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Using Programmed Heating–Cooling Cycles with Racemization in Solution for Complete Symmetry Breaking of a Conglomerate Forming System

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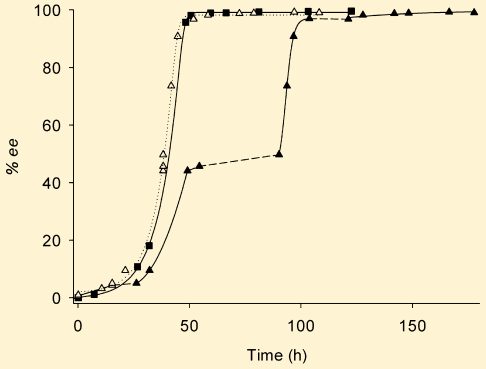
ABSTRACT: A deracemization technique using periodic temperature fluctuations on a conglomerate forming system undergoing a swift racemization in solution is demonstrated. The method uses heating and cooling periods of the suspension in order to create cycles of partial dissolution of the crystal phase followed by crystal regrowth: this enables symmetry breaking in the solid phase. The technique is an effective, simple, and cheap operation, and can promote understanding of the effects of dissolution and recrystallization on chiral symmetry breaking in the solid phase. The heating period leads to the decrease of the size of crystals and the destruction of small crystals; the surviving crystals can then grow during the cooling period. A succession of such cycles allows the autocatalytic transformation from a racemic suspension into pure enantiomer, with an enantiomeric excess (*ee*) > 99% within a few days. The results demonstrate a possible mechanism for the emergence of homochirality of molecules of biological significance on Earth.



INTRODUCTION

Access to pure enantiomers remains an important scientific and industrial issue. Recently, a new crystallization process called Viedma ripening was designed.[1] Viedma showed that it was possible to completely break the symmetry of a racemic mixture of D- and L-crystals of $NaClO_3$ by using a continuous grinding technique in suspension. Though achiral in solution, $NaClO_3$ has the special feature to crystallize in the chiral space group $P2_13$,[2] giving two kinds of enantiomorphous crystals. An older technique named total symmetry breaking, which was described by Kipping and Pope in 1898, was used to obtain an enantiomeric excess over 90% by seeding a saturated solution of $NaClO_3$ with solid composed of pure enantiomorphous crystals.[3] In 2008, the first example of the total symmetry breaking of an intrinsically chiral component, an amino acid derivative, was jointly given by a Dutch consortium and the group of Blackmond by combining Viedma ripening and *in situ* racemization in solution.[4] After this initial research, further chiral organic compounds have been deracemized.[5−10] Unfortunately, the number of candidates is limited by the important restrictions of this process: compounds must crystallize as a conglomerate (i.e., a physical mixture of the two enantiomers) and must undergo a fast racemization in solution under the same operating conditions. The number of publications on the topic has also significantly increased as researchers attempt to explain how racemic suspensions in contact with a saturated solution and a racemizing agent are able to evolve toward an enantiopure final state. Additionally, the full resolution of the mechanism of the deracemization could give the keys to understand why only one enantiomer of many natural chiral compounds is prevalent in nature. The understanding of how biological systems may have naturally become homochiral is one of the most important questions for scientists.[11−14]

Numerous studies have been carried out to explain the mechanism of chiral symmetry breaking of the crystal phase. After vigorous debates, the current standard model involves the combination of Ostwald ripening and the reincorporation of chiral clusters by crystals of the same chirality.[5,10,15−17] Indeed, attrition produced by grinding enables the production of a high number of chiral clusters that increase the exchange of matter between particles and thus the rate of the evolution of the *ee* of the solid phase. Moreover, due to the minimization of the energy surfaces, the smaller particles produced by grinding are quickly dissolved to the benefit of the growth of the larger ones (Ostwald ripening) which also speeds up the evolution of the *ee*. Numerous computer models have been produced to simulate the evolution of such a process by taking in account the reincorporation of clusters, the effect of Ostwald ripening, the size dependent solubility, the agglomeration of particles,

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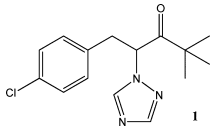
and of course, the crystallization as a conglomerate together with fast racemization in solution.[18−23] These studies also demonstrated that the grinding and the resulting processes were not necessary to complete deracemization, but they serve to significantly accelerate the evolution of the *ee*.[5] Ripening occurs somewhere between the solubility of an infinite size crystal and the solubility of a nucleus, which will result in slow kinetics since these two limits are very close and both dissolution and growth processes will occur at very low levels of supersaturation.

