Journal of Coordination Chemistry

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/gcoo20

Corrins and porphyrins: two of nature's pigments of life

Helder M. Marques

To cite this article: Helder M. Marques (2024) Corrins and porphyrins: two of nature's pigments of life, Journal of Coordination Chemistry, 77:11, 1161-1210, DOI: 10.1080/00958972.2024.2343109

To link to this article: https://doi.org/10.1080/00958972.2024.2343109

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

Published online: 22 Apr 2024.

Submit your article to this journal

Article views: 96

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at https://www.tandfonline.com/action/journalInformation?journalCode=gcoo20

JOURNAL OF COORDINATION CHEMISTRY
2024, VOL. 77, NO. 11, 1161–1210
https://doi.org/10.1080/00958972.2024.2343109

REVIEW ARTICLE

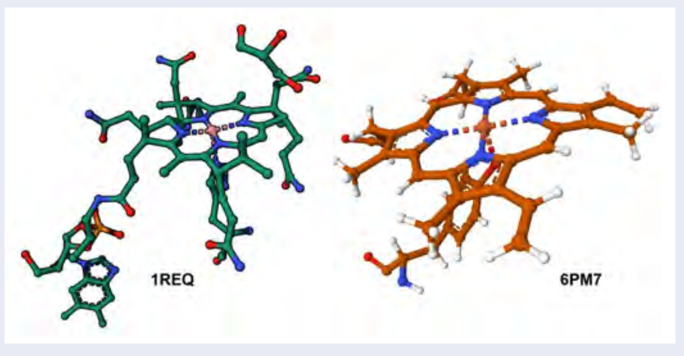
OPEN ACCESS

Corrins and porphyrins: two of nature's pigments of life

Helder M. Marques

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

ABSTRACT
Given the relative scarcity of cobalt in the earth's crust, its retention in biological systems, principally (but not exclusively) in the cobalt corrinoids or derivatives of vitamin B_{12}, may be surprising. The chemistry of these compounds and the much more widely utilized iron porphyrins, is compared and contrasted and an attempt made to explain the retention of cobalt chemistry in biology.



ARTICLE HISTORY
Received 31 December 2023
Accepted 5 February 2024

KEYWORDS
Cobalt; cobalt corrinoids; B_{12}; iron; iron porphyrins; hemes; hemoproteins

1. Introduction

Corrins (the cobamides, or cobalt corrinoids, derivatives of cyanocobalamin, [CNCbl], vitamin B_{12}) and porphyrins are tetrapyrrole macrocycles usually containing cobalt and iron, respectively; they are two of the "pigments of life" [1] (Figure 1). Some naturally occurring and synthetic tetrapyrroles are shown in Figure 2.

The structure of several cobamides is shown in Figure 3. The total synthesis of vitamin B_{12} (which is actually an artefact of the isolation of the cobalamin from liver and has to be converted to its biologically active forms *in vivo*) by Woodward and Eschenmoser [3] remains a landmark in synthetic organic chemistry. Some iron porphyrins, also referred to as hemes, are shown in Figure 4.

CONTACT Helder M. Marques Helder.Marques@wits.ac.za Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, South Africa
Dedicated to the memory of Professor O.I. Koifman

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

Figure 1. The pigments of life: (a) corrins; (b) porphyrins (exemplified here by protoporphyrin IX); (c) hydrocorphin; (d) chlorin.

One of the distinguishing features of the cobalt corrinoids and the iron porphyrins are their intense UV-visible spectra (Figure 5). In all cases, the spectra are dependent on the axial ligands present (and hence, in the case of iron porphyrins, on the spin state of the metal – cobalt in the corrinoids is always low spin irrespective of its oxidation state) and the oxidation state of the metal. It has been suggested that a complete understanding of the electronic transitions of these compounds will assist in development of their application in, for example, energy conversion and drug delivery systems [6].

Iron plays a key role in biology. The very low solubility of Fe(III) means that nature has had to develop transport and storage systems to harness the chemistry of this key element [9]. Iron porphyrins are widespread in nature fulfilling many functions [10–14]

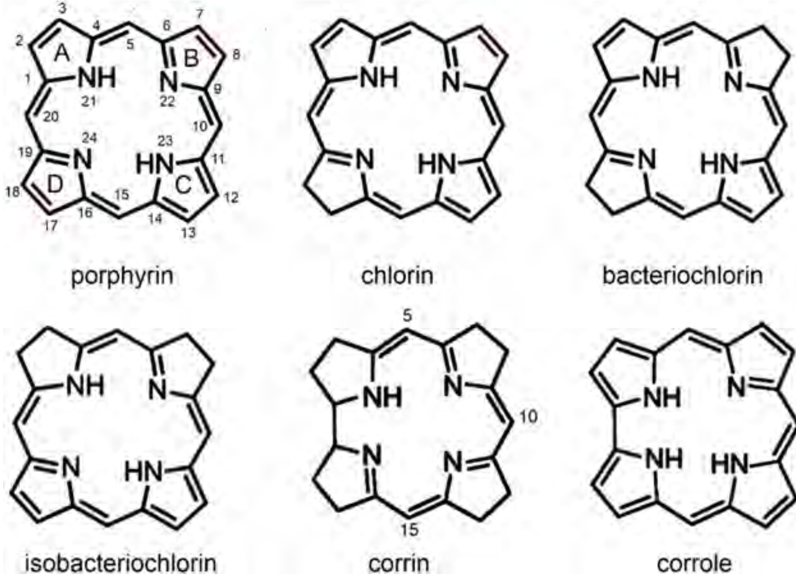


Figure 2. Selected tetrapyrroles. Chlorins are partially hydrogenated porphyrins and have the same oxidation state of the tetrapyrrole macrocycle as chlorophylls, the magnesium-containing tetrapyrroles in chloroplasts (Figure 1(d)). Bacteriochlorins, found in some bacteriochlorophylls, feature two reduced pyrrole rings. Isobacteriochlorins are found in nature as sirohydrochlorin, an intermediate in the biosynthesis of siroheme, found in the active site of sulfite reductase which converts sulfite to sulfide, which is incorporated in homocysteine. Corroles are synthetic analogs of corrins featuring a more extensive delocalized π electron system.

(including, and by no means limited to, the transport and storage of dioxygen [15–18]; electron transport [19–21]; as redox partners to other enzymes [22–25]; and as catalysts in the oxidases [26–29], peroxidases [27,30–33], catalases [34–36] and the superfamily of the cytochromes P450 [27,37–40] (Figure 6); in photosynthesis [42–44] and (using siroheme, a porphyrin with reduced A and B rings, see Figure 2), in the reduction of nitrite [45–47] and sulfite [47–49]). There is evidence of porphyrins in the fossil record [50]. For example, heme has been identified by TOF-MS in the blood contained in the abdomen of a 26 million year old, middle Eocene, female mosquito [51], and a recent report suggests blood sucking by mosquitos dates back to at least the early Cretaceous [52].

Corrins are much less widespread than porphyrins in nature and appear to occupy a small but nevertheless important niche in biology. Many organisms, including bacteria, archaea, and eukaryotes, but not plants, require them for growth. Only some bacteria and archae carry out their *de novo* synthesis [53–55]. Higher organisms have to absorb B_{12} from their diet or procure it in symbiotic relationships [56], and there is an elaborate absorption and transportation system [57,58].

Vitamin B_{12} itself, cyanocobalamin [CNCbl], has no known function and has to be converted into its biologically active form. The chemistry of the cobalt corrinoids is focused on the Co(II)|Co(III) couple (in the 5′-deoxyadenosylcobalamin [AdoCbl]-dependent enzymes) and the Co(I)|Co(III) couple (in the methylcobalamin [MeCbl]-dependent enzymes). Co(IV) does not appear to have a role in biology [59]. (Cobalt corroles can be oxidized to low spin d^5 Co(IV) [60], analogous to low spin d^5 Fe(III)

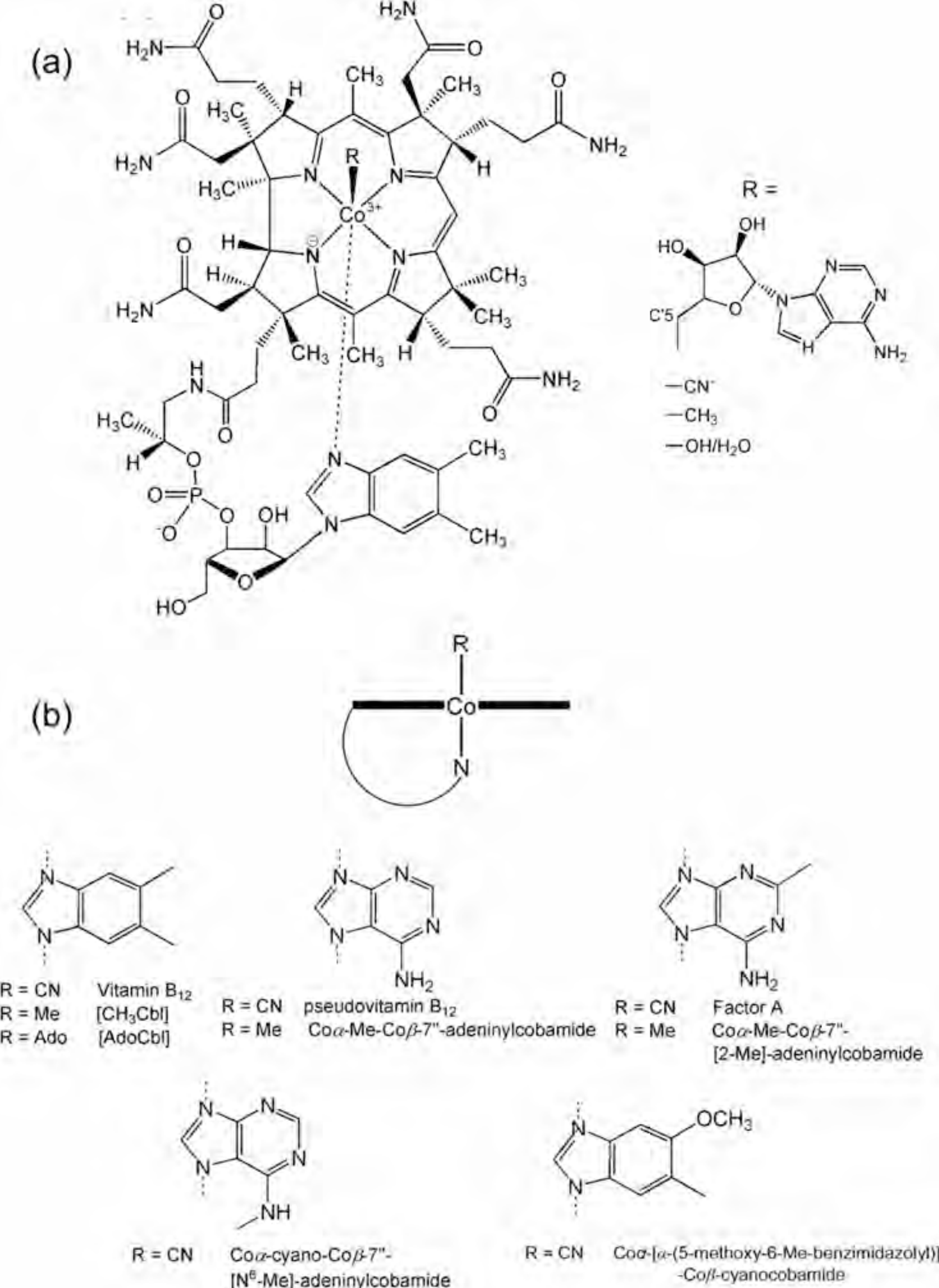


Figure 3. (a) The structure of the cobalamins (adapted from [2]). In adenosylcobalamin, [AdoCbl], or coenzyme B_{12}, the ligand occupying the upper (β) coordination site, $R = 5'$-deoxyadenosyl. Cyanocobalamin or vitamin B_{12} itself, [CNCbl], has $R = CN^-$. Methylcobalamin, [CH_3Cbl] or [MeCbl], has $R = CH_3^-$; in aquacobalamin, or vitamin B_{12a}, [H_2OCbl]$^+$, $R = H_2O$ and in hydroxocobalamin, [HOCbl], $R = OH^-$. The lower (α) axial ligand is 5,6-dimethylbenzimidazole (bzm). (b) Examples of the variability of the lower ligand of the cobalt corrinoids.

Figure 4. Hemes differ in the composition of the side chains of the porphyrin. The unusual farnesyl group in heme *o* is apparently important for anchoring the heme to the protein [4]. The conversion of a methyl group in heme *o* to a formyl group in heme *a* results in an increase of the redox potential by 180 mV [4, 5]. This high potential heme is used in the terminal oxidases. In heme *d* one of the double bonds of a pyrrole ring has been reduced so it is actually a chlorin rather than a porphyrin.

porphyrins [61]). Both [MeCbl] and [AdoCbl] feature a Co–C bond (Figure 3). Some examples of reactions catalyzed by these cofactors are shown in Figure 7.

[MeCbl] is the cofactor in several methyltransferases (Figure 7). The Co–C bond undergoes heterolytic cleavage, forming the "supernucleophile" cob(I)alamin, $[Cbl(I)]^-$ [63] and a methyl carbocation that is transferred to a nucleophilic acceptor. The reaction therefore involves Co formally cycling between a +1 and a +3 oxidation state (Equations 1 and 2).

$$\mathrm{Co(I) + R{-}CH_3 \rightarrow Co(III){-}CH_3 + R^-} \tag{1}$$

$$\mathrm{Co(III){-}CH_3 + R'^{+} \rightarrow Co(I) + R'{-}CH_3} \tag{2}$$

An example of an enzyme relying on this cofactor is 5-methyltetrahydrofolate-homocysteine methyltransferase methionine synthase (sometimes simply referred to as methionine synthase, MS, and termed MetH in bacteria). It catalyzes the transfer of a methyl group from 5-methyltetrahydrofolate (Me–THF) to homocysteine (Hyc) for methionine synthesis [64–66]. [MeCbl] also features as the cofactor in several enzymes

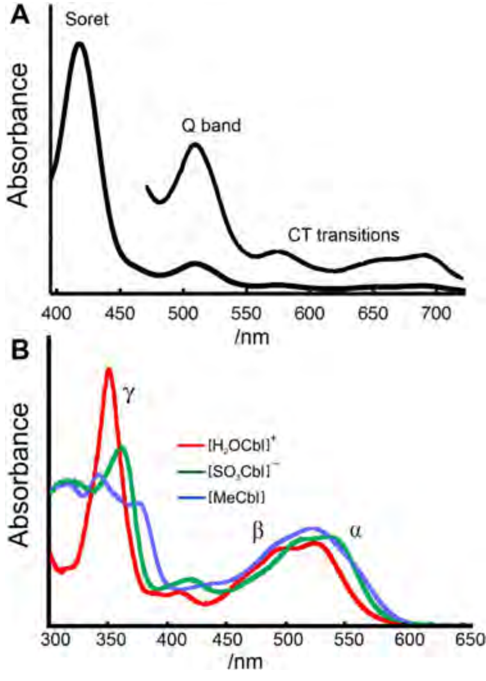


Figure 5. Representative uv-vis spectra of **A,** a ferric porphyrin (adapted from [6]) and **B,** some cobalamins (adapted from [7]). The Soret band of a porphyrin is due to a $S_0 \rightarrow S_2$ transition of the porphyrin, while the Q band is a $S_0 \rightarrow S_1$ transition. The weak longer wavelength bands are due to charge transfer transitions. The most prominent bands of a cobalamin are due largely to corrin $\pi \rightarrow \pi^*$ transitions, but virtually all transitions involve some contribution from the metal d orbitals [8]. Soft donor ligands increase electron density on the metal ion which raises the energy of the metal 3d orbitals. They are therefore able to mix with corrin π orbitals which increases the number of electronic transitions that occur in the γ region of the spectrum.

in the CO_2 fixing pathway in methanogenic archaea [67] and acetogenic bacteria [68]. An additional cofactor (Zn(II) or an [Fe_4S_4] cluster) is often present.

The adenosylcobalamin ([AdoCbl], $R = 5'$-deoxyadenosyl, Figure 3(a)) -dependent enzymes include the carbon skeleton mutases, eliminases, and aminomutases (Figure 7). The reactions are initiated by the homolytic cleavage of the Co–C bond of [AdoCbl], and the resulting Ado$^\bullet$ radical is the species that reacts with the substrate. Formally, Co cycles between the +3 and +2 oxidation states.

There are two enzymes in humans that require B_{12} chemistry. Methylmalonyl CoA mutase uses [AdoCbl] and converts methylmalonyl CoA into succinyl CoA, and methionine synthase, which uses [MeCbl], and features in the recycling of tetrahydrofolate by means of methionine synthesis from homocysteine. B_{12} deficiency is a serious condition that can result in damage to the myelin sheath of nerves and in megaloblastic anemia [69–75].

Biosynthesis of corrins and porphyrins initially follows a common porphobilinogen pathway [76] (Figure 8). The biosynthesis starts with uroporphyrinogen III which arises from the tetramerization of the biological pyrrole porphobilinogen [1]. Uroporphyrinogen III is the precursor of all natural porphyrinoids such as heme, siroheme and F_{430}. This has been extensively studied and reviewed [53,77–87] and

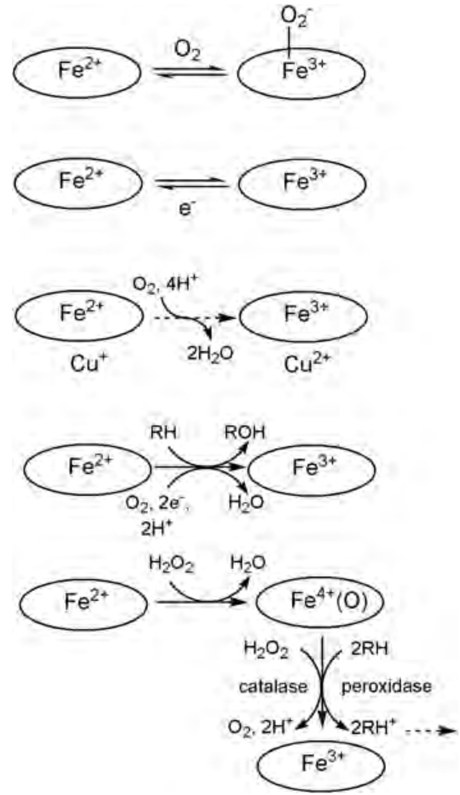


Figure 6. Examples of the roles played by hemoproteins (adapted from [41]).

recently summarized [88]. It has been suggested (see [89] and references therein) that since many bacteria are able to synthesize corrinoids while primitive anaerobes such as acetogens and methanogens are unable to synthesize porphyrins, the biosynthesis of corrins predates that of porphyrins, and corrin chemistry has its origins in prebiotic chemistry. It has been shown [90] that when coordinated to smaller metal ions (Co, Ni) rather than Fe, ring contraction of a corphinoid, giving rise to the direct linking of rings A and B, a feature of the corrinoids, occurs quite readily, as indeed do many of the complex structural elements that characterize the corrin ring of the corrinoids. The occurrence of this seemingly complex macrocyclic structure in nature is therefore not surprising.

Besides their role in biology, cobalt corrinoids and iron porphyrins have other interesting properties. By virtue of their aromaticity, porphyrin-based materials have been explored for potential application in materials science [91,92] and as electrochemical sensors [93]. Porphyrin-based covalent-organic and metal-organic frameworks have also attracted attention because of their promising CO_2 capture capabilities [94]. Isomeric annulated, expanded and contracted porphyrins are being explored for their unusual chemical and physical properties [95]. Under some conditions, metalloporphyrins can be contracted to form metallocorroles [96–99]. B_{12} conjugates can be used for oral delivery of protein drugs [100], while B_{12}-modified polymeric micelles can be exploited for oral delivery of drugs that have a low water solubility [101], and the application of B_{12}-based supermolecular nanoentities (SMEs) is beginning to be

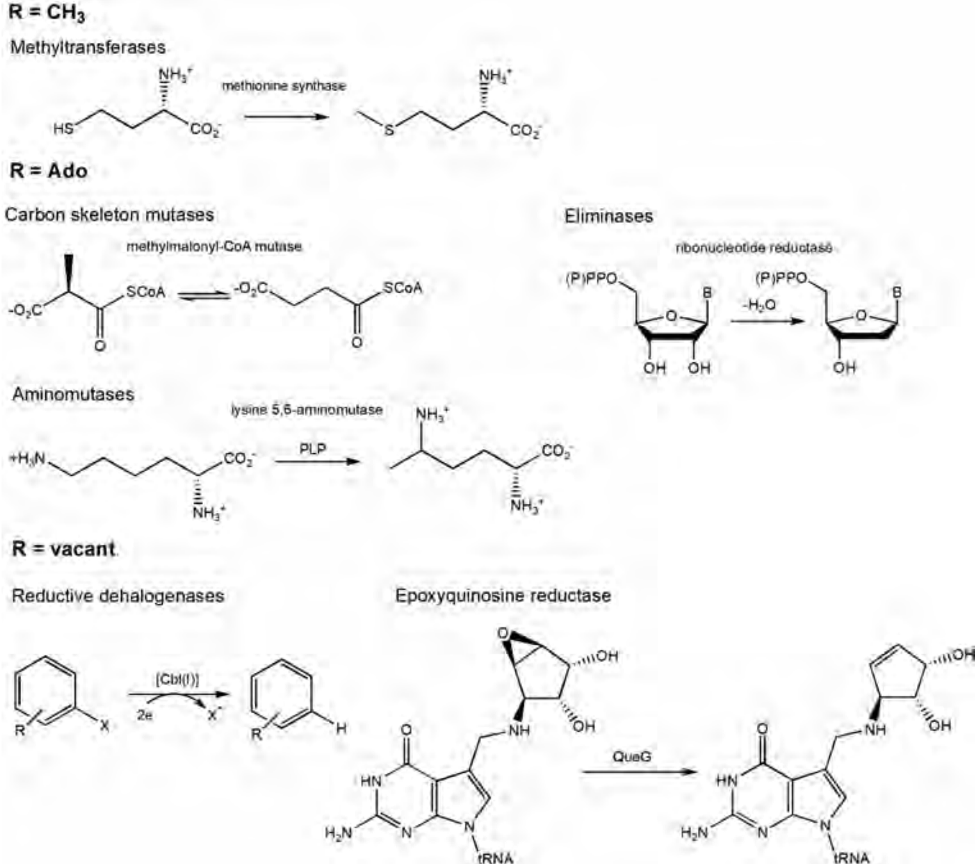


Figure 7. The most common reactions catalyzed by the cobalamins in biological systems. R refers to the upper (β) ligand of the corrinoid (Figure 3). Adapted from [62].

explored [102,103]. Antivitamins B_{12} [86,104–106], inert cobalamins such as 2-phenylethynyl-cobalamin [107], induce functional B_{12} deficiency; by reducing the synthesis of B_{12}, they impair bacterial growth and when added to sulfonamides, they enhance their antibiotic action [108]. They also show promise as antineoplastic agents [109].

Iron is geologically a common element and constitutes some 80% of the inner and outer cores of Earth [110], and is the fourth most abundant element in the crust [111]; cobalt is much less common (15–30 ppm in the crust) [112]. That nature has retained cobalt corrinoid chemistry suggesting the ability of the cobalt corrinoids to perform some unusual chemistry, chemistry perhaps not accessible by iron porphyrins. The difference between these related but different tetrapyrroles is the focus of this review. Given the immense scope of heme [11,14] and corrin chemistry [7,113,114], this review draws on illustrative examples and is by no means comprehensive.

