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Did nature also choose arsenic?

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Abstract: All known life requires phosphorus (P) in the form of inorganic phosphate (PO_4^{3-} or P_i) and phosphate-containing organic molecules. P_i serves as the backbone of the nucleic acids that constitute genetic material and as the major repository of chemical energy for metabolism in polyphosphate bonds. Arsenic (As) lies directly below P on the periodic table and so the two elements share many chemical properties, although their chemistries are sufficiently dissimilar that As cannot directly replace P in modern biochemistry. Arsenic is toxic because As and P are similar enough that organisms attempt this substitution. We hypothesize that ancient biochemical systems, analogous to but distinct from those known today, could have utilized arsenate in the equivalent biological role as phosphate. Organisms utilizing such 'weird life' biochemical pathways may have supported a 'shadow biosphere' at the time of the origin and early evolution of life on Earth or on other planets. Such organisms may even persist on Earth today, undetected, in unusual niches.

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Phosphorus (P) ranks just behind hydrogen, oxygen, carbon and nitrogen (H, O, C and N) in a quantitative list of the most important elements in biology (Voet & Voet 1990). However, P is usually less available to life than these other elements, particularly in the oceans. H and O are available in any aqueous solution, while C and N can be found in gaseous compounds that are readily distributed through the atmosphere and that can be converted into highly soluble chemical forms. Although there is some speculation about extraterrestrial input of P to Earth, early life may have been mainly dependent on crustal elemental sources (Pasek 2008). In contrast, while P is a relatively common element in the Earth's crust (0.1 % by weight) (Winter 2007), there is no gas phase P compound analogous to CO_2, CH_4, N_2 or NH_3, and common phosphate minerals such as apatite ($Ca_5(PO_4)_3(OH, F, Cl)$) are only sparingly soluble (Stumm & Morgan 1996). The distribution of bioavailable P at the Earth's surface is therefore extremely heterogeneous. Although there is some speculation about extraterrestrial input of P to Earth, early life may have been mainly dependent on crustal elemental sources (Pasek 2008). In this way, P is similar to many of the so-called 'micronutrient' elements that are required in biology in trace amounts (e.g. Fe, Cu, Mn and Zn). As a result, the distribution of life at the Earth's surface is often determined by the distribution of P, which is why phosphate (PO_4^{3-}) fertilizers are commonly used to compensate for low P concentrations.

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Twenty years ago, Westheimer explained why life as we know it is based on P (Westheimer 1987). A critical feature is the acid–base chemistry of P in the 5+ oxidation state (P(V)) in the form of phosphoric acid (H_3PO_4), which dictates that the dominant soluble forms of P at biological pH (~7–8) are the charged species $H_2PO_4^-$, HPO_4^{2-} and PO_4^{3-} (collectively, these species and H_3PO_4 are referred to as 'inorganic phosphorus' or P_i). Charged molecules are more easily contained within lipid membranes than are uncharged molecules, and hence evolution selected for biomolecules that include functional groups derived from P_i and other weak acids such as carboxylic acids and amino acids (Davis 1958). However, P_i is unique even among these weak acids because it can maintain a negative charge at physiological pH even when bonded to two other molecular units. Hence, as the building block for adenosine triphosphate (ATP) and adenosine diphosphate (ADP), P_i prevents chemically stored energy from escaping the cell. Similarly, the repeating phosphodiester linkages in deoxyribonucleic acid (DNA) effectively make DNA a polyanion, so that P_i helps cells retain the genetic material. The negative repeating charge of DNA is also a key factor in its physical stability in the way it prevents folding of the linear strand, thereby protecting template-like behaviour (Benner & Hutter 2002). Hence, P_i is well suited as a component of both metabolic and genetic molecules.

However, other elements share key chemical properties with P. Of these arsenic (As) in the (V) oxidation state warrants closer inspection. Inorganic As(V), like P(V), is negatively charged over a range of physiological pH conditions, as $H_2AsO_4^-$, $HAsO_4^{2-}$, or AsO_4^{3-} (i.e. arsenate or As_i). In fact,

