Intrinsic properties and reactivities of mononuclear nonheme iron–oxygen complexes bearing the tetramethylcyclam ligand

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ABSTRACT

Iron–oxygen species, such as iron(IV)-oxo, iron(III)-superoxo, iron(III)-peroxo, and iron(III)-hydroperoxo complexes, are key intermediates often detected in the catalytic cycles of dioxygen activation by heme and nonheme iron enzymes. Our understanding of the chemistry of these key intermediates has improved greatly by studies of the structural and spectroscopic properties and reactivities of their synthetic analogues. One class of biomimetic coordination complexes that has proven to be particularly versatile in studying dioxygen activation by metal complexes is comprised of FeIV=O and FeIII=O2(H) complexes of the macrocyclic tetramethylcyclam ligand (TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane). Several recent advances have been made in the synthesis and isolation of new iron–oxygen complexes of this ligand, their structural and spectroscopic characterization, and elucidation of their reactivities in various oxidation reactions. In this review, we summarize the chemistry of the first structurally characterized mononuclear nonheme iron(IV)-oxo complex, in which the FeIV=O group was stabilized by the TMC ligand. Complexes with different axial ligands, [FeIV( O)(TMC)(X)]+, and complexes of other cyclam ligands are discussed as well. Very recently, significant progress has also been reported in the area of other iron–oxygen intermediates, such as iron(III)-superoxo, iron(III)-peroxo, and iron(III)-hydroperoxo complexes bearing the TMC ligand. The present results demonstrate how synthetic and mechanistic developments in biomimetic research can advance our understanding of dioxygen activation occurring in mononuclear nonheme iron enzymes.
1. Introduction

The cytochromes P450 (CYP 450) are a versatile group of heme-based mono-oxygenases with vital functions for human health, including the biodegradation and metabolism of toxic compounds in the body as well as the biosynthesis of hormones [1–7]. They utilize molecular oxygen at a heme center and react via oxygen atom transfer to substrates, leading to C–H hydroxylation, C≡C epoxidation, aromatic hydroxylation, and heteroatom oxidation [8,9]. The CYP 450s contain a central heme active site that is linked to the protein via a thiolate bridge from a cysteinate residue [10,11]. The catalytic cycle of the CYP 450s starts from the resting state (Fig. 1A) [12–14], where a water molecule fills the sixth binding position of the metal. Upon substrate binding into the active site, the water molecule is released and a five-coordinate high-spin ferric species with a vacant coordination site for dioxygen binding is formed (Fig. 1B). After the reduction of the ferric heme by reduced putidaredoxin to a five-coordinate high-spin ferrous heme (Fig. 1C), dioxygen binds to the heme in a ferric–superoxo form (Fig. 1D) and picks up another electron and proton to form a ferric-hydroperoxo species (Fig. 1E) that is protonated to give an iron(IV)-oxo heme π-cation radical oxidant (Fig. 1F), which is the active species of the enzyme and also known as Compound I (Cpd I). Due to the high reactivity and short lifetime of Cpd I, it has been difficult to trap and characterize it with spectroscopic methods, but recently Rittle and Green collected the first pieces of evidence from Mössbauer and UV–vis spectroscopic experiments [15]. However, its participation as active oxidant in the catalytic cycle was inferred from indirect evidence [16,17] and high-level computational studies [18–22] for a long time. Until recently, there was considerable discussion in the literature regarding the reactivity and stability of Cpd I versus Cpd I′. Some site-directed mutagenesis studies seemed to implicate the ferric-hydroperoxo species as active oxidant [23]. A series of computational and experimental biomimetic studies, however, contradicted this conclusion and reasoned that Cpd I is a superior oxidant over the ferric-hydroperoxo species at least in heme enzymes and iron porphyrin models [24–27]. In CYP 450 enzymes, the second reduction step is rate-determining and dioxygen-bound intermediates are short-lived (see Fig. 1). As a consequence, biochemical studies into the mechanism and reactivity of Cpd I have been hampered by its short lifetime, and research has been redirected to biomimetic model complexes instead.

A mononuclear FeIV–O species is also believed to be the key oxidant of nonheme iron enzymes that activate dioxygen at a nonheme FeII site. These enzymes carry out substrate hydroxylation, halogenation, and other reactions involving C–H bond activation for a variety of purposes, including biosynthetic functions, DNA repair, and cellular oxygen sensing. Many of these enzymes, including several α-ketoglutarate- (αKG) and pterin-dependent oxygenases for which such a high-valent Fe intermediate has been trapped in recent years, contain a 2His1carboxylate ligand motif that links the metal to the protein. The catalytic cycle of one representative enzyme, taurine:α-ketoglutarate dioxygenase (TadD) [28–34], is shown in Fig. 2 and starts from a resting state where the three remaining Fe coordination sites are occupied by water molecules, and upon co-substrate binding, namely αKG, two water molecules are replaced and the third water molecule is released when substrate (taurine) enters the binding site (Fig. 2A). Subsequently, molecular oxygen binds to the metal in the ferric–superoxo form (Fig. 2B′), which is an elusive intermediate that has been proposed by computational modeling to attack the α-keto position of αKG to form a bicyclic ring-structure (Fig. 2C′) [35,36]. Decarboxylation then leads to a high-valent iron(IV)-oxo species with succinate bound (Fig. 2D′), which reacts with substrate via hydrogen atom (H-atom) abstraction from the substrate to give a ferric-hydroxo complex (Fig. 2E′). Rebound of the hydroxyl group finally leads to the alcohol product (Fig. 2F′). The iron(IV)-oxo species, in contrast to Cpd I of the CYP 450s, appears to have a lifetime that is long enough to enable spectroscopic characterization, and work by Hausinger, Krebs, and Bollinger provided compelling evidence of its spectroscopic and catalytic properties [37–39]. In particular, D′ was characterized by spectroscopic techniques as a high–spin FeIV−O species, and its kinetics were followed spectroscopically. Further studies with deuterated substrate gave evidence of an elevated kinetic isotope effect for the reaction and implicated a rate determining H-atom abstraction reaction in the process. To gain further insights into nonheme iron(IV)-oxo species, a range of biomimetic model complexes was studied and characterized, which revealed considerable differences in activity between nonheme iron and heme complexes.

One of the first biomimetic model systems where an iron(IV)-oxo species was trapped and characterized structurally was a mononuclear nonheme iron(IV)-oxo complex of the tetraaza-macroyclic TMC ligand (TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) [40]. This iron complex has since been intensely studied, and valuable insights into its physical properties, axial ligand influences, and reactivities with substrates have been gained from this work. Furthermore, reactivity studies of several [FeIV(O)(TMC)(X)]n+ complexes (X=a neutral or anionic ligand), [FeIII(O2T)(TMC)]+, and [FeIII(O2H)(TMC)]3+ have unveiled consid-

![Fig. 1. Proposed catalytic cycle of cytochrome P450 enzymes.](image-url)
erable differences with respect to analogous intermediates in the catalytic cycle of CYP 450 enzymes. In this review, we will give an up-to-date overview of experimental and computational studies of [FeIV(O)(TMC)(X)]2+, [FeIII(O2)(TMC)]+ and [FeII(O2H)(TMC)]2+ complexes and their comparison to CYP 450 intermediates.

2. Iron(IV)-oxo complexes of TMC and related macrocyclic ligands

Among the Fe–O2 intermediates supported by the TMC ligand, the iron(IV)-oxo complex [FeIV(O)(TMC)(NCCH3)]2+ was the first to be identified and isolated. Extensive spectroscopic and structural studies of this complex provided detailed insights into its electronic structure and the intrinsic properties of the FeIV=O unit. Also described in this section are iron(IV)-oxo complexes of other macrocyclic ligands that are closely related to TMC and complexes resulting from axial ligand substitution.

