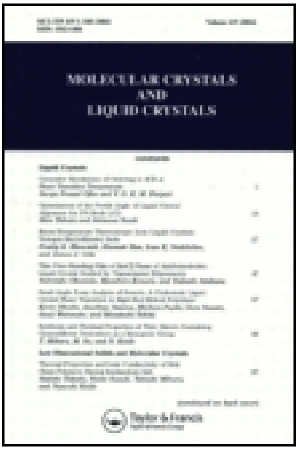

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Preferential Enrichment and Crystal Structure

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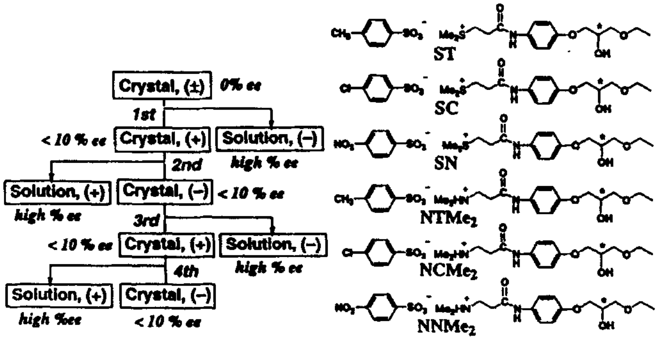
Comparison of three different stable crystal structures of (±)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]dimethylammonium *p*-nitrobenzenesulfonate [(±)-$NNMe_2$], and its *p*-chlorobenzene-sulfonate [(±)-$NCMe_2$] and *p*-toluenesulfonate [(±)-$NTMe_2$] derivatives is described. The first two racemates exhibited the phenomenon of the Preferential Enrichment, but the last one failed to do. It is clear that the nature of the para substituent on the benzenesulfonate group greatly affects the crystal structure and thereby governs the occurrence of the Preferential Enrichment; i.e., substitution by an electron-withdrawing group leads to the formantion of an ordered racemic compound crystal or a fairly ordered racemic mixed crystal of the two enantiomers, while the presence of an electron-donating group results in the formation of a highly disordered racemic mixed crystal.

Keywords: preferential enrichment; enantiomeric resolution; mixed crystal; racemic compound; disorder

INTRODUCTION

Recently we have reported the first case of accomplishment of enantiomeric resolution by simple recrystallization of a series of racemic compounds [(±)-ST,[1,2] SC,[3] SN[4], $NNMe_2$[5] and $NCMe_2$[6], although in principle this type of enantiomeric resolution has been believed to be impossible for more than a century since the mechanical resolution of enantiomeric conglomerates by Pasteur[7] and the discovery of the "preferential crystallization" by Gernetz.[8] We have referred to this new enantiomeric resolution phenomenon as the "**Preferential Enrichment**" in the mother liquor. Preferential Enrichment has the following features: 1) Repeated recrystallization of the racemate and each crop of deposited crystals results in a remarkable alternating enrichment of the two enantiomers up to 100% *ee* in the mother liquors (***enantiomeric enrichment in the mother liquors***). 2) When nonracemic crystals with low *ee* values are recrystallized, the resulting deposited crystals always have the opposite chirality (***reversal of chirality in the deposited crystals***) as shown in Scheme 1. 3) Only the racemates or nonracemates with low *ee* values have to be crystalline, since highly enantiomerically enriched materials are obtained from the mother liquor. These unique features are quite different from those of the preferential crystallization of conglomerates in which considerable enantiomeric enrichment occurs in the deposited crystals.[9]

The investigation of the crystal properties of ST[1,2] and $NNMe_3$[10] has suggested that (1) the presence of polymorphism between a metastable mixed crystal of the two enantiomers and a stable racemic compund crystal and thereby (2) the transformation of the metastable polymorph into the stable one are responsible for the phenomenon of the "Preferential Enrichment." In order to predict the overall mode of the polymorphic transformation associated closely with the mechansim of the Prererential Enrichment, it is essential to elucidate each stable crystal structure of the componds, which show the phenomenon of the Preferential Enrichment, and compare it with the metastable one if available. Here we report three different crystal structures of three compounds ($NNMe_2$, $NCMe_2$ and $NTMe_2$) obtained by slight modification of the molecular structure; 1) an ordered racemic compound crystal, 2) a fairly ordered racemic mixed crystal and 3) a highly disordered racemic mixed crystal, where the first two cases effected the Preferential Enrichment but the last one failed to do.



SCHEME 1 Preferential Enrichment.