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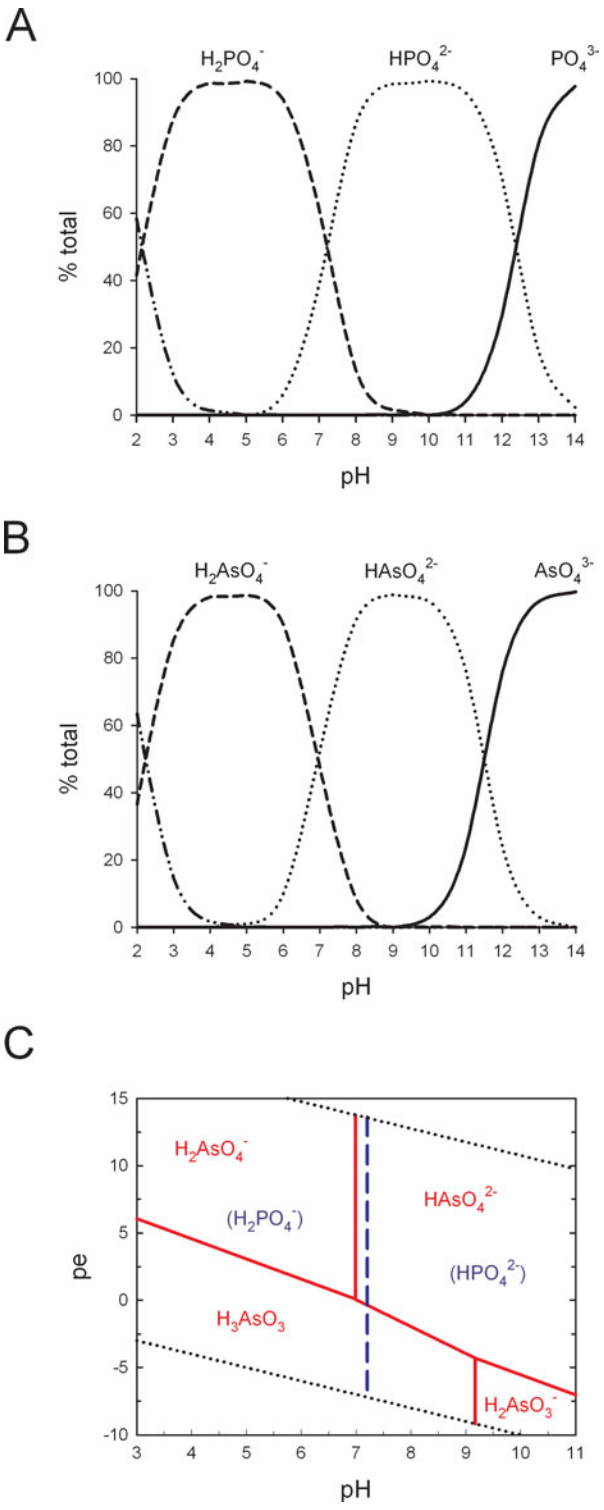


Fig. 1. pH and redox potential (pe) are the most important factors controlling arsenic speciation. Phosphate (A) and arsenate (B) speciation are shown as a function of pH for the (V) oxidation states. H_3PO_4 or H_3AsO_4 (dashed and dotted line), $H_2PO_4^-$ or $H_2AsO_4^-$ (dashed line), HPO_4^{2-} or $HAsO_4^{2-}$ (dotted line) and PO_4^{3-} or AsO_4^{3-} (solid line) are all indicated as a percentage of total P_i or As_i. The distribution curves in (A) and (B) show that As_i and P_i have similar charge and speciation under biologically relevant pH (Westall *et al.* 1976; Allison *et al.* 1991; Serkiz *et al.* 1996). Redox speciation is shown on a pe-pH diagram for aqueous arsenic species (C) in the systems P–O_2–H_2O and As–O_2–H_2O at 25 °C and 1 bar total pressure. Arsenic (solid lines) and phosphorus (dashed line) species have been overlaid within the bounds of the O_2–H_2O redox couple (dotted lines). On such a diagram, phase boundaries represent the conditions at which the activities of the species on each side of the boundary are equal (Morel & Hering 1993; Smedley & Kinniburgh 2002). Under dysoxic conditions (pe ≈ 0) and at neutral to mildly alkaline pH, the dominant As species is $HAsO_4^{2-}$ suggesting that it would be present under conditions possibly relevant to the early evolution of life on Earth.

the dissociation constants for H_3AsO_4 are so similar to those of H_3PO_4 that As_i and P_i follow strikingly similar speciation patterns (Figure 1A and B). Also, like P_i, As_i is capable of retaining a negative charge even when it bonds to two other molecules. Owing to these similarities, known life cannot easily distinguish between As_i and P_i. Thus, arsenate is taken up by cells via phosphate transporters and can substitute for P_i in the early steps of many P_i-based metabolic pathways (Braunstein 1931; see Table 1). For example, As is generally thought to decouple oxidative phosphorylation, the production of ATP using energy released by oxygen-consuming redox reactions, because no ATP is produced in phosphate-depleted, arsenate-rich mitochondrial particles even though oxygen uptake continues. This observation suggests that arsenate substitutes for phosphate in the early steps of this process (Crane & Lipmann 1953). These similarities account in large measure for the biological toxicity of As_i.

