

Review

The Bioinorganic Chemistry of the First Row d-Block Metal Ions—An Introduction

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Abstract: The role played by the metal ions of the first row of the block in biology is discussed using illustrative examples, and covering current thinking in the field. This will be of interest to current researchers in bioinorganic chemistry, as well as to senior undergraduate and novice postgraduate students entering the field.

Keywords: bioinorganic chemistry; d-block metal ions; metals in biology; catalysis; electron transfer; metalloenzymes; oxygen transport and storage

1. Introduction

Living systems on Earth primarily rely on a limited number of elements, notably C, H, N, O, P, and S. Together with Ca, these elements comprise approximately 98% of the human body by mass. Adding Na, Mg, Cl, and K brings the total close to 100% [1–4]. Despite their trace presence, d-block metal ions play crucial roles in biological processes, a concept underscored by the term *metallome* [5,6]. It has even been hypothesised that metal ions such as Fe, Mn, and Zn were essential for the actual emergence of modern metabolism [5,7]. In humans, metals like Mn, Fe, Co, Cu, and Zn are essential, while Cr and V offer some benefits [8,9]. The essentiality of Ni for humans is unclear, though it is vital for other life forms [10,11].

Many of these metal ions are biologically significant because of their variable oxidation states, with notable examples being Mn, Fe, Co, Ni, and Cu from the first row of the d block. Others, like Zn, primarily serve structural roles but also contribute to catalysis. Maintaining metal ion homeostasis is essential: a deficiency can harm the organism, but an excess is equally detrimental [12–17]. Indeed, while some elements may be beneficial at pharmacological concentrations, most are toxic at higher levels [17–19].

Trace metal ions in cells generally do not exist as free ions but as complexes, which falls under the domain of inorganic chemistry, particularly coordination chemistry. Understanding the role of metal ion complexes is central to bioinorganic chemistry, the intersection of inorganic chemistry and biology [20–26]. Despite their trace concentrations, these metals are integral to evolution, performing a variety of vital biological tasks [27–29]. Roughly one-third of all enzymes depend on metal ions for either catalytic function or structure [30,31]. Nature is also adaptable. Many enzymes can use different metal ions in their active sites. The superoxide dismutases and the ribonucleotide reductases, both of which will be discussed in this article, are examples. This adaptability to fluctuating metal availability has been important in the development of life on Earth [32].

Ions with closed-shell electron configurations, such as Na⁺, K⁺, Ca²⁺, and Zn²⁺, play diverse roles, including maintaining protein structure, catalysing reactions as Lewis acids,



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and regulating electrolyte and fluid balance. Metals with variable oxidation states, including Mn, Fe, Co, and Cu, facilitate redox catalysis, electron transport, oxygen transport and storage, defence against reactive oxygen, nitrogen, and sulphur species, and enzyme-catalysed reactions requiring changes in oxidation states [33].

The d-block metal ions important in biology are trace elements. An early definition of trace elements by Arnon and Stout [34], originally focused on plants, can be extended to other life forms:

- Without these elements, a plant cannot complete its life cycle.
- These elements are part of the essential constituents or metabolites of the plant.
- Deficiency of these elements leads to diseases, which can be corrected by their reintroduction.

Other definitions exist, such as the following:

- “An element is essential when a deficient intake consistently results in impaired function, and supplementation at physiological levels, but not others, restores optimal function” [1].
- “An element is considered essential if it has a defined biochemical function, and its absence results in death or reproductive failure, reversible by dietary supplementation” [35].
- The European Food Safety Authority (EFSA) defines an essential nutrient as “any substance an organism must consume from the diet to support normal health, development, and growth” [36].

A more comprehensive definition is provided in the classic textbook *Trace Elements in Human and Animal Nutrition* by Eric Underwood [37]:

A trace element is essential if it fulfils the following criteria:

- is present in all healthy tissues of living organisms;
- exists in relatively constant concentrations across individuals;
- causes physiological and structural abnormalities in its absence, which are reversible upon reintroduction;
- leads to specific biochemical changes when deficient, correctable by reversing the deficiency.

It is important to note the concept of partially essential or beneficial elements [38–40] and that the essentiality of elements varies across life forms. For example, while boron is essential for higher plants [41], it appears to be non-essential for animals (although this has been contested [41,42]); conversely, selenium is essential for animals, while its role in plants is unclear [38,43,44].

This article provides an introduction to bioinorganic chemistry, focusing on the first-row d-block metals and their biological (and sometimes medicinal) roles, whether essential or not. Using illustrative examples, it endeavours to reflect current thinking in the field to encourage deeper exploration and appreciation of ongoing developments. Given the breadth of the topic, the discussion is necessarily selective and illustrative rather than exhaustive. Moreover, this article should be particularly useful for the senior undergraduate and novice postgraduate student entering the field. Heavier metals like Mo and W, also important in biology, will be discussed elsewhere.

2. Scandium

Scandium is a relatively rare element found in the Earth’s crust, soil, and water bodies, typically dispersed in small quantities. It is often present in aluminosilicate minerals, including clays, micas, and pyroxenes [45].

Scandium is not known to be essential for biological systems, and due to its low bioavailability, it is generally considered non-toxic [46]. Its increasing industrial use has raised concerns about its potential environmental impact [47] and further research

on its exposure risks is warranted [48]. Its potential toxicity in humans has been extensively reviewed [49].

Scandium oxide (Sc_2O_3) is probably non-toxic, supporting cell viability, growth, and proliferation [48,50]. Although certain bacteria are sensitive to scandium at millimolar concentrations, eukaryotic cells are not [51]. Scandium does not bioaccumulate; its concentration in plants is typically lower than in the surrounding soil, with higher levels found in roots compared to leaves and seeds [52].

The ionic radius of Sc^{3+} (74.5 pm) is larger than that of high-spin, six-coordinate Fe^{3+} (64.5 pm) [53], yet Sc^{3+} can still bind to human serum transferrin (HSTf), the mammalian iron transport protein, albeit with weaker affinity ($\log K_1 = 14.6$ (2) and $\log K_2 = 13.3$ (3) for Sc^{3+} [54] compared to 22.7 and 22.1 [55] or 22.5 and 21.4 [56] for Fe^{3+}). Sc^{3+} also interacts with other proteins, such as α -globulins [57], and β -globulins [58], and it forms complexes with ATP, such as $\text{Sc}(\text{ATP})_2$ [59].

Complexes of Sc^{3+} have been explored for their antiviral, antibiotic, and antineoplastic activities. A diphthalocyanine complex of Sc^{3+} exhibits antiviral activity [60]. Coupling of Sc^{3+} with epoxypolysaccharide (EPS) derivatives improves the anti-metastatic properties of EPS [61]. Some complexes of scandium with europium oxide nanorod metallocene complexes exhibit anti-proliferative activity against some breast cancer and prostate cancer cell lines [62].

Sc^{3+} chelated with EDDHA (ethylenediamine- N,N' -bis(2-hydroxyphenylacetic acid)) binds to human serum albumin (HSA), likely through a bridging interaction involving EDDHA's phenolic groups [57]. Other chelators, such as NTA, EDTA, DTPA, and CDTA (NTA, nitrilotriacetic acid; EDTA, ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CDTA, cyclohexanediaminetetraacetic acid) do not form such complexes [63]. In mice, scandium behaves differently depending on its compound: Sc-EDTA is rapidly excreted in urine via the kidneys, whereas ScCl_3 accumulates in the liver and spleen [64]. Urinary scandium excretion may serve as a biomarker for environmental or occupational exposure [46,65]. Elevated circulating Sc^{3+} levels have been associated with chronic renal failure [66], and hair analysis suggests correlations between increased Sc^{3+} levels and health conditions such as diabetes and obesity [67].

In cellular systems, Sc^{3+} interacts with actin, a cytoskeletal protein critical for cell motility and structural integrity, displacing native Mg^{2+} and forming amorphous aggregates [68]. $\text{ScF}_x^{(x-3)-}$ can inhibit the ATPase activity of myosin, another key cytoskeletal protein involved in cellular motility, by interacting with its subfragment 1 [69].

There is interest in the use of the positron emitters ^{44}Sc ($t_{1/2} = 3.97$ h) and ^{47}Sc ($t_{1/2} = 3.4$ d) for theranostic applications [70–73]; with its short lifetime, ^{44}Sc (and ^{43}Sc) is useful for PET imaging while ^{47}Sc is useful for therapy. Suitable chelates are required, with DOTA (1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetic acid) as the current gold standard [73–75].

There is probably merit in the further exploration of Sc^{3+} complexes for their antiviral, antibiotic, and antineoplastic activities which might lead to the development of novel treatment regimes.

3. Titanium

Titanium plays no known biological role [76]. Humans typically ingest approximately 0.8 mg of titanium daily, primarily through food [77], but most of it passes through the body unabsorbed. Blood titanium levels in humans average around $45 \mu\text{g L}^{-1}$ [78]. Titanium alloys are highly biocompatible and widely utilised in joint replacements and dental implants [79–81] with negligible effects on blood titanium levels [78], although there is recent evidence of elevated titanium levels in the blood of patients after spinal surgery

and implants [82]. It has been suggested that titanium implants can contribute to peri-implantitis through mechanisms such as foreign body reactions and DNA methylation [83] and the chemical treatment of the implants may be appropriate [84]. A re-evaluation of the design of titanium alloys for use in implants may be necessary [85].

In oxidising environments, titanium predominantly exists as Ti^{4+} [86], with an ionic radius of 0.605 Å (for six-coordinate Ti^{4+} [53]), which is an intermediate between six-coordinate Al^{3+} (0.535 Å) and high-spin Fe^{3+} (0.645 Å).

3.1. Biomedical Applications

While titanium plays no role in biology, many of its compounds have been used in biomedical applications. Some examples are discussed here—and the list is by no means comprehensive.

Titanium compounds such as titanocene dichloride, Cp_2TiCl_2 (Figure 1), exhibit anti-tumour properties [87–93]. The anti-tumour property is thought to be a consequence of the accumulation of these compounds in nucleic acid-rich regions, particularly the chromatin of tumour cells, where they bind irreversibly to DNA via phosphate oxygen and, to a lesser extent, nitrogen bases [94,95]. This inhibits cell growth.

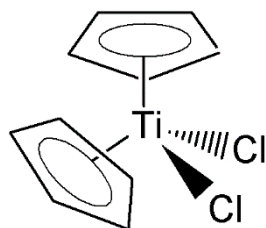


Figure 1. Titanocene dichloride, $(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCl}_2$.

A recent review underscores the multifaceted nature of titanium's anticancer activity [96]. The mechanism of action for titanium-based anticancer drugs extends beyond DNA binding. Proposed mechanisms include inhibition of mitochondrial activity, induction of paraptosis via kinase activation, topoisomerase inactivation, apoptosis, and iron deprivation.

Ti^{4+} is transported to cancer cells by HSTf, forming complexes with the N and C lobes of HSTf [97]. Its strong Lewis acidity and higher charge density enable it to bind more strongly to HSTf than Fe^{3+} ($\log K_1 = 26.8$ and $\log K_2 = 25.7$ compared to 22.7 and 22.1 [55] or 22.5 and 21.4 [56] for Fe^{3+}). Cancer cells overexpress transferrin receptors [98], and their low intracellular pH facilitates Ti^{4+} release and DNA complexation.

The exploration of titanium complexes in oncology is the subject of ongoing research [90,91,95,96,99,100] and future interesting findings can be expected.

Titanium oxide nanoparticles have significant photocatalytic potential which generates high levels of reactive oxygen species (ROS). They are therefore potential antibacterial and anticancer agents [101,102]. In fungi, TiO_2 nanoparticles cause damage to the cells by impairing their ROS-scavenging system [103]. In *E. coli*, TiO_2 photocatalysis leads to damage of cell walls due to lipid and protein peroxidation, increasing their fluidity, and ultimately leading to cell lysis [104,105]. TiO_2 nanoparticles in the size range 10–100 nm penetrate tumour cells with minimal uptake by healthy cells. They induce oxidative stress and can be used in cancer therapy [106,107].

An interesting biomedical application of titanium is $\text{Ti}_3\text{C}_2\text{T}_x\text{-MXene}$, a two-dimensional material of the MXene family (a layered material of general formula $\text{M}_{n+1}\text{AX}_n$, M = a transition metal such as Ti or Nb, A = Al, Si, or Ga, X = C and/or N). These can serve as carriers

of poorly hydrophilic drugs to cancer cells and are also useful in photoacoustic imaging and photothermal therapy [108].

BaTiO₃ is a nano-acoustic sensitiser that can be used in sonodynamic therapy, a process that utilises sound waves to activate a sonosensitiser to generate localised effects that target cancer cells. The effects include tumour cell senescence, ferroptosis, and glutathione depletion [109].

3.2. Enzyme Inhibition

The five-coordinate Ti⁴⁺ complex TiO(SO₄)(H₂O) potently inhibits trypsin-like serine proteases (enzymes that cleave peptide bonds in proteins [110,111]) by binding directly to Asp189 at the substrate binding pocket's base [112]. The specificity of this interaction is noteworthy as it excludes the chymotrypsin subclass, where the amino acid serine replaces aspartate. This distinction underscores the nuanced selectivity of TiO(SO₄)(H₂O) in targeting specific protease families, which could have significant implications for therapeutic applications, especially in conditions where trypsin-like proteases are dysregulated.

Titanium complexes inhibit lipoprotein lipase (LPL) [113], which is important given LPL's critical role in lipid metabolism and its implications in conditions such as obesity and cardiovascular diseases [114].

Some hydrazide complexes of Ti(III) and Ti(IV) inhibit tyrosinases (which control the production of melanin) and lipoxygenases (which oxygenate polyunsaturated fatty acids and regulate inflammatory responses). They therefore are potentially useful in cosmetic and therapeutic applications for skin disorders (tyrosinase inhibition) [114] and anti-inflammatory therapies (lipoxygenase inhibition) [115].

The immobilisation of the bacterial metalloprotease serratiopeptidase onto TiO₂ nanoparticles is a significant advancement in enzyme engineering [116]. This process not only enhances the enzymatic stability of serratiopeptidase, which is known for its ability to degrade a variety of proteins, but also amplifies its antibacterial properties. The incorporation of TiO₂ nanoparticles provides a robust support matrix that can protect the enzyme from denaturation and degradation, thereby prolonging its functional lifespan. Exploiting such synergies between materials science and biological chemistry could lead to innovative applications in biomedicine, particularly in developing targeted therapies against bacterial infections, where serratiopeptidase's proteolytic activity can be harnessed to disrupt bacterial cell walls or biofilms.

3.3. Antibiotic Properties

Titanium complexes show promise as antibiotics [117]. For example, the Ti⁴⁺ complex Ti(deferasirox)₂ (Figure 2) demonstrates activity against methicillin-resistant *Staphylococcus aureus* with minimal human cell toxicity. Its antibiotic effect may stem from transmetalation with labile Fe³⁺, inhibiting iron bioavailability and hence ribonucleotide reductase [117]. It has also been suggested that titanium is a natural antibiotic, mobilised by acid-producing bacteria [118]. Metal oxide nanoparticles, including TiO₂ nanoparticles, also show promising antibiotic properties [119–122].

3.4. Role in Agriculture

Titanium stimulates plant growth, as observed with Tytanit[®], a Ti⁴⁺ complex of ethylene glycol and terephthalic acid used in agriculture [123]. Low concentrations of titanium enhance chlorophyll content, photosynthesis, nutrient uptake, stress tolerance, and crop yield [124–127]. These effects may involve an antagonistic interaction with iron, whereby titanium induces iron acquisition gene expression, so enhancing plant growth [124]. However, caution is necessary; excessive titanium can disrupt iron homeostasis, leading to

phytotoxicity [128]. TiO₂ nanoparticles can be used to extend the shelf life of fruit by removing bacteria [129].

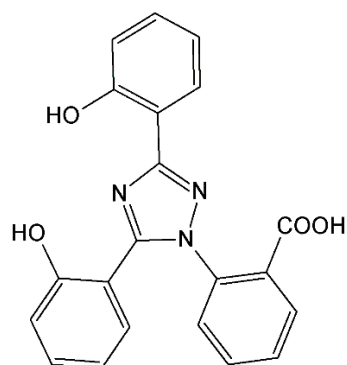


Figure 2. The structure of desferasirox.

3.5. Potential Biological Roles

Although titanium's biological role remains unconfirmed, it is known that some marine organisms sequester titanium [86]; there is a distinct possibility that this is merely an artefact of increasing levels of TiO₂ nanoparticles in aquatic ecosystems [130,131]. Suggestions have been advanced on how such a role—if it indeed exists—might be uncovered [76,132,133]. Hypothetical roles include leveraging its Lewis acidity for enzyme catalysis by deprotonating substrates in the active site of an enzyme; participation in redox electron transfer chains with suitable ligands to tune the Ti⁴⁺ | Ti³⁺ couple; as the active site of a redox metalloenzyme; or serving as an antimicrobial agent via singlet oxygen (¹O₂) and superoxide (O₂^{•−}) generation under UV irradiation, as mentioned above. Titanium alloys could serve as temporary organs in organ transplant patients until a suitable donor is found [134]. Future studies may uncover new functions for titanium in biology.

4. Vanadium

Vanadium, with an abundance of 136 ppm in the Earth's crust [135], is relatively widespread and plays a small but significant role in biological systems [136–142]. While vanadium exhibits oxidation states ranging from −3 to +5 [135], only the +3, +4, and +5 states are known to participate in biological processes.

The role of vanadium in higher life forms is still unclear, but there is speculation that vanadium, in the form of oxidovanadium (IV) complexes may have played a significant role in the prebiotic world [143]. Some bacteria use V⁵⁺–H₂VO₄[−] as an electron acceptor during respiration [140,144]. Intestinal bacteria of the sea squirt *Ciona robusta* accumulate V⁵⁺, reducing it to V⁴⁺, which is of considerable interest for possible bioremediation and biomineralization [145–148] and indeed might be extended in the future for mining in extra-terrestrial ore bodies [149].

Another notable role of vanadium is in the haloperoxidases of algae (*Ascophyllum nodosum*), fungi (*Curvularia inaequalis*), and certain cyanobacteria [142,150]. These enzymes catalyse the oxidation of halides to hypohalous acids, which may provide a defence mechanism against predators or parasites.

Vanadium is involved in nitrogenase enzymes, enabling bacteria like *Azotobacter* to fix nitrogen, converting it to NH₃. In some cases, vanadium substitutes for molybdenum, as observed in the nitrate reductase of *Pseudomonas isachenkovii* [151]. Ascidians and fan worms accumulate vanadium from seawater, possibly as a defence mechanism against predators [152].

Vanadium has potential therapeutic applications for treating diabetes, parasitic diseases, and cancer [153–158]. This will not be discussed in this article.

4.1. Vanadium in Respiration

As mentioned, some bacteria use V^{5+} ($H_2VO_4^-$) as an electron acceptor during respiration [140,144]. Understanding the processes is important for bioremediation efforts [146,159] since V^{5+} is toxic to humans. There are also potential bioengineering applications of these organisms as exoelectrogens in energy applications [160].

Geobacter metallireducens, a bacterium present in subsurface soil and which has served as a model for the physiology of microbes involved in biogeochemical recycling of metals [147], converts $H_2VO_4^-$ to $VO(OH)_2$ using lactate (or acetate) as a reductant (Figure 3, [140,144]). Other bacteria that occur in soils and groundwater, such as *Shewanella*, also oxidise V^{5+} (such as HVO_4^{2-}) to V^{4+} (as VO^{2+} or insoluble $VO(OH)_2$) using formate, lactate, or citrate as a reductant (Equation (1)).

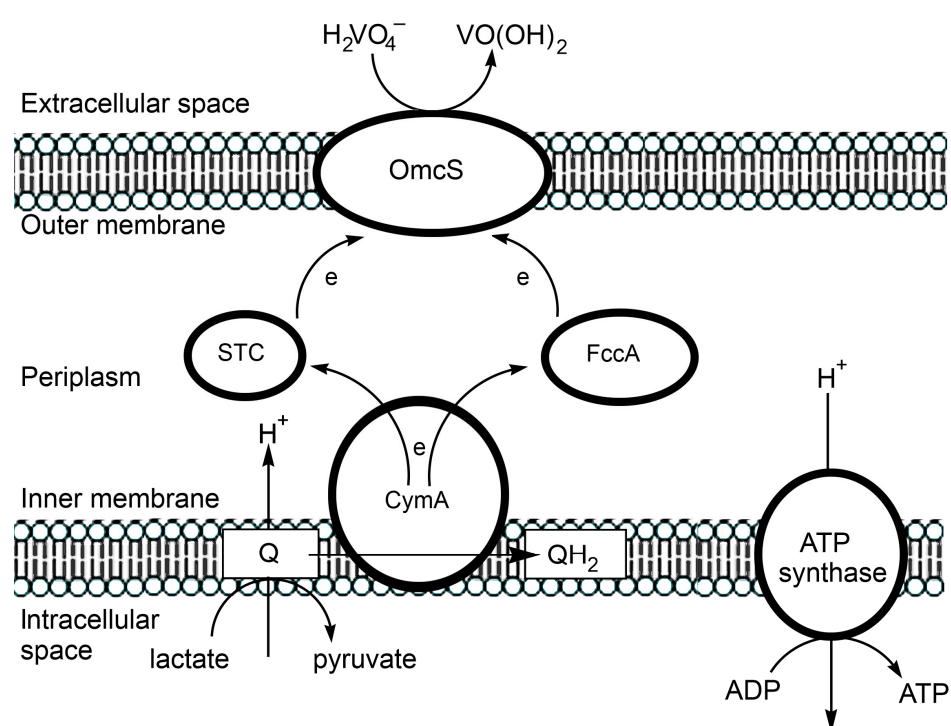


Figure 3. Electron transfer across a bacterial cellular membrane. The process begins with the oxidation of lactate or acetate at the cytosolic membrane and terminates with the reduction of vanadate at the outer membrane. Q/QH₂ is menaquinone/-hydroquinone. Refer to the text for other abbreviations. The electron transport from the cytosolic to the outer membrane is accomplished by a cascade of cytochrome *c*-type haemoproteins. The H⁺ transport into the intracellular space is coupled to the formation of ATP.

Lactate, present in the cytosol, is oxidised to pyruvate by lactate dehydrogenase, a reaction that generates a limited amount of ATP, the primary energy currency of the cell. The electrons released are transferred to the quinol dehydrogenase CymA, a *c*-type tetrahaem protein [161], which oxidises reduced quinones such as menaquinone-7. CymA subsequently transfers these electrons to periplasmic cytochromes, including a small tetrahaem cytochrome (STC), which facilitates electron transfer between the inner and outer membranes [162]. Electrons are also directed to fumarate reductase (FccA) [163,164].

Both STC and FccA contribute to electron delivery to an outer membrane-associated complex. In *Geobacter* species, this complex includes OmcS, a six-haem cytochrome implicated in transmembrane electron transfer (see [165] and the references therein). OmcS

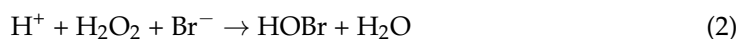
facilitates the export of electrons across the outer membrane to the extracellular environment, where the reduction of H_2VO_4^- to $\text{VO}(\text{OH})_2$ occurs.

This electron transport process is coupled to proton translocation from the cytosol to the periplasm, generating a proton-motive force across the inner membrane [166]. This electrochemical gradient is subsequently utilised by ATP synthase to drive ATP synthesis. For a detailed mechanistic overview of proton pumping in *Geobacter*, see [167].

Other bacteria that occur in soils and groundwater, such as *Shewanella*, also oxidise V^{5+} (such as HVO_4^{2-}) to V^{4+} (as VO^{2+} or insoluble $\text{VO}(\text{OH})_2$) using formate, lactate, or citrate as a reductant (Equation (1)).

4.2. Haloperoxidases

Haloperoxidases have been known for over 25 years [168] and new haloperoxidases are still being discovered [169], or may yet be discovered [170]. They are widely distributed in seaweeds, cyanobacteria, fungi, and phytoplankton [171]. These enzymes catalyse the two-electron oxidation of halides (and thiocyanate) to hypohalous acids by a peroxide (Equation (2), using Br^- and H_2O_2 as an example) [172]. (Sometimes, perhaps arbitrarily [150], haloperoxidases that oxidise Cl^- , Br^- , and I^- are termed chloroperoxidases; the bromoperoxidases oxidise Br^- and I^- ; while the iodoperoxidases act on I^- exclusively.)



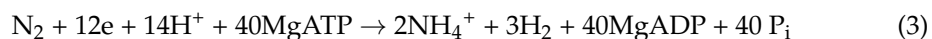
The hypohalide can subsequently halogenate an organic substrate, such as an aromatic compound, in the process converting a strong aromatic C-H bond into a C-halogen bond, a process facilitated by the structure of the protein which enables the binding of the substrate [173].

There is interest in these enzymes as they are useful synthesis tools that complement more traditional methods in organic synthesis and biosynthesis [174–180], and there are also potential bioengineering and biocatalysis applications [181]. There is medical interest as an increased level of haloperoxidases and halogenative stress is associated with Parkinson's disease [182].

One of the active sites of the hexameric vanadate-dependent bromoperoxidase from the algae *Ascophyllum nodosum* (Protein Data Base, PDB, reference code 5AA6 [183]) is shown in Figure 4. A His residue serves as the axial ligand of the metal, while the oxides of VO_4^{3-} (or H_2VO_4^-) interact with several amino acids of the protein.

An outline of the proposed reaction mechanism of a bromoperoxidase is shown in Figure 5 [183]. (See [150] for a more complete description.)

The reaction catalysed by V-Nase, unlike Mo-Nase, uses a significant fraction of the reducing equivalents to produce H_2 (Equation (3)) and can indeed act purely as a hydrogenase in the absence of N_2 .



By comparison, Mo-Nase consumes sixteen equivalents of MgATP and generates only one equivalent of H_2 per equivalent of N_2 reduced; it is a much more specific enzyme [190]. The reducing equivalents come from central metabolism and ATP hydrolysis [191] and are delivered to the substrate-reducing site via a $[\text{Fe}_8\text{S}_7]$ relay (called the P-cluster) from an iron protein containing a $[\text{4Fe-4S}]$ cluster [192]. The P-cluster of V-Nase is more readily reduced than that of Mo-Nase [193] and perhaps consists of fragmented iron–sulphur clusters rather than being a fully formed cluster [194]. In the resting state of V-Nase the $[\text{VFe}_7\text{S}_8\text{C}(\text{CO}_3)]$ cluster includes a bridging CO_3^{2-} , which is linked to the protein through cysteine, histidine, and a homocitrate coordinated to V (Figure 6).

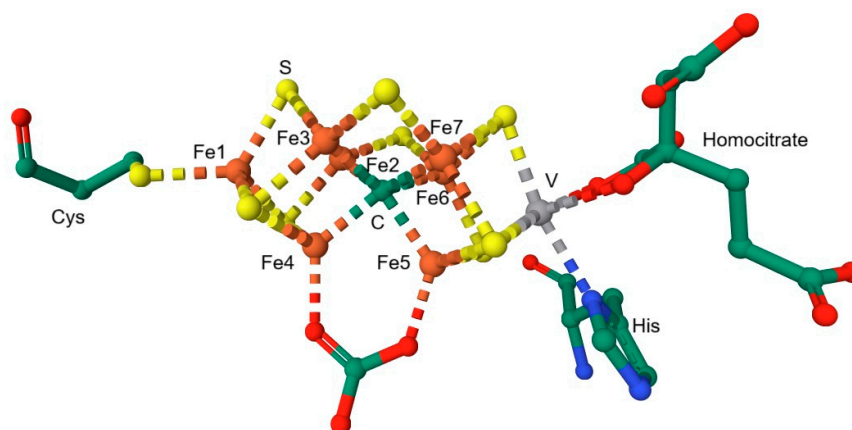


Figure 6. The active site $[\text{VFe}_7\text{S}_8\text{C}]$ cluster of a vanadium nitrogenase (PDB 5N6Y [190]).

Nitrogenases are sensitive to and inhibited by O_2 . Recent cryo-EM reports [195,196] show that when O_2 levels increase, a small protein, FeSII, is oxidised and forms a protective complex with two MoFe nitrogenases, and that this can grow into extended filaments. The nitrogenase is inactive under these conditions. Once O_2 levels drop, the complex dissociates as FeSII is reduced, and nitrogenase activity is restored. This protective strategy may well apply to V-Nase as well.

The substrate-reducing site of Mo-Nase contains (formally) three Fe^{2+} and four Fe^{3+} ions, and a $\text{d}^3 \text{Mo}^{3+}$, making up a $[\text{MoFe}_7\text{S}_9\text{C}]^-$ cluster [197] with a quartet ground state [198], although delocalisation of electron density makes the allocation of charges a moot point. In the substrate-reducing cluster of V-Nase, a carbonate rather than a sulphide bridges two of the iron centres. Vanadium is present as $\text{d}^2 \text{V}^{3+}$ with 3Fe^{2+} and 4Fe^{3+} and a triplet ground state [199].

All three nitrogenase enzyme types can perform the reductive elimination of H_2 . Details will differ depending on the enzyme type and there is by no means certainty about the mechanistic details.

It is known that N_2 activation occurs after a four-electron reduction of the cofactor (with—formally—all Fe^{3+} reduced to Fe^{2+}) [200]. Two hydrides leave as H_2 just prior to binding of N_2 [201]. There is evidence (for Mo-Nase) of both terminal and bridging S-H stretching frequencies, observed using surface-enhanced infrared absorption spectroscopy on Mo-Nase attached to gold electrodes, which served as the source of electrons for enzyme turnover [202]. A minimal scheme is shown in Figure 7 [203].

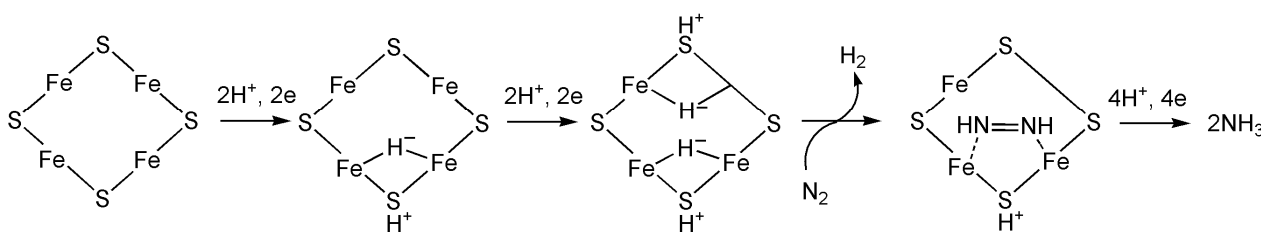


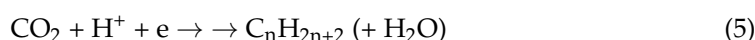
Figure 7. The reductive elimination of H_2 leads to conversion of N_2 to NH_3 by the nitrogenases.

Recent DFT modelling of the mechanism of V-Nase indicates that there is one additional step in V-Nase between the ground state and the state that binds N_2 (referred to as the E_4 state) since V^{3+} can be reduced to V^{2+} whilst the equivalent reduction of Mo^{3+} does not occur. The oxidation state of the cofactor prior to N_2 binding is (V^{2+} , 5Fe^{2+} , 2Fe^+) in V-Nase but (Mo^{3+} , 5Fe^{2+} , 2Fe^+) in Mo-Nase; see [198] for details. Another difference is the initial binding site of N_2 in the two enzymes—to Fe6 in V-Nase, but to Fe4 in Mo-Nase; see Figure 6 for the numbering of the Fe atoms. (It should be borne in mind that predictions using DFT methods can depend on the functional and basis set used, as demonstrated when modelling the formation of H_2 during enzyme turnover of Mo-Nase [204].)

The rate-determining step in Mo-Nase, and probably in V-Nase as well, is the protonation of bound N_2 . An intermediate in the catalytic cycle of V-Nase featuring a μ^2 -bridging ligand, purportedly nitrogen, has been reported [205] and sheds some light on the mechanism of the nitrogenases, although QM/MM calculations [206,207] suggest that it is likely to be OH^- rather than NH_2^- or NH^- that occupies the active site.

Why one equivalent of H_2 is produced by Mo-Nase per enzyme turnover, but three equivalents during V-Nase turnover, is not clear. Clearly, this unproductive step is the penalty paid for having to use vanadium instead of molybdenum under molybdenum-starved conditions.

In addition to the reduction of N_2 to NH_4^+ (Equation (3)), V-Nase, unlike the Mo-dependent enzymes, is also capable of reducing CO and CO_2 to hydrocarbons with chain lengths of 2–7 [189,208–211] (for example, Equations (4) and (5) [212]), and the reduction of alkenes (Equation (6)).



The difference in the chemistry of V-Nase and Mo-Nase is probably a consequence of differences in the overall structure of the protein [190]. The crystal structure of V-Nase with CO bridging two Fe ions of the active site, and replacing one of the sulphides, has been reported [213]. But the formation of a C–C bond implies that two CO molecules must be coordinated to the active site—and the crystal structure of such a complex has indeed appeared (PDB 7AIZ) [209]. The active site is shown in Figure 8.

4.3. Vanadium in Marine and Fungal Systems

Ascidians and fan worms accumulate vanadium from seawater, likely as a defence mechanism against predators [152]. In fan worms, VO^{2+} binds to and suppresses a nucleoside diphosphate kinase, an enzyme which helps maintain the balance of nucleotide pools in the cell [214]. Ascidians take up vanadium in the form of H_2VO_4^- ; this is reduced to VO^{2+} in two successive steps, and finally by CysMet to V^{3+} after binding to the lysine residues of vanabin (a cysteine-rich vanadium-binding metalloprotein),

Equation (7) [215]. (Cys is the reductant while Met is thought to ensure the structural integrity of the reaction environment).

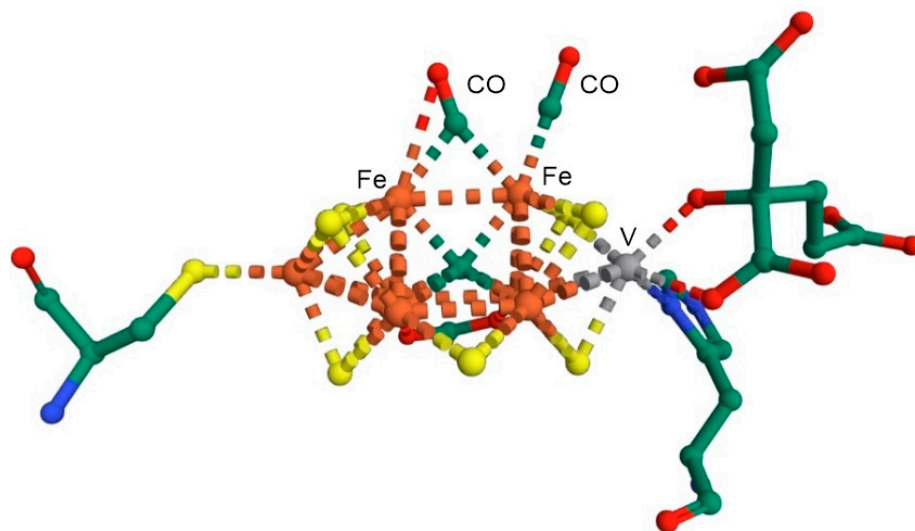
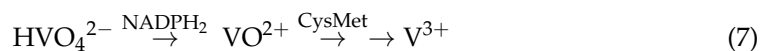


Figure 8. The active site of a V-Nase with two bound CO ligands (PDB 7AIZ [209]).