CRYSTAL STRUCTURE OF AN ORDERED RACEMIC COMPOUND CRYSTAL

As already reported, (±)-$NNMe_2$ showed the phenomenon of the Preferential Enrichment.[5] The single crystal was prepared under much more diluted conditions than those used for the Preferential Enrichment experiment; slow crystallization from the two-fold saturated 2-propanol solution at 25°C afforded an adequate single crystal with a size of 0.35 x 0.20 x 0.15 mm. The crystalline form of (±)-$NNMe_2$ has proved to be a racemic compound composed of a pair of *R* and *S* molecules in the unit cell (Z=2) of a centrosymmetric space

TABLE I Space group and lattice parameters.

compound	space group	Z	a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)
(±)-$NNMe_2$	$P\bar{1}$	2	10.062	15.365	8.439	97.56	91.48	70.85
(±)-$NCMe_2$	$P\bar{1}$	2	9.896	15.250	8.496	98.20	91.88	71.15
$NCMe_2$§	$P1$	2	9.917	15.248	8.502	98.26	92.27	71.13
(±)-$NTMe_2$	$P2_1/c$	4	12.699	8.645	22.341	-	91.99	-

§ca. 40% *ee*. R, Rw, V($Å^3$): 0.054, 0.087, 1221.5 for (±)-$NNMe_2$; 0.043, 0.070, 1200.9 for (±)-$NCMe_2$; 0.044, 0.042, 1203.9 for $NCMe_2$ (ca. 40% *ee*); 0.051, 0.069, 2451.2 for (±)-$NTMe_2$.

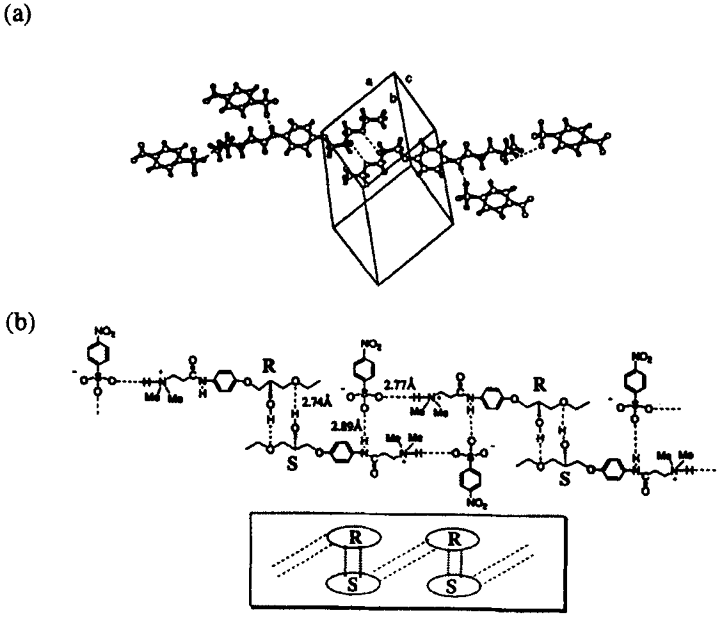


FIGURE 1 (a) Molecular and crystal structure and (b) schematic representation of the intermolecular hydrogen bonding mode of (±)-$NNMe_2$.

group $P\bar{1}$ (Table 1 and Fig. 1). There are three kinds of intermolecular hydrogen bonds; one is between the hydroxy group and the ethoxy oxygen atom (O—O distance: 2.74 Å) in a pair of *R* and *S* molecules resulting in the formation of a head-to-head cyclic dimer, and two other hydrogen bonds were observed between an oxygen atom of one sulfonate group and the amide NH (N—O distance: 2.89 Å) and between another oxygen atom of the same sulfonate group and the ammonium hydrogen atom in the neighbouring long-chain cation (N—O distance: 2.77 Å). Thus, by virtue of these hydrogen bonds, one-dimensional heterochiral chain (::::R=S::::R=S:::::R=S::::) is formed in the crystal lattice (Fig. 1b).

