Homochirality as Fixed Point of Prebiotic Chemistry

Raphaël PLASSON[1], Hugues BERSINI[2] and Auguste COMMEYRAS[1]

[1] OMEMF, CC17, Université Montpellier II, Place E. Bataillon, 34095 Montpellier Cedex 5, FRANCE
[2] IRIDIA, ULB, 50 avenue F. Roosevelt, CP194/6, 1050 Bruxelles, BELGIUM
rplasson@univ-montp2.fr

Abstract

The purpose of this work is to highlight the ability of a prebiotic system of activation/polymerization/depolymerization (APD) of amino acids to have non-racemic fixed points, similarly to Frank's model, and thus to evolve spontaneously toward homochirality. Chemical kinetic simulations of reaction sets, from simple isolated polymerization systems to complete APD systems in presence of inversion reactions, are developed in order to understand the mechanisms of amplification of asymmetry. The results emphasize the emergence of autocatalysis thanks to the synergetic action between epimerization and APD reactions, allowing spontaneous symmetry breaking from racemic state. The APD system appears to be an original nonequilibrium chemical system model, as an extension of the Frank's model based on prebiotically relevant chemical reactions.

Introduction

One of the most fascinating characteristics of the molecular constituents of all living beings is a property called homochirality: these molecules are chiral — that is they are not identical to their mirror image, as a right hand compared to a left hand — and only one of either "right" or "left" form naturally exists. In order to describe the chirality of molecules, we will limit ourselves to the L/D nomenclature of Fischer. For example, the proteinic amino acids are L, while the ribose of ribonucleic acids is always D. This property is fundamental for molecular structures: a peptide characterized by the same sequence of amino acids as a given protein, but with a random distribution of D and L amino acids, will never adopt the three-dimensional conformation of the protein. Knowing that it is the conformation of the protein which determines its function, it is broadly accepted that homochirality of the molecular constituents of cells can be considered as a prerequisite for life (Avetisov and Goldanskii, 1991).

Homochirality is a very interesting phenomenon in the origin of life, since for symmetry reasons, prebiotic compounds are synthesized in an equally distributed L/D mixture (called a "racemic" mixture). As a matter of fact, this racemic situation should be quite attracting and stable in the long term, as the inversion of chiral centers tends to equilibrate L and D concentrations. How could the biomolecules have escaped from this attractor ? Two families of hypothesis have been proposed to explain the emergence of homochirality. The first one, exogenous, relies on the external origin of asymmetry (asymmetrical weak force, environmental asymmetry, ...) and will not be considered further in this paper. The second one, endogenous, relies on intrinsic properties of the chemical system (e.g. difference of affinity between L and D shaped compounds (stereoselectivity) or autocatalytic processes).

One of the most used models in the prebiotic field relies on the principle of amplification and accumulation of asymmetry. A series of experiments (Blair and Bonner, 1981; Hitz and Luisi, 2003) illustrates how a small difference in L and D concentrations can be multiplied in peptides by the stereoselective polymerization of amino acids derivatives. What is still unsatisfactory with this explanatory schema is that racemic and non-racemic remain stable situations, nothing is qualitatively new and the non-racemization of polymers just reflects the non-racemization of initial concentrations. Adopting the terminology of dynamical systems, this model is a conservative one in which any initial condition will lead to a different outcome. Such systems cannot produce homochirality in the long term (Bonner, 1999).

A more exciting model relies on autocatalytic reactions, in which each L or D form catalyzes its own formation. This model was first developed by Frank (Frank, 1953). From this perspective, Decker (Decker, 1974) described the minimal chemical open systems that can exist in several steady states. The formalism was extended by Kondepudi (Kondepudi and Nelson, 1984), and similar ones are currently developed (Iwamoto, 2003). All these models describe open-flow systems of autocatalytic synthesis of chiral compounds, according to the following scheme:

$$\mathrm{F} \longrightarrow X_L \qquad F + X_L \longrightarrow 2X_L \qquad (1)$$

$$\mathrm{F} \longrightarrow X_D \qquad F + X_D \longrightarrow 2X_D \qquad (2)$$

$$X_L + X_D \longrightarrow P \qquad (3)$$

In contrast with the precedent case, the initial racemic state

becomes unstable, and a non-racemic state can spontaneously emerge as the attracting fixed point. This new dynamics is now dissipative, and every initial condition will lead to a non-racemic situation, favoring excess of either L or D.

