Submarine hydrothermal vents are rich in hydrogen ($H_2$), an ancient source of electrons and chemical energy for life. Geochemical $H_2$ stems from serpentinization, a process in which rock-bound iron reduces water to $H_2$. Reactions involving $H_2$ and carbon dioxide ($CO_2$) in hydrothermal systems generate abiotic methane and formate; these reactions resemble the core energy metabolism of methanogens and acetogens. These organisms are strict anaerobic autotrophs that inhabit hydrothermal vents and harness energy via $H_2$-dependent $CO_2$ reduction. Serpentinization also generates native metals, which can reduce $CO_2$ to formate and acetate in the laboratory. The enzymes that channel $H_2$, $CO_2$, and dinitrogen ($N_2$) into methanogen and acetogen metabolism are the backbone of the most ancient metabolic pathways. Their active sites share carbon–metal bonds which, although rare in biology, are conserved relics of primordial biochemistry present at the origin of life.
and provides a hydrophobic pocket where cofactor and substrate can react [13]. The popular idea of an RNA world [14] arose around the concept that cofactors preceded enzymes in evolution and were originally connected to RNA molecules as the precursors of proteins [15]. Thioesters have long been recognized as being central to metabolism [8, 16]. The thioester bond is long and easily cleaved [17], making them highly reactive [18]. Thioester bonds have a high free energy of hydrolysis (~43 kJ/mol), higher than that of ATP (~31 kJ/mol) [8], which is often generated from thioesters in metabolism. Thioesters are thought to have preceded phosphates as energy currencies in evolution [16, 19] and they can be synthesized in the laboratory from carbon monoxide (CO) and methyl sulfide in the presence of FeS [20], compounds that were likely present on the primordial Earth [8]. FeS clusters are traditionally viewed as primitive catalysts in metabolism because they are completely inorganic and because metal sulfides would have been common on the early Earth [21, 22]. Reduced FeS clusters are also a currency of chemical energy [23, 24], similar to thioesters and ATP. They are also highly enriched in genomic reconstructions of the metabolism of the last universal common ancestor (LUCA) [25], which used the acetyl-CoA pathway and lived off gases, harnessing energy by reducing CO2 with H2 [26]. Physiology is rich in continuity because some 4 billion years after the origin of life [27], the same chemical energy that powered LUCA still fuels the growth of modern methanogens and acetogens that inhabit the crust today [28–32].

If the continuity principle holds at the active sites of enzymes, then enzymes with which anaerobes access CO2, N2, and H2 at the interface between the environment and biology can provide insights into the nature of primordial metabolism. Here, I discuss ancient enzymes at the core of metabolism because they are completely inorganic and because metal sulfides

**Glossary**

- **Acetogens**: organisms that generate acetate (and water) as the sole end-product of their main bioenergetic reaction (sometimes also called homoacetogens). All acetogens characterized so far belong to the bacteria.
- **Autotrophy**: a trophic ( nutritional) mode in which the cell satisfies its carbon needs from CO2. The opposite of autotrophy is heterotrophy, a trophic mode in which the cell satisfies its carbon needs from reduced organic compounds.
- **Bioenergetic reactions**: energy-releasing reactions that cells use to conserve chemical energy. The most common currency of biochemical energy is ATP, but there are other energy currencies used in cell metabolism, including acyl phosphates, thioesters, reduced ferredoxin, or ion gradients.
- **Continuity thesis**: a philosophical construct that separates scientific from vitalistic thought on the nature of self-organization. It unites theories viewing the origin of life as inherently probable based on their shared premise that physical and chemical constraints apply uniformly across the transition from inanimate to living matter. It distinguishes them from theories viewing the origin of life as so improbable that supernatural influence was required for life to arise from the elements on the early Earth.
- **Electron bifurcation (flavin based)**: a soluble mechanism of energy conservation that generates reduced ferredoxin as the energy currency. In flavin-based electron bifurcation, an electron pair is split at a flavoprotein. One electron is transferred energetically ‘downhill’ to an acceptor with a more positive midpoint potential than the donor, the other is transferred energetically ‘uphill’ to an acceptor with a more negative midpoint potential, a low potential ferredoxin in cases studied so far.
- **Last universal common ancestor (LUCA)**: a hypothetical entity envisaged by some as an organism, envisaged by others as a geochemically supported chemical reaction, that had
The key enzymes of the acetyl-CoA pathway are CO dehydrogenase (CODH) and acetyl-CoA synthase (ACS) [47]. Although there are over 400 known reactions in metabolism that involve the assimilation or dissimilation of CO₂, there is only one portal for CO₂ entry into metabolism: the CODH reaction [48]. CODH synthesizes CO from CO₂ [42,43]. The role of CO in metabolism is specific; energy is released by the acetyl-CoA pathway during the conversion of a CO-derived carbonyl group to a carboxylate [48], while the other CO₂ fixation routes reduce carboxylate groups to carbonyls [40,43,46].
ACS condenses a methyl group and CO to an acetyl group that is covalently bound to the enzyme and removed by the thiol of coenzyme A to yield the energy-rich thioester acetyl-CoA [49,50]. The methyl group is donated to ACS via methylcobalamin in the corrinoid FeS protein, CoFeS [51–54], which performs an unusual metal-to-metal methyl transfer reaction. The teams of Steve Ragsdale and Holger Dobbek have generated high-resolution structures of the active sites of CODH [55–57], ACS [56,58–60], and CoFeS [51,52,54]. Importantly, all three active sites are ancient, tracing to the genome of the LUCA [25]. More importantly, in the context of this paper, all three active sites represent organometallic compounds; that is, they contain carbon–metal bonds (Figure 1). The acetyl-CoA pathway can even be emulated by reactions between native metals and CO₂ in laboratory experiments, narrowing the gaps between the geochemical and biochemical reactions of carbon (Box 1).

