Unusual Disordered Crystal Structure of a Racemate Exhibiting a Novel Enantiomeric Resolution: Preferential Enrichment**

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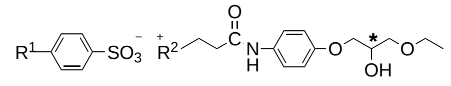
Recently we reported the first case of enantiomeric resolution by simple recrystallization of a series of racemic compounds ((±)-ST,[1, 2] (±)-SC[3] and (±)-SN[4]), although in principle this type of enantiomeric resolution was believed to be impossible for more than a century since the mechanical resolution of enantiomeric conglomerates by Pasteur[5] and the discovery of the "preferential crystallization" technique by Gernetz.[6,7] We refer to this new phenomenon of enantiomeric resolution as "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)[1–4] (Figure 1). An X-ray crystallographic analysis of the racemic single crystals (0 % *ee*) of ST and SC indicated that their stable crystalline forms are composed of a regular packing of the *R* and *S* enantiomers in the crystal lattice (space group $P\bar{1}$, $Z = 2$).[1–3] In addition, it was shown that several related racemic (disordered) mixed crystals[8] in which the same sites are occupied by molecules of the *R* and *S* enantiomers in equal amounts do not exhibit preferential enrichment.[4] Here we report another new case of preferential enrichment in which the stable crystalline form of the racemate is the (disordered) mixed crystal, which, however, is composed of a weakly ordered arrangement of the two enantiomers and contains the centrosymmetric heterochiral cyclic dimer (*R*,*S*) as the major component (ca. 54 %) in the crystal lattice.



ST, R^1=CH$_3$ R^2=Me$_2$S **SN**, R^1=NO$_2$ R^2=Me$_2$S
SC, R^1=Cl R^2=Me$_2$S **NC**, R^1= Cl R^2=Me$_2$NH

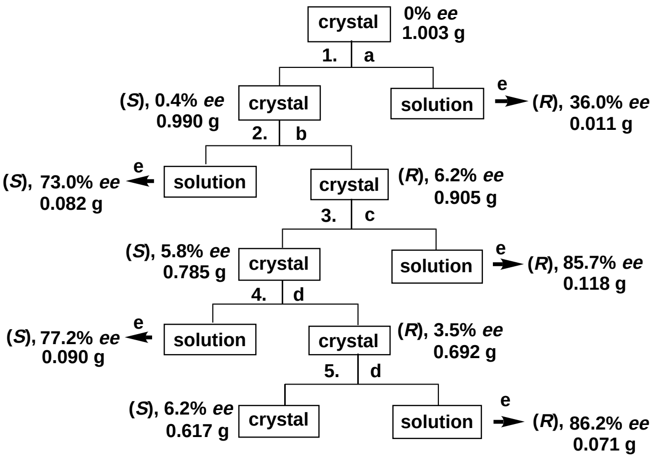


Figure 1. Preferential enrichment of NC. The crystals were dissolved in EtOH by heating. The saturated solution was cooled to 25 °C, stirred until crystallization began, and then allowed to stand for the stated period of time. Crystallization conditions: a) EtOH (10 mL), 25 °C, 17 d; b) EtOH (10 mL), 25 °C, 5 d; c) EtOH (10 mL), 25 °C, 3 d; d) EtOH (8 mL), 25 °C, 3 d; e) removal of the solvent by evaporation. The *ee* values of the mother liquors and crystals were determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H, 0.46 × 25 cm) and a mixture of hexane, EtOH, CF$_3$COOH, and Et$_2$NH (800/200/5/1) as the mobile phase.

