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Modeling non-heme iron proteins

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Synthetic modeling studies of non-heme iron proteins continue to contribute to our understanding of the mechanism of these proteins. Recently, mononuclear Fe(IV)=O complexes have been prepared and characterized to model the same species that are proposed to be the reactive intermediates in reactions involving mononuclear non-heme iron proteins. Generation of such species for the oxidation of organic substrates has also been demonstrated. Other advances include successful modeling of the structural and functional aspects of diiron non-heme proteins with the use of terphenyl-based carboxylate ligands and the development of several iron-based reagents that catalyze oxidation reactions with the use of various oxidants, including dioxygen.

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Abbreviations

cyclam	1,4,8,11-tetraazacyclotetradecane
MMO	methane monooxygenase
OTf	CF_3SO_3
PaPy$_3$H	*N*-[*N*,*N*-bis(2-pyridylmethyl)aminoethyl]-2-pyridinecarboxamide; H is the dissociable amide proton
Ph$_3$P	triphenylphosphine
PhINTs	phenyl-*N*-tosylimidoiodinane
PhIO	iodosylbenzene
RNR	ribonucleotide reductase
TMC	1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane
TPA	tris(2-pyridylmethyl)amine
Tp^{Ph2}	hydrotris(3,5-diphenylpyrazol-1-yl)borate

Introduction

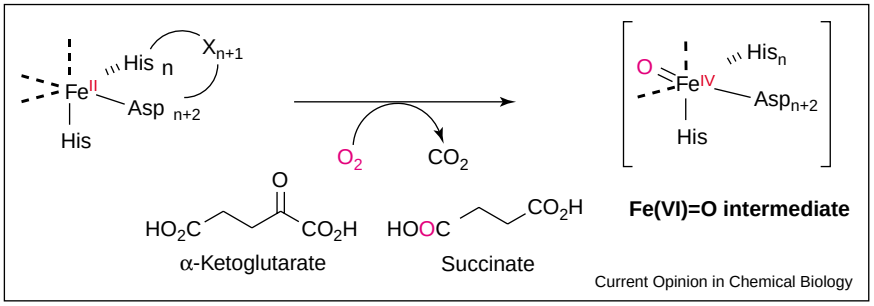
Proteins containing non-heme iron centers are widespread in nature. They perform a broad range of functions, particularly activating dioxygen for the oxidation of various substrates. Most of these reactions are challenging for chemists to realize in the laboratory. For example, various mononuclear non-heme iron proteins catalyze impressive functionalizations of inert C–H bonds of different substrates [1,2]. In the reaction of reduced iron(II) with dioxygen, it is believed that an iron(IV)-oxo species is generated in these proteins as the reactive oxidant. Cofactors that can supply two additional electrons are often used by these proteins to fully activate the dioxygen molecule. Diiron-containing proteins also perform important oxidation functions [3–5]. A good example is methane monooxygenase (MMO) [5], which converts methane into methanol using dioxygen as the oxidant, a reaction that would have a significant impact if it could be realized with a small molecular catalyst under mild conditions. Synthetic small-molecule models that mimic the active site environments or reaction intermediates of these proteins provide important tools for understanding these enzymatic processes. Knowledge gained from these model studies could lead to the design of practical catalysts that catalyze similar reactions and, consequently, much effort has been made to model the non-heme iron proteins. Because of space limitations, this review only summarizes recent advances made in the field of synthetic modeling of dioxygen-activation non-heme iron proteins.

Synthetic models for mononuclear non-heme Fe(IV)=O intermediates

The mononuclear non-heme site usually consists of three ligands from protein residues, two histidines and one carboxylate, around the iron center [6,7]. It is generally agreed that a probable mechanism involves the generation of an intermediate Fe(IV)=O species as the reactive oxidant in the reaction of the reduced Fe(II) with dioxygen [2,6]. Cofactors, such as α-ketoglutarate, are often used to supply two more electrons to facilitate the formation of this high-valent iron(IV) species, as illustrated in Figure 1. However, this intermediate has not been well characterized in protein systems. Thus, emphasis has been placed on obtaining Fe(IV)=O complexes that can act as a model for the intermediate species in reactions containing mononuclear non-heme iron enzymes. A model complex would enable the study of the electronic properties of the Fe(IV)=O unit and give insight into the mechanism of the iron-centered oxidation reactions.

