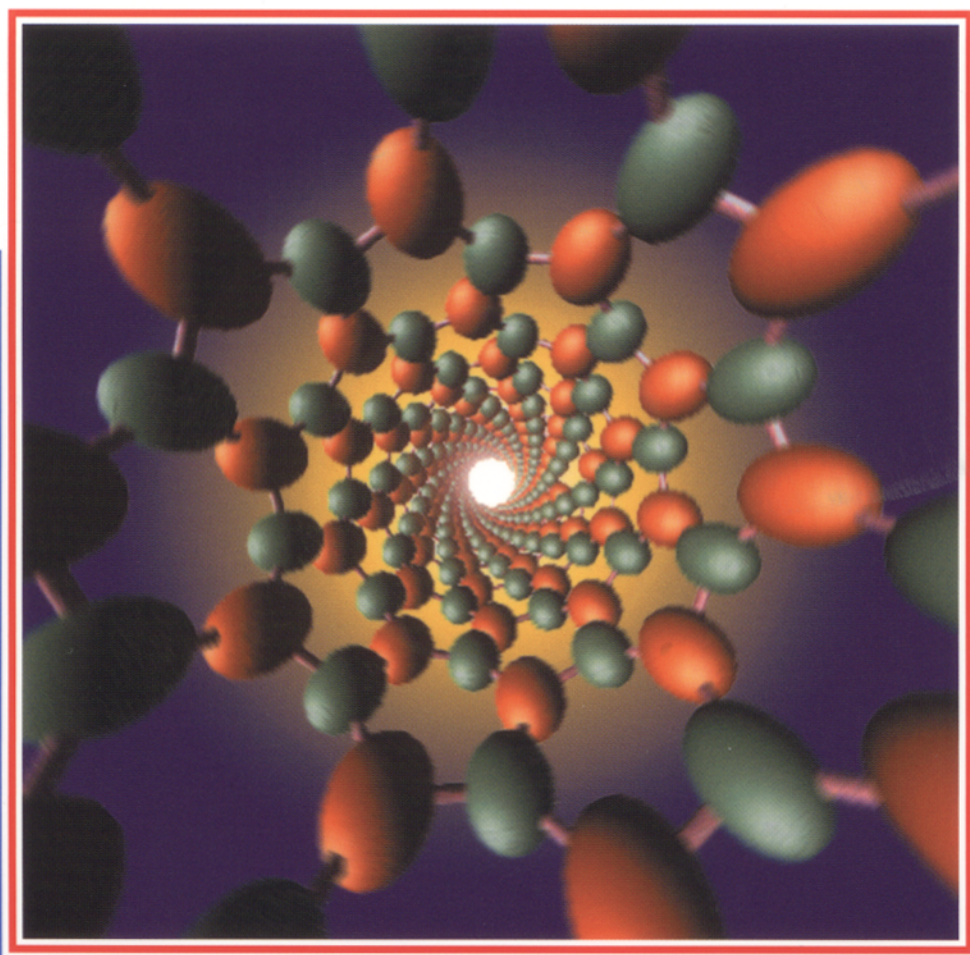


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11

On One Hand But Not The Other: The Challenge of the Origin and Survival of Homochirality in Prebiotic Chemistry

Patrick Frank, William A. Bonner, and Richard N. Zare

What are the facts of life? One of the most striking is that all known living systems involve the same types of polymers, i.e., three varieties of homochiral biopolymers. That is, each variety is composed of unique molecular building blocks having the same three-dimensional handedness. Thus, with rare exceptions, the proteins found in cells are composed exclusively of the l-enantiomers of 19 optically active amino acids (Fig. 11.1).^{*} Similarly, only D-ribose and 2-deoxy-D-ribose sugars are found in the nucleic acid polymers that make up the RNAs and DNAs, which are essential for protein synthesis in the cell and for the transmission of genetic information from one generation to the next.

What is the origin of biological chirality and how did it successfully propagate itself to dominance? The riddle is at once intriguing, central, and profound. It has been persuasively argued and is now widely accepted that homochirality of biopolymers is essential for the existence of life, and that life would be impossible in its absence. [4] Thus the solution to the riddle of terrestrial homochirality may well be intimately related to how life on Earth originated.

Was Nature's selection of these stereochemical structures a random event, or was it the consequence of determinate processes? Although the presence of amino acids and other organic molecules on primitive Earth has been attributed to both endogenous and exogenous sources, [5,6] the origin of the chiral bias of prebiotic molecules remains a fundamental mystery. A mystery perhaps even more central to the origin of life is the mechanism that brought into dominance and survival any putative small chiral molecular excess on early Earth.

* The prefixes D and L refer to absolute spatial configurations, which do not necessarily designate how plane polarized light is rotated or how circularly polarized light is preferentially absorbed. The latter are denoted by the prefixes d (dextrorotatory) and l (levorotatory). The observation that a chiral compound can be assigned to d or l can vary with wavelength and other factors. For example, at the sodium D line, eight of the naturally occurring

L-amino acids are d and ten are l at 25°C in water solution. At shorter wavelengths, near 200 nm, all nineteen L-amino acids absorb preferentially left-handed versus right-handed circularly polarized radiation. See: L. Fowden, P. M. Scopes, and R. N. Thomas, *J. Chem. Soc. (C)* 1971, 833-840; and L. I. Katzin and E. Gulyas, *J. Am. Chem. Soc.* 1968, 90, 247-251.

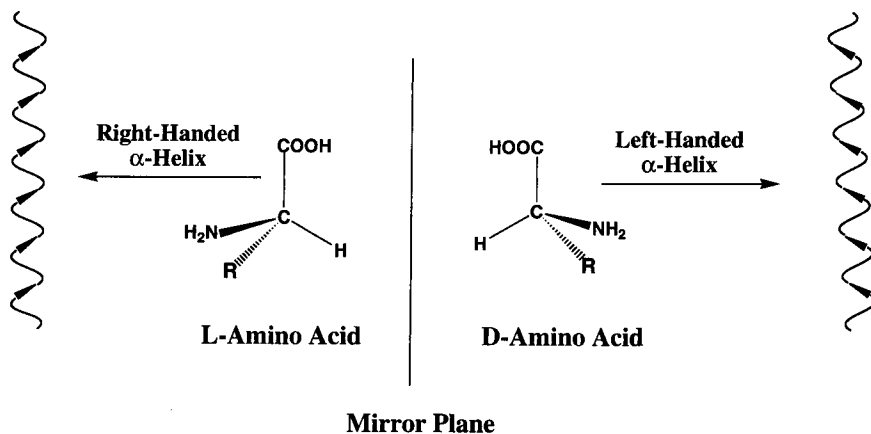


Fig. 11.1 Mirror-image relationship of the amino acids. All amino acids (except glycine) can exist in one of two mirror-symmetric forms, called enantiomers. Proteinogenic amino acids are almost exclusively the L-enantiomer. With some exceptions, biopolypeptides fold into right-handed α -helices. [1,2] In all cases,

polypeptides composed of D-amino acids fold into helices of opposing handedness. [3] The *bolded* and *hashed* bonds are above and below the plane of the drawing, respectively. "R" represents the pendant group that distinguishes one amino acid from another.

The traditional starting point for a solution to the mystery of terrestrial homochirality has been a search for factors capable of spontaneously breaking molecular symmetry, thus causing a stereochemical preference. One possibility is that Nature has a built-in preference for one handedness over another and that this preference is reflected in the homochirality of biopolymers. Indeed, we shall see that such an energetic preference does exist, although it is so small compared to the thermal energy of the ambient surroundings that its presence may not be determining. Another possibility is that some statistical fluctuation led to the preferential selection of one enantiomer over the other in a racemic system, that is, a system composed of equal amounts of left-handed and right-handed molecules. A third possibility is that prebiotic chemical systems have been exposed to some external set of conditions that have broken their chiral symmetry in such a manner as to favor particular stereochemical structures over their mirror images. Suggested examples [4] of such symmetry-breaking external conditions involve exposure to circularly polarized light of just one handedness, exposure to polarized β -radiation, or subjection to crossed force fields (electric and magnetic, or gravitational and rotational) of one origin or another. Once some form of primitive self-replicating chiral molecular system was established, its ability to reproduce itself and to metabolize its surroundings caused one type of handedness to become dominant over the other.

Almost 140 years ago Pasteur showed how a racemic mixture could be separated into its chiral constituents. Ever since, theories such as the three possibilities above have been proposed to explain an abiotic origin for molecular chirality in living systems. At the present time, however, no agreement exists about which explanation is best. In each of these scenarios, we can imagine production of some initial enantiomeric excess (e.e.).

One crucial question is not whether some small initial e.e. can be generated, but how such a small e.e. can be amplified so that one enantiomer eventually dominates completely over the other. The second crucial question is how a homochiral dominance, once established, can survive. These are the questions that challenge us in our search to explain the homochirality of terrestrial biopolymers.

In what follows we first review some of the mechanisms that have been proposed for establishing initial enantiomeric excesses in a racemic mixture of optically active stereoisomers. Next, we summarize experiments that have been performed to find ways in which such small enantiomeric excesses can become amplified to afford highly enantiomerically enriched yields. Then we discuss ways in which homochirality could have persisted in the challenging environment of early Earth. Finally, we synthesize several lines of evidence into a research outline directed toward developing a self-consistent theory for the origin and survival of homochirality, and thus of life. The end of the 20th century marks nearly 100 years since the first critical comments on the chemical origin of life were made by Chamberlin and Chamberlin. [7] It seems fitting, after the intense, brilliant, and optimistic work of so many people, that the end of the century that witnessed such work might see the emergence of a scientifically credible research outline. Such a research outline should promise all the elements of a viable, testable, and self-consistent theory for the origin of life.

