"III Congreso Latinoamericano de Astrobiología (2021)"
Revista Mexicana de Astronomía y Astrofísica Serie de Conferencias (RMxAC), **55**, 15–20 (2023)

https://doi.org/10.22201/ia.14052059p.2023.55.03

III Latin American Congress of Astrobiology (3CLA)(Virtual-Modality, August 3-6, 2021)
Editors: Leticia Carigi, Sandra I. Ramírez Jiménez, Miguel Chávez Dagostino, and Millarca Valenzuela - DOI: https://doi.org/10.22201/ia.14052059p.2023.55.03

HOW DOES PREBIOTIC CHEMISTRY GO?

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RESUMEN

En el intento de reconstruir en el laboratorio etapas previas al origen de la vida desde una perspectiva clásica de atrás, al inicio con moléculas muy simples, hacia adelante, ya con el origen de sistemas auto replicantes, considerando que un proceso de síntesis química precedió a la vida, se han tenido grandes avances desde la propuesta de Oparin-Haldane, que sirvió de base al famoso experimento de Stanley Miller, pero también grandes dificultades e intensos debates. Ya casi a un siglo que estos aspectos fueron propuestos, muchas de las preguntas centrales aún siguen sin una adecuada respuesta. Por ello, se han presentado nuevas aproximaciones en las síntesis de compuestos de importancia prebiótica, especialmente la coevolución de varias moléculas conformando redes capaces de tener un proceso de evolución química.

ABSTRACT

In the attempt to reconstruct stages before the origin of life in the laboratory from a classic bottom-up perspective, from relatively simple molecules at the beginning to the self-replicating systems, a process of chemical synthesis preceding life, called chemical evolution, was proposed. Since the Oparin–Haldane proposal, significant advances have been made, which served as the basis for Stanley Miller's famous experiment, but great difficulties and intense debates have also arisen. Almost a century after these aspects were proposed, many of the central questions remain without adequate answers. Therefore, new approaches have been presented to synthesize compounds of prebiotic importance, especially involving the co-evolution of various molecule-conforming networks capable of chemical evolution.

Key Words: astrobiology — chemical evolution — pre-biotic astrochemistry

1. EVOLUTION OF THE PLANET AND THE ORIGIN OF LIFE

Earth has changed from its formation to the present. Among the phases of the Earth's evolution is the Precambrian, during which the most important events that changed Earth from a lifeless planet to a world full of life occurred (Ramphal 2010).

Life is a particular and unique system as a continuation of the universe's evolutionary process. It is a piece of complex machinery assembled for millions of molecules. The idea that a cell is the fundamental biological unit and its evolution into more complex forms were revolutionary concepts at the end of the 19th century. They are now cornerstones of biology. Parallels exist between biological evolution and evolution at the molecular level. The simplest molecules formed more of the complex ones as parts of cell components. Any definition of life requires minimum characteristics for something to be considered alive, which are also overly complicated to define. The consensus view of the minimum properties that a system should have is compartmentalization, metabolism, and replication (Ruiz-Mirazo 2014). Each of these processes requires organic molecules and their abiotic generation, which are essential for the development of life. This topic has yielded insights into the steps prior to the appearance of life.

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2. MINIMAL REQUIREMENTS FOR A CELL

2.1. *Compartments*

Among the essential requirements for the emergence of life are compartments. The membrane's presence prevents a chemical process from dispersing into the surrounding environment. In addition, encapsulation decreases volume, which increases the concentration of reactants inside. Furthermore, the compartment provides individuality and an isolated environment for reaction networks to develop. For these and other reasons, researchers consider membrane encapsulation at an early stage in prebiotic chemical evolution as an essential requirement for the emergence of life. Conceptually, a membrane may be the most readily formed of the major cellular components (Segré et al. 2001; Szostak et al. 2001; Deamer et al. 2002; Schrum et al. 2010; Deamer 2011).

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2.2. *Metabolism*

The primitive cell should have a system capable of being energetically autonomous. For this reason, scientists favor an alternative route to the origin of life–based chemical reactions occurring within hydrothermal systems.