Previously, Wieghardt and co-workers [8] obtained a green compound ($\lambda_{max} = 676$ nm), stable for at least 30 min at −80 °C, by exposing a mononuclear [(cyclam-acetato)Fe(III)(O_3SCF_3)]PF_6 compound to a stream of oxygen and ozone. This green species, present in a mixture of complexes, was assigned to be a monomeric Fe(IV)=O complex (**1**, Figure 2) through spectroscopic characterizations. More recently, also through spectroscopic studies, Que *et al.* demonstrated that a Fe(IV)=O unit (**2**, Figure 2) can be supported by the tetradentate ligand tris(2-pyridylmethyl)amine (TPA) [9,10•]. By

Figure 1



Proposed Fe(VI)=O intermediate in mononuclear non-heme iron proteins.

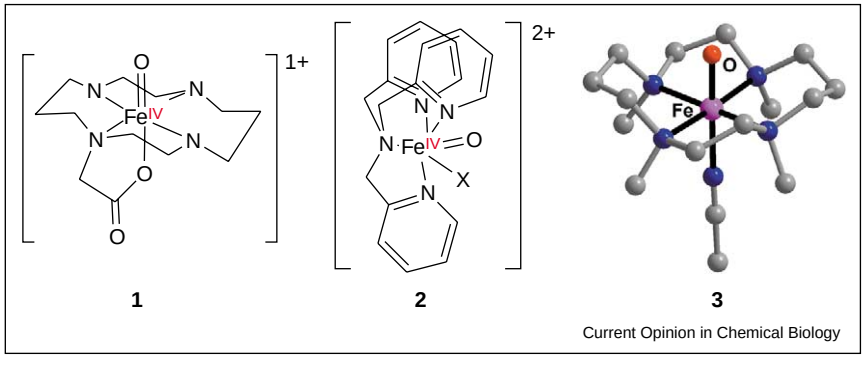
two different methods, an intermediate species $[Fe(IV)(O)(TPA)]^{2+}$ was prepared. First, by reacting $[Fe(II)(TPA)(NCCH_3)_2]^{2+}$ with one equivalent of peracetic acid in CH_3CN at −40 °C, a pale green complex that is stable for several days at −40 °C was obtained [10•]. This species was shown to contain an Fe(IV)=O unit with an iron(IV)–oxo bond distance to be ~1.67 Å, as revealed from spectroscopic characterizations. The same compound was also prepared by adding various Lewis bases to [Fe(III)(TPA)(OO*t*Bu)] [9]. In the first case, the Fe(IV)=O intermediate was shown to react with thioanisole or cyclooctene at −40 °C. 100% of thioansisole oxide or 30% of cyclooctene oxide was obtained, demonstrating that the complex $[Fe(IV)(O)(TPA)]^{2+}$ is effective in transferring the oxygen atom [10•].

By using a sterically bulky macrocyclic ligand, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (TMC), a non-heme Fe(IV)=O complex was stabilized by Que and co-workers [11••]. Reacting $[Fe(II)(TMC)(OTf)_2]$ with one equivalent of iodosylbenzene (PhIO) in CH_3CN resulted in the formation of an iron(IV) species in greater than 90% yield at −40 °C. The tetravalent state of the iron was revealed from Mössbauer studies. This compound displays a near infrared absorption at $\lambda_{max} = 820$ nm ($\varepsilon = 400\ M^{-1}\ cm^{-1}$). Crystals of this compound were obtained and the structure revealed a Fe(IV)=O unit in $[Fe(IV)(O)(TMC)(NCCH_3)](OTf)_2$ (**3**, Figure 2). The iron(IV)–oxygen bond length is 1.646(3) Å, much shorter than that found for an Fe(III)=O complex [12]. This Fe(IV)=O complex was capable of transferring the terminal oxo to triphenylphosphine (Ph_3P) to give Ph_3PO, although its oxidation ability requires further evaluation (see also Update). Nevertheless, the structural characterization of this first Fe(IV)=O model compound represents a significant achievement in modeling intermediates believed to be present in non-heme iron proteins. It strengthens the credibility of its presence as an intermediate in non-heme iron catalysis.