2.1. Synthesis and characterization of mononuclear nonheme iron(IV)-oxo complexes

The [FeIV(O)(TMC)(NCCH3)]2+ complex was first prepared in acetonitrile solution by oxygen atom transfer from iodosylenzene (PhIO) to the corresponding iron(II) complex, [FeII(TMC)(NCCH3)]2+ (Eq. (1)). It was readily identified as a new intermediate by a band in the near-IR region of its absorption spectrum (λmax = 824 nm).

\[
[\text{Fe}^{II}(\text{TMC})(\text{NCCH}_3)]^{2+} + \text{PhIO} \rightarrow [\text{Fe}^{IV}(\text{O})(\text{TMC})(\text{NCCH}_3)]^{2+} + \text{Phl}
\]  

(1)

Single crystals of the triflate salt of this highly oxidized complex were obtained at −40 °C, and its structure was established by X-ray crystallography (Fig. 3a), which revealed an Fe–O distance of 1.646(3) Å [40]. This very short distance is consistent with strong σ and π bonding between the Fe center and the O atom and a formal bond order of 2 (Fig. 3b). Notably, it is significantly shorter than the Fe–O distances in diiron(III) complexes with bridging oxo ligands [41,42]. The crystal structure also showed that the FeIV=O group is sterically shielded by the macrocyclic TMC ligand, providing a rationale for the remarkable stability of this compound (t1/2 ≈ 10 h at 25 °C) [43].

The complex was further characterized by peaks in its electrospray ionization mass spectrum (ESI MS) attributable to [FeIV(O)(TMC)(NCCH3)]2+ and [FeIV(O)(TMC)(OTf)]2+ (OTf = CF3SO3−), by a 57Fe Mössbauer quadrupole doublet having a low isomer shift (δ) of 0.17 mm s−1, and by an FeO stretching vibration (νFeO) at 835 cm−1. The value for νFeO represents the average of data obtained by three different vibrational techniques (i.e., 834 cm−1 by IR, 839 cm−1 by resonance Raman (rRaman), and 831 cm−1 by nuclear resonance vibrational spectroscopy (NRVS)), which exhibit 16O-isotope shifts of ca. 35 cm−1 as expected for a diatomic νFeO mode. In addition, NRVS-active FeNα and FeNαx stretching and OFeNα bending modes were identified in the range of ca. 300–650 cm−1 [44].

To shed some light on the origin of the unique near-IR absorption band of [FeIV(O)(TMC)(NCCH3)]2+, Decker and Solomon [45–47] carried out detailed variable-temperature magnetic circular dichroism (VT MCD) spectroscopic studies. From group theory, five d–d ligand-field transitions are expected for an axially distorted S = 1 FeIV=O complex [C4v, d4; Fig. 4]. Three bands were observed

Fig. 2. Proposed catalytic cycle of taurineα-ketoglutarate dioxygenase.

Fig. 3. Molecular structures of iron(IV)-oxo complexes of the TMC ligand. (a) Crystallographically determined structure and (b) schematic drawing of [FeIV(O)(TMC)(NCCH3)]2+ and (c) crystallographically determined structure of a Sc(OH)3-bound FeIV(O)(TMC) complex. (TMC:FeIV(O)(µ-O)Sc(OH)(OTf)3). Hydrogen atoms have been omitted. Carbon, gray; nitrogen, blue; oxygen, red; iron, scarlet; scandium, orange; sulfur, yellow; fluorine, green.
Fig. 4. Ligand-field splitting diagram and spin- and electric-dipole allowed d–d transitions for an S = 1 FeIV–O complex (Cu) with assignments of the spectroscopically observed bands.

in the low-energy region of the MCD spectra (<16,000 cm⁻¹) and assigned to the following three transitions: 3dₓᵧ → 3d₁₂₋₋₋₋_-₋₁₋ (band I), 3dₓᵧ → 3dₓᵧ₋₋₋₋₋₋ (band II), and 3dₓᵧ₋₋₋₋₋₋ → 3dₓᵧ₋₋₋₋₋₋ (band III), where the z axis is defined by the Fe–O bond. In support of this assignment, band II displays a fine structure that could be attributed to a vibronic progression in the FeO stretching mode, because the excitation of an electron from a nonbonding orbital (3dₓᵧ) into Fe–O π* orbitals (3dₓᵧ₋₋₋₋₋₋) causes a weakening of the Fe–O π bond. Two additional bands associated with 3dₓᵧ₋₋₋₋₋₋ → 3dₓ₋₋₋₋₋₋ (band IV) and 3dₓᵧ → 3dₓ₋₋₋₋₋₋ transitions (band V) were found at higher energies. By correlating the energies of the bands observed in the MCD and absorption spectra, the broad feature in the near-IR region of the absorption spectrum was revealed to be a composite of the three low-energy d–d transitions (bands I, II, and III), with band III being the most intense (Fig. 5). On the basis of this analysis, the near-IR absorption band can be viewed as a fingerprint signature of S = 1 FeIV–O complexes.

Several other macroyclic ligands related to TMC were successfully used for the generation of mononuclear FeIV=O complexes, including tetradeinate ligands with different substituents and ring sizes (e.g., 14-membered TBC, 1,4,8,11-tetrazenyl-1,4,8,11-tetraacyclotetradacene), 15-membered TAPM, 1,4,8,12-tetramethyl-1,4,8,12-tetraacyclotetradacene, and 15-membered TAPM, 1,4,8,12-tetraacyclotetradacene [48,49] as well as pentadentate ligands with neutral and anionic donor groups (Chart 1; Table 1). One early example, which actually pre-dates all of the other complexes reviewed here, is the [FeIV(O)(cyclam)-ac]⁺ (cyclam-acH = 1,4,8,11-tetraacyclotetradacene-1-acetic acid) complex from Wieghardt’s group [50] having a carboxylate group appended to the cyclam scaffold. Noteworthy are also [FeIV(O)(TMC-py)]²⁻ (TMC-py = 4,8,11-trimethyl-1-(2-pyridylmethyl)-1,4,8,11-tetraacyclotetradacene) reported by Banse and coworkers [51], which represents another crystallographically characterized example, and [FeIV(O)(TMCS)]⁺ (TMCSH = 4,8,11-trimethyl-1,4,8,11-tetraacyclotetradacene-1-ethanethiol) with a pendant thiolate donor (see Section 2.4.2) [52,59].

While PhIO has often been the oxidant of choice for the preparation of iron(IV)-oxo complexes, H₂O₂ [40,54], O₃ [50], and peroxycarboxylic acids [53,55] have also been employed. However, H₂O₂ may have limited utility, because it also can function as a reductant toward nonheme iron(IV)-oxo complexes as was shown very recently [56]. The biologically relevant oxidant (i.e., O₃) has now increasingly been used to access iron(IV)-oxo complexes. In one case, [FeIV(TMC)(NCCH₃)]²⁺ was found to react with O₃ in the presence of alcohols or ethers, where the FeIV complex has lower redox potentials than in acetonitrile only [57]. The complex-to-dioxo stoichiometry of 2:1 was suggestive of a dinuclear O₂ activation pathway proceeding through a (μ-1,2-peroxo)diiron(III) species and subsequent homolytic O–O bond cleavage to afford two equivalents of the iron(IV)-oxo complex. Alternatively, [FeIV(TMC)(NCCH₃)]²⁻ could react with O₃ in acetonitrile to give [FeIV(O)(TMC)(NCCH₃)]²⁻ when both a reductant, such as BPh₄⁻ [51] and NADH (dihydronicotinamide adenine dinucleotide) analogues (e.g., BNAH (1-benzyl-1,4-dihydronicotinamide) and AcrH₂ (10-methyl-9,10-dihydroacridine) derivatives) [58], and an acid, such as HClO₄, were present. These results indicated that both an electron and a proton were required for O₂ activation (Section 3). Interestingly, [FeIV(O)(TMC)(NCCH₃)]²⁻ was also generated from [FeIV(TMC)(NCCH₃)]²⁻ and O₂ in the presence of substrates with weak C–H bonds, suggestive of the involvement of hydrogen atom transfer from the substrate to an iron–oxygen species (Section 3) [59].

