

# The Origin and Early Evolution of Life: Prebiotic Chemistry, the Pre-RNA World, and Time

## Review

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In the last few years, there have been a number of developments in origin of life studies that merit review. We will discuss primitive atmospheres, submarine vents, autotrophic versus heterotrophic origin, the RNA and pre-RNA worlds, and the time required for life to arise and evolve to cyanobacteria. Topics such as prebiotic synthesis, template polymerizations, and evolution of specific metabolic pathways will not be discussed here.

### The Primitive Atmosphere

There is no agreement on the composition of the primitive atmosphere, with opinion varying from strongly reducing ( $\text{CH}_4 + \text{N}_2$ ,  $\text{NH}_3 + \text{H}_2\text{O}$ , or  $\text{CO}_2 + \text{H}_2 + \text{N}_2$ ) to neutral ( $\text{CO}_2 + \text{N}_2 + \text{H}_2\text{O}$ ).

There is no geological evidence either way, although it is generally accepted that  $\text{O}_2$  was absent. It is beyond the scope of this review to explore this question, except to comment that atmospheric chemists mostly favor high  $\text{CO}_2 + \text{N}_2$ , whereas prebiotic chemists mostly favor more reducing conditions. Reducing conditions are required for the synthesis of amino acids, purines, pyrimidines, and sugars, and such syntheses are very efficient (Stribling and Miller, 1987). The robustness of this type of chemistry is supported by the occurrence of most of these biochemical compounds in the  $4.6 \times 10^9$ -year-old Murchison meteorite, a carbonaceous chondrite, which comes from an asteroid. The meteorite analysis results make it plausible, but do not prove, that such syntheses also occurred on the primitive Earth. Based on what is known about prebiotic chemistry, if the Earth was not reducing, then the organic compounds would have to be brought to it by dust particles, comets, and meteorites (Anders, 1989; Chyba et al., 1990). The amounts that can be brought in this way and survive passage through the atmosphere are quite small, and may not have been sufficient for the origin of life.

The temperature of the primitive Earth during the period of the origin of life is unknown. The entire planet is generally thought, without direct evidence, to have remained molten for several hundred million years after its formation  $4.6 \times 10^9$  years ago (Wetherill, 1990). The oldest sedimentary rocks in the Greenland Isua formation have been heated to  $500^\circ\text{C}$ , so the evidence on the conditions at that time has largely been destroyed. The sediments in the Australian Warrawoona formation  $3.5 \times 10^9$  years old contain very convincing cyanobacteria-like microfossils (Schopf, 1993). Some atmospheric

models incorporate high partial pressures of  $\text{CO}_2$  to raise the temperature of the Earth by a greenhouse effect and thus prevent the complete freezing of the oceans (Kasting, 1993). However, a frozen Earth has some advantages for prebiotic chemistry (Bada et al., 1994). But again, there is no direct evidence either way. In addition, processes relevant to the origin of life may have taken place in environments different from the terrestrial average, e.g., hot springs, eutectic sea water, or drying lagoons.

### Submarine Vents

Shortly after the discovery of submarine vents, or hot springs, at oceanic ridge crests (Corliss et al., 1979), a theory of the origin of life in these vents was proposed (Corliss et al., 1981). Considerable attention has been given to this theory (Holm, 1992) and the other possible roles of vents in the origin of life, but it seems unlikely that the vents played a role in prebiotic synthesis of organic compounds or polymers.

The hot springs arise by sea water being forced down into the sediments for several kilometers, heated by magma, and pushed through the vents at  $350^\circ\text{C}$ . A great deal of water is involved, with the whole ocean passing through them every ten million years. The theory proposes that organic synthesis took place during the passage of vent water down the  $350^\circ\text{C}$  to  $2^\circ\text{C}$  gradient, followed by synthesis of peptides and other polymers, and the conversion of these polymers to living organisms in the temperature gradient. The steps in this theory have been examined and shown not to work (Miller and Bada, 1988). For example, organic compounds are decomposed at  $350^\circ\text{C}$  rather than synthesized, and polymers such as peptides, RNA, and DNA are hydrolyzed rapidly rather than synthesized at vent temperatures. The submarine vents did play a role in the events leading to the origin of life, but this role was in regulating the composition of the ocean and possibly the atmosphere, and, more importantly, the destruction of organic compounds produced in the atmosphere. This means that organic compounds would not accumulate over very long periods of time, and therefore the vent destruction sets a time frame for the origin of life of approximately ten million years (Stribling and Miller, 1987; Lazcano and Miller, 1994).