Functional model of mononuclear non-heme iron centers

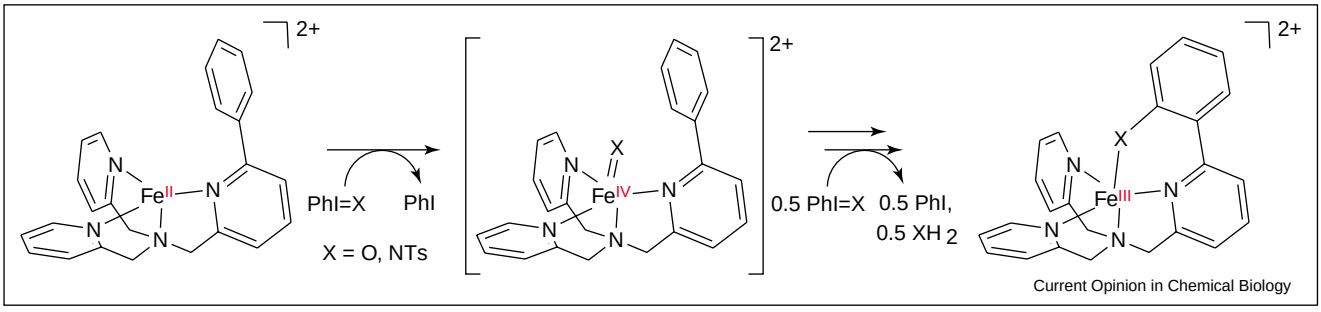
Fully activating one molecule of dioxygen to generate Fe(IV)=O with a mononuclear iron(II) molecule requires two additional electrons from outside sources. This process is typically challenging to achieve catalytically. Thus, two-electron oxidants such as hydrogen peroxide and PhIO are frequently used in reactions with mononuclear iron(II) compounds. High-valent iron-based reactive oxidants can be prepared from these reactions. Que *et al.*

Figure 2



Spectroscopically (**1** and **2**) and structurally (**3**) characterized Fe(IV)=O model compounds. The molecular structure of **3** is shown.

Figure 3

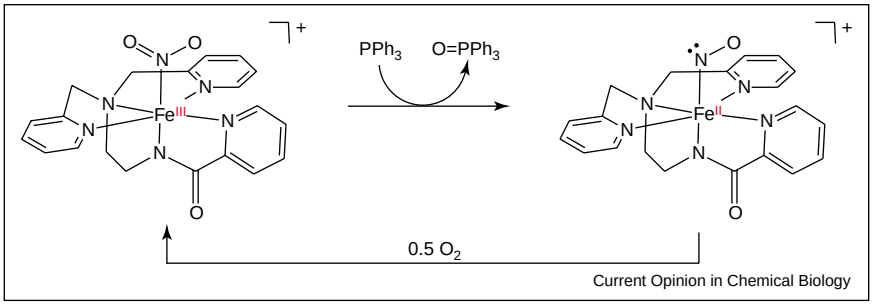


Intramolecular hydroxylation (X = O) and amination (X = NTs) reactions with a model mononuclear iron compound. An Fe(IV)=X species was proposed to be the reactive intermediate that electrophilically attacks the arene group on the ligand.

