Chiral Resolution

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# Fast Attrition-Enhanced Deracemization of Naproxen by a Gradual In Situ Feed**

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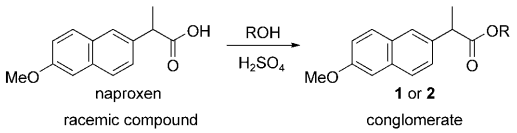
*In memory of Egbert Havinga, born 100 years ago*

Routes to create enantiomerically pure compounds starting from prochiral or racemic components are a principal issue in the discussion on the emergence of prebiotic chiral molecules. Such routes to single-handedness are also of paramount practical importance today, especially for economical high-yielding processes to pharmaceutical compounds that often must be registered in enantiomerically pure form.[1]

Louis Pasteur demonstrated that enantiomorphous crystals (a racemic conglomerate) of a tartrate salt could be separated manually.[2] Crystallization of a conglomerate is an attractive option to obtain enantiomerically pure materials, provided a better means of separation than manual crystal sorting is available. Resolution by crystallization is much more attractive if simultaneous racemization of the unwanted enantiomer occurs. This combination of crystallization and racemization in solution results in a so-called total spontaneous resolution,[3] for which enantiopure seeds are introduced into a clear supersaturated solution in which racemization takes place. These seeds grow further, resulting in an increasing amount of enantiopure solid material, until the solution is depleted of racemate. To reduce the nucleation rate of the undesired enantiomer, the supersaturation can be lowered by introducing many secondary nuclei of the desired enantiomer by stirring.[4,5] In principle, all chiral material that crystallizes can be converted into the desired enantiomer. The theoretical yield in enantiopure solid phase is thus 100% and in practice only limited by solubility. To prevent the unwanted enantiomer from nucleating, however, the crystallization conditions, and in particular the temperature, need to be controlled well.

The recent demonstration of a complete deracemization using crystallization with abrasive grinding under near-equilibrium conditions is a remarkably simple and much more reliable technique to reach an enantiomerically pure end state for these systems.[6] Recently we determined the rate-determining parameters for this deracemization process.[6d] In particular, we found that the deracemization time increases linearly with the amount of solids in the slurry. Furthermore, the time needed for the system to overcome the threshold of the autocatalytic process could be minimized by starting from an enantioenriched solid phase.[6c] Would it therefore be beneficial to start with a small amount of solids having a large enantiomeric excess (*ee*), and then gradually feed the slurry under isothermal conditions with racemic material? In this way, the solid phase can sustain a high *ee*, resulting in a high deracemization rate. Overall, this procedure should shorten the time required to reach an enantiopure solid phase.

Although the gradual feeding can be realized mechanically, the target molecule can be alternatively synthesized in situ, making the practical execution very simple. To show the practical applicability, the non-steroidal anti-inflammatory drug (*S*)-naproxen is used as an example (Scheme 1).




***Scheme 1.*** Esterification of naproxen to the methyl ester **1** (R = Me) or ethyl ester **2** (R = Et).

Naproxen itself crystallizes as a racemic compound, and is therefore not suitable for a resolution as described above.[7] Remarkably, its methyl ester **1** and ethyl ester **2**, both readily prepared by acid-catalyzed esterification of naproxen (Scheme 1), do crystallize as racemic conglomerates, that is, as separate enantiomorphous phases.[7b,8] Both esters can easily be racemized under basic conditions. However, spontaneous resolution as described by Arai et al. by seeding a clear saturated solution of (*RS*)-**1** with (*S*)-**1** and crystallization by cooling gave poor results.[8]

Herein we describe the complete deracemization of naproxen methyl ester **1** by abrasive grinding of a nearly

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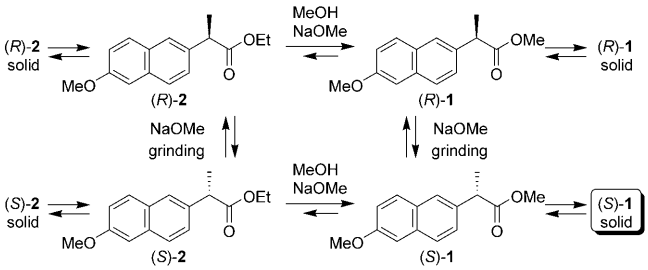
racemic crystal suspension by an in situ feed via transesterification of solid racemic ethyl ester **2** (Scheme 2). Under basic racemization conditions with methanol as a solvent, com-