The surprising occurrence of hyperthermophiles growing at temperatures as high as  $110^\circ\text{C}$  (not at  $350^\circ\text{C}$ ) near the vents (Forterre, 1996 [this issue of Cell]), as well as of tube worms and clams growing near the vents at  $37^\circ\text{C}$ , cannot be used as an argument for the origin of life at elevated temperatures, anymore than the present abundance of life on the Earth at  $2^\circ\text{C}$  in the ocean or  $37^\circ\text{C}$  in mammals indicates an origin at these temperatures (Miller and Lazcano, 1995).

### Heterotrophic or Autotrophic Origins

The Oparin-Haldane heterotrophic theory of the origin of life has been widely accepted on the basis that a heterotrophic organism is simpler than an autotrophic

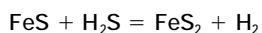
one, and prebiotic synthesis experiments show how easy it is under reducing conditions to produce organic compounds, many of which are used in present biology. There are, however, some recent examples of autotrophic proposals made for a variety of reasons.

One reason for proposing an autotrophic origin is the CO<sub>2</sub>-rich model of the primitive Earth's atmosphere (Kasting, 1993). High pressures of CO<sub>2</sub> (10–100 atm) imply the absence of reducing conditions and organic compound synthesis, and therefore it would be necessary for the first organisms to biosynthesize their organic compounds, or to make use of the very small amounts of organic compounds brought in by comets and meteorites.

An autotrophic theory involving nonenzymatic reactions patterned after present biochemical pathways of intermediate metabolism has been proposed (Hartmann, 1975). According to this scheme, the citric acid cycle started with acetyl-CoA by two CO<sub>2</sub> fixations. The development of such a system is envisioned to require clays, transition state metals, and UV light. Although there are a few biosynthetic reactions that will proceed nonenzymatically, most do not. Cyclic pathways need to be very efficient or they will stop working. An example is the Krebs cycle, which stops unless the oxalacetate lost by nonenzymatic decarboxylation is replaced. Non-cyclic pathways are less bothered by this problem, but, in any case, this idea has never been given an experimental test.

Cairns-Smith (1982) proposed a clay mineral theory in which the genetic information is contained in the pattern of ions in the clay mineral lattice, and reproduction is accomplished by crystal growth. The mineral system is converted to the present biological one by an unspecified process called genetic takeover. There has been no experimental support for this theory after 20 years, although there were some promising reports that have not been confirmed.

The most elaborate autotrophic theory is that of Wächtershäuser (1992, and references therein), in which biosynthesis and polymerization are postulated to take place on the surface of FeS and FeS<sub>2</sub>. The reaction



is a very favorable one ( $\Delta G^\circ = -9.23$  kcal/mol;  $E^\circ = -620$  mV at pH 7 and 25°C), so the FeS/H<sub>2</sub>S combination is a strong reducing agent. According to this scheme, both enzymes and nucleic acids are the evolutionary outcome of such surface-contained archaic metabolism. The FeS/H<sub>2</sub>S has been used to reduce double bonds,  $\alpha$ -ketoglutarate to glutamic acid, thiols to hydrocarbons, et cetera, (Hafenbradl et al., 1995, and references therein). However, the FeS/H<sub>2</sub>S system does not reduce CO<sub>2</sub> to amino acids, purines, or pyrimidines, even though there is more than adequate free energy to do so (Keefe et al., 1995). But the reduction of CO<sub>2</sub> is precisely what is required of an autotrophic theory. The FeS/H<sub>2</sub>S system may have been used to reduce prebiotic compounds synthesized by other energy sources in reducing atmospheres, thereby being a component of a heterotrophic theory of the origin of life and Oparin's primitive soup.

There have been so many unsuccessful attempts to produce prebiotic organic compounds with CO<sub>2</sub>+N<sub>2</sub>+H<sub>2</sub>O mixtures (in the absence of hydrogen) that one wonders whether successful prebiotic syntheses are possible under such conditions. Those who propose autotrophic theories need to provide experimental evidence of how organic compounds can be produced, and how such systems can work. This is quite a challenge, since even heterotrophic entities, which need only take their compounds from the environment, are difficult to envision.

