# Homochirality and the Need for Energy

**Raphaël Plasson · Axel Brandenburg**

**Abstract** The mechanisms for explaining how a stable asymmetric chemical system can be formed from a symmetric chemical system, in the absence of any asymmetric influence other than statistical fluctuations, have been developed during the last decades, focusing on the non-linear kinetic aspects. Besides the absolute necessity of self-amplification processes, the importance of energetic aspects is often underestimated. Going down to the most fundamental aspects, the distinction between a single object—that can be intrinsically asymmetric—and a collection of objects—whose racemic state is the more stable one—must be emphasized. A system of strongly interacting objects can be described as one single object retaining its individuality and a single asymmetry; weakly or non-interacting objects keep their own individuality, and are prone to racemize towards the equilibrium state. In the presence of energy fluxes, systems can be maintained in an asymmetric non-equilibrium steady-state. Such dynamical systems can retain their asymmetry for times longer than their racemization time.

## Introduction

Understanding how asymmetric chemical systems can be formed spontaneously is one key element for the description of the onset of life. The emergence of

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homochirality has been developed as a kinetic phenomenon, describing chemical competition in the presence of autocatalytic phenomena (Frank 1953; Kondepudi and Nelson 1983). In this context, asymmetric states can be described as originating from statistical fluctuations, amplified and maintained actively in non-equilibrium steady states thanks to high-order autocatalytic reactions (Plasson et al. 2007).

In recent years the interest in energetic aspects of homochirality has become apparent (Kondepudi and Kapcha 2008; Blackmond and Matar 2008; Plasson and Bersini 2009). Assuming the presence of efficient autocatalytic processes, we will mainly focus here on the energetic aspects that must be taken into account in a far-from-equilibrium context. By focusing on simple examples that are partly motivated by recent experiments of different groups, we address the question where the energy responsible for the symmetry breaking behaviors originates from.

We shall first discuss the significance of symmetry versus asymmetry of chemical systems, emphasizing the underlying apparent paradox of homochiral phase stability that is the source of many misunderstandings. Developing the dynamic aspect of asymmetric systems, a detailed picture about the energetic requirements for their generation is given. In particular, the necessity of energy for creating microscopic and macroscopic asymmetry, and for maintaining this asymmetry in a stable steady state are highlighted. Concrete examples from the literature will be developed to illustrate these energy needs.

**Symmetry of Chemical Systems**

We shall assume that the fundamental laws of physics are symmetric,[1] the purpose of this article being to describe how asymmetric states can emerge from symmetric laws. Following Curie's Principle (Curie 1894),[2] this may seem at the first glance impossible, but because of the discrete nature of matter, statistical fluctuations are an unavoidable source of asymmetry, apt to be amplified by appropriate mechanisms (Siegel 1998; Plasson et al. 2007).

And indeed, it is easy to realize that asymmetry can be naturally obtained as long as a chemical compound is sufficiently complex. It only requires four different groups to be attached to one atom of carbon to obtain a chiral molecule. It is sufficient to build *one* sufficiently complex molecule to generate *microscopic* asymmetry. However, this is not sufficient to build macroscopically ordered asymmetry. A sufficiently

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[1]This is of course not strictly true, because of the existence of the violation of symmetry by weak force (Mason and Tranter 1985; Chandrasekhar 2008; Pagni 2009). However, it is widely accepted in the community that the influence of this asymmetry can be neglected in the presence of autocatalytic mechanisms, that only require initial statistical fluctuations to bootstrap the process (Avalos et al. 2000; Bonner 2000; Lahav et al. 2006; Lente 2007).

[2]"Lorsque certaines causes produisent certains effets, les éléments de symétrie des causes doivent se retrouver dans les effets produits. Lorsque certains effets révèlent une certaine dissymétrie, cette dissimétrie doit se retrouver dans les causes qui lui ont donné naissance. La réciproque de ces deux propositions n'est pas vraie, au moins pratiquement, c'est-à-dire que les effets produits peuvent être plus symétriques que les causes." (When some causes produce some effects, the elements of symmetry of the causes must be found in the produced effects. When some effects possess some asymmetry, this asymmetry must exist in the causes that produced the effects. The reciprocal of these two propositions is not true, at least in practice, that is the produced effects can be more symmetric than the causes.).

**Fig. 1** Temporal conversion of a chiral molecule. It stays half of its life time in each of the two configurations on a timescale larger that the reaction half time, passing by a symmetric intermediate (0)*

$$(+) \xrightleftharpoons[k]{k} (-)$$
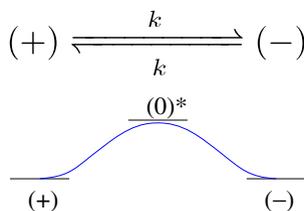
large collection of objects will lose its ordered asymmetry: Curie's Principle suggests that, on average, the same quantity of both configurations will be created. Here appears an apparent paradox: one object is asymmetric, one collection of objects is symmetric. How can this problem be solved?

Symmetry of an Object

An object is asymmetric if it is not similar to its image by the corresponding symmetry operation. In the present case, we are talking of chiral objects, that are different from their mirror image. This can be applied to amino acids, nucleotides, crystals, and other objects, but to keep it general we shall now talk about "+" and "−" compounds (that can represent R and S compounds, P and M helices, etc.).

Because of the symmetry of physical laws, a chiral molecule is exactly as stable as its enantiomer (its mirror image molecule). It will interconvert to its mirror image on a given timescale (that may be very small or very large). The kinetic rate (or inversion probability) is the same in both directions for symmetry reasons. In practice, the asymmetry of an object persists only on a timescale smaller than its interconversion time. At larger timescales, they spend half of the time in one configuration, and half of the time in the other configuration (see Fig. 1). They are symmetric on average, despite being pointwise asymmetric on a given timescale. This is typically the case of tri-substituted amines, or of the asymmetric conformation of symmetric molecules, that are theoretically asymmetric but that do not possess any chiral properties at ambient temperature. Strictly speaking, a chiral object should thus be considered as in a frozen state, whose asymmetry exists only temporarily. However, this frozen state is purely academic in the cases where the rate of inversion can be neglected. This is especially the case for macroscopic objects, like crystals, whose spontaneous inversion is not possible.[3]

Symmetry of a Collection of Objects

Real systems, and especially chemical systems, will generally not be composed of one unique object, but of a large number of them. Let us take a system composed of $n$

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[3]Some precautions must be taken there. For example, if a crystal of L-amino acid cannot invert into the mirror crystal of D-amino acid, amino acids can racemize in solid form (non-crystalline), even if this process is much slower than in solution. For example, while the half life of aspartic acid in $100\,°C$ water is 30 days in free form and 1 to 3 days in proteins, it will still racemize on timescales of $10^4 - 10^5$ years in solid form, like in fossils or carbonate sediments (Bada 1985).

