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*Published in:*  
Angewandte Chemie International Edition

*DOI:*  
[10.1002/anie.200905215](https://doi.org/10.1002/anie.200905215)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2009

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Noorduyn, W. L., Vlieg, E., Kellogg, R. M., & Kaptein, B. (2009). From Ostwald Ripening to Single Chirality. *Angewandte Chemie International Edition*, 48(51), 9600-9606. <https://doi.org/10.1002/anie.200905215>

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# From Ostwald Ripening to Single Chirality

Wim L. Noorduin, Elias Vlieg, Richard M. Kellogg, and Bernard Kaptein\*

ablation · chiral resolution · conglomerates ·  
crystallization · deracemization

**A** century ago Wilhelm Ostwald received the Nobel Prize for Chemistry. Although Ostwald was never significantly involved with the phenomenon of chirality, one of his discoveries, Ostwald ripening, is thought to be involved in a recently discovered method in which grinding-induced attrition is used to transform racemic conglomerates virtually quantitatively into a single enantiomer. In this Minireview the basic concepts developed by Ostwald will be introduced, followed by a summary of the current status of grinding-induced asymmetric transformations. We will see how close Ostwald himself came to discovering this technique.

## 1. Wilhelm Ostwald

This year marks the centennial of the award of the 1909 Nobel Prize for Chemistry to Friedrich Wilhelm Ostwald (1853–1932) for his work on catalysis, chemical equilibria, and reaction velocity (Figure 1). At the end of the 19th century, chemistry in Germany was dominated by synthetic organic chemists. Physical chemistry—general chemistry as Ostwald called it—was still in its infancy. Together with van't Hoff (Nobel Prize 1901) and Arrhenius (Nobel Prize 1903), with whom he collaborated at the University of Leipzig, Ostwald recognized the need for a fundamental understanding of many of the basic issues of chemistry. Ostwald was the author of many textbooks on physical chemistry, of which the *Lehrbuch der Allgemeinen Chemie* (1885) was the standard. Together with van't Hoff he founded the first journal for physical chemistry, the *Zeitschrift für Physikalische Chemie*.

Ostwald's work on catalysis built on the work of Berzelius, who had introduced the term catalyst. At that time, scattered information on catalyzed chemical conversions was available, such as the transformation of starch into dextrins and sugars

by acid, but such transformations were regarded as individual phenomena rather than examples of a mutual relationship. Ostwald recognized the general principle of catalysis by acids and bases, and realized that they

accelerate chemical conversions but remain chemically unchanged.<sup>[1]</sup> For a historical overview of the life of Ostwald we recommend the essay by Ertl which appeared recently in *Angewandte Chemie*.<sup>[2]</sup>

Although Ostwald had a lasting collaboration with van't Hoff, who published his seminal work on the three-dimensional arrangement of molecules in 1874, he did not really become involved with stereochemistry and chirality.<sup>[3]</sup> It is, therefore, a remarkable display of interdisciplinarity that theories developed by Ostwald around 1900 now contribute to a recently discovered method to transform certain racemates autocatalytically and virtually quantitatively into a single enantiomer. We start with Ostwald's seminal work on the growth and stability of crystals.



Figure 1. Wilhelm Ostwald.

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## 2. Ostwald's Rule of Stages and Ostwald Ripening

In 1897 Ostwald reported a study of the nucleation of crystals in droplets. He observed that some compounds first nucleated in a less-stable crystal structure and then later on converted into a more-stable polymorph.<sup>[4]</sup> This observation was generalized as the “rule of stages”: “... *dass beim Verlassen irgend eines Zustandes und dem Übergang in einen stabileren nicht der unter vorhandenen Verhältnissen stabilste aufgesucht wird, sondern der nächstliegende*”. Put in modern terms, the less-stable polymorph will nucleate first, and later converts into the most stable polymorph, sometimes via structures of intermediate stability.

In subsequent studies, Ostwald observed that a saturated solution containing large and small crystals is supersaturated with respect to the large crystals and undersaturated with respect to the small ones. In 1900 he bolstered this theory by studying the influence of the crystal size on the solubility.<sup>[5,6]</sup> He first measured the solubility of crystals in contact with a stagnant saturated solution and then added “Tariiergranate” (probably small metal balls used for weighing on a counter-balance) and ground the slurry for a few days. An increase in the solubility was observed during the grinding of the crystals. This is attributed to the Gibbs–Thomson effect, which states that small particles have a higher solubility than large ones.<sup>[7]</sup> The difference in solubility is a direct consequence of the surface to volume ratio of the particles, as the system minimizes its total surface free energy.

