Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 11435–11442, October 1996
Chemistry

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected on April 25, 1995.

Mirror symmetry breaking at the molecular level

(prebiotic chemistry/molecular evolution/homochirality/enantioselectivity/origin of life)

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ABSTRACT **Reasoning from two basic principles of molecular physics, $\hat{P}$ invariance of electromagnetic interaction and the second law of thermodynamics, one would conclude that mirror symmetry is retained in the world of chiral molecules. This inference is fully consistent with what is observed in inorganic nature. However, in the bioorganic world, the reverse is true. Mirror symmetry there is definitely broken. Is it possible to account for this phenomenon without going beyond conventional concepts of the kinetics of enantioselective processes? This study is an attempt to survey all existing hypotheses concerning this phenomenon.**

Operation of mirror reflection, or space inversion $\hat{P}$, enables one to classify any molecular structure under either of two groups. One group involves molecules having neither symmetry planes nor symmetry centers, i.e., noninvariant with respect to $\hat{P}$. These molecules occur in the form of two mirror antipodes (L and D enantiomers), possess optical activity, and are called chiral (from the Greek word $\chi\varepsilon\iota\rho$, meaning hand). Among members of the other group are achiral molecules having either symmetry planes or symmetry centers. These molecules are invariant with respect to $\hat{P}$ and are optically inactive.

The main characteristic of the chemistry of chiral compounds is associated with $\hat{P}$ invariance of electromagnetic interaction. This type of interaction as a rule dominates coupling of intramolecular electrons and nuclei, and therefore, the states of a chiral molecule are described by a symmetric double-well potential with minima corresponding to the L and D configurations (1).

In compounds with an asymmetry center, e.g., with a carbon atom bonded to four different substituents, the characteristic time of tunneling between L and D is much greater than that of elementary chemical reactions initiated, e.g., by thermal excitation at room temperature. Therefore, the L and D configurations can be regarded as quasistationary states of a chiral molecule on ordinary chemical time scales. The enantiomers have the same ground-state energies and, hence, the same reactivities. This is the most representative feature of the chemistry of chiral compounds, which stems from the symmetry properties of electromagnetic interaction.

Another important peculiarity is thermally initiated over-barrier transitions between the states of enantiomers (thermally induced racemization which even in the absence of other processes leading to cleavage and formation of bonds results in the formation of a thermodynamically equilibrium, racemic state, i.e., the state corresponds to the equal amounts of the L and D enantiomers).

This assumption is in line with what is observed in nonliving nature. Spontaneous synthesis of chiral compounds during volcanic eruptions, under extraterrestrial conditions, and in experiments modeling primeval stages of Earth's evolution yields racemic mixtures (2, 3).

However, in living nature, the situation changes dramatically. Broken mirror symmetry of bioorganic objects was first noticed by Louis Pasteur and led him to the conclusion that the molecular substrate of life was not only chiral but also asymmetric (4).

What can be said about it now that relatively simple organisms have been studied in so much detail that apparently the only question that remains unanswered is how all these organisms could arise?

It is common knowledge that polymer constituents of the double-stranded DNA structure may involve millions of nucleotide links, that similar RNA chains incorporate hundreds and even thousands of nucleotide monomers, and that polymer chains of enzymes usually consist of several hundred amino acid links. DNA and enzymes play essentially different roles; DNA macromolecules are informational carriers, whereas macromolecules of enzymes are functional carriers. RNA plays a part of an intermediary between DNA and enzymes and occasionally takes on the duties of either of the sides (5, 6).

However, from the "chiral" viewpoint, all these biopolymers feature a remarkable trait, namely, nucleotide links of RNA and DNA incorporate exclusively D-ribose and D-deoxyribose, respectively, whereas enzymes involve solely L enantiomers of amino acids. In other words, the primary structures of DNA, RNA, and enzymes are homochiral. This property is inherent in all informational and functional biocarriers without exception.

Control exerted over enantiomers in the course of biosynthesis of RNA, DNA, and enzymes is so exact that for every 10^6 to 10^8 DNA links, there is less than one failure. The strict control would be impossible without certain enzymes that, whenever necessary, accomplish enantioselective functions. It is these enzymes that (*i*) recognize enantiomers of a chiral substrate, as in Pasteur's experiments on growing bacteria in racemic nourishing media, and (*ii*) exercise control over enantiomers of chiral compounds immediately in the course of their biosynthesis.

Thus, there are two main aspects of chiral specificity of the bioorganic world. The first structural aspect is homochirality of informational and functional carriers playing the key role in biological replication, and the second functional aspect is enantioselectivity of functions responsible for replication of homochiral macromolecules.

Problems

Chirality of the bioorganic world is usually perceived as breaking of mirror symmetry on the molecular level, revealing itself first by the existence of the "chirality sign" and lack of any traces of "mirror antipode" of life (7–9). This poses another question, namely, where should we look for the source of

Abbreviations: AF, advantage factor; FR, factor of racemization.

symmetry breaking: in the chemical, prebiotic, or biological stages of evolution?

We place the accent on another problem, namely, on the origin of homochiral macromolecules whose complexity is commensurate with that of informational and functional carriers in the bioorganic world. The answer to this question will clarify to some extent, if not completely, the cause of breaking of mirror symmetry of the biosphere as a whole.

Complexity of Homochiral Structures. Consider macromolecular chains of N links, formed by L and D monomers. Number M of all possible sequences of L and D links equals 2^N and grows exponentially with N. M becomes commensurate with the characteristic span of fluctuations of the number of particles ($\approx 10^{-12}$) in laboratory conditions at $N \approx 40$. This implies that whenever N does not exceed a couple of dozens, the experimental conditions can be so chosen that the produced polymer chains will involve the full spectrum of possible sequences of links, including homochiral.

Homochiral macromolecules of this length will be called the structures of the chemical level of complexity. The question of their origin is not particularly intricate, because, provided that the chemical mechanism by which links are assembled is preset, the probability of any sequence of links is finite, even if links are chosen arbitrarily. In other words, formation of homochiral structures of the chemical level of complexity requires no enantioselective functions.

