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Enantiomer-Specific Oriented Attachment: Formation of Macroscopic Homochiral Crystal Aggregates from a Racemic System**

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Dedicated to Professor Mark M. Green on the occasion of his birthday

In 1910, Liesegang proposed that the coarsening of silver halide single crystals in photographic emulsions might occur not only by "Ostwald ripening", in which larger crystals grow by adding individual molecules dissolved from smaller crystals, but also by larger-scale aggregation in which "*…two or more undissolved fragments would be cemented together by intermediary dissolved material*".[1] Over the last 20 years such nonclassical crystallization, in which nano- or microcrystals undergo oriented attachment to form single crystal aggregates, has received significant support, particularly from studies using static or dynamic electron microscopy.[2–4]

Even more recently, enantiomer specificity during oriented attachment of chiral crystals of subcritical size has been implicated in "Viedma ripening," the process by which a racemic slurry transforms to a single enantiomer upon grinding or boiling.[5] Amplification of the enantiomer ratio results when subcritical crystals of the major enantiomer are less likely to dissolve than those of the minor enantiomer, because they are more likely to be rescued from dissolution by fusing with the more prevalent crystals of the same hand.[6]

We now report efficient enantiomer-specific oriented attachment (ESOA) for crystals of nearly millimeter dimensions to form large, homochiral aggregates that facilitate a Pasteur-like manual separation of enantiomorphs. We also provide strong evidence that homochiral aggregates of macroscopic $NaClO_3$ crystals are formed by ESOA, not by the alternative mechanisms of epitaxial recrystallization.

As a racemic mixture of many small $NaBrO_3$ crystals in a saturated aqueous solution is warmed, or boiled, or shaken with warming, the crystals undergo Ostwald ripening and then begin to aggregate when the size of individual crystals reaches the range of 0.2–0.5 mm, ultimately forming clusters containing several tens of crystals (Figure 1). Optical examination shows that the crystals within an individual cluster are of the same hand, although some clusters include one or a few crystals of the opposite hand.[7]

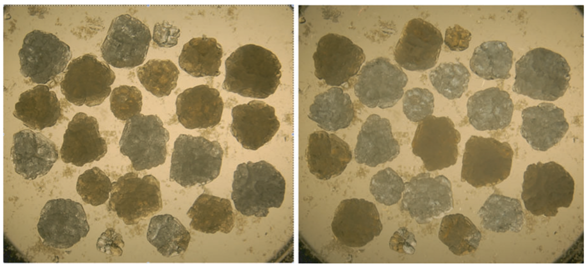

Figure 1. Thousands of *d*- and *l*-$NaBrO_3$ crystals in a saturated boiling solution evolve into large crystal aggregates. These two images show same sample held between polarization filters uncrossed by a few degrees in opposite directions. Clusters are correspondingly dark or bright, indicating that almost every aggregate is composed of crystals of a single hand. The two lowest aggregates include crystals of both hands. Crystal size: circa 5–10 mm.

After boiling for 24 h, many $NaBrO_3$ aggregates assume the form of truncated tetrahedra that mimic the morphology of individual crystals (Figure 2). Edges of the individual crystals within a cluster are nearly parallel, but their lattices are not perfectly aligned. Optical goniometry (Supporting Information, Powerpoint File S1) showed that the orientation of individual crystals within a cluster depart from their average by 1 to 2°, although some diverge by as much as 3°.

Although $NaClO_3$ crystals do not undergo analogous ESOA upon boiling, they do so upon shaking with modest warming (Supporting Information, Movie S2). Increasing the temperature increases the size and chiral uniformity of aggregates and accelerates aggregation (24 h at 40 °C, 10 h at 60 °C, 2 h at 85 °C). Neither the individual $NaClO_3$ crystals nor their aggregates display the tetrahedral morphology of $NaBrO_3$.