2. Oxidation states

Some metal ions (Fe, Co, Cu and Ni, for example) are incorporated in biological systems because the chemistry in which they are involved relies on their accessing a

Figure 8. The initial steps in the biosynthesis of porphyrins and corrins. Adapted from [76].

number of oxidation states. One of the features of the heme-containing enzymes is their ability to alternate between Fe(II) and Fe(III) (and in some cases Fe(IV)). It is interesting to note that, cycling between Fe(I) and Fe(III), myoglobin (Mb) is capable of catalyzing the electrochemical reduction of N_2O and N_3^- on a graphite electrode [115].

In addition to the iron porphyrins there are many non-heme iron catalysts [116–118], perhaps most notably the iron-sulfur clusters [119–121]. The very nature of the cluster means that the assignment of a formal oxidation state to each Fe is difficult. For example, in the nitrogenase iron protein, the iron sulfur cluster in the zero oxidation state, $[4Fe{:}4S]^0$, iron is best described as being in the 2+ oxidation state; but in the oxidized $[4Fe{:}4S]^{2+}$ form, the metal is characterized as being in a valence-delocalized +2.5 state [122]. The important oxidation states of cobalt are Co(III) and Co(II) in the [AdoCbl]-dependent enzymes and Co(III) and Co(I) in the [MeCbl]-dependent enzymes.

Many other metal ions are exploited in biology because of a variable oxidation state. For example, coenzyme F_{430} is a Ni-containing hydrocorphin (Figure 1) found, for example, in methyl-coenzyme M reductase which converts CH_3–S–CoM and coenzyme B, CoB–SH, to CoM–S–S–CoB [123]. Two proposed reaction mechanisms involve Ni(I) and Ni(II), or Ni(I), Ni(II) and Ni(III) [124]. A second example is copper. The multi-copper oxidases feature a copper site that accepts electrons from its substrate and transfers them to a multi-copper site responsible for electron transfer to O_2 and its reduction to H_2O. Copper cycles between Cu(I) and Cu(II) [125,126].

3. Electronic structure

In its +3 oxidation state, the cobalt ion in the corrinoids is usually low spin and six-coordinate under aerobic conditions. There is a report [127] that the methylcorrinoid

in the methyl transferase from the bacterium *Sporomusa ovata* in which bzm of the cobalamins (Figure 3) attached to the α-ribose moiety of the *f* side chain is replaced by p-cresol, with a His residue of the protein in the α coordination site of the metal [128], is high spin; this is very unusual. The Co(II) form, cob(II)alamin, [Cbl(II)], or B_{12r}, is also low-spin and is usually five-coordinate in neutral solution with a vacant β coordination site with the unpaired electron density in $3d_z2$. There are exceptions. For example, reduction of cobalamin with dithionite produces a six-coordinate Co(II) species with SO_2^- in the β coordination site [129–131]. If the β coordination site is occupied, the bond to bzm is weakened. Protonation of bzm leads to a base-off [Cbl(II)] which is five-coordinate in a coordinating solvent, with a solvent molecule occupying an axial coordination site, as demonstrated by EPR and ENDOR methods [132]. A further one-electron reduction produces cob(I)alamin ($[Cbl(I)]^-$, B_{12s}; this is most often four-coordinate [133]. The ground state wavefunction of $[Cbl]^-$ is an admixture of d^8 Co(I) and d^7 Co(II)/corrin π radical [134,135] with significant destabilization of $3d_z2$; this, together with the partial biradical nature of the Co(I) state, may be an important reason for its 'supernucleophilicity' [63].

Recent quantum mechanical charge field molecular dynamics (QMCF MD) calculations [136] indicate that in aqueous solution a Co(II) porphyrin is high-spin and five coordinate, whereas the corresponding Co(III) complex prefers a low-spin, six-coordinate geometry. The ability of corrin to maintain Co(II) and Co(III) in a low-spin state is probably an important aspect of the biological chemistry of the cobalt corrinoids (*vide infra*). The Fe(III) analog of B_{12} undergoes ligand substitution reactions analogous to those undergone by $[H_2OCbl]^+$ and can be reduced to Fe(I) but not methylated [137]. A ferric corrin would therefore not catalyze the reactions catalyzed by [MeCbl].

Crucial to the majority of the chemistry of the cobalt corrinoids is the Co–C bond, as elaborated on below. An analysis of the electron densities of [AdoCbl] and [MeCbl], based on high resolution, low temperature X-ray diffraction studies, and DFT calculations with an analysis of the topological properties of the Co–C bonds, showed there is very little difference in the properties of the Co–C bonds of the two compounds [138]. Clearly it is the protein that controls the nature of the bond breaking of its cofactor. So a Co–C has to be stable to exist prior to initiation of the catalyzed reaction, yet flexible enough to allow for either a homolytic or a heterolytic cleavage. It has been suggested [139] that resistance of the Co–C bond to hydrolysis is one of the reasons for the use of organocobalt corrinoids in biology. Theoretical calculations found a Co–C bond to be between 33 and 48 kJ mol^{-1} more resistant to hydrolysis than a Fe–C bond [140].

The spin state of iron in the porphyrins depends on the oxidation state and the coordination number of the metal. Thus the metal in four-coordinate Fe(II) porphyrins is of intermediate spin ($S = {}^3/_2$). The delocalization of electron density between the metal center and the π system of the porphyrin stabilizes the triplet spin state over the high spin quintet state ($S = {}^5/_2$) [141]. Five-coordinate complexes of Fe(II) and Fe(III) porphyrins are typically high spin and six-coordinate complexes are low spin ($S = {}^1/_2$) [140,142]. In many iron porphyrins these spin states are quite close in energy [141,143].

4. Redox properties

At around pH 7 the Co(III)|Co(I) redox potential of $[H_2OCbl]^+$ is 0.200 V (vs SHE) and that of the Co(II)|Co(I) couple is −0.647 V [144]. The coenzymes [MeCbl] and [AdoCbl] are more difficult to reduce because of the donation of electron density by the alkyl ligand to the metal (–1.36 V for [MeCbl] [145,146]; −1.07 V for [AdoCbl] [147]). The Fe(III)|Fe(II) couple of the porphyrins ranges from −0.4 V to 0.4 V [13]. (The iron-sulfur proteins, $(FeS)_n$, span a very wide range, −0.7 V to 0.45 V, while the Cu(II)|Cu(I) couple in blue copper proteins ranges from 0.18 V to 0.75 V [13]). The thermodynamic stability of water (pH 7), its "electrochemical window," ranges from −0.41 V (for the $2H^+|H_2$ couple) to 0.82 V ($O_2|H_2O$), 25 °C, pH 7. That biological systems can operate outside this window illustrates how the structure of the redox center and that of the protein hosting that center, or by coupling a redox process intimately with a reaction, can overcome the thermodynamic limitations imposed by an aerobic aqueous environment. The occurrence of the strong reductant Co(I) in biological process is such an example.

The redox chemistry of cobalt porphyrins is rather more complex [148]. A Co(II) porphyrin has the metal ion in a low spin d^7 configuration. Redox processes may be (predominantly) metal-centered or ring-centered as shown in an investigation of the redox properties of a series of cobalt tetraaryl porphyrins (with substituents at the meso positions of the porphyrin and on the pyrrole rings) [149]. The initial reduction in CH_2Cl_2 of the meso-benzo Co(II) porphyrin leads to the formation of Co(I) which rapidly attacks the solvent producing a Co(III)–CH_2Cl^- species. With a meso-benzo porphyrin, the reduction produces a Co(II) porphyrin with a π-anion porphyrin radical. Oxidation of the meso-benzo porphyrin produces a Co(III) porphyrin, but with a meso-butano porphyrin, the product is Co(II) with a π-cation porphyrin ring.

Porphyrins readily stabilize Fe(II) and Fe(III) – the most important oxidation states in their biological roles – and Fe(IV)=O species are known [150], but Fe(I) is highly reactive and only generated transiently [148], for example, electrochemically [151,152]. The redox potential of iron porphyrins such as the cytochromes is controlled by a number of factors [153]. This is particularly important for them to assume their functional position in structures such as electron transport chains. The primary coordination sphere of the metal, i.e. the porphyrin, its identity and structure, and the axial ligands, are of primary importance. For example, bis-His ligation, which predominates in the *b*-type cytochromes, tends to result in a hemoprotein with a more negative potential than one with His and Met ligation, the predominant coordination motif in the *c*-type cytochromes. Mutation of cytochrome b_{562} from *E. coli*, with replacement of Met by His, decreases the midpoint potential by 260 mV at pH 7 [154]. However, the way the primary coordination sphere interacts with the secondary coordination sphere is also important [155–157], as is the folding of the protein. Another important factor is the extent of exposure of the cofactor to solvent, with tuning of the reduction potential by up to 500 mV [158,159]; the more hydrophobic the environment of the cofactor the greater the stability of the neutral Fe(II) cofactor relative to the cationic Fe(III) cofactor. The actual type of porphyrin seems to have a minimal effect. For example, replacing a *c*-type heme with a *b*-type heme modulates the potential only by between 23 and 75 mV [160,161].

5. Nature's exploitation of organometallic chemistry

The biological chemistry of the cobalt corrinoids is centered principally on the cobalamins and is dominated by the formation and cleavage of a Co–C bond [7,54,58,62,81,114,162–176]. There are other, more recently discovered functions of the cobalt corrinoids in nature such as riboswitches and photoreceptors. A riboswitch is a regulatory segment of a mRNA molecule that binds a small molecule; this results in a change in production of the proteins encoded by the mRNA [177–179]. [AdoCbl] functions as a riboswitch [180–183]. There is some evidence that cobalamin riboswitches are quite promiscuous, responding to a wide range of corrinoids [184].

Another relatively recent discovery are [AdoCbl]-dependent photoreceptors. They are used by some bacteria as a transcriptional repressor [185–187]. For example, CarH mediates the light-dependent expression of DNA coding for the transcription of proteins required for the synthesis of carotenes in some non-photosynthetic bacteria. Both cobalamin-dependent riboswitches and photoreceptors rely on the absorption of visible range radiation by a cobalamin.

As mentioned, the chemistry of the cobalt corrinoids is focused on the Co(II)|Co(III) couple (in the [AdoCbl]-dependent enzymes) and the Co(I)|Co(III) couple (the [MeCbl]-dependent enzymes). Crucial to the chemistry catalyzed by the organocobalamins, [RCbl], is the ability of a Co–C bond to undergo either heterolytic cleavage to form Co(I) and R^+ or Co(III) and R^-, or homolytic cleavage to Co(II) and $R^\bullet$. (Theoretical calculations suggest that it is conceivable that Co–C bond dissociation occurs by the oxidation of a cobalt corrinoid to a species which has some Co(IV) character and some Co(III)-π-cation character [188], but there is as yet no experimental evidence to support this.) Clearly a relatively weak Co–C bond is required for such chemistry to occur. The bond dissociation energy for heterolysis of the Co–CH_3 in [MeCbl] is 155 kJ mol^{-1} [189]. That for homolysis in [AdoCbl] is about 125 kJ mol^{-1} [190,191].

The observation of a Co–C bond in [AdoCbl] was a surprise [192] since such bonds were believed to be unstable towards hydrolysis. This provided a major impetus for the organometallic chemistry of tetrapyrroles (see for example [193–197]), and complexes such as $[Co(NH_3)_5(CH_3)]^{2+}$, once thought to be unattainable, were prepared [198]. The similarity of its UV-vis spectrum to that of $[Co(NH_3)_6]^{3+}$ as well as the similarity in its ^{60}Co nmr shift [198] strongly suggests that the Co–C bond is best described as a bond between Co(III) and a carbanion. It has been estimated [199] that $\log K \approx 27$ for substitution of H_2O in $[H_2OCbl]^+$ by CH_3^-.

It is instructive to compare these values with those determined with Fe(III) porphyrins. Alkyl complexes of Fe(III) porphyrins are low spin [200,201]. Based on a study of the kinetics of thermolysis of [Porph-Fe(CH_3)] (Porph = tetra(*p*-toluyl)porphyrinato), Riordan and Halpern [202] estimated the Fe(III)–CH_3 bond dissociation energy to be 88 kJ mol^{-1}, significantly weaker than the Co–CH_3 bond in [MeCbl]. Equilibration of solutions of [Porph-Fe(R)] (Porph = tetraphenylporphyrinato; R = ethyl, butyl) with CO leads to homolysis of the Fe–C bond and formation of an Fe–CO intermediate, and attack by the caged alkyl radical [200]. Similar results were obtained with CO_2 with formation of a carboxylate complex. The ability of iron porphyrin compounds to be able to perform cobalt corrinoid-type chemistry is therefore in doubt. There is a role for organoiron compounds in biology, nevertheless. They are intermediates in

lipoxygenase oxidations [203], and they are found in the heme inactivation in hemoglobin, myoglobin, cytochrome P450 and catalase by the suicide inhibitor, phenylhydrazine [204,205]. Organoiron complexes are also important as CO-releasing molecules, and as antimalarials and antineoplastic agents [206].

Metal-carbon bonds in biology, while perhaps rare, are not unusual; as Martin has pointed out [207], the enzymes that channel H_2, CO_2 and N_2 into methanogen and acetogen metabolism, probably conserved relics of primordial chemistry, have active sites that are known (or are likely) to feature metal-carbon bonds. Apart from [MeCbl] and [AdoCbl] these include the C cluster of carbon monoxide dehydrogenase (CODH, Ni–C(O)O–Fe) [208–210]; acetyl-CoA synthase (ACS, Ni–CO) [210–212]; the M cluster of nitrogenase (Fe–C–Fe) [213–215]; Fe–CO in [Fe]-hydrogenase [216,217], [Fe-Fe] hydrogenase H cluster [216,218,219], and [Fe-Ni]-hydrogenase [216,220]; and Fe–Ado in the radical *S*-adenosyl methionine (SAM) intermediate omega [221,222]. Co(I) porphyrins are highly reactive towards alkyl and aryl halides, with formation of a Co–C bond [223]. Oxidation of Co(III) porphyrins to form π-cation and dication complexes is possible (for example [223–226]).

The [AdoCbl]-dependent enzymes include the carbon skeleton mutases, eliminases, and aminomutases (Figure 7). The reactions are initiated by the homolytic cleavage of the Co–C bond of [AdoCbl], and the resulting $Ado^{\bullet}$ radical is the species that reacts with the substrate. Formally, Co cycles between the $+3$ and $+2$ oxidation states. As mentioned above, in humans methylmalonyl CoA mutase uses [AdoCbl] and converts methylmalonyl CoA into succinyl CoA.

Methionine synthase uses [MeCbl] and features in the recycling of tetrahydrofolate by means of methionine synthesis from homocysteine in humans. The methionine synthases form part of the S–adenosylmethionine (SAM) biosynthesis and regeneration cycle. However, while undoubtedly useful, and hence retained in nature, a cobalamin enzyme is not absolutely essential to catalyze such reactions; in plants this function is performed by a cobalamin-independent enzyme, and many microorganisms express both cobalamin-dependent and cobalamin-independent forms of the enzyme.

In methionine synthase the transfer of the methyl group from 5-methyltetrahydrofolate (CH_3–THF) to homocysteine occurs with Co(I) as an intermediate (Figure 9) [64–66,228]. The enzyme-catalyzed reactions are accelerated by between 10^6 to nearly 10^8 times compared to realistic protein-free methyl transfer reactions [229]. The role of a strictly conserved Ser-Asp-His triad (where His replaces bzm in the α coordination site of the cobalamin) is crucial [229].

Oxidation of Co(I) to Co(II) during enzyme turnover by O_2 or reactive oxygen species requires a regeneration cycle. Co(II) corrinoids themselves are readily oxidized to Co(III) by a wide variety of oxidants. The reaction with O_2 proceeds *via* intermediate formation of coordinated superoxide [230], a species that can be detected by EPR [230–233]. Cobalt corrinoids have been investigated as catalysts for the oxygen reduction reaction (ORR) at the cathode of a polymer electrolyte fuel cell [234]. There is some uncertainty whether the corrin survives the severe pyrolysis conditions used to prepare the cathode material (pyrolysis with carbon black at 700 °C), however, although there was minimal formation of metallic cobalt (unlike cobalt and iron porphyrins which yielded metallic particles). DFT calculations [235] suggest that a

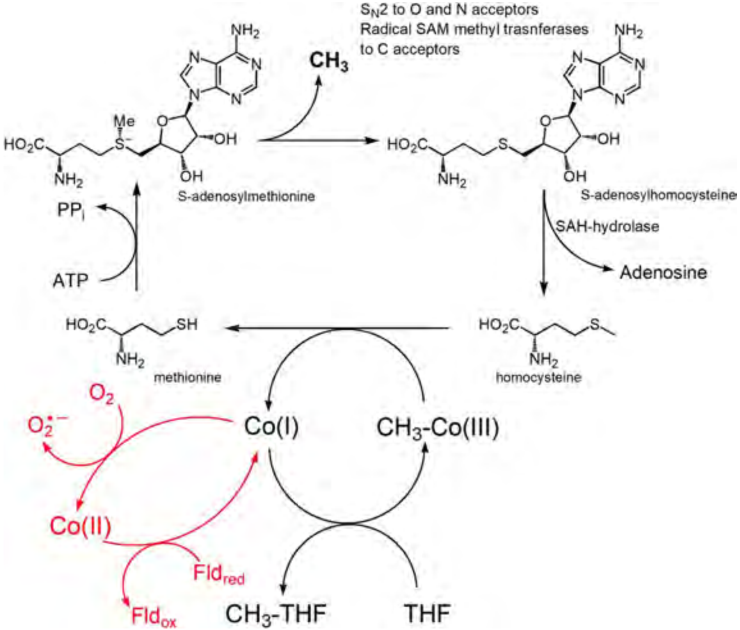


Figure 9. The transfer of a methyl group from 5-methyltetrahydrofolate to homocysteine, producing methionine, catalyzed by methionine synthase. A regeneration cycle (red) is required when about once every 2000 enzyme cycle turnovers [227] oxidation of Co(I) to Co(II) occurs. Adapted from [65].

Co-corrin (modelled with all corrin ring substituents as H and with no axial ligands) was a better catalyst for the ORR than the neutral complex, or a complex reduced by two equivalents.

Myoglobin with the heme group replaced by a Co(II)-tetrahydrocorrin has been prepared and crystallized as a potential model for the methyl transferases [236,237]. The metal ion is coordinated by the proximal His ligand of the protein, mimicking the coordination of Fe(II) in the native protein. The metal could be reduced to Co(I) by dithionite, and the crystal structure showed the formation of a four-coordinate Co(I) center, with displacement of the proximal His ligand [238]. Co(I) was methylated by methyl iodide, forming a methylcobalamin analog. This species slowly transfers the methyl group to the distal His, the residue in the heme pocket of Mb responsible for stabilizing the Fe–O_2 through hydrogen bonding [239]. Thus, while certainly able to carry out a methyl transfer reaction, the structure of Mb is not appropriate for interaction with a substrate targeted for methylation.

6. Other methyl transfer reactions in nature

Methyl transfer reactions are not confined to the cobalt corrinoids. In the final step of the acetyl-CoA (Ljungdahl-Wood) pathway of autotrophic carbon assimilation, acetyl-CoA is synthesized from Me^+, CoA and CO. A key reaction is the transfer of a methyl group from a cobalt corrinoid iron-sulfur protein (CoFeSP) to one of two Ni ions in the active site of the Ni- and Fe-containing enzyme acetyl-CoA synthase [240].

$$\text{Me–CoFeSP} + \text{CO} + \text{CoA} \rightarrow \text{CH}_3(\text{CO})\text{CoA} + \text{CoFeSP} \quad (3)$$

The reaction is thought to proceed by transfer of Me^{+}, generating Co(I), which is then remethylated by Me–THF. There is also a regeneration cycle for when the cobalt corrinoid is oxidized to Co(II). While it is generally believed that the transfer of the methyl group from Me–THF to the cobalamin entails the attack of Co(I), based upon molecular docking simulations of subunits from MetH and MtmBC (monomethylamine:CoM methyltransferase) it has been suggested that a radical-based electron transfer mechanism (involving Co(II) and a corrin-based radical) is more likely [241].

A Ni hydrocorphin, F_{430}, is quite competent at performing a methyl transfer reaction analogous to that – superficially, at any rate – carried out by the [MeCbl]-dependent methyl transferases, with Ni(I) acting as an attacking nucleophile. The reaction catalyzed by methyl-coenzyme M reductase (MCR) is important in the global carbon cycle [124,242,243]:

$$\text{CH}_3\text{–S–CoM} + \text{CoB–SH} \rightarrow \text{CoM–S–S–CoB} + \text{CH}_4 \quad (4)$$

The Ni(II)|Ni(I) couple is −0.65 V [244], more negative than the −0.41 V for the $2H^{+}|H_2$ (pH 7) couple that defines the lower limit of nature's "electrochemical window." (F_{430} can be oxidized to Ni(III) with $E^{o} > 1$ V [245]). That it is as high as it is (cf. −1.3 V in Ni-isobacteriochlorins) is a consequence of the structure of the hydrocorphin macrocycle, an interesting example of the importance of the structure of the macrocycle in these metallo-cofactors: (i) the macrocycle is monoanionic (porphyrins and isobacteriochlorines are dianionic); and (ii) there is an electron-withdrawing carbonyl attached to C15 (Figure 1(c)). These two features facilitate the reduction of Ni(II) [86]. Reduction of Ni(II) to Ni(I) in F_{430} places the extra electron density on the metal, producing an $S = 1/2$ species, unlike a Ni porphyrin or a Ni chlorin where the reducing equivalent is largely located on the macrocycle. This may be important if Ni(I) acts as a nucleophile in reactions catalyzed by MCR, analogous to the role of Co(I) in the reactions catalyzed by [MeCbl].

At least four mechanisms have been proposed for the reaction [246], including one where Ni(I) acts at the attacking nucleophile on the methyl of CH_3–S–CoM, generating a Ni(III)–CH_3^{-} species and $^{-}$S–CoM [247]. However, current evidence appears to favor the mechanism shown schematically in Figure 10 [123,124,246]. In the oxidized form of the coenzyme, Ni(II) is axially coordinated by a Gln residue [248–250], but is probably four coordinate in the reduced, Ni(I), active form. The oxidized Ni(II) form is converted to the active Ni(I) form by a multicomponent $[Fe_4S_4]$ protein [251].

Kräutler, Eschenmoser *et al.* [252,253] and more recently Zelder *et al.* [254] have shown that when Ni(II) is confined to a corrin-type system, it stubbornly remains as a diamagnetic square pyramidal d^8 complex even in the presence of coordinating solvents or exogenous ligands such as CN^{-} or SCN^{-}, whereas in the larger hydrocorphin ring it readily undergoes spin crossover to a paramagnetic octahedral complex, perhaps because the larger ionic radius of paramagnetic Ni(II) is not readily accommodated in a corrin. This might offer a rationale for the natural selection of a nickel hydrocorphin rather than a nickel corrin as the cofactor in MCR. However, the Rh analogs of [MeCbl] and [AdoCbl] have been prepared [255], emphasizing the flexibility of the corrin ring and its ability to accommodate larger metal ions [7]; low spin

Figure 10. The likely mechanism of the reaction of CH_3–S–CoM and CoB–SH catalyzed by methyl-coenzyme M reductase. Based on [246, 247].

six-coordinate Co(III) has an ionic radius of 55 pm while that of six-coordinate Rh(III) is significantly larger, 67 pm [256].

