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# A Hypothetical Pathway of Unified Ribonucleotide Formation on the Surface of Meteorite Phosphide Minerals

Ze-Run Zhao <sup>1,†</sup>, Qian-Qian Chen <sup>1,†</sup>, Bing-Yue Zhao <sup>1,†</sup>, Wan-Jun Qin <sup>1</sup>, Qing Liu <sup>1</sup>, Xiao Wang <sup>1,2,\*</sup>

<sup>1</sup> School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

<sup>2</sup> Frontiers Science Center for Critical Earth Material Cycling, Nanjing University, Nanjing 210023, China

<sup>†</sup> Contributed equally

\* Corresponding author: wangxiao@nju.edu.cn

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**Abstract:** A unified and selective prebiotic synthesis to access *N9* purine and *N1* pyrimidine ribonucleotides has been proposed. Metal phosphide in meteorite and a Fe(III)-hydrazine/thiol couple could serve as the key reagents that furnish the desired transformation. The target nucleotides, which are traditionally difficult to obtain via the direct ribose-nucleobase condensation, are expected to be selectively produced via an oxidation-reduction condensation process. A pathway utilizing P(III) derived from phosphide minerals is also suggested, which circumvents several formidable issues in the conventional phosphorylation routes.

**Keywords:** RNA world; prebiotic chemistry; nucleosidation; meteorite; phosphide mineral; oxidation-reduction condensation

## 1. Introduction

The RNA World has been a mainstream hypothesis in the origins of life community [1] and continues to evolve [2,3]. However, the early-stage chemistry of this hypothesis is still challenged by several unsolved problems [4,5]. In particular, the reactivity and selectivity of nucleosidation, the mobilization of phosphorus, and the availability of phosphorus species able to form organophosphates have been the major stumbling blocks [6]. In the structure of an extant nucleoside, it is intriguing that the glycosidic bond links ribose with the least nucleophilic nitrogen of the nucleobase (*N9* of purine and *N1* of pyrimidine). The exocyclic amino groups of adenine, guanine and cytosine are the most reactive but undesired sites for ribosylation. Because of that, the coupling of ribose and nucleobase to afford canonical nucleosides has been synthetically troublesome [7]. Stepwise routes had to be developed to ensure the correct regioselectivity [8–11].

However, the order of reactivity of different nucleophiles can be altered by using an alternative condensation approach. In water in general, pH and coordination specific to metallic species are levers to modulate this reactivity. For example, a nucleophile with a lower  $pK_a$  might have an unusual superiority to the less acidic ones, under the Mitsunobu conditions [12], which activate the alcoholic substrate for nucleophilic substitution. Although the Mitsunobu reaction has hardly been documented in prebiotic chemistry, it has been applied to construct glycosidic bonds in routine organic synthesis [13]. This prompts us to envisage a possible prebiotic variant of the oxidation-reduction condensation that could yield nucleosides with the desired regioselectivity.

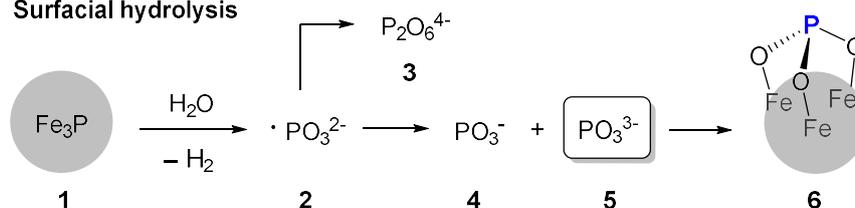
## 2. Results and Discussion

Schreibersite (**1**), in the primary composition of  $(\text{Fe,Ni})_3\text{P}$ , is speculated to be a key extraterrestrial source of phosphorus (Figure 1) [14]. For the utilization of phosphorus, most existing routes suggest the oxidation of phosphonic acid that derived from schreibersite, to P(V) (preferably phosphoric acid) [15]. Schreibersite has been verified as an efficacious reagent for the phosphorylation of nucleosides [16]. However, the strong tendency of binding divalent cations forbids the existence of soluble phosphate and the phosphorylation of nucleosides [17]. To avoid that, others suggest the direct utilization of P(III) to form a nucleoside phosphite, and the H-phosphonate diester linkage is later oxidized to the phosphodiester linkage by  $\text{Fe}^{3+}$  [17]. Schreibersite is also a geochemical source of activated, water-soluble phosphate reagents such as diamidophosphate (DAP) by reacting with  $\text{NH}_3$  in water [18,19], since water might have already existed on Earth about 4.4 billion years ago [20].

