The transformation of the enantiomorphic but intrinsically achiral salt NaClO₃ into single chirality was recently demonstrated by Viedma by simply grinding the crystals in a saturated solution. Broader application of this grinding method to the deracemization of chiral molecules is subject to prerequisites. The enantiomers must crystallize as separate crystals, and possess the ability to be racemized in solution. The proof of principle was demonstrated using a derivative of the amino acid phenylglycine. For both the chiral and nonchiral compounds, the solid phase enriches exponentially.

Although the practical execution of the process is remarkably simple, there has been much debate regarding its mechanistic details. There is consensus about the main processes that take place. Crystals of both enantiomorphs are continuously ground to small fragments, part of which dissolve, while at the same time the remaining larger crystals grow until they are crushed again. In a stagnant solution, Ostwald ripening, a near-equilibrium process for crystals grow until they are crushed again. In a stagnant solution, Ostwald ripening, a near-equilibrium process for which large crystals grow at the cost of smaller ones, leads to one single crystal, and thus of single-handedness. The process slows down extremely when the crystals become larger. During grinding, however, the rate of Ostwald ripening remains high within a steady-state crystal size distribution that is made up of a large number of small crystals. Several models have demonstrated that for Ostwald ripening to show exponential enantioenrichment in the solid phase, it is not sufficient to describe the crystal growth exclusively by incorporation of monomers; an additional autocatalytic growth mode is necessary to explain the observed exponential behavior. The key question thus lies in the details of the transport of material to the final enantiopure solid phase. Herein this process is discussed for chiral molecules, where solution-phase racemization is necessary.

The first attempt to describe Viedma’s experiment in detail was published by Uwaha. The autocatalytic behavior in his model is due to the reincorporation of subcritical chiral clusters in crystals of the same handedness. Recently, Saito and Hyuga proposed a physical interpretation in terms of an enhanced racemization reaction at the surface of the enantiomorphic crystals. In both models, the minor population is completely converted into the major population of the opposite handedness with a rate that follows the experimentally observed exponential behavior.

The exponential behavior is thus an insufficient criterion to choose one of the models, but, as we will demonstrate below, the models can be distinguished by observing the enantiomeric excess (ee) in the solution. Tsogoeva, Mauksch and co-workers have reported enantioenrichment in solution for the enantiomer that forms the minor population in the solid phase during a reversible Mannich reaction. The authors also conclude that surface-assisted racemization is active in that system.

It was our aim to obtain quantitative data that could be numerically compared with the existing theoretical models. Reliably measuring the solution ee during the deracemization is very difficult, and we therefore performed experiments in the absence of racemization for different values of the ee in the solid phase. Using a centrifuge, the solids were separated from the liquid phase, thus allowing the measurement of the solution enantiomeric excess as a function of the solid phase ee for a wide range of compositions. We found that the solution phase has a surprisingly large excess of molecules with the handedness of the minor solid phase, which becomes more pronounced upon enrichment of the solid phase in the opposite enantiomer. This excess forms the driving force for a net flux of molecules from crystals of the minor handedness to crystals of the major handedness in cases where racemization occurs in solution.

As a model compound we used the same amino acid derivative that led to the proof of principle of the method for chiral molecules, namely the imine formed from 2-methyl-
benzaldehyde and phenyl glycinamide (1).13 We started by
grinding nonracemic mixtures of 1 (0.26 g) with various values for
the initial ee in acetonitrile (4.5 g) without racemization

catalysts using glass beads (8.5 g) in a thermostated ultrasonic

Figure 1. Enantiomeric excess in the solution phase as a function of the
solid-phase enrichment. The solution enriches in the handedness
that is opposite to the enantiomer of the major population in the solid
phase. Filled symbols show the results of grinding a solid phase
enriched in (R)-1, leading to a solution phase enriched in (S)-1. The
curve is a fit of Equation (2) to the data (K1 = 17.1, K2 = 9.74).

grinding. As 1 is a racemic conglomerate, thermodynamics
predicts that the supernatant solution phase is racemic for any
solid composition. We might expect a slight enrichment in the
handedness that is abundant in the solid phase if small
amounts of solid material are also accidentaly sampled. In
practice, however, the solution phase is found to be enriched
in the enantiomer that forms the minor population in the solid
phase. This enantioenrichment becomes even more
pronounced the larger the ee in the solid phase (Figure 1).

In an alternative experiment to test whether the solution-
phase ee is indeed the result of the grinding, we waited for
four hours between the grinding and centrifuge steps. In this
case, the solution-phase enantiomeric excess was zero within
the detection limit of the chiral HPLC (ca. 0.5% ee). Therefore, the inverted ee value in the solution phase is the result of continuous grinding of the enantiomERICALLY enriched
conglomerate crystals.