***Scheme 2.*** Chemical and physical equilibria during the simultaneous transesterification and deracemization of racemic **2** into enantiopure **1**.

pound **2** is reversibly converted into **1**. The solubility of **1** (7.7 wt%, 20°C) is appreciably lower than that of **2** (11.9 wt%, 20°C) in this solvent. The reversible conversion and the difference in solubilities can be used to generate a supersaturated solution of **1** by starting from a saturated solution of **2** in contact with solid **2**, thereby gradually feeding the slurry with racemic **1**. In this way, there is no necessity to cool the system to induce nucleation.

We will compare the efficiency of two routes to deracemization of **1**: direct abrasive grinding of **1**, and abrasive grinding using **2** as feeding material (Figure 1). First, (*RS*)-**1**

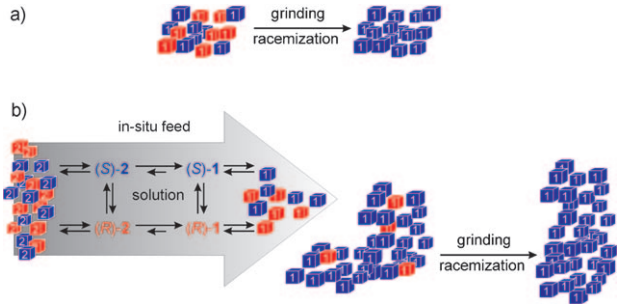



***Figure 1.*** Representations of a) the direct deracemization of **1**, and b) the one-pot deracemization using an in situ gradual feed. In the latter process, racemic solid **2** dissolves and is transformed into (less-soluble) racemic **1**. (*RS*)-**1** precipitates, thereby nurturing an already highly enriched solid phase of **1**, which is readily deracemized under abrasive grinding conditions.[10]

was deracemized using abrasive grinding without the gradual feed. For this process, solution–solid mixtures of methanol and (*RS*)-**1**, together with glass beads, were ground using a thermostated standard ultrasonic cleaning bath. Solution racemization was initiated using sodium methoxide. Figure 2 shows that an initial enantiomeric excess as low as 1.5% leads to exponential evolution of an enantiopure (*S*)-**1** solid phase.[9] Under these conditions **1** is completely stable, and no decomposition products were observed. As can also be seen from Figure 2, starting with 20% *ee* results in complete deracemization in 1.5–2 days. To combine this abrasive

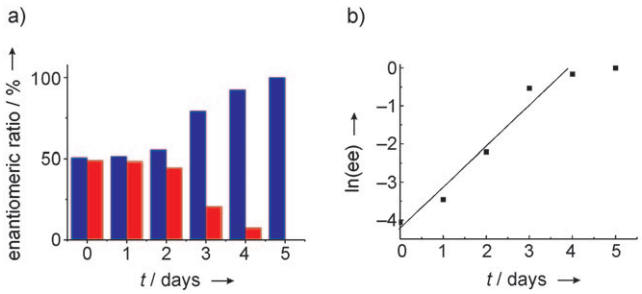



***Figure 2.*** a) Evolution of the solid-phase *ee* value in the (*S*)-enantiomer (blue) at the cost of the (*R*)-enantiomer (red) of **1** under abrasive grinding. The rate of increase in the solid-phase *ee* is exponential (b).

grinding deracemization with a gradual feed using the in situ transesterification reaction (Scheme 2), a solid mixture of 92 mol% (*RS*)-**2** and 8 mol% (*S*)-**1** was partially dissolved in MeOH/NaOMe and ground using glass beads and magnetic stirring at 700 rpm.[11] Sodium methoxide initiates both the solution phase racemization and the conversion of compound **2** into **1** by transesterification. As the solubility of **1** is lower and the solvent shifts the esterification equilibrium towards the side of **1**, all solid material of **2** is converted into **1** (Figure 3, dashed line), following Dimroth's principle.[10,12]

