

## 23.6: Applications of Coordination Compounds

Chelating Agents for Poising (EDTA)

Biomolecules (Porphorins and Hemoglobin)

Drugs and Health (cis-Platin)

### Learning Objectives

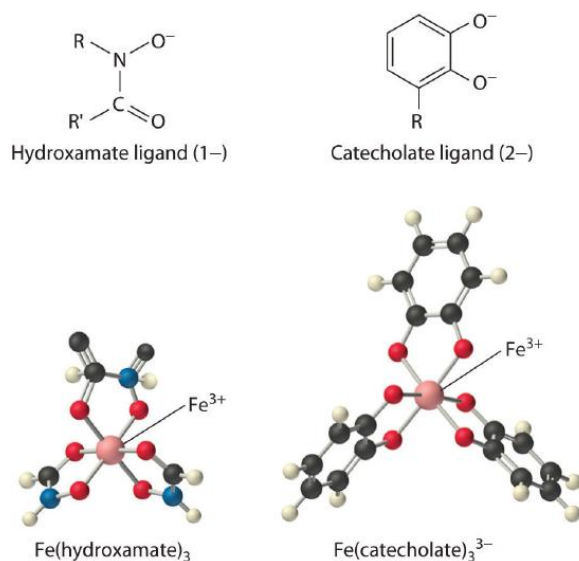
- To become familiar with some of the roles of transition-metal complexes in biological systems.

In this section, we describe several systems that illustrate the roles transition metals play in biological systems. Our goal is for you to understand why the chemical properties of these elements make them essential for life. We begin with a discussion of the strategies organisms use to extract transition metals from their environment. The section continues with a brief discussion of the use of transition metals in reactions that involve the transfer of electrons, reactions of small molecules such as  $O_2$ , Lewis-acid catalysis, and the generation of reactive organic radicals.

### Uptake and Storage of Transition Metals

There are three possible dietary levels for any essential element: deficient, optimal, and toxic, in order of increasing concentration in the diet. If the concentration of an essential element in the diet is too low, an organism must be able to extract the element from the environment and concentrate it. If the concentration of an essential element in the diet is too high, an organism must be able to limit its intake to avoid toxic effects. Moreover, organisms must be able to switch off the uptake process rapidly if dietary levels rise suddenly, and they must be able to store essential elements for future use.

Three distinct steps are involved in transition metal uptake. First, the metal must be “mobilized” from the environment and brought into contact with a cell in a form that can be absorbed. Second, the metal must be transported across the cell membrane into the cell. Third, the element must be transported to its point of utilization within a cell or to other cells within the organism. In our discussion, we focus on the uptake, transport, and storage of iron, which illustrates the most important points. Because iron deficiency (anemia) is the most widespread nutritional deficiency known in humans, the uptake of iron is especially well understood.



*Iron complexes in biological systems. Iron(III) forms very stable octahedral complexes with hydroxamate and catecholate ligands.*

The solubility of metal ions such as  $Fe^{3+}$ , which form highly insoluble hydroxides, depends on the pH and the presence of complexing agents. In an oxygen-containing atmosphere, iron exists as Fe(III) because of the positive reduction potential of  $Fe^{3+}$  ( $Fe^{3+} + e^- \rightarrow Fe^{2+}$ ;  $E^\circ = +0.77$  V). Because ferric hydroxide  $[Fe(OH)_3]$  is highly insoluble ( $K_{sp} \approx 1 \times 10^{-39}$ ), the equilibrium concentration of  $Fe^{3+}(aq)$  at pH 7.0 is very low, about  $10^{-18}$  M. You would have to drink  $2 \times 10^{13}$  L of iron-saturated water per day

(roughly  $5 \text{ mi}^3$ ) to consume the recommended daily intake of Fe for humans, which is about 1 mg/day. Animals such as humans can overcome this problem by consuming concentrated sources of iron, such as red meat, but microorganisms cannot.

Consequently, most microorganisms synthesize and secrete organic molecules called siderophores to increase the total concentration of available iron in the surrounding medium. Siderophores are generally cyclic compounds that use bidentate ligands, such as the hydroxamate and catecholate groups shown here, to bind  $\text{Fe}^{3+}$  in an octahedral arrangement. Typical siderophores are ferrichrome, a cyclic peptide produced by fungi, and enterobactin, a cyclic ester produced by bacteria (Figure 23.6.1). Attaching the three iron ligands to a cyclic framework greatly increases the stability of the resulting  $\text{Fe}^{3+}$  complex due to the chelate effect described in Section 23.4. The formation constants for the  $\text{Fe}^{3+}$  complexes of ferrichrome and enterobactin are about  $10^{32}$  and  $10^{40}$ , respectively, which are high enough to allow them to dissolve almost any Fe(III) compound.

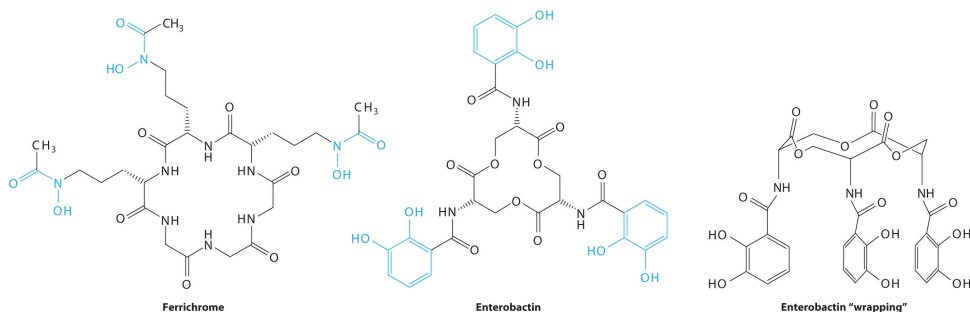


Figure 23.6.1: Siderophores. Ferrichrome (a) and enterobactin (b) are siderophores that use hydroxamate and catecholate ligands, respectively, to bind  $\text{Fe}^{3+}$ . The “wrapped” drawing of enterobactin (c) shows how the cyclic ester framework places the three catecholate ligands in the correct orientation to bind to a single  $\text{Fe}^{3+}$  ion, which is an application of the chelate effect. The actual structure of ferrichrome is similar to that of enterobactin, with the three hydroxamate ligands adjacent to one another for optimal binding of  $\text{Fe}^{3+}$ . Note: For clarity, most or all hydrogen atoms have been omitted in this and the following structures.