Preferential enrichment of the ammonium analogue of (±)-SC, (±)-{2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl}dimethylammonium *p*-chlorobenzenesulfonate [(±)-NC], was effected by recrystallization from a fivefold supersaturated solution in ethanol or 2-propanol at 25 °C. Both the alternating enantiomeric enrichment in the mother liquors (up to 86 % *ee*) and the reversal of chirality in the deposited crystals were observed (Figure 1). The X-ray powder diffraction pattern of the racemate was similar to but clearly different from that of the pure enantiomer. Furthermore, the melting point of the racemate (124.4–130.0 °C) determined by differential scanning calorimetry (DSC) is higher than that of the pure enantiomer (73.5–96.2 °C). From these results, we predicted that the stable crystalline form of the racemate of NC would be a racemic compound, as was observed for related compounds.[1–4]

Single crystals of the racemate and the *S*-enriched nonracemic material (ca. 40 % *ee*) were obtained by crystallization without stirring from twofold supersaturated 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 crystal structure of the racemate of NC was solved in the space group $P\bar{1}$, because the single crystals obtained were composed of almost the equal amounts of the two enantiomers with an *ee* value of less than 0.4 % (HPLC analysis). The unique molecular arrangement of *R* and *S* enantiomers is shown in Figures 2 and 3. Contrary to our expectation, the stable

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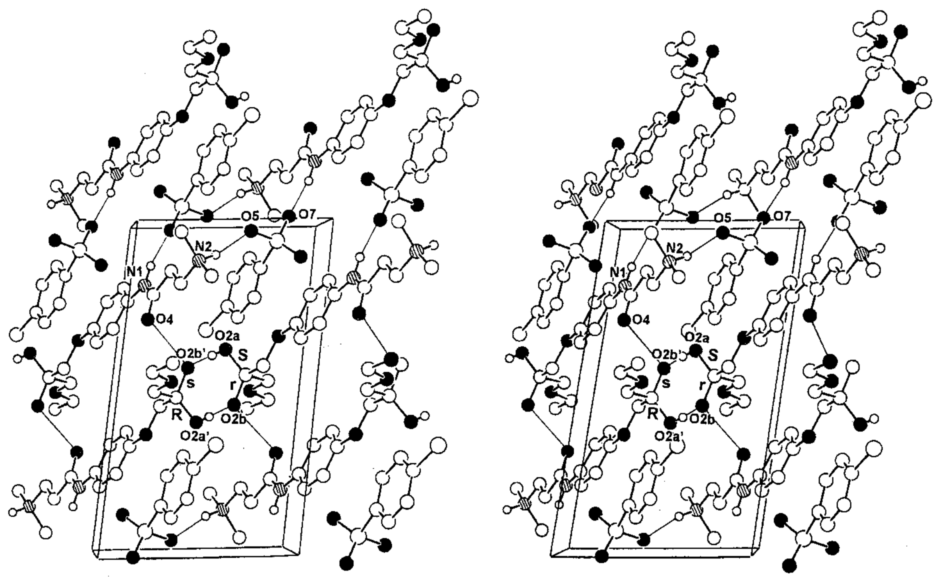

Figure 2. Crystal structure of (±)-NC viewed down the *a* axis (stereoview). The *b* axis is vertical, and the *c* axis is horizontal. The carbon, oxygen, and nitrogen atoms are represented by open, full, and hatched circles, respectively. Hydrogen atoms are omitted for clarity except for those of hydroxyl and amido groups. Hydrogen bonds are indicated by thin lines. **R** and **r** represent the more and less highly occupied sites of the *R* enantiomers, and **S** and **s** the corresponding sites of the *S* enantiomer.

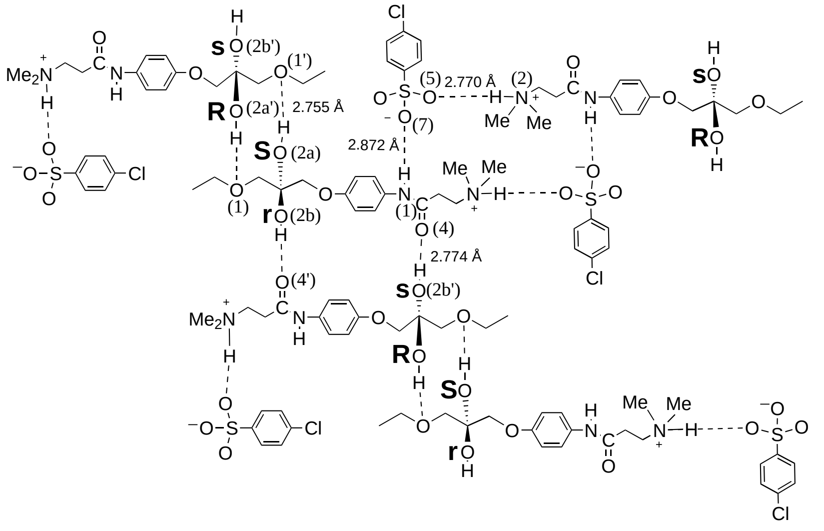

Figure 3. Schematic representation of the various types of intermolecular hydrogen bonds in the crystal of (±)-NC.