Relevant properties of the iron(IV)-oxo complexes reviewed here, including the [FeIV(O)(TMC)(X)]²⁻ complexes (Section 2.2), are summarized in Table 1. They generally exhibit (i) characteristic low-intensity bands in the near-IR region with absorption maximum wavelengths ranging from 750 to 900 nm (ε, 100–400 M⁻¹ cm⁻¹), (ii) FeO stretching vibrations in the range of 810–860 cm⁻¹, and (iii) low Fe Mössbauer isomer shifts (δ) [60,61]. The large and positive zero-field splittings (D, 20–35 cm⁻¹) are consistent with an S = 1 ground state [62,63]. Because the lifetime of many of these complexes are too short to allow the growth of single crystals, their metal–ligand distances have been determined by Fe K-edge EXAFS (extended X-ray absorption fine structure) analysis, with Fe–O distances falling in the range of 1.64(2)–1.70(2) Å. In the pre-edge region of the Fe K-edge X-ray absorption spectra, the iron(IV)-oxo complexes display relatively intense peaks associated with 1s → 3d transitions, whose energies and intensities are sensitive to the oxidation state and coordination geometry, respectively, of the Fe center. The peak energies (ca. 7114–7115 eV) usually are about 0.5–1 eV higher than those of related FeIII complexes and about 1–1.5 eV higher than those of the
Table 1
Properties of iron(IV)-oxo complexes of TMC and related macrocyclic ligands. a

<table>
<thead>
<tr>
<th>Complex</th>
<th>Fe—O (Å)b</th>
<th>Fe—N/O (Å)c,d</th>
<th>E_pre-edge (eV)d</th>
<th>XAS pre-edge areae</th>
<th>νFeO (cm⁻¹)f</th>
<th>ΔνFeO (cm⁻¹)f</th>
<th>δ (mm s⁻¹)g</th>
<th>ΔE (mm s⁻¹)g</th>
<th>D (cm⁻¹)h</th>
<th>λmax (nm)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral donor set, [Fe\textsuperscript{IV}OL\textsubscript{5}]\textsuperscript{2+}</td>
<td>1.646</td>
<td>2.091\textsuperscript{14}</td>
<td>7114.1</td>
<td>26</td>
<td>841</td>
<td>35</td>
<td>0.17</td>
<td>1.24</td>
<td>26.95\textsuperscript{1e}</td>
<td>750</td>
<td>[49]</td>
</tr>
<tr>
<td>[FeO<a href="NCCH%5Ctextsubscript%7B3%7D">TAPH</a>]\textsuperscript{2+}</td>
<td>1.64</td>
<td>2.08</td>
<td>cis 2.118</td>
<td>trans 2.058</td>
<td>7114.14</td>
<td>835\textsuperscript{1f}</td>
<td>35\textsuperscript{1f}</td>
<td>0.14</td>
<td>0.78</td>
<td>27.5</td>
<td>806, 1026</td>
</tr>
<tr>
<td>[FeO(TMC)(NCCH\textsubscript{3})]\textsuperscript{2+}</td>
<td>1.647</td>
<td>2.083\textsuperscript{14}</td>
<td>826</td>
<td>34</td>
<td>0.18</td>
<td>1.08</td>
<td>29</td>
<td>834</td>
<td>[51]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metal-ion bound, [L\textsubscript{4}Fe\textsuperscript{IV}((/SYN)-O)M\textsuperscript{III}X\textsubscript{5}]\textsuperscript{h}</td>
<td>1.754</td>
<td>2.175\textsuperscript{1h}</td>
<td>[FeO(TMCS)]\textsuperscript{+}</td>
<td>1.64</td>
<td>2.06</td>
<td>7114.1</td>
<td>25</td>
<td>831</td>
<td>0.19</td>
<td>1.28</td>
<td>330, 830, 990</td>
</tr>
<tr>
<td>Monoanionic donor set, trans-[Fe\textsuperscript{IV}OL\textsubscript{4}X]\textsuperscript{+}</td>
<td>1.64</td>
<td>2.08</td>
<td>7114.2</td>
<td>31</td>
<td>854</td>
<td>37</td>
<td>0.20</td>
<td>1.39</td>
<td>31</td>
<td>836, 940, 990</td>
<td>[43,73]</td>
</tr>
<tr>
<td>[FeO(TMC)]\textsuperscript{1+}</td>
<td>1.67</td>
<td>2.07</td>
<td>7114.7</td>
<td>26</td>
<td>822</td>
<td>30</td>
<td>0.16</td>
<td>0.42</td>
<td>31</td>
<td>350, 845, 1010</td>
<td>[73]</td>
</tr>
<tr>
<td>[FeO(TMC)]\textsuperscript{2+}</td>
<td>1.65</td>
<td>2.07</td>
<td>7114.3</td>
<td>24</td>
<td>820</td>
<td>34</td>
<td>0.16</td>
<td>0.60</td>
<td>30</td>
<td>387, 850, 1050</td>
<td>[72,73]</td>
</tr>
<tr>
<td>[FeO(TMC)]\textsuperscript{3+}</td>
<td>1.66</td>
<td>2.08</td>
<td>7114.4</td>
<td>24</td>
<td>814</td>
<td>34</td>
<td>0.17</td>
<td>0.70</td>
<td>29</td>
<td>407, 850, 1050</td>
<td>[72,73]</td>
</tr>
<tr>
<td>[FeO(TMC)]\textsuperscript{4+}</td>
<td>1.68</td>
<td>2.10</td>
<td>7115.1</td>
<td>20</td>
<td>0.15</td>
<td>0.25</td>
<td>31</td>
<td>858</td>
<td>[73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[FeO(TMCS)]\textsuperscript{1+}</td>
<td>1.70</td>
<td>2.09</td>
<td>7114.3</td>
<td>18</td>
<td>0.19</td>
<td>-0.22</td>
<td>35</td>
<td>460, 570, 860</td>
<td>[52,53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[FeO(TMCSO\textsubscript{2})]\textsuperscript{+}</td>
<td>1.64</td>
<td>2.06</td>
<td>7114.1</td>
<td>25</td>
<td>831</td>
<td>0.19</td>
<td>1.28</td>
<td>330, 830, 990</td>
<td>[53]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Structures of ligands are shown in Chart 1.
b Distances from EXAFS are given with three significant figures and distances from X-ray crystallography with four significant figures.
c For crystallographically determined Fe—N distances, the position of the N atom with respect to the oxo ligand is indicated (cis or trans); average values are given for equatorial Fe—N distances.
d Fe K-edge XAS pre-edge peak energies, E\textsubscript{pre-edge} (referenced to an Fe foil calibration point of 7112.0 eV), and intensities (observed peak areas).
e From resonance Raman spectroscopy, unless noted otherwise; \(^{18}O\)-isotope shifts, Δν\textsubscript{FeO} = (Fe\textsuperscript{16}O) − (Fe\textsuperscript{18}O).
f Average from IR, resonance Raman, and NRV spectroscopy [40,44,73].
g From EPR spectroscopy [61].
h Isomer where oxo ligand is oriented syn with the four TMC N-methyl substituents.

\[ \text{Fe—OH} = 1.94 \text{ Å} \]

\[ \text{Fe—S} = 2.33 \text{ Å} \]
The increased peak intensities (ca. 20–30 area units) are a consequence of the strong and covalent Fe–O bonding interaction, which results in axial distortion of the Fe coordination geometry and 3d_{z^2}-4p_{xy} mixing.