Siderophores increase the  $[\text{Fe}^{3+}]$  in solution, providing the bacterium that synthesized them (as well as any competitors) with a supply of iron. In addition, siderophores neutralize the positive charge on the metal ion and provide a hydrophobic “wrapping” that enables the  $\text{Fe}^{3+}$ –siderophore complex to be recognized by a specific protein that transports it into the interior of a cell. Once it is inside a cell, the iron is reduced to  $\text{Fe}^{2+}$ , which has a much lower affinity for the siderophore and spontaneously dissociates.

In contrast, multicellular organisms can increase the concentration of iron in their diet by lowering the pH in the gastrointestinal tract. At pH 1.0 (the approximate pH of the stomach), most Fe(III) salts dissolve to form  $\text{Fe}^{3+}(\text{aq})$ , which is absorbed by specific proteins in the intestinal wall. A protein called transferrin forms a complex with iron(III), allowing it to be transported to other cells. Proteins that bind tightly to Fe(III) can also be used as antibacterial agents because iron is absolutely essential for bacterial growth. For example, milk, tears, and egg white all contain proteins similar to transferrin, and their high affinity for  $\text{Fe}^{3+}$  allows them to sequester iron, thereby preventing bacteria from growing in these nutrient-rich media.

Iron is released from transferrin by reduction to  $\text{Fe}^{2+}$ , and then it is either used immediately (e.g., for the synthesis of hemoglobin) or stored in a very large protein called ferritin for future use (Figure 23.6.2). Ferritin uses oxygen to oxidize  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , which at neutral pH precipitates in the central cavity of the protein as a polymeric mixture of  $\text{Fe}(\text{OH})_3$  and  $\text{FePO}_4$ . Because a fully loaded ferritin molecule can contain as many as 4500 Fe atoms, which corresponds to about 25% Fe by mass, ferritin is an effective way to store iron in a highly concentrated form. When iron is needed by a cell, the  $\text{Fe}^{3+}$  is reduced to the much more soluble  $\text{Fe}^{2+}$  by a reductant such as ascorbic acid (vitamin C). The structure of ferritin contains channels at the junctions of the subunits, which provide pathways for iron to enter and leave the interior of a molecule.

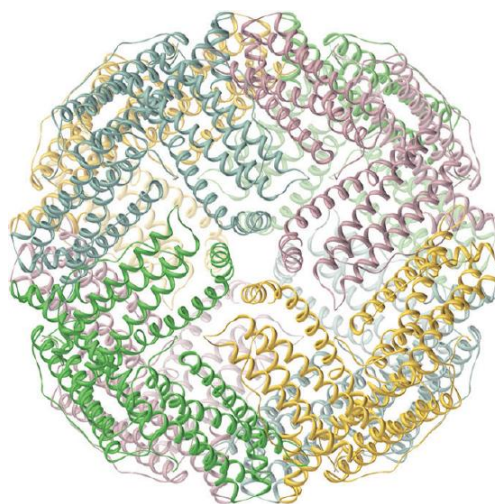


Figure 23.6.2: Ferritin, an Iron Storage Protein. A schematic drawing of the structure of iron-loaded ferritin, showing the almost spherical protein shell inside which the iron hydroxide/phosphate core is formed.

## Metalloproteins and Metalloenzymes

A protein that contains one or more metal ions tightly bound to amino acid side chains is called a metalloprotein; some of the most common ligands provided by amino acids are shown here. A metalloprotein that catalyzes a chemical reaction is a metalloenzyme. Thus all metalloenzymes are metalloproteins, but the converse is not true. Recent estimates suggest that more than 40% of all known enzymes require at least one metal ion for activity, including almost all the enzymes responsible for the synthesis, duplication, and repair of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid).

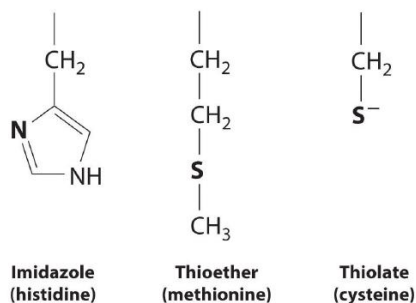


Figure 23.6.2b: Ligands used in biological systems. These metal ligands are commonly found in metalloproteins.

## Electron-Transfer Proteins

Proteins whose function is to transfer electrons from one place to another are called electron-transfer proteins. Because they do not catalyze a chemical reaction, electron-transfer proteins are not enzymes; they are biochemical reductants or oxidants consumed in an enzymatic reaction. The general reaction for an electron-transfer protein is as follows:



Because many transition metals can exist in more than one oxidation state, electron-transfer proteins usually contain one or more metal ions that can undergo a redox reaction. Incorporating a metal ion into a protein has three important biological consequences:

1. The protein environment can adjust the redox potential ( $E^0$ ), of the metal ion over a rather large potential range, whereas the redox potential of the simple hydrated metal ion  $[M_n^{+}(\text{aq})]$ , is essentially fixed.
2. The protein can adjust the structure of the metal complex to ensure that electron transfer is rapid.
3. The protein environment provides specificity, ensuring that the electron is transferred to only the desired site.

Three important classes of metalloproteins transfer electrons: blue copper proteins, cytochromes, and iron-sulfur proteins, which generally transfer electrons at high ( $> 0.20$  V), intermediate ( $\pm 0$  V), and low ( $-0.20$  to  $-0.50$  V) potentials, respectively (Table 23.12). Although these electron-transfer proteins contain different metals with different structures, they are all designed to ensure rapid electron transfer to and from the metal. Thus when the protein collides with its physiological oxidant or reductant, electron

transfer can occur before the two proteins diffuse apart. For electron transfer to be rapid, the metal sites in the oxidized and reduced forms of the protein must have similar structures.

Table 23.6.1: Some Properties of the Most Common Electron-Transfer Proteins

Protein	Metal Center	M/e- Transferred	Reduction Potential (V)
iron-sulfur proteins*	$[\text{Fe}(\text{SR})_4]^{2-}$	1 Fe	-0.1 to +0.1
	$[(\text{RS})_2\text{FeS}_2\text{Fe}(\text{SR})_2]^{2-}$	2 Fe	-0.2 to -0.4
	$[\text{Fe}_3\text{S}_4(\text{SR})_3]^{3-}$	3 Fe	-0.1 to -0.2
	$[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$	4 Fe	-0.3 to -0.5
cytochromes	Fe-heme (low spin)	1 Fe	~0
blue copper proteins†	$[\text{Cu}(\text{Im})_2(\text{SR})(\text{SR}_2)]^-$	1 Cu	$\geq +0.20$

\* A sulfur bound to an organic group is represented as SR.

