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Special Paper

Homochirality in an Early Peptide World

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ABSTRACT

A recently proposed model of non-autocatalytic reactions in dipeptide formation that leads to spontaneous symmetry breaking and homochirality was examined. The model is governed by activation, polymerization, epimerization, and depolymerization of amino acids. Symmetry breaking was determined to result primarily from the different rates of reactions that involve homodimers and heterodimers, *i.e.*, stereoselective reactions, and the fact that epimerization can only occur on the N-terminal residue and not on the C-terminal residue. This corresponds to an auto-inductive cyclic process that works only in one direction. It is argued that epimerization mimics autocatalytic behavior as well as mutual antagonism, both of which are known to be crucial for the production of full homochirality. Key words: Prebiotic chemistry—Asymmetric synthesis—Autocatalysis. Astrobiology 7, 725–732.

INTRODUCTION

HOMOCHIRALITY OF ALMOST ALL amino acids (left-handed) and sugars (right-handed) is undoubtedly a striking property of all life on Earth and an essential requirement for the assembly of functional polymers (either polypeptides or nucleic acids). Indeed, the origin of homochirality is often thought to be closely associated with the origin of life itself (Avetisov, 1991; Bada, 1995). Conversely, the amino acids of dead organisms gradually lose their preferred handedness. This well-known property of amino acids is sometimes used as an approximate dating method (Hare and Mitterer, 1967; Bada *et al.*, 1970). We use here the term homochirality rather than the more exact expression, biological chirality. (See Palyi *et al.*, 1999, 2004; Caglioti *et al.*, 2006; for a review see also Keszthelyi, 1995.) Since the chemistry of right- and left-handed molecules is the same, it is conceivable that life could have been based on molecules whose handedness would be reversed. The selection of the two possible chiralities would then be a matter of chance and depend essentially on the presence of a minute initial excess of one type of handedness over the other. The size of the initial excess, however small, would be of little consequence, provided that the growth rate was sufficiently large and a mechanism that amplifies any excess exponentially over time existed.

In a recent paper, Plasson *et al.* (2004) raised the possibility that homochirality may have been attained in an early peptide world via a sequence

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of reactions that ultimately produce dipeptides of only one handedness. They considered a closed, recycled system in which the total number of building blocks was unchanged. In their model, monomers and dimers are coupled via activation, polymerization, and depolymerization reactions, and the activation is mediated via the formation of N-carboxyanhydrides. Crucial to this model is the fact that the reaction rates for producing homodimers are different from those producing heterodimers (*i.e.*, they are stereospecific). The fact that epimerization occurs only on the N-terminal residue and not on the C-terminal residue is also of importance. Their model carries the name APED, which denotes activation, polymerization, epimerization, and depolymerization reactions. What is remarkable is that, apparently, no autocatalysis is required, but the homochiralization process is based on what they call auto-induction. The preferential epimerization on the N-terminal residue is an empirically known fact (Kriausakul and Mitterer, 1980), though for some peptides preferential epimerization may also occur on the C-terminal residue (Kriausakul and Mitterer, 1983).

Since the seminal paper by Frank (1953), it has been considered that, on quite general grounds, two distinct ingredients are needed for establishing molecular symmetry breaking: autocatalysis and an inhibitory effect Frank called mutual antagonism. Later, Sandars (2003) identified such an inhibitory effect as enantiomeric cross-inhibition in template-directed polycondensation of polynucleotides (Joyce, 1984). However, autocatalytic reactions are currently known to exist only for a small number of non-biological molecules (Soai *et al*., 1995; Blackmond, 2004), but not for short nucleic acids or short peptides, for example. According to the APED model of Plasson *et al*. (2004), the stereoselective reactions that favor the formation of homochiral dipeptides, together with the coupled reaction network of polymerization, epimerization, and depolymerization of amino acids, may produce an auto-inductive reaction cycle that leads to the same symmetry-breaking result as the classical hypothesis of an autocatalytic process with mutual antagonism.

The goal of the present work is to illuminate the similarity between the dipeptide reaction sequence proposed by Plasson *et al*. (2004) and the two governing effects of Frank's model, which are autocatalysis and mutual antagonism, and to investigate the effects of the reaction parameters of the original APED model so as to illustrate its effects on symmetry breaking.

