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Mini-review

From the one-carbon amide formamide to RNA all the steps are prebiotically possible

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ABSTRACT

Formamide provides the raw material and the reaction leads connecting hydrogen cyanide HCN chemistry with higher complexity molecular structures. Formamide is liquid between 4 and 210 °C and, upon heating in the presence of one of several catalysts, affords nucleic bases, acyclonucleosides, carboxylic acids and aminoacids. In formamide in the presence of a source of phosphate, nucleosides are non-fastidiously phosphorylated in every position of the sugar residue, also yielding cyclic nucleotides. Guanine $3',5'$ cyclic nucleotide monophosphates polymerize to oligonucleotides, up to 30 nucleotides long. Adenine $3',5'$ cyclic nucleotide monophosphate reacts similarly but less efficiently. Preformed oligonucleotides may undergo terminal ligation in the absence of enzymes, thus allowing the formation of abiotically obtained long RNA chains.

1. Introduction

It is a shared opinion that life began with an RNA world. The foundations of this hypothesis lay on in the facts that RNA acts as a catalyst in various processes, as in the synthesis of peptide bonds [1,2] and, markedly, as a catalyst of itself. For a collection of reviews on this matter see [3]. The reactions involved in self-catalysis suggest scenarios in which generation of RNA sequences would be an initially spontaneous process, followed by replication and, in the appropriate physical–chemical frame, by molecular evolution. The scenario is still highly unfocused and entire domains remain elusive.

One important area relates to the possible involvement in the RNA world of aminoacids and of peptides. As noted [4], α-aminoacid *N*-carboxyanhydrides (NCAs) are activated peptide monomers and might have performed as energy carriers owing to their ability to activate inorganic phosphate and nucleotides (*ibidem*). On the other hand, the ability of very simple RNAs in carrying out important functions in peptide bond formation has been reported [5,6]. Whether the answer to the synthesis of the first peptide bonds is a private affair of activated aminoacids (for which chemical and thermodynamic possibilities are not lacking [7]) or whether simple initial RNAs were instrumental to the formation of peptide bonds since the very beginning, is an open problem. The fact remains that the evolution of the extant coded genetic system [8–10] necessarily required the contemporaneous presence of both RNA and peptides in an environment such as to facilitate their cooperative interaction.

The reverse seems not to be necessary. RNA is apparently endowed with the capacity of self-generation and catalysis. The cooperation between peptides and RNA possibly kick-started the evolution of a system in which RNA was auto-generating and reproducing. This consideration highlights another basic unresolved question: where the energy for making RNA was coming from, how was it harnessed and made available? Classically this problem goes under the question mark "genetics-first or metabolism-first?".

We wish to indicate a potential chemical frame in which the formation and the permanence of several participants to these processes are conceivable and that, most relevantly, could accommodate their contemporaneous occurrence and their eventual interaction. Our reasoning started from the consideration that life is a robust chemical process. Thus, its unprotected start and its continued existence had necessarily to be based not only on robust chemistry but also on easily available materials.

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2. Formamide

NH_2COH formamide contains in its structure the four most common elements of the Universe, with the exception of the inert helium. These elements are those required for the synthesis of biomolecules. Phosphorus and sulphur present in nucleic acids and proteins play precise roles even though structural and functional alternatives are conceivable [11–13].

Formamide is an ubiquitous molecule [14], present in comets [15], in Solar System satellites [16], in the interstellar medium [17]. What makes it attractive as a potential source of a prebiotic process is that

(i) The major pathway leading to its synthesis consists in the reaction between H_2O and HCN hydrogen cyanide, the two most abundant three-atoms combinations, respectively inorganic and organic, in space (www.astrochemistry.net). HCN would thus be the primary source of chemical energy in this frame. The synthesis, stability and degradation chemistry of formamide was reviewed [18,19].

(ii) Formamide is liquid between 4 and 210 °C, with very limited azeotropic effects [20], thus being easily concentrated by evaporation of water.

(iii) It increases micelle formation of ionic surfactants (sodium stearate, sodium palmitate, ecc.) suggesting a role in supramolecular organization correlated with the solvophobicity of the system [21].

As result of a search lasted more than a decade [22–29], we have reported in a prebiotic perspective that all the necessary nucleic bases are afforded by formamide in a simple experimental setup, essentially consisting of warming formamide in a sealed vessel for 24–48 h at 140–160 °C in the presence of a catalyst.

The catalysts tested [22–29] were representative of numerous classes of terrestrial minerals, namely: metal oxides as calcium carbonate $CaCO_3$, alumina Al_2O_3, silica SiO_2, zeolite Y-type; titanium dioxide TiO_2; cosmic dust analogues (CDAs) of terrestrial olivines (from fayalite to forsterite); phosphate minerals; iron sulphur and iron-copper sulphur minerals; borates; zirconium minerals. Minerals from the meteorite Murchison were also tested.

