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Supporting Information

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**The Driving Mechanism Behind Attrition-Enhanced
Deracemization****

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Supplementary information

We here introduce a simple model for the enantiomeric enrichment during grinding of conglomerate crystals in contact with a racemizing or achiral solution that follows the work by Uwaha^{S1} and McBride and Tully^{S2}, but is adapted to allow for a difference in solute concentration of both enantiomers. In the model the crystal size distribution is simplified by considering only two sizes: big crystals (containing B_R and B_S molecules altogether) and small clusters, (containing C_R and C_S molecules altogether). Figure S1 schematizes the various processes involved in the deracemization procedure, which is described by the following set of coupled differential equations:

$$\frac{\partial B_R}{\partial t} = a(M_R - M_{B,eq})B_R - bB_R + cB_R C_R, \quad (1a)$$

$$\frac{\partial C_R}{\partial t} = a'(M_R - M_{C,eq})C_R + bB_R - cB_R C_R, \quad (1b)$$

$$\frac{\partial M_R}{\partial t} = -a(M_R - M_{B,eq})B_R - a'(M_R - M_{C,eq})C_R - r(M_R - M_S), \quad (1c)$$

$$\frac{\partial B_S}{\partial t} = a(M_S - M_{B,eq})B_S - bB_S + cB_S C_S, \quad (1d)$$

$$\frac{\partial C_S}{\partial t} = a'(M_S - M_{C,eq})C_S + bB_S - cB_S C_S, \quad (1e)$$

$$\frac{\partial M_S}{\partial t} = -a(M_S - M_{B,eq})B_S - a'(M_S - M_{C,eq})C_S - r(M_S - M_R), \quad (1f)$$

$$T = B_R + C_R + M_R + B_S + C_S + M_S = \text{constant} . \quad (1g)$$

The meaning of the variables and constants in this set of equations is summarized in Table 1.

We presume an ablation rate (i.e. formation rate of small chiral clusters by grinding) proportional to the number of large crystals of each enantiomer, bB . As fractured crystals are studded with growth steps and the advancement rate of steps is proportional to supersaturation^{S3}, we consider linear growth kinetics. This means that the growth/dissolution rate of the large/small crystals is proportional to the difference in actual solute concentration with the equilibrium concentration of the large/small crystals, $a(M - M_{eq})$. As a consequence of the Gibbs-Thomson effect the equilibrium concentration of the solution in contact with the small crystals, $M_{C,eq}$ is larger than that of the large crystals, $M_{B,eq}$. The incorporation rate of the small clusters into the large crystals of the same handedness is second order, proportional to both the number of large crystals and the number of clusters, i.e. cBC . We assume no incorporation of small clusters into large crystals of opposite handedness. Finally, we assume that the racemization rate of the enantiomers in the solution is proportional to the difference in concentration of each enantiomer, $r(M_R - M_S)$.

Figure S1. Schematic view of the processes involved during grinding of a slurry of conglomerate crystals. In the absence of racemization in solution $r = 0$ and no transfer of M_R to M_S or vice versa takes place.

Table S1: Variables and constants used in equations 1 - 6. All numbers and rates have relative meaning only.

B_R, B_S	Number of molecules in big crystals of the (R) or (S) enantiomer
C_R, C_S	Number of molecules in small, chiral clusters of the (R) or (S) enantiomer
M_R, M_S	Number of monomer molecules of the (R) or (S) enantiomer in solution
t	Time
$M_{B,eq}$	Equilibrium number of molecules in solution in contact with the big crystals of each enantiomer
$M_{C,eq}$	Equilibrium number of molecules in solution in contact with the small clusters of each enantiomer
a, a'	Rate constants for growth and dissolution
b	Rate constant for ablation of big crystals
c	Rate constant for incorporation of chiral clusters into big crystals
r	Rate constant for racemization in solution
T	Total number of molecules