11.1

Symmetry Breaking and Chiral Induction

Chiral molecules have a nonsuperposable mirror image (see Fig. 11.1) and so possess intrinsic handedness in three-dimensional space. In a perfectly symmetric, chirally unbiased world, each handed version (enantiomer) must exist with an equal probability. The observed preference of one enantiomer over the other in biomolecules implies that this symmetry has been broken. The initial induction of a symmetry-breaking chiral excess is the *sine qua non* of eventual chiral dominance. Several mechanisms have been proposed to bring about chiral symmetry breaking.

11.1.1

Is it Intrinsic?

More than forty years ago, Lee and Yang [8] observed anomalies in the decay patterns of theta and tau mesons, which suggested to them that parity was not conserved for certain weak interactions involved in the β -decay of radioactive nuclei. This Nobel-prize-winning prediction was experimentally validated by Wu et al., [9] who found that the longitudinally polarized electrons emitted during the β -decay of ^{60}Co nuclei had a notable (40%) left-handed bias, i.e., their spins were predominantly antiparallel to their directions of motion. These experiments established that parity violation and symmetry breaking occurred at the nuclear level.

In 1957 Vester and Ulbricht attempted to couple this parity violation on the nuclear level to events at the molecular level. Vester et al. [10,11] suggested that cir-

cularly polarized gamma rays produced when longitudinally polarized β -decay electrons impinge on matter might, in the presence of suitable organic substrates, engender stereoselective photochemical reactions, synthetic or degradative, that would lead to chiral products having an enantiomeric excess.

A more subtle aspect of this broken symmetry, however, is its effect on the energies of D- and L- enantiomers, which, previous to the work of Lee and Yang, were assumed to be energetically identical. In 1966 Yamagata [12] proposed what might be called the Yamagata PVED-induced chirality hypothesis. He argued that the D- and L-forms of chiral molecules would have slightly different energies and thus different probabilities for chemical reaction because of parity violation. Yamagata argued further that this parity violation energy difference (PVED) would account for the asymmetric appearance of biomolecules on Earth.

In 1974 Garay and Hrasko [13] contended that PVEDs between enantiomers would, in the course of millions of years of evolution, lead to almost complete selection of one isomer, and in 1975 Letokhov [14] asserted that PVED-generated rate differences as small as 10^{-16} would over 10^8 to 10^9 years be "quite sufficient for full selection of either of the two stereoisomeric forms of all the amino acids that occur in animate nature." In 1983 Kondepudi and Nelson [15] claimed that a value of $\Delta E/kT$ of 10^{-17} to 10^{-15} is "sufficient to have a strong chiral selectivity."

Building on an early theoretical scheme by Frank [16] (see below) for the spontaneous autocatalytic symmetry breaking in which enantiomers act as catalysts for their own production, Kondepudi and Nelson [17–20] further suggested a generalized scheme by which the minor excess of one enantiomer, caused by PVED, might lead to a state of enantiomeric homogeneity. They then calculated that a period as short as 15 000 years could cause chiral domination. [19] In 1989 MacDermott and Tranter [21] maintained that "this amplification time would be reduced from 10^4 years to just one year if the PVED were increased to $10^{-16} kT$ ", i.e., by a factor of only ten.

The traditional treatment of molecules relies upon a molecular Hamiltonian that is invariant under inversion of all particle coordinates through the center of mass. For such a molecular Hamiltonian, the energy levels possess a well-defined parity. Time-dependent states conserve their parity in time provided that the parity is well defined initially. Such states cannot be chiral. Nevertheless, chiral states can be defined as time-dependent states that change so slowly, owing to tunneling processes, that they are stationary on the time scale of normal chemical events. [22] The discovery of parity violation in weak nuclear interactions drastically changes this simple picture, [14, 23–28] For a recent review, see Bouchiat and Bouchiat. [29]

A proper treatment of molecular chirality must include parity-violating forces in the quantum chemistry calculations, even though the corresponding parity-violating molecular potentials are extremely small – on the order of $10^{-18\pm3}$ kJ/mol for molecules composed of light elements. Such forces may be neglected for almost all purposes except the treatment of chiral molecules. This computational task, however, is not readily carried out. Among the best calculations to date appears to be the recent work of Bakasov, Ha, and Quack, [30] who report that they are unable to calculate the energy difference at the stage of refinement they have reached, although their

calculations do show that the difference between the parity-violating potentials is more than an order of magnitude greater than previously estimated. Lazzeretti and coworkers [31, 32] have reached the same conclusion. Even so, Bakasov et al. find that the values of the PVEDs for sugars and amino acids are uncertain even as to their sign. Therefore, at the present level of theory, it is far from established that the energy differences of enantiomers arising from parity-violating weak nuclear forces can account for the homochirality of biopolymers. Recent highly precise PVED calculations comparing D- and L-alanine indicate the continued force of this conclusion. [30a]

11.1.2

Is it Fluctuational?

In 1981 Nicolis and Prigogine [33] considered the behavior of far-from-equilibrium racemic mixtures that can bifurcate randomly into a direction of an enantiomeric singularity on passing through a critical point. They showed that such systems are profoundly sensitive to environmental asymmetries that at the critical point can cause the system to adopt one handedness over the other.

Are examples of such systems to be found in nature? Indeed, crystallization of silica within cooling magma tubes exhibits just this behavior. Although silica is not chiral on the atomic scale, it can crystallize from a melt into one of two helical structures that are morphologically chiral. [34] The choice of which of the two crystallographic helices is expressed is purely a fluctuational episode producing a nucleation event within the cooling, saturated melt. Figure 11.2 shows an example of single crystals of left- and right-handed quartz.

The observed distribution of chirality among quartz crystals within the Earth is extremely close to 50:50, as would be expected from a randomly selected sample of



Fig. 11.2 Single crystals of morphologically enantiomeric quartz. Note the mirror symmetry of the facets on the respective crystals. Unlike amino acids, the component silicon dioxide molecules have no chirality. The spontaneous resolution of quartz into crystals of opposite morphological handedness is an example of local symmetry breaking in the environment.

limited size if terrestrial quartz had no net chiral excess. [35] For example, in the largest study to date (of 27 053 naturally occurring quartz crystals), 49.83% of these (13 481) were found to be left-handed, and 50.17% (13,572) were found to be right-handed. [36]

Spontaneous resolution seems to be a general phenomenon, because it is also observed to occur from solutions of achiral sodium chlorate, which crystallizes into morphologically chiral crystals. In the same way as quartz, however, any given spontaneous crystallization produces nearly equal numbers of left- and right-handed sodium chlorate crystals. The explanation for this behavior is that the primary crystallization nuclei that form throughout a cooling concentrated solution must occur with a random distribution of the two morphological chiralities.

In an interesting finding, however, Kondepudi, Kaufman, and Singh [37] reported that, when stirred, aqueous solutions of sodium chlorate would deposit crystals that were overwhelmingly of one chirality or the other. The rationale for this was that stirring dispersed the initial crystallization nucleus throughout the solution into a multitude of secondary crystallization nuclei. These secondary nuclei, of the same handedness as the primary nucleus, induced rapid and complete crystallization of the solute into a single chiral form. Although the chirality of the initial nucleus was randomly selected, the choice, once made, determined the chiral fate of the process. Recently, Kondepudi, Laudadio, and Asakura [38] have extended these findings to 1,1'-binaphthyl.

As found for quartz, however, such processes occurring across the Earth will necessarily sum to zero net chirality. That is, because the choice of nucleating chirality is random, the chirality of the crystals deposited from disturbed solutions is also random, and over a large number of such events, the outcomes must sum to equality.

In the organic regime, Niori et al. [39] observed that certain large self-associating molecules that in solution have a shape like a recurved bow can spontaneously assemble into macroscopic chiral regions of one handedness or the other. This work has recently been extended by Walba and coworkers, [40] who showed that similar molecules can form observable chiral domains despite the lack of any molecular chiral center. The chirality of the domains alternate in the fluid, and so there is no net chiral induction. Likewise, racemic mixtures of chiral amphiphiles dissolved in lipid monolayers can spontaneously segregate into D- and L-enriched regions. [41, 42] Similar behavior occurs in monolayers of racemic (R)(S)-2-bromohexadecanoic acid on graphite. The racemic monolayer was observed to spontaneously segregate into alternating chiral domains that were directly visualized using scanning tunneling microscopy. [43]

From these examples, it becomes clear that molecular symmetry can spontaneously break into chiral domains in the absence of any external force or seed. However, in every known case, the net symmetry remains intact, and the overall chirality sums to zero in the environment. Nevertheless, the spontaneous formation of macroscopic chiral regions in systems of associating achiral molecules is of interest to those who contemplate induction of molecular chirality in the context of prebiotic reaction chemistry.

11.1.3

Is it Extrinsic?

Other means exist to break symmetry than a way intrinsic to weak nuclear forces. For example, it is well known that chiral molecules are characterized by circular dichroism (CD), that is, left circularly polarized light (left CPL) and right circularly polarized light (right CPL) are not absorbed equally by the two enantiomers. Because of CD, CPL from an external source is able to engender asymmetric stereo-selection in the photodegradations, photochemical syntheses, or photochemically induced interconversions of chiral molecules, thereby leading to small e.e.s. Such processes and the theory behind them, which stem from the pioneering asymmetric photolyses reported by Kuhn and Braun [44] over 70 years ago, have been more recently reviewed in detail. [45]

On Earth, light from the sun can exhibit weak (ca. 0.2%) left circular polarization at sunrise and right circular polarization at sunset. Light scattering from atmospheric aerosols and particulates induce this polarization difference. These differences, as discussed by Bonner, [46] would sum to zero over a completely flat Earth. Where the terrain is tilted, however, a net circular polarization of light could result. Thus, photolysis of racemic terrestrial organics exposed on some eastward-facing slope could be invoked to rationalize the appearance of chirality on Earth. This explanation, although it cannot be ruled out, does seem to be a form of special pleading after the fact.