7. Non-corrin cobalt in nature

The biological chemistry of cobalt is not confined to the cobalt corrinoids. While not widely exploited compared to iron or copper, cobalt is used by a number of enzymes. The occurrence, function, and what is known about their reactions has been reviewed [257,258]. The enzymes include methionine aminopeptidase, prolidase, nitrile hydratase, thiocyanate hydrolase, glucose isomerase, methylmalonyl-CoA carboxytransferase, aldehyde decarbonylase, lysine-2,3-aminomutase, and bromoperoxidase (Figure 11).

Proteins that bind Co(II) usually use His and Glu residues for this purpose [259]. In many cases other metal ions such as Mn(II) and Fe(II) are found in similar enzymes from other sources and perform precisely the same chemistry. Clearly, Co is not absolutely essential for carrying out this chemistry.

Methionine aminopeptidase is an enzyme found in prokaryotes and eukaryotes that cleaves the N-terminal methionine from polypeptide chains [260]. It contains two Co(II) ions, probably bridged by OH^-, coordinated by the side chains of five amino acid residues. It functions as a bimetallic catalyst for a hydrolytic reaction, with bridging OH^- acting as the attacking nucleophile, similar to the function of bovine amino peptidase which contains two Zn(II) ions and the *E. coli* enzyme proline aminopeptidase that contains two Mn(II) ions.

Methionine aminopeptidase

Prolidase

Nitrile hydratase

R—C≡N → R—C(=O)NH$_2$

Thiocyanate hydrolase

$SCN^- + 2H_2O \rightarrow COS + NH_3 + OH^-$

Glucose isomerase

D-glucose → D-fructose

D-xylose → D-Xylulose

MethylmalonlyCoA carboxytransferase

L-methylmalonylCoA + pyruvic acid → propanylCoA + oxolactic acid

Aldehyde decarbonylase

Lysine 2,3-aminomutase

Bromoperoxidase

$H_2O_2 + HBr \rightarrow HBrO + H_2O$

$HBrO + RH \rightarrow RBr + H_2O$

Figure 11. Reactions catalyzed by Co-containing enzymes that do not depend upon a cobalt corrinoid. Adapted from [257, 258].

Prolidase [261–263], which catalyzes the degradation of dipeptides in which the penultimate residue is Pro, also contains two Co(II) ions (one of which is lost during purification but which is required for catalytic function to be restored). Two Asp, two Glu and a His residue appear to form the metal binding site.

Nitrile hydratase catalyzes the hydration of nitriles to amides [264]. The enzyme is composed of α and β subunits, and each $\alpha\beta$ pair contains one Co(III) ion as the prosthetic group. The crystal structure for the nitrile hydratase from *Pseudonocardia thermophila* JCM 3095 [265] shows cobalt coordinated through the S-donors of Cys111 and Cys113 which have been post-translationally modified to $CysSO_2H$ and to CysOH. Cys108, Ser112 and H_2O place Co(III) in a distorted octahedral site. The active site is similar to that of the iron-containing nitrile hydratases. Given its kinetic inertness, low spin Co(III) probably functions as a Lewis acid in the catalyzed reaction. A similar coordination environment in the iron-dependent nitrile hydratase stabilizes Fe(III), inhibiting its ability to bind O_2, and ensuring its role as a Lewis acid [265], probably using the metal-bound OH^- to deprotonate H_2O in the active site, with the resultant OH^- acting as the attacking nucleophile on the substrate. Modified nitrile hydratases have been developed as potential industrial catalysts [266].

Closely related to nitrile hydratase is thiocyanate hydrolase, purified from the eubacterium *Thiobacillus thiocapsa*, which catalyzes the hydrolysis of SCN^- to COS, NH_3 and OH^- [267,268]. Low spin Co(III) is five coordinate (*i.e.* the OH^- – or H_2O – found in nitrile hydratase is missing) so it is feasible that SCN^- binds directly to the metal [258], although the kinetic inertness of Co(III) takes this mechanistic proposal questionable.

Glucose isomerase is a commercially important enzyme that isomerizes D-glucose to D-fructose. It contains Co(II) in a distorted octahedral environment with N- and O-donor ligands from the amino acids of the protein [269,270].

Methylmalonyl-CoA carboxytransferase catalyzes the transfer of a carboxyl group from methylmalonyl-CoA to pyruvate to form propionyl-CoA and oxaloacetate. It contains a high spin Co(II) in a distorted octahedral environment in its active site [271].

Aldehyde decarboxylase is reported to contain one cobalt porphyrin per $\alpha\beta$ subunit [272], but this conclusion has been questioned [273]; cobalt porphyrins are not usually found in the aldehyde decarboxylases.

An enzyme which uses a reactive adenosyl-metal cofactor, mimicking the chemistry of the [AdoCbl]-dependent enzymes, is lysine 2,3-aminomutase [274]. Although it contains a high spin Co(II) in an octahedral environment, it is thought that *S*-adenosylmethionine methylates a reduced [Fe-S] cluster which then generates the adenosyl radical. This is captured and stabilized by interaction with the Co(II) center [275].

Bromoperoxidase from *Pseudomonas putida* contains cobalt, although the enzymes from other organisms use other metal ions (zinc, iron) [276–278].

Cobalt porphyrins are found in some bacteria, although their function, if any, is unknown. While Co is essential for prokaryotes and mammals, for example, its role in the biological chemistry of plants in only now beginning to be elucidated [279].

Moura *et al.* [280] reported that a protein containing a cobalt porphyrin was isolated from the sulfite-reducing organism *Desulfovibrio gigas* but its function was not determined. A similar cobalt porphyrin-containing protein was isolated from

Desulfovibrio desulfuricans [281] but its function also was not determined. Battersby and Sheng [282] subsequently showed that the cofactor is a Co(III)-isobaceteriochlorin. There is evidence that a cobalt porphyrin-containing enzyme isolated from the planktonic microalga *Botryococcus braunii* catalyzes decarbonylation of aldehydes, the final step in hydrocarbon biosynthesis [272], but this has been questioned [273]. There are cases known (for example, the DGCR8 protein, essential for processing canonical microRNA primary transcripts) where cobalt-protoporphyrin IX can mimic the function of the native heme cofactor [283]. The iron porphyrin of cytochrome P450 can be replaced with a cobalt porphyrin, but this does compromise the stability of the protein [284].

8. Activation of the Co-C bond

The Co–C bond in [AdoCbl] is remarkably stable towards thermolysis in aqueous solution, with $\Delta G^{\ddagger} = 124\,\text{kJ mol}^{-1}$ and $k = 10^{-7}$–$10^{-9}\ \text{s}^{-1}$ at 37 °C [285,286]. Since [AdoCbl]-dependent enzymes have k_{cat} of 2–300 s^{-1} [190,287,288], this means that the enzyme accelerates the rate of Co–C bond cleavage by up to 10^{13} times. How this is achieved was clearly a key question in B_{12} chemistry [289] with many suggestions advanced, including the upward flexing of the corrin (*vide infra*) or distortion of the Co–C–C angle by the protein [290,291], or a combination of these effects, including the coupling of Co–C bond cleavage to Ado–H bond formation [292]. There is now much greater clarity: it is the action of the protein on the cofactor that causes this remarkable effect when the enzyme binds the substrate [293–295]. While the detailed mechanism of the reaction will vary between different enzyme classes (carbon skeleton mutases, eliminases, class II ribonucleotide reductases, and amino mutases) broadly the reaction proceeds as follows [296]: (i) the substrate binds in the vicinity of the [AdoCbl] coenzyme; (ii) this induces changes in the conformations of the enzyme and the coenzyme, bringing the substrate and [AdoCbl] into close proximity and facilitating their interaction; (iii) these conformational changes induce geometric changes in the coenzyme by steric interactions, facilitating the homolysis of the Co–C bond to form cob(II)alamin and Ado$^{\bullet}$, and the radical is kept in the vicinity of the metal, which reduces the bond dissociation energy, with the structure stabilized by electrostatic and van der Waals interactions; (iv) the generated adenosyl radical initiates the radical chemistry required for the transformation of the substrate, details of which depend on the enzyme in question; and (v) the departure of the product and reformation of the Co–C bond completes the catalytic cycle.

An example of an [AdoCl]-catalyzed reaction, that of methylmalonyl-coenzyme A mutase (MCM), is shown in Figure 12.

The side chains of the corrin ring play an important role in stabilizing Ado$^{\bullet}$ in some of the enzymes. In others, hydrogen bonding between the side chains of amino acid residues of the protein and Ado$^{\bullet}$ play an important role in stabilizing the post-homolysis product and in positioning the substrate for reaction with Ado$^{\bullet}$ [295]. A series of neopentylcobalamins with a variety of groups attached to the *c* side chain were synthesized and the kinetics of the thermolysis of the neopentyl ligand examined [298]. There was virtually no effect on $\Delta H^{\ddagger}$ but $\Delta S^{\ddagger}$ increased with the bulk of the *c* side

chain while molecular mechanics calculations suggested there was no effect on the Co–C bond length or the Co–C–C bond angle. Increasing the bulk of the side chain reduces the ground state entropy, leading to the suggestion that enzyme-induced restriction of the motion of the acetamide side chains in the ground state, and relief of these restrictions in the transition state, could be a significant contributor to the enhanced rate of Co–C bond homolysis [298]. In methylmalonyl coenzyme A mutase the acetamide side chains are located in relatively open pockets of the protein and, with the exception of the *e* propionamide side chain, appear not to be hydrogen bonded to the amino acid residues of the protein [299]. The motion of the side chains might be restricted by a conformation change of the protein during enzyme turnover, partially contributing to homolysis of the Co–C bond [300]. The bulkiness of the Ado ligand is clearly important; the methyl group in [MeCbl] is too small for this corrinoid to act as the cofactor in these reactions [294].

Metal-carbon bonds are by no means confined to the cobalt corrinoids. Porphyrins containing metal–carbon bonds of many metals are known [195]. Synthetic routes include the reaction of chloro- or dichlorometalloporphyrins with alkyllithium or alkylmagnesium halides,

$$[\mathrm{PorphFeCl}] + \mathrm{RM(X)} \rightarrow [\mathrm{PorphFeR}] + \mathrm{ClM(X)} \tag{5}$$

(X = halide, or absent if M = Li) or the reaction of low-valent metalloporphyrin with alkyl halides,

$$[\mathrm{PorphFe^{I}}] + \mathrm{RX} \rightarrow [\mathrm{PorphFe^{III}R}] + \mathrm{X^-} \tag{6}$$

Fe(II) porphyrins undergo oxidative addition with alkylating agents involving the (formal) transfer of one electron.

Figure 12. The reaction catalyzed by methylmalonyl-coenzyme A mutase (MCM). Adapted from [288, 297].

$$[PorphFe^{II}] + RX \rightarrow [PorphFe^{III}X] + R^{\bullet} \text{ (slow)} \quad (7)$$

$$[PorphFe^{II}] + R^{\bullet} \rightarrow [PorphFe^{III}R] \text{ (fast)} \quad (8)$$

The resulting alkyl (or aryl) porphyrins are usually low-spin complexes, but may occur in an equilibrium mixture of high-spin and low-spin forms, depending on the donor properties of R and the basicity of the porphyrin itself [301,302]. However, the Fe–C bond of alkylporphyrins is susceptible to an insertion reaction as, for example, in their reaction with SO_2:

$$[PorphFe^{III}R] + SO_2 \rightarrow [PorphFe^{III}(SO_2R] \quad (9)$$

Cobalt porphyrins containing a Co–C bond can be prepared by reaction with an alkyl- or aryllithium compound (X = halide) or by the reaction on a Co(I) porphyrin with an alkyl or aryl halide [195].

$$[PorphCo^{III}X] + RLi \rightarrow [PorphCo^{III}R] + LX \quad (10)$$

$$[PorphCo^{I}]^{-} + RX \rightarrow [PorphCo^{III}R] + X^{-} \quad (11)$$

However, as mentioned in Section 3, a Fe–C bond is much more susceptible to hydrolysis than a Co–C bond.

9. Comparing porphyrins and corrins – the macrocycle and its cis effect

That Co(III) actually plays a significant role as a catalyst in biology is perhaps surprising. Low spin Co(III), along with Cr(III), is the quintessential kinetically inert metal ion from the first row of the d block because of the large ligand field contribution to the activation energy [303,304]. Both Fe(II) and Fe(III) are orders of magnitude more labile [305] and, on the face of it, much more suited for a role as a catalyst in biology. It is perhaps obvious that the corrin ligand must control and modify the fundamental properties of the metal ion. Indeed, the kinetic lability of Co(III) in the cobalt corrinoids suggests that the corrin macrocycle may impart significant lability to the metal ion, perhaps conferring on it some measure of labile Co(II)-like character [7]. It has been known for many years that a clear elucidation of the oxidation state of a metal ion in a complex with ligands that have a delocalized electronic structure is problematic [306–308] and that the nature of the tetrapyrrole ligand controls and modifies the properties of the metal ion [309]. There is a strong interaction between the cobalt ion and the corrin as shown by the significant differences in ^{59}Co and ^{13}C nmr signals of two polymorphs of cyanocobalamin [310,311].

A metal ion such as Cr(III) can be accommodated in a porphyrin and Cr(III) porphyrin complexes are well known (for example [312,313]) and continue to attract attention (for example [314–317]). It is probable that Cr(III) can be accommodated in a corrin as well; even though the ionic radius of Cr(III), 0.615 Å [256], is larger than that of six-coordinate low spin Co(III), 0.545 Å, it is smaller than that of five-coordinate low spin Co(II), 0.67 Å or Rh(III), 0.665 Å, both of which are readily accommodated by a corrin, in for example cob(II)alamin (although the metal is displaced by 0.12 Å from the mean plane of the four equatorial N donors towards the 5,6-dimethylbenzimidazole (bzm)

ligand) [318] and in the Rh(III) analog of adenosylcobalamin, [AdoRhCbl] [319], respectively.

It has been suggested [320] that the hole size of a tetrapyrrole is important in controlling and modifying the properties of the metal ion, suggesting a fundamental difference between porphyrins and corrins. The average metal–N_{corrin} bond lengths of low spin Co(III) and low spin Co(II) corrins are identical (c. 1.90 Å) [7]. There is little variation in the metal–N_{corrin} bond length with a change in the spin state of Co [321,322]. This is not the case with porphyrins which show a dependence of the metal–N_{porph} bond lengths on the spin state of the metal [322]. This ensures that in cobalt corrins there is virtually no impact on the reorganization energy associated with the change in oxidation state, and so must contribute to an efficient conversion between (formally) Co(III) and Co(II) in the [AdoCbl]-dependent enzymes, provided that (as in the [AdoCbl] enzymes) the reduction is accompanied by a decrease in coordination number.

On the other hand, one of the important functions of iron porphyrins in biology is to act as electron transfer agents in electron transport chains [323]. Theoretical calculations show that the inner sphere reorganization energy for the Co(III)|Co(II) couple in a cobalt corrinoid with two axial imidazole ligands is very large (197 kJ mol^{-1}) because of the location of the unpaired electron density in $3d_z2$, whereas for the Fe(III)|Fe(II) couple in an iron porphyrin this is a very modest 8 kJ mol^{-1}, rationalizing why cobalt corrinoid complexes are not used as biological electron transfer agents [140]. Furthermore. DFT calculations, using the BP86 functional, suggest 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 [140], rationalizing the occurrence of the matching of the metal to the macrocycle in nature [142].

Cr(III) is an important trace element and aids in normal insulin function; chromium imbalance affects sugar metabolism. It has been associated with the glucose tolerance factor (GTF) isolated from brewer's yeast and its role may be to supply Cr(III) to cells deficient in the metal ion [324]. Cr(III) is involved in the breakdown of lipids and carbohydrates by interfering with the insulin signaling pathways [325], and it stimulates fatty acid and cholesterol synthesis. Chromium deficiency has been associated with a diabetic-like condition, impaired growth, decreased fertility and increased risk of cardiovascular diseases [326–328]. However, to be involved in the reactions catalyzed by the cobalt corrinoids, it would have to form Cr(II) and Cr(I), both of which are highly reducing and control of their reactivity would be difficult [199]. That Cr serves no function in biological Co-type chemistry is therefore not surprising.

The rate of ligand substitution on a Co(III) corrinoid is significantly faster than in cobaloximes, porphyrins, tetraammine or bis-ethylenediamine systems [7]. For example, the rate of substitution of H_2O in aquahydroxocobinamide [329] is nearly two orders of magnitude faster than for aquahydroxo-Co(III)hematoporphyrin [308]. Even more dramatic is the rate of hydrolysis (25 °C, substitution of NH_3 by H_2O) of $[(NH_3)(CN)Cbi]^+$, $k_{aq} > 0.3\ s^{-1}$ [330] (Cbi = cobinamide; cobinamides are incomplete corrinoids that lack the nucleotide tail, with hydrolytic cleavage of the nucleotide side chain at the phosphate group) compared to trans-$[Co(cyclam)Cl(NH_3)]^{2+}$,

$k_{aq} = 4.6 \times 10^{-11}$ s^{-1} (25 °C) [331] (cyclam = 1,4,8,11-tetra-azacyclo-tetradecane), a difference of nearly 10 orders of magnitude. (Cyanide and chloride have a similar trans labilizing effect [332].) The corrin clearly has a marked cis effect and there is clear evidence for the electronic communication between the equatorial ligand and the axial ligands in the corrinoids [333–336].

Perturbing the electronic structure of the corrin can provide further evidence for the cis effect of the macrocycle [7]. For example, if the H at C10 of a cobalamin is replaced by electron-withdrawing NO, this completely deactivates the metal ion towards ligand substitution by pyridine [337]. The replacement of the C10H by Cl [338] or Br [339] of a cobalamin results in a decrease in the rate of substitution of H_2O by N_3^-, imidazole and pyridine due to smaller values of $\Delta H^‡$ which fail to compensate for more negative values of $\Delta S^‡$, a consequence of an earlier transition state along the reaction coordinate, which is the result of a lower charge density on the metal, making it a better electrophile towards the incoming and the departing ligand. For a detailed discussion of such effects, and a comparison of the kinetics of ligand substitution on corrins, corrins in which the conjugated π system has been interrupted, analogs where the corrin macrocycle has been cleaved, and porphyrin analogs of cobalamin, see [7].

Despite their extended conjugation, porphyrins are very flexible and not necessarily planar [41,340], a flexibility that is often important for their function. This flexibility is key to the allosteric behavior of hemoglobin, with the movement of iron into the porphyrin plane on binding of O_2 [341]. Several workers have noted that there is a correlation between the redox potential of a cytochrome and the distortion from planarity of its heme group [342,343]; for example, in yeast iso-1-cyt *c*, the Fe(II) form has a saddle conformation, a deformation that becomes more pronounced in the oxidized form. This results in significant changes to the hydrogen bonding network around the cofactor, to the orientation of a heme propionate side chains, and to the iron-Met bond length, which increases by 0.08 Å (although the iron-His bond length merely increases by 0.02 Å, probably within the uncertainty in its crystallographic determination). Of course, there is always an element of doubt whether solid state structures are really representative of the active, *in vivo* structures. In this case, the crystallographic observations have been largely verified by nmr studies [344–347]. Another example is cytochrome $P450_{BM-3}$, the prokaryote enzyme originally from *Bacillus megaterium* which catalyzes the hydroxylation of several long-chain fatty acids; reduction from Fe(III) to Fe(II) causes very significant structural changes in the protein [348]. However, significant structural differences between the oxidized and reduced forms do not always occur [349].

Cytochrome b_5 from a variety of species exists in two isoforms of the heme group, A and B, where the B form has the heme rotated by 180° about the C5-C15 axis (Figure 2). The A/B ratio varies from 20 in chicken cyt b_5 [350] to 1 in rat liver outer mitochondrial membrane cyt b_5 [351]. The redox potential of the A and B forms of bovine erythrocyte cyt b_5 differ only by about 27 mV, which probably is not physiologically significant [352].

An interesting parallel has been drawn between iron porphyrins and cobalt corrinoids; the first can act as reversible oxygen carriers, the latter as reversible free radical

carriers [291]. Porphyrins and corrins do share some similar non-biological catalytic properties. The reductive dehalogenases (RDases), enzymes that contain two iron-sulfur clusters and a cobalt corrinoid, catalyze reactions in which a halogen atom is removed from an organic substrate [353,354]. The cofactor is bound with water (or hydroxide) in the β coordination site of Co. They degrade both naturally-occurring [355] and anthropogenic organohalogens in the environment [356]. The mechanism probably involves cob(I)alamin as attacking nucleophile [353,357]. Cobalt corrinoids, cobalt porphyrins and ferric porphyrins have all been shown to be effective non-enzymatic catalysts for the reductive dechlorination of chlorohydrocarbons [358–362]. B_{12} is a somewhat more effective catalyst for the reduction of NO to N_2O by dithiothreitol than cobalt hematoporphyrin or cobalt protoporphyrin IX [363].

Given the very diverse biological function of iron porphyrin-containing proteins (O_2 transport and storage, electron transfer agents, and catalysts in many reactions) how this diversity of function is achieved has been a theme of bioinorganic chemistry research for many years (see for example [364]).

While the chemistry of the cofactor of a metalloprotein is of course vital, its intrinsic properties are controlled and modified by the protein to which it is bound to form the enzyme [365]: the protein provides the reaction medium; it is the scaffold for the arrangement of the reactants and the catalytic site; it may provide ligands that bind the metal ion or metal-containing cofactors in place; it may exert a conformation influence of the cofactors, perhaps bind them in an entatic state; and it mediates the interaction with other components in a supramolecular biological system. So the structure of the protein, the identity of the proximal axial ligand [366], and the nature of the amino acid side chains in the immediate vicinity of the distal side of the prosthetic group are undoubtedly important. The distortions of the porphyrin itself influence the redox properties of the prosthetic group [367], as also seen in the chlorophylls [368]. The ease of oxidation of an iron porphyrin increases with its deviation from planarity [368–371]. Despite their delocalized electronic structure, porphyrins are flexible [364,372–375], a flexibility that is seen, for example, in the cytochromes [376] and which may be related to their biological function [364]. Credence for this is provided by the observation that the nature and extent of the distortions tends to be preserved for a given type of hemoprotein from different species [364], striking examples being the very marked saddle distortions of 25 peroxidases and ruffled conformations of the cytochromes *c* from, for example, rice, horse and tuna. Of course, as Shelnutt *et al.* have pointed out [364], the porphyrin's conserved distortion from planarity may simply be a consequence of the conserved tertiary structure of a particular enzyme across a multitude of species.

Theoretical calculations indicated that in a four-coordinate metalloporphyrin the nature of the distortion of the porphyrin from planarity (Figure 13) depends on the size of the metal ion and its spin state [377]. A porphyrin can host P(V) by adapting a severe *ruf* conformation; a low spin Ni(II) porphyrin is either moderately ruffled or planar; high spin Fe(II) porphyrins are also moderately ruffled; a Zn(II) porphyrin is planar; while a Pb(II) porphyrin is domed. A survey of crystallographic structures indicated than a planar or near planar porphyrin core will have metal–N_{porph} bond lengths between 1.96 and 2.08 Å and calculations suggested that minimum strain occurs with

metal–N_{porph} bonds of 2.035 Å, in agreement with an observation that the ideal length for such a bond is between 2.01 and 2.04 Å [378].