#### **Autotrophic Hyperthermophiles: They May Be Ancient, but They Are Hardly Primitive**

Another reason for postulating an autotrophic origin of life is that the deepest branches of the universal tree of life are occupied by anaerobic sulfur-dependent hyperthermophiles that fix CO<sub>2</sub> by a reductive Krebs cycle. It is then assumed that this metabolism is primordial, rather than a result of extensive development (Maden, 1995). However, it is important to distinguish between ancient and primitive. Hyperthermophiles may be cladistically ancient, but they are hardly primitive relative to the first living organisms. They contain the same elaborate protein biosynthesis and most of the enzymes of modern organisms. They seem to be no more primitive in their replication and translation apparatus and metabolic abilities than mesophiles (Miller and Lazcano, 1995).

Truly primitive organisms would be those of the RNA world or some of their immediate descendants in which a simplified version of the DNA/protein system had already appeared. In principle, the latter could be recognized because they would branch off early in a universal tree of life, and would be endowed with simpler replication and translation machinery demonstrably not due to secondary adaptations. However, no such organisms have been found. The study of hyperthermophiles is an invaluable source of information on early biological evolution and the nature of the last common ancestor of all extant life forms, but an extrapolation into prebiotic times should not be taken for granted. Since the metabolic processes of the RNA world and the chemical reactions of prebiotic times were different from present day metabolism, phylogenetic information from extant protein sequences can not be applied to understand them.

#### **Computer Experiments on Origin of Life**

There has been a school of workers applying computer modeling to origin of life processes (Kauffman, 1993). These computer simulations (referred to in some circles as experiments *in silico*, in contrast with *in vitro* or *in vivo*) can model Darwinian evolution and the emergence of order from chaotic systems. However, these calculations have so far not provided guidelines for origin of life studies because they do not take into account the specific properties of individual organic compounds and polymers, e.g., the base pairing of AU and GC.

#### **Pre-RNA Worlds**

The discovery of catalytic RNA gave credibility to prior suggestions that the first living organisms were self-replicating RNA molecules with catalytic activity, a situation called the RNA world (Gesteland and Atkins, 1993).

This idea has become widely accepted, but as will be shown below, it is unlikely that RNA itself with AUGC and a ribose phosphate backbone is a prebiotic molecule. We will refer to the period when the informational macromolecule had a backbone different from ribose phosphate and possibly different bases as the pre-RNA world. The pre-RNA world is assumed to have the same essential characteristic of the RNA world—phenotype and genotype both reside in the same polymer, so no protein or related catalysts are required to be synthesized. Work on nucleic acids with hexoses, instead of pentoses and pyranoses, in place of furanoses suggest that a wide variety of informational macromolecules are possible, even when restricted to sugar phosphate backbones (Eschenmoser, 1994). The most interesting nonsugar alternative is peptide nucleic acid (PNA). This has a backbone of ethylenediamine monoacetic acid, with the bases attached by an acetic acid, and it binds strongly to DNA (Nielsen, 1993). The monomers of PNA are likely prebiotic compounds, but it is not clear whether the polymer can be formed. Since many other alternatives are possible, RNA itself may have been the evolutionary outcome of a series of different genetic polymers.

#### The Chemical Stability of Ribose: Implications for the Origin of Life

Recent results show that RNA itself is an unlikely prebiotic molecule. The first problem is that there is no prebiotic reaction that gives largely ribose rather than a mixture of many sugars, including those with branched chains (Shapiro, 1988), although there is one promising prebiotic process that might be feasible using glycolaldehyde phosphate as a starting reagent (Müller et al., 1990).

The second problem is that sugars decompose very rapidly on the geological timescale. Thus, the half-life for ribose decomposition is 73 min at 100°C and pH 7, and 44 years at 0°C and pH 7. Other sugars are similarly unstable at 100°C and pH 7, with the rate approximately proportional to the amount of free aldehyde in the sugar. Examples are ribose 5-phosphate ( $t_{1/2} = 9$  min), deoxyribose ( $t_{1/2} = 225$  min), and ribose 2,4-diphosphate ( $t_{1/2} = 31$  min) (Larralde et al., 1995).

The instability problem could be overcome if the ribose nucleosides could have formed early, because nucleosides are quite stable owing to the absence of free aldehyde in its sugar. However, there is no efficient prebiotic synthesis of purine ribosides and no prebiotic synthesis of pyrimidine nucleosides at all. Added to these problems is the fact that any prebiotic synthesis of ribose or nucleosides would give a racemic mixture, and all template polymerization experiments so far show enantiomeric cross inhibition. This is where the presence of activated L nucleosides in a template polymerization of activated D nucleosides causes chain termination during polymerization (Joyce et al., 1987).