crystalline form of (±)-NC is not a racemic compound, but the racemic (disordered) mixed crystal. It is surprising that a racemate existing as a stable racemic (disordered) mixed crystal can exhibit preferential enrichment.[4] To gain an insight into this unexpected result, we investigated the crystal structure of (±)-NC in detail and compared it with that of the nonracemic crystal.

The crystal structure of (±)-NC is characterized by hydrogen bonds between the hydroxyl group and the oxygen atom of the ethoxy or amido group of the long-chain cation, and between the ammonium and amido NH groups of the long-chain cation and the sulfonate groups of the anion. Interestingly, the hydroxyl group on an asymmetric carbon atom (C4) is disordered over two positions. Constrained refinement of these two positions gave occupancy factors of 0.737 and 0.263 for O2a and O2b, respectively. Hence, either the *R* or the *S* enantiomer can be located at the same site in the crystal lattice. The occurrence of the racemic (disordered) mixed crystal is explained in terms of the presence of a site in the crystal lattice that can accomodate O2a and O2b and allow the interaction of both O2a and O2b with hydrogen-bond acceptors. 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 Figures 2 and 3. The hydroxyl group of **R** (HO2a′) and **S** (HO2a) forms hydrogen bonds with the ethoxy oxygen atom (O1 or O1′) of the symmetry-related **S** and **R** molecules, respectively; this leads to the formation of a head-to-head cyclic dimer around a center of symmetry at ½, ½, ½ (probability: 0.737 × 0.737 = 0.543); the lengths of the hydrogen bonds are 2.755(3) Å for O2a′–O1 and O2a–O1′. Similarly, the hydroxyl groups of **r** (HO2b) and **s** (HO2b′) form hydrogen bonds with the carbonyl oxygen atoms (O4′ and O4) of the symmetry related molecules to give a side-by-side cyclic dimer around a center of symmetry at 1, ½, 1 and 0, ½, 0 (probability: 0.263 × 0.263 = 0.069); the lengths of the hydrogen bonds are 2.774(8) Å for O2b⋯O4′ and O2b′⋯O4. The major hydrogen-bonding mode between **R** and **S** molecules and the minor one between **r** and **s** molecules were observed in the related compounds (±)-SC[3] and (±)-ST,[1, 2] respectively. 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. For a crystal grown from a different batch, the occupancy factors were 0.747 for O2a and 0.253 for O2b.

Although the initial structure determination showed that the nonracemic crystal was isomorphous with that of (±)-NC, and *E* statistics and the *N*(*z*) cumulative probability distribution[10a] were consistent with the existence of a center of symmetry, the crystal structure of *S*-enriched nonracemic NC was solved and refined in the space group *P*1, since the *ee* value of the crystals was about 40% by HPLC analysis. The

Hamilton test indicated that the space group of the nonracemic crystal is $P1$ at the 99.5% significance level.[10b] The crystal structure of the mixed crystal of *S*-enriched nonracemic NC was isomorphous with that of (±)-NC (Figure 2). The hydroxyl 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 Figure 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′). An *ee* value of 41% was calculated for this nonracemic crystal. The X-ray powder diffraction pattern of this nonracemate is intermediate between those of the racemate and the pure enantiomer. Therefore, it can be assumed that with increasing fraction of *S* enantiomers in the crystal, the occupation of the sites HO2a and HO2b′ increases and that of HO2a′ and HO2b decreases (Figures 2 and 3), so that the crystal structure of the pure *S* enantiomer is approached. Thus, the stable crystalline form of nonracemic NC is proved to be the (disordered) mixed crystal composed of different amounts of the two enantiomers.