The grinding increases the amount of small crystals and thus the total surface free energy, thereby increasing the solubility. Therefore, in a stagnant solution the small crystals dissolve and the large crystals grow larger: Ostwald ripen-

ing.<sup>[8]</sup> To express it as an aphorism: “The rich get richer and the poor get poorer”.

## 3. Ostwald Ripening: A Route to Enantiopurity

As a result of the Gibbs–Thomson effect resulting in Ostwald ripening, the end state of the process is a saturated solution in contact with one single crystal. This has an interesting consequence for a system of chiral crystals in contact with a liquid phase, wherein they can either lose their chirality at a molecular level or, if intrinsically chiral, can undergo reversible racemization to interconvert between two enantiomers. The thermodynamically most stable state is one single, and therefore enantiopure, crystal!<sup>[9]</sup> In other words, Ostwald ripening always leads to complete enantiopurity. Such an enantiopurification process is readily observed in a stagnant solution of sodium chlorate ( $\text{NaClO}_3$ ; Figure 2). Although the dissolution of the small crystals is relatively fast, the ripening of the larger crystals greatly slows down the arrival at the single-crystal end state. It turns out that a way to overcome this slowing down of Ostwald ripening for large crystals is to fragment them continuously into many small crystals by stirring or milling. This is exactly the surprising but successful experiment that Viedma performed in 2005.<sup>[10]</sup>

Viedma studied the primary nucleation of  $\text{NaClO}_3$ , continuing the work of Kondepudi et al.<sup>[11]</sup> on total spontaneous resolution, which was described for the first time by Havinga in 1941 for quarternary ammonium salts.<sup>[12]</sup> Kondepudi et al. had reported that the crystallization of a clear *supersaturated* solution of  $\text{NaClO}_3$  under vigorous stirring resulted in a solid phase that in most experiments was



Wim Noorduin studied chemistry at the Radboud University in Nijmegen (The Netherlands). He is currently completing his PhD in the research group of Prof. E. Vlieg on the separation of chiral molecules through the combination of chemical reactions and crystallization.



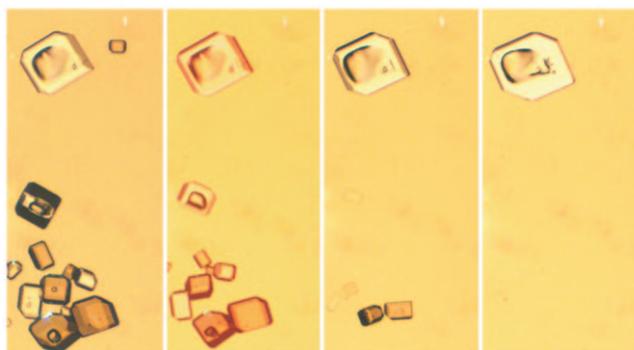
Richard M. Kellogg obtained his PhD in 1965 at the University of Kansas (USA) with Prof. E. S. Huyser. He is currently co-director of the contract research organization Syncom BV, after a long time as professor of organic chemistry at the University of Groningen. His research interests lie in the areas of stereochemistry, bioorganic chemistry, and catalysis.



Elias Vlieg obtained his PhD in physics in 1988 at the University of Leiden (The Netherlands) on work performed with Prof. J. F. van der Veen at the FOM institute AMOLF in Amsterdam. He is currently professor in Solid-State Chemistry at the Radboud University Nijmegen (The Netherlands). As head of the Applied Materials Science group, he is further involved in the practical applications of GaN and of III-V semiconductors for thin-film solar cells. His research interests include chiral separation, nanowires, protein crystallization, additives, self-assembly, and the atomic-scale structure of solid–liquid interfaces.



Bernard Kaptein obtained his PhD in organic chemistry in 1989 at the University of Groningen (The Netherlands) under the supervision of Prof. R. M. Kellogg. He is currently working as a senior scientist at DSM Pharmaceutical Product in Geleen (The Netherlands). His research interests are stereochemistry, crystallization, biocatalysis, and the chemistry of amino acids.

