Metastability in Supersaturated Solution and Transition towards Chirality in the Crystallization of NaClO₃**

Zoubir El-Hachemi,* Joaquim Crusats, Josep M. Ribó,* J. Michael McBride, and Sabino Veintemillas-Verdaguer*

Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

Reports on spontaneous deracemization of crystal mixtures of achiral or racemizing compounds (Viedma deracemization)[1] are arousing strong interest not only because of their potential applications but also for understanding spontaneous emergence of chirality in chemical scenarios.[2] The systems that may undergo such deracemizations involve compounds that crystallize as enantiopure crystals (racemic conglomerates)[3] but are achiral or racemize rapidly in solution. The experimental conditions that promote such deracemizations are wet grinding of a racemic conglomerate in contact with its saturated solution and, if necessary, addition of a catalyst to accelerate racemization of the compound in the liquid phase. The results cannot be explained by dynamic kinetic resolution, because the assumption of a single parent crystal does not apply when a mixture of enantiomeric crystals is ground. Moreover, they cannot be explained by a second-order dynamic kinetic resolution process,[4] nor by enantioselective inhibition of crystal growth under the influence of a chiral minor component,[5] because of the absence of a second chiral compound.

For systems such as NaClO₃ and 1,1′-binaphthyl, there are reports of crystallizations that, under the action of strong stirring, yield polycrystalline mixtures of composition near to homochirality.[6] Such results have been interpreted by the one-single-parent-crystal assumption together with a crystal growth dominated by secondary nucleation processes; the strong stirring creates new seeds by fracturing crystals.[7] However, a recent report[8] that describes a homochiral

outcome in the crystallization of NaClO₃ from boiling solutions suggests that the deracemization might also occur at the level of subcritical clusters. Notice that chiral amplification by secondary nucleation by no means precludes amplification at the level of subcritical clusters. In fact, some results in these previous reports indicate that the enantiomeric excess of crystals increases with the initial supersaturation,[6] which, as we will show, is consistent with a significant role of the metastable stage preceding primary nucleation.

Several mechanisms have been proposed to explain Viedma deracemization.[9] However, it is important to understand the thermodynamic aspects and constraints that allow such deracemizations to occur. As we have previously discussed,[10] in the initial stagnant conditions the system is in a chemical equilibrium that is determined solely by interactions between individual crystals and the solvated chemical compound. Solid-to-solution interaction does not distinguish between the enantiomorphic crystals. Under these conditions the enantiomorphic solids are thermodynamically identical, and the system is defined by one component in addition to the solvent; there is only one solid phase. This is the long-accepted chemical interpretation in respect to the available degrees of freedom that explain the experimental chemical behavior of these systems.[11] Under Viedma deracemization conditions, we proposed that erosion of the crystals would lead to clusters that, in their interaction with other crystals or with each other, would recognize each other as different thermodynamic phases, that is, an enantiomeric discrimination would occur between the two enantiomorphic solid phases.[10] Consequently, under constant grinding the system is taken out of equilibrium and evolves towards a final stationary state that, according to the published reports, is homochiral or nearly homochiral. Note, however, that certain experimental conditions may lead to a racemic stationary state of different composition than the stagnant conditions, or even to oscillations. Customary failure to publish "negative" results inhibits evaluating the range of possibilities.

We have now conducted experiments to determine whether, in the crystallization of NaClO₃ from boiling solutions, deracemization can occur at the level of subcritical clusters during the metastable stage previous to crystal growth.

