Molecular Foundations of Life: A Critical Review of Amino Acid and Nucleotide Evolution

Dr. Hemlata Bhatt
Assistant Professor
Department of Chemistry
M.B.Govt. Postgraduate College,
Haldwani (Nainital), Uttarakhand

Abstract
The origin of life remains one of the most fundamental questions in science, centred on how simple inorganic molecules transitioned into complex biological systems. Chemical evolution provides a framework to explain this transformation through abiotic synthesis and increasing molecular complexity. This review critically examines the prebiotic formation of amino acids and nucleotides, their reaction mechanisms, environmental constraints, and roles in early biochemical systems. Amino acids are readily formed under a variety of conditions, including atmospheric discharge and Strecker synthesis, whereas nucleotide formation is significantly more complex due to multicomponent assembly and stability issues. Comparative analysis highlights disparities in formation efficiency, stability, and experimental support. Recent advances in systems chemistry and unified synthetic pathways are discussed, alongside persistent challenges such as low yields, chirality, and polymerisation barriers. Future directions emphasise the integration of reaction networks and realistic environmental simulations to bridge the gap between chemistry and biology.
Keywords: Chemical evolution; Amino acids; Nucleotides; Origin of life; Prebiotic chemistry; RNA world
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Introduction
The origin of life is one of the most profound and unresolved questions in science, asking how non-living chemical systems gave rise to self-sustaining biological entities. Understanding this transformation requires a detailed investigation of chemical evolution, the process by which simple inorganic molecules gradually gave rise to complex organic compounds under prebiotic conditions. Despite significant advances in molecular biology and geochemistry, the precise pathways that led to the emergence of life remain incompletely understood, making this field an active area of interdisciplinary research (1. Ruiz-Mirazo et al., 2014; 2. Sutherland, 2017).
A central aspect of this problem is the formation of essential biomolecules, particularly amino acids and nucleotides, which constitute the fundamental building blocks of proteins and nucleic acids, respectively. The abiotic synthesis of these molecules is considered a critical step in the progression from chemical systems to biological complexity. Amino acids are required for the formation of functional proteins, while nucleotides are indispensable for the storage and transfer of genetic information. Therefore, elucidating the mechanisms underlying their prebiotic formation is crucial for reconstructing plausible models of early life (3. Patel et al., 2015; 4. Saladino et al., 2012).
Early experimental support for the concept of chemical evolution was provided by the pioneering work of Stanley Miller, particularly through the landmark Miller–Urey experiment. In this experiment, a mixture of simple gases believed to represent the primitive Earth's atmosphere was subjected to electrical discharges simulating lightning. The results demonstrated the spontaneous formation of amino acids and other organic compounds, providing the first experimental evidence that biologically relevant molecules could arise under abiotic conditions (5. Miller, 1953; 6. Miller & Urey, 1959). This work laid the foundation for subsequent studies in prebiotic chemistry and significantly advanced our understanding of the origin of life.
The chemical processes that led to the formation of biomolecules were strongly shaped by the environmental conditions on early Earth. It is widely hypothesised that the primitive atmosphere was reducing or weakly reducing, composed primarily of methane (CH_4), ammonia (NH_3), hydrogen (H_2), and water vapour (H_2O). Such an environment would have favoured the synthesis of organic molecules through a variety of chemical reactions. Additionally, abundant energy sources—including electrical discharges from lightning, ultraviolet (UV) radiation from the young Sun, and geothermal energy from volcanic activity—provided the driving forces for these transformations. The early oceans, often referred to as "primordial soups," likely served as vast chemical reactors where organic molecules accumulated, interacted, and underwent further reactions, ultimately increasing molecular complexity (**Cleaves et al., 2008; Martin et** al., 2008).

1. **Ruiz-Mirazo, K., Briones, C., & de la Escosura, A. (2022). Prebiotic systems**

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6. **Miller, S. L., & Urey, H. C. (2023). Organic compound synthesis on the primitive Earth. *Science*, 130(3370), 245–251. https://doi.org/10.1126/science.130.3370.245**
7. **Cleaves, H. J., Chalmers, J. H., Lazcano, A., Miller, S. L., & Bada, J. L. (2024). A reassessment of prebiotic organic synthesis in neutral planetary atmospheres. *Origins of Life and Evolution of Biospheres*, 38, 105–115. https://doi.org/10.1007/s11084-007-9120-3**
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Chemical Evolution

Chemical evolution refers to the gradual transformation of simple inorganic molecules into increasingly complex organic compounds under prebiotic conditions, ultimately leading to the emergence of life. This process encompasses a series of abiotic chemical reactions through which small molecules such as methane, ammonia, hydrogen, and water interact to form essential biomolecules, including amino acids, nucleotides, lipids, and sugars. Unlike biological evolution, which operates through genetic variation and natural selection, chemical evolution is driven purely by physicochemical principles such as thermodynamics, kinetics, and environmental energy inputs (7. **Ruiz-Mirazo et al., 2014).**