### Complete hydrolysis



### Surfacial hydrolysis

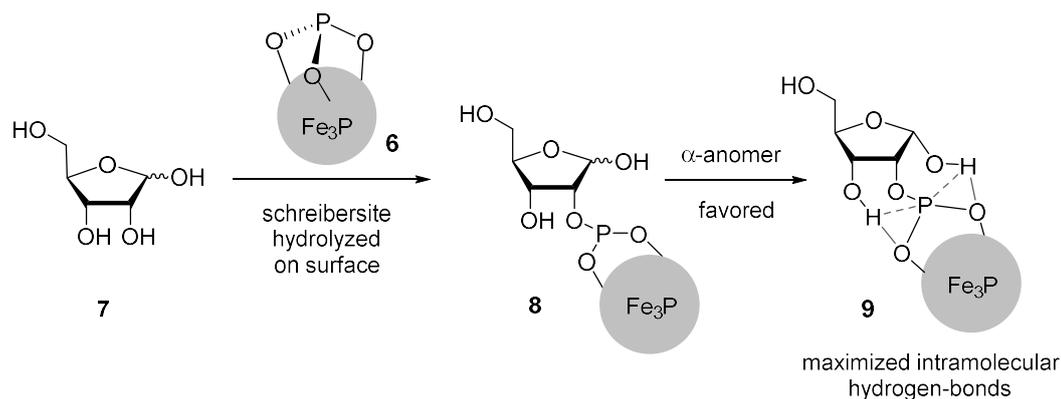


**Figure 1.** Schreibersite and the possibly partially hydrolyzed surface.

Previous chemical syntheses of nucleotides were mainly achieved through nucleoside formation followed by subsequent phosphorylation, or nucleosidation of pre-phosphorylated ribose, or via a stepwise route involving smaller building blocks. Pasek investigated the phosphorylation of nucleosides using meteorite as a phosphorus source under basic conditions [16]. Carell completed the prebiotic synthesis of ribonucleotides in the presence of struvite [21]. Kim and Benner developed a regioselective synthesis of nucleotide via the nucleophilic attack by purine's N9 or pyrimidine's N1 to ribose-1',2'-cyclic phosphate [22]. The pre-activated ribose was prepared under conditions such as the presence of amidotriphosphate derived from cyclic trimetaphosphate [23]. Cronin studied the promotion effect of amino acids to the nucleosidation of the pre-phosphorylated ribose [24]. Furukawa reported the synthesis of ribose 5'-phosphate in the presence of urea and borate [25]. Sutherland constructed the ribose skeleton via the addition of 2-amino-oxazole, glyceraldehyde and cyanoacetylene, followed by treating anhydronucleoside with sodium dihydrogen phosphate to generate 2',3'-cyclic pyrimidine monophosphate [9]. These are undoubtedly momentous examples which demonstrate high prebiotic relevance. Here, we are curious to propose a route to access nucleotide, with most synthetic steps occurring on the same mineral surface. According to Pasek's research, the hydrolysis of  $\text{Fe}_3\text{P}$  affords  $\text{Fe}_3\text{O}_4$  and  $\text{H}_3\text{PO}_3$ , with hydrogen gas emission [14] (Figure 1). However, the solubility of schreibersite in water is limited, so its surface might first