In 2011, Viedma and Cintas showed that boiling suspensions of sodium chlorate can also lead to chiral symmetry breaking of the crystals.[24] They suggested that dissolution/crystallization cycles due to the temperature gradient existing between the bottom of the flask (in contact with a hot plate) and the top of the flask (in contact with atmosphere at ambient temperature) are responsible for the process of deracemization. Recent modeling performed by Iggland and Mazzotti[25] has shown that simultaneous growth of crystals larger than the critical size and dissolution of crystals smaller than the critical size may be able to produce relatively fast chiral symmetry breaking. It should be emphasized that this process (a form of ripening) is very distinct from growth and dissolution cycles due to temperature gradient where essentially all the crystals in the suspension grow in the lower temperature part of the gradient and dissolve (either partially or totally) in the upper temperature part. It is possible that similar effects occur in suspensions undergoing grinding. Indeed, attrition induces localized volumes of high energy/temperature in the system, which leads to the dissolution/recrystallization phenomenon.

This paper aims at contributing to a better understanding of deracemization in heterogeneous systems. This study is focused on the effect of temperature fluctuations at near ambient conditions in a gently stirred system on the deracemization of a model compound, 1-(4-chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pentan-3-one **1** (Figure 1). This compound,



1

Figure 1. Chemical structure of **1**.

a precursor of Paclobutrazol, a plant growth inhibitor,[26] is known to crystallize as a stable conglomerate without detectable solid solution and can be easily racemized using an alkaline aqueous solution.[27] The deracemization of this compound was previously described in the literature at 25 °C.[6] This compound was thus an appropriate candidate to study the possibility to perform deracemization by means of temperature cycles at near ambient conditions to simulate the natural temperature cycling and in order to address the question of how chiral symmetry breaking occurs

■ EXPERIMENTAL SECTION

Materials. Racemic 1-(4-chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pentan-3-one (**1**) was synthesized according to the literature.[28]

Distilled water was used for deracemization experiments. HPLC-grade *n*-heptane and ethanol, and reagent-grade methanol were purchased from Fisher Scientific.

Deracemization Experiments. The deracemizations were carried out as follows: in a 50 mL round-bottom thermostatted flask, **1** was suspended in a methanol/water mixture (80/20 wt %, 25 g) and then the racemising agent, sodium hydroxide (0.2 g, i.e., 8 g per kg of solvent), was added. An oval magnetic stirrer operated at 500 rpm was used to ensure a uniform distribution of particles and temperature in the heterogeneous system, and then a temperature program (TP) was applied. Different masses of **1** and different TPs (Figure 2) were used to achieve the symmetry breaking in the study, as summarized in Table 1. The first temperature program TP1 consisted of four steps: holding

Table 1. Required Number of Cycles and Required Time to Achieve Complete Symmetry Breaking (Defined As Reaching an *ee* > 98%) for the Experiments Described

	TP	total mass of **1** (g)	required time to complete deracemization (h)	number of cycles required to complete deracemization
experiment I	1	3.3	91	91
experiment II	2	2.5	51	86
experiment III	3	2.5	51	121
experiment IV	4	2.5	51	67
experiment V	2	1.8	32	55