Our results clearly contradict the enhanced surface
racemization model of Saito, which predicts a zero solution
ee without racemization.10 To compare the experimental
results with the model of Uwaha, we adapted the cluster
model to cover the absence of racemization. The crystal size
distribution in an actual system is simplified by considering
only two sizes: large crystals and small clusters (Figure 2).13

The clusters represent the fragments resulting from ablation.
The set of coupled differential equations that describe the
development of the total number of molecules in the

Figure 2. Representation of the continuous growth and dissolution of

crystals during abrasive grinding, according to McBride.9 During

the grinding, crystals are continuously fragmented into clusters. The
reincorporation of small clusters occurs more frequently for the major
population in the solid phase (process c). As a result, a higher fraction
of clusters of the minor population dissolve, leading to an increase in
molecules of this handedness in the solution phase. Under racemizing
conditions, this concentration difference allows a net flux of molecules
of the minor population to molecules of the major chirality. Thus, the
final result is a complete conversion of the crystals of the minor
handedness into crystals of the chirality that initially forms the major
population.

\[
\frac{\partial N_R}{\partial t} = a (N_R - N_{eq}) N_R - b N_R + c N_S C_R
\]

\[
\frac{\partial N_S}{\partial t} = a' (N_R - N_{eq}) N_R - b N_R - c N_S C_R
\]

\[
\frac{\partial N_C}{\partial t} = -a (N_R - N_{eq}) N_R - a' (N_R - N_{eq}) C_R
\]
the two populations of crystals (Figure 2). The grinding causes the ablation of small fragments from the crystals. According to the Gibbs–Thomson effect, the small fragments or clusters have a higher solubility than the larger crystals.[18] As a result, the smallest clusters dissolve, thereby nurturing the larger crystals: Ostwald ripening. The modeling shows that in Equation (1), the parameter $c$ has to be non-zero to achieve an $ee$ in the solution phase as observed in the experiments (see the Supporting Information). This fact implies that there is a direct route from clusters to crystals of the same handedness, irrespective of the actual transfer mechanism of the molecules. Entire clusters could be incorporated, but the results (and mathematics) are the same if, for example, only a fraction of the cluster would transfer to the crystal. These situations correspond to different values of the rate constant $c$. The only difference between the practical execution of the deracemizations and the results presented herein is the presence or absence of a racemization catalyst. Without racemization, the solution contains an enantiomeric excess that is the inverse of that in the solid phase. In the presence of a racemization catalyst, that is, in a deracemization process, this enantiomeric excess erodes, resulting in an overall net flux of molecules from crystals of the minor handedness towards crystals of the major form. From that perspective, the measurements presented herein can be considered as snapshots of several moments in the deracemization process. In this manner, the inverted enantiomeric excess in the solution phase is the driving force for the deracemization process. Although we have focused on chiral systems, the cluster incorporation model also explains the observed exponential enantiomeric enrichment in acyclic systems such as NaClO$_3$.[3]

The solution $ee$ is a consequence of the fact that for the minority solid phase, the clusters have a lower probability of encountering a crystal of the same handedness. This probability can also be lowered by adding more solvent. An interesting and paradoxical consequence is that upon addition of solvent to a ground slurry, the concentration in the solution increases. We indeed observe this phenomenon of reverse dilution (see the Supporting Information). In a deracemization experiment, the initial 50:50 mixture of left- and right-handed solid converts into 100% single chirality. Reverse dilution then leads to a lower concentration in the final solution corresponding to an energetically more favorable state.

Currently, grinding-induced deracemization is being explored as a practical route to produce enantiomerically pure compounds that can be used in the manufacture of pharmaceuticals. It also provides a scenario for the evolution of single chirality as is found in nature.[12,19-23] Furthermore, a wide variety of procedural approaches, including circularly polarized light, shifted crystal size distributions, and chiral additives have been shown to change at will a racemic mixture of conglomerate crystals to a predetermined handedness.[1,23-25] Although the rate-determining parameters have been identified, pinning down the driving force for this asymmetric transformation has remained a challenge.[3,4,12,14] The major question has been why there is a net flux of molecules of the minor handedness in the solid phase towards the major form.

Herein, we have demonstrated experimentally that in the absence of racemization, a concentration inversion in the solution exists during the grinding of a slurry containing an enantioenriched racemic conglomerate. Upon racemization, this solution phase $ee$ drives molecules towards the handedness that already forms the major population in the solid phase.

From these results, we conclude that deracemization of racemic conglomerates can be explained by including four processes: 1) racemization in the solution (not needed for achiral systems), 2) Ostwald ripening; that is, large crystals growing at the expense of smaller crystals, 3) enantioselective (partial) incorporation of clusters, and 4) attrition. The enantioselective cluster incorporation as proposed by Uwaha is a realization of the concept of chiral recognition.[24]

There has been some debate as to whether the current process should be called Ostwald ripening or not. It is interesting to note that Liesegang, when he introduced the term Ostwald ripening in 1911, suggested that large crystals could grow from small ones either by coalescence or by transport of material through dissolution, which is equivalent to the route through clusters and monomers, respectively, as shown herein.[20] Also in a stagnant solution, clusters will be present as a consequence of the dissolution of the smaller crystals, but these will not play an important role during ripening. The continued attrition during grinding experiments, however, results both in a large number of clusters and frequent encounters between clusters and crystals. This factor appears to be essential to explain the exponential increase in solid-phase $ee$.

The attrition leads to a non-equilibrium crystal size distribution. To stress the difference with the equilibration process of Ostwald ripening, we propose calling this novel route to single chirality Viedma ripening. The reverse dilution forms the thermodynamic driving force in Viedma ripening, whilst the solution-phase racemization provides the kinetic pathway.

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[15] Similar results were obtained after 16 h of grinding.

[16] Under racemizing conditions in the solution, surface-assisted racemization might still play a role. The present results indicate that the incorporation of clusters forms the dominant deracemization mechanism, at least in our system.

[17] In our model, the clusters dissolve and are in that sense subcritical, but they are formed through ablation and not by nucleation. Primary nucleation is unimportant during grinding and is excluded in the model.


