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## Research Paper

## Origins of building blocks of life: A review



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## ABSTRACT

How and where did life on Earth originate? To date, various environments have been proposed as plausible sites for the origin of life. However, discussions have focused on a limited stage of chemical evolution, or emergence of a specific chemical function of proto-biological systems. It remains unclear what geochemical situations could drive all the stages of chemical evolution, ranging from condensation of simple inorganic compounds to the emergence of self-sustaining systems that were evolvable into modern biological ones. In this review, we summarize reported experimental and theoretical findings for prebiotic chemistry relevant to this topic, including availability of biologically essential elements (N and P) on the Hadean Earth, abiotic synthesis of life's building blocks (amino acids, peptides, ribose, nucleobases, fatty acids, nucleotides, and oligonucleotides), their polymerizations to bio-macromolecules (peptides and oligonucleotides), and emergence of biological functions of replication and compartmentalization. It is indicated from the overviews that completion of the chemical evolution requires at least eight reaction conditions of (1) reductive gas phase, (2) alkaline pH, (3) freezing temperature, (4) fresh water, (5) dry/dry-wet cycle, (6) coupling with high energy reactions, (7) heating-cooling cycle in water, and (8) extraterrestrial input of life's building blocks and reactive nutrients. The necessity of these mutually exclusive conditions clearly indicates that life's origin did not occur at a single setting; rather, it required highly diverse and dynamic environments that were connected with each other to allow intra-transportation of reaction products and reactants through fluid circulation. Future experimental research that mimics the conditions of the proposed model are expected to provide further constraints on the processes and mechanisms for the origin of life.

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## 1. Introduction

When, where, and how did life on Earth originate? These questions on the origin of life are among the biggest unsolved problems in natural science. Recent progress in geological research has provided significant constraints on the first question: time of the origin of life. The Earth was formed about 4.53 billion years (Gyr) ago through gravitational accretions of a large number of 10-km-sized objects, with the moon-forming impact being late and the most catastrophic event (Canup and Asphaug, 2001; Kleine et al., 2005; Wood et al., 2006). After the giant impact, the surface of the primitive Earth cooled rapidly from rock-melting-temperature (~2000 K) to below the boiling point of liquid water

(400–500 K) on a timescale of 1–10 million years (Nisbet and Sleep, 2001; Sleep, 2010). As a consequence, a hydrosphere and continental crust were formed as early as 4.3 Gyr ago (Mojzsis et al., 2001; Wilde et al., 2001; Harrison et al., 2005). The primordial ocean was occasionally vaporized by massive meteorite impacts called the “late heavy bombardment” during the first hundreds of million years of the Earth's history (Sleep et al., 1989; Marchi et al., 2014). Liquid water is essential for life, and organic molecules are typically unstable at temperatures higher than 100 °C, therefore it is unlikely that life could have survived the bombardment period, particularly before 4.2 Gyr ago (Nisbet and Fowler, 1996; Nisbet and Sleep, 2001). Nonetheless, geochemical investigations of graphitic carbons in early Archean sedimentary rocks have indicated that life on the Earth began before 3.8 Gyr ago (Mojzsis et al., 1996; Rosing, 1999; Ohotomo et al., 2014). Geological occurrences of graphite from the Isua supracrustal belt indicate the possible existence of planktonic organisms at >3.7 Gyr ago (Rosing, 1999). If the interpretation is correct, the origin and early evolution of life would have occurred long before that. The geological evidence is

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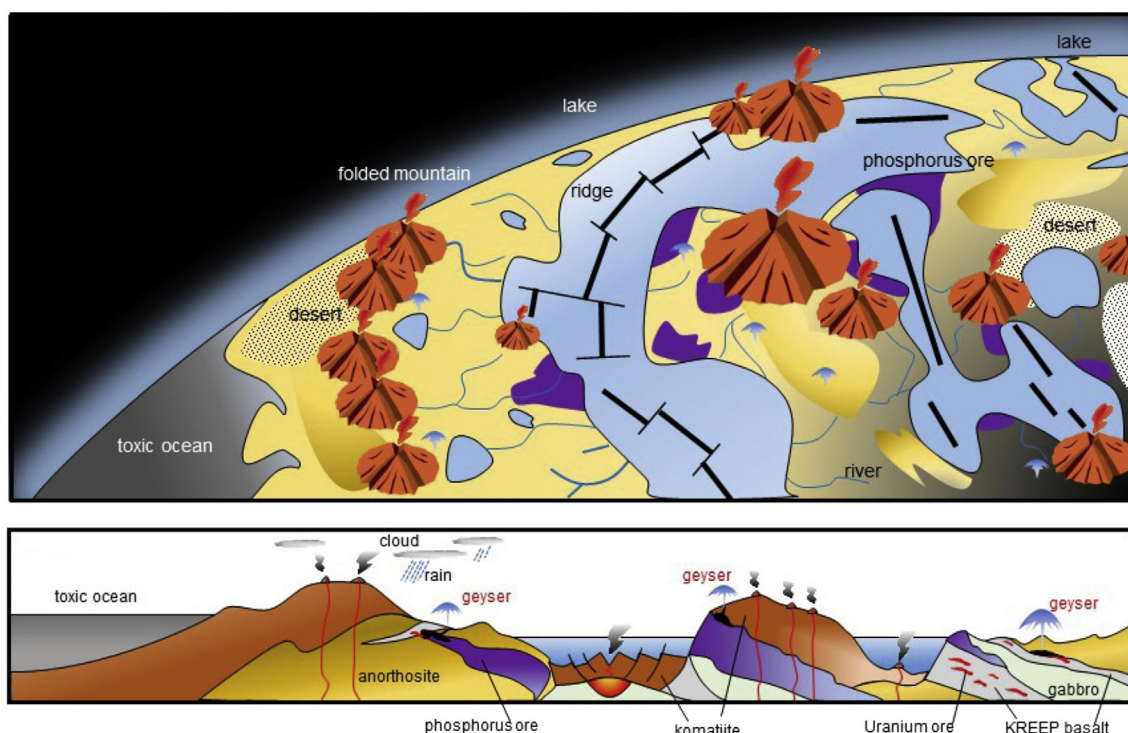
consistent with an estimate from a phylogenetic analysis of molecular divergence among Archaea (Battistuzzi et al., 2004). A molecular clock analysis suggested that the first divergence within Archaea occurred as far back as 4.11 Gyr ago, implying even earlier dates for the last common ancestor of living organisms. Based on these multiple lines of information, the beginning of life on the Earth is inferred to be between 4.1 and 4.2 Gyr ago.

Then, where did life on Earth originate? To date, various environments have been proposed as plausible sites for life's origin, including oceans, lakes, lagoons, tidal pools, submarine hydrothermal systems, etc. But no single setting can offer enough chemical and physical diversity for life to originate. This idea was recently proposed by Stueken et al. (2013), suggesting that chemical evolution required complex interactions among diverse geochemical processes. In accord with the suggestion, Dohm and Maruyama (2015) proposed a new concept of a habitable environment. The concept, "Habitable Trinity", involves coexisting atmosphere, water, and landmass with continuous material circulation between the three of them that is driven by the Sun. This setting is one of the minimum requirements for the emergence of life. Elements consisting of life body (C, H, O, N, and nutrients) are provided from the three components: atmosphere (C and N), water (H and O), and a landmass (nutrients). Although the presence and composition of primitive continents have been under vigorous debate (Harrison, 2009), Maruyama et al. (2013) speculated that a huge landmass had existed on the Hadean Earth (Fig. 1). It was comprised of dozens of kilometer thick anorthositic crust with local cover and dikes of KREEP (Kalium, Rare Earth Elements, and Phosphorus) basalt composition, similar to that observed on the moon. On the continental surface, serpentine-hosted hydrothermal systems distributed with localized H<sub>2</sub>-rich alkaline environments. In a pond near the geothermal field, ample and continuous supplies of nutrient elements (e.g., K and P) were provided by weathering, erosion and transportation of nutrient-enriched rocks. The shores of the pond favor dehydration reactions leading to biomolecule

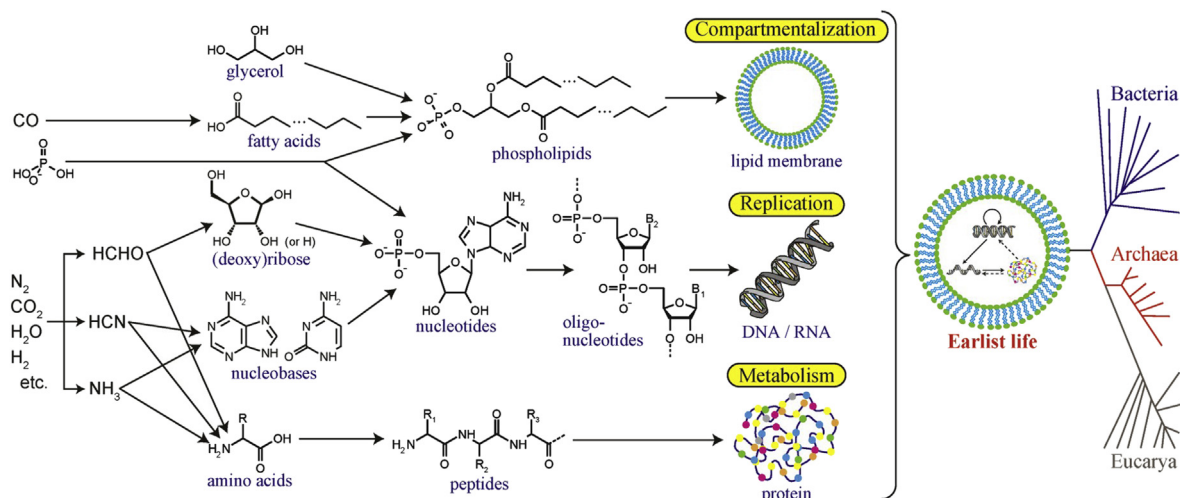
polymerization through wetting–drying cycles (Mulikidjanian et al., 2012a,b; Stueken et al., 2013). The geothermal fields also enabled the involvement of solar light as an energy source and diverse organic substances that were produced through atmospheric reactions or delivered by extraterrestrial objects. The proposed environment appears to include almost all geochemical situations proposed so far that favor the chemical evolution of life. Therefore, it would be worth considering whether the terrestrial environment is enough to drive all stages of chemical evolution, ranging from condensation of simple inorganic molecules (e.g., CO<sub>2</sub>) to the emergence of the earliest life. To this end, we also need to consider the last question: how did life on Earth originate?

Life is generally characterized by the following three functions: (1) compartmentalization: the ability to keep its components together and distinguish itself from the environment, (2) replication: the ability to process and transmit heritable information to progeny, and (3) metabolism: the ability to capture energy and material resources, staying away from thermodynamic equilibrium (Fig. 2; Nakashima et al., 2001; Ruiz-Mirazo et al., 2004, 2014). All these functions are operated by biopolymers such as DNA, RNA, protein, and phospholipids (Fig. 2). Phospholipids are made of two fatty acids esterified to a glycerol phosphate molecule. DNA and RNA are made of nucleosides (composed of (deoxy)ribose and nucleobases) bound by phosphodiester linkages, while proteins are made of amino acids linked together by peptide bonds (Fig. 2). It is typically assumed that these vital components were synthesized abiotically, accumulated somewhere, condensed into polymers, interacted mutually, and eventually evolved into a self-sustaining system through natural phenomena on the primitive Earth. A considerable number of laboratory simulations have been made to explore the most plausible conditions for these processes, especially for the synthesis, accumulation, and polymerization steps of organic monomers.

The aim of this review is to provide a framework for thinking about geochemical situations necessary for life to originate from



**Figure 1.** Schematic diagram of a Hadean surface environment proposed by Maruyama et al. (2013) and Santosh et al. (2017).



**Figure 2.** Structures, components, and abiotic synthetic pathways of bio-macromolecules operating three fundamental functions of life (replication, compartmentalization, and metabolism).

mixtures of simple inorganic compounds (e.g.,  $\text{CO}_2$ ,  $\text{N}_2$ ,  $\text{H}_2\text{O}$ ,  $\text{H}_3\text{PO}_4$ ) on the Hadean Earth. To date, a number of varied environments have been proposed as being favorable for prebiotic chemistry (Deamer et al., 2006; Ricardo and Szostak, 2009; Benner et al., 2012; Mulikidjanian et al., 2012a,b). However, these discussions have focused on a limited stage of chemical evolution, or emergence of a specific chemical function of proto-biological systems. To cover all stages, we first summarize reported experimental and theoretical findings for prebiotic chemistry, including availability of biologically essential elements (N and P), abiotic formation of life's building blocks (amino acids, ribose, nucleobases, fatty acids, and nucleotides), their polymerizations to bio-macromolecules (peptides and oligonucleotides), and emergence of biological functions of replication and compartmentalization. These summaries are used to make a list of reaction conditions necessary to complete the chemical evolution from the beginning to the end. A relevant geochemical setting for each condition is then discussed while considering the Hadean surface environments proposed in the literature (e.g., Maruyama et al., 2013). It should be noted that the origin and early evolution of metabolism have been discussed over the last twenty years (Wächtershäuser, 1988; Russell et al., 1994; Braakman and Smith, 2013). However, laboratory simulations on this topic have still focused on syntheses of simple metabolic intermediates (e.g., pyruvate) and amino acids (e.g., Cody et al., 2000; Guzman and Martin, 2009; Huber et al., 2012). Many uncertainties remain about how proto-metabolic systems emerged and evolved into modern counterparts. Inclusion of this process as a part of the whole scenario must be done later, at a time when sufficient experimental support is available in the literature. It is also noteworthy that it is possible life started with different inventories of organic/inorganic compounds that are not used in modern biochemistry (e.g., Cairns-Smith, 1982). Owing to a lack of experimental support, our survey does not refer to the works done on this topic. Evaluations of the availability, reactivity, and function of the “standard” building blocks of life as we know it should provide an important insight to elucidate the components as well as the geological settings for the origin of life.

Prior to proceeding to the prebiotic chemistry that led to the origin of life, we briefly survey three standard hypotheses; (1) prebiotic soup theory, (2) hydrothermal origin of life, and (3) extraterrestrial origin of life. Because many laboratory simulations have been done following these three, this review accordingly focuses on chemical reactions under conditions relevant to these hypotheses.

## 2. Origin of life hypothesis

### 2.1. Prebiotic soup theory

Over time, philosophers and scientists have proposed many different theories for the origin of life. The best-known theory is the “Prebiotic soup” theory hypothesized by Oparin in 1924 (Oparin, 1957). In this theory, organic compounds were created in a reductive atmosphere from the action of sunlight and lightning. The compounds were then dissolved in the primitive ocean, concentrated, and underwent polymerization until they formed “coacervate” droplets. The droplets grew by fusion with other droplets, were split into daughter droplets by the action of tidal waves, and developed the ability to catalyze their own replication through natural selection, which eventually led to the emergence of life. Later on, the relevance of coacervates to the origin of life was questioned because coacervates have no permeability barrier, so they lack the capacity for nutrient uptake and waste release that are essential functions for encapsulated metabolism (Monnard and Deamer, 2002; Thomas and Rana, 2007). However, the scientific merits of Oparin's proposal are not in its details, but in the possibility to test its plausibility with rigorous scientific investigation (Pereto, 2005). By changing its details with refinements of scientific knowledge, the scenario has become a starting point of many modern theories for the origin of life. It has been argued, for instance, that the concentration process of organic molecules could have occurred more effectively in tidal pools, icy environments and/or on mineral surfaces rather than in bulk oceanic water (Bada and Lazcano, 2002). Tidal pools would allow processing as well as concentrations of a huge variety of reactants transported by rivers, the ocean, and the atmosphere. Tidal pools have at least four characteristics advantageous for prebiotic organic synthesis: accumulation of heavy detrital minerals, evaporation–concentration cycles, a gradient in water activity, and high porosity (Stueken et al., 2013). Mineral surfaces could have played an important role in polymerization of organic monomers (Lambert, 2008; Cleaves et al., 2012). As many as 1000 mineral species have been estimated to be present on Earth at the time of life's origin, 4.5–4.0 billion years ago (Cleaves et al., 2012). Given the ubiquity of mineral–water interfaces on the Earth's surface, it is almost impossible to envision prebiotic chemistry scenarios leading to the origin of life, but involving no interfacial processes. A difficulty of this scenario arises from the assumption that life started with primordial



heterotrophic systems in an organic-rich reductive soup. Through changing the assumption of the primitive atmospheric composition from highly reducing to neutral (Kasting, 1993; Delano, 2001; Trail et al., 2011) (although we still lack any robust evidence of its exact condition; Zahnle, 1986; Tian et al., 2011), the focus in our search has shifted to other locations that could have been more likely to have provided an ample and continuous supply of reducing elements.

## 2.2. Hydrothermal origin of life

The discovery of thermophilic organisms in association with deep-sea hydrothermal systems in the late 1970s (Corliss et al., 1979) led to a new idea that life might have originated in hydrothermal systems on the primitive Earth (Takai et al., 2006; Martin et al., 2008; Sousa et al., 2013). The perceived benefits afforded to early life in this environment include protection from intense asteroid bombardment and UV radiation, and a source of thermal and chemical energy, along with potentially catalytic minerals (Baross and Hoffman, 1985; Holm, 1992). Evidence that supports this scenario has been provided from various research fields. For instance, geologists have detected evidence for microbial methanogenesis from fluid inclusions in 3.5-Gyr-old hydrothermal precipitates (Ueno et al., 2006). Using molecular biological approaches, biologists have demonstrated that the thermophilic microbial inhabitants of the active seafloor populate the deepest branches of the universal phylogenetic tree (Reysenbach and Shock, 2002). Chemists have claimed that, on both theoretical and experimental bases, the physical and chemical conditions that are characteristic of the deep-sea hydrothermal systems are favorable for abiotic synthesis of biochemically significant organic molecules (Shock, 1990, 1992a; Shock and Schulte, 1998).

More recently, a new type of vent system, the Lost City hydrothermal field, was discovered in 2000 more than 15 km from the spreading axis of the Mid-Atlantic Ridge (Kelley et al., 2001, 2005). Unlike vent systems that are located directly on the spreading zone, the water circulating these off-axis vents makes no contact with magma, and emerges at a temperature of around 70–90 °C. Its fluid composition is derived from exothermic reactions between seawater and uplifted mantle peridotite, rather than from interactions between seawater and cooling basalts (Martin and Fyfe, 1970; Lowell and Rona, 2002; Emmanuel and Berkowitz, 2006). The peridotite–seawater reactions associated with the oxidation of iron produce alkaline fluids (pH 9–11) that are rich in H<sub>2</sub> and CH<sub>4</sub> and other low-molecular-mass hydrocarbons (Proskurowski et al., 2008; Konn et al., 2009).

Russell and colleagues have proposed that life arose within alkaline hydrothermal vents similar to those of the Lost City (Russell et al., 1994; Russell, 2003, 2007; Martin and Russell, 2007; Russell et al., 2010, 2014). A proposed beneficial characteristic for life there is the proton gradient at the interface between the alkaline effluent (pH 10–11) and the possibly slightly acidic Hadean ocean (pH 5–6) (Macleod et al., 1994; Morse and Mackenzie, 1998). Such proton gradients could have provided a geochemically-generated chemiosmotic potential that may have served as a template upon which biological chemiosmotic gradients evolved, provided the two were physically separated by a semiporous barrier, such as a layer of sulfide minerals at a hydrothermal vent. Alkaline effluent might also provide biologically important heavy metals such as Mo and W because their sulfide species (e.g. MoS<sub>4</sub><sup>2−</sup>) are soluble at alkaline pH, but not at neutral pH (Martin and Russell, 2007; Helz et al., 2014). Mo and W are known to catalyze the transfer of O<sup>2−</sup> from substrate onto water or vice versa (S + H<sub>2</sub>O ↔ SO + 2H<sup>+</sup> + 2e<sup>−</sup>) at the active sites of oxido reductases (Doring and Schulzke, 2010). These reactions are part of the carbon,

nitrogen and sulfur metabolism and are fundamentally important for all organisms (Doring and Schulzke, 2010).

At the same time, however, some scientists have questioned this scenario because biomolecules are unstable under high temperature conditions (White, 1984; Miller and Bada, 1988). High pH also presents problems in terms of the availability of inorganic carbon. High pH results in the precipitation of carbonate minerals and the near complete removal of aqueous inorganic carbon species, leaving few carbon sources that can be fixed into biomass (Schrenk and Brazelton, 2013). Several uncertainties remain regarding accumulation and polymerization of organic molecules at the vent–ocean interface. Additionally, although thermophiles near the hydrothermal systems distribute at the deepest branches of the phylogenetic tree, it is conceivable that they are not the universal ancestor, but only the survivors from early Archean high-temperature regimes generated by severe impact events (Miller and Lazcano, 1995; Sleep and Zahnle, 1998; Nisbet and Sleep, 2001). Moreover, cell cytoplasm has a largely different ionic composition from that of sea water (e.g., the K<sup>+</sup>/Na<sup>+</sup> ratio of modern cell is orders of magnitude higher than the level of sea water (Mulikidjanian et al., 2012a)). Consequently, this scenario is not without controversy (Bernhardt and Tate, 2012), though it persists as an active topic of study in both field (e.g., Nakamura et al., 2010) and laboratory (e.g., Barge et al., 2014) investigations.

## 2.3. Extraterrestrial origin of life

Another important source of organic compounds on the primitive Earth is delivery by extraterrestrial objects (meteorites, comets, and interplanetary dust particles (IDPs)) (Anders, 1989; Chyba et al., 1990). It has been estimated that the delivery of organic carbon by IDPs at the time of 4.0 Gyr ago was in the order of 10<sup>8</sup> kg yr<sup>−1</sup>, or 10<sup>16</sup> kg per 100 million years (Chyba and Sagan, 1992). Given that there is about 6 × 10<sup>14</sup> kg of organic matter in the present biosphere, it is likely that the role of extraterrestrial organics was significant (Ruiz-Mirazo et al., 2014). Carbonaceous chondrites contain a wide variety of organic compounds including amino acids, purines, pyrimidines, sugar-like compounds, and long-chain monocarboxylic acids with amphiphilic properties (Pizzarello et al., 2006; Zaia et al., 2008; Burton et al., 2012). These compounds could have been used as a component of primitive life.

It is also conceivable that life originated elsewhere in the universe where conditions were favorable, and transferred to the Earth after the surface conditions became tranquil (Sharov, 2006; Price, 2010). The apparently short timespan between the cooling of the Earth and the appearance of modern-looking microbes (4.2–3.8 Gyr ago) has been taken as evidence supporting this idea (Nicholson, 2009). Kirschvink has proposed a Martian origin for the terrestrial life (Kirschvink and Weiss, 2003). Arguments that support this idea include that (1) higher concentrations of nutrients such as boron (Kirschvink et al., 2006; Stephenson et al., 2013) and phosphate (Adcock et al., 2013; Pasek, 2013) were more likely to exist on early Mars than on the Earth with chemically available forms, (2) the physicochemical conditions (water content, redox state, temperature, etc.) on the early Mars could have been better for the evolution of early biochemical systems than those of early Earth (Sleep and Zahnle, 1998; Kirschvink and Weiss, 2003), and (3) meteorites are capable of transferring life from the surface of Mars to the surface of Earth without subjecting it to sterilizing temperature and solar UV (Weiss et al., 2000). These ideas raise the possibility that life did not necessarily evolve on each planet it occurs on, but rather in a single location, and then spread about the galaxy to other star systems via cometary and/or meteorite impact. However, criticisms always exist; for instance, “the idea merely

shifts the problem of the origin of life to a different location" (Bada and Lazcano, 2002; Bada, 2004).

In addition to the above, various sites for the origin of life have been proposed, including transient melt zones in a frozen ocean (Bada et al., 1994), hydrothermal systems within volcanos (Wächtershäuser, 2006) and subterranean lithic zones (Nakazawa et al., 1993). Although each setting has advantages in some stages of chemical evolution, unsolved problems also remain. For instance, high temperature (150–400 °C) and high pressure (5 MPa–5.5 GPa) conditions have been shown to favor the polymerization of amino acids in a dry state (Ohara et al., 2007; Otake et al., 2011; Furukawa et al., 2012). The results support the idea that life arose in a deep subsurface (Nakazawa et al., 1993). However, it is unclear how amino acids were accumulated and purified in such an extreme environment. So far, there is no plausible scenario that can explain all the stages of the origin of life.

### 3. Availability of nitrogen and phosphorus

#### 3.1. Nitrogen fixation

Nitrogen is an essential element for life and is central in the structure of protein, RNA, DNA, and other vital substances. The atmosphere ( $\sim 3.9 \times 10^{21}$  gN) is the major reservoir of nitrogen at the Earth's surface, where it is present in the form of di-nitrogen gas ( $N_2$ ) (Bebout et al., 2013). The ocean and biosphere also store huge amounts of nitrogen ( $6.6 \times 10^{17}$  gN and  $4.3 \times 10^{15}$  gN, respectively; Chapin et al., 2002), but the contributions are several orders of magnitude less than the atmosphere.  $N_2$  is virtually inert owing to a high activation energy to break  $N \equiv N$  triple covalent bond ( $941 \text{ kJ mol}^{-1}$ ; Howard and Rees, 1996). Therefore, to be made available for living organisms,  $N_2$  must be converted into chemically accessible forms such as ammonium ( $NH_4^+$ ) or nitrate ( $NO_3^-$ ) ions. In the present Earth, the nitrogen fixation is mainly driven by biological or anthropogenic processes ( $2.5 \times 10^{14}$  and  $1.6 \times 10^{14}$  gN  $yr^{-1}$ , respectively; Gruber and Galloway, 2008). But prior to the evolution of nitrogen-fixing organisms (3.5 Gyr ago; Nishizawa et al., 2014), abiotic processes would have been the only fixation mechanisms. The nature and relative abundance of nitrogen compounds formed through abiotic processes depend on the oxidation state of the atmosphere. A reducing atmosphere rich in hydrogen ( $H_2$ ) and methane ( $CH_4$ ) generates hydrogen cyanide (HCN) and glycolonitrile ( $HOCH_2CN$ ) as major N-containing compounds (Schlesinger and Miller, 1983a; Zahnle, 1986; Stribling and Miller, 1987). In contrast, if the primitive atmosphere was more neutral, composed of carbon dioxide ( $CO_2$ ) and  $N_2$ , the main form of fixed nitrogen is nitric oxide (NO). The most important geochemical process of NO production could have been volcanic lightning ( $10^{12}$ – $10^{13}$  gN  $yr^{-1}$ ; Navarro-Gonzalez et al., 1998). Other proposed mechanisms for  $N_2 \rightarrow NO$  conversion includes post-impact plumes ( $\sim 10^{12}$  gN  $yr^{-1}$ ; Kasting, 1990), thunderstorm lightning ( $\sim 3.0 \times 10^{11}$  gN  $yr^{-1}$ ; Navarro-Gonzalez et al., 2001), subaerial volcanos ( $10^{10}$ – $10^{12}$  gN  $yr^{-1}$ ; Mather et al., 2004), cosmic rays ( $10^9$ – $10^{10}$  gN  $yr^{-1}$ ; Nicolet, 1975), and corona discharge ( $\sim 1 \times 10^9$  gN  $yr^{-1}$ ; Nna-Mvondo et al., 2005). NO would then have converted to nitrate ( $NO_3^-$ ) and nitrite ( $NO_2^-$ ) through a series of photochemical and aqueous phase reactions (Mancinelli and McKay, 1988; Summers and Khare, 2007). These nitrogen oxides can be reduced to ammonia ( $NH_4^+$ ) through interactions with Ni/Fe/Cu metals and alloys, magnetite and iron sulfides in aqueous solution (Summers, 2005; Brandes et al., 2008; Smirnov et al., 2008; Singireddy et al., 2012; Summers et al., 2012). Nitrite is also readily reduced to  $NH_4^+$  by  $Fe^{2+}$  at neutral pH (Summers and

Chang, 1993; Summers, 1999). Other sources of reduced nitrogen proposed so far include photochemical reduction of  $N_2$  to  $NH_3$  in the presence of titanium oxide ( $TiO_2$ ) (Bickley and Vishwanathan, 1979; Henderson-Sellers and Schwartz, 1980), HCN production in a  $CO_2/N_2$  atmosphere via the action of UV radiation ( $4 \times 10^{10}$  gN  $yr^{-1}$ ; Tian et al., 2011), and direct reduction of  $N_2$  to  $NH_4^+$  in aqueous solution catalyzed by Ni/Fe metals and iron sulfide (FeS) (Schoonen and Xu, 2001; Dorr et al., 2003; Smirnov et al., 2008). The efficiency of  $N_2$  reduction to  $NH_4^+$  in aqueous solution is low (0.04%, Dorr et al., 2003; 2.5%, Smirnov et al., 2008). Given the low solubility of  $N_2$  in water (0.65 mM in equilibrium with 1 bar  $N_2(g)$  at 25 °C; Shock et al., 1989), this process would have been a minor source of  $NH_4^+$  for prebiotic synthesis. How much ammonia could have been accumulated in the primitive ocean? Summers and Chang (1993) estimated a steady state concentration of  $NH_4^+$  in the primitive ocean to be 3.6–70  $\mu M$ , assuming a production rate of NO from  $N_2(g)$  ( $1.4 \times 10^{11}$  mol  $yr^{-1}$ ), a conversion efficiency of NO to  $NO_2^-$  in the ocean (33%), a concentration of  $Fe^{2+}$  in the ocean (190 nM), a reduction rate of  $NO_2^-$  to  $NH_4^+$  ( $3.6 \times 10^{10}$  mol  $yr^{-1}$ ), and photochemical and/or hydrothermal destruction of  $NH_4^+$ . The concentration is much higher than the modern oceanic level ( $<0.1 \mu M$ ; Amend and Shock, 1998), but still much lower than those used in abiotic synthesis experiments of biomolecules (e.g.,  $\geq 50$  mM for amino acid synthesis; Aubrey et al., 2009). It is also noteworthy that  $NH_4^+$  concentrations in modern aqueous environments are generally low (e.g.,  $<6 \mu M$  at the Lost City hydrothermal field; Lang et al., 2013) except for fluids that pass through organic-rich sediments (e.g., Lilley et al., 1993). Detected  $NH_4^+$  are mostly attributed to biological origin; no appreciable flux of abiogenic  $NH_3$  has been apparent even though the environment is sufficiently reducing to have an equilibrium N-speciation dominated by  $NH_3$ . Consequently, it is unclear whether nitrogen fixation starting from  $N_2$  gas could have produced enough ammonia to sustain prebiotic synthesis of biomolecules necessary to initiate life.

Another important reservoir of nitrogen on Earth is the mantle (Canfield et al., 2010). Although the size of the mantle reservoir is still poorly constrained, some estimates have shown a possibility that the nitrogen abundance in the mantle is more than twice as much as the present atmospheric nitrogen level (Goldblatt et al., 2009; Bebout et al., 2013). The solubility of nitrogen is very sensitive to the redox state of the mantle. Under a relatively oxidized condition such as the present Earth's upper mantle (at approximately the fayalite–magnetite–quartz (FMQ) oxygen buffer level; Frost and McCammon, 2008), nitrogen exists predominantly as  $N_2$ , and hence presents a low solubility in basaltic melt similar to that of noble gases ( $<1$  ppm; Libourel et al., 2003). In contrast, under more reducing conditions (below the iron–wüstite (IW) buffer), nitrogen is mainly in the form of  $NH_4^+$ , and shows a drastic increase in solubility with decreasing oxygen fugacity ( $fO_2$ ) (Libourel et al., 2003). It has been argued that, at the time of accretion and core formation of the Earth, the magma ocean on Earth could have been very reducing, with the oxygen fugacity being 2–4 log units below the IW buffer (Wood et al., 2006; Rubie et al., 2011; Scaillet and Gaillard, 2011). Therefore, a significant fraction of the nitrogen on Earth could have originally been dissolved in the magma ocean, and been released from the solidifying magma ocean in the form of  $NH_4^+$  (Li et al., 2013; Li and Keppler, 2014). A recent geochemical study suggested that the oxygen fugacity of the Hadean continental crust increased rapidly to the present-day level in the first 0.5 Gyr of Earth's history (Yang et al., 2014). The partial pressure of  $N_2$  in the Earth's early atmosphere (at least 3.5 Gyr ago) has been argued to be similar to the present value or even higher (Goldblatt et al., 2009; Marty et al., 2013; Wordsworth and Pierrehumbert, 2013). Assuming that an amount equivalent to the present atmospheric nitrogen ( $\sim 3.9 \times 10^{21}$  gN; Bebout et al., 2013) was released from

the primitive mantle over a timescale of  $5 \times 10^8$  years, an  $\text{NH}_4^+$  flux of  $\sim 10^{13}$  gN yr $^{-1}$  is calculated. The value is lower than the modern rate of biological nitrogen fixation by a factor of 10 ( $2.5 \times 10^{14}$  gN yr $^{-1}$ ; Gruber and Galloway, 2008). However, at a local environment such as terrestrial geothermal fields, the release of nitrogen could have provided an ample and continuous supply of  $\text{NH}_4^+$  during the Hadean era.

Extraterrestrial input could have provided additional ammonia onto the primitive Earth. Carbonaceous chondrites contain  $\text{NH}_3$  with concentrations up to 18.85  $\mu\text{mol}$  per gram of meteorite (Pizzarello et al., 1994, 2008; Pizzarello and Holmes, 2009). The largest portion of organic matter in carbonaceous chondrites is present as a complex insoluble organic material (IOM); however, a significant amount of  $\text{NH}_3$  has been extracted from IOM upon a hydrothermal treatment (Pizzarello et al., 2011; Pizzarello and Williams, 2012). For IOM in CR2, the most primitive and least altered chondrites, a hydrothermal heating at 300 °C and 100 MPa for 6 days released ammonia in the amount of 10  $\mu\text{g}$  per 1 mg of IOM, which accounted for nearly 60% of the nitrogen in the IOM prior to the treatment (Pizzarello et al., 2011). The  $\text{NH}_3$  content in other extraterrestrial objects (comet and IDPs) are not well known. The N/C molar ratios in the organic phase of IDPs are in the range from 0.05 to 0.1, which are similar to those in carbonaceous chondrites (0.03–0.1) (Pizzarello et al., 2006). The delivery of organic carbon by extraterrestrial objects about 4 Gyr ago has been estimated to be  $\sim 10^{11}$  g yr $^{-1}$ , with IDPs' contribution being the most significant (Chyba and Sagan, 1992). If all delivered organic nitrogen were in the form of  $\text{NH}_3$ , or were converted to  $\text{NH}_3$  upon subsequent aqueous alteration on the Earth, the ammonia input is calculated to be  $\sim 10^{10}$  g yr $^{-1}$ . The estimation is over optimistic; but is still much lower than the  $\text{NH}_3$  production on the early Earth (see above). Extraterrestrial input would therefore be a minor source of ammonia for the chemical evolution of life.

### 3.2. Phosphorous fixation

Phosphorous (P) is the fifth most important element in biology, just behind hydrogen, oxygen, carbon and nitrogen (Pasek and Lauretta, 2005). It constitutes biomolecules that play central roles in replication and information (RNA and DNA), metabolism (ATP, NADPH and other coenzymes), and structure (phospholipids) (Pasek, 2008). On Earth, phosphorus is the 11th most abundant element, occurring as fully oxidized orthophosphate ( $\text{PO}_4^{3-}$ ) within igneous and metamorphic rocks (0.15–0.2 wt.%), and as well-separated crystalline masses formed by differentiation from cooling basic magma (Maciam, 2005; Bryant et al., 2009). Representative phosphate minerals found in the lithosphere are apatite ( $\text{Ca}_5(\text{PO}_4)_3\text{X}$ ); hydroxylapatite ( $\text{X} = \text{OH}$ ), chlorapatite ( $\text{X} = \text{Cl}$ ), fluorapatite ( $\text{X} = \text{F}$ ), whitlockite ( $\text{Ca}_3(\text{PO}_4)_2$ ), graftonite ( $(\text{Fe,Mn,Ca})_3(\text{PO}_4)_2$ ), and sarcopside ( $(\text{Fe,Mn,Ca})_7(\text{PO}_4)_4\text{F}_2$ ), the apatite group being by far the most ubiquitous (Maciam, 2005). The ocean is an important reservoir of phosphorus ( $6.3 \times 10^{16}$  g), but the content is much lower than those on land ( $4.3 \times 10^{20}$  g) and on the ocean floor ( $3.9 \times 10^{20}$  g) owing to its low solubility controlled by phosphate minerals (Van Cappellen and Ingall, 1996). The solubility products ( $K_{sp}$ ) of chlorapatite, merrillite ( $\text{Ca}_9\text{Mg}(\text{PO}_4)_7$ ), and whitlockite are  $10^{-22}$ ,  $10^{-39}$ , and  $10^{-39}$ , respectively (Adcock et al., 2013), indicating that the concentration of  $\text{HPO}_4^{2-}$  equilibrated with these minerals are  $4.6 \times 10^{-9}$  M,  $8.5 \times 10^{-9}$  M, and  $5.2 \times 10^{-8}$  M, respectively, in the presence of 1 mM  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Cl}^-$  at 25 °C and neutral pH. Because of the low solubility, the vital element is often the limiting nutrient in ecosystems (Oelkers and Valsami-Jones, 2008; Pasek, 2013). The low-solubility problem would also arise in a primitive aquatic environment. Evaporation of

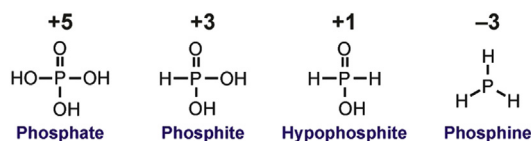
seawater cannot lead to an increase of phosphate concentration, but to precipitation of phosphate minerals because it also increases the concentration of divalent cations (Schwartz, 2006). The same situation would occur in concentration by freezing (Keefe and Miller, 1995).

Yamagata et al. (1991) reported detection of polyphosphates from a fumarole of the volcano Mt. Usu in Hokkaido, Japan. The concentrations reported for orthophosphate, pyrophosphate ( $\text{H}_4\text{P}_2\text{O}_7$ ), and tripolyphosphate ( $\text{H}_5\text{P}_3\text{O}_{10}$ ) were 1.13, 0.45, and 0.37  $\mu\text{M}$ , respectively. These concentrations are so low that it is unlikely that they could have contributed directly to the chemical evolution. So far, no geochemical process that led to abiotic production of polyphosphates in high yield on the Earth has been discovered (Keefe and Miller, 1995).

Phosphorous forms a variety of redox state P compounds including orthophosphate ( $\text{H}_3\text{PO}_4$ ;  $\text{P}^{5+}$ ), phosphite ( $\text{H}_3\text{PO}_3$ ;  $\text{P}^{3+}$ ), hypophosphite ( $\text{H}_3\text{PO}_2$ ;  $\text{P}^{1+}$ ), and phosphine ( $\text{H}_3\text{P}$ ;  $\text{P}^{-3}$ ) (Fig. 3; Pasek, 2008). Phosphite is more soluble than orthophosphate by a factor of  $\sim 1000$  over similar pH and temperatures (Schwartz, 2006; Pasek, 2008). Additionally, phosphite is much more reactive than orthophosphate, capable of forming condensed phosphates as well as phosphorylated organic compounds having C–P and C–O–P linkages without condensing agents (Pasek et al., 2007). For instance, ammonium phosphite ( $(\text{NH}_4)_2\text{HPO}_3$ ) readily reacts with uridine (2:1 molar ratio) to generate uridine-5'-phosphite at 60 °C in dry conditions (De Graaf and Schwartz, 2005). The yield attained about 20% (based on uridine) within 24 h, whereas no detectable 5'-UMP were obtained from ammonium phosphate under the same conditions.

Phosphite is thermodynamically unstable with respect to oxidation to orthophosphate on the Earth's surface. Nonetheless, it has been observed in various aquatic environments, including geothermal pools (Pech et al., 2009, 2011), eutrophic lakes (Han et al., 2012, 2013), and a bay area (Pasek et al., 2014). The origin of phosphite is both biogenesis and abiogenesis. A mechanism of abiotic formation of phosphite is reduction of phosphate from the action of lightning (Glindemann et al., 1999; De Graaf and Schwartz, 2000; Pasek and Block, 2009). Another abiotic source of phosphite is corrosion of phosphide minerals (e.g., schreibersite;  $(\text{Fe,Ni})_3\text{P}$ ) in water (Pasek and Lauretta, 2005). Schreibersite readily oxidizes in water to form a mixed-valence series of P compounds including phosphite as a primary product (Pasek and Lauretta, 2005). Mixing of schreibersite with organics in water produces a variety of phosphorylated organic compounds; a mild heating of synthetic  $\text{Fe}_3\text{P}$  powder (1 g) with aqueous solution of glycerol (25 mL, 0.5 M) at 65 °C for 2 days generates glycerol-phosphate in 2.5% yield (Pasek et al., 2013).

