



A role for phosphorus redox in emerging and modern biochemistry

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Phosphorus is a major biogeochemical element controlling growth in many ecosystems. It has presumably been an important element since the onset of life. In most chemical and biochemical considerations, phosphorus is synonymous with phosphates, a pentavalent oxidation state that includes the phosphate backbone of DNA and RNA, as well as major metabolites such as ATP. However, redox processing of phosphates to phosphites and phosphonates, and to even lower oxidation states provides a work-around to many of the problems of prebiotic chemistry, including phosphorus's low solubility and poor reactivity. In addition, modern phosphorus cycling has increasingly identified reduced P compounds as playing a role, sometimes significant, in biogeochemical processes. This suggests that phosphorus is not redox-insensitive and reduced P compounds should be considered as part of the phosphorus biogeochemical cycle.

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Introduction

The element phosphorus is part of a suite of major biochemical elements, often termed 'CHONPS' for carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur. Within this group, phosphorus is unique in that there exists no significant volatile P gas (although the gas phosphine, PH_3 , has been recognized as a potential player in the phosphorus cycle [1]), and terrestrial redox reactions of the element have historically been considered to be limited to the lab of the synthetic chemist [2^{**}], though the astrochemist is not similarly bound [3,4]. In contrast, redox chemistry drives the biogeochemical cycles of the other major elements, and volatile phases are the norm for

most of them (e.g. through photosynthesis and nitrogen fixation).

Within modern life, phosphorus is a key part of nucleic acids as it serves as the phosphate backbone of DNA and RNA, plays a critical role in metabolism as ATP and similar coenzymes and transfers chemical energy, and supports cellular structure as phospholipids [5]. These roles are conserved across all domains of life, and indicate a role for phosphorus in antiquity. Given the importance of phosphorus to biochemistry, it seems plausible that phosphorus played a role in the very earliest stages of life or even at life's onset.

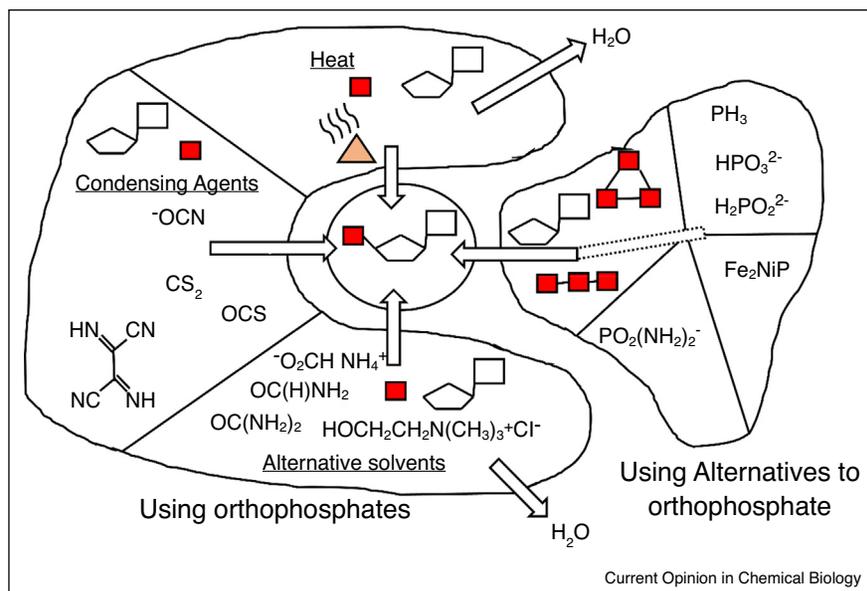
Phosphorus in the origin of life

Before the onset of modern enzymatic biochemistry, the first biomolecules had to arise from abiotic processes, such as the Miller-Urey process [6,7], formose chemistry [8], and HCN polymerization [9]. Phosphorylated molecules, were they present, would have had to have come ultimately through the reaction of a mineral of some sort—as effectively all phosphorus originates from minerals—with an organic substrate.

Therein lies the most significant problem with prebiotic phosphorylation: unlike the other biogenic elements, there is no major volatile form (limiting gas-phase reactions such as those suggested by Miller and Urey [7]), and redox reactions are considered rare for phosphorus. Hence phosphates are generally poorly reactive, and because most phosphorylation reactions release water in an aqueous solvent, phosphorylation is thermodynamically unfavored. This coupled with the poor solubility of phosphate minerals has led origins of life researchers to propose that prebiotic chemistry is confounded by a 'Phosphorus Problem' [2^{**},10,11]. Phosphorylation of organics ultimately must take place via a dehydration reaction, and in most cases necessitate higher concentrations of phosphate than would be possible compared with phosphate from early phosphate mineral dissolution. It is hence hard to envision such conditions in an early ocean.