2.3. *Information*

Another important minimal component of a cell is the capacity to pass information to its descendants. The biomolecules in charge of that mission are the nucleic acids. These are complex molecules that present four nucleic acid bases, a sugar, and a phosphate group. This aspect involves how entities had the capacities for multiplication, variation, and heredity.

3. THE SCENERY OF THE EARLY EARTH

What was the early Earth like? The environmental conditions in the primitive Earth are a matter of relevant importance. Despite the scientific advance, the conditions of the Earth remain without an exact definition. This problem is due to the lack of geological information from that time. The chemical and physical conditions present in the early Earth should be reconstructed based on geological records and theoretical environmental models (Valdivia-Silva et al. 2013). The critical aspects relevant to the origin of life are related to the atmosphere, ocean, and continents, among others.

3.1. *Time Scale*

Changes have occurred since the origin of the universe and the formation of our planet. In this way, the conditions were established for the emergence of life on Earth. Evidence-based U-Pb, Hf-W, and Sm-Nd isotopic measurements suggest that the Earth was formed at about 4750 Ma (Tilton & Steiger 1965). An unknown phenomenon took place in this crucial period, from which the transformation originated from inorganic matter to organic matter and later to life.

3.2. *Atmosphere*

The Earth's atmosphere and oceans were formed from the impact of in-falling planetesimals degassing on the planet. The primitive atmosphere supplied the raw materials for organic compounds to be synthesized. Regarding the atmosphere's nature, widely different views have been expressed concerning its constitution and redox character. Models of atmospheric evolution suggest that the Archean atmosphere was composed mainly of CO_2, H_2O and N_2 (Kasting & Ackerman 1986; Kasting 1993; Walker 1990). The nature of the composition, with higher atmospheric CO_2 levels, is critical because carbon dioxide is an effective infrared absorber that could have warmed the Earth's surface by contributing to the greenhouse effect (Kasting & Ackerman 1986). Additionally, it is consistent with the Archean sun's lower luminosity, in that above-freezing temperatures were maintained by this CO_2-rich atmosphere on the early Earth (Caldeira & Kasting 1992).

When and how did the atmosphere start to accumulate molecular oxygen? It is generally agreed that the primitive atmosphere did not contain more than a trace of free oxygen. Three sources of oxygen are considered plausible: the photodissociation of water vapor by solar UV radiation in the upper layers of the atmosphere (Canuto et al. 1983). The second is a biotic source. Specifically, by cyanobacteria, photosynthetic organisms produced oxygen as a byproduct and first appeared 3500 Ma ago. They became widespread in the Proterozoic. The photosynthetic activity was primarily responsible for the rise of atmospheric oxygen (Holland 2006). The third source proposed by Draganić et al. 1991 included the decomposition of ocean waters by potassium-40 radiation. Geological evidence such as the distribution of pyritic conglomerates over time suggests that oxygen production by cyanobacteria did not immediately result in a significant increase of atmospheric oxygen. Instead, three oxygen sinks consumed the molecular oxygen: 1) reaction with volcanic gases, 2) facultative aerobic microbes that used oxygen, and 3) burial in the iron-rich layers of banded iron formations (BIFs). Ultimately, about 2000–1800 Ma, a stable aerobic environment was established after atmospheric oxygen levels rose. This oxygen level was the "first pollution crisis" that hit the Earth, at about 2200 Ma.

3.3. *Oceans*

The composition and pH of the primitive oceans are essential information for determining the prevailing conditions of the early Earth. Evidence of liquid surface water from the isotopic analysis of detrital zircons from 4300 to 4400 Ma showed that liquid water could have existed (Wilde et al. 2001). In the beginning, the pH of this ocean was driven by the volatile fraction of the atmosphere. The CO_2 present produced an acidic pH. Later, inorganic salts dissolved changed to alkaline pH. Nevertheless, the question of where Earth's original water came from has been fraught with controversy.