The structure and reactivity of one Fe^{IV}=O complex was substantially altered by coordination to a strong Lewis acid. Reaction of [Fe^{IV}(O)(TMC)(NCH$_3$)$_3$]$^{2+}$ with Sc(OH)$_3$ led to the isolation of the metal-ion bound iron(IV)-oxo complex [TMC][Fe^{IV}(µ-O)(O)Sc(OH)(OTf)$_3$]$_2$ [66]. The crystal structure revealed that the Fe center is five-coordinate and the oxo ligand occupies the coordination site syn with the four N-methyl substituents of the TMC ligand (Fig. 3c). The Fe–O distance is with 1.754 Å significantly longer than for the other two crystallographically characterized complexes, which was attributed to a weakening of the Fe–O bond due to the coordination of the Lewis-acidic Sc$^{III}$ center. Although this distance would also be consistent with an oxo-bridged Fe$^{III}$ complex [41,42], it is still shorter than the 1.82 Å distance of the Fe$^{IV}$=O group reported for the protonated compounds II of chloroperoxidase [67,68] and cytochrome P450 119 [69]. Another example of a syn isomer was characterized spectroscopically [70].

2.2. Trans-Influences in [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes

Systematic investigations of the influence of anionic ligands on the spectroscopic properties of Fe$^{IV}$=O complexes were reported for two series of complexes, [Fe$^{IV}$(O)(TPA)(X)]$^+$ (TPA = tris(2-pyridylmethyl)amine) [71] and [Fe$^{IV}$(O)(TMC)(X)]$^+$ [43,72,73], where the X ligand is coordinated to the Fe$^{IV}$ center in cis or trans position relative to the oxo ligand. These complexes were accessed by exchange of the neutral solvent ligands in the parent complexes, [Fe$^{IV}$(O)(TPA)(NCH$_3$)$_3$]$^{2+}$ and [Fe$^{IV}$(O)(TMC)(NCH$_3$)$_3$]$^{2+}$.

For the [Fe$^{IV}$(O)(TPA)(X)]$^{2+}$ complexes with different equatorial ligands, the ligand-field band in the near-IR region shifts to lower energies ($\lambda_{max}$ = 724–800 nm) with decreasing ligand-field strength of the X ligand according to the spectrochemical series [71]. On the other hand, the spectral changes caused by axial ligand substitution in [Fe$^{IV}$(O)(TMC)(NCH$_3$)$_3$]$^{2+}$ are more complex as they involve not only an energy shift but also a redistribution of absorption intensities (Fig. 5). Thus, [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes with various carboxylate (X = CF$_3$CO$_2$ and CH$_3$CO$_2$ [43,74]) and pseudohalide ligands (X = NCS$^-$, NCS$^-$, N$_3$-, CN$^-$, and OH$^-$ [70,72,73]) trans to the oxo ligand exhibit $\lambda_{max}$ values of 800–860 nm and broader absorption envelopes with additional peaks that extend beyond 1000 cm$^{-1}$ (Table 1). For [Fe$^{IV}$(O)(TMC)(NCH$_3$)$_3$]$^{2+}$ and [Fe$^{IV}$(O)(TMC)(OC)(OCH$_3$)$_3$]$^{2+}$, the perturbations were analyzed by MCD spectroscopy and attributed to variations in energies and intensities of two of the five d–d transitions, i.e., 3d$_{xy}$ – 3d$_{xy}$ (band II) and 3d$_{xy}$ – 3d$_{xy}$ (band III), which, in turn suggest that the 3d$_{xy}$ orbitals are destabilized by Fe–O=C(O)CF$_3$ π interactions [46]. Aside from the pronounced modulation of the Fe$^{IV}$=O near-IR signature, some of the [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes (X = NCO$^-$, NCS$^-$ and N$_3$-) as well as [Fe$^{IV}$(O)(TMC)$^-$ and [Fe$^{IV}$(O)(TMC)$_3$]$^{2+}$ (TMC$_2$SO$_4$H = 4,8,11-trimethyl-1,4,8,11-tetraazaacyclooctadeca-1-ethanesulfonic acid) possess distinct absorption peaks in the UV–vis region that are associated with charge transfer transitions [53,72,73].

In contrast to the electronic modulation, the Fe–O distance was rather insensitive to the identity of the trans ligand [d(Fe–O) = 1.64–1.68 Å for [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$]. The FeO stretching mode proved to be a more sensitive reporter. The values of $v_{\text{FeO}}$ span a range of 40 cm$^{-1}$ and decrease with increasing basicity of the axial ligand (CF$_3$CO$_2$ $< $ CH$_3$CN $< $ CN–$\approx$ NCO$^-$$\approx$ NCS$^-$$< $ N$_3^-$), indicating that a stronger trans donor weakens the Fe=O bond. A similar relationship between $v_{\text{FeO}}$ and donor strength of axial ligand was reported for iron(IV)-oxo porphyrin complexes [75–77]. The changes in the $v_{\text{FeO}}$ value could also be used to estimate changes in the Fe–O distance. Green [78] had previously demonstrated that Badger’s rule, an empirical relationship between bond length (r$e$) and stretching frequency ($v_{\text{FeO}}$), can be applied to the Fe–O bonds of heme and nonheme iron complexes (Eq. (2), where C$\text{\scriptsize{E}}$ and d$\text{\scriptsize{E}}$ refer to theoretically derived constants). Based on this relationship, the 40 cm$^{-1}$ range found for $v_{\text{FeO}}$ in [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes is correlated with a distance range of 0.02 Å, which is in agreement with the distances experimentally observed by X-ray crystallography and EXAFS analysis [73].

$$r_e = \frac{C_f}{\left(v_{\text{FeO}}\right)^2} + d_E$$

The $^{57}$Fe Mössbauer isomer shifts and XAS (X-ray absorption spectroscopy) pre-edge peak energies of the [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes remain fairly constant and substantiate the Fe$^{IV}$ oxidation state assignment. But the quadrupole splittings ($\Delta E_Q$) and XAS pre-edge peak areas vary with the X ligand, presumably due to varying extent of axial distortion [73].

2.3. Reactivities of [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes

Since [Fe$^{IV}$(O)(TMC)(NCH$_3$)$_3$]$^{2+}$ was the first synthetic iron(IV)-oxo species to be stabilized and characterized, it led to a variety of reactivity studies with different substrates. Summarized in Fig. 6 are chemical reactions investigated with [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes. Initially, the oxidation of PPh$_3$ by [Fe$^{IV}$(O)(TMC)(NCH$_3$)$_3$]$^{2+}$ was studied [40], because it is a facile reaction requiring a small activation energy. Subsequent studies utilized thiiaanisole, and its sulfoxidation by the iron(IV)-oxo complex [26,72,79,80] was investigated giving evidence of a direct oxygen atom transfer mechanism in line with what was proposed for CYP 450 enzymes [81,82]. Using a selection of para-substituted sulfides, reactivity trends were determined and the measured rate constants were plotted as a function of the Hammett parameters, which gave Hammett $\rho$ values between –1.4 and –2.5 [26,80]. These highly negative Hammett $\rho$ values implicate electrophilic character of the Fe=O group, as concluded before for sulfoxidation reactions by other metal-oxo species [83–85].

