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OXYGEN ACTIVATION BY MONONUCLEAR Mn, Co, AND Ni CENTERS IN BIOLOGY AND SYNTHETIC COMPLEXES

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Abstract

The active sites of metalloenzymes that catalyze O₂-dependent reactions generally contain iron or copper ions. However, several enzymes are capable of activating O₂ at manganese or nickel centers instead, and a handful of dioxygenases exhibit activity when substituted with cobalt. This minireview summarizes the catalytic properties of oxygenases and oxidases with mononuclear Mn, Co, or Ni active sites, including oxalate-degrading oxidases, catechol dioxygenases, and quercetin dioxygenase. In addition, recent developments in the O₂ reactivity of synthetic Mn, Co, or Ni complexes are described, with an emphasis on the nature of reactive intermediates featuring superoxo-, peroxy-, or oxo-ligands. Collectively, the biochemical and synthetic studies discussed herein reveal the possibilities and limitations of O₂ activation at these three “overlooked” metals.

Keywords

Manganese Cobalt Nickel Dioxygen activation Model complexes Metalloenzymes

Introduction

As attested by the articles in this special issue, the on-going tale of O₂ activation by metalloenzymes has featured two metals as the principal protagonists: iron (both heme and nonheme) and copper. Indeed, our fundamental understanding of biological O₂ activation has been shaped, in large part, through the study of a handful of enzymatic prototypes, such as cytochrome P450, methane monooxygenases, tyrosinase, and the α -ketoglutarate-dependent dioxygenases. Because of this, it is easy to forget that other transition metals have had distinguished “bit-parts” in this 60-year-old saga. Manganese, cobalt, and nickel are redox-active elements that occupy positions adjacent to iron and copper on the periodic table, and all three metals are capable of activating O₂ in biological environments. For example, many organisms employ manganese-dependent oxidases to degrade the toxic metabolite oxalate,¹ and a manganese-containing catechol dioxygenase catalyzes a critical step in the catabolism of aromatic compounds.² Certain soil bacteria are able to degrade the compound quercetin—a flavonol released into the environment by decomposing plant material—due to a nickel-dependent dioxygenase.³ And while no known enzyme requires cobalt to activate O₂ in vivo, cobalt-substituted dioxygenases generated in vitro have exhibited robust activities that rival the native enzymes.⁴

Furthermore, an impressive number of synthetic Mn, Co, and Ni complexes have been reported that harness the power of O₂ to perform oxidative transformations. Some of these complexes were prepared with biomimetic intent, whereas others were generated solely for the purpose of developing novel O₂-dependent chemistry. Regardless, investigations into the reactivities and spectroscopic properties of these complexes have illuminated key features of the relevant enzymes. Synthetic studies have also revealed unique aspects of O₂ activation at Mn, Co, and Ni sites that suggest alternative “plot lines” that were not pursued in the evolution of metal-dependent oxygenases.

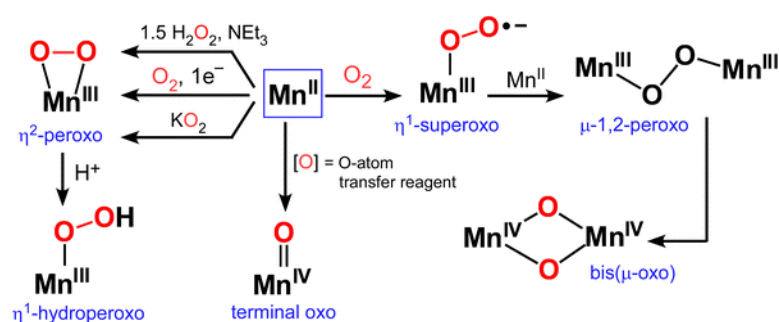
The goal of the present minireview is to summarize recent advances in our understanding of O₂ activation at nonheme mononuclear Mn, Co, and Ni centers in both biological and synthetic contexts (manganese-containing ribonucleotide reductases, which feature a dinuclear active site, are treated elsewhere in this special issue). The scope of the review is limited to (bio)chemical systems that involve direct reaction of the metal center with O₂. Thus, we have excluded enzymes that employ reduced O₂-derivatives (O₂^{•-}, H₂O₂) as substrates, such as catalase (Mn) or superoxide dismutase (Mn, Ni), along with those that operate by substrate activation mechanisms (e.g., manganese-containing lipoygenases, and nickel acireductone dioxygenase). Before delving into a discussion of specific enzymes and related models, we will first consider general aspects of the O₂ activation mechanisms commonly employed by these three transition metals, as elucidated through the study of synthetic complexes.

Dioxygen activation pathways for mononuclear Mn, Co, and Ni complexes

Manganese

As illustrated in Scheme [1](#), mononuclear Mn sites are capable of supporting an assortment of superoxo-, (hydro)peroxo-, and oxo-bound intermediates similar to those observed in heme and nonheme iron enzymes.

Superoxomanganese(III) complexes are often proposed as the first intermediates formed upon reaction of Mn(II) with O₂, although well-characterized examples are rare due to generally short lifetimes. By employing stopped-flow absorption spectroscopy at reduced temperatures, Kovacs and Rybak-Akimova observed the putative superoxomanganese(III) intermediate (complex **1** in Fig. 1) generated by treatment of a five-coordinate Mn(II)-thiolate complex with O₂.^{5,6} This species quickly reacts with a second equivalent of Mn(II) to afford a dimanganese(III) complex bridged by a *trans*- μ -1,2-peroxide ligand. Lang et al. succeeded in obtaining a crystal structure of a Mn(III) complex (**2**) featuring a superoxide ligand in an end-on (η^1) binding mode (Fig. 1).⁷ The unique stability of **2** is attributed to the steric bulk of the calix⁴arene supporting ligand, which prevents dimerization. The Mn/O₂ unit exhibits an unusual linear geometry (Mn–O–O bond angle of 180°) due to π ··· π and electrostatic interactions between the superoxide anion and NMe₃⁺-substituted phenyl rings of the calix⁴arene “bowl”. The lengthy Mn–O(O) bond of 2.444 Å indicates that the superoxide ligand is only weakly bound to the Mn(III) center.



Scheme 1. Dioxygen reactivity of mononuclear Mn species

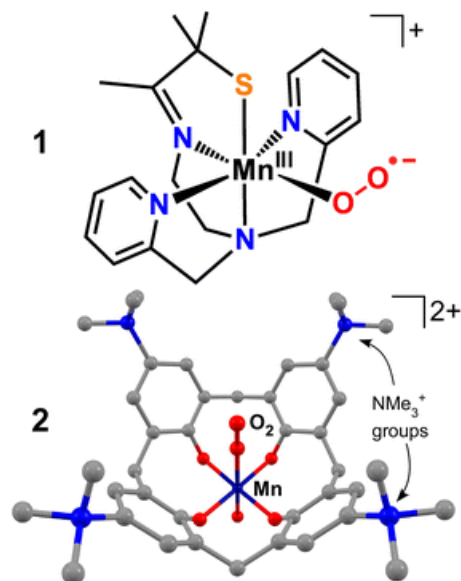


Fig. 1 Schematic representation (**1**) and X-ray crystal structure (**2**) of superoxomanganese complexes prepared by the Kovacs^{5,6} and Lang⁷ groups, respectively

Synthetic nonheme Mn(III) complexes with side-on (η^2) peroxide ligands—first reported by Kitajima and Morooka in 1994⁸—are generally prepared by treatment of Mn(II) precursors with superoxide or H₂O₂ (Scheme 1).^{9,10} The Borovik group, however, was able to derive a peroxomanganese(III) complex (**3**; Fig. 2) from direct reaction

of a Mn(II) complex with O₂ in the presence of an H-atom donor, which presumably serves to reduce the transient superoxomanganese(III) intermediate.^{11,12,13} Regardless of the ancillary ligand, η²-peroxomanganese(III) complexes are rather unreactive and conversion to a dioxomanganese (V) species has not been achieved. The [Mn³⁺(η²-O₂)]⁺ unit is sufficiently nucleophilic to perform the deformylation of aldehydes (e.g., cyclohexanecarboxaldehyde) to produce formate and oxidized products.^{11,12,14,15,16,17} A recent study of a bispidine-supported [Mn³⁺(η²-O₂)]⁺ complex revealed an alternative deformylation mechanism that involves the initial hydrogen-atom transfer from the aldehyde substrate to the peroxide ligand.¹⁸

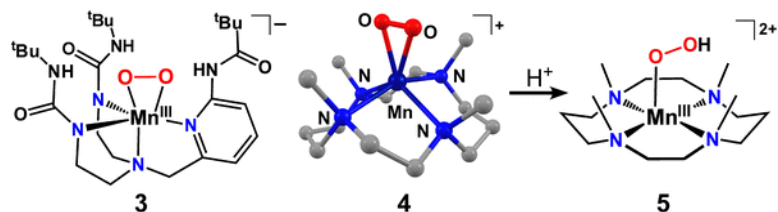


Fig. 2 Peroxomanganese(III) complexes prepared by the Borovik (**3**)¹¹ and Nam (**4** and **5**)^{14,21} groups. The coordinates of **4** were obtained from the published crystal structure

The peroxide bond is also activated by treatment with Lewis acids; for example, addition of Mn(II) has been shown to yield bis(μ-oxo-)dimanganese(III,IV) “diamond cores” via O–O bond cleavage.¹⁹ Similarly, Jackson and coworkers demonstrated that the η²-peroxomanganese(III) complex [Mn(O₂)(Me₂EBC)]⁺ decays in the presence of Mn(II) starting material to yield a mixture of Mn(IV)-oxo and Mn(III)-OH species (Me₂EBC = 4,11-dimethyl-1,4,8,11-tetraaza-bicyclo[6.6.2]hexadecane)²⁰ Recently, Nam et al. trapped an end-on manganese(III)-hydroperoxide intermediate (**5**) via addition of acid to [Mn(η²-O₂)(14-TMC)]⁺ (**4**),¹⁴ where 14-TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (Fig. 2).²¹ Reactivity studies indicated that protonation enhances the ability of the manganese peroxide moiety to perform electrophilic chemistry, such as oxygen atom transfer (OAT) reactions.

The long-standing interest in high-valent oxomanganese species arises, in large part, from their relevance to putative intermediates in the oxygen-evolving mechanism of photosystem II. An impressive number of binuclear Mn(IV)₂ and Mn(III)Mn(IV) complexes with μ-oxido ligands have been reported, and some were prepared via aerobic oxidation of Mn(II) precursors.^{22,23,24,25,26} This reaction likely occurs by the initial formation of a dimanganese(III)-peroxide intermediate, followed by O–O bond cleavage (Scheme 1). Interestingly, synthetic chemists have yet to trap a *mononuclear* Mn(IV)-oxocomplex using O₂ as the sole oxidant. Nearly, all of the currently available oxomanganese complexes, such as **6** in Fig. 3, were prepared by treating Mn(II) precursors with O-atom transfer reagents, such as iodosylbenzene (PhIO), peroxy acids, or H₂O₂.^{27,28,29,30,31,32} Borovik and coworkers, however, have developed an alternative route to mononuclear high-valent oxomanganese complexes. Using a tripodal ligand capable of stabilizing terminal oxometal units through multiple H-bonding interactions (Fig. 3), a monomeric oxomanganese(III) complex (**7**) was generated via reaction with O₂.³³ Stepwise oxidation of this complex by ferrocenium yielded Mn(IV)-oxo and Mn(V)-oxo derivatives (**8** and **9**, respectively), as confirmed by EPR spectroscopy and DFT calculations.^{34,35,36}

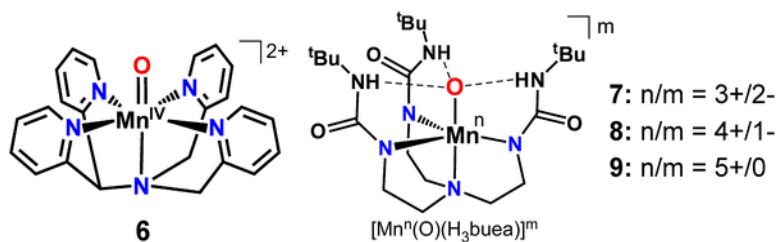
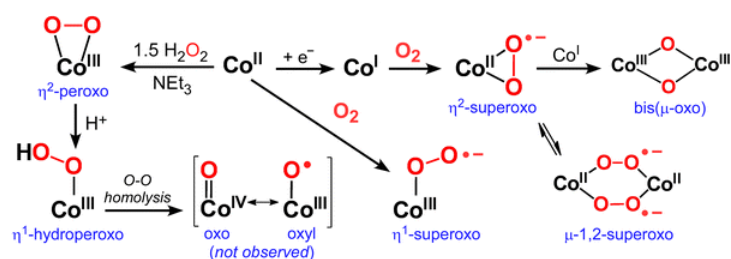


Fig. 3 Schematic representations of oxomanganese complexes **6–9**^{27,33,34,35,36}

Two mononuclear Mn(V)-oxo species have been generated by aerobic oxidation of Mn(III) complexes bearing highly anionic, square-planar macrocycles similar to porphyrins. The corrolazine-based oxomanganese(V) complex of Goldberg was prepared by a free-radical mechanism initiated by photoactivation of the Mn(III) precursor in the presence of O₂.^{37,38} The tetraamido-based oxomanganese(V) complex of Nam and Fukuzumi is proposed to arise from homolytic O–O cleavage of a manganese(IV) (hydro)peroxide intermediate formed after O₂ binding to Mn(III).³⁹ While notable, these mechanisms differ from manganese-based O₂ activation at nonheme sites in nature, which begin by reaction of O₂ with Mn(II) centers.

