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A chiral switch: balancing between equilibrium and non-equilibrium states

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Herein we introduce a "chiral switch" – a sequence of operations that alternate between equilibrium and non-equilibrium conditions to switch the absolute configuration of a chiral center. The generality and practical potential of the technique are demonstrated with three unnatural α-amino acid precursors.

Mechanisms that control symmetry breaking and propagation of chirality are relevant for discussions as diverse as the origin of life or practical routes to enantiomerically pure building blocks for construction of pharmaceuticals. Today, a wide variety of compounds can be obtained in high enantiomeric excess (*ee*) *via* absolute asymmetric synthesis, crystallization-induced transformation *etc*.[1–5] Recently discovered Viedma ripening is rapidly evolving as a practical mechanism that enables complete chiral symmetry breaking.[6–10] During Viedma ripening a solid phase of the racemate is completely converted into a single enantiomer *via* racemization in the liquid phase and continuous dissolution/recrystallization. Viedma ripening requires *a racemizable conglomerate*: (a) the compound must crystallize as a mechanical mixture of enantiomerically pure crystals, *i.e.* racemic conglomerate, and (b) the enantiomers must interconvert in the liquid phase, *i.e.* the compound must undergo racemization. Although the fundamental mechanistic details of the process are still a subject of discussion, the scope of practical application of this process is rapidly broadening. A range of racemizable conglomerates has been identified and used for the synthesis of relevant enantiopure building blocks by means of Viedma ripening.[11–17] A general methodology for the synthesis of enantiopure α-amino acids via design and identification of racemizable conglomerates has also been reported.[18]

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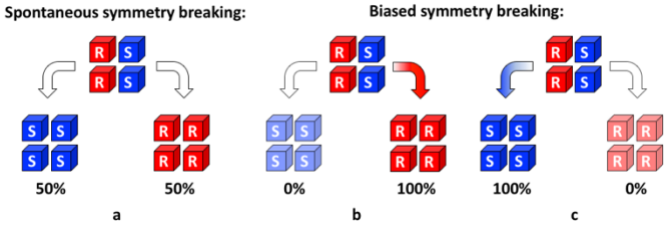


Figure 1. Probability of symmetry breaking process to an excess in one of the two enantiomers: *a*) Spontaneous symmetry breaking - there is no enantiomeric preference for the process, stochastic outcome; *b,c*) Biased symmetry breaking - the presence of widely abundant enantioenriched impurities continuously direct the process towards the same outcome: *b)* towards (*R*); *c)* towards (*S*).

Viedma ripening processes can be directed towards the configuration of choice by deliberate creation of an initial *ee* in the desired enantiomer, thus providing controlled symmetry breaking. If no chiral additive is used, "uncontrolled" spontaneous symmetry breaking occurs. In theory, spontaneous symmetry breaking has no enantiomeric preference for a specific chirality. It is therefore assumed to be dependent on random fluctuations only, thus resulting in a stochastic outcome with equal probabilities for directing the deracemization towards either (*R*)- or (*S*)- enantiomers (Fig. 1a). In practice, however, preferential symmetry breaking has been observed in the majority of Viedma ripening experiments. The process was found to be biased towards either (*R*)- or (*S*)-enantiomer with the probability of the same outcome up to 100% (Fig. 1b and Fig. 1c, respectively), when even more than a hundred experiments were performed.[19] This preference has been attributed to minute amounts of enantiomerically enriched impurities that are widely abundant.[20] Such biased symmetry breaking causes practical challenges. Oftentimes, there is no way to access the desired enantiomer relying on spontaneous symmetry breaking. It has been shown that high intensive attrition may help to overcome this problem,[21] but a major drawback is the potential formation of undesired amorphous phases.[22] Therefore, it would be highly beneficial to develop an approach that enables a "chiral switch" - conversion of one enantiomer into the opposite one.

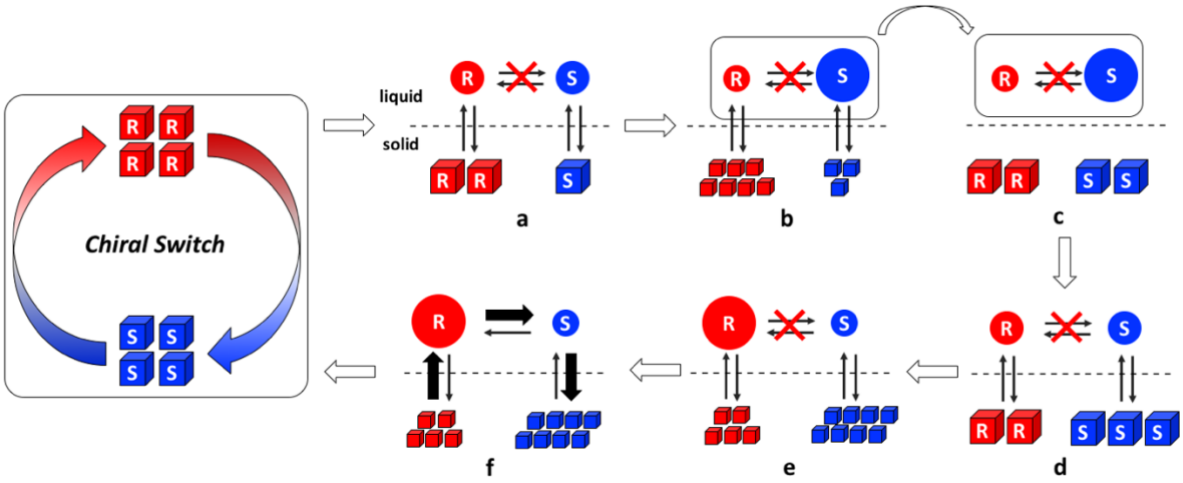
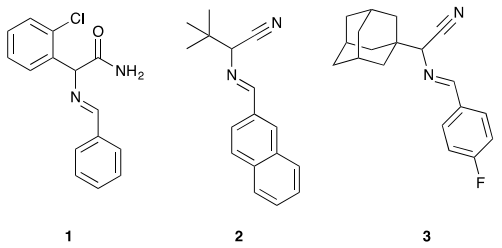