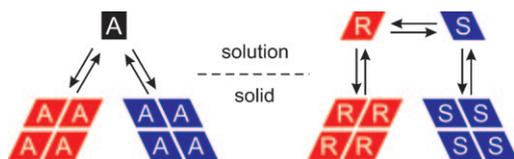


**Figure 2.** Polarized light microscopy images of  $\text{NaClO}_3$  crystals in equilibrium with a saturated solution showing the process of Ostwald ripening, in which large crystals grow at the cost of smaller ones. The chirality of the crystals can be determined by rotating one of the crossed polarizers slightly either clockwise or anticlockwise. On doing this, the L or D crystals become dark. The images from left to right, obtained over a period of two months, show that Ostwald ripening inexorably results in the emergence of one large crystal of single handedness.<sup>[9]</sup>

dominated by crystals of one handedness. McBride et al. were able to videotape the process, and showed that after the first unique initial primary nucleation event, the secondary nucleation induced by the stirring resulted in propagation of many small crystallites of the same handedness.<sup>[13]</sup> Viedma, however, observed that the symmetry breaking in  $\text{NaClO}_3$  works even when the primary nucleation is very fast, thus resulting in the nucleation of many crystals of both enantiomers. Since the subsequent secondary nucleation caused by the stirring would result in seed crystals of both enantiomorphs, Viedma argued that secondary nucleation alone cannot fully explain the observed symmetry breaking.<sup>[14]</sup> This argumentation was further supported by the surprising observation that a single chiral solid phase still emerged even when starting from a prepared slurry with a mixture of racemic crystals and using isothermal abrasive grinding conditions with glass beads.<sup>[10]</sup> Thus, even grinding of a  $\text{NaClO}_3$  slurry (and later also of  $\text{NaBrO}_3$ ) in contact with a saturated solution under near equilibrium conditions still resulted in the transformation of a mixture of enantiomorphous crystals into crystals of single handedness. The handedness of the final solid was found to vary randomly between left and right for different experiments.<sup>[15]</sup>

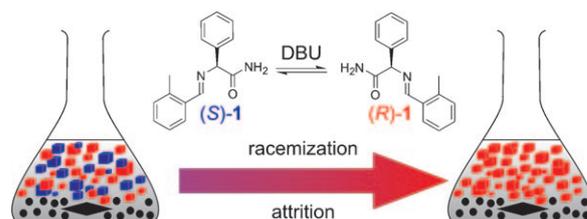
The success of this near-equilibrium process relies on the fact that the solids of different handedness can nurture each other via the achiral solution (Scheme 1).

Could this grinding technique also be applied to intrinsically chiral molecules? The equivalent of this process for an



**Scheme 1.** Comparison between solid–solution equilibria for an intrinsically achiral molecule (left) and an intrinsically chiral molecule (right) subject to racemization in the liquid phase.

intrinsically chiral molecule is separate crystallization of the enantiomers, in other words racemic conglomerate behavior, combined with a solution-phase racemization reaction (Scheme 1).<sup>[16]</sup> A chiral molecule incorporated into a crystal of single handedness can dissolve, racemize to the opposite handedness, and then be incorporated in a crystal with this opposite handedness. Together with the Blackmond research group we decided to test this idea by using amino acid derivative **1**.<sup>[17]</sup> We knew from previous work that **1** was a conglomerate, that it was nicely crystalline, and that it could readily be racemized in solution with the base DBU (Scheme 2). In a series of more than 100 experiments, carried



**Scheme 2.** Deracemization of (R,S)-**1** by abrasive grinding. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.<sup>[18]</sup>

out in four different laboratories, complete deracemization of the solid phase was observed within approximately 30 days.<sup>[18,19]</sup> Unexpectedly, however, all experiments provided the R enantiomer; the behavior of the system was not random. Although chiral influences such as parity violation energy difference (PEVD) or circularly polarized light (CPL) may be considered as causes of symmetry-breaking processes, so far the working hypothesis has been that minute amounts of chiral impurities of natural origin enantioselectively hamper the growth of crystals of one handedness, thereby driving the process to the unhampered enantiomer of the opposite handedness.<sup>[18,20,21]</sup> This effect, however, could be overruled and the outcome directed at will to either enantiomer by starting from a small imbalance in the enantiomers in the solid phase or by adding enantiopure additives.<sup>[18]</sup>