† See Figure 23.6.2b for the structure of imidazole (Im).

### Blue Copper Proteins

Blue copper proteins were first isolated from bacteria in the 1950s and from plant tissues in the early 1960s. The intense blue color of these proteins is due to a strong absorption band at a wavelength of about 600 nm. Although simple  $\text{Cu}^{2+}$  complexes, such as  $[\text{Cu}(\text{H}_2\text{O})_6]^{2+}$  and  $[\text{Cu}(\text{NH}_3)_4]^{2+}$ , are also blue due to an absorption band at 600 nm, the intensity of the absorption band is about 100 times less than that of a blue copper protein. Moreover, the reduction potential for the  $\text{Cu}^{2+}/\text{Cu}^+$  couple in a blue copper protein is usually +0.3 to +0.5 V, considerably more positive than that of the aqueous  $\text{Cu}^{2+}/\text{Cu}^+$  couple (+0.15 V).

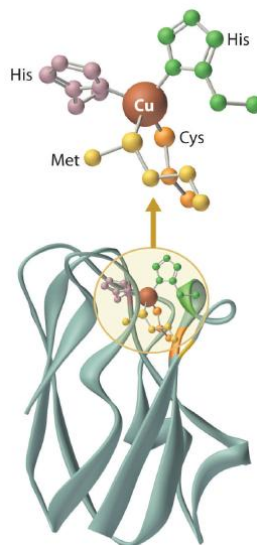


Figure 23.6.3: A Blue Copper Protein. In both the oxidized and reduced forms of a blue copper protein, the copper is coordinated by four ligands (two histidine imidazole nitrogen atoms, a cysteine thiolate sulfur, and a thioether sulfur of a methionine) in a roughly tetrahedral arrangement.

The copper center in blue copper proteins has a distorted tetrahedral structure, in which the copper is bound to four amino acid side chains (Figure 23.6.3). Although the most common structures for four-coordinate  $\text{Cu}^{2+}$  and  $\text{Cu}^+$  complexes are square planar and tetrahedral, respectively, the structures of the oxidized ( $\text{Cu}^{2+}$ ) and reduced ( $\text{Cu}^+$ ) forms of the protein are essentially identical. Thus the protein forces the  $\text{Cu}^{2+}$  ion to adopt a higher-energy structure that is more suitable for  $\text{Cu}^+$ , which makes the  $\text{Cu}^{2+}$  form easier to reduce and raises its reduction potential.

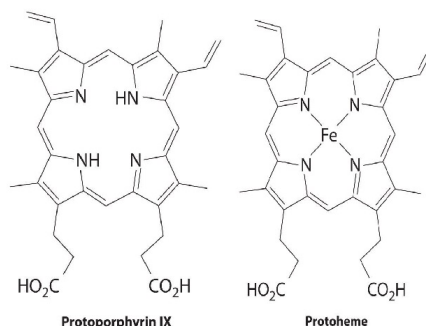
Moreover, by forcing the oxidized and reduced forms of the metal complex to have essentially the same structure, the protein ensures that electron transfer to and from the copper site is rapid because only minimal structural reorganization of the metal center is required. Kinetics studies on simple metal complexes have shown that electron-transfer reactions tend to be slow when the structures of the oxidized and reduced forms of a metal complex are very different, and fast when they are similar. You will see that

other metal centers used for biological electron-transfer reactions are also set up for minimal structural reorganization after electron transfer, which ensures the rapid transfer of electrons.

## Cytochromes

The cytochromes (from the Greek cytos, meaning “cell”, and chroma, meaning “color”) were first identified in the 1920s by spectroscopic studies of cell extracts. Based on the wavelength of the maximum absorption in the visible spectrum, they were classified as cytochromes a (with the longest wavelength), cytochromes b (intermediate wavelength), and cytochromes c (shortest wavelength). It quickly became apparent that there was a correlation between their spectroscopic properties and other physical properties. For examples, cytochromes c are generally small, soluble proteins with a reduction potential of about +0.25 V, whereas cytochromes b are larger, less-soluble proteins with reduction potentials of about 0 V.

All cytochromes contain iron, and the iron atom in all cytochromes is coordinated by a planar array of four nitrogen atoms provided by a cyclic tetradentate ligand called a porphyrin. The iron–porphyrin unit is called a heme group. The structures of a typical porphyrin (protoporphyrin IX) and its iron complex (protoheme) are shown here. In addition to the four nitrogen atoms of the porphyrin, the iron in a cytochrome is usually bonded to two additional ligands provided by the protein, as shown in Figure 23.6.4



A cytochrome. Shown here is protoporphyrin IX and its iron complex, protoheme.

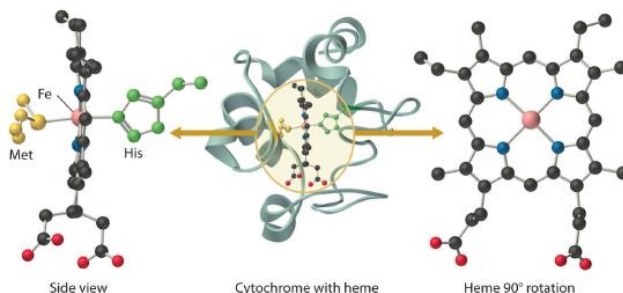


Figure 23.6.4: A Cytochrome c. In a cytochrome c, the heme iron is coordinated to the nitrogen atom of a histidine imidazole and the sulfur atom of a methionine thioether, in addition to the four nitrogen atoms provided by the porphyrin.

In contrast to the blue copper proteins, two electron configurations are possible for both the oxidized and reduced forms of a cytochrome, and this has significant structural consequences. Thus  $\text{Fe}^{2+}$  is  $d^6$  and can be either high spin (with four unpaired electrons) or low spin (with no unpaired electrons). Similarly,  $\text{Fe}^{3+}$  is  $d^5$  and can also be high spin (with five unpaired electrons) or low spin (with one unpaired electron). In low-spin heme complexes, both the  $\text{Fe}^{2+}$  and the  $\text{Fe}^{3+}$  ions are small enough to fit into the “hole” in the center of the porphyrin; hence the iron atom lies almost exactly in the plane of the four porphyrin nitrogen atoms in both cases. Because cytochromes b and c are low spin in both their oxidized and reduced forms, the structures of the oxidized and reduced cytochromes are essentially identical. Hence minimal structural changes occur after oxidation or reduction, which makes electron transfer to or from the heme very rapid.