ESSENTIALS OF THE APED MODEL

In their original paper, Plasson *et al*. (2004) considered eight pairs of reactions, including those for the activation and deactivation of both left- and right-handed amino acids, spontaneous polymerization of activated amino acids into hetero- and homodimers, epimerization (*i.e.*, spontaneous conversion of the handedness of one monomer residue in a polymer to another) of the amino acids in the N-terminal position of the dimers, and depolymerization of the dimers. Reaction coefficients a and b were designated for activation and deactivation reactions, respectively. Coefficients p and h were designated for polymerization and depolymerization of homodimers, respectively, and coefficient e was designated for productive epimerization of the N-terminal amino acid to form homodimers. The non-stereospecific reaction rates that involve corresponding heterodimer reactions were quantified by reaction rates αp, βh, and γe. A pictorial overview of the original set of reactions considered by Plasson *et al*. (2004) is given in Fig. 1.

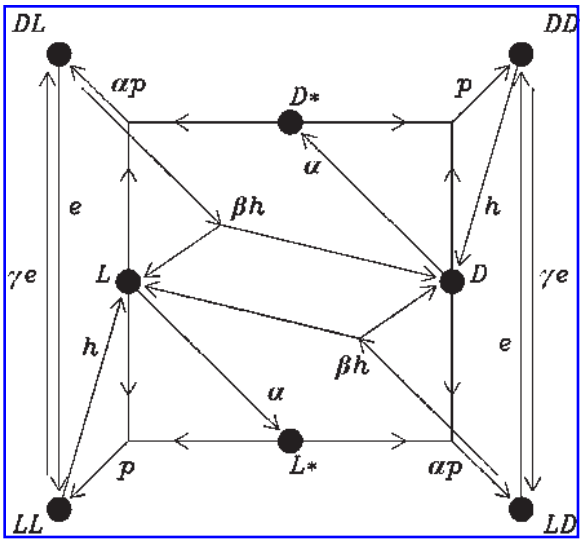

FIG. 1. Representation of the original set of reactions for producing homochirality. Here, *D* and *L* denote right- and left-handed monomers, *D** and *L** are their activated forms, *DD* and *LL* are homochiral dimers, and *DL* and *LD* are heterochiral dimers. Reaction coefficients are denoted by lowercase latin letters while greek letters indicate the departure from full stereospecificity.

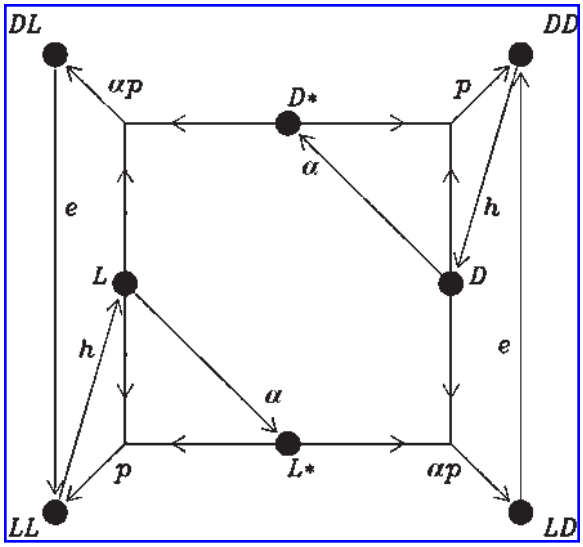

FIG. 2. Summary of the minimal subset of reactions of the APED model.

The full set of all optional reactions is rather complex and hard to analyze, so Plasson *et al.* (2004) also considered an extreme and unrealistic case where the depolymerization and epimerization reactions were fully stereospecific ($\beta = \gamma = 0$) and only the polymerization reaction varied between different degrees of stereospecificity (αp). Under these presumed conditions, 5 pairs of reactions determine the development of the symmetry state and are adequate to obtain the remarkable effect of homochiralization in their model.

