ACS chemical biology

Perspective

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The Ubiquity of Iron

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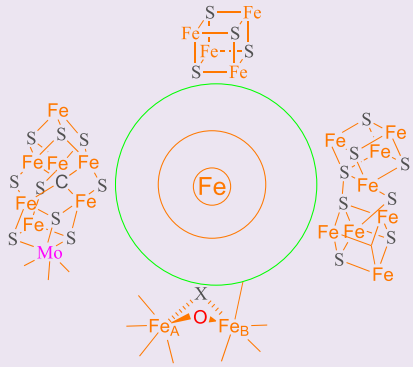
ABSTRACT: The importance of iron in living systems can be traced to the many complexes within which it is found, to its chemical mobility in undergoing oxidation–reduction reactions, and to the abundance of iron in Earth's crust. Iron is the most abundant element, by mass, in the Earth, constituting about 80% of the inner and outer cores of Earth. The molten outer core is about 8000 km in diameter, and the solid inner core is about 2400 km in diameter. Iron is the fourth most abundant element in Earth's crust. It is the chemically functional component of mononuclear iron complexes, dinuclear iron complexes, [2Fe–2S] and [4Fe–4S] clusters, [Fe–Ni–S] clusters, iron protophorphyrin IX, and many other complexes in protein biochemistry. Metals such as nickel, cobalt, copper, and manganese are present in the crust and could in principle function chemically in place of iron, but they are scarce in Earth's crust. Iron is plentiful because of its nuclear stability in stellar nuclear fusion reactions. It seems likely that other solid planets, formed by the same processes as Earth, would also foster the evolution of life and that iron would be similarly important to life on those planets as it is on Earth.



A recent issue of *Current Opinion in Chemical Biology* for April 2011, which is devoted to Bioinorganic Chemistry, focuses attention on iron in biochemistry. The opening sentence of the Editorial reads "Iron, the most abundant metal in the earth, dominates the field of inorganic prosthetic groups in proteins".[1] This sentence understates the importance of iron in the Earth, of life on Earth, and of the evolution of life. As used here, *understates* refers to the fact that iron not only is the most abundant metal in the Earth but is in fact the most abundant element by mass in the Earth. The core of Earth, comprising the inner and outer cores, is 7–8000 km in diameter and contains many elements, but iron dominates the core.

IRON AND THE EARTH

Iron is prevalent in Earth because of the physics of nuclear fusion. Earth and presumably other solid planets originated from accretion of matter arising from a primordial supernova. The predominance of iron within this matter is a consequence of the physics of nucleosynthesis in dying stars. Fusion of lighter elements to form heavier ones in late-stage stellar evolution produces a net release of energy up to elements in the iron group (Fe, Co, Ni). Nuclear fusion to form elements heavier than iron and nickel absorbs energy and therefore is not sustaining. A major sequence in the complicated fusion chain of nucleosynthesis involves the alpha process whereby the equivalent of a helium nucleus is fused to the precursor element. The masses increase by 4 units up to mass number 56. The ^{56}Ni that is produced in this chain decays to ^{56}Fe *via* ^{56}Co through sequential electron captures with production of characteristic γ rays. Thus, iron becomes a major component of dying stars that have or acquire sufficient mass to undergo a cataclysmic supernova. Consequently iron is abundant in the debris resulting from supernovae of all types.[2]

Figure 1 depicts the approximate relative diameters of the inner and outer cores, the mantle, and the crust of Earth. The core is very hot, and for this reason the outer core is molten. However, the inner core is solid because of the high pressure, 330 GPa or 3.5×10^6 atm, despite the temperature of 5700 °C.[3,4]