Cobalt

The O₂-activation landscape of cobalt is summarized in Scheme 2. The ability of square-planar Co(II) complexes featuring porphyrin, phthalocyanine, tetrazamacrocyclic, and Schiff-base (e.g., salen) ligands to *reversibly* bind O₂ has been studied extensively for decades, and the findings are described in several helpful reviews.^{40,41,42,43} These Co/O₂ adducts, which consist of a low-spin Co(III) center bound to a η^1 -superoxide ligand (**10** in Fig. 4), have often served as models of Fe/O₂ species in dioxygen carrier proteins; yet the former exhibits greater stability, on average, due to the kinetic inertness of Co(III). In addition, numerous Co(II)-salen catalysts have been developed for the aerobic oxidation of phenols and olefins.^{44,45,46,47,48} The key step in the catalytic cycle generally involves H-atom transfer (HAT) from a weak O–H or C–H bond to the cobalt(III)-bound superoxide ligand, thereby initiating a radical-based oxidation mechanism.^{49,50} When supported by neutral amine-based ligands, mononuclear superoxocobalt(III) intermediates are usually not observed due to fast reaction with a second Co center, thereby yielding dicobalt(III) complexes with μ -1,2-(su)peroxide ligands.^{51,52,53,54}



Scheme 2 Dioxygen reactivity of mononuclear Co species

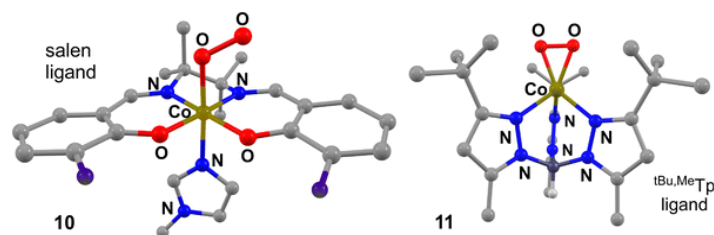


Fig. 4 X-ray crystal structures of superoxocobalt complexes **10** and **11**^{55,56}

In 1990, Theopold and coworkers reported the crystal structure of a mononuclear cobalt(II) complex (**11**) featuring a side-on (η^2) superoxide ligand.⁵⁵ The complex was prepared via oxidative addition of O₂ to a low-valent cobalt(I) center supported by the hydrotris(3-*tert*-butyl-5-methyl-pyrazolyl)borate (Tp^{tBu,Me}) ligand (Fig. 4). When a less sterically bulky Tp ligand was employed, the [Co(η^2 -O₂)] adduct dimerized at low temperatures to yield a dicobalt(II) complex with two *trans*- μ - η^1 : η^1 superoxide ligands (Scheme 2).⁵⁷ The O–O bond lengths measured by X-ray crystallography for these Tp-based complexes range between 1.26 and 1.36 Å, suggesting that the putative Co(II)-superoxo-units possess partial Co(III)-peroxide character. In certain cases, treatment of the mononuclear [Co(η^2 -O₂)(Tp)] adduct with a second Co(I) equivalent yielded a dicobalt(III) bis(μ -oxo) species, which likely arises from O–O homolysis of a dicobalt(II) μ - η^2 : η^2 -peroxide intermediate.^{58,59} Other structurally characterized [Co₂(μ -O)₂]²⁺ complexes derived from reaction with O₂ have featured bidentate β -diketiminato,⁶⁰ guanidinato,⁶¹ or monodeprotonated ureayl ligands.⁶² Hikichi et al. have shown that dicobalt(III) bis(μ -oxo) intermediates are potent oxidants capable of hydroxylating the isopropyl substituents of the Tp ligand.^{59,63,64}

Mononuclear peroxocobalt(III) complexes have been prepared by one of two routes: (1) direct reaction of Co(I) centers with O₂ or (2) treatment of Co(II) precursors with H₂O₂ under basic conditions. Meyer et al. used the former approach to prepare [Co(O₂)(TIMEN^{xy})]⁺ (**12**; Fig. 5), where TIMEN^{xy} is a tripodal *N*-heterocyclic carbene ligand.^{65,66} The strong σ -donating ability of the carbene groups favors a peroxocobalt(III) configuration over the superoxocobalt(II) alternative adopted by Tp-based complexes. Nam and coworkers followed the H₂O₂/NEt₃ route to prepare complexes, such as complex **13** in Fig. 5, featuring X-TMC macrocycles of varying sizes (*X* = 12, 13, 14, or 15, where *X* is the number of atoms in the cyclam ring).^{67,68} In all structurally characterized examples, the peroxide ligand coordinates to Co(III) in a side-on (η^2) fashion with an O–O bond distance of \sim 1.43 Å. The η^2 -peroxocobalt(III) complexes are sluggish oxidants with limited ability to perform hydroxylation, HAT, or OAT reactions; however, they are competent to perform oxidative nucleophilic reactions with aldehydes.^{67,68,69} Nam et al. have shown that treatment of [Co(η^2 -O₂)]⁺ complexes with acids provides a spectroscopically observable cobalt(III)-hydroperoxide species capable of both electrophilic and nucleophilic oxidation reactions.^{68,70} When the 15-TMC ligand is employed, decay of the cobalt(III)-hydroperoxide species is accompanied by hydroxylation of the methyl group of the TMC ligand.⁶⁸ Mechanistic evidence suggests that the hydroxylation is performed by a short-lived oxocobalt(IV) or oxylcobalt(III) intermediate (not observed) arising from O–O bond homolysis (Scheme 2).

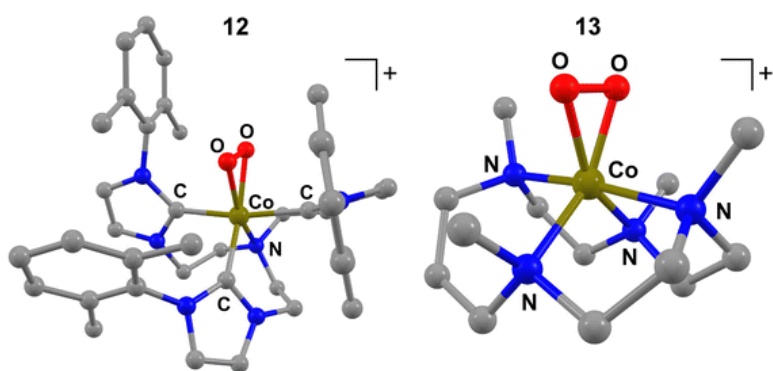


Fig. 5 X-ray crystal structures of η^2 -peroxocobalt(III) complexes prepared by the Meyer (**12**)^{65,66} and Nam (**13**)⁶⁷ groups

Although cobalt complexes with terminal oxoligands are frequently invoked as transient intermediates in the decay of cobalt-(alkyl/hydro)peroxide species, attempts to isolate such an entity have not been successful to date.^{55,57,58,59,71,72,73,74} This shortcoming is not surprising given the intrinsic instability of terminal oxometal

complexes of groups 9–11 (often referred to as the “oxowall” for tetragonal structures).⁷⁵ The nearest analogs of these elusive species are a handful of mononuclear Co(III) and Co(IV) complexes featuring [Co–O–M] units, where M is a redox-inactive metal ion like Sc(III). For example, Ray and coworkers found that treatment of [Co²⁺(TMG₃tren)(OTf)]⁺ with a derivative of PhIO triggers hydroxylation of the tripodal TMG₃tren supporting ligand (TMG₃tren = tris[2-(*N*-tetramethylguanidyl)ethyl]amine).⁷⁶ The oxocobalt species (**14**) in Fig. 6 was trapped by addition of Sc³⁺ at low temperatures. Data gathered using EPR and X-ray absorption spectroscopies suggested that **14** features a [Co⁴⁺(μ-O)Sc³⁺] core with an *S* = 3/2 ground state, although [Co³⁺(μ-O*)Sc³⁺] and [Co³⁺(μ-OH)Sc³⁺] assignments have also been proposed.^{73,77} Using a similar approach, Ray and Nam generated a series of *S* = 1/2 [Co⁴⁺(μ-O)Mⁿ⁺] complexes (**15^M**; M = Sc³⁺, Y³⁺, Ce³⁺, Zn²⁺) via reaction of PhIO with the square-planar [Co³⁺(TAML)]⁻ complex (TAML = tetraamido macrocyclic ligand) in the presence of redox-inactive metal ions (Fig. 6).⁷⁸ The **15^M** complexes are capable of performing both HAT and OAT reactions, with reactivity increasing with the Lewis acidity of the redox-inactive metal ion.

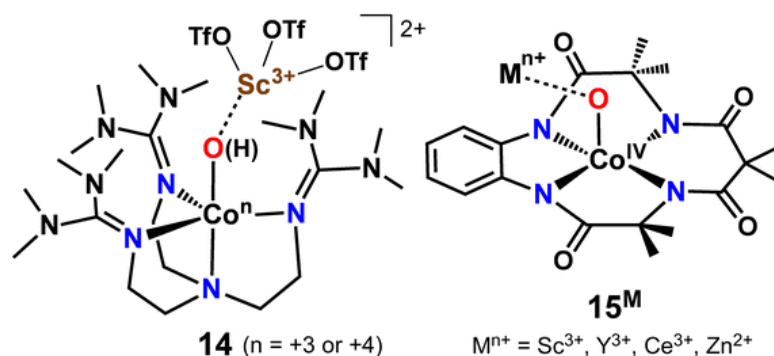


Fig. 6 Schematic representations of putative oxocobalt complexes prepared by Ray and coworkers^{76,78}

Nickel

Nickel(II) complexes are generally unreactive towards O₂ unless electron-rich ligands are employed to depress the Ni^{2+/3+} redox potential. For example, Kimura and Martell reported a series of nickel(II) complexes with dioxopentaaza macrocyclic ligands capable of catalyzing oxygen insertion reactions under aerobic conditions.^{79,80,81} Although never isolated, superoxonickel(III) species were proposed as the active intermediates in the oxygenation mechanisms. Nickel(II)-thiolate complexes are also known to react with O₂ to afford the corresponding metallosulfoxides and metallosulfones. Mechanistic evidence suggests that these reactions involve direct reaction of O₂ with the thiolate ligand without oxidation of the nickel(II) center.⁸²

Much of the nickel-dioxygen chemistry reported in the past 15 years has harnessed the enhanced O₂ reactivity of electron-rich Ni(I) precursors. In 2001, Riordan described the synthesis of a dinickel(III) bis(μ-oxo) complex (**16**; Fig. 7) from the reaction of O₂ with [Ni⁺(CO)(PhTt^{tBu})], where PhTt^{tBu} = phenyltris((*tert*-butylthio)methyl)borate.^{83,84,85} Resonance Raman (rR) and X-ray absorption spectroscopies affirmed the presence of the [Ni₂³⁺(μ-O)₂] core.⁸⁶ The formation of **16** was presumed to follow the conventional superoxo→peroxo→bis(μ-oxo) pathway involving the initial formation of a 1:1 Ni:O₂ adduct, followed by reaction with a second Ni(I) equivalent and O–O bond homolysis. In support of this mechanism, a monomeric η²-superoxonickel(II) species (**17**; Fig. 7) was obtained by reaction of O₂ with [Ni⁺(CO)(PhTt^{Ad})], which features bulky adamantyl (Ad) groups on the PhTt supporting ligand to prevent dinucleation.⁸⁷ Treatment of **17** with [Ni⁺(CO)(PhTt^{tBu})] afforded the asymmetric dimer, [(PhTt^{Ad})Ni³⁺(μ-O)₂Ni³⁺(PhTt^{tBu})].