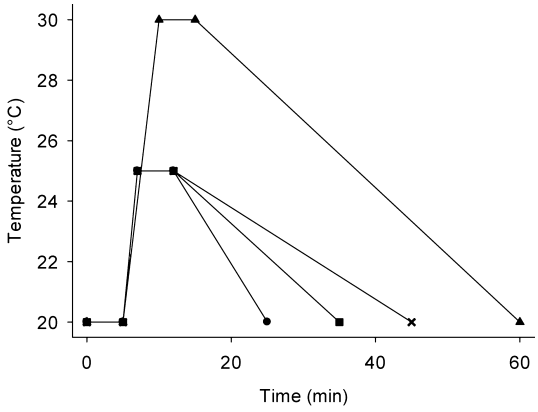


Figure 2. The different temperature programs. ▲ TP1, ■ TP2, ● TP3, and × TP4.

at 20 °C for 5 min, ramping up to 30 °C over a period of 5 min, holding at 30 °C for 5 min, and then ramping down to 20 °C over a period of 45 min. The second temperature program TP2 starting by holding the temperature of the suspension at 20 °C for 5 min, then ramping it up to 25 °C over a period of 2 min, then holding it at 25 °C for 5 min, and finally ramping it down to 20 °C over 23 min. The third temperature program TP3 and fourth temperature program TP4 were identical to TP2 with the exception that the final ramp from 25 to 20 °C occurred over periods of 13 min (TP3) and 33 min (TP4). These temperature cycles were continued over a large number of cycles until deracemization was substantial. The suspension was partially dissolved during the heating period. The remaining crystals then recrystallize and grow during the cooling period by consumption of the supersaturation in the solution phase. The recrystallized amount is the same as the mass lost during the heating step.

HPLC. The *ee* was monitored by chiral HPLC.[6] Samples were taken off at the end of cycles (at 20 °C) using a plastic pipet. The solid was then filtered under a vacuum and washed with a sufficient amount of water to remove the rest of the sodium hydroxide (the solubility of **1** in water at 20 °C is lower than 0.1%[6]). A small amount of solid (ca. 5 mg) was then dissolved into 1 mL of ethanol. A 20 μL sample of this solution was injected into a Chiracel OC column (250 × 4.6 mm) using a solution of 5 vol% ethanol in *n*-heptane as eluent at a flow rate of 1.5 mL·min^{-1}. The two enantiomers were detected at retention

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times of ca. 8 and ca. 10 min using UV detection at a wavelength of 227 nm.

Solubility. Solubilities of the racemic mixture and of the pure enantiomer of **1** were determined at different temperatures using the gravimetric method. Without racemization (i.e., in a 80/20 methanol/water mixture), the solubilites of the racemic mixture and of the pure enantiomer are 5.0% and 2.4%, respectively at 25 °C and are in accordance with Meyerhoffer's rule. Under racemizing conditions, the solubilities of the racemic mixture and of the pure enantiomer are very close (Table 2), probably because both the solid phases are in equilibrium with a racemic liquid phase. The presence of sodium hydroxide seems to decrease the solubility of **1**. It should be noted that HPLC analyses confirmed that the chirality of the solid phases was the expected chirality (racemic for determination of the solubility of racemic **1**, enantiomerically pure for determination of the solubility of pure enantiomer of **1**) and that the liquid phases (that is to say, the dry extracts) were racemic.

Table 2. Solubilities of 1 in an 80/20 wt % Methanol/Water Mixture Containing 8 g of NaOH per kg of Solvent[a]

temperature (°C)	solubility of the racemic mixture **1** (%)	solubility of pure enantiomer of **1** (%)
20	3.9	3.6
25	4.6	4.4
30	5.8	5.5

[a]Solubilities are given in mass of **1** per 100 g of saturated solution.

Enantiomeric Excess (*ee*) in the Solid Phase. Enantiomeric excess in the solid phase is defined in terms of the predominant enantiomer at complete deracemization (at the end of the experiment). The experimental results demonstrated that the deracemization was random; the final product of the deracemization could be either of the *R*-form or the *S*-form of the compound. The presentation here is focused on the absolute value of the *ee* in order to compare the results more conveniently.