Phosphide minerals are the major P carriers in iron meteorites, pallasites, and enstatite chondrites (Pasek, 2008; Bryant et al., 2013). IDPs and ordinary and carbonaceous chondrites contain P as both phosphate and phosphide (Pasek and Lauretta, 2008). During the impact period of the Hadean era, therefore, significant amounts of reduced P could have been delivered to the primitive Earth. Pasek and Lauretta (2008) estimated the extraterrestrial input of P during the putative late-heavy bombardment (between ca. 4.0 and 3.8 Gyr ago) to be  $2 \times 10^8$  kg yr $^{-1}$ . Iron meteorites and



**Figure 3.** Structures of inorganic P compounds having different redox states (+5, +3, +1, and –3).



IDPs were expected to be the major carriers. If the input of P was distributed evenly on the Earth's surface, the resultant surface concentration of P is very low ( $4 \times 10^{-4} \text{ g yr}^{-1} \text{ m}^{-2}$ ). However, localized impact events associated with iron meteorites could have created high local concentrations of activated P compounds, on the order of  $10^2 \text{ g yr}^{-1} \text{ m}^{-2}$  (Pasek and Lauretta, 2008). It is noteworthy that shock heating by meteorite impact can convert phosphate to reduced ( $\text{P}^0$ ) species (Friel and Goldstein, 1976; Yakovlev et al., 2006). Anorthosites on the Moon surface contain schreibersite as the major P-bearing mineral, with scarce amounts of phosphate minerals such as apatite and whitlockite ( $\text{Ca}_3(\text{PO}_4)_2$ ) (Yakovlev et al., 2006).

Contrary to meteorites, occurrence of phosphide minerals in a terrestrial environment is limited owing to their thermodynamic and kinetic instabilities. Exceptions reported so far include schreibersite, found as trace inclusions in natural metallic iron from the Disko Island, Greenland (Klock et al., 1986), 200- $\mu\text{m}$ -size grains of barringerite ( $\text{Fe}_2\text{P}$ ) in garnet peridotite from China (Yang et al., 2005), and schreibersite grains in fulgurites formed by cloud-to-ground lightning strike (Essene and Fisher, 1986; Pasek et al., 2012). Recently, a rich occurrence of iron-nickel phosphides were found in pyrometamorphic rocks from Israel and Jordan (Britvin et al., 2015). The phosphide minerals were inferred to be of terrestrial origin, formed from natural phosphates and trevorite ( $\text{NiFe}_2\text{O}_4$ ) at temperatures higher than  $1050^\circ\text{C}$  (Britvin et al., 2015). The solid-state reduction of phosphate to phosphide requires

highly reducing and elevated temperature ( $\geq 400^\circ\text{C}$ ) conditions. In industry, the reduction is achieved in high-temperature gaseous hydrogen and methane in the presence of mineral catalysts (Burns et al., 2007; Prins and Bussell, 2012). If geothermal environments on the Hadean Earth were reducing enough for the occurrence of high concentrations of  $\text{CH}_4$  and  $\text{H}_2$ , phosphate reduction at localized reductive sites could have been a significant source of reduced P at the time of the origin of life.

## 4. Prebiotic synthesis of building blocks of life

### 4.1. Amino acid

Amino acids are the building blocks of proteins, composed of amino ( $-\text{NH}_2$ ) and carboxyl ( $-\text{COOH}$ ) groups together with a side-chain specific to each amino acid. Most protein amino acids are L- $\alpha$ -amino acids attaching a hydrogen atom to the  $\alpha$ -carbon. Because of their simpler structures compared to other biological components (e.g., nucleobases and ribose), abiotic synthesis of amino acids has been studied in great detail through both experimental and theoretical investigations (Table 1).

#### 4.1.1. Terrestrial synthesis of amino acids

One of the most important parts of experiments for abiotic amino acid synthesis is the Miller–Urey experiment (Miller, 1953).

**Table 1**  
Summary of abiotic synthesis of the 20 protein amino acids.

Amino acids	Terrestrial origin				Extraterrestrial origin			
	Spark discharge	Irradiation (UV, X-ray, etc.)	Shock heating	Hydrothermal synthesis	C1 (C11, CM1, CR1)	C2 (CM2, CR2, Tagish Lake)	C3 (CR3, CH3, CB)	Others (MMs <sup>a</sup> , comet)
Gly	a, b, k, l, r, v, ae, an, aq, aw, az, bf, au, ay	d, i, m, t, u, aa, ab, ad, af, ah, aj, ap	h, bb, bi	c, e, g, n, o, p, q, w, x, y, ai, as, ba	av, be, bh, bk	s, z, ak, al, ar, at, av, ax, bd, be, bh	be, bh, bj	ac, am, ao, bc
Ala	a, b, k, l, r, v, ae, an, aq, au, ay, az, bf	d, i, m, t, u, aa, ab, ad, af, aj, ap	h, bi	c, e, g, n, p, q, w, x, y, ai, as, ba	av, be, bh, bk	s, z, ag, ak, al, ar, at, av, ax, bd, be, bh	be, bh, bj	ac, am, ao
Arg	—	—	—	n	—	—	—	—
Asp	a, l, r, v, ae, au, ay, az, bf	i, m, t, u, aa, ab, ad, af, ah, aj	c, e, g, n, o, p, x, y, ba	av	s, z, al, ar, av, be, bh, bk	ak, at, bd, be, bh	ac, am, ao, bj	—
Asn	—	ap	—	—	—	—	—	—
Cys	—	m	—	x	—	—	—	—
Gln	—	—	—	—	—	—	—	—
Glu	l, r, v, au, ay, az, bf	i, m, aa, ab, ad, af, aj	e, g, n, p, x, y, ba	av	bk	z, ak, al, ar, at, av, bd, be, bh	be, bh, bj	ac, am, ao
His	aq, au	—	—	n	—	—	—	—
Ile	l, au, bf	m	—	e, n, x, y	—	s, al, bd, bh	bh	—
Leu	l, bf	m	h	e, n, y	—	s, z, al, at, bd, bh	bh	—
Lys	aq	—	—	y	—	—	—	—
Met	k, j, bf, bg	f	—	n, x	—	—	—	—
Phe	ay	—	—	y	—	bd	—	—
Pro	l, aq, au, aw	m	—	g, y	bh	al, bd, bh	bh	—
Ser	l, r, v, aq, au, aw, ay, az, bf	i, m, u, t, aa, ab, ad, af, aj, ap	—	c, e, g, n, o, p, x, y, ba	av, be, bh, bk	s, al, ar, at, av, bd, be, bh	be, bh, bj	ac, am, ao
Thr	l, bf	m, t, u, aj	—	c, e, n, p, y	—	s, al, bd, bh	bh	—
Trp	—	—	—	—	—	—	—	—
Tyr	—	—	—	—	—	bd, bh	bh	—
Val	l, r, aq, au, aw, ay, bf	m	h	g, n, y	be, bk	s, ag, al, ar, at, bd, be, bh	bh, bj	am, ao

a, Miller (1953); b, Miller (1955); c, Oro et al. (1959); d, Groth and Weyssenhoff (1960); e, Lowe et al. (1963); f, Steinman et al. (1968); g, Fox and Windsor (1970); h, Bar-Nun et al. (1970); i, Sagan and Khare (1971); j, Khare and Sagan (1971); k, Van Trump and Miller (1972); l, Ring et al. (1972); m, Becker et al. (1974); n, Hatanaka and Egami (1977); o, Kamaluddin et al. (1979); p, Yanagawa et al. (1980); q, Yanagawa et al. (1982); r, Schlesinger and Miller (1983a); s, Cronin and Pizzarello (1986); t, Kobayashi et al. (1989); u, Kobayashi et al. (1990); v, Hirose et al. (1990–1991); w, Yanagawa and Kobayashi (1992); x, Hennet et al. (1992); y, Marshall (1994); z, Engel and Macko (1997); aa, Utsumi and Takahashi (1998); ab, Kobayashi et al. (1998); ac, Brinton et al. (1998); ad, Kobayashi et al. (1999); ae, Miyakawa et al. (1999); af, Takahashi et al. (1999); ag, Pizzarello and Cronin (2000); ah, Shi et al. (2001); ai, Islam et al. (2001); aj, Kobayashi et al. (2001); ak, Kminek et al. (2002); al, Shimoyama and Ogasawara (2002); am, Glavin et al. (2004); an, Plankensteiner et al. (2004b); ao, Matrajt et al. (2004); ap, Civis et al. (2004); aq, Plankensteiner et al. (2006); ar, Glavin et al. (2006); as, Huber and Wächtershäuser (2006); at, Martins et al. (2007); au, Ruiz-Bermejo et al. (2007a); av, Botta et al. (2007); aw, Janda et al. (2008); ax, Pizzarello et al. (2008); ay, Johnson et al. (2008); az, Cleaves et al. (2008); ba, Aubrey et al. (2009); bb, Furukawa et al. (2009); bc, Elsila et al. (2009); bd, Pizzarello and Holmes (2009); be, Glavin et al. (2011); bf, Parker et al. (2011a); bg, Parker et al. (2011b); bh, Pizzarello et al. (2012); bi, Martins et al. (2013); bj, Burton et al. (2013); bk, Burton et al. (2014).

<sup>a</sup> MM, micro meteorite.

By activating an electric discharge in a highly reducing gas mixture of  $\text{CH}_4$ ,  $\text{NH}_3$  and  $\text{H}_2$ , which at the time was believed to be representative of the primitive atmosphere, Miller produced protein-amino acids including Gly, Ala and Asp along with two non-proteinones,  $\beta$ -alanine and amino-*n*-butyric acid (Miller, 1953; Lazcano and Bada, 2003). The result provided direct experimental support for the “Prebiotic soup” theory proposed by Oparin. Recent re-analyses of the extracts from the Miller–Urey experiments in the 1950’s detected 23 amino acids, far more than the five reported originally (Johnson et al., 2008; Parker et al., 2011a,b). Amino acids have also been synthesized from gas mixtures using various types of energy sources including UV (e.g., Steinman et al., 1968; Sagan and Khare, 1971), X-ray (e.g., Utsumi and Takahashi, 1998; Takahashi et al., 1999), and proton irradiation (e.g., Kobayashi et al., 1990, 1999) (Table 1). An important characteristic of the products is that they are not a random mixture of organic compounds; rather, a relatively small number of compounds (including amino acids) are formed in high yields (Bada and Lazcano, 2003). The preferential synthesis of  $\alpha$ -amino acids occurs through a variation of the Strecker reaction (Strecker, 1850). The reaction starts from gas-phase production of HCN and aldehydes, followed by condensation of these molecules with  $\text{NH}_3$  to form  $\alpha$ -aminonitriles in aqueous solution. Subsequent hydrolysis of the nitrile group to the carboxyl group generates  $\alpha$ -amino acids (Fig. 4a) (Miller and Orgel, 1974; Ruiz-Mirazo et al., 2014). The structure of aldehyde determines the structure of amino acid; Gly is formed from formaldehyde (HCHO), Ala from acetaldehyde ( $\text{CH}_3\text{CHO}$ ), whereas Ser

from glycolaldehyde ( $\text{HOCH}_2\text{CHO}$ ) (Miller and Orgel, 1974). Asp is formed from condensation of cyanoacetylene ( $\text{HCCCN}$ ) with ammonium cyanide ( $\text{NH}_4\text{CN}$ ), followed by hydrolysis of the nitrile group to the carboxyl group (Fig. 4b; Sanchez et al., 1966a; Miller and Orgel, 1974). Cyanoacetylene is the second major product from a  $\text{CH}_4/\text{N}_2$  gas mixture by the action of electric discharge (up to 8.4% of the principal product, HCN) (Sanchez et al., 1966b). The Strecker route does not directly produce non- $\alpha$ -amino acids; hence another mechanism is necessary to explain their synthesis.  $\beta$ -amino acids have been proposed to form from  $\alpha,\beta$ -unsaturated nitriles by the addition of ammonia to the double bond (Michael addition), as from acrylonitrile in the case of  $\beta$ -alanine (Fig. 4d; Buc et al., 1945; Pizzarello et al., 2006). Although they are energetically less favored,  $\gamma$ - and  $\delta$ -amino acids can also be synthesized by the same process from  $\beta,\gamma$ - and  $\gamma,\delta$ -unsaturated nitriles, respectively (Pizzarello et al., 2006). Fig. 4 also presents abiotic synthetic pathways of other amino acids reported by Friedmann and Miller (1969a) for Val and Ile, by Van Trump and Miller (1972) for Met and Glu, by Friedmann and Miller (1969b) for Phe and Tyr, and by Shen et al. (1990) for His.

Effect of gas composition on the yield and variety of amino acids has been examined by Schlesinger and Miller (1983b). They showed that reducing gas mixtures of  $\text{CH}_4$ ,  $\text{H}_2$ , and  $\text{N}_2$  generate amino acids in excellent yields (up to 4.7% of the initial carbon), whereas only  $6 \times 10^{-4}\%$  yield of amino acids were obtained from  $\text{CO}_2$  and  $\text{N}_2$ . In the former system, identified amino acids include Gly, Ala, Asp, Glu, Ser, and Val, whereas Gly was almost the only amino acid produced

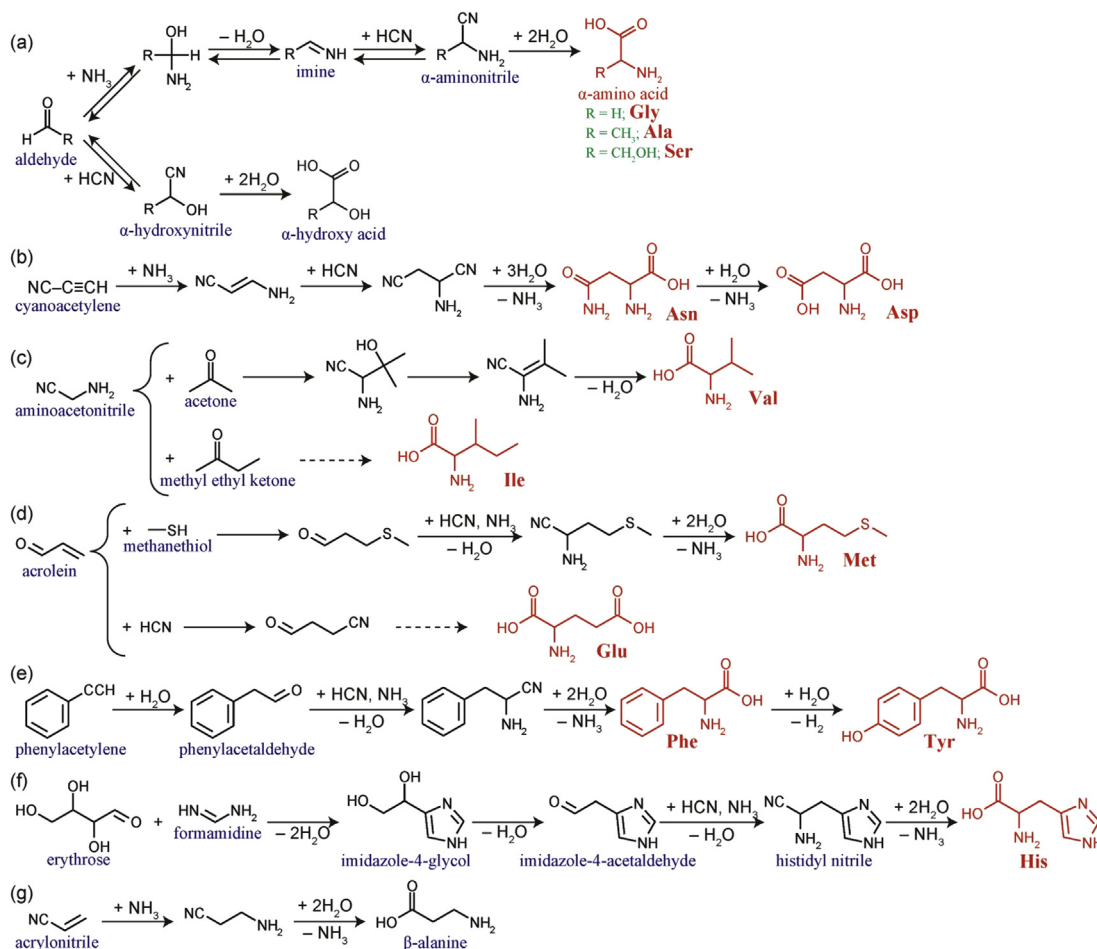


Figure 4. Abiotic synthetic pathways of amino acids and hydroxy acids.



from the latter gas mixture. More recently, however, using a  $\text{N}_2/\text{CO}_2$  gas mixture, Cleaves et al. (2008) demonstrated that the yield of amino acids increased hundreds of times as much as previously reported (up to 2.5% of the initial nitrogen) when the pH of the collecting solution was buffered to maintain a value close to 7, and oxidation inhibitors such as  $\text{Fe}^{2+}$  were added to the solution (Cleaves et al., 2008). Produced amino acids include Gly, Ala, Asp, Gly, Ser, and some non-protein amino acids ( $\beta$ -alanine,  $\gamma$ -aminobutyric acid, and  $\alpha$ -aminoisobutyric acid). Amino acid synthesis from the atmosphere therefore greatly depends on the oceanic conditions (pH and dissolved species) as well as the redox state of the primitive atmosphere.

$\alpha$ -Hydroxy acids are another major class of products in the Miller–Urey type experiments (Miller and Orgel, 1974). Unlike amino acids, their synthesis does not involve  $\text{NH}_3$  (Fig. 4). At equilibrium, therefore, the concentration ratio of  $\alpha$ -hydroxynitrile (a precursor of  $\alpha$ -hydroxy acids) and  $\alpha$ -aminonitrile (a precursor of  $\alpha$ -amino acids) is a linear function of the concentration of free  $\text{NH}_3$ ; (e.g.,  $[\text{aminoacetoneitrile}]/[\text{glycolonitrile}] = 21 [\text{NH}_3]$  at 25 °C; Moutou et al. (1995)). Because the mole fraction of  $\text{NH}_3$  increases with increasing pH through deprotonation of  $\text{NH}_4^+$  ( $pK_a = 9.24$  at 25 °C and 7.40 at 100 °C (Shock and Helgeson, 1988; Shock et al., 1989)),  $\alpha$ -aminonitriles predominate over  $\alpha$ -hydroxy nitriles under alkaline pH if  $\text{NH}_3$  is abundantly present in the system. It is also noteworthy that formaldehyde strongly accelerates the hydrolysis of  $\alpha$ -aminonitriles, and hence kinetically shifts the  $\alpha$ -aminonitrile/ $\alpha$ -hydroxynitrile equilibrium in favor of the formation of  $\alpha$ -amino acids (Taillades et al., 1998). In the case of the aminoacetoneitrile/glycolonitrile system, the ratio of their hydrolysis rates is given as  $4.2 \times 10^6 [\text{H}_2\text{CO}][\text{NH}_3]$  at 25 °C (Taillades et al., 1998). If the product “ $[\text{H}_2\text{CO}][\text{NH}_3]$ ” is larger than  $2.4 \times 10^{-7}$ , the formation rate of Gly can exceed that of glycolic acid. The value is still higher than the product of estimated concentrations of  $\text{H}_2\text{CO}$  ( $1 \times 10^{-3}$  M; Pinto et al., 1980) and  $\text{NH}_4^+$  (3.6–70  $\mu\text{M}$ ; Summers and Chang, 1993) in the primitive ocean. However, sufficient concentrations of these compounds could have been met in a local reducing environment, such as a shallow pond in the proximity of a lightning-rich volcanic eruption (Bada, 2004, 2013).

#### 4.1.2. Hydrothermal systems of amino acids

Another possible source of abiotic amino acids is submarine hydrothermal systems (SHSs) (Table 1). It has been shown that high concentrations of  $\text{NH}_3$ , HCN and  $\text{H}_2\text{CO}$  ( $\geq 50$  mM) are excellent starting conditions for the hydrothermal synthesis of amino acids (yields;  $>1\%$  of initial nitrogen) because they are basic components for the Strecker synthesis (Hennet et al., 1992; Marshall, 1994; Islam et al., 2001). HCN is formed from the condensation of  $\text{H}_2\text{CO}$  and  $\text{NH}_2\text{OH}$  ( $\text{H}_2\text{CO} + \text{NH}_2\text{OH} \rightarrow \text{HCN} + 2\text{H}_2\text{O}$ ) (Oro et al., 1959; Kamaluddin et al., 1979); hence amino acids (mainly Gly) are also synthesized from the two compounds without HCN (Oro et al., 1959; Kamaluddin et al., 1979). Contrary to the apparent great successes, some researchers questioned these experiments because of a low probability of the occurrence of the reaction conditions under the primitive SHSs (Aubrey et al., 2009; McCollom, 2013a). No HCN and  $\text{H}_2\text{CO}$  have been observed in modern hydrothermal systems. A thermodynamic calculation by LaRowe and Regnier (2008) showed that the stabilities of HCN and  $\text{H}_2\text{CO}$  relative to  $\text{CO}_2$ ,  $\text{N}_2$  and  $\text{H}_2$  (or  $\text{CO}$ ,  $\text{N}_2$  and  $\text{H}_2$ ) drastically decrease with increasing temperature.  $\text{NH}_4^+$  has been detected in modern hydrothermal systems, but has mostly been attributed to biogenic origins (Lilley et al., 1993). Regarding the duration time of heating, laboratory experiments typically use heating times on the order of minutes to hours, whereas residence times in axial hydrothermal systems range from years (Kadko et al., 2007; Coumou et al., 2008) to decades (Turekian and Cochran, 1986). Those in lower

temperature off-axis diffuse flow systems are possibly on the order of ten thousands of years (Fruh-Green et al., 2003). Consequently, amino acid formation from  $\text{NH}_3$ , HCN and  $\text{H}_2\text{CO}$  might be possible on the Hadean Earth, but would require special environmental situations, such as concentration of these precursors by evaporation or freezing and rapid heating–cooling cycles to prevent undesirable reactions toward the equilibrium. Both the situations are difficult to attain in SHSs.

Fluids from modern SHSs contain  $\text{CO}_2$  (up to 200 mM) and  $\text{CH}_4$  (up to 3.4 mM) as major carbon species (Kelley et al., 2001; Tivey, 2007) along with trace amounts of  $\text{CO}$  (up to 5  $\mu\text{M}$ ; Charlou et al., 2002). So far, there is no experimental evidence that amino acids were directly produced from  $\text{CO}_2$  (Keefe et al., 1995) although a possibility has been proposed that  $\text{CO}_2$  reduction by  $\text{FeS}$  and  $\text{H}_2\text{S}$  through a sequence of proto-metabolic reactions leads to the formation of amino acids (Wächtershäuser, 1990, 2000). Amino acid formation from  $\text{CH}_4$  in hydrothermal solution has been experimentally demonstrated by Yanagawa and Kobayashi (1992). However, observed amino acids were only Gly and Ala with very low concentrations (1.99 and 0.75  $\mu\text{M}$ , respectively, which correspond to  $2.4 \times 10^{-4}\%$  and  $1.4 \times 10^{-4}\%$  of initial carbon) even though their experiment started from unrealistically high concentrations of  $\text{CH}_4$  (40 atm),  $\text{N}_2$  (40 atm) and  $\text{NH}_3$  (54 mM) together with a variety of metal cations ( $\text{Fe}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$ ) as catalysts. Thermodynamically, synthesis of amino acids from  $\text{CH}_4$  requires much larger amounts of extra energy than those from  $\text{CO}_2$  because  $\text{CH}_4$  formation from  $\text{CO}_2$  is a strong thermodynamically favorable reaction ( $\Delta_r G^\circ$  for the reaction “ $\text{CO}_2 + 4\text{H}_2 \rightarrow \text{CH}_4 + 2\text{H}_2\text{O}$ ” is  $-195 \text{ kJ mol}^{-1}$  at 25 °C and 250 bar (calculated using the relevant thermodynamic data reported by Helgeson and Kirkham (1974), Shock et al. (1989), and Shock and Helgeson (1990))). For  $\text{CO}$ , the primitive SHSs could have provided a much higher concentration than the present level. Using a high concentration of  $\text{CO}$  (1–75 bar) together with 1.33–2 mM  $\text{CN}^-$ , Huber and Wächtershäuser (2006) produced Gly and Ala (up to 0.17 and 0.015 mM, respectively) by conducting a hydrothermal experiment under alkaline pH (9–12.5) in the presence of Ni/Fe precipitates (sulfides and hydroxides) at 100 °C. One concern for the  $\text{CO}$ -driven synthesis is that  $\text{CO}$  rapidly reaches equilibrium with  $\text{CO}_2$  at high temperature conditions (e.g., the half-life for  $\text{CO}$  oxidation to  $\text{CO}_2$  at 350 °C is  $\sim 2$  min; McCollom and Seewald, 2003; Seewald et al., 2006). If the residence time of high-temperature fluid in the primitive SHSs was sufficiently long for the  $\text{CO}$ – $\text{CO}_2$  equilibrium, thermodynamic drives for abiotic synthesis of amino acids from  $\text{CO}$  and  $\text{CO}_2$  will be similar.

Taken together, current scientific knowledge denies the possibility that the primitive SHSs provided amino acids in sufficient concentrations to support the chemical evolution of life.

#### 4.1.3. Extraterrestrial input of amino acids

Since the first detection from the Murchison (CM2) meteorite in the early 1970s (Kvenvolden et al., 1970; Oro et al., 1971), extraterrestrial amino acids have been observed in various types of carbonaceous chondrites (Pizzarello et al., 2006), comets (Elsila et al., 2009), and micrometeorites (Brinton et al., 1998). To date, over 80 kinds of amino acids have been identified in carbonaceous chondrites, including 12 protein-amino acids of Ala, Asp, Glu, Gly, Ile, Leu, Phe, Pro, Ser, Thr, Tyr, and Val (Sephton, 2002; Glavin et al., 2011; Burton et al., 2012). Their total abundances in chondrites range from 0.2 ppm (CB chondrite; Burton et al., 2013) to 2400 ppm (CR2 chondrite; Pizzarello and Shock, 2010). CR2s are the most primitive, least altered chondrites (Cody and Alexander, 2005; Alexander et al., 2010), and typically have a higher concentration of amino acids than chondrites that experienced more severe aqueous or thermal alteration in meteorite parent bodies (Burton et al., 2012). The amount and variation of amino acids in comets

and IDPs are not well known, but comets contain about 10 times the amount of organics found in carbonaceous chondrites (Delsemme, 1991; Alexander et al., 2007). Organic matter in carbonaceous chondrites and comets has been inferred to have formed from a common precursor material that originated in the outer Solar system and/or in the interstellar medium (Alexander et al., 2007; Herd et al., 2011). Therefore, amino acid concentration in comets could amount to the order of 10,000 ppm, a value several times higher than those in CR2 chondrites.

An important characteristic of meteoritic amino acids is enantiomeric excess of the left-handed amino acids over the right-handed counterparts (Burton et al., 2012). The L-amino acid excess was first discovered in the four stereoisomers of 2-amino-2,3-dimethylbutanoic acid in the Murchison meteorite (Cronin and Pizzarello, 1997). Since then, several  $\alpha$ -dialkyl amino acids (isovaline,  $\alpha$ -methylnorleusine,  $\alpha$ -methylvaline,  $\alpha$ -methylnorvaline, and  $\alpha$ -methylisoleucine) were found to have slight to significant L-excesses ranging from nearly 0 to 60% (Glavin and Dworkin, 2009; Pizzarello et al., 2012; Burton et al., 2013). In contrast to  $\alpha$ -hydrogen amino acids found in biology,  $\alpha$ -dialkyl amino acids are highly resistant to racemization (conversion of one enantiomer to the other) under aqueous and radiogenic conditions (Burton et al., 2012). Therefore, these amino acids could have preserved their enantiomeric properties for a long period since their delivery onto the primitive Earth, and contributed to the origin of biological homochirality by transferring their asymmetry to the  $\alpha$ -hydrogen protein amino acids or other prebiotic compounds (Pizzarello and Weber, 2004). In fact,  $\alpha$ -methyl amino acids are known to have strong helix inducing and stabilizing effects (Altmann et al., 1988). The property could have supported the stereoselectivity of secondary structures of long peptides (Brack and Spach, 1981).

Amino acids could have been formed on the primitive Earth through meteorite impacts and comets (Bar-Nun et al., 1970; Goldman et al., 2010). However, yields of amino acids from non-reducing gas mixtures (e.g., CO<sub>2</sub> and N<sub>2</sub>) are extremely low (<<1%). For instance, Furukawa et al. (2009) observed 24 picomolar Gly ( $\sim 10^{-6}\%$  of initial carbon) produced from a high-velocity impact into a mixture of solid carbon, water, ammonia and Fe and Ni metals. Martins et al. (2013) applied a shock impact ( $\sim 7$  km/s) into an ice mixture mimicking the ice present in comets, comprised of NH<sub>4</sub>OH, CO<sub>2</sub> and CH<sub>3</sub>OH in the molar ratio of 9.1:8:1. Some amino acids were observed with their total yield of 3900 ng ( $\sim 8 \times 10^{-5}\%$  of initial carbon). The contribution of the impact event to the origin of life on Earth would therefore be minor.

## 4.2. Peptide

Polymerization of amino acids to peptides requires the removal of water molecules from the amino and carboxyl groups of the reaction partners ( $-\text{NH}_3^+ + -\text{OOC}- \rightarrow -\text{NHOC}- + \text{H}_2\text{O}$ ). As a consequence, the peptide synthesis in water is both a thermodynamically and kinetically unfavorable process. For dimerization of the simplest amino acid “Gly” to glycylglycine (GlyGly) in water at 25 °C and neutral pH, the required Gibbs energy is 14.84 kJ mol<sup>-1</sup>, and the equilibrium constant is  $2.51 \times 10^{-3}$  (Kitadai, 2014). The value indicates that less than 0.01% of Gly is converted into GlyGly unless the initial Gly concentration is extremely high (e.g., >100 mM). The equilibrium constant increases at higher temperatures (Shock, 1992b; Kitadai, 2014). Thus, some researchers argued that polymerization of amino acids occurred in SHSs on the primitive Earth (e.g., Imai et al., 1999; Lemke et al., 2009). Such reactions proceed more readily at alkaline pH (Zamaraev et al., 1997; Sakata et al., 2010). The occurrence of high temperatures and alkaline solutions has been observed in serpentine-hosted hydrothermal systems (Kelley et al., 2001, 2005; Suda et al.,

2014), which could have prevailed under the primitive ocean floor (Shibuya et al., 2010). However, temperature increase also favors decomposition of amino acids (Qian et al., 1993; Cox and Seward, 2007; McCollom, 2013a). The temperature dependences of decomposition rates of amino acids are typically greater than those of polymerization; the activation energies of dimerization and decarboxylation of Gly are 88 kJ mol<sup>-1</sup> (Sakata et al., 2010) and 138.4 kJ mol<sup>-1</sup> (Li and Brill, 2003), respectively. Consequently, it is unclear whether SHSs could sustain the abiotic formation of peptides necessary to initiate life.

To overcome the difficulties noted above, several mechanisms have been proposed including (1) a solid-state reaction based on melting of amino acids (Fox and Harada, 1958, 1960; Fox, 1964), (2) chemical modifications of amino acids using condensation agents such as cyanates (Flores and Leckie, 1973), cyanamides (Steinman et al., 1964, 1965a, 1966; Steinman and Cole, 1967), imidazole (Sawai et al., 1975; Sawai and Orgel, 1975a; Weber et al., 1977; Ferris et al., 1996), linear and cyclic polyphosphates (Rabinowitz et al., 1969; Chung et al., 1971; Yamanaka et al., 1988), and nucleoside triphosphate (ATP, CTP, GTP and UTP) (Weber et al., 1977; Rishpon et al., 1982), and (3) heterogeneous systems involving mineral surfaces and metal cations working as catalysts and/or condensation agents (Basiuk et al., 1990–1991; Rimola et al., 2005, 2007; Napier and Yin, 2006; Kitadai et al., 2011, 2017; Kitadai, 2017). Later on, it was argued that the occurrences of the former two mechanisms on the primitive Earth were unlikely or had at most only a marginal probability of taking place at specific locations. Therefore, the present review does not include the two topics; their realizations in a primitive Earth environment has been discussed in Rode (1999), Rode and Suwannachot (1999), and Fitz et al. (2007).

### 4.2.1. Peptide synthesis in tidal pools

The effects of metal cations on the polymerization of amino acids have been thoroughly studied by Rode and co-workers simulating tidal pool environments (e.g., Schwendinger and Rode, 1989, 1991). In the “salt-induced peptide formation” (SIPF), they showed that amino acids polymerized effectively in wetting–drying cycles at temperatures between 60 and 90 °C and with acidic pH (2–3) in the presence of NaCl and Cu<sup>2+</sup>. NaCl acts as a dehydration agent of amino acid to peptide in the process of drying, whereas Cu<sup>2+</sup> catalyzes the reaction. Various other metal cations (Ca<sup>2+</sup>, Mg<sup>2+</sup>, Cd<sup>2+</sup>, Co<sup>2+</sup>, Fe<sup>2+</sup>, Mn<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>, Al<sup>3+</sup>, Cr<sup>3+</sup>) have also been examined for their catalytic efficiencies in a similar reaction system, but no enhancement of peptide formation has been observed (Schwendinger and Rode, 1989; Rode and Schwendinger, 1990). The SIPF reaction produces certain amino acid linkages preferentially, rather than random sequences with equal probability (Rode et al., 1997). For instance, some L-amino acids give better yields of dipeptides than the D-forms. The stereoselectivity was first discovered for Ala with a slight preference of L-Ala over D-Ala in dimerization (9%; Plankensteiner et al., 2004a). Later on, Val was found to have much better performance in the SIPF reaction (the L-/D-D ratio of >7.75; Plankensteiner et al., 2005a). As another example,  $\alpha$ -amino acids have been shown to have different polymerization behaviors compared to  $\beta$ - and  $\gamma$ -analogs.  $\alpha$ -amino-butylic acid preferably linked to glycine when competing with the  $\beta$ -analog in a short reaction time, although longer reaction times favor the  $\beta$ -containing peptides because they resisted hydrolysis better than their  $\alpha$ -counterparts (Schwendinger et al., 1995). Such selective polymerizations could have biased the sequence of proteins formed on the primitive Earth (Rode, 1999; Rode and Suwannachot, 1999; Rode et al., 2007). Another important feature of this system is that some amino acids catalyze the formation of homo-dipeptides of other amino acids. This effect, called “mutual amino acid catalysis”, is achieved effectively with Gly, His, and Gly

dipeptides (GlyGly and diketopiperadine; DKP) (Suwannachot and Rode, 1999; Plankensteiner et al., 2002, 2005b,c; Reiner et al., 2006; Fitz et al., 2008; Li et al., 2008, 2010a,b).

A drawback of this system is that only short peptides are formed in the process (up to tri-peptide from mono-amino acids). Yields of peptides are not significant; the maximum yields of homodipeptides reported so far are 6.90% for Ala (Suwannachot and Rode, 1998), 0.7818% for Arg (Li et al., 2010a), 0.5% for Asp (Plankensteiner et al., 2002), 8.56% for Gly (Saetia et al., 1993), 0.30% for Leu (Suwannachot and Rode, 1999), 8.66% for Lys (Reiner et al., 2006), 2.87% for Met (Li et al., 2008), 14.41% for Pro (Reiner et al., 2006), 3.5% for Ser (Plankensteiner et al., 2005c), 0.014% for Trp (Reiner et al., 2006), and 2.23% for Val (Reiner et al., 2006). A combination with oxide minerals and clays improves the situation (Le Son et al., 1998; Rode et al., 1999), but is still insufficient to make polypeptides have ordered secondary structures.

#### 4.2.2. Amino acid polymerization in volcanic hydrothermal environments

Longer peptides with better yields have been obtained in experiments simulating volcanic hydrothermal environments. Huber and Wachtershauser (1998) conducted a heating experiment of 50 mM amino acids (Gly, Phe, and Tyr) with 1 bar CO and 50 mM H<sub>2</sub>S (or CH<sub>3</sub>SH) at 100 °C in the presence of (Fe,Ni)S precipitates. After 1–4 days heating under alkaline pH (8–9.5), they observed the formation of dimers in the yield up to 6.2%, together with trace amounts of trimers. Because amino acid polymerization is thermodynamically unfavorable in aqueous solution, their results indicate that any thermodynamically favorable reaction co-existed in that system, and coupled with the polymerization to drive. Later detailed analyses of reaction intermediates revealed that the driving force was hydrolysis of carbonyl sulfide (Huber et al., 2003; Leman et al., 2004) ( $\Delta_r G^\circ$  for “COS(g) + H<sub>2</sub>O(l) → H<sub>2</sub>S(g) + CO<sub>2</sub>(g)” is  $-21.45 \text{ kJ mol}^{-1}$ ; calculated using the relevant thermodynamic data reported by Wagman et al. (1982). COS is formed from the condensation of CO and H<sub>2</sub>S, and reacts with the amino group of an amino acid to give the amino acid thiocarbamate (Fig. 5). Intramolecular cyclization of this molecule forms the  $\alpha$ -amino acid N-carboxyanhydride (NCA). NCA then reacts with another amino acid and subsequent decarboxylation produces dipeptides (Fig. 5). A

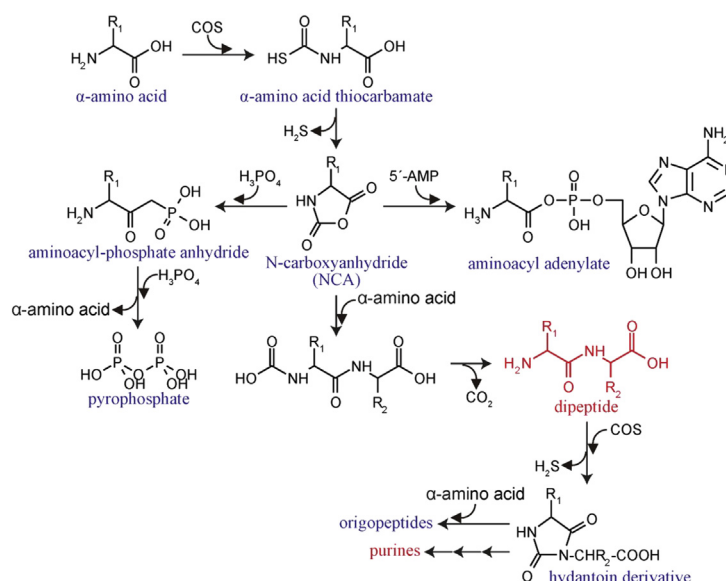
similar condensation process also occurs between COS and dipeptides to give longer peptides (Fig. 5). The COS-mediated condensation was substantially enhanced in the presence of metal cations (Pb<sup>2+</sup>, Fe<sup>2+</sup> or Cd<sup>2+</sup>) and oxidizing agents (Leman et al., 2004). When 70 mM phenylalanine thiocarbamate was mixed with 100 mM potassium ferricyanide (K<sub>3</sub>Fe(CN)<sub>6</sub>) at room temperature, 63% yield of dipeptide was obtained in 5 min, along with 13% tripeptide, 3% tetrapeptide, and trace amounts of penta- and hexapeptides (Leman et al., 2004).

Importantly, COS mediates the aminoacyl bond formation between amino acids and phosphates via NCAs (Fig. 5; Biron and Pascal, 2004; Leman et al., 2006). The reaction also occurs between NCAs and nucleoside monophosphates to give aminoacyl nucleotides (Fig. 5; Biron et al., 2005; Leman et al., 2006). The aminoacyl bond has a high hydrolysis energy; hence an incubation of orthophosphate with COS and amino acids generates pyrophosphate as well as aminoacyl phosphate anhydrides (Fig. 5; Leman et al., 2006). It is also worth noting that the hydantoin derivative resulting from a glycine peptide has a close structural similarity to the imidazole ring of the purine bases (Fig. 5; Huber et al., 2003). These connections between peptides and nucleic acids via COS, a simple volcanic gas, suggests that the present-day's linkage between protein enzyme and DNA/RNA replication is a consequence of their co-evolution from the very beginning of the origin of life.

The present level of COS in volcanic gases is only up to 0.09% (Symonds et al., 1994). However, a recent geochemical study suggested that the Hadean continental crust was significantly more reducing than its present condition by the  $fO_2$  value up to  $\sim 8 \text{ log units}$  (Yang et al., 2014). Such reducing crust generates highly reducing volcanic exhalations with high molar ratios of CO/CO<sub>2</sub>, H<sub>2</sub>S/SO<sub>2</sub>, and NH<sub>3</sub>/N<sub>2</sub> (Mikhail and Sverjensky, 2014; Yang et al., 2014). The COS-driven peptide bond formation and phosphate activation, could therefore have been a significant driving force for the chemical evolution of life.