Accumulated vanadium activates glucose-6-phosphate dehydrogenase, which catalyses the conversion of D-glucose-6-phosphate to 6-phospho-D-glucono-1,5-lactone.

Poisonous *Amanita* mushrooms contain the eight-coordinate V^{4+} complex amavanadin, $[\text{V}[\text{NO}[\text{CH}(\text{CH}_3)\text{CO}_2]_2]_2]^{2-}$ (Figure 9). The function of amavanadin is unclear [140]; it can act as both a catalase and a peroxidase [140,216,217] (Equations (8) and (9), where the oxidation state of vanadium in amavanadin is shown in each case).

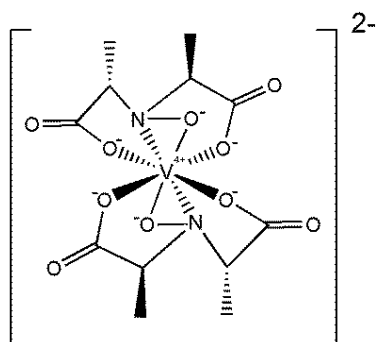
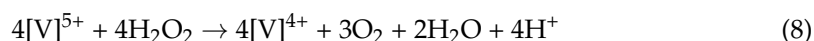


Figure 9. Amavanadin, found in *Amanita* mushrooms.

4.4. Vanadium and Human Biology

As far as is known at present, vanadium plays no essential role in human biology [218]. Vanadium uptake in humans occurs primarily from dietary sources, and it is absorbed from the gastrointestinal tract [219], although other routes are possible [154]. Once absorbed, vanadium is transported in the bloodstream bound to, for example, HSTf [220] or HSA [221].

been linked to diabetes-like symptoms, impaired growth, reduced fertility, and increased cardiovascular risk [253–255].

Within animal cells, Cr^{3+} binds to a low molecular weight peptide known as the chromium-binding substance (LMWCr), or chromodulin, which comprises Asp, Cys, Glu, and Gly residues [256,257]. This peptide cooperatively binds four Cr^{3+} ions ($K_f = 10^{21} \text{ M}^{-1}$, Hill coefficient = 3.47) [258–260], and exhibits a high degree of specificity for Cr^{3+} [261]. Variable-temperature magnetic susceptibility measurements, along with X-ray absorption spectroscopy and EPR studies [262], indicate the presence of a binding site for a single Cr^{3+} ion, as well as an asymmetric trinuclear Cr^{3+} cluster bridged by oxo ligands. The precise physiological role of chromodulin, however, remains speculative.

Cr^{3+} -loaded chromodulin (homochromodulin) binds to the insulin receptor on insulin-sensitive cells, thereby promoting insulin binding [263]. It is proposed that this interaction enhances insulin receptor activity by prolonging tyrosine kinase signalling, ultimately leading to improved glucose uptake [264]. Homochromodulin may thus function as a secondary messenger, amplifying insulin signalling [258]. It is well established that Cr^{3+} is translocated from the bloodstream to peripheral tissues in response to elevated insulin levels [247,258]. The enhancement of insulin receptor β -subunit kinase activity may involve the phosphorylation of three tyrosine residues, along with the activation of downstream effectors such as PI3-kinase and Akt [265,266]. When insulin concentration decreases, homochromodulin is released from the cell to relieve its effect.

Recent evidence [267] indicates that the activity of Cr^{3+} is predominantly in the mitochondria where eight Cr^{3+} -binding proteins have been identified. The proteins are associated with the activity of ATP synthase. The binding of Cr^{3+} suppresses its activity and this leads to the activation of adenosine monophosphate-activated protein kinase (AMPK) [268,269], which has been termed the “guardian of metabolism and mitochondrial homeostasis” [270,271]. This activation improves the metabolism of glucose, protecting mitochondria from fragmentation due to hyperglycaemia [272]. It has been argued, though, that how the inhibition of ATP synthase arises is still an open question [273].

Conversely, Cr^{6+} is toxic to virtually all life forms [274–282] and the effect of Cr^{6+} and its biological effects have been extensively reviewed [238,250,283]. Several bacteria (e.g., *Pseudomonas*, *Bacillus*, *Escherichia*) can enzymatically reduce Cr^{6+} to Cr^{3+} using NADH or other electron donors, undoubtedly as a protective mechanism, although this process does generate reactive oxygen species [284–289].

6. Manganese

Manganese is a geochemically abundant transition metal, with an average crustal concentration of approximately 1000 ppm [290]. It is distinguished by its capacity to adopt a wide spectrum of oxidation states, ranging from +2 (as in d^{10} $[\text{Mn}(\text{NO})_3\text{CO}]$) through to +7 (d^0 as in $[\text{MnO}_4]^-$) [135]. Nonetheless, the oxidation states most frequently encountered in nature span from +2 to +7 (see Figure 11). Given both its prevalence and the versatility of its redox chemistry, the centrality of manganese to a range of biological processes is to be expected [291].

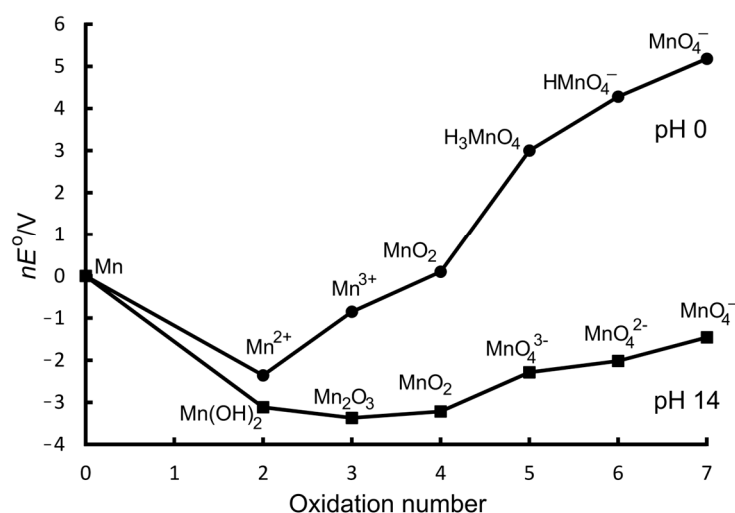


Figure 11. Frost diagram of manganese.

As an essential trace element, manganese is indispensable across diverse biological taxa. In mammals, it plays a critical role in the metabolism of amino acids, lipids, proteins, and carbohydrates, and is also requisite for normal reproductive function [292–294]. A wide array of Mn-dependent enzymes has been characterised, encompassing oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases [295]. In photosynthetic organisms, manganese assumes a pivotal role within the oxygen-evolving complex (OEC) of the thylakoid membrane in chloroplasts, where it facilitates the terminal photooxidation of water during the light-dependent phase of photosynthesis [296,297].

The most common Mn oxidation states in biological systems are +2, +3, and +4. These states exhibit diverse coordination geometries, predominantly with N and O donor ligands. Ligand identity significantly influences the redox potential of the metal. Mn²⁺ is the most prevalent oxidation state, and it is almost always high-spin ($S = 5/2$); low-spin ($S = 1/2$) Mn²⁺ complexes are known but uncommon due to the high pairing energy required [298–301].

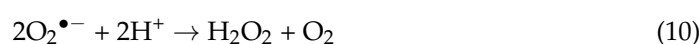
In humans, dietary intake serves as the primary source of Mn, and maintaining Mn homeostasis is crucial to prevent overloading and toxicity [302–306]; overloading affects mostly the brain, altering cognitive functions and locomotion [307–309].

Several transporters are known (or suspected) to facilitate Mn transport within the body [3,292,310–312]. These include the divalent metal ion transporter (DMT-1), which mediates the transport of Fe²⁺ and other divalent metal ions across plasma membranes and out of endosomes [313]; the zinc transporter families ZNT and ZIP [310,311,314]; and HSTf, which transports Mn in its +3 oxidation state [315]. In plasma, most Mn²⁺ binds to globulin and albumin [292].

What follows is a brief discussion of several Mn-dependent enzymes, highlighting the diverse biological functions of this essential metal ion.

6.1. Superoxide Dismutase

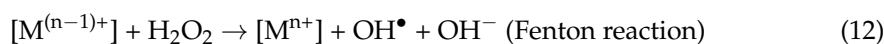
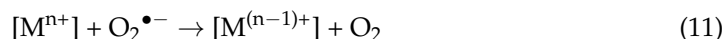
Superoxide dismutase (SOD) is a crucial enzyme in a living system's defence against oxidative stress [316]. It is responsible for the conversion of O₂^{•−} to H₂O₂ and O₂ with proton-coupled electron transfer (PCET, Equation (10)).



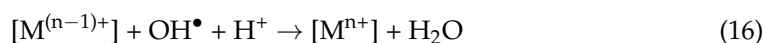
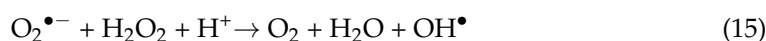
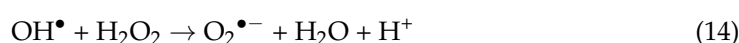
The formation of reactive oxygen species (ROS), including singlet oxygen ¹O₂, superoxide O₂^{•−}, hydrogen peroxide H₂O₂, and (especially) hydroxyl radical OH[•], is inevitable

in an oxidising atmosphere and was a challenge that life on Earth had to overcome to survive [317]. The main challenge is $\text{OH}^\bullet$ which reacts virtually indiscriminately with many biomolecules, including DNA, membranes, and proteins [318].

ROS production is sometimes (mistakenly) attributed to the Haber–Weiss cycle, catalysed by a metal ion complex $[\text{M}^{n+}]$ (Equations (11)–(13)).

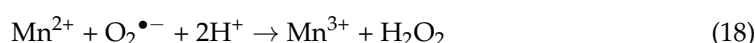


However, $\text{O}_2^{\bullet-}$ reacts faster with itself than with H_2O_2 [319,320]. The Fenton reaction is important because it initiates a chain reaction (Equations (14) and (15)), which is then terminated (Equation (16)).



Given this crucial role, SODs are widespread in living systems. Some bacteria have an MN-SOD [321,322]. Mn-SOD is found in the mitochondrial matrix of eukaryotes; its role is vital for maintaining the viability of mitochondria [323], having to deal with the $\text{O}_2^{\bullet-}$ produced by electrons leaking from the mitochondrial electron transport chain [324]. A SOD with a Cu–Zn active site is found in the extracellular matrix and cytosol of eukaryotes [325,326]. Superoxide dismutases are key to preserving health [327–329]. Fe-SODs are found in bacteria and the chloroplasts of plants [330–332]. A Ni-SOD is found in prokaryotes [333].

SOD is an example of an oxidoreductase enzyme that couples the concerted transfer of protons and electrons (PCET). The overall reaction catalysed by Mn-SOD is given in Equations (17) and (18) [334].



In a typical Mn-SOD, the metal ion has a distorted trigonal bipyramidal structure with three His, one Asp, and an H_2O (or OH^-) as ligands (Figure 12). The outer coordination sphere of human Mn-SOD contains five amino acid residues (two Tyr, His, Gln, and Glu, which is itself hydrogen-bonded to a Trp) which may be important in proton shunting to the active site.

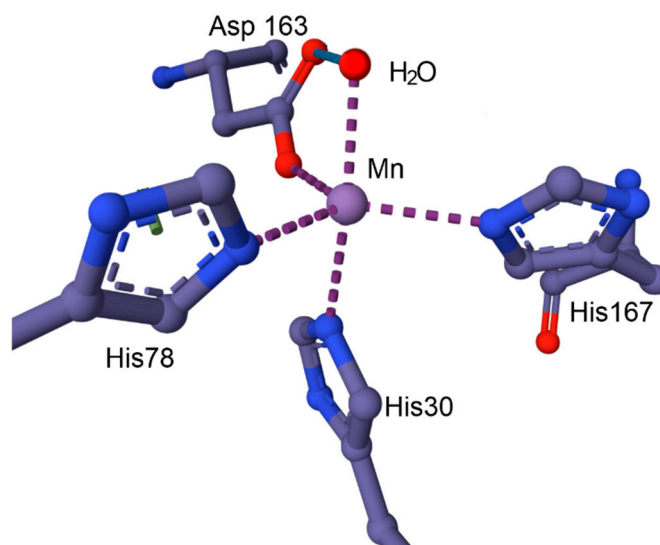


Figure 12. The active site of Mn-SOD from *Trichoderma reesei* [335].

It has been suggested that the substrate binds opposite the Asp ligand to form a six-coordinate intermediate [336–338]. An alternative suggestion [339,340] is that the substrate displaces Asp from the metal's coordination site and that the six-coordinate complex, observed with ligands such as N_3^- [341], is actually an inactive form of the enzyme. Lys and Arg residues form a positive surface near the active site and are thought to contribute electrostatically to guiding the substrate to the metal ion [342].

Using the results from neutron diffraction studies, a possible mechanism for the coupling of proton transfer to electron transfer in human Mn-SOD has been proposed recently from the direct visualisation of active site protons in the Mn^{2+} and Mn^{3+} redox states of the enzyme [343]. Proton transfer occurs among the coordinated H_2O , a solvent H_2O , and amino acids (two Tyr, a His, and Glu) that constitute the secondary coordination sphere of the metal ion and is driven by changes in the metal's oxidation state as it cycles between Mn^{3+} and Mn^{2+} (Figure 13). It is still unclear whether the reactions proceed through an inner sphere mechanism where there is direct bonding between the metal and $\text{O}_2^{\bullet-}$ and O_2 in the second step (as shown in Figure 13), or whether the reactions proceed through an outer sphere mechanism [325,342,344]. Indeed, QM/MM calculations, complemented with CASSCF/CASPT2/MM single-point energy calculations, suggest that the first step proceeds through an inner sphere mechanism, and the second step through an outer sphere mechanism with His or Tyr serving as proton donors for the formation of H_2O_2 [345].

There is a potential problem having an enzyme that generates H_2O_2 : whilst it is important as a signalling molecule [346], over-production will lead to deleterious effects. For example, H_2O_2 is a potent apoptotic agent and there is a causal link between cellular H_2O_2 and enhanced apoptosis, the driving force behind auto-antigenic exposure and chronic immune activation in systemic lupus erythematosus [347]. Fortunately, MnSOD is itself inhibited by H_2O_2 , ensuring a steady-state H_2O_2 concentration. In the inhibited state, HO_2^- replaces the OH^- ligand of the resting state of the enzyme [348]. A disturbance of this steady-state concentration is characteristic of several diseases [349].

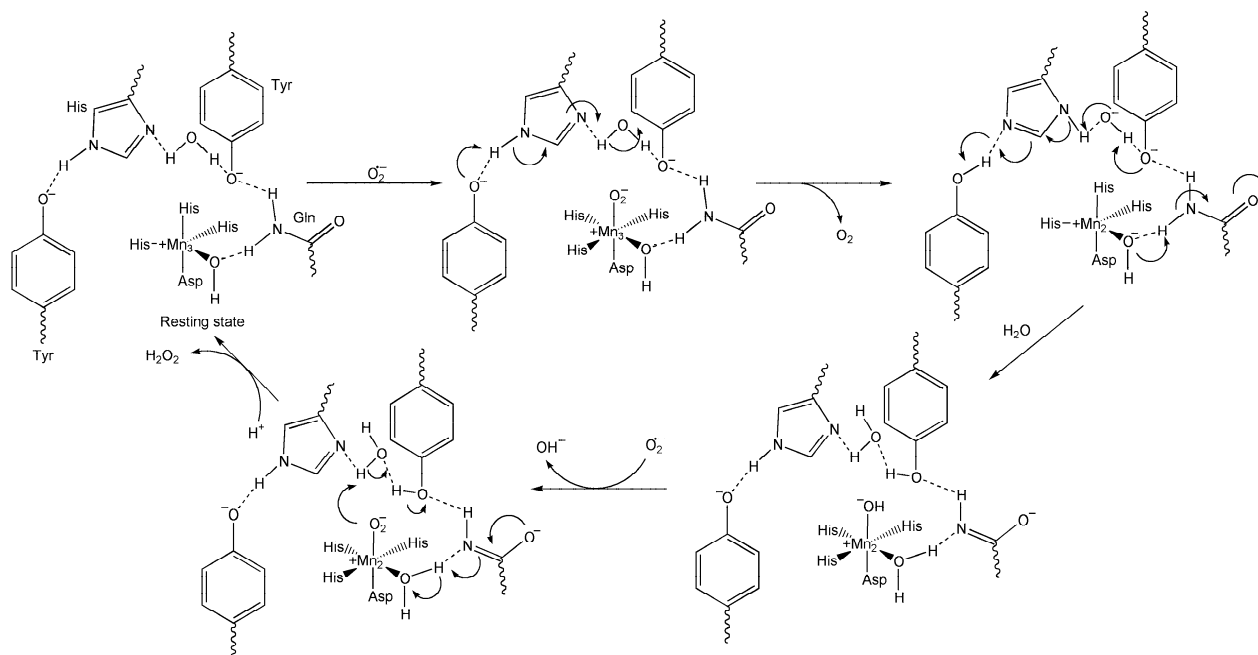


Figure 13. A possible mechanism, based on neutron diffraction observations, for the action of Mn-SOD, converting two equivalents of superoxide to hydrogen peroxide and oxygen during each enzyme turnover [343]. The movement of protons is a response to the change in the oxidation state of the metal.

6.2. Photosystem II

Possibly one of the earliest uses of manganese by living systems was in Photosystem II (PSII, water-plastoquinone oxidoreductase) [291,350], a system responsible for using light to oxidise water to O_2 and four reducing equivalents (Equation (19)) and located in the thylakoid membrane of cyanobacteria, plants, and algae. Manganese deficiency is detrimental to the growth of crops [351].



In the process, protons are pumped into the lumen, and the proton gradient thus created is used to drive the synthesis of ATP by ATP synthase. A schematic of the redox-active cofactors and the electron transfer chain in PSII of cyanobacteria is given in Figure 14 (adapted from [352]).

Light energy is captured by antenna complexes, known as light-harvesting complexes (LHC) in plants, typically composed of (bacterio)chlorophylls and (bacterio)pheophytins [353]. This energy is then transferred to the two branches, D1 and D2, of the reaction centre (RC). The D1 branch contains the oxygen-evolving complex (OEC), which features a cubic Mn_3CaO_5 structure with an additional Mn ion connected through a μ -oxo bridge (Figure 15). How the manganese cluster is assembled has been reviewed and summarised [354]. The LHC can respond to a variation in energy flux. Under conditions of high light intensity, quenching mechanisms are activated to prevent photodamage [355–358]. Replacement of Mn by one or more Fe ions leads to a decrease in activity (with 3 Mn and 1 Fe) or activity but only as far as producing H_2O_2 rather than O_2 [359]. Mn is clearly essential for optimum functioning of the LHC.

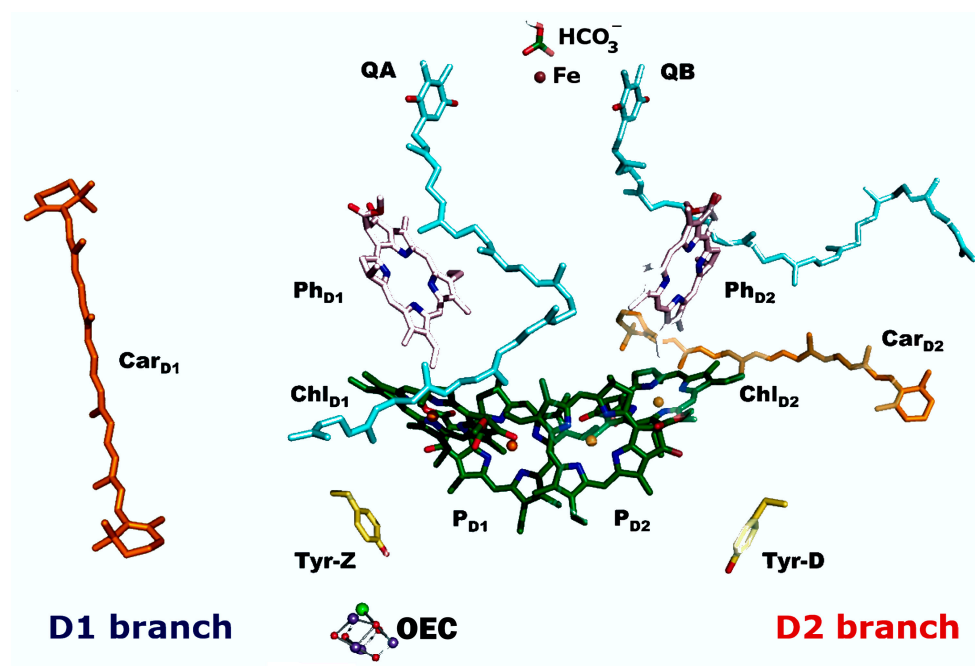


Figure 14. The D1 and D2 branches of PSII (adapted from [352]).

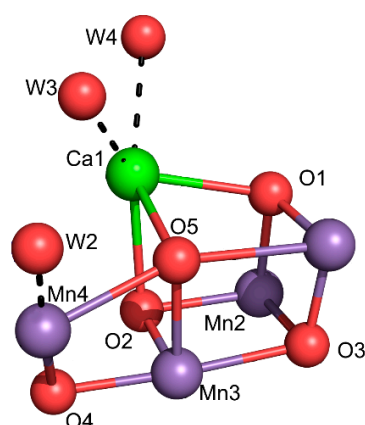


Figure 15. The OEC of PSII from the cyanobacterium *T. vulcanis*, PDB code 3WU2 [360]. W = H₂O. Adapted from <https://commons.wikimedia.org/w/index.php?curid=47294160>, accessed on 16 February 2025.

The OEC structure is nearly identical across plants, algae, and cyanobacteria, suggesting it dates to the early evolution of photosynthetic organisms that triggered the Great Oxidation Event approximately 2.7 billion years ago. This event transformed Earth's atmosphere from mildly reducing to oxidising [361–363]. The OEC is surrounded by amino acid residues, including tyrosine Y_Z, two Cl[−] ions (which are essential for electron transfer from H₂O to the manganese cluster, probably by blocking a proton exit channel [364–366]), and several water molecules [360,367–370]. Additionally, the RC houses a “special pair” of chlorophyll-*a* molecules (P_{D1} and P_{D2}), two chlorophyll-*a* molecules (Chl_{D1} and Chl_{D2}), two pheophytin-*a* molecules (Ph_{D1} and Ph_{D2}), two quinones (Q_A and Q_B), and a bicarbonate ion coordinated to a non-haem iron. The D1 branch also contains a carotenoid, Car_{D1}.

Charge separation occurs at Chl_{D1} (commonly referred to as P680) upon the absorption of light. Photoexcited P680* reduces pheophytin Phe_{D1}, initiating a series of electron transfers via Q_A and Q_B that ultimately reduce a plastoquinone. P680⁺ is a potent oxidant ($E \approx -1.3$ V) and oxidises tyrosine Y_Z. The oxidised tyrosine drives the cyclic mechanism responsible for oxidising H₂O to O₂ within the OEC. Changes in protein conformation are

important for controlling the entire process and in effect control the rate of electron transfer of the system [371,372].

Water oxidation in the OEC proceeds through five distinct S states: the Kok–Joliot cycle (Figure 16) [373]. With each step, the Mn_4CaO_5 cluster in the OEC is incrementally oxidised, and after the fourth step, O_2 is released. Electrons from the cluster are transferred via Tyr_Z to P680⁺, reducing it back to P680, thereby completing the cycle. The role of Ca^{2+} appears to be to stabilise a hydrogen bonding network connecting two water molecules with tyrosine Y_Z [374,375], and substitution with other metal ions leads to decrease in activity (when Ca^{2+} is substituted by Sr^{2+}) or no activity at all (when substituted by other cations). The oxidation of Tyr_Z lowers the energy barrier for proton transfer from the OEC along a pathway of conserved carboxylate groups and water molecules [366]. There is evidence that some singlet oxygen, $^1\text{O}_2$, may be produced as an unwanted product of the process of O_2 evolution [376].

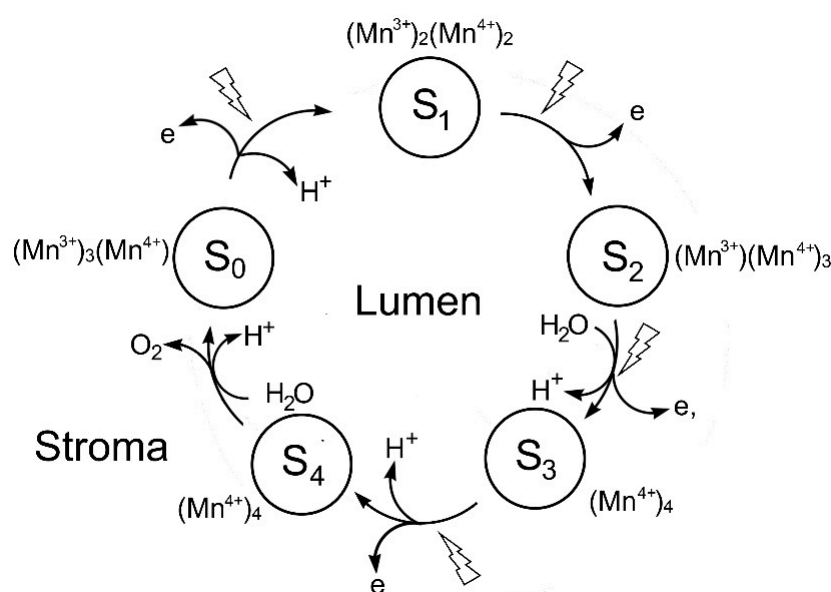


Figure 16. The Kok–Joliot cycle of the OEC of PSII with *possible* oxidation states of the four Mn ions [377,378]. While there is general agreement on the structures of S₀, S₁, and S₂, the structures of S₃ and S₄ are uncertain.

The oxidation states of Mn in each of the five states is still a matter for conjecture and the subject of ongoing research, undoubtedly prompted not only by the desire to understand one of the fundamental reactions of nature, but also by the promise (hope?) that such knowledge may be invaluable in the development of artificial photosynthesis systems as we move (and we must!) from a carbon-based energy economy [354,379]. The “low oxidation (LO)” model features an (Mn³⁺)₃(Mn⁴⁺) cluster, whilst the “high oxidation (HO)” model features an (Mn³⁺)(Mn⁴⁺)₃ cluster [380–382]. Evidence from photoactivation of PSII microcrystals suggests that the S₀ state corresponds to (Mn³⁺)₃(Mn⁴⁺), the S₂ state to (Mn³⁺)(Mn⁴⁺)₃, and the S₃ state to (Mn⁴⁺)₄ [383]. This is supported by computational modelling [384]. For a detailed analysis of the S₂ state, see [385]. The S₄ state is a transient intermediate, and its structure is uncertain [377,378]. Details of the S₁–S₂–S₃ transitions obtained using serial femtosecond crystallography (SFX) have recently become available [379,386]. SFX captures snapshots of proteins in action at near-atomic resolution whilst avoiding the inevitable damage from X-rays in traditional XRD methods [379]. For a comprehensive review of the literature on structure determination of the Mn_4CaO_5 cluster from experimental and computational methods, see [379].

One possible mechanism is shown in Figure 17, using the HO model. The formation of the O-O bond occurs in S_4 . For another possible mechanism, based on quantum chemical calculations, see [387]. An alternative proposal invokes the +3, +4, and +7 oxidation states of Mn [378]—all well-established stable oxidation states of the metal (Figure 11). Whatever the mechanism of the reaction, it is clear that what is being exploited to effect the oxidation of H_2O to O_2 are the variable oxidation states of manganese [388].

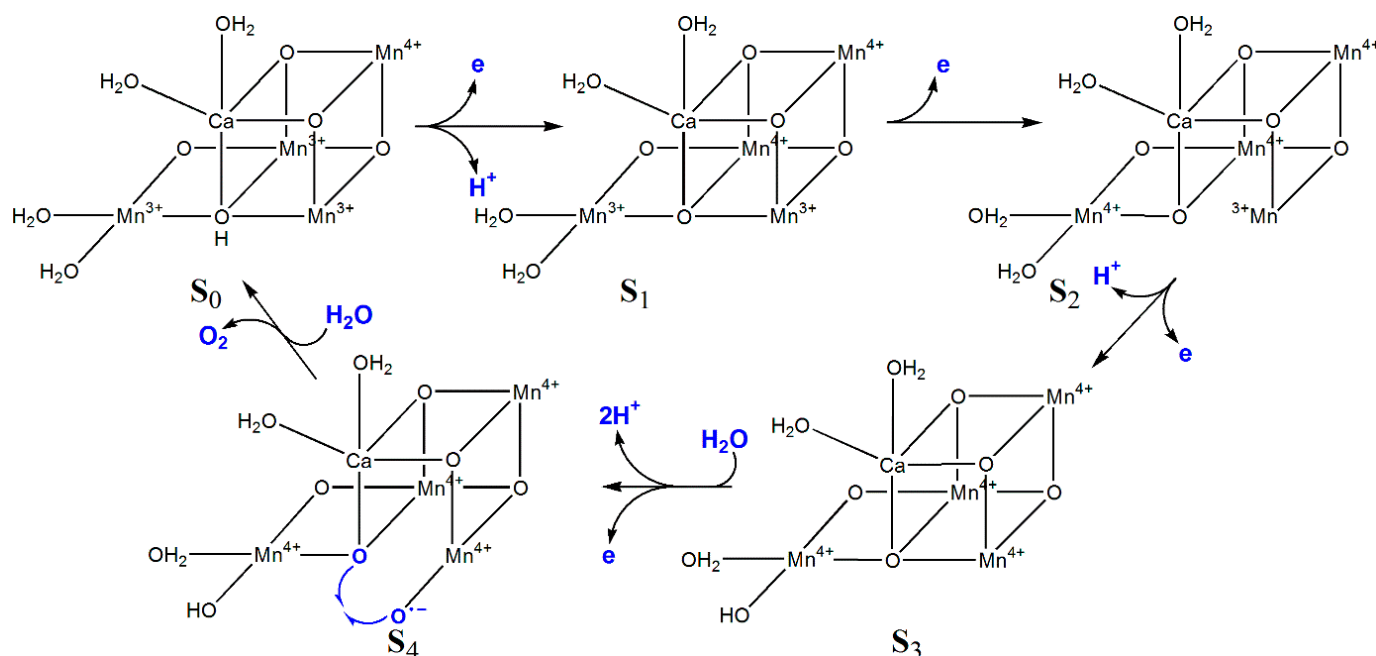


Figure 17. A possible mechanism for the evolution of oxygen at the OEC. (Adapted from [377]).

6.3. Examples of Other Mn-Containing Enzymes That Involve a Change in the Metal's Oxidation State

Iron is much more commonly used than manganese in metalloenzymes where there is a change in the oxidation state of the metal during enzyme turnover, perhaps because of its greater natural abundance during the early stages of the evolution of life and its lower redox potential [291]. Nevertheless, there are many enzymes that use the redox chemistry of manganese. Some illustrative examples follow.

6.3.1. Ribonucleotide Reductase (RNR)

There are three classes of these enzymes; they all catalyse the conversion of nucleotides to deoxynucleotides, the building blocks of DNA [389]. The reactions involve the generating of a Cys radical by some means, and all RNRs basically follow the same reaction mechanism (Figure 18) [390].

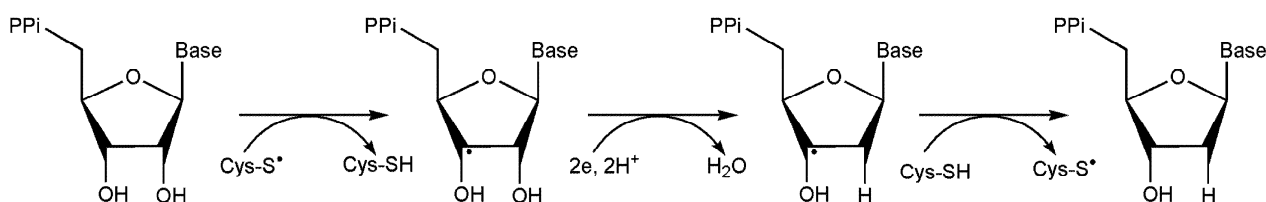


Figure 18. The reaction mechanism of a ribonucleotide reductase. A Cys $^{\bullet}$ radical initiates the reaction by abstracting the 3'-H of the substrate; the reaction is initiated by a one-electron oxidation. Ribose 2'-OH is released as water on a two-electron reduction. The abstracted H, present on Cys, is returned to the 3' position and the Cys $^{\bullet}$ radical is regenerated.

The capacity to generate the reactive $\text{Cys}^\bullet$ is stored remotely within the enzyme, spatially separated from the relatively accessible active site. The precise location of this radical-generating machinery varies among the three classes of RNRs [391,392].

Class I RNRs are heterodimeric enzymes composed of two distinct subunits. The larger subunit, variously designated R1, NrdA, or NrdI, is the site of ribonucleotide reduction, whereas the smaller subunit (R2, NrdB, or NrdF) is responsible for radical generation. In the latter, a stable tyrosyl radical is located in proximity to a binuclear metal centre. Class I RNRs are further categorised into five subclasses, based on the metal composition of the bimetallic site [393].

Class II RNRs generate the required radical through homolytic cleavage of the Co–C bond in adenosylcobalamin, [AdoCbl], whereby the resulting adenosyl radical ($\text{Ado}^\bullet$) directly initiates the formation of $\text{Cys}^\bullet$ [394].

By contrast, Class III RNRs utilise a distinct mechanism involving the reductive cleavage of the 5'-C–S bond in S-adenosyl-L-methionine, catalysed by a dedicated activating enzyme. The resulting $\text{Ado}^\bullet$ radical generates a glycyl radical ($\text{Gly}^\bullet$), which in turn oxidises a Cys residue in a reversible manner.

A schematic representation of tyrosyl radical generation near a dimanganese centre in the Class Ib RNR from the Gram-positive bacterium *Bacillus subtilis* is shown in Figure 19 [395]. Unlike the diiron variants of Class Ib RNRs, dimanganese enzymes are unreactive towards O_2 . Instead, they require the reduced form of a flavodoxin-like protein, NrdI_{hq} (hq = hydroquinone), which is oxidised to the semiquinone form, NrdI_{sq} (sq = semiquinone), and in the process reduces O_2 to $\text{O}_2^{\bullet-}$ [396]. The superoxide radical subsequently interacts with the bimetallic centre to form an $\text{Mn}^{3+}-(\text{O})(\text{OH})-\text{Mn}^{4+}$ intermediate, which serves to oxidise a nearby tyrosine residue to yield $\text{Tyr}^\bullet$.