have utilized mononuclear iron complexes of TPA and other related ligands as models for reactions, including hydroxylation of alkanes, epoxidation and *cis*-dihydroxylation of olefins, and sulfoxidation of organic sulfides by peroxides [13]. Recent study of olefin *cis*-dihydroxylation by H_2O_2 suggests that two types of oxidants with electrophilic and nucleophilic characters can form in the catalysis with TPA and 6-Me_3-TPA ligands, respectively [13]. The presence of high-valent iron–oxo species in these reactions was indicated. An α-phenyl substituent was installed on one of the pyridine ligands of TPA in the hope of 'trapping' the reactive iron–oxo intermediate. Indeed, reacting the mononuclear iron(II) compound of 6-PhTPA with *t*BuOOH resulted in an efficient intramolecular *ortho*-hydroxylation of the phenyl substituent [14•]. Experimental results suggest that an Fe(IV)=O intermediate formed, which hydroxylated the phenyl group. The same result was obtained when PhIO was used as the oxidant (Figure 3) [15••]. When the nitrene transfer reagent phenyl-*N*-tosylimidoiodinane (PhINTs) was used, intramolecular aromatic amination was observed, which suggests the formation of an Fe(IV)–imido intermediate (Figure 3) [15••]. The same strategy was also applied to a mononuclear Fe(II) α-keto carboxylate complex with a sterically hindered tridentate ligand hydrotris(3,5-diphenylpyrazol-1-yl)borate (Tp^{Ph2}). Complex $[Fe^{II}(Tp^{Ph2})(O_2CC(O)CH_3)]$ reacted with dioxygen, resulting in the hydroxylation of a single *ortho* phenyl position of the Tp^{Ph2} ligand [16]. It suggests that the iron(II)-bound α-keto carboxylate assisted in the generation of an Fe(IV)=O intermediate that attacked the phenyl ring. The same mechanism is believed to be used by mononuclear non-heme iron proteins that utilize α-ketoglutarate as the cofactor [2,7].

Although iron-containing heme complexes with an iron–nitro unit had been shown to transfer oxygen atoms to substrates such as PPh_3, Me_2S and styrene, no non-heme iron complexes had been found that could perform such oxygen transfers. Mascharak *et al.* have introduced the first non-heme iron complex $[(PaPy_3)Fe(NO_2)](ClO_4)$ with a bound nitrite group, which transferred an oxygen atom to PPh_3 (Figure 4) [17••]. With $[(PaPy_3)Fe(NO)](ClO_4)$ as an intermediate species, the reaction of $[(PaPy_3)Fe(NO_2)](ClO_4)$ and PPh_3 in MeCN at 45 °C under anaerobic conditions led to the production of Ph_3PO. This novel oxygen-atom transfer with a nitrosyl-to-nitrite conversion is catalytic with dioxygen and an excess of PPh_3.

Figure 4



A non-heme iron(III)-nitro species promotes catalytic O-atom transfer to PPh_3 with the use of O_2 as the oxidant.

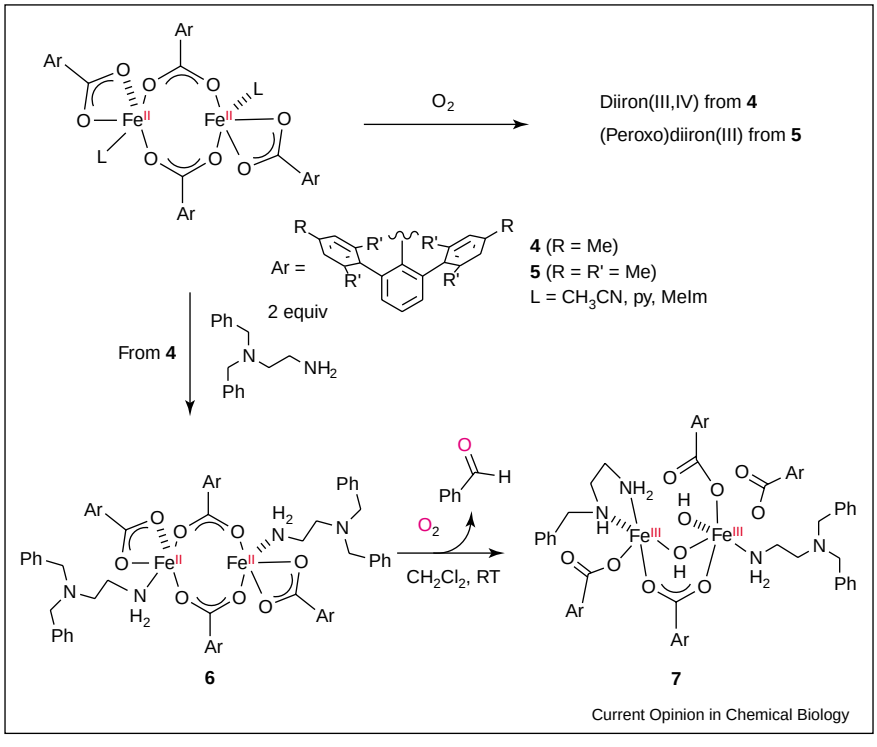
Sterically hindered carboxylates and carboxylate mimics for modeling non-heme diiron centers