This problem has been addressed through four main routes (Figure 1) in the literature: by heating, use of condensing agents, condensed phosphates, and alternative solvents [2^{**}]. Each of these has its advantages, and some have significant problems. Heating [12,13] can cause degradation of organics [14], and most must be heated above 100 °C to promote condensation.

Figure 1



Prebiotic phosphorylation routes explored in prior work. The goal molecule shown here is a nucleotide, with phosphate shown as the red rectangle. Most phosphorylation routes utilize phosphate as the monomer (PO_4^{3-} , or its protonated forms). Both heating and use of alternative solvents drive off water, which either evaporates (heating) or has a sparingly low activity (alternative solvents). Use of alternatives to phosphates include condensed phosphates, reduced phosphorus compounds, amidophosphates, and phosphide minerals. Many of these overcome some of the difficulties of prebiotic phosphorylation but require geochemical justification of their starting material.

Condensing agents [15] are those compounds that promote the condensation of phosphate and an organic and include cyanate [16], but most aren't phosphate-specific, and few have been shown to work adequately in water. Condensed phosphates overcome the phosphate-specific problem [17], but there are few known polyphosphate minerals [18], suggesting they may be sparse. Recent work has shown amidophosphates as excellent phosphorylating agents, but again, a geologic source is unknown [19,20]. Alternative solvents such as formamide work quite well for promoting condensation as the production of water is no longer thermodynamically uphill [21–23], but the prevalence of alternative solvents compared to water is unknown [24].

Because of the broad issues of phosphorylation in prebiotic chemistry, some researchers have suggested alternatives to phosphate at the onset of the origin of life [25]. Alternatives that have been investigated include arsenate [26] and glyoxylate [27]. From the perspective of geochemistry phosphate is generally superior, as phosphate tends to be more common than arsenate and does not induce further chirality, unlike glyoxylate. However, recently there have been suggestions that phosphate may have altogether not even been present at the origin of life [28], though that begs the question of when modern biochemistry arose.

Phosphorus redox in prebiotic chemistry

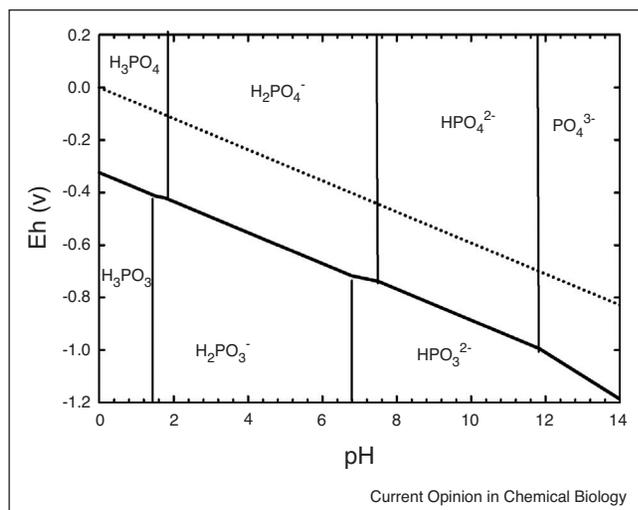
A novel route to phosphorylation may lie in the rather unexplored natural redox chemistry of phosphorus. Although most geochemists consider phosphate and phosphorus to be synonyms, new evidence suggests lower redox states of phosphorus may both be ubiquitous and biogeochemically important (see subsequent section).

The transformation of phosphate to a lower redox state of phosphorus such as phosphite or hypophosphite results in a few positive effects. Firstly, the lower redox states of phosphorus are much more soluble under similar conditions than the equivalent phosphates. For instance, calcium phosphite is $1000\times$ as soluble as calcium phosphate, and calcium hypophosphite is about $10^6\times$ as soluble. In addition, since reduced P compounds are thermodynamically unstable, they might be more reactive towards some organic reagents than phosphate. These arguments were made over half a century ago by Addison Gulick [29].

The reduced phosphorus argument was quickly stymied by the experimentalist leaders in the field [7]. Gulick's hypothesis neglected the essentials of geochemistry: under the redox conditions where water is present, no reduced P species should be possible (assuming equilibrium chemistry, see Figure 2).

With the denunciation of reduced P [7], little was done to explore reduced P in nature over the next few decades.

Figure 2



An Eh-pH diagram showing the relationship between the typical most reducing conditions found in the environment (where $2\text{H}^+ + 2\text{e}^- = \text{H}_2(\text{g})$, represented by the dashed line) and where reduction of phosphate to phosphite occurs. This reduction reaction is below the stability field of water.