CRYSTAL STRUCTURE OF A FAIRLY ORDERED RACEMIC MIXED CRYSTAL

Preferential Enrichment was reported to occur for (±)-$NCMe_2$.[6] Single crystals of the racemate and the *S*-enriched nonracemic material of ca. 40% ee were obtained by crystallization from two-fold saturated racemic and nonracemic (65% *ee*) solutions in 2-propanol at 25°C, respectively, followed by very slow evaporation of the solvent, and were subjected to X-ray crystallographic analysis. The stable crystalline form of (±)-$NCMe_2$ was not a racemic compound but a racemic mixed crystal, although the crystal structure was solved in the space group $P\bar{1}$ because the single crystals obtained were composed of almost the equal amouonts of the two enantiomers with an *ee* value of less than 0.4% by HPLC analysis (Table 1 and Fig. 2). The crystal structure was characterized by intermolecular hydrogen bonds between the hydroxy group of the long-chain cation and the oxygen atom of the ethoxy or amide carbonyl group in the neighbouring long-chain cation, and between the ammonium and amide NH groups of the long-chain

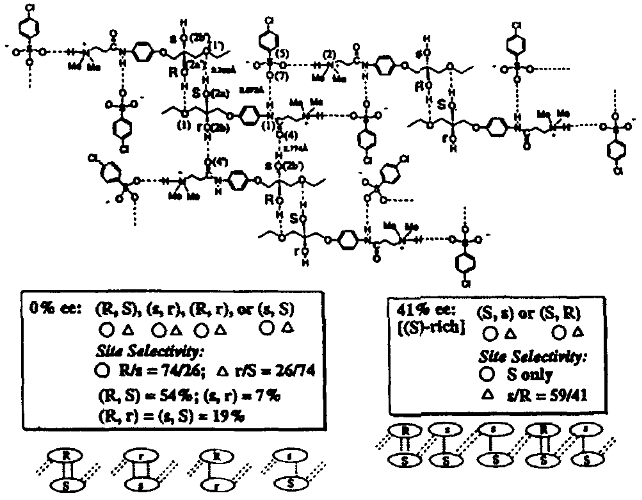


FIGURE 2 Schematic reprersentation of intermolecular hydrogen bonding mode in the crystal of (±)-NCMe$_2$.

cation and the sulfonate groups of the anion.

Although the crystal structure of (±)-NCMe$_2$ was similar to that of (±)-NNMe$_2$, interestingly, the hydroxy group on an asymmetric carbon atom is disordered over two positions with the occupancy factors of 0.737 and 0.263 for O2a and O2b, respectively (Fig. 2). Hence, either the *R* or the *S* enantiomer can be located at the same site in the crystal lattice. The *R* and *S* enantiomers in the sites with higher occupancy factors are designated **R** and **S** (occupancy factor: 0.737 each), and those in sites with lower occupancy factors **r** and s (occupancy factor: 0.263 each) in Fig. 2. The hydroxy groups of **R** (HO2a') and **S** (HO2a) form hydrogen bonds with the ethoxy oxygen atoms (O1 and O1') of the symmetry-related **S** and **R** molecules, respectively; this leads to the formation of a head-to-head cyclic dimer (probability: 0.737 x 0.737 = 0.543); the lengths of the hydrogen bonds are 2.755 Å for O2a'—O1 and O2a—O1'. Similarly, the hydroxy groups of **r** (HO2b) and **s** (HO2b') form hydrogen bonds with the carbonyl oxygen atoms (O4' and O4) of the symmetry-related **s** and **r** molecules, respectively, to give a side-by-side cyclic dimer (probablity: 0.263 x 0.263 = 0.069); the lengths of the hydrogen bonds are 2.774 Å for O2b—O4' and O2b'—O4. The rest of the crystal consists of equal amounts of *R* and *S* enantiomers that do not form cyclic dimers. The values of the occupancy factors were reproducible for the racemic crystals of $NCMe_2$.

The crystal structure of *S*-enriched nonracemic $NCMe_2$ was isomorphous with that of (±)-$NCMe_2$ (Table 1 and Fig. 2) and was solved and refined in the space group $P1$, since the *ee* value of the crystals was about 40% by HPLC analysis. The hydroxy groups are disordered around a pseudo-center of symmetry, but the initial refinement showed that one of the two independent molecules is essentially ordered and has the *S* configuration. At this stage, the occupancy factor of the OH group (O2a in Fig. 2) with *S* configuration was fixed at 1.0, and that with *R* configuration (O2b) was removed from the atom list. The occupancy factors of the hydroxyl groups belonging to the other of the two independent molecules were refined to 0.59 for the *R* configuration (O2a') and to 0.41 for the *S* configuration (O2b'). Thus, the stable crystalline form of nonracemic $NCMe_2$ has proved to be the mixed crystal composed of different amounts of the two enantiomers.