Many studies addressed the enzymatically relevant and mechanistically important reaction of aliphatic C–H abstraction by nonheme iron(IV)-oxo complexes. Typical substrates used in the reactions include alkylaromatic compounds with weak C–H bonds, such as xanthene (BDE$_{\text{C–H}}$ = 75.5 kcal mol$^{-1}$),
9,10-dihydroanthracene (DHA, \( \text{BDE}_{\text{C-H}} = 77 \text{ kcal mol}^{-1} \)), 1,4-cyclohexadiene (\( \text{BDE}_{\text{C-H}} = 80 \text{ kcal mol}^{-1} \)) \cite{86-88}. Due to the relatively low oxidizing power of many biomimetic nonheme iron(IV)-oxo complexes, these alkyolaromatic compounds turned out to be excellent substrates for mechanistic studies on C–H bond activation reactions \cite{83,86,89-91}. Studies on the axial ligand effect of \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{N}3)]^+ \) in C–H abstraction and oxygen atom transfer reactions highlighted the fact that electron-donating anionic ligands enhance the H–atom abstraction ability of the iron-oxo species \cite{92}. A plot of the second-order rate constants against the \( \text{BDE}_{\text{C-H}} \) values of the substrates gave a linear correlation. Moreover, the reactions proceeded with a high kinetic isotope effect (KIE) of >10 for hydrogen atom abstraction from xanthene and DHA. The identity of the axial ligand in \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) also affected reduction potentials and reorganization energies in electron transfer processes, as different reduction potentials were determined for \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCH3})]^{2+} \) \((\text{E}_{\text{red}} = 0.39 \text{ V and } \lambda = 2.37 \text{ eV})\), \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{OC}(\text{O})(\text{CF}3))]^{+} \) \((\text{E}_{\text{red}} = 0.13 \text{ V and } \lambda = 2.12 \text{ eV})\), and \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{Ni})]^{+} \) \((\text{E}_{\text{red}} = -0.05 \text{ V and } \lambda = 1.97 \text{ eV})\) \cite{93}.

As shown in Fig. 6, nonheme iron(IV)-oxo complexes, including \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \), mediate alcohol oxidation, N-dealkylation, olefin oxidation, and aromatic hydroxylation reactions. The iron(IV)-oxo complexes activate alcohols exclusively by H-atom abstraction from the \( \alpha \)-CH bonds of the alcohols, and the C–H bond cleavage is the rate-determining step \cite{94,95}. The oxidative N-dealkylation reaction was proposed to occur via an electron transfer–proton transfer (ET–PT) mechanism \cite{96,97} that proceeds with an initial electron transfer followed by a proton transfer to give an overall hydrogen atom abstraction. Although it has been shown that the nonheme iron(IV)-oxo complexes, \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TPA})(\text{NCH3})]^{2+} \) and \( [\text{Fe}^{\text{IV}}(\text{O})(\text{BN-TPEN})]^{2+} \) \((\text{BN-TPEN} = \text{N}-\text{benzyl-N,N,N-tris}(2\text{-pyridylmethyl})\text{ethane}-1\text{-2-diamine})\), react with olefins to give the corresponding epoxide products (e.g., the formation of cyclooctene oxide in the oxidation of cyclooctene) \cite{49,55,58}, the mechanism of the reaction remains elusive. In aromatic hydroxylation reactions, Nam and co-workers have proposed that the aromatic ring oxidation by \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TPA})(\text{NCH3})]^{2+} \) and \( [\text{Fe}^{\text{IV}}(\text{O})(\text{BN-TPEN})]^{2+} \) does not occur via a H-atom abstraction mechanism but involves an initial electrophilic attack on the \( \pi \)-system of the aromatic ring to produce a tetrahedral radical or a cationic \( \sigma \)-complex \cite{99,100}.

The \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{NCH3})]^{2+} \) complex was also used in elucidating the mechanism of oxygen exchange between high-valent metal-oxo species and labeled water (Scheme 1) \cite{101}, because \(^{18}\text{O}\)-labeled water experiments have frequently been carried out to obtain indirect insight into the nature of the reactive intermediates involved in catalytic oxygenation reactions \cite{102–105}. In this study, direct evidence that nonheme iron(IV)-oxo complexes exchange their oxygen atom with \( \text{H}_2{^{18}}\text{O} \) was obtained for the first time by monitoring changes of the iron(IV)-oxo species by electrospray ionization mass spectrometry. The degree of the oxygen exchange depended markedly on the concentration of \( \text{H}_2{^{18}}\text{O} \) and the reaction temperature but not on the presence of a trans axial ligand. Thus, a mechanism for the oxygen-atom exchange in nonheme iron(IV)-oxo models was proposed that does not proceed via the trans oxo-hydroxo tautomerism pathway proposed for high-valent metal-oxo porphyrins \cite{106} but by a variant involving a cis-dihydroxoiron(IV) transition state.

### 2.4. DFT calculations on iron(IV)-oxo complexes

#### 2.4.1. \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) complexes

To understand the reactivity patterns of the \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) complexes and in particular the effect of the axial ligand on the reaction rates and mechanisms, a series of detailed density functional theory (DFT) calculations were done and established two-state-reactivity type mechanisms \cite{107–109}. High-lying occupied and low-lying virtual orbitals of \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{Cl})]^{1+} \) are shown in Fig. 7. The lowest metal 3d orbital is the \( \pi^*_{yz} \) orbital that is located in the plane of the nitrogen atoms of the TMC ring and is nonbonding and doubly occupied. Slightly higher in energy are a pair of degenerate \( \pi^*_{xz} \) orbitals for the antibonding interactions of 3d_{xz,yz} on iron with 2p_{xy} on the oxygen atom. With a halide as an axial ligand, these two orbitals also mix with 3p_{xy} atomic orbitals on the halide, which is absent with neutral ligands such as acetonitrile. Higher lying and virtual are the \( \sigma^*_{xz} \) orbital for the antibonding interactions along the Fe–O bond and the \( \sigma^*_{xy} \) orbital for the antibonding interaction of the metal with the nitrogen atoms of the TMC group. Experimental studies characterized all \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) intermediates irrespective of the axial ligand as triplet spin states with \( \pi^*_x \pi^*_x \pi^*_y \) orbital occupation. Higher in energy is a quintet spin state with \( \pi^*_x \pi^*_x \pi^*_y \sigma^*_xy \sigma^*_xz \) configuration, which is the ground state in enzymatic nonheme iron(IV)-oxo complexes \cite{110}. DFT calculations generally give the triplet and quintet spin state close in energy and environmental perturbations and/or solvent effect can change their ordering and relative energies slightly.