Few experimental systems have shown such behavior of symmetry breaking: crystallization of sodium chlorate (Kondepudi et al., 1990), synthesis of cobalt complexes (Asakura et al., 2000), organometallic synthesis of pyrimidyl alkanol (Soai et al., 2001), etc. All these systems are based on direct autocatalytic reactions. Unfortunately, these experiments are far from the prebiotic field.

The simulations presented in this paper try to conserve the spirit of Frank's model, while based on prebiotic data and knowledge, in the field of peptides and amino acids reactivity (Taillades et al., 1999), for determining the ability of a prebiotic closed system to evolve toward homochirality, even in the absence of initial imbalance. A set of six types of chemical reactions are included in the simulation, which all together can lead to the autocatalytic effect giving rise to homochirality. The next section will describe the six types of reactions, and the third one will present and discuss results of simulations, where the reactions will be successively introduced. We will show that while only deactivation and polymerization is enough to obtain amplification of asymmetry, the whole set of reactions becomes necessary to obtain, like in Frank's model, a dissipative dynamics and an autocatalytic spontaneous generation of homochirality.

The Activation/Polymerization/Depolymerization Model

The activation/polymerization/depolymerization (APD) system involves three kinds of chemical species (X, X* and X_n, X being either L or D), and six kinds of reactions, summed up on Fig. 1.

Involved Species:

1. X represents the amino acids, that is the non-activated monomers, unable to polymerize by itself. X can be of configuration either L or D;
2. X* represents the activated monomers, which only in their active form can polymerize. They can be of configuration either L or D;
3. X_n represents the peptides, that is the polymer, composed of a sequence of L or D monomers.

Involved Reactions:

1. *Activation* corresponds to the conversion of X to X*:

$$X \xrightarrow{k_a} X^* \qquad (4)$$

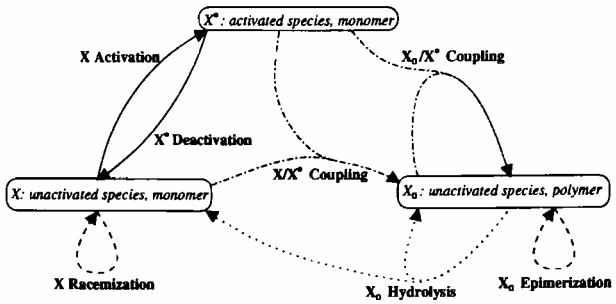

Figure 1: System of activation/polymerization/depolymerization of amino acids: a model of closed dissipative prebiotic system.

2. *Deactivation* corresponds to the conversion of X* to X:

$$X^* \xrightarrow{k_d} X \qquad (5)$$

3. *Polymerization* corresponds to the reaction of X* with either X or X_n, leading to the peptide elongation on the left side (by convention). For a given peptide, the kinetic constant $k_n^=$, between X* and the peptide's left side of same configuration (Eq. 7 and Eq. 8), is greater than the kinetic constant $k_n^{\neq}$, between X* and the peptide's left side of opposite configuration (Eq. 6 and Eq. 9).

$$L^* + DX_{n-1} \xrightarrow{k_n^{\neq}} LDX_{n-1} \qquad (6)$$

$$L^* + LX_{n-1} \xrightarrow{k_n^=} LLX_{n-1} \qquad (7)$$

$$D^* + DX_{n-1} \xrightarrow{k_n^=} DDX_{n-1} \qquad (8)$$

$$D^* + LX_{n-1} \xrightarrow{k_n^{\neq}} DLX_{n-1} \qquad (9)$$

4. *Peptide hydrolysis* corresponds to the conversion of one peptide to two shorter peptides or amino acids. Hydrolysis can take place between two residues of either same configurations (Eq. 10 and Eq. 13) or opposite configurations (Eq. 11 and Eq. 12). Here again, according to the difference in intensity of the values of the two constant rates, this reaction can be more or less stereoselective. Experimental data is lacking on this specific fact.

$$X_nLLX_m \xrightarrow{k_h^=} X_nL + LX_m \qquad (10)$$

$$X_nLDX_m \xrightarrow{k_h^{\neq}} X_nL + DX_m \qquad (11)$$

$$X_nDLX_m \xrightarrow{k_h^{\neq}} X_nD + LX_m \qquad (12)$$

$$X_nDDX_m \xrightarrow{k_h^=} X_nD + DX_m \qquad (13)$$

5. *Racemization* corresponds to the conversion between L and D.