chiral objects, having $m$ of "+" type and $(n - m)$ of "−" type. There is a large number of different ways to build such a system. The number of equivalent combinations is:

$$c_m = \frac{n!}{(n - m)!m!}. \tag{1}$$

There are $c_m$ equivalent systems of $n$ objects with $m$ of "+" type, each having the same probability $p_k = 1/c_m$, and their entropy is (Le Bellac et al. 2004, p. 59, Eq. 2.46):

$$S_m = -\sum_{k=1}^{c_m} p_k \ln p_k \tag{2}$$

$$= \ln c_m. \tag{3}$$

For very large systems, this can be evaluated by using the Stirling approximation, $\ln(n!) \approx n \ln n - n$, and by introducing the enantiomeric excess $ee = (2m - n)/n$:

$$S = \ln(n!) - ln(m!) - ln((n - m)!) \tag{4}$$

$$\approx n \ln n - m \ln m - (n - m) \ln(n - m). \tag{5}$$

This expression can be simplified by writing $\alpha = (1 + ee)/2$ and $\beta = (1 - ee)/2 = 1 - \alpha$, so that $m = \alpha n$ and $(n - m) = \beta n$:

$$S = n \ln n - \alpha n \ln(\alpha n) - \beta n \ln(\beta n) \tag{6}$$

$$= n \ln n - \alpha n \ln \alpha - \alpha n \ln n - \beta n \ln \beta - \beta n \ln n \tag{7}$$

$$= -(\alpha \ln \alpha + \beta \ln \beta)n \tag{8}$$

The corresponding macroscopic molar entropy is:

$$S = -k_b \mathcal{N}_a (\alpha \ln \alpha + \beta \ln \beta) \tag{9}$$

$$= -R(\alpha \ln \alpha + \beta \ln \beta) \tag{10}$$

These entropies are plotted in Fig. 2.

This value is zero for homochiral systems (i.e. for $m = 0$ or $m = n$, that is $ee = \pm 1$), and maximum for racemic systems (i.e. for $m = n/2$, that is $ee = 0$). This implies an entropic stabilization of the racemic state, equal to:

$$\Delta S = S_{n/2} - S_0 \tag{11}$$
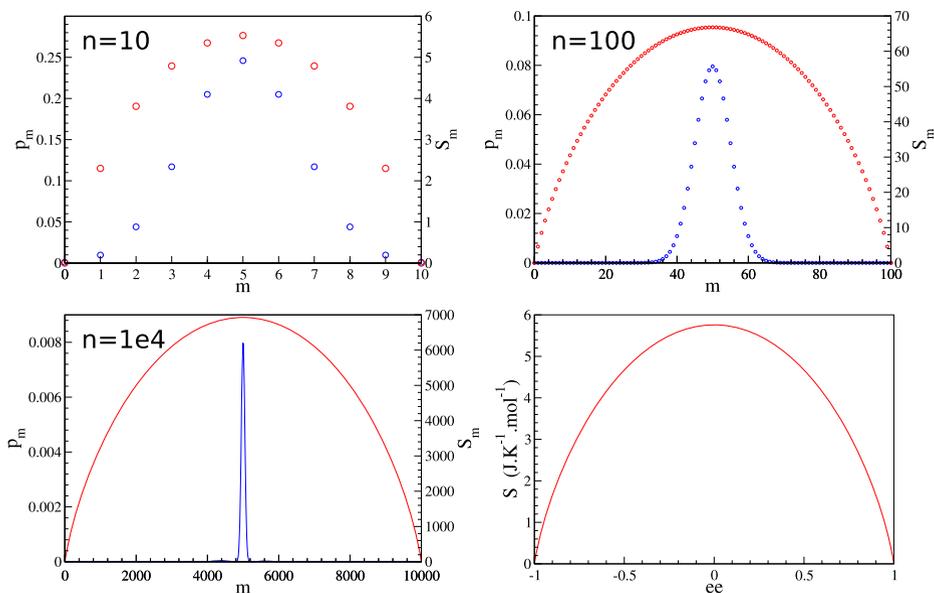
$$= \ln \frac{n!}{\left(\frac{n}{2}!\right)^2}. \tag{12}$$

For very large systems, this can be again evaluated by using the Stirling approximation:

$$\Delta S = \ln(n!) - 2 \ln \left(\frac{n}{2}!\right) \tag{13}$$

$$\approx n \ln n - n - 2 \left(\frac{n}{2} \ln \frac{n}{2} - \frac{n}{2}\right) \tag{14}$$

$$= n \ln 2. \tag{15}$$

**Fig. 2** Entropic stabilization (red, Eq. 3) and statistical distribution (blue, Eq. 1) for a non-interacting ensemble of $n = 10$, 100 and 10000 chiral objects containing $m$ configurations of type $+$ and $(n - m)$ configurations of type $-$, and entropy of mixing for a macroscopic system of chiral objects as a function of the enantiomeric excess (Eq. 10). The statistical distribution of a macroscopic system is too narrow to be represented

The corresponding macroscopic molar entropy stabilization of the racemic state is:

$$\Delta S = k_b \mathcal{N}_a \ln 2 \tag{16}$$

$$= R \ln 2 = 5.76 \, \mathrm{J \, K^{-1} \, mol^{-1}}, \tag{17}$$

where $k_b$ is the Boltzmann constant, $\mathcal{N}_a$ the Avogadro's number, and $R$ the ideal gas constant. This value corresponds to the entropy of mixing of half a mole of compounds "$+$" and of half a mole of compounds "$-$".[4]

In total, there are $\sum_{m=1}^{n} c_m = 2^n$ systems of $n$ compounds. All these systems are energetically equivalent because of the symmetry between $+$ and $-$ compounds. Among all these systems, for each $m$, there are $c_m$ systems that are totally equivalent (i.e. that cannot be distinguished from each other). The proportion of systems having $m$ of type $+$ is $c_m/2^n$: that represents a Gaussian distribution of the systems of $n$ compounds, centered on $m = n/2$, with a standard deviation $\sigma = \sqrt{n}/2$. The racemic state is the more stable state, as it is entropically stabilized, and the statistical fluctuations correspond to a standard deviation for the enantiomeric excess of $\sigma_{ee} = 1/\sqrt{n}$ (Hill 1962; Siegel 1998; Faglioni et al. 2005).

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[4]It may seem surprising that a thermodynamic stabilization is obtained despite the absence of any interaction between the compounds, and that the value is independent of the nature of the compounds. This is referred in the literature as the "Gibbs Paradox", and many interpretations have been developed (Jaynes 1992; Lin 1996; Ben-Naim 2007; Pérez-Madrid 2004; Lin 2008; Swendsen 2008).