Subsequently, the H-atom abstraction ability of the \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) complexes was calculated with DFT methods using a range of model substrates \cite{107–109}, and Fig. 8 displays the aliphatic hydroxylation mechanism of the benzyl position of ethylenebenzene by \( [\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{X})]^{n+} \) \((\text{X} = \text{NCH3} \text{ or } \text{Cl}^{-})\) with data taken from ref 109. The reaction starts from a reactant complex (R) between iron(IV)-oxo species and substrate and proceeds with a H-atom abstraction via a transition state (TS_{Hx}) leading to an iron(II)-hydroxo with a nearby radical (A). Rebound of the hydroxo group to the ethylenebenzene radical restgroup is barrierless and leads to alcohol products (P). The overall exothermically
is large for the oxidant with X = NCH$_3$ but considerably less than that for X = Cl$^-$. This affects the complete reaction pathway, whereby all barriers and intermediates are lower in energy for the reaction starting with [Fe$^{IV}$(O)(TMC)(NCH$_3$)]$^{2+}$ as compared to those starting with [Fe$^{IV}$(O)(TMC)(Cl)]$^+$. Note that although the triplet spin reactants are the ground state, the actual mechanism takes place on the quintet spin state, which implies a spin state crossing from triplet to quintet prior to the H-atom abstraction. Thus, in the triplet spin state, the electron transfer fills a π$^*$ orbital with a second electron, whereas in the quintet spin state a complete exchange stabilized metal 3d-system is formed that results in favorable high-spin over intermediate-spin reactivity. Nevertheless, the DFT calculations confirm the conclusions derived from experiment that [Fe$^{IV}$(O)(TMC)(NCH$_3$)]$^{2+}$ is a better oxidant than [Fe$^{IV}$(O)(TMC)(Cl)]$^+$ in H-atom abstraction reactions.

Optimized geometries are typical for structures calculated for H- abstraction barriers for a range of substrates and iron(IV)-oxo oxidants [111–119] and show that the substrate attacks the iron(IV)-oxo group from the top. This follows from the electron transfer processes, whereby an electron is shuttled from substrate into the σ$^*_z$ orbital along the Fe=O bond [120]. The imaginary frequencies in the transition state are large (>900 cm$^{-1}$), which implicates that the reaction will proceed with a considerable kinetic isotope effect and tunneling [114,115,121]. Despite the fact that both rate determining transition states $^5$TS$_{HA,NCH_3}$ and $^5$TS$_{HA,Cl}$ refer to a H-atom abstraction barrier with significant radical character on the substrate, the intermediates show considerable differences in electron occupation. Thus, $^5$A$_{Cl}$ is a radical intermediate with π$^{ax,ay}_x$ π$^{ax,az}_x$ π$^{ay,ay}_y$ π$^{ay,az}_y$ π$^{az,az}_z$ σ$^{az,az}_x$ configuration with an S = 2 on the metal antiferromagnetically coupled to a substrate radical. On the other hand, $^5$A$_{NCH_3}$ represents a cationic intermediate that is the result of a formal hydride transfer from substrate to oxo group with π$^{ax,ay}_x$ π$^{ax,az}_x$ π$^{ay,ay}_y$ π$^{ay,az}_y$ σ$^{az,az}_x$ configuration. Note that the second electron transfer that is part of the hydride transfer is only transferred after the transition state and en route to the intermediate.

Another process studied in detail relates to the aromatic hydroxylation of arenes by [Fe$^{IV}$(O)(TMC)(X)]$^{2+}$ complexes. An example of two calculated energy profiles of ethylene hydroxylation by [Fe$^{IV}$(O)(TMC)(NCH$_3$)]$^{2+}$ and [Fe$^{IV}$(O)(TMC)(Cl)]$^+$ are shown in Fig. 9. The mechanisms are the same irrespective of the axial ligand and follow a mechanism devised for Cpd I of CYP 450 [100,122].
with an electrophilic addition leading to a σ-complex (B) via a transition state \( \text{TS}_{\text{trans}} \). Thereafter, the ipso–proton is resubstituted to one of the nitrogen atoms of the TMC ring to form a phenolate bound to iron(III) with a protonated TMC ligand. Rebound of the proton to phenolate gives phenol products (P_3). The latter steps proceed fast and with virtually no barrier heights, so that the initial barrier via \( \text{TS}_{\text{trans}} \) is rate determining. The imaginary frequencies in the transition states are considerably lower than those found for hydrogen atom abstraction reactions and lead to almost no or slightly inverse kinetic isotope effects.

Although the mechanistic features of the reactions starting with \([\text{Fe}^{IV}(O)(\text{TMC})(\text{NCCH}_3)]^{2+}\) and \([\text{Fe}^{IV}(O)(\text{TMC})(\text{Cl})]^+\) are the same, there are considerable differences in electronic properties along the reaction mechanism. Thus, in analogy to the H-abstraction barriers discussed above, the initial electrophilic addition leads to a single electron transfer from the arené to the metal and gives partial radical character to the arené in the transition state. With Cl− as axial ligand, this state relaxes to a radical intermediate (\( \text{B}_{\text{Cl}} \)), whereas a second electron transfer takes place en route from \( \text{TS}_{\text{trans,NCCH}_3} \) to form a cationic intermediate \( \text{B}_{\text{NCCH}_3} \). These differences in radical versus cationic pathways were allocated to differences in orbital energy level of the \( \pi_{\text{xy}} \) orbital, which is higher in energy for \( \text{R}_{\text{Cl}} \) and thereby affects the electron affinity of the oxidant and consequently the electron transfer processes. Therefore, the axial ligand has a profound effect on the orbital energy levels and in particular the one involving metal 3d-interactions. It affects the spin state ordering and energies as well as the electron abstraction ability of the oxidant. As such, it has a dominant effect on reactivity patterns.

Further studies on the relative reactivities of \([\text{Fe}^{IV}(O)(\text{TMC})(\text{X})]^+\) complexes in H-atom abstraction and oxygen atom transfer reactions found computational trends according to the electrophilicity of the oxidant [123]. At first glance, these studies seemed to contradict experiment; however, when blending of rate constants for triplet and quintet states was taken into account, the correct trends were observed. This implies that full spin equilibration occurs and that the spin orbit coupling between the triplet and quintet spin states may affect rate constants and reactivity patterns.

2.4.2. A complex of a thiolate-appended TMC ligand, \([\text{Fe}^{IV}(O)(\text{TMC})]^+\)

Comparative studies by Dawson and co-workers [124] on peroxidase and CYP 450 enzymes highlighted differences in the axial ligand bound to the heme, whereby the axial thiolate ligand in the CYP 450 s was proposed to induce a ‘push-effect’, but the axial histidine ligand in peroxidases gives a ‘pull-effect’ of electrons. Since then many studies on iron porphyrins have tried to quantify the axial ligand effect [66,125–127]. In particular, Gross and Nimni [125] found a trans-influence of the axial ligand that affected spectroscopic parameters including FeO stretching frequencies as well as a trans-effect on the rate constants of styrene epoxidation. Subsequently, Nam and co-workers have demonstrated that iron(IV)–oxo porphyrin π-cation radicals, \([\text{Fe}^{IV}(O)(\text{Porp}^*\text{CH}_3)]^+\) and \([\text{Fe}^{IV}(O)(\text{Porp}^*\text{NCCH}_3)]^+\), exhibit different reaction patterns depending on the identity of the axial ligand, as shown, for example, in the selectivity for cis– versus trans-olefins in olefin epoxidation, the oxidizing power in alkane C–H bond activation, and the regioselectivity of aromatic ring versus aliphatic C–H hydroxylation in the oxidation of ethylbenzene [128–131]. These results demonstrate unambiguously that iron(IV)–oxo porphyrin π-cation radicals can exhibit diverse reaction patterns under different circumstances.