We first consider the case of one single enantiomer without racemization in the solution ($r = 0$). In steady state, when $t \rightarrow \infty$ and $\partial x / \partial t = 0$ ($x = M, B$ and C) the set of equations (1) reduce to

$$0 = a(M - M_{B,eq})B - bB + cBC, \quad (2a)$$

$$0 = a'(M - M_{C,eq})C + bB - cBC, \quad (2b)$$

$$T = B + C + M. \quad (2c)$$

If the grinding process involves Ostwald ripening only such that the process only involves the growth with monomers and no clusters are incorporated into the larger crystals (i.e. $c = 0$), then solving this set of equations for M gives

$$M = M_{B,eq} + \frac{b}{a}. \quad (3)$$

Figure S2. Steady-state number of molecules in liquid as a function of the total number of molecules in the solid for a single enantiomer system expressed in arbitrary units. $a = 3$, $b = 0.5$, $c = 0.2$, $M_{B,eq} = 1.0$; $M_{C,eq} = 1.1$.

It is clear that in the case of no cluster incorporation the number of molecules in the liquid is independent of the total amount of material, T . For two enantiomers (R) and (S) this implies that the ee of the molecules in the liquid, $ee_l = (M_R - M_S) / (M_R + M_S) = 0$ and thus is independent of the ee of the solid phase $ee_s = ((B_R + C_R) - (B_S + C_S)) / (B_R + C_R + B_S + C_S)$. This is contrary to the experiments.

Including incorporation of the small clusters into the large crystals ($c \neq 0$) and taking $a = a'$ (same rate constants for growth and dissolution), we obtain for $t \rightarrow \infty$ a solute content of

$$M(S) = \frac{-a(M_{B,eq})^2 + aM_{B,eq}M_{C,eq} + cSM_{B,eq} - bM_{B,eq} + bM_{C,eq}}{-aM_{B,eq} + aM_{C,eq} + cS}. \quad (4)$$

where $S = B + C$, the total number of molecules in the solid phase.

As shown in figure S2, an increase in the total amount of solid S leads to a decrease in the number of solute molecules going down from $M_{C,eq}$ at $S = \frac{a}{r}(M_{C,eq} - M_{B,eq}) - \frac{b}{r}$, where all large crystals are dissolved to $M_{B,eq}$ at $S \rightarrow \infty$. This increase qualitatively agrees with our experiments.

As the changes in the absolute solute concentration are limited, they are not easily measured directly. Therefore, mixtures of both enantiomers are used in the experiments, which allows for relative measurements by determining the enantiomeric excess of the solution, ee_l , as a function of its solid value ee_s . For our model this implies that both enantiomers (R) and (S) are introduced in the system, which do not racemize in the solution (i.e. $r = 0$). The total amount of solid is composed of S_R molecules of the (R) enantiomer and S_S molecules of the (S) enantiomer: $S = S_R + S_S$. For $t \rightarrow \infty$ and still assuming $a=a'$ we arrive at the following set of equations:

$$0 = a(M_R - M_{B,eq})B_R - bB_R + cB_R C_R, \quad (5a)$$

$$0 = a(M_R - M_{C,eq})C_R + bB_R - cB_R C_R, \quad (5b)$$

$$S_R = B_R + C_R, \quad (5c)$$

$$0 = a(M_S - M_{B,eq})B_S - bB_S + cB_S C_S, \quad (5d)$$

$$0 = a(M_S - M_{C,eq})C_S + bB_S - cB_S C_S, \quad (5e)$$

$$S_S = B_S + C_S. \quad (5f)$$

Solving M_R and M_S from this set of equations for given S_R , S_S and expressing $ee_l = (M_R - M_S)/(M_R + M_S)$ as a function of $ee_s = (S_R - S_S)/(S_R + S_S)$ gives the following relationship:

$$ee_l = \frac{-ee_s}{K_1 - K_2 ee_s^2} \quad (6a)$$

with

$$K_1 = [4ab(M_{C,eq} - M_{B,eq})^2 + 4a^2 M_{B,eq} (M_{C,eq} - M_{B,eq})^2 + 2bcS(M_{C,eq} - M_{B,eq}) + 4acSM_{B,eq}(M_{C,eq} - M_{B,eq}) + c^2 S^2 M_{B,eq}] / 2bcS(M_{C,eq} - M_{B,eq}) \quad (6b)$$

and

$$K_2 = cSM_{B,eq} / 2b(M_{C,eq} - M_{B,eq}). \quad (6c)$$

This relationship is shown in Figure S3. Its profile is very similar to the experimental curve in the main text.