**Ancient Metabolic Networks**

The acetyl-CoA pathway requires high concentrations of reduced low potential ferredoxin to operate [10,23,42,43,61–63]. The acetyl-CoA pathway and ferredoxin are both replete with metals, and both figure prominently in studies of biochemical pathway evolution. Metabolic pathways themselves should contain information about how they interacted with, and emerged from, the ancient environment [12]. Each genome encodes a collection of enzymes that supports life, and those enzymes catalyze reactions that connect substrates, generating a metabolic network for each organism. Goldford *et al.* [16] recently probed metabolic networks to see whether there

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**Figure 1. Carbon–Metal Bonds.** (A) Carbon dioxide (CO₂) fixation: the structure of the carbon–nickel bond in the carbon monoxide dehydrogenase (CODH) reaction intermediate shown is according to Dobbek *et al.* [55], Jeoung and Dobbek [59], and Can *et al.* [49,50]. The structure of carbon–nickel bonds in the acetyl-CoA synthase (ACS) A-cluster is redrawn from Svetlitchnyi *et al.* [58] and Can *et al.* [49]. Methylcobalamin, a cofactor in the CO₂ fixation pathway, performs metal-to-metal methyl transfer from corrinoid iron sulfur protein (CoFeS) to the A cluster of ACS [51,52]. (B) N₂ fixation: the structure of the carbon–iron bond in the nitrogenase M cluster is redrawn from Hu and Ribbe [83], Anderson *et al.* [77], Raugei *et al.* [85], and Cao *et al.* [86]. (C) H₂ oxidation: the structures of carbon–iron bonds in [Fe–Ni] hydrogenase [87,88], [Fe] hydrogenase [88,89], and [Fe–Fe] hydrogenase [88,90,91]. (D) Radical formation: the structures of adenosylcobalamin and the radical S-adenosyl methionine (SAM) intermediate omega are redrawn from [83,99,100]. Active sites and cofactors that trace to the last universal common ancestor (LUCA) [25] are indicated with a dot. Carbon–metal bonds are highlighted in black.
are traces of biochemical reactions that might have existed before ATP became the universal energy currency. For that, they looked at metabolic networks to see whether an ancient core remains if all the ATP-dependent reactions are removed. They found such a core comprising 260 metabolites connected by 315 reactions, some of which were still energetically uphill. Those energetically uphill reactions did not involve ATP but did involve two currencies of ancient metabolic energy instead: thioesters and FeS-dependent reactions.