Why, despite these similarities, has the possibility of As-based life been discounted? The primary chemical objection is that As_i-based compounds hydrolyse much more rapidly than their P_i counterparts (Westheimer 1987). In particular, polyarsenates hydrolyse orders of magnitude faster than do polyphosphates. However, this objection is not decisive. For example, the same type of problem exists for nucleic acids. As we shall argue, chemically exceptional aquatic environments and natural selection both offer solutions, particularly when considered in the context of prebiotic chemistry and the evolution of early life (Levy & Miller 1998). Similar logic could apply here.

The relative instability of polyarsenates does not rule out a role for As_i in environments in which it is present at much higher concentrations than P_i. Such settings could sustain elevated steady-state concentrations of polyarsenates and other As-based biomolecules versus P-based analogues despite the faster reaction rates of the former. Intriguingly, such environments include both terrestrial and deep-sea hydrothermal systems (Von Damm 1990; Wilkie & Hering 1998; Langner *et al.* 2001) where life is conjectured to have originated (Corliss *et al.* 1979; Martin & Russell 2003) and where the last common ancestor may have avoided surface-sterilizing meteor impacts of the Late Heavy Bombardment (Maher & Stevenson 1988; Miller & Bada 1988; Sleep & Zahnle 1998). In these systems, As and many other elements react with hydrogen sulphide to precipitate as sulphide minerals, forming the famous 'chimneys' of undersea 'black smoker' volcanoes. The surfaces of these minerals, rich in bioessential

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Table 1. *Evidence of arsenate substitution for phosphate by modern, extant biochemical processes*

Reaction or enzyme	Arseno-analogue	Phosphate compound	Reference
Adenylate deaminase	5′AMAs	5′AMP	Lagunas *et al.* (1984)
Adenylate kinase	5′AM(CH_2)As	AMP	Adams *et al.* (1984)
Aspartate aminotransferase	Pyridoxal arsenate	Pyridoxal phosphate	Ali & Dixon (1992)
Chloroplastic electron transport	ADP-As	ATP	Avron & Jagendorf (1959)
Glucose-6-phosphate dehydrogenase	Glucose-6-arsenate	Glucose-6-phosphate	Gresser (1981)
Hexokinase	ADP-As	ATP	Gresser (1981), Moore *et al.* (1983)
Human red blood cell sodium pump	As_i	P_i	Kenney & Kaplan (1988)
Mitochondrial O_2 consumption	As_i	P_i	Crane & Lipmann (1953)
Myokinase	AMAs	AMP	Lagunas *et al.* (1984)
RNA Polymerase	Pyroarsenate	Pyrophosphate	Rozovskaya *et al.* (1984)
R. rubrum light induced phosphorylation	ADP + As_i	ADP + P_i	Slooten & Nuyten (1983)
Phosphoenolpyruvate mutase	Arsenopyruvate	Phosphonopyruvate	Chawla *et al.* (1995)
Phosphotransacetylase	As_i	P_i	Kyrtopoulos & Satchel (1972)
Protein synthesis	ADP-As hydrolysis	ATP hydrolysis	Ozawa *et al.* (1970)
Purine nucleoside phosphorylase	As_i	P_i	Kline & Schramm (1993)

trace metals and S, and bathed in fluids containing dissolved volatiles such as CO_2 and N_2 (Forrest *et al.* 2005), are widely recognized as a promising environment for prebiotic catalytic chemistry and early life (Schoonen & Xu 2001; Brandes & Devol 2002). Importantly, As, unlike P, forms sulphide minerals, rendering it far more accessible than P for (bio)-chemical reactions occurring on hydrothermal sulphide mineral surfaces. Although present in these minerals in a highly reduced form, arsenite (AsO_3^{3-}) and arsenate are thermodynamically and kinetically stable even in anoxic waters at pH > 7, as long as the concentration of sulphide is low (Berner 1981; Smedley & Kinniburgh 2002; Oremland *et al.* 2004). Such chemical conditions probably typified the Archean oceans (Canfield 2005), so that As_i could have been available near the surfaces of As-rich sulphide minerals where As sulphides dissolved in seawater.

