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Review

High-valent nonheme iron-oxo complexes: Synthesis, structure, and spectroscopy

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ABSTRACT

High-valent iron-oxo intermediates have often been implicated, and in some cases identified, as the active oxidant in oxygen activating nonheme iron enzymes. Recent synthetic efforts have yielded pivotal insights into the generation of oxoiron(IV and V) complexes, and allowed thorough investigation of their spectroscopic, structural, and electronic properties. Furthermore, insight into the mechanisms by which nonheme iron sites activate dioxygen to yield high valent iron-oxo intermediates has been obtained. This review covers the great successes in iron-oxo chemistry over the past decade, detailing various efforts to obtain iron-oxo complexes in high yield, and to delve into their diverse structural and spectroscopic properties.

Abbreviations: 15-cyclam, 1,4,8,12-tetraazacyclopentadecane; 15-TMC, 1,4,8,12-tetramethyl-1,4,8,12-tetraazacyclopentadecane; 6-MeTPA, (6-methyl-2-pyridylmethyl)bis(2-pyridylmethyl)amine; 6-Me_3TPA, tris(6-methyl-2-pyridylmethyl)amine; BisPi1, 2,4-(2-pyridyl)-3-(2-pyridylmethyl)-7-methyl-3,7-diazabicyclo[3.3.1]nonanone; BisPi2, 2,4-(2-pyridyl)-3-methyl-7-(2-pyridylmethyl)-3,7-diazabicyclo[3.3.1]nonanone; BisPi3, 2,4-(2-pyridyl)-3,7-methyl-3,7-diazabicyclo[3.3.1]nonanone; Bn-TPEN, *N*-benzyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,2-diaminoethane; BPMCN, *N*,*N*′-dimethyl *N*,*N*′-bis(2-pyridylmethyl)-*trans*-1,2-diaminocyclohexane; BPMEN, *N*,*N*′,-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane; BPMPN, *N*,*N*′,-dimethyl-*N*,*N*′,-bis(2-pyridylmethyl)-1,3-diaminopropane; BQCN, *N*,*N*′-dimethyl-*N*,*N*′-bis(8-quinolylmethyl)*trans*-1,2-diaminocyclohexane; BQEN, *N*,*N*′-dimethyl-*N*,*N*′-bis(8-quinolyl)-diaminoethane; cyclam-CH_2CO_2, 1-carboxymethyl-1,4,8,11-tetraazacyclotetradecane; H_3buea, 1,1,1-tris[(*N*′-*tert*-butylureaylato)-*N*-ethyl]aminato; H_4B*, 3,3,6,6,9,9-hexamethyl-3,4,8,9-tetrahydro-1H-1,4,8,11-benzotetraazacyclotridecine-2,5,7,10(6H,11H)-tetraone; HPA, 1,2-bis{[2-[bis(2-pyridylmethyl)aminomethyl]-6-pyridyl]}ethane; ^{iPr}BIP, 2,6-bis(*N*,*N*′-2,6-diisopropyl-phenyl)acetaldiminopyridine; L^8Py_2, *N*,*N*′-bis(2-pyridylmethyl)-1,5-diazacyclooctane; Me-TPEN, *N*-methyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,2-diaminoethane; Me-TPPN, *N*-methyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,3-diaminopropane; ^{Me,H}Pytacn, 1,4-dimethyl-7-(2′-pyrid*N*′ylmethyl)-1,4,7-triazonane; Me_3NTB, tris((*N*-methylbenzimidazol-2-yl)methyl)amine; N3S2, 2,6-bis-(2-methylthiophenyliminomethyl)pyridine; N4Py, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine; ^{n}Bu-P2DA, *N*-(1′,1′-bis(2-pyridyl)pentyl)iminodiacetate; PyMAC, 2,7,12-trimethyl-3,7,11,17-tetra-azabicyclo[11.3.1]heptadeca-1(17),13,15-triene; QBPA, (2-quinolylmethyl)bis(2-pyridylmethyl)amine; SR-TPA, tris(3,5-dimethyl-4-methoxypyridyl-2-methyl)amine; TBC, 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclotetradecane; TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane; TMC-Py, 1-(2-pyridylmethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane; TMCS, 1-(2-mercaptoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane; $TMCSO_2$, 1-(2-sulfinatoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane; TMG_2dien, 2′,2′-(2,2′-(methylazanediyl)bis(ethane-1,2-diyl))bis(1,1,3,3-tetramethylguanidine; TMG_3tren, 1,1,1-tris(2-[*N*2-(1,1,3,3-tetramethylguanidino)]ethyl)amine; TPA, tris(2-pyridylmethyl)amine; tpa^{Ph}, tris(5-phenylpyrrol-2-ylmethyl)amine); TPEN, *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)ethylenediamine.

