

Chiral Symmetry Breaking During Crystallization: Complete Chiral Purity Induced by Nonlinear Autocatalysis and Recycling

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We report experimental results that show a large and symmetric population of *D* and *L* crystals moving into complete chiral purity, with one of the enantiomers completely disappearing. The results indicate (i) a new symmetry breaking process incompatible with the hypothesis of an initial single chiral phase or “mother crystal,” (ii) that total symmetry breaking and complete chiral purity can be achieved from a system that initially includes both enantiomers, and (iii) that this is achieved through a nonlinear autocatalytic-recycling process.

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Introduction.—Chiral symmetry breaking occurs when a physical or chemical process that does not have preference for the production of one or other enantiomer spontaneously generates a large excess of one of the two enantiomers: left-handed (*L*) or right-handed (*D*). From the energetic point of view, these two enantiomers can exist with an equal probability and inorganic processes involving chiral products commonly yield a racemic mixture of both (*L*) and (*D*) enantiomers [1]. However, life on earth utilizes only one type of amino acids and only one type of natural sugars: (*L*)-amino acids and (*D*)-sugars. The fact that biologically relevant molecules exist only as one of the two enantiomers is a fascinating example of complete symmetry breaking in chirality and has long intrigued many scientists.

With a few exceptions, the symmetry breaking produced by different natural mechanisms has proved giving small enantiomeric excess (EE) [2], ranging from the 20% found experimentally for asymmetric photolysis to the 10^{-17} alleged theoretically for parity violating energy difference between enantiomers. This means that to reach total chiral purity, mechanisms to enhance any initial imbalance in chirality are absolutely essential [3].

In 1953, Frank [4] suggested that a form of autocatalysis in which each enantiomer catalyses its own production, while suppressing that of its mirror image, might have nonlinear dynamics leading to the amplification of small initial fluctuations in the concentrations of the enantiomers. Many theoretical models are proposed afterwards, but they are often criticized as lacking any experimental support [5]. Recently, asymmetric autocatalysis of pyrimidyl alkanol has been studied intensively [6–9]. The enhancement of EE was confirmed [7], and its temporal evolution was explained by the second-order autocatalytic reaction [8,9]. But only with the nonlinear autocatalysis, chirality selection is not complete; the value of EE stays less than 100% and total chiral symmetry breaking is not achieved. In a recent theoretical model Saito [10] shows that in a closed system the nonlinear autocatalysis amplifies the

initial small enantiomeric excess, but eventually the simple backreaction can promote the decomposition of less abundant enantiomer to the reactant, which is recycled to produce the more abundant type. Through this recycling process, the complete chiral purity would be achieved.

In this Letter we show the first experimental case where total symmetry breaking and complete chiral purity is achieved from a system where both enantiomers are present since the beginning.

First, we show with laboratory experiments how an isothermal saturated solution of sodium chlorate (NaClO_3) with a large population of *D* and *L* crystals moves into complete chiral purity: (i) any small initial crystal enantiomeric excess (CEE) eventually gives rise to total crystal purity disappearing the less abundant enantiomer (100% CEE); (ii) “symmetric” proportion of both enantiomeric crystals gives rise to total symmetry breaking and crystal purity disappearing randomly one of the two enantiomers. We study the key factors that promote this behavior.

Second, up to now it was believed that any case of total symmetry breaking during crystallization occurs via production of secondary crystals of the same handedness from a single “mother crystal” that seeds the solution. However, our results show a case of total symmetry breaking incompatible with the latter idea; i.e., we are dealing with an entirely different process. Furthermore, the experimental results show that complete symmetry breaking and chiral purity can be achieved from an initial system with both enantiomers. Therefore, the findings demand a new explanation for this process of total symmetry breaking and open the debate on this fascinating phenomenon.

Finally, we present arguments indicating that our experimental data can be explained by the model of “complete chiral purity induced by nonlinear autocatalysis and recycling.”