RESULTS

First, experiments were carried out to give the proof that temperature cycles at near ambient conditions were able to totally break the symmetry of the solid phase. TP1 and TP2, respectively experiment I (Figure 3a) and experiment II (Figure 4a), were applied to a suspension of **1**. After a few dozens of hours (ca. 90 h and ca. 50 h, respectively) and cycles (ca. 90 cycles and ca. 85 cycles, respectively), the solid phase became enantiomerically pure. The time required to achieve complete deracemization in the solid phase using the temperature cycling technique is shorter than when using grinding by small glass beads at constant temperature, which requires around a week for complete deracemization. These results indicate that it is possible to achieve total symmetry breaking of the solid phase by using cyclic temperature fluctuations in the system. The behavior of the conversion is a sigmoidal curve with an exponential part as illustrated by the curve $\ln(ee) = f(t)$ (see Figure 3b).

TP2 is shorter than TP1 and with smaller temperature fluctuations (between 20 and 25 °C instead of 20 and 30 °C for TP1). Therefore, for a usual ds/dT — variation of solubility versus temperature — there is no need for a high temperature gradient to break the symmetry.

It is known that grinding due to a magnetic stirrer is also able to perform deracemization.[29] Similar experiments were thus conducted in the same operating conditions than experiments I and II but with some periods of constant temperature to demonstrate that the symmetry breaking found in this study was due to temperature cycling rather than grinding. Experiment I′ was carried out at constant temperature (20 °C) for the first 142 h, and then TP1 cycles were applied (Figure 3a). No evolution of the *ee* is visible in the absence of temperature cycles during the observation period. But, once TP1 is applied, symmetry breaking of the solid phase significantly increases, leading to complete deracemization at ca. 90 temperature cycles (90 h) after the initiation of the temperature program. Figure 3b shows that the linear part of the curve $\ln(ee) = f(t)$ of experiment I and I′ is parallel, meaning that the evolution of the *ee* is not disturbed by the initial constant temperature period.

In the case of experiment II′, three periods of constant temperature were applied between periods of temperature cycles (Figure 4a). The evolution of the *ee* of the solid phase when the temperature is constant is much slower (almost without evolution) than during the TP2 periods even at high values of *ee* (≈45%). When merging the TP2 periods together (removing data at constant temperature), the evolution of *ee* in the solid phase (dotted line) is similar to the continuous use of TP2 throughout the experiment. The curves $\ln(ee) = f(t)$ are also superimposable (Figure 4b).

The fast evolution of the *ee* observed in this study is therefore due to the temperature fluctuations applied to the suspension and not due to the grinding ensured by the magnetic stirrer.

The effect of the cooling rate on the evolution of *ee* of the solid was investigated; the temperature programs TP2, TP3,

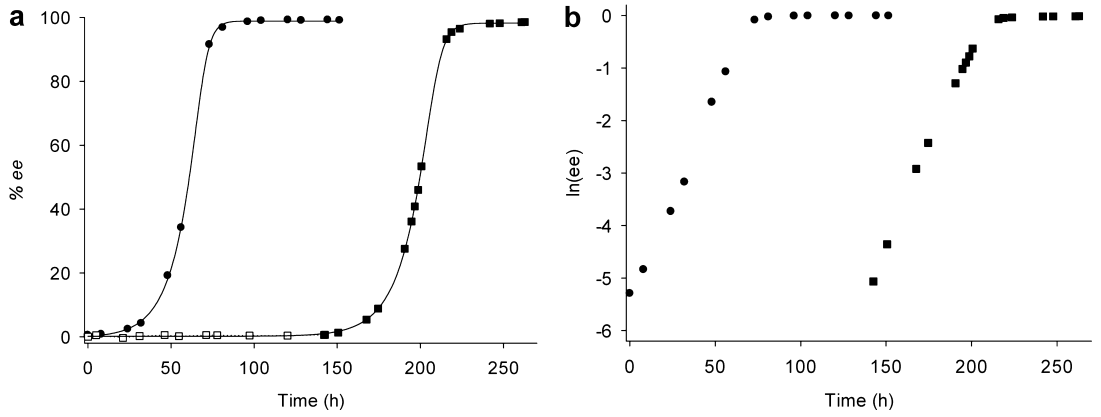

Figure 3. Deracemization by using TP1. (a) Evolution of *ee* versus time. (b) Evolution of ln(*ee*) versus time. ● Experiment I, □ Experiment I′ - constant temperature period (20 °C), ■ Experiment I′ - TP1 period.