Figure S3. ee_l as a function of ee_s ; $a = 3$, $b = 0.5$, $c = 0.2$, $M_{B,eq} = 1.0$, $M_{C,eq} = 1.1$, $S = 15$. The constants K_1 and K_2 in equation (6a) are 44.4 and 30 respectively.

In the experiments the total amount of molecules is kept fixed, i.e. $S + M_R + M_S$ is kept constant. However, as $M_R + M_S$ is close to $M_{B,eq} + M_{C,eq}$, which is constant, we can also approximate S as a constant for the different experiments.

To follow the process of deracemization in time, the set of equations (1) is numerically integrated using the finite difference method. From this we derived the development of ee_s and ee_l as a function of time for two different values of the rate constant for racemization in solution, r . A large

r approximates $r \rightarrow \infty$, which is the situation in which the solute molecules are achiral, like the case of NaClO_3 ^{S4}. A smaller r holds for the case of intrinsically chiral molecules in the solution, which are racemized by a racemization catalyst, as described in our paper. Results for two different r values are given in Figures S4 and S5.

It can readily be seen that for both cases ee_s increases exponentially with time until it approaches unity, i.e., a pure enantiomer:

$$ee_s = ee_s(t=0)\exp(kt). \quad (7)$$

This agrees with the experiments reported in literature^{S5-7}. The rate constant k is larger for the larger racemization rate, r . It can also be recognized that the solute concentration of the enantiomer that forms the minor population in the solid phase is higher than that of the solid enantiomer in excess. This difference in solute concentration provides the actual driving force for the conversion toward the solid enantiomer in excess and thus powers the system toward single chirality. The driving force is larger for smaller r , but because of the smaller racemization rate constant, r , the process nevertheless proceeds slower.

Figure S4. ee_s (left) and ee_l (right) as a function of time. $a = 3$, $b = 0.5$, $c = 0.2$, $r = 25$, $M_{B,eq} = 1.0$, $M_{S,eq} = 1.1$, $S + M_R + M_S = 15$.

Figure S5. ee_s (left) and ee_l (right) as a function of time. $a = 3$, $b = 0.5$, $c = 0.2$, $r = 2$, $M_{B,eq} = 1.0$, $M_{S,eq} = 1.1$, $S + M_R + M_S = 15$.

Measuring the solubility increase upon addition of extra solvent to a grinding slurry

First a stock solution was prepared containing 8.35 g MeCN and 0.25 g anisole as an internal standard. This solution was carefully sealed. Subsequently in a 10 mL reaction vial were added 8.5 g glass beads ($\varnothing$ 2.5 mm), 0.30 g (*RS*)-**1** and 2.2 g internal standard. The slurry was ground in an Elma Transsonic T470/H ultrasonic cleaning bath that was kept at a constant temperature of 20 °C (room temperature) using a cooling spiral that was attached to a Julabo F25 thermostat bath. After two hours of grinding 2.2 mL of the slurry was collected, divided over two centrifuge tubes and immediately centrifuged at 13,000 rpm for 2 minutes. From the upper layer ca. 10 μ L of the clear supernatant was carefully removed and analyzed using chiral HPLC. To the remaining slurry in the reaction vessel was added 3 mL of the stock solution and the slurry was ground for an additional 2 hours. Solution samples were collected as before using the centrifuge step and analyzed using HPLC. As can be observed from Figure S6, the overall concentration of racemic **1** (13.5 (*R*) and 15.2 (*S*) min.) increases as compared to the anisole (3.7 min.) concentration upon adding stock solution to the grinding slurry (see also Figure S7). Using a calibration line shows that upon the extra addition of solvent to the ground slurry, the concentration in the solution increases from 2.37 wt% to 3.14 wt% as compared to 2.2 wt% for an unground mixture of racemic (*RS*)-**1** crystals in contact with MeCN.

Figure S6: HPLC analysis before (left) and after (right) addition of the stock solution showing an increase in the (*RS*)-**1**/anisole ratio.

Figure S7: Schematic representation of increase of the concentration in the solution upon decreasing the concentration of solid material in the solution of a ground slurry.

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