Because solar CPL is weak and variable, Rubenstein and coworkers [47] looked further afield and suggested that the discriminating CPL could have originated from the polarized synchrotron radiation of neutron stars. In this mechanism, further extended by Bonner and Rubenstein [48] and Greenberg, [49] irradiation of interstellar grain mantles by circularly polarized ultraviolet starlight would produce an enantiomeric excess in the organic materials of interstellar dust clouds. This handedness would reverse along with the hemispheric polarity of the CPL field across the ecliptic of the neutron star. Planets within solar systems newly formed by condensation of these irradiated dust clouds would then be seeded with molecules of one e.e. or the other by meteoric infalls of dust, comets, and carbonaceous chondrites. This process is thus envisioned to have provided the initial chiral impetus toward a general planetary chiral excess. Which chirality dominates life is, in this theory, a matter of happenstance.

11.2

Experimental Studies of Chiral Induction

Clearly what we need are verifying experimental demonstrations to help us select among the various mechanisms outlined above for the appearance of a small enantiomeric excess (e.e.) within a mixture of two enantiomers. Only after such an initiating event can an e.e. be amplified into the state of homochirality and enantiomeric purity necessary to permit the emergence of self-replicating biopolymers. In what

follows we review briefly a number of experimental systems that have focused on abiotic e.e. induction. We consider both their generality and their inherent plausibility in the light of what we know about early Earth.

11.2.1

Intrinsic Mechanisms

The hypothesis that polarized β -emission could induce a chiral excess in racemic mixtures was tested experimentally by its originators in the presence of several β -emitting nuclides, [10, 11] but no polarimetric evidence was found for an enantiomeric excess of chiral products. Nevertheless, this work provided the impetus for numerous other investigations, which have been recently reviewed elsewhere. [50] There is some experimental evidence demonstrating that a preferred molecular chirality results from spin-polarized subatomic particles through induced chemical transformations. Tokay et al. [51] reported that after a year of autoradiolysis the β -decay of solid racemic mixtures of ^{14}C -enriched D,L-leucine exhibited an excess of the L-isomer. This result was suggested to indicate preferential decarboxylation of the D-isomer due to the polarization of the emitted β -particle. A more recent report suggests that spin-polarized radiation can influence the outcome of the crystallization of aqueous sodium chlorate. [52] In the described experiments, β -radiation produced an excess of NaClO_3 crystals exhibiting clockwise rotation, whereas excess crystals of opposite habit were produced using positrons. These results could indicate an alternative route to the appearance of a chiral excess on early Earth, that is, β^\pm -induced phase transformations.

Despite the theoretical difficulties outlined above, some small PVED between enantiomers does exist, on the order of $10^{-18\pm 3}$ times the average thermal energy (kT) at room temperature per light-atom molecule. In a mole of a racemic mixture of amino acids, for example, this energy difference leads to an excess of approximately a million molecules of the more energetically stable enantiomer. Thus, we are led to search experimentally for how such minuscule excesses could be translated into a macroscale preference. As yet, another challenge, the measurement of the energy differences associated with the different enantiomers (PVEDs) so far eludes our detection abilities.

In his 1966 paper discussing PVEDs, Yamagata [12] postulated that the small reaction rate differences between enantiomers might be enhanced by "an accumulation principle" in a sequential series of polymerization steps. In 1974, Thiemann and Darge [53] investigated the possibility that PVED effects might be observable during polymerization reactions. They conducted polymerizations of the N-carboxyanhydrides of scrupulously racemized samples of alanine, α -aminobutyric acid, and lysine, and then measured the optical activity of each resulting polymer polarimetrically. All of the polymers showed rotations at 310 nm that ranged between -0.00025° and -0.00084° . These rotations were claimed to indicate a relative difference in the polymerization rates for L- and D-amino acids of about 8×10^{-6} . From these results it is clear that the evidence for PVED accumulation is small to nonexistent.

In 1974 Wagener [54] suggested a number of physical methods that might be exploited to detect any inherent PVED-induced chiral excess. These included chromatography, ion exchange, electrophoresis, polymerization, and crystallization. Analyzing the suitability of each, he concluded that fractional precipitation was the most promising procedure. Immediately thereafter, Thiemann [55] tested this conclusion by examining the fractional precipitation of D,L-asparagine. The results were ambiguous in that repeated recrystallizations below 7.5° yielded a small excess of the D-isomer in the precipitate, whereas above 8° the reverse was true.

The significance of a PVED in influencing the outcome of a chemical reaction remains controversial, and Bonner [56] has recently reviewed experimental work directed toward demonstrating PVED effects. In 1970 Thiemann and Wagener [57] studied the fractional crystallization of sodium ammonium D,L-tartrate, examining the initial fractions for optical activity. In ten such experiments they observed a rotation of approximately -0.001° at 280 nm, and concluded that the effect was caused by a difference of 10^{-5} in the lattice energies of the enantiomorphic crystals. In 1973 Yamagata [58] proposed refinements of such crystallization experiments, but unfortunately these were not implemented. Two years later Kovács and Garay [59] reexamined the crystallization of sodium ammonium D,L-tartrate, but now in the presence of the β -rays from codissolved ^{32}P -phosphate. They observed a slight preference for crystallization of the L-enantiomer in the presence of the radioactive ^{32}P , but control experiments lacking the ^{32}P showed no selectivity whatsoever, and offered "No support ... in favor of any measurable energy content difference between optical isomers." [60] These negative results may reflect, however, the use of light atoms in the search.

PVED scales strongly with the nuclear charge Z . Recently PVED-derived atomic chirality has been directly measured in the gas phase for cesium ($Z = 55$) and thallium ($Z = 81$). [61, 62] Relativistic calculations indicate that PVED effects produced in molecules containing multiple heavy atoms should be several orders of magnitude larger than PVEDs of molecules containing only light atoms. [63] Enzymes containing transition metal sulfide clusters at the catalytic site are candidates for such chemistry. Possibly of significance is that such enzyme systems are considered to be among the first that were utilized within the earliest living systems.

11.2.2

Fluctuational Mechanisms

In 1969 Calvin [64] proposed a scheme for autocatalytic symmetry breaking, which he called "stereospecific autocatalysis". Calvin's mechanism has been validated experimentally in the context of the total spontaneous resolution during the crystallization of racemic mixtures. During crystallization, crystals of one enantiomer may spontaneously separate, leaving the other enantiomer in solution. If the possibility of the equilibration of the enantiomers in solution exists and if the enantiomer in solution can convert rapidly to the enantiomer that is crystallizing before crystallization is complete, then the entire racemate may deposit as a single enantiomer. At least half a dozen examples of Calvin's stereospecific autocatalysis involving such

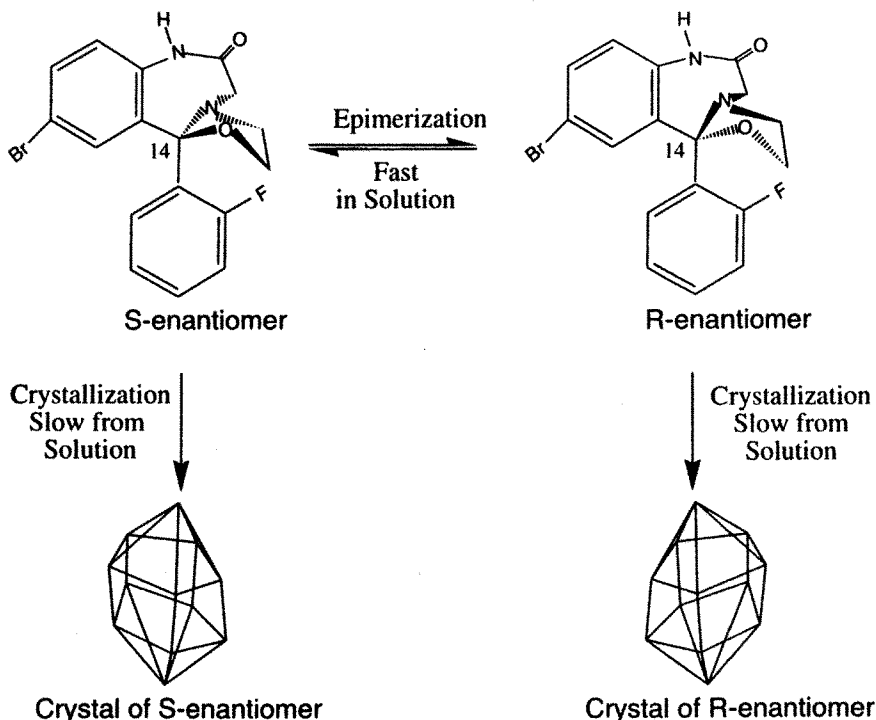


Fig. 11.3 In solution, the molecule bromo-fluoro-1,4-benzodiazepinooxazole rapidly epimerizes between two enantiomers, denoted by R and S, caused by bond rearrangement at the carbon atom of position 14. Epimerization is fast relative to crystallization. If one enantiomer is removed from solution, Le Chatelier's principle

will cause the equilibrium to shift producing more of that enantiomer in solution. Thus, fluctuational nucleation of one enantiomer can produce a spontaneous resolution by crystallization. The *bolded* and *hashed* bonds are above and below the plane of the drawing, respectively.

spontaneous resolution under racemizing conditions (SRURC) have substantiated the mechanism. [65]

SRURC is such an interesting example of the facile formation of chiral induction from racemic mixtures in the absence of any external symmetry-breaking agent that it deserves special attention. One of the best studied examples is the crystallization of bromo-fluoro-1,4-benzodiazepinooxazole (Fig. 11.3), which possesses a single asymmetric carbon atom at C14 and a potentially asymmetric bridgehead nitrogen atom at N4.