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3.4. *Energy Sources*

Several energy sources have been proposed as having induced chemical changes in the raw materials that formed organic compounds upon the primitive Earth. The variety and intensity of the action may have caused different products. In the laboratory, most of these forms of energy are used to simulate primitive conditions. Some characteristics are needed to consider an energy source as a potential source for prebiotic synthesis. It must be available, abundant, and efficient to induce chemical reactions. Different energy sources have been proposed as having contributed to the synthesis of organic matter. Ultraviolet light from the sun, which produces total energy of 260,000 $cal\ cm^{-2}\ yr^{-1}$ (Miller 1953), is the most important, and up to now, life on our planet today is dependent on the Sun for its energy. Other energy sources are the heat from volcanoes and hot springs, radioactivity, and discharges from lightning (Valdivia-Silva et al. 2013).

3.5. *The raw material*

The answer to such questions about the raw material is complex, considering the information provided by astronomers. The raw materials available were H, He, O, C, N, Ne, and S, the most abundant elements in the universe. Present-day life is based on carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus atoms (C H, O, N, S, and P). These elements are the bioorganic molecules forming the simple precursors that constitute the primitive scenario. The sources for these compounds could have been exogenous, through contributions from extraterrestrial bodies like comets or meteorites, or indigenous to the Earth, formed via synthesis from simple precursors. They evolved into more complex molecules and biomolecules.

3.6. *The earliest evidence for life*

In a journey into the Precambrian eon, on Akilia Island in Greenland, the oldest stromatolite-like structures were discovered in the 3700-Ma-old Isua supracrustal belt (Nutman et al. 2016). Other earliest life forms could be traced by studying the relatively well-preserved rock, 3500 to 3300 Ma in age, found in the Warrawoona formation (Shopf & Packer 1987; Shopf 1993). By this stage in the evolution of life, life took a complex microbial form.

4. HYPOTHESES ON THE ORIGIN OF LIFE

Hypotheses exist to explain the origin of life on Earth. Nevertheless, none of these views gained a unanimous preferential position over the others,

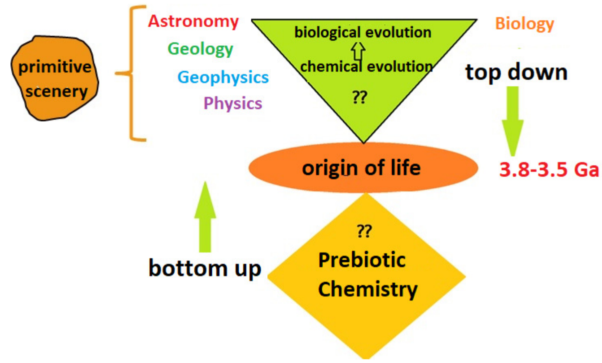

Fig. 1. General aspect and approaches to the origin of life.

and each has its shortcomings. Considering that the number of molecules necessary for life is reduced, any hypothesis should account for the abiotic supply of monomers necessary for the first biological system. This topic requires a basic understanding of the role these molecules have at present.

The hypotheses on the origins of life underlying specific physical and chemical properties can be grouped into two main ideas. One focuses on Heterotroph/genetics first. This hypothesis has RNA or DNA replication as an essential condition for Darwinian evolution and heterotrophic cells. The second idea focuses on autotrophic/metabolism first, also called chemoautotrophic theory. Both approaches still have unanswered questions.

The Oparin–Haldane hypothesis (Oparin 1938; Haldane 1928) proposes that life originated from chemical and physical processes and a hypothetical synthesis period called chemical evolution. This period was necessary for the building block of cells to exist. In this way, the study of chemical evolution encompasses physical and chemical events that resulted in molecules of biological importance forming before living things appeared. The medium's physicochemical factors facilitated the chemical evolution process. This hypothesis exists in the context of a heterotrophic origin of life. It considers that the conditions of the primitive Earth were different from the present. Especially the reductive character of the atmosphere, basic pH in the oceans, moderate temperature, several energy sources, and heterotrophic cells that cannot produce their food instead of taking nutrition from the environment.

