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From formamide to RNA: the roles of formamide and water in the evolution of chemical information

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Abstract

In pursuing the origin of informational polymers, we followed the assumption that their spontaneous formation could only have occurred: (i) if all the components were present at the same site and in the same reaction, and (ii) if the thermodynamics of the processes involved favored a polymerized over a monomeric state of the precursors. A plausible scenario satisfying both assumptions is provided.

Keywords: Formamide; Water; Nucleic bases; Nucleotides; RNA origin; Molecular evolution

1. Introduction

The origin of informational polymers is not known. Faced by the great complexity of extant nucleic acids and by the ensuing difficulty of following a top-down approach, we have chosen an Occam's razor attitude. Thus, we started from the consideration that the simpler the precursor molecules and processes involved, the higher the probability that relevant prebiotic polymerizations might have actually taken place. Following this logic, we asked the question: does a unitary and simple physical–chemical frame exist in which nucleic bases may form and evolve to their open or closed nucleoside forms, and in which nucleosides may be phosphorylated, oligomerize and possibly ligate to yield larger oligonucleotide fragments? If these processes could take place in the same context and with comparable efficiencies, a plausible scenario for the onset of complex chemical information would be sketched.

With this aim, we analyzed the chemistry of formamide H_2NCOH and observed that it condenses into a large panel of nucleic bases, i.e. purine, adenine, hypoxanthine, N^9-formylpurine, N^9,N^6-diformyladenine, acyclonucleosides, cytosine, hydroxypyrimidine, 4(3H)-pyrimidinone, uracil, thymine, 5-hydroxymethyluracil, 5′-aminoimidazole-4-carboxamide and 5′-formaminoimidazole-4-carboxamideand related compounds, i.e. urea, parabanic acid and carbodiimide, by simply heating between 90 and 160 °C in the presence of a variety of catalysts, i.e. silica, alumina, $CaCO_3$, TiO_2, zeolites, common clays, kaolin, montmorillonites, olivines and phosphate minerals [30,35]. Each catalyst yields a specific panel of compounds, and the chemical processes involved have been described [33,35]. The very fact that, regardless of the catalyst involved, formamide condenses into nucleic bases establishes its versatility and fertility as a prebiotic precursor. Formamide

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also yields acyclonucleosides [28], potentially solving the longstanding problem of the poor reactivity between nucleic bases and ribose. The other reaction catalyzed by formamide that is particularly relevant in a prebiotic context is the efficient phosphorylation of nucleosides, as determined for adenosine and cytosine using soluble phosphates or phosphate minerals as phosphate source [7]. Thus, formamide chemistry is suited to fulfill both the roles of single and general precursor for the initial steps of nucleic syntheses. The relevant chemical properties of formamide are discussed below.

We reasoned that, along the path of increasing chemical complexity based on formamide chemistry, from the one-carbon atom H_2NCOH to phosphorylated nucleosides [35], at one point prebiotic evolution had to shift to water-based processes. The argument is twofold: (i) extant nucleic acids are structurally adapted to and conditioned by water, not by formamide, and (ii) water was enormously more abundant than formamide.

Thus, we previously analyzed nucleoside phosphorylation, oligomerization and ligation in water and in formamide. Data obtained showed that: (i) formamide, an efficient catalyst for phosphorylation [7], is essentially inert in oligomerization, and that (ii) both phosphorylation and oligomerization of adenosine actively take place in water.

Thus, nucleoside phosphorylation might have been the prebiotic step in which the take-over by water chemistry could have occurred.

2. Formamide chemistry

Cellular life necessarily requires both a genetic and a metabolic apparatus. Different scenarios have been suggested for their origin. In the case of informational molecules (DNA and RNA), the chemistry of hydrogen cyanide (HCN) that received the highest attention in the past only focused on the synthesis of nucleic acid bases. Other relevant topics, such as the synthesis of nucleosides and their phosphorylation to nucleotides, remained substantially undisclosed. On the other hand, the most representative models suggested for the emergence of metabolism, such as the Wächtershäuser hypothesis for the chemoautotrophic origin of secondary metabolism [44], deal with the primitive carbon-fixation pathway of CO_2 into simple carboxylic acid derivatives, neglecting the formation of nucleic acid components. In this perspective, the search for a possible unitary frame that could link the genetic and metabolic origin-of-life scenarios remains an important goal. The chemistry of formamide shows new and useful properties for attaining this objective, such as: a) the role of a multifunctional prebiotic precursor; b) chemiomimesis; and c) organocatalysis.

2.1. Formamide as a multifunctional prebiotic precursor

In contrast to other chemicals previously studied as starting materials for the synthesis of biomolecules, the chemistry of formamide can be fine-tuned by the presence of a large panel of minerals and metal oxides modelling the complexity of the environment of early Earth. These inorganic compounds catalyze the thermal condensation of formamide and, at the same time, its partial degradation to low molecular weight derivatives, including HCN, formaldehyde (HCOH), formic acid (HCOOH), carbon oxides (CO_x) and ammonia (NH_3). These compounds are, in principle, reagents for the synthesis of sugars, peptides and other relevant biomolecules [27], e.g., during the process of condensation of formamide in the presence of mineral phosphates, glycine, the simplest α-amino acid, was recovered at appreciable yields, in addition to cytosine, uracil, adenine and hypoxanthine [33] (Fig. 1). While the nucleic acid bases are synthesized by polymerization of formamide (the formamide dimer being the first intermediate), glycine derives from a different reaction pathway, a Strecker condensation, between HCN, formaldehyde and ammonia, all of them generated in situ from thermal degradation of the same formamide. From this point of view, formamide behaves as a multifunctional prebiotic precursor whereby selectivity of transformation depends on the physical and chemical properties of the surface of the mineral used as a catalyst and on the difference in rate constants of possible side reactions. This effect was of particular relevance in the case of the hitherto unreported one-pot synthesis of nucleoside derivatives under plausible prebiotic conditions, obtained simply by heating neat formamide in the presence of titanium dioxide (TiO_2) [28]. Under these experimental conditions, two apparently independent reactions, polymerization of formamide to nucleic acid bases and formose condensation [5] of formaldehyde to sugars, cross-link in an unexpected way by means of N-formyl purines as intermediates, to afford acyclonucleosides a different number of carbon atoms in the side-chain. These data suggest a scenario for the origin of nucleosides that is more efficient than the traditional approach, i.e. the formation of the glycosidic bond between newly formed nucleic acid bases and sugars by a formal dehydration process [3], highly disfavored by thermodynamic concerns.

2.2. Chemiomimesis as a new perspective for molecular evolution

Analyzing the composition of the mixtures of products obtained by the condensation process of formamide, instances are observed of the chemiomimesis concept. Chemiomimesis refers to the possibility that primitive chemical processes could be templates for successive evolution of complex biological machinery [10]. This is the case for prebiotic synthesis of hypoxanthine from formamide in the presence of montmorillonites. Montmorillonites are naturally occurring clays characterized by a charged multilayer structure. These minerals are able to adsorb formamide with a twofold-positive effect: an increase in its local concentration favoring the process of condensation, and activation of both electrophilic and nucleophilic centers in the molecule by means of coulombic and hydrogen bonding interactions. The treatment of formamide with montmorillonites at 160 °C, a model resembling volcanic scenarios, yielded a panel of nucleic acid bases, including hypoxanthine, and some imidazole