#### 4.3. Ribose

Ribose is a monosaccharide containing five carbon atoms that, in its open chain form, has an aldehyde functional group at one end



**Figure 5.** COS-mediated chemical evolution of peptides and nucleotides.

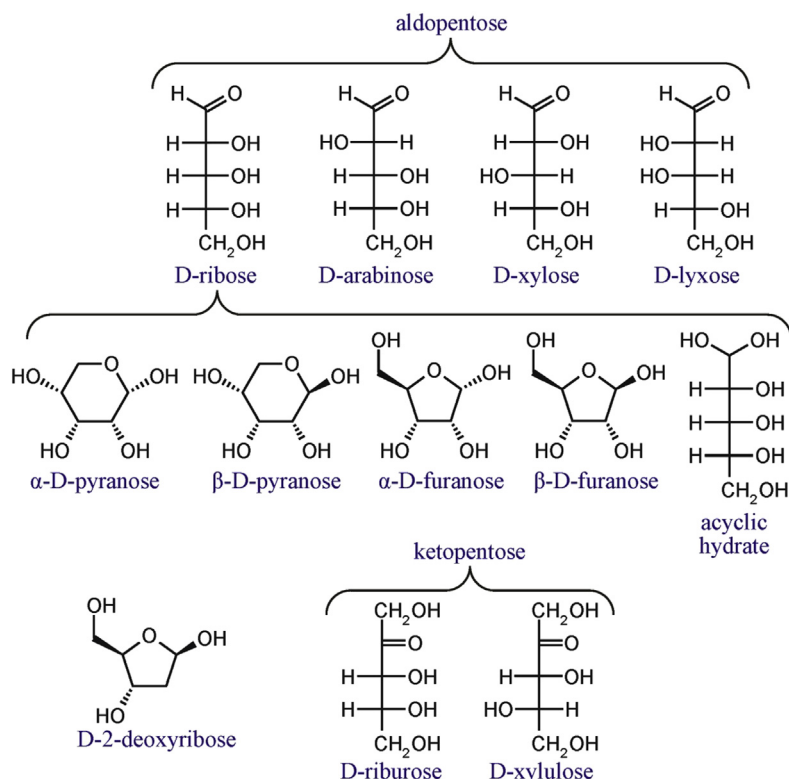


(aldopentose; Fig. 6). Like many monosaccharides, ribose exists in water as an equilibrating mixture of different structural forms. In D<sub>2</sub>O at 28 °C, for instance, D-ribose is present as the six different forms of  $\alpha$ -pyranose,  $\beta$ -pyranose,  $\alpha$ -furanose,  $\beta$ -furanose, an open chain hydrate, and an open chain dehydrate with their relative abundances of 59, 20, 7, 13, 0.09, and 0.04%, respectively (Drew et al., 1998). The  $\beta$ -D-furanose form is extensively used in biological systems as a component of RNA, ATP and NADH. The deoxyribose derivative found in DNA differs from ribose by having a hydrogen atom in place of the hydroxyl group at the C2' carbon.

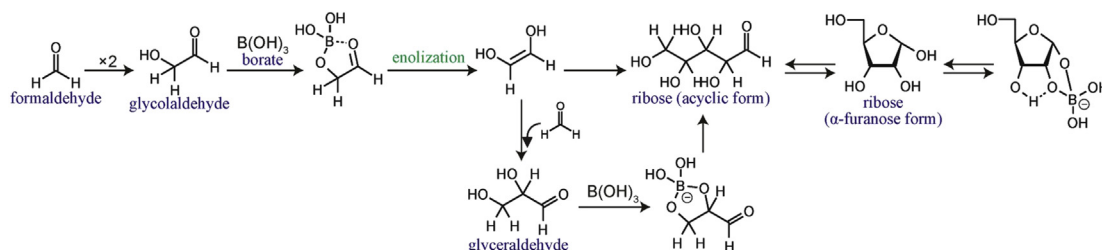
The best studied mechanism relevant to the prebiotic synthesis of ribose is the formose reaction (Breslow, 1959) that was originally discovered by Butlerow more than 150 years ago (Butlerow, 1861). This reaction is a series of polymerizations of formaldehyde (H<sub>2</sub>CO) starting from a very slow conversion of two H<sub>2</sub>CO molecules to glycolaldehyde, followed by a rapid fixation of HCHO to yield carbohydrates as intermediates on the way to more complex, tarry mixtures (Fig. 7). It proceeds with three types of reactions characteristic of compounds having a C=O (carbonyl) group: (1) deprotonation of the carbon atom next to the C=O (“enolization”) to give an enediolate, (2) attack of the resulting enediolate nucleophile on a C=O electrophile to form a new C–C bond (“aldol addition”), and (3) retroaldol fragmentation of higher species to generate lower carbohydrates (Kim et al., 2011; Ritson and Sutherland, 2012). The polarity inversion of intrinsically electrophilic carbonyl carbon of H<sub>2</sub>CO to nucleophile requires highly alkaline conditions (pH > 10) with Ca<sup>2+</sup> as a catalyst. As a consequence, to make the initial step of the formose reaction (2H<sub>2</sub>CO → glycolaldehyde) possible, laboratory experiments have typically been conducted in Ca(OH)<sub>2</sub> suspensions at pH 10–11 and 60–80 °C (Benner et al., 2012).

Several problems have been recognized for the ribose synthesis via the formose reaction (Shapiro, 1988; McCollom, 2013b). First, ribose is merely an intermediate product among a broad suite of compounds including sugars with more or fewer carbons, as well as

structural isomers with the same number of carbons as ribose (Decker et al., 1982). As a consequence, the yield of ribose is typically less than 1% (Shapiro, 1988). Second, reaction time is a critical factor controlling the yield and structure of sugars. The formose reaction initially shows a lag period in which slow conversion of H<sub>2</sub>CO occurs. During this period, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, and C<sub>7</sub> carbohydrates accumulate (Ricardo et al., 2006). This lag period is then followed by a rapid loss of H<sub>2</sub>CO, after which the sample solution turns yellow, then brown. Further incubation generates mixtures that progressively become an insoluble product termed tar. The yield of sugars reaches a maximum at the “yellowing point”, and then declines (Shapiro, 1988); thus, the reaction must be stopped at this point to obtain formose sugars. Third, the formose reaction requires a high concentration of H<sub>2</sub>CO ( $\geq 0.1$  M). The concentration of H<sub>2</sub>CO in the primitive ocean has been estimated to be 10<sup>−3</sup> M by Pinto et al. (1980), assuming its production in a reducing atmosphere and an accumulation period of 10<sup>7</sup> years (no decomposition of H<sub>2</sub>CO in the ocean was taken into account). The value would be an overestimation because H<sub>2</sub>CO readily undergoes a variety of reactions in aqueous solution (Cleaves, 2008). A possible loss channel for H<sub>2</sub>CO is the Cannizzaro reaction, which converts two H<sub>2</sub>CO molecules into one molecule of formate (HCOO<sup>−</sup>) and one molecule of methanol (CH<sub>3</sub>OH) (Benner et al., 2012). At such low concentrations ( $\leq 10^{-3}$  M), no sugar products have been observed even in the presence of effective catalytic minerals and salts (Gabel and Ponnamperna, 1967; Reid and Orgel, 1967; Cairns-Smith et al., 1972; Schwartz and De Graaf, 1993). Fourth, ribose rapidly decomposes in aqueous solution. The half-life of ribose is 73 min at 100 °C and pH 7.0, and 44 years at 0 °C and pH 7.0 (Larralde et al., 1995). The instability of ribose has led some researchers to explore the possibility that ribose and other sugars were not components of the first genetic material, and were preceded by simpler and more stable compounds, such as peptide nucleic acids (Nielsen, 1993; Larralde et al., 1995; Nielson et al., 2000).



**Figure 6.** D-ribose and some pentoses with similar structure.



**Figure 7.** The role of borate in the selective synthesis of ribose through the formose reaction as described by Benner et al. (2012).

Recognition of these problems has led experimentalists to explore more effective catalysts for the ribose synthesis, which are expected to be present on the primitive Earth. Several inorganic ions have been found to enhance the yields of pentoses (including ribose) in the formose reaction, including borate (Ricardo et al., 2004), silicate (Lambert et al., 2010a) and lead (Zubay, 1998). The most promising mechanism reported so far is the borate-mediated ribose synthesis. In the presence of  $\text{Ca}(\text{OH})_2$  (0.5 M, pH ~12), a solution of glycolaldehyde and glyceraldehyde rapidly turns brown (1 h at 25 °C and 10 min at 45 °C) (Ricardo et al., 2004). When the same incubation is done with borate minerals of ulexite ( $\text{NaCaB}_5\text{O}_9 \cdot 8\text{H}_2\text{O}$ ), kernite ( $\text{Na}_2\text{B}_4\text{O}_7$ ), or colemanite ( $\text{Ca}_2\text{B}_6\text{O}_{11} \cdot 5\text{H}_2\text{O}$ ), the solution does not turn brown, even after 2 months (Ricardo et al., 2004). A chromatographic analysis confirmed a selective formation of ribose from the mixture (Ricardo et al., 2004).

Borate forms a complex with organic molecules that carry 1,2-dihydroxyl groups (Benner, 2004). Although glycolaldehyde does not have the functional unit, it binds borate with its hydroxyl-ketone groups (Fig. 7; Benner et al., 2012). The complexation increases the rate of enolization, and facilitates aldol reactions to form glyceraldehyde as a nucleophile (Benner et al., 2012). Borate then suppresses enolization of glyceraldehyde, and prevents it from acting as a nucleophile (Benner, 2004). Glyceraldehyde nevertheless remains electrophilic, so it reacts with the enediolate of glycolaldehyde to form pentoses (Fig. 7; Benner, 2004). Once formed, the cyclized forms of the pentoses make stable, less reactive complexes with borate because they lack reactive  $\text{C}=\text{O}$  groups (Benner, 2004). The borate complex of ribose is especially stable because of a network of hydrogen bonding permitted by its stereochemistry (Fig. 7; Kim et al., 2011). If equilibration is possible, ribose and two pentuloses (ribulose and xylulose) accumulate as the predominant pentoses from a mixture (Benner et al., 2012). Silicate also forms complexes with sugars through the 1,2-dihydroxyl unit, and stabilizes them (Lambert et al., 2010a,b; Vazquez-Mayagoitia et al., 2011). But the stabilizing effect is weak compared to borate (Kim and Benner, 2010; Kim et al., 2011).

Boron is a quintessential crustal element, enriched in the upper continental crust compared to other reservoirs (Grew et al., 2011). Some terrestrial environments show marked enrichment in boron; for instance, a highly evolved granitic pegmatite from southeastern Manitoba, Canada contains boron with the concentration as much as 213 ppm on average (Stilling et al., 2006). If a granitic continental crust had differentiated at the time of the origin of life, borate-rich conditions sufficient to stabilize ribose could have occurred (e.g., in

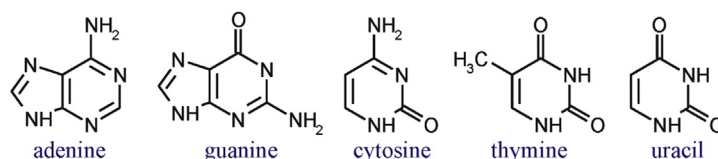
an intermountain dry valley; Benner et al., 2012) and played a positive role in the chemical evolution.

Another issue to be addressed is the chirality problem; a biological system exclusively uses D-ribose, whereas abiotic experiments synthesize both D- and L-ribose in equal amounts. A potential solution to this problem is the asymmetric formation of sugars catalyzed by enantiomeric amino acids (Pizzarello and Weber, 2004). Pizzarello and Weber (2004) found that non-racemic Ala and isovaline influenced chiral configurations of tetrose formed from glycolaldehyde condensation. The largest enantiomeric excess (ee) of 10.6% was observed for D-threose with L-isovaline catalyst. The catalytic effect is more effective in the case of di- and tri-peptides than single amino acids, with ee in the tetrose products of over 80% (Weber and Pizzarello, 2006). LL-dipeptides of branched amino acids (e.g., L-Ile-L-Val) are better catalysts than those of unbranched counterparts (Pizzarello and Weber, 2010). L-ee of amino acids has been observed in carbonaceous chondrites (Pizzarello et al., 2012), so the exogenous delivery of L-enriched amino acids during the impact period of the early Earth could have provided a continuous chiral influence in prebiotic sugar synthesis.

#### 4.4. Nucleobase

Fig. 8 shows structures of primary nucleobases found in DNA and RNA; adenine (A), cytosine (C), guanine (G), thymine (T) and uracil (U). A, C, G, and T appear in DNA, whereas T is replaced by U in RNA. T and U are identical except that U lacks the 5' methyl group (Fig. 8). A and G belong to the double-ringed class of molecules called purines, whereas C, T, and U are all pyrimidines. Although DNA and RNA contain dozens of modified nucleobases in addition to the five primary ones (e.g., 5-methylcytosine ( $\text{m}^5\text{C}$ ), 7-methylguanosine ( $\text{m}^7\text{G}$ )), this review focuses on the synthesis of the five bases under simulated prebiotic conditions.

To date, a number of possible precursors, conditions, and catalysts have been tested experimentally for the abiotic synthesis of nucleobases, as is summarized in Table 2 and illustrated in Fig. 9. The first synthesis of A was reported by Oro in 1960 (Oro, 1960), who heated highly concentrated  $\text{NH}_4\text{CN}$  (1–15 M) for several days at temperatures up to 100 °C. After removal of a black polymer and treatment of the supernatant with HCl, A was identified in the yield of 0.5% of the initial  $\text{NH}_4\text{CN}$  (Oro and Kimball, 1961). Later on, a similar experiment with detailed product analysis showed that G was also synthesized from  $\text{NH}_4\text{CN}$  (10 M) by heating at 80 °C for



**Figure 8.** Structures of the primary nucleobases found in DNA and RNA.

**Table 2**Summary of abiotic synthesis of adenine (**A**), cytosine (**C**), guanine (**G**), thymine (**T**), and uracil (**U**).

Starting material <sup>a</sup>	Experimental conditions <sup>b</sup>	Catalyst	Product	Ref.
0.010 mole malic acid, 0.015 mole urea	100–140 °C, 15–120 min	0.5–16.0 mL polyphosphoric acid	<b>U</b> ( $\leq 9\%$ based on urea)	a
1–15 M NH <sub>4</sub> CN	27–100 °C, 2 d	–	<b>A</b> ( $\leq 0.5\%$ )	b
4 M NH <sub>4</sub> OH under 300 mmHg CH <sub>4</sub> and 0–100 mmHg H <sub>2</sub>	Electron irradiation, 100 °C, 45 min	–	<b>A</b> (0.012–0.001% based on CH <sub>4</sub> )	c
4 mL HCN, 10 mL NH <sub>3</sub>	120 °C, 20 h	–	<b>A</b> (15% based on HCN)	d
1.0 M KCN, 0.1 M cyanoacetylene	100 °C, 1 and 7 d	–	<b>C</b> (1–5%)	e
0.002–0.1 M cyanoacetylene, 0.004–1.0 M KNCN	100 °C, 12 h, pH ~9.5	–	<b>C</b> ( $\leq 7.6\%$ )	f
1 M cyanoacetylene, 1 M urea	100 °C, 20 h, pH 9.6	–	<b>C</b> (4.8%)	
CO/H <sub>2</sub> /NH <sub>3</sub> gas mixture (1:2:0.4, 650 mL at 2 atm)	600 °C, 1.5 h, followed by heatings at lower temperatures (75–310 °C) for several tens of hours	Iron meteorite (150 mg), alumina (50 mg), and silica (50 mg)	<b>A</b> (0.16%), <b>G</b> (0.09%), <b>C</b> (0.05%)	g
Uracil, paraformaldehyde, hydrazine (all 0.005 mole)	70 °C, 3 d, in an ammoniacal solution (pH 9)	–	<b>T</b> (0.1%)	h
CO/H <sub>2</sub> /NH <sub>3</sub> gas mixture (1:1:1–0.4, 600–700 mL at 1–6 atm)	500–700 °C, 0.5 h, followed by heatings at 100–400 °C for 1–14 d	Iron meteorite (500 mg) and alumina (30 mg)	<b>A</b> , <b>G</b> , <b>T</b> (not quantified)	i
0.01 M of 2,4-diaminopyrimidine	100 °C, 12 and 48 d, pH 7, 9, or 11	–	<b>C</b> (not quantified), <b>U</b> ( $\leq 36\%$ )	j
2.5 mmol propiolic acid, 2.5 mmol urea	85 °C, 4 h	Polyphosphoric acid (4.0 g)	<b>U</b> (75%)	k
	100–105 °C, 7 h	Sulfuric acid (5 mL)	<b>U</b> (59%)	
	–	Orthophosphoric acid	No <b>U</b> was detected	
5,6-dihydrouracil (50 mg) in 5 mL of H <sub>2</sub> O	UV irradiation, 48 h, in N <sub>2</sub> gas saturated with H <sub>2</sub> O	1 g montmorillonite, illite, vermiculite, kaolinite, silica gel, quartz, basalt, granite or CaCO <sub>3</sub>	<b>U</b> ( $\leq 22\%$ )	l
5,6-dihydrouracil (50 mg) in 5–10 mL H <sub>2</sub> O	UV irradiation, 48 h, in N <sub>2</sub> gas saturated with H <sub>2</sub> O	1 g montmorillonite	<b>U</b> ( $\leq 22\%$ )	m
5,6-dihydrothymine (50 mg) in 5–10 mL H <sub>2</sub> O	–	–	<b>T</b> (12%)	
0.1 M NH <sub>4</sub> CN (pH 9.2)	r.t., 4–12 m	–	<b>A</b> ( $\leq 0.04\%$ based on HCN)	n
Orotic acid ( $6.4 \times 10^{-4}$ or $6.5 \times 10^{-5}$ M)	UV irradiation (254 nm), 1–120 h	$6.4 \times 10^{-4}$ M of Fe <sup>3+</sup> or Cu <sup>2+</sup>	<b>U</b> ( $\leq 17.3\%$ )	o
Acetylene dicarboxylic acid (0.5–2.0 mmole), urea (1.0 mmole)	100 °C, 8 h	200 mg phosphate	<b>U</b> ( $\leq 6.3\%$ )	p
0.01 M NH <sub>4</sub> CN, 0.01 M glyconitrile	–2 °C, 60–100 d, pH 9.2	–	<b>A</b> ( $\leq 0.02\%$ )	q
NH <sub>4</sub> CN (0.1 or 1 M)	r.t., 6 m, pH 9.2	–	<b>U</b> (0.001–0.005%)	r
NH <sub>3</sub> (200 torr), CH <sub>4</sub> (150 torr), C <sub>2</sub> H <sub>6</sub> (50 torr)	Spark discharge, 25–28 °C, 48 h	–	<b>A</b> (0.0010%), <b>G</b> (0.00017%) (based on total carbon)	s
0.001 M cyanoacetaldehyde, 0–20 M urea	100 °C, $\leq 30$ h	–	<b>C</b> ( $\leq 53\%$ )	t
0.1 M NH <sub>4</sub> CN	–20 °C, 25 y	–	<b>A</b> (0.038%), <b>G</b> (0.0035%)	u
10 M NH <sub>4</sub> CN	80 °C, 24 h	–	<b>A</b> (0.028%), <b>G</b> (0.0007%)	
0.1 M NH <sub>4</sub> CN (pH ~9.2)	–78 °C, 25 y	–	<b>A</b> (0.04%)	v
	–20 °C, 25 y	–	<b>A</b> (0.038%)	
0.001 M cyanoacetaldehyde, 0.01 M urea (pH 7)	60–100 °C, 2–16 d, dry conditions	–	<b>C</b> ( $\leq 0.23\%$ ), <b>U</b> ( $\leq 0.08\%$ )	w
0.001 M cyanoacetaldehyde, 2 M urea (pH 7)	4 °C, 4 m	–	<b>C</b> (0.010%), <b>U</b> (0.046%)	
	–20 °C, 2 m	–	<b>C</b> (0.005%), <b>U</b> (0.02%)	
0.12 mole FA	160 °C, 48 h	0.057 g CaCO <sub>3</sub> , silica, alumina, kaolin, or zeolite (Y type)	<b>A</b> ( $\leq 0.9$ mg), <b>C</b> ( $\leq 4.4$ mg) (per 1 g FA)	x
0.15 M HCN, 0.1 M NH <sub>3</sub>	–78 °C, 7 y	–	<b>A</b> ( $\leq 0.029\%$ ), <b>G</b> ( $\leq 0.0067\%$ ), <b>U</b> ( $\leq 0.0017\%$ )	y
0.1 M NH <sub>4</sub> CN	–20 °C, 3 m	–	<b>A</b> (0.0094%)	
0.01M NH <sub>4</sub> CN	–	–	<b>A</b> (0.01%)	
0.001M NH <sub>4</sub> CN	–	–	<b>A</b> (0.0042%)	
1 g ammonium formate, 2 g HCN tetramer	110 °C, 3 d	–	<b>A</b> (18%)	z
0.12 mole FA	160 °C, 48 h	0.1 g TiO <sub>2</sub>	<b>A</b> ( $< 1$ mg), <b>C</b> ( $< 1$ mg), <b>T</b> ( $< 1$ mg) (per 1 g FA)	aa
0.12 mole FA	160 °C, 48 h	0.1 g montmorillonite	<b>A</b> ( $\leq 22.0$ mg), <b>C</b> (18.0 mg), <b>U</b> (2.0 mg) (per 1 g FA)	ab
0.12 mole FA	160 °C, 48 h	0.1 g Fe <sub>2</sub> SiO <sub>4</sub> , Mg <sub>0.5</sub> Fe <sub>1.5</sub> SiO <sub>4</sub> , MgFeSiO <sub>4</sub> , Mg <sub>1.5</sub> Fe <sub>0.5</sub> SiO <sub>4</sub> or Mg <sub>2</sub> SiO <sub>4</sub>	<b>C</b> ( $\leq 68.6$ mg), <b>U</b> ( $\leq 4.5$ mg) (per 1 g FA)	ac
0.001 M cyanoacetaldehyde, 1 M guanide·HCl	0 °C, 2 m, pH 8.1	–	<b>C</b> (0.05%), <b>U</b> (10.8%)	ad
5 mL H <sub>2</sub> O under CH <sub>4</sub> /N <sub>2</sub> /H <sub>2</sub> atmosphere (4:3:3; 1200 mbar in total)	Electric discharge, 72 h	Aqueous aerosol	<b>A</b> (0.011% based on total carbon)	ae
0.12 mole FA	160 °C, 48 h	0.1 g Fe <sub>1-x</sub> S, FeS <sub>2</sub> , FeCuS <sub>2</sub> , FeCu <sub>5</sub> S <sub>4</sub> , (Fe,Cu,Sb) <sub>3</sub> S, or CuS	<b>A</b> ( $\leq 1.80$ mg per 1 g FA)	af
0.1 M urea (pH 7.1) under a N <sub>2</sub> /H <sub>2</sub> /CH <sub>4</sub> atmosphere (3:3:4; 1 atm in total)	A freeze (–5 °C)–thaw (5 °C) cycle, 3w, with spark discharge during the first 72 h	–	<b>C</b> (4.2%), <b>U</b> (1.9%), <b>A</b> (0.15%) (based on urea)	ag
0.12 mole FA	160 °C, 48 h	0.1 g ZrO <sub>2</sub> , CeZrO <sub>4</sub> , ZrSiO <sub>4</sub> , Li <sub>2</sub> ZrO <sub>3</sub> , PbZrO <sub>3</sub> , BaZrO <sub>3</sub> or ZrO(NO <sub>3</sub> ) <sub>2</sub>	<b>A</b> ( $\leq 0.08$ mg per 1 g FA)	ah



Table 2 (continued)

Starting material <sup>a</sup>	Experimental conditions <sup>b</sup>	Catalyst	Product	Ref.
FA with 10 mM diaminomaleonitrile, diaminofumaronitrile, or aminoimidazolecarbonitrile	130 °C, 48 h, with and without UV irradiation (254 nm)	CaCO <sub>3</sub> or Na <sub>4</sub> P <sub>2</sub> O <sub>7</sub> (4.4 wt.% FA)	<b>A</b> (≤500 µg per 1 g formamide), <b>G</b> (not quantified)	ai
0.12 mole FA	100–160 °C, 12–96 h	50 mg goethite, akaganeite, or hematite	<b>A</b> (≤3.764 mg), <b>C</b> (≤3.034 mg) (per 1 g FA)	aj

a, Fox and Harada, 1961; b, Oro and Kimball, 1961; c, Ponnamperuma et al., 1963a; d, Wakamatsu et al., 1966; e, Sanchez et al., 1966b; f, Ferris et al., 1968; g, Hayatsu et al., 1968; h, Stephen-Sherwood et al., 1971; i, Hayatsu et al., 1972; j, Ferris et al., 1974; k, Harada and Suzuki, 1976; l, Chittenden and Schwartz, 1976; m, Schwartz and Chittenden, 1977; n, Ferris et al., 1978; o, Ferris and Joshi, 1979; p, Subbaraman et al., 1980; q, Schwartz et al., 1982; r, Voet and Schwartz, 1982; s, Yuasa et al., 1984; t, Robertson and Miller, 1995; u, Levy et al., 1999; v, Levy et al., 2000; w, Nelson et al., 2001; x, Saladino et al., 2001; y, Miyakawa et al., 2002b; z, Hill and Orgel, 2002; aa, Saladino et al., 2003; ab, Saladino et al., 2004; ac, Saladino et al., 2005b; ad, Cleaves et al., 2006; ae, Ruiz-Bermejo et al., 2007b; af, Saladino et al., 2008; ag, Menor-Salvan et al., 2009; ah, Saladino et al., 2010; ai, Barks et al., 2010; aj, Shanker et al., 2011.

<sup>a</sup> FA, formamide.

<sup>b</sup> d, day; h, hour; m, month; min, minute; w, week; y, year; r.t., room temperature.

24 h, but the yield was 10 to 40 times less than that of **A** (Levy et al., 1999). The reaction starts from polymerization of four HCN molecules to diaminomaleonitrile (Fig. 9). The HCN tetramer then reacts with formamidine, a condensation product of HCN and NH<sub>3</sub>, to give 4-aminoimidazole-5-carbonitrile (Orgel, 2004). Subsequent condensations of this compound with small molecules (e.g., H<sub>2</sub>O, HCN, C<sub>2</sub>N<sub>2</sub>) produce a variety of purines including **A** and **G** (Orgel, 2004). The rate of HCN polymerization is proportional to the square of the HCN concentration. In contrast, hydrolysis of HCN to formic acid and ammonia (HCN + 2H<sub>2</sub>O → HCOOH + NH<sub>3</sub>) is first-order in HCN (Sanchez et al., 1967). Consequently, polymerization occurs dominantly over hydrolysis in a concentrated HCN solution, whereas hydrolysis predominates in a dilute one; the two reactions become equally important for the HCN concentration between 0.01 and 0.1 M at pH 8–9 and 0–60 °C (Sanchez et al., 1967). The value is several orders of magnitude higher than the steady state concentration of HCN in the primitive ocean estimated by Miyakawa et al. (2002a) ( $7 \times 10^{-13}$  M at 100 °C and pH 8, and  $2 \times 10^{-6}$  M at 0 °C and pH 8). Because HCN is more volatile than water, evaporation of seawater cannot concentrate HCN if the pH is lower than the *pK*<sub>a</sub> of HCN (9.2 at 25 °C). Instead, eutectic freezing is an effective mechanism to concentrate HCN (Sanchez et al., 1966b). When a HCN-water mixture is cooled to the eutectic temperature (−21 °C), the eutectic contains an extremely high concentration of HCN (78 wt.%) (Miyakawa et al., 2002b). It has been shown that cooling a dilute

solution of HCN to below 0 °C leads to the formation of **A** and **G** (Schwartz et al., 1982; Levy et al., 1999, 2000), even when the initial NH<sub>4</sub>CN concentration is as low as 0.001 M (Miyakawa et al., 2002b). Such a freezing event would rarely happen in the primitive ocean, but might have occasionally occurred in localized aquatic environments (e.g., a shallow pond) on the Hadean continent. One concern for these experiments is that the examined HCN solutions contain no salt, which would have been present in the primitive environments. Salts possibly influence the stability of HCN and the eutectic temperature and hence, the polymerization behavior of HCN (Miyakawa et al., 2002b; McCollom, 2013b).

HCN polymerization does not generate pyrimidine. Because bonds between carbon and a hetero atom (e.g., C–N, C=O) are more readily constructed than a C–C bond, pyrimidine syntheses have typically been started from C<sub>3</sub> compounds such as cyanoacetylene and its hydrolysis product, cyanoacetaldehyde (Shapiro, 1999). It has been shown that cyanoacetylene generates **C** (up to 19% yield) by a condensation with potassium cyanate (KNCO) at 100 °C for 24 h (Ferris et al., 1968). The yield decreases with the reactant concentrations, but 1% yield was still obtained from 0.002 M cyanoacetylene and 0.004 M KNCO (Ferris et al., 1968). Cyanoacetylene is the second major N-containing product from a CH<sub>4</sub>/N<sub>2</sub> gas mixture from the action of electric discharge (up to 8.4% of the principal product, HCN) (Sanchez et al., 1966a). Cyanate is formed from the hydrolysis of cyanogen (Wang et al., 1987), which

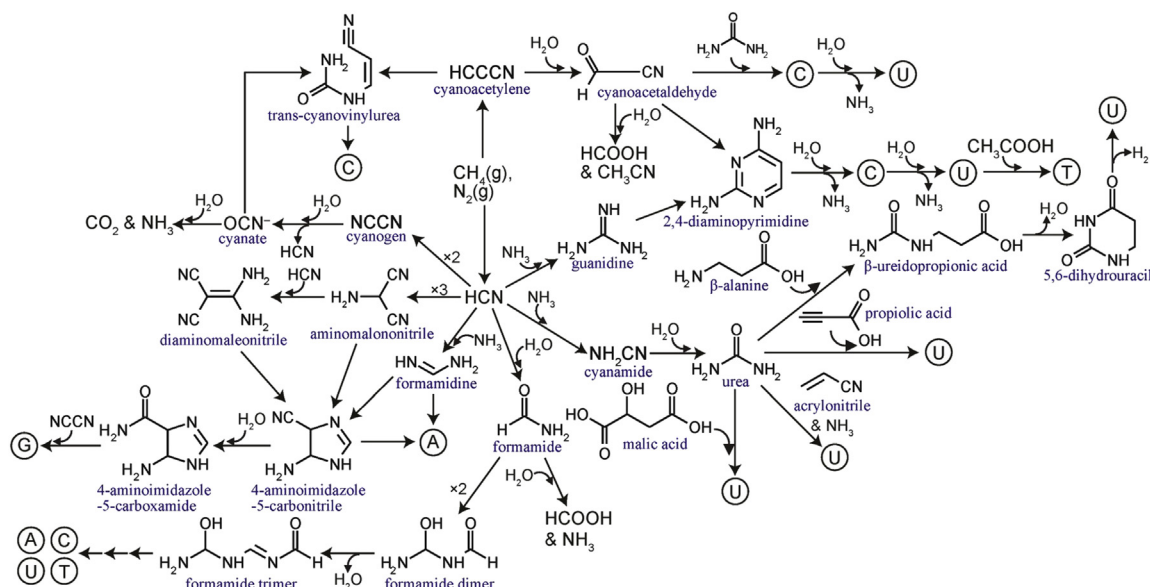


Figure 9. Reaction pathways for abiotic synthesis of adenine (A), cytosine (C), guanine (G), thymine (T), and uracil (U).

is generated by a high-temperature heating (770–975 °C) of HCN and acetylene ( $C_2H_2$ ) in the gas phase (Krebaum, 1966). A drawback of this system is the instability of cyanoacetylene. Cyanoacetylene hydrolyzes to cyanoacetaldehyde with a half-life ( $t_{1/2}$ ) of 10 days at pH 9 and 30 °C (Ferris et al., 1968, 1974).

Cyanoacetaldehyde is more stable than cyanoacetylene ( $t_{1/2}$  = 31 years at pH 9 and 30 °C; Ferris et al., 1974). It produces **C** and **U** in incubation with urea or guanidine (Ferris et al., 1974; Robertson and Miller, 1995). The reaction with urea requires a concentrated urea solution (>0.1 M; Shapiro, 1999) or a dry condition (Nelson et al., 2001), whereas that with guanidine yields both **C** and **U** even from the reactant concentrations as low as 0.005 M (Ferris et al., 1974). Guanidine is formed from  $NH_4CN$  on the action of heating (Lowe et al., 1963) and UV irradiation (Lohrmann, 1972). Once formed, guanidine can continue to exist in water for a long period ( $t_{1/2}$  =  $5 \times 10^5$  years at pH 9 and 30 °C; Ferris et al., 1974). Thus, the cyanoacetaldehyde–guanidine system could have offered an effective route to the pyrimidine synthesis that was significant for the origin of life (Ferris et al., 1974).

Purines and pyrimidines have also been synthesized by heating pure formamide at 100–160 °C in the presence of mineral catalysts (Saladino et al., 2012a,b). In contrast to HCN, formamide has a high boiling point (210 °C) with a limited azeotropic effect with water (Ruiz-Mirazo et al., 2014). The stability in water is relatively high compared to other HCN derivatives ( $t_{1/2}$  = 199 years at 25 °C and 7.3 days at 120 °C under neutral pH; Slebocka-Tilk et al., 2002). Thus, formamide could have been readily concentrated in lagoons or drying ponds on the primitive Earth.

Moreover, various routes for the prebiotic synthesis of **U** have been proposed, including the reaction of urea with malic acid (Fox and Harada, 1961), acrylonitrile (Oro, 1963), propionic acid (Harada and Suzuki, 1976), and  $\beta$ -alanine (Chittenden and Schwartz, 1976; Schwartz and Chittenden, 1977). Photo-decarboxylation of orotic acid produces **U** (Ferris and Joshi, 1979). Hayatsu et al. (1968, 1972) synthesized **U** with a Fischer-Tropsch-type reaction of  $CO/H_2/NH_3$  gas mixtures.

Note that nucleobases have relatively short lifetimes in aqueous solution; the half-lives of **A**, **C**, **G**, **T** and **U** at 100 °C and pH 7 are 1 year, 19 days, 0.8 years, 56 years and 12 years, respectively (Levy and Miller, 1998). To accumulate nucleobases in prebiotic environments, they must be synthesized at higher rates than their decomposition. It is unlikely that such a situation was met in bulk ocean water (Shapiro, 1995, 1999). However, localized reducing environments with highly concentrated HCN and its derivatives could have favored the formation and accumulation of nucleobases.

Carbonaceous chondrites contain a variety of purines and pyrimidines including **A**, **G**, and **U**, with their total concentration up to 500 ppb (Callahan et al., 2011; Burton et al., 2012). It is unlikely that these extraterrestrial nucleobases played a significant role in life's origin because of their very low concentrations. However, the findings of meteoritic nucleobases show clear evidence that they can be formed abiotically through geochemical processes. Elucidation of their formation mechanism would provide important hints for the chemical evolution of nucleobases on the primitive Earth.

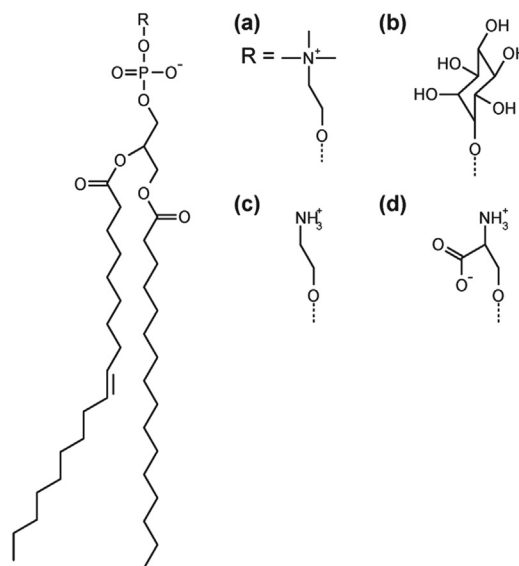
#### 4.5. Fatty acid

All biological cells are bound by lipid membranes. Cell membranes provide a semipermeable barrier that retains and protects genetic materials and metabolic activities within the cellular space, while potentially allowing small molecules to diffuse in and out of the cell (Chen and Walde, 2010; Schrum et al., 2010). They also provide a physical boundary between self and non-self, which is necessary to prevent the random interaction of replicator enzymes

(replicases) and to reduce the problem of inactive parasites. These properties are a minimum requirement for Darwinian evolution (Szostak et al., 2001).

Modern cell membranes are composed primarily of double-chain amphiphiles, particularly glycerol phosphate phospholipids (Fig. 10; Lombard et al., 2012). Because of their geometry, phospholipid membranes lack the dynamic properties required for membrane growth and division, as well as for the uptake of charged compounds by passive diffusion (e.g., the permeability of  $K^+$  is in the range of  $10^{-10}$  to  $10^{-12}$  s/cm; Paula et al., 1996). Modern cells control these functions with complex biochemical machinery incorporated into the membrane structures. However, because such biochemical machinery cannot be expected to exist as a component of primitive protocells, phospholipids are not a good candidate for the first membrane component. Fatty acids, a single-chain amphiphile, have versatile properties that allow both membrane growth and nutrient uptake. Membranes composed of fatty acids have relatively high permeability to ions and small molecules ( $K^+$  permeability coefficient is on the order of  $10^{-6}$  s  $cm^{-1}$ ; Chen and Szostak, 2004), while retaining encapsulated biopolymers such as oligonucleotides (Apel et al., 2002; Chen et al., 2005). They can undergo repeated cycles of growth and division without the loss of cell contents (Zhu and Szostak, 2009; Budin et al., 2012). Additionally, fatty acid membranes allow rapid permeation of ribose compared with other aldopentoses or hexoses (Sacerdote and Szostak, 2005). The kinetic advantage could have allowed faster assimilation of ribose from the surrounding environment to the primitive cells. Moreover, condensations of fatty acids with glycerol and phosphate have been shown to yield phospholipids under hypothetical prebiotic conditions (Hargreaves et al., 1977; Rao et al., 1982, 1987). This observation provides a conceptually simple route for the transition from primitive to modern membranes. For these reasons and others, fatty acids have been recognized as the most appropriate building blocks for the membranes of early cells (Schrum et al., 2010; Blain and Szostak, 2014).

The most widely invoked pathway for the formation of fatty acids in geochemical environments is the Fischer-Tropsch synthesis (FTS) (MuCollom and Seewald, 2007; McCollom, 2013c). The reaction mechanism was originally explored by Franz Fischer and Hans



**Figure 10.** Structures of representative glycerol phosphate phospholipids observed in biological membranes. (a) phosphatidylcholine; (b) phosphatidylinositol; (c) phosphatidylethanolamine; (d) phosphatidylserine.

Tropsch in the 1920s (Fischer and Tropsch, 1926) as a means of synthesizing hydrocarbons from a gas mixture of CO and H<sub>2</sub> in a surface-catalyzed process. FTS exclusively produces linear saturated hydrocarbons that decrease in abundance with an increasing number of carbons (McCormick, 2013b). Fatty acids and fatty alcohols are minor by-products of FTS. FTS proceeds effectively in the gas phase, but also occurs in a high-temperature and high-pressure aqueous solution that resembles deep-sea hydrothermal environments. At the optimal temperature conditions (150–250 °C), fatty acids up to C<sub>22</sub> have been observed from solutions of formic (HCOOH) and oxalic acid (HOOC–COOH) (McCormick et al., 1999; Rushdi and Simoneit, 2001; McCormick and Seewald, 2006). These acids decompose rapidly to CO<sub>2</sub> and H<sub>2</sub> under hydrothermal conditions, and hence were used as carbon and hydrogen sources to circumvent practical difficulties of adding these volatile gases to water. Later on, however, these experiments were questioned on the basis that organic syntheses occurred not in solution, but either in the vapor headspace in fixed-volume reactors, or in the H<sub>2</sub>-rich vapor bubbles formed on the surfaces of solids in reactors (McCormick, 2013b,c). Subsequent experiments with no gas phase in reaction vessels showed that the products in water were dominantly CH<sub>4</sub> with small amounts of light hydrocarbons (up to C<sub>5</sub>), even in the presence of mineral catalysts (McCormick and Seewald, 2001, 2003; Foustoukos and Seyfried, 2004; Ji et al., 2008). The yields of CH<sub>4</sub> are generally low, even in strongly thermodynamically favorable conditions and after extended reaction times (~0.5% conversion by 1062 h heating at 390 °C; Foustoukos and Seyfried, 2004, ~0.5% conversion by 2086 h heating at 260 °C; McCormick and Seewald, 2003). One exception is an experimental report by Horita and Berndt (1999), where an almost complete conversion of CO<sub>2</sub> to CH<sub>4</sub> was observed within 350 h at 300 °C in the presence of Ni/Fe-alloy (awaruite). In sub-seafloor environments, Ni/Fe-alloys are formed through hydrothermal alteration of ultramafic rocks (Alt and Shanks, 2003; Klein and Bach, 2009). Thus, the Ni/Fe-alloy-catalyzed synthesis could well be a key mechanism controlling the CH<sub>4</sub> concentration in serpentine-hosted hydrothermal systems such as Lost City (0.13–0.28 mM; Kelley et al., 2001) and Rainbow (2.5 mM; Charlou et al., 2002). Note that the catalytic activity of Ni/Fe-alloy observed by Horita and Berndt (1999) is exclusive for CH<sub>4</sub> synthesis because no ethane and propane were observed over the detection levels of analysis. In accordance with this result, the concentration of light hydrocarbons (C<sub>2</sub>H<sub>6</sub>, C<sub>3</sub>H<sub>8</sub>, etc.) in submarine hydrothermal fields are typically much smaller than that of CH<sub>4</sub> (the molar ratio of CH<sub>4</sub>/C<sub>2</sub>H<sub>6</sub>+C<sub>3</sub>H<sub>8</sub>+...) ranges from ~100 to >8000; McCormick and Seewald, 2007). Consequently, the role of hydrothermal systems in the formation of membrane-forming compounds remains elusive.