The discovery of naturally occurring phosphonates [30], contemporaneous with Miller's early prebiotic studies, was viewed primarily as a biochemical oddity. The first discovery that violated the paradigm of phosphorus = phosphate was the discovery of natural phosphine in a pig slurry plant, nearly 30 years later [31]. Further, the discovery of phosphonates in the meteorite Murchison [32]—considered by many to be an analog to plausible prebiotic chemistry—demonstrated that not all phosphorus was phosphates. In the years that followed, several arguments were made for phosphonate and phosphite in prebiotic chemistry, though a reduced source was lacking [33,34]. It has been in the last two decades that research has revealed that there exist several routes to providing reduced phosphorus compounds to the oxidizing earth's surface. These include meteoritic delivery of phosphide minerals [35,36], reduction of phosphate to phosphite by lightning [37], and reduction of phosphate to phosphite by low-temperature (<200 °C) metamorphic heating [38]. There also exists some evidence that such processes were active in the Archean [38,39].

This latter reaction merits some further discussion. Iron (II) is capable of reducing phosphate to phosphite by oxidizing to iron(III) at ~160–200 °C. If iron and phosphate are associated in the environment as sediments, then this reaction occurs readily as sediments sink and are heated during the early stages of metamorphism. Water can preferentially remove phosphite relative to phosphate due to the significantly higher solubility of iron phosphite, and hence this phosphite may accumulate in the ocean. Such a process, if coupled to slow abiotic and biotic

oxidation rates, could have resulted in an abundance of phosphite in the earth early oceans.

If there were an abiotic source of reduced P on the early earth, then perhaps this was the original reactant that led to organophosphorus molecules. For instance, hypophosphite has been shown to react with aldehydes, including pyruvate to make C–P bonds [40]. In addition, phosphide minerals have been shown to oxidize and phosphorylate nucleosides [41]. This oxidation also produces polyphosphates such as pyrophosphate and triphosphate as side products [42], and these compounds were not considered especially common in the prebiotic environment in prior studies [18] as they had no known geologic source.

Phosphorus redox in the modern biogeochemical system

Reduced oxidation state phosphorus overcomes many of the issues for prebiotic phosphorylation. Several of the discoveries that led to redox of phosphorus being proposed as a route around the 'Phosphate Problem' in the origin of life are also relevant to modern phosphorus biogeochemical cycling studies. In the last few years reduced phosphorus compounds have been identified to be both ubiquitous in the environment, and to be major players in some environments.

The inorganic routes to forming reduced phosphorus compounds include both natural and anthropogenic sources. As discussed earlier, phosphite is formed naturally by lightning [37], corrosion of naturally occurring iron-based and nickel-based metals and metallic minerals [35], and by the concomitant oxidation of ferrous iron [38]. The latter is likely the single largest abiotic source active on the surface of the earth today. In addition to these natural sources, anthropogenic sources include rusting of iron metal, and production of elemental phosphorus for use in industry [43,44].

The first indications that there is a reduced phosphorus cycle came in 1959 with the discovery of the molecule 2-aminoethylphosphonate in a sea anemone [30]. Subsequently this phosphonate and others were found to be ubiquitous across the domains of life [45], though a biochemical rationale for their production remains unclear as they are formed—at considerable metabolic cost—from phosphoenolpyruvate [46].

One of the simplest of the organic phosphonates is methylphosphonate ($\text{CH}_3\text{-PO}_3^{2-}$). Methylphosphonate is a metabolic product in the biodegradation of most organic phosphonates [47], and is the penultimate molecule en route to oxidation to phosphates, along with the molecule hydroxymethylphosphonate [48,49]. This molecule is ultimately broken down enzymatically to yield phosphate and methane, and serves as the largest source of methane in the oxygenated ocean [48–53]. To this end,

a phosphonate molecule appears to control a major carbon source in the environment [54**]. Recently, a separate organism has been shown to use phosphite to fix CO₂, the seventh pathway of its kind [55*].

Given the prevalence of the organic reduced P molecules, it would seem as though there might be an interplay with the inorganic reduced P molecules. The inorganic analog to the organic phosphonates is the ion phosphite (HPO₃²⁻). This ion is kinetically stable and can serve as a substitute for phosphate under phosphate-starvation for several microbial lineages [56–58]. The utilization of phosphite and hypophosphite rely on one of three genes, two of which use O₂ as the oxidant, and the other uses NAD⁺ [59]. The ability to use reduced P compounds appears to be present in 1–10% of all microbial lineages in many environments [60*,61], suggesting a source somewhere in the environment of these compounds.