Figure 2. A stepwise schematic illustration of the "chiral switch" approach. *a)* A slurry of an enantiomerically enriched conglomerate in equilibrium: an *ee* in the solid phase, while the liquid phase is racemic; *b)* non-equilibrium: the liquid phase shows an *ee* in the enantiomer that represents minority population in the solid phase; *c)* the isolated liquid phase (*2b*) is added to the racemate; *d)* equilibration of the slurry, leads to 0% *ee* in the liquid phase, and as a result, the solid phase becomes enriched in the enantiomer that represented minority population in the starting material (*2a*); *e)* non-equilibrium: the liquid phase is enriched in the opposite enantiomer as compared to the solid phase; *f)* racemization catalyst is added, deracemization is directed towards majority population in the solid phase.

We realize that Viedma ripening may inherently have embedded mechanisms that switch the chirality from one configuration to the opposite one. To illustrate this, we consider a suspension of an enantiomerically enriched conglomerate (for example in the (*R*)-enantiomer). It is well known that under conditions of thermodynamic equilibrium, the liquid phase of such a suspension exhibits 0% *ee*.[23] However, during continuous grinding of the suspension, the liquid phase becomes enantiomerically enriched in the opposite (*S*)-enantiomer.[24] Thus, grinding of an enantiomerically enriched conglomerate slurry results in an inverse *ee* in the liquid phase. This observation has been explained in terms of different growth/dissolution rates for the two enantiomorphs under grinding. In short, grinding pumps energy to the system and crystals are continuously broken into smaller ones. Consistent with the Gibbs-Thompson effect, the smaller crystals dissolve and nurture the growth of the larger ones,[25] until these are broken into small fragments again. The input of mechanical energy thus leads to a continuous growth/dissolution process. However, the growth/dissolution rates for both enantiomorphic solid phases also depend on the amounts of solids, as has been described in a kinetic model that fits the experimental observations.[24] Since the (*R*)-enantiomer is in excess, there is larger surface area of (*R*)-enantiomer in the solid phase. This greater surface area incorporates more molecules and crystal fragments of the same configuration from solution, providing faster growth of the majority enantiomorph in the solid phase. Consequently, the liquid phase becomes more depleted in the (*R*)-enantiomer, thus resulting in an excess of the minority (*S*) enantiomer in the liquid phase. This phenomenon has been assigned with a key role in the driving mechanism of Viedma ripening. [24,26–29]

This remarkable example demonstrates that a system may show completely different behavior under *equilibrium* versus *non-equilibrium* conditions. Whereas under thermodynamic equilibrium the liquid phase *ee* must be 0%, non-equilibrium conditions enable new degrees of freedom for deliberate manipulation of this composition (i.e. $ee \neq 0$).

Exploiting this insight, we develop the concept of a "chiral switch" (Fig. 2) that offers a systematic approach to access material enriched in the desired enantiomer even if preferential symmetry breaking favors formation of the undesired one. This approach is based on a rational sequence of manipulations with equilibrium and non-equilibrium states of the system. The concept of the chiral switch works for either enantiomer. For simplicity, we illustrate the situation when the (*R*)-enantiomer is available, but the (*S*)-enantiomer is desired. Combining (*R*) with the racemate and solvent yields a mechanical mixture of both enantiomorphs in contact with the liquid phase (Fig.2a). Note that no racemization occurs. Under equilibrium conditions, the solid phase is enantiomerically enriched ($ee \neq 0\%$), whereas the liquid phase remains racemic ($ee = 0\%$).[23] Under non-equilibrium grinding conditions, the solid phase remains enriched in the major (*R*)-enantiomer. However, the enantiomorphs have different growth/dissolution rates consistent with the driving mechanism of Viedma ripening.[24] As a result, the liquid phase becomes enriched in the (*S*)-enantiomer that represents the minority population in the solid phase (Fig. 2b). Note, if the grinding is stopped, the system re-equilibrates rapidly, thus leading to a complete vanishing of the liquid phase inverse *ee* within minutes.[30] To preserve this inverse *ee*, the liquid phase is rapidly isolated (Fig. 2b). Subsequently, this enriched liquid phase is combined with a new portion of solid racemate (Fig. 2c). When the resulting slurry reaches thermodynamic equilibrium, it returns to typical conglomerate behavior: the liquid phase exhibits 0% *ee* and, as a result, the solid phase is enriched in the desired (*S*) enantiomer (Fig. 2d). Thus, the inverse *ee* created in the liquid phase is transferred to the solid phase. If this slurry is brought under non-equilibrium conditions by means of attrition, the



