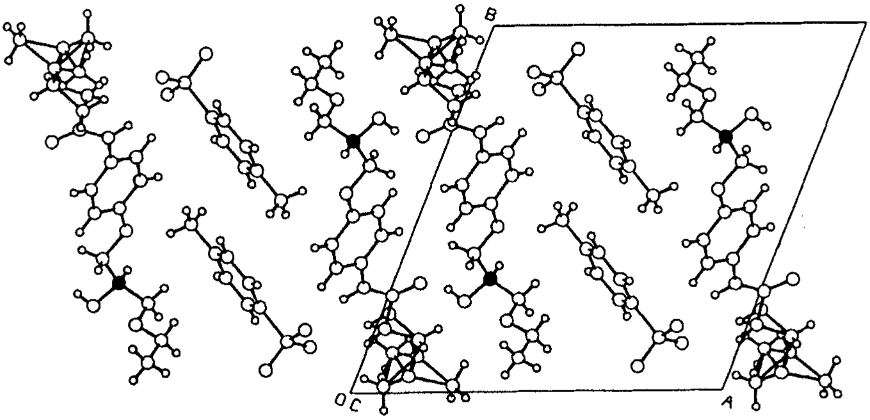


FIGURE 1 Molecular and crystal structure of (±)-ST. Black circles represent the asymmetric carbon atoms.

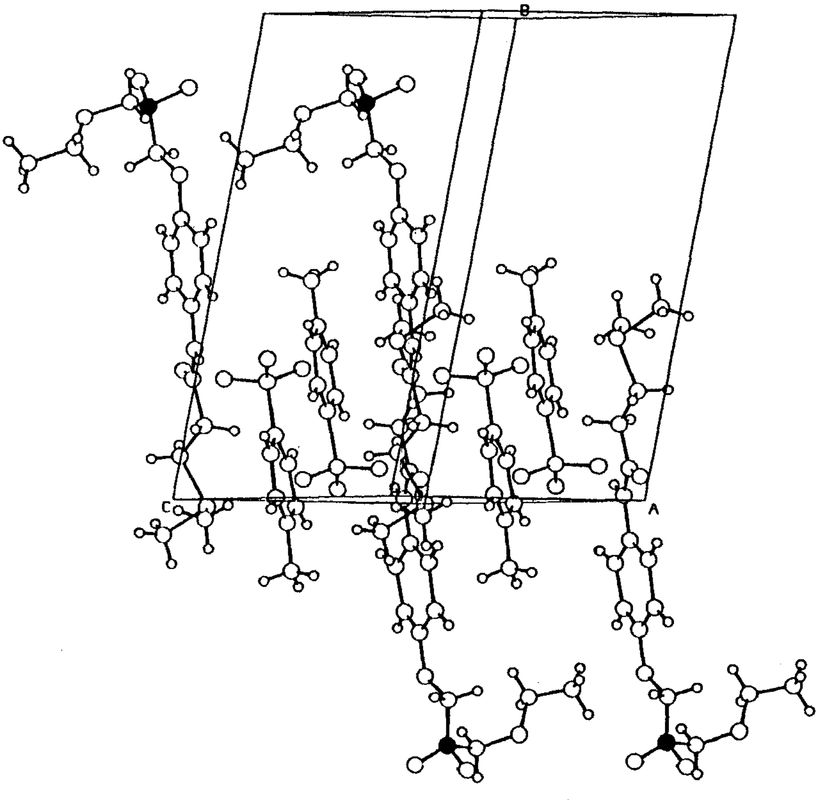
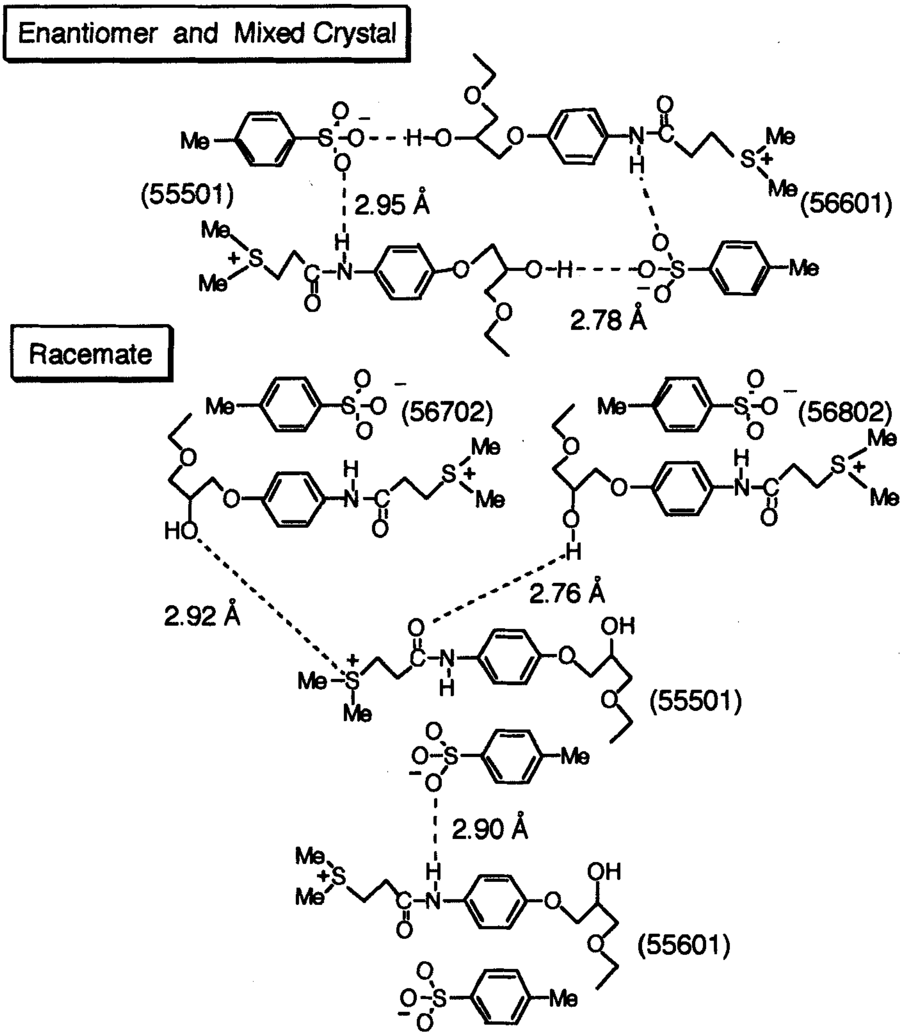