undergo slow and partial corrosion [26,27]. We would expect that the surficial hydrolysis could then give an oxygenated structure like Fe–O–P, with P facing outward. Notably, free phosphorous acid does not favor the trihydroxy form (as P(OH)<sub>3</sub>), which bears lone pair electrons. Instead, it mainly exists as the tetrahedral, dihydroxy form without a lone pair (as HP(O)(OH)<sub>2</sub>). Schreibersite tends to hydrolyze first to a phosphite radical ( $\bullet\text{PO}_3^{2-}$  (2), with a small part dimerized to afford P<sub>2</sub>O<sub>6</sub><sup>4-</sup> (3)), which disproportionates to produce PO<sub>3</sub><sup>-</sup> (4) and PO<sub>3</sub><sup>3-</sup> (5) [28,29]. Among these phosphorus species, PO<sub>3</sub><sup>3-</sup> (5) may be directly bound to the mineral surface rich in Fe<sup>3+</sup> (6). Consequently, the immobilized PO<sub>3</sub><sup>3-</sup> (6) might be a feasible metastable product on the schreibersite surface. PO<sub>3</sub><sup>-</sup> (4) might as well be bound to Fe<sup>3+</sup>, although such a P(V) reagent in a redox-neutral Mitsunobu reaction is not as robust as a phosphine or phosphite [30]. The P(O<sub>Fe</sub>)<sub>3</sub> moiety on the schreibersite surface can be regarded as a protected version of P(OH)<sub>3</sub>, ensuring its lone pair to be reactive like a phosphite [31]. By contrast with the pre-phosphorylation of ribose, this route obtains the available phosphorus source from schreibersite via simple corrosion. Notably, in contemporary synthesis of nucleic acids, the ribose-phosphate linkage is routinely constructed by the introduction of P(III) group followed by an oxidation process [17,32].

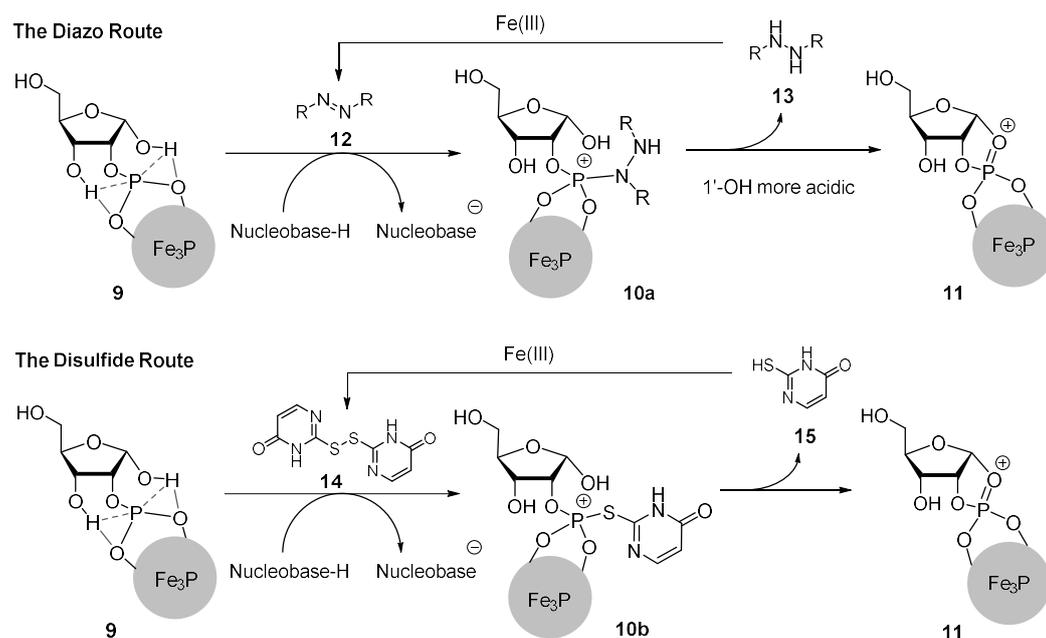
The formation of pyrimidine and purine could be traced to key small molecules such as HCN, NH<sub>3</sub> and CO [33–35]. Nucleobases have also been found in meteorites [36]. Our lab has demonstrated that ribose can be selectively enriched and stabilized on metal-containing minerals out of a complex formose mixture [37]. We also recently succeeded in the selective synthesis of *N*9 purine nucleoside by using an insoluble mineral as a heterogeneous catalyst [38]. These discoveries, however, are independent and complementary to this discussion. Georgelin and co-workers showed that metal ions on a solid support (e.g., silica) favor the adsorption of furanose, whereas pyranose remains the primary isomer without the addition of metal [39]. In alignment with that, all ribose structures in this route are presented as the furanose form. When exposed to ribose (7), one of the P–O<sub>Fe</sub> bonds is likely to be replaced by P–O<sub>ribose</sub> (8). We would expect the 2'-OH to be preferably phosphonated, since the product can be stabilized by a maximal number of intramolecular hydrogen bonds (Figure 2). The most phosphonated ribofuranose will be the  $\alpha$ -anomer since its 1'-OH is in close proximity to maximize the number of hydrogen bonds (9). This is analogous to the confirmed selective binding of  $\alpha$ -ribofuranose to metal cation over the  $\beta$ -anomer, since the  $\alpha$ -anomer has three –OH groups facing the same direction [40].