Sodium chlorate crystallization.—The achiral molecules of NaClO_3 crystallize as two enantiomeric chiral crystals in the cubic space group $P2_13$ [11]. Hence sodium chlorate

is achiral before crystallization, as it exists in solution as more or less dissociated ions or clusters without a fixed chirality but forms a chiral crystal. About 100 years ago Kipping and Pope [12] demonstrated that solutions of NaClO_3 by seeding can produce total CEE. More recently Kondepudi and others [13] showed that simply stirring during the crystallization of sodium chlorate from solution was sufficient to produce a yield approaching 100% of just one enantiomer. Whereas under normal conditions a distribution of the proportion of one or other enantiomer obtained in a series of experiments falls on a typical Gaussian curve, with the peak yield at 50% of each enantiomer, in the stirred experiments the distribution is bimodal, with the peak yield close to 100% of one or the other enantiomer. Kondepudi suggested that the most important factor in this chiral symmetry breaking is secondary nucleation by which a seed crystal or randomly generated “mother crystal” triggers the production of a large number of secondary crystals at a fast rate if the solution is stirred that are enantiomerically identical to itself. The result of this crystallization process is the generation of crystals with the same handedness (total chiral symmetry breaking). Nevertheless, the hypothesis of an initial single chiral crystal to explain spontaneous chiral symmetry breaking has been disputed recently [14].

Experimental.—Chiral L and D crystals were obtained separately by literature procedures via seeding with the appropriate chiral crystal a supersaturated solution [15]. We prepared samples (12 g) with mixtures of L and D NaClO_3 chiral crystals with 5% CEE (L crystals: D crystals = 5.7000 g:6.3000 g or 6.3000 g:5.7000 g), and samples with symmetric mixtures of both crystals (L crystals: D crystals = 6.0000 g:6.0000 g). Every sample was ground using an agate pestle and a mortar and was placed in a set of 25 mL round-bottom flasks with 10 mL of water. Because of the solubility of NaClO_3 [16], an excess of more than 2 g of crystals remains without dissolving at 24 °C. We added to some solution flasks, 8 g, 6 g, 4 g, or 2 g of small glass balls (3 mm of diameter), that continuously crushed the crystals that were being subjected to stirring by a magnetic bar (3–20 mm) at 600 rpm. Flasks with only solutions and crystals and flasks with solutions, crystals, and glass balls were hermetically closed and maintained at 24 °C with constant agitation. Every solution contains a population of more than a million of crystals. The continuous mechanical abrasion-grinding of crystals by glass balls imposes to crystals a maximum size of about 200 μm that is kept during all the experiment although they grow (it depends fundamentally on the size of the glass balls because the system works like a mill). A parallel experiment was performed: four solution flasks with crystals and 4 g of glass balls were agitated to 200, 400, 600, and 800 rpm, respectively. Samples of solution with crystals (0.1 mL with more than 10 000 crystals) were

removed from the flasks every 2 h and left to grow during a few hours. The experiments are considered finished when chiral crystal purity is achieved. Chiral crystal evolution was determined by their optical activity using a petrographic microscope [13]. The ease with which the L and D crystals could be identified enables us to know when chiral crystal purity has been reached. All experiments have been performed and repeated more than 20 times in successive weeks. The reported results are average values.

Results and discussion.—Crystals in the stirred solutions (no glass balls involved) maintain indefinitely (several days) the initial enantiomeric excess or the initial “symmetry” between both populations of L and D crystals. However, all stirred crystals-solution systems where glass balls (abrasion-grinding process) intervene show a continuous enhancement of CEE, and eventually, total symmetry breaking and complete chiral crystal purity achieved at different times. The time required to achieve chiral purity depends on the number of glass balls present in the system (Fig. 1), and when the number of glass balls is the same, it depends on the speed of agitation (rpm) (Fig. 2). After 8 h, solutions with initial 5% L -CEE show 100% L -CEE, and solutions with initial 5% D -CEE show 100% D -CEE (Fig. 3). Solutions with initial symmetric mixtures of L and D crystals and 4 g of glass balls show total symmetry breaking and chiral purity after 24 h (Fig. 4). The handedness in this last case is L or D (randomly). Nevertheless, any small difference between L and D crystals induces the preferred production of one of them, for example, small differences in the quality of the crystals bias the progressive enantiomeric amplification of a certain handedness.

It is evident from these results that under these conditions complete chiral purity cannot be explained by the model of an initial single chiral crystal, and therefore, a new explanation is required.

The crystal enantiomeric excess can be measured by $\text{CEE} = (N_L - N_D)/(N_L + N_D)$, where N_L and N_D are the number of each enantiomer, that is, a means to quantify the symmetry breaking. Recently Cartwright [17] established with theoretical argument that mechanical crushing of crystals is on the microscale the same mechanism that secondary nucleation. In fact, collisions between one crystal and another or between a crystal and the fluid boundaries (container walls, stirring bar, etc.) break pieces off the surface, and fluid shears, which may also detach fragments from the crystal surface, have each been put forward as responsible for homochiral secondary nucleation [18,19]. The detached fragment will possess the same chirality as the crystal of which they previously formed a part. Thus we can consider that the abrasion-grinding process by the glass balls of our experiments is a sort of “induced” secondary nucleation that generates new fragments of crystals with the same chirality as that of the mother crystal.