Okada and coworkers [66] discovered that the crystallization of this molecule from methanol yielded optically active crystals that were sometimes dextrorotatory and sometimes levorotatory, and that underwent rapid racemization upon redissolving in methanol. They went on to study the kinetics of this process as well as the nature of the different crystalline forms. [67, 69] Bonner [50, 65, 70] has extended and confirmed these observations and conclusions, with special attention to the possibility that the crystallization might provide the means for studying the efficacy of

PVED effects. After much study, Bonner [50] concluded that “the data offer no evidence whatsoever for the efficacy or intervention of PVEDs.”

SRURC has an additional drawback, however, for realistic prebiotic symmetry breaking. A hypothetical solution of equilibrating racemates undergoing total spontaneous resolution by crystallization – for example, from some evaporating tide pool on the primitive Earth – would inevitably racemize on redissolving prior to undergoing the next stage of its prebiotic chemical evolution, barring prior implausible solid-state reactions.

11.2.3

Extrinsic Mechanisms

That chiral molecules can be produced in a CPL field, either from achiral precursors by photo-activated synthesis or by preferential chiral photodestruction of a racemic mixture, is now well demonstrated and has been reviewed. [46] In all cases currently known, however, such processes have proved very inefficient. For example, asymmetric photochemical ring-closures of achiral helicene precursors induced by CPL have produced only about 0.2% e.e. in the products. Likewise, the CPL-induced photolysis of racemic camphor produced about 20% e.e., but only after 99% photodestruction, and photolysis of D,L-glutamic acid produced only 0.22% e.e. after 52% photodecomposition. [71]

Recently, the theory that a terrestrial e.e. could arise from seeding by chiral molecules produced extraterrestrially by stellar CPL, discussed in Section 11.1.3, received strong and direct experimental support. Cronin and Pizzarello [72] resolved the earlier [73] contended [74] claims that a chiral excess of L-amino acids could be extracted from the Murchison meteorite. They did so by looking for, and finding in the meteorite, a chiral excess of several nonbiogenic L- β -methyl-amino acids, including L,L-2-amino-2,3-dimethylpentanoic acid (2- α -2,3-dmpa). These chiral amino acids, undoubtedly of interstellar origin, were further deduced to have originated by way of CPL photolysis of precursor racemic mixtures because no other mechanism could convincingly be adduced to account for the formation of the two chiral centers of 2- α -2,3-dmpa. Bailey et al. [75] have recently disputed the possibility that CPL from neutron stars could be the source of extraterrestrial molecular handedness, but they further reported detecting up to 17% circular polarization in the infrared light emitted from the OMC-1 star-forming region of the Orion nebula. Although not produced by neutron stars, the inferred ultraviolet CPL would be similarly effective in inducing a net e.e. in photolyzed racemic organic precursors within dusty interstellar clouds.

The possible photoresolution of racemic mixtures of chiral molecules by irradiation with CPL under interstellar conditions has also been examined experimentally and discussed critically. [76] These experiments have proven interesting, and significant quantities of biologically familiar amino acids as well as other molecules such as glycerol have been produced. [76, 77] In addition, irradiation of racemic tryptophan with ultraviolet CPL at 10 K has produced sufficient chiral products to allow the estimate that as much as 50% e.e. may be generated in irradiated regions of interstellar molecular clouds. [35] Thus, although the exact source of the extraterres-

trial CPL remains disputed, [79, 80] the likelihood of chiral induction in interstellar molecular clouds by some sort of stellar CPL irradiation field remains very real.

More general experimental support for this idea comes from laboratory studies [81] that have shown that irradiation of realistic models of interstellar and cometary ices containing methanol and formaldehyde, with lesser quantities of ammonia, produced notable amounts of hexamethylenetetramine (HMT). HMT, in turn, is known to produce several amino acids on acid hydrolysis. [82] In addition, irradiation under similar icy conditions of complex polycyclic aromatic hydrocarbons (PAHs), which are believed to make up about 20% of the cosmic carbon budget, [83, 84] produced an extensive variety of organic products. [85] Therefore it can be justifiably imagined that the infall to Earth of organic material from meteoric flux might have delivered not only an e.e. of amino acids but also a wide diversity of chiral organic chemicals. These chemicals were possibly enriched in the L-enantiomer selected by the polarization of the CPL field of the extraterrestrial environment, which would have provided the seed for L-homochirality in proteins.

Crick [86, 87] has conjectured that the early genetic code was G-C rich. This conjecture is based on the enhanced stability of G-C rich duplexes compared to A-T rich duplexes. If this conjecture is correct, several authors [88, 90] have proposed that the earliest genomes coded primarily for the amino acids having G or C in their codon. Together, these authors agree that these amino acids include alanine, aspartic acid, proline and glycine. Interestingly, these four amino acids include one that is hydrophobic (alanine), another that is hydrophilic (aspartic acid), and two that permit (glycine) or require (proline) folding of protein structures. Moreover, three of these amino acids are known to form polypeptides under simple conditions of high salt concentration and dehydration in which metal ions may serve as a catalyst. [91] These four amino acids are aliphatic; and they resist photodegradation compared to other (nonaliphatic or hetero-atom containing) amino acids. A consequence of the resistance to photodegradation is that these amino acids are more likely to persist in an enantiomerically enriched state in the presence of short-wavelength circularly polarized radiation. Thus, the impact of an extrinsic CPL field on racemic mixtures of amino acids rationalizes why the earliest forms of primitive life appear to have been based predominantly on homochiral proteins made up of these four amino acids.

11.3

Chiral Amplification and Takeover

How are the small-to-microscale excesses of one enantiomer over the other, produced by any of the scenarios outlined above, capable of generating a final state of enantiomeric purity? In 1953 Frank [16] developed a mathematical model for the "autocatalytic" random symmetry breaking of a racemic system. He proposed that the reaction of one enantiomer yielded a product that acted as a catalyst for the further production of more of itself and as an inhibitor for the production of its antipode. He showed that such a system is kinetically unstable, which implies that any **random fluctuation producing a transient e.e.** in the 50:50 population of the racemic

reactant would result in the eventual domination of the chiral product from that reactant. This kinetic amplification mechanism has been critically reviewed by Nordén, [92] who corroborated this conclusion. Thus a theoretical system is available in support of the search for an experimental mechanism for amplification of a small enantiomeric excess.

11.3.1

Autoamplification by Polymerization/Depolymerization

In 1957 Wald [93] first proposed that the secondary α -helix structure of a polypeptide chain should bias the selection of amino acid enantiomers toward homochirality as polymerization progressed. In other words, the particular chirality of the α -helix should dictate that the chirality of the new monomers adding to it be of the same handedness as those already making up the helix. This seminal suggestion soon received abundant verification in a variety of prototypical experiments involving base-catalyzed conversions of monomeric amino acid N-carboxyanhydrides (NCAs) into polypeptides. These studies led Bonner and coworkers in the mid-1970s to initiate a series of model experiments designed to explore the further possibility that Wald's mechanism might also be applicable for the e.e. amplification of enantiomerically impure amino acids.

Their studies involved the partial polymerization of NCAs of mixtures of specific amino acids having known e.e.s, followed by determination of the e.e.s of the amino acids in both the resulting polypeptides and in the residual unreacted NCA monomers. [94] In a typical experiment it was found that when an optically impure leucine NCA monomer having an $L > D$ e.e. of 31.2% was polymerized to the extent of 52% to the helical polyleucine peptide, the e.e. of the polymer was enhanced to 45.4%, an increase of 14.2%. In the same experiment the e.e. of the unreacted leucine NCA monomer was depleted to a similar extent. Analogous experiments with valine NCAs of known e.e.s, however, led to a reverse effect, namely, the preferential incorporation of the racemate rather than one enantiomer into the growing polyvaline peptide. This finding was interpreted to be the result of the fact that polyvaline consists of β -sheets rather than α -helices, emphasizing that the Wald mechanism applies only to α -helix polymers. At about the same time Brach and Spach [95] showed that, under proper conditions, β -sheet polymers could also be implicated in the amplification of amino acid e.e.s.

In the above experiments with polyleucines it was also observed that the partial hydrolysis of mixtures of nonhomochiral leucine peptides led to the preferential hydrolysis of those components of the mixtures that were enantiomerically more random. This produced a corresponding e.e. enrichment in the unhydrolyzed polymer. [96] For example, when the above polyleucine sample having an $L > D$ e.e. of 45.4% was 27% hydrolyzed, the residual unhydrolyzed polymer had an e.e. of 55.0%, representing an e.e. increase of 9.6%.

Thus in the two typical experiments cited, a sequential combination of partial polymerization, with its 14.2% e.e. increase, and partial hydrolysis, with its 9.6% e.e. increase, resulted in an impressive overall $L > D$ e.e. enhancement of 23.8%.

This enhancement required just two steps from the initial leucine NCA monomer to the final polyleucine peptide.