Fatty acids up to C<sub>12</sub> have been synthesized from reducing gas mixtures by the action of electric discharge (Allen and Ponnamperna, 1967; Yuen et al., 1981) and UV radiation (Groth and Weyssenhoff, 1960), and from a shock heating experiment mimicking a meteorite impact (Furukawa et al., 2009). Mechanisms of these processes have not yet been investigated.

Another source of fatty acids is carbonaceous chondrite (Sephton, 2002; Pizzarello et al., 2006). In Murchison meteorite, monocarboxylic acids are the most abundant compounds in the soluble organic material (Sephton, 2002). The concentration of the most abundant monocarboxylic acid, propanoic acid (1.83 μmol/g of meteorite; Lawless and Yuen, 1979) is around 58 times greater than the most abundant amino acid, Gly (0.041 μmol/g; Pereira et al., 1975). Monocarboxylic acids in carbonaceous chondrite show high structural diversity; they contain equal concentrations of branched and straight-chain isomers that decrease in abundance with increasing carbon number (Sephton, 2002; Pizzarello et al., 2006). The mechanism of their formation is still not well known,

but is possibly generated from interstellar gas mixtures by UV radiation (Dworkin et al., 2001) and/or a high temperature Fischer-Tropsch-type reaction (Nooner et al., 1976). In aqueous solution, they can spontaneously assemble into membrane vesicles under alkaline pH (pH ≥ 10) (Deamer, 1985).

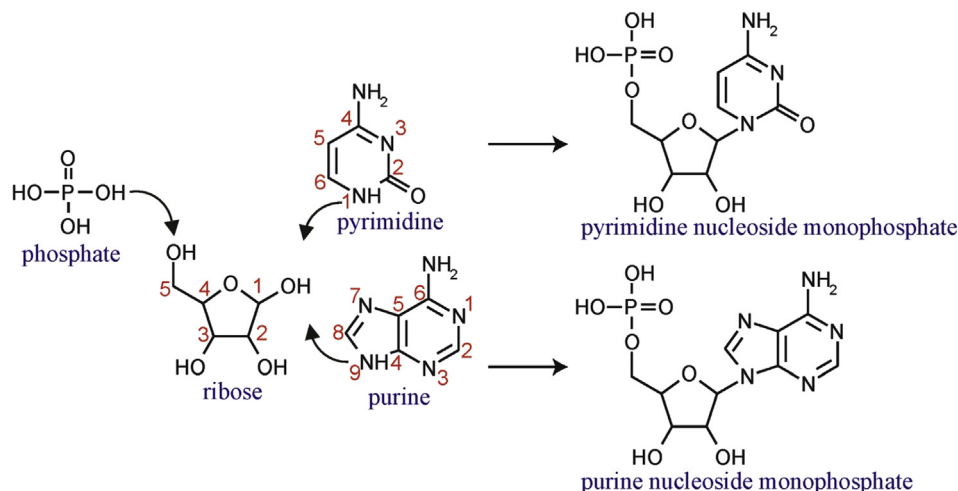
It is noteworthy that the amphiphilic molecules formed through prebiotic processes or delivered by meteorites are both highly heterogeneous in terms of chain length and head group chemistry. Membranes composed of mixtures of amphiphiles often show superior properties to those composed of single pure species. For instance, vesicle formation from nonanoic acid (C<sub>8</sub>H<sub>17</sub>COOH) in water requires its concentration to be at least 85 mM, whereas only 20 mM is necessary when mixed with 2 mM nonanol (C<sub>9</sub>H<sub>19</sub>OH) (Apel et al., 2002). Vesicles composed of fatty acids precipitate in the presence of millimolar concentrations of divalent cations (Mg<sup>2+</sup>, Ca<sup>2+</sup>) (Monnard et al., 2002), but fatty acid/alkyl amine vesicles are resistant to the effects of divalent cations up to 0.1 M (Namani and Deamer, 2008). Moreover, mixtures of fatty acids with the corresponding alcohols and/or glycerol esters form vesicles that are stable over wider ranges of pH (Apel et al., 2002) and temperature (Mansy and Szostak, 2008). The mixtures are more permeable to nutrient molecules such as nucleotides (Mansy et al., 2008). These behaviors are in striking contrast to the situation with genetic polymers, where even low levels of modified nucleotides can lead to strong inhibition of further replication (Mansy and Szostak, 2008; Schrum et al., 2010).

#### 4.6. Nucleotide

The synthesis of nucleotides is the least understood aspect of the prebiotic chemistry reading of RNA and DNA (Orgel, 2004; Saladino et al., 2012b). The difficulty of abiotic synthesis arises from the fact that the building blocks of nucleotides ((deoxy)ribose, nucleobases and phosphate) must be combined with the right regiospecific and stereospecific configurations (Fig. 11). Ribose exists in aqueous solution in four cyclic and two alicyclic forms in which the β-D-furanose isomer, a necessary configuration for the nucleotide synthesis, is a relatively minor component (Fig. 6; Drew et al., 1998). The purine bases must use the nitrogen atom at the N9 position, while the pyrimidines must use the nitrogen at the N1 position, to form a C–N bond with the C1 atom of ribose (Fig. 11). Because nitrogen atoms of purines and pyrimidines are all nucleophiles with the exocyclic amino group being the most reactive (Sutherland, 2010; Saladino et al., 2012b), a simple heating of ribose and the nucleobase results in a multitude of isomeric products. When adenine is heated with D-ribose at 100 °C in dry conditions in the presence of inorganic catalysts (MgCl<sub>2</sub> and trimetaphosphate), the fraction converted into β-adenosine is only ~4% even after a treatment to hydrolyze N6-ribosyl adducts (Fuller et al., 1972a). A better yield of β-ribonucleoside is obtained when hypoxanthine and 2-pyrimidinone are used in a similar experiment (up to 20% and 12%, respectively) because they have no exocyclic amino group in their structures (Fuller et al., 1972b; Bean et al., 2007). In contrast, no direct synthesis of pyrimidine nucleosides from ribose and cytosine or uracil has been reported (Orgel, 2004).

Abiotic synthesis of cytidine and uridine has been achieved by multistep construction of respective bases on a sugar structure. Sanchez and Orgel (1970) synthesized α-cytidine (10–20%) and β-cytosine arabinoside (10%) by a stepwise addition of cyanamide and cyanoacetylene in aqueous solution of D-ribose and D-arabinose, respectively. These pentoses react with cyanamide to yield amino-oxazolines, which then convert into the anhydronucleosides through condensation with cyanoacetylene (Fig. 12). Subsequent rearrangements of chemical bonds lead to the formation of pyrimidine nucleosides (Fig. 12). If D-ribose is replaced by D-ribose-5-



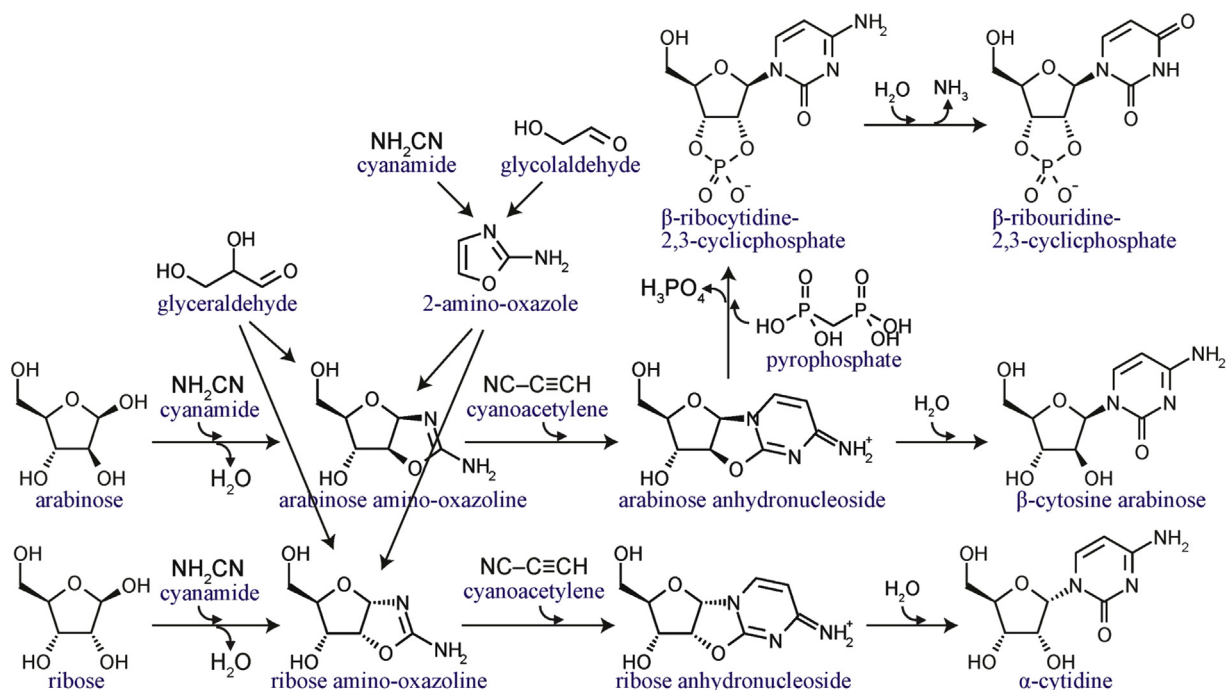


**Figure 11.** Structures of nucleotides and their components (ribose, nucleobase and phosphate) with their carbon atoms labeled.

phosphate in the reaction sequence,  $\alpha$ -cytidine-5'-phosphate is obtained in up to 40% yield (Sanchez and Orgel, 1970).  $\beta$ -cytidine-2',3'-cyclic phosphate has also been obtained from condensation of arabinose-3-phosphate, cyanamide and cyanoacetylene (Ingar et al., 2003). Sugars can be phosphorylated with orthophosphate in water using cyanogen or cyanamide as a condensing agent (Steinman et al., 1964; Halmann et al., 1969). Cyanamide is formed from a dilute aqueous solution of HCN or a HCN-NH<sub>3</sub> mixture by the action of UV irradiation (Schimpl et al., 1965). These experiments therefore suggest a potential solution to the abiotic synthesis of pyrimidine nucleotides.

Many efforts have been devoted to phosphorylate nucleosides to nucleotides under various experimental conditions (Table 3). As is the case for the nucleoside synthesis from corresponding sugar and nucleobase, phosphorylation is thermodynamically unfavorable in water over a wide variety of temperatures and pH. Consequently,

the reaction has mostly been examined in dry conditions (Ponnamperuma and Mack, 1965; Beck et al., 1967; Rabinowitz et al., 1968) or in organic solvents acting as condensing agents such as formamide and acetamide (e.g., Schoffstall, 1976; Schoffstall and Laing, 1985). Phosphorylation occurs in water in the presence of condensing agents, but yields of nucleotides are much lower than those obtained in dry conditions or in pure organic solvents (up to 0.5%, Steinman et al., 1965b; up to 3.6%, Lohrmann and Orgel, 1968). Another approach to phosphorylate nucleosides in water is the usage of condensed phosphate. An excellent yield of adenosine monophosphate has been obtained from a reaction of 0.05 M adenosine with 0.05 M trimetaphosphate under alkaline pH (up to 91.8%; Etaix and Orgel, 1978). Linear polyphosphates (e.g., pyrophosphate and triphosphate) also act as phosphorylating agents, while the efficiencies are small (Schwartz and Ponnamperuma, 1968). These condensed phosphates can be produced from



**Figure 12.** Reaction pathway for abiotic synthesis of pyrimidine nucleotides.

**Table 3**

Summary of phosphorylation of nucleoside (or nucleotide) under simulated prebiotic conditions.

Reactant <sup>a</sup>	Phosphate <sup>b</sup>	Experimental condition <sup>c</sup>	Catalyst	Product (%)	Ref.
<b>A</b> (<1 mM)	Ethyl metaphosphate	UV irradiation at 40 °C for 1 h	–	AMP (0.5), ADP (0.2), ATP (0.1)	a
AMP (<1 mM)			–	ADP (3), ATP (0.3)	
<b>A</b> (2 μmole)	2 μmole NaH <sub>2</sub> PO <sub>4</sub> ·H <sub>2</sub> O	Dry heating at 160 °C for 24 h	–	AMP (3.1)	b
<b>G</b> (2 μmole)			–	GMP (9.8)	
<b>C</b> (2 μmole)			–	CMP (13.7)	
<b>U</b> (2 μmole)			–	UMP (20.6)	
<b>T</b> (2 μmole)			–	TMP (6.3)	
ADP (0.01M)	0.01M H <sub>3</sub> PO <sub>4</sub>	24 h	Dicyanodiamide (0.01M), kaolin (8 mg)	ATP (0.5)	c
<b>U</b>	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> (5 times relative to U)	Dry heating at 65 °C for 9 m	–	UMP (14.6)	d
	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> (20 times relative to U)	Dry heating at 85 °C for 6 m	–	UMP (35.9)	
<b>A</b> (40 mM)	400 mM Na <sub>4</sub> P <sub>2</sub> O <sub>7</sub>	Heated at 100 °C for 5 h in 0.75N NH <sub>4</sub> OH	–	–	e
	400 mM Na <sub>5</sub> P <sub>3</sub> O <sub>10</sub>		–	AMP (1.08)	
<b>U</b>	H <sub>3</sub> PO <sub>4</sub>	Dry heating at 160 °C for 2 h	–	UMP (8.3)	f
	NaH <sub>2</sub> PO <sub>4</sub> ·H <sub>2</sub> O		–	UMP (16.0)	
	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub>		–	UMP (5.9)	
	(NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub>		–	UMP (13.4)	
	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> ·H <sub>2</sub> O		–	UMP (10.5)	
<b>U</b> (0.16 M)	Pi (1 M)	Kept at 37 °C and pH 5–8 for 6 d	HCOSNa (1.6 M)	UMP (≤1.5)	g
		Heated at 65 °C and pH 5–8 for 1 d		UMP (≤2.2)	
<b>U</b> (0.16 M)		Kept at 37 °C and pH 5–8 for 1 d	NC·CONH <sub>2</sub> (1 M)	UMP (≤2.0)	
		Heated at 65 °C and pH 5–8 for 1 d		UMP (≤4.0)	
<b>U</b> (0.1 M)		Heated at 65 °C and pH 5–8 for 30 d	NC·NH <sub>2</sub> (1 M)	UMP (≤2.8)	
<b>U</b> (0.1 M)		Kept at 37 °C and pH 5–8 for 1 d	KOCN (1 M)	UMP (≤1.2)	
<b>U</b> (0.16 M)	Pi (2 M)	Heated at 65 °C and pH 5–8 for 1 d	C <sub>2</sub> H <sub>5</sub> NC (3.8 M)	UMP (≤12)	
<b>U</b> (0.1 M)	Pi (1 M)	Kept at 37 °C and pH 5–8 for 1 d	Carbodiimide (1 M)	UMP (≤3.4)	
		Heated at 65 °C and pH 5–8 for 1 d		UMP (≤3.6)	
<b>A</b> (0.1 M)	Sodium TMP	Heated for 4.5 h	NaOH (0.5 M)	AMP (31)	h
<b>U</b> (0.04 M)	Na <sub>2</sub> HPO <sub>4</sub> (0.04M)	Dry heating at 100 °C for <24 h	Urea (0.4 M), NH <sub>4</sub> HCO <sub>3</sub> (0.2 M), NH <sub>4</sub> Cl (0.4 M)	UMP (≤30.9)	i
	Ca <sub>5</sub> (PO <sub>4</sub> ) <sub>3</sub> OH (40 mg)			UMP (≤24.8)	
<b>C</b> (0.04 M)	Na <sub>2</sub> HPO <sub>4</sub> (0.04M)			CMP (≤30.4)	
<b>A</b> (0.04 M)				AMP (≤28.0)	
<b>G</b> (0.04 M)				GMP (≤16.4)	
<b>T</b> (0.04 M)	Na <sub>2</sub> HPO <sub>4</sub> (0.04 M)	65 °C, ≤16 d, dry condition	Urea (0.4 M), NH <sub>4</sub> Cl (0.4 M)	TMP (≤26.0)	j
		Heating (65 °C, 17 h) and cooling (25 °C, 7 h) cycle (≤25 d in total)		TMP (≤68.2)	
UMP (1 μmole)	(NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> (3 μmole)	Dry heating at 85 °C for ≤7 d	Urea (10 μmole), MgCl <sub>2</sub> (6 μmole)	UDP (≤21.4)	k
UMP (2 μmole)	Hydroxylapatite (1 μmole)	Dry heating at 85 °C for 5 d	Urea (60 μmole), NH <sub>4</sub> Cl (2 μmole), MgCl <sub>2</sub> (4 μmole)	UDP (12.2)	
UMP (2 μmole)	Mg <sub>2</sub> P <sub>2</sub> O <sub>7</sub> (1 μmole)	Dry heating at 85 °C for ≤72 h	NH <sub>4</sub> Cl (1 μmole), MgCl <sub>2</sub> (20 μmole)	UDP (≤13.0)	
CMP (1 μmole)	(NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> (1 μmole)	Dry heating at 85 °C for 72 h	Urea (10 μmole), MgCl <sub>2</sub> (2 μmole)	CDP (24.3)	
TMP (1 μmole)				TDP (24.7)	
GMP (1 μmole)				GDP (16.3)	
AMP (1 μmole)				ADP (20.5)	
<b>U</b> (17.8 mol%)	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> (6.2 mol%)	Dry heating at 100 °C for ≤11 d	Urea (76.0 mol%)	UMP (≤69)	l
<b>A</b> (0.02 M)	(NH <sub>4</sub> ) <sub>2</sub> H <sub>2</sub> PO <sub>4</sub> (0.1 M)	Heated at 70 °C for 15 d in FA	FA	AMP (29), ADP (5)	m
	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> ·2H <sub>2</sub> O (0.1 M)			AMP (26), ADP (6)	
<b>T</b> (0.02 M)	KH <sub>2</sub> PO <sub>4</sub> (0.1 M)			TMP (40), TDP (6)	
<b>U</b> (0.02 M)	KH <sub>2</sub> PO <sub>4</sub> (0.1 M)			UMP (34), UDP (4)	
dG (12.5 mg)	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> (200 mg)	Kept at 37 °C for several weeks in FA	FA (5 mL)	dGMP (19)	n
dA (12.5 mg)				dAMP (21)	
<b>T</b> (12.5 mg)				TMP (10)	
dC (12.5 mg)				dCMP (26)	
AMP (0.02 M)	TMP (0.04 M)	Kept at r.t. for 3 d in dry condition	MgCl <sub>2</sub> (0.1 M)	ADP (2.2), ATP (6.8)	o
		Kept at r.t. for 4 d in dry condition	MgCl <sub>2</sub> (0.1 M), imidazole (0.5 M)	ADP (≤22.9), ATP (≤25.3)	
dA (0.05 M)	TMP (1.0 M)	Kept at r.t. and pH 10.5–12.0 for 15 d	–	dATP (22)	p
dC (0.05 M)			–	dCTP (24)	
<b>T</b> (0.05 M)			–	TTP (22)	
dG (0.05 M)			–	dGTP (20)	
<b>A</b> (0.05 M)	TMP (0.05 M)	Kept at r.t. and pH 8–12 for ≤10 d	–	AMP (≤91.8), ATP (≤3.0)	
<b>A</b> (0.05 M)	TMP (1.0 M)	Kept at r.t. and pH 12–14 for ≤6 d	–	AMP (≤8.5), ATP (≤9.9)	
<b>A</b> (0.02 M; pH4.80–7.21)	KH <sub>2</sub> PO <sub>4</sub> (0.2 M)	Electrical discharge for 1w under CO <sub>2</sub> /H <sub>2</sub> /N <sub>2</sub> atmosphere (2:2:1, 35 cmHg)	–	AMP (0.21)	q
<b>A</b> (0.01 M)	Carbomyl phosphate (0.2M)	Kept 37 °C and pH 7 for 3 h,	Ba <sup>2+</sup> , Ca <sup>2+</sup> , Mn <sup>2+</sup> , Cd <sup>2+</sup> , or Co <sup>2+</sup> (0.2M)	–	r
AMP (0.01 M)				ADP (≤6.9)	
ADP (0.01 M)				ATP (≤17.1)	

(continued on next page)

**Table 3** (continued)

Reactant <sup>a</sup>	Phosphate <sup>b</sup>	Experimental condition <sup>c</sup>	Catalyst	Product (%)	Ref.
<b>A</b> (0.01–0.05 M)	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> (0.01–0.5 M)	Kept at 25–140 °C for 12 h–90 d in FA	FA	AMP (≤32)	s
<b>U</b> (0.05 M)	KH <sub>2</sub> PO <sub>4</sub> (0.1 M)	Heated at 125 °C for 0.5 d in FA		UMP (88)	
<b>C</b> (0.05 M)				CMP (90)	
<b>G</b> (0.05 M)				GMP (32)	
<b>T</b> (0.05 M)	KH <sub>2</sub> PO <sub>4</sub> (0.05 or 0.1 M)	Kept at 46–130 °C for 0.5–15 d in FA		TMP (≤46)	
<b>A</b> (0.05 M)	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> (0.05 M)	Heating at 100 °C for 0.8 d in organic solvents	FA (5 mL) M-methylFA (5 mL) Acetamide (5 mL) N-methylacetamide (5 mL) N,N-dimethylFA (5 mL)	AMP (18), ADP (8) AMP (9), ADP (2) AMP (7) AMP (5) –	t
ADP (0.01 M)	KH <sub>2</sub> PO <sub>4</sub> (0.05 M) KH <sub>2</sub> PO <sub>4</sub> (0.5 M)	Dry heating at 100 °C for 2 d Kept at 25 °C and pH 4–8 for 5 h	Urea 1.0 M NaOCN and CaCl <sub>2</sub> ·2H <sub>2</sub> O	AMP (17.5), ADP (10.5) ATP (≤22)	u
AMP (0.005 M)	KH <sub>2</sub> PO <sub>4</sub> (1 M)	Kept at 4 °C and pH 4–8 for 22 d	NaOCN, CaCl <sub>2</sub> ·2H <sub>2</sub> O, and MgCl <sub>2</sub> ·2H <sub>2</sub> O (1.0 M)	ADP (≤19), ATP (≤7)	
<b>A</b> (0.02 M)	TMP (0.2 M)	Kept at 37 °C for 2 w Dry heating at 60 °C for 2 w Wet–dry cycle at 37 °C	FA (0.3%), MgCl <sub>2</sub> (0.1 M) MgCl <sub>2</sub>	AMP (0.6), ATP (0.6) AMP (0.9), ATP (1.3) AMP (≤10.7), ATP (≤23.7)	v
<b>A</b> (0.025 M)	KH <sub>2</sub> PO <sub>4</sub> (0.05 M) hydroxyapatite Mn <sub>5</sub> (PO <sub>3</sub> (OH)) <sub>2</sub> (PO <sub>4</sub> ) <sub>2</sub> (H <sub>2</sub> O) <sub>4</sub> Cu <sub>2</sub> (PO <sub>4</sub> ) (OH) Cu <sub>3</sub> PO <sub>4</sub> (OH) <sub>3</sub> Cu <sub>5</sub> (PO <sub>4</sub> ) <sub>2</sub> (OH) <sub>4</sub>	Heated at 90 °C in FA	FA, various metal cations FA (1 mL)	AMP (≤7) AMP (≤2.5) AMP (≤0.1) AMP (>6) AMP (>2) AMP (>2.8)	w
<b>A</b> (50 mM)	KH <sub>2</sub> PO <sub>4</sub> (0.05 M) KH <sub>2</sub> PO <sub>4</sub> (0.1 M) KH <sub>2</sub> PO <sub>4</sub> (0.1 or 1 M)	Heated at 90 °C for 24 h in FA Heated at 90 °C for <200 h in 90% FA Heated at 90 °C for <250 h in H <sub>2</sub> O	FA, Cu <sub>2</sub> (CO <sub>3</sub> ) (OH) <sub>2</sub> FA –	AMP (7) AMP (≤25) AMP (≤7)	x

a, Ponnamperuma et al., 1963b; b, Ponnamperuma and Mack, 1965; c, Steinman et al., 1965a,b; d, Beck et al., 1967; e, Schwartz and Ponnamperuma, 1968; f, Rabinowitz et al., 1968; g, Lohrmann and Orgel, 1968; h, Schwartz, 1969; i, Lohrmann and Orgel, 1971; j, Bishop et al., 1972; k, Handschuh et al., 1973; l, Osterberg et al., 1973; m, Schoffstall, 1976; n, Philipp, 1977; o, Lohrmann, 1977; p, Etaix and Orgel, 1978; q, Yamagata et al., 1979; r, Saygin, 1981; s, Schoffstall et al., 1982; t, Schoffstall and Laing, 1985; u, Yamagata, 1999; v, Cheng et al., 2002; w, Constanzo et al., 2007; x, Saladino et al., 2009.

<sup>a</sup> A, adenosine; C, cytosine; G, guanosine; T, thymidine; U, uridine; dA, 2'-deoxyadenosine; dC, 2'-deoxycytidine; dG, 2'-deoxyguanosine.

<sup>b</sup> Pi, phosphate; TMP, trimetaphosphate.

<sup>c</sup> d, day; h, hour; m, month; min, minute; w, week; r.t., room temperature; FA, formamide.

orthophosphate by heating in dry conditions (Rabinowitz et al., 1968; Osterberg and Orgel, 1972) or mixing with organic condensing agents in aqueous solution (Miller and Parris, 1964; Beck and Orgel, 1965; Weber, 1982; Keefe and Miller, 1996).

Phosphorylation occurs at any possible position of the sugar moiety: 2', 3', 5' and 2', 3' or 3', 5' cyclic. When orthophosphate is used as a starting phosphorus compound, preferential functionalization is observed at the 5'-position of ribose or 2'-deoxyribose (Beck et al., 1967; Lohrmann and Orgel, 1971; Osterberg et al., 1973; Schoffstall et al., 1982) because of the higher reactivity of the primary OH group with respect to the secondary ones on the 2'- and 3'-positions (Saladino et al., 2005a). In contrast, trimetaphosphate tends to react with the OH groups at the 2'- and 3'-positions, leading to nucleoside 2'-(or 3'-)monophosphate as a major product (Schwartz, 1969; Etaix and Orgel, 1978).

Note that individual steps of the nucleotide synthesis outlined above have been performed under mutually different experimental conditions. As was described in previous sections, the abiotic synthesis of each nucleotide component (ribose and nucleobases) tends to generate complex mixtures of products with desired compounds being only a small fraction. It is unclear whether or not these problems could be overcome by environmental fluctuations on the primitive Earth; such as purification and concentration of the nucleotide components, mixing the components with condensing agents at the right time and place, and exposing the mixtures to the optimum conditions to form nucleotides (Orgel, 2004; McCollom, 2013b).

More recently, a new synthetic approach for pyrimidine nucleotides was explored by Sutherland and co-workers (Fig. 12; Powner et al., 2009). In their discovered pathway, reactions do not start from ribose and nucleobases, but from a set of much simpler precursors; glycolaldehyde, glyceraldehyde, cyanamide, cyanoacetylene, and phosphate. The pathway begins with a reaction of

glycolaldehyde and cyanamide to form 2-amino-oxazole. The compound then condenses with glyceraldehyde to yield the arabinose amino-oxazoline. Reaction of this molecule with cyanoacetylene gives the arabinose anhydronucleoside as Sanchez and Orgel (1970) demonstrated. Subsequent phosphorylation and rearrangement of chemical bonds results in the formation of β-ribo-cytidine-2',3'-cyclic phosphate.

Phosphate plays important roles in every step of the reaction sequence, acting as a pH buffer, an acid–base catalyst, a chemical buffer for depleting undesired byproducts, as well as being a component of nucleotides. First, phosphate acts as an acid–base catalyst in the formation of 2-amino-oxazole, thereby the reaction proceeds under neutral pH (in the absence of phosphate, alkaline pH is required for the selective formation of 2-amino-oxazole; Cockerill et al., 1976). In 1M phosphate buffer solution at pH 7.0, a mild heating (60 °C for 3 h) of glycolaldehyde (~1 M) and cyanamide (~1 M) produces 2-amino-oxazole in >80% yield (Powner et al., 2009).

The next step, condensation of 2-amino-oxazole with glyceraldehyde, gives all four pentose amino-oxazolines with high stereoselectivity for the ribo- and arabino-isomers (Anastasi et al., 2006). All compounds convert reversibly into the 5-substituted 2-amino-oxazoles, but the lyxose amino-oxazoline is the least stable in the presence of a phosphate catalyst (Powner et al., 2009). Phosphate thus leads to further selective formation of arabino-amino-oxazoline, an important intermediate for subsequent steps of the nucleotide synthesis.

The addition of phosphate also allows a high-yield production of the arabinose anhydronucleoside from arabinose amino-oxazoline and cyanoacetylene (92% yield). In the absence of phosphate, pH rises during the reaction, resulting in hydrolysis of the anhydronucleoside to β-arabinocytidine (Sanchez and Orgel, 1970). Furthermore, excess cyanoacetylene reacts with the hydroxyl



groups of the anhydronucleoside. Phosphate prevents these undesired reactions by maintaining a neutral pH, and by converting the excess cyanoacetylene to cyanovinyl phosphate (Powner et al., 2009). Once the arabinose anhydronucleoside has formed, a dry heating (100 °C for 24 h) with pyrophosphate in the presence of urea and ammonium chloride gives  $\beta$ -ribocytidine-2',3'-cyclic phosphate in 32% yield (Powner et al., 2009). Irradiation of this molecule with UV light (254 nm, 80 h) converts it to  $\beta$ -ribouridine-2',3'-cyclic phosphate (Powner et al., 2009).

The proposed mechanism significantly reduces the problems in the abiotic nucleotide synthesis described above. However, the story remains incomplete because several steps require temporally separated reactants with high concentrations. It is not clear if the production of target molecules is still possible in the presence of impurities (both organic and inorganic) and other closely related components. Compatibility of each reaction condition also remains uncertain. Further refinements of the synthesis pathway are needed for clearer convergence between laboratory simulations and geochemical limitations (McCollom, 2013b).

#### 4.7. Oligonucleotide

The polymerization of nucleotides in water is an unfavorable reaction in both thermodynamics and kinetics. The Gibbs energy necessary to synthesize a mole of phosphodiester bond is 5.3 kcal at 25 °C and pH 7 (Dickson et al., 2000). The value indicates that an equilibrium molar ratio of dimer over monomer of nucleotide is only ~0.01% even when the monomer concentration is as high as 1M. The half-life of the phosphodiester bond of oligonucleotides is in the range of 1 hour–10 day, 2–70 s and 0.01–0.9 s at 100 °C, 200 °C, and 300 °C, respectively (Kawamura, 2004). Consequently, attempts to polymerize nucleotide in aqueous solution result in a

formation of short oligonucleotides in very poor yields (Ogasawara et al., 2000). Alternative approaches proposed so far include a dry heating of nucleotides at high temperature (>100 °C; Morvek, 1967) and mixing with organic activating agents such as cyanamide and water-soluble carbodiimides (Ibanez et al., 1971a,b; Ferris et al., 1989). Both approaches, however, have failed to make oligomers longer than dimers in acceptable yields (Orgel, 2004). Nucleoside 5'-polyphosphates (e.g., ATP) are high-energy phosphate esters, but are unreactive in aqueous solution. The half-life for hydrolysis of ATP to ADP is 6.3 years at 25 °C and neutral pH (Stockbridge and Wolfenden, 2009). A rate of ligation of two oligoribonucleotides aligned on a template RNA, one bearing a 2',3'-hydroxyl and the other a 5'-triphosphate, is only  $5.4 \times 10^{-7}$  per hour, or 210 years for complete ligation at 25 °C and pH 7.4 in the presence of 15 mM  $Mg^{2+}$  (Bartel and Szostak, 1993). The rate is comparable to the rate of hydrolysis of a RNA phosphodiester bond (~90 years at 25 °C; Wolfenden, 2011). These properties may be advantageous for an enzyme-controlled reaction, whereas it is a severe obstacle for non-enzymatic polymerization of nucleotides (Robertson and Joyce, 2012).

In contrast, nucleoside 2',3'- and 3',5'-cyclic phosphates (Fig. 13) are highly reactive for polymerization. The enthalpies of hydrolysis of 2',3'- and 3',5'-cyclic ones are respectively from -7.8 to -9.5 and from -10.5 to -14.1 kcal mol<sup>-1</sup> at 25 °C and neutral pH (Rudolph et al., 1971), indicating that the coupling of the hydrolysis with the formation of a new phosphodiester bond ( $\Delta_r G^\circ = 5.3$  kcal mol<sup>-1</sup>; Dickson et al., 2000) is thermodynamically favorable. Polymerization of the cyclic 2',3'-phosphates requires a dry heating with organic catalysts (Tapiero and Nagyvary, 1971; Verlander et al., 1973; Verlander and Orgel, 1974), whereas active polymerizations have been observed for the cyclic 3',5'-phosphates in water in the absence of catalysts at moderate

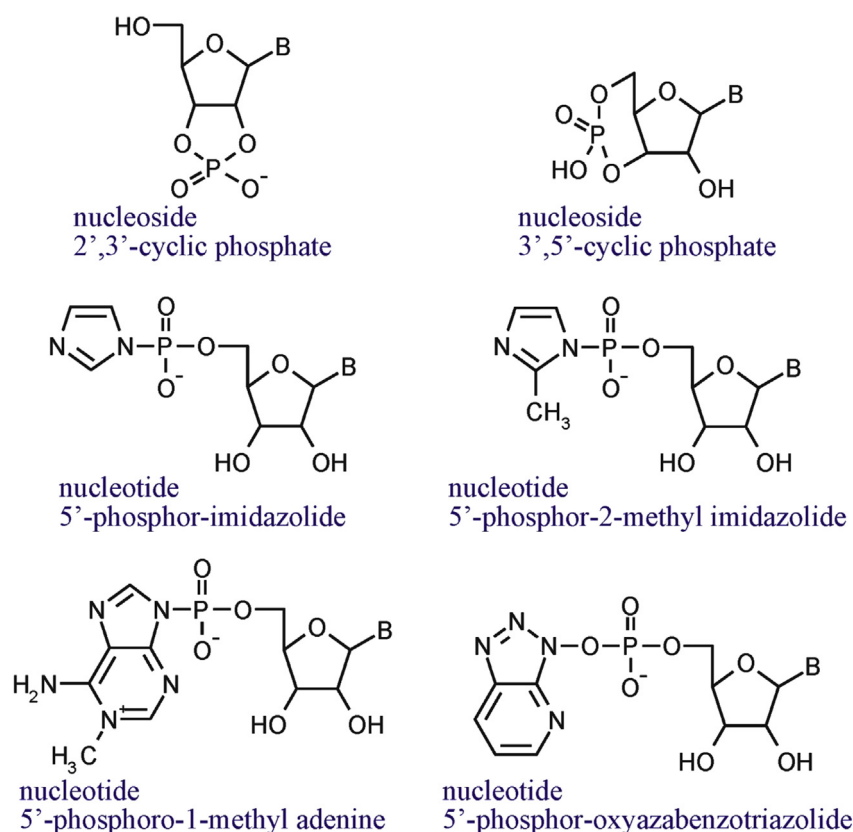


Figure 13. Structures of activated nucleotides.

temperatures (40–90 °C) (Costanzo et al., 2009, 2012). When 1 mM guanosine 3',5'-cyclic phosphate (3',5'-cGMP) was heated in water at 85 °C and pH 8.2, oligomers up to a length of ~25 units were obtained after a short heating duration (one hour) (Costanzo et al., 2009). The cyclic 2',3'-phosphates are the major products of the urea-catalyzed phosphorylation of nucleosides at 100 °C in the solid state (Lohrmann and Orgel, 1971), whereas the cyclic 3',5'-phosphates can be obtained by heating of the corresponding nucleosides with KH<sub>2</sub>PO<sub>4</sub> at 90 °C in formamide (Saladino et al., 2009).

Great success has also been met using a different type of activated nucleotide, nucleoside 5'-phosphorimidazolides (ImpN; Fig. 13). In the presence of inorganic ions such as Pb<sup>2+</sup> and UO<sub>2</sub><sup>2+</sup>, ImpNs polymerize into oligonucleotides of up to 16-mer in aqueous solution (Sawai and Orgel, 1975b; Sawai, 1976; Sawai et al., 1989). The reaction is especially efficient when performed in the eutectic water phase at -18 °C, where most of the water is present as ice (Kanavarioti et al., 2001; Monnard et al., 2003). Using Pb<sup>2+</sup> as a metal catalyst, oligomers as long as 17 mer have been obtained with 90% yield. Phosphorimidazolides can be produced from imidazoles and nucleoside 5'-polyphosphates in dry conditions (Lohrmann, 1977), and thus have been claimed to be present on the primitive Earth. Note that oligomers formed from the activated monomers are normally random mixtures of 2'-5', 3'-5', and 5'-5' bonds, of which only the 3'-5' bond is the biologically relevant linkage. Attempts to increase the proportion of 3',5'-linked oligomers have met with some success (Sawai et al., 1992), but it is still unlikely that condensation of activated nucleotides leads to entirely 3',5'-linked oligomers in water, even in the presence of effective metal catalysts (Robertson and Joyce, 2012).

Ferris and coworkers have investigated the catalytic effect of an abundant clay mineral, montmorillonite, on the synthesis of long oligonucleotides from ImpNs and related activated nucleotides (Ferris et al., 2004; Ferris, 2006). In a typical experiment, ~15 mM ImpN (pH 8) is incubated with 50 mg of Na<sup>+</sup>-montmorillonite in 1 mL solution of 0.2 M NaCl and 0.075 M MgCl<sub>2</sub> at room temperature for several days. HPLC analysis of the reaction products has shown the formation of 2–14 mers, with the chain length depending on the base present in the nucleotide (Ferris and Ertem, 1992, 1993; Ding et al., 1996; Ertem and Ferris, 1996; Kawamura and Ferris, 1999). Recent reassessment with an advanced analytical technique (MALDI-TOF mass spectrometry) detected oligomers of up to 40 monomeric units from mixtures of oligomeric products on montmorillonite (Zagorevskii et al., 2006). Na<sup>+</sup>-montmorillonite accelerates the hydrolysis of the imidazole group of the activated nucleotides by a factor of 35, but provides a much greater enhancement for the polymerization (>1000 times), which results in the net conversion of ImpN to oligonucleotides (Kawamura and Ferris, 1994). Long oligomers have also been obtained using a different type of activated nucleotide in which imidazole is replaced by 1-methyladenine (Fig. 13; Prabaha and Ferris, 1997; Huang and Ferris, 2003). 1-methyladenine is formed from N6-methyladenine by the reversal of the Dimroth rearrangement, and N6-methyladenine from adenine by heating with 20 M methylamine (CH<sub>3</sub>NH<sub>2</sub>) in a sealed ampoule at 100 °C and alkaline pH (up to 50% yields; Levy and Miller, 1999). Once formed, 1-methyladenine reacts with nucleoside 5'-monophosphate to form nucleotide 5'-phosphoro-1-methyladenine in the presence of a water soluble carbodiimide (Prabaha and Ferris, 1997). The activated functional group particularly promotes polymerization of adenosine and uridine, making their oligomers greater than 40-mer in length in 1 day at room temperature in reactions catalyzed by montmorillonite (Huang and Ferris, 2006). Once short oligomers are formed, daily replacements of the supernatant solution of an oligomer–montmorillonite suspension with the fresh activated

monomers results in chain elongation up to 55 monomers long (Ferris et al., 1996; Ferris, 2002).