$$L \underset{}{\overset{k_r}{\rightleftharpoons}} D \qquad (14)$$

6. *Epimerization* corresponds to the conversion of one monomer inside the peptide chain.

$$X_nLX_m \overset{k_e}{\rightleftharpoons} X_nDX_m \qquad (15)$$

This model is based on real chemical reactions which are part of the Commeyras "primary pump" scenario about the prebiotic origin of peptides (Commeyras et al., 2002), but is compatible with other similar APD systems (Huber et al., 2003). Many of the kinetic rates used in the simulations were experimentally measured (Plasson et al., 2002), more particularly the rates concerning and supporting the stereoselectivity of polymerization. This scenario explains the appearance of peptide chains by a succession of activation reactions, taking place in dry phase, and polymerization and depolymerization reactions, possible in wet phase.

Chemical Kinetic Simulation Program

The program used for the kinetic simulations, `Sa3`, is based on numerical integration of a set of chemical equations, by a semi-implicit Runge-Kutta algorithm (Kaps and Rentrop, 1984). It was developed by J.-C. Micheau and D. Lavabre (*IMRCP, Université Paul Sabatier*, Toulouse, FRANCE).

As all considered reactions must be written, it was necessary to limit their number. In this model, the formation of peptides of polymerization degree greater than 4 were neglected. All stereoisomers of peptides up to the tetramers and the corresponding reactions were then considered.

Amplification of Non-Racemic Situations

Polymerization of Non-Racemic X*

In line with Blair and Bonner's experimental results, a first set of simulation shows that an initial excess of one form of X* will be amplified by its accumulation in peptides thanks to the stereoselectivity of the polymerization reactions.

In this first simulation, only the reactions of deactivation and polymerization were taken into account. In the initial conditions, only X* is present, with an excess of 10% of L*. The L excess in monomers is determined by $ee_1 = \frac{([L]+[L^*])-([D]+[D^*])}{([L]+[L^*])+([D]+[D^*])}$, and in homopeptides by $ee_n = \frac{[L_n]-[D_n]}{[L_n]+[D_n]}$ for $n \in [2,4]$.

Because of stereoselectivity of coupling, a majority of homochiral peptides is produced. Homochiral peptides are first generated with a much higher L excess than initially introduced: 20%, 29% and 38% for respectively ee_2, ee_3 and ee_4 (Fig. 2). These values decrease as polymerization go on, but when all L* are consumed, they still remain high: 10%, 14% and 25% for respectively ee_2, ee_3 and ee_4, while final excess of L is only 5%. Stereoselective polymerization allows concentration of the configuration in excess into homochiral polymers.

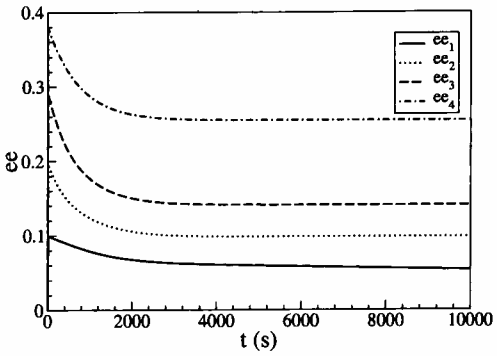

Figure 2: Evolution of ee_n during the polymerization of non-racemic X* ($ee^{init} = 0.1$) calculated by computer simulation using the `Sa3` program (tolerance, 10^{-3}; maximal step, 1 s). Parameters: $k_d = 5 \cdot 10^{-4}$ s^{-1}; $k_1^= = 1.6 \cdot 10^{-2}$ s^{-1}.M^{-1}; $k_1^{\neq} = 1.1 \cdot 10^{-2}$ s^{-1}.M^{-1}; $k_2^= = 6 \cdot 10^{-2}$ s^{-1}.M^{-1}; $k_2^{\neq} = 1.3 \cdot 10^{-2}$ s^{-1}.M^{-1}; $k_3^= = 6 \cdot 10^{-2}$ s^{-1}.M^{-1}; $k_3^{\neq} = 1.3 \cdot 10^{-2}$ s^{-1}.M^{-1}; $[L^*]_0 = 1.1 \cdot 10^{-1}$ M; $[D^*]_0 = 9 \cdot 10^{-2}$ M.