However, for chains of 150 monomer units or so, statistical constraints are rather severe. Indeed, when M is compared with an "astronomical" value, e.g., to the number of bioorganic molecules on the Earth ($\approx 10^{40}$), it is easy to notice that M becomes of the order of this value at $N \approx 130$. This implies that any existing sequence involving 150 links or more is "unique," simply because the universe is too small to accommodate all these sequences, and most of them do not exist at all. On this level of macromolecular complexity, which we call biological (or biochemical) because it is typical for enzymes, RNA, and DNA, the relative number of practicable information sequences is always very small, whatever the physical or chemical conditions may be.

How do specific sequences arise in this case?

An idea of certain important aspects of the evolution of complex information carriers can be gained from the well-known theory of molecular quasispecies (10).

Let there be an array of functions capable of replicating sequences I_i ($i = 1, 2, \ldots, 2^N$) encoded as strings of two letters. Each sequence I_i is replicated with some probability $\Omega_{ii} = p^N$, where p is the relative probability of replication of an individual link. For simplicity, p is assumed to be independent of the link type (letter) and its ordinal number in the sequence.

Replication of sequences I_i may be accompanied by generation of mutant sequences I_k. Their probability equals $\Omega_{ik} \approx q^{d(i,k)}\, p^{N-d(i,k)}$, where $q = (1 - p)$ is the probability of mutation at a single stage of chain assembly, and $d(i, k)$ is the so-called Hamming distance (11), signifying the minimum number of consecutive mutations required to pass from I_i to I_k.

If sequences are copied exactly ($p = 1$), the stationary distribution of probabilities established by selection will be a unique (main) sequence I_0 with the maximum reproducibility. As the precision of copying (p) reduces, the concentration of main sequence I_0 decreases, whereas mutant sequences, on the contrary, increase in number, first by sequences differing from the main one by one mutation, then by two mutations and so forth. When copying precision is comparatively high, i.e., when $q = (1 - p)$ is small and mutations "hop" through short Hamming distances, the stationary distribution has a shape of a peak of a finite width describing the spread of mutant sequences around the main sequence; as the precision reduces, the distribution broadens and shifts to the most probable mutants. Coincident with broadening, mutation hops through long Hamming distances become much more probable because of the exponential growth of the number of ways these hops can be realized. As a consequence, starting from some level of inaccuracy of copying q_c (error barrier), replicative functions will mostly produce mutant copies, and the stationary distribution will become uniform.

Selection of sequences is possible whenever the precision of replicative functions exceeds some threshold value $p_c = (1 - q_c)$ that depends on the length of copied chains,

$$p_c = 1 - \alpha N^{-1}, \qquad [1]$$

where $\alpha \approx 1$. Otherwise, an "errors catastrophe" (10) occurs. To explain the physical meaning of the condition shown in Eq. **1**, it is sufficient to note that as long as the statistics of errors in copying obeys the binomial distribution, the mean number of errors ($<m>$) in a copy of length N equals Nq, and the critical condition (Eq. **1**) simply implies that $<m> \approx 1$, i.e., that the mean number of errors in a copy should not exceed unity. This is the basic condition for evolution of sufficiently complex macromolecules.

Thus, evolution of information carriers of the biological level of complexity is possible only with the availability of some specific functions. Given the set of appropriate specific functions, molecular evolution of the Darwin type (by selection and mutations) may entail "takeover" of the organic medium by some specific sequences. It is noteworthy that condition **1** is essential even for comparatively short macromolecules involving a couple of scores links (e.g., with $N = 50$; ref. 10), i.e., for macromolecular objects of the prebiotic rather than biological stage of evolution.

However, apart from the above functional constraint, Darwinian evolution of macromolecules has the structural restriction.

Homochirality and Matrix Replication. Polymer chains of RNA and DNA are known to be matrices for assembling complementary replicas. This property of biological information carriers underlies replicative function, and any homochiral sequence of nucleotides A, T(U), G, and C is a matrix suitable for assembling a complementary replica from the same A, T(U), G, and C.

Is there a correlation between chirality of links of information carriers and the matrix mechanism of their replication? A qualitative answer was derived (12) from molecular models of two fragments of double-stranded structures [poly(A)·poly(T)] (Fig. 1 *A* and *B*). Both strands of one fragment (Fig. 1*A*) comprise links of the same chirality sign, and each strand serves as a matrix for its complementary replica. In the other fragment (Fig. 1*B*), one strand [poly(A)], like its counterpart in the first fragment, is homochiral; however, the other strand [poly(T)] with a complementary composition involves the so-called "chiral defect," link T differing from the other T links of this chain by its chirality. It turned out that the nitrogenous base of such a mirror antipode incorporated into the poly(T) chain will be at an angle of almost 100° with its normal position suitable for complementary coupling. The result is that the nitrogeneous base of a chiral defect cannot couple with the nitrogen base of the appropriate link of the "perfect" chain without rupture of chemical bonds connecting the chiral defect with the neighboring links. Although the fact that complementary coupling between a chiral defect of the replica and a normal link of the homochiral matrix is impossible,† it is undoubtedly essential; the most important inference stemming from the model (see Fig. 1*B*) is that the replica completely loses the matrix profile in the vicinity of the chiral defect.

The same conclusion follows from the results of *in situ* experiments on abiogenic (enzyme-free) matrix oligomerization of nucleotides (13). The synthesized homochiral matrix chains of nucleotides poly(G) were placed in a solution of nucleotide C, which, in one case, was chirally pure (containing

†The same result is gained by mutations, i.e., by insertion of a homochiral yet noncomplementary partner (e.g., by placing A opposite to A, or T opposite to T).

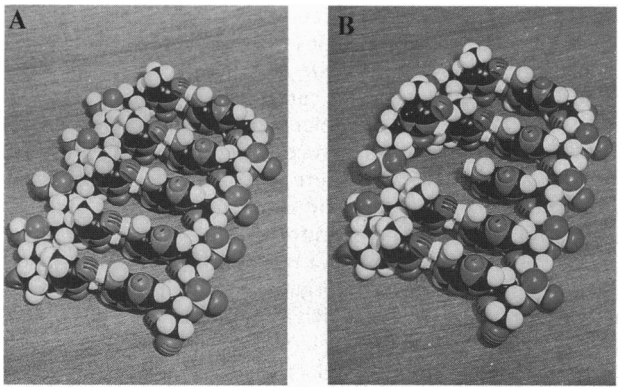

FIG. 1. (*A*) Double-stranded matrix–replica structure for homochiral chains complementing each other [poly(A)·poly(T)]. (*B*) Double-stranded structure with a chiral defect in a poly(T) chain.

enantiomer C in the same configuration as that in the matrix chain) and, in the other case, racemic.