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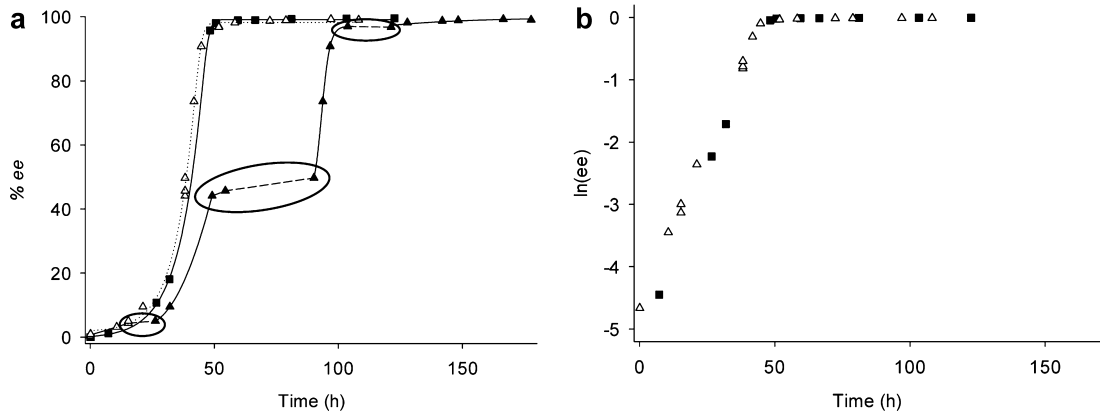

Figure 4. Deracemization by using TP2. (a) Evolution of *ee* versus time. (b) Evolution of ln(*ee*) versus time. ■ Experiment II, ▲ Experiment II′, full line: TP2 periods, dashed line: constant temperature periods (20 °C). (The constant temperature periods are encircled.) △ Experiment II′ ignoring the constant temperature periods.

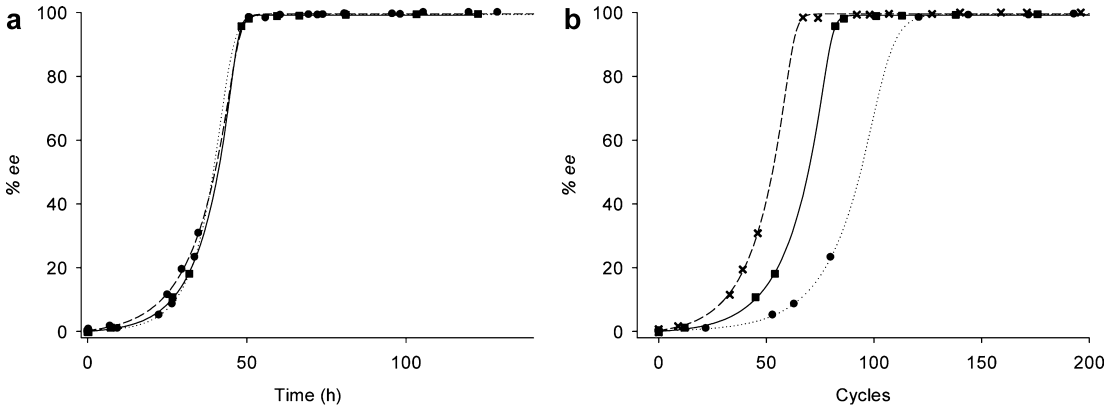

Figure 5. Effect of the cooling rate on deracemizations. (a) Evolution of the *ee* versus time, (b) evolution of *ee* versus the number of heating−cooling cycles. ■ Experiment II (TP2), ● experiment III (TP3), × experiment IV (TP4).