#### Are Polyphosphates Prebiotic?

It also has become clear that polyphosphates and activated phosphates were not abundant prebiotic compounds (Keefe and Miller, 1995). There is no known

polyphosphate mineral known, and only a few kg of calcium pyrophosphate have been found in a deposit in New Jersey. The primitive Earth may have been different, but no one has yet shown how large amounts of polyphosphates could have been produced. Recently, it has been shown that phosphorus pentoxide ( $P_4O_{10}$ ) can be produced by heating volcanic basalts to 1200°C, and small amounts of pyrophosphate and tripolyphosphate have been found in a fumarole near Mount Usa in Hokkaido, Japan (Yamagata et al., 1991). However, the amounts of polyphosphates produced are so small that even greatly increased volcanic activity on the primitive Earth would not make polyphosphates available as useful prebiotic reagents, except by their concentration in very local areas. It could be argued that the first self-replicating systems arose in such rare environments. We consider this to be unlikely, but such a possibility can not be excluded altogether.

It thus follows that polyphosphates are an unlikely prebiotic free energy source and that phosphate esters are unlikely to have been involved in the first genetic material. This is a very strong statement, because of the central role that phosphates play in the metabolism of all known organisms, but this can only be revised when a robust prebiotic process for polyphosphate synthesis or a plausible geochemical mechanism for concentrating them are found. One alternative is thioesters, which are high-energy compounds (de Duve, 1991). Another possibility is the spontaneous synthesis of a polymer from high energy precursors, e.g., the polymerization of glycine nitrile to polyglycine is thermodynamically favorable, although the reaction is sluggish.

#### How Long Did It Take for Life to Appear?

It generally has been assumed that the origin of life took place after extended geological periods of time. Although it is not possible to assign a precise chronology to the events leading to the origin of life, in the last few years estimates of the available time for this to occur have been considerably reduced. There is compelling paleontological evidence that microbial communities were thriving on the primitive Earth  $3.5 \times 10^9$  years ago (Schopf, 1993), and it has been suggested that life may have been killed off as late as  $3.8 \times 10^9$  years ago if the Earth was undergoing impacts from large asteroids (Maher and Stevenson, 1988; Sleep et al., 1989). Thus, only 300 million years appear to be left for the origin and early diversification of life.

It has been argued that such short periods of time make the accumulation of the prebiotic soup unlikely, and therefore should be interpreted as evidence supporting an autotrophic origin of life (Maden, 1995). As argued below, there is no reason to assume that life required enormous periods of time to originate and evolve to the  $3.5 \times 10^9$ -year-old cyanobacteria-like Warrawoona microfossils. The accumulation of organic compounds of abiotic origin in the primitive oceans is balanced by destructive processes, and if prebiotic synthesis stops because of atmospheric changes, then it would not be possible for life to arise after the organic compounds decompose. On the other hand, the chemistry of prebiotic reactions is robust, and does not require

extended periods of time to take place. For instance, the slow step in the Strecker synthesis of amino acids is the hydrolysis of the corresponding amino nitrile to the amide, which has a half-life of 40 years at pH 8 and 0°C (Miller and Van Trump, 1981) (half-lives of 40 years or a process completed in  $10^5$  years are slow by biological standards, but rapid on the geological time scale). An example of a relatively rapid prebiotic synthesis is that of amino acids on the Murchison meteorite parent body, where it apparently occurred in less than  $10^5$  years (Peltzer et al., 1984). Thus, although the buildup of the prebiotic soup may have involved millions of years, the individual reactions to synthesized prebiotic compounds have short half-lives, and there are no known relevant examples of slowly synthesized molecules.