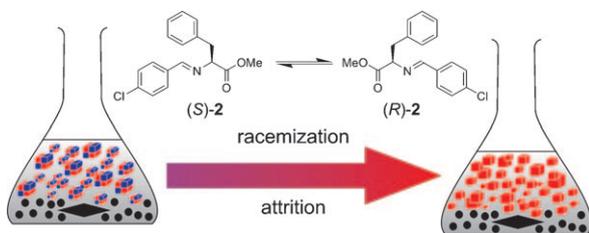
Computer simulations modeling the opposing effects of Ostwald ripening and attrition gave insight into how deracemization works and also provided essential parameters for optimization.<sup>[9,19]</sup> Typically, an exponential increase in the enantiomeric excess (*ee*) with time was found. Moreover, the model allowed us to decrease the time to reach an enantiomerically pure end state from almost a month to less than one day, thus making this a practical route to enantiomerically pure compounds.<sup>[19]</sup>

#### 4. General Applicability

How general is this method? Shortly after our first report Cuccia and co-workers reported that ethylenediammonium sulfate, an achiral compound that forms, analogously to  $\text{NaClO}_3$ , a conglomerate in the solid state, could also be deracemized by attrition-induced grinding.<sup>[22]</sup> In a later report

they also demonstrated that the outcome of the deracemization could be steered by using enantiopure amino acids as additives.<sup>[23]</sup>

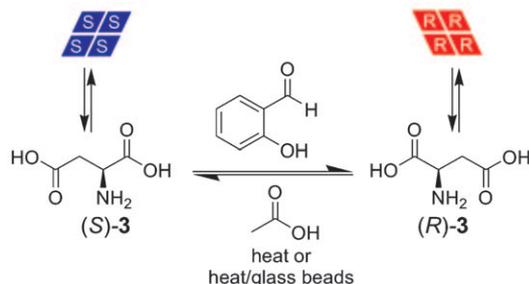
It has been reported in the literature that compound **2**, a derivative of the natural amino acid phenylalanine, is a conglomerate (Scheme 3).<sup>[24]</sup> However, the two enantiomeric



**Scheme 3.** Deracemization of an amino acid derivative displaying epitaxial conglomerate behavior.<sup>[24]</sup>

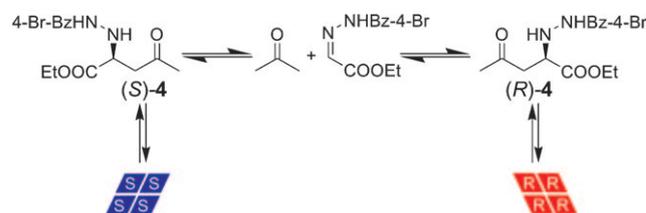
solids of this compound exhibit mutual epitaxial growth, thereby leading to crystals that consist of several blocks of each enantiomer. Such a growth mode inhibits direct resolution by entrainment. We were pleased to observe, however, that a mixture of enantiomers was still converted completely into a single chiral solid phase of the desired handedness under abrasive grinding conditions. Furthermore, the final outcome of the deracemization could be controlled by the initial crystal-size distributions of the two enantiomers. It was found that a population of small crystals which exhibit an enantiomeric excess is able to nurture the population of large crystals of the opposite handedness. These results demonstrate again the Ostwald ripening character of this process, in which large crystals grow at the expense of smaller ones.

Viedma, Blackmond et al. reported that a mixture of enantiopure crystals of aspartic acid **3** in the presence of a catalytic amount of salicylaldehyde (to reversibly form the imine) in acetic acid can also be deracemized by grinding (Scheme 4).<sup>[25]</sup> Interestingly, aspartic acid is a racemic compound, but by creating an artificial mixture of enantiopure crystals the system shows (meta)stable conglomerate behavior. Remarkably, attrition by the use of glass beads was not necessary for the deracemization, although in this case the enantioenrichment rate is slower than exponential. The authors argue that in the absence of vigorous grinding of the crystals, Ostwald ripening is not as efficient as under conditions of continuous ablation.