FIGURE 2 Molecular and crystal structure of mixed crystal of ST (0% ee). Black circles represent the asymmetric carbon atoms. The oxygen atoms were observed as orientational disorder with respective occupancy factors by which the ee value was estimated.

More importantly, recrystallization of (±)-ST in 2-PrOH at 25°C without any crystal seed resulted in the deposition of a mixture of a large amount of the racemic compound crystals and a small amount of the mixed crystals. The mode of the concurrent deposition of the two types of crystals is quite important in terms of the elucidation of the mechanism of the unusual optical resolution phenomenon described above.[8]



SCHEME 2 Intermolecular interactions and distances between two heteroatoms. Parentheses represent ADC (ref 9).

PHYSICOCHEMICAL PROPEERTIES OF ST

The melting point, enthalpy of fusion (ΔHf) and solubility of the racemic compound crystal of ST were compared with those of the enantiomeric crystals and the mixed crystal (Table II). From these results, It has been found that an order of the decreasing thermodynamic stability is as follows: the racemic compound crystal > the enantiomeric crystal > the mixed crystal. Further, the IR, solid state ^{13}C CP/MAS NMR and X-ray powder diffraction spectra of the mixed crystals (0% ee) were compared with those of the

TABLE II Physicochemical date of ST crystals.

	M.p.[a] (°C)	Enthalpy of fusion[a] ΔHf (KJ/mol)	Solubility[b] (mg/mL)
(±)-ST (0% ee)	83.2	34.7	10.6
(+)-ST (98.9% ee)	78. 8	36.4	13.1
(-)-ST (99.8% ee)	77.0	34.4	13.5
Mixed crystal (0% ee)	72.2	31.4	15.0

[a] Determined by DSC. [b] In 2-PrOH at 25°C.