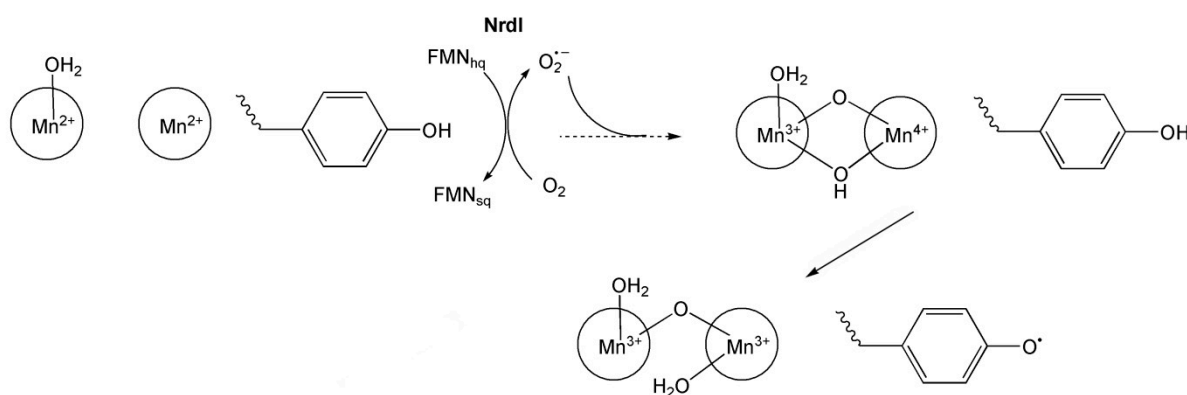


Figure 19. In the class Ib RNRs, a tyrosyl radical is generated near a di-Mn centre. This initiates the formation of $\text{Cys}^\bullet$ (Figure 18). Adapted from [389].

The crystal structure of NrdI from *Mycobacterium tuberculosis* has been elucidated [396], revealing a channel extending from the protein surface to the buried flavin mononucleotide (FMN) cofactor. This structural feature likely facilitates O_2 access to FMN, where it undergoes reduction to form $\text{O}_2^{\bullet-}$.

The use of femtosecond crystallography with an X-ray-free electron laser (to avoid photoreduction) on the NrdI complex from *Bacillus cereus* showed that the FMN moiety is sterically strained, which probably tunes its redox potential to be able to reduce O_2 [397].

There is evidence for such a mechanism from model complexes. Using $[\text{Mn}^{2+}_2(\text{TPDP})(\text{O}_2\text{CPh})_2](\text{BPh}_4)$ (TPDP = 1,3-bis(bis(pyridin-2-ylmethyl)amino)propan-2-ol, Ph = phenyl), Doyle et al. observed the formation of a peroxido- $\text{Mn}^{2+}\text{Mn}^{3+}$ species on its reaction with $\text{O}_2^{\bullet-}$ [398]. It is very likely that such a complex precedes the cleavage of the O–O bond and formation of the $\text{Mn}^{3+}\text{Mn}^{4+}$ complex shown in Figure 19 which then generates the tyrosyl

radical. Indeed, formation of both a peroxido $\text{Mn}^{2+}\text{-O-O-Mn}^{3+}$ species and the subsequent formation of an $\text{Mn}^{3+}\text{-(}\mu\text{-O)(}\mu\text{-OH)-Mn}^{4+}$ species on addition of an H^+ donor was observed with a different model compound [399].

There are many variations. The class Ic RNR from the bacterium *Chlamydia trachomatis*, for example, contains a Phe rather than a Tyr near an $\text{Mn}^{2+}/\text{Fe}^{2+}$ cluster [400,401]. Using Mn instead of Fe provides the enzyme with an oxidised $\text{Mn}^{4+}/\text{Fe}^{3+}$ cluster that has sufficient oxidising power to generate $\text{Cys}^\bullet$ [401]. Pulsed multifrequency EPR spectroscopy of the enzyme from *Geobacillus kaustophilus* provided evidence of an $\text{Mn}^{3+}\text{-(}\mu\text{-O)(}\mu\text{-OH)-Fe}^{3+}$ species [402].

The class Id RNRs from the bacteria *Facklamia ignava* and *Leeuwenhoekiella blandensis* use a similar strategy, but with an $\text{Mn}^{4+}/\text{Mn}^{3+}$ cluster to directly generate $\text{Cys}^\bullet$ without intermediate formation of $\text{Tyr}^\bullet$ [403]. In this case, Tyr is directed away from the bimetallic site, with a Lys residue occupying its usual position. The class Id RNRs do not react directly with O_2 , but instead with one equivalent of $\text{O}_2^{\bullet-}$ or two equivalents of H_2O_2 in addition to a one electron reduction. Clearly, manganese is a useful, but not essential, element to carry out the RNR reactions.

6.3.2. Manganese Peroxidase

The manganese peroxidases (MnPs) are oxidoreductase enzymes produced by white-rot fungi and some bacteria [404,405]. White-rot fungi play an important role in the degradation of solid organic matter in ecosystems [406]. The MnPs are primarily responsible for degrading lignin; their activity has been employed for treating organic pollutants and other contaminants in wastewater streams [405,407,408] and for the biological pre-treatment of biomass [409]. They may be useful for the control of mycotoxins, an important issue in global food safety [410].

A representative of the active site of a manganese peroxidase is shown in Figure 20. (There is some variability in the structure of the active site of these enzymes [404].) The active site comprises an iron porphyrin and an Mn^{2+} ion bound in an octahedral environment by one of the porphyrin propionates, two Glu, one Asp, and two H_2O molecules.

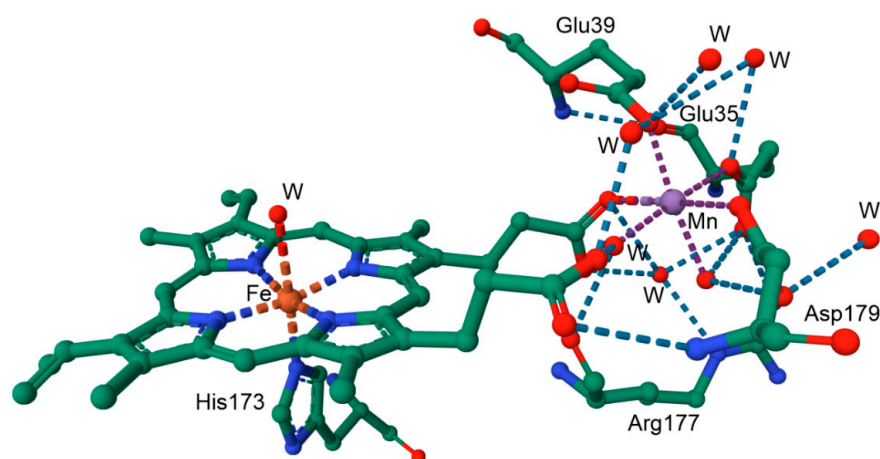


Figure 20. The active site of manganese peroxidase from *Phanerochaete chrysosporium*. W = H_2O . PDB code 3M5Q [411].

MnP features an Mn^{3+} chelate as a mobile oxidising agent. The reaction begins with the two-electron oxidation of the iron porphyrin by H_2O_2 to form an iron hydroperoxide intermediate [412]. Loss of H_2O leads to the formation of an $[\text{Fe}^{4+}=\text{O}]\text{-Porph}^{\bullet+}$ species (referred to as Compound I in the catalytic cycle of the peroxidases). Compound I oxidises one equivalent of Mn^{2+} , complexed by a suitable chelating agent (oxalate, tartrate, lactate, mal-

onate, for example), producing $[\text{Fe}^{4+}=\text{O}]\text{-Porph}$, Compound II. The Mn^{3+} is then released from the enzyme and replaced by Mn^{2+} . Compound II in turn oxidises Mn^{2+} and a second Mn^{3+} chelate is released (Figure 21). The Mn^{3+} chelate acts as a one electron oxidant for a variety of substrates in the environment, including phenols, amines, aromatics, carboxylic acids, thiols, and unsaturated fatty acids. The enzyme, as well as other enzymes such as lignin peroxidase and laccase, may be useful to tackle the degradation of polyethylene and other plastics, which is a serious environmental problem [413–415]. Manganese peroxidase enzymes are known which have Mn^{2+} -independent activity, albeit at significant slower rates [416]. Mn^{2+} is therefore important, but not essential, for the activity of these enzymes.

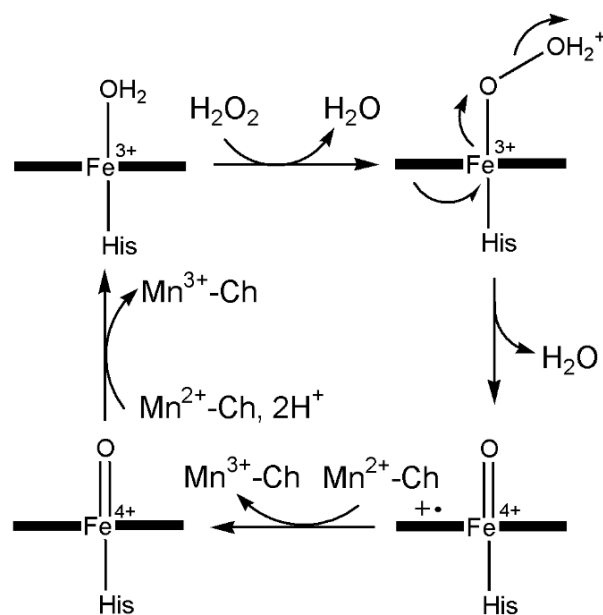


Figure 21. Oxidation of chelated Mn^{2+} to Mn^{3+} by H_2O_2 , catalysed by an iron porphyrin.

6.3.3. Manganese Lipxygenase

Lipxygenases (LOXs) catalyse the oxidation of polyunsaturated fatty acids to hydroperoxides [417]. These non-haem enzymes are widespread in nature [418,419]. The active site metal in LOXs of animals, plants, and prokaryotes contain iron; in fungi, both iron-containing and manganese-containing LOXs are found. A simplified scheme of a typical LOX-catalysed reaction is shown in Figure 22 [420].

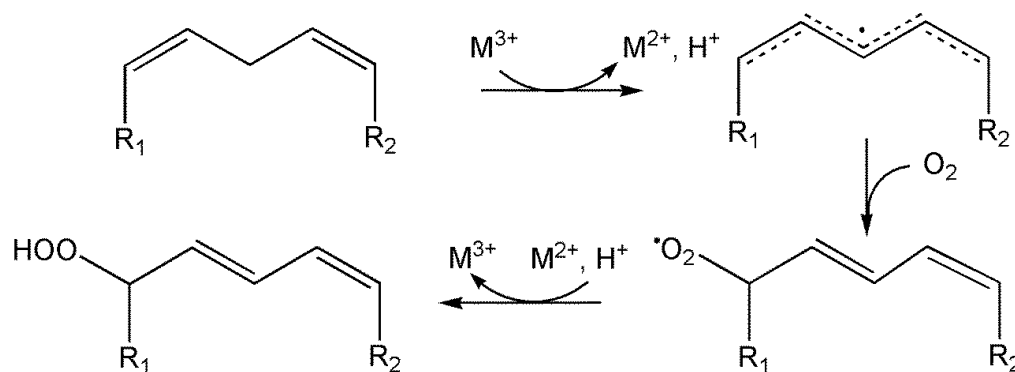


Figure 22. A LOX-catalysed oxidation of a polyunsaturated fatty acid. $\text{M} = \text{Fe}$ or Mn .

The metal binding site of Mn-LOX from *Pyricularia oryzae* is shown in Figure 23. The metal ion (Fe^{3+} or Mn^{3+}) extracts an electron from a 1,4-diene, and a base abstracts the proton. O_2 reacts with the resultant organic radical, forming a peroxy radical. This

abstracts an electron from the reduced metal ion, and picks up a proton from the base, regenerating M^{3+} ($M = Fe$ or Mn) [421].

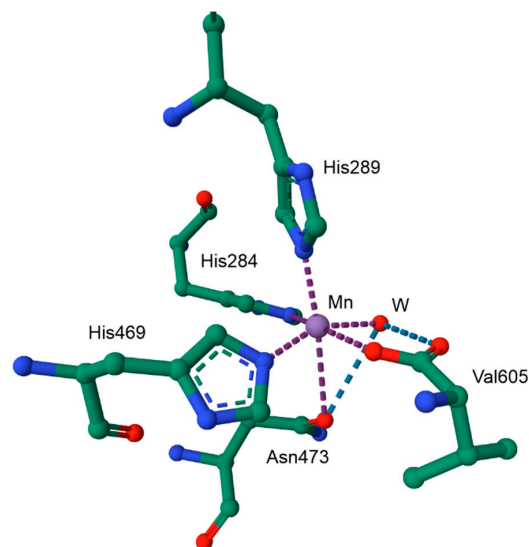


Figure 23. The binding of Mn in LOX (PDB code 5FNO) [422]. W = H_2O .

6.4. Examples of the Non-Redox Bioinorganic Chemistry of Manganese

In addition to exploiting manganese's rich redox chemistry, nature also uses it as a Lewis acid.

The glycosyltransferases and glycosidases catalyse the assembly, processing, and turnover of glycans such as cellulose [423,424]. One example of such an enzyme is β -1,4-galactosyltransferase-1. It catalyses the transfer of galactose from the donor, uridine 5'-(α -D-galactopyranosyl diphosphate) to the acceptor, *N*-acetylglucosamine, producing *N*-acetyl-lactosamine [425]. Mn^{2+} acts as a Lewis acid in the enzyme.

One possible mechanism envisages Mn^{2+} , bound to the diphosphate of the donor, helping to generate an oxocarbenium ion-like transition state in an S_N2 reaction (Figure 24) [426]. (Other mechanisms, including an S_N1 mechanism, are feasible [427].)

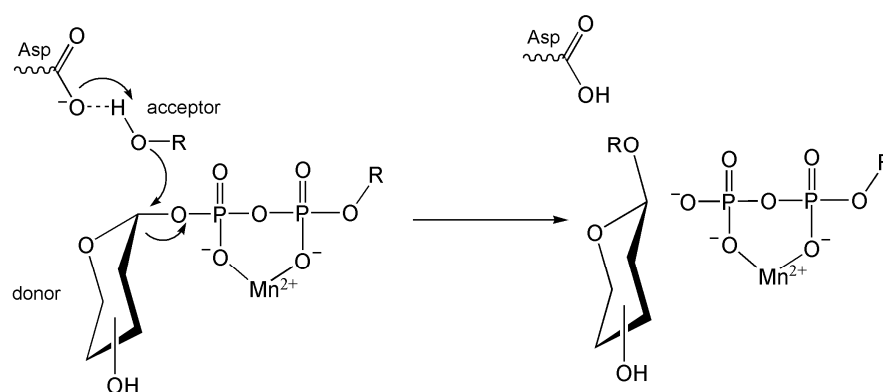


Figure 24. The Lewis base properties of Mn^{2+} exploited to enable attack of ROH to form a new β -1,4-glycosidic bond. An Asp residue in the active site is essential. Adapted from [427].

Arginase is an enzyme in the urea cycle responsible for the hydrolysis of arginine to urea and ornithine (Equation (20)) [428,429]. It performs important cellular functions in the cardiovascular system [430]. Arginase contains a binuclear Mn^{2+} site (Figure 25). The metal ions are important not only for catalysis, but also for maintenance of the proper geometry of the active site [431]. The two Mn^{2+} ions are bridged by H_2O (or OH^-). It is

this coordinated OH^- that initiates a nucleophilic attack on the substrate which is bound nearby (Figure 26); see also [428,432].

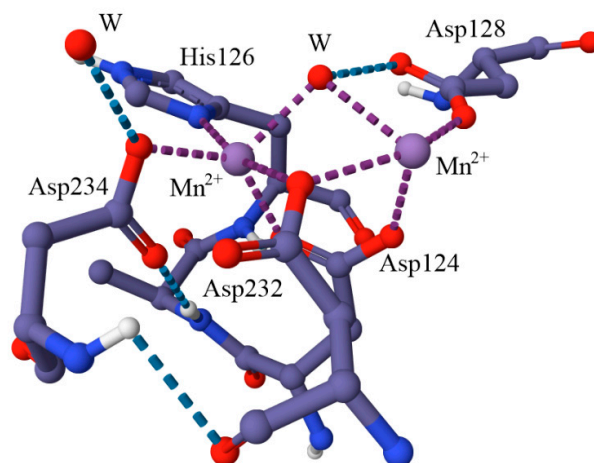
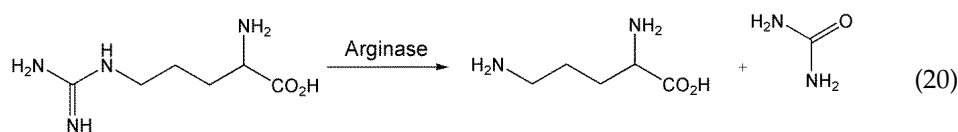


Figure 25. The bimetallic active site of arginase from rat liver (PDB code 1RLA [433]). W = H_2O (or OH^-).

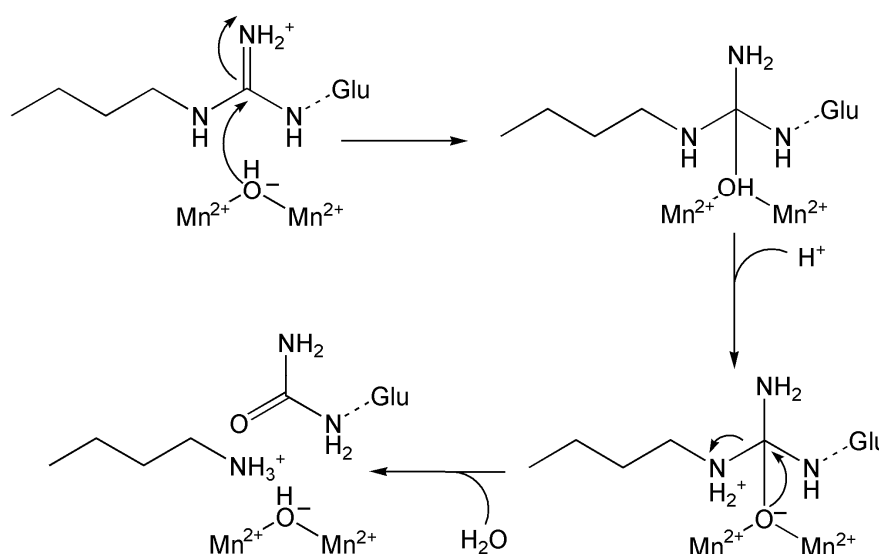


Figure 26. Proposed mechanism for the breakdown of arginine to ornithine and urea by arginase [428,432]. The attacking nucleophile is a metal-activated hydroxide.

7. Iron

Iron-containing systems fulfil many functions in biology [434–439]. Among these are the haem proteins responsible for the transport and storage of dioxygen [440–444]; electron transport [445–447]; redox partners to other enzymes [448–451]; and as catalysts in the oxidases [452–455], peroxidases [453,456–459], catalases [460–462], and the superfamily of the cytochromes P450 [453,463–466] (Figure 27); in photosynthesis [467–469]; and (using siroheme, a porphyrin with reduced A and B rings in the reduction of ni-

trite [470–472] and sulphite [472–474]). The uptake of iron, and its haemostasis, is crucial for human health [475–477].

The predominant oxidation states of iron in biological systems are Fe^{2+} and Fe^{3+} , though Fe^{4+} appears transiently during the reaction cycles of some haemoproteins. Iron-containing complexes are ubiquitous in electron transfer reactions within living organisms. Fe^{3+} is a hard metal ion, preferring hard donor ligands (e.g., hydroxyl, ether, and carboxylate groups), while Fe^{2+} , with intermediate hardness, favours nitrogen and sulphur donors. Both oxidation states exhibit diverse coordination geometries, typically four-, five-, or six-coordinate.

The redox potential of an iron centre can be manipulated by varying the ligands, the coordination geometry, and the environment of the complex, thus affording redox potentials virtually across (or at least near) the entire range of nature's ambient "electrochemical window" (in an aqueous environment, potentials between the oxidation of H_2O with evolution of O_2 and the reduction of H^+ to produce H_2 ; under standard conditions at pH 7 this is +817 mV and −413 mV, respectively.) Both Fe^{3+} and Fe^{2+} are relatively labile (rate constants for H_2O exchange typically 10^2 and 10^6 s^{-1} [478]), and this facilitates rapid ligand exchange when this is required.

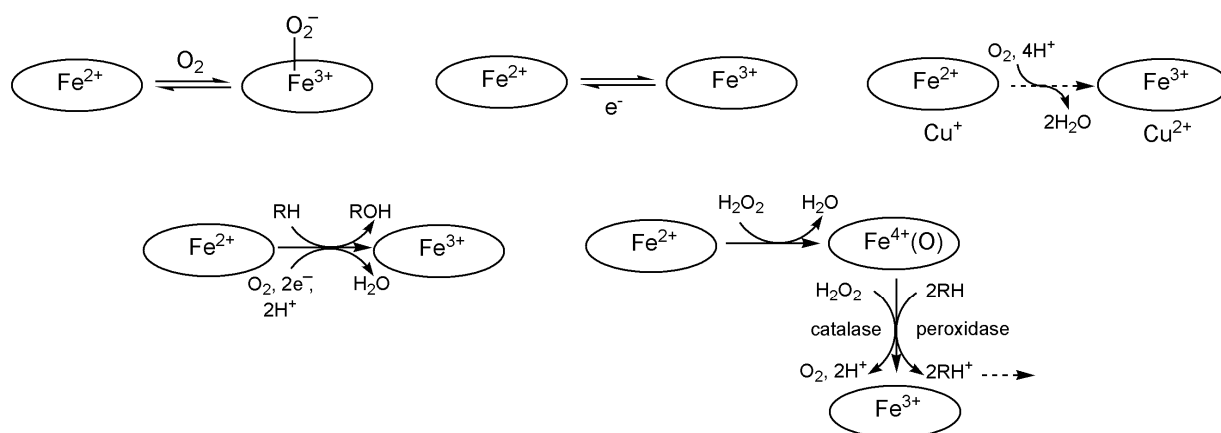


Figure 27. Examples of the roles played by haemoproteins (adapted from [479]).

Iron is abundant on Earth, constituting some 80% of its inner and outer cores [480] and ranks as the fourth most abundant element in the crust [481]. Before the Great Oxidation Event approximately 2.7 billion years ago, Fe^{2+} was abundant in Earth's oceans. However, the GOE, driven by oxygenic photosynthesis by cyanobacteria, transformed the atmosphere from reducing to oxidising [482–485]. (While the advent of the GOE is generally accepted, there is an intriguing recent report on the generating of "dark oxygen"—oxygen produced in the absence of sunlight—in the deep ocean due to a potential difference of up to 950 mV in polymetallic modules which can lead to the electrolysis of water [486].) Fe^{3+} is much less soluble than Fe^{2+} ($K_{\text{sp}} \approx 10^{-39}$, pH 7 [487]), so obtaining this essential metal from the environment was essential. Prokaryotes developed chelators such as ferrichromes and siderophores to bind Fe^{3+} and facilitate its uptake [488–490]. For example, ferrichromes are found among fungi, yeasts, and moulds; bacteria tend to use chelates based on catechols. These ligands feature hard donors to complex hard Fe^{3+} (Figure 28).

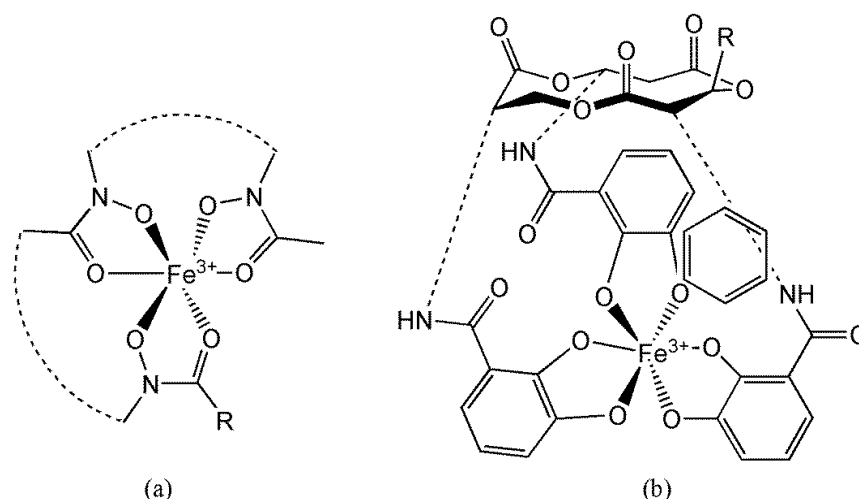


Figure 28. A schematic representation of (a) a ferrichrome chelate and (b) a catechol chelate for Fe^{3+} .

In humans, iron is absorbed in the duodenum and proximal jejunum and is transported by HSTf before being stored in ferritin within the liver, spleen, bone marrow, and other tissues [491]. This tightly regulated process is essential for maintaining iron homeostasis, a critical aspect of human health [492–494]. Iron plays an important role in ferroptosis, a regulated form of cell death [495,496].

HSTf contains two binding sites, one in the N- and the other in the C-lobe of the protein; the sites have a high affinity for Fe^{3+} ($\log K_1 = 22.7$ and 22.1 [55] or 22.5 and 21.4 [56] and $E_{1/2} < -500$ mV [497]). The binding site consists of two Tyr, His, Asp, and a carbonate anion (Figure 29). Carbonate, through hydrogen bonding, modulates the structure of the protein to ensure a high affinity for Fe^{3+} . On binding to the Tf receptor on the cell surface membrane, the acidic environment leads to loss of CO_3^{2-} , and $E_{1/2}$ is then raised by >200 mV, facilitating release of iron as Fe^{2+} , since Tf has a relatively low affinity for this ion ($\log K = 7.6$ [498,499]).

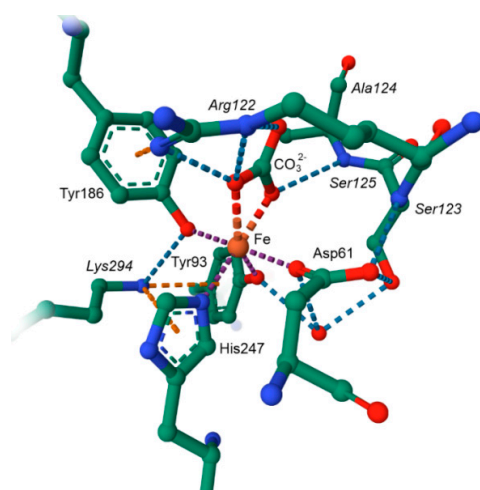


Figure 29. The iron binding site of Tf.

The haemoproteins containing iron coordinated to a porphyrin are used for the transport and storage of O_2 , for its activation, and for electron transfer. Some examples of haems are shown in Figure 30.

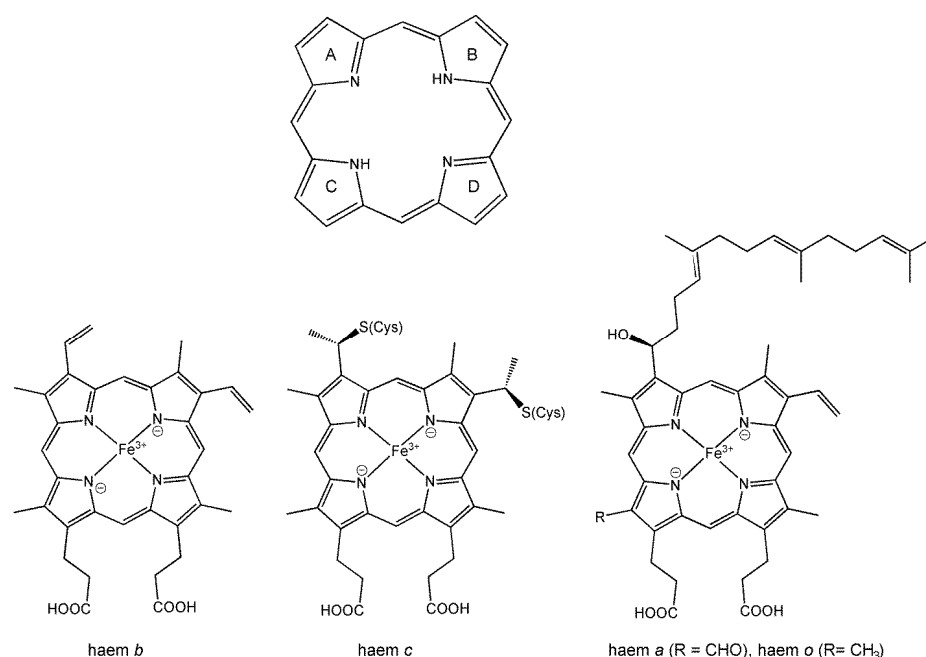


Figure 30. The basic structure of a porphyrin, a tetrapyrrole (**top**), and some common haems (iron porphyrins, (**bottom**), all shown in their ferric form). Different haems have different porphyrin side chains. Haem *c* is covalently linked to two Cys residues of the protein. The haem in haem *o* is anchored to the protein by a farnesyl group. The replacement of a methyl group in haem *o* by a formyl group in haem *a* causes an increase in the redox potential by some 180 mV [500,501]. This high potential haem is then exploited in the terminal oxidases. In haem *d*, one of the double bonds of a pyrrole ring has been reduced so the complex is a chlorin rather than a porphyrin.

There are many ways in which iron-containing proteins can be classified; this is often done to reflect the role played by the metal ion [438]: structural, metal storage and transport, oxygen storage and transport, electron transfer, or catalytic. The reader will appreciate that the bioinorganic chemistry of iron is a vast field, and only selected examples from each are discussed below.

7.1. The Transport and Storage of O₂

The mechanisms by which oxygen is carried by haemoglobin (Hb) and stored by myoglobin (Mb) in higher eukaryotes are well understood (see for example [29,502–505]). While haemoglobin has additional functions [506], its primary role in oxygen transport is complemented by myoglobin's role in oxygen storage.

Mb has a single haem binding site for O₂ and so binds O₂ in a hyperbolic manner, following a standard binding isotherm. Hb is tetramer (with subunits α_1 and α_2 , and subunits β_1 and β_2) and binds O₂ in a sigmoidal manner (Figure 31)—which means that in Hb the affinity of one site depends on whether another site is occupied or not: the behaviour is cooperative. A passage from the Christian Bible, Matthew (13:12), is sometimes quoted as an analogy: “Whoever has will be given more, and they will have an abundance. Whoever does not have, even what they have will be taken from them.” This “Matthew Effect” highlights the principle of increasing returns, which parallels the enhanced binding affinity of haemoglobin as O₂ occupancy increases.

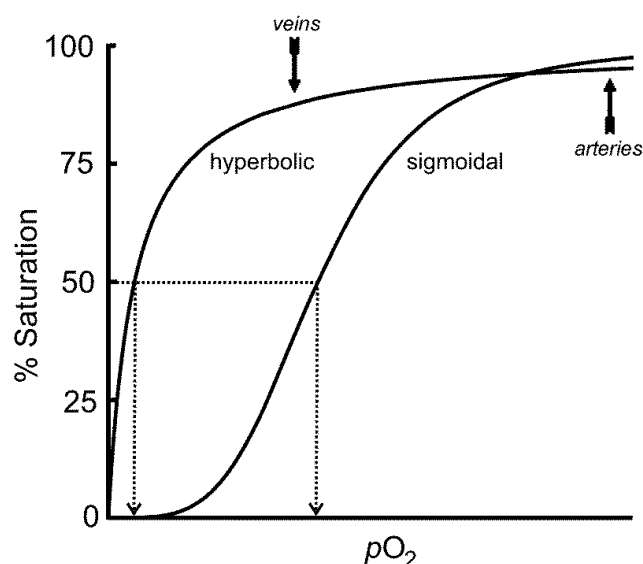


Figure 31. The binding of O_2 in a non-cooperative (hyperbolic) or cooperative (sigmoidal) manner. As an example, the dotted arrows show that half the load of O_2 can be released at a much higher pO_2 if the bonding is cooperative, which is essential for efficient delivery to bodily tissues.

The physiological advantage of cooperative binding is obvious: it would have required a much lower partial pressure of O_2 in the target tissue for the carrier system to release half its O_2 load if the binding were non-cooperative (so a non-cooperative O_2 binder would have too high an affinity for its load to be an effective transport agent). CO_2 binds to terminal amino groups of each of the four subunits of Hb, forming carbaminohaemoglobin; this lowers the affinity of Hb for O_2 and is one of the ways that CO_2 is transported from the tissues to the lungs [507].

The basis of the cooperative behaviour of Hb hinges on the differences in the coordination geometry of a deoxygenated and an oxygenated iron porphyrin. For Hb (and Mb) to bind O_2 , iron must be in its ferrous form. In deoxyHb, Fe^{2+} is five-coordinate, paramagnetic, and displaced from the mean porphyrin plane towards the proximal His ligand [508,509]. OxyHb is diamagnetic with iron in the mean porphyrin plane (see for example [510], and Figure 32). The spin change accompanying the oxygenation of Fe^{2+} incurs a very small energy penalty thanks to the flexibility of the porphyrin [511]. A distal His forms a strong hydrogen bond with bound O_2 , enhancing O_2 affinity, slowing autoxidation, and offering some protection against CO poisoning [512].

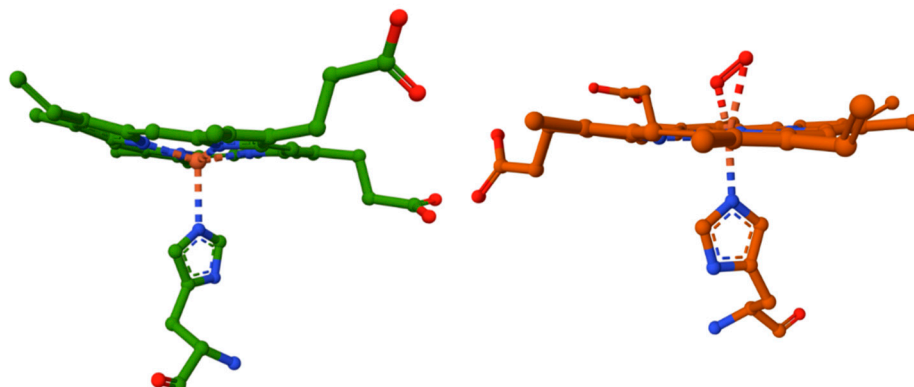


Figure 32. The crystal structures of the iron porphyrin in (left) deoxyHb (PDB: 2HBS) [509] and (right) oxyHb (PDB: 3A0G) [510].

The nature of the Fe–O₂ bond has long been the subject of considerable debate [513–517]. It has been variously described as a resonance hybrid of two structures involving O₂ coordinated to Fe²⁺ [508]; as an Fe³⁺–O₂[−] complex, in which the bond is predominantly ionic, with antiferromagnetic coupling between the unpaired electrons on low-spin Fe³⁺ and O₂[−] [513,515]; or as an intermediate-spin Fe²⁺ species antiferromagnetically coupled to ³O₂ [516,517].

Although substantial direct and indirect evidence, by analogy with cobalt–oxygen porphyrin and corrin complexes, supports the formulation of an Fe³⁺–O₂[−] complex, including vibrational spectroscopy [518,519], fluorescence emission [520], UV-vis [520], EPR [521], Mössbauer [522], and ENDOR measurements [523], other techniques suggest a more nuanced picture. X-ray Kβ emission and K-edge absorption spectroscopy, along with theoretical approaches such as TD-DFT and CASSCF calculations [524], indicate that the iron centre is best described as essentially *S* = 1 Fe²⁺, with limited charge transfer to O₂. This imparts a degree of superoxide character to the bound ligand. The Fe–O₂ bond exhibits notable double-bond character and is characterised by a three-centre, ozone-like electron delocalisation. Although the complex undergoes autoxidation to yield Fe³⁺ and O₂^{•−}, the reaction proceeds relatively slowly, with a half-life of approximately 11 h at pH 7 for MbO₂ [525].