Nucleotides adsorb on montmorillonite via van der Waals' interaction between the silicate layer of the montmorillonite and the purine and pyrimidine bases of the nucleotides at neutral pH (Lailach et al., 1968; Ferris, 2006). The strength of the binding of purine nucleotides is greater than that of the corresponding pyrimidine ones owing to the larger size of the planar purine ring (Ertem and Ferris, 1997). Strong binding to montmorillonite is not a primary factor in oligomer formation (Kawamura and Ferris, 1999), but results in the favorable orientation for the formation of 3',5' phosphodiester bonds. The oligomerization of ImpA, for example, gives a higher proportion of 3',5'-linked products in the presence of montmorillonite (Ferris and Ertem, 1992, 1993), whereas the reaction of pyrimidine nucleotides ImpC and ImpU yields oligomers that are predominantly 2',5'-linked (Ding et al., 1996; Ertem and Ferris, 1997). The mechanism for the catalytic effect is not well understood, but detailed experimental study by Wang and Ferris (2001) suggested that the oligomerization occurs at a limited number of specific active sites within the interlayers of the montmorillonite.

More recently, Deamer and coworkers found that a multi-lamellar lipid matrix strongly accelerates the polymerization of 5'-mononucleoside phosphates (AMP and UMP) in hydration–dehydration cycles (Rajamani et al., 2008; DeGuzman et al., 2014). The synthesis of 25–100 nucleotide-containing polymers were observed, with 3'-5' and 2'-5' linkages randomly existing (DeGuzman et al., 2014). It is noteworthy that vesicle formation from fatty acid micelles is catalyzed by montmorillonite, and that the vesicle can encapsulate clay particles together with surface-adsorbed nucleotide oligomers (Hanczyc et al., 2003). Because montmorillonite preferentially catalyzes the formation of 3'-5'-phosphodiester linkages, these findings indicate the possibility that polymerization on montmorillonite, and subsequent encapsulation within membrane vesicles, could generate nucleotide oligomers with sufficient length and appropriate configuration to initiate the replication system in primitive protocells.

#### 4.8. RNA world

Natural selection through replication and mutation is a key mechanism for evolving complex biochemical systems from simpler ones (Orgel, 2004). The replicating system in contemporary biology consists of DNA, RNA and protein; DNA holds genetic information, RNA translates it to form proteins, and proteins provide the enzymatic activities needed to make DNA and RNA, and to enable them to reproduce themselves. It is highly unlikely, however, that the DNA/RNA/protein system emerged from a random mixture of amino acids and nucleotides that were abiotically formed on the primitive Earth. One possible approach to this dilemma is to pinpoint a single molecular species that acts both as genetic information and as a catalyst that supports its own replication. The most promising candidate is RNA if a mechanism existed on the primitive Earth for the formation of oligoribonucleotides, and if some of these polymers acquired, by chance, the ability to copy their sequences through template-directed ligation of preexisting nucleotides. The RNA-first scenario was initially suggested over 40 years ago (Woese, 1967; Crick, 1968; Orgel, 1968). Since then, it has been the most well-known hypothesis for the origin of the replication system (Gilbert, 1986; Bernhardt, 2012). Support for this hypothesis has come from the discovery of a growing number of catalytic RNA molecules, ribozymes, in extant organisms (Kruger et al., 1982; Guerrier-Takada et al., 1983). Notably, the ribosome's peptidyl transferase center, the active site for peptide bond formation, is composed entirely of RNA (Nissen et al., 2000). Support has also come from *in vitro*

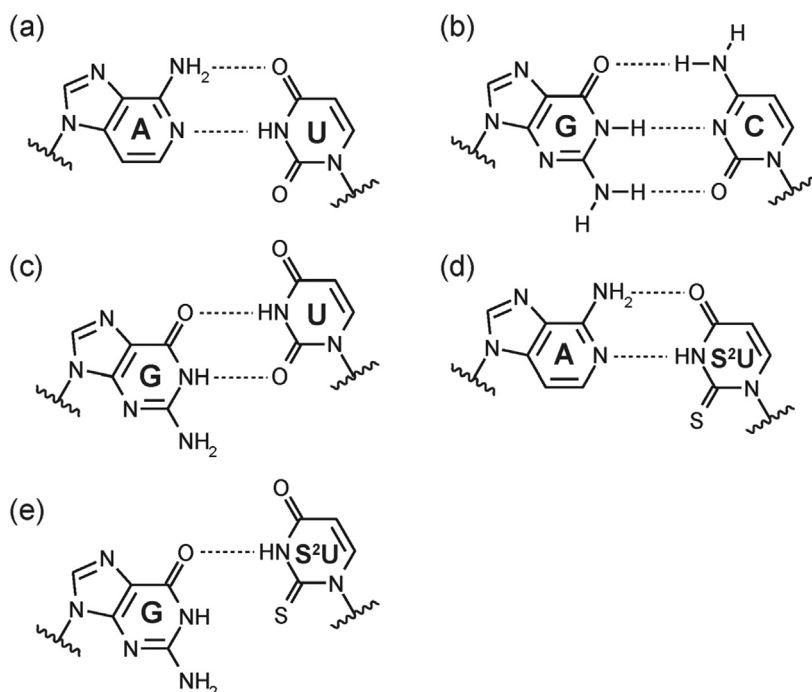
evolution of a wide range of new ribozymes, including both artificial functional RNA molecules and improved versions of certain natural ribozymes (Johnston et al., 2001; Joyce, 2004). The appearance of RNA before DNA is also convincing; nucleotide metabolism synthesizes deoxyribonucleotides from their corresponding ribonucleotides by the reduction of their C2' position, rather than by their *de novo* synthesis from deoxyribose-containing precursors (Stubbe, 1990). A remaining central question is how the first template-dependent RNA polymerase ribozyme could have emerged on the primitive Earth. Considerable efforts have been devoted to this topic of nonenzymatic replication.

The template-directed synthesis of oligonucleotides was first demonstrated in the 1960s using a water-soluble carbodiimide as the condensing agent (Naylor and Gilham, 1966; Sulston et al., 1968a,b, 1969). The reactions were slow and inefficient, and/or led to complex mixtures of isomeric short oligonucleotide products (Orgel, 2004; Blain and Szostak, 2014). More efficient and regio-specific polymerization has been obtained using pre-activated substrates, phosphorimidazolides, or related phosphoramidates (Fig. 13). When guanosine-5'-phosphorimidazolide (ImpG) was incubated with poly(C) templates in the presence of  $Mg^{2+}$  and  $Zn^{2+}$ , products were predominantly 3'-5'-linked oligomers (Bridson and Orgel, 1980), while 2'-5'-linked oligomers were exclusively obtained in the presence of  $Mg^{2+}$  and  $Pb^{2+}$  (Lohrmann and Orgel, 1980). Exclusive formation of 3'-5'-linked oligomers was also observed in the absence of metal ions other than  $Mg^{2+}$  when imidazole is replaced by 2-methylimidazole in the activated nucleotide (Fig. 13; Inoue and Orgel, 1981). More recently, the rates of template copying were significantly improved with oxyazabenzotriazole (OAt; Fig. 13) as the leaving group (Hagenbuch et al., 2005; Vogel and Richert, 2007). When OAt-activated cytosine nucleotides were added onto an RNA template with a primer RNA designed to aid the incorporation of C monomer onto a G residue in the template, almost complete ligation was observed within 20 h at slightly alkaline pH (9.5) (Vogel et al., 2005).

The fidelity of the template-directed condensation of activated nucleotides depends strongly on the sequence and base

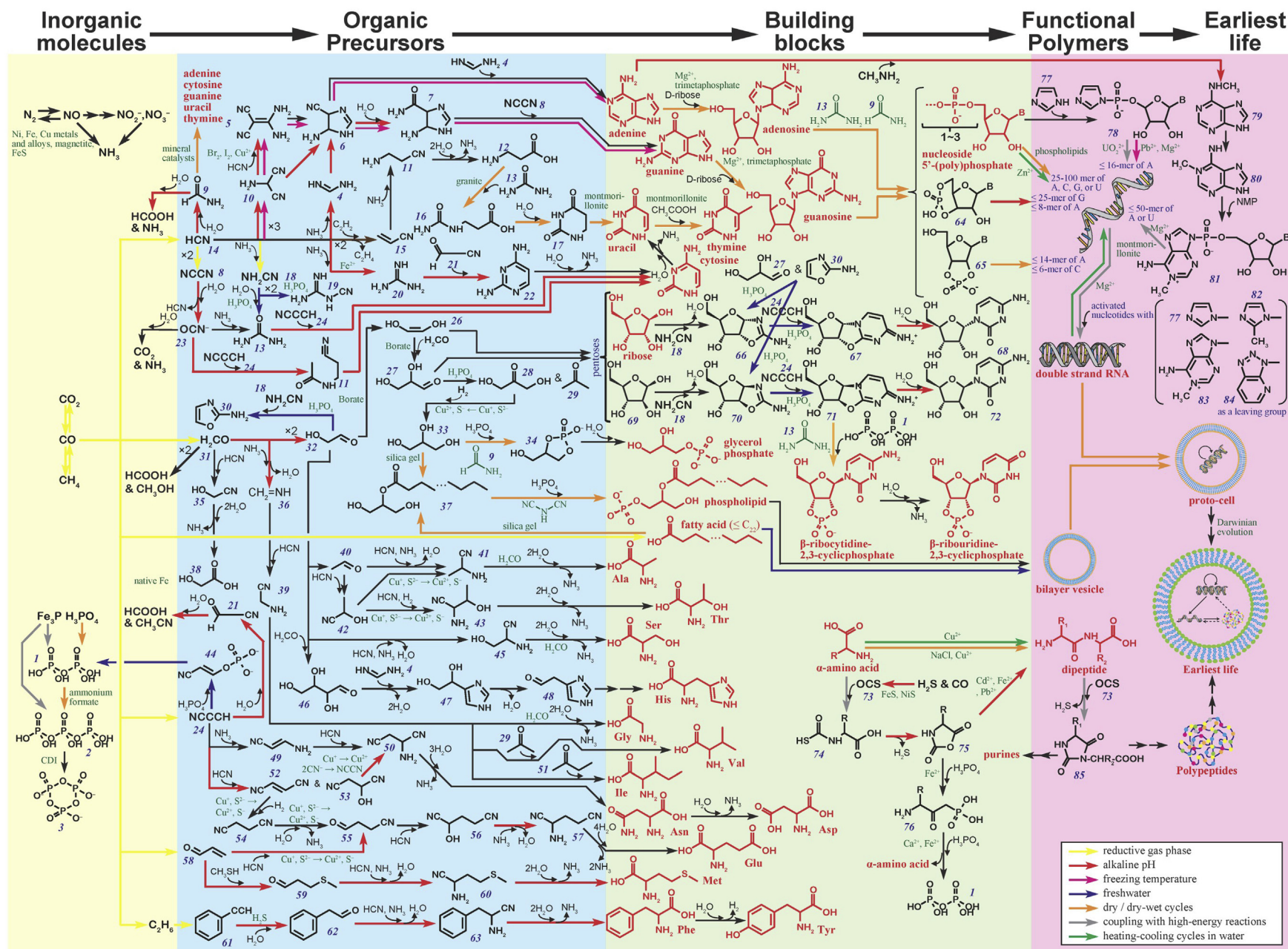
composition of the oligonucleotide template. Formation of poly(G) on poly(C) template is remarkably accurate; if poly(C) is incubated with an equimolar mixture of the four nucleoside 5'-phospho-2-methylimidazolides (2-MelpNs; N = G, A, C, or U), incorporation of non-complementary nucleotides into oligomers is less than 1% (Inoue and Orgel, 1982). Random copolymers containing an excess of C residues lead to the oligomerization of 2-MelpG with the corresponding derivatives of other bases with good efficiency of incorporation (Inoue and Orgel, 1983). A C:G template as long as 14-mer (5'-CCCCGCCGCCGCC-3') has been copied successfully in the yield of ~50% for the sum of truncated products, and <2% for the full-length products (Acevedo and Orgel, 1987). In contrast, U residues in a template are difficult to copy (Inoue and Orgel, 1983; Leu et al., 2011) owing to weak base-pairing between U and A together with the comparable strength of a G:U wobble pair versus an A:U base pair (Fig. 15; Freier et al., 1986; Chen et al., 2012). The presence of multiple A, T or G residues in succession in a template drastically reduces the copying efficiency (Wu and Orgel, 1992). Oligo (C, G)s that do not contain an excess of C residues tend to form intra- and inter-molecular duplex structures that prevent them from acting as templates (Joyce and Orgel, 1986). The problem of template self-structure rules out the possibility of repeated rounds of replication, because a successful template-directed synthesis results in complementary products of G-rich sequences that cannot then serve as good templates (Orgel, 2004; Robertson and Joyce, 2012).

An approach to improving the fidelity of A:U base pairing is to use nucleobase analogs that increase the specificity of the base pair recognition. The G:U wobble pairing (or G:T) is caused by the shift of hydrogen bonding via the 2-exo-oxygen participation within the base pairs (Fig. 14). Because the 2-exo-oxygen atom is not involved in the A:U (or A:T) base pair, replacement of this oxygen by a weaker H-bond acceptor is expected to weaken the wobble pairs selectively, and thereby increase the fidelity of RNA copying. The possibility has been demonstrated by introducing a selenium (Hassan et al., 2010) and a sulfur atom (Zhang et al., 2013) at the 2-position. The substitution with sulfur is particularly effective because it stabilizes the A:U base pair (by 1.1 kcal mol<sup>-1</sup>) as well as



**Figure 14.** Hydrogen-bonding interactions of (a) A:U base-pair, (b) G:C base-pair, (c) G:U wobble pair, (d) A:2-thio-U base pair, and (e) G:2-thio-U wobble pair.





**Figure 15.** Overview of the chemical evolution of life. See [Supplementary Table 1](#) for the mechanism and reactivity of each reaction and for the chemicals' names.



weakening the wobble pairing of **G** and **U** (by 0.3 kcal mol<sup>-1</sup>) (Testa et al., 1999).

Many efforts have been devoted to discovering conditions that lead to the efficient synthesis of 3'-5'-linked oligonucleotides. It is noteworthy, however, that 3'-5'-linked RNA with significant chain length has a very high thermal stability against strand separation. Even an RNA duplex of 30 base-pairs has a melting temperature higher than 100 °C (Engelhart et al., 2013). Because strand separation is required to allow for repeated cycles of template copying, effective means of destabilization of the strand is necessary for the initiation of replication cycles without the help of protein enzyme. Oligonucleotides containing 2'-5' linkages have much lower melting temperatures than natural RNA duplex (Kierzek et al., 1992; Wasner et al., 1998; Engelhart et al., 2013). With lower efficiency than 3'-5' linked RNA, 2'-5' linked oligomers can act as a template for nonenzymatic primer extension with activated nucleotides (Prakash et al., 1997). Moreover, some RNA functions (molecular recognition and catalytic cleavage of phosphodiester bond) have been shown to tolerate random doping of 2'-5'-linkages of up to 25% (Engelhart et al., 2013). The presence of 2'-5' linkages, therefore, may not be a problem, but an important feature that allowed RNA to emerge as the first replicating polymer on the primitive Earth.

In addition to the findings outlined above, considerable progress has been made toward elucidation of prebiotic pathways for non-enzymatic RNA replication (Schrum et al., 2010; Szostak, 2012; Blain and Szostak, 2014). Nevertheless, many problems still remain, such as the slow rate and insufficient fidelity of RNA template-copying, the hydrolysis of activated nucleotides on the same timescale as polymerization, and the fast reannealing of separated RNA strands (Engelhart et al., 2013). Most importantly, although proposed mechanisms for the template-directed polymerization postulate a continuous ample supply of activated monomers from surrounding environments, their occurrences in large amounts on the primitive Earth are unlikely (Orgel, 2004; Robertson and Joyce, 2012). The RNA-first scenario of the origin of life therefore needs further experimental evidence to overcome these difficulties and to discover a convincing abiotic pathway toward self-replicating RNA molecules.

#### 4.9. Protocell

Although the above discussion of the RNA world focused only on the replication properties of nucleic acids, spatial localization by membrane boundary is also an essential function for the emergence of Darwinian evolution (Szostak et al., 2001). Without spatial localization, an active replication ribozyme would act to propagate unrelated sequences as well as its own sequence. Consequently, nutrients from the surrounding environment would be exhausted before further development of the replication ability progressed. But how did early self-replicating molecules combine with membrane vesicles to constitute a unified cell? Did their interaction result in any mutual benefit? The cooperation of genome and membrane that potentially led to Darwinian evolution has been vigorously studied by Szostak and coworkers using RNA oligomers and fatty acid membranes as constituents of model protocells.

A remarkable finding from their laboratory is that the encapsulation of RNA into fatty acid vesicles drives membrane growth through osmotic pressure (Chen et al., 2004). Vesicles encapsulating a high concentration of RNA experienced a significant internal osmotic pressure, leading to the preferential uptake of additional fatty acids into the tensed membrane. This results in vesicle growth at the expense of neighboring vesicles with less internal RNA and hence, a lower pressure. It is conceivable from the

observation that more efficient RNA replication could cause faster cell growth through competition between protocells, and come to dominate the population. The coupling of RNA replication to membrane growth could have been an important mechanism in the beginning of Darwinian evolution during the origin of cellular life (Chen et al., 2004). It is noteworthy, however, that osmotically swollen vesicles tend to form stable spheres, which are difficult to divide (Szostak et al., 2001; Blain and Szostak, 2014). Prebiotically plausible means of protocell division have not been proposed in this model.

More recently, an alternative mechanism to link genomic function to cell growth was discovered that is independent of osmotic pressure. It was shown that the presence of low amounts of phospholipids (Budin and Szostak, 2011) or hydrophobic dipeptides (Adamala and Szostak, 2013a) can drive the competitive growth of fatty acid vesicles. The growth results from the decrease of membrane fluidity and the dissociation rate of fatty acid from membranes with increasing concentrations of these additives. Interestingly, upon mixing with a large excess of pure fatty acid vesicles, the mixed vesicles grow into thread-like filamentous vesicles owing to slow volume increase relative to rapid surface area increase (Budin and Szostak, 2011; Adamala and Szostak, 2013a). Application of a gentle shear force causes division of the filamentous vesicles into multiple small daughter vesicles without significant loss of encapsulated content. Therefore, the ability to synthesize even low levels of phospholipid and short peptides by internal catalytic RNA would impart a large selective advantage to its host protocell for growth through competition for fatty acid molecules.

A major drawback of fatty acid membranes as components of protocells is their instability under the ionic conditions necessary for RNA replication chemistry. Both nonenzymatic and ribozyme-catalyzed RNA polymerization require high concentrations of Mg<sup>2+</sup> (at least 50 mM; Blain and Szostak, 2014), whereas Mg<sup>2+</sup> causes aggregation and precipitation of fatty acid vesicles even at a few millimolar concentrations (Monnard et al., 2002). A recent study by Adamala and Szostak (2013b) provided a potential solution to this apparent incompatibility. They showed that citric acid chelated Mg<sup>2+</sup> such that fatty acid precipitation was substantially reduced, while template-directed RNA copying was only slightly affected. Citrate also protects RNA from Mg<sup>2+</sup>-catalyzed degradation: the presence of citrate with fourfold concentration relative to Mg<sup>2+</sup> (200 mM vs. 50 mM) reduced the rate of RNA fragmentation by a factor of ten. Because citrate is an important intermediate of today's carbon metabolism (tricarboxylic acid cycle), these advantages could have led to the origin of a metabolic system operated by RNA-based organisms (Muller and Tor, 2014).

These results demonstrate that simple chemical and physical interactions between genome and membrane lead to cellular behaviors essential for Darwinian evolution. Once self-replicating RNA and membrane vesicles have been united to form a protocell, any RNA mutation advantageous for vesicle growth would lead to preferential survival of the cell, and could increase the population through natural selection. Repeated cycles of RNA replication would therefore result in higher survivability of the cell with advanced abilities of growth, division, and reproduction. Additionally, cells could have evolved the ability to synthesize their own building blocks (e.g., phospholipid and short peptides) by developing the catalytic activity of RNA. Darwinian evolution starting from the simple vesicle–RNA system, therefore, is a promising route toward the emergence of modern biological systems.

#### 5. Discussion: where did chemical evolution occur?

Fig. 15 presents an overview of the chemical evolution of life, which was constructed based on reported experimental and

theoretical studies for this topic outlined above. The report referred to for each reaction is presented in [Supplementary Table S1](#) together with brief summaries for examined conditions and mechanisms. The overview depicts the chemical evolution as reaction networks categorized into the four stages of (1) condensation of inorganic compounds to reactive organic precursors, (2) conversion of the precursors to biological building blocks, (3) polymer formation by dehydration-condensation of the respective monomers, and (4) emergence and development of biological functions through Darwinian evolution that eventually led to the origin of life. For several reaction steps, certain inorganic ions or minerals play central roles in the reaction progress. These key inorganic materials are written with green font around arrows for the corresponding steps ([Fig. 15](#)). All reactions have been demonstrated to occur in reported simulations ([Table S1](#)); therefore, if these processes could occur on the Hadean Earth with appropriate order and timing, life, or at least life's fundamental functions (e.g., replication and compartmentalization) would emerge from naturally ubiquitous inorganic molecules (CO<sub>2</sub>, N<sub>2</sub>, H<sub>3</sub>PO<sub>4</sub>) without the aid of biological systems.

What environmental settings, or their combinations, can drive all the stages of chemical evolution? The following discussion lists the reaction conditions necessary to complete the chemical evolution based on the overview ([Fig. 15](#) and [Table S1](#)). It should be noted that, for many of the reaction steps, their responses to changing environmental conditions (e.g., temperature and pH) have not been fully understood. Therefore, in many cases it is unclear whether or not the conditions used in the reported studies ([Table S1](#)) are the optimum ones for the reaction progress. Additionally, several steps, particularly at the later stages of chemical evolution, are still highly hypothetical. It remains unclear how functional polypeptides emerged from abiotically formed amino acids with great conformational (e.g.,  $\alpha$ - vs.  $\beta$ -amino acids) and enantiomeric (e.g., L- vs. D-amino acids) variability. A huge gap should exist between the primitive protocell composed of fatty acid and RNA, and the modern DNA/RNA/protein system. Most seriously, the overview ([Fig. 15](#)) might not represent prebiotic processes that actually occurred on the primitive Earth; rather, it was depicted based on current scientific knowledge about the origin of life. Future research might discover new reaction mechanisms that improve yields and selectivity of life's building blocks synthesized abiotically, or be able to link currently unconnectable reaction networks (e.g., photo-redox chemistry developed by [Patel et al., 2015](#); some of their findings are included in [Fig. 15](#)). If such mechanisms are consistent with geological and biological predictions on the primitive Earth and life, the structure of the overview needs to be updated. Despite these uncertainties, the overview is still worth using as a framework for thinking about geochemical situations necessary for the origin of life. Our limited knowledge of chemical evolution is a major obstacle to envision a clear scenario for this topic. However, there is a sufficient amount of information to delineate the range of physical and chemical conditions that can lead to the formation of life's building blocks and their interactions to make biological functions. Refinement of scientific knowledge on biology, geology and chemistry would provide better constraints on the settings and conditions for these processes. It is hoped that such future modification can be facilitated by the framework made in this study. With these thoughts in mind, we tried to make some generalizations.

#### 5.1. Reductive gas phase (brown arrows in [Fig. 15](#))

Gas phase reactions generate a variety of simple but highly versatile compounds including HCN (**14**), H<sub>2</sub>CO (**31**), cyanogen (**8**), cyanamide (**18**), cyanoacetylene (**24**), acrolein (**58**) and

phenylacetylene (**61**) by the action of lighting and radiation (UV, X-ray, etc.) ([Fig. 15](#)). A high temperature heating (150–250 °C) of CO<sub>2</sub> with H<sub>2</sub> in a water vapor phase generates fatty acids with alkyl chains up to C<sub>22</sub> in the presence of mineral catalysts (e.g., native Fe; [McCullom, 2013c](#)). The yields and relative abundances of these products depend greatly on the redox state of atmosphere. A reducing atmosphere rich in H<sub>2</sub> favors their formation, whereas little is obtained from neutral ones dominated by CO<sub>2</sub> and N<sub>2</sub> (e.g., [Schlesinger and Miller, 1983a](#)).

#### 5.2. Alkaline pH (red arrows in [Fig. 15](#))

Composition of the collecting solution also shows significant influence on the yield and variety of synthesized compounds. Alkaline pH and reducing conditions are a good aqueous environment for preferential synthesis of  $\alpha$ -amino acids over  $\alpha$ -hydroxy acids through the Strecker reaction ([Cleaves et al., 2008](#); [Bada, 2013](#)). If favorable aqueous conditions are met, a variety of amino acids are formed in excellent yields (up to several % of starting materials) even from a neutral gas mixture dominated by CO<sub>2</sub> and N<sub>2</sub> ([Cleaves et al., 2008](#)). Alkaline pH (8–10) also favors the conversion of HCN (**14**) to formamidine (**4**), diaminomaleonitrile (**5**), formamide (**9**), aminomalononitrile (**10**), urea (**13**), and guanidine (**20**) and their condensation to nucleobases (adenine and cytosine) ([Fig. 15](#); [Shapiro, 1995](#)). At a pH higher than 10, non-polar molecules extracted from a carbonaceous chondrite spontaneously assemble into membrane vesicles ([Deamer, 1985](#)). The formose production of ribose from H<sub>2</sub>CO (**31**) requires alkaline pH (10–11) with Ca<sup>2+</sup> as a catalyst at the initial stage (H<sub>2</sub>CO (**31**)  $\times$  2  $\rightarrow$  glycolaldehyde (**32**); [Benner et al., 2012](#)). Although ribose decomposes rapidly in alkaline conditions, its stability is greatly enhanced in the presence of borate by forming a complex in its cyclized form ([Ricardo et al., 2004](#)).

#### 5.3. Freezing temperature (pink arrows in [Fig. 15](#))

A drawback of alkaline pH is that many key organic precursors including HCN (**14**), cyanogen (**8**), formamide (**9**), cyanoacetaldehyde (**21**), and cyanoacetylene (**24**) hydrolyze with the rates being first order in OH<sup>−</sup>. Under alkaline conditions, H<sub>2</sub>CO (**31**) readily reacts with HCOOH to give methanol and carbonic acid (H<sub>2</sub>CO + HCOOH + H<sub>2</sub>O  $\rightarrow$  CH<sub>3</sub>OH + H<sub>2</sub>CO<sub>3</sub>; [Morooka et al., 2005](#)). It is therefore unlikely that these precursors enriched in alkaline aqueous environments up to sufficient concentrations for synthesis of life's building blocks (>0.01–0.1 M for HCN polymerization to adenine; [Sanchez et al., 1967](#),  $\geq$ 0.1 M for ribose synthesis from H<sub>2</sub>CO through the formose reaction; see [Section 4.3](#)). Eutectic freezing is an effective means to increase their concentrations ([Sanchez et al., 1966b](#)). At temperatures less than 0 °C, HCN and its derivatives concentrate as eutectics in an ice matrix, thereby their condensations occur effectively to generate various biomolecules (adenine, guanine, cytosine, Gly, Ala, and Asp) even when their initial concentrations are as low as 0.001 M ([Schwartz et al., 1982](#); [Levy et al., 1999, 2000](#); [Miyakawa et al., 2002b](#); [Cleaves et al., 2006](#)). Such conditions also favor the polymerization of activated nucleotides up to 17-mer in the presence of Mg<sup>2+</sup> and Pb<sup>2+</sup> ([Kanavarioti et al., 2001](#); [Monnard et al., 2003](#)). Although pH measurements have not been conducted in the course of freezing, temperature decreases might lead to pH neutralization owing to the precipitation of metal hydroxides (e.g., Mg<sup>2+</sup> + 2OH<sup>−</sup>  $\rightarrow$  Mg(OH)<sub>2</sub>).

#### 5.4. Fresh water (blue arrows in [Fig. 15](#))

Whereas metal cations (e.g., Cu<sup>2+</sup>, Fe<sup>2+</sup>, Mg<sup>2+</sup>, Pb<sup>2+</sup>, and Zn<sup>2+</sup>) show good catalytic efficiencies in many reaction steps ([Fig. 15](#), [Table S1](#)), their presence in water greatly reduces the stability of

fatty acid vesicles. A few millimolar concentrations is enough to see the aggregation effects of  $Mg^{2+}$  and  $Ca^{2+}$  (Monnard et al., 2002). Dissolved metals also cause precipitation of phosphate (e.g.,  $5Ca^{2+} + 3HPO_4^{2-} + H_2O \rightarrow Ca_5(PO_4)_3(OH) + 4H^+$ ). Because phosphate plays a versatile role in aqueous solution as a pH buffer, an acid–base catalyst, a chemical buffer for depleting undesired byproducts, as well as a component of nucleotides and phospholipids (Sutherland, 2010), its availability in water is a key factor for many abiotically important steps (e.g., synthesis of pyrimidine ribonucleotides from cyanamide (18), cyanoacetylene (24), glyceraldehyde (27), and glycolaldehyde (32); Powner et al., 2009). To ensure the phosphate concentration is the same level as it is in laboratory simulations ( $\sim 1$  M), dissolved metals need to be depleted to below micro-molar concentrations.

#### 5.5. Dry/dry-wet cycles (orange arrows in Fig. 15)

Polymerization of life's building blocks involves dehydration (e.g.,  $n$  amino acids  $\rightarrow$  (peptide) $n$  +  $(n-1)H_2O$ ,  $n$  nucleotides  $\rightarrow$  (oligonucleotide) $n$  +  $(n-1)H_2O$ ), and hence occurs effectively under dry conditions or in organic solvents acting as condensing agents (e.g., formamide (9), urea (13), water-soluble carbodiimides). Dry-wet cycles in the presence of  $Cu^{2+}$  and NaCl at 60–90 °C is an effective means to polymerize solid amino acids up to trimer (Rode, 1999). Oligomers of up to 100 monomers long have been synthesized from normal nucleotides (AMP and UMP) in a multilamellar lipid matrix in hydration–dehydration cycles (Rajamani et al., 2008; DeGuzman et al., 2014). Such a cycle also favors encapsulation of macromolecules (e.g., DNA) into lipid vesicles to form proto-cellular structures (Deamer and Barchfeld, 1982). For formamide (9), a dry heating at 100–160 °C in the presence of mineral catalysts generates various purines and pyrimidines including adenine, cytosine, guanine, uracil, and thymine (Saladino et al., 2012a,b). Formamide (9) might be concentrated easily by water evaporation in lagoons and on drying beaches because of the high boiling point (210 °C) with limited azeotropic effects (Saladino et al., 2009) as well as the high stability in water ( $t_{1/2}$  = 199 years at 25 °C and 7.3 days at 120 °C under neutral pH; Slebocka-Tilk et al., 2002). It is also noteworthy that an anhydrous condition favors phosphorylation of organic compounds (Table 3) and condensation of phosphate to polyphosphate (Keefe and Miller, 1996).

#### 5.6. Coupling with high energy reactions (gray arrows in Fig. 15)

Great successes have also been met for dehydration-condensation of biomolecules by coupling with high-energy reactions of activated compounds. Incubation of organic molecules with phosphide minerals (e.g.,  $Fe_3P$ ) in water generates various phosphorylated compounds as well as polyphosphates even at room temperature ( $\sim 20$  °C) (Pasek and Lauretta, 2005; Pasek et al., 2007). Oligonucleotides of up to  $\sim 50$ -mer have been synthesized by incubation of activated monomers (Fig. 15) in the presence of divalent metals (e.g.,  $Mg^{2+}$ ). Thereby synthesized oligomers are typically random mixtures of 2'-5', 3'-5', and 5'-5' linkages, whereas preferential formations of 3',5' phosphodiester bonds have been observed in the presence of montmorillonite for adenosine oligonucleotide (Ferris et al., 2004; Ferris, 2006). Polymerization of amino acids is enhanced by coupling with hydrolysis of COS via the formation of N-carboxyanhydride (NCA) (Huber and Wachtershauser, 1998; Leman et al., 2004). NCA also mediates condensation of amino acids and phosphate to form aminoacyl phosphate (Leman et al., 2006). Because the aminoacyl bond has a high hydrolysis energy, it might have served as an energy currency to drive proto-metabolic reactions.

#### 5.7. Heating-cooling cycles in water (green arrows in Fig. 15)

Once long RNA oligomers are formed, they might serve as a template on which new nucleotides form base pairs (A with U and C with G), resulting in double strands. Separation of double strand RNA requires a high-temperature heating, whereas activated nucleotides are unstable relative to hydrolysis under such conditions. Fluid circulation between cold and warm sides of a pond, located at a geothermal field in a cold region, could be a solution to this dilemma (Ricardo and Szostak, 2009). On the cold side, template-directed synthesis of oligonucleotides occurred on single RNA strands. On the hot side, heat broke the double helix into single strands. Repeated cycles of the template copying might have led to the initiation of an RNA-based replication system. Heating-cooling cycles also favor polymerizations of amino acids (Imai et al., 1999) and nucleotides (Ogasawara et al., 2000) although the efficiencies are low in both yield and length of polymers synthesized.

#### 5.8. Extraterrestrial input

Extraterrestrial objects (meteorites, comets and IDPs) could have delivered a wide variety of organic compounds on the primitive Earth, including amino acids, purines, pyrimidines, sugar-like compounds, and long-chain monocarboxylic acids with amphiphilic properties. They could have also supplied reactive inorganic nutrients such as ammonia and phosphide minerals. If this input was distributed evenly on the Earth's surface, the resultant surface concentrations would be negligibly low. However, the importance of the extraterrestrial materials is not merely the total amount, but their chemical characteristics relevant to the biochemical system. L-enantiomeric excess of amino acids found in carbonaceous chondrites is a clear indication for that relationship (Burton et al., 2012). L-amino acids and their dimers have been shown to catalyze ribose synthesis from glycolaldehyde (32) and glyceraldehyde (27) with the D-enantiomeric excess of up to 44% (Pizzarello and Weber, 2010). Mechanisms for the abiotic synthesis of L-enriched amino acids remain unknown. If their syntheses require conditions that cannot be realized on the Earth's surface (e.g., cosmic-ray irradiation under high vacuum), exogenous delivery of L-enriched amino acids should have been an essential process for the origin of biological homochirality.

The above discussion clearly indicates that no single setting can offer enough chemical and physical conditions for all the stages of chemical evolution. Instead, life's origin requires highly diverse and dynamic environments that are connected with each other to circulate reaction products and reactants. The same conclusion was reached in a recent review for prebiotic chemistry (Stueken et al., 2013). An advantage of the present article is the capability of drawing possible links between geochemical conditions and each reaction step. In the early stages of chemical evolution an alkaline and  $H_2$ -rich environment appears to be a good reaction place. Such conditions have been observed in serpentine-hosted hydrothermal systems on the present Earth (McCollom and Seewald, 2013). So far, much attention has been paid to deep-sea hydrothermal vents as the site of serpentinization (Kelley et al., 2001, 2005). Similar systems have also been found in several terrestrial environments (e.g., Suda et al., 2014). In contrast to deep-sea vents, terrestrial geothermal fields enable the involvement of organic compounds that are produced through atmospheric reaction (Mulikidjanian et al., 2012a). Extraterrestrial input of biologically relevant compounds and elements are also available. This input can be concentrated much more readily on the terrestrial fields than in the ocean; if a shallow pond with an average depth of 30–40 cm is considered ( $\sim 10,000$  times shallower than the modern ocean level), the same flux from the atmosphere results in a much higher



concentration in the pond than in the ocean by a factor of  $\sim 10,000$ . If the geothermal field is located in a cold region, partial freezing of the pond could temporarily shelter reactive compounds from hydrolysis, leading to their accumulation to make the building blocks of life. Beneath the pond, geothermal fluids would leach a variety of elements from rocks into the water. Depending on the rock compositions, fluid–rock interactions could provide vital elements (e.g., K and P) and catalytic metals for prebiotic reactions (e.g.,  $\text{Cu}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Pb}^{2+}$ ). If the fluids react with atmospheric  $\text{CO}_2$  with the pressure as high as 1 bar while maintaining a higher than neutral pH, dissolved metals precipitate as carbonate minerals (e.g.,  $\text{MgCO}_3$ ). Depletion of metals allows for the stable formation of fatty acid vesicles and dissolution of phosphate minerals. If the Hadean terrestrial environments were more reducing than the present-day conditions, with the oxygen fugacity being of a similar level to the IW buffer (Yang et al., 2014), volcanic exhalations could have provided reactive reducing gases such as  $\text{NH}_3$ ,  $\text{HCN}$ ,  $\text{H}_2\text{CO}$ ,  $\text{COS}$  (Mikhail and Sverjensky, 2014; Yang et al., 2014), and allowed deposition of P as phosphide minerals (e.g.,  $\text{Fe}_3\text{P}$ ). If the continent partially differentiated granitic crust, quintessential crustal elements such as boron could have been available in high concentrations (Grew et al., 2011). Moreover, terrestrial geothermal fields are conducive to dehydration, leading to polymerization through hydration–dehydration cycles. During the evaporation process, solution pH tends to decrease owing to rising concentrations of dissolved species (Li et al., 2008), thereby favorable conditions for peptide bond formation (Rode and Schwendinger, 1990) and nucleotide oligomerization (Rajamani et al., 2008) are satisfied even when the solution is not originally acidic. Hydration–dehydration cycles can also lead to encapsulation of biomacromolecules into lipid membranes (Deamer and Barchfeld, 1982). If a geothermal pool is partly covered by ice, the temperature gradient within the pool would cause fluid circulation between the cold and warm sides, so that RNA strands can undergo repeated cycles of growth and division.

## 6. Concluding remarks

Now we could figure out the geochemical inventory necessary to drive all stages of chemical evolution, ranging from nutrient acquisition, organic synthesis, accumulation, polymerization, and their interactions. What geological processes could offer environments that meet all of the requirements? Were such processes occurring on the Hadean Earth? If so, are the occurrences ubiquitous phenomena or rare on other planets in the universe? These questions need to be tackled by future theoretical and experimental investigations.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.gsf.2017.07.007>.

## References

Acevedo, O.L., Orgel, L.E., 1987. Non-enzymatic transcription of an oligodeoxynucleotide 14 residues long. *Journal of Molecular Biology* 197, 187–193.