Reduction at the methine carbons of a porphyrin increases its flexibility [379]. The reduction of neighboring methine positions in F_{430}, the cofactor of the *S*-methyl coenzyme M system which contains Ni(II) and catalyzes the reversible reduction of *S*-methylcoenzyme M (CH_3–S-CoM) with coenzyme B (HS–CoM) to methane and CoM–S–S–CoB in the final step of methanogenesis [380] provides the porphyrin with the flexibility needed to accommodate Ni(I), rationalizing its physiological redox role [381]. The radical nature of the Ni(I)-F_{430} cofactor enables it to reduce the substrate, although it does make the enzyme very susceptible to oxidation by O_2 to Ni(II) or Ni(III), requiring an elaborate reactivation system [381]. The flexible hydroporphyrin readily accommodates both high spin 6-coordinate and low spin four-coordinate Ni(II) [379].

Once thought to be important in the homolysis of the Co–C bond in the [AdoCbl]-dependent enzymes because of steric interaction between the corrin and the Ado ligand, the upward folding (the "mechano-chemical trigger" [290,382], steric [383–387] or "butterfly effect" [291,388]) of the corrin ring is now believed to have at most a minor effect on activation of the bond [292]. A feature of the corrin are the many side chains pointing to its upper and lower faces. There is some evidence that the conformation of these side chains may play an important role during enzyme turnover, either through steric or hydrogen bonding effects [389–391], or, through restriction of their motion, by entropic destabilization of the Co–C bond [298].

The interaction of the acetamide *a* side chain with the adenosyl group is important for maintaining Ado in the catalytic position in diol dehydratase and ethanolamine

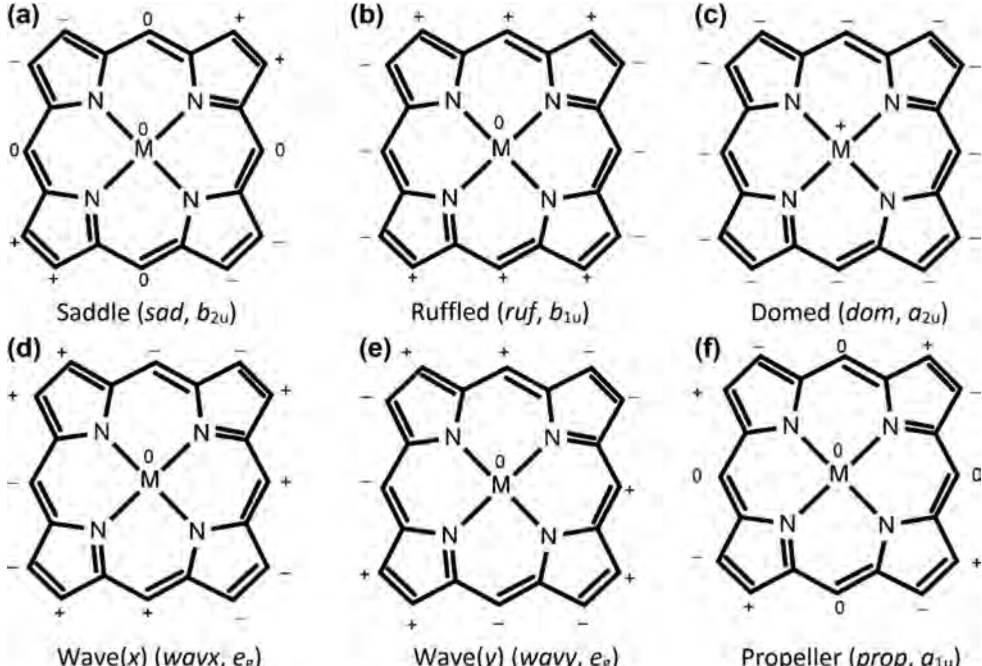


Figure 13. Common departure from planarity of porphyrins above (+) and below (–) the mean porphyrin plane (assuming D_{4h} symmetry for a planar porphyrin). Adapted from [367].

ammonia-lyase [392]. The side chain swings between the original and catalytic positions in a synchronized manner with the radical shuttling between the coenzyme and substrate. If residues that interact directly or indirectly with the *a* side chain are mutated, the rate of unproductive side reactions increases and the enzyme turnover decreases. In a ribonucleotide reductase from *Thermotoga maritima*, the *e* side chain hydrogen bonds to the substrate GDP, locking it in proximity to the [AdoCbl] cofactor [393]. It has been suggested that hydrogen bonding between C19H and 3′-O of the ribose moiety of the Ado ligand aids in the formation of Ado$^{\bullet}$ [394], but the effect is likely to be small [395].

Gryko *et al.* recently demonstrated how side chains are important in a non-enzymatic C–C bond formation reaction, between an alkene and a diazo moiety to produce a mixture of an alkene and an alkane product, catalyzed by a Co(I) corrinoid [396]. Modification of the *c* and *d* side chain substituents had a very significant effect on both the yield and the selectivity of the reaction. The presence of a hydroxyl group in the *c* side chain significantly increased the yield and selectivity (in favor of the alkene product), suggesting that hydrogen bonding with the reactant promotes the selectivity for the alkene over the alkane. The work emphasizes the importance of both steric and electronic effects in the overall course of a cobalt corrinoid-catalyzed reaction.

Another effect that the side chains of a corrin will have is on the kinetics and thermodynamics of the ligand substitution reaction of the upper face of the corrin, for example, the substitution of H_2O by an exogenous ligand. Log *K* for the coordination of imidazole by aquacyanocobinamide (amide side chains), 4.14, decreases to 3.95 for coordination by aquacyanocobester (methyl ester side chains), and to 3.57 when the side chains are propyl esters [330,397–399].

Electrostatic effects are also important. For example, the value of log *K* for coordination of CN^- by aquacyanocobinamide, aquacyanocobester and aquacyanocobyrinic acid (carboxylate side chains) decreases from 6.25(6), to 6.13(5), and to 5.1(4) (21 °C, pH 7.5) as the interaction of coordinated CN^- changes from an attractive interaction with an amide side chain(s), to a hydrophobic interaction, and then to a repulsive interaction [400].

10. The axial ligand

One of the obvious differences between a corrin and a porphyrin is that the macrocycle in the first is much more saturated than the second, and, when coordinated to the metal, is a mono anion while the latter is a dianion (ignoring the side chains). But the axial ligands coordinated to the metal ion are also important. A review of how the properties of the tetrapyrroles of nature are tuned by their axial ligand, based largely on computational modelling, is available [143].

In [MeCbl]-dependent methionine synthase, the bzm base is displaced by a His residue from a Asp-X-His-X-X-Gly sequence [401] (the "base-off/His-on" form), a sequence that is also found in many [AdoCbl]-dependent enzymes. The "base-off/His-on" form is also found in the [AdoCbl] isomerases [299,402,403] and aminomutases [404–406], whereas the isomerases [407–409] and class II ribonucleotide reductases [410] have the "base-on/His-off" form. A question that arises is how important is the axial ligand

in the lower (α) coordination site in controlling and modulating the properties of the cofactor. That [AdoCbl]-catalyzed chemistry is carried out with either His or bzm as axial ligand suggests that the identity of the axial ligand in cobalamin chemistry is of minor importance. Indeed, the very fact that a wide range of Co–N_α bond lengths are found in the crystal structures of cobalamins [7,411] suggests that the bond is quite flexible. Theoretical modelling of glutamate mutase using QM/MM methods [412] indicate that compression of the Co–N_α bond has very little effect on the Co–C bond dissociation energy. Other studies [413,414] support this conclusion.

The identity of the axial ligand is much more important in iron porphyrin chemistry. The cytochromes are widely used as electron transfer agents in electron transport chains in both aerobic and anaerobic environments with iron cycling between Fe(II) and Fe(III). Other functions include involvement in cell apoptosis [415]. All cytochromes involved in electron transfer reactions have iron as a six coordinate, low spin ion. In the *b*-type cytochromes the axial ligands are two His residues; in the *c*-type cytochromes they are His and Met. A His and the α amino group of Tyr occurs in chloroplast cyt *f* [416]. (Bacterioferritin, which is used for iron storage and homeostasis in some bacteria, features bis-Met ligation [417]). The use of neutral axial ligands ensures a low (5–9 kJ mol^{-1}) inner sphere reorganization energy when the oxidation state of the metal changes [418], important for their function as electron transfer agents. The reorganization energy is much higher (20–47 kJ mol^{-1}) if one axial ligand is charged. Such iron porphyrins are typically used as catalysts in biology: the cytochromes P450 (Cys); beef liver catalase (Tyr); nitric oxide synthase (Cys); horseradish peroxidase (His^-); and some peroxidases (Arg). In the cytochromes both Fe(II) and Fe(III) are in their low spin state, further contributing to a low reorganization energy. The reduction potential of the Fe(II)|Fe(III) couple can be tuned by an appropriate choice of axial ligand [418,419]. Thus catalase ($<$0.5 V) $<$ P450 (−0.30 V) $<$ horseradish peroxidase (−0.22 V) $<$ Mb (0.05 V).

11. Binding oxygen

Earth's original atmosphere was reducing in nature [420] and life on Earth, probably dating back to about 3.4 billion years ago [421–423], was anaerobic. However, about 2.7 billion years ago, the action of cyanobacteria (blue-green algae) which are able to perform photosynthesis, photo-oxidizing water through two reaction centers, Photosystems (PS), PSI and PSII [424–426], released O_2 (Equation 12); this gradually reacted with and displaced methane as a major component of the Earth's atmosphere [427,428].

$$nCO_2 + nH_2O \xrightarrow{h\nu} (CH_2O)_n + nO_2 \tag{12}$$

This "Great Oxidation Event" presented a substantial hurdle for life on Earth. While its ability to serve as the oxidant for fuels that drive the production of energy in living systems was clearly an important step in evolution, oxygen also confronts those systems with significant challenges with the formation of reactive oxygen species (ROS), $^1O_2$, O_2^-, H_2O_2, $OH^\bullet$; this leads to oxidative stress, a challenge that had to be overcome to enable the evolution of aerobic multicellular organisms [429]. For example,

oxidative stress leads to inflammation, mitochondrial degeneration and the development of tumors [430–433].

The study of the biological chemistry of dioxygen has attracted a great deal of attention [434]. An important example is the transport and storage of O_2. As neatly summarized by Jensen *et al.* [143] there are several issues involved in the reversible binding of dioxygen to hemoglobin (Hb) and myoglobin (Mb). The tetrameric protein Hb transports O_2 in the circulatory system, while monomeric Mb, present in muscle tissue, facilitates O_2 diffusion and also provides a means for the removal of NO. Firstly, the binding must be reversible but fast. Secondly, since O_2 is a spin triplet, while high spin [PorphFe(III)] is a quintet, and the product is a low spin Fe(III) singlet, the reaction involves a spin crossover, and the nature of the iron-oxygen bond has drawn particular attention.

The study of the binding of O_2 by iron porphyrins as model compounds for Hb and Mb dates back many years (see [435] and references therein). It was established early on that deoxyHb is paramagnetic while oxyHb is diamagnetic [436]. The flexibility of the porphyrin ensures that the spin change which accompanies the oxygenation of Fe(II) incurs a very small energy penalty [377].

The nature of the Fe–O_2 bond became the subject of considerable debate [437–439], described alternatively as a resonance hybrid of two structures (Figure 14(a)) or as an Fe(III)–O_2^- complex with a (predominantly) ionic bond between Fe(III) and O_2^- (Figure 14(b)), with antiferromagnetic coupling of the unpaired electrons on low spin Fe(III) and O_2^-. In between these two extremes were the suggestions of McClure [440] and of Goddard and Olafson [441] of an intermediate spin Fe(II) antiferromagnetically coupled to a triplet O_2.

It is well-established that Co(II) complexes with N-donor ligands, when oxygenated, produce Co(III)-superoxo complexes (for example [442] and references therein). In oxyhemerythrin, O_2 is bound as a peroxide [443]. So transfer of electron density from a metal to bound O_2 is certainly well-established. HbO_2 and MbO_2 are subject to nucleophilic attack by H_2O or OH^- in the heme pocket, resulting in the formation of the Fe(III) forms, metHb and metMb [444]. This auto-oxidation of HbO_2 in the presence of adrenaline results in its oxidation to adrenochrome, a reaction that is inhibited by superoxide dismutase (SOD) [445]. Superoxide is generated during the auto-oxidation of MbO_2 [446]. The mechanism of autoxidation of HbO_2 is predominantly due to dissociation to Fe(III) and O_2^- [447].

There is other evidence for transfer of electron density from Fe(II) to bound O_2. The O–O stretching frequency in HbO_2, 1107 cm^{-1}, is as expected for superoxide (1150–1100 cm^{-1}) [448]. The results of fluorescence emission spectroscopy of MbO_2 are consistent with an equilibrium between a singlet state with coordinated O_2 and a triplet state with coordinated O_2^- [449]. The uv-vis spectrum of HbO_2, by analogy with oxycobalt complexes the structure of which, as established by EPR measurements, is consistent with coordinated O_2^-, suggests coordinated oxygen is best described as O_2^- [450]. The O-O stretching frequency in oxy complexes of Fe(II) and Co(II) are very similar (1107 and 1006 cm^{-1}, respectively) [451], evidence that the nature of bound O_2 in these complexes is very similar. EPR measurements on $CoHb^{17}O_2$ are consistent with some 60% of the unpaired electron density from low spin Co(II) having been

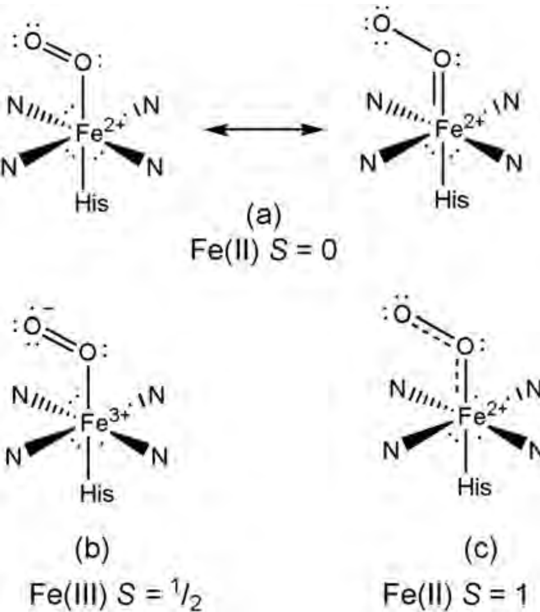


Figure 14. Models for the binding of O_2 in HbO_2 and MbO_2. (a) The resonance hybrid model of Pauling. Fe(II) is envisaged to be d^2sp^3 hybridised (using its d_z2 and $d_x2_{-y}2$ orbitals), with these hybrid orbitals involved in the bonding to its six ligands. The remaining d orbitals accommodate the six d electrons of Fe(II), forming a low spin complex. There is overlap between oxygen π orbitals and d_{xz} and d_{yz} orbitals with partial electron transfer to O_2. (b) The model of Weiss envisages a full electron transfer from iron to oxygen resulting in a (predominantly) ionic bond between low spin Fe(III) and O_2^-. (c) In the models of Clure, and Goodard and Olafson, $S = {}^3/_2$ Fe(II) is antiferromagnetically coupled to a triplet O_2, a structure reminiscent of ozone.

transferred to coordinated O_2 [452]. ^{57}Fe Mössbauer spectra of HbO_2 show quadrupolar splittings, diagnostic of Fe(III) [453]. Continuous wave and pulse EPR and ENDOR investigations of oxygenated Co(II) corrin and porphyrin complexes show that the unpaired electron density resides predominantly on the O_2 ligand [233].

More recent work, as summarized in [454], emphasizes the multiconfigurational character of the iron-oxygen bond, a character which varies depending on experimental conditions. For example, Fe(III)–O_2^- is dominant in HbO_2 in solution, whereas Fe(II)–O_2 is dominant in crystalline HbO_2 [455]. Theoretical calculations (DFT/MM and CASSCF/MM) [456]) support the notion that the iron-oxygen bond has predominant Fe(III)–O_2^- character in MbO_2 although in the gas phase there is a somewhat lower transfer of electron density from iron to oxygen.

A unified version of the nature of the bonding in HbO_2 and MbO_2 has emerged from high-resolution X-ray Kβ emission and K-edge absorption spectroscopy and theoretical calculations (TD-DFT, CASSCF) [457]. The conclusion reached is that iron is essentially $S = 1$ Fe(II) with minor charge transfer to O_2, imparting on the ligand a measure of superoxide character. The iron-oxygen bond has significant double-bond character, and the complex has a three-center, ozone-like, electron delocalization.

The spin state of the metal ion is often an important factor in hemoprotein chemistry. The change in spin state from high spin Fe(II) in deoxyHb to low spin Fe(II) in

oxyHb, which involves the movement of the metal ion from out of the heme plane and into the plane is the basis of the cooperativity behavior of Hb [458,459]. *Af*GcHK is a histidine kinase from *Anaeromyxobacter* sp. Fw109-5 that functions as an oxygen sensor enzyme. Binding of O_2 to its Fe(II) porphyrin center in the protein's sensor domain substantially enhances the autophosphorylation activity of its functional domain [460]. The Fe(III) and Fe(II)-O_2 complexes are active, but the Fe(II) complex is inactive. On substituting the iron protoporphyrin IX with its cobalt analog it was found that Co(III) and Co(II)–O_2 complexes were fully active while the Co(II) complex (which is low spin), unlike the Fe(II) complex (which is high spin), was moderately active. Hence the activity of the enzyme depends on the spin state of the metal center.

Hemoproteins in which the porphyrin is not covalently linked to the protein are amenable to the extraction of the heme group [461], and its replacement by a different cofactor. This has provided many opportunities for assessing structure-function relationships, and the effect of the metal ion and the cofactor on the metalloprotein's function, as well as the development of novel biocatalysts [462] and "designer" metalloproteins with novel function [463]. Another strategy is to grow a strain of *E. coli* under iron-limited, cobalt-rich conditions which results in the incorporation of cobalt protoporphyrin IX into myoglobin, peroxidase, catalase, aldoxime dehydratase and P450 [464,465].

Cobalt corrinoids cannot act as reversible dioxygen carriers, although Co(II) porphyrins, and indeed cobalt-reconstituted Hb and Mb [466,467], can reversibly bind O_2 [466,468–475], best described as predominantly a Co(III) complex of superoxide [476]. Substituting Fe-protoporphyrin IX with a cobalt porphyrin in human adult Hb decreases its O_2 affinity by over a factor of 10 [474]. Aquacobalamin (vitamin B_{12a}) is stable in aerated solutions. At low temperature in methanol solutions, cob(II)alamin (B_{12r}) reacts reversibly with O_2 to form what is best described as a superoxo complex of Co(III) [230,477]. However, near room temperature B_{12r} is rapidly oxidized to Co(III) [478], apparently by disproportionation to Co(III) and Co(I), with the latter being rapidly oxidized by O_2 [479]. Cob(I)alamin (B_{12s}) itself is rapidly oxidized by O_2 and has to be handled under anaerobic conditions.

Oxy compounds of iron porphyrins are important in enzymes, offering protection against oxidative stress, or overcoming the spin-forbidden reaction of triplet O_2 with singlet substrates by complexing oxygen to iron. Examples include the cytochromes P450, which act as monooxygenases or mixed-function oxidases and use pyridine nucleotides as electron donors for the oxidation of organic substrates,

$$\mathrm{NAD(P)H} + \mathrm{O_2} \rightarrow \mathrm{NAD(P)^+} + \mathrm{RO} + \mathrm{H_2O} \tag{13}$$

with electron transfer by means of a flavoprotein or an iron-sulfur protein [480]; heme-containing dioxygenases in which both oxygen atoms of O_2 are incorporated into organic substrates [481]; the catalases [482], which degrade H_2O_2 to H_2O and O_2, thus protecting against oxidative damage to cells; and the peroxidases [483], which catalyze the oxidation of substrates by H_2O_2 and other peroxides,

$$\mathrm{ROOH} + \mathrm{AH_2} \rightarrow \mathrm{ROH} + \mathrm{A} + \mathrm{H_2O} \tag{14}$$

and so are important for the removal of phenolics and peroxides as well as the degradation of mycotoxins.

The cytochromes P450 contain the thiolate of a Cys residue as proximal ligand. This is important for facilitating O–O bond cleavage, for substrate binding, electron transfer and for the correct folding of the protein [484]. The generalized mechanism of the P450s is shown in Figure 15; precise details vary depending on the particular enzyme and, in particular, the substrate RH [480]. A crystal structure of the oxy-ferrous intermediate is available [485]. The occurrence of Compound 0 in the cycle is well established [486] and the existence of Compound I has been kinetically and spectroscopically demonstrated [487].

Co(II) Schiff base complexes are capable of catalyzing the oxidation of organic carbonyls by O_2 [488] and cobalt porphyrins can act as P450-type catalysts for oxidation of toluene [489]. However, substituting the iron porphyrin with a cobalt porphyrin in P450 drastically decreases the thermal stability of the enzyme [284].

Nitrous oxide (N_2O) is known to bind to $[Cbl(I)]^-$ [490], and inactivates methionine synthase [491]. In nature, the reduction of N_2O to N_2 is carried out by the copper-dependent N_2O reductases [492]. Mb reconstituted with cobalt protoporphyrin produces a protein capable of reducing N_2O to N_2, driven electrochemically using a viologen as the electron transfer partner, but there was considerable oxidative damage to the protein scaffold [493]. Thus while a cobalt protoporphyrin is certainly a competent N_2O reductase, this study emphasized the importance of the structure of the protein for executing a particular chemical reaction.

A generalized scheme of reactions catalyzed by the catalases and the peroxidases is shown in Figure 16. (Compound 0 is a transient intermediate.) In the presence of excess peroxide, the ferric enzyme forms Compound III, a ferriperoxidase-superoxide complex [495,496]. In the absence of a reductant, AH_2, peroxidases will convert H_2O_2 into H_2O and O_2 [497], but not very efficiently, essentially becoming trapped as Compound III [498].

It is known that in the catalase reaction both oxygen atoms in the O_2 product that is generated originate from the same H_2O_2 reactant [499]. Catalases contain a distal His residue that serves as an acid-base catalyst and the two hydrogens of H_2O_2 are sequentially transferred to the oxyferryl unit of Compound I [500] (Figure 17(a)) although a direct mechanism (Figure 17(b)) is possible [501] and will operate if the distal His residue is mutated out. QM/MM calculations provide a detailed insight of the electronic rearrangements that occur during the reaction [482]. In either case, the reaction involves the intermediate formation of a Compound II-like species.

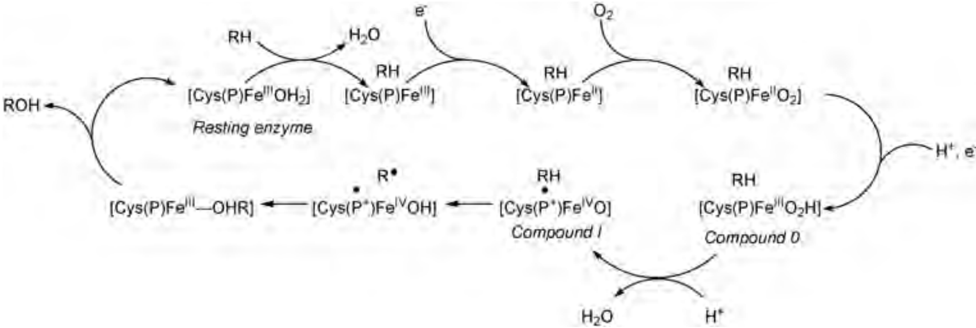


Figure 15. The mechanism of the cytochromes P450. Adapted from [480].