**Figure 2.** Binding of ribose to the surficially hydrolyzed schreibersite.

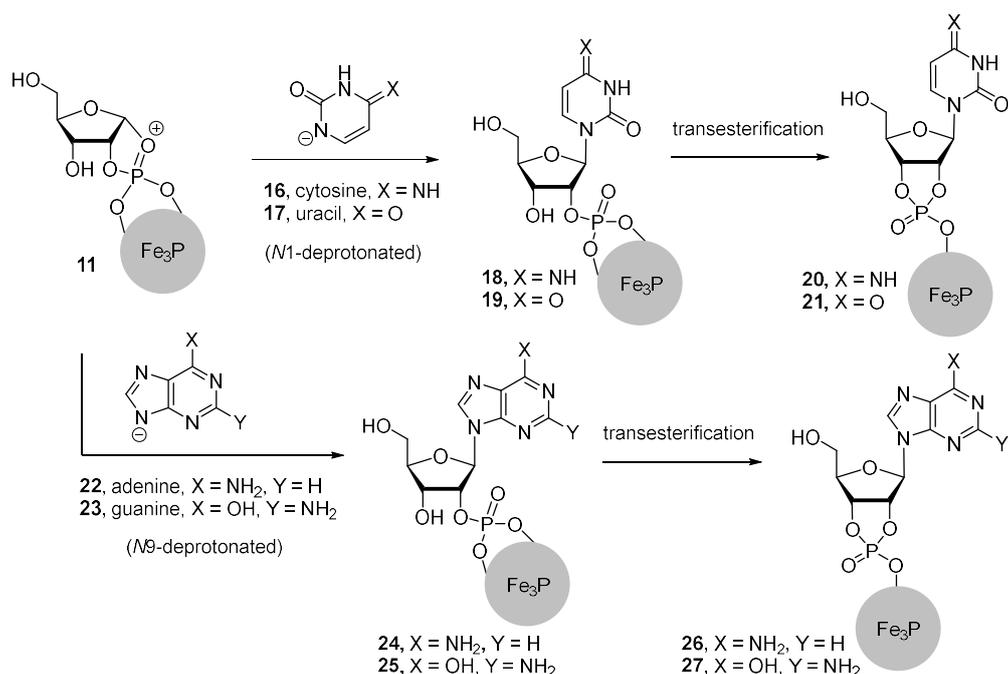
A typical Mitsunobu-type reaction requires a diazo reagent to activate the phosphine or phosphite. The formation of hydrazine and carbohydrazide on the primitive Earth has been studied [41]. Hydrazine can be oxidized to diazo compound in situ by  $\text{Fe}^{3+}$  [42], which is produced concomitantly during the partial hydrolysis of schreibersite. In a mechanistically similar oxidation-reduction condensation developed by Mukaiyama, a phosphine is activated by 2,2'-dipyridyldisulfide [43,44]. This transformation is likely to work with the disulfide of 2-thiouracil (**14**), a prebiotically relevant nucleobase [45]. As the byproduct of the condensation, the thiol can be oxidized back to the disulfide by  $\text{Fe}^{3+}$  [46]. Around the schreibersite surface,  $\text{Fe}^{3+}$  could be much in excess as a stoichiometric oxidant, as compared with the amount of hydrazine or thiol. We would not assert that diazo and disulfide are the most potent reagents, as any prebiotically available, reductive molecules that can activate P(III) might be equally effective.