This oriented aggregation on the millimeter scale is analogous to reports of nonclassical crystal growth on the micrometer and nanometer scales.[2,3] We believe that direct observation of enantiomer specificity is reported here for the

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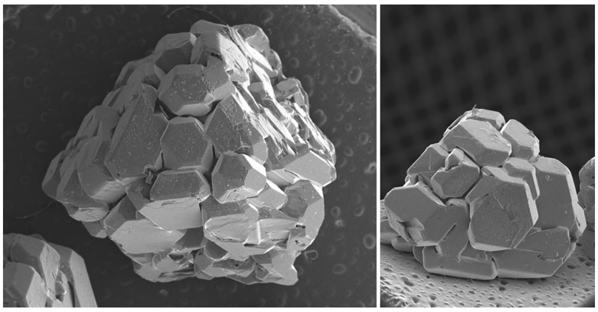

Figure 2. SEM micrographs of $NaBrO_3$ aggregates. Left image: Individual $NaBrO_3$ crystals, mostly of identical handedness, form a polyhedral macrostructure displaying predominantly {111} and $\{11\bar{1}\}$ facets. Right image: In time, larger faces develop, eliminating the boundaries among individual crystalline units. Aggregate size: circa 5 mm.

first time, although it has previously been inferred for subcritical crystals to explain the Viedma ripening phenomenon.[6,8]

We observed narrow bridges (Figure 3) in pairs of $NaClO_3$ crystals collected during the early stages of shaking. Polarized microscopy suggests that these bridges are crystalline and of the same handedness as the crystals being joined, but they obviously contain defects, since the lattices of aggregated crystals are typically misaligned by a few degrees. Apparently these bridges become rigid and strong enough to keep the crystals from being separated by agitation, before the defects can anneal to achieve perfect alignment. Such imperfection might distinguish growth by oriented aggregation of crystals from epitaxial growth involving amorphous clusters. Deposition of individual molecules probably plays an important role in constructing such bridges, and it may be that small crystalline clusters also participate.

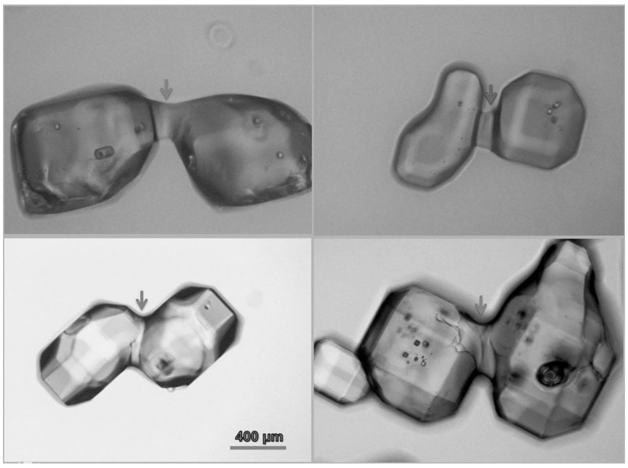

Figure 3. Pairs observed in the early stages of shaking a suspension at 60 °C show crystalline bridges that facilitate homochiral aggregation of $NaClO_3$.

We further minimized the possible role of epitaxy and amorphous intermediates during aggregation by using $NaClO_3$ crystals that had been dyed with aniline blue.[9,10] First a deeply dyed crystal was ground with mortar and pestle, and the resulting powder was added to a saturated solution of $NaClO_3$. Crystals that grew upon slow evaporation of this mixture were nicely faceted and showed a purple core surrounded by a colorless zone of new growth (Supporting Information, Figure S4).

Next, equal amounts of dyed *d*-crystal powder and undyed *l*-crystal powder were well mixed, added to a nearly saturated solution, and shaken with warming to form homochiral macrocrystalline aggregates (Figure 4; Supporting Information, Figure S5). Every *d*-crystal in the resulting aggregates had a dyed core; *l*-crystals showed only superficial dye.

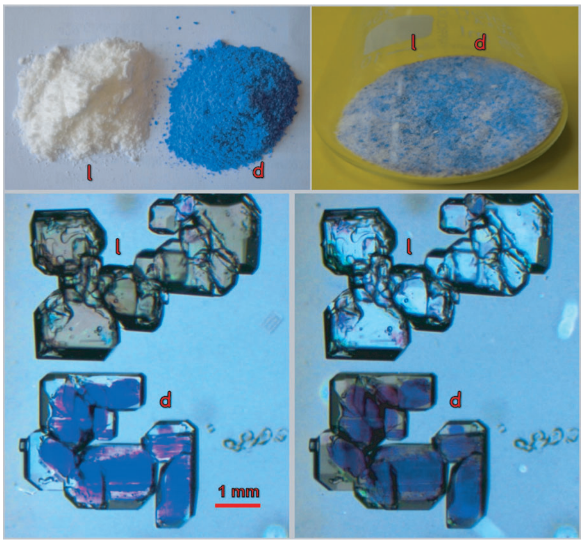

Figure 4. Top: Powders from *l*-$NaClO_3$ crystals and from dyed *d*-$NaClO_3$ crystals were mixed to give a racemate that was suspended in a saturated solution, warmed, and shaken vigorously. Bottom: Polarized-light micrographs with the analyzer rotated to darken *l*-crystals (left), then *d*-crystals (right). All *d*-crystals in the resulting homochiral aggregates (including the small one incorporated by mistake near the top right of the upper *l*-aggregate) show a deep purple core.