Horseradish peroxidase reconstituted with a cobalt porphyrin retains its catalytic activity [471], and there are reports of cobalt complexes and cobalt nanomaterials able to catalyze the oxidation of organic substrates by H_2O_2 (for example, [502–506]), as there are of their catalase activity [507–511]. However, replacement of the iron porphyrin with a cobalt analog leads to an essentially dysfunctional catalase in *Enterococcus faecalis* [512].

Iron porphyrins also couple with other metal ions to form efficient catalysts, such as the heme-copper oxidases. An example is cytochrome *c* oxidase, the terminal enzyme of the respiratory chain located in the membrane of the mitochondria or in the membranes of bacteria and archaea. The reaction catalyzed is the reduction of O_2 to H_2O,

$$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O \quad (15)$$

In the process, protons are pumped across the membrane, generating a proton-motive force that is used in the synthesis of ATP, a cell's energy currency [513]. The final recipient of electrons, and the site of O_2 reduction, is a heme group near a copper ion, itself coordinated by three His residues, one of which is covalently linked to a Tyr (Figure 18). The mechanism of the reaction has been comprehensively reviewed [515].

Some time ago, Collman *et al.* reported an interesting model compound for the O_2 reducing site of cytochrome c oxidase [516]. The model compound consists of a Co(II) porphyrin with a proximal imidazole ligand, and with side chains elaborated to bind a Cu(I) triazacyclononane. The compound binds O_2 to form a bridged peroxide which can then be electrochemically reduced with cobaltocene to two equivalents of H_2O. This demonstrates that, in principal at least, cobalt porphyrins could effectively occupy the site of an oxidase enzyme. The reduction of O_2 to $2H_2O$ can also be effected by

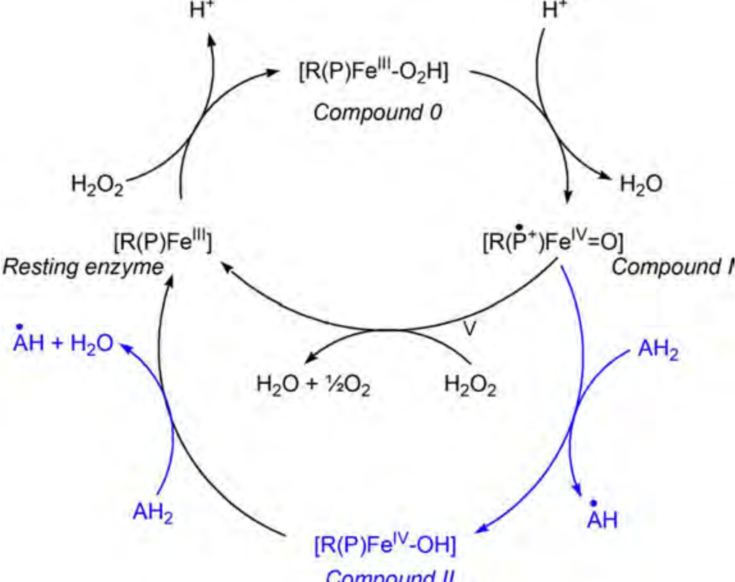


Figure 16. Outline of the mechanisms of (black) the catalases and (blue) the peroxidase. In beef liver catalase, for example, the axial ligand R is Tyr; in horseradish peroxidase it is His. Adapted from [482, 494].

Figure 17. Two feasible mechanisms for the reaction of Compound I with H_2O_2 in the second step of the catalase reaction cycle. Adapted from [499–501].

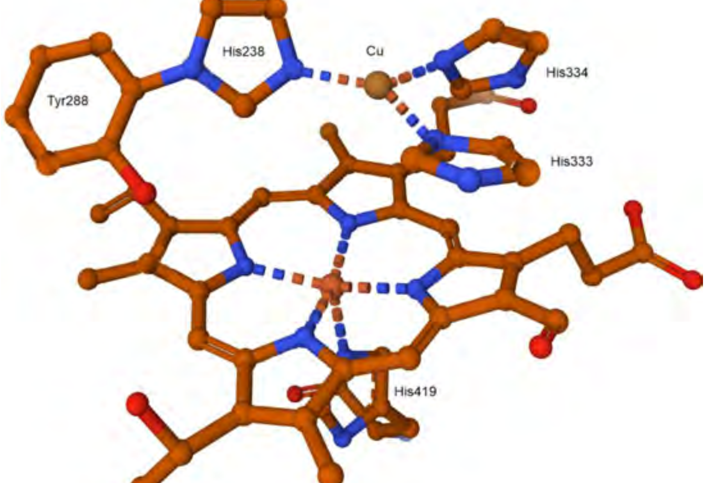


Figure 18. The binuclear active site of the fully reduced form of cytochrome c oxidase from *Rhodobacter sphaeroides*. PDB code: 3FYE [514].

other cobalt compounds such as Co(III) corroles [517] and Co(II) porphyrins [518], and O_2 to H_2O_2 by a variety of cobalt macrocyclic compounds [519].

12. Summary and conclusions

It is intriguing that despite its relative scarcity in the earth's crust, cobalt has been retained by nature to fulfil a range of biological functions, principally (but not exclusively) in reactions catalyzed by the cobalt corrinoids, derivatives of vitamin B_{12}. Iron is geologically much more abundant. Having devised methods for solubilizing, transporting and storage of iron, biology has exploited it (usually as Fe(II) and/or Fe(III)) for many tasks, including the transport and storage of dioxygen, in electron transport chains, in photosynthesis and in many enzymes. This review focused only on the chemistry of the iron porphyrins.

That Co(III), in the form of a Co(III) corrinoid, actually plays a role in biology is surprising – certainly surprising to a coordination chemist! Clearly, the corrin must modify Co(III) to enable cobalt to function as a catalyst in biology. There is a strong interaction between the corrin macrocycle and the metal, perhaps conferring on it a measure of labile Co(II) character. Thus the rate of ligand substitution of a Co(III) corrinoid is much faster than in a porphyrin, a cobaloxime or an equatorial tetraammine system. This cis effect of the corrin can be verified by modifying its structure by, *inter alia*, introducing electron donating or electron withdrawing substituents onto the macrocycle, by interrupting the delocalized π electron system, or cleaving the macrocycle [7].

The biosynthesis of cobalt corrinoids and iron porphyrins share a common porphobilinogen pathway and it has been suggested that the biosynthesis of the corrinoids preceded that of the porphyrins and harks back to prebiotic chemistry since many bacteria synthesize corrinoids but primitive anaerobes such as acetogens and methanogens are unable to synthesize porphyrins.

There are two principal roles for the cobalt corrinoids. The first is in methyl transfer reactions, with [MeCbl] as cofactor, involving the cycling between (formally) Co(I) and Co(III). The second is in the [AdoCbl]-dependent enzymes, including the carbon skeleton mutases, eliminases, and aminomutases, with cycling between Co(II) and Co(III). Both feature a Co–C bond, an unusual, but not unique, exploitation of organometallic chemistry in nature. The Co–C bond undergoes heterolytic cleavage in the [MeCbl]-dependent enzymes, but homolysis in the [AdoCbl]-dependent enzymes. This versatility of the Co–C bond and the availability of the three oxidation states is crucial for the use of cobalt in these systems.

The cobalt corrinoids are required by many organisms, including bacteria, archaea, and eukaryotes, but not plants. The regeneration of methionine from homocysteine catalyzed by a methionine synthase, is carried out both by cobalamin-dependent (for example, in humans) and cobalamin-independent enzymes (in plants). Higher organisms have to absorb B_{12} from their diet or procure it in symbiotic relationships. Since methyl transfer reactions are also catalyzed by, for example, a Ni hydrocorphin in methyl-coenzyme M reductase, this does emphasize that cobalt is not absolutely essential for carrying out such reactions.

To mimic the chemistry of the [MeCbl]-dependent methyl transferases, the cobalt center in myoglobin has been reconstituted with a Co(II)-tetrahydrocorrin. It was found that this can be reduced to Co(I) and methylated with methyl iodide but the methyl group is slowly transferred to the distal His residue of the protein. This emphasizes that not only nature of the prosthetic group but also the architecture of the protein is important. The structure of myoglobin makes it unsuitable as a methyl transferase.

A key feature of the biological chemistry of the cobalt corrinoids is the Co–C bond. Both in [MeCbl] and in [AdoCbl] the bond is very stable towards thermolysis. In the [AdoCbl]-dependent enzymes it is the architecture of the protein and the changes that occur in its conformation on binding of the substrate that induce bond homolysis, placing the resulting $Ado^{\bullet}$ radical in a position to effect the radical chemistry that leads to the transformation of the substrate. The methyl of [MeCbl] is too small for this cofactor to function in the enzymes that use [AdoCbl].

The Fe–C bond in porphyrins is significantly weaker than the Co–C bond of the corrinoids; hence iron porphyrins are ill equipped to perform as catalysts in the reactions catalyzed by cobalt corrinoids. Indeed, organoiron complexes are rare (but not unknown) in biological systems. An Fe(III) corrinoid can be reduced to Fe(I) but not methylated; ferric corrins are therefore incapable of functioning in the [MeCbl]-dependent enzymes. Porphyrins readily stabilize Fe(II) and Fe(III) (and Fe(IV) in some reactions) but Fe(I) is highly reactive and can only be transiently generated.

There are other functions for the cobalt corrinoids, including their use as photoreceptors and riboswitches, and the chemistry of cobalt in plants is only now beginning to be unraveled. There are several enzymes that use non-corrinoid cobalt – and perhaps cobalt porphyrins, although there is some uncertainty about this – at the catalytic site, but in many cases the chemistry they catalyze is equally well catalyzed by other metals. In many of these cases cobalt (usually Co(II)) functions as a Lewis acid rather than a redox center. When an iron porphyrin is replaced by a cobalt porphyrin in some enzymes (such as the DGCR8 protein), function is retained, although in the case of cytochrome P450, for example, the stability of the protein is compromised.

Co(III) in the corrinoids is almost invariably six coordinate while Co(II) is usually five coordinate. In both cases the metal ion is a low spin species, ensuring that there is minimal reorganization energy associated with a change in oxidation state, which is important for rapid reaction at this cofactor. Iron porphyrins, by contrast, feature a metal ion whose spin state depends on the oxidation state of the metal. By contrast, there would be a large reorganization energy associated with the reduction of Co(III) to Co(II) if the metal were to remain six coordinate, whereas the reorganization energy associated with the reduction of low spin six coordinate Fe(III) to low spin six coordinate Fe(II) in an iron porphyrin is very small. This rationalizes the use of iron porphyrins in electron transport chains. Moreover, whereas a change in the oxidation state of an iron porphyrin is largely confined to a change in the oxidation state of the metal, the redox chemistry of cobalt porphyrins is more complex, and may be metal-centered or porphyrin-centered, depending on the structure of the porphyrin. Iron porphyrins, but not cobalt porphyrins, are therefore used in electron transport chains.

The relative flexibility of a porphyrin provides a means of controlling the redox potential of an iron porphyrin, as does the identity of the axial ligands, and the exposure of the cofactor to the solvent. Although it was once thought that the flexibility of the corrin, in the form of an upward fold during turnover in the [AdoCbl]-dependent enzymes was important for the homolysis of the Co–C bond, this is now known to have a minimal effect. However, the conformation of the corrin's side chains probably play a role during enzyme turnover, either through steric or hydrogen bonding effects, or both.

Another factor that might be assumed to be important in controlling function is the identity of the axial ligand. Some [AdoCbl]-dependent enzymes have the bzm ligand displaced by a His residue. But since the chemistry carried out by the "base-off/His-on" and the "base-on/His-off" forms is very similar, this suggests the identity of the axial ligand is not a major factor in B_{12} chemistry. The identity of the axial ligand is much more important in the case of the iron porphyrins. Neutral axial ligands (for example, bis His in the cytochromes *b* and His and Met in the cytochromes *c*) contribute to a low reorganization energy on a change of the metal's oxidation state,

consonant with the function of these hemoproteins in electron transport. Charged ligands (Cys, Tyr, Arg, His^{-}) are found in the hemoproteins that function as catalysts.

Oxycobalt complexes are well-established to be Co(III)-superoxo complexes. Bonding in HbO_2 and MbO_2 is somewhat different; there is minor charge transfer from $S = 1$ Fe(II) to O_2, so the ligand has a small measure of superoxide character. The iron-oxygen bond has significant double-bond character, and the complex has three-center, ozone-like, electron delocalization. This is likely to contribute to the resistance of the oxygen carrier and storage hemoproteins to autoxidation. This of course does occur and nature has developed defense mechanisms (catalase, peroxidase, superoxide dismutase) to cope with the formation of this and other radical oxygen species. While cobalt corrinoids cannot acts as reversible carriers of O_2, Co(II) porphyrins reconstituted into Hb and Mb can indeed reversibly bind O_2, but are subject to more pronounced decomposition to Co(III) and O_2^{-} compared to the iron porphyrins. So it is clear why iron porphyrins function as reversible oxygen carriers, while cobalt corrinoids are reversible radical carriers [291].

By complexing O_2, hemoproteins such as the cytochromes P450 which act as monooxygenases or mixed-function oxidases, overcome the spin-forbidden reaction of triplet O_2 with a singlet substrate. Some hemoproteins, such as horseradish peroxidase, retain their catalytic activity when the iron porphyrin is replaced by a cobalt porphyrin, while others, such as catalase, become dysfunctional.

In conclusion, while it is certainly likely that living systems could evolve in the total absence of cobalt, the cobalt corrinoids in particular seem to have been retained for the small, but important role, they play in nature, a role they fulfill with remarkable efficiency. This was probably a strong driving force for the retention of what seems to be pre-biotic chemistry.

Acknowledgement

A word of thanks to Professor Sergei V. Makarov for the invitation to submit this article to this special issue of JCC, originally in honor of Professor O.I. Koifman on what would have been his 80th birthday, and now, sadly, in his memory.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Funding from the University of the Witwatersrand, Johannesburg, is gratefully acknowledged.

ORCID

Helder M. Marques http://orcid.org/0000-0003-1675-3835

References

[1] A.R. Battersby. *Nat. Prod. Rep.*, **17**, 507 (2000).

[2] B. Kräutler, In *Vitamin B12 and B12 Proteins*, B. Kräutler, D. Arigoni, B.T. Golding (Eds), pp. 2–43, Wiley-VCH, Weinheim (1998).
[3] R.B. Woodward. Synthetic Vitamin B12. In Proceedings of the Third European Symposium on Vitamin B12 and Intrinsic Factors*, Zurich, Switzerland, March 1999*, B. Zagalak, W. Friedrich (Eds), pp. 37–88, Walter de Gruyter, Berlin, Germany (1979).
[4] J. Zhuang, A.R. Reddi, Z. Wang, B. Khodaverdian, E.L. Hegg, B.R. Gibney. *Biochemistry*, **45**, 12530 (2006).
[5] C.J. Reedy, B.R. Gibney. *Chem. Rev*., **104**, 617 (2004).
[6] A.S. Rury, T.E. Wiley, R.J. Sension. *Acc. Chem. Res*., **48**, 860 (2015).
[7] H.M. Marques. *J. Inorg. Biochem*., **242**, 112154(2023).
[8] K. Kornobis, N. Kumar, B.M. Wong, P. Lodowski, M. Jaworska, T. Andruniów, K. Ruud, P.M. Kozlowski. *J. Phys. Chem. A*, **115**, 1280 (2011).
[9] D.H. Busch. *Trans. Kansas Acad. Sci*., **98**, 2 (1995).
[10] P.F. Lindley. *Rep. Prog. Phys*., **59**, 867 (1996).
[11] K.M. Kadish, K.M. Smith, R. Guilard (Eds.). *The Porphyrin Handbook*, Academic Press, San Diego, CA (2003).
[12] E.S. Turilli-Ghisolfi, M. Lualdi, M. Fasano. *Biomolecules*, **13**, 683 (2023).
[13] J. Liu, S. Chakraborty, P. Hosseinzadeh, Y. Yu, S. Tian, I. Petrik, A. Bhagi, Y. Lu. *Chem Rev*, **114**, 4366 (2014).
[14] F.A. Walker, U. Simonis. In *Encyclopedia of Inorganic Chemistry*, R.B. King, R.H. Crabtree, C.M. Lukehart, D.A. Atwood, R.A. Scott (Eds.), John Wiley & Sons, Hoboken, NJ (2005).
[15] E. Antonini, M. Brunori. *Hemoglobin and Myoglobin in Their Reactions with Ligands*, North-Holland, Amsterdam (1971).
[16] M.F. Perutz, G. Fermi, B. Luisi, B. Shaanan, R.C. Liddington. *Acc. Chem. Res*., **20**, 309 (1987).
[17] J.P. Collman, L. Fu. *Acc. Chem. Res*., **32**, 455 (1999).
[18] J.S. Olson. *Mol. Aspects Med*., **84**, 101024 (2022).
[19] G.W. Chong, A.A. Karbelkar, M.Y. El-Naggar. *Curr. Opin. Chem. Biol*., **47**, 7 (2018).
[20] R. Santucci, F. Sinibaldi, P. Cozza, F. Polticelli, L. Fiorucci. *Int J. Biol. Macromol*., **136**, 1237 (2019).
[21] V.L. Davidson. *Acc. Chem. Res*., **33**, 87 (2000).
[22] P.B. Crowley, M. Ubbink. *Acc. Chem. Res*., **36**, 723 (2003).
[23] S. Dell'acqua, S.R. Pauleta, E. Monzani, A.S. Pereira, L. Casella, J.J.G. Moura, I. Moura. *Biochemistry*, **47**, 10852(2008).
[24] R. Hille. *Chem. Rev*., **96**, 2757 (1996).
[25] K. Chen, C.A. Bonagura, G.J. Tilley, J.P. McEvoy, Y.-S. Jung, F.A. Armstrong, C.D. Stout, B.K. Burgess. *Nat. Struct. Biol*., **9**, 188 (2002).
[26] A. Azzi, M. Müller. *Arch. Biochem. Biophys*., **280**, 242 (1990).
[27] J.H. Dawson. *Science*, **240**, 433 (1988).
[28] M.D. Esposti. *Biochim. Biophys. Acta Bioenerg*., **1861**, 148304 (2020).
[29] Y.S. Song, A.J. Annalora, C.B. Marcus, C.R. Jefcoate, C.M. Sorenson, N. Sheibani. *Cells*, **11**, 2930 (2022).
[30] G. Smulevich. *Biochem. Soc. Trans*., **23**, 240(1995).
[31] I.S. Isaac, J.H. Dawson. *Essays Biochem*., **34**, 51 (1999).
[32] G. Battistuzzi, M. Bellei, C.A. Bortolotti, M. Sola. *Arch. Biochem. Biophys*., **500**, 21 (2010).
[33] P.K. Singh, N. Iqbal, H.V. Sirohi, H.R. Bairagya, P. Kaur, S. Sharma, T.P. Singh. *Prog Biophys Mol Biol*, **133**, 49 (2018).
[34] A. Deisseroth, A.L. Dounce. *Physiol Rev*, **50**, 319 (1970).
[35] J. Bravo, I. Fita, P. Gouet, H.M. Jouve, W-l Melik-Adamyan, G.N. Murshudov. *Ser*, **34**, 407 (1997).
[36] M.M. Goyal, A. Basak. *Protein Cell*, **1**, 888 (2010).
[37] M.O. James, S.M. Boyle. *Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol*., **121**, 157 (1998).
[38] H. Vanden Bossche, L. Koymans. *Mycoses*, **41 Suppl 1**, 32 (1998).

[39] I.A. Pikuleva, M.R. Waterman. *J. Biol Chem*, **288**, 17091 (2013).
[40] A.M. Distéfano, N. Setzes, M. Cascallares, D.F. Fiol, E. Zabaleta, G.C. Pagnussat. *Int J. Dev. Biol.*, **65**, 187 (2021).
[41] M. Senge. In K.M. Kadish, K.M. Smith, R. Guilard (Eds.), *The Porphyrin Handbook*, pp. 239–347, Academic Press, New York, NY (2000).
[42] D. Mauzerall. In A. Trebst, M. Avron (Eds.), *Photosynthesis I: Photosynthetic Electron Transport and Photophosphorylation*, pp. 117–124, Springer, Berlin, Heidelberg (1977).
[43] S.G. Boxer. *Biochim. Biophys. Acta*, **726**, 265 (1983).
[44] M. Chen. *Annu. Rev. Biochem.*, **83**, 317 (2014).
[45] T. Yamazaki, H. Oyanagi, T. Fujiwara, Y. Fukumori. *Eur. J. Biochem.*, **233**, 665 (1995).
[46] Y. Zheng, W. Deng, D. Liu, Y. Li, K. Peng, G.H. Lorimer, J. Wang. *J. Inorg. Biochem.*, **237**, 111982 (2022).
[47] M.J. Murphy, L.M. Siegel, S.R. Tove, H. Kamin. *Proc. Natl. Acad. Sci. U S A*, **71**, 612 (1974).
[48] B.R. Crane, L.M. Siegel, E.D. Getzoff. *Biochemistry*, **36**, 12101 (1997).
[49] U. Kappler, J.H. Enemark. *J. Biol. Inorg. Chem.*, **20**, 253 (2015).
[50] M. Tahoun, C.T. Gee, V.E. McCoy, P.M. Sander, C.E. Müller. *RSC Adv.*, **11**, 7552 (2021).
[51] D.E. Greenwalt, Y.S. Goreva, S.M. Siljeström, T. Rose, R.E. Harbach. *Proc. Natl. Acad. Sci. U S A*, **110**, 18496 (2013).
[52] D. Azar, A. Nel, D. Huang, M.S. Engel. *Curr. Biol.*, **33**, 5240 (2023).
[53] J.R. Roth, J.G. Lawrence, T.A. Bobik. *Annu. Rev. Microbiol.*, **50**, 137 (1996).
[54] J.H. Martens, H. Barg, M. Warren, D. Jahn. *Appl. Microbiol. Biotechnol.*, **58**, 275 (2002).
[55] A.I. Scott, C.A. Roessner. *Biochem. Soc. Trans.*, **30**, 613 (2002).
[56] M.T. Croft, A.D. Lawrence, E. Raux-Deery, M.J. Warren, A.G. Smith. *Nature*, **438**, 90 (2005).
[57] R. Banerjee. *ACS Chem. Biol.*, **1**, 149 (2006).
[58] R. Banerjee, C. Gherasim, D. Padovani. *Curr. Opin. Chem. Biol.*, **13**, 484 (2009).
[59] S. Okamoto, L.D. Eltis. *Metallomics*, **3**, 963 (2011).
[60] V.A. Adamian, F. D'Souza, S. Licoccia, M.L. Di Vona, E. Tassoni, R. Paolesse, T. Boschi, K.M. Kadish. *Inorg. Chem.*, **34**, 532 (1995).
[61] M.K. Safo, F.A. Walker, A.M. Raitsimring, W.P. Walters, D.P. Dolata, P.G. Debrunner, W.R. Scheidt. *J. Am. Chem. Soc.*, **116**, 7760 (1994).
[62] J. Bridwell-Rabb, C.L. Drennan. *Curr. Opin. Chem. Biol.*, **37**, 63 (2017).
[63] G.N. Schrauzer, E. Deutsch. *J. Am. Chem. Soc.*, **91**, 3341 (1969).
[64] R. Banerjee, S.W. Ragsdale. *Annu. Rev. Biochem.*, **72**, 209 (2003).
[65] M.L. Ludwig, R.G. Matthews. *Annu. Rev. Biochem.*, **66**, 269 (1997).
[66] M. Kumar, H. Hirao, P.M. Kozlowski. *J. Biol. Inorg. Chem.*, **17**, 1107 (2012).
[67] K. Sauer, R.K. Thauer. In *Chemistry and Biochemistry of B12*, B. Banerjee (Ed.), pp. 655–680, John Wiley & Sons, New York, NY (1999).
[68] S.W. Ragsdale. In R. Banerjee (Ed.), *Chemistry and Biochemistry of B12*, pp. 633–653, John Wiley & Sons, New York, NY (1999).
[69] R. Gräsbeck. *Hematology*, **10 Suppl 1**, 227 (2005).
[70] A. Miller, M. Korem, R. Almog, Y. Galboiz. *J. Neurol. Sci.*, **233**, 93 (2005).
[71] G. Scalabrino, M. Peracchi. *Trends Mol. Med.*, **12**, 247 (2006).
[72] R. Green. *Blood*, **129**, 2603 (2017).
[73] G. Rizzo, A.S. Laganà. In V.B. Patel (Ed.), *Molecular Nutrition*, pp. 105–129, Academic Press, London, UK (2020).
[74] A. Ankar, A. Kumar., *Vitamin B12 Deficiency, StatPearls*, StatPearls Publishing, Treasure Island, FL (2022). https://www.ncbi.nlm.nih.gov/books/NBK441923/
[75] N.M. Rodriguez, K. Shackelford. *Pernicious Anemia, StatPearls*, StatPearls Publishing, Treasure Island, FL (2022). https://www.ncbi.nlm.nih.gov/books/NBK540989/, 2022
[76] A.I. Scott. *J. Org. Chem.*, **68**, 2529(2003).
[77] A.R. Battersby, E. McDonald, J.W. Cornforth, B. Frydman, A. Neuberger, G.W. Kenner. *Philos. Trans. R Soc. Lond. B Biol. Sci.*, **273**, 161 (1976).
[78] A. Battersby. *Science*, **264**, 1551 (1994).
[79] M.J. Warren, E. Raux, H.L. Schubert, J.C. Escalante-Semerena. *Nat. Prod. Rep.*, **19**, 390 (2002).

