

FROM THE BUILDING BLOCKS TO LIFE

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Summary

By analogy with contemporary living systems, some believe that primitive life emerged as a cell-like organized system while others feel the development of the cell occurred at a subsequent step in the evolutionary process. This cell-like system required, at least,

boundary molecules able to isolate the system from the aqueous environment (membrane), catalytic molecules providing the basic chemical work of the cell (enzymes) and information molecules capable to store and to transfer the information needed for reproduction (RNA).

Efficient clay-catalysed condensation of nucleotides into oligonucleotides has been achieved. Non-enzymatic replication of a preformed pyrimidine-rich oligonucleotide active as a template has been demonstrated. It is not generally agreed that ribonucleotides formed spontaneously on the primitive Earth. RNA-analogs containing much simpler structural units but capable of evolving to RNA are also being investigated. A family of RNAs were shown to be able to act simultaneously as informative and catalytic molecules (ribozymes) and have been promoted as the first living systems on Earth (the RNA world). Strong evidence for this proposal has been obtained from the discovery that protein synthesis in the ribosome is catalyzed by RNA. An alternative theory of the origins of life is the initiation of the formation of high concentrations of organics by autocatalytic processes which generated the informational molecules essential for life to begin. Minerals and metal ions may have had an important role in the processes.

Chemical agents, such as carbodiimides, are able to condense amino acids into peptides in water. Minerals have been used to enhance these reactions by binding the amino acids to their surfaces. Chemical reactions capable of selectively condensing the protein amino acids at the expenses of the non-protein ones have been described. When hydrophobic and hydrophilic amino acids alternate in a polypeptide chain, stereoselective and thermostable β -sheet structures are formed. Short peptides have been shown to exhibit catalytic properties.

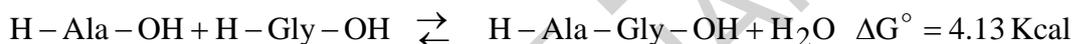
1. Introduction

Contemporary life on Earth stores genetic information in the sequences of DNA and RNA and it evolves through changes in these sequences. Protein enzymes catalyze most of the chemical reactions essential for life. The biological basic functions of information storage and catalysis are fulfilled by biopolymers, i.e. polymers made from repeating monomers, the building blocks of life (see Formation of the Building Blocks of Primitive Life). In the case of RNA the principal monomer unit are derivatives of ribose phosphate to which the heterocyclic bases adenine, guanine (purines) and uracil and cytosine (pyrimidines) are bound to the ribose. Proteins are polymers of amino acids linked by peptide bonds. In contemporary life there are 20 different amino acids in proteins of general formula $\text{NH}_2\text{-CHR-COOH}$ that differ in the structure of the side chain R group. In one scenario for the origin of life, the RNA world, it is proposed that genetic information was stored in RNA and the RNA also catalyzed the biochemical reactions essential for life. The simplest version of this scenario proposes that assemblages of RNA bound to a surface could have functioned as a primitive living system. Since the structural units that make up RNA are quite complicated it has been proposed that the first life contained simpler genetic material that evolved to RNA. In a more classical approach inspired by the molecular machinery of contemporary living systems, it has been suggested that the first primitive life forms emerged as cell-like organized systems. These cell-like systems required, at least, information molecules allowing the storage of the information needed for replication (RNA), catalytic

molecules providing the basic chemical work of the cell (enzymes and ribozymes), and boundary molecules able to isolate the system from the aqueous environment (membranes). A major assumption has been made in assuming that RNA and protein or structures like them were used in the first life on Earth. There is no reason to assume that structures quite different from RNA and protein were used as long as they could have evolved or been transcribed into the biomolecules currently in use. The polymers of HCN come to mind since they contain structural units present in RNA and proteins. Since there are few specific examples of preRNA and preproteins, the discussion here will be limited mainly to proteins and nucleic acids. Possible pathways to boundary molecules on the primitive Earth have been discussed in Chapter Formation of the Building Blocks of Primitive Life.

2. A Primitive Cellular Life

Formally the synthesis of polymers of nucleotide and amino acids appears simple. The condensation reaction consists to eliminate water molecules between monomer units to link them together. However, the formation of either proteins or RNA from their monomers in water is not energetically favored. In water, the peptide bond of proteins is thermodynamically unstable so energy is required to link two amino acids together in an aqueous milieu. For example, the free energy for the condensation of alanine and glycine to form the dipeptide alanyl-glycine in water is 4.13 Kcal/mol at 37°C and pH 7:



The equilibrium constant of the reaction is only about 10^{-3} and the equilibrium concentration of the dipeptide for 1 M solutions of the free amino acids is only slightly above 10^{-5} M. The thermodynamic barrier is very large for the formation of a long chain polypeptide. 1 M solutions in each of the twenty proteinaceous amino acids would yield at equilibrium a 10^{-99} M concentration for a 12 000 Dalton protein. The volume of this solution would have to be 10^{50} times the volume of the Earth to yield one molecule of protein at equilibrium. So energy input was necessary to have made RNA and polypeptides on the primitive Earth.

Initial studies using thermal energy to drive the formation of polymers from monomers were not very successful even if they were carried out in the absence of water. Polymer formation in the presence of water is a more plausible prebiotic scenario than dry heating since it is likely that water was prevalent on the primitive Earth. Polymers can be prepared in the presence of water if activating groups are bound to the reacting monomers or chemical condensing agents are added to provide the requisite free energy for bond formation.