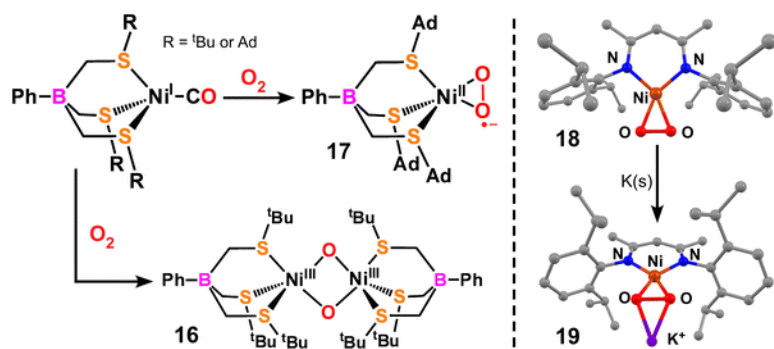


Fig. 7 *Left* Schematic representations of η^2 -superoxonickel(II) and dinickel(III) bis(μ -oxo) complexes (**17** and **16**, respectively) prepared by Riordan and coworkers.^{83,87} *Right* X-ray crystal structures of complexes **18** and **19** generated by Driess et al. The 18-crown-6 ether in the structure of **19** was omitted for clarity^{88,90}

More recently, Driess et al. reported the crystal structure of a square-planar η^2 -superoxonickel(II) complex (**18**; Fig. 7) bearing a β -diketiminato ligand prepared by reaction of a Ni(I) precursor with O_2 .^{88,89} The observed O–O bond distance of 1.35 Å is characteristic of a superoxide ligand. One-electron reduction of **18** using elemental potassium provided an unusual structure (**19**) in which a μ - η^2 : η^2 -peroxide ligand with an O–O bond distance of 1.47 Å serves as a bridge between the nickel(II) center and a potassium ion solvated by 18-crown-6 ether.⁹⁰ Reaction of **18** with a Cu(I) complex was shown to trigger O–O bond cleavage leading to formation of a heterobimetallic $[Cu^{3+}(\mu-O)_2Ni^{3+}]$ core.⁹¹

The *N*-tetramethylcyclam (TMC) framework is capable of supporting both superoxonickel(II) and peroxonickel(III) units, depending on the size of the TMC ring. End-on (η^1) superoxonickel(II) complexes have been synthesized using 13-TMC and 14-TMC.^{92,93} Riordan and coworkers observed that oxygenation of $[Ni^+(14-TMC)]^+$ at low temperature generates a metastable dinickel(II) species (**20**; Fig. 8) with a bridging μ -1,2-peroxide ligand, as determined by rR and DFT analyses.^{94,95} Under conditions of excess O_2 , the mononuclear complex $[Ni^{2+}(\eta^1-O_2)(14-TMC)]^+$ (**21**) is the dominant product.⁹² The same complex was also prepared by addition of excess H_2O_2 and NEt_3 to $[Ni^{2+}(14-TMC)]^{2+}$. Remarkably, reaction of $[Ni^{2+}(12-TMC)]^{2+}$ with the same H_2O_2/NEt_3 combination yielded a η^2 -peroxonickel(III) complex instead of the expected η^1 -superoxonickel(II) species, highlighting the ability of TMC ancillary ligands to modulate the geometric and electronic structures of mononuclear $[NiO_2]^+$ intermediates.^{10,96} Nam and others have shown that $[Ni^{3+}(\eta^2-peroxo)]^+$ complexes, like their Mn and Co congeners, perform the nucleophilic deformylation of aldehydes.^{96,97} By contrast, end-on and side-on superoxonickel(II) complexes are electrophilic and participate in OAT reactions with triphenylphosphine.⁹³

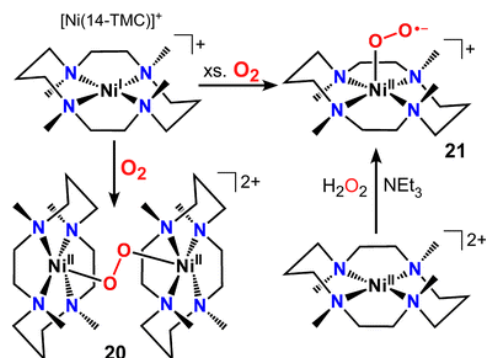


Fig. 8 Peroxodinickel(II) (**20**) and η^1 -superoxonickel(II) (**21**) species obtained using the $[Ni(14-TMC)]^{2+/+}$ framework^{92,95}

The only crystallographically characterized example of a nickel-hydroperoxide complex was recently reported by Gade and coworkers. These researchers found that reaction of O₂ with a pincer-based Ni(I) complex (Fig. 9) yielded a η^1 -superoxonickel(II) complex (**22**) that exists in equilibrium with its dinickel(II) μ -1,2-peroxo-bridged counterpart (**23**).⁹⁸ Treatment of the latter with H₂O₂ provided complex **24** and the resulting crystal structure revealed a square-planar Ni(II) center bound to an end-on hydroperoxide donor. Aerobic decomposition of **24** is accompanied by autoxidation of the pincer ligand to yield a novel alkylperoxo-metallacyclic complex.⁹⁹

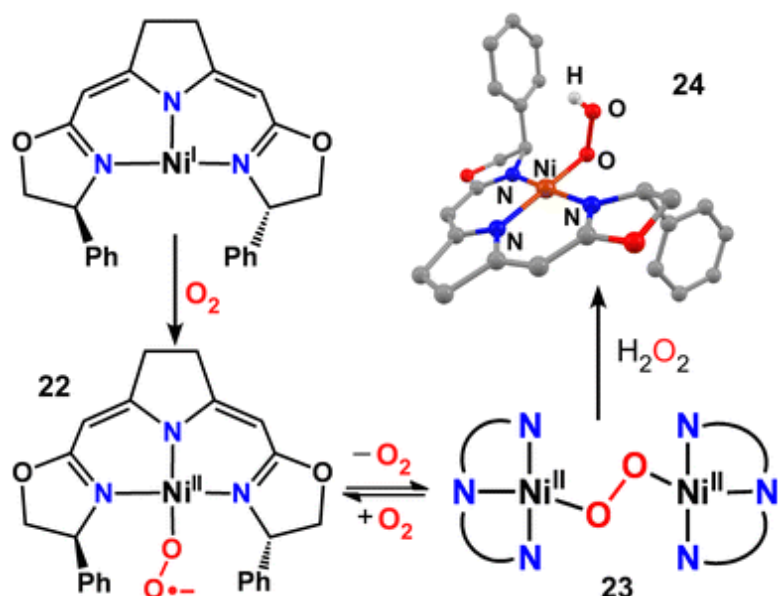


Fig. 9 Series of superoxo-, peroxo-, and hydroperoxo-nickel(II) complexes generated by Gade et al. using a chiral pincer ligand⁹⁸

The same factors that make it challenging to isolate mononuclear oxocobalt species (vide supra) have also prevented, at least so far, definitive characterization of a nickel complex featuring a terminal oxoligand. Transient oxo/oxyl nickel species are likely involved in alkane hydroxylation reactions catalyzed by Ni(II) complexes in the presence of the oxidant *m*-chloroperbenzoic acid (*m*CPBA).^{100,101} The proposed catalytic mechanism involves the initial formation of an acylperoxo-nickel(II) species, followed by O–O bond homolysis to yield the active oxo-nickel(III) or oxynickel(II) intermediate. Ray and coworkers have succeeded in trapping a metastable complex (**25**) that arises from oxidation of [Ni²⁺(TMG₃tren)(OTf)₂] with *m*CPBA at –30 °C.¹⁰² Data gathered using EPR and UV–vis spectroscopies indicate that this species consists of a Ni(III) center bound to a terminal oxo- or hydroxo-ligand, although a conclusive structural determination was not possible due to its instability and low yield of formation (~15 %). Company et al. followed a similar procedure to generate a putative oxynickel(III) species (**26**) supported by a tetradentate bisamidate ligand.^{103,104} Analysis with X-ray absorption spectroscopy (XAS) revealed a nickel–oxygen distance of 1.88 Å, and the preponderance of spectroscopic and computational data favored an oxynickel(III) configuration rather than the oxonickel(IV) alternative. While these results are certainly promising, the assignment of **26** as an oxynickel(III) species remains tentative and additional characterization with structural and spectroscopic methods is required to confirm this hypothesis (Fig. 10).

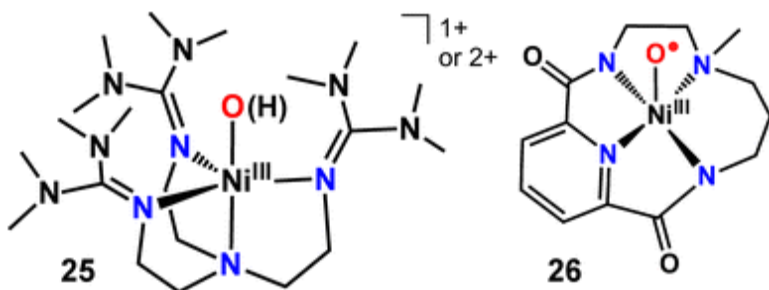
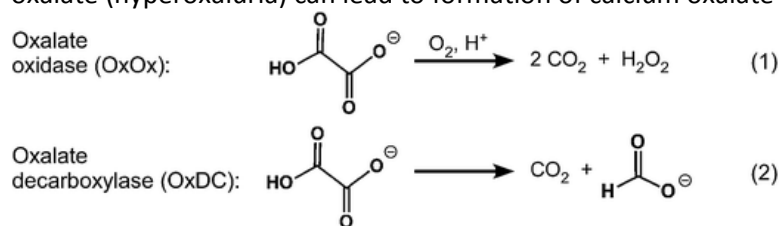


Fig. 10 Schematic representations of putative nickel(III) complexes with hydroxo/oxo (**25**) or oxyl (**26**) ligands^{102,103,104}

Dioxygen activation at mononuclear Mn, Co, and Ni enzymes and model complexes

Manganese oxalate-degrading enzymes

The accumulation of oxalic acid—a byproduct of metabolic pathways in plants, fungi, and microbes—has harmful consequences for nearly all organisms. To mitigate the toxic effects of this organic acid, nature has evolved two classes of manganese-dependent enzymes that degrade oxalate via different reactions.^{1,105,106} Oxalate oxidase (OxOx) catalyzes the oxidation of oxalate to two moles of CO₂ (Eq. 1). Dioxygen serves as the electron and proton acceptor in this process, resulting in concomitant formation of H₂O₂. In contrast, oxalate decarboxylase (OxDC) catalyzes the conversion of oxalate to formate and CO₂ (Eq. 2). Even though the OxDC reaction is merely a disproportionation, the enzyme requires both manganese and O₂ for activity.¹⁰⁷ The OxOx family plays the dominant role in oxalate catabolism in plants.¹⁰⁸ whereas the OxDC family is more common in fungi and bacteria.¹ Humans lack these oxalate-degrading enzymes and thus excessive amounts of dietary oxalate (hyperoxaluria) can lead to formation of calcium oxalate stones in the kidney.¹⁰⁹



Both OxOx and OxDC belong to the functionally diverse superfamily of cupin proteins, and the close structural and sequence similarities between the two enzymes point to a common evolutionary ancestor.^{110,111} A high-resolution X-ray crystal structure published in 2000 revealed that barley OxOx is a homohexamer in which each monomer contains one manganese ion within its jellyroll β-barrel domain.¹¹² Crystal structures of bacterial OxDC's from *Bacillus subtilis* display a similar homohexameric arrangement.^{113,114} However, each OxDC subunit consists of two cupin domains and, therefore, possesses two nearly identical manganese-binding sites, suggesting that OxDC might have arisen from gene duplication of OxOx.¹¹³ Based on structural and mutagenesis studies, it appears that catalytic activity largely occurs at the N-terminal site, while the role of the C-terminal site remains ambiguous.^{114,115,116,117} The active sites of OxOx and OxDC both feature a six-coordinate manganese(II) center bound to one glutamate and three histidine side chains, in addition to two water molecules in a *cis* arrangement (Fig. 11).^{112,113}

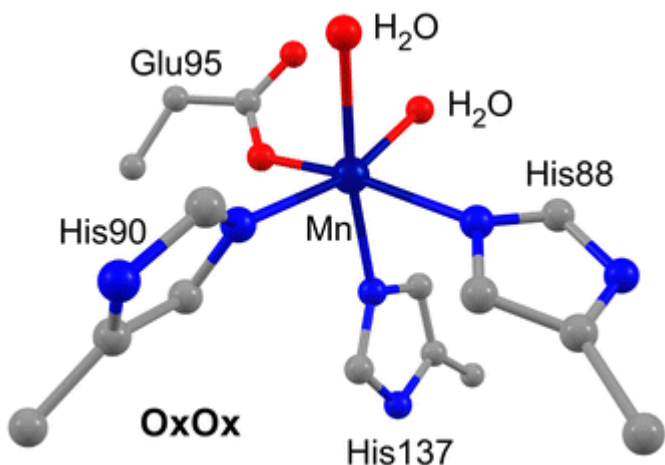
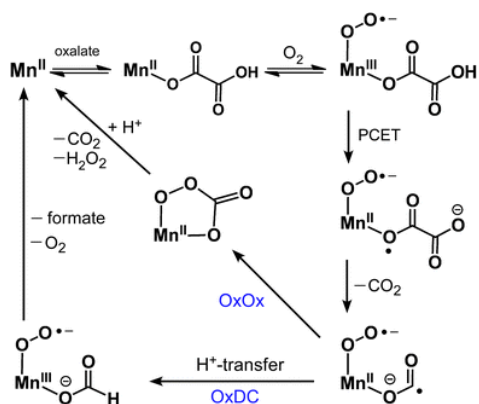


Fig. 11 Manganese active site of OxOx from *Hordeum vulgare* (barley).¹¹² PDB 1F12