The Paradox of Homochiral Phase Stability

The entropic stabilization relies on the fact that there are no enthalpic effects, i.e. that there are no interactions between the objects. But even if both configurations have the same thermodynamic properties for symmetry reasons, the system is more complex when interactions are possible. While retaining the global symmetry of the system, a compound + will interact differently with another + or with a − compound. The symmetry of the laws only implies that the interactions involving ++ and −− are identical (and likewise for the interactions involving +− and −+) but interactions involving ++ and +− may differ.

If heterochiral interactions are favored, then the system evolves to a symmetric phase, each favored +− association losing its asymmetry (e.g. in a racemate crystal). If homochiral interactions are favored, the system evolves to an asymmetric phase (e.g. a conglomerate crystal). However, the situation did not change much: either one unique homochiral phase is obtained (e.g. a unique racemate monocrystal), or several independent phases (e.g. a racemic mixture of racemate monocrystals). The individual objects are interacting, and thus form new larger independent objects to which the entropic stabilization still applies, so the thermodynamic equilibrium is still a racemic mixture of independent asymmetric objects.[5] An intermediate case exists in the case of weak stereoselectivity, as, for example, in the system of crystallization of 1,1'-binaphtyl (Asakura et al. 2002). Stirred crystallization of these compounds generally leads to very noisy distributions, and a single crystal grown from a single seed is not fully homochiral. In this system, the homochiral interactions are only weakly favored, causing the possibility to have inclusions of crystals of the opposite configuration during the crystal growth (Asakura et al. 2004; Plasson et al. 2006; Asakura et al. 2006). This is characterized by the association of several objects (crystal inclusions) weakly interacting between each other within one unique object (the full-grown crystal) that is less asymmetric than expected. Similar systems generating partially homochiral systems can be found, typically in the case of polymers (Hitz and Luisi 2003).

When the interactions are only temporary, the symmetric compounds conserve their individuality, and they will stay racemic *at equilibrium*. Due to the microreversibility of reactions, direct racemization is not necessary: if a pathway exists between the two enantiomers, it will be equivalent to a racemization reaction. Typically, in the system of crystallization of amino acids of Noorduin et al. (2008a, b) a homochiral system of objects is created (crystals), but the chiral compounds keep their individuality in solution, which thus remains racemic.

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[5]At first glance, this may seem to contradict the application of the Gibbs phase rule to these systems, that describes the homochiral phase as the stable one (Crusats et al. 2006, 2007; Blackmond et al. 2007a, b). However, the Gibbs phase rule comes down to determining how many degrees of freedom are available in the system, given the number of parameters and available relations between them. In the context of crystals, this calculation does not take into account the number of crystals of the same configuration and their size distribution. This presupposes that, as a working hypothesis, these parameters are not relevant for describing the properties of the system. In that context, a system with one large crystal is considered equivalent to a system with a large number of small crystals. The Gibbs phase rule can only be applied to describe the stability of one unique phase, unless the parameters describing the distribution of crystals are introduced. This explains our assumption of independent asymmetric objects.

In practice, the interactions will create more or less large "homochiral objects" (like molecules, homochiral blocks within polymers, entire polymers, crystals, etc.) that have a cohesion. Thus, each object is enthalpically stabilized and can thereby overcome the entropic influence. On a large enough scale, the collection of objects will anyway still be globally racemic (i.e. only local homochirality can be obtained). This does not mean that it is impossible to obtain a stable non-racemic mixture of individual objects, but only that this is impossible in the *equilibrium* state: there is a necessity for maintaining the system in non-equilibrium, that is, there is a necessity of energetic exchange.

## Systems Evolution and Stability

The previous description was essentially static, describing what is the more stable state of the system. Let us now develop the dynamic description. We start from a symmetric system that may be either composed of only symmetric objects or of a racemic mixture of asymmetric objects. The purpose here is to understand how it can evolve towards an asymmetric stable steady state.
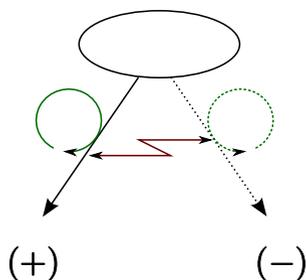
### Creating an Asymmetric State

The first step is to create the asymmetry. This can be a system that creates asymmetric objects either from symmetric objects or by the transformation of asymmetric objects into other asymmetric objects. Alternatively, it can be a system with interconversion between different enantiomers of asymmetric objects.

The first case implies the presence of a source of energy that can be internal (the starting compounds are less stable, allowing their spontaneous transformation) or external (the transformations are coupled to energy exchange allowing the reactions to be performed in the appropriate direction[6]). The second case implies the existence of a pathway allowing the interconversion between asymmetric objects, that is, a racemization process: such a system will reach a racemic state at equilibrium, and must thus be maintained away from this equilibrium, which will require energy.

In any case, an energy consuming process must first be established in order to create an asymmetric state. As the system is initially totally symmetric, a bifurcation towards one or the other configuration is required. If the process leads to an unique asymmetric object (i.e. if all the compounds get aggregated), then the final state can only be homochiral. In other cases, self-amplification processes are necessary. There must then be an autocatalytic formation of the asymmetric compounds (in order to enhance the difference between both configurations) and a mutual inhibition process (in order to destroy compounds of the "bad" configuration). This process is represented in Fig. 3. This is the essence of the Frank's model (Frank 1953; Kondepudi and Nelson 1983). These processes may be indirectly generated within

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[6]How chemical energy can be transferred is explained briefly in the Appendix. The general idea is to couple an energetically unfavored reaction to an energetically favored reaction. This results in a transfer of chemical energy, allowing the system to perform a reaction that cannot be spontaneously performed.

**Fig. 3** Generation of an asymmetric state, starting from a symmetric state (either consisting of asymmetric compounds or of a racemic mixture of symmetric compounds). The generation of the asymmetric compounds must be linked to autocatalytic processes (*half-open arrowed rings*) and to mutual inhibition (*the double-sided zig-zag arrow*)

the chemical network, rather than being direct reactions (Plasson et al. 2004, 2007; Brandenburg et al. 2007).

Maintaining an Asymmetric State

In the presence of a racemization process, the system will tend to destroy the previously built asymmetry, and go back to the equilibrium state. However, if the process that was used to build the asymmetry in the first place can be continuously maintained, then it may be able to oppose the spontaneous racemization process, resulting in the maintenance of a non-equilibrium asymmetric steady state (Plasson 2008; Plasson and Bersini 2009).