The success of these model experiments led Bonner and coworkers to propose a mechanism involving repetitive cyclic sequences of partial polymerization followed by partial depolymerization in which the latter is caused by hydrolysis. Thus, this process is driven by environmental dry and wet cycles that could ultimately have led to homochiral polypeptides on early Earth. [97] Brach and Spach [95] have also proposed a mechanism involving partial hydrolysis for the enantiomeric enrichment of polypeptides having β -sheet secondary structures.

These model experiments involving e.e. amplification of amino acids during polymerization admittedly need prebiotically “unrealistic” substrates as well as carefully contrived experimental conditions. Nevertheless, it is noteworthy that both secondary structures of proteins, α -helices, and β -sheets have been found capable of acting stereoselectively to provide e.e. enhancements during these model polymerizations.

Analogous amplification experiments embodying prebiotically realistic environmental conditions have yet to be reported. Even so, the chiral amplification of non-homochiral peptides could be tested in a biogenically reasonable way by application of a very relevant method recently developed and reported by Imai et al. [98] These workers simulated a hydrothermal submarine vent within a single reactor by continuously circulating an aqueous solution between a high-pressure (24 MPa), elevated-temperature (200–250 K) region and an equally pressurized rapid cold quench. With glycine as solute in pure deionized water, this reactor produced oligomers up to the triglycine stage after only 30 min and up to the hexaglycine stage when Cu^{2+} was present. Diketopiperazine was also produced, and the glycine oligomers were apparently produced by amination of this compound. No other amino acids were reported tested. Extension of similar experiments to racemic amino acid mixtures, however, would directly test the hypothesis that homochiral peptide oligomers might be induced and/or amplified under conditions of dynamic polymerization-depolymerization that reproduce plausible prebiotic conditions.

Recently, Eschenmoser and coworkers [98] have suggested a more elaborate mechanism for spontaneous symmetry breaking. Accompanying their description of the self-assembly of higher oligomers of pyranosyl-RNA by ligative oligomerization of tetranucleotide-2', 3'-cyclophosphates, they postulated that starting with a racemic mixture containing all possible diastereomers sets of such “tetramers with different but mutually fitting base sequences can be expected to co-oligomerize stochastically and generate sequence libraries consisting predominantly of homochiral (D)- and (L)-oligomers.” They then showed how, after reaching a sufficient chain length, the oligomers are “driven beyond a critical level of constitutional complexity,” such that a true racemic mixture of the oligomers is no longer possible. Then, with “internal and external selection pressures” either the homochiral (D)- or (L)-oligomer must eventually predominate. Although these novel suggestions are extrapolated from the authors' solid laboratory observations, they have yet to be demonstrated experimentally. However, these results extend to polynucleotides the findings noted above, that polymerization reactions of racemic materials could produce chiral symmetry breaking and amplification in a way arising naturally out of simple chem-

ical processes. The same concept might apply to polymerization of a racemic mixture of amino acids.

11.3.2

Enantiomeric Amplification by Change of Phase

In the 45 years since its proposal, Frank's autocatalytic mechanism (Section 11.3, above) has spawned numerous theoretical refinements including consideration of such factors as reversibility, racemization, environmental "noise," and parity-violating energy differences. [100, 101] In contrast to the above examples of stereospecific autocatalysis by the SRURC, however, none of these theoretical refinements is supported by experimental evidence. While earlier attempts to validate the Frank mechanism for the autocatalytic amplification of small e.e.s in other experimental systems have generally been unsuccessful, several recent attempts have shown more promising results. [102, 104]

These schemes have been frequently suggested [105–107] as possible mechanisms to achieve the chirally pure "starting point" for prebiotic molecular evolution toward our present homochiral biopolymers. Demonstrably successful amplification mechanisms are the spontaneous resolution of enantiomeric mixtures under racemizing conditions, [509 lattice-controlled solid-state asymmetric reactions, [108] and other autocatalytic processes. [103, 104] Other experimentally successful mechanisms that have been proposed for chirality amplification are those involving "kinetic resolutions" [109] enantioselective occlusions of enantiomers on opposite crystal faces, [110] and lyotropic liquid crystals. [111] These systems are interesting in themselves but are not of direct prebiotic relevance because of their limited scope and the specialized experimental conditions needed for their implementation.

Alternative mechanisms that have been suggested have involved the partial evaporations of [112] or partial precipitations from [55] solutions in which there exist solubility differences between a racemate and its individual enantiomeric constituents. Such studies have given positive results in a few systems and might intuitively be considered plausible in a primitive Earth setting, but their generality at the present level of knowledge unfortunately appears limited. These experiments and those described earlier validating the mechanism of stereospecific autocatalysis have all involved rather exotic chemical systems that are of interest in connection with the Frank hypothesis but seem implausible in any realistic prebiotic environment. All known examples, however, do demonstrate the principle that autoamplification of small spontaneous e.e.s is chemically possible. The experimental charge, therefore, is to seek generalizing examples of the reactions that seem most plausible in a putative prebiotic environment.

11.3.3

Metal-Assisted Enantiomeric Amplification

A recent interesting example of the chiral amplification of a small initial e.e. has been reported by Soai et al. [113, 114] involving the induction of a chiral center in an achiral aldehyde using diisopropylzinc as an alkylating reductant and a very small

e.e. (0.1%) of a chiral effector molecule. The effector molecule is almost certainly a ligand for the zinc. Whichever enantiomer of the effector is in small excess overwhelmingly determines the chirality of the product.

Although the mechanism of this reaction remains unknown, we can visualize how such amplification could occur by assuming that the chirality-amplifying molecule is a tetrahedral zincate that includes two of the chiral effector molecules as ligands. The scheme is illustrated by the reactions depicted in Fig. 11.4.

Chiral effector ligands can be a variety of molecules, including amino acids. The chiral alcohol products of the chiral-transfer reactions in Fig. 11.4 cycle back into these reactions by subsequent complexation with the pool of diisopropyl zinc.

Such a system could proceed to chiral takeover, for example, if the active alkylating agent is the tetrahedral zinc complex (Fig. 11.4), if the initial total concentration of the chiral zinc complexes is small compared to that of the aldehyde reactant, if the tetrahedral *D,L*-zinc complex is more stable thermodynamically than are the tetrahedral *D,D*- and *L,L*-zinc complexes, and if the reaction of the *D,L*- complex with the pyrimidyl aldehyde is kinetically sluggish compared to the reaction rate of the

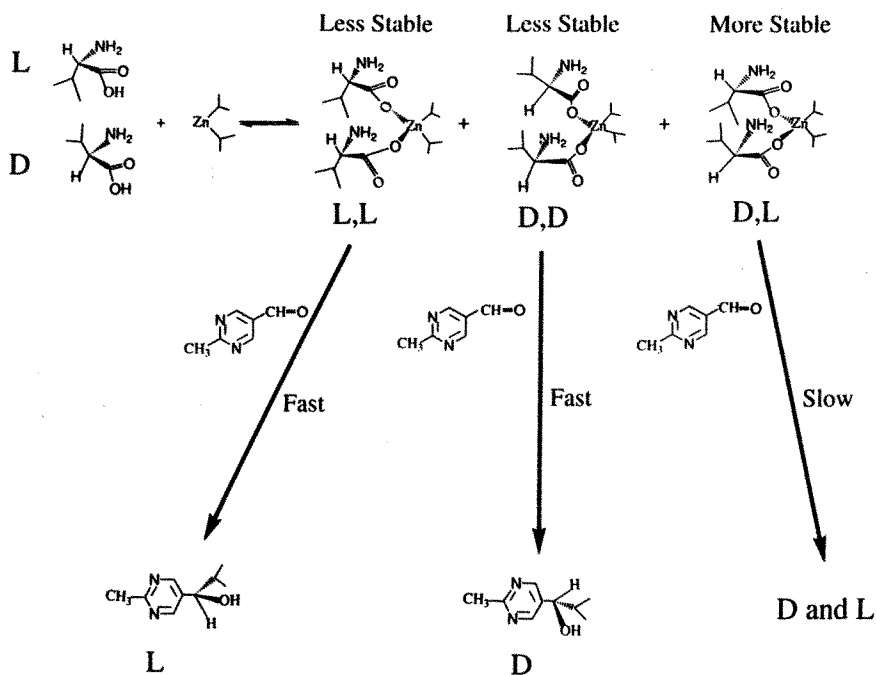


Fig. 11.4 Reaction sequence showing how a small e.e. of the reagent is converted to a large e.e. of the product by a metal-assisted reaction. In the case shown, a 1% e.e. of L-valine produced a 51% e.e. of L-pyrimidine alcohol by the reductive asymmetric transfer of an isopropyl group from zinc to the carbonyl carbon of the

aldehyde. The chiral alcohol product can react with the di-isopropyl zinc in excess to produce additional chirally selective zinc complexes, thus catalyzing its own chiral dominance. The **bolded** and *hashed* bonds are above and below the plane of the drawing, respectively.

homochiral complexes. The last condition would be reasonable if the alkylation involved a rate-determining dissociative step. We can then see that a small initial enantiomeric excess of one chiral effector ligand will eventually dominate because the slightly smaller concentration of the opposite-handed ligand will over time come to be restricted by equilibration into the kinetically sluggish *D,L*-zinc complex. Although the reaction system is prebiotically unrealistic, it nevertheless demonstrates that the principle of runaway autocatalytic amplification of a small chiral excess is not chemically unreasonable.

This reaction has recently been extended into a more realistic prebiotic regime, however, by the finding that an initial symmetry-breaking event can be induced by the surface of a morphologically chiral material such as quartz. Thus, when the reaction in Fig. 11.4 was carried out without any added chiral effector ligand, but in the presence of powdered optically pure crystalline quartz [115] or NaClO₃ crystals, [116] the chirality of the product alcohol was overwhelmingly determined by the morphological symmetry of the mineral. In this reaction, a small chiral excess of the product pyridine alcohol must be produced very early in the reaction. This small initial e.e. could then rapidly dominate the chirality of the final product by the amplification mechanism described qualitatively above.