Our starting assumption, according to a previous report,[8] is that in these systems during the highly concentrated, supersaturated metastable stage, that is, before crystal growth, an enantiomeric excess of chiral subcritical clusters

[*] Dr. Z. El-Hachemi, Dr. J. Crusats, Prof. J. M. Ribó
Department de Química Orgànica and Institute of
Cosmos Science (ICC), Universitat de Barcelona (IEEC-UB)
c. Martí i Franquès 1, 08028-Barcelona Catalonia (Spain)
Fax: (+34) 93-339-7878
E-mail: zelhachemi@ub.edu
        jmribo@ub.edu
Prof. J. M. McBride
Department of Chemistry, Yale University
225 Prospect St., New Haven, CT 06520 8170 (USA)
Dr. S. Veintemillas-Verdaguer
Centro de Astrobiología, CSIC-INTA
Ctra. Ajalvir Km. 4, 28850-Torrejón de Ardoz, Madrid (Spain)
E-mail: sabino@icmm.csic.es

may be generated. Direct analysis of the optical properties of such subcritical nuclei moving in the boiling solution is difficult or even impossible. However, simultaneous collection of several liquid samples at the metastable stage and analysis of the chiral composition of the resulting set of crystals may provide insight into chirality correlation among the subcritical nuclei in the mother solution.

A previous report on the crystallization of $NaClO_3$ in boiling solutions[8] showed that a high enantiomeric excess in the crystal mixture is only obtained when there is a high temperature gradient between the bottom of the flask and the surface of the boiling solution. This gradient implies continuous mass transport between two regions with different saturation concentration values: higher for the hotter region at the bottom and walls and lower at the top of the reaction solution. To test the region of highest cluster concentration, we sampled from the region where crystallization occurs first, that is, near the coolest surface in the middle of the reactor. Figure 1 shows the device used to obtain four samples at
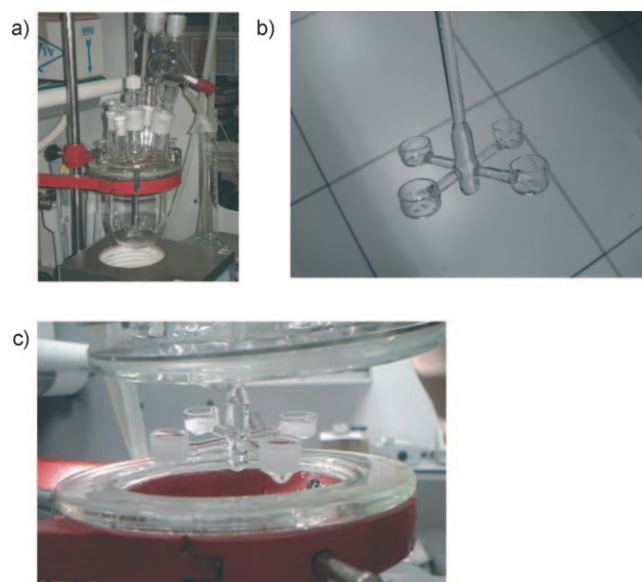

Figure 1. a) Reactor for the crystallization experiments in boiling solutions. b) Detail of the glass rod equipped with four cups, which allows simultaneous collection of four samples from the solution. c) Cups with the crystallized solution.

different sites in the solution. The tiny cups were immersed in the boiling solution before water was distilled from the reactor and held stationary during distillation (see Ref. [8] and the Experimental Section for more details). After a specified amount of water had been distilled from the reactor but before crystallization occurred, the glass rod holding the four cups was raised from the solution to the top of the reactor near to the glass cover, and the electric blanket was disconnected. In some cases the crystallization in the bulk started spontaneously owing to the movement of the rods; these experiments were discarded because of contamination by crystals from the solution. Bulk and cups were both initially free of visible crystals, but crystallization took place suddenly, but independently, after delays of between 30 s and
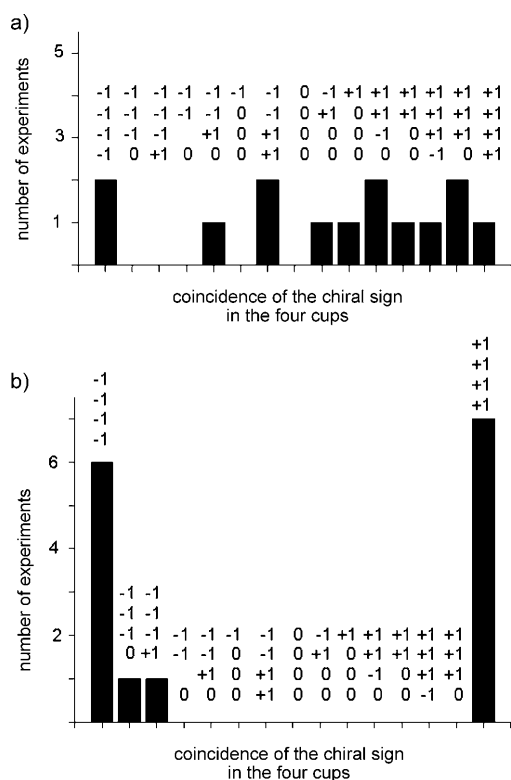
a few minutes as a consequence of cooling. Notice that in the previous report on crystallization in boiling solution,[8] distillation was continued to the point of spontaneous crystallization, which spread throughout the flask within less than 0.1 s of its becoming visible. Now, as expected, crystallization first occurred in the reactor bulk, because of the higher probability of nucleation owing to the higher volume of the solution (ca. 250 mL) compared to the 1.5 mL in each cup.