*Electron transfer reactions occur most rapidly when minimal structural changes occur during oxidation or reduction.*

## Iron–Sulfur Proteins

Although all known bacteria, plants, and animals use iron–sulfur proteins to transfer electrons, the existence of these proteins was not recognized until the late 1950s. Iron–sulfur proteins transfer electrons over a wide range of reduction potentials, and their iron content can range from 1 to more than 12 Fe atoms per protein molecule. In addition, most iron–sulfur proteins contain stoichiometric amounts of sulfide ( $S^{2-}$ ).

These properties are due to the presence of four different kinds of iron–sulfur units, which contain one, two, three, or four iron atoms per Fe–S complex (Figure 23.6.5). In all cases, the  $Fe^{2+}$  and  $Fe^{3+}$  ions are coordinated to four sulfur ligands in a tetrahedral environment. Due to tetrahedral coordination by weak-field sulfur ligands, the iron is high spin in both the  $Fe^{3+}$  and  $Fe^{2+}$  oxidation states, which results in similar structures for the oxidized and reduced forms of the Fe–S complexes. Consequently, only small structural changes occur after oxidation or reduction of the Fe–S center, which results in rapid electron transfer.

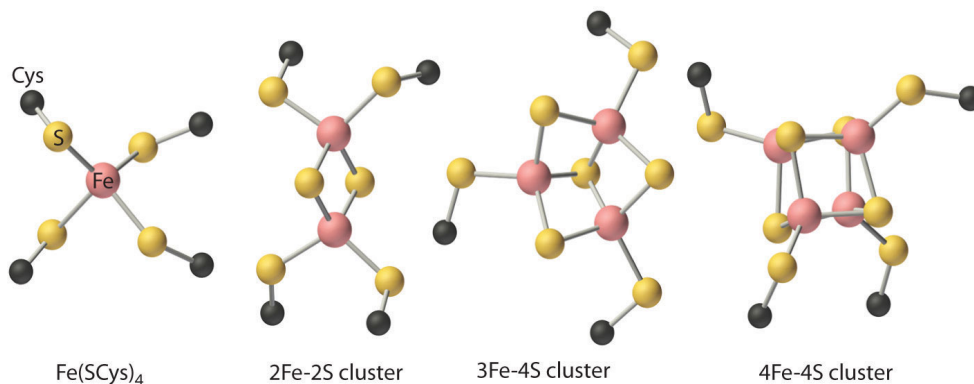


Figure 23.6.5: Fe–S Centers in Proteins: Four kinds of iron–sulfur centers, containing one, two, three, and four iron atoms, respectively, are known in electron-transfer proteins. Although they differ in the number of sulfur atoms provided by cysteine thiolates versus sulfide, in all cases the iron is coordinated to four sulfur ligands in a roughly tetrahedral environment.

## Reactions of Small Molecules

Although small molecules, such as  $O_2$ ,  $N_2$ , and  $H_2$ , do not react with organic compounds under ambient conditions, they do react with many transition-metal complexes. Consequently, virtually all organisms use metalloproteins to bind, transport, and catalyze the reactions of these molecules. Probably the best-known example is hemoglobin, which is used to transport  $O_2$  in many multicellular organisms.

*Under ambient conditions, small molecules, such as  $O_2$ ,  $N_2$ , and  $H_2$ , react with transition-metal complexes but not with organic compounds.*

## Oxygen Transport

Many microorganisms and most animals obtain energy by respiration, the oxidation of organic or inorganic molecules by  $O_2$ . At  $25^\circ C$ , however, the concentration of dissolved oxygen in water in contact with air is only about 0.25 mM. Because of their high surface area-to-volume ratio, aerobic microorganisms can obtain enough oxygen for respiration by passive diffusion of  $O_2$  through the cell membrane. As the size of an organism increases, however, its volume increases much more rapidly than its surface area, and the need for oxygen depends on its volume. Consequently, as a multicellular organism grows larger, its need for  $O_2$  rapidly outstrips the supply available through diffusion. Unless a transport system is available to provide an adequate supply of oxygen for the interior cells, organisms that contain more than a few cells cannot exist. In addition,  $O_2$  is such a powerful oxidant that the oxidation reactions used to obtain metabolic energy must be carefully controlled to avoid releasing so much heat that the water in the cell boils. Consequently, in higher-level organisms, the respiratory apparatus is located in internal compartments called mitochondria, which are the power plants of a cell. Oxygen must therefore be transported not only to a cell but also to the proper compartment within a cell.

Three different chemical solutions to the problem of oxygen transport have developed independently in the course of evolution, as indicated in Table 23.6.2. Mammals, birds, reptiles, fish, and some insects use a heme protein called hemoglobin to transport oxygen from the lungs to the cells, and they use a related protein called myoglobin to temporarily store oxygen in the tissues. Several classes of invertebrates, including marine worms, use an iron-containing protein called hemerythrin to transport oxygen,



whereas other classes of invertebrates (arthropods and mollusks) use a copper-containing protein called hemocyanin. Despite the presence of the hem- prefix, hemerythrin and hemocyanin do not contain a metal–porphyrin complex.

Table 23.6.2: Some Properties of the Three Classes of Oxygen-Transport Proteins

Protein	Source	M per Subunit	M per O <sub>2</sub> Bound	Color (deoxy form)	Color (oxy form)
hemoglobin	mammals, birds, fish, reptiles, some insects	1 Fe	1 Fe	red-purple	red
hemerythrin	marine worms	2 Fe	2 Fe	colorless	red
hemocyanin	mollusks, crustaceans, spiders	2 Cu	2 Cu	colorless	blue

### Myoglobin and Hemoglobin

Myoglobin is a relatively small protein that contains 150 amino acids. The functional unit of myoglobin is an iron–porphyrin complex that is embedded in the protein (Figure 26.8.1). In myoglobin, the heme iron is five-coordinate, with only a single histidine imidazole ligand from the protein (called the proximal histidine because it is near the iron) in addition to the four nitrogen atoms of the porphyrin. A second histidine imidazole (the distal histidine because it is more distant from the iron) is located on the other side of the heme group, too far from the iron to be bonded to it. Consequently, the iron atom has a vacant coordination site, which is where O<sub>2</sub> binds.