The involvement in ancient core metabolism of thioesters, which have a high free energy of hydrolysis and are an energy currency similar to ATP [16], meshes well with the findings of Semenov et al. [18], who constructed thioester-driven systems of oscillating chemical reactions in the laboratory. Furthermore, the involvement of FeS-dependent reactions in the ancient core network [16] fits well with the biochemical axiom that metals and FeS clusters are relics of ancient metabolism [21,22,64–66]. In an origin of life context, FeS clusters are usually discussed as ancient catalysts [22,66–68]. However, their main role in metabolism is not in catalyzing reactions, but rather in enabling electron flow via one-electron-transfer reactions [69,70]. In cells that harness H₂ as a source of electrons for carbon and energy metabolism, electrons enter metabolism via hydrogenases and a soluble FeS protein called ferredoxin, 90% of which is present in the reduced form in growing anaerobes [61] at concentrations of ~80–400 μM [39,71]. The generation of reduced ferredoxin from H₂ is an energetic challenge in its own right and involves the process of flavin-based electron bifurcation, which is the most recently recognized mechanism of biological energy conservation [23,24,61–63]. The ancient core metabolic network uncovered by Goldford et al. [16] underscores the antiquity of the acetyl-CoA pathway, thioesters, and FeS-dependent reactions at the onset of metabolic evolution.

**Tracing Ancient Metabolic Pathways through Genomic Analysis**

Genomes harbor another resource that can be tapped to probe ancient evolution: gene sequences that can be used to generate phylogenetic trees. The standard approach to
investigate early evolution with phylogeny has been to make trees of some conserved component of the cell, such as the ribosome, and to map biochemical pathways or physiological traits onto the tree to infer what might be ancient by scoring the properties of the lineages that branch deep. However, LGT often underlies gene distributions among bacteria and archaea [72] and the evolution of genes that define physiological traits [39].

The LGT problem is quantitatively severe [72,73]. A recent study investigated trees for all 250 000 prokaryotic genes families (clusters) from 2000 genomes that are sufficiently conserved to make trees [25]. Approximately 11 000 of the clusters had homologs in bacteria and Archaea, but 97% of those trees uncovered evidence for LGT between bacteria and archaea [25]. The remaining 3% (355 of the 11 000 present in archaea and bacteria) recovered monophyly for archaea and bacteria [25]. That does not mean that those 355 genes were inherited vertically, but it does mean that they were likely present in the common ancestor of bacteria and Archaea, which in current views was the LUCA.

Those 355 genes shed light on the physiology and habitat of LUCA, depicting it as an anaerobic thermophile that was rich in transition metal clusters, one-electron reactions, radical S-adenosyl methionine (SAM) enzymes, and methyl transferase reactions [25,26]. Regarding ancient metabolism, genomes point in the same direction as the early Earth environments, energetics, and networks described earlier: LUCA used the acetyl-CoA pathway and lived off gases including H2, CO2, CO, and N2 [25,26]. Moreover, the known organometallic bonds of modern metabolism clearly tend to cluster in LUCA (Figure 1) [25,26].

Carbon–Metal Bonds in Nitrogen Fixation
Cell mass is 50% protein and 20% RNA [74], corresponding to 50% carbon and 10% nitrogen by dry weight. Given that proteins and RNA are indispensable for life, the entry of nitrogen into metabolism is crucial to metabolism, both modern and ancient. While H2 and CO2 readily provide carbon energy and electrons for acetogens and methanogens, nitrogen must also be provided for cells to grow. In modern ecosystems, the source of nitrogen is N2, and there is only one enzyme known that can reduce N2: nitrogenase. Nitrogenase is an ancient enzyme [75] the subunits of which trace to LUCA [25,76]. There is only one basic type of nitrogenase active site, which can contain molybdenum (Mo), vanadium (V), or Fe [76,77]. The active site of nitrogenase points to a unique biological solution for a hard chemical problem. The center of the nitrogenase active site harbors a carbide carbon atom that is complexed by iron [78,79]. It is the only biological carbide described to date. Its insertion starts from the methyl group of SAM [80,81], an ancient cofactor that also had a central role in the physiology of LUCA [25]. The nitrogenase active site (Figure 1) has a phenomenal spectrum of enzymatic activities. Not only is it the biological model for the Haber–Bosch process of ammonium synthesis from N2 [36,77], but it also catalyzes industrially relevant reactions involving carbon. These include Fischer–Tropsch reactions (hydrocarbon synthesis from CO2), although sometimes at low rates, as well as reactions of various organic and inorganic nitrogen compounds [82–84]. Nitrogenase accepts electrons from low potential ferredoxin, which is generated in H2-dependent diazotrophs via hydrogenase with the help of electron bifurcation [61–63]. According to current structural models [76,77,85,86], the atom that binds N2 is Fe, not Mo or V (or the Mo-corresponding Fe) in the three nitrogenase isoforms. The carbide, which has not yet been identified in the Fe enzyme [76], is encased in carbon–metal bonds (Figure 1).