If arsenate is present then, in striking contrast to their P_i analogues, As_i biomolecules indeed form spontaneously. For example, *in vitro* mixtures of adenosine (or a deoxy analogue) and As_i readily form As-nucleosides and As-nucleotides (Lagunas *et al.* 1984) (Figure 2). Furthermore, these synthetic 5′AMAs can substitute for 5′AMP in reactions catalysed by the enzymes myokinase and adenylate deaminase (Lagunas *et al.* 1984). Thus, rapid hydrolysis per se may be unproblematic in environments rich in As, as key molecules can be quickly replenished.

It is interesting to speculate that the reactivity of polyarsenates versus polyphosphates might have actually been a virtue in prebiotic chemical systems or ancestral organisms. Owing to the stability of P_i compounds, all known organisms require sophisticated enzymes to catalyse the removal or addition of P_i (phosphatases and kinases, respectively). As_i compounds might have needed less sophisticated molecular machinery to fulfil their biochemical roles in ancient systems, facilitating the development of P_i-like metabolism. It is perhaps no coincidence that it is relatively simple, through site-directed mutagenesis, to change an arsenate reductase to a phosphatase (Rosen 2002). One interpretation of this similarity is that reductases derive from phosphatases. However, an equally plausible interpretation is that the fundamental biochemistry of P_i-based life emerged in an As-rich environment.

Natural selection could have stabilized As_i biomolecules, analogous to the ways that P_i-bearing biomolecules have evolved stability against hydrolysis. The phosphodiester bonds of ribonucleic acid (RNA), for example, are stabilized *in vivo* by 5′ and 3′ end modifications as well as by numerous protein interactions (Deana & Belasco 2005; Slomovic *et al.* 2005; Petrillo *et al.* 2006). Without these mechanisms, the phosphodiester linkages to ribose hydrolyse within seconds under biological conditions (Lindahl 1993; Selinger *et al.* 2003). Moreover, *in vitro* studies replicating thermophilic environments where early life may have resided show the rate of RNA hydrolysis steadily increases as temperature rises from 65 to 100 °C (Eigner *et al.* 1961), approaching reaction rates which are comparable to those for short strands of polyarsenates (Kawamura 1999, 2001a,b; Nagahama & Kawamura 2002; Kawamura *et al.* 2005). It is therefore plausible that As-based life emerged in As-rich environments and, once established, evolved strategies that would enable it to persist.

A second objection to As raised by Westheimer is that it is easily reduced from As(V) to As(III), whereas P is rarely reduced from P(V) at the Earth's surface (Westheimer 1987). Although this difference poses some challenges to As-based metabolism, it also implies some benefits because the redox properties of As provide possible bioenergetic pathways. Indeed, some extant microorganisms exploit this metabolic opportunity (Stolz & Oremland 1999; Rosen 2002; Bhattacharjee & Rosen 2007). As_i can serve as an electron acceptor by anaerobic heterotrophic bacteria that oxidize reduced carbon and produce arsenite (Dowdle *et al.* 1996; Stolz & Oremland 1999; Oremland *et al.* 2002; Oremland & Stolz 2003), in chemolithoautotrophic arsenite oxidizers that fix inorganic carbon and produce arsenate (Ehrlich 2002) or in cyanobacteria and purple bacteria that use arsenite as an electron donor in anaerobic photosynthesis (Kulp *et al.* 2008). Therefore, far from being a liability, the redox