Oligomerization of nucleotides from a chirally pure solution yielded homochiral replicas of poly(C) involving approximately 20 links. However, in a racemic solution, the replica was of the same length as that produced by spontaneous matrixless oligomerization and involved just a few links. An analysis of the distributions obtained in ref. 13 has revealed that in a racemic solution, matrix oligomerization of nucleotides is terminated by the first defect nucleotide whose nitrogeneous base forms hydrogen bridges with a complementary base of the appropriate link of the matrix chain (13, 14).

To a certain extent, this situation is the opposite of that with the molecular models. In the latter case, one of the chains was *a priori* assumed to have a chiral defect with the result that a double-stranded structure (an analog of matrix oligomerization) could not be produced without cleavage of bonds along the defect chain. In the former case, the chiral defect first couples to the appropriate link of the matrix chain; however, its subsequent binding with the neighboring links of the replica chain is impossible for the aforesaid reason.

Thus, in the vicinity of a chiral defect, an informational carrier loses its main property, namely, its ability to be the matrix for a complementary replica. That is where the most outstanding distinction between chiral defects and mutations lies. Mutations, when they appear, also upset the complementary correspondence between the links of the matrix and its replica; however, the mutant replica retains its matrix properties in that it can serve as a matrix for producing its duplicate sequences.

Are the matrix chains necessarily homochiral? Generally, the answer is no. It is not altogether difficult to envision a macromolecular chain with the matrix topography governed by the sequence of alternating L and D units (15, 16). However, in this case too, a chiral defect (i.e., a disturbed sequence of enantiomers) would lead to a similar result, namely, to a loss of matrix properties in the vicinity of a chiral defect. Genetic information is recorded and read by the matrix mechanism irrespective of whether the matrix sequence is homochiral or heterochiral. It is only essential that a sequence of enantiomers be ordered rather than random.

Thus, biological information carriers cannot evolve without specific (with respect to chirality) macromolecular structures and specific (enantioselective) functions assembling these structures.

Complexity of Enantioselective Functions. How does enantioselectivity of the replicating function vary with complexity of homochiral carriers?

Let q be the relative probability of chiral defect arising at an individual stage of chain-link assembly. We denote the parameter allowing for enantioselectivity of the function responsible for the assembly of a homochiral chain by $\gamma = (1 - 2q)$. Assuming that all kinetic parameters of homochiral-chain assembly, having the meaning of rate constants, are proportional to the Arrhenius factor, we obtain $\gamma = \text{th}(\Delta E/2kT)$, where $\Delta E = (E_1 - E_2)$ is the chiral discrimination energy of the enantioselective function performing chain-link fitting, and E_1 and E_2 are the activation barriers for inclusion of a link of erroneous and correct chirality into the chain.

Starting with macromolecules of the prebiotic level of complexity, involving $N \approx 50 \div 150$ units, the average number of chiral defects should not outnumber unity; otherwise, the probability of homochiral-chain formation will be infinitesimal because of the error catastrophe. From Eq. **1**, we obtain

$$\gamma > 1 - 2\alpha N^{-1}, \qquad [2]$$

where $\alpha \approx 1$, i.e., a homochiral chain of N links will be successfully assembled without any error catastrophe, if the energy of chiral discrimination (ΔE) of the replicating function exceeds some threshold value $\Delta E_{\min}$ (Fig. 2).

Functions responsible for generation and evolution of homochiral structures of the chemical level of complexity have no intriguing peculiarities ($\Delta E_{\min} < kT$). Moreover, as noted above, evolution of short homochiral chains is possible even in the absence of enantioselective functions.

In contrast, on the biological level of complexity ($N > 150$), severe limitations are imposed on $\Delta E_{\min}$; the discrimination energy must be well above kT ($\Delta E \approx 6 \div 8kT$). This requirement is met only in a dense medium around interacting molecular fragments, where their mobility is reduced considerably (17–20). Therefore, macromolecular carriers of functions of the biological level of complexity should first be capable of ensuring a rigid and reproducible orientation of interacting molecular fragments during transfer of charge, atoms, or atomic groupings in an elementary event of chemical conversion.

The above properties are inherent in polymer globules. Therefore, in the world of relatively complex macromolecules, complexity of functional carriers does not contravene with requirements on selectivity of their functions. Furthermore, as N ranges from hundreds to millions of links, the threshold discrimination energy changes but slightly, so that physical properties of macromolecular structures, governing the type of functional carriers, remain essentially invariant over the entire biological range of complexity of information carriers. Provided that some class of functionally active structures possesses high functional adaptability, it can sustain evolution of information carriers whose length ranges from thousands of links (RNA-like) to tens of millions of units (DNA-like).

Truly sophisticated constraints arise on the prebiotic level of complexity, i.e., at $N = 50 \div 150$ links. On the one hand, the discrimination energy of enantioselective functions must be well above kT, and hence, macromolecular carriers of these functions, as well as carriers of biochemical functions, should be "dense" and rigid structures. On the other hand, these structures should be able to enhance their enantioselectivity drastically even with an insignificant increase in complexity of information carriers, because the threshold discrimination energy ($\Delta E_{\min}$) increases dramatically with the rise of N.

Polynucleotide matrices, such as RNA, which are now given much attention (21–25) presumably comply with the above requirements. They are amenable to complementary matrix replication and, therefore, undergo natural selection and may, like enzymes, evince specific activity. And, finally, RNA comprises two strands with coupled complementary fragments; in relatively short sequences of nucleotides involving $50 \div 150$ links, stability of complementary fragments heavily depends on the chain length (26).

It is, however, important to emphasize that all properties of polynucleotide matrices, so attractive from the prebiological viewpoint, are inherent only in homochiral chains, because only these chains possess matrix properties, and the major issue is to elicit the origin of homochiral macromolecules.