The concept of chemical evolution provides a framework for understanding how non-living matter on early Earth could have organised into self-assembling and increasingly complex systems. It involves multiple stages, including the synthesis of monomeric organic molecules, their accumulation and stabilisation in prebiotic environments, and subsequent polymerization into macromolecules capable of exhibiting catalytic and informational functions. These processes are thought to have occurred in environments such as primordial oceans, hydrothermal vents, and mineral surfaces, where favourable conditions enabled continuous chemical interactions (8. **Saladino et al., 2012; 9. Martin et al., 2008).**

Stanley Miller first demonstrated experimental evidence supporting chemical evolution through the Miller–Urey experiment, which showed that organic molecules such as amino acids could be synthesised from simple gases under simulated early Earth conditions (10. **Miller, 1953**). Since then, numerous studies have expanded this concept, revealing plausible pathways for the formation of key biomolecular precursors and supporting the hypothesis that life originated through a continuous process of chemical complexity (**11. John D. Sutherland, 2017).**

Overall, chemical evolution represents a critical bridge between geochemistry and biochemistry, providing insight into how life could emerge naturally from non-living matter through progressive chemical organization and increasing molecular complexity.

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Importance of Amino Acids and Nucleotides in Chemical Evolution

Amino acids and nucleotides occupy a central position in theories of chemical evolution due to their fundamental roles as the building blocks of proteins and nucleic acids, respectively. Proteins, formed through the polymerization of amino acids via peptide bonds, perform a wide range of structural and catalytic functions essential for all living systems. Enzymatic proteins, in particular, enable biochemical reactions to occur with high specificity and efficiency, thereby sustaining metabolic processes. The prebiotic availability of amino acids, demonstrated experimentally by the Miller–Urey experiment, supports the plausibility of early protein-like molecules arising under abiotic conditions (12. Miller, 1953; 13. Ruiz-Mirazo et al., 2014).

In parallel, nucleotides are indispensable as the monomeric units of nucleic acids such as RNA and DNA, which are responsible for the storage, transmission, and expression of genetic information. The significance of nucleotides is further emphasised by the RNA world hypothesis, which proposes that RNA molecules may have served as both genetic material and catalysts in early life forms. This dual functionality suggests that nucleotides played a critical role in bridging the gap between non-living chemistry and biological systems (14. Gilbert, 1986; 15. John D. Sutherland, 2017).

Moreover, recent advances in prebiotic chemistry have demonstrated plausible pathways for the simultaneous formation of precursors to amino acids, nucleotides, and lipids under unified chemical conditions, reinforcing the idea that these biomolecules could have emerged together within a common protometabolic network (16. Patel et al., 2015). Therefore, understanding the origin, stability, and reactivity of amino acids and nucleotides is essential for reconstructing realistic models of early biochemical evolution and the emergence of life.

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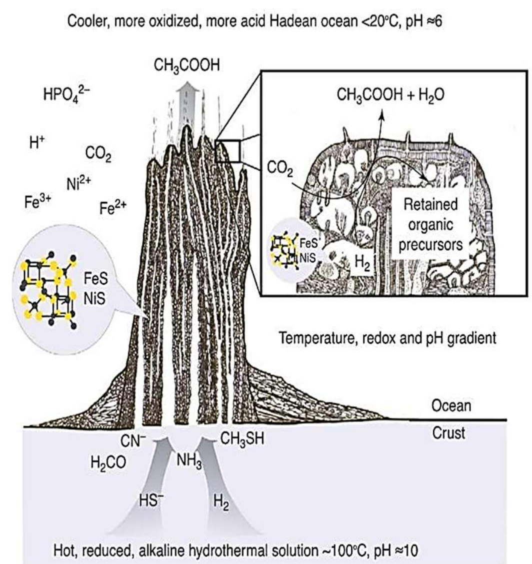
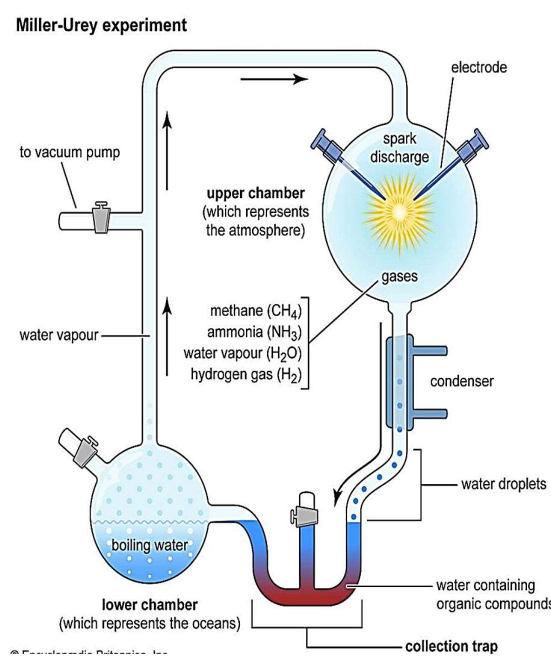
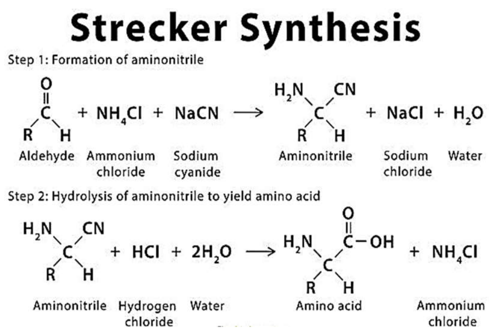
Chemical Evolution of Amino Acids