Carbon–Metal Bonds in Hydrogen Oxidation
Before the origin of photosynthesis, H2 was the source of electrons for primary production [39]. These electrons come into metabolism via the action of the enzyme hydrogenase. Three types of hydrogenase active site are known: [Fe–Ni] hydrogenase [87,88], [Fe] hydrogenase [88,89],
and [Fe–Fe] hydrogenase [88,90,91] (Figure 1). The three proteins are structurally unrelated [88] and their active sites are also different and require different maturases [64,91–93]. Specifically, the [Fe–Ni] active site is found in bacteria and archaea, occurring as a functional module in many enzymes, including soluble hydrogenases [87], membrane-bound hydrogenases related to complex I of the respiratory chain [94], H₂-dependent CO₂ reductase [95], and many others [96]. [Fe–Ni] hydrogenase subunits trace to LUCA [25]; [Fe–Fe] hydrogenase has only been found among bacteria [88] and eukaryotes [97]. It has an essential role in electron bifurcation [61], both in the H₂-oxidizing direction in acetogens [10] and in the H₂-producing direction in fermenters [92,98]. [Fe] hydrogenase has only been found among Archaea so far, where it has an important role in methanogenesis [11]. Given that it relates to LUCA, the distributions of [Fe–Fe] hydrogenase (bacteria) and [Fe] hydrogenase (archaea), in light of their crucial role in H₂-dependent acetogenesis and methanogenesis, suggest an origin of these two hydrogenases at the base of the respective domains, subsequent to divergence from LUCA, but before the origin of free-living H₂-dependent cells (Figure 2). Although they have structurally distinct active sites and unrelated polypeptide sequences, all three hydrogenases harbor carbon–metal bonds (Figure 1), reflecting evolutionary convergence [92] driven by constraints imposed by reaction mechanisms.

![Figure 2](image_url)

**Figure 2. Schematic Depiction of Early Physiological Evolution in a Hydrothermal Setting.** Carbon–metal bonds are involved in the entry of hydrogen (H₂) and dinitrogen (N₂) into metabolism, and in the exergonic pathway of biological carbon dioxide (CO₂) reduction. According to genomic studies, the last universal common ancestor (LUCA) may have inhabited a hydrothermal setting and lived off gases [25,26], because several enzymes and cofactors with carbon-metal bonds trace to LUCA. The [Fe] and [Fe–Fe] hydrogenases do not trace to LUCA but are specific to Archaea and bacteria, respectively, where they have essential roles in the carbon and energy metabolism of hydrogenotrophic methanogens and acetogens (see main text). Abbreviations: ACS, acetyl-CoA synthase; CODH, carbon monoxide dehydrogenase; Hyd, hydrogenase; Nif, nitrogenase; CoFeS, corrinoid iron sulfur protein; SAM, S-adenosyl methionine; Ur-Archaea, archaeal ancestor; Ur-bacteria, bacterial ancestor (‘Ur’ is a German prefix meaning ‘primordial’).
Carbon–Metal Bonds in Ancient Metabolic Pathways

As described earlier, carbon–metal bonds are found in ancient metabolic pathways, linking H₂, CO₂, and N₂ to life in organisms that synthesize their cell mass from these gases. Although it may appear that carbon–metal bonds are common in prokaryotes, few others have been characterized in primary metabolism and both involve cofactors. One is the first organometallic bond characterized, the classical cobalt–carbon bond in adenosylcobalamin, reported in 1961 by Dorothy Hodgkin [99], and the other is the most recent organometallic bond characterized, an iron–carbon bond in the radical SAM reaction intermediate Ω reported by the team of William and Joan Broderick in 2018 [93,100] (Figure 1). Both of these cofactors are involved in generating radicals for enzymes that catalyze reactions with a radical-dependent mechanism, reactions that are particularly common in cofactor biosynthesis [101,102] and particularly prevalent in LUCA [25].

The collection of carbon–metal bonds in Figure 1 is surely incomplete and others will likely come to light. Since 1985, biologically generated carbon–metal bonds were suggested for the acetyl-CoA pathway [47] which is now known to be replete with carbon–nickel bonds [50]. Carbon–nickel bonds had also been discussed as possible reaction intermediates in the mechanism of methyl coenzyme M reductase [103,104], but recent findings reveal a methyl radical intermediate [104,105]. Carbon–metal bonds have also been proposed in O₂-tolerant, Cu- and Mo-dependent CO-oxidizing enzymes [106], which are unrelated to the anaerobic CODH depicted in Figure 1, but the case is unresolved.