Extensive evidence from multiple disciplines has illuminated the mechanism of cooperative O₂ binding by haemoglobin (Hb) (see, for example, [526]). In essence, cooperative binding refers to the phenomenon whereby the binding of O₂ to one haem group increases the affinity of the remaining sites for O₂, as discussed above. The Hb tetramer exists in dynamic equilibrium between a low-affinity ‘tense’ (T) state and a high-affinity ‘relaxed’ (R) state (Figure 33).

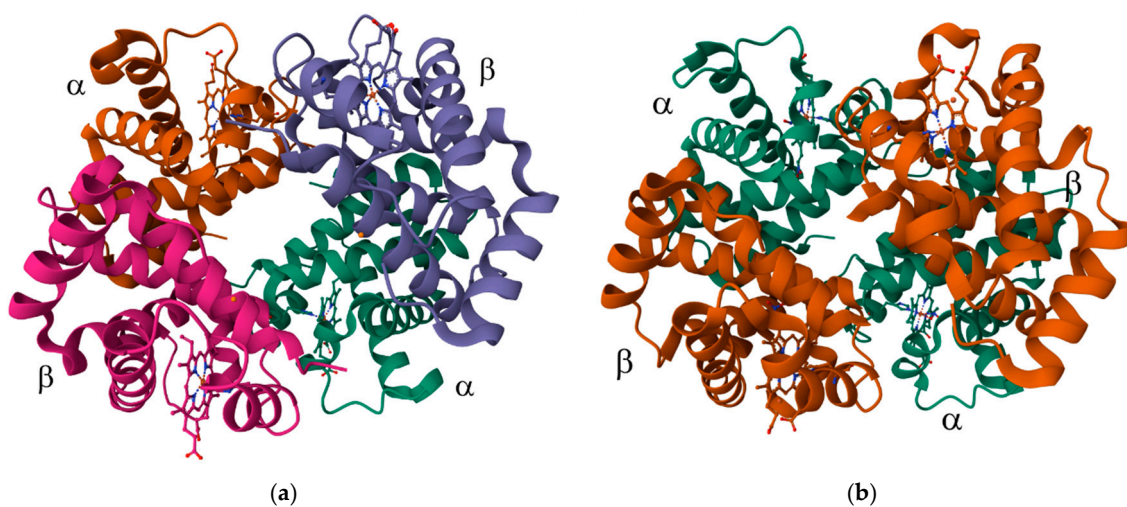


Figure 33. (a) The structure of the low-O₂-affinity T state (human deoxyHb, PDB 2HHB) [527]. (b) The structure of the high-affinity R state (human Hb PDB 3OO5) [528].

As Perutz showed [529,530], there is a set of salt bridges at the interface of the subunits in the T state. The structural changes at haem that accompany O₂ binding (Figure 32) moves the helix of the subunit, breaks the salt bridges, releasing a proton, destabilises the structure of the subunit interface between the α and β subunits, and biases the overall structure towards the R state. When the switch to R occurs, after the binding of the second O₂ molecule, the affinity for O₂ increases. A quantitative description of the Perutz mechanism was later developed by Szabo and Karplus [531]. If Hb remains in the T state, then binding is virtually non-cooperative, as demonstrated by the binding of O₂ to crystals of Hb locked in the T state [532,533]. Flexibility is essentially for the switching between states.

There are many regulators of this conformation change; endogenous regulators include 2,3-diphosphoglycerate (2,3-BPG), CO_2 , protons, and Cl^- , while exogenous regulators include inositol hexaphosphate, inositol tripyrophosphate, and vanillin [534,535].

The binding of O_2 to a ferrous porphyrin involves a change of spin state (oxyhaem is a singlet; O_2 is a triplet; and ferrous haem is a quintet). The process is therefore a spin-forbidden reaction and expected to be very slow; this would obviously be a problem for an oxygen carrier system. Fortunately, ferrous porphyrins have a number of different spin states that lie very close in energy to the ground state quintet [536]. DFT calculations [537] show that a ferrous porphyrin with a His proximal ligand is an excellent system for the binding of triplet O_2 because the seven lowest-lying spin states examined (two singlets, three triplets, a quintet, and a septet) are all within 15 kJ mol^{-1} ; this makes the probability of spin inversion high, facilitating the rapid binding of O_2 . It was estimated that the activation energy barrier for binding of O_2 is $<15 \text{ kJ mol}^{-1}$, and the rate of binding is increased by some 11 orders of magnitude compared to binding to a non-haem Fe^{2+} centre [537,538]. The porphyrin clearly plays a crucial role.

7.2. Electron Transport

The transfer of electrons from a donor to an acceptor is a fundamental process in biological chemistry [324,539,540]. Several notable examples are discussed below.

7.2.1. Cellular Respiration in Mitochondria

A key example of an electron transport chain (ETC) is that involved in mitochondrial respiration in eukaryotic cells [541,542]. In this process, the thermodynamically favourable reduction of oxygen by electron donors such as NADH releases energy. This energy is used to pump protons across the mitochondrial membrane, generating a proton gradient and establishing a proton-motive force [166]. The resulting electrochemical potential drives ATP synthesis via the ATP synthase complex, producing ATP, the cell's primary energy currency (Figure 34). The ETC comprises several iron-containing proteins essential for electron transfer.

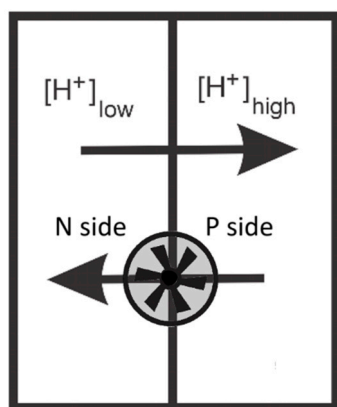
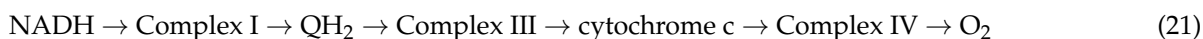


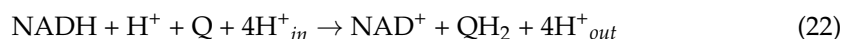
Figure 34. The energy released from the reduction of an electron acceptor by an electron donor is used to pump protons across a membrane against a proton gradient, from the side the membrane with a low $[\text{H}^+]$ (the negative or N side) to the side with a high $[\text{H}^+]$ (the positive or P side). This sets up a proton-motive force which is used by the molecular machine, ATP synthase, to drive the non-spontaneous synthesis of ATP.

7.2.2. Overview of Mitochondrial Respiration

The overall reaction for mitochondrial respiration is given in Equation (21), and a simplified overview is shown in Figure 35.



Complex I (NADH:ubiquinone oxireductase) catalyses the transfer of electrons from NADH, generated in the Krebs cycle, to ubiquinone (coenzyme Q) [543], Equation (22).



Here, *in* and *out* refer to the mitochondrial matrix and the intermembrane space, respectively. Proton pumping also occurs at Complex III (cytochrome *bc*₁) and Complex IV (cytochrome *c* oxidase). The chemiosmotic coupling across these complexes [544,545] establishes a transmembrane potential exploited by Complex V (ATP synthase) to synthesise ATP. Various models have been proposed to explain the coupling of electron transport with proton pumping [544,546–553].

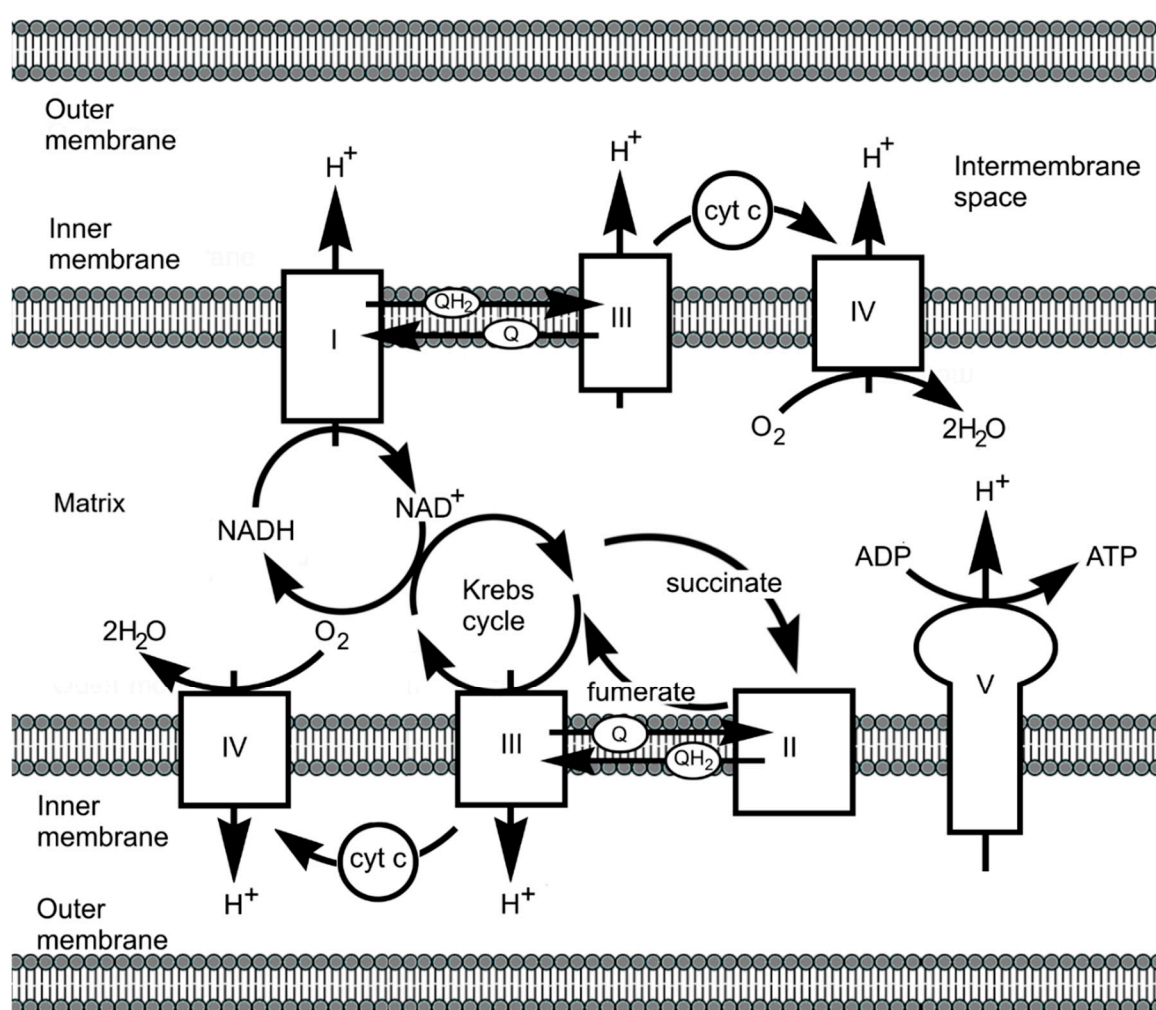


Figure 35. Schematic of the mitochondrial electron transport chain, showing Complexes I through V. Adapted from [554].

Electron donors and acceptors within the mitochondrial ETC have increasing midpoint redox potentials, $E_{1/2}$, providing the thermodynamic impetus for electron flow (Figure 36). Control over these $E_{1/2}$ values is critical to ETC function and is influenced by several factors, most notably the nature of the metal ion involved [555]. For instance, copper-containing proteins operate at the upper end of the biological redox spectrum (350–800 mV for blue copper proteins), while iron–sulphur proteins function at lower potentials (−700

to -100 mV). High-potential iron–sulphur proteins (HiPIPs) occupy an intermediate range (50 – 400 mV), and the iron porphyrin-containing cytochromes span a mid-range potential (-400 to 300 mV).

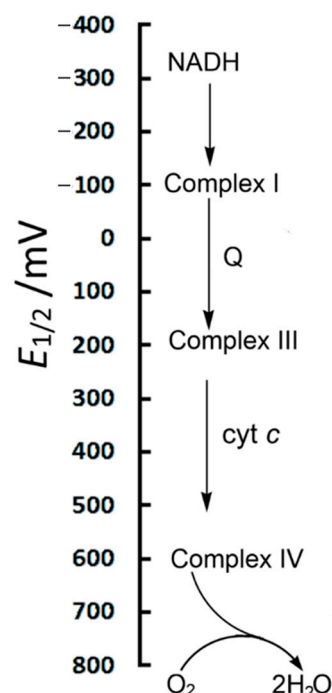


Figure 36. The cascade of electrons from NADH to O_2 in the mitochondrial ETC.

The redox potential of iron–sulphur proteins depends on their accessible oxidation states. HiPIPs, for instance, cycle between $[4Fe-4S]^{2+/3+}$, whereas ferredoxins use the $[4Fe-4S]^{1+/2+}$ couple. Determining the precise oxidation state of the individual ions within a cluster is a moot point, of course, and the clusters are best described as valence-delocalised systems [556,557].

7.2.3. Haems and Electron Transport

The ETC exemplifies the versatility of iron in biology. In Complex I, iron is coordinated within iron–sulphur clusters, coordinated in four positions thanks to the relatively large radius of sulphide ions. By contrast, in haems (iron porphyrins) of Complex III, iron is six-coordinate. The redox potentials of cytochrome *b* and cytochrome *c*₁ haems in Complex III are approximately 120 mV, -30 mV, and 240 mV, respectively [558].

Both high- and low-potential haems utilise His as axial ligands [559], yet the surrounding environments differ. High-potential haems are typically found in solvent-exposed cavities, whereas low-potential haems are shielded from solvents. This illustrates how the microenvironment modulates redox potential. Haems are also more oxygen-tolerant than iron–sulphur clusters and likely evolved later, in response to the rise of atmospheric oxygen driven by cyanobacterial photosynthesis [560]; iron–sulphur clusters, by contrast, are much more oxygen-sensitive and are thought to have emerged earlier in life's evolution [15,561].

In *b*-type haems, the porphyrin ring is embedded within a hydrophobic pocket, with axial ligands maintaining its orientation. In *c*-type haems, the porphyrin is covalently attached to the protein via thioether bonds to Cys residues [562].

7.2.4. Iron–Sulphur Clusters

Iron–sulphur clusters span a broad range of $E_{1/2}$ values, from <-600 mV (e.g., $[7Fe-8S]$ in some ferredoxins) to $> +460$ mV (e.g., $[4Fe-4S]$ in HiPIPs). These clusters are essential in

respiratory and photosynthetic electron transport [563–565] and their existence likely echoes prebiotic chemistry [566]. Typically coordinated by Cys (or occasionally His) residues, they are often buried within proteins to mitigate oxygen sensitivity. Examples of these clusters and their common oxidation and spin states are shown in Figure 37.

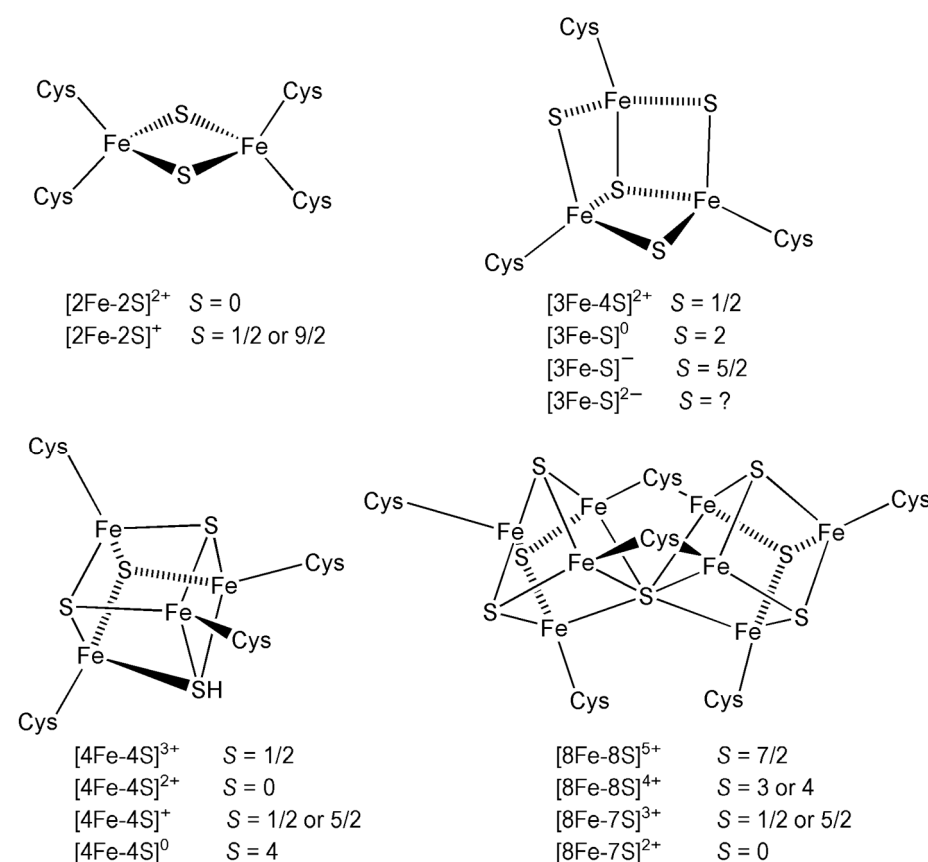


Figure 37. Some iron–sulphur clusters found in biological systems (adapted from [563]).

These clusters generally access two oxidation states and mediate one-electron transfer. In addition to electron transfer, they play catalytic roles (e.g., in aconitase), serve as signalling molecules, and contribute to magnetic sensing in birds [567,568].

Cysteine commonly acts as a terminal ligand, though in cases such as the Rieske centre of Complex III, two His and two Cys residues provide coordination [569]. The protonation state of His residues introduces pH-dependence to $E_{1/2}$, and hydrogen bonding between the cluster and its protein environment provides additional fine-tuning [570]. Rhomboidal $[2\text{Fe}-2\text{S}]$ clusters coordinated solely by Cys residues tend to have pH-independent $E_{1/2}$ values, as the ligands retain their negative charge over the physiological pH range.

Replacing two Cys ligands with His in the Rieske centre increases the potential from -240 mV (Complex I) to approximately 150 mV [571]. Such ligand substitution, combined with structural adjustments by the protein matrix [572], provides a means for precise tuning of the redox potential [573].

Though typically one-electron carriers, some iron–sulphur centres, such as the $[8\text{Fe}-(7/8)\text{S}]$ P-cluster of nitrogenase, can mediate two-electron transfer processes [574,575]. Some nitrogenase variants contain an $[8\text{Fe}-9\text{S}]$ structure, formed by two $[4\text{Fe}-4\text{S}]$ units bridged by a sulphide [576,577].

Nature demonstrates exquisite control over $E_{1/2}$ values through ligand identity, protein environment, and redox-linked protonation equilibria. Rieske centres exemplify this, with protonation of His residues significantly altering $E_{1/2}$ by as much as 450 mV [573]. By

contrast, iron–sulphur clusters coordinated by four Cys ligands exhibit lower potentials due to the influence of the four negatively charged ligands, resembling the potential of a fully deprotonated Rieske centre. The Rieske centres in Complex III, for instance, have high, pH-dependent $E_{1/2}$ values, typically around 350 mV at pH 7. On the other hand, ferredoxins in bacterial oxygenases, which participate in the catabolism of aromatic compounds, display lower $E_{1/2}$ values (around -150 mV) that appear to be independent of pH.

Electrostatic interactions between the metal centre and the surrounding protein influence both $E_{1/2}$ and the pK_a of ligands. Oxidation state and ligand protonation are often coupled, with the pK_a of the oxidised state up to five units lower than that of the reduced state [573,578]. These effects facilitate precise redox potential tuning within the ETC.

Minimising structural reorganisation during redox transitions reduces reorganisation energy (λ), a key determinant of electron transfer rates, as described by the Marcus theory of outer sphere electron transfer [579] (see Section 10.1). The value of λ is influenced by the local environment, with aqueous media increasing it [580]. Protein architecture also matters: β -sheets, being more rigid than α -helices, support a more efficient electron transfer process [580].

The importance of structure is well-illustrated by the [2Fe–2S] and [4Fe–4S] clusters of some ferredoxins, as well as the [Fe(Cys)₄] centre in rubredoxins, the iron–sulphur proteins involved in one-electron transfer in many biological reactions. In these clusters, the similar energies of Fe(3d) and S(3p) orbitals result in significant covalent character, which facilitates easy changes in oxidation state [557]. Importantly, the oxidation state changes in each iron centre do not substantially alter its essentially tetrahedral structure; changes in λ are therefore minimised [581].

It should be appreciated that the redox properties of metal centres in vivo often differ markedly from those in vitro [437,582,583], owing to influences such as the coordination geometry, protein matrix, solvent accessibility, and conformational dynamics [555,584–589].

To summarise, the key factors that control the $E_{1/2}$ of an iron–sulphur centre include the following:

- *Ligand identity and coordination*
 - The type of ligands (e.g., Cys or His) strongly influences $E_{1/2}$.
 - Cys ligands, being negatively charged, generally lower $E_{1/2}$, while harder His ligands, as in Rieske centres, raise $E_{1/2}$.
- *Protein environment and electrostatic effects*
 - The surrounding protein matrix, including electrostatic interactions and hydrogen bonding, fine-tunes the redox potential.
 - Burial within a hydrophobic environment, proximity to charged residues, and the extent of exposure to solvent significantly impacts $E_{1/2}$.
- *Protonation states and pH dependence*
 - Protonation states of coordinating ligands, especially His, introduce pH-dependent shifts in $E_{1/2}$.
 - In Rieske centres, deprotonation of His can lower $E_{1/2}$ by up to 450 mV.
- *Cluster type and delocalisation*
 - The specific iron–sulphur cluster (e.g., [2Fe–2S], [4Fe–4S]) and the accessibility of oxidation states (e.g., valence delocalisation) affect $E_{1/2}$.
 - HiPIPs exhibit higher potentials due to cycling between [4Fe–4S]^{2+/3+}, while ferredoxins operate between [4Fe–4S]^{1+/2+}.

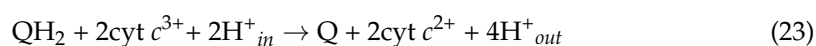
7.2.5. From Complex I to Complex IV

The entry point to Complex I, a large assembly of polypeptides with a combined mass of approximately 1 MDa, involves the reduction of flavin FMN to FMNH₂ by NADH, resulting in the production of NAD⁺. The $E_{1/2}$ of FMN within Complex I is ≈ -340 mV, significantly lower than that of free FMN (-207 mV) [590]. This illustrates once again how the redox potential of a given species can be modulated and finely tuned by its surrounding protein environment.

Electrons subsequently pass through a chain of eight iron–sulphur clusters [591,592] (perhaps the echo of prebiotic chemistry [542,593–595]), eventually reducing ubiquinone (coenzyme Q, $E_{1/2} = 100$ mV) to ubiquinol (QH₂). The QH₂ generated is then utilised by Complex III to reduce cytochrome *c* ($E_{1/2} = 260$ mV) in the intermembrane space. Finally, cytochrome *c* donates electrons to Complex IV, where O₂, $E_{1/2} = 820$ mV, is reduced to water (see Figure 35).

The iron–sulphur clusters located at the beginning of the chain exhibit $E_{1/2}$ values of about -250 mV, whereas the terminal cluster possesses the highest potential in the chain, ≈ -100 mV, as would be expected.

The reaction catalysed by Complex III is given in Equation (23), and that catalysed by Complex IV in Equation (24).



Complex II (succinate–quinone oxidoreductase) provides an alternative entry point for electrons into the electron transport chain.

One of the challenges faced by living organisms in an oxidising environment is the formation of reactive oxygen species (ROS), including singlet oxygen (¹O₂), superoxide (O₂^{•−}), H₂O₂, and especially the hydroxyl radical (OH[•]) [317,596]. Complex III exemplifies this issue. Under normal physiological conditions, it operates in a low-ROS-producing steady state. However, in the absence of oxygen (anoxia), the complex adopts an alternative steady state characterised by elevated ROS production [597]. This high-ROS state may persist for some time even after re-exposure to oxygen-rich conditions. It is important to recognise, however, that low concentrations of O₂^{•−} and H₂O₂ play essential roles in mitochondrial signalling, which modulates mitochondrial function [598]; it is the accumulation of these species that poses a physiological threat. ROS are also generated at Complex I [599].

An outline of the mechanism of Complex III is shown in Figure 38 [600–602]. The reaction catalysed by Complex III begins with the [2Fe–2S] centre of the Rieske iron–sulphur protein accepting an electron from ubiquinol QH₂, resulting in the formation of Q^{•−} and the release of two protons into the intermembrane space. The Rieske protein then transfers the electron to cytochrome *c*₁, which subsequently reduces cytochrome *c*. Meanwhile, the semiquinone radical passes its remaining electron to the low-potential cytochrome *b*_L of cytochrome *b*, which in turn reduces the high-potential cytochrome *b*_H. Cytochrome *b*_H then donates an electron to a second ubiquinone molecule, forming another semiquinone intermediate. During a second turnover of the cycle, this semiquinone is further reduced by a second electron from cytochrome *b*_H, regenerating QH₂. The binding of QH₂ on the intermembrane-space-facing side of the complex initiates another catalytic cycle. The semiquinone radicals generated in this process can react with molecular oxygen, producing O₂^{•−} [603].

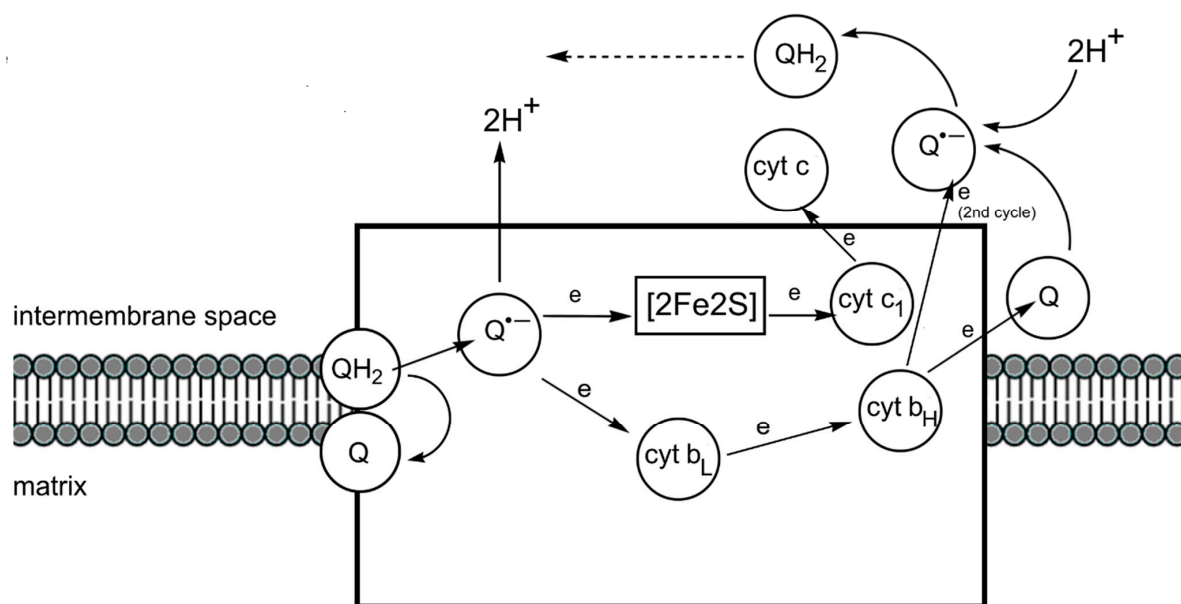


Figure 38. Schematic of the reactions of Complex III [600–602].

Mitochondrial cytochrome *c* oxidase (Complex IV) [604] contains a binuclear copper centre (Cu_A) coordinated by Cys, Met, His, and Glu residues. The complex receives electrons from cytochrome *c* ($E_{1/2} \approx 250$ mV), which are first transferred to haem *a*. The electrons then proceed to haem a_3 (homologous to haem *b* in some reductase families), which is positioned adjacent to a Cu_B centre coordinated by three His residues ($E_{1/2} \approx 800$ mV). Molecular oxygen binds in a bridging configuration between Cu_B and the iron centre of haem a_3 , and is effectively reduced by two electrons to O_2^{2-} , with Fe^{2+} and Cu^+ each donating one electron (see Figure 39). This two-electron reduction strategy circumvents the otherwise spin-forbidden nature of the direct reduction of $^3\text{O}_2$ by singlet-state NADH—a reaction that would otherwise proceed very slowly. The cooperative action of the iron and copper centres allows for a rapid, spin-allowed two-electron reduction of molecular oxygen [605].

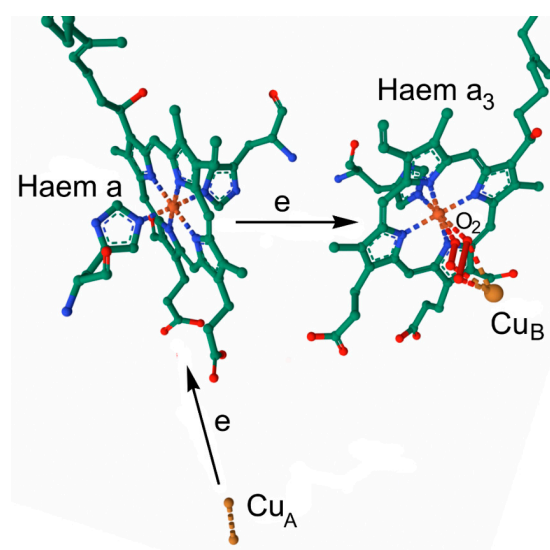


Figure 39. Electron transfer through Complex IV. Electrons flow from a dicopper centre to haem *a*, and from there to haem a_3 with nearby Cu_B . Illustrated is the structure from fully oxidised bovine heart cytochrome *c* oxidase (PDB 5XDQ) [606]. Bound O_2 (disordered over two positions) is coordinated by the iron of haem a_3 and Cu_B .

The entire catalytic cycle consists of six stages: R, A, P, F, O, and E [607] (Figure 40). Stage P can be further divided into two sub-stages, P_M and P_R. Each proton uptake by the catalytic cytochrome *a*₃-Cu_B centre is coupled with the transfer of a proton across the membrane from the high-pH (negative or N) side to the low-pH (positive or P) side (see Figure 34). Under physiological conditions, the reduction of O₂ to 2H₂O releases about 210 kJ of energy. The stoichiometric efficiency of this energy conversion into ATP synthesis ranges between 75% and 90% [607,608].

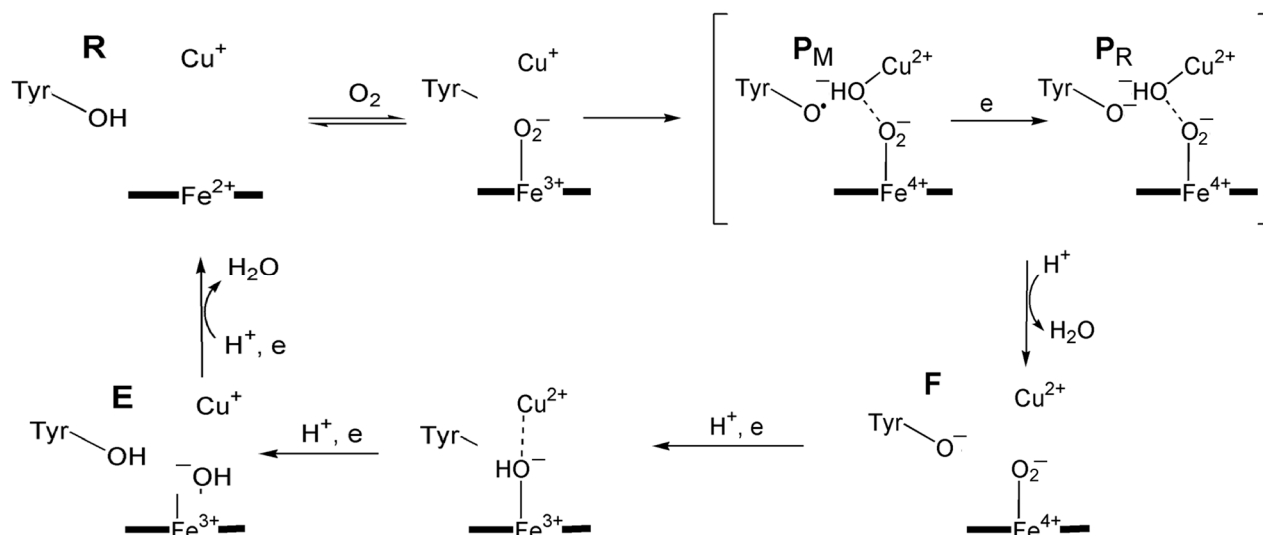


Figure 40. An outline of the catalytic cycle of cytochrome *c* oxidase (see [607] for greater detail).

7.3. An Example of an Iron Enzyme: The Cytochromes P450

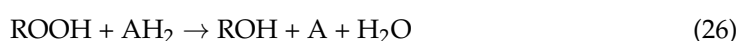
The oxy compounds of iron porphyrins play a crucial role in various enzymes, providing protection against oxidative stress and enabling the spin-forbidden reaction between ³O₂ and singlet substrates by coordinating oxygen to iron. This mechanism is one way to overcome this spin-forbidden reaction, as seen in cytochrome *c* oxidase (see Section 7.2).

The cytochrome P450 superfamily is a prime example [609–613]. These enzymes function as monooxygenases or mixed-function oxidases, using pyridine nucleotides as electron donors to facilitate the oxidation of organic substrates (Equation (25)):



They are potentially useful for biotechnology applications, especially in the design of biosensors [614]. Their ability to catalyse the formation of C-N and C-S bonds holds promise for their use in biosynthetic applications [615]. P450 is capable of catalysing oxidative dehalogenation reactions, opening up the possibility of using them to oxidise organofluorine pollutants [616]. P450 is one way in which herbivorous insects cope with toxic alkaloids that plants deploy to try to ward them off [617].

Other examples of oxy compounds of iron porphyrins include haem-containing dioxygenases, which incorporate both oxygen atoms from O₂ into organic substrates [618]; catalases, which degrade H₂O₂ into H₂O and O₂, thus protecting cells from oxidative damage [619]; nitrite reductases which reduce nitrite to nitric oxide or ammonia [471]; and peroxidases, which catalyse the oxidation of substrates using H₂O₂ or other peroxides, playing a critical role in removing phenolic compounds, peroxides, and degrading mycotoxins (Equation (26)) [620,621].



The P450 enzymes feature a thiolate group from a Cys residue as a proximal ligand to iron. This is essential for cleaving the O–O bond, facilitating substrate binding, electron transfer, and ensuring proper protein folding [622]. Electron transfer in the P450 catalytic cycle is mediated by a flavoprotein or an iron–sulphur protein [612,623].

The generalised mechanism of the P450s is shown in Figure 41; precise details vary depending on the enzyme in question and, in particular, the substrate RH [612]. Clearly, the efficient transfer of electrons from NAD(P)H to the haem centre is essential to ensure catalytic efficiency [624].