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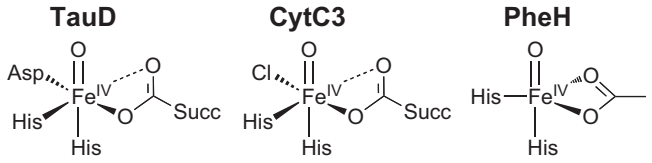

Fig. 1. Proposed structures for Fe^{IV}=O intermediates for TauD, CytC3, and PheH.

1. Introduction

Mononuclear nonheme iron centers are found in a superfamily of enzymes that activate O_2 to carry out metabolically vital oxidative transformations [1,2]. Most of these enzymes utilize an iron center coordinated to a 2-His-1-carboxylate facial triad motif [3–6] to catalyze substrate oxidations, including hydroxylation, halogenation, desaturation, epoxidation and *cis*-dihydroxylation. Electron donors for O_2 activation include the commonly used reductant NADH, as well as α-ketoglutarate (α-KG) [7], tetrahydrobiopterin [8,9], and ascorbate [10,11]. For some enzymes like isopenicillin N synthase (IPNS), the substrate undergoes $4-e^-$ oxidation, providing all necessary electrons required for O_2 activation [12–14]. An Fe^{IV}=O species is the oxidant most commonly postulated for these enzymes, while a *cis*-HO—Fe^{V}=O oxidant is proposed for the Rieske dioxygenases that catalyze *cis*-dihydroxylation of arene double bonds [1,15,16].

Not until 2003 was experimental evidence reported for the putative Fe^{IV}=O oxidizing intermediate in this enzyme superfamily [17–19]. Using a combination of stopped-flow absorption and rapid-freeze-quench Mössbauer spectroscopies, Bollinger, Krebs and co-workers identified an intermediate called 'J' in the catalytic cycle of taurine dioxygenase (TauD), an α-KG-dependent enzyme [20]. Intermediate 'J' exhibits an intense UV band (Table 1, λ_{max} = 318 nm; ε = 1500 M^{-1} cm^{-1}) and a Mössbauer quadrupole doublet (δ = 0.30 mm/s; ΔE_Q = −0.88 mm/s) associated with an S = 2 Fe^{IV} center [17]. Evidence for the Fe=O moiety was obtained with resonance Raman spectroscopy, showing an ^{18}O-isotope sensitive band at 821 cm^{-1} [21], and EXAFS analysis, demonstrating an Fe—O bond of 1.62 Å [22]. These values compare well with those of corresponding Fe^{IV}=O species in heme enzymes [23], and, as detailed herein, with synthetic nonheme Fe^{IV}=O complexes that were synthesized within the same time frame. The most striking evidence for the oxidizing nature of the trapped intermediate was that its lifetime could be significantly extended in the presence of deuterated substrate [24]. This result demonstrated that C—H bond cleavage by 'J' was rate-determining. On the basis of spectroscopic and computational analysis, it is postulated that TauD 'J' has the iron coordination environment shown in Fig. 1 [25]. Since this breakthrough result, the Bollinger/Krebs group has characterized Fe^{IV}=O intermediates for three other α-KG-dependent enzymes (Table 1), prolyl-4 hydroxylase (P4H) [26] and the halogenases CytC3 [27,28] and SyrB2 [29], as well as for the pterin-dependent phenylalanine (PheH) [30] and tyrosine hydroxylases (TyrH) [31].

