

Crystal structure of a new racemate showing Preferential Enrichment: evidence for the existence as a racemic mixed crystal composed of the two enantiomers

Hiroki Takahashi,^a Rui Tamura,^{*a} Shinsuke Yabunaka^a and Takanori Ushio^b

^a Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan.

Fax: +81 75 753 7915; e-mail: tamura@fischer.jinkan.kyoto-u.ac.jp

^b Taiho Pharmaceutical Co. Ltd., 224-2 Hiraishi Ebisuno, Kawauchi-cho, Tokushima, 771-0194, Japan.

Fax: +81 88 665 6347; e-mail: taka-ushio@taiho.co.jp

10.1070/MC2003v013n03ABEH001796

With the use of X-ray diffraction analysis, new racemate **4** showing Preferential Enrichment has been found to exist as a fairly ordered racemic mixed crystal composed of the two enantiomers in the crystalline state.

Preferential Enrichment is an unusual enantiomeric resolution phenomenon, which is in sharp contrast with the spontaneous resolution of racemic conglomerates¹ with respect to the mode of enantiomeric resolution. Preferential Enrichment has the following four unique features (Figure 1):² (1) Repeated crystallization of the racemate and each crop of the resulting crystals from the 4 to 25-fold supersaturated solution leads to a remarkable alternating enrichment of the two enantiomers up to 100% *ee* in the mother liquors. (2) At the same time, whenever recrystallization is carried out, the resulting deposited crystals always display the opposite chirality with a full reproducibility. (3) Racemates or nonracemates with low *ee* values (< 10% *ee*) are more suitable starting materials for Preferential Enrichment than those with higher *ee* values, achieving a very efficient resolution. Therefore, only the racemates or nonracemates with low *ee* values have to be crystalline to carry out the Preferential Enrichment experiment. (4) No addition of seed crystals is necessary at all.

On the basis of the X-ray crystal structures of a series of ammonium sulfonates showing Preferential Enrichment, we have concluded that the crystalline nature of the racemates of compounds showing Preferential Enrichment should be classified as a racemic mixed crystal (in other words, pseudoracemate or solid solution) composed of the two enantiomers.^{2,3} From this result and the fact that these compounds show the unique binary melting point phase diagrams implying the existence of two polymorphs, the mechanism of Preferential Enrichment 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 a nonracemic

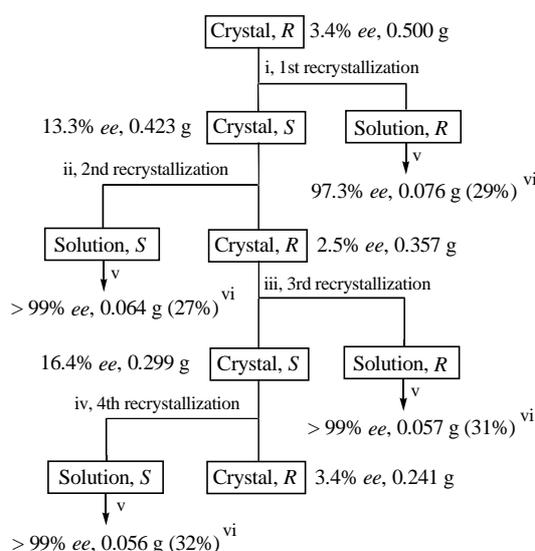


Figure 1 Preferential Enrichment of compound **4**. Conditions: i, EtOH (1.5 ml) at 5 °C for 24 h; ii, EtOH (1.3 ml) at 5 °C for 24 h; iii, EtOH (1.0 ml) at 5 °C for 24 h; iv, EtOH (0.7 ml) at 5 °C for 24 h; v, removal of the solvent by evaporation; vi, recovery (%) of the enriched enantiomer.