The origin of these unique crystal structures of racemic and nonracemic NC might be accounted for, at least in part, by the third intermolecular hydrogen-bonding mode in the crystals. The tails of the long-chain cations interact strongly with the sulfonate groups of the anions through a hydrogen bond/salt bridge N2−H ⋯ O5−S (N2 ⋯ O5 2.770(3), O5−S 1.452(2) Å) and the hydrogen bond N1−H ⋯ O7 (N1 ⋯ O7 2.872(3), O7−S 1.436(2) Å) to give a cyclic dimer (Figures 2 and 3). These interactions should also play an important role in determining the arrangement of NC molecules in the crystal.

Although the stable crystalline form of racemic NC is a (disordered) mixed crystal of the two enantiomers, which was considered undesirable for the preferential enrichment, due to the weakly ordered arrangement of the two enantiomers with the centrosymmetric cyclic dimer structure (*R*,*S*) as the major component in the crystal lattice, preferential enrichment was obtained. This discovery could expand the range of applications of preferential enrichment.

Experimental Section

(±)-NC: A mixture of the precursor (±)-{2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl}dimethylamine (1.52 g, 4.90 mmol) and *p*-chlorobenzenesulfonic acid (1.20 g, 6.23 mmol) in acetone (20 mL) was stirred for 15 h at 55 °C, cooled to 25 °C and then 5 °C, and filtered. The residue was washed with a small amount of diethyl ether to give (±)-NC as a white solid (1.94 g, 79% yield, 0% *ee*). The *ee* value was determined by HPLC analysis. (*S*)-(+)-NC was similarly prepared from (*S*)-(+)-epichlorohydrin. The specific rotation $[\alpha]_D^{25}$ (2.03, MeOH) was +1.7° (standard deviation 0.2).

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[9] The X-ray data were collected on a Rigaku AFC7R four-circle diffractometer ($T = 296$ K). The structures were solved by direct methods (SHELX86) and subsequent Fourier recycling (DIRDIF94), and refined by full-matrix least-squares refinement against $|F|$, with all hydrogen atoms fixed at calculated positions. Empirical absorption corrections were applied. All calculations were performed with the crystallographic software package teXsan (Molecular Structure Corporation, **1985**, **1992**). Crystal data for (±)-NC: $C_{22}H_{31}O_7N_2SCl$, $M_r = 503.01$, triclinic, space group $P\bar{1}$, $a = 9.896(1)$, $b = 15.250(2)$, $c = 8.496(3)$ Å, $\alpha = 98.20(1)$, $\beta = 91.88(1)$, $\gamma = 71.15(1)°$, $V = 1200.9(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.391$ g cm^{-3}, Mo$_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $\mu = 2.91$ cm^{-1}, $2\theta_{max} = 50°$, $R = 0.043$, $Rw = 0.070$, 4224 independent reflections, 3379 observed reflections ($I > 2.0\sigma(I)$), 303 refined parameters, maximum residual electron density 0.34 e Å^{-3}. The disordered O2a and O2b atoms were refined anisotropically and isotropically to give thermal factors of 3.4 Å^2 (B_{eq}) and 5.0 Å^2 (B_{iso}), respectively. The thermal ellipsoid of O2a is not anomalous. Crystal data for (*S*)-(+)-enriched nonracemic NC: $a = 9.917(2)$, $b = 15.248(2)$, $c = 8.502(1)$ Å, $\alpha = 98.26(1)$, $\beta = 92.27(1)$, $\gamma = 71.13(1)°$, $V = 1203.9(4)$ Å^3, triclinic, space group $P1$, $Z = 2$, $\rho_{calcd} = 1.387$ g cm^{-3}, Cu$_{K\alpha}$ radiation ($\lambda = 1.54178$ Å), $\mu = 26.07$ cm^{-1}, $2\theta_{max} = 120.1°$, $R = 0.039$, $Rw = 0.049$, 3571 independent reflections, 2761 observed reflections ($I > 2.0\sigma(I)$), 595 refined parameters, maximum residual electron density 0.32 e Å^{-3}. The disordered O2a′ and O2b′ atoms were refined isotropically to give thermal factors of 3.4 and 5.0 Å^2, respectively. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101049. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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