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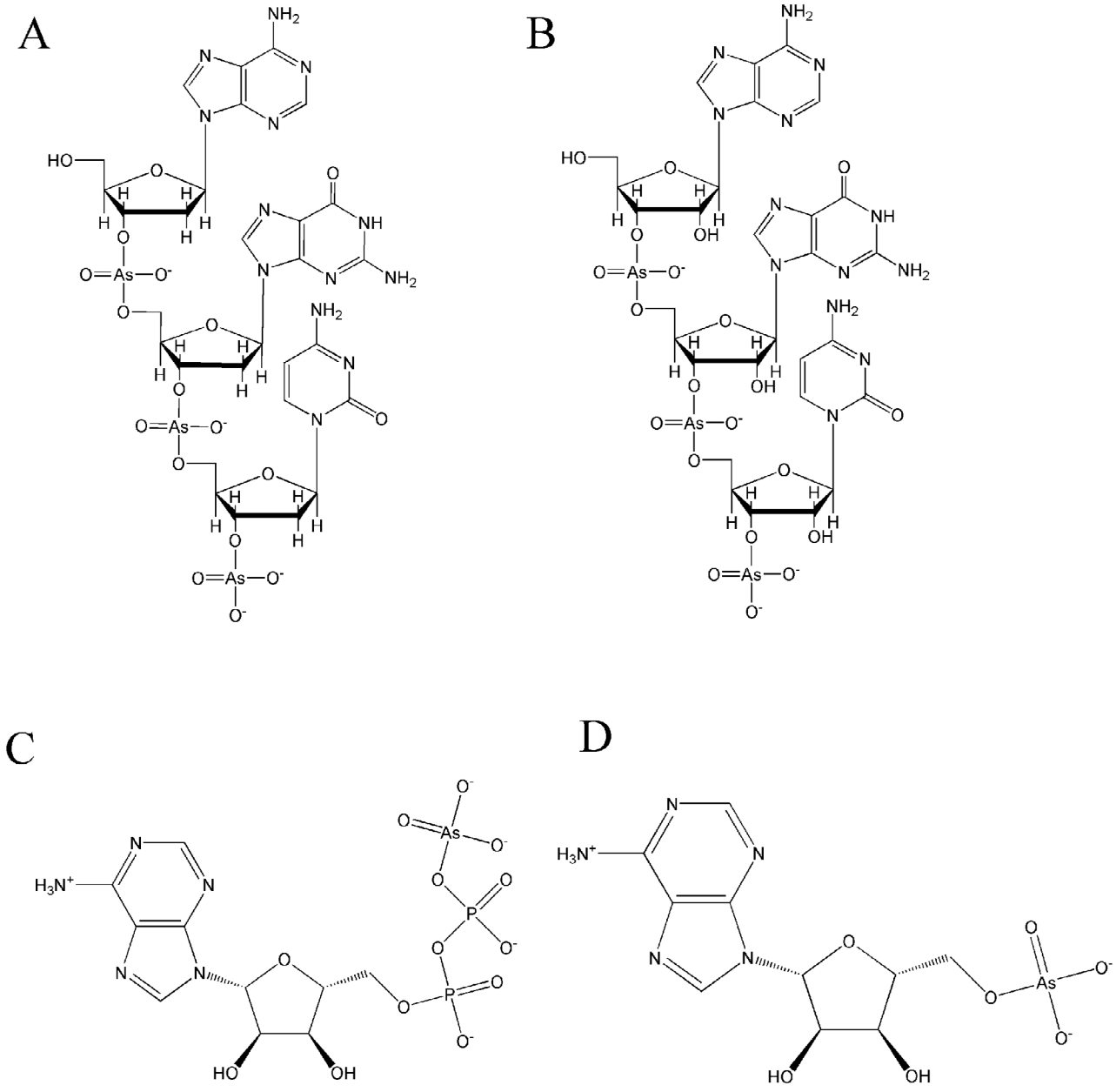


Fig. 2. Examples of both described and yet undetected arsenate containing biological molecules (at pH 7): (A) As-deoxyribonucleic acid (As-DNA); (B) As-ribonucleic acid (As-RNA); (C) adenosine diphosphate arsenate (ADP-As); and (D) adenosine monoarsenate (AMAs).

character of As potentially makes it more biochemically versatile than P.

Once life ventured forth from its As-rich primordial home, the balance of advantage probably tipped in favour of P because P is typically 10 000 times more abundant than As at the Earth's surface. However, As-based life could even survive today in restricted pockets where As is present in abundance, such as shallow and deep-sea hydrothermal systems or at Mono Lake (Von Damm 1990; Pilcher *et al.* 1999; Oremland *et al.* 2002, 2004; Roesler *et al.* 2002).

In conclusion, there seems to be no knockout argument against As-based life, and considerable circumstantial evidence to suggest its plausibility. In recent years, astrobiologists have devoted considerable attention to exploring the possibility of alternative forms of extraterrestrial life (dubbed 'weird life') (Baross 2007). Curiously, little thought has been devoted to the possibility that the Earth may have once also harboured weird life. It is a tantalizing prospect that an ancestral, alternative form of life might even continue to lurk in modern As-rich Earth habitats forming an extant 'shadow biosphere' (Cleland & Copley 2006; Davies *et al.* 2009). A search of such environments would seem to be a promising initial step to test this hypothesis. In view of the extensive consideration given to the possibility of emergent life on other planets, it would be ironic if we overlooked a candidate right here on Earth.

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