Addition of Racemic X* to Non-Racemic Homochiral Dipeptide X_2

Only the reactions inverting L in D (and symmetric) can amplify the global excess of L or D (defined by $ee^{tot} = \left(\frac{[L^{tot}]-[D^{tot}]}{[L^{tot}]+[D^{tot}]}\right)$. Among these reactions are the racemization and the epimerizations.

In a new set of simulations, we add the racemization and modify the initial concentrations: an equal concentration of L* and D*, and an excess of homochiral dipeptide LL ($ee_{2,0} = 10\%$).

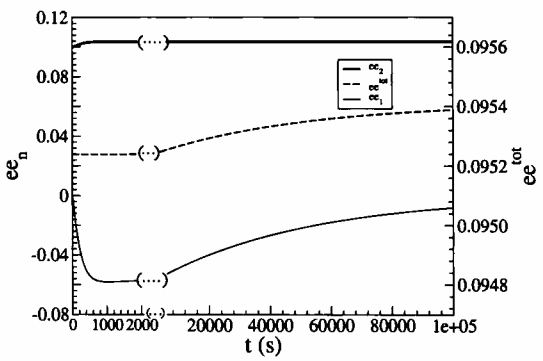

Figure 3: Evolution of ee_n and ee^{tot} during addition of racemic X* to non-racemic homochiral dipeptide ($ee_2^{init} = 0.1$). Same parameters as in Fig. 2, but initial conditions, $[L^*]_0 = 1 \cdot 10^{-2}$ M; $[D^*]_0 = 1 \cdot 10^{-2}$ M; $[LL]_0 = 1.1 \cdot 10^{-1}$ M; $[DD]_0 = 9 \cdot 10^{-2}$ M, and with addition of $k_r = 5 \cdot 10^{-5}$ s^{-1}.

As X* reacts on an excess of homochiral dipeptides, the main formed products are homochiral tripeptides coming from X^*X_2 coupling, and amino acids coming from X* hy-

drolysis. Two phenomena deserve some attention (Fig. 3).

At first, because of stereoselectivity, most of L* reacts on LL, and most of D* reacts on DD. As X* is initially racemic, about the same quantity of LL and DD are consumed. Thus, the absolute concentration difference between LL and DD remains roughly constant, while the total concentration of LL and DD decreases. This implies the increase of ee_2.

Secondly, as there are more LL than DD, L* is more quickly consumed than D*. Thus, during polymerization, concentration of D* is higher than the one of L^*, so that deactivation produces more D than L. At the completion of the reaction, an excess of D is obtained. Compensating for the D/L disequilibrium, the racemization increases consequently the total concentration $[L^{tot}]$, and decreases the total concentration $[D^{tot}]$: the global L excess increases.

While replicating the results of the previous simulation, namely the amplification of the L excess in the peptides, a new global effect occurs, thanks to the presence of racemization: the increase of the global L excess. This result shows that in some conditions, racemization may be able to enhance non-racemic situations rather than to tend to racemic state, via an "inversion of population" phenomenon. But still, we are in the presence of a simple amplification, with no qualitative change: the dynamics is still conservative.

Spontaneous Emergence of homochirality

Closed APD System

The preceding study has shown the ability of a simple system to amplify a first excess in either L or D. While keeping with classical prebiotic chemistry, would it be possible to obtain similar results to the Frank's Model: homochirality as a new fixed point of a now dissipative dynamics ?

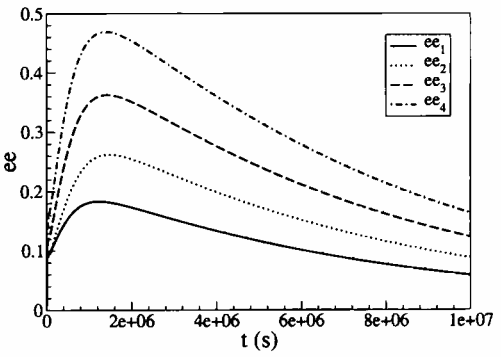

Figure 4: Evolution of ee_n in an APD system ($ee_2^{init} = 0.1$). Same parameters as in Fig. 3, but integration parameters, tolerance, 10^{-3}; maximal step, 10^4 s; and with addition of $k_a = 1 \cdot 10^{-3}\ s^{-1}$; $k_h^{=} = 1 \cdot 10^{-5}\ s^{-1}$; $k_h^{\neq} = 1 \cdot 10^{-6}\ s^{-1}$.