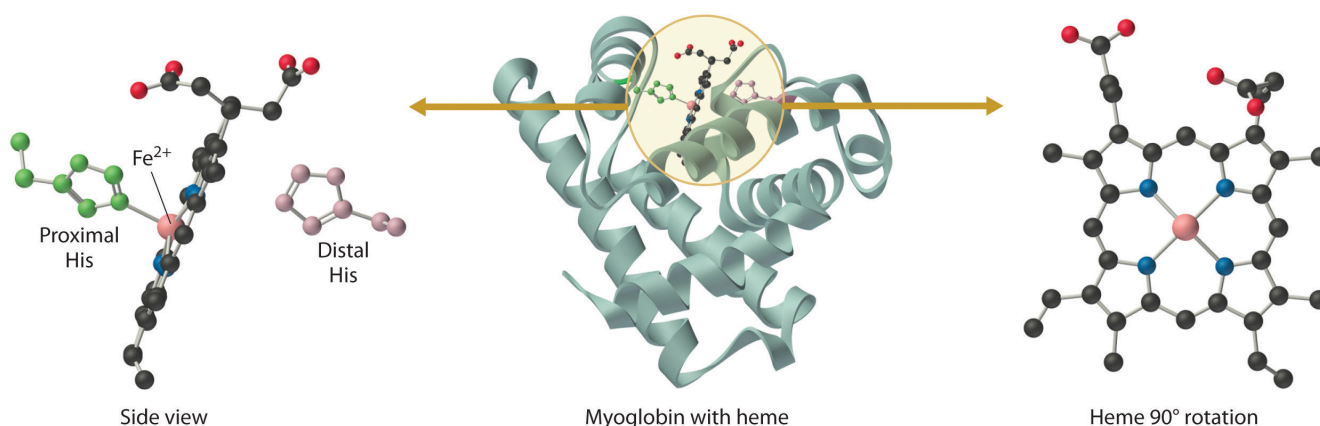


Figure 23.6.6: The Structure of Deoxymyoglobin, Showing the Heme Group. The iron in deoxymyoglobin is five-coordinate, with one histidine imidazole ligand from the protein. Oxygen binds at the vacant site on iron.

In the ferrous form (deoxymyoglobin), the iron is five-coordinate and high spin. Because high-spin Fe<sup>2+</sup> is too large to fit into the “hole” in the center of the porphyrin, it is about 60 pm above the plane of the porphyrin. When O<sub>2</sub> binds to deoxymyoglobin to form oxymyoglobin, the iron is converted from five-coordinate (high spin) to six-coordinate (low spin; Figure 26.8.2). Because low-spin Fe<sup>2+</sup> and Fe<sup>3+</sup> are smaller than high-spin Fe<sup>2+</sup>, the iron atom moves into the plane of the porphyrin ring to form an octahedral complex. The O<sub>2</sub> pressure at which half of the molecules in a solution of myoglobin are bound to O<sub>2</sub> (P<sub>1/2</sub>) is about 1 mm Hg (1.3 × 10<sup>−3</sup> atm).

*A vacant coordination site at a metal center in a protein usually indicates that a small molecule will bind to the metal ion, whereas a coordinatively saturated metal center is usually involved in electron transfer.*

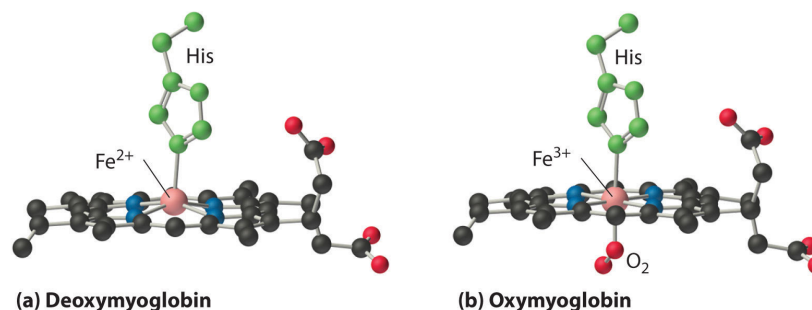


Figure 23.6.7: Oxygen Binding to Myoglobin and Hemoglobin. (a) The  $\text{Fe}^{2+}$  ion in deoxymyoglobin is high spin, which makes it too large to fit into the “hole” in the center of the porphyrin. (b) When  $\text{O}_2$  binds to deoxymyoglobin, the iron is converted to low-spin  $\text{Fe}^{3+}$ , which is smaller, allowing the iron to move into the plane of the four nitrogen atoms of the porphyrin to form an octahedral complex.

Hemoglobin consists of two subunits of 141 amino acids and two subunits of 146 amino acids, both similar to myoglobin; it is called a tetramer because of its four subunits. Because hemoglobin has very different  $\text{O}_2$ -binding properties, however, it is not simply a “super myoglobin” that can carry four  $\text{O}_2$  molecules simultaneously (one per heme group). The shape of the  $\text{O}_2$ -binding curve of myoglobin (Mb; Figure 23.6.7) can be described mathematically by the following equilibrium:



$$K_{\text{diss}} = \frac{[\text{Mb}][\text{O}_2]}{[\text{MbO}_2]} \quad (23.6.3)$$

In contrast, the  $\text{O}_2$ -binding curve of hemoglobin is S shaped (Figure 23.6.8). As shown in the curves, at low oxygen pressures, the affinity of deoxyhemoglobin for  $\text{O}_2$  is substantially lower than that of myoglobin, whereas at high  $\text{O}_2$  pressures the two proteins have comparable  $\text{O}_2$  affinities. The physiological consequences of the unusual S-shaped  $\text{O}_2$ -binding curve of hemoglobin are enormous. In the lungs, where  $\text{O}_2$  pressure is highest, the high oxygen affinity of deoxyhemoglobin allows it to be completely loaded with  $\text{O}_2$ , giving four  $\text{O}_2$  molecules per hemoglobin. In the tissues, however, where the oxygen pressure is much lower, the decreased oxygen affinity of hemoglobin allows it to release  $\text{O}_2$ , resulting in a net transfer of oxygen to myoglobin.

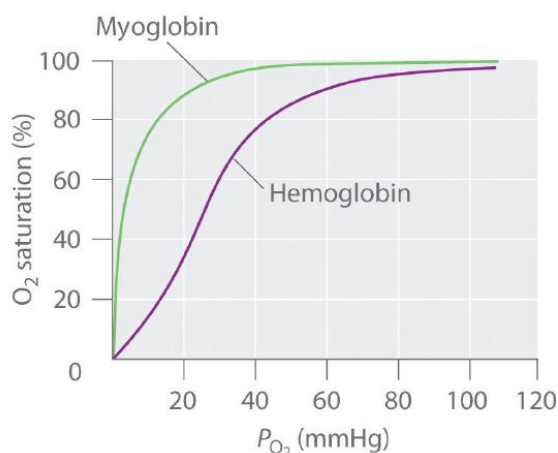


Figure 23.6.8: The  $\text{O}_2$ -Binding Curves of Myoglobin and Hemoglobin. The curve for myoglobin can be described by a simple equilibrium between deoxy- and oxymyoglobin, but the S-shaped curve for hemoglobin can be described only in terms of a cooperative interaction between the four hemes.