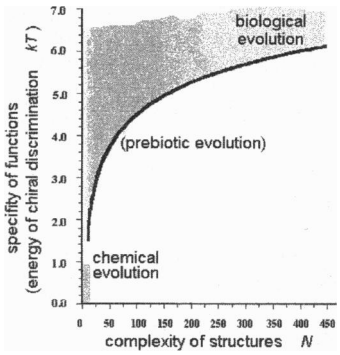

FIG. 2. Limitations on the energy of chiral discrimination of enantioselective functions. The shaded region corresponds to assembly of homochiral sequences of length N.

Scenarios

Presently, there are two dramatically different approaches accounting for the advent of homochiral macromolecules. One approach is based on the assumption that the first to arise in an original racemic organic medium were functional carriers insensitive to chirality, which ensured evolution of complex macromolecules. However, further in evolution of this initially "achiral biosphere," informational and functional carriers, promoted by some unknown factor, underwent radical changes to form a new class of homochiral structures, which had conquered all accessible organic area (27, 28). In other words, this model treats chiral specificity of the bioorganic medium as a consequence of evolution of structures and functions of the biological level of complexity.

The second approach is the reverse of the first approach. Its underlying assumption is that mirror symmetry of the organic medium was somehow broken already in the stage of chemical evolution, and certain homochiral structures formed as a result of polymeric takeover of such asymmetric medium, and afterwards they gave rise to informational and functional carriers of the biochemical level of complexity (14, 28–34). In other words, chiral specificity of the bioorganic world develops as a result of mirror symmetry breaking in the course of evolution of structural and functional carriers at the chemical level of complexity.

Regardless of the way by which structural and functional carriers acquired chiral specificity, evolution of complex homochiral macromolecules could take place only under certain conditions. One of these conditions stems from constraints imposed to avoid the error catastrophe.

Two Hypotheses: Specificity of Functions or Specificity of a Medium? Consider the process of assembling chains in the asymmetric surroundings, i.e., in a medium with chiral polarization $\eta = (x_L - x_D)/(x_L + x_D)$ (here, x_L and x_D are the concentrations of enantiomers). In this case, relative probability q of a chiral defect per chain-assembly step depends not only on enantioselectivity γ of the chain-growth mechanism but also on chiral polarization of the medium η. Then the condition (Eq. **1**) required to avoid the error catastrophe, acquires the following form:

$$\eta > 1 - \frac{\alpha'(1+\gamma)}{N(1-\gamma)}, \qquad [3]$$

where $\alpha' \approx 1$ (33).

This simple inequality gives an idea of how the properties of the medium η and the enantioselectivity of functions γ should vary to sustain continuous complication (rise of N) of macromolecules in the course of their evolution. The values of η and γ at which the number of chiral defects does not exceed unity closely approximate $\eta = 1$ and $\gamma = 1$ in the range with the characteristic width of N^{-1}. The result is obvious, because η and γ are the two independent parameters similarly affecting the probability of chiral defect generation. Note that for macromolecules of the prebiotic level of complexity ($N \approx 50 \div 150$), this range is already quite narrow.

Thus, to preclude the error catastrophe during assembly of complex homochiral macromolecules, no matter at what stage (prebiotic or biological) this process occurs, it is necessary that either the organic medium where macromolecular carriers are generated be chirally pure or the functions that assemble homochiral structures be enantiospecific.

In compliance with the above two approaches to the genesis of chiral specificity of the bioorganic world, there are only two routes of evolution (Fig. 3) which fit the condition shown in Eq. **3**.

Scenario of Evolutional Selection. Evolution in a racemic medium pursues route 1 (see Fig. 3); specific functions of the biochemical level of complexity arising in the course of evolution precede homochiral carriers of these functions. Assuming that this hypothesis is true, we have to find at least one chirally nonspecific type of macromolecular carriers that, like enzymes, can perform specific functions. By analogy with RNA, it is safe to assume that the sought-for type is exemplified by the world of achiral matrix structures. On the chemical level of complexity, such structures do exist (35–37). However, the narrowest "bottleneck" here is not chemical constructions but the lack of the least idea as to which "evolution coordinate" should be chosen to avoid the error catastrophe on the prebiotic level.

No less important is the question how the "great mutations" that changed the mechanisms of recording, reading, and translation of genetic information could occur in the course of evolution of a hypothetical achiral biosphere. Note that the doctrine of molecular evolution by natural selection fails to account for such events, and while these questions remain unanswered, the evolutionary theory of chiral specificity of the bioorganic world will remain an ad hoc hypothesis.

Scenario of Asymmetric Origination. From inequality (3), it becomes clear what factors can favor the asymmetric path of the appearance of homochiral carriers (Fig. 3, route 2).

First, the medium formed at the stage preceding the stage of polymeric takeover should be not simply asymmetric but also chirally pure, for which purpose natural mechanisms of strong violation of mirror symmetry of geochemical or cosmochemical areas are required.

Second, the medium should remain chirally pure not only at the stage of polymeric takeover and formation of homochiral macromolecules but also while certain homochiral macromolecules develop into informational and functional carriers (e.g., enzymes and RNA-like carriers) and later during their evolution, up to the point of initiation of enantiospecific functions sustaining replication of homochiral structures. It is not until these functions come into play that the need for a chirally pure medium is eliminated.

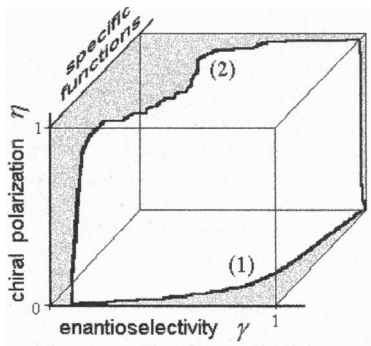

FIG. 3. Two types of evolutionary trajectories: trajectories corresponding to the hypothesis of natural selection [(1)], and trajectories corresponding to the hypothesis of asymmetric conception [(2)].

To sum up, all stages of molecular evolution, from polymeric takeover of the organic medium to origination of informational and functional carriers of the biochemical level of complexity, should occur under conditions of chiral purity. Therefore, the second important point is stability of mechanisms of mirror symmetry breaking to evolutionary processes leading to the appearance of enantiospecific functions.

Asymmetric Factor or Spontaneous Breaking of Symmetry?