Several proteins including MMO, ribonucleotide reductase (RNR) and stearoyl-acyl carrier protein Δ^9 desaturase use two iron atoms to perform diverse oxidizing functions [2,3,5]. The two iron atoms are typically ligated by four carboxylates and two histidine imidazole ligands from the active site protein side chain residues. The iron atoms are positioned close to one another by one or two bridging carboxylates. Potentially, the two iron atoms at the reduced iron(II) state can offer all four electrons that are required to fully activate a dioxygen molecule, which has been proposed to be the case for MMO. The extra complexity of the dinuclear core structure makes these diiron-containing proteins more challenging to model, both structurally and functionally, compared with mononuclear iron proteins. A significant breakthrough came several years ago when sterically bulky terphenyl-based carboxylate ligands were adopted to assemble the diiron core. Two research teams independently discovered that a dinuclear iron(II) center with four bulky carboxylates and two nitrogen-based ligands can be obtained through self-assembly [18–20].

Lippard and Lee successfully prepared a diiron(II) compound (**4**, Figure 5) with four carboxylates and two nitrogen ligands with the use of a sterically bulky 2,6-di(*p*-tolyl)benzoate as the carboxylate ligand [18]. The ligand environment of proteins with the diiron in the reduced states was duplicated with this compound. Upon reacting with dioxygen, this compound can be converted into a novel bis(μ-hydroxo)bis(μ-carboxylato)diiron(III) complex. At essentially the same time, another team led by Tolman and Que independently discovered that a diiron(II) structure (**5**, Figure 5) can also be assembled by using a slightly different bulky 2,6-dimesitylbenzoate [19]. Although similar in structure, the two systems behave differently upon treatment with dioxygen at low temperatures. With the more bulky 2,6-dimesitylbenzoate, complex **5** reacted with dioxygen to give a purple species in non-coordinating solvents [19]. Spectroscopic studies on this purple species suggested that it is a (peroxo)diiron(III,III) complex, although the same species derived from the reaction with $^{18}O_2$ showed only a 14 cm^{-1} shift in the Raman spectrum, which is substantially less than that predicted for a pure O–O stretch (50 cm^{-1}). Recently, the same team also reported the generation of an asymmetric (peroxo)diiron(III,III) species starting from a diiron(II) supported by a less bulky *ortho*-dibenzyl substituted terphenyl-carboxylate [21•].

Reacting diiron(II,II) complex **4** with dioxygen at −78 °C in CH_2Cl_2 resulted in a mixture of complexes. On the

Figure 5

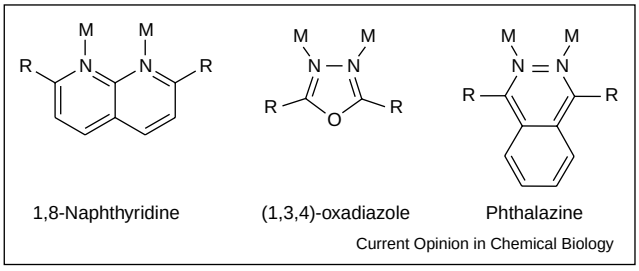


Overview of O_2 reactions performed by diiron complexes that are supported by sterically bulky terphenyl-based carboxylates. An oxidative N-dealkylation of one of the ligands in complex **6** was observed after the treatment of **6** with O_2.

