



## How life began on Earth: a status report

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### Abstract

There are two fundamental requirements for life as we know it, liquid water and organic polymers, such as nucleic acids and proteins. Water provides the medium for chemical reactions and the polymers carry out the central biological functions of replication and catalysis. During the accretionary phase of the Earth, high surface temperatures would have made the presence of liquid water and an extensive organic carbon reservoir unlikely. As the Earth's surface cooled, water and simple organic compounds, derived from a variety of sources, would have begun to accumulate. This set the stage for the process of chemical evolution to begin in which one of the central facets was the synthesis of biologically important polymers, some of which had a variety of simple catalytic functions. Increasingly complex macromolecules were produced and eventually molecules with the ability to catalyze their own imperfect replication appeared. Thus began the processes of multiplication, heredity and variation, and this marked the point of both the origin of life and evolution. Once simple self-replicating entities originated, they evolved first into the RNA World and eventually to the DNA/Protein World, which had all the attributes of modern biology. If the basic components water and organic polymers were, or are, present on other bodies in our solar system and beyond, it is reasonable to assume that a similar series of steps that gave rise of life on Earth could occur elsewhere.

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### 1. Introduction

One of the major scientific questions that confront humanity is whether life exists beyond Earth. If the conditions and processes that resulted in the origin of life on Earth are common elsewhere, then it is reasonable to expect that life could be widespread in

the Universe. It is generally assumed that there are two fundamental requirements for life as we know it: the presence of liquid water and organic polymers, such as nucleic acids and proteins. Water's unique properties (excellent solvent, exceptionally large liquid temperature range, etc.) make it an ideal medium for chemical reactions to take place. Polymers are needed to carry out the central biological functions of replication and catalysis. Without these vital components, as far as we know, life is impossible.

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The origin and early evolution of life on Earth can be divided into several stages [1–3]: the prebiotic epoch; the transition to primitive biotic chemistry (the pre-RNA World); the evolution of the early biotic chemistry of the pre-RNA World into self-replicating RNA molecules (the RNA World); and the evolution of the RNA World into modern DNA/protein biochemistry (DNA/Protein World) which was a common ancestor of all subsequent life on Earth. The appearance of the first molecular entities capable of multiplication, heredity and variation, which probably occurred in the later part of the pre-RNA World, marked the point of the origin of both life and evolution.

It is only the two end members in this series, the prebiotic epoch and the DNA/Protein World, that we know the most about [3]. We can readily investigate in the laboratory, using a variety of plausible geochemical conditions, the possible routes by which compounds of biological interest could have been produced on Earth. Meteorites can be studied to determine what clues they contain about natural abiotic organic chemistry. The genes and proteins of modern organisms can be dissected in order to ascertain information about their possible origins. The first time that direct evidence of life's existence would have been preserved in the form of physical fossils in ancient rocks occurred in the DNA/Protein World when the compartmentalization of the biochemical machinery by cell-like membrane structures comparable to those used in modern biology likely became widespread. Fossilized structures that resemble single-cell organisms similar to modern day cyanobacteria have been found in rocks formed 3.5 billion years ago (Ga) [4], although whether these structures are indeed ancient fossils or artifacts has recently become controversial [5]. Rocks older than 3.5 Ga have been so extensively altered by metamorphic processes that any molecular or fossilized evidence of earlier life has apparently been largely obliterated (for example, see [6]).

To evaluate how life may have begun on Earth, we must access what the Earth was like during its early history and under what conditions the processes thought to be involved in the origin of life took place. Considerable progress has been made in our knowledge of the early Earth and in how the transition from abiotic to biotic chemistry may have occurred. Nevertheless, there are still enormous gaps in our understanding of how the simple organic compounds

associated with life as we know it reacted to generate the first living entities and how these in turn evolved into organisms that left behind actual evidence of their existence in the rock record.

## 2. Origin of life theories

Two views on how the transition from abiotic organic compounds to autonomous self-replicating molecules capable of evolving by natural selection into ones of increasing efficiency and complexity took place are presently dominant [1]:

- (a) *The prebiotic soup theory*: Organic compounds in the primordial oceans, derived from a variety of possible sources, underwent polymerization producing increasingly complex macromolecules, some of which by chance were capable of catalyzing their own self-replication. These simple self-replication entities evolved into increasingly complex ones and eventually into organisms with modern biochemistry.
- (b) *The metabolist theory*: A primitive type of “metabolic life” characterized by a series of self-sustaining reactions based on monomeric organic compounds made directly from simple constituents ( $\text{CO}_2$ , CO) arose in the vicinity of mineral-rich hydrothermal systems. According to this theory, at first, “life” did not have any requirement for informational molecules. As the system of self-sustaining reactions evolved in complexity, genetic molecules were somehow incorporated in order for metabolic-based life to develop into biochemistry as we know it.

Besides these two dominant theories, there have also been numerous suggestions that life began elsewhere and was transported to Earth (for example, see [7]), but this only shifts the problem of the origin of life to a different location.

According to the modern version of the prebiotic soup theory [1], organic compounds derived from “homegrown” chemical synthetic reactions on Earth and the infall of organic rich material from space accumulated in the primordial oceans. These compounds then underwent further reactions in the primal broth, producing ones with increasing molecular

complexity. Some of these reactions took place at interfaces of mineral deposits with primitive ocean water, while others occurred when the primitive ocean constituents were concentrated by various mechanisms, such as evaporation in shallow water regions or the formation of eutectic brines produced during the freezing of parts of the oceans.