Two new types of reactions are introduced: the activation one, possible if the system is no more isolated but energetically open, and the depolymerization one, allowing constant regeneration of basic materials to be recombined. The addition of these two types of reactions introduces reactive loops in the system, which are well-known to promote dynamical irreversibility and to induce new stable configurations.

The experimental results (Fig. 4) show that departing from the same excess of LL, the system now converges to a single global fixed point, in which all compounds are racemic. Instead of being amplified, the dynamic evolution of the system re-establishes a perfect symmetrical situation and looses the memory of the initial condition. The system has turned out to be dissipative but with no self-amplification of the initial unbalanced presence of L or D. However, a transitory period still shows this amplification, even stronger than in the previous simulations. Depolymerization being much slower than polymerization, a rough intuitive explanation is that the system first behaves like in the absence of depolymerization.

Emergence of an Autocatalytic Set

So far, it has been shown that an APD system can temporarily amplify a first L or D excess, but no stable symmetry breaking can be observed, as the fixed point remains racemic. The addition of the last type of reaction, epimerization, is then introduced in the model in order to see how the symmetry breaking can be obtained. This new reaction type aims at favoring the appearance of homopeptides so as to, indeed, amplify an initial unbalanced situation. For simplicity, only one reaction of epimerization is introduced, applied exclusively on LDL and DLD tripeptides, all other epimerization reactions still being neglected.

$$\mathrm{LDL} \xrightarrow{k_e} \mathrm{LLL} \qquad \mathrm{DLD} \xrightarrow{k_e} \mathrm{DDD} \tag{16}$$

As Eq. 16 is considered with equal constant rates k_e for both reactions, the whole system remains symmetric. Supposing that homochiral peptides are more stable than heterochiral peptides, these reactions should be faster than the reverse reactions.

These epimerization reactions may have very interesting potential in an APD system, as shown Eq. 17 for LDL epimerization to LLL. Embedded in such a system, LDL comes from a multi-step activation/polymerization of two L and one D, and LLL is to be hydrolyzed into three L. This set of reactions can then be reduced to a conversion of D to L, consuming and regenerating two L, that is an autocatalytic inversion of D. In this scope, if this path can become more efficient than the non-catalyzed amino acid inversion, the whole racemic system may become unstable.

$$\begin{array}{ccccccc} 2\,\mathrm{L}+\mathrm{D} & \rightarrow & \mathrm{LDL} & \rightarrow & \mathrm{LLL} & \rightarrow & 3\,\mathrm{L} \\ 2\,\mathrm{L}+\mathrm{D} & & & \longrightarrow & & & 2\,\mathrm{L}+\mathrm{L} \end{array} \tag{17}$$

The simulation is done starting with racemic X*. As seen in Fig. 3, the system remains racemic for a long time, when

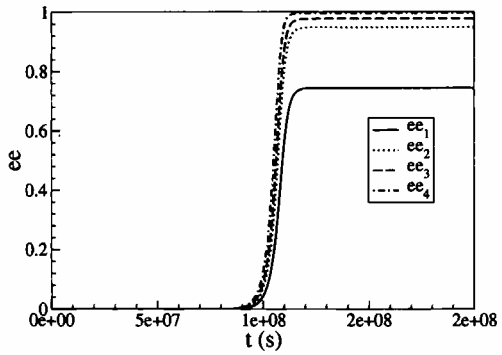

Figure 5: Evolution of ee_n in an APD system in presence of selective epimerization of peptides ($ee^{init} = 0$). Same parameters as in Fig. 4 but initial conditions, $[L^*]_0 = 1 \cdot 10^{-2}$ M; $[D^*]_0 = 1 \cdot 10^{-2}$ M; and with addition of $k_e = 1 \cdot 10^{-3}$ s^{-1}.

an exponential raising of L excess occurs, driving the concentrations to a non-racemic state, with high global L excess. This time, the racemic state is unstable, and the fixed points are non-racemic.

Several systems have been studied for different k_e values. For low values, the system always remains racemic (Fig. 6). For such cases, the autocatalytic inversion of amino acids is slower than the uncatalyzed inversion: the racemic state is stable. But up to a critical value of k_e, a bifurcation occurs, and strong L or D excesses are obtained. The system switches from a globally stable to a locally stable one, in which a certain memory of the initial condition is preserved. Whatever the amount of initial excess of L or D, the final homochiral situation will conserve the sign of the excess. For such cases, the autocatalytic inversion of amino acids becomes faster than the non-catalytic one. This bifurcation phenomenon turns out to be similar to the Frank's model.