This sort of analysis could be extended to any metal-catalyzed chemistry in which a large runaway chiral excess is induced in the product by way of a small chiral excess of the molecules that serve as ligands to the metal. It is only necessary that the *D,L*-metal center be kinetically slower and thermodynamically more stable than the *D,D*- or *L,L*-complexes in order that any small e.e. of a chiral ligand be translated into chiral dominance of the reaction product. That the initial e.e. resulting in chiral takeover within a reacting system can be induced by asymmetric mineral surfaces indicates that a general chemical route to the asymmetry of life may exist.

11.3.4

Amplification by Molecular Propagation from a Chiral Center

In 1994 Wittung et al. [117] reported a provocative mechanism of chiral amplification involving achiral polymers of peptide nucleic acids (PNAs). PNAs are nonribose-containing polymers consisting of chains of poly-[*N*_α-(carboxymethylnucleotide)-*N*_α-(2 ethylamido)glycinamide] (Fig. 11.5). These molecules can form complementary base-paired helical duplexes completely analogous to those of DNA and RNA. Using circular dichroism (CD) spectroscopy these workers showed that a preferred helical handedness could be induced into an achiral PNA duplex polymer by appending a single chiral amino acid to the glycinamide terminus of each chain. Development of a CD spectrum, and thus molecular chirality, only occurred when PNA polymers with complementary nucleotides were mixed. Unmodified PNA polymers formed duplexes that did not develop a preferred helical handedness in solution. The helicity of the PNA duplex was completely determined by the chiral handedness of the amino acid tail. Although only PNA decamers were studied, there is no reason to think that longer PNA polymer chains would not behave similarly. Recent synthetic results [118] have indicated a plausible prebiotic route to the

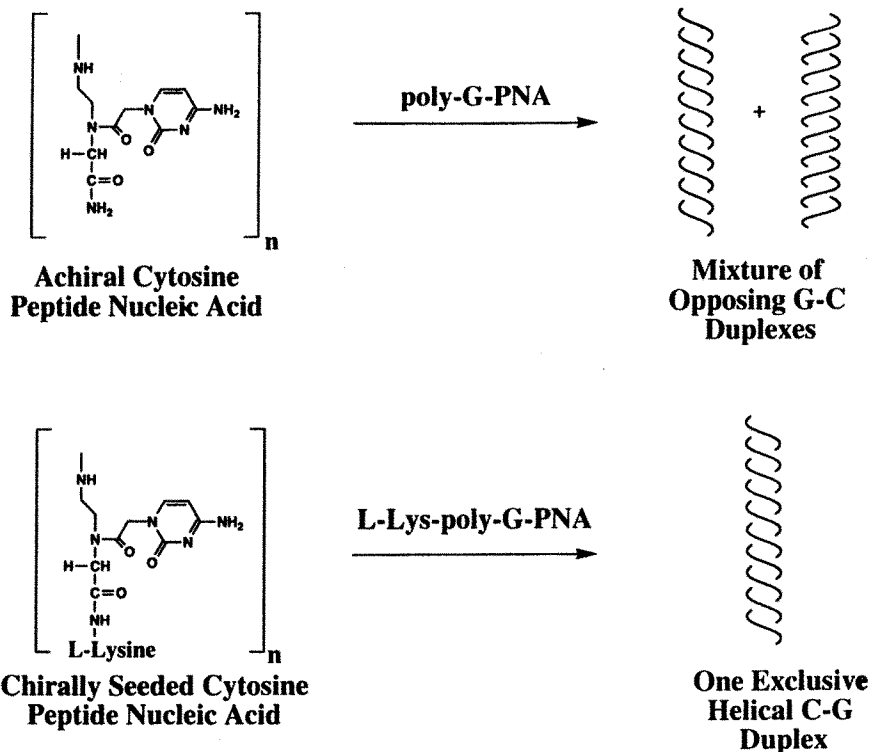


Fig. 11.5 Induction and amplification of chirality in an achiral polymer. Peptide nucleic acids are DNA analogs that can fold into helical duplexes that mimic biogenic nucleic acid biopolymers. With an appended chiral amino acid, a PNA decamer folded into

only (or predominantly) one of the two helical possibilities. This behavior demonstrates that a localized chiral center can induce global chirality in a polymer. The example shown is a simplification of the actual experiment.

production and polymerization of the PNA backbone, raising the possibility that such molecules were involved in early pre-RNA information storage.

11.3.5

Amplification by CPL Photoinduction

Another mechanism of chiral amplification that extends over an even larger scale has been reported by Huck et al. [119] The molecule 12-(9'H-thioxanthene-9'-ylidene-12H-benzo[a]xanthene (Fig. 11.6), which has no chiral center, nevertheless exists, like the helicenes, in two chiral forms defined by their enantiomeric configurations. Consistent with the discussion in Section 11.2.3, a small net handedness (ca. 0.7%) could be induced in racemic solutions of this molecule by use of ultraviolet CPL. However, introducing 20 wt% of this molecule, which contained a 1.5% chiral excess of one roto-enantiomer, into a nematic phase of liquid crystals produced macroscopic (100 μm) regions of a chiral cholesteric liquid crystal phase. The

chemical evolution while floating freely in the oceans. Instead, **they must** have evolved only after their concentration and protection by sequestration into indigenous and robust precellular structures. We examine briefly some of the suggestions that have been offered to accomplish this sheltering.

11.4.1

Porous Minerals

In 1967, J. D. Bernal [126] elaborated his earlier ideas that life could have originated in estuarine or shoreline clays by way of the adsorption, and concentration therein, of prebiotic organic molecules. The chemistry and porous morphology of clays **have** been reviewed in the context of prebiotic chemistry. [127] In particular, the porosity of clays and the consequent high availability of catalytic sites that can adsorb organic molecules and activate them through complexation by metal ions, or by protonation, is discussed. These ideas led to considerable experimentation, which has been reviewed. [47] Although no chiral preference by clays has been reliably detected, the concentration of organics by these materials and the catalytic transformation of adsorbed organics are well verified.

Ideas regarding involvement of clays in the origin of life were explicitly advanced by Cairns-Smith, [128, 129] who suggested that life emerged from an association of organic molecules adsorbed into the interlayers of clays such as montmorillonite or kaolin. In his scheme, the original self-replicating elements were mineral systems derived from the clays themselves, a concept for which there is some experimental support. [130] These were eventually to be replaced, first by clay-organic systems, and then by purely organic autocatalytic reaction systems, from which later life emerged. Cairns-Smith also proposed that the metallic sites found on the edges and corners of clay materials could have promoted the emergence of organic self-replicating systems by way of selection among the products and processes of a multitudinous catalytic chemistry.

These schemes expressly included the idea that clays and porous minerals adsorbed, absorbed, and ultimately concentrated any extant organics from a dilute oceanic broth on the early Earth. This idea is critical because it is difficult to imagine that the kind of polymerization and chiral amplification processes discussed above could or would have occurred in a water solution not much more than millimolar in organics. [131]

Smith and coworkers recently proposed a specific and novel mineral-based solution to the problem of dilution and diffusion of prebiotic reactants. They **have** suggested [132–134] the uptake of organics within the micron-sized three-dimensional cross-linked network of pores found to exist within the top 50 μm , or so, of alumina-depleted, silica-rich weathered feldspar surfaces. These surfaces incorporate cavities typically about 0.5 μm in diameter along with cross inter-connections of about 0.2 μm . The nominal area of the weathered feldspar surface is apparently multiplied by a factor of about 130 arising from this network. The similarity of these pores to the catalytic sites in zeolite-type materials is pointedly mentioned.

The weathering of feldspars produces silica-rich surfaces that are naturally lipophilic. Such surfaces are ideal for the uptake and concentration of amino acids, polymers, and amphiphilic (surface-active) organic molecules. Amphiphiles, including fatty acids, phospholipids, and sterols, are large nonpolar hydrocarbons that include one or more small polar groups and are surface-active at an air-water interface. That is, they self-organize into monolayers with their hydrophilic polar groups extending into, and with their hydrophobic nonpolar groups remaining out of, the water surface. Thus lipophilic silica-rich surfaces may not actually be necessary for uptake of amphiphiles because the surface-active nature of amphiphiles, peptides, carboxylic acids, and amino acids may be sufficient to transform even a polar alumina-rich surface into one that is lipophilic. [135, 136]

The point is also made [134] that the very high surface areas and the richly interconnected three-dimensional networks of these micron-sized spaces, coupled with periods of desiccation, could together have produced microenvironments rich in catalytically produced complex chemicals and possibly membrane-enclosed vesicles of bacterial size. These processes would provide the proximate concatenation of lipid vesicular precursors with the complex chemicals that would ultimately produce the autocatalytic and self-replicating chiral systems. A 2.5 km² granite reef is estimated to contain possibly 10¹⁸ "catalytic microreactors, open by diffusion to the dynamic reservoir of organic molecules ... but protected from the dispersive effects of flow and convection" [134] as well as protected from the high flux of ultraviolet radiation impinging on the early Earth. [123, 137]

11.4.2

Amphiphilic Vesicles

Above a critical concentration certain amphiphiles may aggregate into membranous micelles, which are globular structures with a nonpolar interior and with a polar surface that interfaces the aqueous environment. At still higher concentrations micelles may fuse into multilamellar structures composed of bilayers. [138]

Micelles are capable of self-replication if an appropriate chemical reaction occurs within the micelle itself that produces more of the same amphiphile that forms the micelle. Such self-replication has been demonstrated for both ordinary micelles in an aqueous medium [139] as well as for "reverse micelles," [140] which are spherules of water stabilized by an amphiphile in an organic solvent. Some of the prebiotic potentialities of replicating membranous vesicles have been investigated, [141] and they have been characterized as "minimum protocells." [142]

A critical property of minimum protocells in the prebiotic environment would be their ability to sequester other molecules, including macromolecules. [142] In 1982, Deamer and Barchfeld [143] subjected phospholipid vesicles to dehydration-rehydration cycles in the presence of either monomeric 6-carboxyfluorescein molecules or polymeric salmon sperm DNA molecules as extraneous solutes. The experiment modeled a prebiotic tidal pool containing dilute dispersions of phospholipids in the presence of external solutes, with the dehydration-rehydration cycles representing episodic dry and wet eras. They found that the vesicles formed after rehydration

encapsulated both the small fluorescein molecule and the polymer, with the extent of encapsulation following the amount of original liposome.