Consider the simplest model of an organic medium involving two subsystems, Q, in which some achiral substrate produces the L and D monomers, and P, in which polymer chains are assembled (Fig. 4) (33). The systems communicate by transport of enantiomers from Q into P, and this process is defined by its enantioselectivity γ and intensity $K_P = \tau_0\tau_p^{-1}$ (the ratio of characteristic time τ_0 of chemical conversions in Q to characteristic time τ_p of assembling of macromolecules in subsystem P). Variation of γ and K_p from $(\gamma, K_p) \ll 1$ to $(\gamma, K_p) \approx 1$ corresponds to formation of enantioselective functions of the biochemical level of complexity in the prebiotic stage of evolution.

Breaking of Symmetry on the "Thermodynamic Branch." Let the processes that occur in the course of chemical evolution ($K_p = 0$), and yield chiral products, hold subsystem Q on the thermodynamic branch, i.e., in the absence of asymmetric impacts, subsystem Q tends to a racemic state with characteristic relaxation time τ. Dimensionless parameter $K_r = \tau_0\tau_r^{-1}$ is a measure of the racemization factor (RF) (32).

In this case, the asymmetric state of Q may arise solely under some chiral (asymmetric) field. The field strength is measured by the advantage factor (AF) (32), $g = |(k_i^L - k_i^D)/(k_i^L + k_i^D)|$, where k_i^L and k_i^D are the rate constants for mirror-conjugated channels of the reaction in Q that is susceptible to asymmetric impact. Note that $\tau_0 \approx (k_i^L + k_i^D)^{-1}$.

Regardless of the type of chemical reactions dominating relaxation to thermodynamic equilibrium (to a racemic state) under conditions of chiral field-off (no AF), the chiral polarization of the states of Q exposed to AF can, as demonstrated in (32), be estimated by the solutions of a simple equation

$$-K_r\eta + g(1 - \eta^2) = 0. \quad [4]$$

Therefore, the chiral polarization on the thermodynamic branch depends on the AF-to-RF ratio. Strong violation of mirror symmetry ($\eta \approx 1$) can appear even at small AF ($g \ll 1$), provided that $(g/K_r) \gg 1$.

Enantioselective ability is inherent in various naturally occurring chiral objects, e.g., circularly polarized light ($g \approx 10^{-2}$) or surface of minerals with a chiral structure (e.g., in quartz, $g \approx 10^{-2} \div 10^{-4}$). Many asymmetric factors, sometimes even exotic, like those induced by $\hat{P}$ noninvariant weak interaction ($g \approx 10^{-12} \div 10^{-17}$), have been invoked to account for the assumed asymmetric generation of homochiral carriers. We are not going to discuss here which factor is the most significant, because these factors were thoroughly reviewed in ref. 38. We just assume that a chirally pure medium, formed in some geo- or cosmochemical area exposed to a physical chiral field, is ready for its polymeric takeover. Polymers conquering this medium form an asymmetric polymer world (subsystem P) in which homochiral macromolecules involve monomers of a certain chirality sign. Whenever evolution of such a polymer world pursues the route leading to enantiospecific functions, the stationary states of Q are governed by the equation

$$-K_r\eta + (g - K_p\gamma)(1 - \eta^2) = 0, \quad [5]$$

which implies that advantage factor g is now opposed by enantioselective pressure $K_p\gamma$, for which polymer subsystem P exerts on the monomer medium due to enantioselective (unsymmetrical) transfer of L and D monomers from Q to P.

For the Q state to be sustained chirally pure in the course of evolution of polymer subsystem P, the following simple inequality,

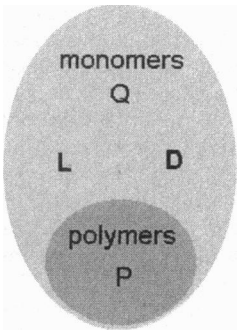

FIG. 4. The simplest model of an evolving prebiotic medium.

$$(g - K_p\gamma)/K_r \gg 1, \quad [6]$$

which depends not only on RF and AF but also on the enantioselective pressure, must be true. The condition shown in Eq. **6** may be met even early in the evolution, when $(g/K_r) \gg 1$ and enantioselective functions are lacking ($\gamma \ll 1$ and $K_p \ll 1$). Therefore, at $(g - K_p\gamma)/K_r \approx N$, homochiral chains formed by polymer evolution and distribution throughout the medium are relatively long ($\approx N$). However, further on, with the advent of enantiospecific functions ($K_p\gamma \to 1$), condition **6** breaks down, first because $g \ll 1$. The chirally pure state of the medium is maintained throughout the stage of enantioselective-function formation only at $g \approx 1$, i.e., it is maintained by the asymmetric factors whose enantioselective action is commensurate with that of functions of the biochemical level of complexity. However, such physical chiral factors are simply nonexistent.

This result suggests that if a chirally pure state does arise under chemically enhanced asymmetric impact in some geo- or cosmochemical area, it cannot persist for long; it fails at the subsequent stage with the advent of enantioselective functions. Hence, homochiral macromolecules cannot form on the thermodynamic branch of chemical evolution, mainly because of the error catastrophe which occurs as the monomer surroundings lose their chiral purity in going to structures of the biological level of complexity.

Nonequilibrium Systems. Far from thermodynamic equilibrium, symmetry of macroscopic states of chemical systems can be spontaneously broken (29–34, 38–40). Here, the case in point is the loss of stability of a symmetric (racemic) state and origination of steady asymmetric (chirally polarized) states. This breaking of symmetry is caused by nonlinear kinetics of chemical processes (which determines the type of staple attractors far from equilibrium), rather than by external asymmetric field.