- Adamala, K., Szostak, J.W., 2013a. Competition between model protocells driven by an encapsulated catalyst. *Nature Chemistry* 5, 495–501.
- Adamala, K., Szostak, J.W., 2013b. Nonenzymatic template-directed RNA synthesis inside model protocells. *Science* 342, 1098–1100.
- Adcock, C.T., Hausrath, E.M., Forster, P.M., 2013. Readily available phosphate from minerals in early aqueous environments on Mars. *Nature Geoscience* 6, 824–827.
- Alexander, C.M.O.D., Fogel, M., Yabuta, H., Cody, G.D., 2007. The origin and evolution of chondrites recorded in the elemental and isotopic compositions of their macromolecular organic matter. *Geochimica et Cosmochimica Acta* 71, 4380–4403.
- Alexander, C.M.O.D., Newsome, S.D., Fogel, M.L., Nittler, L.R., Busemann, H., Cody, G.D., 2010. Deuterium enrichments in chondritic macromolecular material – implications for the origin and evolution of organics, water and asteroids. *Geochimica et Cosmochimica Acta* 74, 4417–4437.
- Allen, W.V., Ponnampuram, C., 1967. A possible prebiotic synthesis of monocarboxylic acids. *Currents in Modern Biology* 1, 24–28.
- Alt, J.C., Shanks, W.C., 2003. Serpentinization of abyssal peridotites from the MARK area, Mid-Atlantic Ridge: sulfur geochemistry and reaction modeling. *Geochimica et Cosmochimica Acta* 67, 641–653.
- Altmann, E., Altmann, K.H., Nebel, K., Mutter, M., 1988. Conformational studies on host-guest peptides containing chiral  $\alpha$ -methyl- $\alpha$ -amino acids. *International Journal of Peptide Research* 32, 344–351.
- Amend, J.P., Shock, E.L., 1998. Energetics of amino acid synthesis in hydrothermal ecosystems. *Science* 281, 1659–1662.
- Anastasi, C., Crowe, M.A., Powner, M.W., Sutherland, J.D., 2006. Direct assembly of nucleoside precursors from two- and three-carbon units. *Angewandte Chemie International Edition* 45, 6176–6179.
- Anders, E., 1989. Pre-biotic organic matter from comets and asteroids. *Nature* 342, 255–257.
- Apel, C.L., Deamer, D.W., Mautner, M.N., 2002. Self-assembled vesicles of monocarboxylic acids and alcohols: conditions for stability and for the encapsulation of biopolymers. *Biochimica et Biophysica Acta* 1559, 1–9.
- Aubrey, A.D., Cleaves, H.J., Bada, J.L., 2009. The role of submarine hydrothermal systems in the synthesis of amino acids. *Origins of Life and Evolution of the Biosphere* 39, 91–108.
- Bada, J.L., 2004. How life began on Earth: a status report. *Earth and Planetary Science Letters* 226, 1–15.
- Bada, J.L., 2013. New insights into prebiotic chemistry from Stanley Miller's spark discharge experiments. *Chemical Society Reviews* 42, 2186–2196.
- Bada, J.L., Lazcano, A., 2002. Some like it hot, but not the first biomolecules. *Science* 296, 1982–1983.
- Bada, J.L., Lazcano, A., 2003. Prebiotic soup—revisiting the Miller experiment. *Science* 300, 745–746.
- Bada, J.L., Bigham, C., Miller, S.L., 1994. Impact melting of frozen oceans on the early Earth: implications for the origin of life. *Proceedings of the National Academy of Sciences of the United States of America* 91, 1248–1250.
- Barge, L.M., Kee, T.P., Doloboff, I.J., Hampton, J.M.P., Ismail, M., Poukashanian, M., Zeytounian, J., Baum, M.M., Moss, J.A., Lin, C.K., Kidd, R.D., Kanik, I., 2014. The fuel cell model of abiogenesis: a new approach to origin-of-life simulations. *Astrobiology* 14, 254–270.
- Bar-Nun, A., Bar-Nun, N., Bauer, S.H., Sagan, C., 1970. Shock synthesis of amino acids in simulated primitive environments. *Science* 168, 470–472.
- Barks, H.L., Buckley, R., Grieves, G.A., Mauro, E.D., Hud, N.V., Orlando, T.M., 2010. Guanine, adenine, and hypoxanthine production in UV-irradiated formamide solutions: relaxation of the requirements for prebiotic purine nucleobase formation. *ChemBioChem* 11, 1240–1243.
- Baross, J.A., Hoffman, S.E., 1985. Submarine hydrothermal vents and associated gradient environments as sites for the origin and evolution of life. *Origins of Life* 15, 327–345.
- Bartel, D.P., Szostak, J.W., 1993. Isolation of new ribozymes from a large pool of random sequences. *Science* 261, 1411–1418.
- Basiuk, V.A., Gromovoy, T.Y., Golovaty, V.G., Glukhoy, A.M., 1990–1991. Mechanisms of amino acid polycondensation on silica and alumina surfaces. *Origins of Life and Evolution of the Biosphere* 20, 483–498.
- Battistuzzi, F.U., Feijao, A., Hedges, S.B., 2004. A genomic timescale of prokaryote evolution: insights into the origin of methanogenesis, phototrophy, and the colonization of land. *BMC Evolutionary Biology* 4, 44.
- Bean, H.D., Sheng, Y., Collins, J.P., Anet, F.A.L., Leszczynski, J., Hud, N.V., 2007. Formation of a  $\beta$ -pyrimidine nucleoside by a free pyrimidine base and ribose in a plausible prebiotic reaction. *Journal of the American Chemical Society* 129, 9556–9557.
- Bebout, G.E., Fogel, M.L., Cartigny, P., 2013. Nitrogen: highly volatile yet surprisingly compatible. *Elements* 9, 333–338.
- Beck, A., Orgel, L.E., 1965. The formation of condensed phosphate in aqueous solution. *Proceedings of the National Academy of Sciences of the United States of America* 54, 664–667.
- Beck, A., Lohrmann, R., Orgel, L.E., 1967. Phosphorylation with inorganic phosphates at moderate temperatures. *Science* 157, 952.
- Becker, R.S., Hong, K., Hong, J.H., 1974. Hot hydrogen atoms reactions of interest in molecular evolution and interstellar chemistry. *Journal of Molecular Evolution* 4, 157–172.
- Benner, S.A., 2004. Understanding nucleic acids using synthetic chemistry. *Accounts of Chemical Research* 37, 784–797.
- Benner, S.A., Kim, H.J., Carrigan, M.A., 2012. Asphalt, water, and the prebiotic synthesis of ribose, ribonucleosides, and RNA. *Accounts of Chemical Research* 45, 2025–2034.



- Bernhardt, H., 2012. The RNA world hypothesis: the worst theory of the early evolution of life (except for all the others). *Biology Direct* 7, 23.
- Bernhardt, H.S., Tate, W.P., 2012. Primordial soup or vinaigrette: did the RNA world evolve at acidic pH? *Biology Direct* 7, 4.
- Bickley, R.I., Vishwanathan, V., 1979. Photocatalytic induced fixation of molecular nitrogen by near UV radiation. *Nature* 280, 306–308.
- Biron, J.P., Pascal, R., 2004. Amino acid N-carboxyanhydrides: activated peptide monomers behaving as phosphate-activating agents in aqueous solution. *Journal of the American Chemical Society* 126, 9198–9199.
- Biron, J.P., Parkes, A.L., Pascal, R., Sutherland, J.D., 2005. Expeditious, potentially primordial, aminoacylation of nucleotides. *Angewandte Chemie International Edition* 44, 6731–6734.
- Bishop, M.J., Lohrmann, R., Orgel, L.E., 1972. Prebiotic phosphorylation of thymidine at 65 °C in simulated desert conditions. *Nature* 237, 162–164.
- Blain, J.C., Szostak, J.W., 2014. Progress toward synthetic cells. *Annual Review of Biochemistry* 83, 11.1–11.26.
- Botta, O., Martins, Z., Ehrenfreund, P., 2007. Amino acids in Antarctic CM1 meteorites and their relationship to other carbonaceous chondrites. *Meteoritics and Planetary Science* 42, 81–92.
- Braakman, R., Smith, E., 2013. The compositional and evolutionary logic of metabolism. *Physical Biology* 10, 011001.
- Brack, A., Spach, G., 1981. Enantiomer enrichment in early peptides. *Origins of Life* 11, 135–142.
- Brandes, J.A., Hazen, R.M., Yoder Jr., H.S., 2008. Inorganic nitrogen reduction and stability under simulated hydrothermal conditions. *Astrobiology* 8, 1113–1126.
- Breslow, R., 1959. On the mechanism of the formose reaction. *Tetrahedron Letters* 21, 22–26.
- Bridson, P.K., Orgel, L.E., 1980. Catalysis of accurate poly(C)-directed synthesis of 3'-5'-linked oligoguanylates by  $Zn^{2+}$ . *Journal of Molecular Biology* 144, 567–577.
- Brinton, K.L.F., Engrand, C., Glavin, D.P., Bada, J.L., Maurette, M., 1998. A search for extraterrestrial amino acids in carbonaceous Antarctic micrometeorites. *Origins of Life and Evolution of the Biosphere* 28, 413–424.
- Britvin, S.N., Murashko, M.N., Vapnik, Y., Polekhovsky, Y.S., Krivovichev, S.V., 2015. Earth's phosphides in Levant and insights into the source of Archean prebiotic phosphorus. *Scientific Reports* 5, 8355.
- Bryant, D.E., Greenfield, D., Walshaw, R.D., Johnson, B.R.G., Herschy, B., Smith, C.L., Wang, L., Pasek, M.A., Kee, T.P., 2009. Electrochemical studies of iron meteorites: phosphorus redox chemistry on the early Earth. *Internal Journal of Astrobiology* 8, 27–36.
- Bryant, D.E., Greenfield, D., Walshaw, R.D., Johnson, B.R.G., Herschy, B., Smith, C., Pasek, M.A., Telford, R., Scowen, I., Munshi, T., Edwards, H.G.M., Cousins, C.R., Crawford, I.A., Kee, T.P., 2013. Hydrothermal modification of the Sikhote-Alin iron meteorite under low pH geothermal environments. A plausibly prebiotic route to activated phosphorus on the early Earth. *Geochimica et Cosmochimica Acta* 109, 90–112.
- Buc, C.R., Ford, J.H., Wise, E.C., 1945. An improved synthesis of  $\beta$ -alanine. *Journal of the American Chemical Society* 67, 92–94.
- Budin, I., Szostak, J.W., 2011. Physical effects underlying the transition from primitive to modern cell membranes. *Proceedings of the National Academy of Sciences of the United States of America* 108, 5249–5254.
- Budin, I., Debnath, A., Szostak, J.W., 2012. Concentration-driven growth of model protocell membranes. *Journal of the American Chemical Society* 134, 20812–20819.
- Burns, S., Hargreaves, J.S.J., Hunter, S.M., 2007. On the use of methane as a reductant in the synthesis of transition metal phosphides. *Catalysis Communications* 8, 931–935.
- Burton, A.S., Stern, J.C., Elsila, J.E., Glavin, D.P., Dworkin, J.P., 2012. Understanding prebiotic chemistry through the analysis of extraterrestrial amino acids and nucleobases in meteorites. *Chemical Society Reviews* 41, 5459–5472.
- Burton, A.S., Elsila, J.E., Hein, J.E., Glavin, D.P., Dworkin, J.P., 2013. Extraterrestrial amino acids identified in metal-rich CH and CB carbonaceous chondrites from Antarctica. *Meteoritics & Planetary Science* 48, 390–402.
- Burton, A.S., Grunsfeld, S., Elsila, J.E., Glavin, D.P., Dworkin, J.P., 2014. The effects of parent-body hydrothermal heating on amino acid abundances in CI-like chondrites. *Polar Science* 8, 255–263.
- Butlerow, A., 1861. Formation synthetique d'une substance sucrée. *Comptes Rendus de l'Académie des Sciences* 63, 145–147.
- Cairns-Smith, A.G.C., 1982. *Genetic Takeover*. Cambridge University Press, New York.
- Cairns-Smith, A.G., Ingram, P., Walker, G.L., 1972. Formose production by minerals: possible relevance to the origin of life. *Journal of Theoretical Biology* 35, 601–604.
- Callahan, M.P., Smith, K.E., Cleaves, H.J., Ruzicka, J., Stern, J.C., Glavin, D.P., House, C.H., Dworkin, J.P., 2011. Carbonaceous meteorites contain a wide range of extraterrestrial nucleobases. *Proceedings of the National Academy of Sciences of the United States of America* 108, 13995–13998.
- Canfield, D.E., Glazer, A.N., Falkowski, P.G., 2010. The evolution and future of Earth's nitrogen cycle. *Science* 330, 192–196.
- Canup, R.M., Asphaug, E., 2001. Origin of the moon in a giant impact near the end of the Earth's formation. *Nature* 412, 708–712.
- Chapin, F.S., Matson, P.A., Mooney, H.A., 2002. *Principles of Terrestrial Ecosystem Ecology*. Springer, New York.
- Charlou, J.L., Donval, J.P., Fouquet, Y., Jean-Baptiste, P., Holm, N., 2002. Geochemistry of high  $H_2$  and  $CH_4$  vent fluids issuing from ultramafic rocks at the Rainbow hydrothermal field (36°14'N, MAR). *Chemical Geology* 191, 345–359.
- Chen, I.A., Szostak, J.W., 2004. Membrane growth can generate a transmembrane pH gradient in fatty acid vesicles. *Proceedings of the National Academy of Sciences of the United States of America* 101, 7965–7970.
- Chen, I.A., Walde, P., 2010. From self-assembled vesicles to protocells. *Cold Spring Harbor Perspectives in Biology* 2, a002170.
- Chen, I.A., Roberts, R.W., Szostak, J.W., 2004. The emergence of competition between model protocells. *Science* 305, 1474–1476.
- Chen, I.A., Salehi-Ashtiani, K., Szostak, J.W., 2005. RNA catalysis in modern protocell vesicles. *Journal of the American Chemical Society* 127, 13213–13219.
- Chen, J.L., Dishler, A.L., Kennedy, S.D., Yildirim, I., Liu, B., Turner, D.H., Serra, M.J., 2012. Testing the nearest neighbor model for canonical RNA base pairs: revision of GU parameters. *Biochemistry* 51, 3508–3522.
- Cheng, C., Fan, C., Wan, R., Tong, C., Miao, Z., Chen, J., Zhao, Y., 2002. Phosphorylation of adenosine with trimetaphosphate under simulated prebiotic conditions. *Origins of Life and Evolution of the Biosphere* 32, 219–224.
- Chittenden, G.J.F., Schwartz, A.W., 1976. Possible pathway for prebiotic uracil synthesis by photodehydrogenation. *Nature* 263, 350–351.
- Chung, N.M., Lohrmann, R., Orgel, L.E., 1971. The mechanism of the trimetaphosphate-induced peptide synthesis. *Tetrahedron* 27, 1205–1210.
- Chyba, C., Sagan, C., 1992. Endogenous production, exogenous delivery and impact-shock synthesis of organic molecules: an inventory for the origins of life. *Nature* 355, 125–132.
- Chyba, C.F., Thomas, P.J., Brookshaw, L., Sagan, C., 1990. Cometary delivery of organic molecules to the early Earth. *Science* 249, 366–373.
- Civis, S., Juha, L., Babankova, D., Cvacka, J., Frank, O., Jehlicka, J., Kralikova, B., Krasa, J., Kubat, P., Muck, A., Pfeifer, M., Skala, J., Ullschmied, J., 2004. Amino acid formation induced by high-power laser in  $CO_2/CO-N_2-H_2O$  gas mixtures. *Chemical Physics Letters* 386, 169–173.
- Cleaves, H.J., 2008. The prebiotic geochemistry of formaldehyde. *Precambrian Research* 164, 111–118.
- Cleaves, H.J., Nelson, K.E., Miller, S.L., 2006. The prebiotic synthesis of pyrimidines in frozen solution. *Naturwissenschaften* 93, 228–231.
- Cleaves, H.J., Chalmers, J.H., Lazcano, A., Miller, S.L., Bada, J.L., 2008. A reassessment of prebiotic organic synthesis in neutral planetary atmospheres. *Origins of Life and Evolution of the Biosphere* 38, 105–115.
- Cleaves, H.J., Scott, A.M., Hill, F.C., Leszczynski, J., Sahai, N., Hazen, R., 2012. Mineral-organic interfacial processes: potential roles in the origins of life. *Chemical Society Reviews* 41, 5502–5525.
- Cockerill, A.F., Harrison, D.R.G., Osborne, D.J., Prime, D.M., Ross, W.J., Todd, A., Verge, J.P., 1976. An improved synthesis of 2-amino-1,3-oxazoles under basic catalysis. *Synthesis* 591–593.
- Cody, G.D., Alexander, C.M.O.D., 2005. NMR studies of chemical structural variation of insoluble organic matter from different carbonaceous chondrite groups. *Geochimica et Cosmochimica Acta* 69, 1085–1097.
- Cody, G.D., Boctor, N.Z., Filley, T.R., Hazen, R.M., Scott, J.H., Sharma, A., Yoder, H.S., 2000. Primordial carbonylated iron-sulfur compounds and the synthesis of pyruvate. *Science* 289, 1337–1340.
- Constanzo, G., Saladino, R., Crestini, C., Ciciriello, F., Mauro, E.D., 2007. Nucleoside phosphorylation by phosphate minerals. *The Journal of Biological Chemistry* 282, 16729–16735.
- Corliss, J.B., Dymond, J., Gordon, L.I., Edmond, J.M., von Herzen, R.P., Ballard, R.D., Green, K.K., William, D., Bainbridge, A., Crane, K., van Andel, T.H., 1979. Submarine thermal springs on the Galapagos Rift. *Science* 203, 1073–1083.
- Costanzo, G., Pino, S., Ciciriello, F., Mauro, E.D., 2009. Generation of long RNA chains in water. *Journal of Biological Chemistry* 284, 33206–33216.
- Costanzo, G., Saladino, R., Botta, G., Giorgi, A., Scipioni, A., Pino, S., Mauro, E.D., 2012. Generation of RNA molecules by a base-catalysed click-like reaction. *ChemBioChem* 13, 999–1008.
- Coumou, D., Driesner, T., Heinrich, C.A., 2008. The structure and dynamics of mid-ocean ridge hydrothermal systems. *Science* 321, 1825–1828.
- Cox, J.S., Seward, T.M., 2007. The reaction kinetics of alanine and glycine under hydrothermal conditions. *Geochimica et Cosmochimica Acta* 71, 2264–2284.
- Crick, F.H.C., 1968. The origin of the genetic code. *Journal of Molecular Biology* 38, 367–379.
- Cronin, J.R., Pizzarello, S., 1986. Amino acids of the Murchison meteorite. III. Seven carbon acyclic primary  $\alpha$ -amino alkanic acids. *Geochimica et Cosmochimica Acta* 50, 2419–2427.
- Cronin, J.R., Pizzarello, S., 1997. Enantiomeric excesses in meteoritic amino acids. *Science* 275, 951–955.
- De Graaf, R.M., Schwartz, A.W., 2000. Reduction and activation of phosphate on the primitive Earth. *Origins of Life and Evolution of the Biosphere* 30, 405–410.
- De Graaf, R.M., Schwartz, A.W., 2005. Thermal synthesis of nucleoside H-phosphonates under mild conditions. *Origins of Life and Evolution of the Biosphere* 35, 1–10.
- Deamer, D.W., 1985. Boundary structures are formed by organic components of the Murchison carbonaceous chondrite. *Nature* 317, 792–794.
- Deamer, D.W., Barchfeld, G.L., 1982. Encapsulation of macromolecules by lipid vesicles under simulated prebiotic conditions. *Journal of Molecular Evolution* 18, 203–206.
- Deamer, D., Singaram, S., Rajamani, S., Kompanichenko, V., Guggenheim, S., 2006. Philosophical Transactions of the Royal Society B 361, 1809–1818.
- Decker, P., Schweer, H., Pohlmann, R., Bioids, X., 1982. Identification of formose sugars, presumably prebiotic metabolites, using capillary gas chromatography/gas chromatography-mass spectrometry of n-butoxime trifluoroacetates on OV-225. *Journal of Chromatography* 224, 281–291.

- DeGuzman, V., Vercoutere, W., Shenasa, H., Deamer, D., 2014. Generation of oligonucleotides under hydrothermal conditions by non-enzymatic polymerization. *Journal of Molecular Evolution* 78, 251–262.
- Delano, J.W., 2001. Redox history of the Earth's interior since ~3900 Ma: implications for prebiotic molecules. *Origins of Life and Evolution of the Biosphere* 31, 311–341.
- Delsemme, A.H., 1991. Nature and history of the organic compounds in comets: an astrophysical review. In: Newburn, R.L., Neugenbauer, M., Rahe, J. (Eds.), *Comets in the Post-Halley Era*, vol. 1. Kluwer Academic, Dordrecht, pp. 377–428.
- Dickson, K.S., Burns, C.M., Richardson, J.P., 2000. Determination of the free-energy change for repair of a DNA phosphodiester bond. *The Journal of Biological Chemistry* 275, 15828–15831.
- Ding, P.Z., Kawamura, K., Ferris, J.P., 1996. Oligomerization of uridine phosphorimidazolides on montmorillonite: a model for the prebiotic synthesis of RNA on minerals. *Origins of Life and Evolution of the Biosphere* 26, 151–171.
- Dohm, J.M., Maruyama, S., 2015. Habitable trinity. *Geoscience Frontiers* 6, 95–101.
- Doring, A., Schulzke, C., 2010. Tungsten's redox potential is more temperature sensitive than that of molybdenum. *Dalton Transactions* 39, 5623–5629.
- Dorr, M., Kassbohrer, J., Grunert, R., Kreisel, G., Brand, W.A., Werner, R.A., Geilmann, H., Apfel, C., Robl, C., Weigrand, W., 2003. A possible prebiotic formation of ammonia from dinitrogen on iron sulfide surfaces. *Angewandte Chemie International Edition* 42, 1540–1543.
- Drew, K.N., Zajicek, J., Bondo, G., Bose, B., Serianni, A.S., 1998. <sup>13</sup>C-labeled aldopentoses: detection and quantitation of cyclic and acyclic forms by heteronuclear 1D and 2D NMR spectroscopy. *Carbohydrate Research* 307, 199–209.
- Dworkin, J.P., Deamer, D.W., Sandford, S.A., Allamandola, L.J., 2001. Self-assembling amphiphilic molecules: synthesis in simulated interstellar/precometary ices. *Proceedings of the National Academy of Sciences of the United States of America* 98, 815–819.
- Elsila, J.E., Glavin, D.P., Dworkin, J.P., 2009. Cometary glycine detected in samples returned by Stardust. *Meteoritics & Planetary Science* 44, 1323–1330.
- Emmanuel, S., Berkowitz, B., 2006. Suppression and stimulation of seafloor hydrothermal convection by exothermic mineral hydration. *Earth and Planetary Science Letters* 243, 657–668.
- Engel, M.H., Macko, S.A., 1997. Isotopic evidence for extraterrestrial non-racemic amino acids in the Murchison meteorite. *Nature* 389, 265–268.
- Engelhart, A.E., Powner, M.W., Szostak, J.W., 2013. Functional RNAs exhibit tolerance for non-heritable 2'-5' vs. 3'-5' backbone heterogeneity. *Nature Chemistry* 5, 390–394.
- Ertem, G., Ferris, J.P., 1996. Synthesis of RNA oligomers on heterogeneous templates. *Nature* 379, 238–240.
- Ertem, G., Ferris, J.P., 1997. Template-directed synthesis using the heterogeneous templates produced by montmorillonite catalysis. A possible bridge between the prebiotic and RNA world. *Journal of American Chemical Society* 119, 7197–7201.
- Essene, E.J., Fisher, D.C., 1986. Lightning strike fusion: extreme reduction and metal-silicate liquid immiscibility. *Science* 234, 189–193.
- Etaix, E., Orgel, L.E., 1978. Phosphorylation of nucleosides in aqueous solution using trimetaphosphate: formation of nucleoside triphosphates. *Journal of Carbohydrates, Nucleosides, Nucleotides* 5, 91–110.
- Ferris, J.P., 2002. Montmorillonite catalysis of 30–50 mer oligonucleotides: laboratory demonstration of potential steps in the origin of the RNA world. *Origins of Life and Evolution of the Biosphere* 32, 311–332.
- Ferris, J.P., 2006. Montmorillonite-catalyzed formation of RNA oligomers: the possible role of catalysis in the origins of life. *Philosophical Transactions of the Royal Society B* 361, 1777–1786.
- Ferris, J.P., Ertem, G., 1992. Oligomerization of ribonucleotides on montmorillonite: reaction of the 5'-phosphorimidazolide of adenosine. *Science* 257, 1387–1389.
- Ferris, J.P., Ertem, G., 1993. Montmorillonite catalysis of RNA oligomer formation in aqueous solution. A model for the prebiotic formation of RNA. *Journal of the American Chemical Society* 115, 12270–12275.
- Ferris, J.P., Joshi, P.C., 1979. Chemical evolution. 33. Photochemical decarboxylation of orotic acid, orotidine, and orotidine 5'-phosphate. *The Journal of Organic Chemistry* 44, 2133–2137.
- Ferris, J.P., Sanchez, R.A., Orgel, L.E., 1968. Studies in prebiotic synthesis III. Synthesis of pyrimidines from cyanoacetylene and cyanate. *Journal of Molecular Biology* 33, 693–704.
- Ferris, J.P., Zamek, O.S., Altbuch, A.M., Freiman, H., 1974. Chemical evolution XVIII. Synthesis of pyrimidines from guanidine and cyanoacetaldehyde. *Journal of Molecular Evolution* 3, 301–309.
- Ferris, J.P., Joshi, P.C., Edelson, E.H., Lawless, J.G., 1978. HCN: a plausible source of purines, pyrimidines and amino acids on the primitive Earth. *Journal of Molecular Evolution* 11, 293–311.
- Ferris, J.P., Ertem, G., Agarwal, V., 1989. Mineral catalysis of the formation of dimers of 5'-AMP in aqueous solution: the possible role of montmorillonite clays in the prebiotic synthesis of RNA. *Origins of Life and Evolution of the Biosphere* 19, 165–178.
- Ferris, J.P., Hill Jr., A.R., Liu, R., Orgel, L.E., 1996. Synthesis of long prebiotic oligomers on mineral surfaces. *Nature* 381, 59–61.
- Ferris, J.P., Joshi, P.C., Wang, K.J., Miyakawa, S., Huang, W., 2004. Catalysis in prebiotic chemistry: application to the synthesis of RNA oligomers. *Advances in Space Research* 33, 100–105.
- Fischer, F., Tropisch, H., 1926. The direct synthesis of petroleum hydrocarbons with standard pressure. *Berichte der Deutschen Chemischen Gesellschaft* 59, 830–831.
- Fitz, D., Reiner, H., Rode, B.M., 2007. Chemical evolution toward the origin of life. *Pure and Applied Chemistry* 79, 2101–2117.
- Fitz, D., Jakschitz, T., Rode, B.M., 2008. The catalytic effect of L- and D-histidine on alanine and lysine peptide formation. *Journal of Inorganic Biochemistry* 102, 2097–2102.
- Flores, J.J., Leckie, J.O., 1973. Peptide formation mediated by cyanate. *Nature* 244, 435–437.
- Foustoukos, D.I., Seyfried, W.E., 2004. Hydrocarbons in hydrothermal vent fluids: the role of chromium-bearing catalysts. *Science* 304, 1002–1005.
- Fox, S.W., 1964. Thermal polymerization of amino-acids and production of formed microparticles on lava. *Nature* 201, 336–337.
- Fox, S.W., Harada, K., 1958. Thermal copolymerization of amino acids to a product resembling protein. *Science* 128, 1214.
- Fox, S.W., Harada, K., 1960. The thermal copolymerization of amino acids common to protein. *Journal of the American Chemical Society* 82, 3745–3751.
- Fox, S.W., Harada, K., 1961. Synthesis of uracil under conditions of a thermal model of prebiological chemistry. *Science* 133, 1923–1924.
- Fox, S.W., Windsor, C.R., 1970. Synthesis of amino acids by the heating of formaldehyde and ammonia. *Science* 170, 984–986.
- Freier, S.M., Kierzek, R., Jaeger, J.A., Sugimoto, N., Caruthers, M.H., Neilson, T., Turner, D.H., 1986. Improved free-energy parameters for predictions of RNA duplex stability. *Proceedings of the National Academy of Sciences of the United States of America* 83, 9373–9377.
- Friedmann, N., Miller, S.L., 1969a. Synthesis of valine and isoleucine in primitive Earth conditions. *Nature* 221, 1152–1153.
- Friedmann, N., Miller, S.L., 1969b. Phenylalanine and tyrosine synthesis under primitive Earth conditions. *Science* 166, 766–767.
- Friel, J.J., Goldstein, J.I., 1976. An experimental study of phosphate reduction and phosphorus-bearing lunar metal particulates. *Proceeding of 7th Lunar and Planetary Science Conference* 751–775.
- Frost, D.J., McCammon, C.A., 2008. The redox state of Earth's mantle. *Annual Review of Earth and Planetary Sciences* 36, 389–420.
- Fruh-Green, G.L., Kelley, D.S., Bernasconi, S.M., Karson, J.A., Ludwig, K.A., Butterfield, D.A., Baschi, C., Proskurowski, G., 2003. 30,000 years of hydrothermal activity at the Lost City vent field. *Science* 301, 495–498.
- Fuller, W.D., Sanchez, R.A., Orgel, L.E., 1972a. Studies in prebiotic synthesis VI. Synthesis of purine nucleosides. *Journal of Molecular Biology* 67, 25–33.
- Fuller, W.D., Sanchez, R.A., Orgel, L.E., 1972b. Studies in prebiotic synthesis VII. Solid-state synthesis of purine nucleosides. *Journal of Molecular Evolution* 1, 249–257.
- Furukawa, Y., Sekine, T., Oba, M., Kakegawa, T., Nakazawa, H., 2009. Biomolecule formation by oceanic impacts on early Earth. *Nature Geoscience* 2, 62–66.
- Furukawa, Y., Otake, T., Ishiguro, T., Nakazawa, H., Kakegawa, T., 2012. Abiotic formation of valine peptides under conditions of high temperature and high pressure. *Origins of Life and Evolution of the Biosphere* 42, 519–531.
- Gabel, N.W., Ponnamperna, C., 1967. Model for origin of monosaccharides. *Nature* 216, 453–455.
- Gilbert, W., 1986. The RNA world. *Nature* 319, 618.
- Glavin, D.P., Dworkin, J.P., 2009. Enrichment of the amino acid L-isovaline by aqueous alteration on CI and CM meteorite parent bodies. *Proceedings of the National Academy of Sciences of the United States of America* 106, 5487–5492.
- Glavin, D.P., Matrajt, G., Bada, J.L., 2004. Re-examination of amino acids in Antarctic micrometeorites. *Advances in Space Research* 33, 106–113.
- Glavin, D.P., Dworkin, J.P., Aubrey, A., Botta, O., Doty, J.H., Martins, Z., Bada, J.L., 2006. Amino acid analysis of Antarctic CM2 meteorites using liquid chromatography–time of flight–mass spectrometry. *Meteoritics and Planetary Science* 41, 889–902.
- Glavin, D.P., Callahan, M.P., Dworkin, J.P., Elsila, J.E., 2011. The effects of parent body processes on amino acids in carbonaceous chondrites. *Meteoritics & Planetary Science* 45, 1948–1972.
- Glindeemann, D., De Graaf, R.M., Schwartz, A.W., 1999. Chemical reduction of phosphate on the primitive Earth. *Origins of Life and Evolution of the Biosphere* 29, 555–561.
- Goldblatt, C., Claire, M.W., Lenton, T.M., Matthews, A.J., Watson, A.J., Zahnle, K.J., 2009. Nitrogen-enhanced greenhouse warming on early Earth. *Nature Geoscience* 2, 891–896.
- Goldman, N., Reed, E.J., Fried, L.E., William Kuo, I.F., Maiti, A., 2010. Synthesis of glycine-containing complexes in impacts of comets on early Earth. *Nature Chemistry* 2, 949–954.
- Grew, E.S., Bada, J.L., Hazen, R.M., 2011. Borate minerals and origin of the RNA world. *Origins of Life and Evolution of the Biosphere* 41, 307–316.
- Groth, W.E., Weyssenhoff, H.V., 1960. Photochemical formation of organic compounds from mixtures of simple gases. *Planetary and Space Science* 2, 79–85.
- Gruber, N., Galloway, J.N., 2008. An earth-system perspective of the global nitrogen cycle. *Nature* 451, 293–296.
- Guerrier-Takada, C., Gardiner, K., Marsh, T., Pace, N., Altman, S., 1983. The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35, 849–857.
- Guzman, M.I., Martin, S.T., 2009. Prebiotic metabolism: production by mineral photoelectrochemistry of  $\alpha$ -ketocarboxylic acids in the reductive tricarboxylic acid cycle. *Astrobiology* 9, 833–842.
- Hagenbuch, P., Kervio, E., Hochgesand, A., Plutowski, U., Richert, C., 2005. Chemical primer extension: efficiency determining single nucleotides in DNA. *Angewandte Chemie International Edition* 44, 6588–6592.
- Halmann, M., Sanchez, R.A., Orgel, L.E., 1969. Phosphorylation of D-ribose in aqueous solution. *The Journal of Organic Chemistry* 34, 3702–3703.

- Han, C., Geng, J., Xie, X., Wang, X., Ren, H., Gao, S., 2012. Detection of phosphite in a eutrophic freshwater lake by suppressed conductivity ion chromatography. *Environmental Science & Technology* 46, 10667–10674.
- Han, C., Geng, J., Ren, H., Gao, S., Xie, X., Wang, X., 2013. Phosphite in sedimentary interstitial water of lake Taihu, a large eutrophic shallow lake in China. *Environmental Science & Technology* 47, 5679–5685.
- Hanczyc, M.M., Fujikawa, S.M., Szostak, J.W., 2003. Experimental models of primitive cellular compartments: encapsulation, growth, and division. *Science* 302, 618–622.
- Hands Schuh, G.J., Lohrmann, R., Orgel, L.E., 1973. The effect of  $Mg^{2+}$  and  $Ca^{2+}$  on urea-catalyzed phosphorylation reactions. *Journal of Molecular Evolution* 2, 251–262.
- Harada, K., Suzuki, S., 1976. The new synthesis of uracil and 1,3-dimethyluracil. *Tetrahedron Letters* 17, 2321–2322.
- Hargreaves, W.R., Mulvihill, S.J., Deamer, D.W., 1977. Synthesis of phospholipids and membranes in prebiotic conditions. *Nature* 266, 78–80.
- Harrison, T.M., 2009. The Hadean crust: evidence from >4 Ga zircons. *Annual Review of Earth and Planetary Sciences* 37, 479–505.
- Harrison, T.M., Blichert-Toft, J., Muller, W., Albarede, F., Holden, P., Mojzsis, S.J., 2005. Heterogeneous Hadean hafnium: evidence of continental crust at 4.4 to 4.5 Ga. *Science* 310, 1947–1950.
- Hassan, A.E.A., Sheng, J., Zhang, W., Huang, Z., 2010. High fidelity of base pairing by 2-selenothymidine in DNA. *Journal of the American Chemical Society* 132, 2120–2121.
- Hatanaka, H., Egami, F., 1977. The formation of amino acids and related oligomers from formaldehyde and hydroxylamine in modified sea mediums related to prebiotic conditions. *Bulletin of the Chemical Society of Japan* 50, 1147–1156.
- Hayatsu, R., Studier, M.H., Oda, A., Fuse, K., Anders, E., 1968. Origin of organic matter in early solar system—II. Nitrogen compounds. *Geochimica et Cosmochimica Acta* 32, 175–190.
- Hayatsu, R., Studier, M.H., Matsuoka, S., Anders, E., 1972. Origin of organic matter in early solar system—VI. Catalytic synthesis of nitriles, nitrogen bases and porphyrin-like pigments. *Geochimica et Cosmochimica Acta* 36, 555–571.
- Helgeson, H.C., Kirkham, D.H., 1974. Theoretical prediction of the thermodynamic behavior of aqueous electrolytes at high pressures and temperatures: I. summary of the thermodynamic/electrostatic properties of the solvent. *American Journal of Science* 274, 1089–1198.
- Helz, G.R., Erickson, B.E., Vorlicek, T.P., 2014. Stabilities of thiomolybdate complexes of iron; implications for retention of essential trace elements (Fe, Cu, Mo) in sulfide waters. *Metallomics* 6, 1131–1140.
- Henderson-Sellers, A., Schwartz, A.W., 1980. Chemical evolution and ammonia in the early Earth's atmosphere. *Nature* 287, 526–528.
- Hennet, R.J.C., Holm, N.G., Engel, M.H., 1992. Abiotic synthesis of amino acids under hydrothermal conditions and the origin of life: a perpetual phenomenon? *Naturwissenschaften* 79, 361–365.
- Herd, C.D.K., Blinova, A., Simkus, D.N., Huang, Y., Tarozo, R., Alexander, C.M.O.D., Gyngard, F., Nittler, L.R., Cody, G.D., Fogel, M.L., Kebukawa, Y., Kilcoyne, A.L.D., Hilt, R.W., Slater, G.F., Glavin, D.P., Dworkin, J.P., Callahan, M.P., Elsil, J.E., De Gregorio, B.T., Stroud, R.M., 2011. Origin and evolution of prebiotic organic matter as inferred from the Tagish lake meteorite. *Science* 332, 1304–1307.
- Hill, A., Orgel, L.E., 2002. Synthesis of adenine from HCN tetramer and ammonium formate. *Origins of Life and Evolution of the Biosphere* 32, 99–102.
- Hirose, Y., Ohmuro, K., Saigoh, M., Nakayama, T., Yamagata, Y., 1990–1991. Synthesis of biomolecules from  $N_2$ , CO, and  $H_2O$  by electric discharge. *Origins of Life and Evolution of Biospheres* 20, 471–481.
- Holm, N.G., 1992. Why are hydrothermal systems proposed as plausible environments for the origin of life? *Origins of Life and Evolution of the Biosphere* 22, 5–14.
- Horita, J., Berndt, M.E., 1999. Abiogenic methane formation and isotopic fractionation under hydrothermal conditions. *Science* 285, 1055–1057.
- Howard, J.B., Rees, D.C., 1996. Structural basis of biological nitrogen fixation. *Chemical Reviews* 96, 2965–2982.
- Huang, W., Ferris, J.P., 2003. Synthesis of 35–40 mers of RNA oligomers from unblocked monomers. A simple approach to the RNA world. *Chemical Communications* 1458–1459.
- Huang, W., Ferris, J.P., 2006. One-step, regioselective synthesis of up to 50-mers of RNA oligomers by montmorillonite catalysis. *Journal of the American Chemical Society* 128, 8914–8919.
- Huber, C., Wachtershauser, G., 1998. Peptides by activation of amino acids with CO on (Ni,Fe)S surfaces: implications for the origin of life. *Science* 281, 670–672.
- Huber, C., Wachtershauser, G., 2006.  $\alpha$ -hydroxy and  $\alpha$ -amino acids under possible Hadean, volcanic origin—life conditions. *Science* 314, 630–632.
- Huber, C., Eisenreich, W., Hecht, S., Wachtershauser, G., 2003. A possible primordial peptide cycle. *Science* 301, 938–940.
- Huber, C., Kraus, F., Hanzlik, M., Eisenreich, W., Wachtershauser, G., 2012. Elements of metabolic evolution. *Chemistry – A European Journal* 18, 2063–2080.
- Ibanez, J.D., Kimball, A.P., Oro, J., 1971a. Possible prebiotic condensation of mononucleotides by cyanamide. *Science* 173, 444–446.
- Ibanez, J.D., Kimball, A.P., Oro, J., 1971b. Condensation of mononucleotides by imidazole. *Journal of Molecular Evolution* 1, 112–114.
- Imai, E., Honda, H., Hatori, K., Brack, A., Matsuno, K., 1999. Elongation of oligopeptides in a simulated submarine hydrothermal system. *Science* 283, 831–833.
- Ingar, A.A., Luke, R.W.A., Hayter, B.R., Sutherland, J.D., 2003. Synthesis of cytidine ribonucleotides by stepwise assembly of the heterocycle on a sugar phosphate. *ChemBioChem* 4, 504–507.
- Inoue, T., Orgel, L.E., 1981. Substituent control of the poly(C)-directed oligomerization of guanosine 5'-phosphorimidazolide. *Journal of the American Chemical Society* 103, 7666–7667.
- Inoue, T., Orgel, L.E., 1982. Oligomerization of (Guanosine 5'-phosphor)-2-methylimidazolide on poly(C) an RNA polymerase model. *Journal of Molecular Biology* 162, 201–217.
- Inoue, T., Orgel, L.E., 1983. A nonenzymatic RNA polymerase model. *Science* 219, 859–862.
- Islam, M.N., Kaneko, T., Kobayashi, K., 2001. Determination of amino acids formed in a supercritical water flow reactor simulating submarine hydrothermal systems. *Analytical Sciences* 17, 1631–1634.
- Janda, M., Morvova, M., Machala, Z., Morva, I., 2008. Study of plasma induced chemistry by DC discharges in  $CO_2/N_2/H_2O$  mixtures above a water surface. *Origins of Life and Evolution of Biospheres* 38, 23–35.
- Ji, F., Zhou, H., Yang, Q., 2008. The abiotic formation of hydrocarbons from dissolved  $CO_2$  under hydrothermal conditions with cobalt-bearing magnetite. *Origins of Life and Evolution of the Biosphere* 38, 117–125.
- Johnson, A.P., Cleaves, H.J., Dworkin, J.P., Glavin, D.P., Lazcano, A., Bada, J.L., 2008. The Miller volcanic spark discharge experiment. *Science* 322, 404.
- Johnston, W.K., Unrau, P.J., Lawrence, M.S., Glasner, M.E., Bartel, D.P., 2001. RNA-catalyzed RNA polymerization: accurate and general RNA-templated primer extension. *Science* 292, 1319–1325.
- Joyce, G.F., 2004. Directed evolution of nucleic acid enzymes. *Annual Review of Biochemistry* 73, 791–836.
- Joyce, G.F., Orgel, L.E., 1986. Non-enzymatic template-directed synthesis on RNA random copolymers Poly(C,G) templates. *Journal of Molecular Biology* 188, 433–441.
- Kadko, D., Gronvold, K., Butterfield, D., 2007. Application of radium isotopes to determine crustal residence times of hydrothermal fluids from two sites on the Reykjanes Peninsula, Iceland. *Geochimica et Cosmochimica Acta* 71, 6019–6029.
- Kamaluddin, Yanagawa, H., Egami, F., 1979. Formation of molecules of biological interest from formaldehyde and hydroxylamine in a modified sea medium. *Journal of Biochemistry* 85, 1503–1507.
- Kanavarioti, A., Monnard, P.A., Deamer, D.W., 2001. Eutectic phases in ice facilitate nonenzymatic nucleic acid synthesis. *Astrobiology* 1, 271–281.
- Kasting, J.F., 1990. Bolide impacts and the oxidation state of carbon in the earth's early atmosphere. *Origins of Life and Evolution of the Biosphere* 20, 199–231.
- Kasting, J.F., 1993. Earth's early atmosphere. *Science* 259, 920–926.
- Kawamura, K., 2004. Behavior of RNA under hydrothermal conditions and the origin of life. *International Journal of Astrobiology* 3, 301–309.
- Kawamura, K., Ferris, J.P., 1994. Kinetic and mechanistic analysis of dinucleotide and oligonucleotide formation from the 5'-phosphorimidazolide of adenosine on Na<sup>+</sup>-montmorillonite. *Journal of the American Chemical Society* 116, 7564–7572.
- Kawamura, K., Ferris, J.P., 1999. Clay catalysis of oligonucleotide formation: kinetics of the reaction of the 5'-phosphorimidazolides of nucleotides with the non-basic heterocycles uracil and hypoxanthine. *Origins of Life and Evolution of the Biosphere* 29, 563–591.
- Keefe, A.D., Miller, S.L., 1995. Are polyphosphates or phosphate esters prebiotic reagents? *Journal of Molecular Evolution* 41, 693–702.
- Keefe, A.D., Miller, S.L., 1996. Potentially prebiotic syntheses of condensed phosphates. *Origins of Life and Evolution of the Biosphere* 26, 15–25.
- Keefe, A.D., Miller, S.L., McDonald, G., Bada, J., 1995. Investigation of the prebiotic synthesis of amino acids and RNA bases from  $CO_2$  using  $FeS/H_2S$  as a reducing agent. *Proceedings of the National Academy of Sciences of the United States of America* 92, 11904–11906.
- Kelley, D.S., Karson, J.A., Blackman, D.K., Fruh-Green, G.L., Butterfield, D.A., Lilley, M.D., Olson, E.J., Schrenk, M.O., Roe, K.K., Lebon, G.T., Rivizzigno, P., the AT3-60 Shipboard Party, 2001. An off-axis hydrothermal vent field near the Mid-Atlantic Ridge at 30°N. *Nature* 412, 145–149.
- Kelley, D.S., Karson, J.A., Fruh-Green, G.L., Yoerger, D.R., Shank, T.M., Butterfield, D.A., Hayes, J.M., Schrenk, M.O., Olson, E.J., Proskurowski, G., Jakuba, M., Bradley, A., Larson, B., Ludwig, K., Glickson, D., Buckman, K., Bradley, A.S., Brazelton, W.J., Roe, K., Elend, M.J., Delacour, A., Bernasconi, S.M., Lilley, M.D., Baross, J.A., Summons, R.E., Sylva, S.P., 2005. A serpentine-hosted ecosystem: the lost city hydrothermal field. *Science* 307, 1428–1434.
- Khare, B.N., Sagan, C., 1971. Synthesis of cysteine in simulated primitive conditions. *Nature* 232, 577–579.
- Kierzek, R., He, L., Turner, D.H., 1992. Association of 2'-5' oligoribonucleotides. *Nucleic Acids Research* 20, 1685–1690.
- Kim, H.J., Benner, S.A., 2010. Comment on the silicate-mediated formose reaction: bottom-up synthesis of sugar silicates. *Science* 329, 902–a.
- Kim, H.J., Ricardo, A., Illangoon, H.I., Kim, M.J., Carrigan, M.A., Frye, F., Benner, S.A., 2011. Synthesis of carbohydrates in mineral-guided prebiotic cycles. *Journal of the American Chemical Society* 133, 9457–9468.
- Kirschvink, J.L., Weiss, B.P., 2003. Mars, panspermia, and origin of life: where did it all begin? *Journal of Geography* 112, 187–196.
- Kirschvink, J.L., Weiss, B.P., Beukes, N.J., 2006. Boron, ribose, and a martian origin for terrestrial life. *Geochimica et Cosmochimica Acta* 70, A320.
- Kitadai, N., 2014. Thermodynamic prediction of glycine polymerization as a function of temperature and pH consistent with experimentally obtained results. *Journal of Molecular Evolution* 78, 171–187.
- Kitadai, N., 2017. Dissolved divalent metal and pH effects on amino acid polymerization: a thermodynamic evaluation. *Origins of Life and Evolution of Biospheres* 47, 13–37.