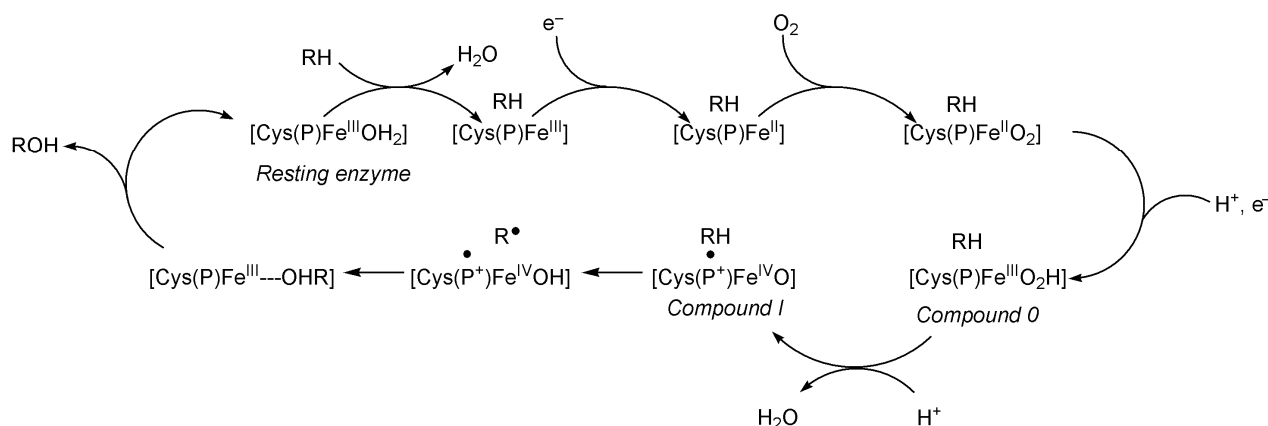


Figure 41. A generalised mechanism of the cytochromes P450. In the scheme, (P) represents the porphyrin equatorial ligand.

There is experimental evidence for some of the intermediates: a crystal structure of the oxy-ferrous intermediate, $[\text{Cys(P)Fe}^{\text{II}}\text{O}_2]$, is available [625]; the occurrence of Compound 0, $[\text{Cys(P)Fe}^{\text{III}}\text{O}_2\text{H}]$, in the cycle is well established [626–629]; and the occurrence of Compound I, $[\text{Cys(P}^+\text{)Fe}^{\text{IV}}\text{O}]$, which features the porphyrin as a radical cation and iron in the +4 oxidation state, has been demonstrated kinetically and spectroscopically [630,631].

Another important iron-containing enzyme is nitrogenase. It contains a multi-iron and molybdenum active site [632]. Found in nitrogen-fixing bacteria and archaea, nitrogenase catalyses the conversion of N_2 to NH_3 and plays a crucial role in the global nitrogen cycle. Its structure and the mechanism of the reaction will be discussed elsewhere when the biological chemistry of the second and third row of the d block is addressed.

8. Cobalt

Cobalt is not a very common element in the Earth's crust (15 to 30 ppm) [633]. That Co^{3+} plays a small, albeit important, role in biology—and that it features as the active site of several enzymes—may be surprising. Virtually all six-coordinate complexes of Co^{3+} are low-spin, and low-spin Co^{3+} and Cr^{3+} are the outstanding examples of kinetically inert metal ions from the first row of the d block because of the large ligand field contribution to the activation energy [634,635]. The residence time of H_2O in $\text{Co}^{3+}_{\text{aq}}$ [636] and $\text{Cr}^{3+}_{\text{aq}}$ [637] is of the order of 10^5 s, compared to 10^{-5} s for $\text{Fe}^{3+}_{\text{aq}}$ and $\text{Ti}^{3+}_{\text{aq}}$ [638] and 10^{-8} s for $\text{Co}^{2+}_{\text{aq}}$ [639]. Clearly cobalt in biology is involved in some unusual chemistry that is perhaps not readily accessible by other enzymatic systems based on, for example, iron porphyrins.

The most prominent role played by Co^{3+} is in the enzymes containing a cobalt corrinoid (a derivative of cyanocobalamin, $[\text{CNCbl}]$, vitamin B_{12}) as cofactor (Figure 42) [394,640–643]. These include methionine synthase, essential for the biosynthesis of methionine [644]; methylmalonyl-coenzyme A mutase, which is essential for the metabolism of amino acids (isoleucine, valine, methionine, and threonine), of odd-chain fatty acids, and of cholesterol [645]; ribonucleotide reductase, which converts ribonucleotides to deoxyribonucleotides in some bacteria [646];

and reductive dehalogenases, found in certain anaerobic bacteria, which break down halogenated hydrocarbons [647]. The structure and electronic properties of the cobalt corrinoids have been studied by a wide range of experimental and computational techniques (for recent examples, see [394,648–663]).

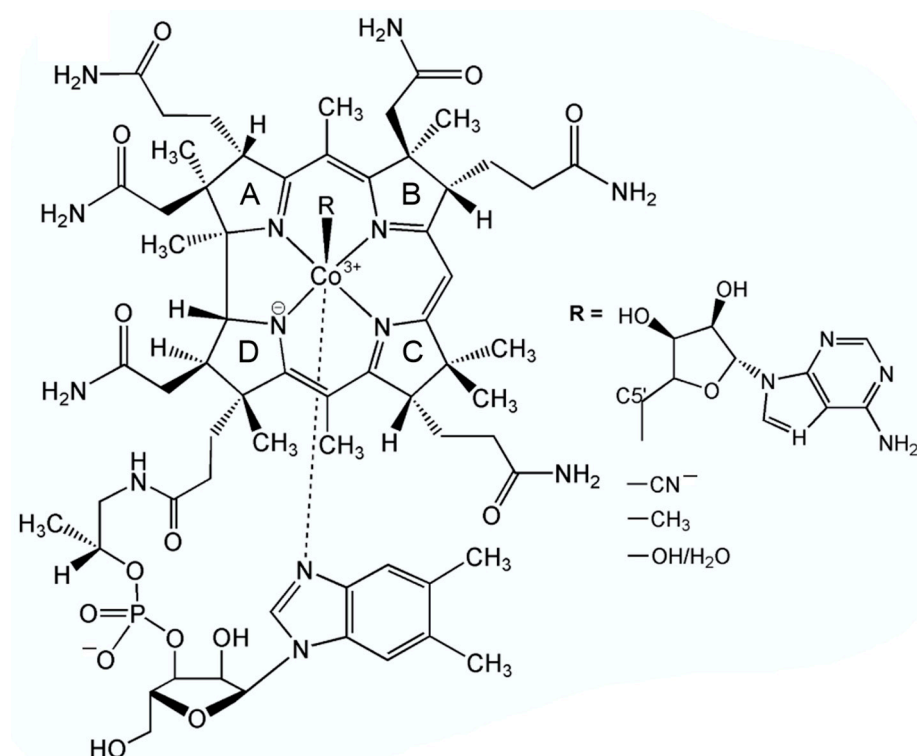


Figure 42. The structure of the cobalamins, the corrinoids that contain a nucleotide loop that ends in a base that coordinates the lower (α) face of the corrin. The usual base is 5,6-dimethylbenzimidazole, dm-bzm. In adenosylcobalamin, [AdoCbl], or coenzyme B₁₂, the ligand occupying the upper (β) coordination site, R = 5'-deoxyadenosyl. Cyanocobalamin or vitamin B₁₂ itself, [CNCbl], has R = CN⁻. Methylcobalamin, [MeCbl], has R = CH₃⁻; in aquacobalamin, or vitamin B_{12a}, [H₂OCbl]⁺, R = H₂O and in hydroxocobalamin, [HOCbl], R = OH⁻. There are derivatives of B₁₂ with different β ligands [394].

[CNCbl] itself plays no role in biology and is an artefact of the isolation of B₁₂ produced by bacterial fermentation [664]. It must be converted into its active forms before being used in its biological roles. Bacteria, archaea, and eukaryotes, but not plants, require B₁₂ for growth [665–667]. That plants do not require B₁₂ suggests that cobalt's role in biology is, in theory, not essential.

The biological chemistry of cobalt probably dates to the origins of life [668,669]. There is recent evidence from phylogenomic analyses of the proteins involved in B₁₂ synthesis that B₁₂ metabolism was retained in the last common land plant ancestor [670], but plants now have an alternative methionine synthase that does not require B₁₂. There is also evidence that corrin synthesis probably dates back to the last universal common ancestor of all life forms (LUCA) and that corrin synthesis played a role in the origin of free-living cells [671].

Higher organisms have to absorb B₁₂ from their diet or procure it in symbiotic relationships [672] and there is a complex absorption and transportation system for B₁₂ and its derivatives [673–676]. B₁₂ is produced industrially by bacterial fermentation with an annual global market value of some \$280 M [677,678] and is widely used in vitamin supplements and in pharmaceutical preparations.

Much has been written about cobalt corrinoid chemistry (see for example [394,679,680]), but there are several cobalt-containing enzymes not based on B₁₂. In these the metal ion typically activates H₂O to catalyse a hydrolytic reaction [640,681–684]. These enzymes include

methionine aminopeptidase [685], prolidase [686], nitrile hydratase [687], thiocyanate hydrolase [688], glucose isomerase [689], methylmalonyl-CoA carboxytransferase [690], aldehyde decarboxylase [691], lysine-2,3-aminomutase [692,693], and bromoperoxidase [694]. There are also relatively recent discoveries on the role of cobalt corrinoids as photo-receptors in light-dependent gene regulation [695–698] (prompting an investigation into the photolytic properties of organocobalamins [697,699–701]), as B₁₂-sensing riboswitches in, for example, *Mycobacterium tuberculosis* [702], and in modulating the structure of microbial communities and their response to toxic substances in the human gut [703–705] and in marine environments [706]. We will focus on the biological chemistry of the cobalt corrinoid-containing enzymes.

Cobalt in excess is toxic to humans [707–709], but B₁₂ deficiency has severe health consequences including anaemia, neurological consequences, birth defects, and cell ageing [710–714]. B₁₂ is also thought to protect DNA against genotoxicity by xenobiotic metabolites [715]. So-called “antivitamins-B₁₂” are of interest for their ability to induce B₁₂ deficiency in organisms, from the resistant bacteria that plague some hospitals, to laboratory mice [716–720]. They contain for example a large organic ligand such as PhCH₂CH₂- or an alkynyl ligand (R-C≡C-); or a metal other than Co such as Rh; or a corrin ring with an interrupted conjugation (referred to as a stable yellow corrinoid). They resist the biological B₁₂ tailoring that leads to the formation of the cobalamin active forms. They may even prove to be useful as growth inhibitors of tumour cells.

The inherent inertness of Co³⁺ is altered by coordination with the corrin macrocycle, which features a 13-atom, 14-electron π -electron delocalised system. In cobalt corrinoids, Co³⁺ undergoes ligand substitution reactions at relatively fast rates [394], suggesting that the corrin macrocycle significantly enhances the lability of the metal ion. This effect may arise from the corrin imparting a degree of labile Co²⁺-like character to the cobalt centre. The challenge of assigning a formal oxidation state to a metal ion in a complex of ligands with a delocalised electronic system has long been recognised [721–723]. The corrin ligand, in effect, is nature’s solution to overcoming the inertness of Co³⁺.

The biosynthesis, uptake, metabolism, and biochemical reactions of the cobalamins in biological systems is well-documented ([666,674,679,724–739]). An overview of the biochemistry requiring a cobalt corrinoid is shown in Figure 43 [737].

As mentioned, vitamin B₁₂ itself is biologically inactive and must be converted to the active form, methylcobalamin ([MeCbl]) or 5'-deoxyadenosylcobalamin ([AdoCbl]), which both feature a Co–C bond. This is the key to the chemistry of the B₁₂-dependent enzymes. The Co–C bond in Co³⁺–R[−] can undergo heterolytic (Equations (27) and (28)) or homolytic cleavage (Equation (29)):



The reactions are readily mimicked with many protein-free alkyl cobalt corrinoids and are an intrinsic property of these organometallic complexes [394,740]. Strategies that mimic B₁₂ organometallic chemistry have been widely explored and applied in synthetic organic chemistry [741,742].

The biological chemistry of cobalt centres primarily on the Co³⁺ | Co⁺ and Co³⁺ | Co²⁺ couples, with Co⁴⁺ appearing to play no known role. Biological reactions involving homolytic cleavage of a Co–C bond must be tightly regulated, as Co²⁺ corrinoids are readily oxidised to Co³⁺. Moreover, reactions with strong oxidants such as H₂O₂ can disrupt the conjugated π -system of the corrin macrocycle, resulting in the formation of stable yellow corrinoids [394,743,744].

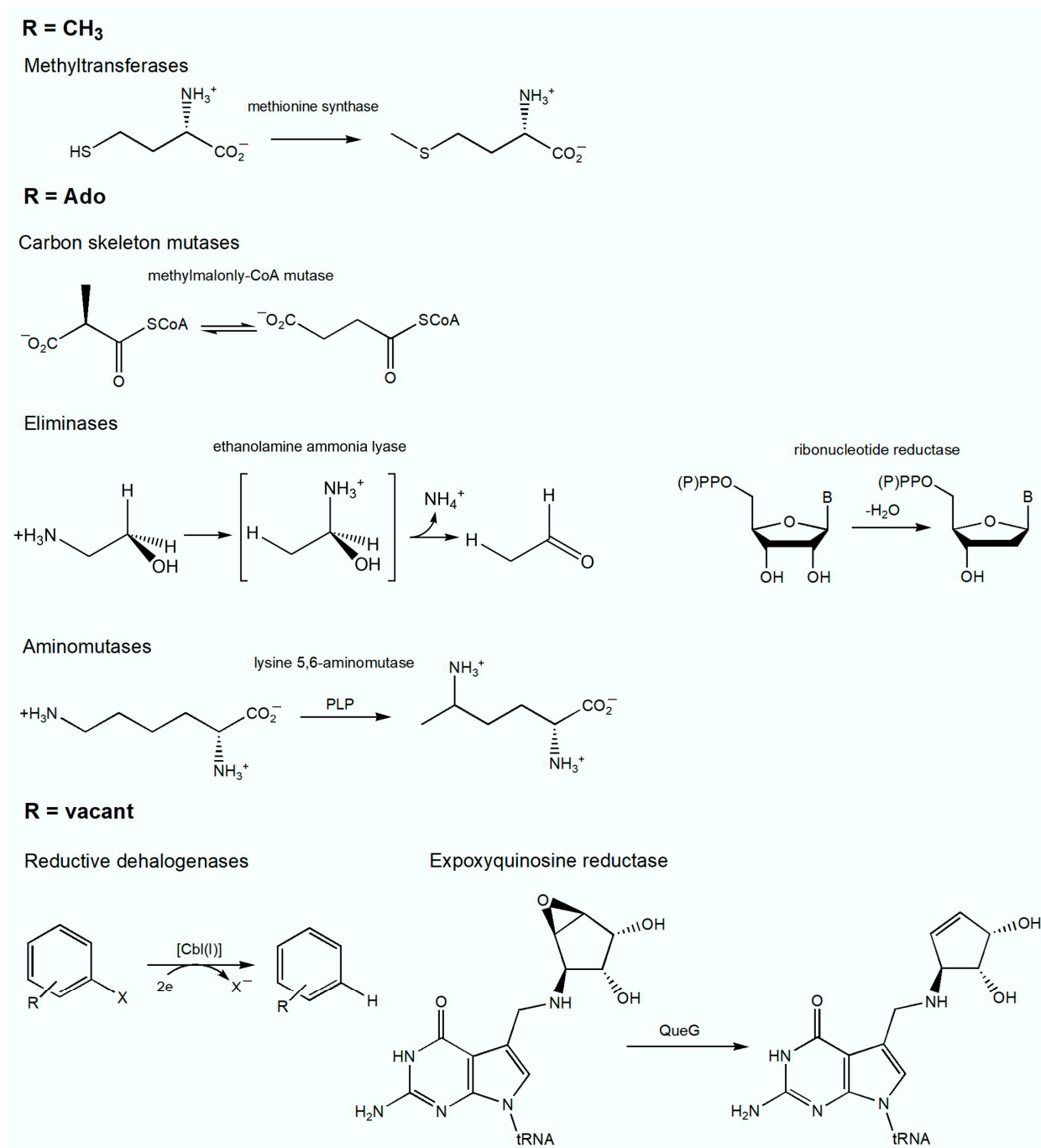


Figure 43. Examples of cobalamin-dependent proteins as defined by the nature of the upper ligand (adapted from [737]). [MeCbl]-dependent methyl transferases catalyse the transfer of a methyl cation to a substrate. [AdoCbl]-dependent enzymes include carbon skeleton mutases, eliminases, and aminomutases. [AdoCbl] is also involved in light-dependent gene regulation of the carotenoid (Car) biosynthetic operon via the transcriptional regulator CarH. A third type of Cbl-dependent enzymes, which includes the reductive dehalogenase PceA and the queuosine biosynthetic enzyme QueG, do not have an upper axial ligand and are denoted as “open”-Cbl-dependent enzymes.

Both [MeCbl] and [AdoCbl] are comparatively resistant to reduction due to the electron-donating properties of the axial alkyl ligand of the cobalt centre (−1.36 V for [MeCbl], pH 7 [745,746]; −1.07 V for [AdoCbl] [747], in contrast to 0.200 V for the $\text{Co}^{3+} | \text{Co}^{+}$ and −0.647 V for the $\text{Co}^{2+} | \text{Co}^{+}$ couple of $[\text{H}_2\text{OCbl}]^{+}$ [748]).

These redox potentials lie well outside the ambient thermodynamic stability window of water, which spans from −0.41 V (for the $2\text{H}^{+} | \text{H}_2$ couple) to 0.82 V ($\text{O}_2 | \text{H}_2\text{O}$, 25 °C,

pH 7). This demonstrates how coupling redox processes to subsequent chemical transformations enables circumvention of the thermodynamic constraints imposed by an aerobic aqueous environment, an essential strategy for harnessing the strong reducing power of the Co^+ state.

Given that the biological reactivity of cobalt corrinoids hinges upon homolytic or heterolytic cleavage of the $\text{Co}-\text{C}$ bond, it follows that this bond must be relatively weak. The bond dissociation energy for heterolysis of the $\text{Co}-\text{CH}_3$ in $[\text{MeCbl}]$ is 155 kJ mol^{-1} [749]. That for homolysis in $[\text{AdoCbl}]$ is even more modest, about 125 kJ mol^{-1} [750,751].

Humans possess two enzymes that utilise cobalamin chemistry. Methionine synthase (MS), which employs $[\text{MeCbl}]$, is involved in the regeneration of tetrahydrofolate via the synthesis of methionine from homocysteine. Methylmalonyl-CoA mutase, which requires $[\text{AdoCbl}]$, catalyses the conversion of methylmalonyl-CoA to succinyl-CoA.

8.1. The $[\text{MeCbl}]$ -Dependent Enzymes

These enzymes catalyse the heterolytic cleavage of the $\text{Co}-\text{CH}_3$ bond to form the “supernucleophile” cob(I)alamin, $[\text{Cbl(I)}]^-$ [752], and a methyl carbocation that is transferred to a nucleophilic acceptor. An example is methionine synthase, MS (called MetH in bacteria). It receives the cobalt corrinoid cofactor (as aquacobalamin or hydroxocobalamin) from the human cobalamin trafficking protein MMADHC (also called CblC) [753,754]. This is then reduced to $[\text{Cbl(II)}]$ and methylated by methyltetrahydrofolate ($\text{CH}_3\text{-THF}$), forming methylcobalamin, $[\text{CH}_3\text{Cbl}]$, the active cofactor of the enzyme.

During enzyme catalysis, MS catalyses the transfer of a methyl group from 5-methyltetrahydrofolate ($\text{CH}_3\text{-THF}$) to homocysteine (Hcy) for methionine synthesis [755–758] (Figure 44) and achieves a rate enhancement of between 10^6 to nearly 10^8 times compared to realistic protein-free methyl transfer reactions [759]. Impairment to MS activity has severe health consequences [760]. See [761] for a detailed discussion of the chemistry of MS.

The SAM-dependent methyltransferases are also capable of catalysing many other reactions [762] including, for example, the fluoromethylation of unactivated carbon centres through intermediate formation of $[\text{CH}_2\text{FCbl}]$ [763], a challenging reaction in synthetic organic chemistry; the methylation of high-value small molecules; the transfer of other alkyl groups; the targeted labelling of oligonucleotides and proteins [764]; and Friedel–Crafts alkylations [765].

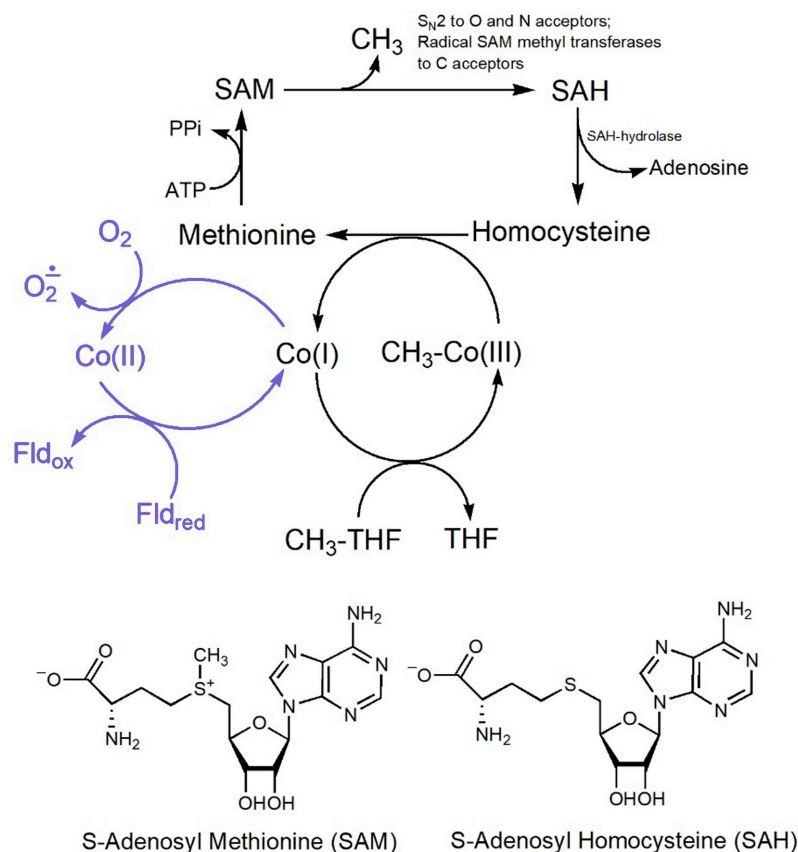
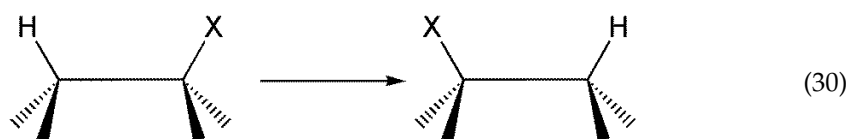


Figure 44. The transfer of a methyl group from 5-methyltetrahydrofolate to homocysteine, producing methionine, catalysed by methionine synthase. Occasionally, Co(I) is oxidised by O₂ or reactive oxygen species (ROS) to inactive cob(II)alamin, [Cbl(II)] [766] (in blue). Function is restored by reduction of Co(II) to Co(I) by methionine synthase reductase (MSR), a diflavin reductase. It uses both FAD and FMN as intramolecular electron carriers during catalysis [767].

8.2. The [AdoCbl]-Dependent Enzymes

The [AdoCbl]-dependent enzymes catalyse the exchange of a hydrogen atom on one carbon atom of the substrate with an electron-withdrawing group X on a neighbouring carbon atom (Equation (30)). The reactions hinge on the homolysis of the Co-C bond between the metal and the Ado ligand, and formation of an Ado[•] radical [768].



There are three classes of [AdoCbl]-dependent enzymes [732,769]. The Class I enzymes, the mutases, catalyse a carbon skeleton rearrangement in which the migrating group is a carbon fragment. An example is methylmalonyl-CoA mutase (MCM); see Figure 43. AdoCbl is synthesised from [Cbl(II)] in a reductive adenosylation reaction catalysed by adenosyltransferase, which also acts as an escort and delivers AdoCbl to MCM [770].

The Class II enzymes include the eliminases [771], which catalyse the migration and subsequent elimination of a hydroxyl or amino group (the reaction catalysed by ethanolamine ammonia-lyase is shown in Figure 43), and ribonucleoside-triphosphate reductase [772], which catalyses the reduction of ribonucleoside triphosphates (Figure 43). Ribonucleotide reductase catalyses a reduction reaction, rather than a rearrangement

reaction, although the removal of the 2'-OH group of the substrate is like the reactions catalysed by the eliminases. Finally, the Class III enzymes, the aminomutases, catalyse the migration of an amino group to an adjacent carbon (the reaction of lysine-5,6-aminomutase on DL-lysine is shown in Figure 43).

In the Class I and Class III enzymes, the dmbzm base of [AdoCbl] is displaced from the α coordination site by a His residue of the protein (referred to as the “base-off/His-on form”), and the nucleotide loop is buried in a hydrophobic pocket. [MeCbl] is bound in a similar manner in methionine synthase [773]. In the Class II enzymes, [AdoCbl] is bound with the axial dmbzm ligand coordinated to the metal (the “base-on/His-off form”). That the chemistry catalysed by the [AdoCbl]-dependent enzymes is carried out with either dmbzm or His as an axial ligand suggests that the identity of the axial ligand in cobalamin chemistry is of minor importance (but see below). There is both experimental evidence [394,774] and evidence from theoretical calculations [775] indicating that the bond between cobalt and its proximal ligand is quite flexible and has little influence on the Co–C bond dissociation energy [776,777].

The loss to the Ado moiety from the AdoCbl-dependent enzymes and formation of hydroxocobalamin leads to loss of enzyme activity, and organisms have strategies to reactivate the enzymes [778].

The reaction of MCM is used to illustrate a typical reaction catalysed by an [AdoCbl]-dependent enzyme (see Figure 43). A schematic of the reaction is shown in Figure 45.

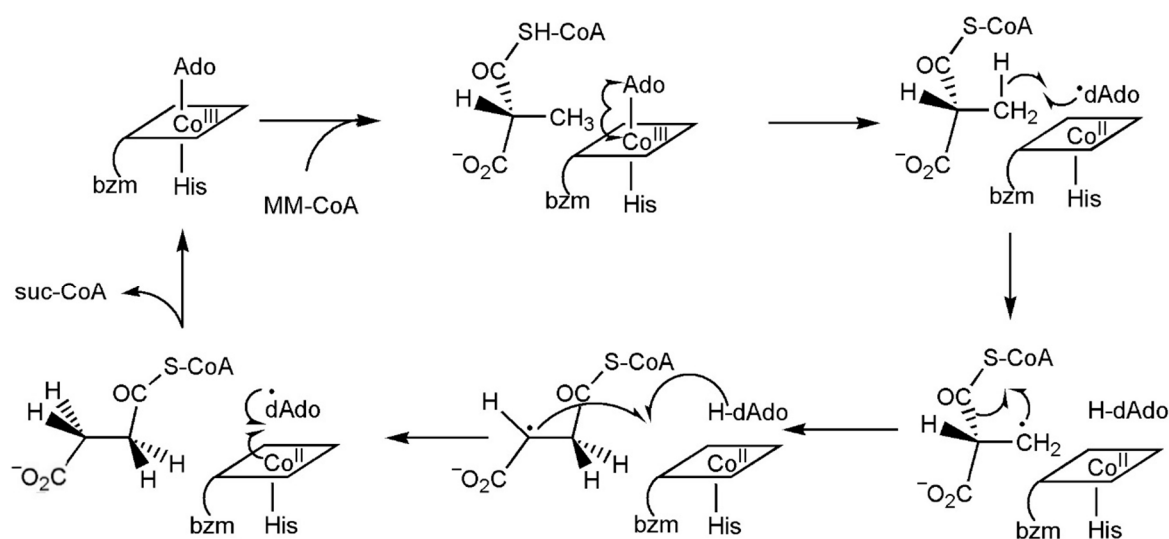


Figure 45. The reaction catalysed by methylmalonyl-coenzyme A mutase (MCM).

In the first step of the reaction, the Co–C bond between cobalt and the adenosyl moiety is cleaved, producing an Ado• radical [779,780]. This radical abstracts a hydrogen atom from the substrate, generating a substrate radical [781]. Remarkably, the enzyme accelerates this reaction by approximately 12 orders of magnitude [750,782,783]. The mechanism behind this extraordinary rate enhancement has been a subject of debate and speculation [784–791], and it appears to vary between enzymes. For instance, in ethanolamine ammonia-lyase, time-resolved, full-spectrum EPR analysis shows that $\Delta H^\ddagger$ is identical to that in aqueous solution, but $\Delta S^\ddagger$ is ten times larger; the catalysis is entropy-driven [792] and is probably the consequence of changes in the interactions between the active site residues and the Ado ligand when the enzyme binds the substrate [793]. Similarly, entropy drives the formation of the Co(II)-cysteine thiyl radical ion pair in ribonucleotide triphosphate reductase [794]. However, in methylmalonyl-CoA mutase, the driving force is primarily enthalpic [779].

Several factors contribute to this rate enhancement [795]. First, stabilisation of the post-homolysis products, Co^{2+} and the $\text{Ado}^\bullet$ radical, through van der Waals and electrostatic interactions with the protein, plays a significant role ([796] and references therein). Additionally, the proximal histidine ligand is part of a hydrogen-bonded network known as the catalytic triad (DXHXGXK or DXHXGXN in 2-methyleneglutarate mutase) [797–799]. Proton uptake by the catalytic triad reduces charge donation by the proximal ligand, so stabilising the Co^{2+} state. Other contributing factors include [800] the following: (i) a reduction in the bond dissociation energy of the Co–C bond in the enzyme compared to free [AdoCbl]; (ii) moderate stabilisation of the protein when the cofactor is in its dissociated form; and (iii) steric interactions with protein residues which deform the coenzyme, decreasing its bond dissociation energy.

8.3. The Reductive Dehalogenases

Reductive dehalogenases (RDases) catalyse the removal of halogen atoms from organic substrates (Figure 46) [801,802]. These enzymes are capable of degrading both naturally occurring [647] and anthropogenic organohalogen compounds present in the environment [803]. To date, no homologous enzymes have been identified in humans.

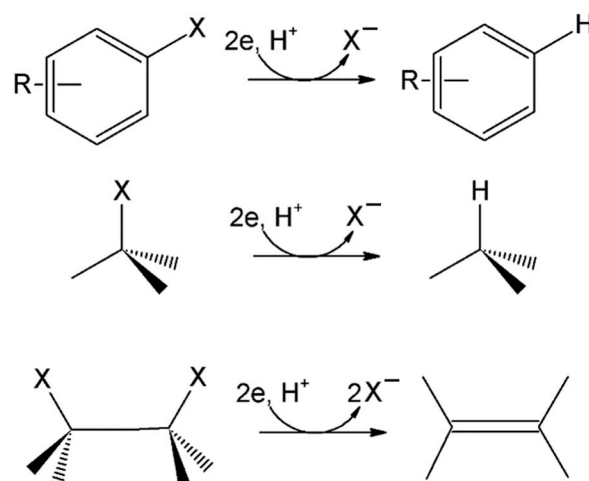


Figure 46. Some examples of reactions catalysed by the RDases.

Several mechanistic pathways have been proposed for RDase-catalysed reactions, all of which feature Co^+ as the nucleophile that initiates an attack on the substrate [801,804].

Typically, RDases contain two iron–sulphur clusters—either two [4Fe–4S] clusters or one [4Fe–4S] and one [3Fe–4S]—in addition to a cobalt corrinoid cofactor, in which a water molecule (or hydroxide ion) occupies the β axial coordination site of cobalt. The electron source for these reductive reactions can include reduced metal ions such as iron, tin, or zinc [805], or metal-containing porphyrinoid cofactors such as cobalamin, coenzyme F_{430} , or haemin [805]. However, for the majority of RDases, the identity of the physiological electron donor remains unresolved [647].

8.4. Why Corrin, and Why Cobalt?

Perhaps the first question that arises when contemplating the biological chemistry of B_{12} and its derivatives is why the corrin ring, an apparently much more complex structure than, for example, a porphyrin, has been retained in nature [806]. And why use a kinetically inert metal ion as the prosthetic group of an enzyme?

The biosynthesis of the corrins and the porphyrins initially follows a common pathway [807,808], which begins with the tetramerisation of the biological pyrrole porphobilinogen [809] and the formation of the tetrapyrrole uroporphyrinogen III. The paths

then deviate to the porphyrins and the corrinoids. Many bacteria are able to synthesise corrinoids while primitive anaerobes such as acetogens and methanogens are unable to synthesise porphyrins; this suggests that the biosynthesis of corrins has its origins in pre-biotic chemistry and actually predates that of porphyrins ([810] and references therein). Many of the apparently complex structural elements that characterise a corrin, including the ring contraction that leads to the direct link between rings A and D, arise quite readily when a corrin precursor, a corphinoid, is coordinated to a smaller metal ion such as Co or Ni, but not Fe [811]. So, the occurrence in nature of the seemingly complex macrocyclic structure of a corrin in nature is probably not surprising.

As mentioned above, the corrin appears to confer on inert Co^{3+} some measure of labile Co^{2+} character—much more so than does a porphyrin, for example, since ligand substitution reactions at a Co^{3+} corrin are much faster than at a Co^{3+} porphyrin [394]. Co^{3+} corrinoid complexes are six-coordinate; Co^{2+} complexes are usually five-coordinate; and Co^+ complexes are four-coordinate. However, in each case the metal is retained in a predominantly low-spin state (see [394] for a discussion of the ground state electronic configuration of these complexes). Crystallographic evidence shows that reduction of six-coordinate low-spin Co^{3+} to five-coordinate low-spin Co^{2+} has virtually no effect on the average bond length between the metal and the N donors of the corrin [394]. There is consequently little influence on the reorganisation energy, one of the major factors that controls the rate of an electron transfer reaction [579]. This clearly contributes to an efficient conversion between (formally) Co^{3+} and Co^{2+} in the [AdoCbl]-dependent enzymes and undoubtedly plays a role in the fast kinetics of their reactions.

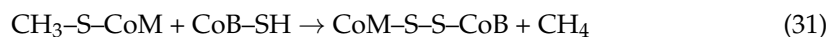
In iron porphyrins, the spin state of the metal ion depends on its oxidation state and its coordination number. Six-coordinate Fe^{2+} and Fe^{3+} porphyrins are usually low-spin ($S = 1/2$), whereas when five-coordinate, the metal ion is typically high-spin ($S = 5/2$) [812,813]. In four-coordinate Fe^{2+} porphyrins, the delocalisation of electron density between the metal centre and the π system of the porphyrin stabilises the intermediate-spin state ($S = 3/2$) over the high-spin state [814]. Moreover, porphyrins show a dependence of the metal– N_{porph} bond lengths on the spin state of the metal [815]. The Fe^{3+} analogue of B_{12} can be reduced to Fe^+ , but cannot be methylated [816]. A ferric corrin therefore could not catalyse the reactions catalysed by [MeCbl]. A Fe^+ porphyrin is highly reactive and can be generated only transiently [817]—for example, electrochemically [818,819].