From the assortment of simple organic compounds in the primitive oceans, geochemical processes next resulted in the synthesis of polymeric molecules. As the variety of polymers (oligomers) that were assembled from the simple monomers by polymerization processes became more varied, some by chance acquired functions, such as the ability to catalyze other reactions. With the rise of catalytic molecules, increasingly complex macromolecules were produced and eventually by chance molecules with the ability to catalyze their own imperfect replication appeared. Although these first replicators at first probably represented only a tiny fraction of the large array of macromolecules, with the ability to catalyze their own replication, they would have soon become increasingly more abundant. This would have marked the transition from purely abiotic chemistry to primitive biochemistry. These first self-replicating molecular entities began the evolutionary cascade that next led to the RNA World and then to the DNA/Protein World that had all the characteristics of modern biochemistry. The chance aspects of this scenario have been used to argue that the prebiotic soup theory is flawed and unscientific [8], but chance events have shaped the course of life's evolution several times throughout its history, with the Cretaceous/Tertiary impact-induced extinction event 65 million years ago (Ma) being one striking example.

In contrast to the prebiotic soup theory, the metabolist theory claims that life at its beginning was nothing more than a continuous chain of sulfide mineral catalyzed self-sustaining chemical reactions with no requirement for genetic information [8–11]. This theory has recently become popular, as some researchers have questioned the validity of the prebiotic soup theory. 'Metabolic life' is rightfully referred to as "Life as we don't know it" [11]: life as we know it is based on both chemistry *and* information. In an attempt to incorporate informational molecules into the metabolist scheme, it has recently been suggested that an elaborate cascade of metabolic reactions entrained within sulfide minerals around hydrothermal vents developed all the way to

RNA molecules and even primitive cells [12]. However, given the transient, short-lived nature of hydrothermal systems, the plausibility of this process under geochemical conditions seems questionable.

In principle, self-sustaining autotrophic reactions conceivably could have arisen in any type of environment as long as the reactant/product molecules survived long enough to continue to be part of the overall reaction chain. Of the various reaction schemes that have been proposed, however, none have been demonstrated to be autocatalytic with one possible exception [13]. The exception is the formose reaction, where the formation of a diverse variety of sugars from formaldehyde in the presence of alkaline catalysts apparently involves an autocatalytic cycle that can result in the continuous autocatalytic synthesis of sugars as long as there is an unlimited supply of formaldehyde [13].

Advocates of the metabolist theory generally favor hydrothermal environments (for example, see [9,14]). However, even if the metabolic-type reaction schemes that have been proposed were feasible, they would not have been unique to hydrothermal temperatures. Reactions that take place rapidly at elevated hydrothermal temperatures would also occur at the more moderate temperatures characteristic of the overall surface of the Earth, albeit at slower rates. The central issue is which temperature regime is more geochemically relevant. A germane example is petroleum, which is mainly produced by a series of reactions that take place as buried sedimentary organic matter is subjected to geochemical processing over time scales of several million years. Although petroleum can be produced at hydrothermal temperatures of 300 to 350 °C in periods as short as 100 years [15], the majority of the Earth's petroleum was formed at peak temperatures of ~120 °C, which demonstrates the dominance of the lower temperature regimes at least in the geochemical processes associated with petroleum formation [16].

The potential importance of autocatalytic reactions should not be underestimated, however. Self-sustaining reaction chains could have played an important role in enriching the prebiotic soup in molecules that were perhaps not readily synthesized by other abiotic reactions or which were unstable and thus need to be continuously and rapidly synthesized in order to be available for subsequent reactions. In this sense, the prebiotic soup and metabolist theories are synergistic and complementary.

### 3. The primitive Earth

During the final planetesimal accretionary phase of the Earth and especially in the period immediately following the moon forming impact event at 4.51 Ga, the Earth's surface was likely covered with a liquid rock, or magma, ocean [17]. Any water at the surface would have been present as steam in the atmosphere. These high temperatures would have incinerated any organic compounds, derived from whatever sources. Thus, in its earliest history, the Earth was likely devoid of an organic carbon reservoir, especially in comparison to the modern Earth where 20–30% of the surficial carbon is present as organic matter.

Although the rock record of the Earth prior to ~3.9 Ga is not preserved, oxygen isotopic analyses of the 4.3 to 4.4 Ga detrital zircons indicate that temperatures had apparently decreased to the point that liquid water was present on the Earth's surface about 100–200 million years after accretion [18,19]. Earth's water is thought to have been derived mainly from degassing of hydrated minerals initially present in the mantle and to a lesser extent from the infall of asteroids and comets [20]. If the Earth's water did indeed mainly come from degassing of the mantle as the early Earth underwent differentiation, then most of the water on the surface today ( $10^{21}$  l) was probably released early in Earth's history. Although the composition of early ocean water is not known, if all the salt deposits presently stored on the continents along with that present in saline groundwaters was originally in the oceans, the salt content of the primitive oceans could have been nearly twice that today [21].

Based on the ancient zircon evidence, Earth during the period 4.4 to 4.0 Ga may have been cool enough to allow for the presence of extensive liquid water oceans for long periods [22]. Based on the lunar cratering record, during this same period, the Earth was apparently relatively free of ocean vaporizing or sterilizing impacts [23]. When liquid water started to accumulate, temperatures would have become cool enough to allow for the survival of organic compounds derived from various sources. It was thus likely that during this presumably relatively quiescent interval between 4.4 and 4.0 Ga, some of the key steps in the origin of life may have occurred (see Fig. 1).