The catalytic cycles of OxOx and OxDC are initiated by coordination of oxalate to the Mn(II) center, displacing one or both of the H₂O molecules found in the resting state. It is generally assumed that oxalate binds in a monodentate fashion, and this hypothesis is supported by crystal structures of OxOx featuring the substrate-analog glycolate¹¹⁸ and a cobalt-substituted OxDC/oxalate complex.¹¹⁹ Oxalate coordination serves to lower the Mn^{3+/2+} redox potential, thus facilitating formation of a Mn/O₂ adduct with η¹-superoxomanganese(III) character.¹²⁰ In the OxOx/OxDC mechanisms favored by both Richards and Bornemann, O₂ binding is followed by a key proton-coupled electron transfer (PCET) step involving deprotonation of the oxalate ligand and transfer of an electron from oxalate to the nascent Mn(III) center (Scheme 3).^{114,121,122} The end-result is a putative superoxomanganese(III)-(oxalate radical anion) intermediate common to both OxOx and OxDC. Because one-electron oxidation of oxalate dramatically weakens its C–C bond,¹²³ this intermediate undergoes spontaneous decarboxylation to generate CO₂ and a manganese-bound formyl radical anion. At this point, the mechanisms of OxOx and OxDC diverge. The formyl radical either couples with the superoxo-ligand to yield a manganese(II)-peroxycarbonate species (OxOx) or undergoes protonation by a conserved second-sphere Glu162 residue to afford a manganese(III)-formate intermediate (OxDC).^{114,121,122} In support of this proposal, Bornemann and coworkers demonstrated that *B. subtilis* OxDC can be converted into an oxidase by mutating four residues (including Glu162) in the flexible lid of the N-terminal site.¹²⁴ Furthermore, radical-trapping EPR experiments have confirmed the presence of superoxo- and oxalate-derived radicals during catalysis.^{124,125,126} and the OxDC mechanism shown in Scheme 3 is consistent with heavy-atom isotope effect measurements.^{122,127}



Scheme 3 Proposed catalytic mechanisms for OxOx and OxDC

The publication of the enzymatic structures has stimulated the development of synthetic models of the OxOx and OxDC active sites. In 2005, Berreau and coworkers prepared a mononuclear Mn(II) complex (**27**) with a N3O donor set provided by the chelate bpppa (Fig. 12), in which the oxygen donor is provided by the 2-amido substituent of one of the pyridine rings.¹²⁸ Attempts to generate the oxalate-bound form of **27** afforded a dimanganese(II) complex, $[\text{Mn}^{2+}(\mu_2\text{-oxalate})(\text{bpppa})_2]^{2+}$, that features a bridging oxalate dianion. Subsequently, Berreau et al. generated a series of $[\text{Mn}^{2+}(\text{N3O})(\text{X})(\text{MeOH})]^+$ complexes ($\text{X} = \text{Cl}^-, \text{Br}^-, \text{I}^-$) using bpppa and a related derivative to mimic the 3His/1Glu coordination of the enzymes.¹²⁹ No reactivity studies with O_2 were reported. The Pecoraro and Chavez groups have both prepared structural models of the resting active sites using 1,4,7-triazacyclononane (TACN) ligands with pendant acetate groups.^{130,131} Chavez found that complex **28** (Fig. 12) binds oxalate in solution and exposure to O_2 results in catalytic decomposition of oxalate to CO_2 (2 equiv. of CO_2 per oxalate ion). However, further analysis found that the catalytically active species is likely $[\text{Mn}^{3+}(\text{oxalate})_2]^-$, not complex **28**.¹³⁰

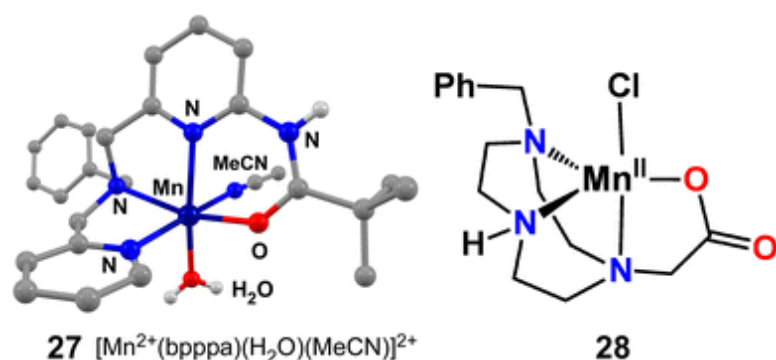
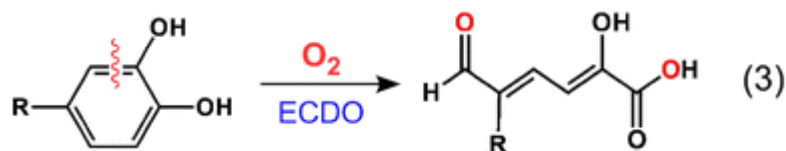


Fig. 12 X-ray crystal structure (**27**) and schematic representation (**28**) of synthetic models of the OxOx/OxDC active sites^{128,130}

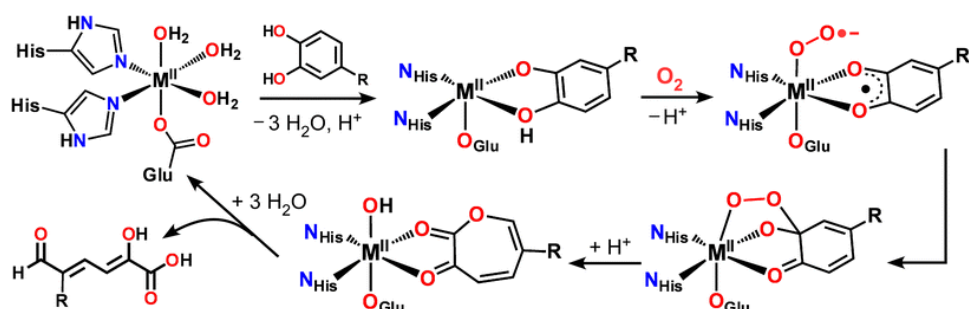
Extradiol catechol dioxygenases

The aerobic degradation of biomolecules by soil bacteria requires a variety of metal-containing dioxygenases that incorporate both atoms of O_2 into the product.^{132,133,134} Extradiol catechol dioxygenases (ECDOs) catalyze the oxidative scission of the C–C bond adjacent to the vicinal dihydroxy unit of catechol-containing substrates, as shown in Eq. 3.^{135,136} While the majority of ECDOs feature a mononuclear iron(II) active site, homoprotocatechuate-2,3-dioxygenases (HPCDs) from *Bacillus brevis*¹³⁷ and *Arthrobacter globiformis* (Mn-MndD)¹³⁸ contain a manganese(II) center instead. Iron-containing HPCD (Fe-HPCD) and Mn-MndD exhibit 83 % sequence identity and crystallographic studies revealed that the active-site structures are nearly superimposable to beyond 15 Å from the metal centers.^{139,140} In the resting states of both enzymes, the divalent metal ion is bound to one glutamate and two histidine residues in a facial geometry (the so-called 2-His-1-carboxylate facial triad¹⁴¹); three labile H_2O ligands complete the metal coordination sphere.



Regardless of the active-site metal, all ECDOs are thought to follow a common mechanism (Scheme 4) that has been elucidated through a combination of crystallographic, spectroscopic, kinetic, and computational

studies.^{132,142,143,144} The catalytic cycle begins with displacement of the H₂O molecules by the monodeprotonated substrate, which coordinates in a bidentate fashion. The resulting M(II) center is then capable of binding O₂ in the vacant site adjacent to the bound substrate. On the basis of experimental and computational evidence, it has been proposed that formation of the M/O₂ adduct is coupled to oxidation of the bound substrate, yielding a superoxo-M(II)-semiquinone (SQ) species (Scheme 4).^{145,146,147,148,149,150,151} Studies of relevant model complexes have confirmed that such an intermediate is feasible due to the “noninnocent” nature of dioxolene ligands.^{152,153,154,155,156,157} However, spectroscopic studies of Fe-HPCD employing mutant enzyme and/or unactivated substrate have failed to detect a catalytically viable Fe(II)/SQ species,^{158,159,160} and a recent density functional theory (DFT) analysis of the iron-based mechanism favored a superoxo-Fe(III)-catecholate description instead.¹⁶¹ Thus, the precise electronic structure of the M/O₂ adduct remains a matter of dispute, and we will return to this topic below. Nevertheless, it is clear that the next step in the catalytic cycle involves formation of a metal(II)-alkylperoxide intermediate, followed by Criegee rearrangement with ring insertion of an oxygen atom. Hydrolysis of the resulting lactone finally yields the aliphatic product (Scheme 4).



Scheme 4 Proposed catalytic mechanism for extradiol catechol dioxygenase

During the past decade, important insights into the O₂ activation mechanism of ECDOs have been gained through the preparation of enzymes reconstituted with a nonphysiological metal in the active site. Since these studies were the subject of a recent review article published in this journal,⁴ we will provide only a cursory overview of the major findings here. In a seminal 2008 paper, the Que and Lipscomb groups described a methodology for “swapping” the metal ions Fe-HPCD and Mn-MndD, thereby generating manganese-substituted HPCD (Mn-HPCD) and iron-substituted MndD (Fe-MndD).¹⁴⁰ Subsequent efforts by the same groups yielded cobalt-substituted HPCD (Co-HPCD).¹⁶² Comparison of HPCD crystal structures collected for the wild-type (WT) and metal-substituted enzymes revealed that the active-site structures are identical regardless of the metal ion present (Mn, Fe, or Co).^{140,162} Kinetic measurements determined that the steady-state catalytic parameters for the four Fe- and Mn-containing enzymes (Fe-HPCD, Mn-MndD, Fe-MndD, and Mn-HPCD) were quite similar, indicating that metal-substitution has little effect on enzyme activity.¹⁴⁰ This result is surprising, because the Mn^{3+/2+} redox potential is intrinsically higher than the Fe^{3+/2+} potential by approximately 0.7 V,¹⁶³ and the identical first and second coordination spheres of HPCD and MndD preclude the possibility of redox tuning by the active site. If the mechanism required one-electron transfer from the M(II) ion to O₂, one would expect Mn-HPCD and Mn-MndD to be less active than their iron-containing counterparts, not equally active. To rationalize this apparent inconsistency, the authors argued that the ECDO mechanism does not, in fact, require a well-defined change in metal oxidation state upon O₂ binding; instead, the metal ion merely serves to shuttle an electron from the catecholate substrate to O₂, giving rise to the elusive O₂⁻/M(II)/SQ intermediate in a concerted step.^{140,164}

The metal-substituted HPCDs have been utilized in attempts to trap and characterize reactive intermediates. The reaction of Mn-HPCD with O₂ generates two short-lived intermediates that were observed by EPR spectroscopy in samples prepared via rapid freeze-quench experiments.¹⁶⁵ EPR analysis indicated that the first-formed species (**Int1**) consists of a Mn(III) center bound to an unidentified radical, perhaps superoxide or semiquinone. The later-forming intermediate (**Int2**) is an Mn(II) species and was assigned to the alkylperoxide intermediate in Scheme 4. These results would seem to contradict the theory, described above, that the oxidation state of the metal center does not change during ECDO catalysis. However, the low yield of **Int1** (5 %) and a lack of structural information make it difficult to draw firm mechanistic conclusions.

The kinetic parameters measured for Co-HPCD differ from those reported for Fe- and Mn-HPCD in ways that are informative. The Co^{3+/2+} redox potential is predicted to be ~ 1.15 V higher than the Fe^{3+/2+} potential for ions in the same coordination environment, which accounts for the very low affinity of Co-HPCD for O₂ under turnover conditions ($K_M^{O_2} = 1200 \mu\text{M}$, compared with ~50 μM for Fe- and Mn-HPCD).¹⁶² However, this diminished O₂ affinity is partially offset by a larger k_{cat} -value for Co-HPCD under conditions of O₂ saturation; indeed, k_{cat} is highly dependent on the solution concentration of O₂. Taken together, these results suggest that the rate-determining step is O₂-binding/activation for Co-HPCD, whereas product release is known to be rate-limiting for Fe-HPCD. A possible explanation for these mechanistic differences became apparent in EPR studies of Co-HPCD using an electron-poor substrate, 4-nitrocatechol (4NC).¹⁶⁶ While the Co-HPCD/4NC complex features a high-spin ($S = 3/2$) Co(II) center, exposure to O₂ affords a low-spin ($S = 1/2$) signal characteristic of a superoxocobalt(III) species. This spin-state change may impose a kinetic barrier to O₂ binding in Co-HPCD that is not present in Fe- and Mn-HPCD, where the metal ions remain high-spin throughout the catalytic cycle. A superoxocobalt(III) species is not observed when the native substrate is employed. It was proposed that the more activated substrate rapidly transfers an electron to the Co(III) center to yield a putative high-spin O₂⁻/Co(II)/SQ species.¹⁶⁶ This hypothesis found support in a recent QM/MM study of the Co-HPCD mechanism by Lai and coworkers.¹⁶⁷

By studying both wild-type and metal-substituted enzymes with a variety of experimental and computational methods, a largely consistent picture of O₂ activation in ECDOs has emerged. The broad similarities in catalysis between Mn-, Fe-, and Co-HPCD, despite the vastly different redox potentials of the respective metal ions, clearly indicate that O₂ binding requires a significant amount of electron transfer from the catecholate substrate, although partial or transient oxidation of the metal centers may also be involved.⁴ On-going efforts to trap and characterize catalytic intermediates will likely provide additional insights into the mechanisms of these finely-tuned enzymes.