This minimal subset of reactions is shown in Fig. 2. It includes activation (proportional to the rate constant a), polymerization (proportional to the rate constant p), epimerization (proportional to the rate constant e), and depolymerization (proportional to the rate constant h). In addition, polymerization to produce heterodimers (proportional to the rate constant αp) is critical for the APED mechanism to work. Unfortunately, even this minimal subset of reactions is still rather complex, so to understand what happens it is useful to consider meaningful limits in parameter space in which this subset of equations can be solved analytically while retaining the main mechanism of homochiralization. The resulting minimal set of equations necessary to retain this effect is summarized in the left-hand column of Box 1; the remaining reactions are shown in the upper portion of the right-hand column. In the lower portion of the right-hand column, we have included two additional reactions such as racemization ($L \leftrightarrow D$) with reaction rate r, and epimerization on the C-terminal position (Kriausakul

1. Original reactions (essential)

A: activation:

$$L \xrightarrow{\alpha} L^*, \quad D \xrightarrow{\alpha} D^*, \tag{1}$$

P: polymerization:

$$L^* + L \xrightarrow{p} LL, \quad D^* + D \xrightarrow{p} DD, \tag{2}$$

$$L^* + D \xrightarrow{\alpha p} LD, \quad D^* + L \xrightarrow{\alpha p} DL, \tag{3}$$

E: epimerization:

$$LD \xrightarrow{e} DD^*, \quad DL \xrightarrow{e} LL, \tag{4}$$

D: depolymerization:

$$LL \xrightarrow{h} L + L, \quad DD \xrightarrow{h} D + D. \tag{5}$$

2. Original reactions (non-essential)

deactivation:

$$L^* \xrightarrow{b} L, \quad D^* \xrightarrow{b} D, \tag{6}$$

epimerization (reverse reaction):

$$DD \xrightarrow{\gamma e} LD, \quad LL \xrightarrow{\gamma e} DL, \tag{7}$$

depolymerization of mixed dimers:

$$LD \xrightarrow{\beta h} L + D, \quad DL \xrightarrow{\beta h} D + L. \tag{8}$$

3. Additional reactions (non-essential)

racemization:

$$L \xrightarrow{r} D, \quad D \xrightarrow{r} L, \tag{9}$$

epimerization on C-terminal residue:

$$LD \xrightarrow{g} LL, \quad DL \xrightarrow{g} DD, \tag{10}$$

$$LL \xrightarrow{\xi g} LD, \quad DD \xrightarrow{\xi g} DL. \tag{11}$$

BOX. 1. Summary of essential and non-essential reactions of the APED model.

and Mitterer, 1983) with reaction rates g and ξg for homochiral and heterochiral dimers, respectively.

Below, we illuminate the mechanism by which homochirality is achieved. This is best seen when writing the essential APED reactions in sequential form in one line, *i.e.*,

$$D^* + L \xrightarrow{\alpha p} \mathrm{DL} \xrightarrow{e} LL \xrightarrow{h} L + L,$$

$$L^* + D \xrightarrow{\alpha p} LD \xrightarrow{e} DD \xrightarrow{h} D + D.$$

Thus, as long as the reaction rates for epimerization and depolymerization are not the limiting factors, we have essentially the reactions

$$D^* \xrightarrow{\alpha p[L]} L \quad \text{and} \quad L^* \xrightarrow{\alpha p[D]} D.$$

This way of writing these reactions emphasizes the roles of L and D in catalyzing the conversion of D^* into L and L^* into D, respectively. Plasson *et al*. (2004) introduced the term auto-induction instead of autocatalysis to emphasize the fact that autocatalysis in the normal sense is not thought to be possible with biological polymers as short as dimers (see the discussion in the introduction). Thus, we can say that L auto-induces the conversion of D^* into L, and D auto-induces the conversion of L^* into D. In addition, there are reactions of the form

$$L^* + L \longrightarrow LL \longrightarrow L + L,$$

$$D^* + D \longrightarrow DD \longrightarrow D + D.$$

Again, these reactions simulate the autocatalytic conversion of L^* into L by L, and of D^* into D by D. These reactions, in the given conditions with fully stereoselective depolymerization and epimerization reactions, can lead to full and sustained homochirality in situations where the value of α is between 0 and 1, *i.e.*, the polymerization reaction is partially stereoselective (Plasson *et al*., 2004).