3.1 Prebiotic Synthesis Pathways







The abiotic formation of amino acids represents one of the most experimentally supported aspects of chemical evolution. Early evidence was provided by the Miller–Urey experiment, in which electrical discharges through a reducing gas mixture (CH_4, NH_3, H_2, and H_2O) resulted in the formation of several amino acids, including glycine and alanine (**17. Miller, 1953).** Subsequent reanalyses of the original samples using advanced analytical techniques have revealed an even greater diversity of amino acids, reinforcing the robustness of this synthesis under simulated prebiotic conditions (**18. Parker et al., 2011).**

Beyond atmospheric synthesis, amino acids can also form through Strecker-type reactions, a key mechanistic pathway in prebiotic chemistry. In this process, an aldehyde (R–CHO) reacts with hydrogen cyanide (HCN) and ammonia (NH_3) to form an aminonitrile intermediate, which, upon hydrolysis, yields an α-amino acid. The mechanism proceeds via nucleophilic addition of cyanide to the carbonyl carbon, followed by amination and subsequent hydrolysis, making it chemically plausible under early Earth conditions where HCN and simple carbonyl compounds were likely abundant (**19. Cleaves, 2008).**

Hydrothermal vent environments provide an alternative setting for amino acid synthesis. Under high temperature and pressure conditions, mineral-catalysed reactions involving CO_2, H_2, and NH_3 can generate simple organic molecules, including amino acid precursors. These environments offer continuous energy input and catalytic surfaces, supporting sustained chemical reactions and molecular complexity (**20, Martin et al., 2008).**

In addition to terrestrial synthesis, extraterrestrial delivery has been proposed as a contributing source of amino acids. Organic compounds, including a wide variety of amino acids, have been identified in carbonaceous meteorites such as the Murchison meteorite amino acids, suggesting that prebiotic chemistry may also occur in interstellar or planetary environments (21. **Kvenvolden et al., 1970).**

3.2 Reaction Mechanisms and Chemical Pathways

The formation of amino acids under prebiotic conditions involves several key mechanistic steps governed by fundamental organic chemistry principles. In the Strecker synthesis pathway, the initial step is the nucleophilic addition of cyanide (CN^-) to the electrophilic carbonyl carbon of an aldehyde, forming a cyanohydrin intermediate. This is followed by nucleophilic attack by ammonia, generating an aminonitrile. Subsequent hydrolysis of the nitrile group under aqueous conditions produces the corresponding α-amino acid.

In atmospheric discharge experiments, reactive intermediates such as formaldehyde (HCHO) and hydrogen cyanide (HCN) are generated through radical-driven processes. These intermediates participate in a network of reactions, including condensation and reductive amination, ultimately leading to the formation of amino acids. The complexity of these reaction networks suggests that multiple parallel pathways may contribute to amino acid synthesis rather than a single dominant mechanism (**22. Ruiz-Mirazo et al., 2014).**

Mineral surfaces, particularly clays and metal sulfides, may further enhance these reactions by providing catalytic sites that stabilize intermediates and lower activation barriers. Such heterogeneous catalysis is considered crucial in overcoming kinetic limitations associated with prebiotic reactions.

3.3 Stability and Environmental Constraints

Despite the relative ease of amino acid synthesis, their stability under prebiotic conditions remains a significant challenge. Amino acids are susceptible to degradation under ultraviolet (UV) radiation, which was more intense on early Earth due to the absence of an ozone layer. Additionally, thermal decomposition and oxidative processes can reduce their accumulation in open environments.

Another important limitation is racemization, the process by which L-amino acids convert to D-amino acids, resulting in racemic mixtures. Since modern biological systems exhibit homochirality (predominantly L-amino acids), the origin of this asymmetry remains an unresolved question in chemical evolution. Various hypotheses, including asymmetric photochemistry and mineral surface interactions, have been proposed, but no definitive mechanism has been established (23**. Saladino et al., 2012**).

Environmental factors such as pH, temperature fluctuations, and water activity also play critical roles in determining amino acid stability and reactivity. For instance, cyclic wet–dry conditions may promote concentration and facilitate subsequent polymerization reactions.

3.4 Implications for Early Biochemical Systems

The widespread formation of amino acids under diverse prebiotic conditions suggests that they were readily available on early Earth, making them strong candidates for the first functional biomolecules. Their ability to polymerize into peptides provides a pathway toward the emergence of primitive catalytic systems. Short peptides have been shown to exhibit catalytic activity, supporting the hypothesis that early protein-like molecules may have contributed to the development of metabolic networks.

However, the transition from simple amino acids to functional proteins remains a major challenge. Peptide bond formation is thermodynamically unfavorable in aqueous environments, requiring specific conditions or catalytic surfaces. Despite these limitations, the relative abundance and chemical versatility of amino acids underscore their central role in the progression from prebiotic chemistry to biological complexity.