The Fe^{3+} – CH_3 bond dissociation energy in a porphyrin is only 88 kJ mol^{-1} [820], significantly weaker than the Co – CH_3 bond in [MeCbl]. So, while a metal–carbon bond that is not too strong is important, it cannot be too weak. The Fe – C bond in complexes of the type $[(\text{porph})\text{Fe}^{3+}\text{--R}^-]$, R = ethyl, butyl) is readily homolysed in the presence of CO or CO_2 to form an intermediate Fe^{2+} – CO or Fe^{3+} – CO_2^- complex which is then attacked by the caged alkyl radical [821]. One of the likely reasons for the use of a Co – C bond in biology is its resistance to hydrolysis, which is important in an aqueous environment [822]. Theoretical calculations show that a Co – C bond is between 33 and 48 kJ mol^{-1} more resistant to hydrolysis than an Fe – C bond [812].

Clearly, iron porphyrin compounds cannot perform cobalt corrinoid-type chemistry, rationalising the occurrence of cobalt in biology.

Organometallic chemistry in biology, while not common, is by no means confined to the chemistry of the cobalt corrinoids. Some examples are the M cluster of nitrogenase (Fe – C – Fe) [823–825]; Fe – CO in [Fe]-hydrogenase [826,827], Fe –Ado in the radical *S*-adenosyl methionine (SAM) intermediate omega [828,829]; and the C cluster of carbon monoxide dehydrogenase (CODH, Ni – $\text{C}(\text{O})\text{O}$ – Fe) [830–832]. Nor are methyl transfer reactions in biology confined to the cobalt corrinoids. For example, F_{430} , a Ni hydrocorphin, is

the active site in methyl-coenzyme M reductase (MCR) which catalyses the reaction shown in Equation (31). This is an important reaction in the global carbon cycle [833–835].



In the reaction, Ni^+ acts as the attacking nucleophile on the S-CH₃ bond of CoMSCH₃ [834,836,837], in a manner analogous to the action of Co^+ in the [MeCbl]-dependent enzymes.

As discussed in Section 7, an important function of six-coordinate iron porphyrins in biology is to act as electron transfer agents in electron transport chains. The reorganisation energy for the $\text{Fe}^{3+} | \text{Fe}^{2+}$ couple in such a case is a very modest 8 kJ mol^{−1}; for the $\text{Co}^{3+} | \text{Co}^{2+}$ couple in a cobalt corrinoid with two axial His ligands this is an untenable 197 kJ mol^{−1} because of the location of the unpaired electron density in $3d_z^2$ [812]. Cobalt corrinoids would not be suitable for this function. DFT calculations also show that for the oxidation states +1 through +3, and for virtually all axial ligands investigated, cobalt corrin and iron porphyrin systems are thermodynamically more stable than iron corrin and cobalt porphyrin systems [812], offering an explanation for the matching of the metal to the macrocycle in nature [813].

An important function of iron porphyrin-containing proteins is the transport and storage of O₂ (Section 7). This is chemistry that cannot be performed by the cobalt corrinoids. At low temperatures, cob(II)alamin will indeed bind O₂, forming what is essentially a $\text{Co}^{3+}\text{-O}_2^-$ complex; however, near-room temperature cob(II)alamin is rapidly oxidised to Co^{3+} [838,839]. Cob(I)alamin is very rapidly oxidised by O₂. Co^{2+} porphyrins, and cobalt-reconstituted Hb and Mb [840,841], can reversibly bind O₂ [840,842–849], but substituting Fe-protoporphyrin IX with a cobalt porphyrin in human adult Hb decreases its O₂ affinity by over a factor of 10 [848].

Living systems could probably have evolved in the total absence of cobalt; nevertheless, cobalt corrinoids fulfil an important, albeit niche, role in nature. A memorable—if somewhat simplistic—parallel has been drawn between iron porphyrins and cobalt corrinoids: the first act as reversible oxygen carriers, the latter as reversible free radical carriers [850,851].

9. Nickel

Nickel is not a particularly abundant element in the Earth's crust (≈ 75 ppm), but it is an essential trace element for various prokaryotes, algae, fungi, and plants [10,837,852–854]. Its role as a trace element in animals, including humans, however, remains to be fully established [10].

Whilst an essential trace element for some life forms, in high concentrations nickel is toxic and there is considerable concern about the effect of high levels of nickel from anthropogenic sources [10,855–860]. For instance, nickel can displace Mg^{2+} from the active site of GTPase, rendering the enzyme inactive [10,855].

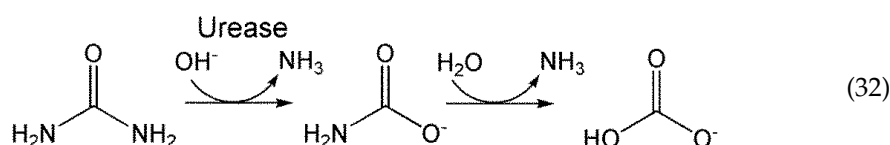
In biological systems, nickel predominantly exhibits oxidation states of +1, +2, and +3 [861]. Nickel's primary biological function is as a redox-active metal or as a structural anchor for nucleophiles, such as OH^- , at the active site of specific enzymes. These have been found in archaea, bacteria, plants, and primitive eukaryotes, and include acireductone dioxygenase, CO-dehydrogenase, glyoxalase, lactate racemase, methyl-coenzyme M reductase, Ni-superoxide dismutase (Ni-SOD), [NiFe] hydrogenase, prolyl cis-trans isomerase, and urease [10,854].

To illustrate nickel's biological roles, we will examine specific Ni-containing enzymes: one where nickel serves a structural role, two where its redox properties are exploited, and

one where its function is not yet fully understood. The general mechanism of superoxide dismutases (SODs), discussed in Section 6, likely applies to Ni-SOD as well [333,862].

9.1. Urease

Urease plays an important role in the global nitrogen cycle, where it catalyses the decomposition of urea to ammonia and carbamate (Equation (32)), with a rate enhancement of some 10^{14} or higher [863], making it one of the most efficient enzymes known. It is also used by pathogens to infect host cells [864], and the increase in pH can have a negative effect on human health [865]. *Helicobacter pylori* [866,867], *Staphylococcus aureus* [868], and *Mycobacterium tuberculosis* [869] are examples of pathogens that contain urease. Urease-utilising species have evolved an elaborate delivery system to ensure that toxic Ni is delivered to the enzyme active site without diffusing into the cytoplasm [867,870–873].



It has been known since the 1970s that urease requires two Ni atoms in each of its subunits for catalytic activity [874]. The number of subunits in urease varies across different organisms [875]. In the active site of urease, two Ni^{2+} ions are positioned approximately 3.5 Å apart, bridged by a hydroxide ion and a carbamylated Lys residue. The active site structure from *Klebsiella aerogenes* (KAU) (PDB 1FWJ [876]) is shown in Figure 47, along with a schematic representation.

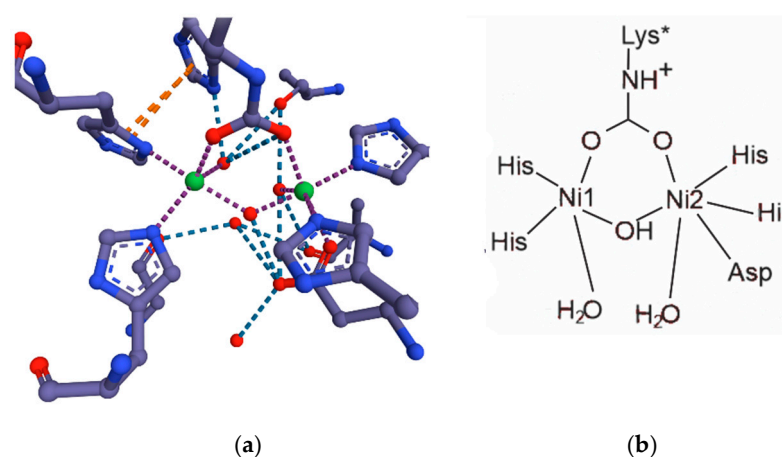


Figure 47. (a) The active site of the urease from *Klebsiella aerogenes* (PDB 1FWJ [876]). (b) Schematic of the active site. Lys* is a carbamylated Lys residue.

In this structure, Ni1 is coordinated by two His residues and a water molecule, while Ni2 is coordinated by two His residues, a monodentate Asp, and H_2O . Additionally, a third water molecule is located near the active site. These water molecules are typically labelled W1, W2, and W3. When urea binds at the active site, it displaces W1 and W3, and its carbonyl group coordinates with Ni1. The specific coordination mode of urea—whether it binds monodentately through its carbonyl group or through one of its NH_2 groups to Ni2—has been a subject of debate [877–880].

Either the coordinated OH^- or deprotonated W2 acts as the nucleophile, attacking bound urea. The Ni^{2+} ions in urease do not perform a redox function. Instead, they serve as Lewis acids, playing key roles in (i) coordinating and anchoring the substrate; (ii) increasing the electrophilicity of the urea carbonyl group; and (iii) stabilising the attacking nucleophile.

Over the years there have been several proposals for the mechanism of the reaction, as well documented by Mazzei et al. [875]. Computational modelling (QM and QM/MM MD [881]) favours—but of course does not prove—the mechanism shown in Figure 48, involving bidentate coordination of urea. See [880] for alternative proposals based on the results from the urease activity of models of the active site.

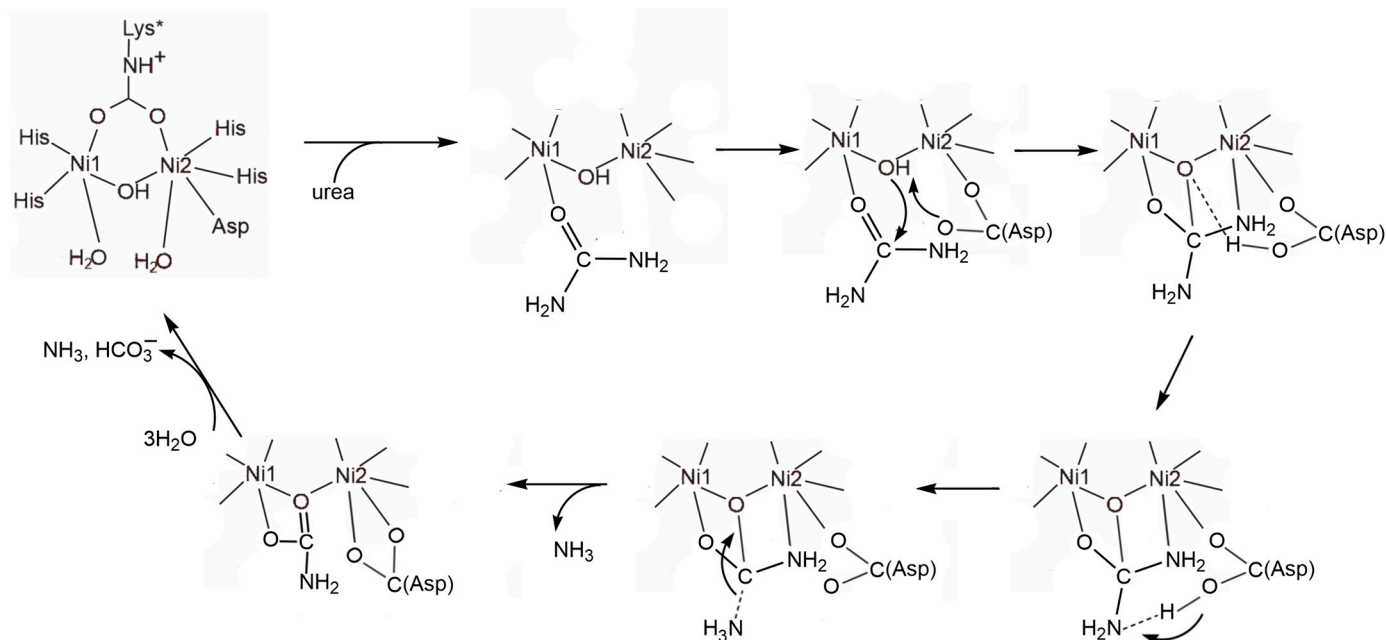
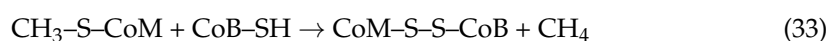


Figure 48. A possible mechanism for the conversion of urea to ammonia and carbamate by urease. Carbamate spontaneously decomposes to bicarbonate and ammonia.

However, as pointed out by Mazzei and co-workers [882], understanding the dynamics of an enzyme requires knowledge of its entire conformational space. Using cryo-EM methods, they demonstrated the importance of the mobility of a mobile flap in the urease from *Sporosarcina pasteurii* in flipping between the inactive open-flap state and the closed-flap, catalytically efficient, state of the enzyme. Both a Cys and His residue on the flexible flap are essential for catalytic function [883,884].

9.2. Methyl-Coenzyme M Reductase

Methyl-coenzyme M reductase (MCR) catalyses the terminal step of methane formation in the energy metabolism of all methanogenic archaea, and the terminal step in the anaerobic oxidation of methane; these are important reactions in the global carbon cycle [833–835,885,886]. In the reaction, methyl-coenzyme M ($\text{CH}_3\text{-S-CoM}$) and coenzyme B (CoB-SH) are converted into methane and a heterodisulphide (Equation (33)).



The enzyme also catalyses the reverse reaction, the anaerobic activation, and oxidation of CH_4 , which entails the cleaving of a C-H bond. The active site contains a Ni hydrocorphin, F_{430} (Figure 49).

In the reaction catalysed by MCR, Ni must be in its +1 oxidation state to function effectively [887,888]. Ni^+ acts as a nucleophile, and one of the key roles of the hydrocorphin macrocycle is to stabilise and make this oxidation state accessible. In F_{430} , the standard reduction potential of the $\text{Ni}^{2+} | \text{Ni}^+$ redox couple is -0.65 V [889]. Although this is more negative than the -0.41 V of the $2\text{H}^+ | \text{H}_2$ couple at pH 7 (the lower limit of nature's "electrochemical window"), it is significantly higher than, for instance, the -1.3 V observed

in a Ni-isobacteriochlorin complex. This illustrates how the structure of a macrocycle can fine-tune the redox potential of a metal complex, bringing it into a useful biological range.

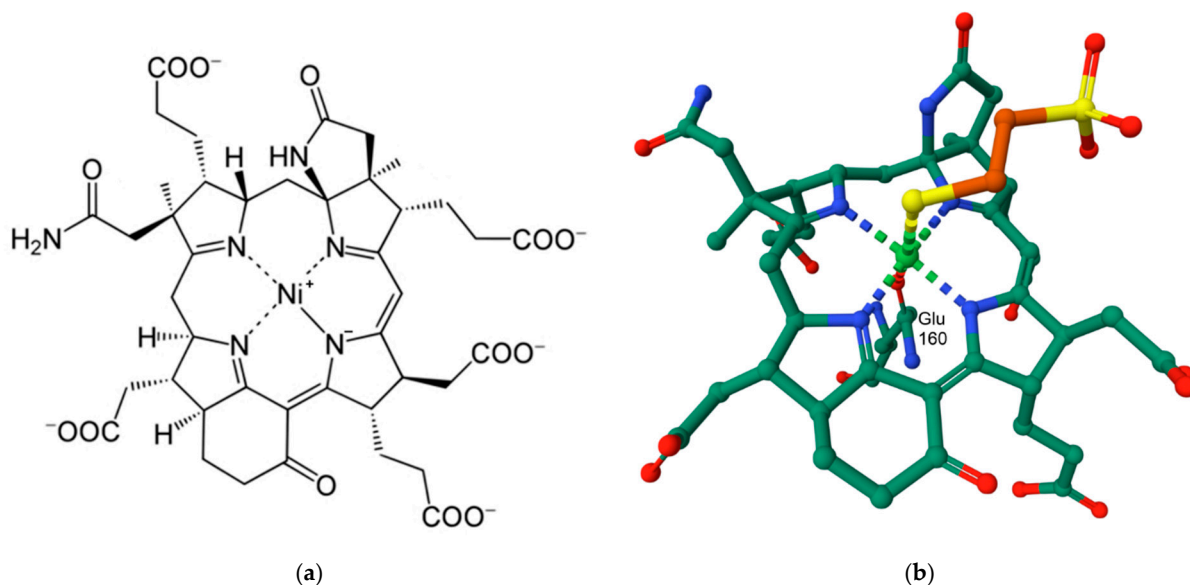


Figure 49. (a) Structure of a nickel-containing hydrocorphin, F₄₃₀. (b) F₄₃₀ from the crystal structure of methyl-coenzyme M reductase from *Methanosarcina barkeri* (PDB 1E6Y [890]) with Glu160 and the substrate mimic thioethane-sulphonic acid as axial ligands.

Several structural features of F₄₃₀ facilitate the reduction of Ni²⁺ to Ni⁺. First, the macrocycle is a monoanion, in contrast to porphyrins and isobacteriochlorins, which are dianions. Second, there is an electron-withdrawing carbonyl group attached to the C15 meso position (Figure 49), which further aids the reduction of Ni²⁺ [641]. When Ni²⁺ is reduced, the added electron density resides on the metal, forming an $S = 1/2$ species. This differs from Ni porphyrin or Ni chlorin complexes, where the reducing equivalent is mainly located on the macrocycle, weakening the metal's ability to act as a nucleophile. In MCR the nucleophilic activity of Ni⁺ is crucial, allowing it to behave similarly to cob(I)alamin, which serves as a “supernucleophile” in methylcobalamin-dependent chemistry (see Section 8).

The requirement for the Ni⁺ state makes the enzyme highly sensitive to oxidation by O₂ or other oxidants. To address this, methanogens employ an ATP-dependent enzymatic system to reactivate the enzyme when it is oxidised [888].

Several mechanisms have been proposed for the MCR-catalysed reaction [836,891–893], with current evidence supporting the mechanism depicted schematically in Figure 50 [834,836,837,894]. In the oxidised form of the coenzyme, Ni²⁺ is axially coordinated by a Gln residue [890,895,896] (Figure 49), but it likely becomes four-coordinate in the reduced, Ni⁺-active form. The conversion of the oxidised Ni²⁺ form to the active Ni⁺ form is facilitated by a multicomponent [4Fe–4S] protein [897]. An electric field aligned along the CH₃-S-CoM thioether bond facilitates its homolytic bond cleavage [898], emphasising that it is not only the structure of the active site, but of the protein as a whole, that is important for the activity of an enzyme.

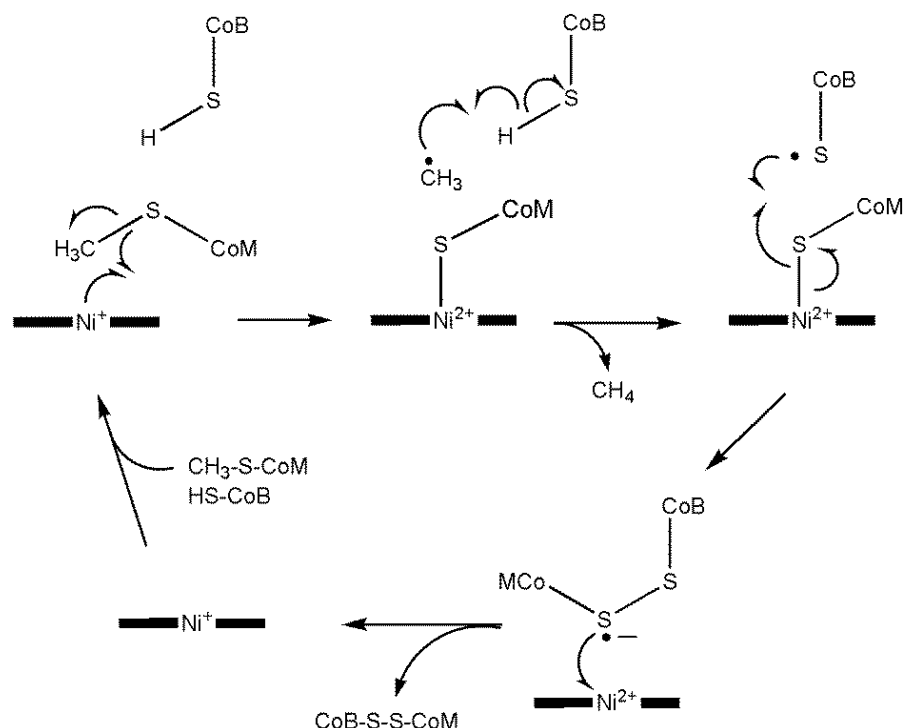
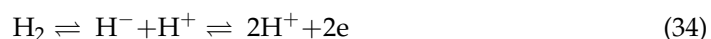


Figure 50. A possible mechanism of the reaction of $\text{CH}_3\text{-S-CoM}$ and CoB-SH catalysed by methyl-coenzyme M reductase.

9.3. NiFe Hydrogenases

Hydrogenases are enzymes that catalyse the reversible oxidation of H_2 [899–903]. They typically contain a bimetallic active site ($[\text{NiFe}]$ or $[\text{FeFe}]$) and catalyse the reaction shown in Equation (34).



It is speculated that Complex I of the mitochondrial electron transport chain may have evolved from a primordial hydrogenase [542,595]. There is considerable interest in these enzymes as it may be feasible to exploit them—or model their chemistry—in biofuel cells to produce H_2 [902,904].

The NiFe active site features an Fe ion coordinated by a CO and two CN^- ligands. Two thiolates of Cys residues bridge the two metals ions, and Ni is terminally coordinated by two Cys residues [905]. The CN^- ligands are synthesised from carbamoylphosphate by maturases and the CO arises from N^{10} -formyl-tetrahydrofolate [906]. Details from the crystal structure of the NiFe hydrogenase from *Cupriavidus necator* are shown in Figure 51 [907].

The formal oxidation states of the metals of the active site in the reduced (active) form of the enzyme are Fe^{2+} and Ni^{2+} . During the catalytic cycle, Fe remains in the low-spin, +2 oxidation state ($S = 0$) [899] while Ni cycles between (formally) the oxidation states +3, +2, and +1 (Figure 52) [908]. In addition, an electron transport chain of iron–sulphur clusters leads from the active site to the surface of the protein where electrons are passed on to the electron acceptor, cytochrome c_3 [909] (Figure 51).

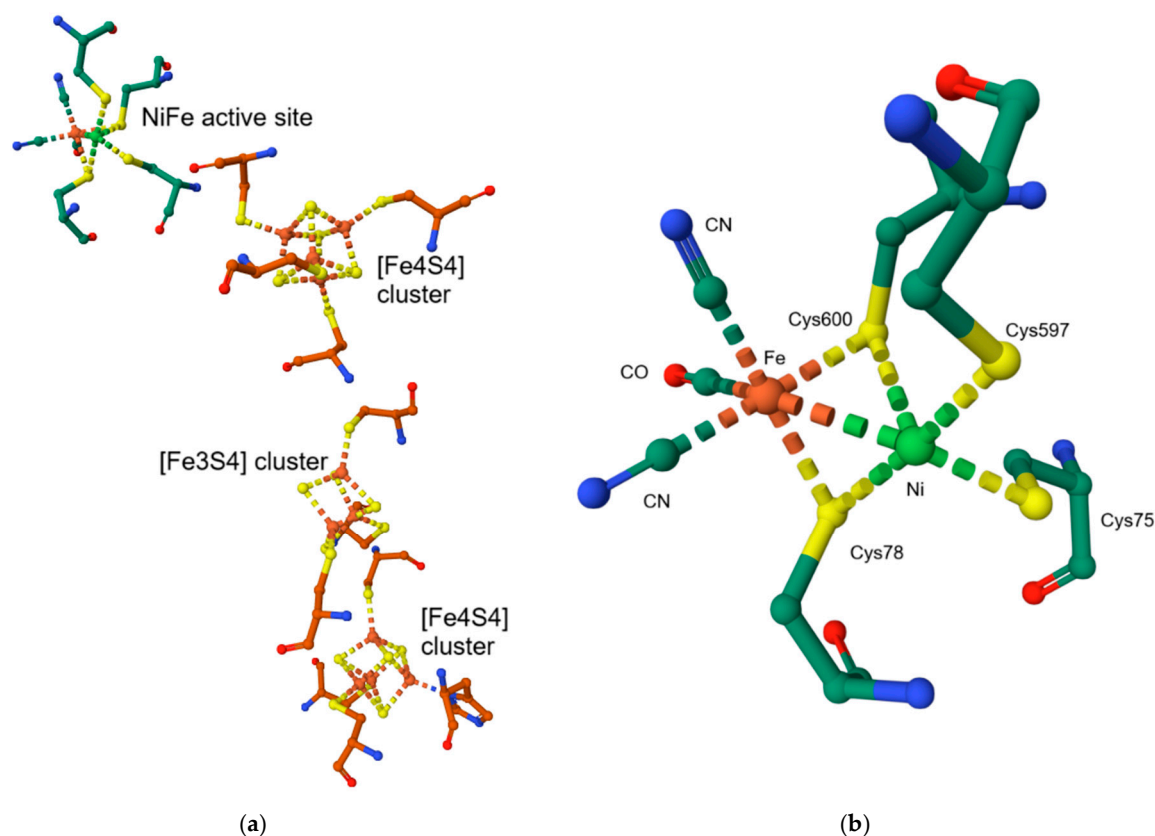


Figure 51. The [NiFe] hydrogenase from *C. necator* (PDB 8POV [907]). (a) The chain of iron–sulphur clusters and the NiFe active site. (b) The NiFe active site.

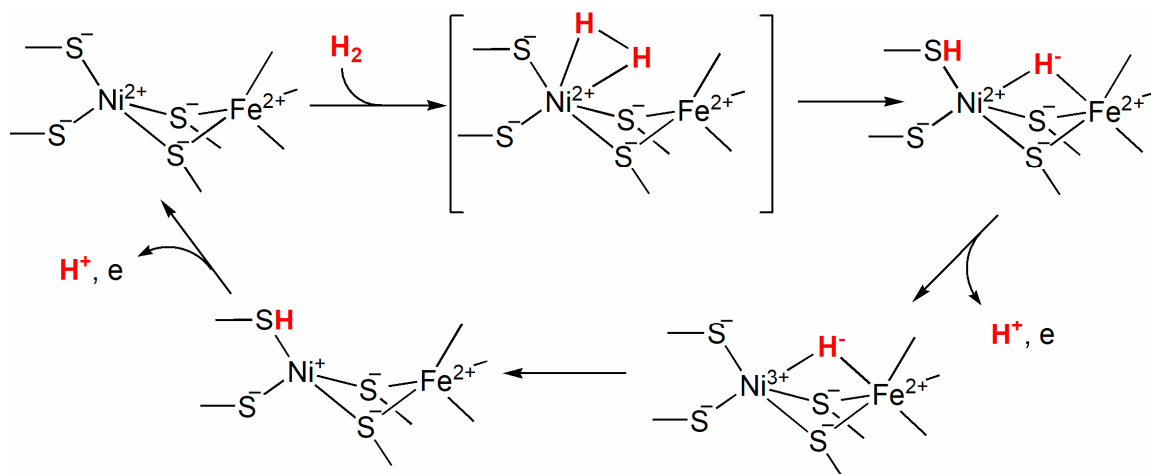


Figure 52. Possible mechanism of the oxidation of H_2 by NiFe hydrogenase [908].

The initial site of H_2 binding is probably Ni^{2+} , as suggested by QM/MM calculations [910]. Enzyme efficiency is ensured by coupling the proton and electron transfer processes (involving a Cys ligand of Ni and the carboxylate of a neighbouring Glu residue) [911,912]. There is also considerable knowledge, if not yet a complete understanding, of the gas-access tunnel in the enzyme (for details see [902]). A possible mechanism is shown in Figure 52.

9.4. Lactate Racemase

Lactate racemase is a Ni-containing enzyme that isomerises L-lactate to D-lactate (Equation (35)). The active site contains a nickel-pincer nucleotide (NPN) as a cofactor, with two S atoms and a C atom bonded to nickel, a cofactor that is used in a large family of α -hydroxyacid racemases and epimerases [913] (Figure 53). How NPN is biosynthesised has been described [914,915].

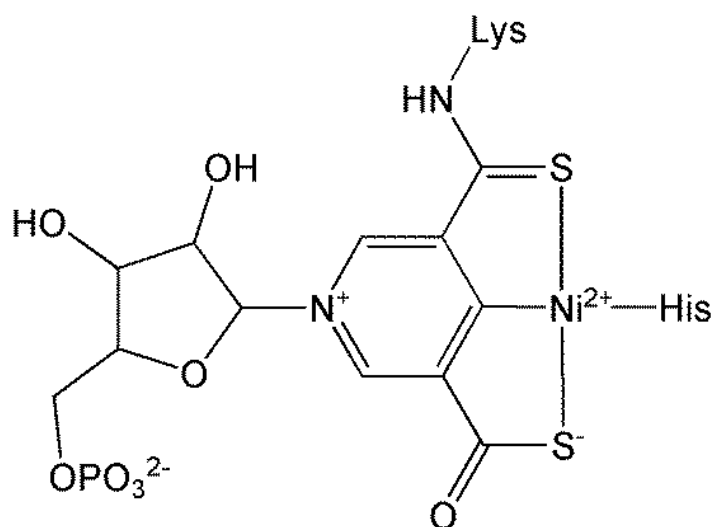
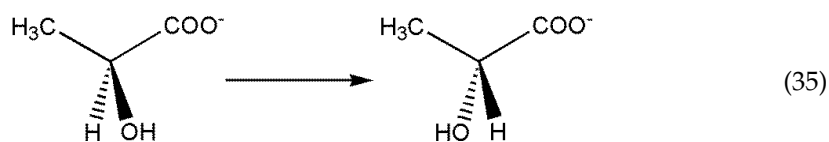


Figure 53. The nickel-pincer nucleotide (NPN) cofactor of lactate racemase.

There is still debate concerning the mechanism of the reaction, with proposals including a proton-coupled electron transfer mechanism in which nickel, originally in the +3 oxidation state, oxidises lactate to form a transient $\text{CO}_2^{\bullet-}$ radical anion and is reduced to Ni^{2+} (Figure 54a) [916], and a proton-coupled hydride transfer mechanism, with nickel in the +2 oxidation state, featuring the transient formation of pyruvate (Figure 54b) [917–920]. The experimental evidence (rather than computational results) appears to favour the latter proposal: there is no evidence of an EPR signal for Ni^{3+} , and pyruvate is detected in quenched solutions of lactate racemase [920]. The inactivation of the enzyme by NaBH_4 also favours this proposal [921].

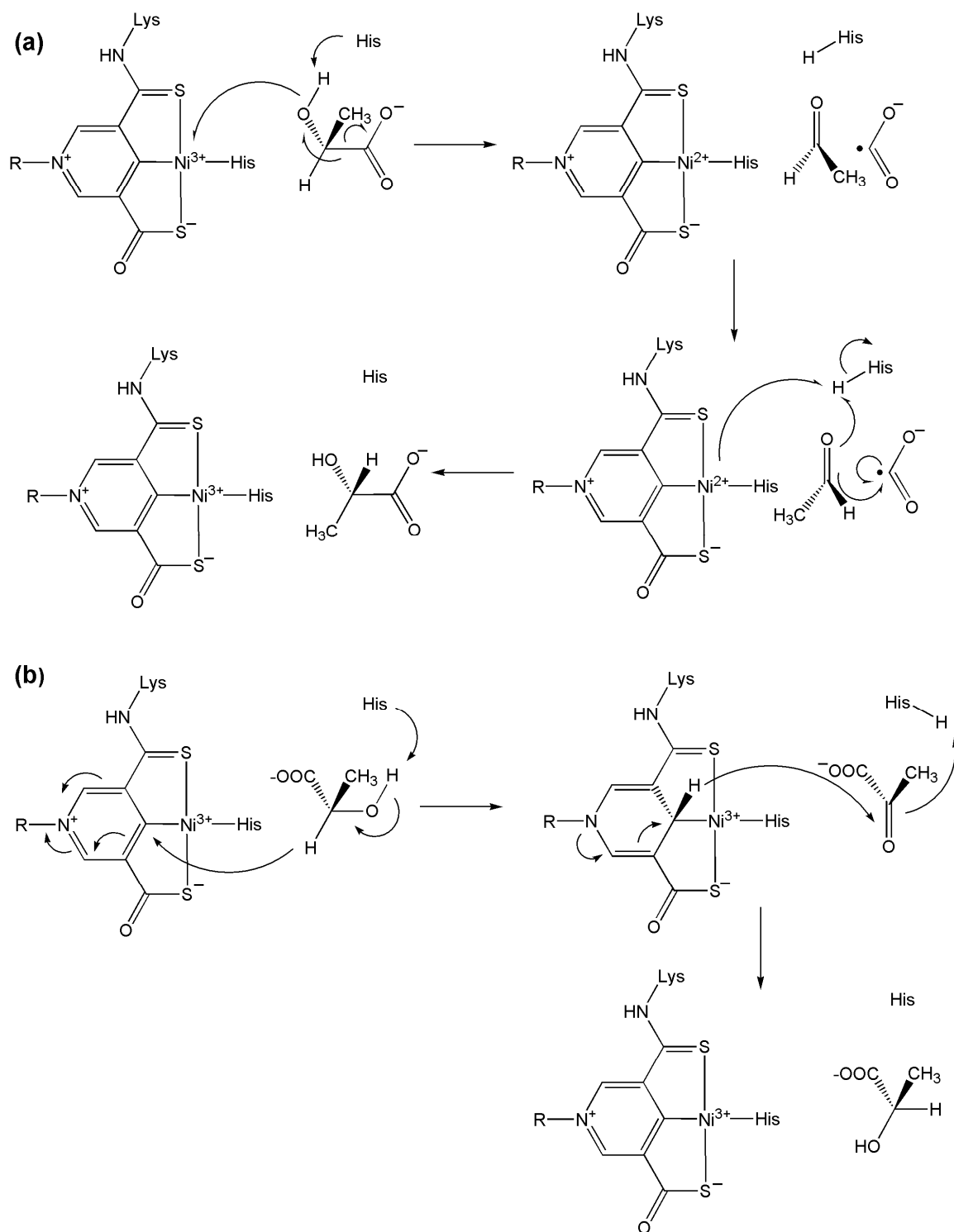


Figure 54. Possible mechanisms for the conversion of L-lactate to D-lactate by lactate racemase: (a) proton-coupled electron transfer; (b) proton-coupled hydride transfer. The location of the hydride could be on C, as shown, or on nickel [920].

10. Copper

Copper is relatively scarce in the Earth's crust, with a concentration of 27 ppm [922]. Nevertheless, with two readily accessible oxidation states, +2 and +1, copper has been integrated into a wide range of biological systems [923–926]. While Cu^+ would have been sequestered as an insoluble sulphide in Earth's primordial reducing atmosphere, Cu^{2+} became more accessible in an oxidising environment following the Great Oxidation

Event, due to its moderate solubility in mildly acidic solutions (K_{sp} of $\text{Cu}(\text{OH})_2 = 2.2 \times 10^{-20}$ [927]). Iron-based biochemistry likely predates copper-based biochemistry [926,928]. However, it has been proposed that copper, along with other metals, played a critical role in prebiotic chemistry [929–934]. For instance, the copper-catalysed condensation of amino acids may have contributed to the formation of prebiotic peptides [929], and Cu^{2+} may have been involved in the activation of nucleotides [930].