In summary, the symmetry breaking described by the APED model seems to simulate autocatalytic behavior, even though the molecules themselves do not possess catalytic activity. In addition, the reactions that involve the conversion from D^* to L and from L^* to D via stereoselective epimerization (if $\gamma = 1$) reflect also mutual antagonism, but in an explicitly productive manner without producing achiral "waste" (degradation product). The chemical basis for these stereospecific reaction rates is not clear, but polymerization and epimerization reactions have been experimentally shown to behave in a stereospecific manner, which favors the formation of homodimers (Bartlett and Jones, 1957; Lundberg and Doty, 1956; Commeyras *et al*., 2002; Plasson, 2003) and could be caused, for instance, by a stereochemical stacking effect of the two amino acids. To put this on a more mathematical basis, we consider now the kinetic equations of a minimal subset of the APED model. For simplicity, deactivation and depolymerization of heterodimers, as well as epimerization to produce heterodimers, are neglected. This corresponds to the presumed initial setting $b = \beta = \gamma = 0$ in Plasson *et al*. (2004). The resulting set of equations is given in Box 2.

We now use explicitly the assumption that epimerization and depolymerization are not the limiting factors in the reaction and that these two reactions are much faster than the activation step, *i.e.*, both e and h are large compared with a. We consider this case mainly to illuminate the nature of the multi-step auto-inductive reaction displayed above. Thus, DL evolves rapidly via LL

$$\frac{\mathrm{d}}{\mathrm{d}t}[L] = -a[L] - p([L^*] + \alpha[D^*])[L] + 2h[LL], \qquad \frac{\mathrm{d}}{\mathrm{d}t}[LL] = p[L^*][L] + e[DL] - h[LL],$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[D] = -a[D] - p([D^*] + \alpha[L^*])[D] + 2h[DD], \qquad \frac{\mathrm{d}}{\mathrm{d}t}[DD] = p[D^*][D] + e[LD] - h[DD],$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[L^*] = a[L] - p([L] + \alpha[D])[L^*], \qquad \frac{\mathrm{d}}{\mathrm{d}t}[DL] = \alpha p[D^*][L] + e[DL],$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[D^*] = a[D] - p([D] + \alpha[L])[D^*], \qquad \frac{\mathrm{d}}{\mathrm{d}t}[LD] = \alpha p[L^*][D] + e[LD]].$$

BOX. 2. Kinetic equations corresponding to the minimal subset of equations essential for the APED model to work.

into $L + L$, and, LD evolves rapidly via DD into $D + D$. Mathematically, this is achieved by removing the time derivatives for the last four of the essential reaction equations. This reduces the number of explicitly time-dependent equations to four. The resulting system of equations is written in Box 3.

This new, reduced system of equations permits a simple and interesting interpretation in that it, too, can be associated with chemical reactions:

$$D^* + L \longrightarrow L + L,\ L^* + D \longrightarrow D + D,$$

$$L^* + L \longrightarrow L + L,\ D^* + D \longrightarrow D + D.$$

These reactions, together with the corresponding activation steps, are depicted in Fig. 3 and are indeed equivalent to the multi-step reactions discussed above. Qualitatively, the process can be explained as follows: A small initial excess of, say, [L] over [D] enhances the supply of [L] from [D^*], which appears to mimic autocatalysis. The diminished level of [D^*] enhances the losses of [D] toward [D^*] because of the minus sign in the corresponding rate $a - p[D^*]$. The reduced level of [D] appears to mimic "productive" mutual antagonism. This also decreases the losses of [L^*] toward [D], so [L^*] stays high; hence, losses of [L] toward [L^*] are minimized because of the minus sign in the corresponding reaction rate $a - p[L^*]$.

The equations can be reduced further to only two explicitly time-dependent equations if we also assume that p is large ($cp >> a$, where c is the total concentration of all building blocks, which is a constant in this model). It turns out

$$\frac{d}{dt}[L] = -a[L] + p([L^*] + \alpha[D^*])[L],$$

$$\frac{d}{dt}[D] = -a[D] + p([D^*] + \alpha[L^*])[D],$$

$$\frac{d}{dt}[L^*] = a[L] - p([L] + \alpha[D])[L^*],$$

$$\frac{d}{dt}[D^*] = a[D] - p([D] + \alpha[L])[D^*].$$

BOX. 3. Kinetic equations corresponding to the reduced set of equations containing the essentials of the APED model.