[80] J.C. Escalante-Semerena. *J. Bacteriol.*, **189**, 4555 (2007).
[81] S.J. Moore, M.J. Warren. *Biochem. Soc. Trans.*, **40**, 581 (2012).
[82] A.R. Battersby. *Acc. Chem. Res.*, **26**, 15 (1993).
[83] A.I. Scott. *Acc. Chem. Res.*, **11**, 29 (1978).
[84] A. Battersby, F.J. Leeper. In *Chemistry and Biochemistry of B12*, B. Banerjee (Ed.), pp. 507–535, John Wiley & Sons, New York, NY (1999).
[85] A.I. Scott, C.A. Roessner, P.J. Santander. In *Chemistry and Biochemistry of B12*, R. Banerjee (Ed.), pp. 537–556, John Wiley & Sons, New York, NY (1999).
[86] B. Kräutler, B.M. Jaun. In *Fundamentals of Porphyrin Chemistry: A 21st Century Approach*, P.J. Brothers, M.O. Senge (Eds.), pp. 777–814, Wiley, Hoboken, NJ (2022).
[87] R.M. Graham, E. Deery, M.J. Warren. In *Tetrapyrroles: Birth, Life and Death*, M.J. Warren, A.G. Smith (Eds.), pp. 286–299, Landes Bioscience, and Springer Science + Business Media, Austin, TX (2009).
[88] T. Schubert. *World J. Microbiol. Biotechnol.*, **33**, 93 (2017).
[89] A. Eschenmoser. *Chem. Soc. Rev*, **5**, 377 (1976).
[90] A. Eschenmoser. *Angew. Chem. Int. Ed. Engl.*, **27**, 5 (1988).
[91] K.S. Suslick, N.A. Rakow, M.E. Kosal, J.-H. Chou. *J. Porphyrins Phthalocyanines*, **04**, 407 (2000).
[92] L.P. Cook, W. Wong-Ng, G. Brewer. In *Advances in Materials Science for Environmental and Energy Technologies V*, T. Ohji, R. Kanakhala, J. Matyáš, N. Marijooran, G. Pickrell, W. Wong-Ng (Eds.), pp. 201–221, Wiley & Sons, Hoboken, NJ (2016).
[93] T.V. Basova, D.V. Belykh, A.S. Vashurin, D.D. Klyamer, O.I. Koifman, P.O. Krasnov, T.N. Lomova, I.V. Loukhina, E.V. Motorina, G.L. Pakhomov, M.S. Polyakov, A. S. Semeikin, P.A. Stuzhin, A. S. Sukhikh, V.V. Travkin. *J. Struct. Chem.*, **64**, 766 (2023).
[94] S. Kumar, M.Y. Wani, C.T. Arranja, J. d e Silva, B. Avula, A.J.F.N. Sobral. *J. Mater. Chem. A*, **3**, 19615 (2015).
[95] T. Sarma, P.K. Panda. *Chem. Rev.*, **117**, 2785 (2017).
[96] B. Patra, S. Sobottka, S. Mondal, B. Sarkar, S. Kar. *Chem. Commun. (Camb)*, **54**, 9945(2018).
[97] B. Patra, S. Mondal, S. Kar. In R.A. Scott (Ed.), *Encyclopedia of Inorganic and Bioinorganic Chemistry*, pp. 1–24, Wiley, Hoboken, NJ (2023).
[98] A. Mahammed, Z. Gross. *J. Am Chem Soc*, **145**, 12429 (2023).
[99] A. Kumar, D. Kim, S. Kumar, A. Mahammed, D.G. Churchill, Z. Gross. *Chem. Soc. Rev.*, **52**, 573 (2023).
[100] G.J. Russell-Jones. *Crit. Rev. Ther. Drug Carrier Syst.*, **15**, 557 (1998).
[101] M.F. Francis, M. Cristea, F.M. Winnik. *Biomacromolecules*, **6**, 2462 (2005).
[102] L.A. Maiorova, N. Kobayashi, D.S. Salnikov, S.M. Kuzmin, T.V. Basova, O.I. Koifman, V.I. Parfenyuk, V.A. Bykov, Y.A. Bobrov, P. Yang. *Langmuir*, **39**, 3246 (2023).
[103] I.A. Dereven'kov, L.A. Maiorova, O.I. Koifman, D.S. Salnikov. *Langmuir*, **39**, 17240 (2023).
[104] N. Mahwish, L.K. Bairy, S. Srinivasamurthy. *J. Pharmacol. Pharmacother*, **13**, 5 (2022).
[105] B. Kräutler. *Chemistry*, **21**, 11280 (2015).
[106] B. Kräutler. *Chemistry*, **26**, 15438 (2020).
[107] M. Ruetz, R. Salchner, K. Wurst, S. Fedosov, B. Kräutler. *Angew Chem. Int. Ed. Engl.*, **52**, 11406 (2013).
[108] M.B. Guzzo, H.T. Nguyen, T.H. Pham, M. Wyszczelska-Rokiel, H. Jakubowski, K.A. Wolff, S. Ogwang, J.L. Timpona, S. Gogula, M.R. Jacobs, M. Ruetz, B. Kräutler, D.W. Jacobsen, G.-F. Zhang, L. Nguyen. *PLoS Pathog*, **12**, e1005949 (2016).
[109] F. Zelder, M. Sonnay, L. Prieto. *ChemBioChem.*, **16**, 1264 (2015).
[110] P.A. Frey, G.H. Reed. *ACS Chem. Biol.*, **7**, 1477 (2012).
[111] K.H. Wedepohl. *Geochim. Cosmochim. Acta*, **59**, 1217 (1995).
[112] O. Pourret, M.-P. Faucon. In *Encyclopedia of Geochemistry: A Comprehensive Reference Source on the Chemistry of the Earth*, W.M. White (Ed.), pp. 1–4, Springer International Publishing, Cham (2017).
[113] B. Kräutler. *Biochem*, **56**, 323(2012).

[114] R. Banerjee (Ed.), *Chemistry and Biochemistry of B12*, Wiley, New York (1999).
[115] M. Bayachou, L. Elkbir, P.J. Farmer. *Inorg. Chem.*, **39**, 289 (2000).
[116] J.A. Kovacs. *Chem. Rev.*, **104**, 825 (2004).
[117] E.I. Solomon, A. Decker, N. Lehnert. *Proc. Natl. Acad. Sci. U S A*, **100**, 3589 (2003).
[118] A. Timmins, S.P. De Visser. *Catalysts*, **8**, 314 (2018).
[119] A.D. Read, R.E.T. Bentley, S.L. Archer, K.J. Dunham-Snary. *Redox Biol.*, **47**, 102164 (2021).
[120] M. Cardenas-Rodriguez, A. Chatzi, K. Tokatlidis. *J. Biol. Inorg. Chem.*, **23**, 509 (2018).
[121] D.C. Johnson, D.R. Dean, A.D. Smith, M.K. Johnson. *Annu. Rev. Biochem.*, **74**, 247 (2005).
[122] B.B. Wenke, T. Spatzal, D.C. Rees. *Angew Chem. Int. Ed. Engl.*, **58**, 3894 (2019).
[123] J.L. Boer, S.B. Mulrooney, R.P. Hausinger. *Arch. Biochem. Biophys.*, **544**, 142 (2014).
[124] T. Wongnate, S.W. Ragsdale. *J. Biol. Chem.*, **290**, 9322 (2015).
[125] I. Bento, L.O. Martins, G. Gato Lopes, M. Arménia Carrondo, P.F. Lindley. *Dalton Trans.*, 3507 (2005).
[126] K.Y. Djoko, L.X. Chong, A.G. Wedd, Z. Xiao. *J. Am. Chem. Soc.*, **132**, 2005 (2010).
[127] E. Stupperich, R. Konle, M. Lehle. In *Vitamin B12 and B12-Proteins*, B. Krautler, D. Arigoni, B. Golding (Eds.), pp. 179–187, Wiley-VCH, Weinheim, Germany (1998).
[128] E. Stupperich, H.J. Eisinger, B. Kräutler. *Eur J. Biochem*, **172**, 459 (1988).
[129] D.S. Salnikov, R. Silaghi-Dumitrescu, S.V. Makarov, R. van Eldik, G.R. Boss. *Dalton Trans*, **40**, 9831 (2011).
[130] D.S. Salnikov, I.A. Dereven'kov, S.V. Makarov, E.S. Ageeva, A. Lupan, M. Surducan, R. Silaghi-Dumitrescu. *Rev. Roum. Chim.*, **57**, 353 (2012).
[131] K. Mieda-Higa, A.A. Mamun, T. Ogura, T. Kitagawa, P.M. Kozlowski. *J Raman Spectroscopy*, **51**, 1331 (2020).
[132] S. Van Doorslaer, G. Jeschke, B. Epel, D. Goldfarb, R.-A. Eichel, B. Kräutler, A. Schweiger. *J. Am. Chem. Soc.*, **125**, 5915 (2003).
[133] J.M. Pratt. *The Inorganic Chemistry of Vitamin B12*, Academic Press, London (1972).
[134] K.P. Jensen. *J. Phys. Chem. B*, **109**, 10505 (2005).
[135] N. Kumar, M. Alfonso-Prieto, C. Rovira, P. Lodowski, M. Jaworska, P.M. Kozlowski. *J. Chem. Theory Comput.*, **7**, 1541 (2011).
[136] S. Jamal, Z. Naz, S.T. Moin, T.S. Hofer. *J. Phys. Chem. B*, **127**, 5072 (2023).
[137] R. Bieganowski, W. Friedrich. *FEBS Lett.*, **97**, 325 (1979).
[138] S. Mebs, J. Henn, B. Dittrich, C. Paulmann, P. Luger. *J. Phys. Chem. A*, **113**, 8366 (2009).
[139] J.M. Pratt. *Pure Appl. Chem.*, **65**, 1513 (1993).
[140] K.P. Jensen, U. Ryde. *ChemBioChem.*, **4**, 413 (2003).
[141] G. Li Manni, A. Alavi. *J. Phys. Chem. A*, **122**, 4935 (2018).
[142] K.P. Jensen, U. Ryde. *J. Porphyrins. Phthalocyanines.*, **09**, 581 (2005).
[143] K.P. Jensen, P. Rydberg, J. Heimdal, U. Ryde. In *Computational Modeling for Homogeneous and Enzymatic Catalysis*, K. Morokuma, J. Musaev (Eds.), pp. 27–56, John Wiley & Sons Inc., New York, NY (2008).
[144] K.A. Rubinson, H.V. Parekh, E. Itabashi, H.B. Mark. *Inorg. Chem.*, **22**, 458 (1983).
[145] D. Lexa, J.M. Saveant. *J. Am. Chem. Soc.*, **100**, 3220 (1978).
[146] D. Lexa, J.M. Saveant. *Acc. Chem. Res.*, **16**, 235 (1983).
[147] R.L. Birke, Q. Huang, T. Spataru, D.K. Gosser. *J. Am. Chem. Soc.*, **128**, 1922 (2006).
[148] B. Dozza, B.M. Rodrigues, I. Tisoco, V.B. de Souza, L. Angnes, B.A. Iglesias. *Microchem. J.*, **183**, 108041 (2022).
[149] L. Ye, Y. Fang, Z. Ou, S. Xue, K.M. Kadish. *Inorg. Chem.*, **56**, 13613 (2017).
[150] H. Fujii. *Coord. Chem. Rev.*, **226**, 51 (2002).
[151] D. Lexa, J. Mispelter, J.M. Saveant. *J. Am. Chem. Soc.*, **103**, 6806 (1981).
[152] J.-P. Battioni, D. Dupré, D. Mansuy. *J. Organomet. Chem.*, **328**, 173 (1987).
[153] Z. Zheng, M.R. Gunner. *Proteins*, **75**, 719 (2009).
[154] S. Hay, T. Wydrzynski. *Biochemistry*, **44**, 431 (2005).
[155] L. Banci, I. Bertini, G. Quacquarini, O. Walter, A. Díaz, M. Hervás, M.A. de la Rosa. *J. Biol Inorg Chem*, **1**, 330 (1996).
[156] S.E.J. Bowman, K.L. Bren. *Inorg. Chem.*, **49**, 7890 (2010).

[157] A.M. Berghuis, J.G. Guillemette, M. Smith, G.D. Brayer. *J. Mol. Biol.*, **235**, 1326 (1994).
[158] F.A. Tezcan, J.R. Winkler, H.B. Gray. *J. Am. Chem. Soc.*, **120**, 13383 (1998).
[159] E. Stellwagen. *Nature*, **275**, 73 (1978).
[160] E.J. Tomlinson, S.J. Ferguson. *Proc. Natl. Acad. Sci. U S A*, **97**, 5156 (2000).
[161] P.D. Barker, J.C. Ferrer, M. Mylrajan, T.M. Loehr, R. Feng, Y. Konishi, W.D. Funk, R.T. MacGillivray, A.G. Mauk. *Proc. Natl. Acad. Sci. U S A*, **90**, 6542 (1993).
[162] B. Kräutler, D. Arigoni, B. Golding (Eds.), *Vitamin B12 and B12-Proteins*, Wiley-VCH, Weinheim (1998).
[163] T. Toraya. *Cell. Mol. Life Sci.*, **57**, 106 (2000).
[164] E.N.G. Marsh, D.E. Holloway. *Subcell. Biochem.*, **35**, 351 (2000).
[165] E.N.G. Marsh. *Bioorg. Chem.*, **28**, 176 (2000).
[166] E.N.G. Marsh, C.L. Drennan. *Curr. Opin. Chem. Biol.*, **5**, 499 (2001).
[167] P.A. Frey. *Annu. Rev. Biochem.*, **70**, 121 (2001).
[168] R. Banerjee. *Biochemistry*, **40**, 6191 (2001).
[169] K. Gruber, C. Kratky. *Curr. Opin. Chem. Biol.*, **6**, 598 (2002).
[170] K.L. Brown. *Chem. Rev.*, **105**, 2075 (2005).
[171] D. Heldt, A.D. Lawrence, M. Lindenmeyer, E. Deery, P. Heathcote, S.E. Rigby, M.J. Warren. *Biochem. Soc. Trans.*, **33**, 815 (2005).
[172] K. Gruber, B. Puffer, B. Kräutler. *Chem. Soc. Rev.*, **40**, 4346 (2011).
[173] S.J. Moore, A.D. Lawrence, R. Biedendieck, E. Deery, S. Frank, M.J. Howard, S.E.J. Rigby, M.J. Warren. *Proc. Natl. Acad. Sci. U S A*, **110**, 14906 (2013).
[174] T.A. Mattes, E. Deery, M.J. Warren, J.C. Escalante-Semerena. In *Encyclopedia of Inorganic and Bioinorganic Chemistry*, R.A. Scott (Ed.), pp. 1–24, John Wiley & Sons, Hoboken, NJ (2017).
[175] D.R. Monteverde, L. Gómez-Consarnau, C. Suffridge, S.A. Sañudo-Wilhelmy. *Geobiology*, **15**, 3 (2017).
[176] L. Randaccio, S. Geremia, N. Demitri, J. Wuerges. *Molecules*, **15**, 3228 (2010).
[177] R.T. Batey. *Curr. Opin. Struct. Biol.*, **16**, 299 (2006).
[178] A. Serganov, D.J. Patel. *Annu. Rev. Biophys.*, **41**, 343 (2012).
[179] R.R. Breaker. *Biochemistry*, **61**, 137 (2022).
[180] A. Nahvi, N. Sudarsan, M.S. Ebert, X. Zou, K.L. Brown, R.R. Breaker. *Chem. Biol.*, **9**, 1043 (2002).
[181] M. Mandal, R.R. Breaker. *Nat. Rev. Mol. Cell Biol.*, **5**, 451 (2004).
[182] A. Nahvi, J.E. Barrick, R.R. Breaker. *Nucleic Acids Res.*, **32**, 143 (2004).
[183] J.E. Johnson, F.E. Reyes, J.T. Polaski, R.T. Batey. *Nature*, **492**, 133 (2012).
[184] K.J. Kennedy, F.J. Widner, O.M. Sokolovskaya, L.V. Innocent, R.R. Procknow, K.C. Mok, M.E. Taga. *mBio*, **13**, e0112122 (2022).
[185] J.M. Ortiz-Guerrero, M.C. Polanco, F.J. Murillo, S. Padmanabhan, M. Elías-Arnanz. *Proc. Natl. Acad. Sci. U S A*, **108**, 7565(2011).
[186] S. Padmanabhan, M. Jost, C.L. Drennan, M. Elías-Arnanz. *Annu. Rev. Biochem.*, **86**, 485 (2017).
[187] S.M. Chemaly. *S. Afr. J. Sci.*, **112**, 9 (2016).
[188] N. Kumar, J. Kuta, W. Galezowski, P.M. Kozlowski. *Inorg Chem.*, **52**, 1762 (2013).
[189] B.D. Martin, R.G. Finke. *J. Am. Chem. Soc.*, **114**, 585 (1992).
[190] R.G. Finke, B.P. Hay. *Inorg. Chem.*, **23**, 3041 (1984).
[191] R.G. Finke. In *Vitamin B12 and B12-Proteins*, B. Krautler, D. Arigoni, B.J. Golding (Eds.), pp. 383–402, Wiley-VCH, Weinheim, 1998.
[192] P.G. Lenhert, D.C. Hodgkin. *Nature*, **192**, 937 (1961).
[193] P.J. Brothers, J.P. Collman. *Acc. Chem. Res*, **19**, 209 (1986).
[194] R. Guilard, C. Lecomte, K.M. Kadish. In *Metal Complexes with Tetrapyrrole Ligands I. Structure and Bonding*, J.W. Buchler (Ed.), pp. 205–268, Springer, Berlin, Heidelberg (1987).
[195] R. Guilard, K.M. Kadish. *Chem. Rev.*, **88**, 1121 (1988).
[196] M.J. Białek, K. Hurej, H. Furuta, L. Latos-Grażyński. *Chem. Soc. Rev.*, **52**, 2082 (2023).

[197] P.J. Brothers. In *Advances in Organometallic Chemistry*, pp. 223–321, Academic Press, New York (2000).
[198] P. Kofod. *Inorg. Chem*, **34**, 2768 (1995).
[199] J.M. Pratt. In R. Banerjee (Ed.), *Chemistry and Biochemistry of B12*, pp. 73–112, John Wiley & Sons, New York, NY (1999).
[200] I.M. Arafa, K. Shin, H.M. Goff. *J. Am. Chem. Soc.*, **110**, 5228 (1988).
[201] P. Cocolios, G. Lagrange, R. Guilard. *J. Organomet. Chem.*, **253**, 65 (1983).
[202] C.G. Riordan, J. Halpern. *Inorg. Chim. Acta*, **243**, 19 (1996).
[203] E.J. Corey, S.W. Wright, S.P.T. Matsuda. *J. Am. Chem. Soc*, **111**, 1452 (1989).
[204] P.R. Ortiz de Montellano, O. Augusto, F. Viola, K.L. Kunze. *J. Biol Chem*, **258**, 8623 (1983).
[205] D. Lancon, P. Cocolios, R. Guilard, K.M. Kadish. *J. Am. Chem. Soc*, **106**, 4472 (1984).
[206] M.P. Coogan, P.J. Dyson, M. Bochmann. *Organometallics*, **31**, 5671 (2012).
[207] W.F. Martin. *Trends Biochem. Sci.*, **44**, 807 (2019).
[208] H. Dobbek, V. Svetlitchnyi, L. Gremer, R. Huber, O. Meyer. *Science*, **293**, 1281 (2001).
[209] J.-H. Jeoung, H. Dobbek. *Science*, **318**, 1461 (2007).
[210] M. Can, F.A. Armstrong, S.W. Ragsdale. *Chem. Rev.*, **114**, 4149 (2014).
[211] V. Svetlitchnyi, H. Dobbek, W. Meyer-Klaucke, T. Meins, B. Thiele, P. Römer, R. Huber, O. Meyer. *Proc. Natl. Acad. Sci. U S A*, **101**, 446 (2004).
[212] M. Can, L.J. Giles, S.W. Ragsdale, R. Sarangi. *Biochemistry*, **56**, 1248 (2017).
[213] L. Cao, O. Caldararu, U. Ryde. *J. Chem. Theory Comput.*, **14**, 6653 (2018).
[214] Y. Hu, M.W. Ribbe. *Angew Chem. Int. Ed. Engl.*, **55**, 8216 (2016).
[215] S. Raugei, L.C. Seefeldt, B.M. Hoffman. *Proc. Nail. Acad. Sci. USA*, **115**, E10521 (2018).
[216] R.K. Thauer, A.-K. Kaster, M. Goenrich, M. Schick, T. Hiromoto, S. Shima. *Annu. Rev. Biochem.*, **79**, 507 (2010).
[217] S. Shima, O. Pilak, S. Vogt, M. Schick, M.S. Stagni, W. Meyer-Klaucke, E. Warkentin, R.K. Thauer, U. Ermler. *Science*, **321**, 572 (2008).
[218] J.W. Peters, W.N. Lanzilotta, B.J. Lemon, L.C. Seefeldt. *Science*, **282**, 1853 (1998).
[219] J.N. Betz, N.W. Boswell, C.J. Fugate, G.L. Holliday, E. Akiva, A.G. Scott, P.C. Babbitt, J.W. Peters, E.M. Shepard, J.B. Broderick. *Biochemistry*, **54**, 1807 (2015).
[220] A. Volbeda, M.-H. Charon, C. Piras, E.C. Hatchikian, M. Frey, J.C. Fontecilla-Camps. *Nature*, **373**, 580 (1995).
[221] A.S. Byer, H. Yang, E.C. McDaniel, V. Kathiresan, S. Impano, A. Pagnier, H. Watts, C. Denler, A.L. Vagstad, J. Piel, K.S. Duschene, E.M. Shepard, T.P. Shields, L.G. Scott, E.A. Lilla, K. Yokoyama, W.E. Broderick, B.M. Hoffman, J.B. Broderick. *J. Am. Chem. Soc.*, **140**, 8634 (2018).
[222] W.E. Broderick, B.M. Hoffman, J.B. Broderick. *Acc. Chem. Res.*, **51**, 2611 (2018).
[223] X. Ke, R. Kumar, M. Sankar, K.M. Kadish. *Inorg. Chem.*, **57**, 1490 (2018).
[224] A. Wolberg, J. Manassen. *J. Am. Chem. Soc.*, **92**, 2982 (1970).
[225] L.A. Truxillo, D.G. Davis. *Anal. Chem.*, **47**, 2260 (1975).
[226] K.M. Kadish, L.A. Bottomley, D. Beroiz. *Inorg. Chem.*, **17**, 1124 (1978).
[227] K.R. Wolthers, N.S. Scrutton. *Biochemistry*, **46**, 6696 (2007).
[228] R.G. Matthews. *PPP*, **16**, 53 (2009).
[229] R.G. Matthews. *Acc. Chem. Res.*, **34**, 681 (2001).
[230] J.H. Bayston, N.K. King, F.D. Looney, M.E. Winfield. *J. Am. Chem. Soc.*, **91**, 2775 (1969).
[231] A. von Zelewsky. *Helv. Chim. Acta*, **55**, 2941 (1972).
[232] E. Joerin, A. Schweiger, H.H. Guenthard. *J. Am. Chem. Soc.*, **105**, 4277 (1983).
[233] S. Van Doorslaer, A. Schweiger, B. Kräutler. *J. Phys. Chem. B*, **105**, 7554 (2001).
[234] S.-T. Chang, C.-H. Wang, H.-Y. Du, H.-C. Hsu, C.-M. Kang, C.-C. Chen, J.C.S. Wu, S.-C. Yen, W.-F. Huang, L.-C. Chen, M.C. Lin, K.-H. Chen. *Energy Environ. Sci.*, **5**, 5305 (2012).
[235] W.-F. Huang, S.-T. Chang, H.-C. Huang, C.-H. Wang, L.-C. Chen, K.-H. Chen, M.C. Lin. *J. Phys. Chem. C*, **124**, 4652 (2020).
[236] Y. Morita, K. Oohora, E. Mizohata, A. Sawada, T. Kamachi, K. Yoshizawa, T. Inoue, T. Hayashi. *Inorg. Chem.*, **55**, 1287 (2016).
[237] K. Oohora, A. Onoda, T. Hayashi. *Acc. Chem. Res.*, **52**, 945 (2019).