This process cannot be costless in terms of energy. If an asymmetric state, characterized by an enantiomeric excess *ee*, is maintained in a steady state, it means that different concentrations $c_+$ and $c_-$ of + and − will be maintained. As a consequence, the racemization reaction (with an identical kinetic constant $k$ in both directions, because of the microreversibility), is not anymore in detailed balance, as $kc_+ \neq kc_-$. This generates a continuous reaction flux, maintained by the incoming energy, that will continuously lead to an entropy production $\sigma$ (Kondepudi 2008). The incoming energy flux $\varepsilon$ must at least compensate $T\sigma$, that is:

$$\sigma = R(kc_+ - kc_-) \ln \frac{kc_+}{kc_-} \tag{18}$$

$$\Rightarrow \quad \varepsilon \geq T\sigma \tag{19}$$

$$\geq TRk(c_+ - c_-) \ln \frac{2c_+/c_t}{2c_-/c_t} \tag{20}$$

$$\geq kRTc_t \cdot ee \ln \frac{1 + ee}{1 - ee} \tag{21}$$

with $c_t = c_+ + c_-$ and $ee = (c_+ - c_-)/c_t$. More energy will be required for systems with fast racemization, high maintained enantiomeric excess, and high concentrations in compounds. Inversely, no energy is required for maintaining racemic systems ($ee = 0$) or frozen systems ($k = 0$). It can be noted that for maintaining strictly homochiral systems ($ee = \pm 1$), an infinite amount of energy is required, whatever the value of $k$.

This is compensated by the fact that the mathematical function describing $\varepsilon$ is very steep when approaching $\pm 1$ (See Fig. 4).

Such dynamic systems are fundamental to obtaining stable systems of non-racemic compounds under racemizing conditions, as this is typically the case for amino acids and peptides in aqueous solution. In this domain, biosystems are especially efficient: while racemization of amino acid derivatives in living matter can occur on the timescale of its life span (Masters et al. 1977), the process of life managed to maintain a very high enantiomeric excess in organic compounds during billions of years.

Propagating the Asymmetry in Space

The chemical processes in realistic settings take place in a spatially extended domains (chemical reactors, in oceans, near shore lines, in the atmosphere, in the porous interface to the Earth's crust, etc). In at least some of those cases it is possible to treat the chemistry by adding spatial diffusion and/or advection terms. The system is thus described as a collection of local systems, able on their own to consume energy for generating and maintaining an asymmetric state as described above, and that can additionally interact with neighboring local systems and influence them, or be influenced by them. The relevant equations take then the form of partial differential equations of the form

$$\frac{\partial X_i}{\partial t} + \mathbf{u} \cdot \nabla X_i - \kappa_i \nabla^2 X_i = \text{reaction terms}, \tag{22}$$

where the concentrations $X_i$ are not only functions of time, but also of spatial coordinates $\mathbf{r}$. Here, $u(\mathbf{r}, t)$ is the advective velocity and $\kappa_i$ is the molecular diffusivity.

In systems with only reaction-diffusion equations, the typical solutions tend to be of the form of propagating fronts. This behavior seems to be quite general and independent of the detailed chemistry, and have now been obtained by various groups (Saito and Hyuga 2004; Brandenburg and Multamäki 2004; Multamäki and Brandenburg 2005; Hochberg and Zorzano 2006; Gleiser 2007; Giaquinta and Hochberg 2008; Gleiser and Walker 2009).



**Fig. 4** Profile of the minimal energy required for maintaining a given *ee* for different values of the product $kRTc_t$
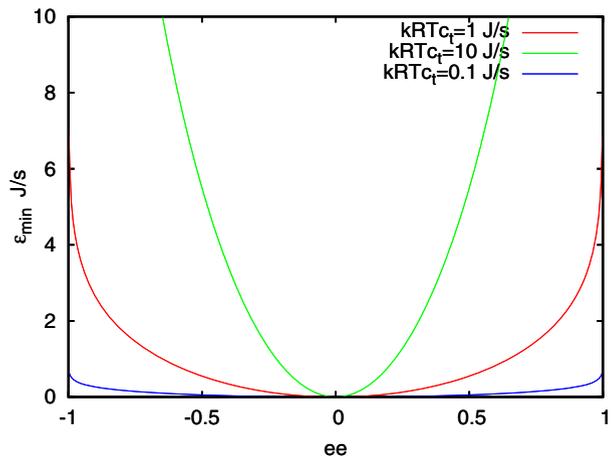
Initially, the diffusion does not have much time to operate: in the initially racemic mixture some local systems bifurcate to one configuration, and some other bifurcate to the opposite one, while the total system remains globally racemic. These different regions are initially well separated and will then spread by simple diffusion into the still racemic regions. This process may already be quite slow, but what happens next is even slower, because once two regions of opposite chirality come into contact, the propagation of the front slows down. This leads to a system with homochiral regions, separated by thin racemic walls.

The regions in contact will compete with each other. Their interface propagates in the direction of the curvature, because the inner front is shorter than the outer one; linear interfaces are stables. The propagation speed is constant in time, and therefore the globally averaged enantiomeric excess grows linearly in time, and is proportional to the number of the still topologically separated regions in space. Eventually, different regions in space merge, so the number of topologically separated regions in space decreases with time, and the growth of the global e.e. slows down. Eventually, if the system is of finite size, one single configuration may be established everywhere, but several space regions of opposite configuration can coexist, separated by stable racemic walls.

Here again, if each local system can be considered as single objects when isolated, they can be fused with other objects (the neighboring systems) to generate larger objects (the homochiral zones). In the final stable state there is either one completely interconnected homochiral zone (i.e. one single object), or there is a coexistence of several zones (i.e. multiple objects) that will be globally racemic for sufficiently large systems. This propagation of the asymmetry can be enhanced by the advection phenomenon: adding mechanical motions able to stir the system will perturb the interfaces and increase the transport speed of compounds inside the system, leading thus much faster to one unique configuration in all space locations (Brandenburg and Multamäki 2004; Multamäki and Brandenburg 2005). The effects of noise, which corresponds to a stochastic loss of chirality in random locations, can however offset this effect either partially or completely (Gleiser 2007; Gleiser and Walker 2009).

## The Need for Energy

Figure 5 gives the main frameworks for obtaining a stable non-racemic state. The fundamental need for energy can originate from an initial excess of chemical energy (Fig. 5A), from an exchange of matter with the surroundings (Fig. 5B), or from an exchange of energy with surroundings (Fig. 5C).

The first category corresponds to the frozen systems. They are static systems that are initially placed in a non-equilibrium state, possessing an excess of free internal energy, and that evolve spontaneously towards a more stable state. No more processes happen in this final state, as all energy has been consumed, and no further exchanges occur. This system will be prone to processes of racemization and is bound to racemize in the long term. The asymmetric state is formed under kinetic control, but the symmetric state will be slowly reached under thermodynamic control (Mc Naught and Wilkinson 1997), as the real equilibrium state.