The crust, mantle, and core of Earth all contain large amounts of iron, but most is in the core, ~8000 km in diameter with 80% iron.[5] One theory holds that the inner core, 2400 km in diameter, consists of a "nearly perfectly aligned aggregate of hcp (hexagonal close-packed) crystals of iron.[6] Physical evidence in support includes seismic sound measurements proving that the core is anisotropic. The only known crystalline form of iron that displays anisotropy at the temperature and pressure of the core is the hexagonal close-packed crystal.[6−9] The compositions of the inner and outer cores suggests that iron might be the most abundant element in the Earth, and this is borne out by detailed geologic analysis showing that the iron content of the Earth is 32% by weight.[10,11]

Earth's mantle also contains large amounts of iron. A lesser percentage of iron is found on Earth's surface than in the core, but it is still the fourth most abundant element (6.3%) in the crust. The other major elements in the crust are oxygen (47%), silicon (26%), aluminum (8.1%), calcium (5.0%), magnesium (2.9%), sodium (2.3%), and potassium (1.5%).

IMPORTANCE OF IRON TO LIFE

The central role of iron in living cells and organisms is widely known but not fully appreciated. Broadly defined, the biochemical reactions in a living cell may be regarded as

Received: June 29, 2012
Accepted: July 30, 2012
Published: July 30, 2012

   dx.doi.org/10.1021/cb300323q | *ACS Chem. Biol.* 2012, 7, 1477–1481

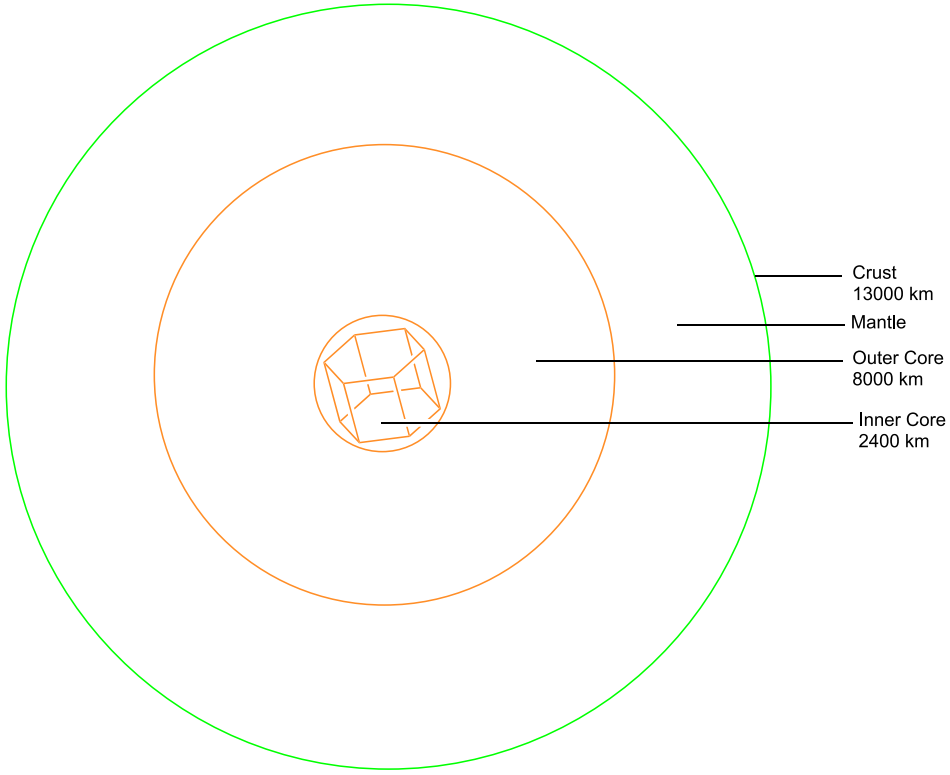


Figure 1. Schematic representation of approximate relative diameters of substructures in Earth. The inner core consists of aligned hcp crystals of iron and is represented here as a single hexagonal solid. The inner and outer cores consist of about 80% iron. The outer core is molten. The mantle is solid rock, and the crust contains about 6.3% iron, the fourth most abundant element in the crust.

cellular metabolism. Many branches of metabolism deal with the full range of cellular processes, energy production, biosynthesis, replication, and locomotion. Iron contributes to each of these processes. Iron even participates in the regulation of gene expression.[12] This summation seeks to explain salient aspects of the importance and significance of iron to life on Earth.