The Sun is estimated to have been ~30% less luminous than today during the early history of the

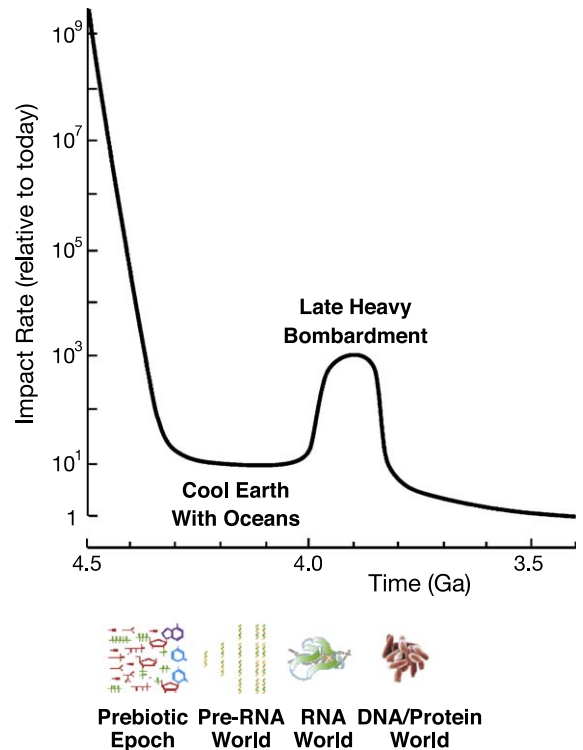


Fig. 1. The impact history of the early Earth and the various stages involved in the origin and evolution of life. Based on [2,22].

Earth, which gives rise to the so-called faint young Sun paradox [24]: without a significantly enhanced greenhouse effect relative to the modern Earth, global surface temperatures would have been  $-40$  °C because of a planetary albedo near that of ice [25]. Consequently, the Earth could have become a permanently frozen planet early in its history. Although it was first suggested nearly 25 years ago that atmospheric  $\text{CO}_2$  levels  $10^3$  to  $10^4$  times modern levels provide one solution to the frozen Earth dilemma, recent considerations of the early carbon cycle suggest that before extensive tectonic recycling of crustal sediments became common, most of the carbon on the Earth's surface would have remained buried in the crust and mantle as calcium carbonate [26]. Thus,  $\text{CO}_2$  may not have been present in the atmosphere at levels adequate to prevent global glaciation, unless other greenhouse gases were present. Apparently,  $\text{CO}_2$  levels were insufficient to prevent global glaciation at around 2.45 to 2.22 Ga and at ~600 Ma when the Sun was ~17% and ~6%, respectively, less luminous than today [24,25]. Without enhanced greenhouse warming associated with higher  $\text{CO}_2$  levels, the

widespread occurrence of an ocean ice cover could have been common in the early history of the Earth [27]. The presence of methane and ammonia in the atmosphere provides a potential solution to the faint early Sun/frozen over early ocean problem (for example, see [28]). However, these gases would have been prone to rapid UV photolysis and thus might not have accumulated to sufficiently high concentrations to prevent ocean freezing.

Even if the Earth's early oceans were totally ice covered, the oceans would not have completely frozen [27]. Heat from the Earth's interior leaking through the oceanic crust would have provided a heat source to the deep ocean beneath the ice layer. A similar heat source today provides sufficient basal heat to produce large subsurface lakes such as Lake Vostok at the base of the Antarctic ice sheet. Using a simple one-dimensional heat flow model and assuming a heat flow of  $\sim 3$  times the present day value, it has been estimated that the ice thickness on an ice covered early ocean would have been  $\sim 300 \pm 100$  m.

Bolide impacts could have played a role in melting the iced-over primitive ocean. Bolide induced melting could have been especially important during the 3.8 to 4.0 Ga 'late heavy bombardment' period [29] and helped promote the transition to a more permanently ice-free ocean. Bolide impacts could have also, however, had some unwanted dire consequences with respect to the transition to an ice free early Earth. Impacts may have generated an opaque equatorial debris ring that, because of its shadow, caused reduced solar insolation at low latitudes [30]. This in turn could have triggered the onset of glaciations and the return of global ice.

It was under these uncertain, chaotic, seemingly adverse and tumultuous conditions that the ingredients for life somehow accumulated and the first primitive life forms emerged on the Earth.

### 3.1. *The Prebiotic Epoch*

In 1953, Stanley L. Miller demonstrated the ease by which important biomolecules, such as amino and hydroxy acids, could be synthesized under what were viewed at the time as plausible primitive Earth conditions (see [31] for a summary of this classic experiment). A key aspect of the experiment was the formation of hydrogen cyanide (HCN), aldehydes and

ketones produced during the sparking of the reduced gases  $H_2$ ,  $CH_4$  and  $NH_3$ . The formation of these reagents suggested that the compounds were produced by the Strecker–Cyanohydrin reaction, first discovered in 1850 by the German chemist Adolph Strecker. The actual synthesis takes place in aqueous solution, implying that on the early Earth, amino acids could have been produced in bodies of water, provided the necessary reagents were present. Only  $\alpha$ -hydroxy acids are formed in the absence of ammonia. Thus, the concentration of ammonia in the primitive oceans would have been critical in determining whether amino acids would have been synthesized by this process.