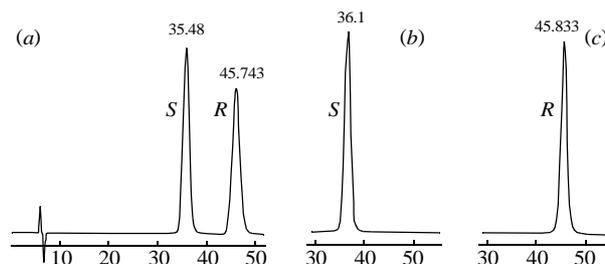


Figure 2 Determination of the *ee* value of **4** by HPLC analysis; (a) racemic sample, (b) *S*-rich mother liquor of > 99% *ee* and (c) *R*-rich mother liquor of > 99% *ee*. Analytical conditions: column, Daicel Chiralcel OD-H (0.46×25 cm); solvent, a mixture of hexane, EtOH, CF₃COOH and Et₂NH (800:200:5:1); flow rate, 0.5 ml min⁻¹; temperature, 25 °C; detector, a UV-VIS spectrometer (254 nm).

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. Processes (3) and (4) are considered to be directly responsible for the enrichment of one enantiomer in the mother liquor.²

However, thus far we have not obtained any evidence for the existence as a racemic mixed crystal with regard to analogous sulfonium sulfonates **1–3** similarly showing Preferential Enrichment because their melting point phase diagrams were not available due to the poor crystallinity of the sulfonium salts with medium to high *ee* values and the obtained crystal structures of racemic **1** and **2** were a completely ordered racemic mixed crystal which can hardly be distinguished from a racemic compound.^{4–7}

Here we report that sulfonium sulfonate **4** makes a new entry into the compounds showing Preferential Enrichment, and the crystal structure of the racemate is exactly classified as a fairly ordered racemic mixed crystal with a certain extent of orienta-

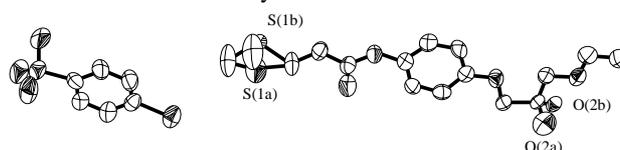


Figure 3 An ortep diagram of the molecular structure of (±)-**4** with the orientational disorder of the hydroxy group [O(2a) and O(2b)] and the positional disorder of the sulfonium sulfur atom [S(1a) and S(1b)]. Displacement ellipsoids are plotted at the 50% probability level.

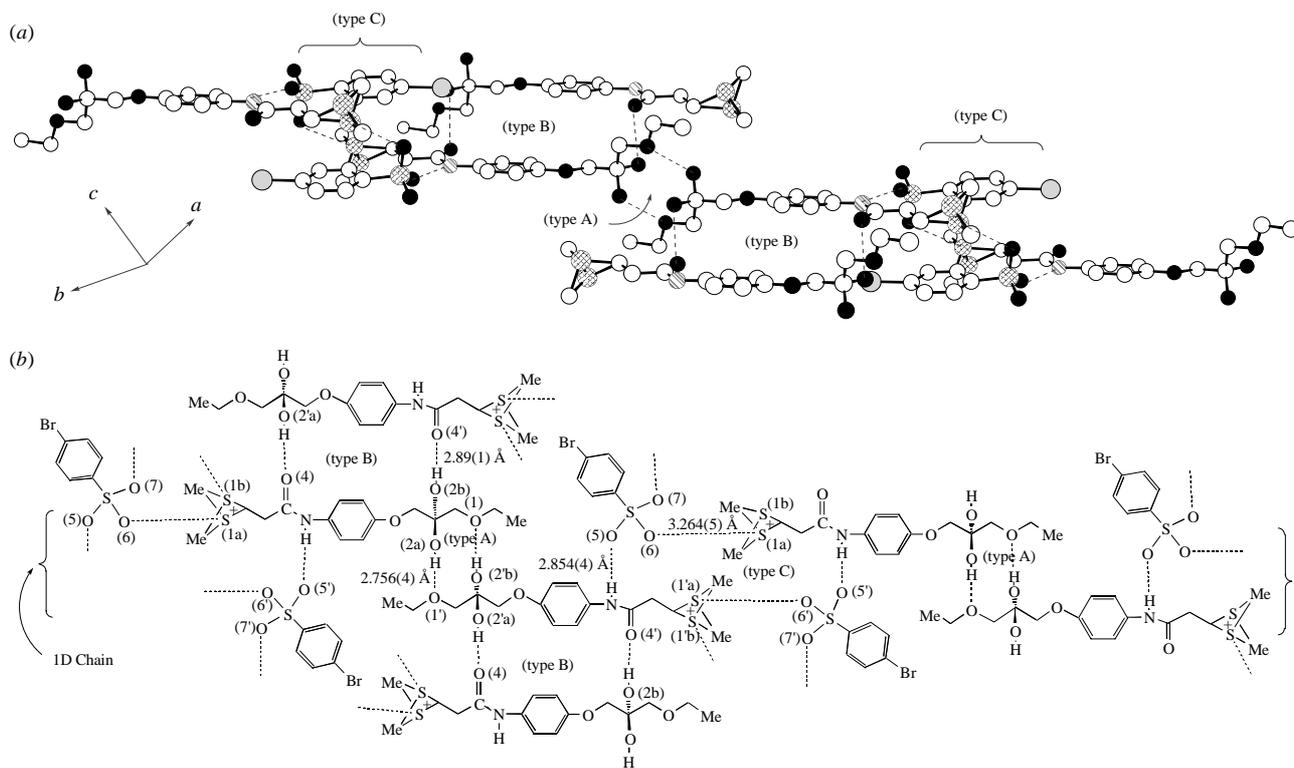
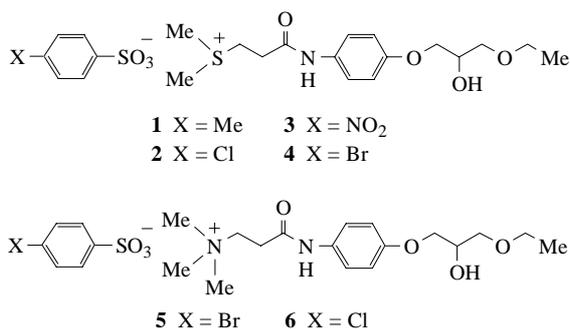