[238] T. Hayashi, Y. Morita, E. Mizohata, K. Oohora, J. Ohbayashi, T. Inoue, Y. Hisaeda. *Chem. Commun. (Camb)*, **50**, 12560 (2014).
[239] J.S. Olson, A.J. Mathews, R.J. Rohlfs, B.A. Springer, K.D. Egeberg, S.G. Sligar, J. Tame, J.-P. Renaud, K. Nagai. *Nature*, **336**, 265 (1988).
[240] T. Svetlitchnaia, V. Svetlitchnyi, O. Meyer, H. Dobbek. *Proc. Natl. Acad. Sci. U S A*, **103**, 14331 (2006).
[241] S. Malinowski, A.P. Ghosh, S. Edwards, J. Jaroszynska-Wolinska, P.M. Kozlowski. *J. Mol. Graph Model*, **104**, 107831 (2021).
[242] E.C. Duin. In R.H. Kretsinger, V.N. Uversky, E.A. Permyakov (Eds.), *Encyclopedia of Metalloproteins*, pp. 1410–1418, Springer, New York, NY (2013).
[243] H. Chen, Q. Gan, C. Fan. *Front Microbiol.*, **11**, 578356 (2020).
[244] C. Holliger, A.J. Pierik, E.J. Reijerse, W.R. Hagen. *J. Am. Chem. Soc.*, **115**, 5651 (1993).
[245] B. Juan, R.K. Thauer. In A. Sigel, S. Sigel., R.K.O. Sigel (Eds.), *Metal Ions Life Science: Nickel and Its Surprising Impact in Nature*, pp. 323–356, John Wiley & Sons, Chichester, UK (2007).
[246] T. Wongnate, D. Sliwa, B. Ginovska, D. Smith, M.W. Wolf, N. Lehnert, S. Raugei, S.W. Ragsdale. *Science*, **352**, 953 (2016).
[247] Y. Zhou, D.A. Sliwa, S.W. Ragsdale. In K.M. Kadish, K.M. Smith, R. Guilard (Eds.), *Handbook of Porphyrin Science*, pp. 1–44, World Scientific, Singapore (2012).
[248] W. Grabarse, F. Mahlert, S. Shima, R.K. Thauer, U. Ermler. *J. Mol. Biol.*, **303**, 329 (2000).
[249] T. Wagner, J. Kahnt, U. Ermler, S. Shima. *Angew Chem. Int. Ed. Engl.*, **55**, 10630 (2016).
[250] E.C. Duin, T. Wagner, S. Shima, D. Prakash, B. Cronin, D.R. Yáñez-Ruiz, S. Duval, R. Rümbeli, R.T. Stemmler, R.K. Thauer, M. Kindermann. *Proc. Natl. Acad. Sci. U S A*, **113**, 6172 (2016).
[251] D. Prakash, Y. Wu, S.-J. Suh, E.C. Duin. *J. Bacteriol.*, **196**, 2491 (2014).
[252] A. Fässler, A. Pfaltz, P. Michael Müller, S. Farooq, C. Kratky, B. Kräutler, A. Eschenmoser. *Helv. Chim. Acta.*, **65**, 812 (1982).
[253] C. Kratky, A. Fässler, A. Pfaltz, B. Kräutler, B. Jaun, A. Eschenmoser. *J. Chem. Soc, Chem. Commun.*, 1368 (1984).
[254] C. Brenig, L. Prieto, R. Oetterli, F. Zelder. *Angew Chem. Int. Ed. Engl.*, **57**, 16308 (2018).
[255] V.B. Koppenhagen, B. Elsenhans, F. Wagner, J.J. Pfiffner. *J. Biol. Chem.*, **249**, 6532 (1974).
[256] R.D. Shannon. *Acta Cryst. A*, **32**, 751 (1976).
[257] E. Sakuradani, M. Kobayashi, T. Ashikari, S. Shimizu. *Eur. J. Biochem.*, **261**, 812 (1999).
[258] T.C. Harrop, P.K. Mascharak. In *Encyclopedia of Metalloproteins*, R.H. Kretsinger, V.N. Uversky, E.A. Permyakov (Eds.), pp. 684–690, Springer New York, New York, NY (2013).
[259] V.V. Khrustalev, T.A. Khrustaleva, V.V. Poboinev, C.I. Karchevskaya, E.A. Shablovskaya, T.G. Terechova. *Metallomics*, **11**, 1743 (2019).
[260] W.T. Lowther, B.W. Matthews. *Biochim. Biophys. Acta*, **1477**, 157 (2000).
[261] I. Eni-Aganga, Z.M. Lanaghan, M. Balasubramaniam, C. Dash, J. Pandhare. *Front Mol. Biosci.*, **8**, 723003 (2021).
[262] M. Ghosh, A.M. Grunden, D.M. Dunn, R. Weiss, M.W.W. Adams. *J. Bacteriol.*, **180**, 4781 (1998).
[263] M.J. Maher, M. Ghosh, A.M. Grunden, A.L. Menon, M.W.W. Adams, H.C. Freeman, J.M. Guss. *Biochemistry*, **43**, 2771 (2004).
[264] A. Miyanaga, S. Fushinobu, K. Ito, T. Wakagi. *Biochem. Biophys. Res. Commun.*, **288**, 1169 (2001).
[265] T.C. Harrop, P.K. Mascharak. *Acc. Chem. Res.*, **37**, 253 (2004).
[266] S. Martinez, X. Yang, B. Bennett, R.C. Holz. *Biochim. Biophys. Acta Proteins Proteom.*, **1865**, 107 (2017).
[267] Y. Katayama, K. Hashimoto, H. Nakayama, H. Mino, M. Nojiri, T-a Ono, H. Nyunoya, M. Yohda, K. Takio, M. Odaka. *J. Am. Chem. Soc.*, **128**, 728 (2006).
[268] T. Arakawa, Y. Kawano, Y. Katayama, H. Nakayama, N. Dohmae, M. Yohda, M. Odaka. *J. Am. Chem. Soc.*, **131**, 14838 (2009).

[269] H. Ben Hlima, S. Bejar, J. Riguet, R. Haser, N. Aghajari. *Appl. Microbiol. Biotechnol.*, **97**, 9715 (2013).
[270] K.H. Nam. *Appl. Sci*, **12**, 428 (2022).
[271] P.R. Hall, R. Zheng, L. Antony, M. Pusztai-Carey, P.R. Carey, V.C. Yee. *Embo J.*, **23**, 3621 (2004).
[272] M. Dennis, P.E. Kolattukudy. *Proc. Natl. Acad. Sci. U S A*, **89**, 5306 (1992).
[273] E.N.G. Marsh, M.W. Waugh. *ACS Catal.*, **3**, 2515 (2013).
[274] R.M. Petrovich, F.J. Ruzicka, G.H. Reed, P.A. Frey. *J. Biol. Chem.*, **266**, 7656 (1991).
[275] R.M. Petrovich, F.J. Ruzicka, G.H. Reed, P.A. Frey. *Biochemistry*, **31**, 10774 (1992).
[276] G. Genchi, G. Lauria, A. Catalano, A. Carocci, M.S. Sinicropi. *Biology (Basel)*, **12**, 1335 (2023).
[277] N. Itoh, N. Morinaga, T. Kouzai. *Biochim. Biophys. Acta*, **1207**, 208 (1994).
[278] T. Ohshiro, S. Nakano, Y. Takahashi, M. Suzuki, Y. Izumi. *Phytochemistry*, **52**, 1211 (1999).
[279] X. Hu, X. Wei, J. Ling, J. Chen. *Front Plant Sci.*, **12**, 768523 (2021).
[280] J.J.G. Moura, I. Moura, M. Bruschi, J. Le Gall, A.V. Xavier. *Biochem. Biophys. Res. Commun.*, **92**, 962 (1980).
[281] E.C. Hatchikian. *Biochem. Biophys. Res. Commun.*, **103**, 521 (1981).
[282] A.R. Battersby, Z.-C. Sheng. *J. Chem. Soc. Chem. Commun.*, 1393 (1982).
[283] I. Barr, S.H. Weitz, T. Atkin, P. Hsu, M. Karayiorgou, J.A. Gogos, S. Weiss, F. Guo. *Chem. Biol.*, **22**, 793 (2015).
[284] A. Mondal, M. Das, S. Mazumdar. *Inorg. Chim. Acta*, **487**, 398 (2019).
[285] B.P. Hay, R.G. Finke. *J. Am. Chem. Soc.*, **108**, 4820 (1986).
[286] K.L. Brown, X. Zou. *J. Inorg. Biochem.*, **77**, 185 (1999).
[287] R. Padmakumar, R. Padmakumar, R. Banerjee. *Biochemistry*, **36**, 3713 (1997).
[288] S. Chowdhury, R. Banerjee. *Biochemistry*, **39**, 7998 (2000).
[289] M.L. Ludwig, C.L. Drennan, R.G. Matthews. *Structure*, **4**, 505 (1996).
[290] G.N. Schrauzer, J.H. Grate. *J. Am. Chem. Soc.*, **103**, 541 (1981).
[291] J. Halpern. *Science*, **227**, 869 (1985).
[292] J.M. Sirovatka, A.K. Rappé, R.G. Finke. *Inorg. Chim. Acta*, **300-302**, 545 (2000).
[293] N. Shibata, T. Toraya. *ChemBioChem.*, **24**, e202300021 (2023).
[294] K.P. Jensen, U. Ryde. *J. Am. Chem. Soc.*, **127**, 9117 (2005).
[295] G.D. Román-Meléndez, P. von Glehn, J.N. Harvey, A.J. Mulholland, E.N.G. Marsh. *Biochemistry*, **53**, 169 (2014).
[296] E.N.G. Marsh, G.D. Román Meléndez. *Biochim Biophys Acta*, **1824**, 1154 (2012).
[297] G.H. Reed. *Curr. Opin. Chem. Biol.*, **8**, 477 (2004).
[298] K.L. Brown, S.F. Cheng, H.M. Marques. *Inorg. Chem.*, **34**, 3038 (1995).
[299] F. Mancia, N.H. Keep, A. Nakagawa, P.F. Leadlay, S. McSweeney, B. Rasmussen, P. Bösecke, O. Diat, P.R. Evans. *Structure*, **4**, 339 (1996).
[300] H.M. Marques, K.L. Brown. *Coord. Chem. Rev.*, **225**, 123 (2002).
[301] R. Guilard, B. Boisselier-Cocolios, A. Tabard, P. Cocolios, B. Simonet, K.M. Kadish. *Inorg. Chem.*, **24**, 2509 (1985).
[302] A. Tabard, P. Cocolios, G. Lagrange, R. Gerardin, J. Hubsch, C. Lecomte, J. Zarembowitch, R. Guilard. *Inorg. Chem.*, **27**, 110 (1988).
[303] C.L. Rollinson, J.C. Bailar, H.J. Emeléus, R. Nyholm. *The Chemistry of Chromium, Molybdenum and Tungsten.* Pergamon International Library of Science, Technology, Engineering and Social Studies, Elsevier Science, Oxford, UK (2015).
[304] F. Basolo, R.G. Pearson. *Mechanisms of Inorganic Reactions: A Study of Metal Complexes in Solution*, Wiley, New York, NY (1958).
[305] S.F. Lincoln. *Helv. Chim. Acta.*, **88**, 523 (2005).
[306] R. Williams, E. Billig, J.H. Waters, H.B. Gray. *J. Am. Chem. Soc.*, **88**, 43 (1966).
[307] F. Rohrscheid, A.L. Balch, R.H. Holm. *Inorg. Chem.*, **5**, 1542 (1966).
[308] E.B. Fleischer, S. Jacobs, L. Mestichelli. *J. Am. Chem. Soc.*, **90**, 2527 (1968).
[309] J.H. Fuhrhop, J. Subramanian, J.W. Buchler. *Phil. Trans. Roy. Soc. Lond. B*, **273**, 335 (1976).
[310] A. Medek, L. Frydman. *J. Am. Chem. Soc*, **122**, 684 (2000).

[311] S.M. Chemaly, L.A. Jack, L.J. Yellowlees, P.L.S. Harper, B. Heeg, J.M. Pratt. *Dalton Trans*, 2125 (2004).
[312] E.B. Fleischer, T.S. Srivastava. *Inorg. Chim. Acta*, **5**, 151 (1971).
[313] G.N. La Mar, F.A. Walker. *J. Am. Chem. Soc.*, **95**, 6950 (1973).
[314] S.C. Jeoung, D. Kim, D.W. Cho, M. Yoon. *J. Phys. Chem. A*, **104**, 4816 (2000).
[315] M. Inamo, K. Eba, K. Nakano, N. Itoh, M. Hoshino. *Inorg. Chem.*, **42**, 6095 (2003).
[316] R. Cao, K.E. Thomas, A. Ghosh, R. Sarangi. *RSC Adv.*, **10**, 20572 (2020).
[317] A. Kechiche, T. Fradi, O. Noureddine, M. Guergueb, F. Loiseau, V. Guerineau, N. Issoui, A. Lemeune, H. Nasri. *J. Mol. Struct*, **1250**, 131801 (2022).
[318] B. Kraeutler, W. Keller, C. Kratky. *J. Am. Chem. Soc.*, **111**, 8936 (1989).
[319] F.J. Widner, A.D. Lawrence, E. Deery, D. Heldt, S. Frank, K. Gruber, K. Wurst, M.J. Warren, B. Kräutler. *Angew Chem. Int. Ed. Engl.*, **55**, 11281 (2016).
[320] A.M. Stolzenberg, M.T. Stershic. *J. Am. Chem. Soc*, **110**, 6391 (1988).
[321] C. Rovira, X. Biarnés, K. Kunc. *Inorg. Chem.*, **43**, 6628 (2004).
[322] C. Rovira, K. Kunc, J. Hutter, M. Parrinello. *Inorg. Chem.*, **40**, 11 (2001).
[323] E.C. Johnson, T. Niem, D. Doolphin. *Can. J. Chem.*, **56**, 1381 (1978).
[324] J.B. Vincent. *J. Nutr.*, **124**, 117 (1994).
[325] M.-H. Lai. *J. Clin. Biochem. Nutr.*, **43**, 191 (2008).
[326] S. Wallach. *J. Am. Coll. Nutr.*, **4**, 107 (1985).
[327] R.A. Anderson. *Diabet. Metabol.*, **26**, 22 (2000).
[328] S. Wilbur, H. Abadin, M. Fay, D. Yu, B. Tencza, L. Ingerman, J. Klotzbach, S. James. *Toxicological Profile for Chromium*, Agency for Toxic Substances and Disease Registry, Atlanta, GA (2012). https://www.ncbi.nlm.nih.gov/books/NBK158851/
[329] D.A. Baldwin, E.A. Betterton, J.M. Pratt. *J. Chem. Soc. Dalton Trans.*, 217 (1983).
[330] G.C. Hayward, H.A.O. Hill, J.M. Pratt, R.J.P. Williams. *J. Chem. Soc. A*, 196 (1971).
[331] W.K. Lee. BSc special thesis, University of Hong Kong (1972).
[332] C.K. Poon. *Coord. Chem. Rev.*, **10**, 1 (1973).
[333] J.M. Pratt, R.G. Thorp. In *Advances in Inorganic Chemistry and Radiochemistry*, H.J. Emeléus, A.G. Sharpe (Eds.), Vol. 12, pp. 375–427, Academic Press, New York, NY (1969).
[334] C.B. Perry, H.M. Marques, S. Afr. *J. Chem*, **58**, 9 (2005).
[335] K.S. Conrad, T.C. Brunold. *Inorg. Chem.*, **50**, 8755 (2011).
[336] A.S. Eisenberg, I.V. Likhtina, V.S. Znamenskiy, R.L. Birke. *J. Phys. Chem. A*, **116**, 6851 (2012).
[337] H.M. Marques, L. Knapton, X. Zou, K.L. Brown. *J. Chem. Soc. Dalton Trans.*, 3195 (2002).
[338] L. Knapton, H.M. Marques. *Dalton Trans.*, 889 (2005).
[339] N. Ghadimi, C.B. Perry, M. Fernandes, P.P. Govender, H.M. Marques. *Inorg. Chim. Acta*, **436**, 29 (2015).
[340] J.L. Hoard. *Ann. N Y Acad. Sci.*, **206**, 18 (1973).
[341] C. Ciaccio, A. Coletta, G. De Sanctis, S. Marini, M. Coletta. *IUBMB Life*, **60**, 112 (2008).
[342] A.M. Berghuis, J.G. Guillemette, G. McLendon, F. Sherman, M. Smith, G.D. Brayer. *J. Mol. Biol.*, **236**, 786 (1994).
[343] A.M. Berghuis, G.D. Brayer. *J. Mol. Biol.*, **223**, 959 (1992).
[344] P.X. Qi, D.L. Di Stefano, A.J. Wand. *Biochemistry*, **33**, 6408 (1994).
[345] P.X. Qi, J.L. Urbauer, E.J. Fuentes, M.F. Leopold, A.J. Wand. *Nat. Struct. Biol.*, **1**, 378 (1994).
[346] A.E. García, G. Hummer. *Proteins*, **36**, 175 (1999).
[347] P.X. Qi, R.A. Beckman, A.J. Wand. *Biochemistry*, **35**, 12275 (1996).
[348] S. Modi, M.J. Sutcliffe, W.U. Primrose, L.-Y. Lian, G.C.K. Roberts. *Nat. Struct. Biol.*, **3**, 414 (1996).
[349] Y. Matsuura, T. Takano, R.E. Dickerson. *J. Mol. Biol.*, **156**, 389 (1982).
[350] K.B. Lee, G.N. La Mar, L.A. Kehres, E.M. Fujinari, K.M. Smith, T.C. Pochapsky, S.G. Sligar. *Biochemistry*, **29**, 9623 (1990).
[351] M. Rivera, C. Barillas-Mury, K.A. Christensen, J.W. Little, M.A. Wells, F.A. Walker. *Biochemistry*, **31**, 12233 (1992).