The gas phosphine was the first major inorganic reduced P species detected from natural sources on the surface of the earth, and its origin was unclear [31]. Several researchers argued for a biotic origin, others preferred an abiotic origin. In most cases, a biotic origin was hinted, as many phosphine sources are from highly reducing environments such as animal waste plants and wetlands [62–65]. Recently, it appears the reduced P compounds such as phosphite and hypophosphite may ultimately be the source of phosphine in the atmosphere. The disproportionation of the reduced P compounds is predicted to produce the concentration of phosphine that has been observed in atmospheric measurements based on thermodynamics [66]. Indeed, recent experimental observations show the clear

production of phosphine from hypophosphite disproportionation [67].

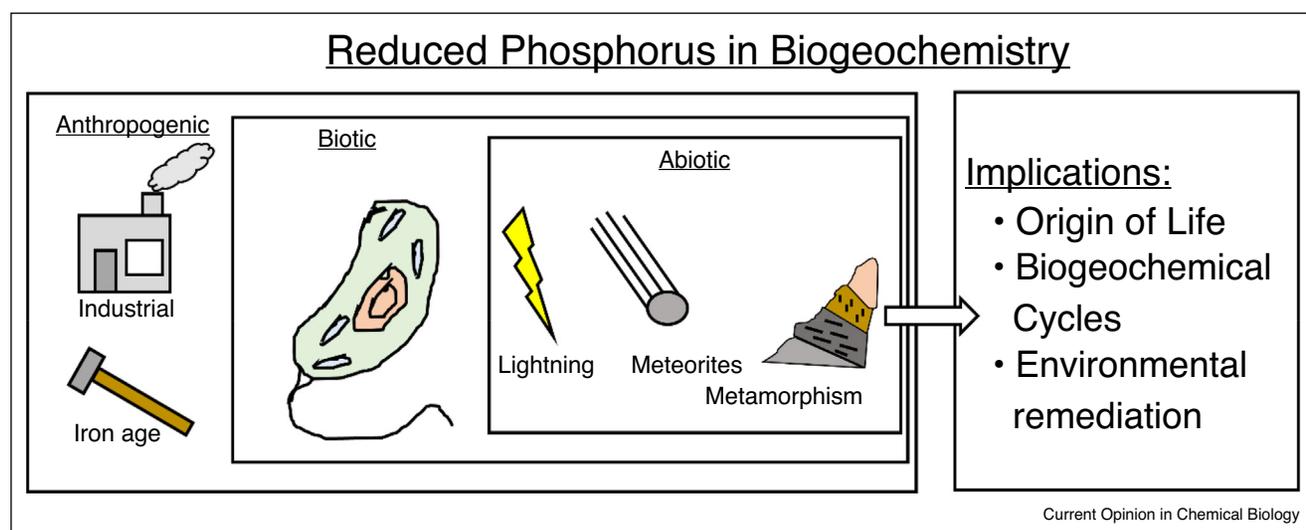
Presented here is a hypothesis: that the ion phosphite and hypophosphite originate from organic phosphonates. The exact production of these molecules is unclear and remains undemonstrated, but if a route to phosphite production from phosphonates can be demonstrated, then such a demonstration would tie the organic and inorganic reduced P biochemistries together and demonstrate a full phosphorus redox cycle.

Summary and implications

There is a clearly a presence of reduced P in modern biochemistry. Its origin is unclear, but there is a growing body of work that has demonstrated that phosphonates are both biologically important and are important on the global environmental scale. The case for inorganic reduced P is less clear, but it seems likely that there exists an interplay between phosphonates and phosphite, though the chemical linkage between the two has eluded discovery.

The biogeochemical cycle of phosphorus needs to be evaluated with redox as a player (Figure 3). Redox may not be universally important in all environments, but in those cases where phosphorus is a key substance of interest, identifying and considering reduced P reactions is a critical step. For instance, reduced P is not typically analyzed for in wastewater remediation facilities, and the two major routes for phosphate quantification—molybdenate coprecipitation and struvite formation—fail to capture reduced P [68]. As such these species may not even be considered in modern environmental reclamation

Figure 3



Routes to reduction of phosphate may be grouped roughly according to onset in history, from before the origin of life to before the origin of industry to modern day.

schemes. This may point to a ‘leak’ in our phosphorus biogeochemical cycle consideration that may be due in part to redox [69**]. It is the hope of this paper that readers will consider redox when encountering phosphorus in biogeochemistry.

Conflict of interest statement

Nothing declared.

Acknowledgements

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