1 2 3

Scheme 1. Chemical structures of the used conglomerates.

liquid phase becomes enriched in the (*R*)-enantiomer that represents the minority population in the solid phase (Fig. 2e). Finally, introduction of the racemization catalyst drives deracemization towards the desired (*S*)-enantiomer that represents majority population in the solid phase (Fig. 2f), thus accomplishing a complete chiral switch.

We demonstrate the validity of this concept using three recently reported conglomerate forming precursors of unnatural α-amino acids **1**, **2** and **3** (Scheme 1).[18,31] All these compounds were previously designed and identified as racemizable conglomerates suitable for Viedma ripening. To achieve this, both the physical (crystallinity) and chemical (acidity) properties were optimized by modification of the chemical structure while still preserving the target chiral moiety.[18] In particular, conglomerate formation statistically occurs only for 5-10% of chiral organic compounds and remains unpredictable.[32] To overcome this bottleneck, libraries of imines with enhanced acidity compared to the parent amines were prepared by simple condensation of aromatic aldehydes with precursors of the corresponding α-amino acids and screened for conglomerate behavior.

Identical experiments were performed with both enantiomers of all three compounds. An enantiomerically enriched mixture was artificially created, by simple mixing of an enantiomer with the corresponding racemate. Then, glass beads and a solvent suitable for the deracemization of the compound were added.[18,31] The resulting mixture was sonicated at 20°C for two hours to grind the crystals. Subsequently, the liquid and solid phases were rapidly separated by filtration and analyzed by HPLC on a chiral column. As expected, an inverse *ee* of 0.2 – 3.4% was observed in all experiments (Table 1). This enrichment in the desired enantiomer was used to direct the subsequent deracemization. For this, the isolated enriched liquid phase was added to the corresponding racemate. The slurry was sonicated in the presence of glass beads for an hour, and the racemization catalyst - 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The resulting reaction mixture was sonicated at 20°C for 24 hours to achieve complete deracemization towards the desired enantiomer in the solid phase (Table 1). In all experiments, we confirm that this series of operations results in a chiral switch from the (*R*)- to the (*S*)-enantiomer, and *vice versa*. It is noteworthy that even the lowest inverse *ee* of 0.2-0.8% (*on the edge of the HPLC detection limit*)[33] observed with compound **2** was sufficient to direct the deracemization towards the desired enantiomer.

Table 1. Summary of the Chiral Switch experiments

Initial solid (*ee*, %)*	*Non-equilibrium* conditions		Chiral Switch outcome, (*ee*, %)
	Liquid phase (*ee*, %)	Solid phase (*ee*, %)	
(*S*)-1 (43.5)	(*R*)-1 (3.1)	(*S*)-1 (50.6)	(*R*)-1 (99.8)
(*R*)-1 (43.5)	(*S*)-1 (3.4)	(*R*)-1 (50.0)	(*S*)-1 (99.9)
(*S*)-2 (50.0)	(*R*)-2 (0.2)	(*S*)-2 (61.7)	(*R*)-2 (99.3)
(*R*)-2 (50.0)	(*S*)-2 (0.8)	(*R*)-2 (60.9)	(*S*)-2 (98.7)
(*S*)-3 (50.0)	(*R*)-3 (2.3)	(*S*)-3 (52.6)	(*R*)-3 (99.5)
(*R*)-3 (50.0)	(*S*)-3 (1.9)	(*R*)-3 (51.9)	(*S*)-3 (99.1)

* calculated based on the weighed amounts of racemates and enantiomerically pure materials used.

In summary, we introduce here a "chiral switch" – a powerful approach to convert an enantiomerically enriched racemizable conglomerate into the opposite absolute configuration. Based on an analysis of liquid/solid phase behavior, we have rationally designed a sequence of operations that alternate between equilibrium and non-equilibrium conditions to switch the absolute configuration of the chiral center.

We note that this switch is relevant to the propagation of chirality under presumed prebiotic conditions. Such a switch allows one to overcome biased symmetry breaking for production of the desired enantiomer without the intervention any extra chiral influences. In practical terms, we foresee that this simple technique may potentially be applied to a wide range of compounds of interest via their reversible conversion into racemizable conglomerates.

Conflicts of interest

There are no conflicts to declare.

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33 We observed that even an ee value of 0.2% in the liquid phase is sufficient dictate the final outcome. However, this enantiomeric excess is too small to be accurately measured by HPLC (the limit is approximately 0.5% ee).