As reported,[8] crystallization of the boiling solution occurs at a density of $2 \, g \, mL^{-1}$, that is, at a molar ratio $H_2O/NaClO_3$ of about 2.1. In boiling conditions, the solutions approach this supercritical state after the extraction of about 75 mL of water from the initial 220 mL of solution containing 400 g $NaClO_3$. Two different sets of experiments were performed, one extracting only 60–69 mL of water (molar ratio of $H_2O/NaClO_3$ ca. 2.39–2.25), and the other extracting 70–80 mL (molar ratio of $H_2O/NaClO_3$ ca. 2.25–2.09).

The chirality of the crystals as determined from the optical rotatory dispersion (ORD) spectra of Nujol mull dispersions is shown in Figure 2. In the case of the series with less water extracted (60–69 mL) the four cups do not always show the same chiral sign (Figure 2a and Figure 3a). However, when the amount of water extracted (70–80 mL) approaches the critical value, the chiral sign of the four cups is the same in 14
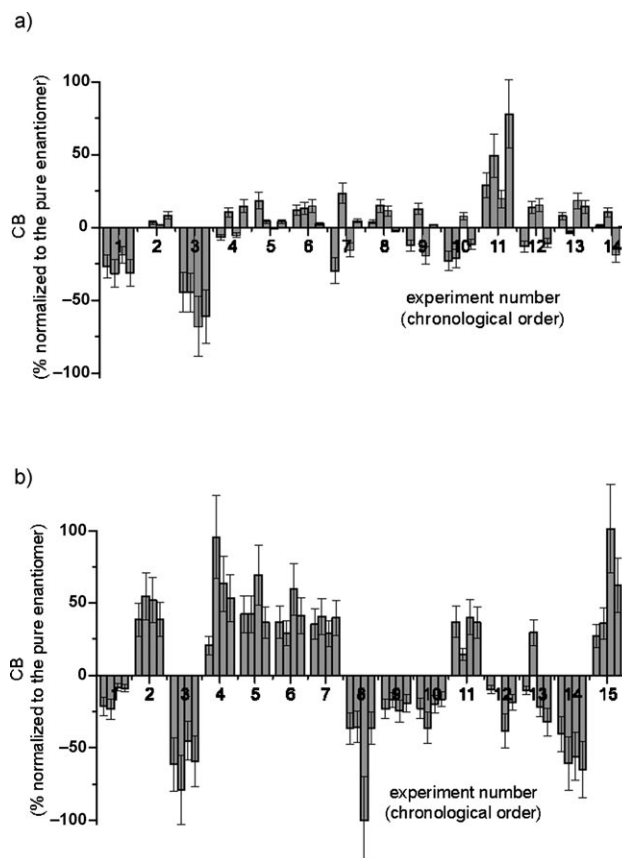
Figure 2. CB values at 230 nm in percent normalized to the value for a pure $NaClO_3$ crystal (ca. 7000 mdeg g^{-1}). a) Samples collected after removing 60–69 mL of water. b) Samples collected after removing 70–80 mL of water (see the Experimental Section).