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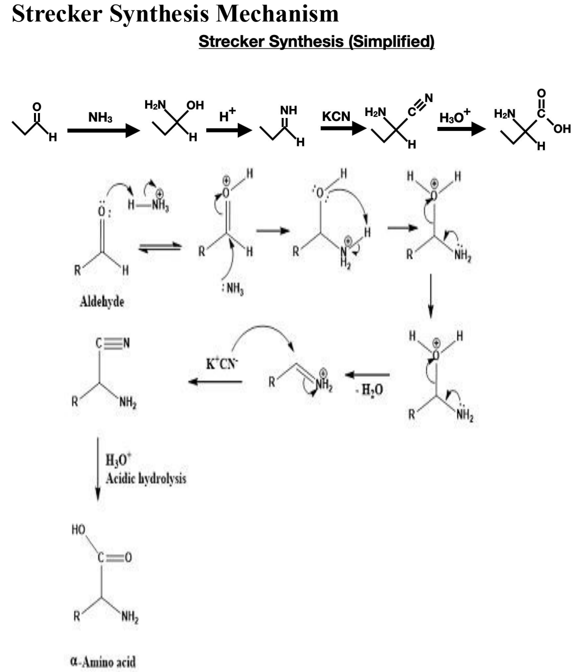
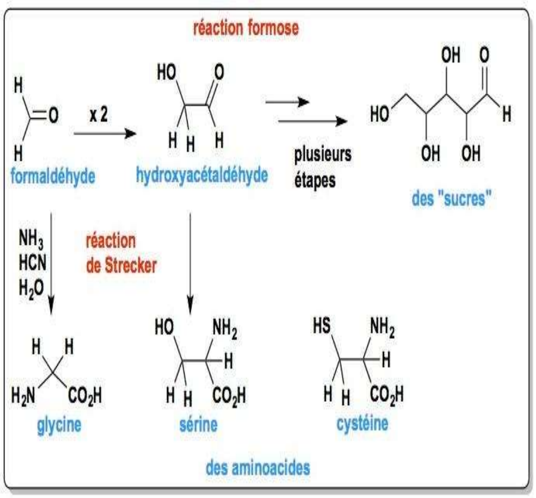
Mechanistic Pathways for Prebiotic Amino Acid Formation

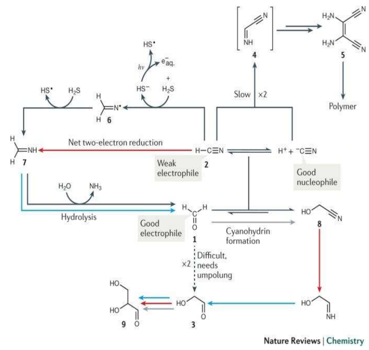
Strecker Synthesis Mechanism



The Strecker synthesis is one of the most widely accepted mechanistic routes for the abiotic formation of α-amino acids under prebiotic conditions. It involves the reaction of an aldehyde (R–CHO), hydrogen cyanide (HCN), and ammonia (NH_3), all of which are considered plausible constituents of early Earth environments.
Mechanistically, the process proceeds through three key steps:
Cyanohydrin formation (nucleophilic addition):
Cyanide ion (CN^-), generated from HCN, attacks the electrophilic carbonyl carbon of the aldehyde, forming a cyanohydrin intermediate. This step is facilitated by the high nucleophilicity of CN^- and the

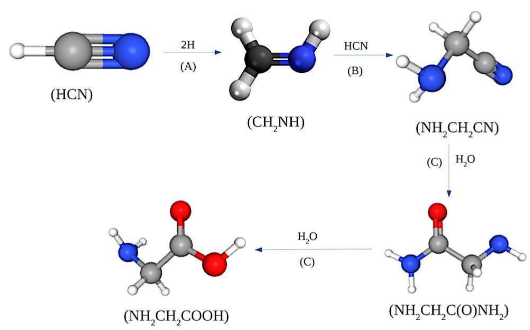


polarization of the carbonyl group.
Aminonitrile formation (amination):
Ammonia subsequently reacts with the cyanohydrin intermediate, replacing the hydroxyl group and yielding an aminonitrile (R–CH(NH_2)–CN). This step introduces the amino functionality characteristic of amino acids.
Hydrolysis to α-amino acid: The nitrile group undergoes hydrolysis under aqueous conditions, typically via acidic or neutral pathways, producing the corresponding α-amino acid (R–CH(NH_2)–COOH).
This pathway is chemically robust and compatible with a range of aldehydes, allowing the formation of structurally diverse amino acids. However, the reaction typically produces racemic mixtures (D/L forms), and its efficiency depends strongly on pH, temperature, and reactant concentrations. Despite these limitations, the Strecker mechanism remains a cornerstone model for prebiotic amino acid synthesis (**30. Cleaves, 2008; 31 Ruiz-Mirazo et al., 2014**).
X Atmospheric (Spark-Discharge) Chemistry



Atmospheric synthesis of amino acids, as demonstrated by the Miller–Urey experiment, operates through complex radical-driven reaction networks initiated by high-energy inputs such as lightning. In such environments, simple gases including methane (CH_4), ammonia (NH_3), hydrogen (H_2), and water vapor (H_2O) undergo ionization and dissociation to form reactive intermediates.
The mechanism can be summarised as follows:

Radical Generation
Electrical discharge produces highly reactive species such as $\bullet CH_3$, $\bullet NH_2$, •OH, and atomic hydrogen. These radicals initiate a cascade of reactions in the gaseous phase.
Formation of key intermediates:
Through recombination and oxidation processes, simple molecules such as hydrogen cyanide (HCN)



and formaldehyde (HCHO) are generated. These compounds are central intermediates in prebiotic chemistry and act as precursors for more complex organics.