The second and third categories are the dynamic systems: the final steady state is non-isolated, continuously exchanging energy or matter with its surroundings. This minimum of required energy is actually very low. For example, taking the
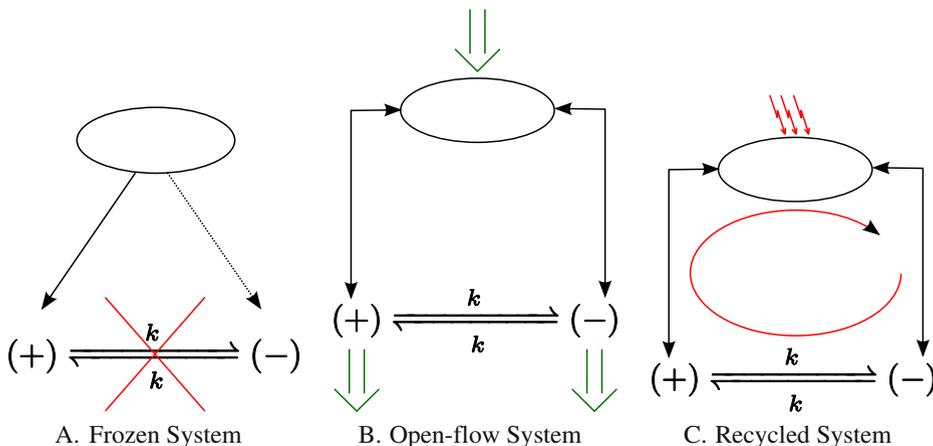
**Fig. 5** Three frameworks for obtaining a stable non-racemic state. **A** An isolated system that can evolve from a symmetric state to an asymmetric state may be stable as long as the racemization process can be neglected. **B** An open flow system can maintain an asymmetric steady state, refueling continuously in freshly synthesized asymmetric compounds, as long as a complete "flush" of the system is avoided (Cruz et al. 2008). **C** A non-isolated recycled system can maintain an activated deracemization process, opposed to the spontaneous racemization process (Plasson 2008)

racemization rates of aspartic acid from Bada (1972), it corresponds to a minimum consumption of energy of $\varepsilon_{min} = 1.3 \cdot 10^{-7}$ J s$^{-1}$ per mole of amino acid maintained in an enantiomeric excess of 99% at 25 °C, and of $1.6 \cdot 10^{-3}$ J s$^{-1}$ at 100 °C. In acidic or basic conditions, kinetic rates—and thus $\varepsilon_{min}$—can be about ten times larger.

However, no matter how low this value is, it is non-zero. This means that if the quantity of available energy is limited, then the asymmetric state will be able to be maintained only until energy is remaining, that is during the interval time $\Delta t \leq E_{tot}/\varepsilon_{min}$. Moreover, it is important to note that the value of $\varepsilon$ is a *minimum* prerequisite. It represents only the energy that is dissipated by the racemization process. Complete chemical systems are likely to require much more energy, as each reaction of the full network, that is required for the deracemization process, dissipates energy on their own. In the example of the recycled system of activated polymerization-depolymerization of amino acid (Plasson et al. 2004), for which the energetic analysis has recently been performed in detail (Plasson and Bersini 2009), the energy dissipated by the racemization reactions represents about only 0.1% of the total consumed energy.

## Application to Some Example Systems

### The Soai Reaction: Closed Systems

The simpler way to generate a non-racemic system in the laboratory is to work in a closed system, from an unstable initial state, and let it evolve spontaneously toward a frozen state. The Soai reaction (Soai et al. 1995) describes exactly this process. The system initially contains very reactive compounds, generating much more stable

compounds in a quasi-irreversible reaction. Due to a very efficient autocatalytic mechanism, symmetry breaking can be observed, forming an asymmetric alcohol with a very high enantiomeric excess, starting from only symmetric compounds.

This final asymmetric state is a frozen state that only exists temporarily. On larger timescales, taking into account the reversibility of the reactions, there must be a long term racemization of the system (Crusats et al. 2009). By the time the system has reached the asymmetric state, it has consumed all its energy, and then it slowly goes back to the equilibrium state. The formation of an asymmetric state is only possible as long as energy is available, that drives the reactions in autocatalytic loops.

Reversible reactions have been invoked for describing the mechanism of bifurcation in chemical systems based on the Mannich reaction (Mauksch et al. 2007a, b; Mauksch and Tsogoeva 2008), presenting similar symmetry breaking behavior. This approach was criticized, as reversible reactions must lead to the racemization of the system in the long term (Blackmond and Matar 2008; Blackmond 2009). However, if precautions are taken into account, the presence of reversible reactions, as opposed to irreversible ones, is not a major drawback for these systems (Plasson 2008; Plasson and Bersini 2009). It is crucial to identify the presence of energy: if energy is present in excess from the beginning, then the reversible system is capable of reaching a non-racemic state, but this one will naturally racemize itself on a timescale that may or may not be important; if energy is continuously exchanged with the surroundings, then a non-racemic steady state can be maintained.

## Generating Asymmetry During Crystallization: from Closed to Recycled Systems

Generating microscopic asymmetry from a symmetric system has been known for a long time, using conglomerate crystallization of sodium chlorate (Kipping and Pope 1898). The same system was used later to generate macroscopic asymmetry (Kondepudi et al. 1990), the bifurcation being generated by secondary nucleation induced by stirring (McBride and Carter 1991).

The problem with crystallization is that the initially "bad seeds" are not eliminated, as crystals are formed once and for all. More recently, variations of these systems[7] have allowed a total deracemization, starting from a racemic mixture of homochiral crystals (Viedma 2005; Viedma et al. 2008). In this system, some mechanisms are present that can generate the destruction of crystals: a continuous attrition of the crystals, due to a strong crushing by glass beads, and a process of Ostwald ripening (Noorduin et al. 2008a, b).

The process of Ostwald ripening (Voorhees 1985) relies on the fact that large crystals are more stable than small ones. A system containing several crystals of different sizes will evolve slowly, the smaller crystals disappear while larger crystals are growing (Noorduin et al. 2008a). This is explained by realizing that, eventually, one unique crystal will be obtained, and the system will thus reach a frozen homochiral state, with one unique asymmetric object that cannot evolve anymore (see Fig. 6A). A direct consequence of this "single object" final state is a dynamic that is intrinsically dependent of the system size, a larger system requiring proportionally more time to reach completion (Saito and Hyuga 2009).

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[7]There are systems that are either based on the original systems of sodium chlorate crystallization, or on a variant of amino acid crystallization in racemizing environment.