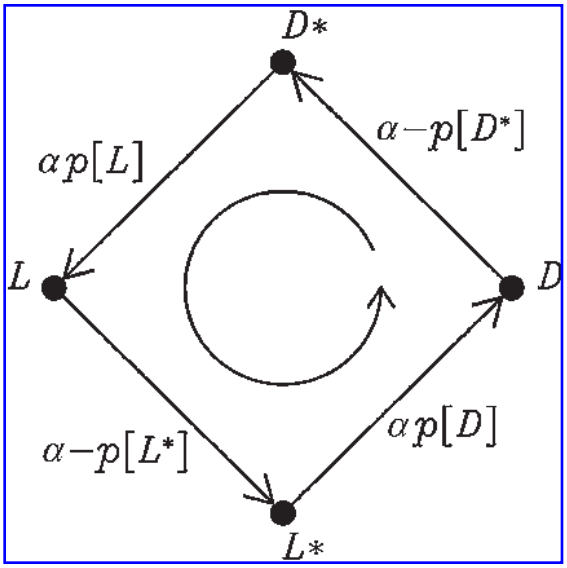

FIG. 3. Representation of the reduced set of reactions leading to homochirality. Note the counterclockwise sense of the reaction sequence.

that the enantiomeric excess (e.e.) obeys the equation

$$\frac{d}{dt}(\text{e.e.}) = \lambda \times (\text{e.e.})$$

where λ is the growth rate, which is given by

$$\lambda = \frac{2a\alpha(1-\alpha)[L][D]}{(1+\alpha^2)[L][D] + \alpha([L]^2 + [D]^2)}.$$

For the racemic solution, the growth rate of the instability toward homochirality is

$$\lambda = 2a\alpha\frac{1-\alpha}{(1+\alpha)^2}$$

Evidently, and in agreement with Plasson *et al.* (2004), the growth rate is positive as long as $\alpha < a_{\text{crit}}$, where $a_{\text{crit}} = 1$ is the maximum possible value for achieving homochirality in the reduced model. Once one of the two homochiral states has been reached, either [D] or [L] vanish; hence $\lambda = 0$, which terminates further growth.

We see that the enantiomeric excess shows exponential growth whenever α is between 0 and 1. It is remarkable that this criterion is so general and, apparently, independent of the values of the other parameters. However, it should be remembered that several restrictive approximations have been made in arriving at this result; most notably that h, e, and p were assumed large, and β and γ were assumed = 0.

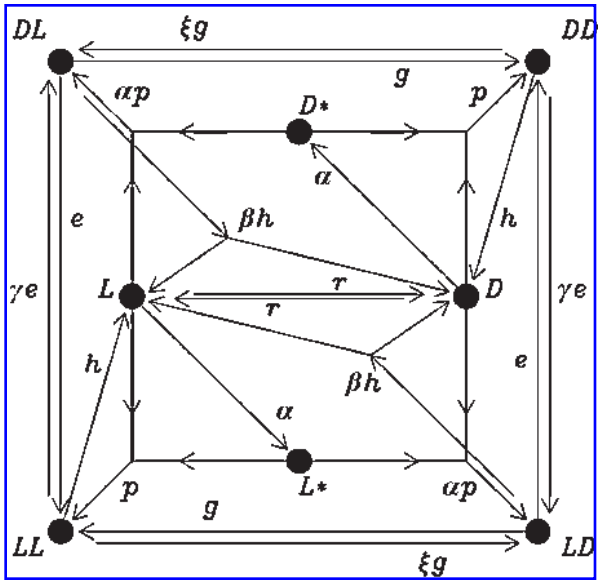

FIG. 4. Representation of the full and expanded set of reactions leading to homochirality.

In Fig. 4, we show an expanded set of reactions, and we demonstrate in Fig. 5 that, even for smaller values of h, e, and p, and also for finite values of β and g, the criterion is unchanged and only the values of the growth rates change. The only reaction that changes this criterion is the racemization reaction, characterized by the parameter r. If r is larger than $0.12a$, only the racemic solution is possible (see Fig. 6), but if r is less than $0.12a$, there is a finite interval of α where a homochiral (right- or left-handed) solution is possible. For $r = 0.05$, for example, homochirality is only possible when α is in the interval between 0.06 and 0.80 (Fig. 6).