Whatever the nature of the first genetic polymer, it is clear that hydrolysis must have limited its accumulation in the primitive environment. An informational polymer must have a lifetime comparable with that of the organism (Westheimer, 1987) or, at least, with the time required for its replication. Even if a slow addition of monomers to a genetic polymer is envisioned, the rate of polymer synthesis nonetheless must be rapid compared with hydrolysis rates, especially if a significant amount of genetic information is to be contained in the polymer. Thus, a 100-base long RNA molecule needs to be synthesized at least 100 times faster than the hydrolysis rate of a single phosphodiester bond. Even if highly stable precursors to the ribose phosphate backbone of RNA are proposed for the pre-RNA world, the bases themselves will decompose over long periods of time. For example, cytosine hydrolyses to uracil with a half-life of 300 years at pH 7 and 25°C in single-stranded DNA (Lindahl, 1993). Adenine, which is usually thought to be very stable, deaminates to hypoxanthine with a half-life of 204 days at 100°C and pH 7 (Shapiro, 1995). This is only about ten times slower than cytosine ( $t_{1/2} = 21$  days at 100°C and pH 7). Given these stability constraints, there is no reason to assume that the self-organization of prebiotic compounds into a system capable of undergoing Darwinian evolution involved extended periods of time. We envision a maximum upper limit of  $5 \times 10^6$  years, because this is the half-life for destruction of organic compounds in the oceans owing to their passage through the submarine vents (Lazcano and Miller, 1994).

These stability calculations can also be used to set an upper limit for the amount of time available for protein biosynthesis to appear. Although the emergence of translation was once considered the central issue in the origin of life, the discovery and characterization of ribozymes, including the specific binding of amino acids to RNA molecules (Yarus, 1993) and the possibility that peptidyl-transferase activity resides in the RNA component of the ribosome (Noller et al., 1992) have given credence to the idea that a rudimentary form of protein synthesis originated in the RNA world. How this took place is unknown, but it could not have been delayed for extended periods of time owing to the decomposition of both RNA and amino acids in aqueous solutions, which is significant even at low temperatures. Although alanine decomposes slowly by irreversible decarboxylation ( $t_{1/2} = 10^9$  years at 25°C), other amino acids are

rather unstable. Serine and threonine have half-lives of approximately  $10^3$  years at 25°C, whereas histidine and tyrosine decompose at a much faster rate. This problem would have been avoided if amino acid biosyntheses were accomplished by ribozymes. It has been suggested that this may be the case in histidine biosynthesis (White, 1976), but no evidence supporting this claim is available.

### The Role of Gene Duplication in Early Cell Evolution

There is still a gap between descriptions of prebiotic events and the last common ancestor. Intermediate stages must have involved simpler organisms with much smaller genomes. The question is whether it is possible to infer some of their major characteristics. It has long been recognized that most genetic information is not essential for cell growth and division. Statistical analysis of ~80 randomly selected chromosomal loci for *Bacillus subtilis* has led to the suggestion that the minimum cellular genome size is of the order of 562 kb (Itaya, 1995). This figure is comparable with the size of the *Mycoplasma genitalium* genome, which is 580 kb long and codes for 482 genes (Fraser et al., 1995). The compactness of mycoplasma genomes can easily be understood in terms of their parasitic lifestyle, but it is somewhat surprising that the streamlining processes have not greatly affected the length of the genes or the number involved in protein synthesis and DNA replication (Fraser et al., 1995; Bork et al., 1995).

It is unlikely that such a large array of sequences involved in replication, transcription, and translation were already present in the first DNA/protein organisms. Most enzymes are recognized to have arisen by gene duplication. The uncertainty is the number of enzymes that did not arise in this manner, i.e., the starter types. In some cases, the starter types may stem from slow nonenzymatic reactions where the protein improves on a previously sluggish process, e.g., pyridoxal catalyzed transaminations.

Based on the similarity of many biochemical reactions, and on the observation that many proteins of related function share the same ancestry within a given organism, we estimate that the number of starter types ranged from 20–100, but the reader might want to make her or his own list of minimal enzymes. Analysis of the currently available databases, including the recently completed entire genome sequences of *Haemophilus influenzae* (Fleischmann et al., 1995) and *Mycoplasma genitalium* (Fraser et al., 1995), has shown that a large proportion of each organism's genes are related to each other as well as to genes in distantly related species. All known life forms share a common pool of highly conserved genetic information that was shaped to a considerable extent by paralogous gene duplications and divergence events predating the prokaryote-eukaryote divergence.

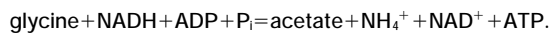
A few examples of the wide variety of such gene duplications involved in the translation and replication machineries include: the *Escherichia coli* ribosomal proteins, which are the result of gene duplications; the elongation factors; aminoacyl tRNA synthetases, which are the result of gene duplication events of two major

starter types; and DNA polymerases (cf. Lazcano and Miller, 1994).