[352] F.A. Walker, D. Emrick, J.E. Rivera, B.J. Hanquet, D.H. Buttlaire. *J. Am Chem Soc*, **110**, 6234 (1988).
[353] K.A.P. Payne, C.P. Quezada, K. Fisher, M.S. Dunstan, F.A. Collins, H. Sjuts, C. Levy, S. Hay, S.E.J. Rigby, D. Leys. *Nature*, **517**, 513 (2015).
[354] E. Miller, G. Wohlfarth, G. Diekert. *Arch. Microbiol.*, **166**, 379 (1996).
[355] M. Fincker, A.M. Spormann. *Annu. Rev. Biochem.*, **86**, 357 (2017).
[356] C. Holliger, D. Hahn, H. Harmsen, W. Ludwig, W. Schumacher, B. Tindall, F. Vazquez, N. Weiss, A.J.B. Zehnder. *Arch. Microbiol.*, **169**, 313 (1998).
[357] R.-Z. Liao, S.-L. Chen, P.E.M. Siegbahn. *ACS Catal.*, **5**, 7350 (2015).
[358] T.S. Marks, J.D. Allpress, A. Maule. *Appl. Environ. Microbiol.*, **55**, 1258 (1989).
[359] U.E. Krone, R.K. Thauer, H.P.C. Hogenkamp, K. Steinbach. *Biochemistry*, **30**, 2713 (1991).
[360] C.A. Schanke, L.P. Wackett. *Environ. Sci. Technol.*, **26**, 830 (1992).
[361] T.S. Marks, A. Maule. *Appl. Mircobiol. Biotechnol.*, **38**, 413 (1992).
[362] S. Lesage, H. Xu, L.J. Durham. *Hydrol. Sci. J.*, **38**, 343 (1993).
[363] W.T. Potter, J. Cho, K.L. Sublette. *Technol.*, **40**, 355 (1994).
[364] J. A. Shelnutt, X.-Z. Song, J.-G. Ma, S.-L. Jia, W. Jentzen, C.J. Medforth, C.J. Medforth. *Chem. Soc. Rev.*, **27**, 31 (1998).
[365] R. Huber. *Eur J. Biochem.*, **187**, 283 (1990).
[366] H. Senn, K. Wüthrich. *Q Rev. Biophys.*, **18**, 111 (1985).
[367] C. Olea, Jr., J. Kuriyan, M.A. Marletta. *J. Am. Chem. Soc.*, **132**, 12794 (2010).
[368] K.M. Barkigia, L. Chantranupong, K.M. Smith, J. Fajer. *J. Am. Chem. Soc.*, **110**, 7566 (1988).
[369] M. Ravikanth, D. Reddy, A. Misra, T.K. Chandrashekar, K. Tavarakere. *J. Chem. Soc., Dalton Trans*, 1137 (1993).
[370] M. Ravikanth, T.K. Chandrashekar. *Struct. Bonding (Berlin)*, **82**, 105 (1995).
[371] K.M. Kadish, E. Van Caemelbecke, F. D'Souza, C.J. Medforth, K.M. Smith, A. Tabard, R. Guilard. *Inorg. Chem.*, **34**, 2984 (1995).
[372] L.D. Sparks, C.J. Medforth, M.-S. Park, J.R. Chamberlain, M.R. Ondrias, M.O. Senge, K.M. Smith, J.A. Shelnutt. *J. Am. Chem. Soc.*, **115**, 581 (1993).
[373] X.Z. Song, W. Jentzen, S.L. Jia, L. Jaquinod, D.J. Nurco, C.J. Medforth, K.M. Smith, J.A. Shelnutt. *J. Am. Chem. Soc.*, **118**, 12975 (1996).
[374] B.S. Cheng, O.Q. Munro, H.M. Marques, R. Scheidt. *J. Am. Chem. Soc.*, **119**, 10732 (1997).
[375] B. Szyszko, M.J. Białek, E. Pacholska-Dudziak, L. Latos-Grażyński. *Chem. Rev.*, **117**, 2839 (2017).
[376] J.D. Hobbs, J.A. Shelnutt. *J. Protein Chem.*, **14**, 19 (1995).
[377] O.Q. Munro, J.C. Bradley, R.D. Hancock, H.M. Marques, F. Marsicano, P.W. Wade. *J. Am. Chem. Soc.*, **114**, 7218 (1992).
[378] E.B. Fleischer. *Acc. Chem. Res.*, **3**, 105 (1970).
[379] W.A. Kaplan, K.S. Suslick, R.A. Scott. *J. Am. Chem. Soc.*, **113**, 9824 (1991).
[380] M. Krüger, A. Meyerdierks, F.O. Glöckner, R. Amann, F. Widdel, M. Kube, R. Reinhardt, J. Kahnt, R. Böcher, R.K. Thauer, S. Shima. *Nature*, **426**, 878 (2003).
[381] R.K. Thauer. *Biochemistry*, **58**, 5198 (2019).
[382] J.H. Grate, G.N. Schrauzer. *J. Am. Chem. Soc.*, **101**, 4601 (1979).
[383] R.H. Abeles, D. Dolphin. *Acc. Chem. Res.*, **9**, 114 (1976).
[384] J.S. Krouwer, B. Holmquist, R.S. Kipnes, B.M. Babior. *Biochim. Biophys. Acta.*, **612**, 153 (1980).
[385] Y. Tamao, R.L. Blakley. *Biochemistry*, **12**, 24 (1973).
[386] S.M. Chemaly, J.M. Pratt. *J. Chem. Soc. Dalton Trans.*, 2259 (1980).
[387] J. M. Pratt. *J. Mol. Catal.*, **23**, 187 (1984).
[388] J.P. Glusker. In D. Dolphin (Ed.), *B12*, pp. 23–107, Wiley-Interscience, New York (1982).
[389] T. Toraya, E. Krodel, A.S. Mildvan, R.H. Abeles. *Biochemistry*, **18**, 417 (1979).
[390] V.B. Pett, M.N. Liebman, P. Murray-Rust, K. Prasad, J.P. Glusker. *J. Am. Chem. Soc*, **109**, 3207 (1987).
[391] T. Toraya, A. Ishida. *Biochemistry*, **27**, 7677 (1988).
[392] N. Shibata, Y. Sueyoshi, Y. Higuchi, T. Toraya. *Angew. Chem.*, **130**, 7956 (2018).

[393] K.-M. Larsson, D.T. Logan, P. Nordlund. *ACS Chem. Biol.*, **5**, 933 (2010).
[394] B. Durbeej, G.M. Sandala, D. Bucher, D.M. Smith, L. Radom. *Chemistry*, **15**, 8578 (2009).
[395] P. Friedrich, U. Baisch, R.W. Harrington, F. Lyatuu, K. Zhou, F. Zelder, W. McFarlane, W. Buckel, B.T. Golding. *Chemistry*, **18**, 16114 (2012).
[396] M. Karczewski, M. Ociepa, K. Pluta, K. ó Proinsias, D. Gryko. *Chemistry*, **23**, 7024 (2017).
[397] G.I.H. Hanania, D.H. Irvine. *J. Chem. Soc.*, 5694 (1964).
[398] M.S.A. Hamza. *J. Inorg. Biochem.*, **69**, 269 (1998).
[399] M.S.A. Hamza, M.A. Elawady, H.M. Marques, S. Afr. *J. Chem.*, **61**, 68 (2008).
[400] C. Männel-Croisé, F. Zelder. *Inorg. Chem.*, **48**, 1272 (2009).
[401] C.L. Drennan, S. Huang, J.T. Drummond, R.G. Matthews, M.L. Ludwig. *Science*, **266**, 1669 (1994).
[402] R. Reitzer, K. Gruber, G. Jogl, V.G. Wagner, H. Bothe, W. Buckel, C. Kratky. *Structure*, **7**, 891 (1999).
[403] N. Kurteva-Yaneva, M. Zahn, M.T. Weichler, R. Starke, H. Harms, R.H. Müller, N. Sträter, T. Rohwerder. *J. Biol. Chem.*, **290**, 9727 (2015).
[404] K.R. Wolthers, C. Levy, N.S. Scrutton, D. Leys. *J. Biol. Chem.*, **285**, 13942 (2010).
[405] M. Ruetz, G.C. Campanello, M. Purchal, H. Shen, L. McDevitt, H. Gouda, S. Wakabayashi, J. Zhu, E.J. Rubin, K. Warncke, V.K. Mootha, M. Koutmos, R. Banerjee. *Science*, **366**, 589 (2019).
[406] F. Berkovitch, E. Behshad, K.H. Tang, E.A. Enns, P.A. Frey, C.L. Drennan. *Proc. Natl. Acad. Sci. U S A*, **101**, 15870 (2004).
[407] M. Yamanishi, M. Yunoki, T. Tobimatsu, H. Sato, J. Matsui, A. Dokiya, Y. Iuchi, K. Oe, K. Suto, N. Shibata, Y. Morimoto, N. Yasuoka, T. Toraya. *Eur. J. Biochem.*, **269**, 4484 (2002).
[408] N. Shibata, H. Tamagaki, N. Hieda, K. Akita, H. Komori, Y. Shomura, S. Terawaki, K. Mori, N. Yasuoka, Y. Higuchi, T. Toraya. *J. Biol. Chem.*, **285**, 26484 (2010).
[409] N. Shibata, J. Masuda, T. Tobimatsu, T. Toraya, K. Suto, Y. Morimoto, N. Yasuoka. *Structure*, **7**, 997 (1999).
[410] M.D. Sintchak, G. Arjara, B.A. Kellogg, J. Stubbe, C.L. Drennan. *Nat. Struct. Biol.*, **9**, 293 (2002).
[411] C.B. Perry, H.M. Marques, S. Afr. *J. Sci.*, **100**, 368 (2004).
[412] K.P. Jensen, U. Ryde. *J. Mol. Struct. (THEOCHEM)*, **585**, 239 (2002).
[413] T. Andruniow, M.Z. Zgierski, P.M. Kozlowski. *J. Am. Chem. Soc.*, **123**, 2679 (2001).
[414] N. Dölker, F. Maseras, A. Lledós. *J. Phys. Chem. B.*, **107**, 306 (2003).
[415] R.M. Kluck, E. Bossy-Wetzel, D.R. Green, D.D. Newmeyer. *Science*, **275**, 1132 (1997).
[416] S.E. Martinez, D. Huang, M. Ponomarev, W.A. Cramer, J.L. Smith. *Protein Sci.*, **5**, 1081 (1996).
[417] F. Frolow, A.J. Kalb, J. Yariv. *Nat. Struct. Biol.*, **1**, 453 (1994).
[418] E. Sigfridsson, M.H.M. Olsson, U. Ryde. *J. Phys. Chem. B*, **105**, 5546 (2001).
[419] S. Amanullah, A. Singha, A. Dey. *Coord. Chem. Rev.*, **386**, 183 (2019).
[420] J.F. Kasting, J.L. Siefert. *Science*, **296**, 1066 (2002).
[421] E.J. Javaux, C.P. Marshall, A. Bekker. *Nature*, **463**, 934 (2010).
[422] T.R.R. Bontognali, A.L. Sessions, A.C. Allwood, W.W. Fischer, J.P. Grotzinger, R.E. Summons, J.M. Eiler. *Proc. Natl. Acad. Sci. U S A*, **109**, 15146 (2012).
[423] M.M. Tice, D.R. Lowe. *Nature*, **431**, 549 (2004).
[424] T.L. Hamilton, D.A. Bryant, J.L. Macalady. *Environ. Microbiol.*, **18**, 325 (2016).
[425] S. Rexroth, M.M. Nowaczyk, M. Rögner. In P.C. Hallenbeck (Ed.), *Modern Topics in the Phototrophic Prokaryotes: Metabolism, Bioenergetics, and Omics*, pp. 163–191, Springer International Publishing, Cham (2017).
[426] R. Mittler, S. Vanderauwera, N. Suzuki, G. Miller, V.B. Tognetti, K. Vandepoele, M. Gollery, V. Shulaev, F. Van Breusegem. *Trends Plant Sci.*, **16**, 300 (2011).
[427] P. Sánchez-Baracaldo, T. Cardona. *New Phytol.*, **225**, 1440 (2020).
[428] M.R. Warke, T. Di Rocco, A.L. Zerkle, A. Lepland, A.R. Prave, A.P. Martin, Y. Ueno, D.J. Condon, M.W. Claire. *Proc. Natl. Acad. Sci. U S A*, **117**, 13314 (2020).
[429] W.W. Fischer, J. Hemp, J.S. Valentine. *Curr. Opin. Chem. Biol.*, **31**, 166 (2016).

[430] S. Miriyala, I. Spasojevic, A. Tovmasyan, D. Salvemini, Z. Vujaskovic, D. St. Clair, I. Batinic-Haberle. *Biochim. Biophys. Acta*, **1822**, 794 (2012).
[431] G. Pizzino, N. Irrera, M. Cucinotta, G. Pallio, F. Mannino, V. Arcoraci, F. Squadrito, D. Altavilla, A. Bitto. *Oxid. Med. Cell. Longevity*, **2017**, 8416763 (2017).
[432] H. Sies, C. Berndt, D.P. Jones. *Annu. Rev. Biochem.*, **86**, 715 (2017).
[433] K. Aramouni, R. Assaf, A. Shaito, M. Fardoun, M. Al-Asmakh, A. Sahebkar, A.H. Eid. *J. Cell Physiol.*, **238**, 1951 (2023).
[434] E.-I. Ochiai. *J. Inorg. Nucl. Chem.*, **37**, 1503 (1975).
[435] J.P. Collman, J.I. Brauman, K.S. Suslick. *J. Am. Chem. Soc.*, **97**, 7185 (1975).
[436] L. Pauling, C.D. Coryell. *Proc. Natl. Acad. Sci. U S A*, **22**, 210 (1936).
[437] J.J. Weiss. *Nature*, **202**, 83 (1964).
[438] L. Pauling. *Nature*, **203**, 182 (1964).
[439] J.J. Weiss. *Nature*, **203**, 183 (1964).
[440] D.S. McClure. *Rad. Res.*, **2**, 218 (1960).
[441] W.A. Goddard, B.D. Olafson. *Proc. Natl. Acad. Sci. U S A*, **72**, 2335 (1975).
[442] V.M. Miskowski, J.L. Robbins, I.M. Treitel, H.B. Gray. *Inorg. Chem.*, **14**, 2318 (1975).
[443] J.B.R. Dunn, D.F. Shriver, I.M. Klotz. *Biochemistry*, **14**, 2689 (1975).
[444] K. Shikama. *Prog. Biophys. Mol. Biol.*, **91**, 83 (2006).
[445] H.P. Misra, I. Fridovich. *J. Biol. Chem.*, **247**, 6960 (1972).
[446] T. Gotoh, K. Shikama. *J. Biochem.*, **80**, 397 (1976).
[447] A. Mal, I.B. Chatterjee. *J. Biosci.*, **16**, 55 (1991).
[448] C.H. Barlow, J.C. Maxwell, W.J. Wallace, W.S. Caughey. *Biochem. Biophys. Res. Commun.*, **55**, 91 (1973).
[449] A.S. Koster. *J. Chem. Phys.*, **63**, 3284 (2008).
[450] J.B. Wittenberg, B.A. Wittenberg, J. Peisach, W.E. Blumberg. *Proc. Natl. Acad. Sci. U S A*, **67**, 1846 (1970).
[451] J.C. Maxwell, W.S. Caughey. *Biochem. Biophys. Res. Commun.*, **60**, 1309 (1974).
[452] R.K. Gupta, A.S. Mildvan, T. Yonetani, T.S. Srivastava. *Biochem. Biophys. Res. Commun.*, **67**, 1005 (1975).
[453] G. Lang, W. Marshali. *Proc. Phys. Soc*, **87**, 3 (1966).
[454] K.L. Bren, R. Eisenberg, H.B. Gray. *Proc. Natl. Acad. Sci. U S A*, **112**, 13123 (2015).
[455] S.A. Wilson, E. Green, I.I. Mathews, M. Benfatto, K.O. Hodgson, B. Hedman, R. Sarangi. *Proc. Natl. Acad. Sci. U S A*, **110**, 16333 (2013).
[456] H. Chen, M. Ikeda-Saito, S. Shaik. *J. Am. Chem. Soc.*, **130**, 14778 (2008).
[457] N. Schuth, S. Mebs, D. Huwald, P. Wrzolek, M. Schwalbe, A. Hemschemeier, M. Haumann. *Proc. Natl. Acad. Sci. U S A*, **114**, 8556 (2017).
[458] M.F. Perutz. In *Structure and Function Relationships in Biochemical Systems*, F. Bossa, E. Chiancone, A. Finazzi-Agrò, R. Strom (Eds.), pp. 31–48, Springer, Boston, MA (1982).
[459] G. Fermi, M.F. Perutz, B. Shaanan, R. Fourme. *J. Mol. Biol.*, **175**, 159 (1984).
[460] K. Kitanishi, M. Shimonaka, M. Unno. *ACS Omega*, **6**, 34912 (2021).
[461] F.W.J. Teale. *Biochim. Biophys. Acta*, **35**, 543 (1959).
[462] K.L. Stone, S.M. Ahmed. *Inorganics*, **4**, 12 (2016).
[463] C.M. Lemon, M.A. Marletta. *Acc. Chem. Res.*, **54**, 4565 (2021).
[464] L.J. Perkins, B.R. Weaver, A.R. Buller, J.N. Burstyn. *Proc. Natl. Acad. Sci. USA.*, **118**, e2017625118 (2021).
[465] B.R. Weaver, L.J. Perkins, F.O. Fernandez Candelaria, J.N. Burstyn, A.R. Buller. *ACS Synth. Biol.*, **12**, 3369 (2023).
[466] B.M. Hoffman, D.H. Petering. *Proc. Natl. Acad. Sci. U S A*, **67**, 637 (1970).
[467] L.C. Dickinson, J.C.W. Chien. *J. Biol. Chem.*, **248**, 5005 (1973).
[468] H.C. Stynes, J.A. Ibers. *J. Am. Chem. Soc.*, **94**, 1559 (1972).
[469] G.C. Hsu, C.A. Spilburg, C. Bull, B.M. Hoffman. *Proc. Natl. Acad. Sci. U S A*, **69**, 2122 (1972).
[470] F.A. Walker. *J. Am. Chem. Soc.*, **95**, 1154 (1973).
[471] M.Y. Wang, B.M. Hoffman, P.F. Hollenberg. *J. Biol. Chem.*, **252**, 6268 (1977).

[472] R.S. Drago, T. Beugelsdijk, J.A. Breese, J.P. Cannady. *J. Am. Chem. Soc.*, **100**, 5374 (1978).
[473] G.C. Wagner, I.C. Gunsalus, M.Y. Wang, B.M. Hoffman. *J. Biol. Chem.*, **256**, 6266 (1981).
[474] M.C. Marden, L. Kiger, C. Poyart, A.K. Rashid, J. Kister, F. Stetzkowski-Marden, G. Caron, M. Haque, L. Moens. *FEBS Lett.*, **472**, 221 (2000).
[475] E.A. Brucker, J.S. Olson, G.N. Phillips, Y. Dou, M. Ikeda-Saito. *J. Biol. Chem.*, **271**, 25419 (1996).
[476] F.A. Walker. *J. Magn. Reson.*, **15**, 201 (1974).
[477] J.H. Bayston, F.D. Looney, J.R. Pilbrow, M.E. Winfield. *Biochemistry*, **9**, 2164 (1970).
[478] R. Blackburn, D.L. Cox, G.O. Phillips. *J. Chem. Soc. Faraday Trans. 1*, **68**, 1687 (1972).
[479] E.W. Abel, J.M. Pratt, E. Whelan, P.J. Wilkinson. *S. Afr. J. Chem.*, **30**, (1977).
[480] F.P. Guengerich. *ACS Catal.*, **8**, 10964 (2018).
[481] I. Efimov, J. Basran, S.J. Thackray, S. Handa, C.G. Mowat, E.L. Raven. *Biochemistry*, **50**, 2717 (2011).
[482] M. Alfonso-Prieto, X. Biarnés, P. Vidossich, C. Rovira. *J. Am. Chem. Soc.*, **131**, 11751 (2009).
[483] F.K. de Oliveira, L.O. Santos, J.G. Buffon. *Food Res. Int.*, **143**, 110266 (2021).
[484] K. Auclair, P. Moënne-Loccoz, P.R. Ortiz de Montellano. *J. Am. Chem. Soc.*, **123**, 4877 (2001).
[485] I. Schlichting, J. Berendzen, K. Chu, A.M. Stock, S.A. Maves, D.E. Benson, R.M. Sweet, D. Ringe, G.A. Petsko, S.G. Sligar. *Science*, **287**, 1615 (2000).
[486] R.D. Bach, O. Dmitrenko. *J. Am Chem Soc*, **128**, 1474 (2006).
[487] J. Rittle, M.T. Green. *Science*, **330**, 933 (2010).
[488] T. Punniyamurthy, M.M. Reddy, S.J.S. Kalra, J. Iqbal. *Pure Appl. Chem.*, **68**, 619 (1996).
[489] B. Hu, C. Sun, Q. Deng, Z. Liu. *J. Incl. Phenom. Macrocycl. Chem.*, **76**, 345 (2013).
[490] R.G. S. Banks, R.J. Henderson, J.M. Pratt. *J. Chem. Soc. A*, 2886 (1968).
[491] J.F. Nunn. *Trends Pharmacol. Sci.*, **5**, 225 (1984).
[492] D. Richardson, H. Felgate, N. Watmough, A. Thomson, E. Baggs. *Trends Biotechnol.*, **27**, 388 (2009).
[493] T.D. Rapson, S. Warneke, M.M. Musameh, H. Dacres, B. C.T. Macdonald, S.C. Trowell. *RSC Adv.*, **5**, 89003 (2015).
[494] P. Campomanes, U. Rothlisberger, M. Alfonso-Prieto, C. Rovira. *J. Am. Chem. Soc.*, **137**, 11170 (2015).
[495] S. Nakamura, K. Yokota, I. Yamazaki. *Nature*, **222**, 794 (1969).
[496] N.C. Veitch. *Phytochemistry*, **65**, 249 (2004).
[497] L. Vámos-Vigyázó, N.F. Haard. *CRC Crit. Rev. Food Sci. Nutr.*, **15**, 49 (1981).
[498] C. Jakopitsch, A. Wanasinghe, W. Jantschko, P.G. Furtmüller, C. Obinger. *J. Biol. Chem.*, **280**, 9037 (2005).
[499] J. Vlasits, C. Jakopitsch, M. Schwanninger, P. Holubar, C. Obinger. *FEBS Lett.*, **581**, 320 (2007).
[500] I. Fita, M.G. Rossmann. *J. Mol. Biol.*, **185**, 21 (1985).
[501] S. Kato, T. Ueno, S. Fukuzumi, Y. Watanabe. *J. Biol. Chem.*, **279**, 52376 (2004).
[502] L.-J. Peng, C.-Y. Zhang, W.-Y. Zhang, H.-Y. Zhou, F.-Q. Yang. *Physiochem. Eng. Aspects*, **651**, 129744 (2022).
[503] Z. Deng, H. Zhang, P. Yuan, Z. Su, Y. Bai, Z. Yin, J. He. *Catalysts*, **12**, 679 (2022).
[504] Y. Wang, H. Li, L. Guo, Q. Jiang, F. Liu. *RSC Adv.*, **9**, 18815 (2019).
[505] N. Li, W. Lu, K. Pei, W. Chen. *RSC Adv.*, **5**, 9374 (2015).
[506] W. Hu, J-z Li, Y. Wang, J. Du, C-w Hu, X-c Zeng. *J. Disp. Sci. Technol.*, **29**, 1476 (2008).
[507] P. Waldmeier, B. Prijs, H. Sigel. *Zeit. Naturforsch. B*, **27**, 95 (1972).
[508] D.G. Chihichin, V.A. Kotseruba, O.A. Levchenko, G.N. Masanovets, I.I. Seyfullina, G.L. Kamalov. *Russ J. Gen Chem.*, **83**, 915 (2013).
[509] P. Waldmeier, H. Sigel. *Inorg. Chem.*, **11**, 2174 (1972).
[510] M. Yamada, N. Yoshinari, N. Kuwamura, T. Saito, S. Okada, S.P. Maddala, K. Harano, E. Nakamura, K. Yamagami, K. Yamanaka, A. Sekiyama, T. Suenobu, Y. Yamada, T. Konno. *Chem. Sci.*, **8**, 2671 (2017).

[511] B.M. Pires, D.M. Silva, L.C. Visentin, B.L. Rodrigues, N.M.F. Carvalho, R.B. Faria. *PLoS One*, **10**, e0137926 (2015).
[512] M. Brugna, L. Tasse, L. Hederstedt. *FEBS J.*, **277**, 2663 (2010).
[513] J.A. Lyons, F. Hilbers, M. Caffrey. In *Cytochrome Complexes: Evolution, Structures, Energy Transduction, and Signaling, Advances in Photosynthesis and Respiration 41*, W.A. Cramer, T. Kallas (Eds.), pp. 307–329, Springer, Dordrecht, Gernany (2016).
[514] L. Qin, J. Liu, D.A. Mills, D.A. Proshlyakov, C. Hiser, S. Ferguson-Miller. *Biochemistry*, **48**, 5121 (2009).
[515] S. Yoshikawa, A. Shimada. *Chem Rev.*, **115**, 1936 (2015).
[516] J.P. Collman, L. Fu, P.C. Herrmann, X. Zhang. *Science*, **275**, 949 (1997).
[517] K.M. Kadish, L. Frémond, Z. Ou, J. Shao, C. Shi, F.C. Anson, F. Burdet, C.P. Gros, J.-M. Barbe, R. Guilard. *J. Am. Chem. Soc.*, **127**, 5625 (2005).
[518] R. McGuire, Jr., D.K. Dogutan, T.S. Teets, J. Suntivich, Y. Shao-Horn, D.G. Nocera. *Chem. Sci.*, **1**, 411 (2010).
[519] Y.-H. Wang, B. Mondal, S.S. Stahl. *ACS Catal.*, **10**, 12031 (2020).