Attempts to generate structural and functional models of the manganese-dependent ECDOs have been rather limited, lagging far behind biomimetic studies of iron-containing ring-cleaving dioxygenases.^{132,168,169} Que and coworkers used neutral, tetradentate N4 chelates to prepare six-coordinate Mn-MnD models featuring a monoanionic 4-nitrocatecholate ligand, yet O₂ reactivity experiments were not pursued.¹⁷⁰ Other ECDO models have been generated by binding dianionic catecholate ligands to Mn(III) centers.^{171,172,173,174,175,176} The resulting complexes often exhibit valence tautomerization between Mn(III)-catecholate and Mn(II)-semiquinone configurations (Fig. 13), where the latter resembles the O₂⁻/Mn(II)/SQ species proposed for the enzymatic mechanism. Several groups have demonstrated that six-coordinate Mn(II)/SQ complexes serve as intermediates in the catalytic oxidation of catechols to benzoquinones under aerobic conditions (i.e., catechol oxidase activity).^{171,172,173} Hikichi and coworkers also observed small amounts of intradiol and extradiol ring-cleavage products upon reaction of the five-coordinate complex [Mn²⁺(DTBSQ)(Tp^{iPr2})] (**29**; Fig. 13) with O₂ (DTBSQ = 3,5-di-*tert*-butylsemiquinonate).¹⁷⁶

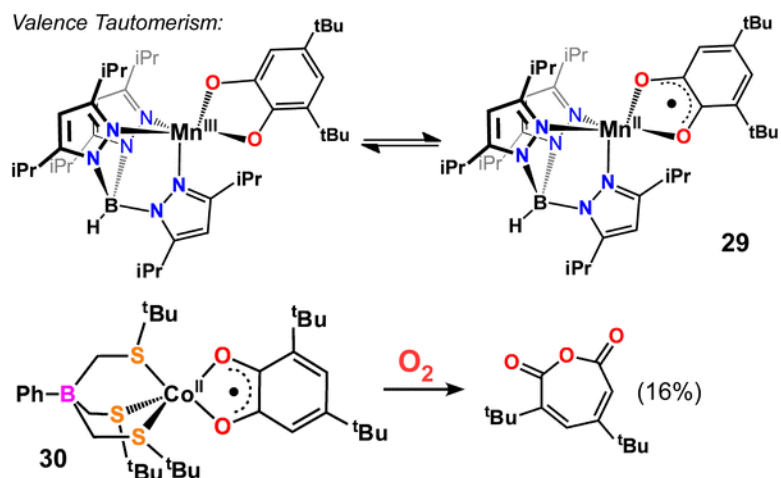
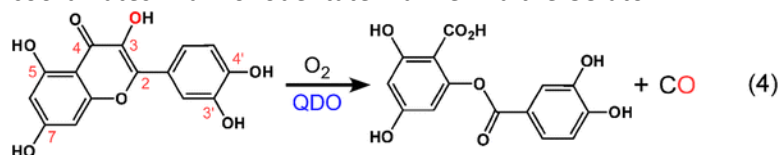


Fig. 13 Synthetic models of extradiol catechol dioxygenases containing manganese (top)¹⁷⁶ and cobalt (bottom)¹⁷⁹

Cobalt dioxolene complexes have attracted considerable scrutiny due to their valence tautomeric behavior,¹⁷⁷ yet the O₂ reactivity of such complexes has not been examined until recently. In an extension of their manganese studies, Hikichi et al. found that [Co²⁺(DTBSQ)(Tp^{Me2})] serves as a catalyst for the aerobic oxidation of *ortho*- and *para*-hydroquinones with simultaneous formation of H₂O₂.¹⁷⁸ More recently, Riordan and coworkers reported that the five-coordinate complex [Co²⁺(DTBSQ)(PhTt^{tBu})] (**30**; Fig. 13) reacts with O₂ to afford the intradiol cleavage product in 16% yield.¹⁷⁹

Quercetin dioxygenases

The aerobic breakdown of plant-derived flavonols by fungi and some bacteria is an important process in soil environments.^{180,181} The first step in the catabolism of quercetin (3,5,7,3',4'-pentahydroxyflavone) involves dioxygenolytic cleavage of the 3-hydroxyflavone ring to yield a depside product and carbon monoxide (Eq. 4). This reaction is catalyzed by quercetin dioxygenases (QDOs), which belong to the cupin superfamily of enzymes.¹⁸² The best-studied QDOs have been isolated from fungi and require copper for activity. Crystallographic studies revealed that the active site of fungal QDO from *Aspergillus japonicus* (QDO^{Aj}) features a mononuclear Cu(II) center bound to the three His residues and one water molecule.¹⁸³ In contrast, an X-ray structure of bacterial QDO from *Bacillus subtilis* (QDO^{Bs}) featured two monoiron(II) active sites per subunit.¹⁸⁴ Both iron centers are pentacoordinate with four protein ligands (one Glu and three facial His) and one H₂O ligand (Fig. 14). However, in the site closest to the C-terminus, the Glu ligand is only weakly bound with an Fe–O_{Glu} distance of 2.44 Å. While QDO^{Bs} is thought to be an iron-containing dioxygenase *in vivo*, it exhibits equal or greater activity with other transition-metal ions, including Mn, Co, Ni, and Cu.¹⁸⁴ The QDO from *Streptomyces* sp. strain FLA (QDO^{FLA}) is similarly “promiscuous”, displaying catalytic activity following the order Ni > Co > Mn (strangely, QDO^{FLA} is inactive with ferrous iron).^{3,185} Crystallographic studies indicate that the active sites of QDO^{Bs} (Fe) and QDO^{FLA} (Ni) provide similar metal coordination environments regardless of metal ion identity.^{184,186} Structures of the enzyme-substrate complexes revealed that the deprotonated substrate coordinates in a monodentate manner via the O3 atom.^{183,186}



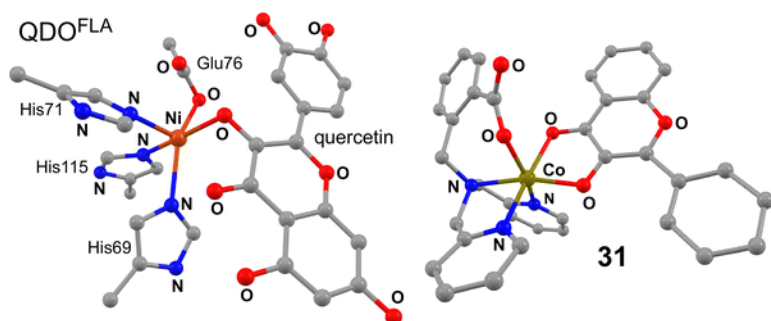
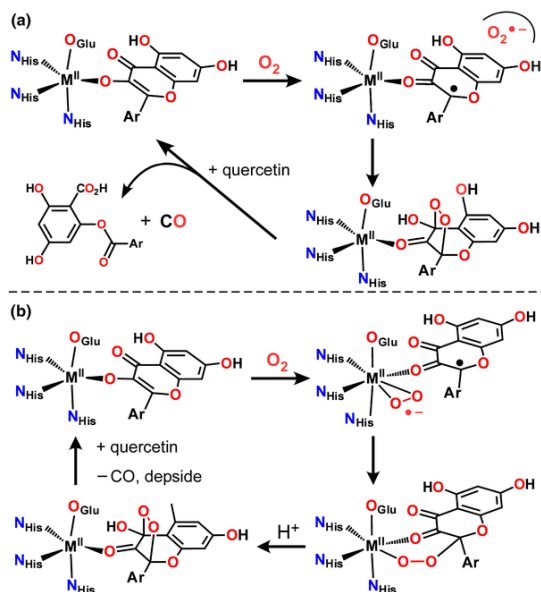


Fig. 14 X-ray crystal structures of the substrate-bound active site of QDO^{FLA} (*left*) and complex **31** (*right*)

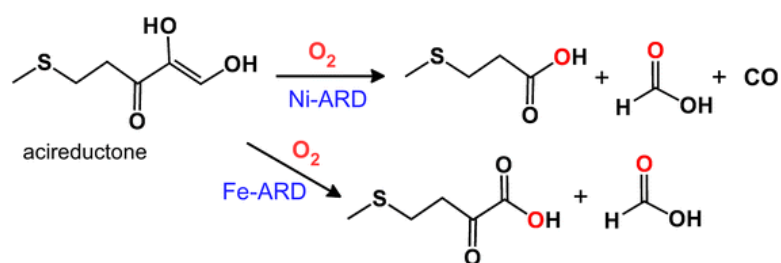
The precise role of the metal center in the O₂ activation mechanism of QDOs has been the subject of much debate.¹⁸⁷ The fact that QDO activity is largely independent of the redox potential of the active-site metal makes it unlikely that the catalytic cycle involves electron transfer from the M(II) center to O₂. Moreover, flavonolate anions are known to react with O₂ to yield QDO-type products in the absence of redox-active ions, leading some to suggest that the metal ion does not bind O₂ at all and simply serves to deprotonate the substrate.¹⁸⁸ As shown in Scheme 5a, such a mechanism could proceed via direct addition of O₂ to the flavonolate ring, or outer-sphere electron transfer to yield superoxide and substrate radicals. In either case, the resulting cyclic peroxide species would decompose via concerted O–C and O–O bond cleavages, affording the depside and CO products. Recently, however, Dobbek and coworkers reported strong evidence in favor of a metal-based O₂ activation mechanism. After exposing crystals of the substrate-bound enzyme to O₂ for short periods of time, the resulting X-ray structure revealed the presence of a Ni/O₂ adduct in the QDO^{FLA} active site.¹⁸⁶ The O₂ ligand is coordinated in a side-on fashion with Ni–O and O–O bond distances of 2.4 and 1.3 Å, respectively. Based on their results, Dobbek et al. proposed the ECDO-like mechanism shown in Scheme 5b, in which O₂ binding yields a superoxo-Ni(II)-(flavonol radical) intermediate, followed by O–C bond formation. A similar mechanism was derived from DFT studies performed by Siegbahn.¹⁸⁹ While it is possible that the crystallographically observed Ni/O₂ is not catalytically relevant, this study provides unambiguous proof that O₂ is capable of coordinating to the metal center of a QDO.



Scheme 5 Two possible catalytic mechanisms for quercetin dioxygenase

The majority of QDO model complexes prepared to date contain copper-flavonolate units, and these efforts have been reviewed by Kaizer et al.¹⁹⁰ In light of the ability of QDOs to operate with non-native metals, several groups have prepared metal(II)-flavonolate complexes using other first-row transition metals.^{191,192,193,194,195,196} In the past few years, Sun and coworkers have reported a series of QDO models (M = Mn, Fe, Co, Ni, Cu, and Zn) supported by a tetradentate N₃O chelate featuring a benzoate donor which closely resembles the enzymatic coordination environments (see complex **31** in Fig. 14).^{197,198,199,200} Unlike the enzyme, however, the flavonolate ligands in Sun's models coordinate in a bidentate manner to afford six-coordinate structures. While reaction rates vary with metal ion, each of these complexes reacts with O₂ at elevated temperatures to yield CO and oxidized ring-cleavage products. Berreau and coworkers also demonstrated that irradiation of metal(II)-flavonolate complexes (M = Mn, Co, Ni, Cu) in the presence of O₂ triggers QDO-like reactivity.¹⁹⁵

There are numerous similarities between QDOs and nickel-containing acireductone dioxygenase (Ni-ARD) which catalyzes an "exit reaction" from the methionine salvage pathway (Scheme 6).^{187,201,202,203} Both enzymes generate CO as a product and contain mononuclear active sites featuring 3His/1Glu coordination of a divalent metal ion.²⁰⁴ Like QDO, Ni-ARD exhibits nearly full activity with non-native metal ions, such as Co(II) and Mn(II).^{204,205} Even more remarkably, an iron-containing ARD (Fe-ARD) is also involved in the methionine salvage pathway, yet the iron and nickel enzymes catalyze different dioxygenation reactions with the same substrate (Scheme 6).²⁰⁵ However, the metal ions of both ARD enzymes are not redox active under catalytic conditions; instead, the mechanism proceeds via direct addition of O₂ to the metal-bound substrate dianion.²⁰⁶ Thus, the Fe- and Ni-ARDs are examples of substrate activation by a metalloenzyme, not O₂ activation. It has been proposed that the unique regioselectivity of the ARDs is due to distinct coordination modes of acireductone to the Fe(II) and Ni(II) centers (the so-called "chelate hypothesis").^{206,207} The chelate hypothesis, however, is not supported by biomimetic studies. The Berreau group has prepared synthetic models of the Fe- and Ni-ARD active sites that exhibit metal-dependent regioselectivity similar to that of the enzymes, even though the acireductone ligand adopts the same coordination mode in the Fe and Ni complexes.^{208,209,210,211,212,213,214,215} Mechanistic studies indicated that the Fe- and Ni-ARD models react with O₂ to generate a common triketone intermediate, and it is the subsequent reactivity of this triketone with the metal complexes and H₂O that accounts for the observed regioselectivity. The chelate hypothesis has also been called into question by computational studies of the Fe- and Ni-ARD mechanisms.²¹⁶



Scheme 6 Reactions catalyzed by Ni- and Fe-containing ARD

Conclusions

Collectively, the studies discussed in this review highlight the relative capabilities of mononuclear Mn, Co, and Ni centers to activate O₂ in both enzymatic and synthetic environments. There are close parallels between the O₂ reaction pathways employed by manganese- and iron-containing systems. Both metals are able to access oxidation states between +2 and +5 under turnover conditions, permitting the formation of high-valent

oxometal intermediates stable enough for spectroscopic and/or crystallographic characterization. However, as noted above, none of the mononuclear oxomanganese(IV) complexes in the literature have been prepared via direct reaction of a Mn(II) center with O₂. The primary obstacle in the Mn(II) + O₂ → Mn(IV)=O reaction appears to be the O–O bond homolysis step. In contrast to iron-based chemistry, there are no reported examples of mononuclear Mn(III)-OOR complexes (R = vacant, H, or alkyl) converting to an observable oxomanganese(IV) species. Instead, O–O homolysis generally requires a second metal center, resulting in dinuclear bis(μ-oxo) structures (Scheme 1). Because of this, high-valent oxomanganese species in O₂-activating enzymes are only found in dinuclear active sites like ribonucleotide reductase, whereas mononuclear oxygenases involving an oxometal(IV) intermediate employ iron exclusively.

