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Molecular Modeling of RNA Nucleotides under Hydrothermal Prebiotic Conditions

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Introduction: The study of RNA formation and its subsequent accumulation and polymerization in the primitive Earth is one of the key issues related to the RNA World hypothesis. In this regard, many efforts have been dedicated to explore RNA synthesis under different plausible prebiotic conditions, comprising the catalytic function of mineral surfaces, the role of salts or lipid compounds, the exposure to drying/wetting cycles, and so forth [1]. However, one of the main challenges is to achieve the formation of RNA monomers (ribonucleotides) that subsequently polymerized to constitute larger RNA oligomers potentially able to perform more complex chemical processes. In this work, we provide quantitative new insights on the chemical reactions of ribonucleotides synthesis under hydrothermal prebiotic environments, performing *ab initio* molecular dynamics simulations explicitly taking into account water molecules and in presence of a biological pentose phosphate precursor (PRPP). Additionally, we exploit free-energy methods [2,3] in combination with a topological approach developed in our team that accurately tracks the chemical bond network along a reaction path [4]. From this framework, we are able to unveil the mechanism of ribonucleotide synthesis in atomistic detail, as well as to quantitatively assess the thermodynamical properties of this chemical process [5]. In addition, we performed NMR and Mass Spectroscopy experiments to detect the formation of ribonucleotides under hydrothermal conditions, complementing the results obtained from our *in silico* studies and confirming their plausability. Our main finding is that a chemical path from the same precursor of ribonucleotide synthesis in current biological systems is observed in plausible hydrothermal prebiotic conditions (see Figure 1).

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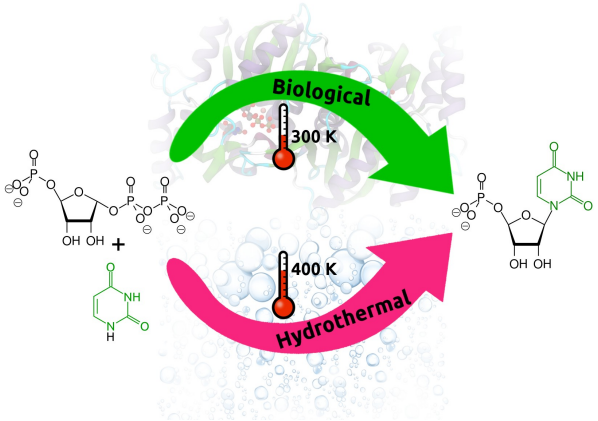

Figure 1 – Ribonucleotide formation from PRPP precursor in current biological systems vs. plausible prebiotic hydrothermal conditions as tested in our simulations and *in situ* NMR experiments. Synthesis in current living forms involves enzyme catalysis by phosphoribosyltransferases.