2.1. Prebiotic RNA

The general consensus among origins of life scientists is that RNA was the most important biopolymer in early, but not necessarily the first, life on Earth. DNA is believed to have appeared after RNA and to have later derived from RNA for the following reasons:

- (a) The ribose structural unit present in RNA monomers was probably formed from formaldehyde or an oligomer of formaldehyde. The prebiotic synthesis of the deoxyribose of DNA requires the reaction of a mix of starting materials.
- (b) The biosynthesis of DNA triphosphates proceeds from RNA triphosphates by a unique free radical reaction pathway in which ribonucleoside reductase, an unusual enzyme, has a central rôle. This enzyme appears to have evolved after RNA formed.
- (c) RNA exhibits catalytic activity as well as information storage so could have served both as a catalyst and storehouse of genetic information in the first life.

Initial attempts to form RNA by heating monomers or by using condensing agents did not yield long oligomers so these studies will not be described. Polymerization studies, which used activated monomers, have been the most successful and these will be reviewed here keeping in mind that, in most instances, potential prebiotic sources of the activated monomers remains to be discovered, as described in Chapter Formation of the Building Blocks of Primitive Life.

2.1.1. The Montmorillonite Clay-catalyzed Synthesis of RNA

The possible role of clays in the prebiotic reactions of organic compounds was first proposed by Bernal (Bernal, 1949). He emphasized the need for the selective concentration of organics by adsorption on surfaces, the protection of the adsorbed organics from solar radiation and the photopolymerization of the adsorbed material. The proposal was extended where it was proposed that clays contained "crystal genes" which were the first life on Earth. It is proposed that these "crystal genes" contained defects that were replicated by crystallization. Currently, there is no direct experimental evidence for "crystal genes".

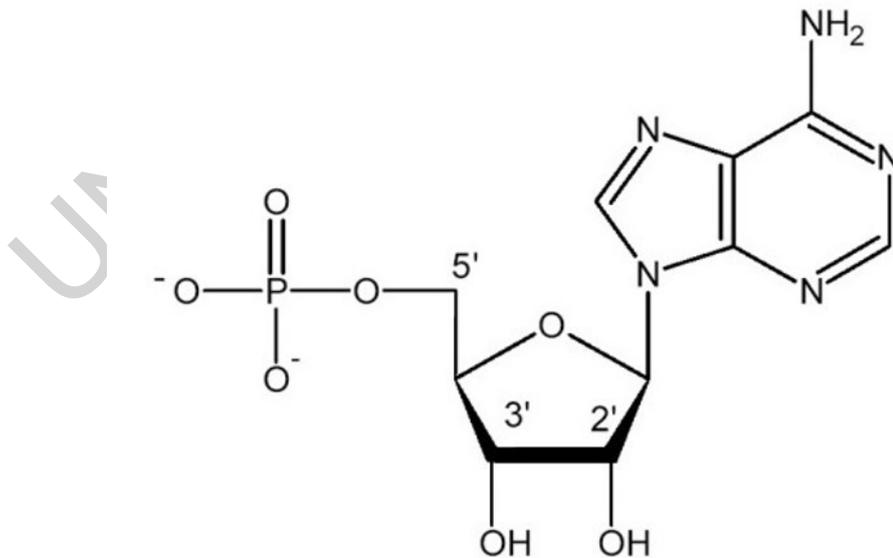


Figure 1. RNA monomer with the 2', 3' and 5' positions for the phosphodiester linkages.

One of the successful applications of Bernal's proposal is the observation that oligomers containing 6 to 14 monomer units are formed when RNA monomers activated on the

phosphate with an imidazole group condense in the presence of montmorillonite (Ferris and Ertem, 1993). The reaction is a general one as shown by the formation of oligomers when the nucleotide base is A, C, G, I or U. Catalysis has the potential for limiting the number of isomers formed. For example the 3',5'-linked phosphodiester bond is favored in the reaction of purine nucleotides on montmorillonite (see Figure 1 for the 2', 3'- and 5'- positions on the nucleotides). The 2', 5'-linkage is favored in the absence of catalysis and in the clay-catalyzed reactions of pyrimidine nucleotides.

Analysis of the dimers formed in the reaction of mixtures of two or more activated nucleotides demonstrated strong sequence selectivity of the dimers formed. The 5'-purine-pyrimidine sequence is favored over the 5'-pyrimidine-purine sequence at the end of the polymer chain by a factor of about 20. In addition, five 5'-sequences (A-C, A-U, G-C, A-A and G-A) are formed in significantly larger amounts (73% total yield) than the eleven others in the reaction of mixtures of the four activated monomers of the nucleotides A, C, G, and U.

The formation of short RNA oligomers by montmorillonite catalysis was the first step in the preparation of the RNAs needed for the initiation of the RNA world. In the second step it was shown that it is possible to generate longer RNAs by elongation of short oligomers. Reactive monomers were added daily to a decamer of A bound to montmorillonite and the progress of the elongation of the primer was followed by gel electrophoresis for fourteen days (Ferris et al., 1996). The length of the polymer increased incrementally up to a 40-50mer in that time period.

The elongation of RNA to chains longer than 40mers could have provided the RNAs that initiated the RNA world. It has been proposed that RNAs containing greater than 40mers would have been able to replicate with sufficient fidelity by template-directed synthesis to maintain the core information content of their sequences (Joyce and Orgel, 1999). In addition, it has been postulated that a 40mer is the minimum chain length required for RNA to catalyze the reactions of other RNA molecules.

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