a)

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-1 -1 -1 -1 -1 -1  -1  0 -1 +1 +1 +1 +1 +1
-1 -1 -1 -1 -1  0  -1  0 +1  0 +1 +1 +1 +1
-1 -1 -1     +1  0 +1  0  0  0 -1  0 +1 +1 +1
-1  0 +1  0  0  0 +1  0  0  0  0 -1  0 +1
```

number of experiments

coincidence of the chiral sign
in the four cups

b)

```
                                                +1
-1                                              +1
-1                                              +1
-1                                              +1
-1

-1 -1
-1 -1
-1 -1  -1 -1 -1   -1  0 -1 +1 +1 +1 +1
 0 +1  -1 -1  0   -1  0 +1  0 +1 +1 +1
       +1  0 +1   0  0  0 -1  0 +1 +1
        0  0  0  +1  0  0  0  0 -1  0
```

number of experiments

coincidence of the chiral sign
in the four cups

Figure 3. Summary of the chiral signs arising in each set of four cups in the experiments of Figure 2. a) 60–69 mL of water removed. b) 70–80 mL of water removed.

of 15 runs and coincides with that of the bulk solution (Figure 2b and Figure 3b).

Furthermore, the circular birefringence (CB) values are higher for the series removing 70–80 mL of water (compare Figure 2a,b). It is difficult to perform accurate measurements of the amount of water extracted, because of the number of ground-glass joints and the large surface area of the flat flange.

The results suggest that mirror symmetry breaking can occur before crystal growth at the metastable stage of supersaturated solution. The differences between the two sets of experiments shown in Figure 2 and Figure 3 indicate that the transition to a chiral state occurs near the onset of crystal growth, when the concentration of subcritical clusters is at a maximum.[12]

It is unlikely that cross contamination through space from the crystals appearing in the bulk solution determined the homochiral sign in the four cups in the runs of Figure 2b, because bulk crystallization was similar in the runs of Figure 2a, in which there was little correlation. Furthermore, the three 70–80 mL runs of Figure 2b (experiments 5, 8 and 12) where the cups crystallized before the bulk[13] showed the same correlation seen in the other experiments. The difference between the runs of Figure 2a,b also makes it unlikely that there was seeding from cup to cup. Furthermore, the cups were separated from one another by more than 3.5 cm, and their contents crystallized before any crystallization could be observed in the small amount of liquid adhering to the connecting rods or to the outside of the cups.

Thus the coincidence of chiral sign for the four cups in the series of experiments where 70–80 mL of water was removed, as compared to the randomness in the series where less water was removed, indicates that when there is sufficient supersaturation mirror symmetry breaking can occur for metastable clusters, that is, before perceptible crystallization, even without grinding.

Obviously, the observed chiral correlation requires a significant concentration of clusters that are large enough to avoid both rapid racemization and rapid accommodation to a larger enantiomeric cluster. To judge the plausibility of such large clusters, we estimated the cluster size distribution according to the classical theory of primary nucleation for ionic salts (see the Supporting Information). The same theoretical framework gives an estimation of the supersaturation limit consistent with the experimental data.[8] The estimated cluster critical size for homogeneous primary nucleation contains $58\,NaClO_3$ units (see the Supporting Information). A significant number of clusters are larger than four unit cells ($16\,NaClO_3$ units), and we think it plausible that racemization is slow above this size. If we simulate heterogeneous primary nucleation (by reducing the $NaClO_3$ solid–solution surface energy), the supersaturation limit, although it necessarily decreases, remains of the same order as that experimentally observed. This heterogeneous nucleation decreases the cluster size at the saturation point, but it shows an important increase of the concentration of the large clusters (see the Supporting Information), which suggests that the change of homogeneous to heterogeneous primary nucleation would not change the influence of cluster–cluster interactions on the emergence of chiral correlation.