It appears that, in 4 billion years of evolution, biology has not evolved an alternative to the CODH/ACS-dependent acetyl-CoA pathway for exergonic CO₂ fixation that lacks carbon–metal bonds; neither has nature found an alternative to the carbon–metal bond in the active site of nitrogenase to funnel N₂ into metabolism. Nature has also so far not revealed an enzymatic reaction that will extract electrons from H₂ without the participation of carbon–metal bonds. Only three metals, Fe, Co, and Ni, have been observed in organometallic bonds so far and include Ni-carboxyl, Ni-carbonyl, Ni-methyl, and Ni-acetyl in CODH/ACS [49,50,55–59], Co-methyl in CoFeS [51–54], Fe-carbide in nitrogenase [77–79,87], Fe-carbonyl, Fe-acetyl, and Fe-nitrile in hydroge- nases [87–91], Co-methylene in adenosylcobalamin [99], and Fe-methylene in the SAM interme- diate Ω [93,100]. In enzymes and in industry, the catalytic activity of Fe, Co, and Ni resides in the ability of the unpaired electrons in their 3d orbitals to undergo back bonding and to forge metastable bonds [48,107].

As microbiologists probe new environments, more carbon–metal bonds might be found. As one possible example, newly characterized acetogens from a serpentinizing system called the Cedars inhabit effluent that is saturated with H₂ [32]. The effluent has a strongly reducing midpoint potential that can reach values of up to −900 mV, easily sufficient to reduce ferredoxin if the right catalysts are available [32]. Although effectively drowning in H₂, the bacteria appear to lack known hydrogenases [32], raising interesting questions, such as whether they access electrons from H₂ by mechanisms that do not require hydrogenases, or whether known hydrogenase side activities of ferredoxin-dependent organometallic enzymes, such as nitrogenase [83] or CODH [108], fill that catalytic void. Alternatively, it is possible that organisms living in environments such as the Cedars have novel hydrogenases that, based on hydrogenases known so far, might be expected to harbor carbon–metal bonds.

Although rare and ancient in biology, carbon–metal bonds are common in chemical industry [36, 77,107], they are always around us and we encounter them every day: imagine a life without steel. Steel is iron containing ~0.1–5% carbon atoms (Figure 3) [109,110]. Carbon–metal bonds are what gives steel greater hardness and tensile strength over iron alone; the more carbon steel
contains, the harder and more brittle it becomes [109]. Many experiments investigating CO₂ reduction under hydrothermal conditions have been reported in which the catalysts investigated had small effects, but the steel-walled reactors themselves appeared to be catalytic in the synthesis of a small amount of reduced carbon compounds (reviewed in [110]). In light of the activities associated with carbon–metal bonds and the biological activities of native metals [111–119] (Box 1), the catalytic properties of steel would appear to have more in common with biology than one might think.

Concluding Remarks and Future Perspectives
Carbon–metal bonds in enzymes and cofactors are ancient, few in number, and crucially positioned at the interface of metabolism and the environment; they have been and still are required for the entrance of carbon, nitrogen, and hydrogen gases into metabolism. However, unlike organic cofactors, thioesters, and FeS clusters found in ancient metabolism, organometallic bonds are not universal among microbes, which leads to a variety of questions regarding their mechanisms and evolution (see Outstanding Questions). Given their insuperably primordial position in metabolism, bringing H₂, CO₂, and N₂ to life, carbon–metal bonds in physiology might well be as old as it gets, a kind of biochemical bedrock.

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Outstanding Questions
What are the molecular mechanisms that microbes use to access native metals as electron donors for growth? Do the mechanisms involve the formation of carbon–metal bonds?

Besides Fe, Ni, and Co, are there other metals that forge bonds with carbon during catalysis or promote biogenic catalysis, either within cells or in the environment?

Newly characterized bacteria that inhabit the Cedars, a serpentinizing system saturated with H₂, appear to lack known hydrogenases. How do they generate reduced ferredoxin?

Why is it that [Fe–Fe] hydrogenase is specific to Archaea while [Fe–Fe] hydrogenase is specific to bacteria?

Cells that access native metals or that live in saturated H₂ environments might be able to circumvent electron bifurcation as a means of generating low potential ferredoxins. Do such routes exist and, if so, what mechanisms and catalysts are involved?
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