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Mechanistic insight into the prebiotic syntheses of pyrimidine ribonucleotide and pyrimidine deoxynucleotide precursors

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ABSTRACT

Density functional theory is utilized to elucidate the detailed mechanisms of the reactions between 2-aminooxazole **O2**/2-aminothiazole **S2** and glyceraldehyde **2**. According to our calculations, in **O2**/**2** system, aminooxazoline **O3** is formed via two steps including C—C formation and cyclization. C—C formation determines the reaction diastereoselectivity and ribo-aminooxazoline is the most favorable product. Although oxazole-hemiaminal **O6** is not detected in the experiment, it is deduced can be formed theoretically. In **S2**/**2** system, aminothiazoline **S3** is hard to be generated because of the less nucleophilic ability of **S2**. The formation of thiazole-hemiaminal **S6** is more favorable than **S3** formation in kinetics but somewhat unfavorable in thermodynamics. However, the transformation from **S6** to thiazole-aminal **S7** is favorable both in kinetics and thermodynamics, which provides a driving force for the formation and transformation of **S6**. Additionally, our calculations indicate that phosphate is very important in assisting proton transfer in all of the transformations.

1. Introduction

The synthesis of canonical nucleotides by abiotic chemical means has been a major goal in origins of life research [1–6]. For decades, the only approach for the synthesis of nucleotides is based on the assumption that their constituent components (nucleobase, sugar and phosphate) are synthesized separately and subsequently assembled [7]. However, attempts to provide experimental support for this have proved to be tough [8,9], because ribose is difficult to form selectively [10,11], and the addition of nucleobases to ribose is inefficient in the case of purines [12] and does not occur at all in the case of the canonical pyrimidines [7]. Over 30 years ago, Orgel and co-workers demonstrated that glycosidic bonds could be formed from adenine and hypoxanthine and D-ribose when dried and heated together [13]. However, this approach proved to be less promising with the other bases. A stepwise synthesis of cytosine on a preformed sugar was first accomplished by Sanchez and Orgel [14], and explored in great detail by the Sutherland recently [15]. However, the reaction conditions were harsh and the yield of the product was low. Bean and co-workers previously reported the first successful synthesis of a pyrimidine nucleoside from a free base and a nonactivated sugar in a plausible prebiotic reaction. Nevertheless, the yield of the β-furanosyl nucleoside was very low (12%) [16]. They subsequently presented a detailed computational study on this reaction with density functional theory, which demonstrated that a Mg^{2+} ion can afford the necessary stabilization to the base [17].

In recent years, Powner and Sutherland creatively discovered a short, high-yielding route to activated pyrimidine ribonucleotides (Scheme 1) [18,19], which bypassed free ribose and nucleobases and could overcome the problems caused by traditional method mentioned above. All of the starting materials for Powner's route, cyanamide **1**, glycolaldehyde **O1**, glyceraldehyde **2**, cyanoacetylene **3** and inorganic phosphate **4**, are plausible prebiotic feedstock molecules. This mixed nitrogenous oxygenous chemistry first generated 2-aminooxazole **O2** which is resulted from the reaction between **1** and **O1**. Pentose aminooxazoline **O3** is produced by adding **2** into **O2**. Reaction between **O3** and **3** gives anhydronucleotide **O4** which subsequently undergoes phosphorylation with rearrangement to furnish activated pyrimidine ribonucleotide, β-ribo cytidine-2′,3′-cyclic phosphate **O5**. According to the experiment, in the presence of phosphate buffer, at pH 7, the ribose and arabinose aminooxazolines ($\mathbf{O3_r}$ and $\mathbf{O3_a}$) are the major products, and the xylose derivative $\mathbf{O3_x}$ is a minor product. The lyxose aminoxazoline is formed in intermediate amounts as an equilibrating mixture of furanose $\mathbf{O3_l}$ and pyranose $\mathbf{O3_{p\text{-}l}}$ isomers.

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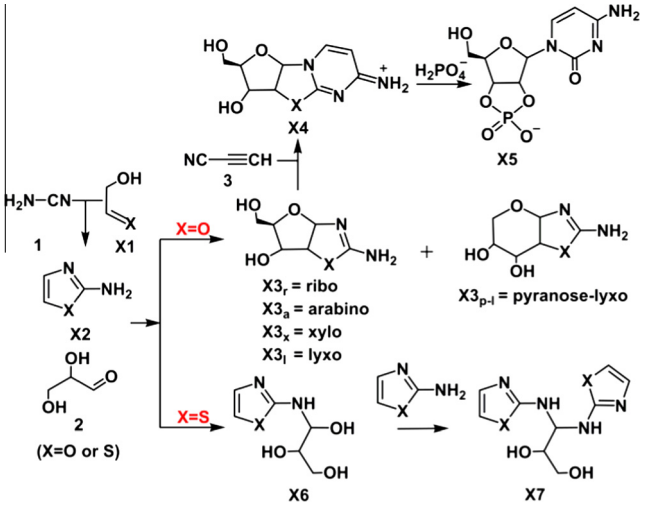


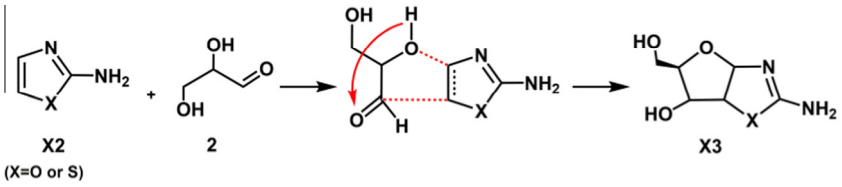
Scheme 1. The proposed prebiotic syntheses of pyrimidine nucleotide and pyrimidine deoxynucleotide by Powner and co-workers.