Multiplicity of Iron Complexes in Proteins. It is useful to consider the sheer number of different chemical classes of iron complexes in living cells. Figure 2 shows a sampling of the many iron complexes in living cells. New ones are being discovered all the time. For example, the structure of the complex of *S*-adenosyl-L-methionine (SAM) with [4Fe-4S] clusters in radical SAM enzymes was discovered within the past decade, although it is an ancient coenzyme.[13] This year, the final assignment of carbide as the central interstitial species in the FeMoco cofactor of nitrogenase completes the structure of this molecule, which is central to the fixation of nitrogen.[14,15] It is interesting that the iron carbide in FeMoco appeared in nature millions of years before the carbonization of iron by man in the manufacture of steel. A very recent article reveals that the nucleolus of plant cells is a "hot spot" of iron.[16] The chemical constitution of nucleolar iron is not yet known. There are many more biological iron coenzymes and prosthetic groups than of any other metal.

Iron complexes facilitate electron transfer, from fast intramolecular processes to the long distances (12−20 Å) separating active sites in macromolecular complexes and across membranes.[17] Iron complexes catalyze oxygenation and dehydrogenation of metabolites. They catalyze isomerization of metabolites; essential steps in DNA and RNA biosynthesis; certain types of DNA repair; and numerous steps in the biosynthesis of vitamins, coenzymes, cofactors, and antibiotics. All of these processes were important in the genesis and evolution of life. Finally, the iron in heme facilitates transport of molecular oxygen in the bloodstreams of higher animals and humans.

The iron-cysteine and iron sulfide complexes at the top of Figure 2 are likely the earliest biological iron complexes in evolution. They are the most efficient and versatile structures engaged in electron transfer and display reduction potentials ranging from +360 to −650 mV. They are essential for oxidation−reduction processes that provide the energy for ATP production and function in critical roles in many other metabolic processes. These simple iron complexes date to the earliest anaerobic Archeae and bacteria and have persisted in their roles in energy production and metabolism since the appearance of molecular oxygen and the evolution of aerobic metabolism.

Mononuclear iron complexes, such as that at the right of the first line in Figure 2,[18] and the oxo-Fe_2 complexes in the second line catalyze oxygenation, dehydrogenation, and reduction of metabolites and xenobiotics. Class I ribonucleotide reductases required for DNA biosynthesis and methane monooxygenases have di-iron complexes that initiate catalysis by generating free radicals.[19−21] The Fe−Ni hydrogenase complex catalyzes the reduction of protons to molecular hydrogen. The C-cluster in bifunctional CO dehydrogenase contains both Fe and Ni, and the A-cluster in this enzyme contains up to three metals, Fe−Zn−Ni, Fe−Cu−Ni, or Fe−Ni−Ni. The latter is thought to be the most biologically active.[22] The [4Fe−4S/SAM complex catalyzes many radical reactions, including complex metabolic reactions; DNA repair; deoxyribonucleotide production in DNA biosynthesis; maturation of RNA; and