basis of spectroscopic studies, it was found that approximately equal amounts of mixed-valent diiron(II,III) (34%) and diiron(III,IV) (36%) formed in the solution [22,23]. The diiron(III,IV) species is a good spectroscopic model for the intermediate X in RNR. The presence of equal amounts of diiron(II,III) and diiron(III,IV) in the product mixture led the authors to suggest that the initial reaction of **4** with dioxygen may have produced a diiron(IV,IV) species. This diiron(IV,IV) species can quickly oxidize one equivalent of diiron(II,II) to give rise to equal amounts of diiron(III,IV) and diiron(II,III) [23]. No direct experimental evidence has been obtained to support this hypothesis. Other mechanistic possibilities cannot be excluded. The terminal nitrogen ligands on **4** can be replaced with monodentate diamine ligands to afford compound **6**. Exposure of a solution of **6** to dioxygen resulted in an oxidative N-dealkylation of one of the diamine ligands (Figure 5) [24••]. Isotope labeling experiments using $^{18}O_2$ indicated that ^{18}O was incorporated into the product PhCHO. This was the first example of such a reaction to be observed for non-heme diiron models. With a bis(μ-hydroxo)(μ-carboxylato) core, the diiron(III,III) product **7** formed from the reaction is analogous to the oxidized active site of MMO. The use of bulky benzoate ligands has led to the uncovering of unprecedented structures and chemistry. More insight into the enzymatic processes could be gained from further exploration of these systems. An interesting aspect of these diiron model systems is that the two nitrogen ligands are *trans* to each other, presumably because the complexes were self-assembled. The proteins always arrange the two imidazole ligands *cis* to each other. Determining whether the asymmetric arrangement of the ligands to the two irons plays any significant role in the dioxygen activation and the oxidation reactions awaits further synthetic modeling studies [25] and direct investigation of the protein systems.

Besides directly using bulky carboxylate ligands to self-assemble diiron structures, multidentate dinucleating ligands have also been designed to prepare more robust dinuclear compounds. The bridging carboxylate ligands in diiron proteins adopt the *syn*, *syn* coordination modes. In mimicking the same bridging mode, it is difficult to directly incorporate a carboxylate group as the bridging unit in a multidentate ligand. Nitrogen analogues that can afford the same or similar bridging modes have been used instead. For instance, 1,8-naphthyridine [26,27], (1,3,4)-oxadiazole [28] and phthalazine [29] have been successfully incorporated as bridging units in dinucleating ligands (Figure 6). These bridging units, with pendant arms bearing chelating ligands, can form stable dinuclear compounds. Hemerythrin models have been prepared from these compounds [27,28], which nicely complemented models derived from carboxylate-based ligands [30]. To further take advantage of these bridging units, sterically bulky and more donating ligands need to be

Figure 6



Selected nitrogen donor-based dinucleating bridging units.

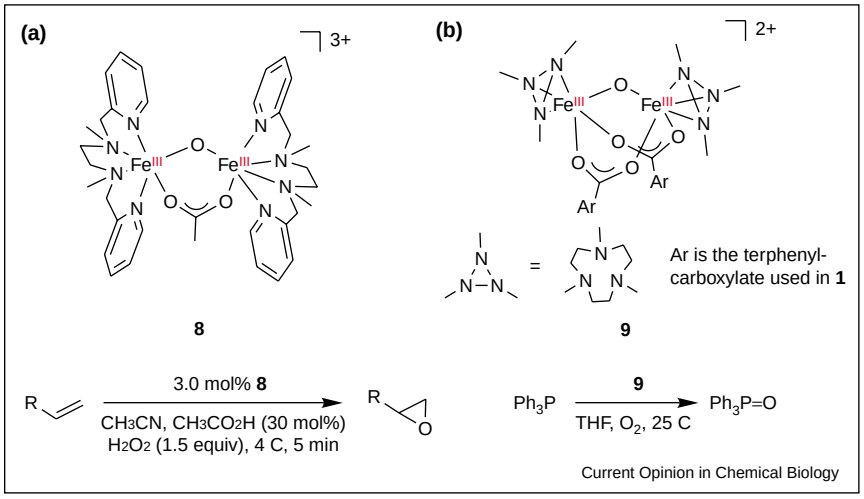
installed as the pendant arms or as ancillary ligands to facilitate the activation of dioxygen and to protect the formed intermediates. Very recent effort in combining 1,8-naphthyridine-based dinucleating ligands with ancillary carboxylate ligands has led to the observation of oxidative N-dealkylation of a diiron(II) model compound upon reacting with dioxygen [31].