**Fig. 6** Energy profile for the evolution of a racemic mixture of conglomerate crystals by simple Ostwald ripening (**A**) and in ground crystallization (**B**). A system containing a racemic mixture of homochiral crystals is entropically stabilized compared to an homochiral mixture of homochiral crystals, for the same size distribution in crystals of the same amount of matter. A system containing a low number of large crystals is enthalpically stabilized compared to a system containing a high number of small crystals, for the same amount of matter. Processes forming larger crystals are spontaneous, while processes forming smaller crystals require some consumption of energy



A: Ostwald ripening

B: Ground crystallization
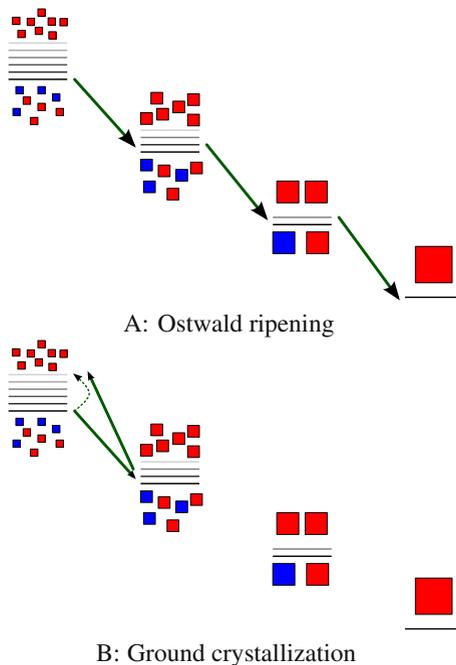
In the Viedma experiments, the spontaneous Ostwald ripening process (that tends to increase the size of the crystals) is counteracted by additional processes that tend to decrease the size of the crystals. As these processes generate less stable crystals, they must be activated by processes consuming energy. The major process is a system of continuous grinding, generated by the addition of crystal beads (Viedma 2005), implying a transfer of mechanical energy into chemical energy. More recently, a similar effect was also induced by temperature gradients (Viedma et al. 2008). This process is faster than the simple Ostwald ripening, and is independent of the system size (Saito and Hyuga 2009).

In these systems, the Ostwald ripening is a downhill process (a spontaneous evolution towards more stable state) where smaller crystals are gradually destroyed in favor of the formation of larger ones. This is an irreversible process, consuming the excess of energy initially present in the system, characterized by an excess of less stable small crystals. Simultaneously, the grinding process is an uphill process, consuming the energy given by the mechanical grinding, where the crystals are partially destroyed to generate smaller (and thus less stable) crystals (see Fig. 6B). The result is the maintaining of a steady-state size distribution. This is not an equilibrium state, as unstable compounds (small crystals) are maintained by a continuous input of energy (the grinding). This implies continuous cycles of reaction of crystal growth/decay, leading to the deracemization of a stable set of crystals. This system constitutes a recycled system as described in Fig. 5C (Plasson 2008).

It can be noted that the case of systems in the absence of attrition crushing, and in the absence of temperature gradient, is reported to be still working, but with a much lower efficiency. According to Viedma et al. (2008), the only possible processes of destruction—still present as an homochiral state is obtained before a single object

is formed—are probably collisions with other crystals, with vessel walls, or with the stirring bar. Here, there is still a system of growth by Ostwald ripening, while the mechanisms of crystal breaking (and thus of energy consumption) are still present, but in much lower quantity. No steady state size distributions are observed, and the crystals are continuously growing. These systems are intermediate cases between the two preceding ones, where part of the energy comes from the Ostwald ripening process, and the other part from the remaining crystal breaking mechanism.

## Conclusion

The emergence of a stable non-racemic state relies on the presence of a usable energy source. Different energy consuming processes are required:

First phase:        Creation of asymmetric objects. The asymmetric object can be a simple molecule, but can also result from the association of other smaller objects (e.g. into polymers or crystal). This first step may not require energy consumption *per se*, as an asymmetric object can be more stable than a symmetric object, but the created asymmetry is only local. Its extent is restricted to the dimension of the object itself. On larger scales, several objects can be independently created, leading to a racemic mixture of chiral objects. If a unique object is obtained, the system can be considered to be in thermodynamic equilibrium if the inversion of the object can be considered as impossible (e.g. in the case of one conglomerate monocrystal); when the racemization of the object is possible, the object is actually kinetically frozen.

Second Phase:       Creation of a macroscopic asymmetric state. This requires either internal energy (the system starts from an initially unstable state, possessing an excess of chemical energy) or external energy (an external source of energy can be coupled to the system, forcing some reaction in a given direction). This energy must be directed toward some self-amplification mechanism, allowing the bifurcation toward one state over another. If the amount of energy is limited (especially in the case of a closed system functioning on an excess of internal energy), the created asymmetric state is unstable and is bound to be racemized with time.

Third phase:        Stabilization of the asymmetric state. If the energy fluxes can be maintained, the deracemization processes can overcome the racemization processes and maintain actively a stable asymmetric state, even on a timescale larger than the racemization timescale. In this case, the deracemizing processes must consume at least the energy that is dissipated by the racemization process.

Fourth phase:       Propagation of asymmetric regions in space: no additional energy is consumed to propagate a given asymmetry in space, on top of the energy consumption by each local systems, as long as simple diffusion can be sufficiently effective. However, the presence of active processes generating macroscopic turbulences inside the system can lead to a more efficient propagation.

The kind of system described above is an obvious example of energy-driven self-organizing system. In that respect, understanding the origin of life implies to identify the potential energy sources, how this energy can be used to generate bifurcation towards non-equilibrium states of lower entropy, and how these states can be maintained. This energetic approach is necessary to understand the evolution and stability of self-organized chemical systems as they have been described until now (Eigen 1971; Gánti 1984; Farmer et al. 1986; Wagner and Ashkenasy 2009).

## Appendix

Energy Transfer

How can chemical energy be transferred into a system? The purpose is to couple a thermodynamically unfavorable reaction (e.g. $C \rightleftharpoons A$) to a more favorable one (e.g. $X \rightleftharpoons Y$), so that the global reaction is favorable (e.g. $C + X \rightleftharpoons A + Y$), forcing the first reaction to be realized. Such transfer of chemical energy is ubiquitous in biochemical systems, the most simple example being the reaction $ATP \rightarrow ADP + P_i$.