and TP4 were compared. They differ only by the duration of the ramp to return to 20 °C (Figure 5). This is a critical parameter since it will determine the evolution of the supersaturation during the crystal growth period; faster cooling rates will lead to larger supersaturation values during the crystallization and therefore a greater likelihood of nucleation during the crystallization period rather than simply growth of existing crystals. The cooling rates of TP2, TP3, and TP4 are 13 °C h^{-1}, 23 °C h^{-1}, and 9 °C h^{-1}, respectively. The results show that the evolution of *ee* over time is unchanged for the three temperature programs used (Figure 5a). The programs have no significant effect on the time required to achieve complete chiral purity. However, when the evolution of *ee* in the solid phase is plotted against the number of heating−cooling cycles (Figure 5b), the evolution of the *ee* is different. The faster cooling rate system requires more cycles than the lower cooling rate system. In the case of a rapid cooling, the creation of a high supersaturation puts the solution point beyond the Ostwald limit,[30] and the enantiomer in minor amount can produce small crystals by secondary nucleation, resulting in a time delay for complete conversion. However, in the case of a slow cooling, the crystallization of the major enantiomer is favored and not limited by the decrease of its concentration due to racemization in the liquid phase.

The effect of the amount of solid to deracemize on the duration of the experiment was studied. Two experiments were carried out in the same operating conditions, except for the initial mass of **1**: 2.5 g (experiment II) and 1.8 g (experiment V) were used. In the two cases, the same mass of solid is dissolved during the heating period. The resulting masses and the resulting supersaturations are therefore the same, as illustrated in Figure 7. It is not surprising that the time required to achieve complete chiral purity is shorter when the mass of solid is smaller (Figure 6), the amount of **1** to deracemize being smaller. However, the relative percentage of

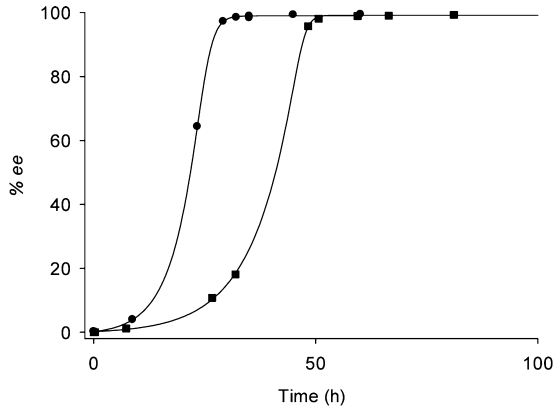

Figure 6. Comparison between two deracemizations carried out in the same experimental conditions, using TP2, except for the total mass of **1**: ■ experiment II: 2.5 g of **1** and ● experiment V: 1.8 g of **1**.

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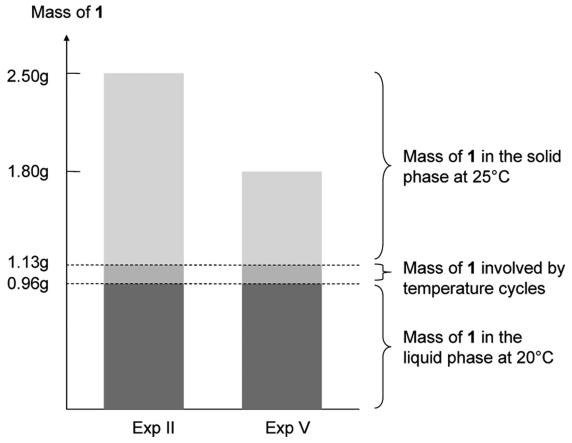

Figure 7. Schematic representation of the distribution of **1** in the different phases of the suspension for the experiments II and V.

solid involved in each cycle is different: ca. 10% of the solid phase is dissolved in the experiment II instead of ca. 20% in the experiment V. It is therefore possible that all the processes that occur due to dissolution/recrystallization are magnified when a higher percentage of solid is involved by the temperature fluctuations, accelerating the evolution of the *ee*.