The S-shaped  $\text{O}_2$ -binding curve of hemoglobin is due to a phenomenon called cooperativity, in which the affinity of one heme for  $\text{O}_2$  depends on whether the other hemes are already bound to  $\text{O}_2$ . Cooperativity in hemoglobin requires an interaction between the four heme groups in the hemoglobin tetramer, even though they are more than 3000 pm apart, and depends on the change in structure of the heme group that occurs with oxygen binding. The structures of deoxyhemoglobin and oxyhemoglobin are slightly different, and as a result, deoxyhemoglobin has a much lower  $\text{O}_2$  affinity than myoglobin, whereas the  $\text{O}_2$  affinity of oxyhemoglobin is essentially identical to that of oxymyoglobin. Binding of the first two  $\text{O}_2$  molecules to deoxyhemoglobin causes



the overall structure of the protein to change to that of oxyhemoglobin; consequently, the last two heme groups have a much higher affinity for  $O_2$  than the first two.

Oxygen is not unique in its ability to bind to a ferrous heme complex; small molecules such as CO and NO bind to deoxymyoglobin even more tightly than does  $O_2$ . The interaction of the heme iron with oxygen and other diatomic molecules involves the transfer of electron density from the filled  $t_{2g}$  orbitals of the low-spin  $d^6$   $Fe^{2+}$  ion to the empty  $\pi^*$  orbitals of the ligand. In the case of the  $Fe^{2+}-O_2$  interaction, the transfer of electron density is so great that the  $Fe-O_2$  unit can be described as containing low-spin  $Fe^{3+}$  ( $d^5$ ) and  $O_2^-$ . We can therefore represent the binding of  $O_2$  to deoxyhemoglobin and its release as a reversible redox reaction:



As shown in Figure 23.6.9 the  $Fe-O_2$  unit is bent, with an  $Fe-O-O$  angle of about  $130^\circ$ . Because the  $\pi^*$  orbitals in CO are empty and those in NO are singly occupied, these ligands interact more strongly with  $Fe^{2+}$  than does  $O_2$ , in which the  $\pi^*$  orbitals of the neutral ligand are doubly occupied.

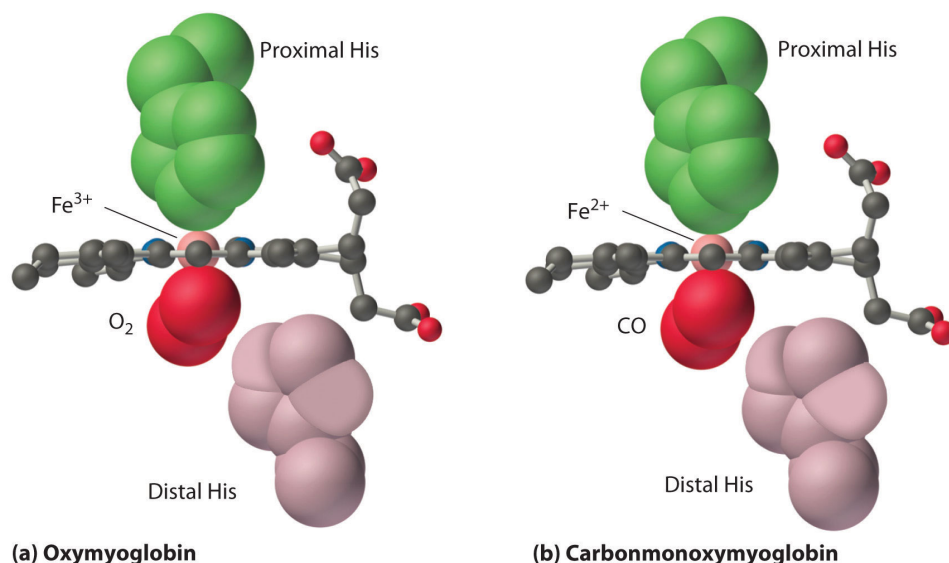


Figure 23.6.9: Binding of  $O_2$  and CO to the Iron of Myoglobin. Because the  $Fe-O-O$  unit is bent, while the  $Fe-C-O$  unit is linear, the imidazole group of the distal histidine in hemoglobin interferes with CO binding and decreases the affinity of hemoglobin for CO.

Although CO has a much greater affinity for a ferrous heme than does  $O_2$  (by a factor of about 25,000), the affinity of CO for deoxyhemoglobin is only about 200 times greater than that of  $O_2$ , which suggests that something in the protein is decreasing its affinity for CO by a factor of about 100. Both CO and NO bind to ferrous hemes in a linear fashion, with an  $Fe-C(N)-O$  angle of about  $180^\circ$ , and the difference in the preferred geometry of  $O_2$  and CO provides a plausible explanation for the difference in affinities. As shown in Figure 23.6.9 the imidazole group of the distal histidine is located precisely where the oxygen atom of bound CO would be if the  $Fe-C-O$  unit were linear. Consequently, CO cannot bind to the heme in a linear fashion; instead, it is forced to bind in a bent mode that is similar to the preferred structure for the  $Fe-O_2$  unit. This results in a significant decrease in the affinity of the heme for CO, while leaving the  $O_2$  affinity unchanged, which is important because carbon monoxide is produced continuously in the body by degradation of the porphyrin ligand (even in nonsmokers). Under normal conditions, CO occupies approximately 1% of the heme sites in hemoglobin and myoglobin. If the affinity of hemoglobin and myoglobin for CO were 100 times greater (due to the absence of the distal histidine), essentially 100% of the heme sites would be occupied by CO, and no oxygen could be transported to the tissues. Severe carbon-monoxide poisoning, which is frequently fatal, has exactly the same effect. Thus the primary function of the distal histidine appears to be to decrease the CO affinity of hemoglobin and myoglobin to avoid self-poisoning by CO.

### Hemerythrin

Hemerythrin is used to transport  $O_2$  in a variety of marine invertebrates. It is an octamer (eight subunits), with each subunit containing two iron atoms and binding one molecule of  $O_2$ . Deoxyhemerythrin contains two  $Fe^{2+}$  ions per subunit and is colorless,

whereas oxyhemerythrin contains two  $\text{Fe}^{3+}$  ions and is bright reddish violet. These invertebrates also contain a monomeric form of hemerythrin that is located in the tissues, analogous to myoglobin. The binding of oxygen to hemerythrin and its release can be described by the following reaction, where the  $\text{HO}_2^-$  ligand is the hydroperoxide anion derived by the deprotonation of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ):



Thus  $\text{O}_2$  binding is accompanied by the transfer of two electrons (one from each  $\text{Fe}^{2+}$ ) and a proton to  $\text{O}_2$ .