Another very active research area is the modeling of high-valent iron–oxo intermediates in diiron enzymes with the use of nitrogen-based tetradentate mononucleating ligands. Various bis(μ-oxo)diiron species have been prepared and characterized; these works have recently been reviewed in detail elsewhere [32]. Among many interesting results, this approach has led to the preparation of a model complex for the putative $Fe(IV)_2(\mu\text{-}O)_2$ diamond core in the MMO intermediate Q [33] and a recent characterization of a unique dihydroxo-bridged diiron(II,III) complex [34] (see also Update).

Other functional models for non-heme diiron centers

Although we are still far from reaching the goal of fully duplicating the functions of dioxygen-activating diiron proteins, several diiron model compounds have emerged recently that show interesting catalytic reactivities. A μ-oxo, carboxylate bridged diiron(III) compound (**8**) was found to catalyze the efficient epoxidation of aliphatic olefins with H_2O_2 at 4 °C (Figure 7) [35••]. A similar reactivity with H_2O_2 has been observed for MMO. Characterization of the intermediate oxidant in this reaction will be very helpful in understanding this chemistry. The iron atoms in the precatalyst are coordination saturated. It will be necessary for the H_2O_2 to interact with the iron atom, presumably through the bridging positions to generate a bridging or terminal oxidant. Interestingly, the isolated compound **8** was inactive in catalyzing the olefin epoxidation reaction [36]. However, in the presence of an excess amount of acid, it became an efficient catalyst [37], further suggesting that the bridging oxo ligand may be replaced by H_2O_2 derived ligands under acidic reaction conditions. A μ-oxo diiron(III,III) complex with phenanthroline ligands was also found to catalyze the

Figure 7



Olefin epoxidation **(a)** and triphenylphosphine oxidation **(b)** reactions catalyzed by (μ-oxo)diiron(III,III) complexes.

epoxidation of terminal olefins with the use of peracetic acid [37]. A mononuclear Mn(II) compound bound with the same tetradentate ligand efficiently catalyzes the epoxidation of electron-deficient olefins with peracetic acid [38]. Alkyl hydroperoxides have been used as oxidants, as well. A diiron(II,II) compound was shown to be capable of catalyzing the heterolytic cleavage of alkyl hydroperoxides to give rise to a putative [Fe(II),Fe(IV)=O] intermediate [39]. This species was able to transfer its oxo group to thioanisole and cyclohexene.

With the use of the bulky carboxylate presented in compound **4**, the same research group assembled a μ-oxo, carboxylate bridged diiron(III,III) compound (**9**) with *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane (Me_3TACN) as the terminal tridentate ligands [40•]. This μ-oxo diiron(III,III) compound exhibits unique oxidative properties. It catalyzed oxidation of Ph_3P to Ph_3PO with the use of dioxygen as the oxidant (Figure 7). The acetate bridged diiron(III,III) analogue exhibited much less reactivity.

Conclusions

Bioinorganic model complexes enable detailed structural, spectroscopic and mechanistic investigations that could be intimately related to protein systems. The characterization of the intermediates and the study of reaction mechanisms from modeling studies have helped in the understanding of enzymatic processes of non-heme iron proteins. Challenges for the future include elucidating the detailed mechanisms of some of the model reactions and to design synthetic systems that can fully duplicate the enzymatic oxidation reactions. The effort to develop iron-based catalysts that perform useful oxidation reactions will continue. These efforts may someday lead to practical catalysts that can catalyze oxidation reactions in the laboratory and in industry.

Update

Recent work from Que *et al.* has shown that Fe(IV)=O complexes can oxidize the C–H bonds of cyclohexane at room temperature [41]. Slep *et al.* [42] reported that several mixed-valent (μ-oxo)bis(μ-carboxylato)diiron(III,IV) complexes were prepared and characterized spectroscopically at −30 °C.

Acknowledgements

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- • of special interest
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