Figure 4 Crystal structure of (\pm) -**4** (a) and its schematic representation (b). The carbon, hydrogen, nitrogen, oxygen, sulfur and bromine atoms are represented by large open, small open, crosshatched, closed, grid and dotted circles, respectively. All hydrogen atoms are omitted in (a). The heterochiral supramolecular 1D chain consists of alternating type A and type C dimers.



tional disorder at the position of the OH group on the stereogenic centre.

Racemic **4** [(\pm) -**4**] was prepared in a similar way to (\pm) -**1**– (\pm) -**3** and subjected to recrystallization from ethanol at a concentration of 0.59 mol dm⁻³ at 5 °C.⁷ As shown in Figure 1, Preferential Enrichment occurred regularly and reproducibly by repeating recrystallization to give enantiomerically enriched materials (29 to 45% recovery for each recrystallization) in the mother liquors in the alternating chirality sense (Figure 2). Thus, by collecting and evaporating the mother liquors with the same chirality, very efficient separation of the two enantiomers (> 98% *ee*) has been achieved.⁸

The single crystal of (\pm) -**4** adequate for X-ray crystallographic analysis was obtained from an about twofold supersaturated solution in isopropanol, followed by slow evaporation of the solvent at 20 °C. The crystal structure of (\pm) -**4** indicates that the stable crystalline form is not a racemic compound but a fairly ordered racemic mixed crystal composed of the two enantiomers (Figures 3 and 4).[†] The hydroxy group on the stereogenic carbon atom and the sulfonium sulfur atom were respectively disordered over two positions; constrained refinement of these two positions gave occupancy factors of 0.69 and 0.31 for O(2a) and O(2b), and 0.73 and 0.27 for S(1a) and S(1b), respectively (Figure 3). Hence, either the *R* or the *S* enantiomer can be located at the same site in the crystal. This crystal struc-

ture is very similar to those of (\pm) -**5**³ and (\pm) -**6**⁹ with respect to the orientational disorder of the hydroxy group. It is characterised by hydrogen bonds between the hydroxy groups and either the ethoxy oxygen atoms [the major type A cyclic dimer; O(2a)–O(1') and O(2'b)–O(1) distance: 2.756(4) Å] or the amide carbonyl oxygen atoms [minor type B cyclic dimer; O(2b)–O(4') and O(2'a)–O(4) distance: 2.89(1) Å] (Figure 4). From the occupancy factors for O(2a) and O(2b), the probabilities of the type A and type B dimers in the crystal were estimated to be 0.48 (0.69×0.69) or lower and 0.10 (0.31×0.31) or lower, respectively. The rest of the crystal consisted of equal amounts of the *R* and *S* enantiomers that did not give cyclic dimers including the stereogenic centres. Furthermore, the interplay between (i) the electrostatic interactions between the sulfonate oxygen atoms and the disordered sulfonium sulfur atoms [O(6')–S(1a) and O(6')–S(1'a) distance: 3.264(5) Å] and (ii) the hydrogen bonds between other oxygen atoms of the same