The temperature difference between the flask and the gas–liquid surface of the solution, together with the intense convective flows produced in the boiling solution, cause rapid mass transport between these two regions. Classical nucleation theory (see the Supporting Information)[14] suggests that the larger clusters from the cooler region would reduce their size in the hotter region; this result implies the recycling of large clusters to small clusters in the mass transport between surface and wall. Moreover, the difference between the cluster size distributions is predicted to increase as water is withdrawn from the system (see the Supporting Information). In summary, the calculation supports a scenario of dynamic recycling of chiral clusters by transport between hotter and cooler regions. Notice that in the wet grinding conditions of most of the reported Viedma deracemization results, as well in aerosol mediated crystallization,[15] recycling from solid to clusters is performed by eroding of crystals. Of course recycling alone cannot lead to mirror symmetry breaking,[9f, 10] which requires pathways involving enantiomeric discrimination (chiral recognition) between the enantiomorphic solid phases. Such discrimination is present, sometimes only implicitly, in all successful mechanistic models for explaining Viedma deracemization (for example in Refs [9a,e–h]). The concentration of nonracemizing clusters in the conditions of these experiments is relatively large, but obviously the concentration of racemizing clusters is much higher. Formation of clusters by coalescence of large nonracemizing clusters with small racemizing clusters of the opposite chiral sign is an

expected process, although it should be slower than the corresponding aggregation between clusters of the same chiral sign.

The results reported herein strongly suggest that the emergence of chirality in deracemization experiments of systems of racemic conglomerates of one chemical component (achiral or racemizing) plus solvent can occur by way of chiral recognition between clusters before the primary nucleation process. Recent observation of chiral inversion between solid and solution phases for this system has been attributed to analogous recognition in slurries that already contain solid.[16] Now that three mechanisms (secondary nucleation, Viedma ripening, and subcritical cluster correlation) have been shown to create nearly homochiral sets of crystals from achiral or racemic samples, it is difficult to assign a mechanism to previous examples of spontaneous symmetry breaking in crystalline systems (e.g., Ref. [17]) without further study.

Experimental Section

General method of crystallization: The experimental setup consists of a 700 mL glass wide-necked cylindrical reactor (flat flange) with a cover with ground-glass joints heated with an electric blanket. A distilling head with stopcock, placed between the reactor and the reflux condenser, allows removal of solvent (Figure 1). A screw cap on the central threaded ground-glass joint of the cover supports a long glass rod which holds four tiny glass cups (1.5 mL volume each; Figure 1) all attached at the same distance (2.5 cm) from the axial glass rod. Teflon sleeves were used instead of lubricant grease for the glass joints. Mounting the cups above their radial supports and far from the axial rod avoids contamination from liquid falling from the supporting rods. The central rod can be shifted vertically and rotated by adjusting the supporting screw cap at the reactor cover to move the cups into or out of the boiling solution. It also allows them to be moved to the top of the reactor to avoid contamination from the solution and the reflux condenser. The cups, when immersed in the solution, were 1 cm from the reactor wall and 2 cm below the solution surface (at the final volume of the solution). Details on the specific experimental conditions are described in the Supporting Information. Before crystallization occurs, the four-cup assembly was raised from the boiling solution to the top of the reactor near the glass cover, and the electric blanket was disconnected. When necessary, the long glass rod, after removal from the solution, was slightly rotated to avoid water from the distilling head dripping into the cups. Crystallization takes place after a few minutes, usually first in the reactor, where the probability of nucleation is much higher than in the cups. Crystals were present only within the cups and in the bulk, not on the supporting bar or the external walls of the cups. In some cases crystallization began as the cups were raised; these experiments were discarded.

Optical rotatory dispersion spectra: The ORD spectra at room temperature were recorded over the range 220–400 nm using a Jasco Spectropolarimeter J-810 and Nujol mull samples prepared according to the procedure reported,[7] as described in detail in the Supporting Information.

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