The O₂ activating potential of mononuclear Co(II) and Ni(II) centers is limited by the inability of these ions to access the +4 oxidation state and stabilize terminal oxide ligands. Thus, it is not surprising that all known O₂-activating enzymes containing Co or Ni employ mechanisms, such as those shown in Schemes 4 and 5, that do not require formation of a high-valent, oxometal intermediate. Instead, the divalent metal ions in ECDO and QDO simply serve as conduits of electron density between the activated substrate and O₂. Nevertheless, synthetic Co and Ni complexes have displayed rich O₂ chemistry that surpasses the narrow reactivity of these metals in biological systems. For example, numerous mononuclear superoxo- and peroxo-cobalt(III) species have been generated via reaction of O₂ with Co(II) and Co(I) complexes. These Co/O₂ adducts react with a second cobalt equivalent to afford dinuclear [Co₂³⁺(μ-O)₂] units (Scheme 2). Because Ni(II) centers exhibit a low affinity for O₂ unless supported by highly anionic chelates, recent Ni/O₂ chemistry has successfully employed Ni(I) precursors to generate superoxo-nickel(II) and dinickel(III) species (Fig. 7). Future synthetic efforts will undoubtedly expand the boundaries of O₂ chemistry for Mn, Co, and Ni complexes, and biochemists will hopefully discover new and surprising metalloenzymes that employ one of these “bit-players” in the drama of O₂ activation.

Notes

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References

- ¹Svedruzic D, Jonsson S, Toyota CG, Reinhardt LA, Ricagno S, Lindqvist Y, Richards NGJ (2005) *Arch Biochem Biophys* 433:176–192 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²Que L Jr, Reynolds MF (2000) *Met Ions Biol Syst* 37:505–525 [PubMed](#) [Google Scholar](#)
- ³Nianios D, Thierbach S, Steimer L, Lulchev P, Klostermeier D, Fetzner S (2015) *BMC Biochem* 16:1–11 [CrossRef](#) [Google Scholar](#)
- ⁴Fielding AJ, Lipscomb JD, Que L Jr (2014) *J Biol Inorg Chem* 19:491–504 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁵Coggins MK, Sun X, Kwak Y, Solomon EI, Rybak-Akimova E, Kovacs JA (2013) *J Am Chem Soc* 135:5631–5640 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁶Kovacs JA (2015) *Acc Chem Res* 48:2744–2753 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁷Liu L-L, Li H-X, Wan L-M, Ren Z-G, Wang H-F, Lang J-P (2011) *Chem Commun* 47:11146–11148 [CrossRef](#) [Google Scholar](#)

- ⁸Kitajima N, Komatsuzaki H, Hikichi S, Osawa M, Moro-oka Y (1994) *J Am Chem Soc* 116:11596–11597 [CrossRef](#) [Google Scholar](#)
- ⁹Leto DF, Jackson TA (2014) *J Biol Inorg Chem* 19:1–15 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁰Cho J, Sarangi R, Nam W (2012) *Acc Chem Res* 45:1321–1330 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹¹Shook RL, Gunderson WA, Greaves J, Ziller JW, Hendrich MP, Borovik AS (2008) *J Am Chem Soc* 130:8888–8889 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹²Shook RL, Borovik AS (2010) *Inorg Chem* 49:3646–3660 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹³Shook RL, Peterson SM, Greaves J, Moore C, Rheingold AL, Borovik AS (2011) *J Am Chem Soc* 133:5810–5817 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴Seo MS, Kim JY, Annaraj J, Kim Y, Lee Y-M, Kim S-J, Kim J, Nam W (2007) *Angew Chem. Int Ed* 46:377–380 [CrossRef](#) [Google Scholar](#)
- ¹⁵Annaraj J, Cho J, Lee Y-M, Kim SY, Latifi R, de Visser SP, Nam W (2009) *Angew Chem. Int Ed* 48:4150–4153 [CrossRef](#) [Google Scholar](#)
- ¹⁶Kang H, Cho J, Cho K-B, Nomura T, Ogura T, Nam W (2013) *Chem Eur J* 19:14119–14125 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁷Geiger RA, Chattopadhyay S, Day VW, Jackson TA (2011) *Dalton Trans* 40:1707–1715 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸Barman P, Upadhyay P, Faponle AS, Kumar J, Nag SS, Kumar D, Sastri CV, de Visser SP (2016) *Angew Chem. Int Ed* 55:11091–11095 [CrossRef](#) [Google Scholar](#)
- ¹⁹Leto DF, Chattopadhyay S, Day VW, Jackson TA (2013) *Dalton Trans* 42:13014–13025 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ²⁰Colmer HE, Howcroft AW, Jackson TA (2016) *Inorg Chem* 55:2055–2069 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹So H, Park YJ, Cho K-B, Lee Y-M, Seo MS, Cho J, Sarangi R, Nam W (2014) *J Am Chem Soc* 136:12229–12232 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ²²Mukhopadhyay S, Mandal SK, Bhaduri S, Armstrong WH (2004) *Chem Rev* 104:3981–4026 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²³Gohdes JW, Armstrong WH (1992) *Inorg Chem* 31:368–373 [CrossRef](#) [Google Scholar](#)
- ²⁴Larson E, Lah MS, Li X, Bonadies JA, Pecoraro VL (1992) *Inorg Chem* 31:373–378 [CrossRef](#) [Google Scholar](#)
- ²⁵Pecoraro VL, Baldwin MJ, Gelasco A (1994) *Chem Rev* 94:807–826 [CrossRef](#) [Google Scholar](#)
- ²⁶Horwitz CP, Winslow PJ, Warden JT, Lisek CA (1993) *Inorg Chem* 32:82–88 [CrossRef](#) [Google Scholar](#)
- ²⁷Chen J, Lee Y-M, Davis KM, Wu X, Seo MS, Cho K-B, Yoon H, Park YJ, Fukuzumi S, Pushkar YN et al (2013) *J Am Chem Soc* 135:6388–6391 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁸Wu X, Seo MS, Davis KM, Lee Y-M, Chen J, Cho K-B, Pushkar YN, Nam W (2011) *J Am Chem Soc* 133:20088–20091 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁹Chen J, Yoon H, Lee Y-M, Seo MS, Sarangi R, Fukuzumi S, Nam W (2015) *Chem Sci* 6:3624–3632 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ³⁰Yoon H, Lee Y-M, Wu X, Cho K-B, Sarangi R, Nam W, Fukuzumi S (2013) *J Am Chem Soc* 135:9186–9194 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ³¹Garcia-Bosch I, Company A, Cady CW, Styring S, Browne WR, Ribas X, Costas M (2011) *Angew Chem. Int Ed* 50:5648–5653 [CrossRef](#) [Google Scholar](#)
- ³²Engelmann X, Monte-Perez I, Ray K (2016) *Angew Chem. Int Ed* 55:7632–7649 [CrossRef](#) [Google Scholar](#)
- ³³Cook SA, Borovik AS (2015) *Acc Chem Res* 48:2407–2414 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ³⁴Parsell TH, Behan RK, Green MT, Hendrich MP, Borovik AS (2006) *J Am Chem Soc* 128:8728–8729 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ³⁵Gupta R, Taguchi T, Lassalle-Kaiser B, Bominaar EL, Yano J, Hendrich MP, Borovik AS (2015) *Proc Natl Acad Sci USA* 112:5319–5324 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ³⁶Taguchi T, Gupta R, Lassalle-Kaiser B, Boyce DW, Yachandra VK, Tolman WB, Yano J, Hendrich MP, Borovik AS (2012) *J Am Chem Soc* 134:1996–1999 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)

- ³⁷Prokop KA, Goldberg DP (2012) *J Am Chem Soc* 134:8014–8017 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ³⁸Sahu S, Goldberg DP (2016) *J Am Chem Soc* 138:11410–11428 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ³⁹Hong S, Lee Y-M, Sankaralingam M, Vardhaman AK, Park YJ, Cho K-B, Ogura T, Sarangi R, Fukuzumi S, Nam W (2016) *J Am Chem Soc* 138:8523–8532 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁴⁰Niederhoffer EC, Timmons JH, Martell AE (1984) *Chem Rev* 84:137–203 [CrossRef](#) [Google Scholar](#)
- ⁴¹Jones RD, Summerville DA, Basolo F (1979) *Chem Rev* 79:139–179 [CrossRef](#) [Google Scholar](#)
- ⁴²Busch DH, Alcock NW (1994) *Chem Rev* 94:585–623 [CrossRef](#) [Google Scholar](#)
- ⁴³Smith TD, Pilbrow JR (1981) *Coord Chem Rev* 39:295–383 [CrossRef](#) [Google Scholar](#)
- ⁴⁴Bailey CL, Drago RS (1987) *Coord Chem Rev* 79:321–332 [CrossRef](#) [Google Scholar](#)
- ⁴⁵Cozzi PG (2004) *Chem Soc Rev* 33:410–421 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁴⁶Nam W, Kim HJ, Kim SH, Ho RYN, Valentine JS (1996) *Inorg Chem* 35:1045–1049 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁴⁷Deng Y, Busch DH (1995) *Inorg Chem* 34:6380–6386 [CrossRef](#) [Google Scholar](#)
- ⁴⁸Simandi LI (2003) *Catal Met Complexes* 26:265–328 [CrossRef](#) [Google Scholar](#)
- ⁴⁹Bakac A (2000) *J Am Chem Soc* 122:1092–1097 [CrossRef](#) [Google Scholar](#)
- ⁵⁰Bakac A (1997) *J Am Chem Soc* 119:10726–10731 [CrossRef](#) [Google Scholar](#)
- ⁵¹Lever ABP, Gray HB (1978) *Acc Chem Res* 11:348–355 [CrossRef](#) [Google Scholar](#)
- ⁵²Gavrilova AL, Qin CJ, Sommer RD, Rheingold AL, Bosnich B (2002) *J Am Chem Soc* 124:1714–1722 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁵³Spingler B, Scanavy-Grigorieff M, Werner A, Berke H, Lippard SJ (2001) *Inorg Chem* 40:1065–1066 [CrossRef](#) [Google Scholar](#)
- ⁵⁴Cho YI, Joseph DM, Rose MJ (2013) *Inorg Chem* 52:13298–13300 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁵⁵Egan JW Jr, Haggerty BS, Rheingold AL, Sendlinger SC, Theopold KH (1990) *J Am Chem Soc* 112:2445–2446 [CrossRef](#) [Google Scholar](#)
- ⁵⁶Avdeef A, Schaefer WP (1976) *J Am Chem Soc* 98:5153–5159 [CrossRef](#) [Google Scholar](#)
- ⁵⁷Reinaud OM, Yap GPA, Rheingold AL, Theopold KH (1995) *Angew Chem Int Ed Engl* 34:2051–2052 [CrossRef](#) [Google Scholar](#)
- ⁵⁸Reinaud OM, Theopold KH (1994) *J Am Chem Soc* 116:6979–6980 [CrossRef](#) [Google Scholar](#)
- ⁵⁹Hikichi S, Akita M, Moro-oka Y (2000) *Coord Chem Rev* 198:61–87 [CrossRef](#) [Google Scholar](#)
- ⁶⁰Dai X, Kapoor P, Warren TH (2004) *J Am Chem Soc* 126:4798–4799 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁶¹Jones C, Schulten C, Rose RP, Stasch A, Aldridge S, Woodul WD, Murray KS, Moubaraki B, Brynda M, La Macchia G et al (2009) *Angew Chem. Int Ed* 48:7406–7410 [CrossRef](#) [Google Scholar](#)
- ⁶²Larsen PL, Parolin TJ, Powell DR, Hendrich MP, Borovik AS (2003) *Angew Chem Int Ed* 42:85–89 [CrossRef](#) [Google Scholar](#)
- ⁶³Hikichi S, Yoshizawa M, Sasakura Y, Komatsuzaki H, Moro-Oka Y, Akita M (2001) *Chem Eur J* 7:5011–5028 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁶⁴Hikichi S, Komatsuzaki H, Akita M, Moro-oka Y (1998) *J Am Chem Soc* 120:4699–4710 [CrossRef](#) [Google Scholar](#)
- ⁶⁵Hu X, Meyer K (2005) *J Organomet Chem* 690:5474–5484 [CrossRef](#) [Google Scholar](#)
- ⁶⁶Hu X, Castro-Rodriguez I, Meyer K (2004) *J Am Chem Soc* 126:13464–13473 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁶⁷Cho J-H, Sarangi R, Kang H-Y, Lee J-Y, Kubo M, Ogura T, Solomon EI, Nam W-W (2010) *J Am Chem Soc* 132:16977–16986 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁶⁸Kim D, Cho J, Lee Y-M, Sarangi R, Nam W (2013) *Chem Eur J* 19:14112–14118 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁶⁹Jo Y, Annaraj J, Seo MS, Lee Y-M, Kim SY, Cho J, Nam W (2008) *J Inorg Biochem* 102:2155–2159 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁷⁰Cho W-Y, Wang B, Lee Y-M, Cho K-B, Shearer J, Nam W (2016) *Dalton Trans* 24:14511–14515 [CrossRef](#) [Google Scholar](#)
- ⁷¹Chavez FA, Mascharak PK (2000) *Acc Chem Res* 33:539–545 [PubMed](#) [CrossRef](#) [Google Scholar](#)