HCN is a critical reagent. Not only is it a central component of the Strecker reaction, but polymerization of HCN itself, even in  $-20$  and  $-78$  °C HCN-rich brines [32], generates important molecules, such as glycine, adenine and guanine. HCN is unstable and hydrolyzes to ammonia and formate, a reaction that is very rapid at elevated temperatures (half-life at 100 °C is  $\sim 1$  day at neutral pH [33]). Based on estimates of the rates of HCN production and hydrolysis, it has been estimated that the steady-state concentration of HCN in the primitive oceans would have been about  $2 \times 10^{-5}$  M at 0 °C and only  $4 \times 10^{-12}$  M at 100 °C at pH 7 [33]. This result strongly suggests that in order for HCN to play a significant role in prebiotic chemistry on the early Earth, temperatures at the time must have been cool.

The hydrolysis of HCN provides a potential source of ammonia in the primitive oceans even if ammonia was absent in the early atmosphere. Ammonia would have been continuously produced in the oceans by HCN hydrolysis, provided there was a continuous source of HCN, which remains uncertain, however. Ammonia may have also been injected into the early oceans by hydrothermal vent discharges [34], although most of the ammonia detected in modern hydrothermal systems is likely derived from the high-temperature decomposition of biologically produced organic matter rather than being abiotic in origin. In addition, ammonia could have been produced in the early oceans by the ferrous iron catalyzed reduction of nitrite [35]. If the primitive oceans were cool and more acidic than today, the ammonia would have been mainly dissolved in the ocean present as  $NH_4^+$ . This implies that even if there was adequate  $NH_4^+$  dissolved in the oceans to support prebiotic reactions, the atmospheric ammonia levels may have been too low to provide for sufficient



greenhouse warming to keep the early Earth's surface temperature above freezing.

One often-overlooked aspect of the Miller experiment is that the main product was oily goo. With a methane-rich atmosphere, oily material would have been produced in huge quantities on the early Earth, forming an oil slick that would have unimaginable on the Earth today. Oily material could have formed a protective layer on the primitive ocean surface that allowed not only for molecules to be protected from destruction by the sun's ultraviolet light [36], but also may have helped promote the condensation of simple monomeric compounds into polymers by acting as an anhydrous solvent [37]. In addition, the oily layer could have decreased the vapor pressure of water and thus the OH radical concentration in the atmosphere. As a consequence, the atmospheric lifetimes of reducing gases, such as methane and ammonia, could have been substantially increased [37].

Since the classic Miller experiment, numerous researchers have demonstrated that a large assortment of organic molecules can be synthesized using a variety of gaseous mixtures and energy sources (for example, see [38,39]). Most of the molecules that play an

essential role in modern biochemistry, such as amino acids, nucleobases, sugars, etc., have been synthesized under plausible geochemical conditions. The conditions employed have ranged from the highly reducing conditions first used by Miller to less reducing mixtures containing CO and CO<sub>2</sub> [40]. However, with neutral atmospheric mixtures containing CO<sub>2</sub> and N<sub>2</sub>, the yields of amino acids and other essential organic compounds is vanishingly low.

Many geoscientists today doubt that the primitive atmosphere had the highly reducing composition used by Miller in 1953. Although reducing conditions may not have existed on a global scale, localized high concentrations of reduced gases may have existed around volcanic eruptions, especially in hot-spot island-arc systems that may have been common on the early Earth. Whether reducing volcanic gases would have been dominant in these systems on the early Earth would depend on the oxidation state of the early mantle, which could have been more reducing than today [41]. The localized release of reduced gases by volcanic eruptions on the early Earth would likely have been immediately exposed to intense lightning (see Fig. 2), which is commonly associated with



Fig. 2. Lightning associated with the eruption of the Galunggung volcano in West Java, Indonesia photographed on October 16, 1982 (taken from [42]).

volcanic eruptions today [42,43]. With present day volcanic gas mixtures, NO is the main product [44], but with more reducing mixtures containing H<sub>2</sub>, CH<sub>4</sub> and N<sub>2</sub>, acetylene, HCN and other prebiotic reagents would have been produced [45]. Thus, in localized volcanic plumes, prebiotic reagents may have been produced, which after washing out of the atmosphere could have become involved in the synthesis of organic molecules. Island-arc systems may have been particularly important in localized Strecker-type syntheses because the reagents could have rained out into tidal areas where they could be concentrated by evaporation or periodic freezing.

An alternative to direct Earth-based syntheses is that the organic compounds needed for the origin of life may have come from extraterrestrial sources, such as interplanetary dust particles (IDPs), comets, asteroids and meteorites [46]. It is well established that carbonaceous meteorites contain a wide assortment of organic compounds [47], including ones, such as amino acids and nucleobases, that play a critical role in biochemistry. The major organic component in carbonaceous chondrites is complex macromolecular material similar to that produced in the spark discharge experiment. The input of this type of material from space could have contributed to the organic goo that may have covered parts of the early Earth and oceans.

Whether extraterrestrial organic material was efficiently delivered intact to the Earth, however, remains an uncertain issue. Because of the high temperatures associated with large impacts, most organic compounds originally present in the bolide should be destroyed, although robust molecules, such as fullerenes, may survive intact [48]. Bolide impacts may have had a beneficial effect on prebiotic chemistry, however: large amounts of methane could have been produced and which in turn could have yielded substantial amounts of HCN by photodissociation reactions [49]. This could have resulted in the bolide impact induced episodic synthesis of some key biomolecules by both the Strecker reaction and direct HCN polymerization.