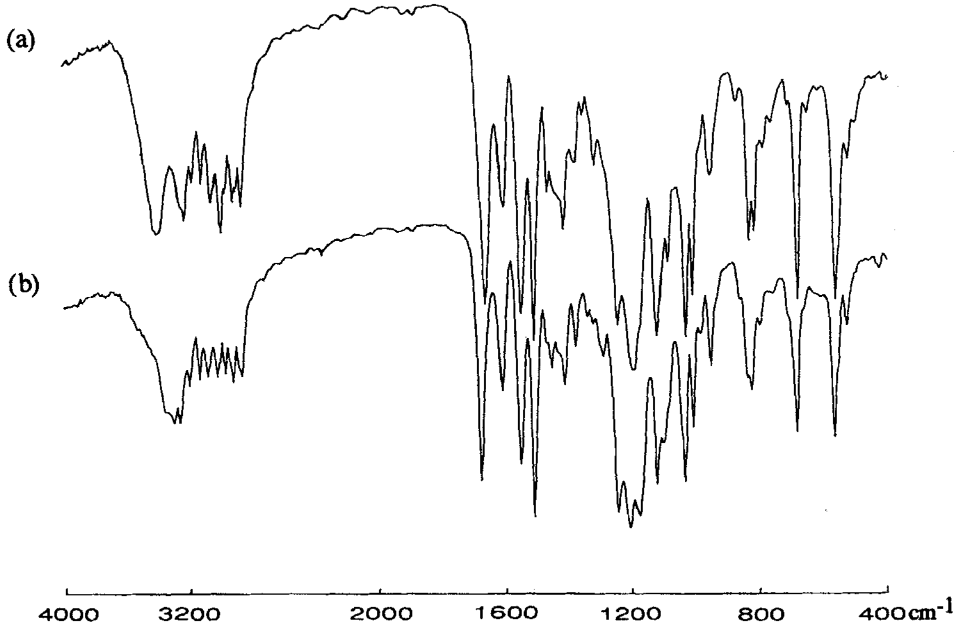


FIGURE 3 Infrared spectra of (a) racemic compound crystals and (b) mixed crystals of ST.

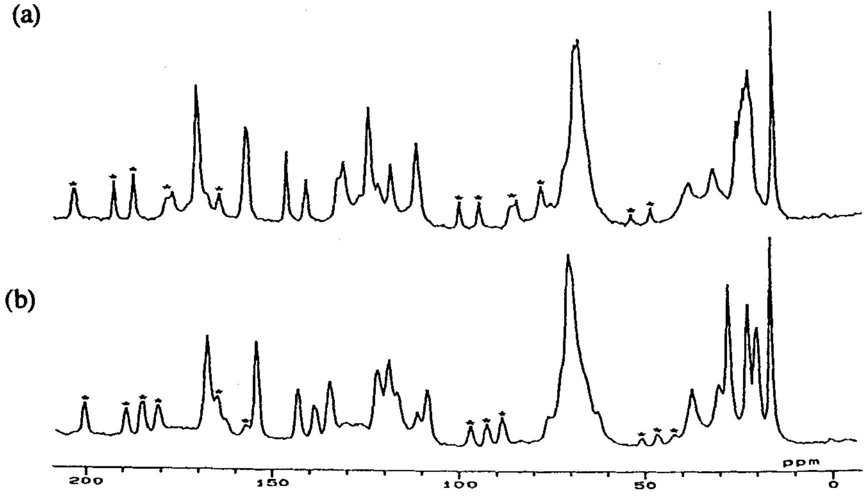


FIGURE 4 ^{13}C CP/MAS NMR spectra of (a) racemic compound crystals and (b) mixed crystals of ST. Asterisk represents side-bands.