4.1. *RNA world*

A reappraisal of the Oparin–Haldane hypothesis postulates that primitive cells, about 3800 Ma ago, had catalytic RNA, which may have arisen

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in an environment that followed a chemical pathway from prebiotically available precursors. RNA molecules functioned as genomes and genome catalysts (Revilla et al. 2020). This hypothesis solves the protein/RNA dilemma, at least herein, favoring RNA, due to the discovery of RNA molecules called ribozymes that have catalytic activity (Cech & Bass 1996). These findings indicate that RNA was able to conduct both information storage and catalysis functions. If correct, this would imply that the first organisms were composed of RNA. This hypothetical biosphere is known as the "RNA world" (Gilbert 1986). Both DNA and protein molecules were formed and evolved throughout evolution to perform a function and do so in a more optimal way than RNA. Thus, one molecule could have served several roles. However, it is difficult for many researchers to think about how a complex system like the genetic machinery could evolve from simple components. This problem is one of the paradigmatic controversies between genetic versus metabolic first.

4.2. *The autotrophic/metabolism first hypothesis*

In this scenario, the first stages involved a primitive metabolism involving developing carbon fixation, with other aspects such as membranes, proteins, and nucleic acids arising later. This idea proposes that life first emerged from a network of chemical reactions occurring within hydrothermal systems (Wächtershäuser 1992, 2006; Russell & Hall 2006). Submarine hydrothermal systems have the basic ingredients for chemical reactions, such as CO_2, H_2S and NH_3, and mineral surfaces, to drive reaction networks to emerge.

5. PREBIOTIC CHEMISTRY

An approach to this topic is to simulate in the laboratory the possible routes for how bioorganic molecules may have been synthesized before the appearance of living beings. Miller (1953) initiated this approach in his classic experiment, giving rise to prebiotic chemistry studies. The information obtained from simulations of chemical reactions, the possible conditions that existed on the primitive Earth, and comparisons with actual organisms may be correlated to understand the early steps in the origin of life.

5.1. *Simulation of how biomolecules formed in the prebiotic Earth*

The understanding of life's origins and evolution has long been dominated by aspects like taking clues from existing biology, extrapolating its molecules and pathways back in time, and determining the geochemical processes that possibly played prominent roles in synthesizing bioorganic compounds. Prebiotic chemistry studies have led to a basic understanding of the formation and stability of a relatively small number of prebiotic molecules in conditions proposed to exist on the early Earth. Some of these conditions are heterogeneous environments, with the presence and participation of minerals that would enable sufficiently complex chemistry, which would have a relevant role in approaching the origin of life (Ramos-Bernal & Negrón-Mendoza 1998). Two critical aspects should be considered in simulated experiments related to chemical evolution on Earth: (1) It is important to simulate a geologically relevant scenario to have a more realistic and plausible environment that could resemble the primitive Earth. Although making this connection is not always an easy task, such constraints would require complex multiphase systems. In this geological framework, it is relevant to consider the contribution of solid surfaces as a catalyst. Among the most important surfaces are silicates, carbonates, sulfides, and clays. (2) For molecules used for biological processes, they must have the same set of compounds during their synthesis. Therefore, it is crucial to have a biased synthesis that leads to this selectivity. A biased character would render a minor sequence compared to a sequence derived from random synthesis (Mosqueira et al. 2002). These considerations generate questions. What could the raw materials for their synthesis be? What molecules were involved, how abundant were they, and how stable were they? The studies focused on prebiotic chemistry provide essential information about the increased complexity of molecules and how they gave rise to emergent properties and could eventually shed light on the origin of life.

5.2. *Achievements and failures*

Monomers and small molecules have been synthesized, starting with simple precursors in the frame of chemical evolution. There are difficulties in finding universal solutions that connect prebiotic chemistry to biological chemistry. Important precursors as amino acids, nitrogen bases, carboxylic acids have been synthesized under possible prebiotic conditions. However, the synthesis of larger molecules has problems, especially those forming important biological polymers such as proteins and nucleic acids. These polymerization syntheses do not proceed in an aqueous medium. They are thermodynamically uphill, giving rise to poor selectivity for the polymer's formation. At this point, it is helpful to rethink the

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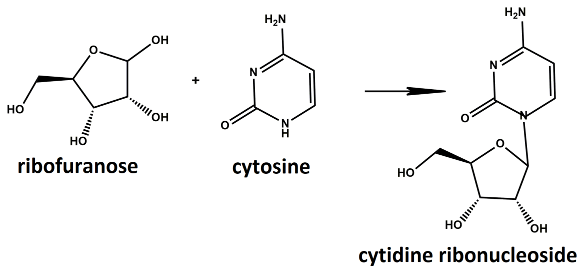

Fig. 2. A traditional synthesis of nucleosides step by step resulting in low yields of the final product.

chemical processes of the synthesis as the sole end goal (Krishnamurthy 2018).