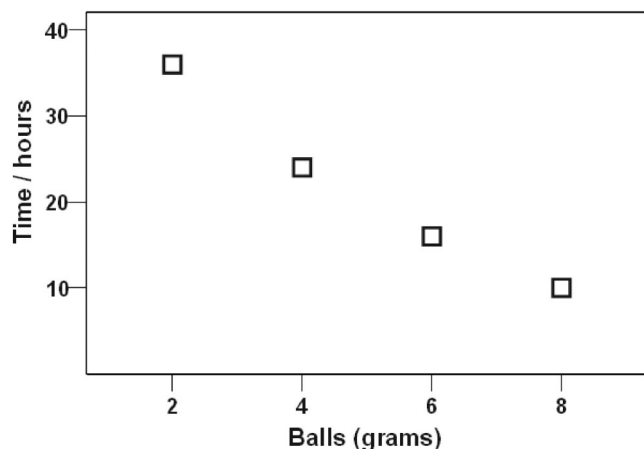


FIG. 1. Solutions with initial symmetric mixtures of *L* and *D* crystals and glass balls show total symmetry breaking and chiral crystal purity. The data show the necessary time to achieve chiral purity depending on the number of balls in the system (600 rpm).

Following the ideas of Frank [4], indicating that a nonlinear autocatalysis amplifies the small initial fluctuations in the concentrations of the enantiomers, Cartwright and co-workers [17] showed with numerical simulations that secondary nucleation can act as just such a nonlinear autocatalytic process. As in the case of chiral crystallization, secondary nuclei possess the same chirality as the mother crystal, so the presence of a crystal of a given chirality catalyzes the production of further crystals with the same chirality. However, in their simulation we can observe that only with the nonlinear autocatalysis chirality selection is not complete and the value of CEE stays less than unity. They assume that to obtain chiral purity we need “a single mother crystal: an ancestral Eve for the whole population.”

Similar results were achieved by Saito and Hyuga [10] with a mathematical model in which substances *A* and *B* react to form substance *C*. Though reactants *A* and *B* are achiral, the product *C* happened to be chiral in two enan-

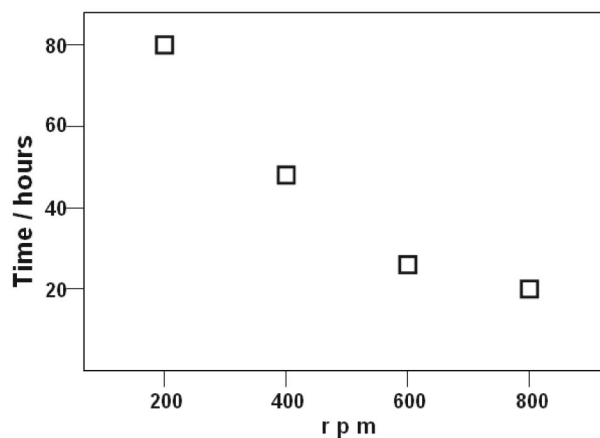
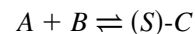
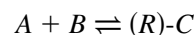


FIG. 2. Solutions with initial symmetric mixtures of *L* and *D* crystals and glass balls show total symmetry breaking and chiral crystal purity. The data show the necessary time to achieve chiral purity depending on the speed of agitation of the system (4 g of balls).

tiometric forms; *R* isomer (*R*)-*C* and *S* isomer (*S*)-*C*.



They found that the EE amplification takes place with a nonlinear autocatalytic chemical reaction. However, the final chirality is not complete: the EE is smaller than 100%. However, the inclusion of the backreaction from the products (*R*)-*C* and (*S*)-*C* to *A* and *B* brings about the drastic change in the results. The component which has a slight advantage starts to dominate, and the other chiral type extinguishes gradually. Eventually, the complete homochirality or chiral purity is achieved.

Because of the combined abrasion-grinding (glass balls) and stirring in our experiments, the left- and right-handed crystals continuously lose tiny fragments of left- and right-

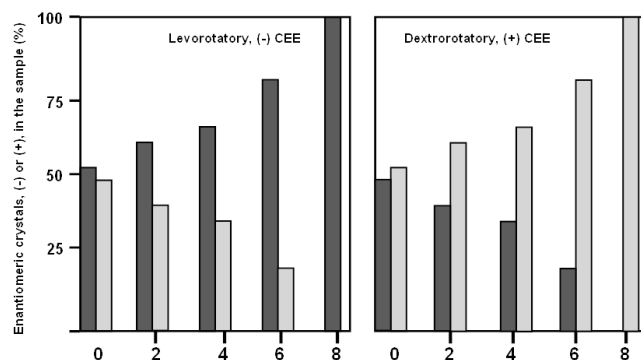


FIG. 3. Solutions with initial 5% *L*-CEE show 100% *L*-CEE, and solutions with initial 5% *D*-CEE show 100% *D*-CEE in 8 h (600 rpm).