With these prerequisites, the ribose-P(III)-schreibersite complex (**9**) will subsequently react with the diazo reagent (**12**) or disulfide (**14**) to form a tetrahedral, cationic intermediate (**10a** or **10b**, Figure 3). This step also triggers the deprotonation of the nucleobase, during which only the sufficiently acidic protons will be removed to give the anionic nucleobase (**16**, **17**, **22** and **23** in Figure 4). As a result, the undesired, more nucleophilic reaction sites of the nucleobases are ruled out, since 4-NH<sub>2</sub> of cytosine, 6-NH<sub>2</sub> of adenine, and 2-NH<sub>2</sub> of guanine are much less prone to deprotonation. Next, the adjacent 1'-OH attacks the positively charged P(V) intermediate **10a** to give the cyclic cation **11**, and kicks out the hydrazine (**13**), which can be oxidized back to **12** by  $\text{Fe}^{3+}$ . The selective participation of 1'-OH is due to its higher acidity than the rest of hydroxyl groups, so that the protonation and leaving of the hydrazide would be more feasible. Alternatively, in the Mukaiyama-type route, 2-thiouracil (**15**) can be converted to the disulfide (**14**) via Fe(III) oxidation.



**Figure 3.** Formation of the cationic P(V) intermediate.

The cationic species **11** should be adequately electrophilic to react with the deprotonated nucleobases, at *N1* of cytosine and uracil, and *N9* of adenine and guanine (Figure 4). In principle, *N3* of cytosine and uracil should be comparably acidic as *N1*, but it is more hindered to react. It can be expected that the nucleosidation step gives exclusively  $\beta$ -furanoside-2'-phosphate of all genetic alphabets (**18**, **19**, **24** and **25**). Owing to the highly electrophilic nature of the positively charged starting material (**11**), this nucleosidation reaction would presumably be more facile than those employing an electronically neutral intermediate. The resulting 2'-phosphate could then undergo transesterification to afford 2',3'-cyclic phosphate (**20**, **21**, **26** and **27**) as the activated form of ribonucleotides, which could oligomerize toward the formation of an RNA strand. It was reported that minerals could catalyze the polymerization of nucleotides to form short-chain oligomers [47]. However, understanding how exactly non-enzymatic polymerization occurs still remains an outstanding challenge [6,48].



**Figure 4.** Substitution by nucleobase and transesterification.

### 3. Conclusion

In summary, we have presented a hypothetical route of a phosphide mineral-based, unified synthesis of ribonucleotide, via a prebiotic version of the oxidation-reduction condensation reaction. The early Earth might experience impacts from both carbonaceous chondrites and metallic meteorites, which provided organic substrates and phosphide minerals respectively. Their collision in close proximity created conditions for the proposed chemical reactions, which did not necessarily happen on the meteorite but on Earth. Overall, the proposed route is expected to answer four levels of questions: (1) Paradox of the canonical glycosidic bond and the poor reactivity of pyrimidine's N1 and purine's N9; (2) Direct utilization of the phosphorus element from a phosphide mineral; (3) Oxidation path from P(III) to P(V); (4) Preference of the  $\beta$ -configuration of canonical ribonucleosides. We hope this route would inspire a plausible solution to the challenges of the nucleosidation and phosphorylation problems for the early-stage chemistry of the RNA World.

**Author contributions:** X.W. conceived and developed the concept. Z.-R.Z., Q.-Q.C., B.-Y.Z., W.-J.Q., Q.L. further developed the synthetic route. All authors wrote the manuscript. Z.-R.Z., Q.-Q.C. and B.-Y.Z. contributed equally.

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