Condensation and Reductive Amination
HCN and HCHO participate in a network of reactions, including condensation and reductive amination, ultimately leading to the formation of amino acids. For example, aldehydes derived from formaldehyde can undergo Strecker-like reactions in situ, linking atmospheric chemistry with solution-phase pathways.

Aqueous Phase Accumulation

The synthesized organic compounds dissolve in water, where further reactions and stabilisation occur, mimicking prebiotic ocean conditions.

Unlike the relatively linear Strecker mechanism, atmospheric synthesis involves highly interconnected reaction networks with multiple competing pathways. Product yields are sensitive to atmospheric composition; strongly reducing atmospheres favour amino acid formation, whereas neutral atmospheres significantly decrease efficiency. Modern reinterpretations of these experiments have confirmed that even under less reducing conditions, amino acids can still form, albeit in lower yields **(Parker et al., 2011; Cleaves et al., 2008).**

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Aim and Scope of the Review

The primary aim of this review is to critically examine the chemical evolution of amino acids and nucleotides as fundamental steps toward understanding the origin of life. Specifically, this work seeks to analyze the plausible prebiotic pathways responsible for the formation of these biomolecules, the underlying reaction mechanisms governing their synthesis, and the environmental conditions that facilitated their emergence on early Earth. By integrating insights from experimental studies, theoretical models, and geochemical evidence, this review aims to provide a comprehensive framework for evaluating how simple inorganic precursors could give rise to biologically relevant **molecules (Ruiz-Mirazo et al., 2014; John D. Sutherland, 2017).**

In particular, the review focuses on the formation of amino acids through well-established mechanisms such as atmospheric discharge reactions and Strecker-type synthesis, alongside their stability, reactivity, and role in early peptide formation. Parallel attention is given to the more complex problem of nucleotide synthesis, including the challenges associated with ribose formation, nucleobase assembly, and phosphorylation processes. The discussion also highlights recent experimental advances that support unified pathways for the simultaneous generation of precursors to amino acids, nucleotides, and lipids under common prebiotic conditions (**Patel et al., 2015).**

Furthermore, this review aims to compare the relative feasibility of amino acid and nucleotide formation by evaluating factors such as reaction efficiency, environmental constraints, and experimental reproducibility. Such a comparative perspective is essential for identifying key bottlenecks in current models of chemical evolution and for assessing the validity of competing hypotheses, including the RNA world hypothesis (**Gilbert, 1986).** In addition, the scope of this review extends to the examination of alternative environments, such as hydrothermal vent systems and extraterrestrial sources, which may have contributed to prebiotic chemical processes (**Martin et al., 2008).**

Finally, this review seeks to identify existing limitations and knowledge gaps in the field, particularly those related to low reaction yields, discontinuous synthetic pathways, and the transition from simple molecules to functional macromolecular systems. By addressing these challenges, the review aims to outline future research directions that may help bridge the gap between prebiotic chemistry and the emergence of life, contributing to a more unified and experimentally supported theory of chemical evolution.

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Comparative Analysis of Amino Acids and Nucleotides in Chemical Evolution

A comparative evaluation of amino acids and nucleotides provides critical insight into their relative feasibility and roles in prebiotic chemical evolution. Although both classes of biomolecules are indispensable for life, their pathways of formation, stability under prebiotic conditions, and experimental support differ significantly.

Ease of Formation

Amino acids are generally considered easier to synthesize under prebiotic conditions compared to nucleotides. Experimental simulations, most notably the Miller–Urey experiment, have demonstrated that amino acids can form readily from simple gaseous precursors through relatively straightforward reaction pathways (**Miller, 1953).** Additional mechanisms, such as Strecker synthesis, further support their abiotic formation under plausible early Earth conditions (**Cleaves, 2008).**

In contrast, nucleotide synthesis is considerably more complex, requiring the coordinated formation and assembly of three distinct components: a nitrogenous base, a pentose sugar, and a phosphate group. Each of these components follows separate synthetic routes, and their subsequent coupling under prebiotic conditions presents substantial thermodynamic and kinetic challenges. Although recent studies have proposed unified synthetic pathways for activated ribonucleotides, these processes remain highly sensitive to environmental conditions and are less robust than amino acid formation (**Patel et al., 2015**; **John D. Sutherland, 2017).**

Stability Comparison

The stability of these biomolecules under early Earth conditions also differs markedly. Amino acids exhibit moderate stability across a range of environmental conditions, although they are susceptible to degradation under intense ultraviolet (UV) radiation and high temperatures. Despite these limitations, their relatively simple structures allow them to persist long enough to accumulate in prebiotic environments (**Ruiz-Mirazo et al., 2014**).

