

## GRINDING TO HOMOCHIRALITY THE MECHANISM OF VIEDMA RIPENING

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The initial source of single-handed molecules in nature has been the object of lively discussion among chemists, physicists, biologists, statisticians, geologists, and theologians for 150 years. A recently recognized candidate is recrystallization with grinding, a phenomenon first reported in 2005 by geologist Cristobal Viedma.<sup>[1]</sup>

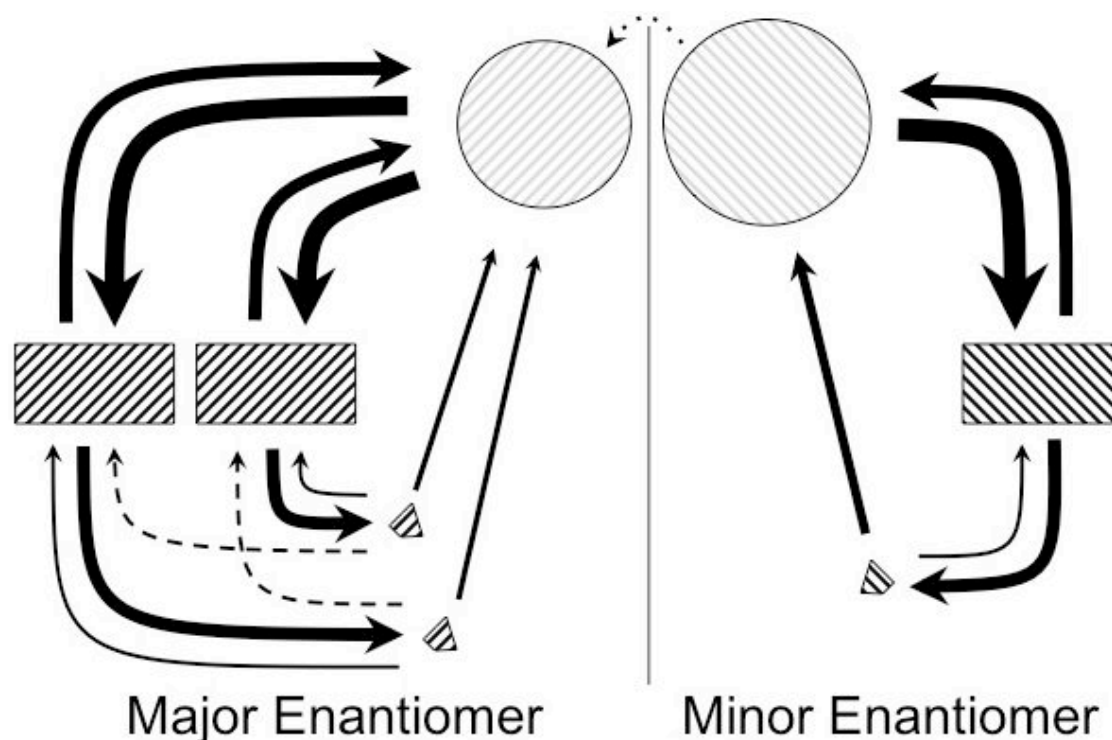
Symmetry-breaking crystallization of solids like sodium chlorate and quartz has been known since the 1850s. During the latter half of the 20th century such phenomena became understood as due to secondary nucleation, where one or a few initial crystals spawn multiple offspring, a process enhanced by stirring.<sup>[2]</sup> Such control requires operating far from equilibrium where the formation of supercritical nuclei is kinetically limiting.

By contrast "Viedma ripening" begins with a slurry containing a near-equilibrium conglomerate of enantiomeric crystals that upon steady, fine grinding spontaneously converts to a single hand. It has been generalized to materials made up of intrinsically chiral molecules, such as amino acid derivatives and pharmaceutical precursors.

While grinding obviously supplies the energy to drive a polycrystalline sample away from the statistically favored racemic composition, the mechanism of its influence has been debated. One school has advocated an interpretation based on Ostwald ripening.<sup>[3]</sup> but the differences between Ostwald- and Viedma ripenings are dramatic, and Ostwald ripening lacks the type of non-linearity and chiral recognition that are required to amplify an enantiomer ratio under the most interesting and relevant conditions.

Recent evidence supports the 1910 suggestion of Liesegang that crystals may grow not only by adding individual molecules or ions, but also by adding crystalline clusters.<sup>[4]</sup> Such growth by enantiomer-specific agglomeration of subcritical clusters generated by steady grinding provides precisely the type of non-linearity and irreversibility necessary to explain Viedma ripening.<sup>[5]</sup> At the same time, Viedma ripening provides what may be the most convincing evidence for crystal growth by incorporation of these tiny crystalline clusters. An independent attempt to demonstrate such incorporation using paramagnetic labeling failed, presumably because of the extremely small size and shortness of life of clusters that can be incorporated rapidly into larger crystals. Grinding maintains a high steady-state concentration of such clusters.

The debate about mechanism of Viedma ripening seems to be resolving in favor of a scheme like that shown in Figure 1.



*Figure 1. Steady-state mass flow in a conglomerate slurry with grinding. Circles denote dissolved enantiomers; rectangles denote enantiomeric crystals; irregular polygons denote enantiomeric subcritical nanocrystals. Arrows denote dissolution, crystal growth, grinding, and enantiomer-specific agglomeration of nanocrystals. The dashed arrows emphasize that there are more agglomerations pathways for the major enantiomer. This retards dissolution via grinding, maintaining a lowered steady-state concentration in solution for the major enantiomer, and driving a steady flow from minor to major (dotted arrow) in solution that leads autocatalytically to chiral purity.*

This scheme predicts that, under grinding, the enantiomer ratio in solution should oppose that in the solid phase, which has been confirmed experimentally.<sup>[6]</sup>

Another line of experimentation suggests that, under reflux, enantiomer-specific agglomeration of subcritical clusters can play an important role in crystal nucleation, even without grinding, and before the appearance of supercritical crystals.<sup>[7]</sup>

Studying Viedma Ripening has reinforced for the speaker five lessons that he had not learned as an undergraduate student of elementary chemistry:

- 1) Solution concentration in a saturated slurry depends on crystal size.
- 2) Single crystals can grow by cluster attachment.
- 3) When a slurry is ground, solution concentration depends inversely on the amount of solid.
- 4) Refluxing can lead to disequilibrium.
- 5) Computer simulation algorithms can be seriously misleading.

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