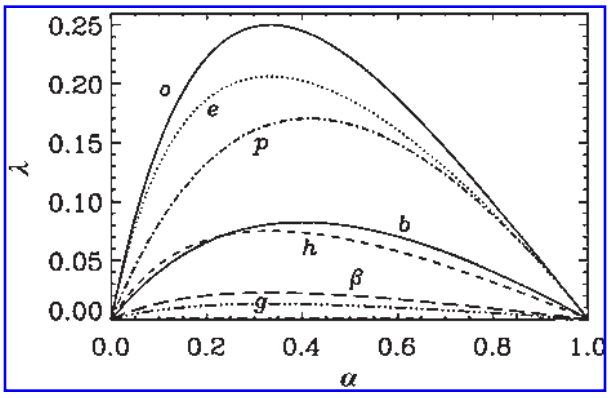

FIG. 5. Growth rate versus α for different parameter combinations. The solid line (denoted o) gives the asymptotic formula described in the text, while for all other curves one parameter is different from a value that would reproduce the asymptotic result ($e = 100a$, $p = 200a/c$, $h = 1000a$, $b = g = \beta = 0$). For the dotted curve (denoted e) we have $e = a$, for the dash-dotted curve (denoted p) we have $p = 2a/c$, for the dashed curve (denoted h) we have $h = a$, for the other solid line (denoted b) we have $b = 100a$, for the long-dashed curve (denoted β) we have $\beta = 1!$ and for the triple dot-dashed curve (denoted g) we have $g = 0.9e$.

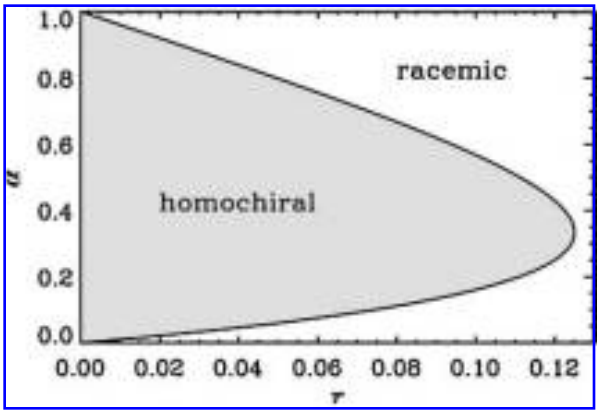

FIG. 6. Chirality regimes as a function of α and the racemization parameter r.

In conclusion, the interpretation of a one-way circular reaction scheme based on the simplified model presented above appears to be robust. We conclude, therefore, that the APED model does indeed capture effects quite analogous to the usual autocatalysis and mutual antagonism phenomena.

TEMPORAL EVOLUTION

If the initial condition were exactly racemic, homochirality would, of course, never emerge. However, such a special initial condition would be quite unrealistic, and there will always be a distribution of the initial value of the e.e. around zero. The width of this distribution decreases with the increasing number of molecules that can interact (the width is $1/\sqrt{n}$ for n molecules).

We illustrate this in Fig. 7 by plotting the evolution of e.e. for two different random initial distributions of molecules. In addition to plotting the distributions of the initial values of e.e., we also show logarithmic and linear plots of the evolution of e.e., which show quite clearly that, after a time of about 7–14 times the value of $1/a = 3$ yr (for $a = 10^{-8}$ s^{-1} quoted by Plasson *et al.*, 2004), full homochirality is achieved. This time depends only logarithmically on the initial e.e., so for