Later, inspired by the low dissociation energy of C—S bond which may result in the chemical differentiation required for the divergent synthesis of DNA and RNA monomers, Powner and co-workers proposed a related pathway for the prebiotic synthesis of 2′-deoxynucleotides [20], in which glycolaldehyde **O1** was substituted by β-mercaptoacetaldehyde **S1**. The reaction between **1** and **S1** gives 2-aminothiazole **S2**. Nevertheless, 2-aminothiazoline **S3**, which might be an important precursor toward pyrimidine deoxynucleotide, is not produced from the reaction between **S2** and **2**. That is to say, pyrimidine deoxynucleotide cannot be obtained from **S2** and **2**, which is strikingly different from that pyrimidine nucleotide can be generated from **O2** and **2**. Experimentally, the reaction reversibly gives thiazole-hemiaminal **S6** and thiazole-aminal **S7**. The experimenters proposed that the facile reversibility of aminal formation might provide a route to the concentration, purification, and stabilization of the necessary aldehyde precursors of nucleotides. Additionally, 2-aminothiazole can take part in a 3-component carbon–carbon bond-forming reaction in water leading to the diastereoselective synthesis of purine precursors whose mechanism has been theoretically studied by us [21].

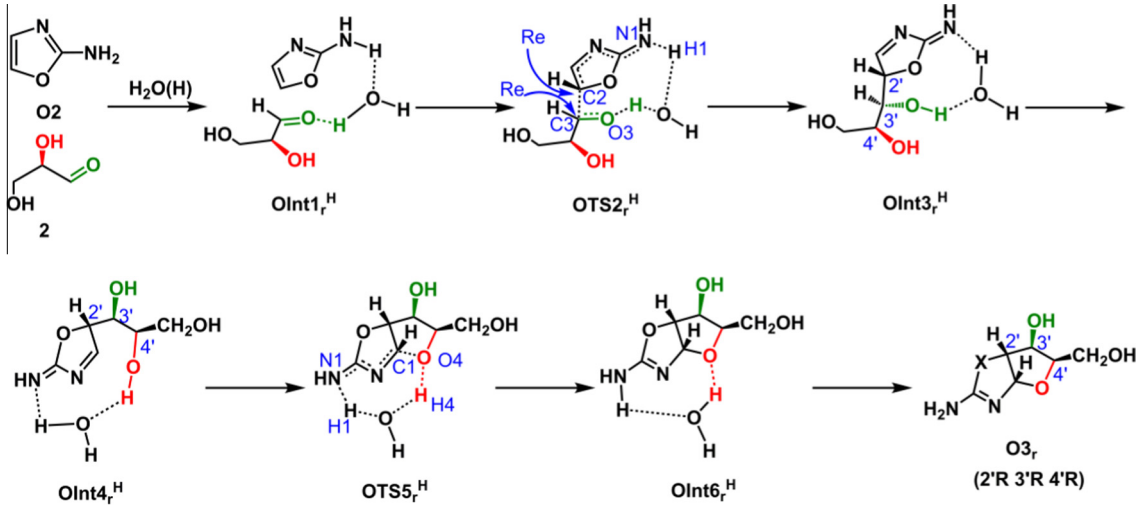
By analyzing the two processes, we can see that the reaction between **2** and **X2** (X = O or S) is the most important step in controlling the diastereoselectivity (ribo, arabino, xlyo and lyxo) and chemoselectivity of the products (2-aminooxazoline, 2-aminothiazoline, hemiaminal and aminal). In order to illuminate the origin of the diastereoselectivity and chemoselectivity, we have conducted a detailed mechanism study of the reactions between **X2** and **2**. We hope our study can provide valuable information in prebiotic synthesis of nucleotides and deoxynucleotides and in the origin of life.

2. Computational details

All structures were optimized in gas phase at the M06-2X/6-311++G(d,p) [22–24] level of theory. Harmonic frequency analysis calculations were subsequently performed to verify the optimized geometries to be minima or transition states. The intrinsic reaction coordinate (IRC) calculations [25,26], at the same level of theory, were performed to evaluate whether there is a connection between the calculated initial states, the transition states, and products. The energies were then improved by M06-2X/6-311++G(d,p) single point calculations with solvent effect accounted by SMD [27–31] solvent model, using water as solvent. The refined energies were



Scheme 2. Possible direct react mechanism between **X2** and **2**.



Scheme 3. The H_2O assisted mechanism of ribo-aminooxazoline $\mathbf{O3_r}$ formation.