For our purposes, it is necessary to deduce a general equation which, like Eq. **5**, models spontaneous breaking of symmetry in chemical systems irrespective of a specific way of its realization. Such an equation for ordering parameter η, allowing for symmetry of chiral system states, was derived in the framework of the bifurcation theory (29, 30, 38, 40) and has the form typical for the classical theory of phase transitions of the second kind

$$-\eta^3 + (1 - \rho)\eta = 0, \quad [7]$$

where $0 \le \rho < \infty$ is the controlling parameter which, in turn, depends on the kinetic parameters of chemical conversion in the system. At $\rho > 1$ (see Fig. 5*a*), there is only one steady state (racemic, $\eta = 0$). This range of ρ values corresponds to the thermodynamic branch of states. However, at $\rho < 1$, the dynamics of the system is governed by asymmetric attractors, mirror-conjugated steady states $\eta = \pm\sqrt{1-\rho}$. As soon as ρ goes below its critical value $\rho_{\bar{n}} = 1$, the racemic state becomes unsteady, and mirror symmetry is broken spontaneously (if the system is initially in the racemic state, either of the two antipodal asymmetric states is equally probable). As the controlling parameter (ρ) decreases, the chiral polarization grows, so that the states become almost chirally pure [$\eta \approx (1 - N^{-1})$, $N \gg 1$] at small $\rho \approx N^{-1}$.

Many schemes of conversion of L and D enantiomers exhibit this property. They, as a rule, model diverse autocatalytic processes (not only relevant chemical reactions but also physical processes, e.g., self-consistent interaction of coherent radiation with optically active molecules) (41–43). Formal rules of selection of the most reliable models to be used in devising theoretical models are reviewed in ref. 32. Important peculiarities of these processes will be discussed below. Here, we shall dwell on the possibility of justifying the hypothesis of asymmetric origin of the biosphere by the idea of spontaneous breaking of mirror symmetry.

Suppose that the kinetics of formation of some classes of chiral organic compounds is such that monomer subsystem Q determined for these classes is able to change steady attractors by the type of spontaneous symmetry breaking. Assume further that in the course of chemical evolution (in the absence of polymer subsystem P), controlling parameter ρ attains the value at which the system reaches the degree of chiral purity necessary for the formation of complex homochiral structures and the polymeric takeover of chirally pure medium leads to the origination of polymeric world able to acquire enantiospecific functions. Assuming that K_p and γ change in the course of P evolution much more slowly than in Q, it is easily shown that the bifurcation equation for the states of subsystem Q takes the form (33, 34)

$$-\eta^3 + (1 - \rho)\eta - K_p\gamma(1 - \eta^2) = 0. \qquad [8]$$

Here, as in Eq. **5**, enantioselective pressure ($K_p\gamma$), exerted by polymer subsystem P on the monomer surroundings, acts as an external chiral field applied to Q.

Now, the problem of evolution stability can be formulated as follows. Let, in the absence of enantiospecific functions ($\gamma \ll 1$, $K_p \ll 1$), (*i*) the controlling parameter become close to 0 ($\rho_{st} \approx N^{-1}$), (*ii*) the system acquire the requisite degree of chiral purity $\eta \approx (1 - N^{-1})$ (image point S in Fig. 5*a*), and (*iii*) the polymer subsystem P contain sufficiently long homochiral chains. As the enantioselective pressure increases ($K_p\gamma \to 1$), the critical value of the controlling parameter ρ_c, at which a branch of steady states of Q (involving image point S) arises, shifts to 0 (see Fig. 5*b*) until it becomes equal to the coordinate of point S, $\rho_c = \rho_{st}$. As this takes place, γ assumes some value γ_c. As γ increases further, S soon "gets off" the branch of steady states, and the monomer medium looses its chiral purity. The question that remains is whether the requisite enantioselectivity [$\gamma \approx (1 - N^{-1})$] of the functions assembling macromolecules in subsystem P will be attained before point S leaves the branch of stable states or not. The answer to this question is the approximate relationship $\gamma_c \approx (1 - N^{-1})$; subsystem Q remains chirally pure over the entire range of enantioselectivity, from $\gamma \ll 1$ to $\gamma \approx (1 - N^{-1})$. If a chirally pure medium arises by spontaneous breaking of mirror symmetry, this mechanism will sustain the medium chirally pure until its constituent macromolecules acquire enantiospecific functions of the biochemical level of complexity. Note that these functions, on the one hand, let the evolutionary processes progress independently of the state of the medium and, on the other, "erase" important information about an entangled sequence of evolutionary events culminated in their generation.

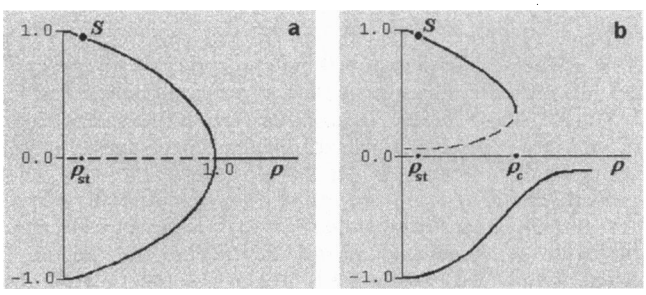

FIG. 5. Chiral polarization η of the stable states of monomer subsystem Q as a function of controlling parameter ρ in the chemical stage of evolution (*a*) and in the prebiotic stage of evolution (*b*). Image point S corresponds to the state of the medium as it is during the primary takeover of the medium by polymers.

Thus, spontaneous breaking of mirror symmetry is the only mechanism that is essentially consistent with the hypothesis of asymmetric genesis of the biosphere. It remains now to determine the processes mediating this scenario.

Mirror Symmetry Breaking Through Autocatalytic Processes

Autocatalytic processes underlying evolution at the biological stage seem to be of certain interest for the stage of prebiotic evolution. Without detracting from the fruitfulness of this hypothesis, we shall demonstrate the difficulties of its application to the problem of the origin of chiral specificity of the bioorganic world.

One difficulty is that incoherent autocatalytic processes do not violate symmetry. Indeed, let L and D be mirror antipodes capable of reproducing themselves,

$$A + \mathrm{L} \xrightarrow{k_1} \mathrm{L} + \mathrm{L},$$
$$A + \mathrm{D} \xrightarrow{k_1} \mathrm{D} + \mathrm{D}. \qquad [9]$$

To reveal the symmetry properties of the processes shown in Eq. **9**, it suffices to introduce variables η and $\theta = (x^{\mathrm{L}} + x^{\mathrm{D}})$, where x_{L} and x_{D} are the concentrations of the antipodes

$$\frac{d\eta}{dt} = 0,$$
$$\frac{d\theta}{dt} = k_1 c_A \theta. \qquad [10]$$

Here, c_A is the concentration of achiral substrate, and k_1 is the rate constant for appropriate conversion. Thus, the mean chiral polarization remains unchanged. By applying this result to evolution of quasispecies, it is easily demonstrated that natural selection occurring in each subclass of antipodal species leads to an array of mutants distributed somehow about the main species. However, chiral polarization of the population as a whole remains on average constant, i.e., equal to its initial value. This is the immediate result of the fact that mirroring does not alter the reproductive ability.