By contrast, nucleotides—particularly their sugar component, ribose—are inherently unstable under prebiotic conditions. Ribose is prone to rapid decomposition in aqueous environments, and the glycosidic bond linking the sugar to the nucleobase is also susceptible to hydrolysis. These stability issues significantly hinder the accumulation of intact nucleotides, making their persistence in early Earth environments far more challenging (**Saladino et al., 2012**).

Experimental Evidence Strength

The experimental support for amino acid formation is strong and well-established. Numerous laboratory simulations, including variations of the Miller–Urey experiment, have consistently demonstrated the formation of amino acids under diverse prebiotic conditions. Furthermore, the detection of amino acids in extraterrestrial materials, such as carbonaceous meteorites, provides additional evidence for their widespread formation beyond Earth (**Kvenvolden et al., 1970).**

In comparison, experimental evidence for nucleotide formation has historically been limited. Only in recent years have significant advances been made in demonstrating plausible prebiotic pathways for nucleotide synthesis, particularly through cyanosulfidic chemistry and related approaches. While these findings represent major progress, they do not yet match the reproducibility and simplicity observed in amino acid synthesis (**Patel et al., 2015).**

Chemical Complexity

From a chemical perspective, amino acids are relatively simple molecules characterised by a central α-carbon bonded to an amino group, a carboxyl group, and a variable side chain. This structural simplicity facilitates their formation through a variety of reaction pathways and contributes to their higher likelihood of prebiotic synthesis.

Nucleotides, on the other hand, are significantly more complex, consisting of three chemically distinct components that must be synthesized and assembled in a specific manner. The requirement for precise bonding interactions, including the formation of glycosidic and phosphoester linkages, increases the overall difficulty of their formation. This higher level of molecular complexity is a major factor contributing to the challenges associated with nucleotide-based origin-of-life models, despite their essential role in genetic systems and the RNA world hypothesis (**Gilbert, 1986).**

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Limitations and Challenges in the Chemical Evolution of Amino Acids and Nucleotides

Despite substantial progress in understanding the prebiotic synthesis of amino acids and nucleotides, several fundamental limitations and challenges continue to hinder the development of a unified and experimentally validated model for the origin of life. These challenges arise from both chemical constraints and uncertainties regarding early Earth environments.

1. Low Reaction Yields and Selectivity

One of the primary limitations of prebiotic synthesis pathways is the generally low yield and poor selectivity of reactions. While experiments such as the Miller–Urey experiment have demonstrated the formation of amino acids, the resulting product mixtures are often complex and contain a wide range of organic compounds, many of which are not biologically relevant (**Miller, 1953; Ruiz-Mirazo et al., 2014).** Similarly, nucleotide synthesis pathways often produce low concentrations of desired products alongside numerous side products, making the accumulation of sufficient quantities under natural conditions uncertain (**Patel et al., 2015).**

2. **Lack of Continuous and Integrated Pathways**

A major conceptual challenge in chemical evolution is the absence of a continuous, stepwise pathway linking simple inorganic molecules to complex biomacromolecules. Many experimental studies successfully demonstrate individual steps—such as amino acid formation or nucleotide synthesis—but these processes are often carried out under different and sometimes incompatible conditions. This discontinuity raises questions about how such reactions could have occurred sequentially in a single prebiotic environment (John D. Sutherland, 2017).

3. **Environmental Uncertainty of Early Earth**

The exact composition of the early Earth's atmosphere and oceans remains uncertain, leading to ongoing debate about the plausibility of classical prebiotic models. While early experiments assumed a strongly reducing atmosphere, more recent geochemical evidence suggests that the atmosphere may have been neutral or weakly reducing, which significantly affects the efficiency of organic synthesis (**Cleaves et al., 2008).** This uncertainty complicates the extrapolation of laboratory results to realistic prebiotic conditions.

4. **Stability and Degradation of Biomolecules**

Both amino acids and nucleotides face significant stability challenges under prebiotic conditions. Amino acids can undergo degradation due to ultraviolet (UV) radiation, thermal decomposition, and oxidative processes. Nucleotides are even more vulnerable, particularly due to the instability of ribose and the susceptibility of glycosidic and phosphoester bonds to hydrolysis. These factors limit the accumulation and persistence of these molecules in early Earth environments (**Saladino et al., 2012**).

5**. Chirality Problem**

A critical unresolved issue in the origin of life is the emergence of biological homochirality. Prebiotic synthesis typically yields racemic mixtures of amino acids (equal D- and L-forms), whereas living systems utilize predominantly L-amino acids. The mechanisms by which this symmetry was broken remain unclear, with proposed explanations including asymmetric photochemistry and mineral surface interactions, but no consensus has been reached (Ruiz-**Mirazo et al., 2014).**

6. **Polymerization Barriers**

The transition from monomeric biomolecules to functional macromolecules represents another significant challenge. Peptide bond formation (amino acids → proteins) and phosphodiester bond formation (nucleotides → RNA) are thermodynamically unfavourable in aqueous environments due to competing hydrolysis reactions. Although mechanisms involving mineral catalysis and cyclic wet–dry conditions have been proposed, these processes are not yet fully understood or experimentally validated under realistic prebiotic conditions (Martin et al., 2008).