**Scheme 4.** Solid-solution equilibria for the deracemization of aspartic acid.<sup>[25]</sup>

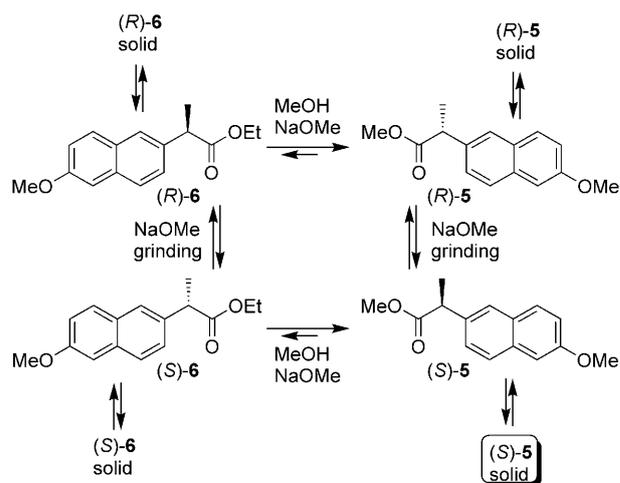
More recently, Tsogoeva et al. reported the deracemization of the racemic compound **4** (Scheme 5).<sup>[26]</sup> In this case, the racemization mechanism was based on the reversibility of the Mannich reaction to interconvert enantiomers in the solution. Attrition by the use of glass beads was also in this case not necessary for the deracemization; normal stirring was sufficient to cause ablation of the crystals. Probably the hardness of the crystals plays an important role.



**Scheme 5.** Deracemization conditions for compound **4** by application of a reversible Mannich reaction.<sup>[26]</sup> Bz = benzoyl.

In light of the successful deracemizations of these amino acid derivatives, we were also interested in whether this grinding method would lend itself to the production of enantiopure pharmaceutical compounds. We successfully used this new deracemization method to develop an alternative chiral synthesis of the nonsteroidal anti-inflammatory drug Naproxen. We demonstrated that the commercially interesting *S* enantiomer could be obtained by applying the technique of grinding under racemizing conditions.<sup>[27]</sup> We could greatly enhance the rate of deracemization by making the less-soluble racemic methyl ester **5** in situ, starting from the more-soluble ethyl ester **6** (Scheme 6). The conversion reaction provides both a gradual feed, according to Dimroth's principle, as well as a supersaturation without the need for cooling.<sup>[28]</sup> The gradual feed of racemic material to an enriched solid mixture combined with the exponential behavior of the conversion rate yields a very efficient process.

Clopidogrel **9** (Plavix) is a large-selling drug used as a platelet aggregation inhibitor (Scheme 7). It is produced as its



**Scheme 6.** Chemical and physical equilibria during the simultaneous transesterification and deracemization of racemic **6** into enantiopure **5**.<sup>[27]</sup>



because of its almost 100% yield as well as its technological simplicity. Although the technique is limited at present to crystalline racemic conglomerates that racemize in solution, opportunities for the rapid screening of derivatives for conglomerate behavior by using a second harmonic generation technique broaden the general applicability.<sup>[30]</sup> From another standpoint, this deracemization method provides a potentially spontaneous pathway to create enantiomerically pure compounds starting from racemic components, and thereby contributes to the discussion of the emergence of prebiotic chiral molecules of single handedness.

From a historical perspective, one might wonder why the stunningly simple method of grinding a slurry of sodium chlorate to enantiomeric purity (the archetypal example of chiral crystallization) was not discovered earlier. Looking back, we can now see how close Ostwald was to Viedma's discovery. The first experiments that formed the basis of "Ostwald's rule of stages" were actually performed using NaClO<sub>3</sub>, and during the experiment he observed the crystals through a polarized light microscope, not only to improve the contrast but also to enjoy the colorful images. On the other hand, he also used the technique of prolonged grinding, but with Hg<sub>2</sub>O slurries, to prove his crystal-ripening theory. Ostwald initially did work with the right compound and also did grind slurries under conditions almost identical to that performed by Viedma more than 100 years later. One can only speculate what would have happened had the careful experimentalist Ostwald performed his solubility experiments under grinding conditions using NaClO<sub>3</sub> instead of the mercury compounds he later chose to use.

*The SNN agency (Cooperation Northern Netherlands) and the European Fund for Regional Development (EFRO) are acknowledged for partial financial support of this work. Prof. D. G. Blackmond is acknowledged for fruitful discussions during the joint collaboration, and Dr. H. Meekes is acknowledged for helpful comments. W.L.N. and E.V. thank COST Action CM0703 for support.*

Received: September 17, 2009

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- [37] We note that when working on practical systems, the observation of enantioenrichment alone cannot be considered as a guarantee that a grinding-induced asymmetric transformation has taken place. For example, if a side reaction in the solution occurs that irreversibly converts the dissolved enantiomers, this results in the dissolution of both solid enantiomers. If there is already an enantiomeric excess in the solid phase, the dissolution of the both enantiomers will result in an enantioenrichment. This enrichment is not due to an asymmetric transformation, however. Therefore, checking the reaction mixture for side products and monitoring the solid-phase crystal structure is crucial for unambiguous demonstration of grinding-induced asymmetric transformation.