- Kitadai, N., Yokoyama, T., Nakashima, S., 2011. Hydration–dehydration interactions between glycine and anhydrous salts: implications for a chemical evolution of life. *Geochimica et Cosmochimica Acta* 75, 6285–6299.
- Kitadai, N., Oonishi, H., Umemoto, K., Usui, T., Fukushima, K., Nakashima, S., 2017. Glycine polymerization on oxide minerals. *Origins of Life and Evolution of Biospheres* 47, 123–143.
- Klein, F., Bach, W., 2009. Fe–Ni–Co–O–S phase relations in predotite–seawater interactions. *Journal of Petrology* 50, 37–59.
- Kleine, T., Palme, H., Mezger, K., Halliday, A.N., 2005. Hf–W chronometry of lunar metals and the age and early differentiation of the moon. *Science* 310, 1671–1674.
- Klock, W., Palme, H., Tobschall, H.J., 1986. Trace elements in natural metallic iron from Disko island, Greenland. *Contributions to Mineralogy and Petrology* 93, 273–282.
- Kminek, G., Botta, O., Glavin, D.P., Bada, J.L., 2002. Amino acids in the Tagish Lake meteorite. *Meteoritics and Planetary Science* 37, 697–701.
- Kobayashi, K., Oshima, T., Yanagawa, H., 1989. Abiotic synthesis of amino acids by proton irradiation of a mixture of carbon monoxide, nitrogen, and water. *Chemistry Letters* 1527–1530.
- Kobayashi, K., Tsuchiya, M., Oshima, T., Yanagawa, H., 1990. Abiotic synthesis of amino acids and imidazole by proton irradiation of simulated primitive Earth atmospheres. *Origins of Life and Evolution of Biospheres* 20, 99–109.
- Kobayashi, K., Kaneko, T., Saito, T., Oshima, T., 1998. Amino acid formation in gas mixtures by high energy particle irradiation. *Origins of Life and Evolution of Biospheres* 28, 155–165.
- Kobayashi, K., Kaneko, T., Saito, T., 1999. Characterization of complex organic compounds formed in simulated planetary atmospheres by the action of high energy particles. *Advances in Space Research* 24, 461–464.
- Kobayashi, K., Masuda, H., Ushio, K., Ohashi, A., Yamanashi, H., Kaneko, T., Takahashi, J., Hosokawa, T., Hashimoto, H., Saito, T., 2001. Formation of bio-organic compounds in simulated planetary atmospheres by high energy particles or photons. *Advances in Space Research* 27, 207–215.
- Konn, C., Charlou, J.L., Donval, J.P., Holm, N.G., Dehairs, F., Bouillon, S., 2009. Hydrocarbons and oxidized organic compounds in hydrothermal fluids from Rainbow and Lost City ultramafic-hosted vents. *Chemical Geology* 258, 299–314.
- Kruger, K., Grabowski, P.J., Zaug, A.J., Sands, J., Gottschling, D.E., Cech, T.R., 1982. Self-splicing RNA: autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena. *Cell* 31, 147–157.
- Kvenvolden, K., Lewless, J., Pering, K., Peterson, E., Flores, J., Ponnampetuma, C., Kaplan, I.R., Moore, C., 1970. Evidence for extraterrestrial amino-acids and hydrocarbons in the Murchison meteorite. *Nature* 228, 923–926.
- Lailach, G.E., Thompson, T.D., Brindley, G.W., 1968. Absorption of pyrimidines, purines, and nucleosides by Li-, Na-, Mg-, and Ca-montmorillonite (clay-organic studies XII). *Clays and Clay Minerals* 16, 285–293.
- Lambert, J.F., 2008. Adsorption and polymerization of amino acids on mineral surfaces: a review. *Origins of Life and Evolution of the Biosphere* 38, 211–242.
- Lambert, J.B., Gurusamy-Thangavelu, S.A., Ma, K., 2010a. The silicate-mediated formose reaction: bottom-up synthesis of sugar silicates. *Science* 327, 984–986.
- Lambert, J.B., Gurusamy-Thangavelu, S.A., Ma, K., 2010b. Response to comment on “The silicate-mediated formose reaction: bottom-up synthesis of sugar silicates”. *Science* 329, 902–b.
- Lang, S.Q., Fruh-Green, G.L., Bernasconi, S.M., Butterfield, D.A., 2013. Sources of organic nitrogen at the serpentinite-hosted Lost City hydrothermal field. *Geobiology* 11, 154–169.
- LaRowe, D.E., Regnier, P., 2008. Thermodynamic potential for the abiotic synthesis of adenine, cytosine, guanine, thymine, uracil, ribose, and deoxyribose in hydrothermal systems. *Origins of Life and Evolution of the Biosphere* 38, 383–397.
- Larralde, R., Robertson, M.P., Miller, S.L., 1995. Rates of decomposition of ribose and other sugars: implications for chemical evolution. *Proceedings of the National Academy of Sciences of the United States of America* 92, 8158–8160.
- Lawless, J.G., Yuen, G.U., 1979. Quantification of monocarboxylic acids in the Murchison carbonaceous meteorite. *Nature* 282, 396–398.
- Lazcano, A., Bada, J.L., 2003. The 1953 Stanley L. Miller experiment: fifty years of prebiotic organic chemistry. *Origins of Life and Evolution of the Biosphere* 33, 235–242.
- Le Son, H., Suwannachot, Y., Bujdak, J., Rode, B.M., 1998. Salt-induced peptide formation from amino acids in the presence of clays and related catalysts. *Inorganica Chimica Acta* 272, 89–94.
- Leman, L., Orgel, L., Ghadiri, M.R., 2004. Carbonyl sulfide-mediated prebiotic formation of peptides. *Science* 306, 283–286.
- Leman, L.J., Orgel, L.E., Ghadiri, M.R., 2006. Amino acid dependent formation of phosphate anhydrides in water mediated by carbonyl sulfide. *Journal of the American Chemical Society* 128, 20–21.
- Lemke, K.H., Rosenbauer, R.J., Bird, D.K., 2009. Peptide synthesis in early Earth hydrothermal systems. *Astrobiology* 9, 141–146.
- Leu, K., Obermayer, B., Rajamani, S., Gerland, U., Chen, I.A., 2011. The prebiotic evolutionary advantage of transferring genetic information from RNA to DNA. *Nucleic Acids Research* 39, 8135–8147.
- Levy, M., Miller, S.L., 1998. The stability of the RNA bases: implications for the origin of life. *Proceedings of the National Academy of Sciences of the United States of America* 95, 7933–7938.
- Levy, M., Miller, S.L., 1999. The prebiotic synthesis of modified purines and their potential role in the RNA world. *Journal of Molecular Evolution* 48, 631–637.
- Levy, M., Miller, S.L., Oro, J., 1999. Production of guanine from  $\text{NH}_4\text{CN}$  polymerizations. *Journal of Molecular Evolution* 49, 165–168.
- Levy, M., Miller, S.L., Brinton, K., Bada, J.L., 2000. Prebiotic synthesis of adenine and amino acids under Europa-like conditions. *Icarus* 145, 609–613.
- Li, J., Brill, T.B., 2003. Spectroscopy of hydrothermal reactions, Part 26: kinetics of decarboxylation of aliphatic amino acids and comparison with the rates of racemization. *International Journal of Chemical Kinetics* 35, 602–610.
- Li, Y., Keppler, H., 2014. Nitrogen speciation in mantle and crustal fluids. *Geochimica et Cosmochimica Acta* 129, 13–32.
- Li, F., Fitz, D., Fraser, D.G., Rode, B.M., 2008. Methionine peptide formation under primordial earth conditions. *Journal of Inorganic Biochemistry* 102, 1212–1217.
- Li, F., Fitz, D., Fraser, D.G., Rode, B.M., 2010a. Arginine in the salt-induced peptide formation reaction: enantioselectivity facilitated by glycine, L- and D-histidine. *Amino Acids* 39, 579–585.
- Li, F., Fitz, D., Fraser, D.G., Rode, B.M., 2010b. Catalytic effects of histidine enantiomers and glycine on the formation of dileucine and dimethionine in the salt-induced peptide formation reaction. *Amino Acids* 38, 287–294.
- Li, Y., Wiedenbeck, M., Shcheka, S., Keppler, H., 2013. Nitrogen solubility in upper mantle minerals. *Earth and Planetary Science Letters* 377–378, 311–323.
- Libourel, G., Marty, B., Humbert, F., 2003. Nitrogen solubility in basaltic melt. Part I. Effect of oxygen fugacity. *Geochimica et Cosmochimica Acta* 67, 4123–4135.
- Lilley, M.D., Butterfield, D.A., Olson, E.J., Lupton, J.E., Macko, S.A., McDuff, R.E., 1993. Anomalous  $\text{CH}_4$  and  $\text{NH}_4^+$  concentrations at an unconsolidated mid-ocean-ridge hydrothermal system. *Nature* 364, 45–47.
- Lohrmann, R., 1972. Formation of urea and guanidine by irradiation of ammonium cyanide. *Journal of Molecular Evolution* 1, 263–269.
- Lohrmann, R., 1977. Formation of nucleoside 5'-phosphoramidates under potentially prebiological conditions. *Journal of Molecular Evolution* 10, 137–154.
- Lohrmann, R., Orgel, L.E., 1968. Prebiotic synthesis: phosphorylation in aqueous solution. *Science* 161, 64–66.
- Lohrmann, R., Orgel, L.E., 1971. Urea–inorganic phosphate mixtures as prebiotic phosphorylating agents. *Science* 171, 490–494.
- Lohrmann, R., Orgel, L.E., 1980. Efficient catalysis of polycytidylic acid-directed oligoguanylate formation by  $\text{Pb}^{2+}$ . *Journal of Molecular Biology* 142, 555–567.
- Lombard, J., Lopez-Garcia, P., Moreira, D., 2012. The early evolution of lipid membranes and the three domains of life. *Nature Reviews Microbiology* 10, 507–515.
- Lowe, C.U., Rees, M.W., Markham, R., 1963. Synthesis of complex organic compounds from simple precursors: formation of amino-acids, amino-acid polymers, fatty acids and purines from ammonium cyanide. *Nature* 199, 219–222.
- Lowell, R.P., Rona, P.A., 2002. Seafloor hydrothermal systems driven by the serpentinization of peridotite. *Geophysical Research Letters* 29, 1531.
- Maciam, E., 2005. The role of phosphorus in chemical evolution. *Chemical Society Reviews* 34, 691–701.
- Macleod, G., McKeown, C., Hall, A.J., Russell, M.J., 1994. Hydrothermal and oceanic pH conditions of possible relevance to the origin of life. *Origins of Life and Evolution of the Biospheres* 24, 19–41.
- Mancinelli, R.L., McKay, C.P., 1988. The evolution of nitrogen cycling. *Origins of Life and Evolution of the Biosphere* 18, 311–325.
- Mansy, S.S., Szostak, J.W., 2008. Thermostability of model protocell membranes. *Proceedings of the National Academy of Sciences of the United States of America* 105, 13351–V13355.
- Mansy, S.S., Schrum, J.P., Krishnamurthy, M., Tobe, S., Treco, D.A., Szostak, J.W., 2008. Template-directed synthesis of a genetic polymer in a modern protocell. *Nature* 454, 122–126.
- Marchi, S., Bottke, W.F., Elkins-Tanton, L.T., Bierhaus, M., Wuenemann, K., Morbidelli, A., Kring, D.A., 2014. Widespread mixing and burial of Earth's Hadean crust by asteroid impact. *Nature* 511, 578–582.
- Marshall, W.L., 1994. Hydrothermal synthesis of amino acids. *Geochimica et Cosmochimica Acta* 58, 2099–2106.
- Martin, B., Fyfe, W.S., 1970. Some experimental and theoretical observations on kinetics of hydration reactions with particular reference to serpentinization. *Chemical Geology* 6, 185–202.
- Martin, W., Russell, M.J., 2007. On the origin of biochemistry at an alkaline hydrothermal vent. *Philosophical Transactions of the Royal Society B* 362, 1887–1925.
- Martin, W., Baross, J., Kelley, D., Russell, M.J., 2008. Hydrothermal vents and the origin of life. *Microbiology* 6, 805–814.
- Martins, Z., Hofmann, B.A., Gnos, E., Greenwood, R.C., Verchovsky, A., Franchi, I.A., Jull, A.J.T., Botta, O., Glavin, D.P., Dworkin, J.P., Ehrenfreund, P., 2007. Amino acid composition, petrology, geochemistry,  $^{14}\text{C}$  terrestrial age and oxygen isotopes of the Shirs 033 CR chondrite. *Meteorite and Planetary Science* 42, 1581–1595.
- Martins, Z., Price, M.C., Goldman, N., Sephton, M.A., Burchell, M.J., 2013. Shock synthesis of amino acids from impacting cometary and icy planet surface analogues. *Nature Geoscience* 6, 1045–1049.
- Marty, B., Zimmermann, L., Pujol, M., Burgess, R., Philippot, P., 2013. Nitrogen isotopic composition and density of the Archean atmosphere. *Science* 342, 101–104.
- Maruyama, S., Ikoma, M., Genda, H., Hirose, K., Yokoyama, T., Santosh, M., 2013. The naked planet Earth: most essential pre-requisite for the origin and evolution of life. *Geoscience Frontiers* 4, 141–165.
- Mather, T.A., Pyle, D.M., Allen, A.G., 2004. Volcanic source for fixed nitrogen in the early Earth's atmosphere. *Geology* 32, 905–908.
- Matrajt, G., Pizzarello, S., Taylor, S., Brownlee, D., 2004. Concentration and variability of the AIB amino acid in polar micrometeorites: implications for the exogenous delivery of amino acids to the primitive Earth. *Meteoritics and Planetary Science* 39, 1849–1858.
- McCollom, T.M., 2013a. The influence of minerals on decomposition of the n-alkyl- $\alpha$ -amino acid norvaline under hydrothermal conditions. *Geochimica et Cosmochimica Acta* 104, 330–357.



- McCollom, T.M., 2013b. Miller-Urey and Beyond: what have we learned about prebiotic organic synthesis reactions in the past 60 years? *Annual Review of Earth and Planetary Sciences* 41, 207–229.
- McCollom, T.M., 2013c. Laboratory simulations of abiotic hydrocarbon formation in Earth's deep subsurface. *Reviews in Mineralogy and Geochemistry* 75, 467–494.
- McCollom, T.M., Seewald, J.S., 2001. A reassessment of the potential for reduction of dissolved CO<sub>2</sub> to hydrocarbons during serpentinization of olivine. *Geochimica et Cosmochimica Acta* 65, 3769–3778.
- McCollom, T.M., Seewald, J.S., 2003. Experimental constraints on the hydrothermal reactivity of organic acids and acid anions: I. Formic acid and formate. *Geochimica et Cosmochimica Acta* 67, 3625–3644.
- McCollom, T.M., Seewald, J.S., 2006. Carbon isotope composition of organic compounds produced by abiotic synthesis under hydrothermal conditions. *Earth and Planetary Science Letters* 243, 74–84.
- McCollom, T.M., Seewald, J.S., 2013. Serpentine, hydrogen, and life. *Elements* 9, 129–134.
- McCollom, T.M., Ritter, G., Simoneit, B.T., 1999. Lipid synthesis under hydrothermal conditions by Fischer-Tropsch-type reactions. *Origins of Life and Evolution of the Biosphere* 29, 153–166.
- Menor-Salvan, C., Ruiz-Bermejo, D.M., Guzman, M.I., Osuna-Esteban, S., Veintemillas-Verdaguer, S., 2009. Synthesis of pyrimidines and triazines in ice: implications for the prebiotic chemistry of nucleobases. *Chemistry – A European Journal* 15, 4411–4418.
- Mikhail, S., Sverjensky, D.A., 2014. Nitrogen speciation in upper mantle fluids and the origin of Earth's nitrogen-rich atmosphere. *Nature Geoscience* 7, 816–819.
- Miller, S.L., 1953. A production of amino acids under possible primitive Earth conditions. *Science* 117, 528–529.
- Miller, S.L., 1955. Production of some organic compounds under possible primitive Earth conditions. *Journal of the American Chemical Society* 77, 2351–2361.
- Miller, S.L., Bada, J.L., 1988. Submarine hot springs and the origin of life. *Nature* 334, 609–611.
- Miller, S.L., Lazcano, A., 1995. The origin of life—did it occur at high temperatures? *Journal of Molecular Evolution* 41, 689–692.
- Miller, S.L., Orgel, L.E., 1974. *The Origins of Life on the Earth*. Prentice-Hall, New Jersey.
- Miller, S.L., Parris, M., 1964. Synthesis of pyrophosphate under primitive Earth conditions. *Nature* 204, 1248–1250.
- Miyakawa, S., Sawaoka, A.B., Ushio, K., Kobayashi, K., 1999. Mechanisms of amino acid formation using optical emission spectroscopy. *Journal of Applied Physics* 85, 6853–6857.
- Miyakawa, S., Cleaves, H.J., Miller, S.L., 2002a. The cold origin of life: A. Implications based on the hydrolytic stabilities of hydrogen cyanide and formamide. *Origins of Life and Evolution of the Biosphere* 32, 195–208.
- Miyakawa, S., Cleaves, H.J., Miller, S.L., 2002b. The cold origin of life: B. Implications based on pyrimidines and purines produced from frozen ammonium cyanide solutions. *Origins of Life and Evolution of the Biosphere* 32, 209–218.
- Mojszisz, S.J., Arrhenius, G., McKeegan, K.D., Harrison, T.M., Nutman, A.P., Friend, C.R.L., 1996. Evidence for life on Earth before 3,800 million years ago. *Nature* 384, 55–59.
- Mojszisz, S.J., Harrison, T.M., Pidgeon, R.T., 2001. Oxygen-isotope evidence from ancient zircons for liquid water at the Earth's surface 4,300 Myr ago. *Nature* 409, 178–181.
- Monnard, P.A., Deamer, D.W., 2002. Membrane self-assembly processes: steps toward the first cellular life. *The Anatomical Record* 268, 196–207.
- Monnard, P.A., Apel, D.L., Kanavarioti, A., Deamer, D.W., 2002. Influence of ionic inorganic solutes on self-assembly and polymerization processes related to early forms of life: implications for a prebiotic aqueous medium. *Astrobiology* 2, 139–152.
- Monnard, A.P., Kanavarioti, A., Deamer, D.W., 2003. Eutectic phase polymerization of activated ribonucleotide mixtures yields quasi-equimolar incorporation of purine and pyrimidine nucleobases. *Journal of the American Chemical Society* 125, 13734–13740.
- Morooka, S., Wakai, C., Matubayasi, N., Nakahara, M., 2005. Hydrothermal carbon-carbon bond formation and disproportionations of C1 aldehydes: formaldehyde and formic acid. *Journal of Physical Chemistry A* 109, 6610–6619.
- Morse, J.W., Mackenzie, F.T., 1998. Hadean Ocean carbonate geochemistry. *Aquatic Geochemistry* 4, 301–319.
- Morvek, J., 1967. Formation of oligonucleotides during heating of a mixture of uridine 2'(3')-phosphate and uridine. *Tetrahedron Letters* 18, 1707–1710.
- Moutou, G., Taillades, J., Benefice-Malouet, S., Commeyras, A., 1995. Equilibrium of  $\alpha$ -aminoacetonitrile formation from formaldehyde, hydrogen cyanide and ammonia in aqueous solution: industrial and prebiotic significance. *Journal of Physical Organic Chemistry* 8, 721–730.
- MuCollom, T.M., Seewald, J.S., 2007. Abiotic synthesis of organic compounds in deep-sea hydrothermal environments. *Chemical Reviews* 104, 382–401.
- Mulkidjanian, A.Y., Bychkov, A.Y., Dibrova, D.V., Galperin, M.Y., Koonin, E.V., 2012a. Origin of first cells at terrestrial, anoxic geothermal fields. *Proceedings of the National Academy of Sciences of the United States of America* E821–E830.
- Mulkidjanian, A.Y., Bychkov, A.Y., Dibrova, D.V., Galperin, M.Y., Koonin, E.V., 2012b. Open question on the origin of life at anoxic geothermal fields. *Origins of Life and Evolution of Biospheres* 42, 507–516.
- Muller, U.F., Tor, Y., 2014. Citric acid and the RNA world. *Angewandte Chemie International Edition* 53, 5245–5247.
- Nakamura, R., Takashima, T., Kato, S., Takai, K., Yamamoto, M., Hashimoto, K., 2010. Electrical current generation across a black smoker chimney. *Angewandte Chemie International Edition* 49, 7692–7694.
- Nakashima, S., Brack, A., Maurel, M.C., Maruyama, S., Isozaki, Y., Windely, B.F., 2001. Introduction to: geochemistry and the origin of life. In: Nakashima, S., Maruyama, S., Brack, A., Windley, B.F. (Eds.), *Geochemistry and the Origin of Life*. Universal Academy Press, Inc., Tokyo, Japan, pp. 1–13.
- Nakazawa, H., Yamada, H., Hashizume, H., 1993. Origin of life in the earth's crust, a hypothesis: probable chemical evolution synchronized with the plate tectonics of the early earth. *Viva Origino* 21, 213–222 (in Japanese with English abstract).
- Namani, T., Deamer, D.W., 2008. Stability of model membranes in extreme environments. *Origins of Life and Evolution of the Biosphere* 38, 329–341.
- Napier, J., Yin, J., 2006. Formation of peptides in the dry state. *Peptides* 27, 607–610.
- Navarro-Gonzalez, R., Molina, M.J., Molina, L.T., 1998. Nitrogen fixation by volcanic lightning in the early Earth. *Geophysical Research Letters* 25, 3123–3126.
- Naylor, R., Gilham, P.T., 1966. Studies on some interactions and reactions of oligonucleotides in aqueous solution. *Biochemistry* 5, 2722–2728.
- Nelson, K.E., Robertson, M.P., Levy, M., Miller, S.L., 2001. Concentration by evaporation and the prebiotic synthesis of cytosine. *Origins of Life and Evolution of the Biosphere* 31, 221–229.
- Nicholson, W.L., 2009. Ancient micronauts: interplanetary transport of microbes by cosmic impacts. *Trends in Microbiology* 17, 243–250.
- Nicolet, M., 1975. On the production of nitric oxide by cosmic rays in the mesosphere and stratosphere. *Planetary and Space Science* 23, 637–649.
- Nielsen, P.E., 1993. Peptide nucleic acid (PNA): a model structure for the primordial genetic material? *Origins of Life and Evolution of the Biosphere* 23, 323–327.
- Nielsen, K.E., Levy, M., Miller, S.L., 2000. Peptide nucleic acids rather than RNA may have been the first genetic molecule. *Proceedings of the National Academy of Sciences of the United States of America* 97, 3868–3871.
- Nisbet, E.G., Fowler, C.M.R., 1996. Some like it hot. *Nature* 382, 404–405.
- Nisbet, E.G., Sleep, N.H., 2001. The habitat and nature of early life. *Nature* 409, 1083–1091.
- Nishizawa, M., Miyazaki, J., Makabe, A., Koba, K., Takai, K., 2014. Physiological and isotopic characteristics of nitrogen fixation by hyperthermophilic methanogens: key insights into nitrogen anabolism of the microbial communities in Archean hydrothermal systems. *Geochimica et Cosmochimica Acta* 138, 117–135.
- Nissen, P., Hansen, J., Ban, N., Moore, P.B., Steitz, T.A., 2000. The structural basis of ribosome activity in peptide bond synthesis. *Science* 289, 920–930.
- Nna-Mvondo, D., Navarro-Gonzalez, R., Raulin, F., Coll, P., 2005. Nitrogen fixation by corona discharge on the early Precambrian earth. *Origins of Life and Evolution of the Biosphere* 35, 401–409.
- Nooner, D.W., Gibert, J.M., Gelpi, E., Oro, J., 1976. Closed system Fischer-Tropsch synthesis over meteoritic iron, iron ore and nickel-iron alloy. *Geochimica et Cosmochimica Acta* 40, 915–924.
- Navarro-Gonzalez, R., McKay, C.P., Mvondo, D.N., 2001. A possible nitrogen crisis for Archean life due to reduced nitrogen fixation by lightning. *Nature* 412, 61–63.
- Oelkers, E.H., Valsami-Jones, E., 2008. Phosphate mineral reactivity and global sustainability. *Elements* 4, 83–87.
- Ogasawara, H., Yoshida, A., Imai, E., Honda, H., Hatori, K., Matsuno, K., 2000. Synthesizing oligomers from monomeric nucleotides in simulated hydrothermal environments. *Origins of Life and Evolution of the Biosphere* 30, 51–526.
- Ohara, S., Kakegawa, T., Nakazawa, H., 2007. Pressure effects on the abiotic polymerization of glycine. *Origins of Life and Evolution of the Biosphere* 37, 215–223.
- Ohotomo, Y., Kakegawa, T., Ishida, A., Nagase, T., Rosing, M.T., 2014. Evidence for biogenic graphite in early Archean Isua metasedimentary rocks. *Nature Geoscience* 7, 25–28.
- Oparin, A.I., 1957. *The Origin of Life on the Earth*. Oliver & Boyd, Edinburgh.
- Orgel, L.E., 1968. Evolution of the genetic apparatus. *Journal of Molecular Biology* 38, 381–393.
- Orgel, L.E., 2004. Prebiotic chemistry and the origin of the RNA world. *Critical Reviews in Biochemistry and Molecular Biology* 39, 99–123.
- Oro, J., 1960. Synthesis of adenine from ammonium cyanide. *Biochemical and Biophysical Research Communications* 2, 407–412.
- Oro, J., 1963. Non-enzymatic formation of purines and pyrimidines. *Federation Proceedings* 22, 681.
- Oro, J., Kimball, A.P., 1961. Synthesis of purines under possible primitive Earth conditions. I. Adenine from hydrogen cyanide. *Archives of Biochemistry and Biophysics* 94, 217–227.
- Oro, J., Kimball, A., Fritz, R., Master, F., 1959. Amino acid synthesis from formaldehyde and hydroxylamine. *Archives of Biochemistry and Biophysics* 85, 115–130.
- Oro, J., Gibert, J., Lichtenstein, H., Wikstrom, S., Flory, D.A., 1971. Amino-acids, aliphatic and aromatic hydrocarbons in the Murchison meteorite. *Nature* 230, 105–106.
- Osterberg, R., Orgel, L.E., 1972. Polyphosphate and trimetaphosphate formation under potentially prebiotic conditions. *Journal of Molecular Evolution* 1, 241–248.
- Osterberg, R., Orgel, L.E., Lohrmann, R., 1973. Further studies of urea-catalyzed phosphorylation reactions. *Journal of Molecular Evolution* 2, 231–234.
- Otake, T., Taniguchi, T., Furukawa, Y., Kawamura, F., Nakazawa, H., Kakegawa, T., 2011. Stability of amino acids and their oligomerization under high-pressure conditions: implications for prebiotic chemistry. *Astrobiology* 11, 799–813.
- Parker, E.T., Cleaves, H.J., Dworkin, J.P., Glavin, D.P., Callahan, M., Aubrey, A., Lazcano, A., Bada, J.L., 2011a. Primordial synthesis of amines and amino acids in a 1958 Miller H<sub>2</sub>S-rich spark discharge experiment. *Proceedings of the National Academy of Sciences of the United States of America* 108, 5526–5531.
- Parker, E.T., Cleaves, H.J., Callahan, M.P., Dworkin, J.P., Glavin, D.P., Lazcano, A., Bada, J.L., 2011b. Prebiotic synthesis of methionine and other sulfur-containing

- organic compounds on the primitive Earth: a contemporary reassessment based on an unpublished 1958 Stanley Miller experiment. *Origins of Life and Evolution of Biospheres* 41, 201–212.
- Pasek, M.A., 2008. Rethinking early Earth phosphorus geochemistry. *Proceedings of the National Academy of Sciences of the United States of America* 105, 853–858.
- Pasek, M., 2013. Early Mars without phosphate limits. *Nature Geoscience* 6, 806–807.
- Pasek, M., Block, K., 2009. Lightning-induced reduction of phosphorus oxidation state. *Nature Geoscience* 2, 553–556.
- Pasek, M.A., Lauretta, D.S., 2005. Aqueous corrosion of phosphide minerals from iron meteorites: a highly reactive source of prebiotic phosphorus on the surface of the early Earth. *Astrobiology* 5, 515–535.
- Pasek, M.A., Lauretta, D., 2008. Extraterrestrial flux of potentially prebiotic C, N, and P to the early Earth. *Origins of Life and Evolution of the Biosphere* 38, 5–21.
- Pasek, M.A., Dworkin, J.P., Lauretta, D.S., 2007. A radical pathway for organic phosphorylation during schreibersite corrosion with implications for the origin of life. *Geochimica et Cosmochimica Acta* 71, 1721–1736.
- Pasek, M.A., Block, K., Pasek, V., 2012. Fulgurite morphology: a classification scheme and clues to formation. *Contributions to Mineralogy and Petrology* 164, 477–492.
- Pasek, M.A., Harnmeijer, J.P., Buick, R., Gull, M., Atlas, Z., 2013. Evidence for reactive reduced phosphorus species in the early Archean ocean. *Proceedings of the National Academy of Sciences of the United States of America* 110, 10089–10094.
- Pasek, M.A., Sampson, J.M., Atlas, Z., 2014. Redox chemistry in the phosphorus biogeochemical cycle. *Proceedings of the National Academy of Sciences of the United States of America* 111, 15468–15473.
- Patel, B.H., Percivalle, C., Ritson, D.J., Duffy, C.D., Sutherland, J.D., 2015. Common origins of RNA, protein and lipid precursors in a cyanosulfidic protometabolism. *Nature Chemistry* 7, 301–307.
- Paula, S., Volkov, A.G., Van Hoek, A.N., Haines, T.H., Deamre, D.W., 1996. Permeation of protons, potassium ions, and small polar molecules through phospholipid bilayers as a function of membrane thickness. *Biophysical Journal* 70, 339–348.
- Pech, H., Henry, A., Khachikian, C.S., Salmassi, T.M., hanrahan, G., Foster, K.L., 2009. Detection of geothermal phosphite using high-performance liquid chromatography. *Environmental Science & Technology* 43, 7671–7675.
- Pech, H., Vazquez, M.G., Buren, J.V., Shi, L., Ivey, M.M., Salmassi, T.M., Pasek, M.A., Foster, K.L., 2011. Elucidating the redox cycle of environmental phosphorus using ion chromatography. *Journal of Chromatographic Science* 49, 573–581.
- Pereira, W.E., Summons, R.E., Rindfleisch, T.C., Duffield, A.M., Zeitman, B., Lawless, J.G., 1975. Stable isotope mass fragmentography: identification and hydrogen–deuterium exchange studies of eight Murchison meteorite amino acids. *Geochimica et Cosmochimica Acta* 39, 163–172.
- Pereto, J., 2005. Controversies on the origin of life. *International Microbiology* 8, 23–31.
- Philipp, M., 1977. Spontaneous phosphorylation of nucleosides in formamide–ammonium phosphate mixtures. *Naturwissenschaften* 64, 273.
- Pinto, J.P., Gladstone, G.R., Yung, Y.L., 1980. Photochemical production of formaldehyde in Earth's primitive atmosphere. *Science* 210, 183–185.
- Pizzarello, S., Cronin, J.R., 2000. Non-racemic amino acids in the Murray and Murchison meteorites. *Geochimica et Cosmochimica Acta* 64, 329–338.
- Pizzarello, S., Holmes, W., 2009. Nitrogen-containing compounds in two CR2 meteorites:  $^{15}\text{N}$  composition, molecular distribution and precursor molecules. *Geochimica et Cosmochimica Acta* 73, 2150–2162.
- Pizzarello, S., Shock, E., 2010. The organic composition of carbonaceous meteorites: the evolutionary story ahead of biochemistry. *Cold Spring Harbor Perspectives in Biology* 2, a002105.
- Pizzarello, S., Weber, A.L., 2004. Prebiotic amino acids as asymmetric catalysts. *Science* 303, 1151.
- Pizzarello, S., Weber, A.L., 2010. Stereoselective synthesis of pentose sugars under realistic prebiotic conditions. *Origins of Life and Evolution of the Biosphere* 40, 3–10.
- Pizzarello, S., Williams, L.B., 2012. Ammonia in the early solar system: an account from carbonaceous meteorites. *The Astrophysical Journal* 749, 161.
- Pizzarello, S., Feng, X., Epstein, S., Cronin, J.R., 1994. Isotopic analyses of nitrogenous compounds from the Murchison meteorite: ammonia, amines, amino acids, and polar hydrocarbons. *Geochimica et Cosmochimica Acta* 58, 5579–5587.
- Pizzarello, S., Cooper, G.W., Flynn, G.J., 2006. The nature and distribution of the organic material in carbonaceous chondrites and interplanetary dust particles. *Meteorites and the Early Solar System II* 625–651.
- Pizzarello, S., Huang, Y., Alexandre, M.R., 2008. Molecular asymmetry in extraterrestrial chemistry: insights from a pristine meteorite. *Proceedings of the National Academy of Sciences of the United States of America* 105, 3700–3704.
- Pizzarello, S., Williams, L.B., Lehman, J., Holland, G.P., Yarger, J.L., 2011. Abundant ammonia in primitive asteroids and the case for a possible exobiology. *Proceedings of the National Academy of Sciences of the United States of America* 108, 4303–4306.
- Pizzarello, S., Schrader, D.L., Monroe, A.A., Lauretta, D.S., 2012. Large enantiomeric excesses in primitive meteorites and the diverse effects of water in cosmochemical evolution. *Proceedings of the National Academy of Sciences of the United States of America* 109, 11949–11954.
- Plankensteiner, K., Righi, A., Rode, B.M., 2002. Glycine and diglycine as possible catalytic factors in the prebiotic evolution of peptides. *Origins of Life and Evolution of the Biosphere* 32, 225–236.
- Plankensteiner, K., Righi, A., Rode, B.M., Gargallo, R., Jaumot, J., Tauler, R., 2004a. Indication towards a stereoselectivity of the salt-induced peptide formation reaction. *Inorganica Chimica Acta* 357, 649–656.
- Plankensteiner, K., Reiner, H., Schranz, B., Rode, B.M., 2004b. Prebiotic formation of amino acids in a neutral atmosphere by electric discharge. *Angewandte Chemie International Edition* 43, 1886–1888.
- Plankensteiner, K., Reiner, H., Rode, B.M., 2005a. Stereoselective differentiation in the salt-induced peptide formation reaction and its relevance for the origin of life. *Peptides* 26, 535–541.
- Plankensteiner, K., Reiner, H., Rode, B.M., 2005b. Catalytic effects of glycine on prebiotic dipeptide and diproline formations. *Peptides* 26, 1109–1112.
- Plankensteiner, K., Reiner, H., Rode, B.M., 2005c. Catalytically increased prebiotic peptide formation: ditryptophan, diisylsine, and diserine. *Origins of Life and Evolution of the Biosphere* 35, 411–419.
- Plankensteiner, K., Reiner, H., Rode, B.M., 2006. Amino acids on the rampant primordial Earth: electric discharges and the hot salty ocean. *Molecular Diversity* 10, 3–7.
- Ponnamperuma, C., Mack, R., 1965. Nucleotide synthesis under possible primitive Earth conditions. *Science* 148, 1221–1223.
- Ponnamperuma, C., Lemmon, R.M., Mariner, R., Calvin, M., 1963a. Formation of adenine by electron irradiation of methane, ammonia, and water. *Proceedings of the National Academy of Sciences of the United States of America* 49, 737–740.
- Ponnamperuma, C., Sagan, C., Mariner, R., 1963b. Synthesis of adenosine triphosphate under possible primitive Earth conditions. *Nature* 199, 222–226.
- Powner, M.W., Gerland, B., Sutherland, J.D., 2009. Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. *Nature* 459, 239–242.
- Prabakar, K.J., Ferris, J.P., 1997. Adenine derivatives as phosphate-activating groups for the regioselective formation of 3',5'-linked oligoadenylates on montmorillonite: possible phosphate-activating groups for the prebiotic synthesis of RNA. *Journal of the American Chemical Society* 119, 4330–4337.
- Prakash, T.P., Roberts, C., Switzer, C., 1997. Activity of 2',5'-linked RNA in the template-directed oligomerization of mononucleotides. *Angewandte Chemie International Edition in English* 36, 1522–1523.
- Price, P.B., 2010. Microbial life in martian ice: a biotic origin of methane on Mars? *Planetary and Space Science* 58, 1199–1206.
- Prins, R., Bussell, M.E., 2012. Metal phosphides: preparation, characterization and catalytic reactivity. *Catalysis Letters* 142, 1413–1436.
- Proskowski, G., Lille, M.D., Seewald, J.S., Fruh-Green, G.L., Olson, E.J., Lupton, J.E., Sylva, S.P., Kelley, D.S., 2008. Abiogenic hydrocarbon production at Lost City hydrothermal field. *Science* 319, 604–607.
- Qian, Y., Engel, M.H., Macko, S.A., Carpenter, S., Deming, J.W., 1993. Kinetics of peptide hydrolysis and amino acid decomposition at high temperature. *Geochimica et Cosmochimica Acta* 57, 3281–3293.
- Rabinowitz, J., Chang, S., Ponnamperuma, C., 1968. Phosphorylation by way of inorganic phosphate as a potential prebiotic process. *Nature* 218, 442–443.
- Rabinowitz, J., Flores, J., Krebsbach, R., Rogers, G., 1969. Peptide formation in the presence of linear or cyclic polyphosphates. *Nature* 224, 795–796.
- Rajamani, S., Vlassov, A., Benner, S., Coombs, A., Olasagasti, F., Deamer, D., 2008. Lipid-assisted synthesis of RNA-like polymers from mononucleotides. *Origin of Life and Evolution of the Biosphere* 38, 57–74.
- Rao, M., Eichberg, J., Oro, J., 1982. Synthesis of phosphatidylcholine under possible primitive Earth conditions. *Journal of Molecular Evolution* 18, 196–202.
- Rao, M., Eichberg, J., Oro, J., 1987. Synthesis of phosphatidylethanolamine under possible primitive Earth conditions. *Journal of Molecular Evolution* 25, 1–6.
- Reid, C., Orgel, L.E., 1967. Synthesis of sugars in potentially prebiotic conditions. *Nature* 216, 455.
- Reiner, H., Plankensteiner, K., Fitz, D., Rode, B.M., 2006. The possible influence of L-histidine on the origin of the first peptides on the primordial Earth. *Chemistry & Biodiversity* 3, 611–621.
- Reysenbach, A.L., Shock, E., 2002. Merging genomes with geochemistry in hydrothermal ecosystems. *Science* 296, 1077–1082.
- Ricardo, A., Szostak, J.W., 2009. Origin of life on Earth. *Scientific American* 301, 54–61.
- Ricardo, A., Carrigan, M.A., Olcott, A.N., Benner, S.A., 2004. Borate minerals stabilize ribose. *Science* 303, 196.
- Ricardo, A., Frye, F., Carrigan, M.A., Tipton, J.D., Powell, D.H., Benner, S.A., 2006. 2-Hydroxymethylboronate as a reagent to detect carbohydrates: application to the analysis of the formose reaction. *The Journal of Organic Chemistry* 71, 9503–9505.
- Rimola, A., Tosoni, S., Sodupe, M., Ugliengo, P., 2005. Peptide bond formation activated by the interplay of Lewis and Brønsted catalysts. *Chemical Physics Letters* 408, 295–301.
- Rimola, A., Sodupe, M., Ugliengo, P., 2007. Aluminosilicate surfaces as promoters for peptide bond formation: an assessment of Bernal's hypothesis by ab initio methods. *Journal of the American Chemical Society* 129, 8333–8344.
- Ring, D., Wolman, Y., Friedmann, N., Miller, S.L., 1972. Prebiotic synthesis of hydrophobic and protein amino acids. *Proceedings of the National Academy of Sciences of the United States of America* 69, 765–768.
- Rishpon, J., O'Hara, P.J., Lahav, N., Lawless, J.G., 1982. Interaction between ATR, metal ions, glycine, and several minerals. *Journal of Molecular Evolution* 18, 179–184.
- Ritson, D., Sutherland, J.D., 2012. Prebiotic synthesis of simple sugars by photoredox systems chemistry. *Nature Chemistry* 4, 895–899.