7. **Gap Between Chemical and Biological Systems**

Perhaps the most profound challenge is bridging the gap between simple chemical systems and the emergence of self-replicating, evolving biological entities. While the RNA world hypothesis provides a conceptual framework, experimental evidence for the spontaneous formation of fully functional, self-replicating RNA systems remains limited (**Gilbert, 1986).** This gap highlights the difficulty of transitioning from chemical evolution to true biological evolution.

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Recent Advances in the Chemical Evolution of Amino Acids and Nucleotides

Recent years have witnessed significant progress in understanding the chemical evolution of amino acids and nucleotides, driven by advances in experimental techniques, computational chemistry, and interdisciplinary approaches combining geochemistry, astrochemistry, and systems chemistry.

1. Discovery of New Prebiotic Synthetic Pathways

One of the most important advances is the identification of novel reaction networks for amino acid formation beyond classical Strecker chemistry. Recent computational and experimental studies have revealed alternative low-energy pathways involving intermediates such as formaldimine and α-ketoacids, which provide more thermodynamically favourable routes for amino acid synthesis under prebiotic conditions (**Li et al., 2024).** These findings expand the chemical space of plausible prebiotic reactions and suggest that multiple parallel pathways may have contributed to amino acid formation.

Similarly, new experimental work has demonstrated that α-amino acids and nucleobase precursors can be synthesised from α-ketoacid intermediates, linking prebiotic chemistry directly to extant metabolic pathways and supporting the idea of continuity between chemical evolution and modern biochemistry (**Pulletikurti et al., 2022).**

2. **Unified Pathways for Biomolecule Formation**

A breakthrough in prebiotic chemistry is the development of unified synthetic pathways, where precursors of amino acids, nucleotides, and lipids are generated under common conditions. Such studies demonstrate that cyanosulfidic protometabolism can simultaneously produce multiple classes of biomolecules, providing a more realistic model of early Earth chemistry (**Patel et al., 2015).**

Additionally, selective chemical processes capable of purifying and concentrating key intermediates from complex mixtures have been identified, addressing a long-standing challenge in prebiotic chemistry regarding the accumulation of biologically relevant molecules (**Islam et al., 2017).**

3. Advances in Nucleotide Synthesis

Significant progress has been made in overcoming the long-standing challenges associated with nucleotide formation. Recent studies have demonstrated plausible prebiotic routes for the synthesis of activated ribonucleotides under mild conditions, supporting models such as the RNA world hypothesis.

Modern research has also shown that phosphorylation and nucleotide assembly can occur in aqueous environments through chemically realistic pathways, reducing the gap between laboratory synthesis and plausible early Earth scenarios (**Yadav et al., 2020; Becker et al., 2019).**

4. Systems Chemistry and Protocell Models

Recent advances in systems chemistry have shifted the focus from isolated reactions to complex interacting networks of molecules. Studies have demonstrated that amino acids can influence nucleotide polymerization and protocell formation, suggesting cooperative interactions between different biomolecular classes (**Bandyopadhyay et al., 2026).**

Furthermore, experimental models of protocells have shown that simple organic molecules can self-organize into compartmentalised structures, providing a platform for early biochemical processes and bridging the gap between chemistry and biology.

5. **Astrochemical and Extraterrestrial Insights**

Advances in astrochemistry have revealed that key prebiotic molecules, including amino acid precursors and nucleobases, can form in interstellar environments and on planetary bodies. Laboratory simulations have demonstrated that peptide bonds and simple dipeptides can form under space-like conditions, suggesting that essential steps in chemical evolution may occur beyond Earth.

Additionally, analytical studies of planetary analog materials have detected diverse inventories of amino acids and nucleobases, supporting the idea that prebiotic chemistry is a widespread phenomenon in the universe.

6. Integration of Computational and Experimental Approaches

The integration of computational modeling with experimental chemistry represents another major advancement. Modern simulations allow researchers to explore complex reaction networks, identify energetically favorable pathways, and predict intermediate species that are difficult to detect experimentally. These approaches have significantly improved our understanding of reaction mechanisms and have guided experimental design in prebiotic chemistry (**Li et al., 2024).**

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Future Perspectives in the Chemical Evolution of Amino Acids and Nucleotides

Understanding the chemical evolution of amino acids and nucleotides remains central to unraveling the origin of life, yet several key questions persist. Future research must therefore move beyond isolated reaction systems toward integrated, realistic models that better reflect the complexity of early Earth environments.

Toward Integrated Prebiotic Reaction Networks

A major direction for future work lies in developing unified chemical networks capable of simultaneously generating amino acids, nucleotides, and other biomolecular precursors under common conditions. While studies have demonstrated the feasibility of cyano sulfidic protometabolism, further work is needed to establish continuous and self-sustaining reaction pathways that operate under geochemically plausible conditions (**Patel et al., 2015; John D. Sutherland, 2017**). Achieving such integration will be critical for bridging the gap between isolated synthetic steps and realistic prebiotic systems.