   If the system is connected to an energy reservoir fueling continuously $X$ compounds, the spontaneous flux $X \rightarrow Y$ will generate an induced flux $C \rightarrow A$, thus maintaining high concentrations of the less stable compound $A$ (see Fig. 7). Such non-equilibrium state is characterized by internal chemical fluxes, maintained by the coupling with external fluxes (Plasson and Bersini 2009).
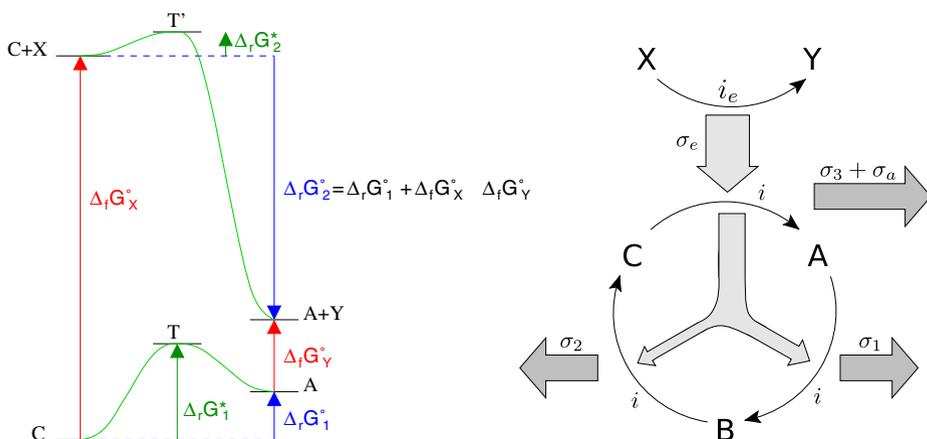


**Fig. 7** How to transfer chemical energy. The thermodynamically unfavorable reaction $C \rightarrow A$ is coupled to the more favorable reaction $X \rightarrow Y$. The corresponding transfer of energy allows the generation of a reaction flux from $C$ to $A$, that can then react on its own generating larger cycle of reactions (e.g. a $A \rightarrow B \rightarrow C \rightarrow A$ cycle.)

Presence of Free Energy

The onset of non-equilibrium reaction network relies on the stable presence of chemical energy. Real chemical systems are generally away from the equilibrium state as they continuously communicate with their surrounding. Diverse forms of available free energy can be found in most abiotic environments, for example induced by the continuous flux of light from the Sun, due to the chemical inhomogeneities of large bodies (e.g. the possibility to obtain fluxes of reduced compounds from the Earth crust (Huber and Wächtershäuser 1998; Cody 2004)), or by the presence of high temperature gradients at the surface of the early Earth (Abramov and Mojzsis 2009). All these natural sources of energy represent potential entry points of energy flux for the prebiotic chemical systems.

## References

Abramov O, Mojzsis SJ (2009) Microbial habitability of the hadean earth during the late heavy bombardment. Nature 459:419–422

Asakura K, Soga T, Uchida T, Osanai S, Kondepudi DK (2002) Probability distributions of enantiomeric excess in unstirred and stirred crystallization of 1,1'-binaphthyl melt. Chirality 14:85–89

Asakura K, Nagasaka Y, Hidaka M, Hayashi M, Osanai S, Kondepudi DK (2004) Chiral symmetry-breaking transition in growth front of crystal phase of 1,1'-binaphthyl in its supercooled melt. Chirality 16:131–136

Asakura K, Plasson R, Kondepudi DK (2006) Experimental evidence and theoretical analysis for the chiral symmetry breaking in the growth front of conglomerate crystal phase of 1,1'-binaphthyl. Chaos 16:037116

Avalos M, Babiano R, Cintas P, Jiménez JL, Palacios JC (2000) From parity to chirality: chemical implications revisited. Tetrahedron Asymmetry 11:2845–2874

Bada JL (1972) Kinetics of racemization of amino acids as a function of pH. J Am Chem Soc 94:1371–1373

Bada JL (1985) Amino acid racemization dating of fossil bones. Annu Rev Earth Planet Sci 13:241–268

Ben-Naim A (2007) On the so-called Gibbs Paradox, and on the real paradox. Entropy 9:132–136

Blackmond D (2007a) Response to "comments on a possible transition to solid-phase homochirality". Chem Eur J 13:10306–10311

Blackmond DG (2007b) "Chiral amnesia" as a driving force for solid-phase homochirality. Chem Eur J 13:3290–3295

Blackmond DG (2009) "If pigs could fly" chemistry: a tutorial on the principle of microscopic reversibility. Angew Chem Int Ed 48:2648–2654

Blackmond DG, Matar OK (2008) A re-examination of reversibility in reaction models for the spontaneous emergence of homochirality. J Phys Chem B 112:5098–5104

Bonner WA (2000) Parity violation and the evolution of biomolecular homochirality. Chirality 12:114–126

Brandenburg A, Multamäki T (2004) How long can left and right handed life forms coexist? Int J Astrobiol 3:209–219

Brandenburg A, Lehto HJ, Lehto KM (2007) Homochirality in an early peptide world. Astrobiol 7:725–732

Chandrasekhar S (2008) Molecular homochirality and the parity-violating energy difference. A critique with new proposals. Chirality 20:84–95

Cody GD (2004) Transition metal sulfides and the origins of metabolism. Annu Rev Earth Planet Sci 32:569–599

Crusats J, Veintemillas-Verdaguer S, Ribó JM (2006) Homochirality as a consequence of thermodynamic equilibrium? Chem Eur J 12:7776–7781

Crusats J, Veintemillas-Verdaguer S, Ribó JM (2007) Comments on a possible transition to solid-phase homochirality. Chem Eur J 13:10303–10305

Crusats J, Hochberg D, Moyano A, Ribó J (2009) Frank model and spontaneous emergence of chirality in closed systems. Chem Phys Chem 10:2123–2131

Cruz JM, Parmananda P, Buhse T (2008) Noise-induced enantioselection in chiral autocatalysis. J Phys Chem A 112:1673–1676

Curie P (1894) Sur la symétrie dans les phénomènes physiques. Symétrie d'un champ électrique et d'un champ magnétique. J Phys 3:393–417

Eigen M (1971) Selforganization of matter and the evolution of biological macromolecules. Naturwiss 58:465–523

Faglioni F, Passalacqua A, Lazzeretti P (2005) Parity violation energy of biomolecules-i: polypeptides. Orig Life Evol Biosph 35:461–475

Farmer JD, Kauffman SA, Packard NH (1986) Autocatalytic replications of polymers. Physica D Nonlinear Phenom 22:50–67

Frank FC (1953) Spontaneous asymmetric synthesis. Biochem Biophys Acta 11:459–463

Gánti T (1984) Coupling of autocatalytic cycles as a possible explanation of chemical oscillations. React Kinet Catal Lett 24:197–202

Giaquinta A, Hochberg D (2008) Chiral symmetry breaking: (i) limited enantioselectivity and (ii) mutual inhibition. Physica D Nonlinear Phenom 237:2563–2576

Gleiser M (2007) Asymmetric spatiotemporal evolution of prebiotic homochirality. Orig Life Evol Biosph 37:235–251

Gleiser M, Walker SI (2009) Toward homochiral protocells in noncatalytic peptide systems. Orig Life Evol Biosph 39:479–493