Many enzymes utilise $\text{Cu}^{2+} | \text{Cu}^+$ chemistry [935–938]. The ability to exploit these two oxidation states, which lie within or near nature's electrochemical window, is a key feature in electron transfer proteins and in catalytic enzymes such as oxidases and oxygenases (Figure 55). As with all metal ions, maintaining copper homeostasis is essential for the health of the organism [939–941].

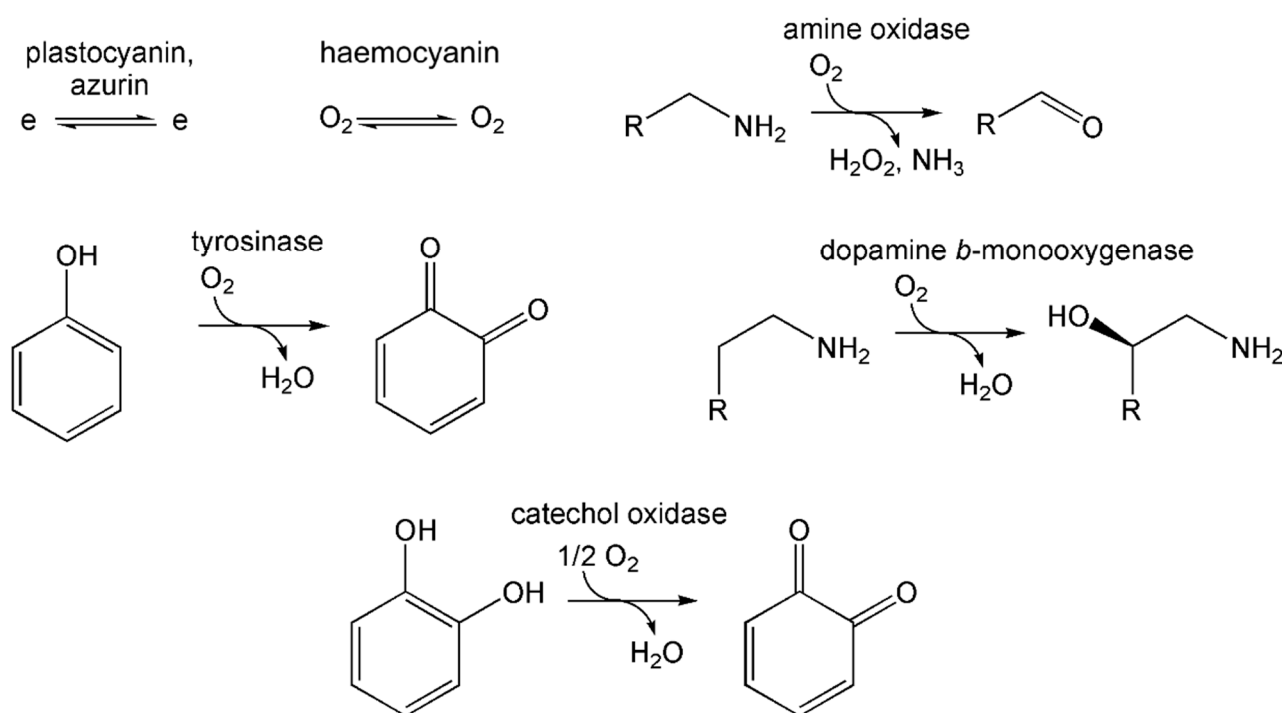


Figure 55. Examples of reactions catalysed by copper metalloproteins and enzymes.

10.1. The Coordination Environment of Copper: The Blue Copper Proteins

Copper is found in a variety of coordination environments within copper-containing enzymes [942–944], several of which are illustrated in Figure 56. One of the most prominent structural motifs employed in copper coordination is the cupredoxin domain, a three-dimensional protein fold utilised in type I (blue copper) proteins [945]. This fold is typically rigid and exhibits minimal conformational change upon metal binding. Notably, however, the apo form of cupredoxin is considerably more flexible, becoming rigid only upon coordination with the metal ion [946]. The primary role of blue copper proteins is to function as outer-sphere, one-electron transfer agents [82,947,948]; an example of such a function in photosynthesis was discussed in Section 7.2.

Copper centres in enzymes may be either mononuclear or multinuclear. Mononuclear type I (class I) centres are typically four-coordinate, featuring a distorted tetrahedral geometry with Cys, two His, and Met as ligands [949] as exemplified by plastocyanin ($E_{1/2} = 370\text{--}400$ mV vs. SHE [950]) (Figure 57).

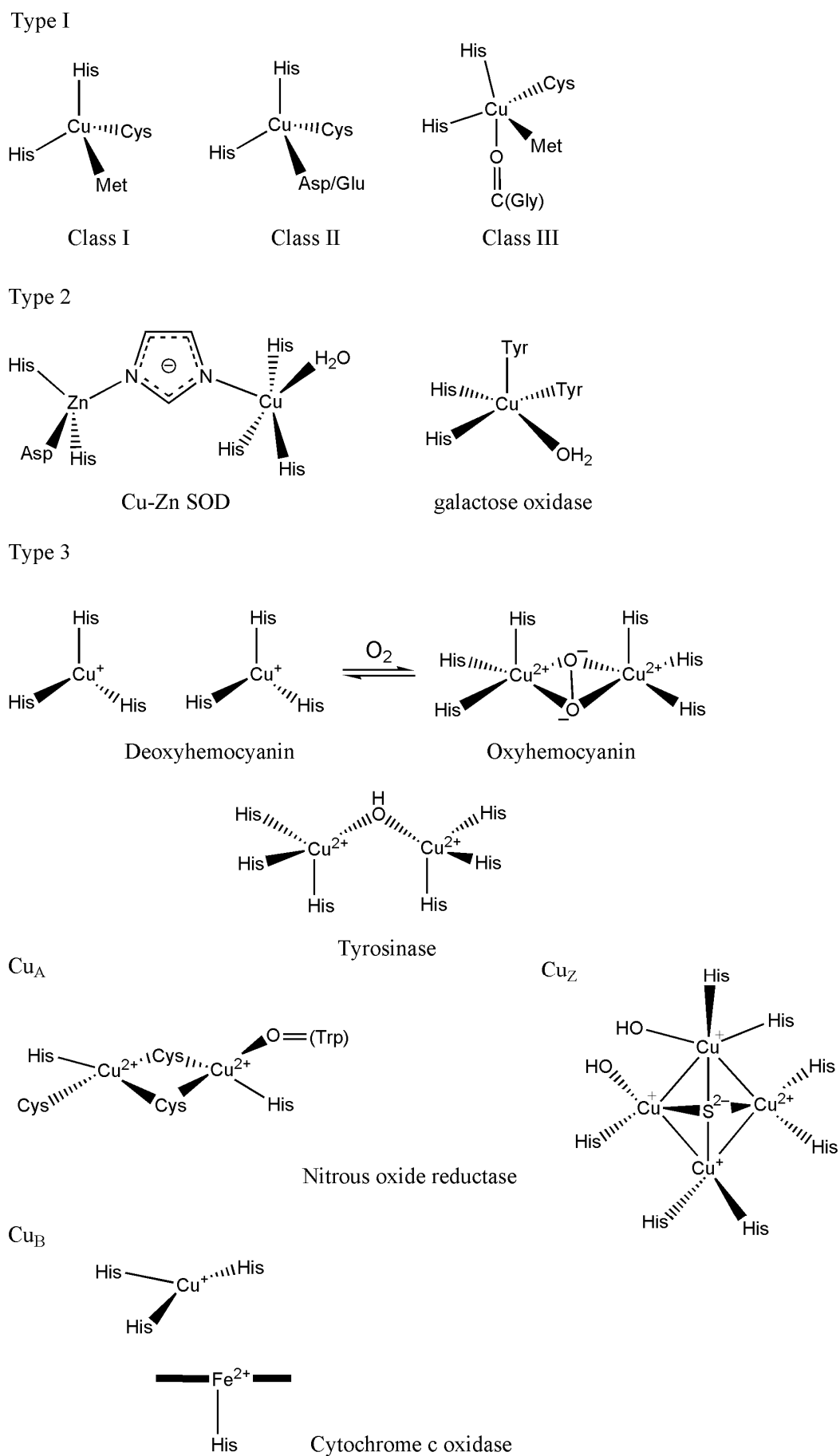


Figure 56. Examples of the coordination environment of copper in copper-containing enzymes.

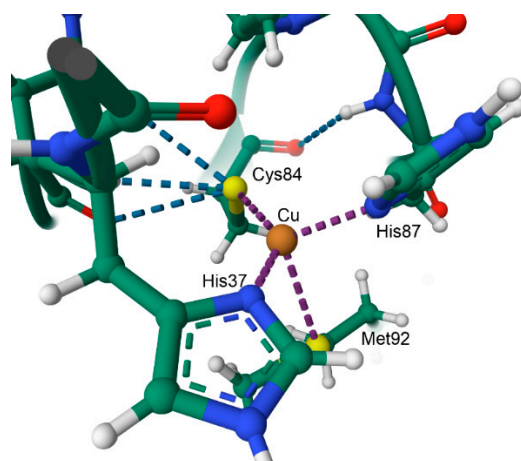


Figure 57. The copper-binding site of plastocyanin.

In these proteins, the copper ion forms strong bonds with the two His and a Cys, while the interaction with Met is comparatively weaker. Typical Cu–Cys and Cu–Met bond lengths are approximately 2.1 Å and 2.9 Å, respectively. The intense blue colour characteristic of these proteins ($\epsilon \approx 5 \text{ mM}^{-1} \text{ cm}^{-1}$) arises from a ligand-to-metal charge transfer (LMCT) transition at 600 nm, specifically from the S(Cys) to Cu^{2+} orbitals, due to a strong π -interaction between $\text{Cu}^{2+}(\text{d}_{x^2-y^2})$ and a sulphur $p\pi$ orbital [951], hence the name “blue copper proteins”.

The covalent character of the $\text{Cu}^{2+}\text{--S}^{2-}$ bond results in partial delocalisation of the unpaired electron onto the sulphur, yielding a significantly reduced $A_{\parallel}$ hyperfine coupling constant in the EPR spectrum (ca. $60 \times 10^{-4} \text{ cm}^{-1}$) compared to the values typically observed for Cu^{2+} complexes (ca. $150 \times 10^{-4} \text{ cm}^{-1}$) [952]. Extensive spectroscopic characterisation, backed up by theoretical studies, has yielded profound insight into the structure and function of these proteins [953].

The coordination geometry of the copper centre in blue copper proteins is intermediate between the tetrahedral preference of $\text{d}^{10} \text{ Cu}^+$ and the square planar preference of $\text{d}^9 \text{ Cu}^{2+}$, placing the metal in what is referred to as an “entatic state” [954–958]. This concept describes a distortion of the ground state coordination geometry to resemble that of the reaction transition state, thereby minimising the reorganisation energy (λ) associated with redox transition, one of the principal barriers to electron transfer, as described by Marcus’ theory [579,959] (see below). Indeed, only minimal structural reorganisation is observed upon redox cycling of the copper centre in blue copper proteins [952]. For comparative analyses of plastocyanin structures from various sources, and for investigations of their solution-phase geometries using NMR spectroscopy, see [960].

The rate of electron transfer, k_{ET} , between an electron donor D and an electron acceptor A is given in Equation (36).

$$k_{\text{ET}} = \frac{2\langle H_{\text{DA}}^0 \rangle^2 e^{-\beta r}}{h} \left(\frac{\pi^3}{4\lambda RT} \right)^{\frac{1}{2}} e^{-\frac{\Delta G^\ddagger}{RT}} \quad (36)$$

In this equation, $\langle H_{\text{DA}}^0 \rangle$ is the Hamiltonian that describes the coupling between the wavefunctions of D and A; β is a parameter reflecting the sensitivity of the coupling to the edge-to-edge distance, r , between D and A; λ is the reorganisation energy; and $\Delta G^\ddagger$ is the Gibbs energy of activation, as defined in Equation (37), where ΔG^0 is the change in Gibbs

energy for an electron transfer from the ground state of D to the ground state of A and is therefore related to the standard reduction potentials of D and A by $\Delta G^\circ = -nFE^\circ$.

$$\Delta G^\ddagger = \frac{1}{4}\lambda \left(1 + \frac{\Delta G^\circ}{\lambda}\right)^2 \quad (37)$$

The magnitude of λ is influenced by the surrounding medium: aqueous environments generally result in larger reorganisation energies [580]. Protein structure also plays a significant role: β -sheets, being relatively rigid, facilitate stronger electronic coupling than the more flexible α -helices [580]. In multicopper oxidases, efficient electron transfer is enabled by strong donor–acceptor coupling [953], consistent with the quadratic dependence $k_{ET} \propto \langle H_{DA}^0 \rangle^2$. A small λ is typically associated with blue copper proteins [961], though this remains a topic of debate [962].

Blue copper proteins exemplify the profound influence of protein structure on the redox potential of the $\text{Cu}^{2+}|\text{Cu}^+$ couple, which is 159 mV in aqueous solution [963]. These potentials vary widely. For instance, laccase (a class I blue copper protein coordinated by two His, Cys, and Met) exhibits redox potentials in the range 400–800 mV, whereas stellacyanin (class II, with 2 His, Cys, and either Asp or Glu) has a lower potential range of 200–350 mV. The $\text{S}(\text{Cys}) \rightarrow \text{Cu}^{2+}$ LMCT transition at 600 nm reflects the contribution of a redox-active molecular orbital (RAMO) in the ground state wavefunction, which is key to long-range, outer-sphere electron transfer [952,953].

Class III blue copper proteins such as azurin possess a five-coordinate copper ion (2 His, Cys, Met, and a backbone carbonyl oxygen, e.g., from Gly), adopting a distorted trigonal bipyramidal geometry. Both the inner and outer coordination spheres contribute to the modulation of the copper centre's redox potential, enabling effective electron transfer between physiological donors and acceptors [952,964–966]. Importantly, redox potential is influenced not only by ligand identity but also by the protein scaffold. For example, in plastocyanin, the redox potential is tuned via the interaction between the Met ligand and Cu^+ in the reduced state [967]. Site-directed mutagenesis has demonstrated that strengthening this interaction leads to an increase in the midpoint redox potential. Furthermore, interactions between the metal ion's primary coordination sphere and its secondary environment influence the spin density on the metal centre, so contributing to the tuning of its redox potential [968,969].

10.2. The Coordination Environment of Copper: Type II and Type III Centres, and the Multicopper Oxidases (MCOs)

Type II copper centres are also mononuclear and have the metal ion in a tetragonal five- or six-coordinate geometry with N and O ligands (Figure 57). Their EPR spectra are consistent with an $S = 1/2$ Cu^{2+} -oxidised ground state, and the absence of an intense LMCT band confirms the absence of Cys in the coordination sphere. Among the copper enzymes with a Type II centre are superoxide dismutase (see below), amine oxidase [970], lysyl oxidase [971], and galactose oxidase [972].

Type III centres are binuclear, with each copper ion coordinated by three His residues. The ions are antiferromagnetically coupled and exhibit no EPR signal. These copper proteins are involved in oxygen transport and activation (for example, haemocyanin [973] and tyrosinase [974], respectively). The copper A centre (Cu_A), found for example in cytochrome *c* oxidase (Section 7) and nitrous oxide reductase [975,976], features two copper ions bridged by Cys residues, with His, Met, Glu, and Trp typically providing the remaining ligands to each four-coordinate metal ion.

A trinuclear centre (TNC), an association of a type I and a type II centre, occurs in enzymes such as ascorbate oxidase [977] and thiocyanate dehydrogenase [978]. The three

metal ions are coordinated by seven His residues. Nitrous oxide reductase has a four-copper ion centre (see below), with His again featuring as the prominent ligand. Copper plays an important role in cytochrome *c* oxidase and in photosynthesis (Section 7). Lytic polysaccharide monooxygenases (LPMOs) use a copper-based oxidative mechanism to cleave glycosidic bonds [979].

Multicopper oxidases (MCOs) oxidise a wide variety of substrates while (usually) reducing O_2 to H_2O [935,980,981]. Examples include laccase (found in fungi and plants and which oxidises diamines and phenols), ascorbate oxidase (found in higher plants; it catalyses the oxidation of ascorbic acid to L-dehydroascorbic acid) and nitrite reductase (a bacterial and fungal enzyme that reduces NO_2^- to NO and H_2O). Other MCOs, termed metallo-oxidases, use Fe^{2+} , Cu^+ , or Mn^{2+} as their source of electrons. They all have multiple copper sites.

Typically, electrons are accepted at a mononuclear copper site, usually a type I site, $[Cu(His_2CysMet)]$, and pass through a His-Cys-His pathway [982] to a multi-copper site some distance from it (≈ 13 Å) where reduction of O_2 (or N_2O) occurs. The evolutionary relationship between MCOs, an ancestry dating back to small mononuclear copper proteins, has been delineated [981,983,984]. The trinuclear cluster of the multicopper oxidase CueO from *E. coli* is shown in Figure 58 [985]. The enzyme is involved in copper tolerance under aerobic conditions [986]. It contains two Cu ions coordinated to three His ligands and solvent H_2O (or OH^-), termed Cu_{T3} , and a Cu ion coordinated to two His residues and a solvent H_2O (or OH^-), termed Cu_{T2} .

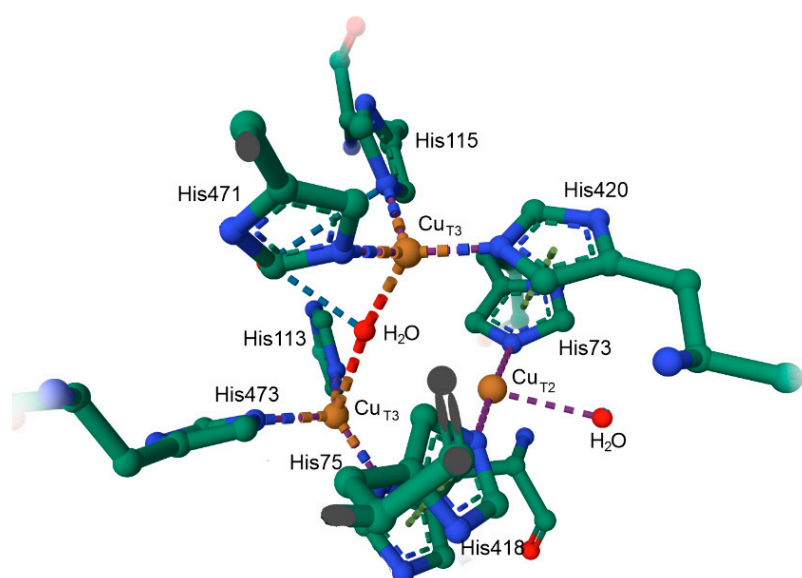


Figure 58. The trinuclear copper site of the multicopper oxidase CueO from *E. coli* (PDB 1KV7 [985]). In the resting state of the enzymes, all copper ions are in the +2 oxidation state.

A proposed mechanism for the reduction of O_2 to H_2O by the multicopper oxidases is shown in Figure 59 [987,988]. The proposal is based on experimental evidence backed by theoretical calculations. The three Cu ions interact with O_2 . This provides the protein with the means of, initially, reducing O_2 to O_2^{2-} , so overcoming the spin-forbidden reduction of 3O_2 by, for example, an organic substrate ($S = 0$), and then to perform four one-electron transfers to the substrate with a minimal release of ROS.

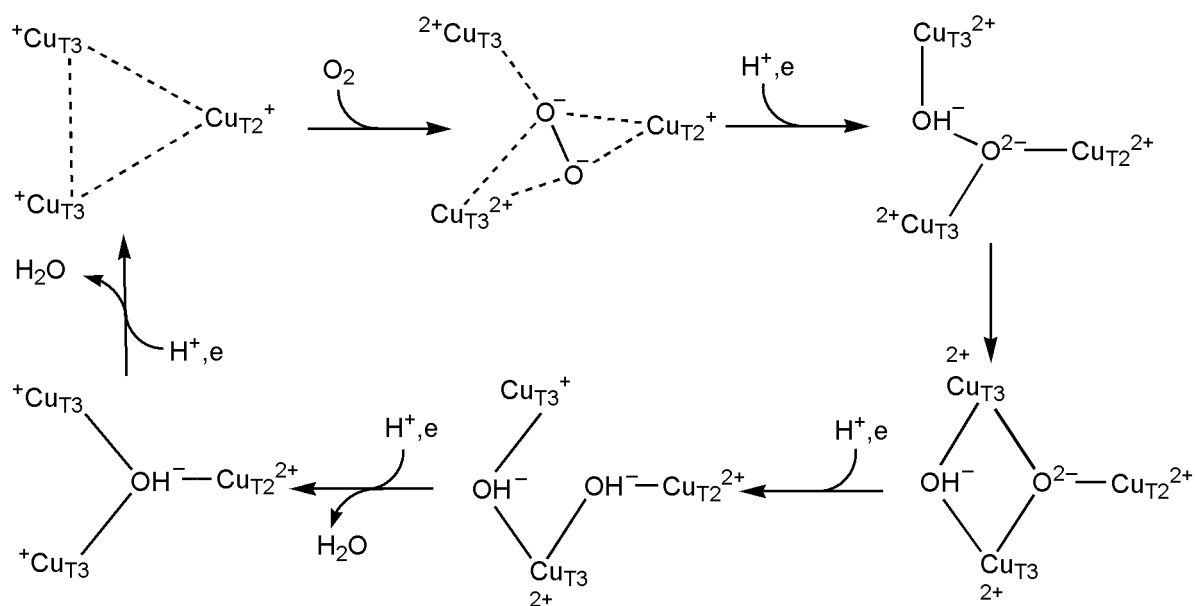


Figure 59. A proposed catalytic cycle for the MCOs. All copper ions are present as Cu⁺ in the reduced state of the enzyme. Binding of O₂ ($k \approx 10^6 \text{ M}^{-1} \text{ s}^{-1}$) leads to formation of bound O₂²⁻ with the oxidation of the two Cu_{T3} ions to the +2 oxidation state [989], and O₂²⁻ interacts with all copper ions [990]. On the uptake of the first electron the O–O bond of peroxide is cleaved (with a small barrier of some 65 kJ mol⁻¹ [980,988,991]. This is the rate-determining step of the entire cycle [988]. On uptake of three more electrons and four protons, and release of 2H₂O, the reduced form of the enzyme is formed, completing the catalytic cycle.

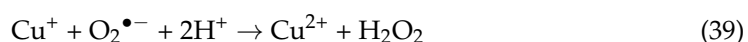
10.3. Some Illustrative Examples of Copper-Based Enzymes

10.3.1. Superoxide Dismutase

The importance of superoxide dismutases was discussed in Section 6. We shall merely consider here the mechanism of the Cu-Zn SODs, widespread among eukaryotes and in some prokaryotes. There are also copper-only superoxide dismutases found for example in bacteria such as *Vibrio cholerae* and *Helicobacter pylori* [992].

The dismutation of superoxides to O₂ and H₂O₂ is clearly the principal function of SOD, but it performs other functions as well; for example, it is a very efficient oxidase of H₂S, which, in excess, is cytotoxic as it inhibits cytochrome *c* oxidase [993]; it boosts the degradation of biomass by glycoside hydrolases, demonstrating its competency to act as an oxidase [994]; and it indirectly leads to the promotion of NADH as a consequence of its antioxidant function [995].

The enzymatic dismutation of O₂^{•-} by Cu-Zn SOD is very rapid ($k \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$) [996], and under normal physiological conditions the rate of enzyme turnover is far from saturation. The reaction is generally thought to take place in two steps (Equations (38) and (39)). The active site of bovine SOD (PDB 1Q0E [997]) is shown in Figure 60 and a possible mechanism is shown in Figure 61. The importance of an Arg residue near the active site is clear. Zinc plays a structural, but not a catalytic role (Zn-depleted SOD is active [998]), and it also plays an important role in ensuring the proper membrane attachment of the enzyme [999]).



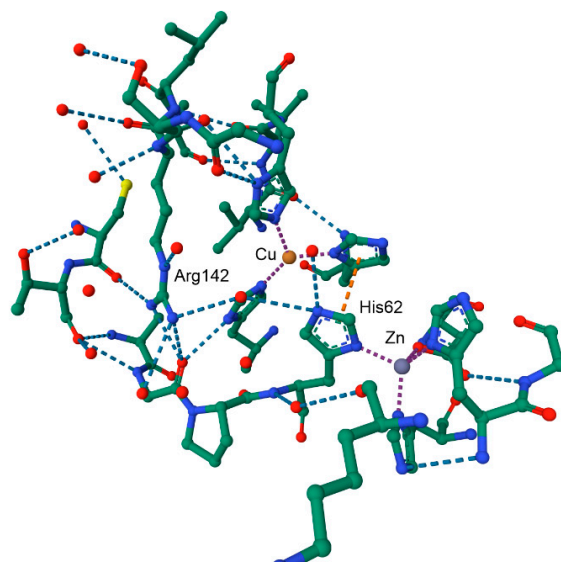


Figure 60. The active site and immediate surroundings of bovine SOD, showing an Arg residue near the copper ion.

Under various physiological conditions Cu-Zn SOD can catalyse a variety of side reactions, using, for example, thiols such as GSH, to generate reactive oxygen species which, in excess, can have deleterious effects [1000].

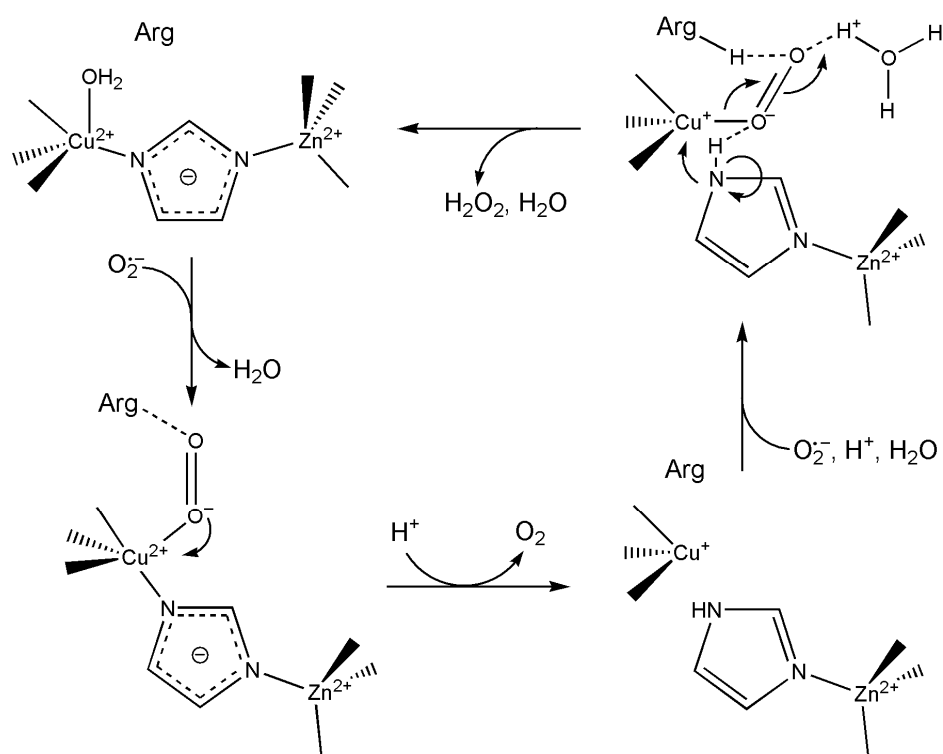
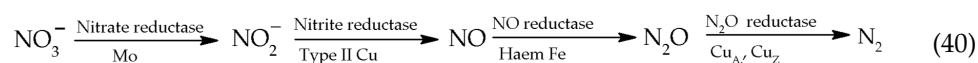


Figure 61. A possible mechanism for the dismutation of superoxide catalysed by SOD [1001]. A conserved Arg residue is important for the reaction [1002]. The H_2O ligand coordinated to Cu^{2+} in the resting enzymes exchanges rapidly with solvent H_2O .

10.3.2. Nitrous Oxide Reductase

The emission of N_2O into the atmosphere, arising in part from the use of fertilisers, is of environmental concern as it is a powerful greenhouse gas [1003]. Bacterial denitrification of soils occurs in four steps (Equation (40)) and is stimulated by high nitrogen input and

low oxygen pressure [1004]; hence, agricultural land is tilled to keep it aerobic. The oxides of nitrogen are used as the terminal electron acceptors in anaerobic respiration by these organisms. Archaea and some fungi also use these enzymes.



Nitrous oxide reductase is the final enzyme in this chain, and catalyses the reaction shown in Equation (41) [1005]. It is not a true MCO as it lacks the TNC of those enzymes but uses a similar proton-coupled electron transfer mechanism to reduce N_2O to N_2 . This is a thermodynamically favourable reaction ($\Delta G^\circ = -340 \text{ kJ mol}^{-1}$) but has a large activation energy ($\Delta G^\ddagger = +250 \text{ kJ mol}^{-1}$) and therefore requires a catalyst.



The enzyme contains two copper sites. The first, termed Cu_A because of its similarity with the Cu_A site of cytochrome *c* oxidase, contains two Cu ions (Figure 62a) and is the entry point for the electrons that are used to reduce N_2O . The second copper centre, Cu_Z , contains four copper ions coordinated by seven His residues and a μ^4 -sulphido ligand which caps the tetranuclear copper core [1006]; this is the catalytic centre of the enzyme [1007,1008] (Figure 62b).

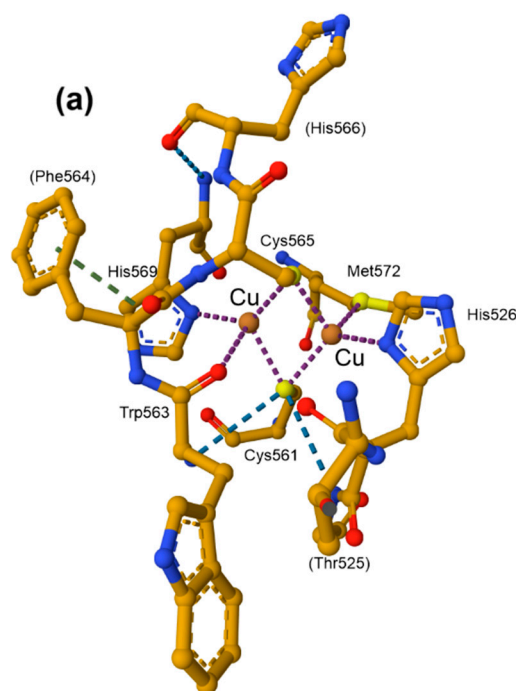


Figure 62. Cont.

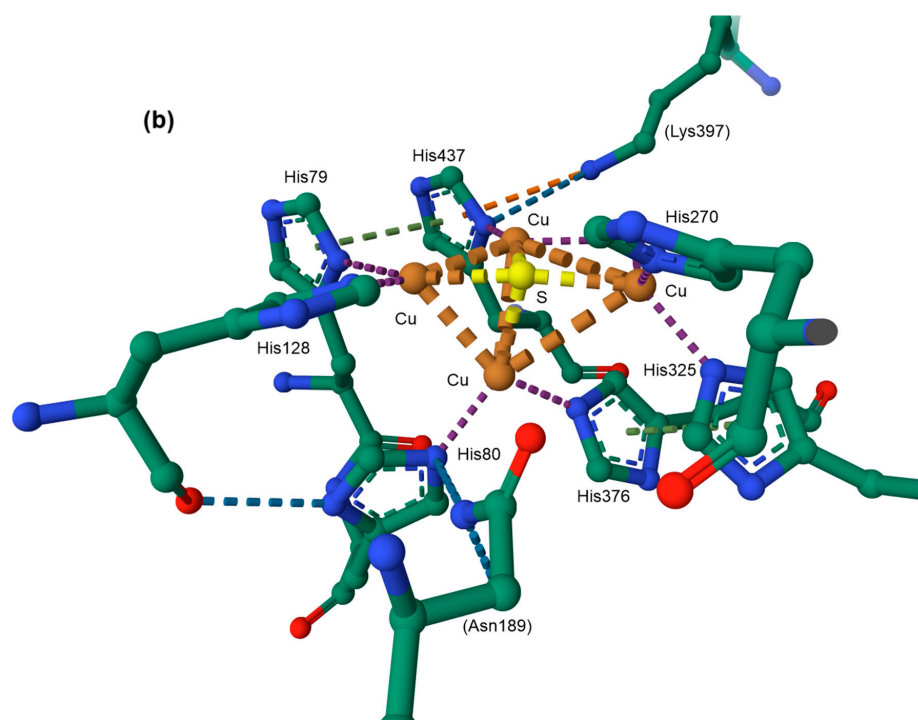


Figure 62. (a) The Cu_A site of nitrous oxide reductase from *Pseudomonas nautica* (PDB 1QNI [1006]). (b) The Cu_Z site, (Cu₄S), often referred to as Cu_Z^{*}, from the same enzyme. Some nitrous oxide reductases contain two sulphur ions in the active site (Cu₄S₂); the site is then usually referred to as Cu_Z. Cu_Z^{*} is associated with aerobic conditions in which one of the sulphides of anaerobic Cu_Z is replaced by H₂O. The two sites (from two different monomers in the homodimeric protein) are some 10 Å apart, facilitating electron transfer.

The Cu_A site is a mixed-valent [Cu^{1.5}Cu^{1.5}] site [1009,1010] with the unpaired electron in the oxidised form delocalised over the two metal ions, which are 2.43 Å apart. LMCT bands (S(Cys) → Cu) occur at 480 and 525–540 nm. The principal function of the site is to provide electrons to the catalytic site, Cu_Z in some enzymes, Cu_Z^{*} in others. This is a proton-coupled transfer, gated by one of the His ligands of the Cu_A site [1011,1012].

The oxidised form of Cu_Z features (formally, anyway) two Cu²⁺ and two Cu⁺ ions and is often termed the “2-hole Cu_Z” site, referring to the two d⁹ Cu²⁺ ions. A single electron reduction produces the one-hole site with the unpaired electron delocalised over the copper ions, as determined by EPR, and with protonation of the bridging sulphide [1013]. The oxidised form of the Cu_Z^{*} site contains three Cu⁺ ions and one Cu²⁺ ion and is therefore termed the “1-hole Cu_Z^{*}” site.

The catalytically active form of the Cu_Z^{*} site is the zero-hole [4Cu⁺] form, which cycles between this and the one-hole [3Cu⁺:Cu²⁺] form; the Cu_Z site cycles between the one-hole [3Cu⁺:Cu²⁺] and the two-hole [2Cu⁺:2Cu²⁺] forms [1014]. Both types of Z site therefore act as sequential one-electron reductants of the N₂O substrate. A possible mechanism for reduction of Cu_Z^{*} by Cu_A and the reduction of N₂O to N₂ has been proposed, Figure 63 [1015] (also [1008] and references therein) and features (like the MCOs) a sequence of proton-coupled electron transfer reactions.

10.3.3. Tyrosinase

Tyrosinase is an enzyme with a type 3 copper centre, responsible for regulating melanin production. It is found in plant and animal tissues, including in melanosomes which are synthesised by melanocytes in the skin. The enzyme catalyses the hydroxylation of monophenols, followed by subsequent oxidation reactions. This includes the conversion

of o-diphenols into o-quinones (Equation (42)) [1016], which are precursors to melanin. These reactions are coupled with the reduction of O_2 to H_2O . The enzymes also are active on aromatic amines [1017].