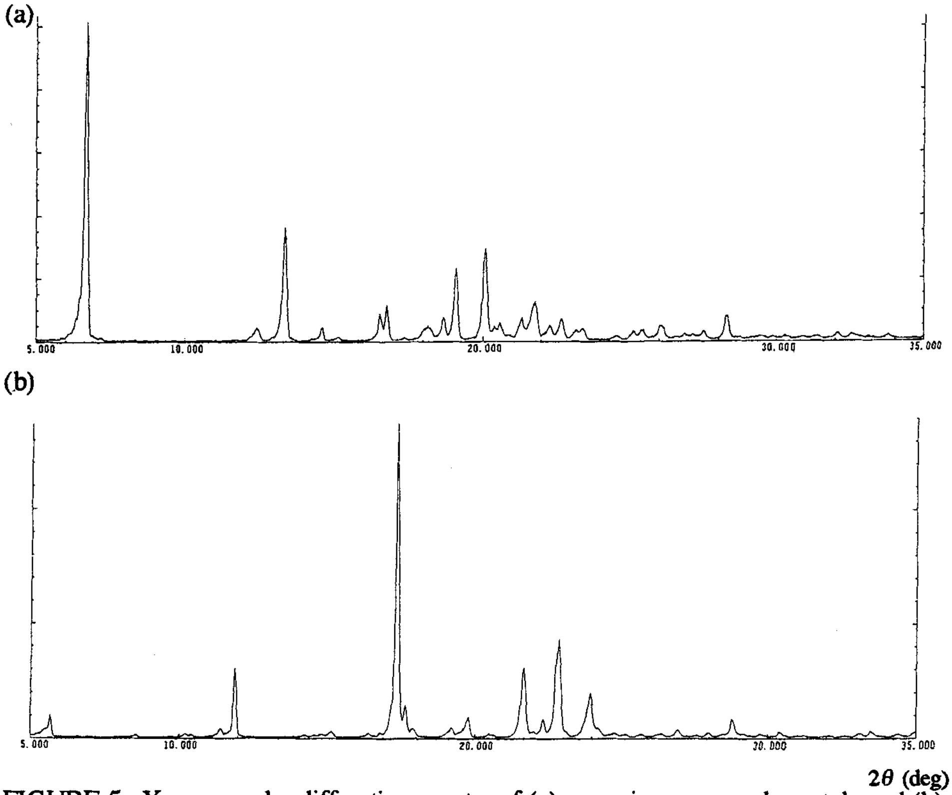


FIGURE 5 X-ray powder diffraction spectra of (a) racemic compound crystals and (b) mixed crystals of ST.

racemic compound crystals (Figure 3-5). These spectral data of the mixed crystals were almost identical with those of the enantiomeric crystals, but distinctly different from those of the racemic compound crystals, as expected from the X-ray crystallographic data shown Table I. Other outstanding differences in the spectral data between the mixed crystals and racemic compound crystals than X-ray powder diffraction patterns are summarized below. (1) The frequency of the C=O (1678 cm^{-1}) stretching vibration in the IR spectrum of the racemic compound crystals was lower than that of the mixed crystals by 13 cm^{-1}, whereas that of the N-H (3299 cm^{-1}) stretching vibration of the mixed crystals was lower than that of the racemic compound crystals by 115 cm^{-1}. (2) The chemical shift of the $\underline{C}$=O in the ^{13}C CP/MAS NMR spectrum of the racemic compound crystals was shifted by 2.8 ppm downfield compared with that of the mixed crystals. These results indicate the existence of fairly strong hydrogen-bonding associated with the C=O group in the racemic compound crystals and the N-H group in the mixed crystals, which is in good agreement with the results of X-ray crystallographic analysis shown in Scheme 2.

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REFERENCES

1. (a) A. Collet, M-j. Brienne and A. Jacques, Chem. Rev., 80, 215 (1980).
   (b) A. Jacques, A. Collet and S. H. Wilen, Enantiomers, Racemates and Resolutions, (Wiley, New York, 1981).
2. P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1-3 (Optical Resolution Information Center, New York, 1978, 1981 & 1984).
3. Toda, F. *Top. Curr. Chem.*, 140, 43 (1987).
4. J. D. Morrison (ed.), Asymmetric Synthesis, Vol. 5, (Academic Press, Orland, 1985).
5. M. Zief and L. J. Crane (eds.), Chromatographic Chiral Separations, Chromatographic Science Series, Vol. 40, (Marcel Dekker, New York, 1988).
6. A. Koda, Y. Yanagihara and N. Matsuura, Agents Actions, 34, 369 (1991).
7. T. Ushio and K. Yamamoto, J. Chromatogr. A, 684, 235 (1994).
8. T. Ushio, R. Tamura, N. Azuma and K. Yamamoto, a manuscript submitted for publication.
9. TEXSAN: Texray Structure Analysis Package, Molecular Structure Corp., 1985.