Deamer and Barchfield suggested that during the dehydration stage the original vesicles shrank and fused together, trapping the solute molecules between the alternating lipid bilayers of a multilamellar sandwich. On rehydration the lamellae swelled, reconstituting larger vesicles that encapsulated a significant percentage of the original monomeric or polymeric solute. They also suggested that if both a template and a monomer were sequestered together, the close contact in the enclosed microenvironment might enhance the efficiency of template-directed replication. This idea anticipates the later suggestion that membranous amphiphile vesicles might provide "an appropriate microenvironment for incorporation and evolution of polymer synthesis systems." [142, 144]

We offer a further suggestion. The dehydration-rehydration encapsulation of macromolecules within vesicles might occur simultaneously with the amplification of an initial e.e. in polypeptides by a partial-polymerization step (during dehydration) and a partial-hydrolysis step (during rehydration). The joint action would permit the evolution from amino acids of low e.e.s into homochiral polypeptides sequestered in the protected interiors of the vesicles. In other words, such encapsulation might augment the above e.e. amplification based on Wald's hypothesis. Although this possibility has not been investigated experimentally, the formation of membranous vesicle protocells along with their ability to self-replicate and to encapsulate exogenous molecules has been convincingly demonstrated experimentally. The conjoint mechanism of encapsulation followed by e.e. amplification could thus constitute a realistic and plausible prebiotic process on the primordial Earth.

The question as to the potential availability of the requisite amphiphilic precursors in the prebiotic environment has been addressed experimentally by Deamer and coworkers, [143, 145] who looked into the uncontaminated Murchison chondrite for the presence of such amphiphilic constituents. Samples of the meteorite were extracted with chloroform-methanol and the extracts were fractionated by thin-layer chromatography, with the finding that some of the fractions afforded components that formed monomolecular films at air-water interfaces, and that were also able to self-assemble into membranous vesicles able to encapsulate polar solutes. These observations clearly demonstrated that amphiphiles plausibly available on the primitive Earth by meteoritic infall have the ability to self-assemble into the membranous vesicles of "minimum protocells."

11.5

Setting the Scene for Life

The circumstances producing an e.e. on the early Earth could well have been capture and amplification of one of the fluctuational mechanisms outlined above, although present evidence favors the meteoric infall of chiral molecules synthesized in interstellar dust clouds. The total flux of organics on the early Earth, delivered to Earth both by way of comets and other bolides, and synthesized by terrestrial mechanisms

is estimated [131] to have been on the order of 7×10^8 kg/yr for a modestly reducing atmosphere composed mostly of CO_2 and dinitrogen. The terrestrial carbon inventory would have included the organics and amphiphiles described above as originating in interstellar molecular clouds and discovered in the Murchison meteorite, and the chiral excesses suggested by the amino acids found within the Murchison meteorite.

The metal-catalyzed amplification of e.e. in small molecules, demonstrated by Soai and coworkers, along with the chiral enrichment of amino acid polymers by sequential polymerization/depolymerization steps, have shown that small enantiomeric excesses in nearly racemic mixtures can be reactively amplified to produce chiral dominance. These real chemical systems, which include plausible prebiotic reactions, experimentally demonstrate the principle of the chiral amplification of a spontaneously broken chiral symmetry in a dynamic and authentic chemical milieu. Therefore amplification to dominance of a small chiral excess of both small and polymeric molecules can be credibly incorporated into an origin-of-life model.

It is presently known that the regions surrounding extant submarine and terrestrial hydrothermal vents are rich in ammonia, hydrogen sulfide, dihydrogen, CO , and the other simple molecules [122, 146–150] thought necessary for biogenic chemistry. [151–155] The extensive organic chemistry accessible in hydrothermal vent systems has been comprehensively reviewed in monographs by several authors in a special issue (Vol. 22, 1992) of "Origins of Life and Evolution of the Biosphere." These circumstances solve the problem that a weakly reducing N_2/CO_2 atmosphere would not have provided the reactive chemicals and reducing environment necessary to produce Miller-Urey chemistry. [131] Under reducing hydrothermal conditions, a rich array of amino acids and organic molecules are expected to be efficiently synthesized. [156, 157] That is, hydrothermal activity on the archaic Earth could have provided a rich variety of chemical "feedstocks" to any conjoining catalytic porous mineral assemblage, wherein stochastic experimentation in biogenic chemistry could occur.

The production and stabilization of long polypeptides on clay surfaces [158–163] from simple evaporation cycles of dilute solutions of amino acids, [164, 165] and from the facile production of amino acids and other organics from simple precursors under a variety of conditions [151, 166–168] is well established. Therefore it is reasonable to extrapolate these laboratory results to prebiotic polymerizations of indigenous amino acids within proposed mineral dikes in a hydrothermal vent-field on early Earth. Libraries of random polypeptides, presumably existent in the critical time just prior to the emergence of the first self-replicating protocell, are known to have members that organize into robustly folded protein-like molecules that are high in α -helical content. [169] Some of these might be expected to have useful catalytic properties.

Similar efficient abiotic syntheses of nucleotide precursors and their polymerization on clays have also been reported [166, 168, 170–174] and reviewed, [175] which allows a provisional extension of the above comments concerning amino acids to these critical molecules as well. Such molecules also have interesting catalytic activity, [176–179] which would be subject to selection. **The uptake and ligation of metal**

ions such as Mg^{2+} is known to confer catalytic activity on even random RNA oligomers. [177, 180]

The early Earth was probably much more geothermally active than the Earth is today. [122] The continents of early Earth were most likely small with vertical profiles at, or near, sea-level. [125, 181] Subaerial (in addition to submarine) tectonic rift zones and hydrothermal vent fields were probably ubiquitous and vigorous. [182] Extensive continental hydrothermal zones enriched in reducing inorganic and organic vent products and subject to wet/dry cycles were probably common. The low-profile shield continents of the early Earth must have been extensively surfaced with basalt and rhyolite, [183] some of which could have been porphyritic.

The partial pressure of CO_2 in the Earth's atmosphere during the early Archaean probably was 10 bars or more (1 bar is approximately 1 atmosphere). [182, 184] The consequent levels of carbonic acid produced acid rain (pH ca. 3.9) and a world ocean with mildly acidic (pH ca. 6) surface waters. [185] The extensive volcanism of the day would have released significant quantities of HCl vapor into the atmosphere, further acidifying rain. [186, 187] Under conditions of heat and acidic waters, which thus probably typified the hydrosphere of the early Earth, chemical weathering of even highly calcic basalt and rhyolite surfaces must have been rapid. [137] Given these circumstances, feldspar inclusions and other phenocrystic mineral assemblages could have rapidly developed the sort of porous networks described above. It is worth observing that once covered with adsorbed organics, internal rock pores would resist further aqueous chemical weathering.

11.6

The Rocky Road to Life?

We are now in a position to offer a speculation on what type of prebiotic chemistry might have occurred, informed by the ideas and observations discussed above. Failing either faster-than-light travel or spectacular advances in optics, we will almost certainly never know by exactly what process life began on Earth. The scientific charge, however, is to derive a plausible theory based upon demonstrable chemistry and verified observations.

The recent developments and ideas in the field of prebiotic chemistry can be combined with the concepts noted here to produce what we regard as a research outline, rather than a detailed hypothesis, directed toward a coherent theory of the origin of complex self-contained, self-replicating chiral assemblies. In what follows we present one possible scenario that is consistent with our current knowledge of chiral induction and amplification and with the nature of early Earth as well as early life. It is exciting that this fundamental question can be formulated in a way that allows systematic experimental testing as we enter the next century.

Credible mechanisms have been identified for the extraterrestrial production and delivery to early Earth of organic molecules and amino acids containing a small e.e. **The subsequent terrestrial sequestration of an initial e.e. and its amplification into dominance** are processes for which biogenically credible mechanisms exist. The

production and propagation of biomimetic chiral organic polymers has also been shown, though only in part plausible in terms of prebiotic mechanisms.

Over the 200 million years or so between the end of the Hadean Age and the first appearance of biological metabolism, [121, 188] organic molecules and amino acids, including a seeding of chiral amino acids, were delivered to Earth by way of carbonaceous chondrites, comets, and interplanetary dust particles. Additional terrestrial organics and amino acids were most likely copiously synthesized in hydrothermal vent systems. The organic materials are suggested to have been absorbed and concentrated by various clays and minerals, with special attention paid to adsorption and uptake by weathered porous feldspars. These feldspar and other porous mineral regimes are considered to have been located in the vicinity of extensive near-shore and subaerial hydrothermal vent fields and thus exposed both to a fluence of reducing and reactive molecules and to thermal flux.