- ⁷²Chavez FA, Rowland JM, Olmstead MM, Mascharak PK (1998) *J Am Chem Soc* 120:9015–9027 [CrossRef](#) [Google Scholar](#)
- ⁷³Ray K, Heims F, Pfaff FF (2013) *Eur J Inorg Chem* 2013:3784–3807 [CrossRef](#) [Google Scholar](#)
- ⁷⁴Ray K, Pfaff FF, Wang B, Nam W (2014) *J Am Chem Soc* 136:13942–13958 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁷⁵Winkler JR, Gray HB (2012) *Struct Bonding* 142:17–28 [CrossRef](#) [Google Scholar](#)
- ⁷⁶Pfaff FF, Kundu S, Risch M, Pandian S, Heims F, Pryjomska-Ray I, Haack P, Metzinger R, Bill E, Dau H et al (2011) *Angew Chem. Int Ed* 50:1711–1715 [CrossRef](#) [Google Scholar](#)
- ⁷⁷Lacy DC, Park YJ, Ziller JW, Yano J, Borovik AS (2012) *J Am Chem Soc* 134:17526–17535 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁷⁸Hong S, Pfaff FF, Kwon E, Wang Y, Seo M-S, Bill E, Ray K, Nam W (2014) *Angew Chem Int Ed* 53:10403–10407 [CrossRef](#) [Google Scholar](#)
- ⁷⁹Kimura E, Machida R (1984) *J Chem Soc Chem Commun* 499–500 [Google Scholar](#)
- ⁸⁰Kimura E, Sakonaka A, Machida R, Kodama M (1982) *J Am Chem Soc* 104:4255–4257 [CrossRef](#) [Google Scholar](#)
- ⁸¹Chen D, Martell AE (1990) *J Am Chem Soc* 112:9411–9412 [CrossRef](#) [Google Scholar](#)
- ⁸²Grapperhaus CA, Darensbourg MY (1998) *Acc Chem Res* 31:451–459 [CrossRef](#) [Google Scholar](#)
- ⁸³Mandimutsira BS, Yamarik JL, Brunold TC, Gu W, Cramer SP, Riordan CG (2001) *J Am Chem Soc* 123:9194–9195 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁸⁴Kieber-Emmons MT, Riordan CG (2007) *Acc Chem Res* 40:618–625 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁸⁵Hikichi S, Yoshizawa M, Sasakura Y, Akita M, Moro-oka Y (1998) In 1998, Akita and Moro-oka reported the crystal structure of a similar dinickel(III) bis(μ -oxo) complex generated by treating a $[\text{Ni}_2^{2+}(\mu\text{-OH})_2]$ precursor with H_2O_2 . *J Am Chem Soc* 120:10567–10568 [CrossRef](#) [Google Scholar](#)
- ⁸⁶Schenker R, Mandimutsira BS, Riordan CG, Brunold TC (2002) *J Am Chem Soc* 124:13842–13855 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁸⁷Fujita K, Schenker R, Gu W, Brunold TC, Cramer SP, Riordan CG (2004) *Inorg Chem* 43:3324–3326 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁸⁸Yao S, Bill E, Milsmann C, Wieghardt K, Driess M (2008) *Angew Chem. Int Ed* 47:7110–7113 [CrossRef](#) [Google Scholar](#)
- ⁸⁹Yao S, Driess M (2012) *Acc Chem Res* 45:276–287 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁹⁰Yao S, Xiong Y, Vogt M, Gruetzmacher H, Herwig C, Limberg C, Driess M (2009) *Angew Chem Int Ed* 48:8107–8110 [CrossRef](#) [Google Scholar](#)
- ⁹¹Kundu S, Pfaff FF, Miceli E, Zaharieva I, Herwig C, Yao S, Farquhar ER, Kuhlmann U, Bill E, Hildebrandt P et al (2013) *Angew Chem Int Ed* 52:5622–5626 [CrossRef](#) [Google Scholar](#)
- ⁹²Kieber-Emmons MT, Annaraj J, Seo MS, VanHeuvelen KM, Tosha T, Kitagawa T, Brunold TC, Nam W, Riordan CG (2006) *J Am Chem Soc* 128:14230–14231 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁹³Cho J, Kang HY, Liu LV, Sarangi R, Solomon EI, Nam W (2013) *Chem Sci* 4:1502–1508 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁹⁴Schenker R, Kieber-Emmons MT, Riordan CG, Brunold TC (2005) *Inorg Chem* 44:1752–1762 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁹⁵Kieber-Emmons MT, Schenker R, Yap GPA, Brunold TC, Riordan CG (2004) *Angew Chem Int Ed* 43:6716–6718 [CrossRef](#) [Google Scholar](#)
- ⁹⁶Cho J, Sarangi R, Annaraj J, Kim SY, Kubo M, Ogura T, Solomon EI, Nam W (2009) *Nat Chem* 1:568–572 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ⁹⁷Kim J, Shin B, Kim H, Lee J, Kang J, Yanagisawa S, Ogura T, Masuda H, Ozawa T, Cho J (2015) *Inorg Chem* 54:6176–6183 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ⁹⁸Rettenmeier CA, Wadepohl H, Gade LH (2015) *Angew Chem Int Ed* 54:4880–4884 [CrossRef](#) [Google Scholar](#)
- ⁹⁹Rettenmeier CA, Wadepohl H, Gade LH (2016) *Chem Sci* 7:3533–3542 [CrossRef](#) [Google Scholar](#)
- ¹⁰⁰Nagataki T, Ishii K, Tachi Y, Itoh S (2007) *Dalton Trans* 1120–1128 [Google Scholar](#)
- ¹⁰¹Nagataki T, Tachi Y, Itoh S (2006) *Chem Commun* 4016–4018 [Google Scholar](#)

- ¹⁰²Pfaff FF, Heims F, Kundu S, Mebs S, Ray K (2012) *Chem Commun* 48:3730–3732 [CrossRef](#) [Google Scholar](#)
- ¹⁰³Corona T, Pfaff FF, Acuna-Pares F, Draksharapu A, Whiteoak CJ, Martin-Diaconescu V, Lloret-Fillol J, Browne WR, Ray K, Company A (2015) *Chem Eur J* 21:15029–15038 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁰⁴Corona T, Company A (2016) *Chem Eur J* 22:13422–13429 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁰⁵Baran EJ (2011) *Adv Plant Physiol* 12:369–389 [Google Scholar](#)
- ¹⁰⁶Requena L, Bornemann S (1999) *Biochem J* 343:185–190 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁰⁷Tanner A, Bowater L, Fairhurst SA, Bornemann S (2001) *J Biol Chem* 276:43627–43634 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁰⁸Lane BG, Dunwell JM, Ray JA, Schmitt MR, Cuming AC (1993) *J Biol Chem* 268:12239–12242 [PubMed](#) [Google Scholar](#)
- ¹⁰⁹Williams HE, Wandzilak TR (1989) *J Urol* 141:742–749 [PubMed](#) [Google Scholar](#)
- ¹¹⁰Dunwell JM, Khuri S, Gane PJ (2000) *Microbiol Mol Biol Rev* 64:153–179 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹¹¹Dunwell JM (1998) *Biotechnol Genet Eng Rev* 15:1–32 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹²Woo E-J, Dunwell JM, Goodenough PW, Marvier AC, Pickersgill RW (2000) *Nat Struct Biol* 7:1036–1040 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹³Anand R, Dorrestein PC, Kinsland C, Begley TP, Ealick SE (2002) *Biochemistry* 41:7659–7669 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁴Just VJ, Stevenson CEM, Bowater L, Tanner A, Lawson DM, Bornemann S (2004) *J Biol Chem* 279:19867–19874 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁵Just VJ, Burrell MR, Bowater L, McRobbie I, Stevenson CEM, Lawson DM, Bornemann S (2007) *Biochem J* 407:397–406 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁶Moomaw EW, Angerhofer A, Moussatche P, Ozarowski A, Garcia-Rubio I, Richards NGJ (2009) *Biochemistry* 48:6116–6125 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁷Angerhofer A, Moomaw EW, Garcia-Rubio I, Ozarowski A, Krzystek J, Weber RT, Richards NGJ (2007) *J Phys Chem B* 111:5043–5046 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁸Opaleye O, Rose R-S, Whittaker MM, Woo E-J, Whittaker JW, Pickersgill RW (2006) *J Biol Chem* 281:6428–6433 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹¹⁹Zhu W, Easthon LM, Reinhardt LA, Tu C, Cohen SE, Silverman DN, Allen KN, Richards NGJ (2016) *Biochemistry* 55:2163–2173 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹²⁰Zhu W, Wilcoxon J, Britt RD, Richards NGJ (2016) *Biochemistry* 55:429–434 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹²¹Saylor BT, Reinhardt LA, Lu Z, Shukla MS, Nguyen L, Cleland WW, Angerhofer A, Allen KN, Richards NGJ (2012) *Biochemistry* 51:2911–2920 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹²²Reinhardt LA, Svedruzic D, Chang CH, Cleland WW, Richards NGJ (2003) *J Am Chem Soc* 125:1244–1252 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹²³Molt RW Jr, Lecher AM, Clark T, Bartlett RJ, Richards NGJ (2015) *J Am Chem Soc* 137:3248–3252 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹²⁴Burrell MR, Just VJ, Bowater L, Fairhurst SA, Requena L, Lawson DM, Bornemann S (2007) *Biochemistry* 46:12327–12336 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹²⁵Imaram W, Saylor BT, Centonze CP, Richards NGJ, Angerhofer A (2011) *Free Radical Biol Med* 50:1009–1015 [CrossRef](#) [Google Scholar](#)
- ¹²⁶Twahir UT, Stedwell CN, Lee CT, Richards NGJ, Polfer NC, Angerhofer A (2015) *Free Radical Biol Med* 80:59–66 [CrossRef](#) [Google Scholar](#)
- ¹²⁷Svedruzic D, Liu Y, Reinhardt LA, Wroclawska E, Cleland WW, Richards NGJ (2007) *Arch Biochem Biophys* 464:36–47 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹²⁸Fuller AL, Watkins RW, Dunbar KR, Prosvirin AV, Arif AM, Berreau LM (2005) *Dalton Trans* 1891–1896 [Google Scholar](#)
- ¹²⁹Fuller AL, Watkins RW, Arif AM, Berreau LM (2006) *Inorg Chim Acta* 359:1282–1290 [CrossRef](#) [Google Scholar](#)