Evidence of extensive gene duplication supports the contention that metabolic pathways were assembled by the so-called "patchwork mechanism," i.e., original biosynthetic routes may have been mediated by primitive enzymes lacking absolute substrate specificity (Jensen, 1976). Sequence analysis of some universally distributed anabolic genes like those in the histidine biosynthetic pathway sequences support this possibility (Fani et al., 1995). In the case of chlorophyll-dependent photosynthesis, evidence of duplication and even double-duplication events has been preserved in ferredoxins, F-type ATPases, the reductases involved in chlorophyll and bacteriochlorophyll biosynthesis, the bacterial photosynthetic reaction center, the two sets of light-harvesting antennae, and photosystems I and II (cf. Lazcano and Miller, 1994).

### Explosive Metabolic Evolution

If it is assumed that life arose in a prebiotic soup containing most, if not all, of the necessary small molecules, then there was a large potential energy supply available on the primitive Earth from different fermentations. It is clear that such compounds could provide both the growth and energy supply of a large number of organisms, but this would rapidly result in the depletion of the available nutrients. Although the usual example of a primordial fermentation is that of glucose (Oparin, 1938), it is unlikely that large quantities of this sugar were available in the primitive environment because of its instability. As noted by Clarke and Elsdon (1980), a more likely early fermentation reaction was that of glycine:



The primitive ocean may have had a glycine concentration between  $10^{-8}$ – $10^{-4}$  M, depending on the efficiency of prebiotic synthesis and whether the ultimate source of organic compounds was endogenous or not. At one mole ATP per mole of glycine, these values correspond to  $10^{25}$ – $10^{28}$  cells. Such high numbers of cells would lead to an exponential decrease in the concentration of the available fermentable organic compounds of prebiotic origin and would bring about a metabolic crisis that could only be overcome by the evolutionary development of light-harvesting autotrophic organisms with  $\text{CO}_2$ -fixing abilities (Lazcano and Miller, 1994).

The time for evolution of the first DNA/protein organisms to oscillatorian-like cyanobacteria is usually thought to be very long, because the latter have rather large genomes of  $6 \times 10^3$  kb to  $8 \times 10^3$  kb (Herdman, 1985) and are usually considered to be very complex. However, many of the evolutionary novelties required for the emergence of oxygenic photosynthesis are the result of duplication and divergence of genes. Assuming that Archean cells had a random rate of duplicon fixation, and a rate of spontaneous gene duplications comparable with the present values of  $10^{-5}$ – $10^{-3}$  gene duplications (Anderson and Roth, 1977), the time required for the development of a 100 kb genome of a DNA/

protein primitive heterotroph into a 7,000-genes filamentous cyanobacteria would require only  $7 \times 10^6$  years (Lazcano and Miller, 1994).

It is well known that only a few weeks are required for the rapid spread of duplicates in bacterial populations under the stress conditions of directed evolution experiments. There appear to be no experimental measurements of the rate of formation and fixation of new enzyme activities resulting from gene duplication. However, recent results on the organophosphate and phosphonate hydrolyzing phosphotriesterase from *Pseudomonas diminuta* and other soil eubacteria suggest that this new enzyme diverged by duplication from the  $\alpha/\beta$  barrel family and reached the diffusion limit in only 40 years (Scanlan and Reid, 1995). Thus, the rate of duplication and fixation of new genes can be surprisingly fast on the geological timescale.

There are a number of additional mechanisms that could have increased the rate of metabolic evolution, including the modular assembly of new proteins, gene fusion events, and horizontal gene transfer as seen in extensive antibiotic resistance in bacteria. Directed evolution experiments have shown that new substrate specificities appear in a few weeks from existing enzymes by recombination events within a gene (Hall and Zuzel, 1980). This suggests that mosaic proteins may have enhanced the catalytic repertoire of ancient organisms.

It is likely that the widespread belief that the origin and early evolution of life were slow processes requiring billions and billions of years stems from the classical Darwinian approach that major changes are slow and proceed in a stepwise manner over extended periods of time. All the evidence reviewed here suggests that stability of monomers and polymers essential for the origin of life strongly limited the possibility of a slow emergence of life. After the explosive metabolic evolution that took place soon after the beginning of life, the basic genetic processes and major molecular traits have persisted essentially unchanged for more than three-and-a-half billion years, perhaps owing to the linkages of the genes involved and the complex interactions between different metabolic routes. At a macroevolutionary level, this represents a case of conservatism that is even more striking than the maintenance of the major animal body plans that appeared at the base of the Cambrian, and which have remained basically unchanged for 600 million years.

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