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Homochirality beyond grinding: deracemizing chiral crystals by temperature gradient under boiling†Cristóbal Viedma^{*a} and Pedro Cintas^b

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A single-chirality solid phase can be obtained in boiling solutions containing a racemic mixture of left- and right-handed enantiomorphous crystals due to dissolution–crystallization cycles induced by a temperature gradient. This phenomenon provides further insights into asymmetric amplification mechanisms under presumably prebiotic conditions.

Mirror-image symmetry breaking, as evidenced by the occurrence of only L-amino acids and D-sugars, constitutes an essential feature of living organisms. Although the appearance of single chirality can be understood by means of different biotic and abiotic hypotheses,¹ there has been a certain consensus on the plausibility of an autocatalytic cycle that exhibits self-recognition and mutual inhibition between enantiomers.² Unfortunately, some elegant asymmetric reactions developed in the laboratory would hardly be compatible with prebiotic scenarios and primitive metabolic pathways.³

Phase transitions provide an alternative path to enantioenrichment as compounds accumulated in a given phase may be sorted out by natural agents and such equilibria are governed by thermodynamic and kinetic effects. The simplest model in this context is most likely the crystallization of sodium chlorate (NaClO₃). Like natural quartz, achiral molecules of NaClO₃ are capable of forming a supramolecular arrangement of either left- or right-handed helicity that leads to a chiral solid (chiral space group *P*2₁3).⁴ While static solutions of NaClO₃ give rise to statistically equal distributions of D- and L-crystals, other perturbations alter significantly this distribution.⁵ As demonstrated by Kondepudi and associates stirring yields mostly enantiomorphous crystals of single handedness.⁶ In this case secondary nuclei grow from a mother crystallite, which may be either D- or L-, thereby leading to homochiral crystallization in a random manner.⁷ Other influences on mirror symmetry breaking include β-radiation, fluid flow effects, or spontaneous resolution in gel media.⁸ The effect of chiral cosolutes, especially sugars, has however been questioned.⁹

El-Hachemi *et al.* demonstrated recently that the effect of stirring in the Kondepudi experiment can be bypassed on inducing crystallization of NaClO₃ in boiling supersaturated solutions, which also leads to optically active crystals of arbitrary chirality.¹⁰ Nucleation was guided by withdrawing water through the distilling head from the reflux system. This strategy is also related to an aerosol–liquid cycle of a supersaturated NaClO₃ solution induced by an ultrasonic generator.^{8d} More recently, Alexander and associates equally showed enantiomorphous segregation of either D- or L-crystals from molten NaClO₃ with stirring.^{11‡}

In 2005 Viedma reported a different scenario for complete enantioenrichment from an initial racemic mixture of D- and L-NaClO₃ crystals under abrasive grinding supplied by glass beads.¹² A continuous process of dissolution–recrystallization takes place coupled with crystal ripening that results in the emergence of a single chiral phase by the conversion of one solid enantiomorph into the other. This protocol has also been successfully applied to several organic molecules that undergo racemization in solution faster than the crystallization step.¹³

Herein, we show that like grinding a slurry of enantiomorphous crystals, a solid phase of single chirality results from boiling solutions left initially in equilibrium with a racemic mixture of D- and L-NaClO₃ crystals. In other words, two populations of solid-phase opposite enantiomorphs cannot coexist in a boiling solution and, as a result, one population disappears in an irreversible transformation that nurtures the other. Unlike grinding, however, the force that promotes the needed dissolution-growth recycling is supplied by a temperature gradient in the heterogeneous mixture. This gradient causes crystal dissolution in one zone of the boiling solution and nucleation-crystal growth in another one. Thus, the present study constitutes a novel strategy that sheds light into the emergence of homochirality in boiling solutions starting from essentially racemic mixtures.

In our experiments, equal amounts of D- and L-crystals are suspended in water and the mixture is gently refluxed (see ESI†). At the boiling temperature an excess of crystals remains without dissolving, which does actually mean equal populations of crystals of both hands. The boiling solution possesses two key characteristics; on the one hand the initial mixture is essentially racemic and, on the other, crystal evolution occurs in a closed system without exchanging matter with the environment.

The temperature at the bottom of the flask in close contact with the hot plate is approximately 120 °C; boiling occurs actually

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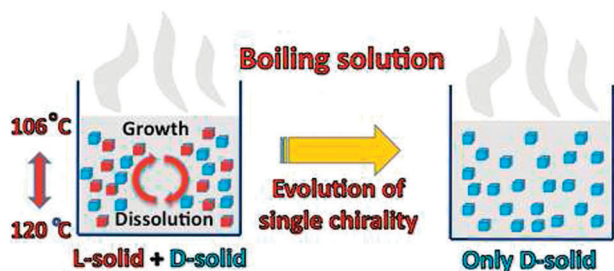


Fig. 1 Deracemization of NaClO_3 under boiling. Cycles of dissolution and crystal growth result in a solid phase of one enantiomorph.

in that zone where one can observe a vigorous dissolution of crystals. However the temperature at the top of the flask decreases significantly (105°C) and this cooler zone favors crystal nucleation. It is worth pointing out the heterogeneous character of the system that consists of two visibly different phases; solid particles settle out at the bottom and shield efficiently the remaining liquid from the boiling temperature (see ESI†). This isolating effect of crystals induces a gradual decrease in temperature along the flask, which clearly contrasts with boiling in homogeneous mixtures. As shown schematically in Fig. 1, crystals dissolve at the hot bottom while the concentrated solution nucleates or grows at the top at a lower temperature. This cycle of dissolution–nucleation could lead ultimately to an anti-Ostwald ripening behavior in which large crystals disappear at the bottom at the expenses of the small ones at the top. Crystals of the same handedness rise inexorably over time at reflux and an initial racemic mixture converts into a solid of single chirality after 24 h. As expected, the resulting handedness varies randomly between left- and right-handed crystals. The procedure is completely reproducible and its robustness has been checked in a series of 60 independent experiments, which lead to 53% cases of L-crystals and 47% of the opposite D-enantiomorph.