- ¹³⁰Pawlak PL, Panda M, Li J, Banerjee A, Averill DJ, Nikolovski B, Shay BJ, Brennessel WW, Chavez FA (2015) *Eur J Inorg Chem* 2015:646–655 [CrossRef](#) [Google Scholar](#)
- ¹³¹Scarpellini M, Gaetjens J, Martin OJ, Kampf JW, Sherman SE, Pecoraro VL (2008) *Inorg Chem* 47:3584–3593 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³²Costas M, Mehn MP, Jensen MP, Que L (2004) *Chem Rev* 104:939–986 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³³Gibson DT, Parales RE (2000) *Curr Opin Biotechnol* 11:236–243 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³⁴Parales RE, Haddock JD (2004) *Curr Opin Biotechnol* 15:374–379 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³⁵Vaillancourt FH, Bolin JT, Eltis LD (2006) *Crit Rev Biochem Mol Biol* 41:241–267 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³⁶Kovaleva EG, Lipscomb JD (2008) *Nat Chem Biol* 4:186–193 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹³⁷Que L Jr, Widom J, Crawford RL (1981) *J Biol Chem* 256:10941–10944 [PubMed](#) [Google Scholar](#)
- ¹³⁸Whiting AK, Boldt YR, Hendrich MP, Wackett LP, Que L Jr (1996) *Biochemistry* 35:160–170 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹³⁹Vetting MW, Wackett LP, Que L Jr, Lipscomb JD, Ohlendorf DH (2004) *J Bacteriol* 186:1945–1958 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴⁰Emerson JP, Kovaleva EG, Farquhar ER, Lipscomb JD, Que L (2008) *Proc Natl Acad Sci USA* 105:7347–7352 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴¹Koehntop KD, Emerson JP, Que L (2005) *J Biol Inorg Chem* 10:87–93 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴²Lipscomb JD (2008) *Curr Opin Struct Biol* 18:644–649 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴³Kovaleva EG, Neibergall MB, Chakrabarty S, Lipscomb JD (2007) *Acc Chem Res* 40:475–483 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴⁴Bugg TDH, Ramaswamy S (2008) *Curr Opin Chem Biol* 12:134–140 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴⁵Arciero DM, Lipscomb JD (1986) *J Biol Chem* 261:2170–2178 [PubMed](#) [Google Scholar](#)
- ¹⁴⁶Emerson JP, Wagner ML, Reynolds MF, Que L Jr, Sadowsky MJ, Wackett LP (2005) *J Biol Inorg Chem* 10:751–760 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴⁷Sanvoisin J, Langley GJ, Bugg TDH (1995) *J Am Chem Soc* 117:7836–7837 [CrossRef](#) [Google Scholar](#)
- ¹⁴⁸Kovaleva EG, Lipscomb JD (2007) *Science* 316:453–457 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁴⁹Spence EL, Langley GJ, Bugg TDH (1996) *J Am Chem Soc* 118:8336–8343 [CrossRef](#) [Google Scholar](#)
- ¹⁵⁰Georgiev V, Borowski T, Blomberg MRA, Siegbahn PEM (2008) *J Biol Inorg Chem* 13:929–940 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵¹Siegbahn PEM, Haeffner F (2004) *J Am Chem Soc* 126:8919–8932 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵²Pierpont CG (2011) *Inorg Chem* 50:9766–9772 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵³Pierpont CG (2001) *Coord Chem Rev* 219:415–433 [CrossRef](#) [Google Scholar](#)
- ¹⁵⁴Bittner MM, Lindeman SV, Fiedler AT (2012) *J Am Chem Soc* 134:5460–5463 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵⁵Bittner MM, Lindeman SV, Popescu CV, Fiedler AT (2014) *Inorg Chem* 53:4047–4061 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵⁶Bittner MM, Kraus D, Lindeman SV, Popescu CV, Fiedler AT (2013) *Chem Eur J* 19:9686–9698 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵⁷Baum AE, Lindeman SV, Fiedler AT (2016) *Eur J Inorg Chem* 2016:2455–2464 [CrossRef](#) [Google Scholar](#)
- ¹⁵⁸Mbughuni MM, Chakrabarti M, Hayden JA, Meier KK, Dalluge JJ, Hendrich MP, Munck E, Lipscomb JD (2011) *Biochemistry* 50:10262–10274 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁵⁹Mbughuni MM, Chakrabarti M, Hayden JA, Bominaar EL, Hendrich MP, Munck E, Lipscomb JD (2010) *Proc Natl Acad Sci USA* 107:16788–16793 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁰Mbughuni MM, Meier KK, Munck E, Lipscomb JD (2012) *Biochemistry* 51:8743–8754 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶¹Christian GJ, Ye SF, Neese F (2012) *Chem Sci* 3:1600–1611 [CrossRef](#) [Google Scholar](#)

- ¹⁶²Fielding AJ, Kovaleva EG, Farquhar ER, Lipscomb JD, Que L Jr (2011) *J Biol Inorg Chem* 16:341–355 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶³Bratsch SG (1989) *J Phys Chem Ref Data* 18:1–21 [CrossRef](#) [Google Scholar](#)
- ¹⁶⁴Miller A-F (2008) *Proc Natl Acad Sci USA* 105:7341–7342 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁵Gunderson WA, Zatsman AI, Emerson JP, Farquhar ER, Que L, Lipscomb JD, Hendrich MP (2008) *J Am Chem Soc* 130:14465–14467 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁶Fielding AJ, Lipscomb JD, Que L (2012) *J Am Chem Soc* 134:796–799 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁷Cao L, Dong G, Lai W (2015) *J Phys Chem B* 119:4608–4616 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁸Bruijninx PCA, Lutz M, Spek AL, Hagen WR, Weckhuysen BM, vanKoten G, Gebbink RJMK (2007) *J Am Chem Soc* 129:2275–2286 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁶⁹Bruijninx PCA, van Koten G, Gebbink RJMK (2008) *Chem Soc Rev* 37:2716–2744 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁷⁰Reynolds MF, Costas M, Ito M, Jo D-H, Tipton AA, Whiting AK, Que L Jr (2003) *J Biol Inorg Chem* 8:263–272 [PubMed](#) [Google Scholar](#)
- ¹⁷¹Triller MU, Pursche D, Hsieh W-Y, Pecoraro VL, Rompel A, Krebs B (2003) *Inorg Chem* 42:6274–6283 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁷²Reddig N, Pursche D, Krebs B, Rompel A (2004) *Inorg Chim Acta* 357:2703–2712 [CrossRef](#) [Google Scholar](#)
- ¹⁷³Hitomi Y, Ando A, Matsui H, Ito T, Tanaka T, Ogo S, Funabiki T (2005) *Inorg Chem* 44:3473–3478 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁷⁴Banu KS, Chattopadhyay T, Banerjee A, Mukherjee M, Bhattacharya S, Patra GK, Zangrando E, Das D (2009) *Dalton Trans* 8755–8764 [Google Scholar](#)
- ¹⁷⁵Caneschi A, Dei A (1998) *Angew Chem. Int Ed* 37:3005–3007 [CrossRef](#) [Google Scholar](#)
- ¹⁷⁶Komatsuzaki H, Shiota A, Hazawa S, Itoh M, Miyamura N, Miki N, Takano Y, Nakazawa J, Inagaki A, Akita M et al (2013) *Chem Asian J* 8:1115–1119 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁷⁷Tezgerevska T, Alley KG, Boskovic C (2014) *Coord Chem Rev* 268:23–40 [CrossRef](#) [Google Scholar](#)
- ¹⁷⁸Ikeda A, Hoshino K, Komatsuzaki H, Satoh M, Nakazawa J, Hikichi S (2013) *New J Chem* 37:2377–2383 [CrossRef](#) [Google Scholar](#)
- ¹⁷⁹Wang P, Yap GPA, Riordan CG (2014) *Chem Commun* 50:5871–5873 [CrossRef](#) [Google Scholar](#)
- ¹⁸⁰Iwashina T (2000) *J Plant Res* 113:287–299 [CrossRef](#) [Google Scholar](#)
- ¹⁸¹Westlake DWS, Roxburgh JM, Talbot G (1961) *Nature* 189:510–511 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸²Fetzner S (2012) *Appl Environ Microbiol* 78:2505–2514 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸³Steiner RA, Kalk KH, Dijkstra BW (2002) *Proc Natl Acad Sci USA* 99:16625–16630 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸⁴Gopal B, Madan LL, Betz SF, Kossiakoff AA (2005) *Biochemistry* 44:193–201 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸⁵Merkens H, Kappl R, Jakob RP, Schmid FX, Fetzner S (2008) *Biochemistry* 47:12185–12196 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁸⁶Jeoung J-H, Nianios D, Fetzner S, Dobbek H (2016) *Angew Chem. Int Ed* 55:3281–3284 [CrossRef](#) [Google Scholar](#)
- ¹⁸⁷Allpress CJ, Berreau LM (2013) *Coord Chem Rev* 257:3005–3029 [CrossRef](#) [Google Scholar](#)
- ¹⁸⁸Kaizer J, Balogh-Hergovich E, Czaun M, Csay T, Speier G (2006) *Coord Chem Rev* 250:2222–2233 [CrossRef](#) [Google Scholar](#)
- ¹⁸⁹Siegbahn PEM (2004) *Inorg Chem* 43:5944–5953 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁹⁰Pap JS, Kaizer J, Speier G (2010) *Coord Chem Rev* 254:781–793 [CrossRef](#) [Google Scholar](#)
- ¹⁹¹Grubel K, Rudzka K, Arif AM, Klotz KL, Halfen JA, Berreau LM (2010) *Inorg Chem* 49:82–96 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁹²Kaizer J, Barath G, Pap J, Speier G, Giorgi M, Reglier M (2007) *Chem Commun* 5235–5237 [Google Scholar](#)
- ¹⁹³Pap JS, Matuz A, Barath G, Kripli B, Giorgi M, Speier G, Kaizer J (2012) *J Inorg Biochem* 108:15–21 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁹⁴Barath G, Kaizer J, Speier G, Parkanyi L, Kuzmann E, Vertes A (2009) *Chem Commun* 3630–3632 [Google Scholar](#)

- ¹⁹⁵Grubel K, Marts AR, Greer SM, Tierney DL, Allpress CJ, Anderson SN, Laughlin BJ, Smith RC, Arif AM, Berreau LM (2012) *Eur J Inorg Chem* 2012:4750–4757 [CrossRef](#) [Google Scholar](#)
- ¹⁹⁶Matuz A, Giorgi M, Speier G, Kaizer J (2013) *Polyhedron* 63:41–49 [CrossRef](#) [Google Scholar](#)
- ¹⁹⁷Sun Y-J, Huang Q-Q, Li P, Zhang J-J (2015) *Dalton Trans* 44:13926–13938 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁹⁸Sun Y-J, Huang Q-Q, Zhang J-J (2014) *Inorg Chem* 53:2932–2942 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ¹⁹⁹Sun Y-J, Huang Q-Q, Zhang J-J (2014) *Dalton Trans* 43:6480–6489 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰⁰Sun Y-J, Huang Q-Q, Tano T, Itoh S (2013) *Inorg Chem* 52:10936–10948 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰¹Maroney MJ, Ciurli S (2014) *Chem Rev* 114:4206–4228 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰²Boer JL, Mulrooney SB, Hausinger RP (2014) *Arch Biochem Biophys* 544:142–152 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰³Pochapsky TC, Ju T, Dang M, Beaulieu R, Pagani GM, OuYang B (2007) *Met Ions Life Sci* 2:473–500 [Google Scholar](#)
- ²⁰⁴Deshpande AR, Wagenpfeil K, Pochapsky TC, Petsko GA, Ringe D (2016) *Biochemistry* 55:1398–1407 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ²⁰⁵Dai Y, Wensink PC, Abeles RH (1999) *J Biol Chem* 274:1193–1195 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰⁶Dai Y, Pochapsky TC, Abeles RH (2001) *Biochemistry* 40:6379–6387 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰⁷Pochapsky TC, Sondej-Pochapsky S, Ju T, Mo H, Al-Mjeni F, Maroney MJ (2002) *Nat Struct Biol* 9:966–972 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²⁰⁸Allpress CJ, Berreau LM (2014) *Eur J Inorg Chem* 2014:4642–4649 [CrossRef](#) [Google Scholar](#)
- ²⁰⁹Allpress CJ, Grubel K, Szajna-Fuller E, Arif AM, Berreau LM (2013) *J Am Chem Soc* 135:659–668 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹⁰Grubel K, Ingle GK, Fuller AL, Arif AM, Berreau LM (2011) *Dalton Trans* 40:10609–10620 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹¹Berreau LM, Borowski T, Grubel K, Allpress CJ, Wikstrom JP, Germain ME, Rybak-Akimova EV, Tierney DL (2011) *Inorg Chem* 50:1047–1057 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹²Rudzka K, Grubel K, Arif AM, Berreau LM (2010) *Inorg Chem* 49:7623–7625 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹³Grubel K, Fuller AL, Chambers BM, Arif AM, Berreau LM (2010) *Inorg Chem* 49:1071–1081 [PubMed](#) [PubMedCentral](#) [CrossRef](#) [Google Scholar](#)
- ²¹⁴Szajna-Fuller E, Rudzka K, Arif AM, Berreau LM (2007) *Inorg Chem* 46:5499–5507 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹⁵Szajna E, Arif AM, Berreau LM (2005) *J Am Chem Soc* 127:17186–17187 [PubMed](#) [CrossRef](#) [Google Scholar](#)
- ²¹⁶Sparta M, Valdez CE, Alexandrova AN (2013) *J Mol Biol* 425:3007–3018 [PubMed](#) [CrossRef](#) [Google Scholar](#)