### Hemocyanin

Hemocyanin is used for oxygen transport in many arthropods (spiders, crabs, lobsters, and centipedes) and in mollusks (shellfish, octopi, and squid); it is responsible for the bluish-green color of their blood. The protein is a polymer of subunits that each contain two copper atoms (rather than iron), with an aggregate molecular mass of greater than 1,000,000 amu. Deoxyhemocyanin contains two  $\text{Cu}^+$  ions per subunit and is colorless, whereas oxyhemocyanin contains two  $\text{Cu}^{2+}$  ions and is bright blue. As with hemerythrin, the binding and release of  $\text{O}_2$  correspond to a two-electron reaction:



Although hemocyanin and hemerythrin perform the same basic function as hemoglobin, these proteins are not interchangeable. In fact, hemocyanin is so foreign to humans that it is one of the major factors responsible for the common allergies to shellfish.

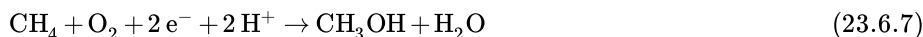
*Myoglobin, hemoglobin, hemerythrin, and hemocyanin all use a transition-metal complex to transport oxygen.*

### Enzymes Involved in Oxygen Activation

Many of the enzymes involved in the biological reactions of oxygen contain metal centers with structures that are similar to those used for  $\text{O}_2$  transport. Many of these enzymes also contain metal centers that are used for electron transfer, which have structures similar to those of the electron-transfer proteins discussed previously. In this section, we briefly describe two of the most important examples: dioxygenases and methane monooxygenase.

Dioxygenases are enzymes that insert both atoms of  $\text{O}_2$  into an organic molecule. In humans, dioxygenases are responsible for cross-linking collagen in connective tissue and for synthesizing complex organic molecules called prostaglandins, which trigger inflammation and immune reactions. Iron is by far the most common metal in dioxygenases; and the target of the most commonly used drug in the world, aspirin, is an iron enzyme that synthesizes a specific prostaglandin. Aspirin inhibits this enzyme by binding to the iron atom at the active site, which prevents oxygen from binding.

Methane monooxygenase catalyzes the conversion of methane to methanol. The enzyme is a monooxygenase because only one atom of  $\text{O}_2$  is inserted into an organic molecule, while the other is reduced to water:



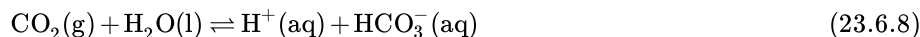
Because methane is the major component of natural gas, there is enormous interest in using this reaction to convert methane to a liquid fuel (methanol) that is much more convenient to ship and store. Because the C–H bond in methane is one of the strongest C–H bonds known, however, an extraordinarily powerful oxidant is needed for this reaction. The active site of methane monooxygenase contains two Fe atoms that bind  $\text{O}_2$ , but the details of how the bound  $\text{O}_2$  is converted to such a potent oxidant remain unclear.

### Metal Ions as Lewis Acids

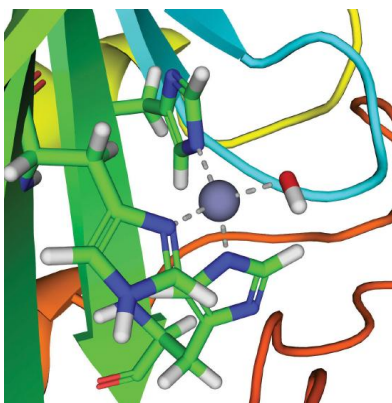
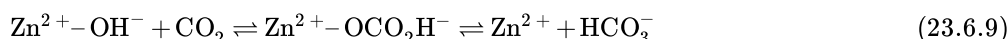
Reactions catalyzed by metal ions that do not change their oxidation states during the reaction are usually group transfer reactions, in which a group such as the phosphoryl group ( $-\text{PO}_3^{2-}$ ) is transferred. These enzymes usually use metal ions such as  $\text{Zn}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Mn}^{2+}$ , and they range from true metalloenzymes, in which the metal ion is tightly bound, to metal-activated enzymes, which require the addition of metal ions for activity. Because tight binding is usually the result of specific metal–ligand interactions, metalloenzymes tend to be rather specific for a particular metal ion. In contrast, the binding of metal ions to metal-activated enzymes is largely electrostatic in nature; consequently, several different metal ions with similar charges and sizes can often be used to give an active enzyme.

*Metalloenzymes generally contain a specific metal ion, whereas metal-activated enzymes can use any of several metal ions of similar size and charge.*

A metal ion that acts as a Lewis acid can catalyze a group transfer reaction in many different ways, but we will focus on only one of these, using a zinc enzyme as an example. Carbonic anhydrase is found in red blood cells and catalyzes the reaction of CO<sub>2</sub> with water to give carbonic acid.



Although this reaction occurs spontaneously in the absence of a catalyst, it is too slow to absorb all the CO<sub>2</sub> generated during respiration. Without a catalyst, tissues would explode due to the buildup of excess CO<sub>2</sub> pressure. Carbonic anhydrase contains a single Zn<sup>2+</sup> ion per molecule, which is coordinated by three histidine imidazole ligands and a molecule of water. Because Zn<sup>2+</sup> is a Lewis acid, the pK<sub>a</sub> of the Zn<sup>2+</sup>–OH<sub>2</sub> unit is about 8 versus 14 for pure water. Thus at pH 7–8, a significant fraction of the enzyme molecules contain the Zn<sup>2+</sup>–OH<sup>–</sup> group, which is much more reactive than bulk water. When carbon dioxide binds in a nonpolar site next to the Zn<sup>2+</sup>–OH<sup>–</sup> unit, it reacts rapidly to give a coordinated bicarbonate ion that dissociates from the enzyme:



*The active site of carbonic anhydrase.*

Thus the function of zinc in carbonic anhydrase is to generate the hydroxide ion at pH 7.0, far less than the pH required in the absence of the metal ion.

