

Summary

The properties of chiral molecules can be different in living organisms for left- and right handed molecules. Therefore, ways to produce molecules of single handedness are of paramount practical importance today, especially for economical, high yielding processes to synthesize pharmaceutical compounds that often must be registered in enantiomerically pure form. Recently a surprisingly simple way to achieve complete chiral resolution for the conglomerate forming salt NaClO_3 was discovered. Viedma demonstrated the inexorable transformation of a racemic solid phase into a solid phase of single chirality by simply grinding the crystals in a saturated solution. Although the exact mechanism was not understood, the conversion relies on the fact that the chiral identity in the solid phase of the intrinsically achiral NaClO_3 is lost upon dissolution (Figure 1). This intriguing result formed the starting point of this PhD research.

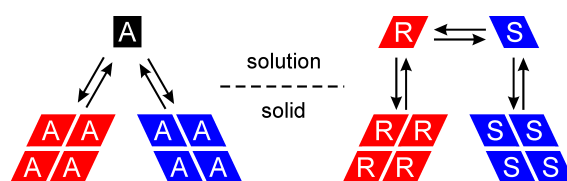


Figure 1. Analogy between solid-solution equilibrium for an intrinsically achiral molecule and a chiral molecule undergoing solution-phase racemization.

The results of Viedma inspired us to apply the technique of abrasive grinding to genuine chiral, consisting of chiral molecules like many pharmaceutical products and their intermediates. To achieve this, a system is needed that first of all forms a conglomerate, and secondly racemizes in solution, in order to maintain a racemic solution during the deracemization process. In Chapter 2 we demonstrate the proof of principle for this method using the imine **1** as a chiral compound, as it is easily racemized in a solution by adding the base DBU (Figure 2). In a series of experiments, showing a complete deracemization of the solid phase in approximately 30 days, the concept was proven. Furthermore, we were able to direct the outcome either by starting from a small enantioimbalance in the solid phase or by adding enantiopure additives.

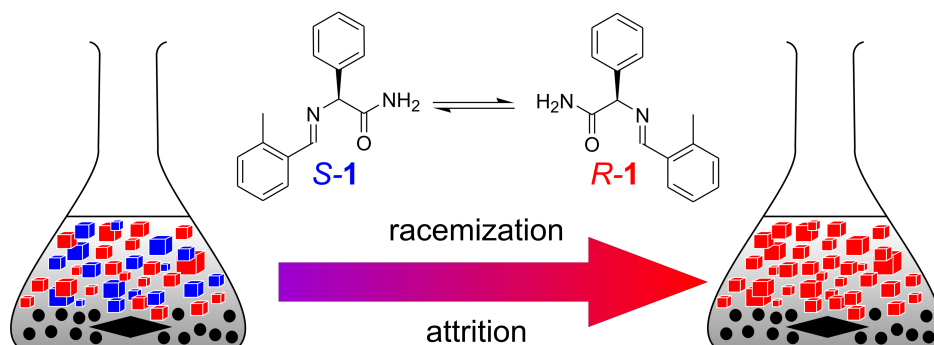


Figure 2. Schematic representation of the deracemization process using abrasive grinding.

We noticed that in the absence of grinding, Ostwald ripening always leads to a solid of single chirality for NaClO₃ (Figure 3, left). Ostwald ripening is a process in which under near equilibrium conditions the larger crystals grow at the cost of the smaller ones. This is a consequence of the Gibbs-Thomson effect, which arises from the fact that large crystals have a lower free energy because of their smaller surface-to-volume ratio. Ostwald ripening, therefore, always leads to a final state consisting of one single crystal that by necessity has a single handedness. This process takes, however, a very long time, up to months, or even years.