The fact that there were nonheme iron enzymes that catalyze substrate oxidations similar to those by heme enzymes (e.g. cytochrome P450) encouraged chemists to investigate the use of synthetic nonheme iron complexes as oxidation catalysts and search for evidence for high-valent Fe=O species in these oxidations (for a review of the extensive work carried out prior to 2000, see [32]). A significant challenge in these earlier studies was to ascertain the involvement of a metal-based oxidant rather than metal-free oxy radical species [32]. A key development was the discovery in 1997 that $[Fe^{II}(TPA)(NCCH_3)_2]^{2+}$ catalyzed stereospecific alkane hydroxylation with H_2O_2 [33]. With *cis*-1,2-dimethylcyclohexane as substrate, the tertiary alcohol product showed complete retention of configuration, thereby excluding an oxy radical as oxidant. Subsequently, this system was also found to catalyze epoxidation and *cis*-dihydroxylation of olefin substrates with high stereoselectivity [34]. An Fe^{III}—OOH intermediate could be trapped and characterized at −40 °C [35], but isotope labeling experiments showed that the alcohol and epoxide products were partially labeled when the oxidations were carried out in the presence of $H_2{}^{18}O$ [34,36]. More importantly, the *cis*-diol product incorporated one oxygen atom from H_2O_2 and the other from H_2O [34], clearly excluding the iron-peroxo species as the oxidant and requiring that it undergo O—O bond cleavage to generate a then unobserved high-valent Fe=O oxidant. These and related observations represented just the tip of the iceberg for the nonheme high-valent Fe=O chemistry to be discovered in subsequent years [37].

A milestone in the synthetic efforts to make high-valent nonheme Fe=O complexes was Borovik's report in 2000 of an unprecedented oxoiron(III) complex, $[Fe^{III}(O)(H_3buea)]^{2-}$ [38]. Its crystal structure shows the tripodal H_3buea supporting ligand provides a tertiary amine and three ureaylate donors that bind the metal center and, more importantly, three N—H functionalities to stabilize the highly basic oxo ligand by hydrogen bonding. This breakthrough marked the start of a decade of intense investigations into nonheme Fe=O chemistry with many excellent reports detailing their generation *and* the characterization of their structural, electronic, and spectroscopic features [37,39–41], which is the subject of this review.

2. S = 1 oxoiron(IV) complexes

2.1. Cyclam and related macrocyclic supporting ligands

The first direct evidence for the generation of a nonheme Fe^{IV}=O complex was reported by Wieghardt at the start of this millennium [42]. Reaction of $[Fe^{III}(cyclam\text{-}CH_2CO_2)(OTf)]PF_6$ with ozone (O_3) at −80 °C in acetone/H_2O yielded a green chromophore (λ_{max} = 676 nm) that was assigned to an S = 1 Fe^{IV} species by Mössbauer spectroscopy (Scheme 1 and Table 1). Unfortunately, further characterization of this novel species was hampered by its low yield (23%). Although no evidence for an Fe^{IV}=O moiety could be obtained, the green chromophore was postulated to be $[Fe^{IV}(O)(cyclam\text{-}CH_2CO_2)]^+$. Its characteristic NIR absorption band and the Mössbauer parameters compare favorably with those of better characterized Fe^{IV}=O complexes subsequently prepared (Table 1), suggesting that its assignment as an Fe^{IV}=O complex was correct.

The high-yield synthesis of $[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$ and the solution of its crystal structure in 2003 represented a significant breakthrough in nonheme Fe^{IV}=O chemistry, as it allowed the thorough characterization of an Fe^{IV}=O species for the first time. $[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$ was generated by the reaction between $[Fe^{II}(TMC)(OTf)_2]$ and iodosylbenzene (PhIO) in CH_3CN at −40 °C, producing the Fe^{IV}=O complex in greater than 90% yield [43]. Interestingly, formation of $[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$ could be monitored by sub-stoichiometric addition of PhIO to a solution of $[Fe^{II}(TMC)(OTf)_2]$ and reached maximum yield at 1 equiv. of oxidant. This observation indicated that $[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$, somewhat surprisingly, did not react with its Fe^{II} precursor to form an Fe^{III}—O—Fe^{III} complex, which is typically the thermodynamic sink for iron complexes [44]. It is likely that steric hindrance prevents formation of the Fe^{III}—O—Fe^{III} byproduct, resulting in the isolation of this novel oxoiron(IV) complex.

$[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$ exhibited a half-life of 10 h at 25 °C and persisted for at least a month at −40 °C, which facilitated its crystallization [43]. $[Fe^{IV}(O)(TMC)(NCCH_3)]^{2+}$ represents the first crystallographically characterized synthetic complex with an