- Robertson, M.P., Joyce, G.F., 2012. The origins of the RNA world. *Cold Spring Harbor Perspectives in Biology* 4, a003608.
- Robertson, M.P., Miller, S.L., 1995. An efficient prebiotic synthesis of cytosine and uracil. *Nature* 375, 772–774.
- Rode, B.M., 1999. Peptides and the origin of life. *Peptides* 20, 773–786.
- Rode, B.M., Schwendinger, M.G., 1990. Copper-catalyzed amino acid condensation in water – a simple possible way of prebiotic peptide formation. *Origins of Life and Evolution of the Biosphere* 20, 401–410.
- Rode, B.M., Suwannachot, Y., 1999. The possible role of Cu(II) for the origin of life. *Coordination Chemical Reviews* 190–192, 1085–1099.
- Rode, B.M., Eder, A.H., Yongyai, Y., 1997. Amino acid sequence preferences of the salt-induced peptide formation reaction in comparison to archaic cell protein composition. *Inorganica Chimica Acta* 254, 309–314.
- Rode, B.M., Son, H.L., Suwannachot, Y., Bujdak, J., 1999. The combination of salt induced peptide formation reaction and clay catalysis: a way to higher peptides under primitive earth conditions. *Origins of Life and Evolution of the Biosphere* 29, 273–286.
- Rode, B.M., Fitz, D., Jakschitz, T., 2007. The first steps of chemical evolution towards the origin of life. *Chemistry & Biodiversity* 4, 2674–2702.
- Rosing, M.T., 1999. <sup>13</sup>C-depleted carbon microparticles in >3700-Ma sea-floor sedimentary rocks from west Greenland. *Science* 283, 674–676.
- Rubie, D.C., Frost, D.J., Mann, U., Asahara, Y., Nimmo, F., Tsuno, K., Kegler, P., Holzheid, A., Palme, H., 2011. Heterogeneous accretion, composition and core-mantle differentiation of the Earth. *Earth and Planetary Science Letters* 301, 31–42.
- Rudolph, S.A., Johnson, E.M., Greengard, P., 1971. The enthalpy of hydrolysis of various 3',5'- and 2',3'-cyclic nucleotides. *The Journal of Biological Chemistry* 246, 1271–1273.
- Ruiz-Bermejo, M., Menor-Salvan, C., Osuna-Esteban, S., Veintemillas-Verdaguer, S., 2007a. The effects of ferrous and other ions on the abiotic formation of biomolecules using aqueous aerosols and spark discharges. *Origins of Life and Evolution of the Biosphere* 37, 507–521.
- Ruiz-Bermejo, M., Menor-Salvan, C., Osuna-Esteban, S., Veintemillas-Verdaguer, S., 2007b. Prebiotic microreactors: a synthesis of purines and dihydroxy compounds in aqueous aerosol. *Origins of Life and Evolution of the Biosphere* 37, 123–142.
- Ruiz-Mirazo, K., Pereto, J., Moreno, A., 2004. A universal definition of life: Autonomy and open-ended evolution. *Origins of Life and Evolution of the Biosphere* 34, 323–346.
- Ruiz-Mirazo, K., Briones, C., de la Escosura, A., 2014. Prebiotic systems chemistry: new perspectives of the origins of life. *Chemical Reviews* 114, 285–366.
- Rushdi, A.I., Simoneit, B.R.T., 2001. Lipid formation by aqueous Fischer-Tropsch-type synthesis over a temperature range of 100 to 400 °C. *Origins of Life and Evolution of the Biosphere* 31, 103–118.
- Russell, M.J., 2003. The importance of being alkaline. *Science* 302, 580–581.
- Russell, M.J., 2007. The alkaline solution to the emergence of life: energy, entropy and early evolution. *Acta Biotheoretica* 55, 133–179.
- Russell, M.J., Daniel, R.M., Hall, A.J., Sherringham, J., 1994. A hydrothermally precipitated catalytic iron sulphide membrane as a first step toward life. *Journal of Molecular Evolution* 39, 231–243.
- Russell, M.J., Hall, A.J., Martin, W., 2010. Serpentinization as a source of energy at the origin of life. *Geobiology* 8, 355–371.
- Russell, M.J., Barge, L.M., Bhartiya, R., Bocanegra, D., Bracher, P.J., Branscomb, E., Kidd, R., McGlynn, S., Meier, D.H., Nitschke, W., Shibuya, T., Vance, S., White, L., Kanik, I., 2014. The drive to life on wet and icy worlds. *Astrobiology* 14, 308–343.
- Sacerdote, M.G., Szostak, J.W., 2005. Semipermeable lipid bilayers exhibit diastereoselectivity favoring ribose. *Proceedings of the National Academy of Sciences of the United States of America* 102, 6004–6008.
- Saetia, S., Liedl, K.R., Eder, A.H., Rode, B.M., 1993. Evaporation cycle experiments – a simulation of salt-induced peptide synthesis under possible prebiotic conditions. *Origins of Life and Evolution of the Biosphere* 23, 167–176.
- Sagan, C., Khare, B.N., 1971. Long-wavelength ultraviolet photoproduction of amino acids on the primitive Earth. *Science* 173, 417–420.
- Sakata, K., Kitadai, N., Yokoyama, T., 2010. Effects of pH and temperature on dimerization rate of glycine: evaluation of favorable environmental conditions for chemical evolution of life. *Geochimica et Cosmochimica Acta* 74, 6841–6851.
- Saladino, R., Crestini, C., Costanzo, G., Negri, R., Mauro, E.D., 2001. A possible prebiotic synthesis of purine, adenine, cytosine, and 4(3H)-pyrimidinone from formamide: implications for the origin of life. *Bioorganic & Medicinal Chemistry* 9, 1249–1253.
- Saladino, R., Ciambecchini, U., Crestini, C., Costanzo, G., Negri, R., Mauro, E.D., 2003. One-pot TiO<sub>2</sub>-catalyzed synthesis of nucleic bases and acynucleosides from formamide: implications for the origin of life. *ChemBioChem* 4, 514–521.
- Saladino, R., Crestini, C., Ciambecchini, U., Cicciello, F., Costanzo, G., Mauro, E.D., 2004. Synthesis and degradation of nucleobases and nucleic acids by formamide in the presence of montmorillonites. *ChemBioChem* 5, 1558–1566.
- Saladino, R., Crestini, C., Costanzo, G., DiMauro, E., 2005a. On the prebiotic synthesis of nucleobases, nucleotides, oligonucleotides, pre-RNA and pre-DNA molecules. *Topics in Current Chemistry* 259, 29–68.
- Saladino, R., Crestini, C., Neri, V., Brucato, J.R., Colangeli, L., Cicciello, F., Mauro, E.D., Costanzo, G., 2005b. Synthesis and degradation of nucleic acid components by formamide and cosmic dust analogues. *ChemBioChem* 6, 1368–1374.
- Saladino, R., Neri, V., Crestini, C., Costanzo, G., Graciotti, M., Mauro, E.D., 2008. Synthesis and degradation of nucleic acid components by formamide and iron sulfur minerals. *Journal of the American Chemical Society* 130, 15512–15518.
- Saladino, R., Crestini, C., Cicciello, F., Pino, S., Costanzo, G., Mauro, E.D., 2009. From formamide to RNA: the roles of formamide and water in the evolution of chemical information. *Research in Microbiology* 160, 441–448.
- Saladino, R., Neri, V., Crestini, C., Costanzo, G., Graciotti, M., Mauro, E.D., 2010. The role of the formamide/zirconia system in the synthesis of nucleobases and biogenic carboxylic acid derivatives. *Journal of Molecular Evolution* 71, 100–110.
- Saladino, R., Crestini, C., Pino, S., Costanzo, G., Mauro, E.D., 2012a. Formamide and the origin of life. *Physics of Life Reviews* 9, 84–104.
- Saladino, R., Botta, G., Pino, S., Costanzo, G., Mauro, E.D., 2012b. Genetics first or metabolism first? The formamide clue. *Chemical Society Reviews* 41, 5526–5565.
- Sanchez, R.A., Orgel, L.E., 1970. Studies in prebiotic synthesis V. Synthesis and photoanomerization of pyrimidine nucleosides. *Journal of Molecular Biology* 47, 531–543.
- Sanchez, R.A., Ferris, J.P., Orgel, L.E., 1966a. Cyanoacetylene in prebiotic synthesis. *Science* 154, 784–785.
- Sanchez, R., Ferris, J., Orgel, L.E., 1966b. Conditions for purine synthesis: did prebiotic synthesis occur at low temperatures? *Science* 153, 72–73.
- Sanchez, R.A., Ferris, J.P., Orgel, L.E., 1967. Studies in prebiotic synthesis II. Synthesis of purine precursors and amino acids from aqueous hydrogen cyanide. *Journal of Molecular Biology* 30, 223–253.
- Santosh, M., Arai, T., Maruyama, S., 2017. Hadean Earth and primordial continents: the cradle of prebiotic life. *Geoscience Frontiers* 8, 309–327.
- Sawai, H., 1976. Catalysis of internucleotide bond formation by divalent metal ions. *Journal of the American Chemical Society* 98, 7037–7039.
- Sawai, H., Orgel, L.E., 1975a. Prebiotic peptide-formation in the solid state. III. Condensation reactions of glycine in solid state mixtures containing inorganic polyphosphates. *Journal of Molecular Evolution* 6, 185–197.
- Sawai, H., Orgel, L.E., 1975b. Oligonucleotide synthesis catalyzed by the Zn<sup>2+</sup> ion. *Journal of the American Chemical Society* 97, 3532–3533.
- Sawai, H., Lohrmann, R., Orgel, L.E., 1975. Prebiotic peptide-formation in the solid state. *Journal of Molecular Evolution* 6, 165–184.
- Sawai, H., Kuroda, K., Hojo, T., 1989. Uranyl ion as a highly effective catalyst for internucleotide bond formation. *Bulletin of the Chemical Society of Japan* 62, 2018–2023.
- Sawai, H., Higa, K., Kuroda, K., 1992. Synthesis of cyclic and acyclic oligocytidylates by uranyl ion catalyst in aqueous solution. *Journal of the Chemical Society, Perkin Transactions 1*, 505–508.
- Saygin, O., 1981. Nonenzymatic photophosphorylation with visible light. *Naturwissenschaften* 68, 617–619.
- Scaillet, B., Gaillard, F., 2011. Redox state of early magmas. *Nature* 480, 48–49.
- Schimpl, A., Lemmon, R.M., Calvin, M., 1965. Cyanamide formation under primitive Earth conditions. *Science* 147, 149–150.
- Schlesinger, G., Miller, S.L., 1983a. Prebiotic synthesis in atmospheres containing CH<sub>4</sub>, CO and CO<sub>2</sub> II. Hydrogen cyanide, formaldehyde and ammonia. *Journal of Molecular Evolution* 19, 383–390.
- Schlesinger, G., Miller, S.L., 1983b. Prebiotic synthesis in atmospheres containing CH<sub>4</sub>, CO and CO<sub>2</sub>. I. Amino acids. *Journal of Molecular Evolution* 19, 376–382.
- Schoffstall, A.M., 1976. Prebiotic phosphorylation of nucleosides in formamide. *Origins of Life* 7, 399–412.
- Schoffstall, A.M., Laing, E.M., 1985. Phosphorylation mechanisms in chemical evolution. *Origins of Life* 15, 141–150.
- Schoffstall, A.M., Barto, R.J., Ramos, D.L., 1982. Nucleoside and deoxynucleoside phosphorylation in formamide solutions. *Origins of Life* 12, 143–151.
- Schoonen, M.A.A., Xu, Y., 2001. Nitrogen reduction under hydrothermal vent conditions: implications for the prebiotic synthesis of C-H-O-N compounds. *Astrobiology* 1, 133–142.
- Schrenk, M.O., Brazelton, W.J., 2013. Serpentinization, carbon, and deep life. *Reviews in Mineralogy and Geochemistry* 75, 575–606.
- Schrum, J.P., Zhu, T.F., Szostak, J.W., 2010. The origins of cellular life. *Cold Spring Harbor Perspectives in Biology* 2, a002212.
- Schwartz, A.W., 1969. Specific phosphorylation of the 2'- and 3'- positions in ribonucleosides. *Chemical Communications* 1393.
- Schwartz, A.W., 2006. Phosphorus in prebiotic chemistry. *Philosophical Transactions of the Royal Society B* 361, 1743–1749.
- Schwartz, A.W., Chittenden, G.J.F., 1977. Synthesis of uracil and thymine under simulated prebiotic conditions. *BioSystems* 9, 87–92.
- Schwartz, A.W., De Graaf, R.M., 1993. The prebiotic synthesis of carbohydrates: a reassessment. *Journal of Molecular Evolution* 36, 101–106.
- Schwartz, A., Ponnampuram, C., 1968. Phosphorylation of adenosine with linear polyphosphate salts in aqueous solution. *Nature* 218, 443.
- Schwartz, A.W., Joosten, H., Voet, A.B., 1982. Prebiotic adenine synthesis via HCN oligomerization in ice. *Biosystems* 15, 191–193.
- Schwendinger, M.G., Rode, B.M., 1991. Salt-induced formation of mixed peptides under possible prebiotic conditions. *Inorganica Chimica Acta* 186, 247–251.
- Schwendinger, M.G., Tauler, R., Saetia, S., Liedl, K.R., Kroemer, R.T., Rode, B.M., 1995. Salt induced peptide formation: on the selectivity of the copper induced peptide formation under possible prebiotic conditions. *Inorganica Chimica Acta* 228, 207–214.
- Schwendinger, M.G., Rode, B.M., 1989. Possible role of copper and sodium chloride in prebiotic evolution of peptides. *Analytical Sciences* 5, 411–414.



- Seewald, J.S., Zolotov, M.Y., McCollom, T., 2006. Experimental investigation of single carbon compounds under hydrothermal conditions. *Geochimica et Cosmochimica Acta* 70, 446–460.
- Sephton, M.A., 2002. Organic compounds in carbonaceous meteorites. *Natural Product Reports* 19, 292–311.
- Shanker, U., Bhushan, B., Bhattacharjee, G., Kamaluddin, 2011. Formation of nucleobases from formamide in the presence of iron oxides: implication in chemical evolution and origin of life. *Astrobiology* 11, 225–233.
- Shapiro, R., 1988. Prebiotic ribose synthesis: a critical analysis. *Origins of Life and Evolution of the Biosphere* 18, 71–85.
- Shapiro, R., 1995. The prebiotic role of adenine: a critical analysis. *Origins of Life and Evolution of the Biosphere* 25, 83–98.
- Shapiro, R., 1999. Prebiotic cytosine synthesis: a critical analysis and implications for the origin of life. *Proceedings of the National Academy of Sciences of the United States of America* 96, 4396–4401.
- Sharov, A.A., 2006. Genome increases as a clock for the origin and evolution of life. *Biology Direct* 1, 17.
- Shen, C., Yang, L., Miller, S.L., Oro, J., 1990. Prebiotic synthesis of histidine. *Journal of Molecular Evolution* 31, 167–174.
- Shi, H.B., Shao, C.L., Yu, Z.L., 2001. Preliminary study on the way of formation of amino acids on primitive Earth under non-reducing conditions. *Radiation Physics and Chemistry* 62, 393–397.
- Shibuya, T., Komiya, T., Nakamura, K., Takai, K., Maruyama, S., 2010. Highly alkaline, high-temperature hydrothermal fluids in the early Archean ocean. *Precambrian Research* 182, 230–238.
- Shimoyama, A., Ogasawara, R., 2002. Dipeptides and diketopiperazines in the Yamato-791198 and Murchison carbonaceous chondrites. *Origins of Life and Evolution of the Biosphere* 32, 165–179.
- Shock, E.L., 1990. Geochemical constraints on the origin of organic compounds in hydrothermal system. *Origins of Life and Evolution of the Biosphere* 20, 331–367.
- Shock, E.L., 1992a. Chemical environments of submarine hydrothermal systems. *Origins of Life and Evolution of the Biosphere* 22, 67–107.
- Shock, E.L., 1992b. Stability of peptides in high-temperature aqueous solutions. *Geochimica et Cosmochimica Acta* 56, 3481–3491.
- Shock, E.L., Helgeson, H.C., 1988. Calculation of the thermodynamic and transport properties of aqueous species at high pressures and temperatures: correlation algorithms for ionic species and equation of state predictions to 5 kb and 1000 °C. *Geochimica et Cosmochimica Acta* 52, 2009–2036.
- Shock, E.L., Helgeson, H.C., 1990. Calculation of the thermodynamic and transport properties of aqueous species at high pressures and temperatures: standard partial molal properties of organic species. *Geochimica et Cosmochimica Acta* 54, 915–945.
- Shock, E.L., Schulte, M.D., 1998. Organic synthesis during fluid mixing in hydrothermal systems. *Journal of Geophysical Research* 103, 28513–28527.
- Shock, E.L., Helgeson, H.C., Sverjensky, D.A., 1989. Calculation of the thermodynamic and transport properties of aqueous species at high pressure and temperatures: standard partial molal properties of inorganic neutral species. *Geochimica et Cosmochimica Acta* 53, 2157–2183.
- Singireddy, S., Gordon, A.D., Smirnov, A., Vance, M.A., Schoonen, M.A.A., Szilagyi, R.K., Strongin, D.R., 2012. Reduction of nitrite and nitrate to ammonium on pyrite. *Origins of Life and Evolution of the Biosphere* 42, 275–294.
- Slebocka-Tilk, H., Sauriol, F., Monette, M., Brown, R.S., 2002. Aspects of the hydrolysis of formamide: revisitation of the water reaction and determination of the solvent deuterium kinetic isotope effect in base. *Canadian Journal of Chemistry* 80, 1343–1350.
- Sleep, N.H., 2010. The Hadean-Archean environment. *Cold Spring Harbor Perspectives in Biology* 2, a002527.
- Sleep, N.H., Zahnle, K., 1998. Refugia from asteroid impacts on early Mars and the early Earth. *Journal of Geophysical Research* 103, 28529–28544.
- Sleep, N.H., Zahnle, K.J., Kasting, J.F., Morowitz, H.J., 1989. Annihilation of ecosystems by large asteroid impacts on the early Earth. *Nature* 342, 139–142.
- Smirnov, A., Hausner, D., Laffers, R., Strongin, D.R., Schoonen, M.A.A., 2008. Abiotic ammonium formation in the presence of Ni-Fe metals and alloys and its implications for the Hadean nitrogen cycle. *Geochemical Transactions* 9, 5.
- Sousa, F.L., Thiergart, T., Landan, G., Nelson-Sathi, S., Pereira, I.A.C., Allen, J.F., Lane, N., Martin, W.F., 2013. Early bioenergetics evolution. *Philosophical Transactions of the Royal Society B* 368.
- Steinman, G., Cole, M.N., 1967. Synthesis of biologically pertinent peptides under possible primordial conditions. *Proceedings of the National Academy of Sciences of the United States of America* 58, 735–742.
- Steinman, G., Lemmon, R.M., Calvin, M., 1964. Cyanamide: a possible key compound in chemical evolution. *Proceedings of the National Academy of Sciences of the United States of America* 52, 27–30.
- Steinman, G., Lemmon, R.M., Calvin, M., 1965a. Dicyandiamide: possible role in peptide synthesis during chemical evolution. *Science* 147, 1574–1575.
- Steinman, G., Kenyon, D.H., Calvin, M., 1965b. Dehydration condensation in aqueous solution. *Nature* 206, 707–708.
- Steinman, G., Kenyon, D.H., Calvin, M., 1966. The mechanism and protobiochemical relevance of dicyandiamide-mediated peptide synthesis. *Biochimica et Biophysica Acta* 124, 339–350.
- Steinman, G., Smith, A.E., Silver, J.J., 1968. Synthesis of a sulfur-containing amino acid under simulated prebiotic conditions. *Science* 159, 1108–1109.
- Stephen-Sherwood, E., Oro, J., Kimball, A.P., 1971. Thimine: a possible prebiotic synthesis. *Science* 173, 446–447.
- Stephenson, J.D., Hallis, L.J., Nagashima, K., Freeland, S.J., 2013. Boron enrichment in Martian clay. *PLoS One* 8, e64624.
- Stilling, A., Cerny, P., Vanstone, P.J., 2006. The Tanco pegmatite at Bernic Lake, Manitoba, XVI. Zonal and bulk compositions and their petrogenetic significance. *Canadian Mineralogist* 44, 599–623.
- Stockbridge, R.B., Wolfenden, R., 2009. The intrinsic reactivity of ATP and the catalytic proficiencies of kinases acting on glucose, N-acetylglucosamine, and homoserine. *The Journal of Biological Chemistry* 34, 22747–22757.
- Strecker, A., 1850. Ueber die kunstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper. *Justus Liebig's Annalen der Chemie* 75, 27–45.
- Stribling, R., Miller, S.L., 1987. Energy yields for hydrogen cyanide and formaldehyde syntheses: the HCN and amino acid concentrations in the primitive ocean. *Origins of Life* 17, 261–273.
- Stubbe, J., 1990. Ribonucleotide reductases: amazing and confusing. *The Journal of Biological Chemistry* 265, 5329–5332.
- Stueken, E.E., Anderson, R.E., Bowman, J.S., Brazelton, W.J., Colangelo-Lillis, J., Goldman, A.D., Som, S.M., Baross, J.A., 2013. Did life originate from a global chemical reactor? *Geobiology* 11, 101–126.
- Subbaraman, A.S., Kazi, Z.A., Choughuley, A.S.U., Chadha, M.S., 1980. Urea-acetylene dicarboxylic acid reaction: a likely pathway for prebiotic uracil formation. *Origins of Life* 10, 343–347.
- Suda, K., Ueno, Y., Yoshizaki, M., Nakamura, H., Kurokawa, K., Nishiyama, E., Yoshino, K., Hongoh, Y., Kawachi, K., Omori, S., Yamada, K., Yoshida, N., Maruyama, S., 2014. Origin of methane in serpentine-hosted hydrothermal systems: the CH<sub>4</sub>-H<sub>2</sub>-H<sub>2</sub>O hydrogen isotope systematics of the Hakuba Haplo hot spring. *Earth and Planetary Science Letters* 386, 112–125.
- Sulston, J., Lohrmann, R., Orgel, L.E., Miler, H.T., 1968a. Nonenzymatic synthesis of oligoadenylates on a polyuridylic acid template. *Proceedings of the National Academy of Sciences of the United States of America* 59, 726–733.
- Sulston, J., Lohrmann, R., Orgel, L.E., Miler, H.T., 1968b. Specificity of oligonucleotide synthesis directed by polyuridylic acid. *Proceedings of the National Academy of Sciences of the United States of America* 60, 409–415.
- Sultson, L., Lohrmann, R., Orgel, L.E., Schneider-Bernloehr, H., Weimann, B.J., 1969. Non-enzymic oligonucleotide synthesis on a polycytidylic acid template. *Journal of Molecular Biology* 40, 227–234.
- Summers, D.P., 1999. Sources and sinks for ammonia and nitrite on the early Earth and the reaction of nitrite with ammonia. *Origins of Life and Evolution of the Biosphere* 29, 33–46.
- Summers, D.P., 2005. Ammonia formation by the reduction of nitrite/nitrate by FeS: ammonia formation under acidic conditions. *Origins of Life and Evolution of the Biosphere* 35, 299–312.
- Summers, D.P., Chang, S., 1993. Prebiotic ammonia from reduction of nitrite by iron (II) on the early Earth. *Nature* 365, 630–633.
- Summers, D.P., Khare, B., 2007. Nitrogen fixation on early Mars and other terrestrial planets: experimental demonstration of abiotic fixation reactions to nitrite and nitrate. *Astrobiology* 7, 333–341.
- Summers, D.P., Basa, R.C.B., Khare, B., Rodoni, D., 2012. Abiotic nitrogen fixation on terrestrial planets: reduction of NO to ammonia by FeS. *Astrobiology* 107–114.
- Sutherland, J.D., 2010. Ribonucleotides. *Cold Spring Harbor Perspectives in Biology* 2, a005439.
- Suwannachot, Y., Rode, B.M., 1998. Catalysis of dialanine formation by glycine in the salt-induced peptide formation reaction. *Origins of Life and Evolution of the Biosphere* 28, 79–90.
- Suwannachot, Y., Rode, B.M., 1999. Mutual amino acid catalysis in salt-induced peptide formation supports this mechanism's role in prebiotic peptide evolution. *Origins of Life and Evolution of the Biosphere* 29, 463–471.
- Symonds, R.B., Rose, W.I., Bluth, G.J.S., Gerlach, T.M., 1994. Volcanic gas studies—methods, results, and applications. *Reviews in Mineralogy* 30, 1–66.
- Szostak, J.W., Bartel, D.P., Luisi, P.L., 2001. Synthesizing life. *Nature* 409, 387–390.
- Szostak, J.W., 2012. The eightfold path to non-enzymatic RNA replication. *Journal of Systems Chemistry* 3, 2.
- Taillades, J., Beuzelin, I., Garrel, L., Tabacik, V., Bied, C., Commeyras, A., 1998. N-carbomoyl- $\alpha$ -amino acids rather than free  $\alpha$ -amino acids formation in the primitive hydrosphere: a novel proposal for the emergence of prebiotic peptides. *Origins of Life and Evolution of the Biosphere* 28, 61–77.
- Takahashi, J., Hosokawa, T., Masuda, H., Kaneko, T., Kobayashi, K., Saito, T., Utsumi, Y., 1999. Abiotic synthesis of amino acids by X-ray irradiation of simple inorganic gases. *Applied Physics Letters* 74, 877–879.
- Takai, K., Nakamura, K., Suzuki, K., Inogaki, F., Nealson, K.H., Kumagai, H., 2006. Ultramafics—hydrothermalism—hydrogenesis—hyperslime (UltraH3) linkage: a key insight into early microbial ecosystem in the Archean deep-sea hydrothermal systems. *Paleontological Research* 10, 269–282.
- Tapiero, C.M., Nagyvary, J., 1971. Prebiotic formation of cytidine nucleotides. *Nature* 231, 42–43.
- Testa, S.M., Disney, M.D., Turner, D.H., Kierzek, R., 1999. Thermodynamics of RNA–RNA duplexes with 2- or 4-thiouridines: implications for antisense design and targeting a group I intron. *Biochemistry* 38, 16655–16662.
- Thomas, J.A., Rana, F.R., 2007. The influence of environmental conditions, lipid composition, and phase behavior on the origin of cell membranes. *Origins of Life and Evolution of the Biosphere* 37, 267–285.
- Tian, F., Kasting, J.F., Zahnle, K., 2011. Revisiting HCN formation in Earth's early atmosphere. *Earth and Planetary Science Letters* 308, 417–423.
- Tivey, M.K., 2007. Generation of seafloor hydrothermal vent fluids and associated mineral deposits. *Oceanography* 20, 50–65.



- Trail, D., Watson, E.B., Tailby, N.D., 2011. The oxidation state of Hadean magmas and implications for early Earth's atmosphere. *Nature* 480, 79–82.
- Turekian, K.K., Cochran, J.K., 1986. Flow rates and reaction rates in the Galapagos Rise spreading center hydrothermal system as inferred from  $^{228}\text{Ra}/^{226}\text{Ra}$  in vesicomid clam shells. *Proceedings of the National Academy of Sciences of the United States of America* 83, 6241–6244.
- Ueno, Y., Yamada, K., Yoshida, N., Maruyama, S., Isozaki, Y., 2006. Evidence from fluid inclusions for microbial methanogenesis in the early Archaean era. *Nature* 440, 516–519.
- Utsumi, Y., Takahashi, J., 1998. Synthesis of amino acids from  $\text{N}_2$ ,  $\text{H}_2\text{O}$  vapor and  $\text{CO}_2$  gas mixture by synchrotron radiation induced photochemical reactions at atmospheric pressure. *Japanese Journal of Applied Physics* 37, L1268–L1270.
- Van Cappellen, P., Ingall, E.D., 1996. Redox stabilization of the atmosphere and oceans by phosphorus-limited marine productivity. *Science* 271, 493–496.
- Van Trump, J.E., Miller, S.L., 1972. Prebiotic synthesis of methionine. *Science* 178, 859–860.
- Vazquez-Mayagoitia, A., Horton, S.R., Sumpter, B.G., Sporer, J., Sporer, J.E., Fuentes-Cabrera, M., 2011. On the stabilization of ribose by silicate minerals. *Astrobiology* 11, 115–121.
- Verlander, M.S., Orgel, L.E., 1974. Analysis of high molecular weight material from the polymerization of adenosine cyclic 2',3'-phosphate. *Journal of Molecular Evolution* 3, 115–120.
- Verlander, M.S., Lohrmann, R., Orgel, L.E., 1973. Catalysts for the self-polymerization of adenosine cyclic 2',3'-phosphate. *Journal of Molecular Evolution* 2, 303–316.
- Voet, A.B., Schwartz, A.W., 1982. Uracil synthesis via HCN oligomerization. *Origins of Life* 12, 45–49.
- Vogel, S.R., Richert, C., 2007. Adenosine residues in the template do not block spontaneous replication steps of RNA. *Chemical Communications* 1896–1898.
- Vogel, S.R., Deck, C., Richert, C., 2005. Accelerating chemical replication steps of RNA involving activated ribonucleotides and downstream-binding elements. *Chemical Communications* 4922–4924.
- Wächtershäuser, G., 1988. Before enzymes and templates: theory of surface metabolism. *Microbiological Reviews* 52, 452–484.
- Wächtershäuser, G., 1990. Evolution of the first metabolic cycles. *Proceedings of the National Academy of Sciences of the United States of America* 87, 200–204.
- Wächtershäuser, G., 2000. Life as we don't know it. *Science* 289, 1307–1308.
- Wächtershäuser, G., 2006. From volcanic origins of chemoautotrophic life to Bacteria, Archaea and Eukarya. *Philosophical Transactions of the Royal Society B* 361, 1787–1808.
- Wagman, D.D., Evans, W.H., Parker, V.B., Schumm, R.H., Halow, L., Bailey, S.M., Churney, K.L., Nuttall, R.L., 1982. The NBS tables of chemical thermodynamic properties. Selected values for inorganic and  $\text{C}_1$  and  $\text{C}_2$  organic substances in SI units. *Journal of Physical and Chemical Reference Data* 11 (Suppl. 2), 1–392.
- Wakamatsu, H., Yamada, Y., Saito, T., Kumashiro, I., Takenishi, T., 1966. Synthesis of adenine by oligomerization of hydrogen cyanide. *Journal of Organic Chemistry* 31, 2035–2036.
- Wang, K.J., Ferris, J.P., 2001. Effect of inhibitors on the montmorillonite clay-catalyzed formation of RNA: studies on the reaction pathway. *Origins of Life and Evolution of the Biosphere* 31, 381–402.
- Wang, Y.L., Lee, H.D., Beach, M.W., Margerum, D.W., 1987. Kinetics of base hydrolysis of cyanogen and 1-cyanoformamide. *Inorganic Chemistry* 26, 2444–2449.
- Wasner, M., Arion, D., Borkow, G., Noronha, A., Uddin, A.H., Parniak, M.A., Damha, M.J., 1998. Physicochemical and biochemical properties of 2',5'-linked RNA and 2',5'-RNA:3',5'-RNA “hybrid” duplexes. *Biochemistry* 37, 7478–7486.
- Weber, A.L., 1982. Formation of pyrophosphate on hydroxyapatite with thioesters as condensing agents. *BioSystems* 15, 183–189.
- Weber, A.L., Pizzarello, S., 2006. The peptide-catalyzed stereospecific synthesis of tetroses: a possible model for prebiotic molecular evolution. *Proceedings of the National Academy of Sciences of the United States of America* 103, 12713–12717.
- Weber, A.L., Caroon, J.M., Warden, J.T., Lemmon, R.M., Calvin, M., 1977. Simultaneous peptide and oligonucleotide formation in mixtures of amino acid, nucleoside triphosphate, imidazole, and magnesium ion. *BioSystems* 8, 277–286.
- Weiss, B.P., Kirschvink, J.L., Baudenbacher, F.J., Vali, H., Peters, N.T., Macdonald, F.A., Wikswo, J.P., 2000. A low temperature transfer of ALH84001 from Mars to Earth. *Science* 290, 791–795.
- White, R.H., 1984. Hydrolytic stability of biomolecules at high temperatures and its implication for life at 250 °C. *Nature* 310, 430–432.
- Wilde, S.A., Valley, J.W., Peck, W.H., Graham, C.M., 2001. Evidence from detrital zircons for the existence of continental crust and oceans on the Earth 4.4 Gyr ago. *Nature* 409, 175–178.
- Woese, C., 1967. *The Genetic Code, the Molecular Basis for Genetic Expression*. Harper and Row, New York.
- Wolfenden, R., 2011. Benchmark reaction rates, the stability of biological molecules in water, and the evolution of catalytic power in enzymes. *Annual Review of Biochemistry* 80, 645–667.
- Wood, B.J., Waler, M.J., Wade, J., 2006. Accretion of the Earth and segregation of its core. *Nature* 441, 825–833.
- Wordsworth, R., Pierrehumbert, R., 2013. Hydrogen-nitrogen greenhouse warming in Earth's early atmosphere. *Science* 339, 64–67.
- Wu, T., Orgel, L.E., 1992. Nonenzymatic template-directed synthesis on hairpin oligonucleotides. 3. Incorporation of adenosine and uridine residues. *Journal of the American Chemical Society* 114, 7965–7969.
- Yakovlev, O.I., Dikov, Y.P., Gerasimov, M.V., 2006. Experimental data on the thermal reduction of phosphorus and iron and their significance for the interpretation of the impact reworking of lunar materials. *Geochemistry International* 44, 847–854.
- Yamagata, T., 1999. Prebiotic formation of ADP and ATP from AMP, calcium phosphates and cyanate in aqueous solution. *Origins of Life and Evolution of the Biosphere* 29, 511–520.
- Yamagata, Y., Matsukawa, T., Mohri, T., Inomata, K., 1979. Phosphorylation of adenosine in aqueous solution by electric discharges. *Nature* 282, 284–286.
- Yamagata, Y., Watanabe, H., Saitoh, M., Namba, T., 1991. Volcanic production of polyphosphates and its relevance to prebiotic evolution. *Nature* 352, 516–519.
- Yamanaka, J., Inomata, K., Yamagata, Y., 1988. Condensation of oligoglycines with trimeta- and tetrametaphosphate in aqueous solutions. *Origins of Life and Evolution of the Biosphere* 18, 165–178.
- Yanagawa, H., Kobayashi, K., 1992. An experimental approach to chemical evolution in submarine hydrothermal systems. *Origins of Life and Evolution of the Biosphere* 22, 147–159.
- Yanagawa, H., Kobayashi, Y., Egami, F., 1980. Genesis of amino acids in the primeval sea. *Journal of Biochemistry* 87, 359–362.
- Yanagawa, H., Makino, Y., Sato, K., Nishizawa, M., Egami, F., 1982. Novel formation of  $\alpha$ -amino acids and their derivatives from oxo acids and ammonia in an aqueous medium. *Journal of Biochemistry* 91, 2087–2090.
- Yang, J.S., Bai, W.J., Rong, H., Zhang, Z.M., Xu, Z.Q., Fang, Q.S., Yang, B.G., Li, T.F., Ren, Y.F., Chen, S.Y., Hu, J.Z., Su, J.F., Mao, H.K., 2005. Discovery of  $\text{Fe}_2\text{P}$  alloy in garnet peridotite from the Chinese continental scientific drilling project (CCSD) main hole. *Acta Petrologica Sinica* 21, 271–276.
- Yang, X., Gaillard, F., Scaillet, B., 2014. A relatively reduced Hadean continental crust and implications for the early atmosphere and crustal rheology. *Earth and Planetary Science Letters* 393, 210–219.
- Yuasa, S., Flory, D., Basile, B., Oro, J., 1984. Abiotic synthesis of purines and other heterocyclic compounds by the action of electrical discharges. *Journal of Molecular Evolution* 21, 76–80.
- Yuen, G.U., Lawless, J.G., Edelson, E.H., 1981. Quantification of monocarboxylic acids from a spark discharge synthesis. *Journal of Molecular Evolution* 17, 43–47.
- Zagorevskii, D.V., Aldersley, M.F., Ferris, J.P., 2006. MALDI analysis of oligonucleotides directly from montmorillonite. *Journal of the American Society for Mass Spectrometry* 17, 1265–1270.
- Zahnle, K.J., 1986. Photochemistry of methane and the formation of hydrocyanic acid (HCN) in the earth's early atmosphere. *Journal of Geophysical Research* 91, 2819–2834.
- Zaia, D.A.M., Zaia, C.T.B.V., De Santana, H., 2008. Which amino acids should be used in prebiotic chemistry studies? *Origins of Life and Evolution of the Biosphere* 38, 469–488.
- Zamaraev, K.I., Romannikov, V.N., Salganik, R.I., Wlasoff, W.A., Khramtsov, V.V., 1997. Modeling of the prebiotic synthesis of oligopeptides: silicate catalysts help to overcome the critical stage. *Origins of Life and Evolution of the Biosphere* 27, 325–337.
- Zhang, S., Blain, J.C., Zielinska, D., Gryaznov, S.M., Szostak, J.W., 2013. Fast and accurate nonenzymatic copying of an RNA-like synthetic genetic polymer. *Proceedings of the National Academy of Sciences of the United States of America* 110, 17732–17737.
- Zhu, T.F., Szostak, J.W., 2009. Coupled growth and division of model protocell membranes. *Journal of the American Chemical Society* 131, 5705–5713.
- Zubay, G., 1998. Studies on the lead-catalyzed synthesis of aldopentoses. *Origins of Life and Evolution of the Biosphere* 28, 13–26.