Alternative experiments have been conducted with enantio-enriched samples that differ by 10% between the populations of enantiomorphous crystals. With such an excess the boiling system is biased to the major enantiomorph, *i.e.* D- or L-enriched mixtures give rise to the exclusive formation of D- NaClO_3 or L- NaClO_3 crystals, respectively.

At first glance, boiling and reflux appear to promote dynamic dissolution and crystallization processes leading to the conversion of one enantiomorph into the other in close analogy to grinding. However, deracemization is now triggered by a concentration–supersaturation gradient, which results otherwise from temperature differences and hence solubilities along the reaction mixture. Remarkably, when the boiling mixture is stirred with a magnetic bar, thereby causing temperature homogenization, any concentration–supersaturation gradient vanishes and as a result the final mixture remains in a racemic state. This result could be counterintuitive, though gradual thermal boiling leading to disequilibrium takes place far from equilibrium, while stirring struggles to restore the equilibrium and under these conditions entropy drives the system toward a racemic state.

To further rule out the role of abrasive grinding, a number of parallel experiments have also been run under agitation using the device shown in Fig. 2 (see ESI†). It consists of a horizontal bar with two Teflon-coated rings at both edges,

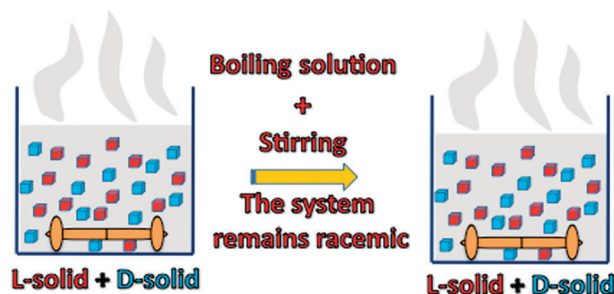


Fig. 2 A racemic mixture of NaClO_3 crystals remains under boiling and smooth agitation without abrasion.

thus smoothly agitating the mixture but preventing the abrasive action of the bar since there is no direct contact between the latter and the remaining crystals. Under such conditions, neither the thermal gradient nor the concomitant nucleation can be established. Only a racemic mixture of large crystals could be detected after prolonged heating.

A major effect under boiling at the bottom of the flask comes presumably from shear forces occurring at the bubble–liquid–crystals interface. This hydrodynamics causes a very strong dissolution process of crystallites with the generation of different entities: achiral molecules, chiral clusters and micro-crystals that rise up cooling, growing and feeding other crystals above them. In fact, a final state of single chirality also happens under the action of efficient mixing and shock waves generated by bubble collapse.^{8e,14} Moreover the boiling process of water is indeed a non-linear phenomenon and there are dynamic interactions: bubble to bubble and bubble to liquid medium.¹⁵

The latter situation is substantially different from that of El-Hachemi *et al.*,¹⁰ who suggest formation of subcritical nuclei (cluster) of the same chirality generated by evaporation. Interesting enough this group recognized the key role played by a temperature gradient between the reactor wall and the air–liquid interface, thus enabling the appropriate recycling of the subcritical nuclei prior to any noticeable crystal growth. The latter will occur after reaching supersaturation, but at that moment the overall system has already a predetermined handedness due to cluster interactions. It is plausible to figure out a process closer to a melt than a conventional boiling solution given the level of saturation above 100°C after water removal.¹⁰ Certainly, crystallization from a melt under stirring has also been known to cause symmetry breaking.¹⁶

The idea that symmetry breaking towards homochiral compositions may begin in the metastable stage preceding crystallization, that is at the level of subcritical clusters, has been previously conjectured by Viedma¹² and Addadi and Lahav.¹⁷ A plausible rationale accounting for deracemization under boiling would thus involve a solution consisting of both achiral NaClO_3 molecules and subcritical chiral clusters of variable size together with microcrystallites. These entities move through the liquid owing to the thermal gradient, thereby creating supersaturation conditions at the cooler zone. Subcritical clusters will then reach a critical size growing from achiral molecules or the above-mentioned chiral clusters. This hypothesis could be consistent with previous theoretical models introduced by Uwaha and Katsuno¹⁸ as well as McBride and Tully.¹⁹ Also, recent experiments unveil indirectly the formation of subcritical clusters as

stereodirecting elements.²⁰ Secondary nucleation, heterogeneous nucleation and ripening should in addition contribute to asymmetric amplification. A mathematical study also shows a final steady-state of single chirality as long as cluster recognition takes place at the level of hexamers.²¹

To conclude, our findings reveal that deracemization of enantiomorphous crystals may actually be occurring under boiling conditions due to dissolution–crystallization cycles induced by a temperature gradient. From an environmental viewpoint, these conditions are credible as hot springs, produced by geothermally-heated groundwater, provide natural scenarios which were presumably abundant in prebiotic periods. It is hoped that controlled boiling favoring sufficient thermal gradient and mass flow may be harnessed for the resolution of chiral compounds of pharmaceutical or industrial interest.

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Notes and references

‡ Interestingly, this experiment also produces racemic D,L-samples, a fact attributed to the existence of several polymorphs, one being achiral and undergoing solid-to-solid transition to a cubic phase (racemic conglomerate of D- and L-domains).

§ Probably, the first credit should be given to Addadi and Lahav, who pointed to the role of discrete clusters of arbitrary chirality in absolute asymmetric photoreactions; see ref. 17.

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