DISCUSSION

The results presented in this study demonstrate conclusively that deracemization can also occur in the absence of abrasive grinding. The evolution of a racemic mixture of a chiral compound to single handedness is possible due to the combination of racemization in solution and dissolution/recrystallization cycles in the system. These temperature fluctuations are responsible for two phenomena that result in an increase of the *ee* of the solid phase: (i) dissolution of the racemic mixture during heating periods, (ii) growth of crystals and entrainment effect during cooling periods.

During the heating periods, according to thermodynamic principles and for low and medium *ee* in the solid phase, only the racemic mixture is dissolved (obviously, if the ee of the solid phase is too high, the enantiomer in excess will be also dissolved). Proportionally, crystals of the less abundant enantiomer are more dissolved than crystals of the enantiomer in excess; the *ee* of the solid phase is therefore magnified. Then, during the cooling periods, a supersaturation is created and the remaining crystals can grow.[31]

For a system in equilibrium without racemization, the initial and the final compositions of a heating/cooling event must be the same: a racemic liquid phase in equilibrium with two mirror related solid phases. The entrainment effect is therefore limited to a short period of time, when the system is out of equilibrium. In the most favorable case, the enantiomer in default is completely dissolved at the highest temperature. The system is autoseeded by the crystals of the single enantiomer remaining in the solid phase.[31−33] The entrainment effect takes place as soon as the system is cooled, and it is exhausted when the mother liquor reaches the metastable solubility of the crystallizing enantiomer. The return to equilibrium corresponds to the crystallization of the second enantiomer, and then the *ee* of the mother liquor decreases down to zero.

With racemization in solution, the composition of the liquid phase is always racemic. Therefore, the entrainment effect has no thermodynamic limit.

A preferential crystallization method called second order asymmetric transition (SOAT)[34] is based on this concept. The combination of a controlled cooling with racemization in solution prevents, up to a certain point, the crystallization of the counter enantiomer and improves the efficiency of the preferential crystallization. If the enantiomeric excess in the solid is not high enough, they are actually two simultaneous SOATs, but the larger the imbalance in the two solid phases the higher the imbalance in the crystal growth so the faster the evolution of toward high *ee*. The net result is therefore an autocatalytic effect.

Viedma previously described a similar model, the "*thermodynamic-kinetic feedback near equilibrium*", to explain the spontaneous chiral symmetry breaking observed for $NaBrO_3$.[33] The appearance of a single handedness was due to a "*feedback between the thermodynamic control of dissolution and the kinetics of the growth process near equilibrium*". This model was described for the slight growth−dissolution cycles that occur at constant temperature (Ostwald ripening), but he suggested that this model could be applied to intrinsically chiral molecules.

Recently, Viedma's research group in collaboration with Blackmond's group gave the proof that deracemization can be achieved only through the use of a temperature gradient, at high temperatures (ca.105 °C), due to the type of heating used, but without grinding.[35] This is likely to be due to a similar mechanism as in the current work, since crystals may cycle through regions of different temperatures; however, the use of deliberate temperature cycling may result in a clearer picture of the mechanism of the deracemization which is still matter of debate.

The general consensus is that Viedma ripening occurs due to Ostwald ripening and the reincorporation of chiral clusters. At the initial stage of the deracemization, a difference between the two enantiomers can be created by any departure from a perfectly symmetric situation: stochastic slight variation of *ee* or of the crystal size distribution due to continuous exchanges of matter between the solid and the liquid phase, presence of an impurity[4] which promotes or disrupts the crystallization of one of the two enantiomers, etc. This imbalance is then progressively increased due to Ostwald ripening and reincorporation of chiral clusters. It is evident however that grinding also introduces fluctuations in energy and therefore fluctuations in temperature in a suspension. Friction induced by glass beads may cause high numbers of small localized cycles of heating/cooling in the system. These fluctuations (with respect to time and space) in temperature will lead to the creation of local dissolution and thus supersaturation after cooling and then entrainment.