[†] Crystallographic data for (\pm) -**4** at 23 °C: C₂₂H₃₀NO₇S₂Br, triclinic, crystal size 0.35×0.25×0.20 mm, space group *P* $\bar{1}$ (#2), *a* = 9.9222(5) Å, *b* = 15.184(2) Å, *c* = 8.9328(9) Å, α = 98.93(1)°, β = 90.682(6)°, γ = 70.089(7)°, *V* = 1248.8(2) Å³, *Z* = 2, *d*_{calc} = 1.501 g cm⁻³, μ (MoK α) = 1.860 mm⁻¹, *F*(000) = 584. The intensities of 5816 reflections were measured on an Enraf-Nonius CAD-4 diffractometer at 23 °C [MoK α (λ = 0.71069 Å) radiation, $\omega/2\theta$ scans, 2.3° < θ < 27°], and 5461 independent reflections were used for further calculations and refinement. The structure was solved by a direct method and refined using the full-matrix least-squares method against *F* in the anisotropic–isotropic approximation. The refinement is converged to *R* = 0.090, *R*_w = 0.068 and GOF = 1.41 for all independent reflections [*R*₁ = 0.051 is calculated against *F* for 2712 observed reflections with *I* > 2 σ (*I*)]. The number of refined parameters is 318. All calculations were performed using the teXsan program.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 208941. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

sulfonate ions and the amide NH groups [O(5)⋯N and O(5')⋯N distance: 2.854(4) Å] gives a head-to-head cyclic dimer (type C). By virtue of these intermolecular interactions, a heterochiral one-dimensional chain is formed. Furthermore, each 1D chain interacts with two adjacent chains by electrostatic interactions between the third oxygen atoms of the same sulfonate ions and the other disordered sulfonium sulfur atoms [O(7)⋯S(1'b) and O(7')⋯S(1b) distance: 3.378 Å] in the adjacent chains, eventually forming a rigid two-dimensional sheet structure.[‡]

References

- 1 J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Krieger, Malabar, FL, 1994.
- [doi>](#)2 R. Tamura, D. Fujimoto, Z. Lepp, K. Misaki, H. Miura, H. Takahashi, T. Ushio, T. Nakai and K. Hirotsu, *J. Am. Chem. Soc.*, 2002, **44**, 13139.
- [doi>](#)3 H. Takahashi, R. Tamura, D. Fujimoto, Z. Lepp, K. Kobayashi and T. Ushio, *Chirality*, 2002, **14**, 541.
- 4 T. Ushio, R. Tamura, H. Takahashi and K. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2372.
- 5 H. Takahashi, R. Tamura, Z. Lepp, K. Kobayashi and T. Ushio, *Enantiomer*, 2001, **6**, 57.
- 6 R. Tamura, T. Ushio, K. Nakamura, H. Takahashi, N. Azuma and F. Toda, *Enantiomer*, 1997, **2**, 277.
- [doi>](#)7 R. Tamura, T. Ushio, H. Takahashi, K. Nakamura, N. Azuma, F. Toda and K. Endo, *Chirality*, 1997, **9**, 220.
- [doi>](#)8 T. Ushio and K. Yamamoto, *J. Chromatogr. A*, 1994, **684**, 235.
- 9 R. Tamura, H. Takahashi, H. Miura, Z. Lepp, Y. Nakajima, K. Hirotsu and T. Ushio, *Supramolecular Chem.*, 2001, **13**, 71.

[‡] The positional disorder of the sulfonium sulfur atom was also observed for (±)-**2**.⁵

Received: 29th April 2003; Com. 03/2122