To understand the ligand binding in CYP 450 enzymes and to mimic this in synthetic analogs, many attempts have been made to create biomimetic model complexes with axial thiolate ligation. One of the first successfully characterized iron(IV)-oxo species with axially ligated thiolate was the \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) complex [52]. Subsequently, this led to a series of experimental and computational studies into the reactivities of \([\text{Fe}^{IV}(O)(\text{TMC})]^+\).

Computational modeling established the electronic properties of \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) and studied C–H abstraction and double bond epoxidation with propene as a model substrate [120]. In contrast to the \([\text{Fe}^{IV}(O)(\text{TMC})(\text{X})]^+\) models described above, calculations on \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) identified it as a high-spin (quintet) ground state slightly below the experimentally assigned triplet spin ground state. Thus, the triplet-quintet energy gap is determined by the relative energies of the \( \pi_{\text{xy}} \) and \( \sigma_{\text{xy},\text{xy}} \) molecular orbitals and when the energy gap narrows the quintet spin state drops below the triplet in energy [123]. In particular, in five-coordinate complexes including the enzymatic noneheme iron(IV)–oxo species, the \( \pi_{\text{xy}}/\sigma_{\text{xy},\text{xy}} \) energy gap is small and a high-spin state is found as the ground state. Another facet of this spin state ordering is the fact that \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) reacts via single-state-reactivity on a quintet spin state surface only.

Thereafter, a comparative study on the regioselectivity of aliphatic hydroxylation versus epoxidation by \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) and \([\text{Fe}^{IV}(O)(\text{Porp}^*\text{SH})]^+\) was performed. Gas-phase epoxidation barriers were a few kcal mol−1 lower in energy than H-atom abstraction barriers from propene by \([\text{Fe}^{IV}(O)(\text{Porp}^*\text{SH})]^+\). On the other hand, reactivity of propene with \([\text{Fe}^{IV}(O)(\text{TMC})]^+\) gave dominant H-atom abstraction reaction instead. This was explained from stereochemical interactions of hydrogen atoms of the TMCs ring with the approaching substrate, whereby the substrate is closer in the epoxidation transition states than in the H-atom abstraction transition states.

3. Iron(III)-superoxo species, \([\text{Fe}^{III}(O_2)(\text{TMC})]^2+\)

Dioxygen activation by a high-spin iron(II) complex in the presence of electron and proton sources in CH₂CN was reported by Nam and co-workers [58]. In this reaction, \([\text{Fe}^{IV}(O)(\text{TMC})(\text{NCCH}_3)]^{2+}\) was generated from \([\text{Fe}^{III}(O)(\text{TMC})(\text{NCCH}_3)]^2\) and O₂ in the presence of NADH analogues, such as BNAH and AcrH₂ derivatives, as an electron source and HClO₄ as a proton source in CH₂CN. The mechanism proposed for O₂ activation is as follows: The reaction is initiated by binding of O₂ to the high-spin iron(II) complex, producing an iron(III)-superoxo species. Subsequently, iron(III)-peroxo and iron(III)-hydroperoxo species are generated by consecutive electron- and proton-transfer reactions (Scheme 2, pathway A).

Finally, homolytic O–O bond cleavage affords the iron(IV)-oxyo species (Scheme 2, pathway C) [91]. It was also reported by Nam and co-workers that \([\text{Fe}^{IV}(O)(\text{TMC})(\text{NCCH}_3)]^{2+}\) could be generated in the reaction of \([\text{Fe}^{IV}(\text{TMC})(\text{NCCH}_3)]^{2+}\) and O₂ in the presence of substrates with weak C–H bonds (e.g., olefins, such as cyclohexene and cyclooctene, and alkylaromatic compounds, such as xanthene and 9,10-dihydroanthracene) [59]. In this reaction, an iron(III)-superoxo intermediate was proposed as an active oxidant that abstracts a H-atom from the substrate (Scheme 2, pathway B). Especially, when the substrates were olefins (e.g., cyclohexene...
and cyclooctene), [FeIV(O)(TMC)(NCCH3)]2⁺ was formed in a high yield because of its low reactivity toward these olefins. In these reactions, the formation of [FeIV(O)(TMC)(NCCH3)]2⁺ was faster with olefins having lower C–H bond dissociation energies [132]; the second-order rate constants for cyclohexene (BDE = 81 kcal mol⁻¹) and cyclooctene (BDE = 85 kcal mol⁻¹) were 1.2 × 10⁻⁴ s⁻¹ and 2.9 × 10⁻⁴ M⁻¹ s⁻¹, respectively. Furthermore, a kinetic isotope effect (KIE) value of 6.3(3) in the formation of [FeIV(O)(TMC)(NCCH3)]2⁺ was obtained using cyclohexene and cyclohexene-d₁₀ as substrates. These results indicated that the C–H bond activation of the olefin by an iron(III)-superoxo species, [FeIII(O₂)(TMC)]⁺, is the rate-determining step in the formation of [FeIV(O)(TMC)(NCCH₃)]²⁺ (Scheme 2, pathway B) [59].

DFT calculations were performed on the H-atom abstraction from cyclohexadiene by [FeIV(O)(TMC)(NCCH₃)]²⁺ and [FeIII(O₂)(TMC)]⁺ [133]. For [FeIV(O)(TMC)(NCCH₃)]²⁺, H- abstraction barriers of 19.7 and 10.6 kcal mol⁻¹ were found for the triplet and quintet spin states, respectively. In contrast to experimental results, however, the barrier heights for H-abstraction from cyclohexadiene by [FeIV(O)(TMC)]²⁺ are much higher in energy. This was explained by differences in spin-inversion-probability, whereby the iron(V)-oxo intermediate stays on the more endothermic triplet spin state, whereas the iron(III)-superoxo intermediate can relax to a more reactive spin state surface.

Apart from studies on iron(III)-superoxo intermediates, calculations also were performed on iron(II)-superoxo, [FeII(O₂)(TMC)]⁺, and nickel(II)-superoxo, [NiII(O₂)(TMC)]⁺, intermediates and their reactivities with substrates [133,134]. The iron(II)-superoxo complex was found to be a sluggish oxidant in aromatic hydroxylation reactions but capable of reacting with aliphatic C–H substrates on a sextet spin state surface with low barriers [135]. Barrier heights for analogous processes catalyzed by [NiII(O₂)(TMC)]⁺ were even higher and it was only found to be a suitable oxidant for substrates with weak C–H bonds (e.g., xanthene or cyclohexadiene) and PPh₃ [134].