dx.doi.org/10.1021/cb300323q | *ACS Chem. Biol.* 2012, 7, 1477−1481

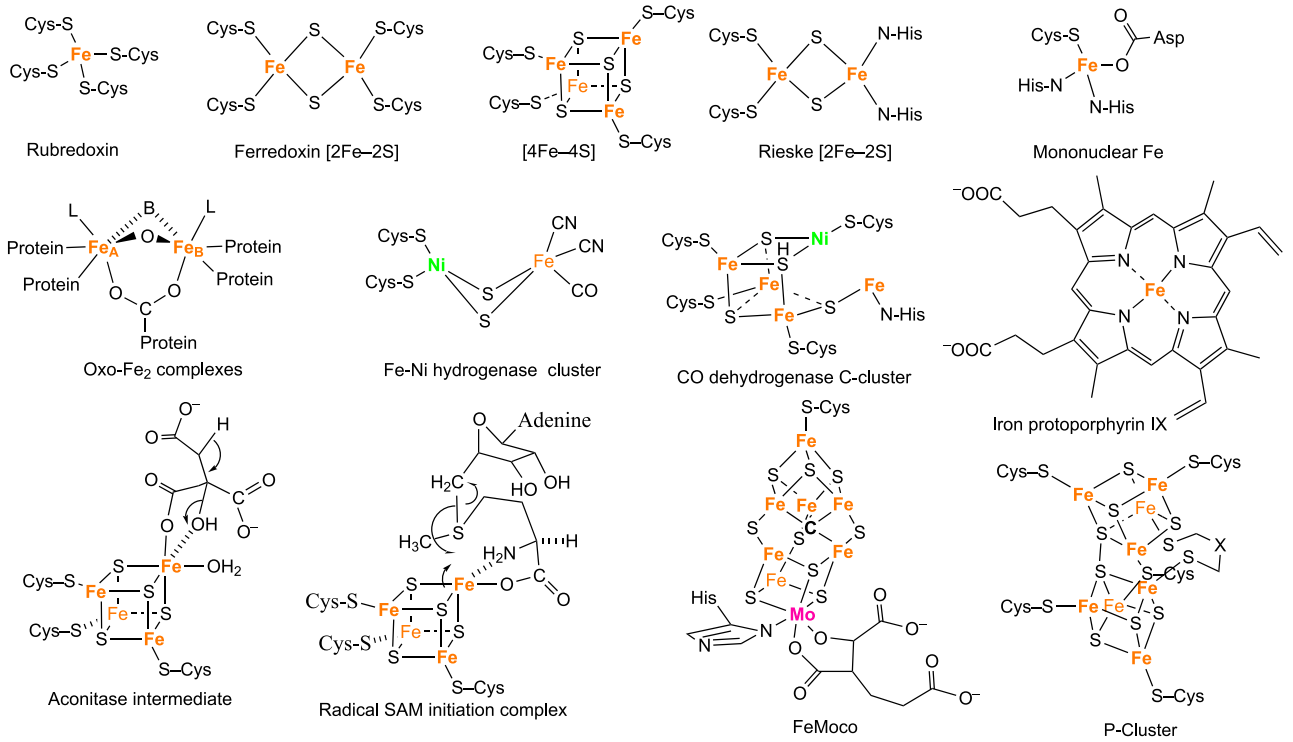


Figure 2. Chemical structures of representative iron complexes in proteins. Rubredoxin, ferredoxin, [4Fe−4S] clusters, and Rieske [2Fe−2S] clusters are found in proteins that function as electron transfer processes. [2Fe−2S] and [4Fe−4S] clusters are also engaged in regulation of the transcription of genes that are under redox control.[12] Mononuclear iron complexes are found in enzymes that catalyze oxygenation reactions. Oxo-Fe_2 complexes catalyze dehydrogenation or reduction of ribonucleotides to deoxyribonucleotides. Fe−Ni hydrogenase and Fe−Fe hydrogenase complexes are found in hydrogenases. The CO dehydrogenase cluster shown is cluster B in carbon monoxide dehydrogenase. The aconitase intermediate occurs as the dehydration intermediate in aconitase. Iron protoporphyin IX is found in heme proteins, cytochromes *c* and *a*, and cytochrome P450. The radical SAM initiation complex is found in radical SAM enzymes. FeMoco and P-cluster are essential cofactors in nitrogenase. The interstitial carbide (C^{4-}) has recently been identified.[14,15]

chemically difficult steps in vitamin, coenzyme, and antibiotic biosynthesis.[13]

Iron protoporphyrin IX in Figure 2 carries out many essential biological functions. It is the coenzyme of cytochrome P450s,[23] which catalyze the oxygenation of many substrates incorporating unactivated and unreactive alkanyl-C−H bonds. It is also the cofactor of peroxidases and catalases. As the cofactor in cytochromes and cytochrome oxidase it facilitates and guides electron transfer processes in ATP biosynthesis. As the prosthetic group in heme, it binds molecular oxygen reversibly and transfers it to cells where it is needed in energy metabolism.