### Enzymes That Use Metals to Generate Organic Radicals

An organic radical is an organic species that contains one or more unpaired electrons. Chemists often consider organic radicals to be highly reactive species that produce undesirable reactions. For example, they have been implicated in some of the irreversible chemical changes that accompany aging. It is surprising, however, that organic radicals are also essential components of many important enzymes, almost all of which use a metal ion to generate the organic radical within the enzyme. These enzymes are involved in the synthesis of hemoglobin and DNA, among other important biological molecules, and they are the targets of pharmaceuticals for the treatment of diseases such as anemia, sickle-cell anemia, and cancer. In this section, we discuss one class of radical enzymes that use vitamin B<sub>12</sub>.

Vitamin B<sub>12</sub> was discovered in the 1940s as the active agent in the cure of pernicious anemia, which does not respond to increased iron in the diet. Humans need only tiny amounts of vitamin B<sub>12</sub>, and the average blood concentration in a healthy adult is only about  $3.5 \times 10^{-8}$  M. The structure of vitamin B<sub>12</sub>, shown in Figure 23.6.10 is similar to that of a heme, but it contains cobalt instead of iron, and its structure is much more complex. In fact, vitamin B<sub>12</sub> has been called the most complex nonpolymeric biological molecule known and was the first naturally occurring organometallic compound to be isolated. When vitamin B<sub>12</sub> (the form present in vitamin tablets) is ingested, the axial cyanide ligand is replaced by a complex organic group.

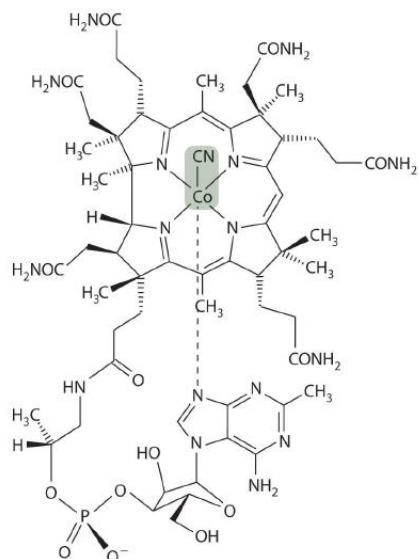
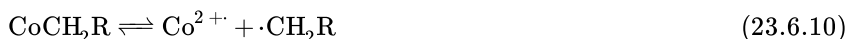
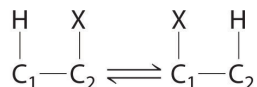


Figure 23.6.10: Vitamin B<sub>12</sub> In the body, the axial cyanide ligand found in the vitamin is replaced by a complex organic unit. Heterolytic cleavage of the Co–C bond in the resulting organometallic complex generates an organic radical for the catalysis of rearrangement reactions.

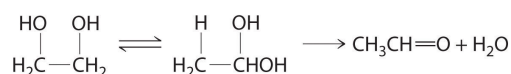
The cobalt–carbon bond in the enzyme-bound form of vitamin B<sub>12</sub> and related compounds is unusually weak, and it is particularly susceptible to homolytic cleavage:



Homolytic cleavage of the Co<sup>3+</sup>–CH<sub>2</sub>R bond produces two species, each of which has an unpaired electron: a d<sup>7</sup> Co<sup>2+</sup> derivative and an organic radical, ·CH<sub>2</sub>R, which is used by vitamin B<sub>12</sub>-dependent enzymes to catalyze a wide variety of reactions. Virtually all vitamin B<sub>12</sub>-catalyzed reactions are rearrangements in which an H atom and an adjacent substituent exchange positions:



In the conversion of ethylene glycol to acetaldehyde, the initial product is the hydrated form of acetaldehyde, which rapidly loses water:



The enzyme uses the ·CH<sub>2</sub>R radical to temporarily remove a hydrogen atom from the organic substrate, which then rearranges to give a new radical. Transferring the hydrogen atom back to the rearranged radical gives the product and regenerates the ·CH<sub>2</sub>R radical.

The metal is not involved in the actual catalytic reaction; it provides the enzyme with a convenient mechanism for generating an organic radical, which does the actual work. Many examples of similar reactions are now known that use metals other than cobalt to generate an enzyme-bound organic radical.

*Nearly all vitamin B<sub>12</sub>-catalyzed reactions are rearrangements that occur via a radical reaction.*

## Summary

Three separate steps are required for organisms to obtain essential transition metals from their environment: mobilization of the metal, transport of the metal into the cell, and transfer of the metal to where it is needed within a cell or an organism. The process of iron uptake is best understood. To overcome the insolubility of Fe(OH)<sub>3</sub>, many bacteria use organic ligands called siderophores, which have high affinity for Fe(III) and are secreted into the surrounding medium to increase the total concentration of dissolved

iron. The iron–siderophore complex is absorbed by a cell, and the iron is released by reduction to Fe(II). Mammals use the low pH of the stomach to increase the concentration of dissolved iron. Iron is absorbed in the intestine, where it forms an Fe(III) complex with a protein called transferrin that is transferred to other cells for immediate use or storage in the form of ferritin.

Proteins that contain one or more tightly bound metal ions are called metalloproteins, and metalloproteins that catalyze biochemical reactions are called metalloenzymes. Proteins that transfer electrons from one place to another are called electron-transfer proteins. Most electron-transfer proteins are metalloproteins, such as iron–sulfur proteins, cytochromes, and blue copper proteins that accept and donate electrons. The oxidized and reduced centers in all electron-transfer proteins have similar structures to ensure that electron transfer to and from the metal occurs rapidly. Metalloproteins also use the ability of transition metals to bind small molecules, such as O<sub>2</sub>, N<sub>2</sub>, and H<sub>2</sub>, to transport or catalyze the reactions of these small molecules. For example, hemoglobin, hemerythrin, and hemocyanin, which contain heme iron, nonheme iron, and copper, respectively, are used by different kinds of organisms to bind and transfer O<sub>2</sub>. Other metalloenzymes use transition-metal ions as Lewis acids to catalyze group transfer reactions. Finally, some metalloenzymes use homolytic cleavage of the cobalt–carbon bond in derivatives of vitamin B<sub>12</sub> to generate an organic radical that can abstract a hydrogen atom and thus cause molecular rearrangements to occur.

### Key Takeaway

- Organisms have developed strategies to extract transition metals from the environment and use the metals in electron-transfer reactions, reactions of small molecules, Lewis-acid catalysis, and the generation of reactive organic radicals.

### Conceptual Problems

- What are the advantages of having a metal ion at the active site of an enzyme?
- Why does the structure of the metal center in a metalloprotein that transfers electrons show so little change after oxidation or reduction?

### Structure and Reactivity

- In enzymes, explain how metal ions are particularly suitable for generating organic radicals.
- A common method for treating carbon-monoxide poisoning is to have the patient inhale pure oxygen. Explain why this treatment is effective.

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