Thus, the core of every discrete component of each *d*-aggregate persisted throughout the experiment as crystalline material of the *d*-configuration. Some crystals within dyed *d*-aggregates contacted their neighbors only through the new, colorless zones (Figure 5), showing that aggregation had occurred during the experiment and could not have existed in the initial powder.

Macroscopic ESOA is not limited to substances like the sodium halates, the chirality of which is due to the packing pattern of intrinsically achiral units. Threonine, a chiral proteinogenic amino acid, crystallizes as a conglomerate and is susceptible to aggregation under conditions similar to those described above. Some batches deposited aggregates with obvious right- or left-helicity (Figure 6).[11] When the right-handed, or left-handed, helices were combined and dissolved in water, polarimetry showed opposite rotations of approximately the same magnitude indicating about 85 % *ee*. Right-handed helices were dextrorotatory and left-handed helices were levorotatory. Because the helices are not

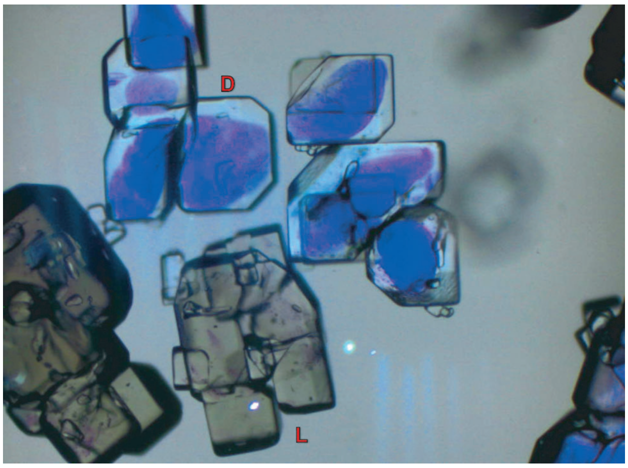

Figure 5. The bright *d*-aggregates, viewed between polaroid filters slightly uncrossed to the right, show dyed cores and contacts through colorless material deposited during shaking.

Figure 6. The macroscopic helicity of threonine aggregates reveals their predominant molecular chirality. Aggregate size: circa 15×3 mm.

enantiopure, the minority component adopts the helical macrosense of the dominant enantiomer.[12]

Much remains to be discovered about the detailed mechanism of ESOA in these systems. For example, it seems likely that the precision and efficiency of joining adjacent crystals should depend on the extent of agitation, on the size, shape, and local concentration of crystals in the suspension, and on the temperature and supersaturation of the solution. Perhaps ESOA of subcritical clusters not only enables Viedma ripening[6,13] but may also play a significant role in normal growth of single crystals by the non-classical mechanism. We are investigating other compounds that crystallize in chiral space groups where the handedness may be easy enough to determine (as by the rotation of the optically isotropic sodium halates or the helicity of threonine aggregates); that enantiomer separation facilitated by aggregation could have practical application at least on modest scale.

Experimental Section

NaBrO$_3$ aggregates: *l*-crystals (10.0 g) and *d*-crystals (10.0 g) were suspended in water (6.0 mL) and placed in a 50 mL Erlenmeyer flask joined to an 80 cm length of 0.8 cm glass tubing as a condenser. The bottom of the flask was coated with aluminum duct tape to promote even heating and placed on a hot plate at 160 °C. Homochiral aggregates were usually obtained within 12–24 h. Increasing the hot plate temperature to 185 °C led to homochiral tetrahedra within 14–24 h. Alternatively, large crystal aggregates could be obtained from identical water suspensions in closed 50 mL flasks heated in a 90 °C silicone oil bath while shaking at 600 rpm with an orbital sander (Supporting Information, Figure S2).

NaClO$_3$ aggregation experiments were conducted in well-closed 50 mL Erlenmeyer flasks containing 10.0 g each of *l*- and *d*-crystals in 6.0 mL water (6.0 mL) and shaken in a 60 °C bath as described above. Homochiral aggregates were obtained after 24 h. At 40 °C, small, predominantly homochiral aggregates resulted after 24 h. At 80 °C, spectacular crystal aggregates appeared within 2–4 h.

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