Nitrogen and Iron. Unlike iron, nitrogen is not abundant in the crust of Earth at only 0.002%. However, nitrogen constitutes 2.6% of the human body. Nitrogen contributes about 16% of the mass in a typical protein and slightly more in DNA. The nitrogen in living cells comes from the atmosphere, which is 78% nitrogen gas. Thus, life depends upon the harvest of nitrogen from the atmosphere by nitrogen fixation, in which N_2 gas is chemically reduced to ammonia (NH_3). Nitrogenase, found in the anaerobic bacteria in root nodules of leguminous plants and in free-living diazotrophs such as *Azotobacter vinelandii*, catalyzes the fixation of nitrogen. The iron complexes FeMoco and P-cluster shown in Figure 2 drive the action of nitrogenase, and a [4Fe−4S] cluster in nitrogenase relays reducing electrons through the P-cluster to FeMoco, the site at which the hydrogenation of N_2 takes place. An iron-containing siroheme and [4Fe−4S] cluster are essential cofactors in ferredoxin-nitrite reductases that carry out a six-electron reduction of nitrite to ammonia occurring in plants, algae, and cyanobacteria. Iron is essential to life by making nitrogen available to all living cells, and this process appeared in nature millions of years before the invention of the Haber Process for the nonenzymatic, hydrogenolytic reduction of N_2 to ammonia.

Carbon and Iron. Carbon is not a dominant element in Earth's crust (0.18%) but constitutes 23% of the human body. Most carbon in the biosphere originates with plants that fix CO_2 from the atmosphere. Carbon dioxide fixation requires ATP, which is produced in photosynthesis. In photosynthetic ATP production, the light harvested by chlorophyll produces highly reducing electrons, which are relayed by the [4Fe−4S] clusters of ferredoxin to sites that generate proton gradients across membranes and energize ATP biosynthesis by photosynthetic ATP synthase. Thus, iron plays an essential role in ATP production and CO_2 fixation.

Iron Chemistry and Life. Iron can exist in eight oxidation states from −2 to +6. In biological cells the most common states are +2 and +3, and the +4 and +5 states are frequently brought into play in oxygenation reactions. The standard reduction potential for free iron is in the medium range, −0.44 V, so that it is easily oxidized to Fe^{2+}, an important state in biochemistry. The standard potential for reduction of Fe^{3+} to Fe^{2+} is +0.77 V, making iron useful for electron transfer reactions in nature. The standard reduction potentials for iron in the complexes shown in Figure 2 are not exactly the same as for free iron and cover a larger range, as pointed out above for the iron−sulfur clusters.

dx.doi.org/10.1021/cb300323q | *ACS Chem. Biol.* 2012, 7, 1477−1481

LIFE AND OTHER METALS

While the midrange reduction potentials for iron complexes and the ability of iron to accept a broad range of ligands enable it to function efficiently in essential biological processes, these properties are not unique to iron. Other transition metals such as nickel (E° = −0.26 V), cobalt (E° = −0.28 V), manganese (E° = −1.17 V), and copper E° = 0.34 V) also bind a broad range of ligands and could in principle function in place of iron. In fact, nickel (Figure 2) and cobalt in vitamin B_{12} do function analogously in a small number of biological reactions. Manganese can function in place of iron in the oxo-Fe_2 complexes,[24,25] and copper proteins function in electron transfer and even reversible binding of molecular oxygen in the case of hemocyanin. Zinc (E° = −0.76 V) is a special case because Zn^{2+} is the only stable oxidized form, so it does not engage in reversible electron transfer.