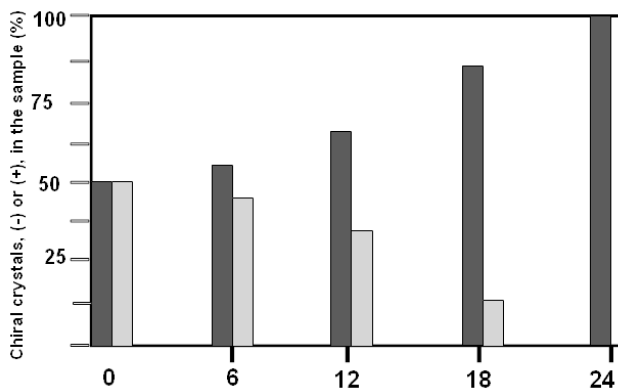


FIG. 4. Initial symmetric mixtures of *D* and *L* crystals and 4 g of balls show total symmetry breaking and chiral purity after 24 h (600 rpm). The handedness in this case is *L* or *D* randomly.

hand microcrystallites or clusters; it is to say that we are dealing with an induced secondary nucleation, and because of this, with a nonlinear autocatalytic phenomenon. On the other hand, we are dealing with a population of crystals in contact with its solution, and therefore, the surface of crystals is subjected a continuous dissolution-crystallization process. Since the abrasion-grinding process results in the continuous generation of microcrystals the effective surface area of crystalline phase continuously increases. Additionally, the thermodynamic prediction of Gibbs-Thompson equation states that solubility of the crystalline phase in a solution is dependent on particle size [20]. Given that solubility of smaller particles is greater than that of the larger ones, a slight concentration gradient exists between particles of different size even near chemical equilibrium. Thus, in the abrasion-grinding process of our system, the finest fraction of microcrystallites or clusters easily dissolves, feeding the larger ones. That is to say, we are dealing with a continuous dissolution-crystallization phenomenon (as expected in any real system), only that in this case the process is highly enhanced by the abrasion-grinding process.

Since the chirality of sodium chlorate is a property of its crystal structure, any molecular arrangement greater than the unit cell is chiral. For NaClO_3 Z (number of molecules in unit cell) = 4 [21]. Thus any molecular group of less than four molecules has not crystal structure, reaching the achiral molecular level. During the dissolution process the final stage of any crystallite or chiral cluster is at this achiral molecular level and therefore can feed other crystals independently of its chirality (the majority enantiomer has more advantage). Thus, in this process the chiral crystals are continuously recycled and complete chiral purity can be achieved.

Very recently Uwaha [22], knowing these experimental results, constructed a simple mathematical model based on a few physical assumptions that mimic our experimental system. The development of this model shows complete chiral symmetry breaking in a dissolution-crystallization process.

Finally, we may speculate that a solution of sodium chlorate, strongly agitated in an isothermal slow evaporation process, can undergo similar pathways at the microscopic scale (microcrystals). At this level the effective surface of solid phase is maximum, resulting in total symmetry breaking that is manifested at the macroscopic level. Additionally, chiral clusters smaller than the critical nucleus size may also be subjected to this symmetry breaking process. In turn, when these clusters reach the critical nucleus size, a chiral symmetry breaking in crystallization from primary nucleation will “inherit” the chiral condition achieved during the prenucleation stage. These hypotheses must be regarded as complementary explanations to the phenomenon of symmetry breaking described in other works [13,14].

Conclusion.—We show experimental data indicating for the first time that complete homochirality and chiral purity can be achieved from an initial system where both enantiomers are present. We suggest that in our system this process becomes possible by the combination of (i) nonlinear autocatalytic dynamic of secondary nucleation and (ii) the recycling of crystallites when they reach the achiral molecular level in the dissolution-crystallization process. In this respect, we propose that chiral purity and total symmetry breaking during crystallization can be achieved without the necessary intervention of an initial single chiral phase. Beyond the specific aspects of these experiments, a significant fact can be established with far reaching implications: final and total chiral purity seems to be an inexorable exigency in the course of some physical processes.

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