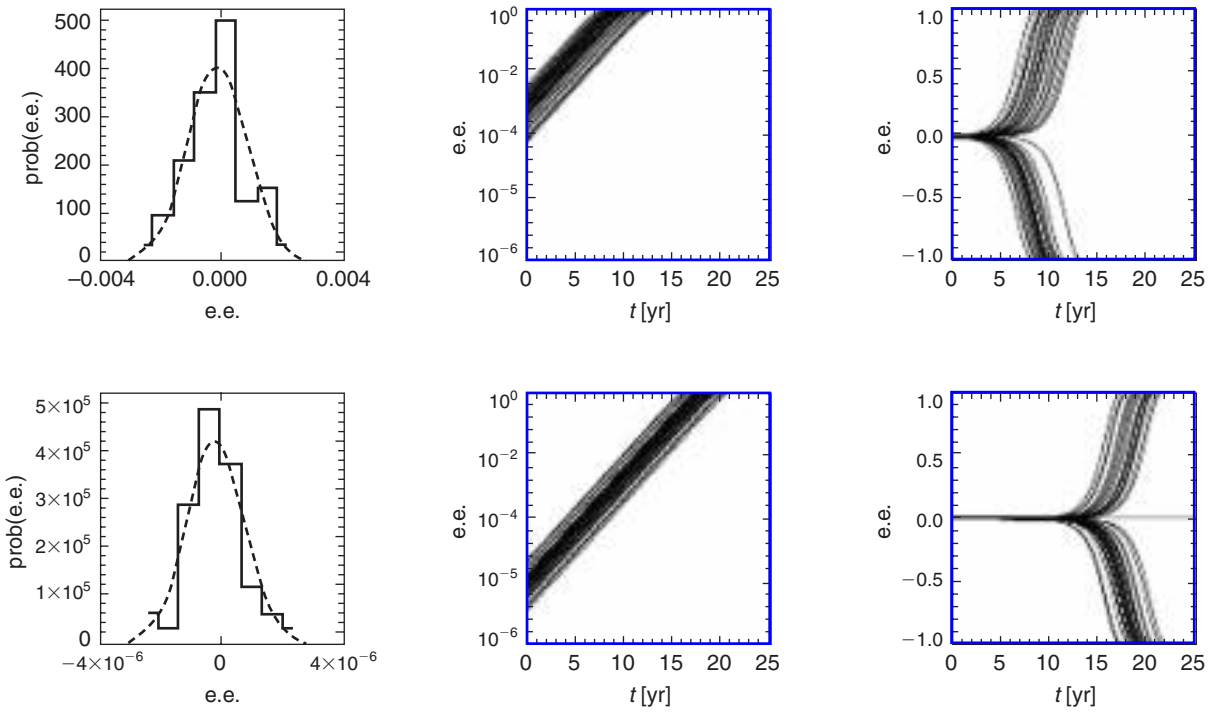

FIG. 7. Two examples of the probability distribution of the initial e.e. for racemic mixtures with 10^6 and 10^{12} molecules together with the resulting evolution of e.e., both in logarithmic and linear representations, using $a = 10^{-8}$ s^{-1}. The dashed lines give a gaussian fit to the distribution function.

e.e. = 10^{-3}–10^{-6} on has log (10^3–10^6) = 7–14 times the value of $1/a$.

FINAL REMARKS

It is not clear under which circumstances the circle of reactions described above could have operated. Is it a phenomenon that might have occurred naturally on the early Earth? This raises the question whether a similar auto-inductive set of reactions might also have worked on ribonucleotides. If so, homochirality may well have been an important condition that enabled the formation of sufficiently long ribonucleotide polymers and, indirectly, the emergence of life. The work of Plasson *et al*. (2004) could be interpreted as pointing in this direction. The other alternative would be that homochirality developed as a consequence of enantiomeric cross-inhibition combined with autocatalysis during a long "struggle" of short, self-replicating RNA molecules for dominance, as envisaged by Sandars (2003) in his model (see also Brandenburg *et al*., 2005). The difficulty here is that autocatalysis would be required, which may be difficult with short nucleic acids.

One can imagine a combination of an early peptide world that provided a homochiral environment along with a developing RNA world where sufficiently long isotactic autocatalytic molecules were synthesized. Although autocatalysis may not have been operational in prebiotic chemistry, the catalysis on clay surfaces remains an interesting and frequently discussed possibility (see, *e.g*., Schwartz, 1996; Yu *et al*., 2001; Cintas, 2002). Nevertheless, it seems likely that, if complete homochirality emerged as a result of spontaneous symmetry breaking of any kind, the crucial ingredients would still be self-amplification and competition, as was the case in the original model of Frank (1953).

ABBREVIATIONS

APED, activation, polymerization, epimerization, and depolymerization; *D*, right-handed monomer; *DD* and *LL*, homochiral dimers; *DL* and *LD*, heterochiral dimers; e.e. enantiomeric excess; *L*, left-handed monomer.

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