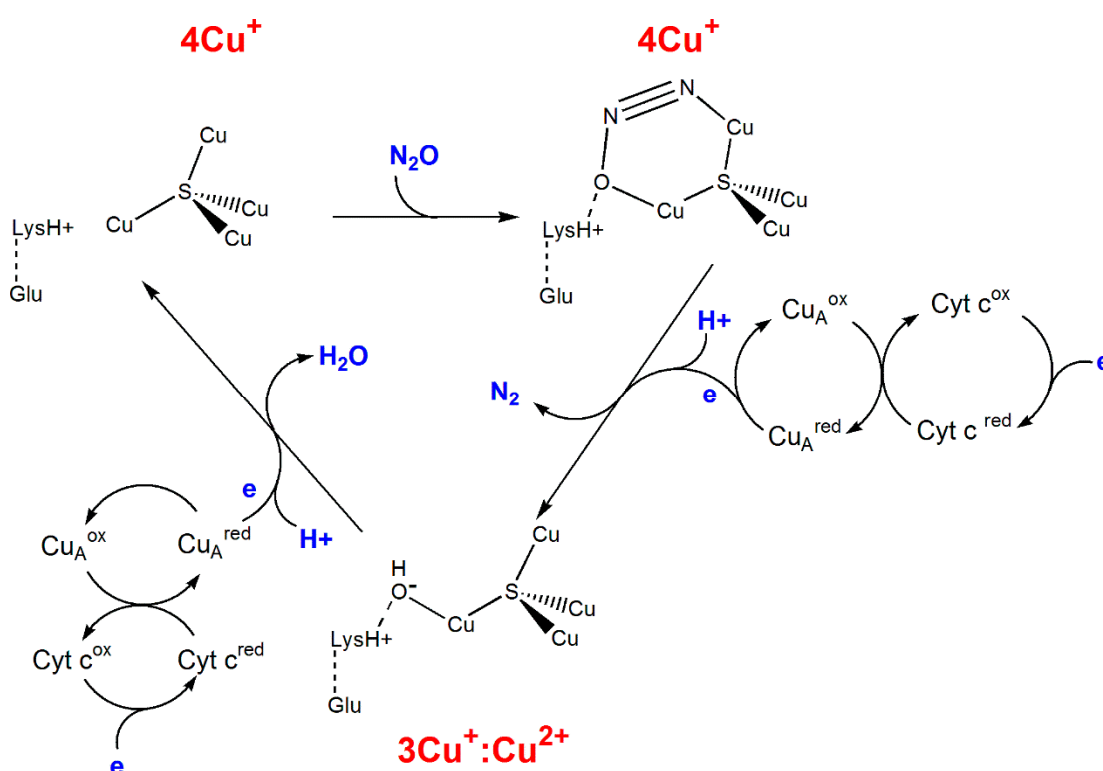
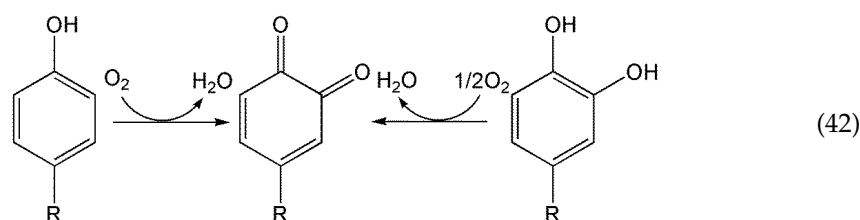


Figure 63. Possible mechanism for the reduction of N_2O at the Cu_Z^* site [1008,1015].

Tyrosinase inhibition is a target for the cosmetics industry to produce products that counter changes in pigmentation, one of the effects of skin ageing [1018]. Flavonoids, compounds that are commonly found in the human diet, are reported to inhibit tyrosinase by binding to the active site of the enzyme [1019], and many other inhibitors—both natural products and synthetic compounds—are known [1020–1024]. Tyrosinase activity can be inhibited by mercury, a common component of skin-whitening creams, but this has very significant health risks [1025].

The action of tyrosinase within the substantia nigra, a part of the brain that controls movement and is involved in chemical signalling, leads to the breakdown of dopaminergic neurons, the main source of dopamine [1026]. Decline in dopamine contributes to the development of Parkinson's disease.

The active form of the enzyme contains two Cu^+ ions which bind O_2 in a $\mu-\eta^2:\eta^2$ side-on manner producing $Cu^{2+}-O_2^{2-}-Cu^{2+}$ [1027]. This species oxidises the substrate. A possible mechanism is shown in Figure 64 [1028,1029].

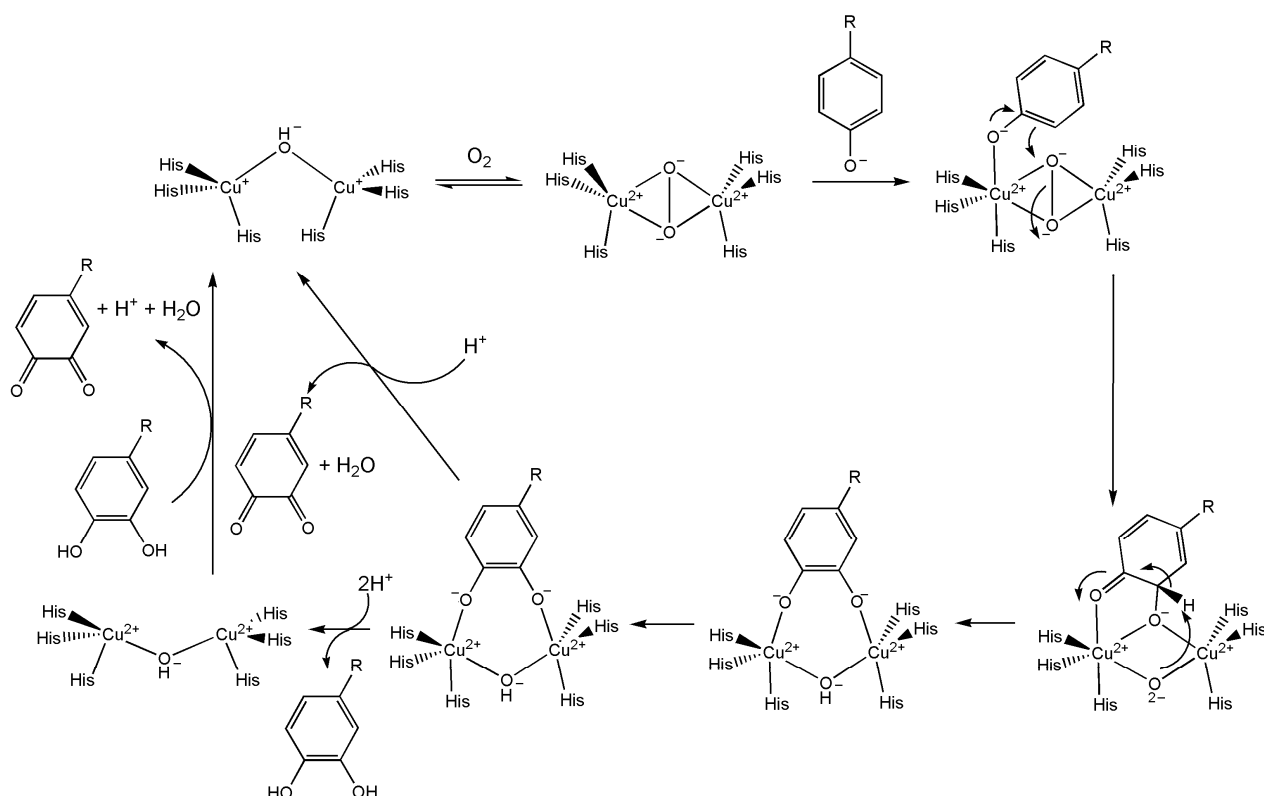


Figure 64. Catalytic cycle of tyrosinase.

11. Zinc

Zinc is important for many life forms including animals, plants, and microorganisms [1030,1031], and important for human health [1032–1035]. Zinc has only one physiologically readily accessible oxidation state, Zn^{2+} , and it functions as a Lewis acid in biological systems [1036,1037].

Zn^{2+} , a d^{10} metal ion with no ligand field stabilisation, has a variable coordination number, from 2 to 8, with 4 and 6 being most common [135]. It is also kinetically labile; the water exchange rate of $[\text{Zn}(\text{H}_2\text{O})_6]^{2+}$ in aqueous solution is $4 \times 10^8 \text{ s}^{-1}$ [1038]. In terms of Pearson's classification of Lewis acids [1039], Zn^{2+} is borderline between a hard and a soft acid and is therefore receptive to a variety of donor ligands. In proteins it is usually coordinated by O, N, and S donors, usually in a distorted tetrahedral or trigonal bipyramidal geometry [1040]. A bioinformatics search of the human genome predicted there are some 2800 human proteins (or some 10% of the human proteome) that are potential Zn^{2+} -binders, with the most abundant being the so-called zinc finger proteins [1041,1042] with Zn^{2+} coordinated by four Cys, or two Cys and two His ligands [1043].

The cellular concentration of Zn^{2+} is high, around $200 \mu\text{M}$ [1044], so the buffering of Zn^{2+} in cells is essential for it not to compete with other metal ions in the metal binding sites of proteins. Free Zn^{2+} (i.e., complexes of Zn^{2+} such as $\text{Zn}(\text{GSH})_2$, $\text{Zn}(\text{citrate})_2$, and Zn-ATP [1044], capable of releasing the metal to the metal binding sites of proteins) is limited to a few hundred pM [1045], with excess zinc stored in vesicular compartments [1046]. There are sophisticated mechanisms that control zinc homeostasis [1047,1048], and an excess of Zn^{2+} (and Cu^{2+}), i.e., metal ion intoxication, is one way in which a host reduces the intracellular survival of pathogens [1049].

Zinc performs many functions in biology [1050]. Zinc-dependent enzymes include DNA and RNA polymerases [1051–1053], proteinases [1054], carbonic anhydrase [1055–1057], and alkaline phosphatase [1058–1060]. Zinc finger proteins, discovered in 1985 [1061], use Zn^{2+} to

stabilise their structure and play an important role in health and in disease [1041,1042,1062]; they are involved in processes such as regulating gene expression by binding to DNA [1041], cellular development [1063], differentiation [1064], and apoptosis [1062]. Shown in Figure 65 is an example of how Zn^{2+} ensures the integrity of the three-dimensional structure of a protein.

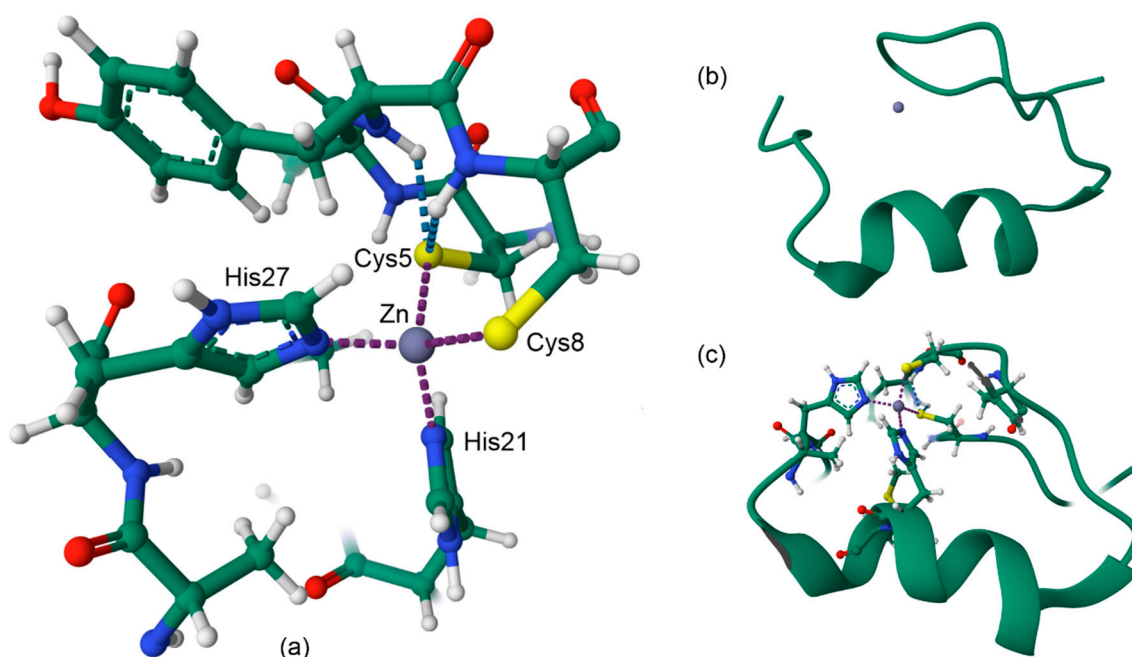


Figure 65. (a) The coordination sphere of Zn^{2+} from a human enhancer-binding protein (PDB 4ZNF [1065]); (b) the overall structure of the protein; (c) illustration of how Zn^{2+} is responsible for maintaining the 3D structure.

Zinc is important for maintaining a healthy immune system [1066] and zinc deficiency can lead to impaired immune response and an increased susceptibility to infections [1067]. As we have seen (Section 10.3.1), Zn^{2+} is a component of the active site of superoxide dismutase and hence plays a role in controlling the concentration of ROS. Zinc is vital for cognitive development and high levels are found in the human brain where it is involved in functions such as neurotransmission and sensory processing, activating both pro-survival and pro-death neuronal signalling pathways [1068]. Zinc is important for tissue repair [1069], hormonal regulation [1070–1072], and reproductive health [1073]. A diet heavy in processed foods may lead to zinc deficiency [1074].

We shall limit our discussion to the role of zinc in a few enzymes other than CuZn-SOD, which was discussed in Section 10.3.1.

In catalytic zinc sites, Zn^{2+} has at least one H_2O ligand, the key component of the site [1040]. This can be deprotonated to hydroxide (as in carbonic anhydrase [1075]), polarised to generate a nucleophile (as in carboxypeptidase A [1076]), or displaced by the substrate (as in alkaline phosphatase [1060]).

11.1. Carbonic Anhydrase

The principal function of Zn^{2+} in enzymes that catalyse hydration or hydrolysis reactions is to stabilise a coordinated OH^- ion as well as to stabilise the developing negative charges in the transition state of the reaction. The enzymes that catalyse the reversible hydration of carbon dioxide to bicarbonate and protons, playing pivotal roles in a variety of biological processes including respiration, calcification, acid-base balance, and CO_2 fixation, are found in many life forms [1077–1079].

An example is human carbonic anhydrase II (CAII) which catalyses the hydration of CO_2 to HCO_3^- and H^+ [1080]. Coordination of H_2O by Zn^{2+} decreases the pK_a of H_2O from 15.7 to around 9, an effect which is augmented by hydrogen bonding between bound OH^- with (in CAII) Thr199. The hydrogen bond also fixes the orientation of OH^- about the $\text{Zn}^{2+}\text{--OH}^-$ bond, optimising it for nucleophilic attack on the substrate, CO_2 , contributing to a near diffusion-controlled limit of enzyme turnover. The active site of CAII, with acetate replacing the active site OH^- , is shown in Figure 66, while an outline of the probable mechanism is given in Figure 67.

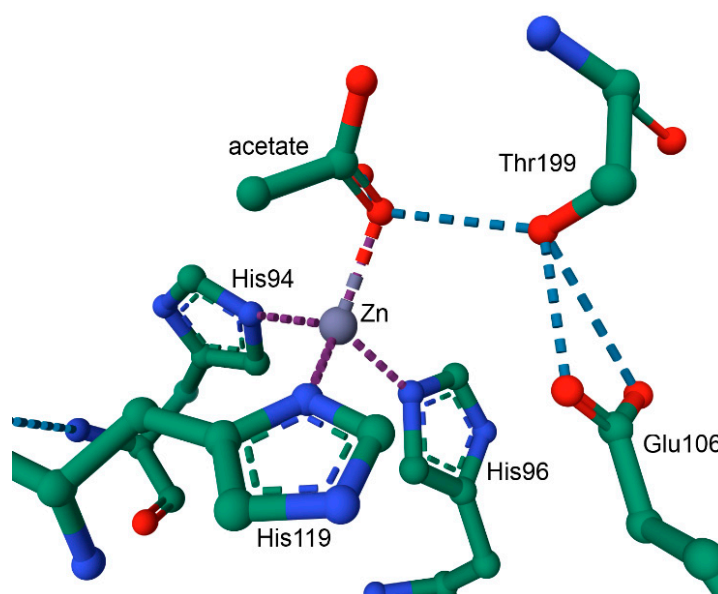


Figure 66. The active site of human CAII (with acetate in the substrate's position), PDB 1XEG [1081].

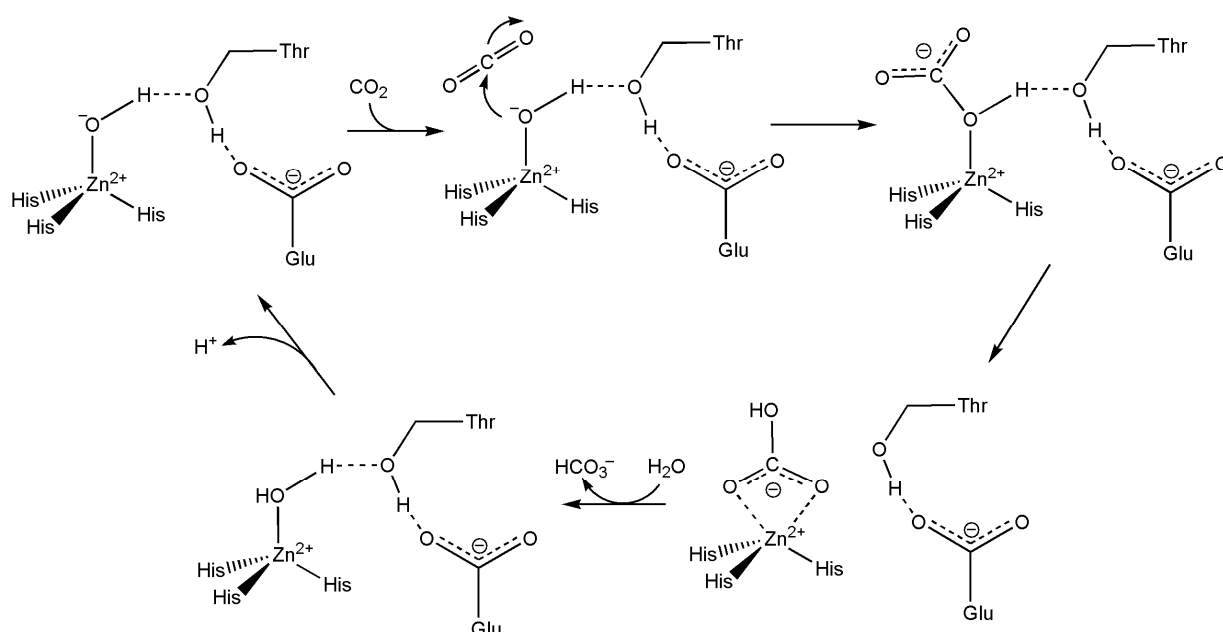
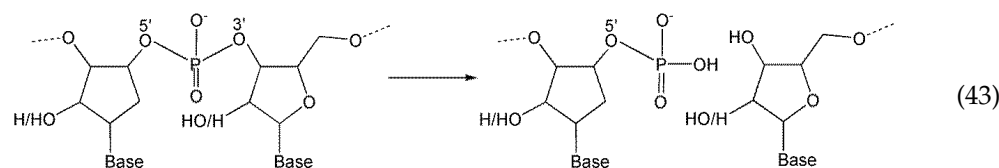


Figure 67. The hydration of CO_2 by CAII. The released H^+ is carried to the enzyme's surface by a His shuttle [1080].

11.2. Zinc-Dependent Phosphoesterases

These enzymes, members of the S1-P1 nuclease family, are found in bacteria, kinetoplasts, fungi and plants; Ca^{2+} -, Mg^{2+} -, and Mn^{2+} -dependent enzymes are also widely

distributed [1082]. They participate in a wide range of biological process where they hydrolyse the P–O3' bond of nucleic acids and mononucleotides (Equation (43)) [1083–1085].



The catalytic site consists of a trinuclear zinc cluster with a Lys or Arg residue, and a nearby site, called Nucleoside Binding Site 1 (NBS1), responsible for binding the substrate. The trinuclear zinc site of the S1 nuclease from *Aspergillus oryzae* (PDB 5FB9) is shown in Figure 68 [1086]. The mechanism of the reaction (Figure 68) entails deprotonation of the bridging water W1, and the resultant hydroxide then acts as the attacking nucleophile on the P–O3' bond [1086–1088].

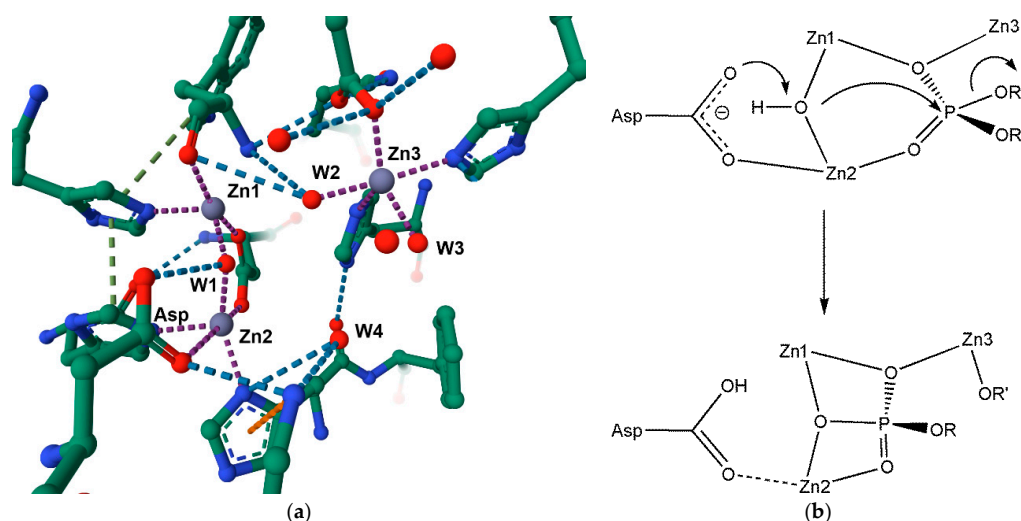
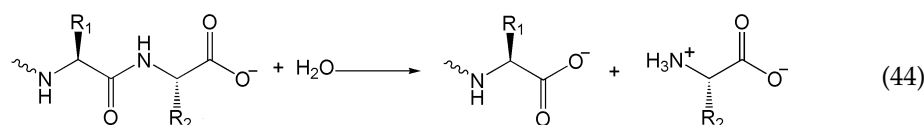


Figure 68. (a) The trinuclear zinc site of S1 nuclease from *Aspergillus oryzae* (PDB 5FB9). (b) The probable mechanism that leads to the cleavage of the P–O3' bond.

11.3. A Zinc Proteinase: Carboxypeptidase A

The most widespread zinc enzymes are hydrolases, referred to as matrix metalloproteinases (MMPs) or zinc proteinases [1047]. Capable of cleaving extracellular matrix proteins, they play a major role in in-cell differentiation, apoptosis, angiogenesis and wound healing [1089]. It is now known that MMPs also have an intracellular function, contributing to the pathogenesis of diseases such as inflammation and cardiovascular renal disorders, and exerting bactericidal and antiviral effects [1054]. One of the most widely studied of these enzymes is carboxypeptidase A [1076,1090,1091]. The enzyme hydrolyses the C-terminal peptide bond of a peptide, releasing the C-terminal amino acid (Equation (44)). It is also capable of hydrolysing esters.



The active site contains Zn^{2+} coordinated by 2 His and a Glu, together with a water molecule. An important Glu residue is in the second coordination shell. Two mechanisms can be envisaged [1092–1096]: one involves attack by Zn-coordinated OH^- (deprotonated

by the second sphere Glu), the other envisages Glu playing the role of the attacking nucleophile. The first is the mechanism used by the enzyme in its proteolysis reactions [1096].

11.4. Alkaline Phosphatase

Co-catalytic zinc enzymes have more than one Zn^{2+} ion (or Zn^{2+} and another metal ion) in proximity that effect the catalytic event. Although only one Zn^{2+} ion plays a role in the catalysis, the other ions are essential (see Section 11.2). Some examples are leucine aminopeptidase (two Zn^{2+} ions) [1097], alkaline phosphatase (two Zn^{2+} and an Mg^{2+}) [1060], and phospholipase C [1098] and nuclease P1 [1085], with three Zn^{2+} ions. In CuZn-SOD, the catalytic site is Cu (see Section 10.3.1), but Zn^{2+} plays an important if indirect role in the catalysis.

Alkaline phosphatase contains two Zn^{2+} ions and one Mg^{2+} ion (Figure 69 shows the active site of the enzyme from *E. coli* with bound phosphate [1099]). The enzyme catalyses the hydrolysis of phosphate esters under alkaline conditions [1100]. One Zn^{2+} (often referred to as Zn_1) is coordinated by two His residues and an Asp residue (and H_2O occupies the remaining two coordination sites in the absence of phosphate); the other (Zn_2) is coordinated by His, Ser102, and two Asp residues (as well as phosphate in the structure shown in Figure 69). The coordination sphere of Mg^{2+} consists of three H_2O , Glu, Thr, and Asp. The PO_4^{3-} is also coordinated by an Arg residue, Arg166.

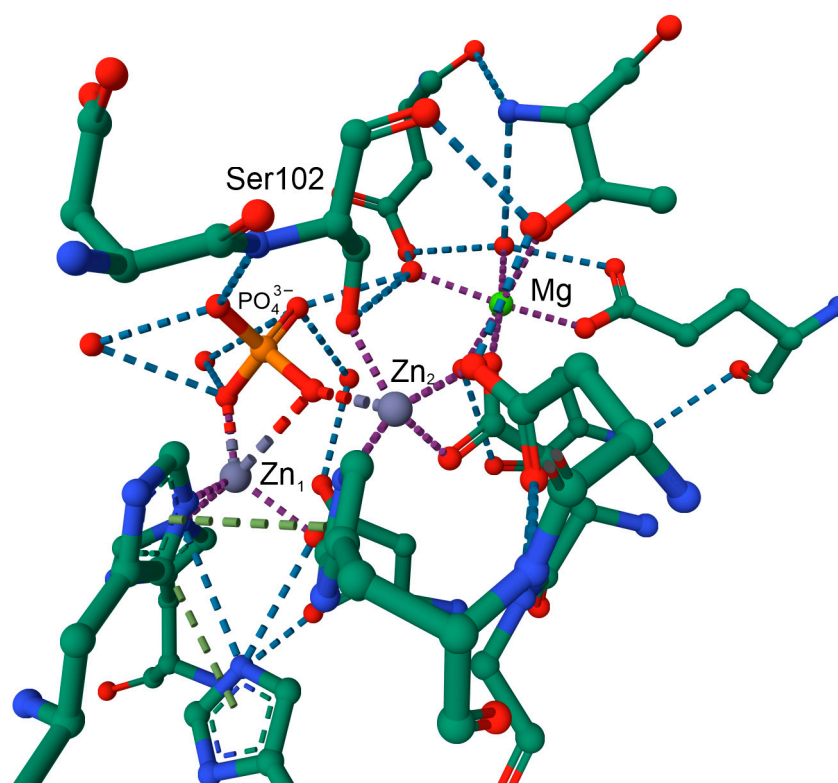


Figure 69. The active site of alkaline phosphatase from *E. coli* (PDB 3TG0 [1099]).

An outline of the mechanism (somewhat simplified) of the hydrolysis of a phosphate monoester, RPO_3^{2-} , is shown in Figure 70 [1060,1101,1102]. The attacking nucleophile is zinc-coordinated Ser-102, leading to the formation of a phosphoseryl intermediate. This is then hydrolysed to produce an enzyme–phosphate complex. If a phosphate acceptor, AOH , is present, the reaction leads to transphosphorylation, $\text{ROPO}_3^{2-} + \text{AOH} \rightarrow \text{ROH} + \text{AOPO}_3^{2-}$. [1060]. The role of the second Zn^{2+} is to coordinate the leaving phosphate as well as activate a solvent water (perhaps as OH^-) for attack on coordinated phosphate in the second step of the reaction. The role of Mg^{2+} is to stabilise the structure of the

enzyme [1103] and to correctly hold the carboxylate of one of the Asp ligands of Zn^{2+} to alternatively donate, and then withdraw, electron density during the reaction [1103,1104].

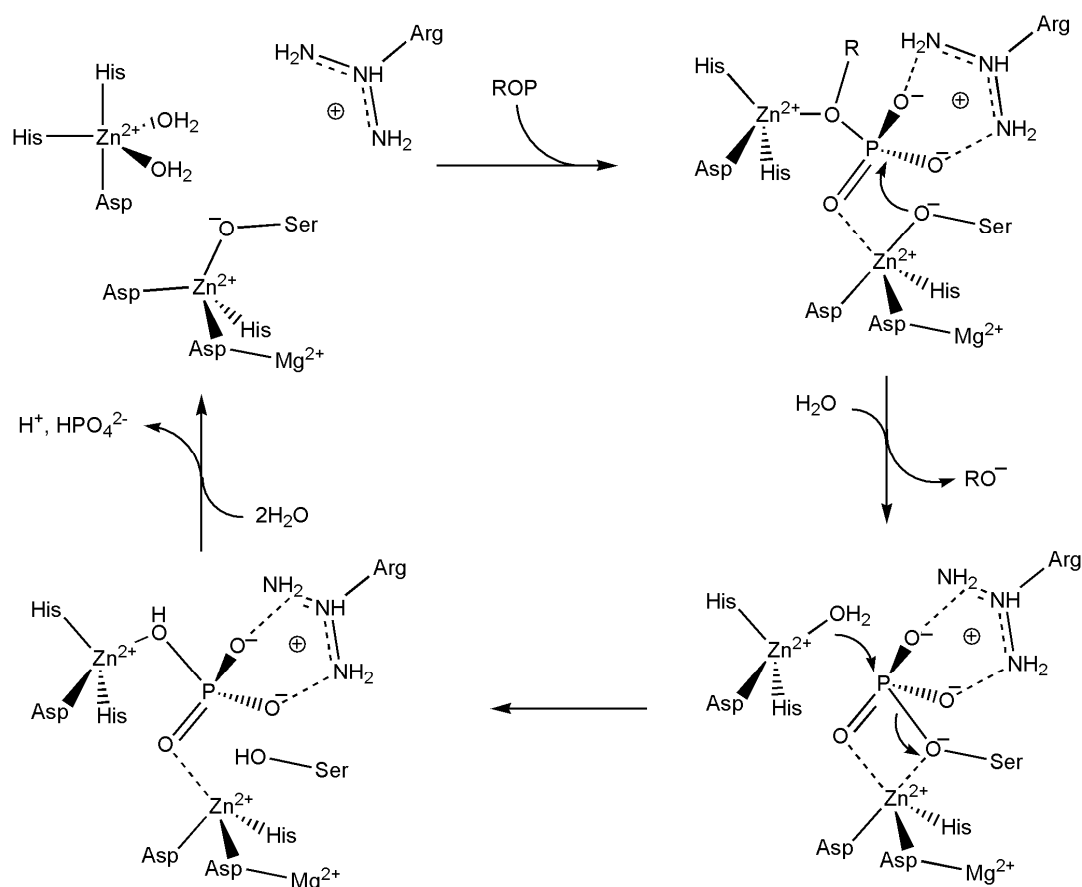


Figure 70. The hydrolysis of a phosphate monoester by alkaline phosphatase.

12. Concluding Remarks

Metal ions constitute by mass a very small percentage of living systems, but they play a crucial role: they are essential trace elements. We have not looked at the role played by the main group metal ions; Na^+ , K^+ , Ca^{2+} , and Mg^{2+} are important in biology. Na^+ and K^+ are involved in many processes including nerve function and nerve impulse transmission [1105,1106], the contraction of muscles [1107,1108], regulating cell volumes [1109,1110], and the regulation of cardiac repolarisation [1111,1112]. Ca^{2+} plays a critical role in, for example, the maintenance of membrane potential [1113,1114], the regulation of the life cycle of a cell [1115,1116], and the activation of many enzymes [1117,1118]. We have seen a number of cases where Mg^{2+} plays a supporting role in catalysts; in addition, the role of Mg^{2+} in the cardiovascular system is critical and there are a number of diseases linked to its deficiency [1119].

The attention here was focused on the elements of the first row of the d block. As far as is known at present, scandium and titanium play no role in biological system. All other elements are essential to one form of life or another or, in some cases, to virtually all life forms. Cobalt, for example, is not required by plants, many fungi and some bacteria, but is vital for animals and many microorganisms. Iron, copper and manganese are widely used by many life forms but there are organisms such as bacteria and archaea that have developed strategies for thriving in, for example, iron-deficient environments using copper or manganese to perform the chemistry usually performed by iron.

There are many metal-containing enzymes, or metalloenzymes, that require metal ions as cofactors. Among the examples discussed was manganese at the heart of Photosystem II, iron in the cytochromes, cobalt in the adenosylcobalamin-dependent enzymes, nickel in urease, copper in superoxide dismutase and zinc in alkaline phosphatase. The metal ions either participate directly in the catalytic process or bind the substrate or activate an entity such as coordinated OH^- to initiate a reaction.

We have seen the key role that iron and copper in particular play in electron transport chains, which are critical for cellular respiration and photosynthesis. The iron–sulphur clusters and cytochromes, and the blue copper proteins, play key roles in the transfer of electrons, facilitating energy production in cells. Iron porphyrins in haemoglobin and myoglobin are vital for the transport and storage of oxygen in animals.

Metal ions may be necessary to stabilise the structure of biomolecules. Zinc fingers, for example are important for protein folding, and they perform many other functions that we have not looked at, including the binding of zinc finger proteins to specific DNA sequences, regulating gene expression [1120,1121] and the regulation of apoptosis [1122,1123].

Bioinorganic chemistry is a very large and interdisciplinary field that explores the role played by metal ions in biological systems, spanning biology and inorganic chemistry. This short overview will hopefully have provided you with a glimpse into some aspects of the discipline: the biological inorganic chemistry of the metals of the first row of the d block—and it will hopefully provide a stimulus for further exploration.

Much has been learned since the pioneering work in the 1960s and 1970s of researchers such as R. J. P. Williams, Harry B. Gray, Richard H. Holm, and Robert H. Crabtree. Insights have been provided into important biological processes involving metal ions, and the discipline has provided the knowledge that has contributed to the development of metal-based drugs and imaging techniques. The development of techniques such as X-ray diffraction crystallography, cryo-electron microscopy, NMR, EPR, and Mössbauer spectroscopy, and, more recently, computational chemistry methods such as density functional theory, have contributed greatly to advances in the field.

But undoubtedly much has still to be learned. The mechanism of many enzymes, such as nitrogenase (involved in nitrogen fixation) and hydrogenase (involved in hydrogen metabolism), remain elusive. Moreover, the rapidly growing area of bioinspired catalysis holds promise for transformative industrial applications.

The future of bioinorganic chemistry lies in the hands of the next generation of researchers and their students who will undoubtedly lead the discipline to new heights in the years ahead.

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