Discussions of exogenous delivery have focused on IDPs because they represent the largest source of extraterrestrial material after large bolide impacts [46]. However, IDPs can be heated to temperatures of 1000 to 1500 °C during atmospheric deceleration, which could cause extensive decomposition of any organic compounds present. In experiments designed to sim-

ulate the atmospheric entry of Murchison-like IDPs [50], it was found that a large fraction of the amino acid glycine vaporized (sublimed) and survived when the grains were heated to 550 °C under partial vacuum. However, other amino acids present in Murchison did not sublime and were completely destroyed. These results suggest that sublimation of glycine present in IDPs may provide a way for this amino acid to survive atmospheric entry heating whereas all other amino acids apparently are destroyed. This is consistent with amino acid analyses of micrometeorites collected from Antarctic ice [51]. These results indicate that <5% of the micrometeorites contain endogenous amino acids. If amino acids were originally present in IDPs at Murchison-like levels, apparently only a small fraction of the amino acids escapes decomposition during atmospheric entry.

It is now generally assumed that the inventory of organic compounds on the early Earth would have been derived from a combination of both direct Earth-based syntheses and input from space. The simple abiotic monomeric organic compounds derived from these sources would have accumulated in the early oceans as well as other bodies of water and provided the raw material for the subsequent reactions.

#### 4. The transition to primitive biotic chemistry

Polymers composed of at least 20–100 monomeric units (mers) are thought to be required in order to have any primitive catalytic and replication functions [2,3]. Thus, polymerization processes taking place on the primitive Earth must have been capable of producing polymers of at least this minimum size.

Polymerization is a thermodynamically unfavorable process. In order to overcome this problem, the selective adsorption of monomers onto mineral surfaces has been suggested as one means of promoting polymerization and this process that has been demonstrated in the laboratory using a variety of simple compounds and activated monomers [52,53]. The potential importance of mineral-assisted catalysis is demonstrated by the montmorillonite-promoted polymerization of activated adenosine and uridine derivatives producing 25–50 mer oligonucleotides [53], the general length range considered necessary for primitive biochemical functions. Adsorption onto surfaces

involves the formation of weak noncovalent van der Waals interactions and thus the mineral-based concentration process and subsequent polymerization would be most efficient at cool temperatures [54,55].

As the length of polymers formed on mineral surfaces increases, they tend to be more firmly bound to the mineral [56]. In order for these polymers to be involved in subsequent interactions with other polymers or monomers, they would need to be released. This could be accomplished by warming the mineral although this would also tend to hydrolyze the absorbed polymers. Polymers could also be released by concentrated salt solutions [52,56], a process that could take place in tidal regions during evaporation or freezing of seawater.

The direct concentration of dilute solutions of monomers could be accomplished by evaporation and by eutectic freezing of dilute aqueous solutions. The evaporation of tidal regions and the subsequent concentration of their organic constituents have been proposed in the synthesis of a variety simple organic molecules (for example, see [57]). Eutectic freezing of dilute reagent solutions has also been found to promote the synthesis of key biomolecules [32]. It has been shown that the freezing of dilute solutions of activated amino acids at  $-20^{\circ}\text{C}$  yields peptides at higher yields than in experiments with highly concentrated solutions at  $0$  and  $25^{\circ}\text{C}$  [58]. In addition, recent studies have shown that eutectic freezing is especially effective in the nonenzymatic synthesis of oligonucleotides [59].

Salty brines could have played a role in the polymerization of amino acids and perhaps other important biopolymers as well. Short peptides have been synthesized using concentrated NaCl solutions containing Cu (II) and 40–50 mM amino acids [60]. Clay minerals, such as montmorillonite, apparently promote the reaction. Again, the evaporation of tidally flushed lagoons or the freezing of the primitive oceans could have produced the concentrated salty brines needed to promote this salt-induced polymerization process.

Hydrothermal systems may have been sites for the formation of short peptides. Because peptide bond formation becomes more favorable at higher temperatures, this reaction is one of the exceptions to the low temperature usually dominates “rule” discussed earlier. Experiments using glycine and other amino acids carried out under simulated high-temperature hydro-

thermal conditions have been shown to produce peptides containing up to 6 amino acid units [61,62]. However, the initial amino acid concentrations in these experiments are unrealistically high (0.1 M) and at more dilute concentrations, the peptide yields would be expected to decrease dramatically. Amino acids rapidly decompose and peptide bonds are rapidly hydrolyzed at elevated temperatures, so long-term survival and steady-state concentration of peptides at elevated temperatures are problematic. This is particularly important with respect to the residence time at high temperature during circulation through hydrothermal systems. The model experiments published to date use short exposure times (i.e., 1+ h) at high temperatures compared to 1–30+ years associated with actual hydrothermal systems [63]. However, autocatalytic cycles, which might take place at temperatures lower than the peak hydrothermal temperatures of  $\sim 350$  to  $400^{\circ}\text{C}$ , could have been important in maintaining a modest steady-state concentration of short peptides [64].