The continuous availability of trillions of independent microreactors greatly multiplied the initial mixture of extraterrestrial organics and hydrothermal vent-produced chemicals into a rich variety of adsorbed and transformed materials, including lipids, amphiphiles, chiral metal complexes, amino acid polymers, and nucleotide bases. Production and chiral amplification of polypeptides and other polymeric molecules would be induced by exposure of absorbed amino acids and organics to dehydration/rehydration cycles promoted by heat-flows beneath a sea-level hydrothermal field or by sporadic subaerial exposure of near-shore vents and surfaces. In this environment the e.e. of chiral amino acids could have provided the ligands required for any metal centers capable of catalyzing enantiomeric dominance. The auto-amplification of a small e.e. of L-amino acids, whether extraterrestrially delivered or fluctuationally induced, thus becomes conceptually reasonable.

Amplification of any enantiomeric excess could rapidly propagate an enantiomeric takeover within the micron-sized cavity of a weathered feldspar microreactor. We can even imagine this process assisted by the spontaneous appearance of an excess of chiral liquid crystal domains of preferred handedness, composed of membranous associations of achiral complex amphiphiles seeded with an e.e. of dissolved chiral molecules, in analogy to the laboratory observations described in Section 11.3. The porous mineral interiors also allow the arguably high likelihood of contingent metal ion-enhanced catalytic reactivity of polypeptides as progenitors to the now ubiquitous metalloproteins, and the likelihood of evolutionary selection among the produced reactivities. This massively parallel process of natural experimentation, as encouraged by networked microporous minerals, implies the likelihood of coevolution [189] and subsequent conjoining of protobiochemical pathways.

These possibilities rectify the proposed subsequent appearance and amplification of chiral autocatalytic molecules and hypercycles. [190] Any autocatalytic systems would propagate [191] throughout an extensive adjoining hydrated porous network already rich in layered amphiphiles, lipids, polymeric materials, amino acids, thiols, and so forth. In addition, amphiphiles are known to be organized into lipid membranes by interaction with the inner surfaces of porous minerals. [136] It is a small organizational jump from these membranes to fully formed lipid vesicles.

As noted above, the occurrence of such chemistry within porous feldspars or other mineral assemblages near chemically rich and strongly reducing hydrothermal vent sites in the early oceans solves two problems. First, it solves the problem of rationalizing polymerization reactions in dilute solutions. Second, it solves the problem of assuming a prolific organic chemistry in the absence of reduced molecules and ammonia in a neutral (though nonoxidizing) [131] early terrestrial atmosphere. This chemistry, occurring both in the vicinity of and within the $\sim 0.5 \mu\text{m}$ cavities of weathered feldspar-like materials in the early Earth, provides the unifying framework for synthesis and containment of the products to critical concentrations.

Prior sequestration of the prebiotic reactions within the micropores of weathered feldspars or other porous rock matrices also avoids many of the other problems of catalysis and dilution encountered by models of chemical biogenesis. That is, this mechanism attains viable evolutionary chemical selection among spatially discrete systems *without* the need to assume an unlikely capture-and-enclosure event involving a pre-existing lipid membrane. [192] Thus autocatalysis of chiral molecules could evolve before the actual appearance of free-floating lipid vesicles.

At the point where amphiphiles were recruited to provide the precursors to cell membranes, stable lipid vesicles could have evolved [141] to enclose autocatalytic chiral hypercycles. Credible models for the subsequent evolution of vesicles containing self-replicating chiral molecules have appeared in the literature. [193, 194] These vesicles could then emerge from the feldspar spaces [134, 192] as micron-sized self-reproducing, energy-metabolizing vesicular systems: protobacteria ready to face the hydrothermal world on their own terms.

Westheimer [195] has stressed the critical importance of phosphorus-containing molecules in promoting biological processes. The cosmic origins and terrestrial geochemistry of phosphorus has been reviewed in the context of biogenic chemistry. [196] The hydrothermal origination of life within porous weathered minerals potentially solves the apparent contradiction of the ubiquity of polyphosphates in biochemistry as contrasted to both the relative rarity of crustal phosphate [197] and the insolubility of native calcium phosphate [apatite: $\text{Ca}_5(\text{PO}_4)_3\text{X}$, ($\text{X}=\text{F}, \text{Cl}, \text{OH}$)] and consequent low average concentration (ca. $2 \mu\text{M}$) of dissolved oceanic phosphate. [198] Phosphate is known to be adsorbed by siliceous clays [199–201] and to have specific affinity for the surface hydroxyls of silica, [202] and is found to be concentrated by several orders of magnitude in the sedimentary and clay deposits of lakes, estuaries, and oceans, over the level of dissolved phosphate. [201, 203] Apatite inclusions have been found within some feldspars [204] and must have been deposited there by absorption and recrystallization of dissolved phosphate. These findings support the idea that primordial phosphate could have been taken up and concentrated by the same silica-rich porous minerals as the primordial organic molecules and amino acids.

As is true today, most phosphate in the primordial crust must have been sequestered in nearly insoluble calcium phosphates and carbonates or in basalts, and only dissolved monomeric phosphate was produced by weathering. [201] However, the volatile polyphosphate P_4O_{10} is known to be a component of volcanic gases. [205] This material originates from the polymerization of phosphate minerals in mag-

matic melts. Tetrapolyphosphate P_4O_{10} hydrolyzes to polyphosphates and trimetaphosphate. Further, aqueous phosphoric acid is known to efficiently polymerize into polyphosphates under conditions of temperature (250–350°C) well within those attained within hydrothermal vent systems. [206] Therefore, the same heat flows inducing the dehydration/hydration cycles that might produce polypeptides at the surface of a hydrothermal system could have also produced polyphosphates at subterranean depths. [207] Delivery of the soluble polyphosphate fraction to the surface by the water flux of this system provides the necessary (and continuous) source of polyphosphates to the prebiotic mix. It is interesting to note that the high CO_2 atmosphere of the early Earth, described above, would have enhanced the solubility of apatite [203] by mild acidification of oceanic waters. The concentration of dissolved phosphate would also have been increased in the oceans of early Earth, relative to the modern pelagic level, because of the comparative scarcity of iron(III). Thus, a relatively rich phosphate-polyphosphate cycle can be plausibly argued to have existed on an early, thermally vigorous, Earth. Once present, the known reactivity of polyphosphates can be utilized in the evolution of any self-replicating system.

These ideas are readily testable and therefore can constitute a research enterprise. For example, the hydrolysis of polyphosphates to monomeric phosphate is relatively fast in weak aqueous acid and warm temperatures. [129, 205] Curiously, however, the same acidity would promote thermal polyphosphate synthesis under the dehydrating conditions of the heated subterranean mineral pores within a hydrothermal system. Measurement of the stability of polyphosphates in microscopic environments where the activity of water might be low would test the phosphate-polyphosphate conjecture made above. If polyphosphates are not stabilized relative to bulk water solutions, as dissolved within micron-sized mineral pores or within vesicles, perhaps in the presence of dissolved organics, then this hypothesis is in danger. Additionally, the proposed production and delivery of polyphosphates by hydrothermal systems can be tested in an appropriate laboratory setting.

Artificial hydrothermal vents might be constructed and supplied with plausible concentrations of simple reactants such as CO , H_2 , NH_3 , and H_2S . Appropriate levels of amino acids including a small chiral excess, along with the sorts of amphiphilic molecules described above, can be rationalized by the findings from the Murchison meteorite. Organic molecules such as found in irradiated interstellar ice models, including HMT, can also be included. The system should include weathered feldspars, which can be modified to include the reduced transition-metal minerals that they are known to contain. [134] Such minerals as Fe,Ni sulfides are likely to have been both present and stable in the environment of early Earth and are known [153, 155] to catalyze formation of organic molecules from simpler precursors.

The entire system, tested first in part and perhaps eventually in full, can subsequently be subjected to cycles of heat and cold, and hydration/desiccation. We might then look for the production of new chiral molecules, the appearance of homochiral dominance among amino acids and their polymers, and perhaps even the eventual emergence of micron-sized lipid vesicles containing catalytic and autocatalytic reaction cycles.

11.7

Concluding Remarks

The universe appears to be self-organizing across all length scales. Evidence of self-organization is obvious in the self-assembly of atoms from quarks and leptons and in the building up of the periodic table by the organization of electrons in shells and subshells. It is apparent from the nature of biopolymers in cells, to neural networks in brains, to organismal development in evolutionary biology and ecology, to the organization of stars in galaxies and even to the scale of the universe itself. Since the pioneering work of Oparin, Eigen, Kaufmann, and others, the origin of life has been regarded as emerging from chemical self-organization of one type or another. Therefore to find an answer to the question “What is life?” it is imperative to answer the question “From whence life?”

At the heart of life, as we know it, are homochiral biopolymers of which RNA, DNA, and the proteins are archetypal. This chapter has considered the question of how homochiral biopolymers can possibly arise from a nearly equal mixture of the chiral monomers. That is, not only how an initiating enantiomeric excess was generated on Earth but, more importantly, what sort of amplification and survival mechanisms might have been able to transform that small enantiomeric excess into the homochiral arrays found in contemporary biomolecules. In the course of exploring this question, we have been led to develop the above outline of what may have happened. We hope that this outline might inspire a series of experiments and eventually evolve into a workable model for this process. This research outline potentially includes all the elements of a viable, testable, and self-consistent theory for the origin of life. Clearly, the question of the origin of life is among the most profound questions asked by human minds. We dare to imagine that during the 21st century a coherent and credible theory of chemical biogenesis will emerge.

11.8

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