Hill TL (1962) Thermodynamics of small systems. J Chem Phys 36:3182–3197

Hitz T, Luisi PL (2003) Chiral amplification of oligopeptides in the polymerization of $\alpha$-amino acid N-carboxyanhydrides in water. Helv Chim Acta 86:1423–1434

Hochberg D, Zorzano MP (2006) Reaction-noise induced homochirality. Chem Phys Lett 431:185–189

Huber C, Wächtershäuser G (1998) Peptides by activation of amino acids with CO on (Ni,Fe)S surfaces: implications for the origin of life. Science 281:670–672

Jaynes ET (1992) The Gibbs Paradox. In: Smith CR, Erickson GJ, Neudorfer PO (eds) Maximum entropy and bayesian methods, pp 1–22

Kipping F, Pope W (1898) Enantiomorphism. J Chem Soc Trans 73:606–617

Kondepudi D (2008) Introduction to modern thermodynamics. In: Entropy production due to chemical reactions, chap 9.5. Wiley, New York

Kondepudi D, Kapcha L (2008) Entropy production in chiral symmetry breaking transitions. Chirality 20:524–528

Kondepudi DK, Nelson GW (1983) Chiral symmetry breaking in nonequilibrium systems. Phys Rev Lett 50:1023–1026

Kondepudi DK, Kaufman RJ, Singh N (1990) Chiral symmetry breaking in sodium chlorate crystallization. Science 250:975–976

Lahav M, Weissbuch I, Shavit E, Reiner C, Nicholson GJ, Schurig V (2006) Parity violation energetic difference and enantiomorphous crystals-caveats; reinvestigation of tyrosine crystallization. Orig Life Evol Biosph 36:151–170

Le Bellac M, Mortessagne F, Batrouni GG (2004) Equilibrium and non-equilibrium statistical thermodynamics. Cambridge University Press, New York

Lente G (2007) The effect of parity violation on kinetic models of enantioselective autocatalysis. Phys Chem Chem Phys 9:6134–6141

Lin SK (1996) Gibbs Paradox of entropy of mixing: experimental facts, its rejection and the theoretical consequences. Electron J Theor Chem 1:135–151

Lin SK (2008) Gibbs Paradox and the concepts of information, symmetry, similarity and their relationship. Entropy 10:1–5

Mason SF, Tranter GE (1985) The electroweak origin of biomolecular handedness. Proc R Soc Lond A 397:45–65

Masters PM, Bada JL, Samuel Zigler J (1977) Aspartic acid racemisation in the human lens during ageing and in cataract formation. Nature 268:71–73

Mauksch M, Tsogoeva SB (2008) Spontaneous emergence of homochirality via coherently coupled antagonistic and reversible reaction cycles. Chem Phys Chem 9:2359–2371

Mauksch M, Tsogoeva SB, Martynova IM, Wei S (2007a) Evidence of asymmetric autocatalysis in organocatalytic reactions. Angew Chem Int Ed 46:393–396

Mauksch M, Tsogoeva SB, Wei S, Martynova IM (2007b) Demonstration of spontaneous chiral symmetry breaking in asymmetric Mannich and Aldol reactions. Chirality 19:816–825

Mc Naught A, Wilkinson A (1997) IUPAC. In: Compendium of chemical terminology ("gold book"), 2nd edn. Blackwell Scientific Publications, Oxford. XML on-line corrected version created by Nic M, Jirat J, Kosata B; updates compiled by Jenkins A. Last update: 2008-09-12; version 2.0.1. "Kinetic control": http://goldbook.iupac.org/K03398.html; "Thermodynamic control": http://goldbook.iupac.org/T06316.html

McBride JM, Carter RL (1991) Spontaneous resolution by stirred crystallization. Angew Chem Int Ed Engl 30:293–295

Multamäki T, Brandenburg A (2005) Spatial dynamics of homochiralization. Int J Astrobiol 4:75–80

Noorduin WL, Meekes H, Bode AAC, van Enckevort WJP, Kaptein B, Kellogg RM, Vlieg E (2008a) Explanation for the emergence of a single chiral solid state during attrition-enhanced Ostwald ripening: survival of the fittest. Cryst Growth Des 8:1675–1681

Noorduin WL, Meekes H, van Enckevort WP, Millemaggi A, Leeman M, Kaptein B, Kellogg RM, Vlieg E (2008b) Complete deracemization by attrition-enhanced Ostwald ripening elucidated13. Angew Chem Int Ed 47:6445–6447

Pagni R (2009) The weak nuclear force, the chirality of atoms, and the origin of optically active molecules. Found Chem 11:105–122

Pérez-Madrid A (2004) Gibbs entropy and irreversibility. Phys A Stat Mech Appl 339:339–346

Plasson R (2008) Comment on "re-examination of reversibility in reaction models for the spontaneous emergence of homochirality". J Phys Chem B 112:9550–9552

Plasson R, Bersini H (2009) Energetic and entropic analysis of mirror symmetry breaking processes in a recycled microreversible chemical system. J Phys Chem B 113:3477–3490

Plasson R, Bersini H, Commeyras A (2004) Recycling Frank: spontaneous emergence of homochirality in noncatalytic systems. Proc Natl Acad Sci USA 101:16733–16738

Plasson R, Kondepudi DK, Asakura K (2006) Three-dimensional description of the spontaneous onset of homochirality on the surface of a conglomerate crystal phase. J Phys Chem B 110:8481–8487

Plasson R, Kondepudi DK, Bersini H, Commeyras A, Asakura K (2007) Emergence of homochirality in far-from-equilibrium systems: mechanisms and role in prebiotic chemistry. Chirality 19:589–600

Saito Y, Hyuga H (2004) Homochirality proliferation in space. J Phys Soc Jpn 73:1685–1688

Saito Y, Hyuga H (2009) Selection of crystal chirality: equilibrium or nonequilibrium? J Phys Soc Jpn 78:104001

Siegel JS (1998) Homochiral imperative of molecular evolution. Chirality 10:24–27

Soai K, Shibata T, Morioka H, Choji K (1995) Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. Nature 378:767–768

Swendsen RH (2008) Gibbs' Paradox and the definition of entropy. Entropy 10:15–18

Viedma C (2005) Chiral symmetry breaking during crystallization: complete chiral purity induced by nonlinear autocatalysis and recycling. Phys Rev Lett 94:065504

Viedma C, Ortiz JE, Torres Td, Izumi T, Blackmond DG (2008) Evolution of solid phase homochirality for a proteinogenic amino acid. J Am Chem Soc 130:15274–15275

Voorhees PW (1985) The theory of Ostwald ripening. J Stat Phys 38:231–252

Wagner N, Ashkenasy G (2009) Symmetry and order in systems chemistry. J Chem Phys 130:164907