As polymerized molecules increased in length and became more complex, some of these began to fold into configurations that could bind and interact with other molecules. Primitive catalysts that promoted a variety of reactions could have thus arisen. Some of these catalytic reactions may have assisted in making the polymerization process more efficient. As the variety of polymeric combinations increased, a large library of random sequences would have been generated. By chance, some of these polymers acquired the ability to catalyze their own imperfect self-replication. Although these self-replicating molecules at first may have been scarce in the overall pool of polymers, because of their ability to catalyze their own replication, they would have become increasingly more abundant and soon dominated. There are now several known examples of self-replicating molecular systems that have been studied in the laboratory and these provide examples of the types of molecular systems that could have given rise to early self-replicating entities [65].

The appearance of the first molecular entities capable of replication, catalysis and multiplication would have marked the origin of both life and evolution. At a minimum, the first living molecular entities must have had the following properties: they could make copies of themselves, although the replication was not exact so mutants that had some



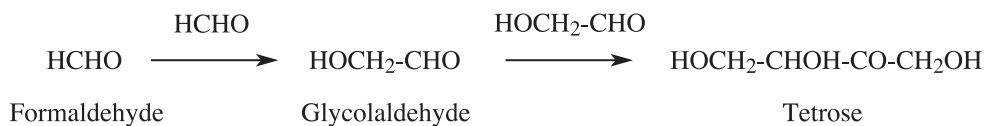
sort of selective advantage might be generated; they could either make ‘activated’ molecules that could be used in the replication process or utilize mineral surfaces to promote replication; and they must ‘live’ long enough to ensure that they survive long enough to be replicated. The challenge is to determine the best candidate system that best fits this minimalist definition.

Because of the huge number of possible random combinations of nucleotides from sugars, phosphate and nucleobases, it is unlikely that a RNA molecule capable of catalyzing its own self-replication arose spontaneously [2]. In addition, the ribose component of RNA is very unstable making its presence in the prebiotic milieu unlikely. Rather than RNA, some type of simpler self-replicator must have come first and several possible contenders have been suggested [2]. It is generally assumed that the first molecular self-replicating living entities must have had the capacity to store information and thus were nucleic acid based, although the component nucleobases and the backbone that held the polymer together were not necessarily the same as those in modern RNA and DNA. Possible candidates include nucleic acid analogues, such as peptide nucleic acid (PNA), where the backbone consists of linked amino acid derivatives, such as *N*-

(2-aminoethyl)glycine or AEG (the nucleobases are attached by an acetic acid linkage to the amino group of glycine) and threose nucleic acid (TNA), where the backbone is made up of L-threose connected by 3', 2' phosphodiester bonds.

PNA is attractive because its backbone is achiral (lacking handedness) which eliminates the need for the selection of chirality before the time of the origin of life. Its components, AEG and nucleobases linked to acetic acid, have been produced under simulated prebiotic conditions [66]. However, PNA is susceptible to an *N*-acyl migration reaction producing a rearranged PNA. This problem could be minimized, however, by blocking the N-terminal position by acetylation, for example.

Based on an extensive study of sugar-based nucleic acids, TNA appears to be superior with respect to its base-pairing attributes, especially with RNA, compared to other possible sugar-based nucleic acids [67,68]. The tetrose sugar in TNA could have been synthesized during the reaction cascade that takes place during the formose reaction. The 4-carbon sugars threose and erythrose could have been readily synthesized by the dimerization of glycolaldehyde, which in turn could have been produced from the dimerization of formaldehyde (see Reaction (1)):



**Reaction 1:** The formation of tetrose sugars from the dimerization of formaldehyde and glycolaldehyde. This is only part of the overall formose series of reactions and both hexoses and pentoses would have been produced by subsequent reactions.

However, in order to avoid the production of a large array of 5- and 6-carbon competing sugars, the reaction would need to somehow be quenched. TNA suffers from the chirality quandary associated with all sugar-based nucleic acid backbones. Although the presence of a 4-carbon sugar in TNA reduces this problem to 2 sugars and 4 stereoisomers, it remains a formidable challenge to demonstrate how oligonucleotides composed of only L-threose could be preferentially synthesized under prebiotic conditions.

It is possible that PNA preceded TNA and in fact assisted in the transition to TNA-based replicating entities. As stated above, the selection of the chiral sugar component of TNA would have required some sort of selection process to be in operation. The incorporation of chiral sugar nucleotides at the end of a PNA chain, that could have occurred simply by chance, can induce chirality into a nucleic acid produced by PNA-induced oligomerization [69]. PNA could have thus assisted in conveying the

critically important biological property of chirality into polymers near the time of the origin of life. This possibility potentially solves an ongoing dilemma about whether the origin of chirality occurred before the origin of life, or whether its origin occurred during the evolution of early living entities.

Regardless of the type of nucleic acid-like analogue, or other type of replicator system, that was used by the first self-replicating entities, polymer stability and survival would have been of paramount importance. Nucleic acids in general have very short survival times at elevated temperatures. The half-life for cleavage of the phosphodiester bonds in RNA has been estimated to be <1000 years at 0 °C [70], <1 day at pH 8, 35 °C [68] and <1 s at 150 °C [71]. DNA is more stable but is still completely fragmented in minutes at 250 °C, in an hour at 150 °C and in  $10^3$  to  $10^4$  years at 0 °C [70,72]. The amino acyl bonds in tRNAs, which are involved in biological protein synthesis, are hydrolyzed in ~10 s at 100 °C [73]. In contrast to elevated temperatures, stabilities would be greatly enhanced at lower temperatures.