Is It Conceivable That a Symmetric Biosphere Exists? Coherent autocatalytic processes may violate mirror symmetry. This idea was first substantiated by Frank (39). One of his models involved two irreversible stages, namely, enantioselective autocatalysis by which achiral substrate A yields mirror antipodes L and D (Eq. **9**) and enantioselective conversion of L and D into catalytically inactive product B is as follows:

$$\mathrm{L} + \mathrm{L} \xrightarrow{k_{-1}} B,$$
$$\mathrm{D} + \mathrm{D} \xrightarrow{k_{-1}} B,$$
$$\mathrm{L} + \mathrm{D} \xrightarrow{k_{-2}} B. \qquad [11]$$

We supplement the above scheme with the following reactions:

$$\mathrm{L} \xrightarrow{k'_{-1}} B,$$
$$\mathrm{D} \xrightarrow{k'_{-1}} B,$$

allowing for the finite lifetime of L and D. With this insignificant supplement, the Frank model also describes evolution of the population of interacting mirror antipodes L and D,

$$\frac{dx_{\mathrm{L}}}{dt} = (k_1 c_A - k'_{-1})x_{\mathrm{L}} - k_{-1}(x_{\mathrm{L}} + x_{\mathrm{D}})x_{\mathrm{L}} - (k_{-2} - k_{-1})x_{\mathrm{L}}x_{\mathrm{D}},$$

$$\frac{dx_D}{dt} = (k_1 c_A - k'_{-1})x_D - k_{-1}(x_D + x_L)x_D - (k_{-2} - k_{-1})x_D x_L. \quad [12]$$

The first term in the right hand side of Eq. **12** allows for proliferation and spontaneous termination of the species, the second, for "demographic pressure" (for the effect of limited resources on the antipodes), and the third, for some sort of "annihilation" (mutual elimination of mirror antipodes destroyed, e.g., by toxic chiral metabolites produced by antipodes).

Eq. **12** has two types of stationary solutions, one corresponding to coexistence of mirror antipodes ($\eta = 0$), and the other, to completely asymmetric population ($\eta = \pm 1$), i.e., the existence of only one of two species. At $(k_{-2} - k_{-1}) < 0$, only one symmetric state $\eta = 0$ exists and is stable; however, at $(k_{-2} - k_{-1}) > 0$, both types of stationary states exist, and among these, only "chirally pure" states $\eta = \pm 1$ are stable (39).

Thus, had prebiotic evolution led to two branches of mirror antipodes, their symmetric coexistence would have been impossible because of biochemical incompatibility of the products of their metabolism.

We emphasize once again that the existence of the asymmetric biosphere, in contrast to the existence of homochiral biomacromolecules, is rather natural than paradoxical.

Chemical Autocatalysis. Let us go back to spontaneous breaking of mirror symmetry at the chemical stage of evolution, a process that underlies the hypothesis of asymmetric origination of life.

The Frank model leads to a true conclusion: that far from thermodynamic equilibrium, autocatalytic processes may destabilize the racemic state. However, chemically, this model is quite formal, because it does not involve any controlling parameter; at any $(k_{-2} - k_{-1}) > 0$, only chirally pure states $\eta = \pm 1$ are stable. This peculiarity of the Frank model is, as will be shown below, associated with absolute enantioselectivity of autocatalytic synthesis of mirror antipodes (Eq. **9**), which is typical for biological rather than for chemical processes.

It would be pertinent to note that the original Frank model has been repeatedly modified (44–50) to introduce the parameter controlling the passage through the critical point; in so doing, the authors of modified models were guided by their personal tastes rather than by general principles of enantioselective catalysis. It was commonly assumed that all parameters, including such "reservoir variables" as the concentration of achiral substrate and mixing rate, could be treated as controlling at least theoretically, and the main problem was to reveal which of them could be varied under different conditions.

Such assumptions may turn out to be essential in view of applying the idea of spontaneous breaking of symmetry to evolution. Indeed, in the previous section dealing with the scenario of asymmetric origination due to spontaneous breaking of symmetry, it was implicitly assumed that controlling parameter ρ could be varied independently of enantioselectivity of the processes defining the assemblage of macromolecular carriers.

Therefore, the question whether ρ and γ are independent variables invites special investigation.

Consider an autocatalytic stage, for which the complete scheme for the chemical processes is as follows:

$$A + \mathrm{L} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{L} + \mathrm{L}, A + \mathrm{L} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{D} + \mathrm{L},$$

$$A + \mathrm{D} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{D} + \mathrm{D}, A + \mathrm{D} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{L} + \mathrm{D}, \quad [13]$$

where k_i are the rate constants for appropriate bimolecular reactions. In contrast to the Frank model, this scheme meets two important requirements, namely, it accounts for two facts: (*i*) that enantioselectivity of any chiral catalyst is limited, so that catalytic effect of each enantiomer leads to formation of both L and D products, and (*ii*) that the kinetic link between mirror conjugate processes arises due to reversibility of the catalytic stage.

Note that Eq. **13** is, in essence, a generalization of the Frank model to catalytic reactions with an arbitrary enantioselectivity at $k_2 = 0$, i.e., in the case of perfectly enantioselective replication, Eq. **13** reduces to Eqs. **9** and **10**.