In a similar way to (±)-$NNMe_2$, there is the third intermolecular hydrogen-bonding mode in the crystals of racemic and nonracemic $NCMe_2$, leading to the formation of one-dimensional chain; the tails of the long-chain cations interact strongly with the sulfonate groups of the anions through two hydrogen bonds (N2—O5 distance: 2.770 Å, N1—O7 distance: 2.872 Å) to give another cyclic dimer structure.

CRYSTAL STRUCTURE OF A HIGHLY DISORDERED RACEMIC MIXED CRYSTAL

It was reported that (±)-NTMe$_2$ failed to show the phenomenon of the Preferential Enrichment.[5] The X-ray crystallographic analysis of (±)-NTMe$_2$ indicated that it is a racemic mixed crystal composed of equal amounts of the two enantiomers ($P2_1/c$, Z=4) and its crystal structure is quite different from that of (±)-NCMe$_2$ (Table 1 and Fig. 3). In the crystal structure, two long-chain cation moieties having the disordered OH groups interact with each other by hydrogen bonds through the intermediary of two sulfonate groups to give a cyclic dimer; an oxygen atom of one sulfonate group interacts with both the disordered two hydroxy groups (O—O distance: 2.85 and 2.96 Å) in one long-chain cation, while another oxygen atom of the same sulfonate group does with one hydroxy group (O—O distance: 2.97 Å) in the same long-chain cation and with an ammonium hydrogen atom (O—N distance: 2.74 Å) in the other long-chain cation. The fact that the occupancy factor of one of the two disordered OH groups is 0.647 and that of the other OH group is 0.353 indicates that there exists the site selectivity for the *R* and *S* molecules in the unit cell to some extent and that the racemic disordered crystal may contain all of the possible sixteen molecular arrangements in the unit cells as shown in Fig. 3. This crystal structure is quite different from those of (±)-NNMe$_2$ and (±)-NCMe$_2$ and this difference is considered to be due to the stronger basicity of the *p*-toluenesulfonate anion than that of the *p*-nitro- and *p*-chlorobenzenesulfonate anions. Furthermore, no formation of one dimensional chain is observed in this highly disordered crystal lattice.

Conclusions

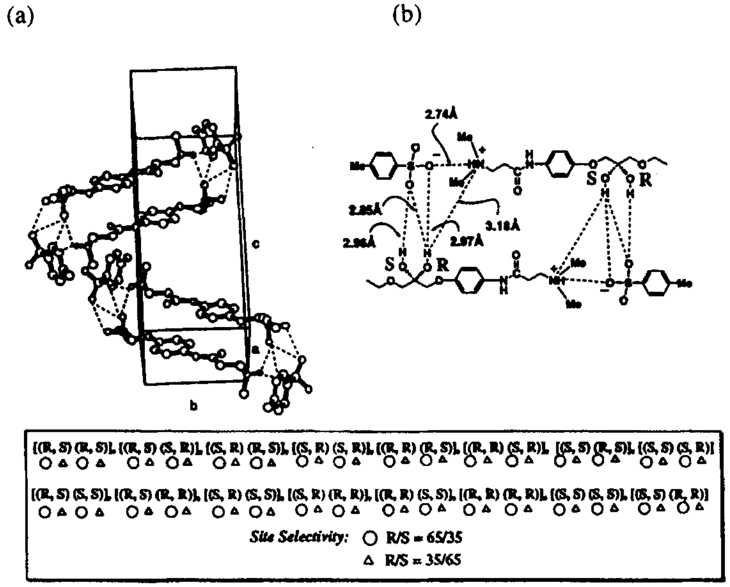


FIGURE 3 (a) Molecular and crystal structure and (b) schematic representation of the intermolecular hydrogen bonding mode of (±)-$NTMe_2$.

It has been indicated that the electronic effects of the para substituent on the benzenesulfonate anion affects the stable crystal structure and thereby governs the occurrence of the Preferential Enrichment. This result is well understood by considering that the polymorphic transformation from less ordered metastable crystal nuclei into more ordered stable crystal ones during crystallization is responsible for the phenomenon of the Preferential Enrichment. Probably, the strong basicity of the sulfonate anion in $NTMe_2$ would result in the formation of less ordered stable mixed crystals by strong intermolecular hydrogen bonds, which are not allowed to transform into more ordered crystals during crystallization. Furthermore, elucidation of the crystal structure of the fairly ordered mixed crystal of $NCMe_2$ has proved to be very useful to understand the common crystal structure of the deposited crystals of a racemic compound type with low *ee* values which are produced by the Preferential Enrichment experiment, because $NCMe_2$ can accommodate excess enantiomers flexibly in the crystal lattice giving crystals with a variety of *ee* values.

Acknowledgments

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