The compounds obtained were: nucleic bases, carboxylic acids, two aminoacids, other simple molecules, as listed below. The only nucleic base formed in the absence of catalysts is purine [22–29]. The bases formed were adenine, cytosine, isocytosine, uracil, 5-hydroxymethyl uracil, thymine, 4(3*H*)-pyrimidinone, hypoxanthine. The synthesis of the imidazoles 5-aminoimidazole-4-carboxamide (AICA) and of 5-formamidoimidazole-4-carboxamide (fAICA) was also observed. Formation of carboxylic acids was observed [22 e through h] encompassing glycolic, oxalic, glyoxylic, malic, oxaloacetic, succinic, fumaric, piruvic, lactic, maleic acids and glyoxylamide (Fig. 1).

Formylglycine, alanine and formylalanine were synthesized in the presence of borates [29]. The formation of urea, carbodiimide, formaldehyde and parabanic acid was also observed. The synthesis of all these molecules was obtained in various compositions and

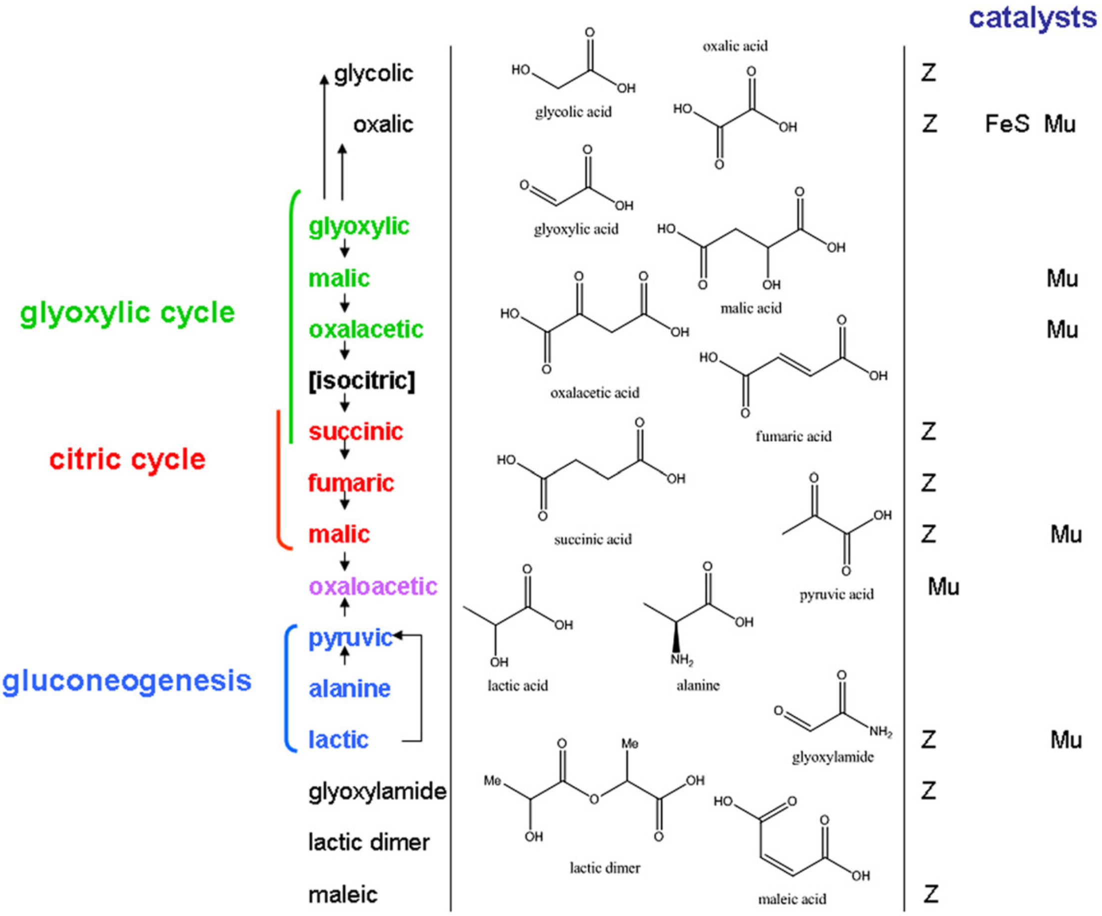

Fig. 1. Carboxylic acids synthesized from formamide by heating in the presence of catalysts. Zirconium minerals (Z) [27], iron sulphur minerals (Fe–S) [26], borate minerals (B) [29], minerals of the Murchison meteorite (M) [28]. Isocitric acid was not detected.