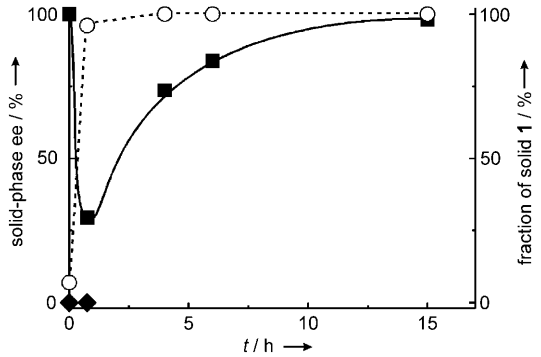



***Figure 3.*** Evolution of the solid-phase *ee* value (left axis) in the (*S*)-enantiomer of **1** (■) and **2** (◆) during the esterification-mediated deracemization. The fraction of **1** in the solid phase (○) corresponds to the right axis. Lines are provided as a guide to the eye.

Simultaneously, crystalline **1** is deracemized as a result of the grinding (Figure 3, solid line). Indeed, the result is a complete conversion of racemic **2** into an enantiomerically pure solid phase of (*S*)-**1**, with a deracemization time of **1** that is reduced dramatically in comparison with the results in Figure 2. This improvement is observed despite the fact that ultrasonic deracemization usually takes less time than in stirred slurries.[6d]

The cascade of events in the present process can be compared with the cooling crystallizations of Kondepudi et al., in which the supersaturation is created by cooling a saturated solution.[4] McBride and Carter argued that in those experiments, the abrasive grinding results in the generation of many small seeds of the same handedness, resulting in a high chiral purity.[5] In our process, this supersaturation is created

by the in situ synthesis of **1**, which has a lower solubility than **2**. Although the secondary nucleation as a result of the grinding will produce many crystals of the same handedness, the racemization of **1** in the solution is not sufficiently fast. Therefore, the unwanted enantiomer also nucleates. However, the resulting solid, which is still rich in the (*S*)-enantiomer, is readily deracemized to 100% enantiomeric purity under the grinding conditions. In the precipitation step, the gradual feeding with racemic **1** by the in situ transesterification of **2** permits avoidance of too large a drop in the solid-state *ee* value. The system remains in the autocatalytic regime, providing a high deracemization rate throughout the process. Paradoxically, relatively slow gradual feeding results in an overall faster evolution to an enantiopure solid **1**.

Various routes have been applied to obtain (*S*)-naproxen, among which the classical resolution using *N*-alkylglucamine with ex-situ racemization of the unwanted enantiomer is currently favored.[1] However, using this large-volume generic drug as an example, we have demonstrated a novel and fast method to obtain enantiomerically pure material by applying an in situ conversion reaction in combination with attrition-enhanced deracemization in a one-pot process. The conversion reaction provides both a gradual feed following Dimroth's principle and a supersaturation without the need for cooling.[10]

In conclusion, a new and industrially attractive route to (*S*)-naproxen in quantitative yield is described, combining in situ transesterification with attrition-enhanced deracemization under isothermal conditions.

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[9] Surprisingly, the cooling crystallizations of Arai et al. only lead to poor enrichments, whereas in the grinding method, complete enantiopurity is reached.[8] This difference can be explained by the relatively slow solution-phase racemization ($t_{1/2} \approx 18$ min). In the case of cooling crystallization, a racemization rate that is slower than the crystallization rate will lead to a supersaturated solution in the undesired enantiomer. This results in the crystallization of the latter, thereby decreasing the enantiopurity of the solid phase. In the case of the grinding process, the relatively slow rate of the racemization process has no influence on the final *ee* value, as in this case the process proceeds under near-equilibrium conditions for which nucleation is rare, if not absent.[6d,i]
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[11] Grinding using a magnetic stirring bar leads to longer deracemization times compared to ultrasonic agitation under otherwise identical conditions.[6d]
[12] Moreover, this allows the process to be started with a large excess of solids of **2**.

  