Despite redox analogies among iron, cobalt, nickel, manganese, and copper, iron is by far the dominant player in biochemical processes. One reason for this bias is likely the abundance of iron in the Earth's crust. At 6.3% of the crust iron is 700 times more plentiful than nickel, 2100 times more than cobalt, 1000 times more than copper, and 57 times more than manganese. Therefore, although other metals display chemical properties that could be exploited to support life, they are too scarce in Earth's crust to compete with iron. Even the recent discovery of mononuclear carbide (C^{4-}) as the interstitial species in FeMoco does not distinguish iron as uniquely suitable to sustain life. Most metals form stable complexes with mono- or binuclear carbide, and interstitial C^{4-} contributes to the hardness and structural rigidity of many alloys, including steel and tungsten carbide, the principal constituent in armor piercing ammunition employed by the military. Interstitial carbide might structurally stabilize the FeMoco cluster and could be expected to do so for other metals as well.

WHY NOT SILICON AND ALUMINUM IN LIFE?

Among the principal elements in Earth's crust, silicon and aluminum are present as aluminates and silicates in greater amounts than iron; however, they are not important in the chemistry of life. Aluminum binds ligands, especially oxygen, very strongly and does not easily exchange ligands. Aluminum exists in nature in the +3 oxidation state and is not easily reduced (reduction potential of −1.66 V). Because Al^{3+} does not easily engage in either electron transfer or ligand exchange, it has not been adopted as a component of living cells.

Silicon is in the same chemical group as carbon and shares an analogous valence electronic configuration with carbon. For this reason, the question arises why silicon cannot support life as well as carbon. There are at least two reasons for this. Certain chemical properties of silicon vary from carbon and would make it impossible for silicon to stand in for carbon. Carbon binds four ligands in a tetrahedral array that display right and left handedness, or stereochemistry. All sugars are constructed with tetrahedral carbon and are right-handed. All amino acids are constructed with tetrahedral carbon and are left-handed. This property of carbon translates into proteins, all of which are constructed with left-handed amino acids. The handedness of proteins allows them to bind molecules upon which they act with a high degree of specificity. Although silicon forms tetrahedral compounds, the right- and left-handed forms tend to be configurationally mobile. Relatively few chiral silanes are known. Thus, left or right-handedness would be difficult to translate into a silicon based protein, and such proteins would likely not have stereochemically defined structures and not be specific in binding molecules.

A perhaps more serious problem for silicon in life is the reactivity of silanes. While the silicates in Earth's crust are structurally stable, silanes are unstable and undergo spontaneous inflammation in the air. This property would make all silicon-based fatty acids and many silicon analogs of amino acids chemically unstable under physiological conditions.

NOT ONLY IRON

Iron is not the only metal required for life. Other common metals in the Earth's crust such as sodium (2.3%), potassium (1.5%), and magnesium (2.9%) are essential cations in all cells. These Group I and II metals do not participate chemically in the complex processes of oxidation−reduction, electron transfer, N_2 reduction or O_2-processing. Magnesium chelates oxyanions in polyphosphates such as ATP and in polynucleotides such as RNA. In plants and photosynthetic bacteria magnesium chelates the heterocyclic bases in chlorophyll. In this function magnesium works very well precisely because it displays chemical properties very different from those of iron. Chlorophyll collects energy from light to generate high potential reducing equivalents and drive biosynthesis in plants and photosynthetic bacteria. Iron would not do as the central chelator because of its propensity to undergo reduction. Magnesium ideally serves the purpose as an excellent chelator but very poor electron acceptor (E° = −2.4 V).

CONCLUSION

Iron is the most abundant element because of its high nuclear binding energy. Together with other transition metals, iron possesses the ligand binding and electron transfer properties essential to many biological processes. Iron dominates these processes, most likely because of its abundance in the Earth.

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Notes

The authors declare no competing financial interest.

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