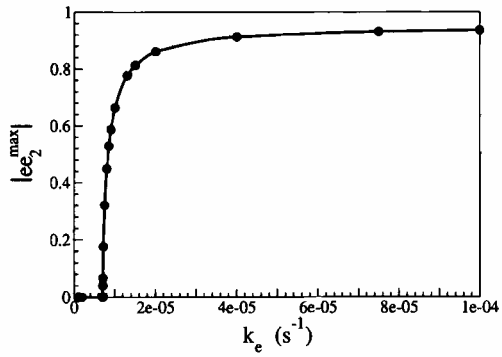

Figure 6: Bifurcation diagram of an APD system in presence of selective peptide's epimerization: variation of final $|ee_2|$ as a function of k_e. Same parameters as in Fig. 5 but k_e.

This critical value is still quite high compared with kinetic rates expected in mild conditions (Schroeder and Bada, 1976). However, this critical value is strongly dependent on a huge number of parameters that were not investigated, and effective epimerization rates may have been much higher in more drastic conditions (Huber et al., 2003).

So, while the basic racemization is opposed to the spontaneous emergence of homochirality, this new contextual form of it, favoring homopeptides, is the simplest autocatalytic effect which can lead to stable and attracting homochirality.

Conclusion

A first key distinction often misunderstood in biological and chemical literature needs to be clarified. The amplification of the initial excess obtained in the first simulations described in the paper is a different dynamical phenomenon from the autocatalytic rupture of symmetry obtained in the last simulation. In the last case, the dynamics is dissipative meaning that the final concentration values are independent of the initial values, and even a simple statistical fluctuation could cause homochirality. The previous simulations have been criticized as a possible explanation of homochirality, as they required a sufficient initial excess, and were wrongly generalized to the second set of simulations, in which the state of homochirality is qualitatively but not anymore quantitatively dependent on the initial conditions.

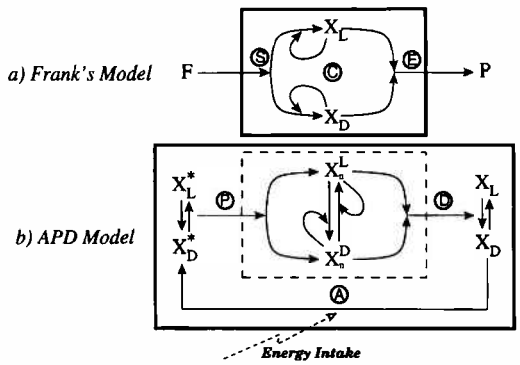

Figure 7: Spontaneous symmetry breaking in nonequilibrium chemical systems. (a) Frank's model: open-flow system, based on synthesis of chiral compounds from achiral compounds Ⓢ, autocatalysis of this synthesis Ⓒ, and elimination of the chiral compounds Ⓔ. (b) APD model: closed system, based on incoming energy flux through activation Ⓐ, complexification of the system with polymerization Ⓟ, and matter recycling with depolymerization Ⓓ.

While Frank's model is an excellent and very analytically detailed illustration of this rupture of symmetry, its prebiotical relevance can be questioned. Our model described in this paper tries to reconcile Frank's hypothesis on the origin of homochirality with the more likely chemical environment of the prebiotic world. It appeared that the polymerization/depolymerization/epimerization system presents im- [illegible] autocatalytic reactions, thanks to the synergy between

all the reactions. This system is similar to the Frank's model, able to amplify asymmetry by consuming activated amino acids by polymerization, and generating non-reactive amino acids by depolymerization (Fig. 7).

The originality of the APD system is to embed this Frank-like open system in a closed system, by recycling materials thanks to energy intake, maintaining the nonequilibrium state. This model no more describes the synthesis of non-racemic chiral compounds from an achiral system, but the conversion of a preexistent racemic mixture of chiral compounds to a non-racemic mixture, and may constitute a "minimum connected, reflexively autocatalytic set" as defined by Steel (Steel, 2000). This system appears to be more robust than classical Frank-like models in a prebiotic perspective. The inversion reactions are no more disadvantages for long-term stability of the non-racemic states (Kondepudi and Asakura, 2001), as they on the contrary become the source of homochirality. The non-racemic state can thus spontaneously emerge, and become long-term stable.

Acknowledgments

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