Assuming that concentration c_A is constant, all necessary information about Eq. **13** can be inferred immediately from solutions of the appropriate kinetic equations. However, for our purposes, it will suffice to specify the bifurcation equation that assumes the following form:

$$-\gamma_+\gamma_-\eta^3 + (\gamma_+ + \gamma_- - 1)\eta = 0, \quad [14]$$

where $\gamma_+ = (k_1 - k_2)/(k_1 + k_2)$ and $\gamma_- = (k_{-2} - k_{-1})/(k_{-2} + k_{-1})$ are the enantioselectivities of direct (+) and reverse (−) reactions. Thus, controlling parameter $\rho = (1 - \gamma_+)(1 - \gamma_-)/\gamma_+\gamma_-$ defined by Eq. **7** depends exclusively on enantioselectivity of catalytic conversions. Critical point $\rho_c = 1$, where the racemic state becomes unstable, is to be determined from simple relationship

$$\gamma_+ + \gamma_- = 1. \quad [15]$$

Note that a chirally pure state appears only when γ_+ (or γ_-) is close to unity. In particular, the state with chiral polarization $\eta \approx (1 - N^{-1})$ is attained at

$$\gamma_+ + \gamma_- > 1, \max\{\gamma_+, \gamma_-\} > (1 - 2N^{-1}). \quad [16]$$

Now we turn to estimating the role of nonselective stages modeled by plain scheme

$$A \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \mathrm{L},$$

$$A \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \mathrm{D} \quad [17]$$

Let us assume that the contribution of the reactions in Eq. **17** is imperceptible. Then critical point $\rho_c = 1$ is preset by the equation

$$(1 - K\delta_+)\gamma_+ + (1 - K\delta_-)\gamma_- = 1, \quad [18]$$

where $K = (k_{-1} + k_{-2})/(k_1 + k_2)$, $\delta_+ = k_3/(k_1 + k_2)c_A$, $\delta_- = k_{-3}/(k_{-1} + k_{-2})c_A$, and $K\delta_+, K\delta_- \ll 1$.

To elicit the physical meaning of the factors preceding γ_+ and γ_- in Eq. **18**, it is necessary to estimate the fraction of catalytic processes at critical point $\rho = \rho_c$. It is readily demonstrated by *in situ* calculations that $(1 - K\delta_+)$ is the fraction of enantioselective reactions in the synthesis, and $(1 - K\delta_-)$ is the fraction of enantioselective events of chiral product decomposition, and therefore, the factors in equation are nothing but "kinetic weights" of enantioselective reactions at the critical point. As the concentration of the achiral substrate c_A increases, the fraction of enantioselective (catalytic) events tends to unity, and therefore, Eq. **15** can be reckoned as the lower boundary of the enantioselectivity of catalytic stages at which critical point ρ_c is attained.

Is there any experimental evidence to support spontaneous symmetry breaking chemical processes? This problem was the subject of many discussions (51–56); however, it was not until recently that the first encouraging report about amplification of enantiomeric excess in an autocatalytic reaction appeared (57).

However, the main conclusion that stems from the conditions for spontaneous breaking of mirror symmetry is that chirally pure medium originates only at high enantioselectivity of catalytic processes. Moreover, the above estimates suggest that chiral purity required to produce homochiral structures of the biochemical level of complexity is attained whenever enantioselectivity of catalytic processes is commensurate with that of biochemical functions.

This inference leads to a basic inconsistency in the hypothesis of asymmetric formation of the biosphere, insofar as the idea of

spontaneous breaking of symmetry was invoked to justify the mechanism of formation of a chirally pure medium at the chemical stage of evolution, i.e., well before enantiospecific functions of the biochemical level of complexity developed.

Conclusion

We had no intent to illuminate every aspect of breaking of mirror symmetry on the molecular level; instead, we restricted ourselves to the problem associated with the origin of the phenomenon of mirror asymmetry of the bioorganic world, which seems to be most intriguing from the physical point of view. This paper is by no means another recurrent review of the multitude of attempts at solving this problem. These attempts were summarized in a number of recent reports (7, 32, 58). We felt it important to highlight severe discrepancies that have arisen.

This paper is concerned with two major topics. (*i*) Was symmetry disturbed in the chemical or in the biological stage of evolution? (*ii*) Was a chiral physical field or spontaneous breaking the cause of symmetry breaking?

First, when speaking of symmetry breaking in the bioorganic world, it should be remembered that this phenomenon manifests itself only at the populational level. Prime attention is commonly given to the choice of the most universal mechanism of asymmetric formation and accumulation of organic compounds under terrestrial or extraterrestrial conditions. However, the paramount question concerning the extent to which hypothetical peculiarities of chemical evolution predetermined origination of only one branch of biological organisms remains untouched.

Over the past century, many explanations for asymmetric accumulation of organic material have been proposed. The question of whether it is possible that the asymmetric synthesis of chiral compounds occurs in nature has already been settled. The answer is yes.

However, the answer to the above question entailed almost no progress in solving the problem concerning the breaking of mirror symmetry of the bioorganic world. This has to do with the lack of knowledge about interrelations between asymmetry of chemical processes involving simple organic molecules and chiral specificity of biological macromolecules.

The basic theoretical problem that arises therewith is evolution of informational structures and specific functions towards increasingly complex forms, and at present, not enough is known about the dynamics of such systems. Therefore, only some assertions can be made concerning the applicability of the hypothesis of the decisive role of mirror symmetry breaking at the chemical stage of evolution in the asymmetric origination of life.

The first inference concerning the above hypothesis is that chiral physical factors, irrespective of whether they are local or global and of conditions under which they reveal themselves, could not violate mirror symmetry of the bioorganic world to any noticeable extent. This is the result of the inability of these factors to sustain stable evolution of homochiral structures toward initiation of enantiospecific functions, mainly because of the growth of enantioselective pressure. Thus, if one turns to the second conventional question, the asymmetrical factor or spontaneous breaking of symmetry, the former should be excluded.

The second inference is that prebiotic evolution can occur as spontaneous breaking of symmetry. However, the most popular version of this scenario (14, 31–34, 59), according to which formation of a chirally pure medium at the chemical stage of evolution and subsequent polymeric takeover of this medium may set a stage for a transition to the prebiotic stage, needs further justification. The point is that, in the case of simple molecules, the requisite chiral purity of the medium is attained only if processes occurring in this medium are commensurate with biochemical functions in their enantioselectivities.

Spontaneous breaking of symmetry applies solely to evolution of the more complex molecules that play the key role in transition from chemical structures and functions to informational and functional carriers of biological level of complexity.

This research was supported, in particular, by grants from the International Science Foundation (M1W000 and M1W300) and the Russian Foundation for Basic Research (95-03-08838).

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