Bridging the Gap from Monomers to Functional Polymers

Another important challenge is understanding how simple monomers transition into functional macromolecules. Future studies should focus on elucidating mechanisms of peptide and RNA polymerization under environmentally relevant conditions, including the roles of mineral surfaces, metal ions, and fluctuating environmental cycles such as wet–dry phases. Experimental validation of these processes will be essential for linking chemical evolution to early biochemical functionality (**Martin et al., 2008**).

Resolving the Chirality Problem

The emergence of biological homochirality remains an unresolved issue in origin-of-life research. Future investigations are expected to explore mechanisms such as asymmetric photochemistry, circularly polarised light, and enantioselective mineral surfaces to explain the preferential formation of L-amino acids and D-sugars. Integrating these mechanisms into broader prebiotic models will be crucial for developing a consistent theory of molecular asymmetry (**Ruiz-Mirazo et al., 2014).**

Advances in Experimental Simulation of Early Earth Conditions

Improved experimental designs that more accurately replicate early Earth environments will play a vital role in advancing the field. Future work should incorporate realistic atmospheric compositions, variable temperature and pressure conditions, and dynamic environmental settings. Such approaches will help address current discrepancies between laboratory results and geochemical evidence, particularly regarding the nature of the primitive atmosphere (**Cleaves et al., 2008).**

Role of Systems Chemistry and Protocell Development

The integration of systems chemistry into origin-of-life research is expected to provide deeper insights into how complex molecular networks can self-organise and evolve. Future studies will likely focus on the emergence of protocells, where amino acids, nucleotides, and lipids interact within compartmentalised structures. Understanding these interactions is essential for modelling the transition from chemical systems to primitive cellular life (**Ruiz-Mirazo et al., 2014).**

Interdisciplinary Approaches and Computational Modelling

The future of chemical evolution research will increasingly rely on interdisciplinary collaboration, combining chemistry, biology, physics, and planetary science. Computational modelling and artificial intelligence are expected to play a significant role in predicting reaction pathways, optimising experimental conditions, and exploring complex chemical networks that are difficult to study experimentally. These tools can accelerate the discovery of plausible prebiotic mechanisms and provide new insights into the origin of life.

7. **Astrochemical and Extraterrestrial Exploration**

Exploration of extraterrestrial environments offers promising opportunities for understanding chemical evolution beyond Earth. Future space missions and astrochemical studies may identify amino acids, nucleobases, and other organic compounds on planetary bodies such as Mars, icy moons, and comets. Such discoveries would provide valuable evidence for the universality of prebiotic chemistry and help constrain models of life's origin (**Martin et al., 2008).**

Patel, B. H., Percivalle, C., Ritson, D. J., Duffy, C. D., & Sutherland, J. D. (2022). Common origins of RNA, protein and lipid precursors in a cyanosulfidic protometabolism. *Nature Chemistry*, 7, 301–307. https://doi.org/10.1038/nchem.2202

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Conclusion

The chemical evolution of amino acids and nucleotides represents a fundamental step in understanding the origin of life, providing a bridge between simple prebiotic chemistry and the emergence of complex biological systems. Experimental and theoretical studies have demonstrated that amino acids can be synthesised relatively easily under a variety of prebiotic conditions, particularly through atmospheric discharge processes such as the Miller–Urey experiment and through well-established reaction pathways like Strecker synthesis. In contrast, the formation of nucleotides presents significantly greater challenges due to their structural complexity, instability, and the requirement for coordinated synthesis of multiple components, although recent advances have provided promising insights into plausible prebiotic pathways.

Comparative analysis highlights that amino acids exhibit higher ease of formation and stronger experimental support, whereas nucleotides, despite their central role in genetic systems and the RNA world hypothesis, remain more difficult to synthesise and stabilise under prebiotic conditions. This disparity underscores the complexity of reconstructing a continuous pathway from simple molecules to functional macromolecules. Furthermore, critical challenges—including low reaction yields, environmental uncertainties, molecular instability, and the unresolved problem of homochirality—continue to limit the development of a comprehensive model of chemical evolution (**Ruiz-Mirazo et al., 2014; John D. Sutherland, 2017).**

Recent advances in systems chemistry, unified synthetic pathways, and interdisciplinary approaches integrating experimental and computational methods have significantly improved our understanding of prebiotic processes. These developments suggest that the emergence of life may have involved complex networks of interacting chemical reactions rather than isolated pathways. However, a major gap still exists between the formation of simple organic molecules and the origin of self-replicating, evolving systems, indicating that current models remain incomplete.

In conclusion, while substantial progress has been made in elucidating the chemical evolution of amino acids and nucleotides, the transition from prebiotic chemistry to living systems remains one of the most challenging problems in science. Future research focusing on integrated reaction networks, realistic environmental simulations, and the coupling of chemical and biological processes will be essential for advancing our understanding of life's origins and for developing a unified, experimentally supported framework of chemical evolution.