5.3. *Systems chemistry*

New approaches have been presented to synthesize compounds of prebiotic importance, integrating chemical systems to make processes more efficient within a plausible geological scheme and simultaneously studying multiple variables. This approach is known as systems chemistry, which involves taking advantage of new technologies to propose chemical systems with multiple functions from which unconventional paths could originate. Research in this area is still fragmented and beginning (Powner & Sutherland 2011; Ruiz-Mirazo 2014). Previous schemes for synthesizing compounds related to life's origin have been followed by the sequential addition of others, rather than the emergence of life based on a mixture of all classes of molecules. The goals of system chemistry are to use chemical clues from multiple subsystems, search for the relevant geochemical conditions, and try to solve the central questions that remain unanswered. Limitations of traditional synthetic chemistry to the problem of life's origins are apparent through the lack of the synthesis of biopolymers. Simultaneously, the potential of new methodologies matches plausible geochemistry constraints, from which the origins of life scenarios can be inferred. An important consideration is having a basic understanding of the formation and stability of molecules on the early Earth, considering thermodynamics, and chemical kinetics, as the driving forces.

5.4. *Advantages over the traditional method*

The systems chemistry approach presents advantages because the synthesis routes are more robust than those involved in the traditional synthesis of each compound are. Some controversies like genetics versus metabolism first are overcome because it involves the co-evolution of a heterogeneous system.

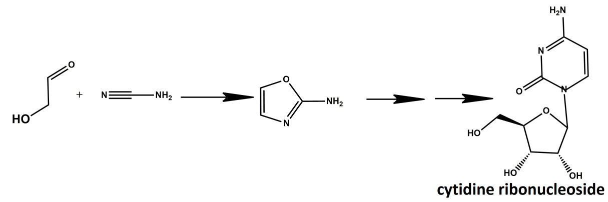

Fig. 3. Synthesis of a nucleoside in a system chemistry approach, with a good yield of the product.

In addition, when formed in a complex medium, the molecules may have chemical interactions and form a network that transforms into a proto-biological system.

These systems have diverse components: thermodynamic and kinetic aspects govern them, and the reactions must be far from chemical equilibrium. Moreover, the limits for the system will be given by minerals or proto membranes. The compartments decreased dilution and increased the interaction among the components inside of the compartment. An example of system chemistry is the formation of a nucleoside.

6. REMARKS

Prebiotic chemistry encompasses the simulation at the laboratory of the possible processes that yield the synthesis of biomolecules. Since the experiment of Miller, many compounds of relevance for life have been formed. However, there are still necessary steps in the area that do not have an answer. A new approach to prebiotic chemistry is system chemistry. That is starting to synthetize compounds in a geological frame, using non-conventional reagents and pathways not directed associated with extant biological compounds, and obtain some of the building blocks of life in much more efficient ways. As L. Orgel wrote, which remains highly topical, "Prebiotic chemistry remains such a diverse field that it is by no means clear where the next breakthroughs will occur" (Orgel 2004).

Acknowledgments: I gratefully acknowledge the support of PAPIIT IN110919 project. I thank for the support received with gratitude and affection to my colleagues from the laboratory: Q. C. Camargo, Dr. K. Cervantes, Dr. J. Cruz, Dr. A. Heredia, Dr. A. López, MEMS I. Mejia, Dr. A. Meléndez, M.Sc. P. Molina, Dr. S. Ramos, and Dr. H. Vázquez, for the tremendous support in the working group and the students associated with the LEQ, who are essential parts of the laboratory.

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