The stability of TNA is apparently similar to that of DNA [68]. The stability of PNA has been partly investigated and provided the *N*-acyl migration reaction can be minimized, the amide linkage in PNA should have a stability at neutral pH similar to that of peptide bonds in proteins [74]. This suggests that in environments with temperatures of around 25 °C, its survival time would be in the range of  $10^4$ – $10^5$  years.

Salty brines may have played a role in early nucleic acid survival. The stabilities of several tRNAs were significantly increased in 1–2 M NaCl solution in comparison to that in pure water [75]. The stability of DNA also increases with increasing salt concentration (Fig. 3). If this trend is applicable to other nucleic acid analogues, such as PNA and TNA, then salt solutions would have provided a protective environment that could have enhanced the survival of early self-replicating molecular entities.

Stability limitations suggest that the origin of simple nucleic acid-based living entities would likely only have been feasible in cool, perhaps salty environments on the early Earth. The first living entities that arose, regardless of the process, may not have survived the high temperatures generated by subsequent bolide impacts, however (see Fig. 1). Simple self-replicating entities may have originated several times before

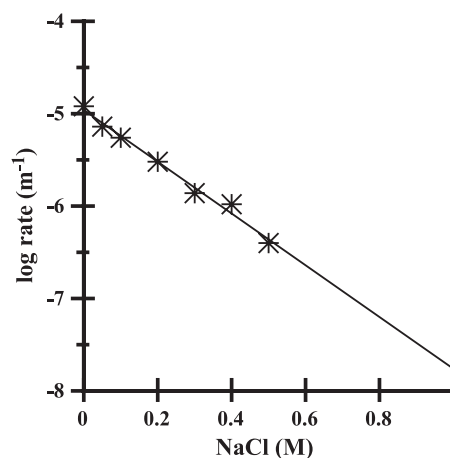


Fig. 3. The rate ( $\text{m}^{-1}=\text{minutes}^{-1}$ ) of depurination of adenine in DNA at pH 4.5 and 60 °C as a function of sodium chloride concentration. The rate for guanine is 2–3 times faster (taken from [74]).

conditions became tranquil enough for periods sufficiently long to permit their survival and evolution into more advanced life.

#### 4.1. The transition to modern biochemistry

The evolution of the first living molecular living entities into ones based entirely on RNA (the RNA World) would have been the next step in the evolution towards modern biochemistry. RNA has been found to be an all-in-one molecule that cannot only store information but also catalyze reactions [2]. Laboratory-based “test tube evolution” experiments have demonstrated that catalytic RNA molecules (ribozymes) have the capacity to carry out a wide range of important biochemical reactions [2,76]. The RNA World could have had a large repertoire of catalytic RNA molecules perhaps functioning in concert with one another. Although the complex series of reactions needed to permit multiplication, genetic transfer and variation required in the RNA World has so far not been demonstrated in the laboratory, optimism remains because of the relative immaturity of this area of research [2,76].

The invention of protein synthesis and the encapsulation of reaction machinery needed for replication may have taken place during the RNA World. Four of the basic reactions involved in protein biosynthesis are catalyzed by ribozymes and it has been noted that the complimentary nature of these reactions is not likely

accidental but rather suggestive that they had a common origin most likely in the RNA World [77]. If this was the case, then the origin of a primitive nucleobase code used for protein biosynthesis had its origin in the RNA World although the bases used in the early code could have been different from the ones used today [78].

RNA molecules adsorbed onto clays, such as montmorillonite, which can catalyze the formation of RNA oligomers, can be encapsulated into fatty acid vesicles whose formation in turn is accelerated by the clay [79]. By incorporating additional fatty acid micelles, these vesicles can grow and divide while still retaining a portion of their contents needed to support RNA replication. In this manner, some of the basic machinery needed for RNA self-replication could have been compartmentalized into prototype cells.

By the time RNA-based life appeared on Earth, the supply of simple abiotic organic compounds derived from the sources discussed above had likely greatly diminished. Many of the components of the primordial soup would have been converted into polymers including those associated with living entities and thus the raw materials needed to sustain primitive life had become largely exhausted. This implies that the origin of simple metabolic-like pathways must have arisen at this point in order to ensure a supply of the components needed to sustain the existence of the primitive living entities. This is where the self-sustaining autotrophic reactions discussed in the “metabolist theory” could have played an important role. The metabolic pathways needed to produce essential components required by primitive living entities were perhaps originally nonenzymatic or semienzymatic autocatalytic processes that later became fine tuned as ribozymatic and protein-based enzymatic processes became dominant [80,81]. The amount of organic carbon produced via the autotrophic fixation of CO<sub>2</sub>, CH<sub>4</sub> and simple organic compounds such as formic and acetic acids by metabolic processes in the RNA World could have far exceeded the amounts of organic compounds remaining, or still being supplied, from either homegrown processes or extraterrestrial sources under the best conditions. At this point, the reservoir of organic material present on the Earth shifted from one totally characterized by compounds of abiotic origin to one made up of components synthesized by early biotic processes.