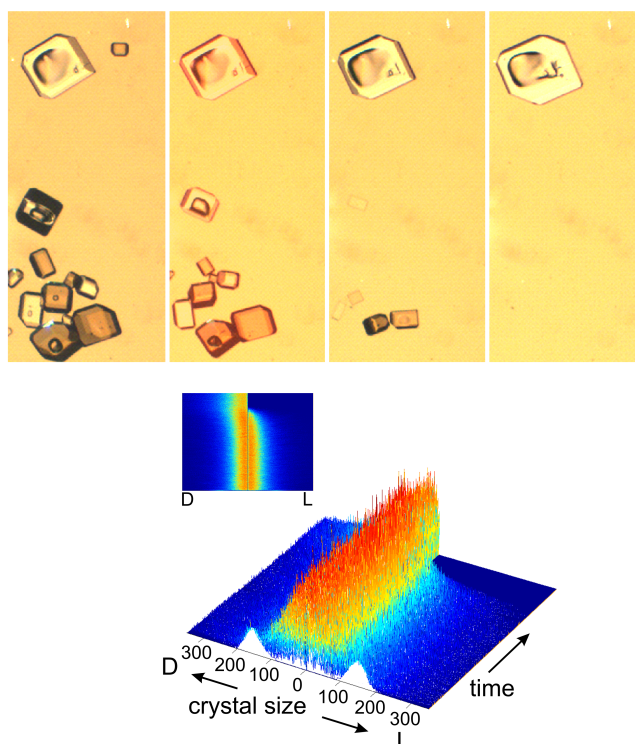


Figure 3. Left: Ostwald ripening of NaClO₃ crystals as observed under a microscope. By using polarizers, the crystals of one handedness are dark and the other light. The end result is a single crystal with single chirality. Right: the result of a computer simulation in which an initial racemic mixture of crystals evolves towards chiral purity.

To further elucidate the accelerating mechanism behind the grinding technique we performed a computer simulation study (Chapter 3). The continuous abrasion of the crystals to small fragments in the deracemization experiments turned out to indeed accelerate the deracemization process. The computer simulations showed that an excess in one of the enantiomers as a result of stochastic fluctuations or of chiral additives, will force the deracemization process to a 100% chiral purity of the solid state (Figure 3). Moreover, the simulations revealed the relevant parameters for the optimization of the deracemization process. In further experiments, choosing suitable conditions inspired by the simulation results, we were able to decrease the deracemization time from approximately 30 days to less than one day, making this a practical route to enantiomerically pure materials (Chapter 4).

Next the research focussed on finding different molecules to show the general applicability of this method. First, a derivative of the natural amino acid phenyl

alanine was deracemized (Chapter 5). However, for this compound, the two enantiomeric solids exhibit mutual epitaxial growth, leading to crystals that consist of several blocks of each enantiomer. Such a growth mode inhibits direct resolution by entrainment. We were pleased to observe, however, that under abrasive grinding conditions a mixture of enantiomers was still converted completely into a single chiral solid phase of the desired handedness.

Using the nonsteroidal anti-inflammatory drug Naproxen as an example of commercially interesting molecule we demonstrated that the commercially relevant (*S*)-enantiomer could be obtained by applying the technique of grinding under racemizing conditions (Chapter 6).

We realized that if we could enantioselectively hamper the growth of one of the two enantiomers using a chiral additive, these crystals could not recover from the grinding, thereby remaining small. This would allow a resolution of the enantiomers without the necessity of the racemization reaction in the solution. In Chapter 7 this idea was tested using a derivate of the amino acid alanine. In case an additive stereoselectively hampers the crystal growth, the crystal size distribution shifts towards smaller sizes for that enantiomer. The enantioselective hampering follows the ‘rule of reversal’, that is, the additive (*R*)-1 blocks (*R*)-2, resulting in a monopolization of large (*S*)-2 crystals and *vice versa*. The large crystals can then be separated by applying a simple washing step in which the small crystals of the undesired handedness are washed away, yielding an enantiopure solid phase of large crystals.

The findings so far also touch on the fundamental scientific issue of the origin of the single handedness of biomolecules in the prebiotic world. Various deterministic scenarios for the evolution of biological homochirality, as found in left-handed amino acids and right-handed sugars, have been proposed. Circularly polarized light (CPL), a phenomenon that is also observed during star formation, is one of the possible actors for such mechanisms. As we knew that the grinding deracemization technique is extremely sensitive to chiral influences, we decided to investigate the use of CPL to direct the final outcome. Indeed, in Chapter 8 we demonstrate that it is possible to transform under grinding conditions a racemic mixture of left- and right-handed crystals into crystals of single chirality hand, with a handedness depending on the rotation sense of the circularly polarized light. The observed deterministic deracemization is attributed to the enantioselective photochemical formation of a chiral crystal growth inhibitor.

Routes to enantiomerically pure molecules are of cardinal importance in the pharmaceutical and food industry. Compared to asymmetric synthesis and separation of enantiomers, the near equilibrium deracemization method is a promising technique with virtually 100% yield. Although the technique is limited to racemic conglomerates that racemize in solution, screening of derivatives on that property broadens the general applicability. From another perspective, the deracemization method outlines a possible pathway to the homochirality found in nature, thereby contributing to the discussion on the emergence of prebiotic chiral molecules.