In this report, we demonstrate deracemization using a technique that is not dependent on grinding. The phenomenon of dissolution/growth in our system has been induced by controlled temperature cycles similar to those occurring in nature. All crystals are simultaneously dissolved during the heating period; the same mass of the two enantiomers is affected. The crystals remaining after the heating cycle are then grown during the cooling period by consuming the excess of the solute molecules in the supersaturated solution. Since the solution has rapid racemization, the supersaturation of the *R*- and *S*-components are equal throughout the crystallization period and the entrainment effect can efficiently occur. Possible mechanisms for the phenomena do not necessarily require an initial asymmetry in either the solution or the crystalline phase;

a very slight imbalance stochastically created by statistical fluctuations is sufficient to trigger the evolution of the whole system. It is possible that there are different histories involved in the nucleation and growth of the two populations (due to the stochastic nature of some of the phenomena) which may have been carried over from events occurring before the temperature cycles where initiated that may result in an imbalance in the kinetics of the two enantiomorphs.

The results may also have implications for the origin of the homochirality of biologically significant molecules on Earth.

Natural temperature cycles occur over short time intervals due to natural convection and buoyancy induced flow, and over longer time intervals due to diurnal and annual temperature cycles. Thus, if deracemization can occur due only to repeated temperature cycles at near ambient conditions, it seems a highly likely cause for homochirality in nature. There is no need for a racemization agent in the liquid phase for the deracemization in a crystalline phase to occur, since amino acids will naturally racemize in solution over very long periods of time, which is plausible since geological time frames were available for the event.

Another well-known theory is that undersea volcanic vents (hydrothermal vents) might have been the original source of life on earth, and this has been reviewed recently by Holm.[36] These vents will result in strong temperature gradients due to the temperature difference between the vent and the surrounding deep water, creating buoyancy flow. This creates a natural temperature cycle for pockets of fluid around the vent and potentially has led to a deracemization event due to these temperature cycles. It can be noted that such systems have the necessary precursor compounds required to form amino acids and also suitable reaction conditions.

■ CONCLUSIONS

This work presents a possible mechanism of complete chiral symmetry breaking occurring in the system via temperature fluctuations, and this is independent from grinding. The dissolution and recrystallization phenomena induced by temperature fluctuations in the system are enough to break the symmetry and finally to achieve complete deracemization. The interplay between (i) dissolution and regrowth with dispersion of rates,[37] (ii) racemization in solution, and (iii) the entrainment effect seems to be responsible for this process.

The heating/cooling cycle can be produced by several procedures, such as friction caused by glass beads in agitated systems or sonication, causing localized energy inputs into the system, temperature programming via the use of a thermostat, or temperature fluctuations in nature. Their effects are therefore to be added to the effect of the other phenomena, such as Ostwald ripening or reincorporation of clusters.

Our results help to fill crucial gaps in the understanding of the mechanism of the deracemization process.

To optimize this novel procedure, the temperature programming has to be adjusted. Optimal programming may use large temperature swings for the initial cycles in order to initiate the breaking of symmetry, followed by smaller temperature variations in later cycles where the preferred enantiomer has a significant excess. In the latter situation, only a small amount of crystal needs to be dissolved to remain in the biphasic domain at high temperature: crystals of a single enantiomer in equilibrium with a racemic saturated solution. This procedure should produce an optimum set of conditions, and the evolution of enantiomeric excess may tend toward an exponential increase to 100%, for conglomerates without partial solid solution,[38] rather than the sigmoidal shape as found in this work.

A combination of techniques using preferential crystallization in addition to periodic temperature fluctuations in order to completely deracemize conglomerate systems may accelerate the complete deracemization and yield high product purity and yield for industrial applications.

This method could also lead to a variety of industrial applications for deracemization; the process involving cycles of growth and dissolution due to temperature fluctuations is easier to implement at a large scale than a continuous grinding.

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Notes

The authors declare no competing financial interest.

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