The main limitation in the RNA World would have been the extreme instability of RNA. This implies that

RNA molecules must have been very efficient in carrying out self-replication reactions in order to maintain an adequate inventory of molecules needed for survival. The instability of RNA could have been the primary reason for the transition to the DNA/Protein World where, because of the increased stability of the genetic molecules, survival would have been less dependent on polymer stability. In the RNA World, ribozymes may have arisen that could catalyze the polymerization of DNA and in this manner, information stored in RNA could be transferred to the more stable DNA [2]. Because of their superior stability, much longer DNA oligomers could have accumulated and this provided for an enhanced storage capacity of information that could be passed on to the next generation of living entities. In addition, using test-tube evolution strategies, deoxyribozymes, the DNA analogues of ribozymes, have been discovered [82]. This may imply that some DNA molecules inherited catalytic properties from ancestors in the RNA World. Before long, RNA which once played the singular role of replication and catalysis was replaced by the more efficient and robust DNA/Protein World wherein RNA was demoted to a role of messenger/transcriber of DNA stored information needed for protein biosynthesis.

Although DNA is more stable than RNA, it is still rapidly degraded at elevated temperatures. In addition, protein enzymes denature rapidly at elevated temperatures. This must have at least initially limited the environments where DNA/Protein-based life could survive for any significant period of time and, as was the case for other earlier nucleic-acid-based living entities, survival would have been the most favorable under cool conditions. Nevertheless, several researchers have advocated high temperatures, especially those associated with hydrothermal vent systems, as the environment where DNA/Protein-based entities first arose. Proponents for a high temperature transition cite the fact that the universal tree of extant life appears to be rooted in hyperthermophilic organisms. Thus, if the last universal common ancestor (LUCA) to all modern biology was a hyperthermophile, then it is concluded that the first DNA/Protein-based life must have arisen in a similar type of environment. However, this argument is flawed for several reasons. First, the recognition that the deepest branches in rooted universal phylogenies are occupied by hyperthermophiles is controversial and does not provide by itself

conclusive proof of a high-temperature origin of DNA/Protein-based life [83]. In addition, lateral gene transfer of thermoadaptive traits has apparently greatly compromised the genetic record present in modern organisms, which makes any conclusions about the environment where the DNA/Protein World originated questionable [84]. In addition, an analysis of protein sequences has found only one enzyme, reverse gyrase, that is specific to hyperthermophiles; other proteins are apparently not ancestral to these organisms and are likely simply heat-adapted versions of those present in cooler temperature organisms [85]. Even if the LUCA was a hyperthermophile, there are alternative explanations for their basal distribution, such as the possibility that hyperthermophily is an evolutionary relic from early Archean high-temperature regimes associated with severe bolide impact events during the late heavy bombardment period (see Fig. 1). In this latter case, heat-loving DNA/Protein-based life was simply the major survivor of an impact-induced catastrophe that destroyed the bulk of the early DNA/Protein World.

## 5. Future challenges

Although the overall scenario presented here provides a framework of the processes involved in the appearance of life on Earth, there are still many details that need to be fully elucidated. One of the most challenging areas is determining what types of polymerization processes could have given rise to nucleic acid-based molecules, especially ones with catalytic properties. For example, although appealing as possible candidates for the first self-replicating molecular living entities, both PNA and TNA have negative aspects, mainly the lack of any demonstrated oligerization process for efficiently producing these nucleic acid analogues under plausible prebiotic conditions. In addition, the reactions needed to permit multiplication, genetic transfer and variation required in PNA, TNA and RNA Worlds have not been achieved in the laboratory and this represents a formidable challenge. The time of the origin of chirality, although discussed here as arising during early evolution of life, remains largely unknown.

Perhaps the biggest uncertainty is whether a metabolic-like set of self-sustaining chemical reactions can be considered ‘alive’ and whether this type of

chemistry preceded information-based chemistry associated with life as we know it. This prospect is highly debatable and although there are compelling reasons that genetic informational molecules were a vital component of the first living entities on Earth, there is considerable polarization on this issue [86]. As discussed here, metabolic-type reactions likely contributed important molecules during the prebiotic epoch and thus could have had a central role in the processes that gave rise to the origin of life. However, whether “metabolic life” could have truly existed by itself and preceded life as we know it is controversial. This issue has important implications with respect to searching for life beyond Earth. How would we recognize simple metabolic-based life elsewhere and how would we go about testing to determine if it was compatible or hazardous to life as we know it on Earth?

## 6. Conclusions

Much remains unknown about the actual processes and sequence of events that gave rise to the first living entities on Earth. Someday, an artificial molecular-based self-replicating entity will probably be created in the laboratory and this will allow us to study some of the attributes of primitive “living” systems. However, there is no guarantee that this will in any way be representative of the types of early living entities that may have first appeared on the early Earth.

The exploration of extraterrestrial worlds may provide some of the missing information about how life began on Earth and its earliest stages of evolution. There are compelling reasons to believe that the core organic components used by living organisms on Earth, polymers made of amino and nucleic acids, would be part of biochemistry elsewhere, although the exact structural makeup of these key molecules may be different [87]. If the abiotic chemistry and its subsequent evolution into primitive living molecular entities discussed here is widespread, we may find examples of some of the stages associated with this process perhaps on Mars, Europa or on some of the extra-solar Earth-like planets that may abound in the Universe.

Searching for signs of extraterrestrial life in our solar system should be fairly straightforward because we can send spacecraft to directly explore promising bodies and if positive results are obtained, eventually return



samples to Earth for direct analyses. Several missions by ESA and NASA are being planned to just this, and hopefully, in the not-too-distant future, we may know whether life on Earth is unique to our solar system. Detecting life on Earth-like planets outside our solar system will likely remain a daunting challenge for some time, however [88].

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