4. Iron(III)-peroxo and -hydperoxo complexes, [FeIII(O₂)(TMC)]⁺ and [FeIII(O₂H)(TMC)]²⁺

4.1. Synthesis, characterization, and interconversion of iron–oxygen intermediates

An iron(III)-peroxo complex, [FeIII(O₂)(TMC)]⁺, was prepared by reacting the corresponding iron(II) complex with H₂O₂ in the presence of base [91,136]. The blue intermediate persisted for several hours at 0 °C, and the greater thermal stability of [FeIII(O₂)(TMC)]⁺ allowed for the isolation of crystals, which were used for a structure determination and spectroscopic and reactivity studies. The electronic absorption spectrum of [FeIV(O₂)(TMC)]⁺ shows a distinct absorption band at 750 nm (ε = 600 M⁻¹ cm⁻¹). The raman spectrum of the iron(III)-peroxo complex revealed upon 778-nm excitation in acetone-d₆ at 77 K, exhibits two 18O-isotope-sensitive bands at 825 and 487 cm⁻¹. The X-ray crystal structure of [FeIII(O₂)(TMC)]ClO₄ revealed a mononuclear iron complex with a side-on bound O₂²⁻ ligand. The iron center is coordinated in a distorted octahedral geometry arising from the triangular FeOO moiety with a small bite angle of 45.03(17)° (Fig. 10a). The FeOO geometry is similar to that of the crystallographically characterized 1:1 Fe₂O₂ adduct of naphthalene dioxygenase (NDO), where dioxygen binds side-on to the iron center in the active site (1.75 Å resolution, r$_{O-O}$ = 1.45 Å) [137]. Furthermore, the structurally determined O–O distance of 1.463(6) Å and the raman data are indicative of peroxo character of the OO group [138–140]. It is worth noting that all four N-methyl groups point to the same side of the FeN₄ plane as the peroxo moiety, as observed in other metal(III)-peroxo complexes [141–143]. In the case of the Sc³⁺-bound iron(IV)-oxo complex, [(TMC)FeIV(µ-O)(Sc(OH)(OFT))₄], the N-methyl groups are also syn with the oxo ligand (Fig. 3c) [66], whereas those in [FeIV(O)(TMC)(NCCH₃)]²⁺ are anti to the oxo ligand and Fig. 3a) [40]. In addition, no axial ligand binds to the Fe ion trans to the peroxo ligand in [FeIV(O)(TMC)]⁺, which is similar to other metal(III)-peroxo complexes [141–143] as well as the Sc³⁺-bound FeIV(O)(TMC) complex [66], but different from the [FeIV(O)(TMC)(NCCH₃)]²⁺ complex [40].

Addition of a slight excess amount of HClO₄ to a solution of [FeIII(O₂)(TMC)]⁺ in acetone/CF₃CH₂OH (3:1) at −40 °C immediately produced a violet intermediate, [FeIII(O₂H)(TMC)]²⁺ (Fig. 10b). Subsequently, this iron(III)-hydperoxo species was converted to the corresponding iron(IV)-oxo complex, [FeIV(O)(TMC)]²⁺ (Scheme 3). The iron(III)-hydperoxo complex, [FeIII(O₂H)(TMC)]²⁺, was characterized using a variety of spectroscopic methods; the EPR spectrum of a frozen acetone/CF₃CH₂OH (3:1) solution of the complex measured at 10 K shows signals at g = 6.8, 5.2, and 1.96, which is consistent with a high-spin (S = 5/2) FeIII species [144,145]. The raman spectrum of the [FeIII(O₂H)(TMC)]²⁺ complex exhibits two 18O-isotope-sensitive bands at 658 and 868 cm⁻¹ for the FeO and OO stretching vibrations, respectively [91]. The structural information obtained by XAS/EXAFS and DFT calculations indicates that an end-on, high-spin [FeIII(O₂H)(TMC)]²⁺ complex with syn orientation of OOH⁻ and N-methyl groups does not bind an oxidant ligand trans to the OOH⁻ ligand [91].

Concerning the conversion of [FeIII(O₂H)(TMC)]²⁺ into [FeIV(O)(TMC)]²⁺, two plausible mechanisms are considered for hydperoxido O–O bond cleavage in [FeIV(O)(TMC)]²⁺: One involves heterolytic O–O bond cleavage to generate an FeIV=O species, followed by one-electron reduction to give the FeIV=O complex (Scheme 4, pathways A and B). The second possible mechanism involves homolytic O–O bond cleavage in [FeIII(O₂H)(TMC)]²⁺ to afford [FeIV(O)(TMC)]²⁺ and a hydroxyl radical (Scheme 4, pathway C). Que and co-workers have proposed the former mechanism based on the observation that the formation rate of [FeIV(O)(TMC)]²⁺ from [FeIV(O₂H)(TMC)]²⁺ in CH₃CN solution was accelerated with increasing proton concentration [146]. In contrast, Nam and co-workers have proposed the homolytic O–O bond cleavage mechanism based on the observation that the rate of hydperoxido O–O bond cleavage in [FeIII(O₂H)(TMC)]²⁺ was independent of the proton concentration for the acetone/CF₃CH₂OH solvent system [91]. Additional evidence in support of the O–O bond homolysis mechanism was obtained by carrying out reactions in the presence and absence of substrates; the yields of the [FeIV(O)(TMC)]²⁺ product formed in the presence and absence of substrates were the same (Scheme 4, pathways A and D).
suggesting that a highly reactive iron(V)-oxo species was not generated in the O–O bond cleavage of [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+} [91].

4.2. Reactivity comparison

The reactivities of the iron(III)-peroxo and iron(III)-hydroperoxo complexes were examined in both nucleophilic and electrophilic reactions and then compared to those of the iron(IV)-oxo complex (Scheme 3). When the nucleophilic character of the three intermediates, [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+}, [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+}, and [Fe\textsuperscript{IV}(O)(TMC)(NCCH\textsubscript{3})]\textsuperscript{2+}, was tested in aldehyde deformatory reactions [147], the iron(III)-hydroperoxo species showed the greatest reactivity in the deformatory of 2-phenylpropionaldehyde (2-PPA), and the reactivity order of [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+} > [Fe\textsuperscript{III}(O)(TMC)]\textsuperscript{2+} > [Fe\textsuperscript{IV}(O)(TMC)(NCCH\textsubscript{3})]\textsuperscript{2+} was observed [91]. Interestingly, formation of [Fe\textsuperscript{IV}(O)(TMC)(NCCH\textsubscript{3})]\textsuperscript{2+} was observed in the reaction of [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+} and 2-PPA, proposing that the reaction is initiated via the nucleophilic attack of the iron(III)-hydroperoxo species on the carbonyl carbon of 2-PPA, followed by O–O bond cleavage of the peroxyhemiacetal leading to the formation of the iron(IV)-oxo species [91]. The high reactivity of the iron(III)-hydroperoxo species in nucleophilic reactions, compared to the side-on iron(III)-peroxo species (i.e., [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{+}), was ascribed to the end-on binding mode of the hydroperoxo ligand [147,148]. The reactivity of [Fe\textsuperscript{III}(O\textsubscript{2}H)(TMC)]\textsuperscript{2+} was further investigated using primary (1–CHO), secondary (2–CHO), and tertiary (3–CHO) aldehydes, and the observed reactivity order of 1–CHO > 2–CHO > 3–CHO supports the nucleophilic character of the iron(III)-hydroperoxo species.

The electrophilic character of the iron(III)-peroxo, iron(III)-hydroperoxo, and iron(IV)-oxo complexes was also investigated in the oxidation of alkylnaphthalene and weak C–H bonds, such as xanthene and 9,10-dihydroanthracene. While the iron(III)-peroxo complex did not show any significant spectral changes upon addition of the substrates, the iron(III)-hydroperoxo and iron(IV)-oxo complexes reacted with DHA, showing that these iron–oxygen intermediates are capable of abstracting an H-atom from DHA with similar reactivity in this C–H bond activation reaction. Thus, as summarized in Scheme 3, the iron(III)-peroxo and iron(IV)-oxo complexes show reactivities in nucleophilic and electrophilic reactions, respectively. Interestingly, the high-spin iron(III)-hydroperoxo complex is an active oxidant in both nucleophilic and electrophilic reactions.

Recent comparative studies on the reactivity of nonheme iron(III)-hydroperoxo and iron(IV)-oxo with an N4Py (N,N-bis(2-pyridylmethyl)-N-[bis(2-pyridyl)methyl]amine or Bn-TPEN ligand system in substrate halogenation reactions showed higher activity for the nonheme iron(III)-hydroperoxo than for the iron(IV)-oxo complexes [149]. Thus, the reaction of tetrabutylammonium bromide with iron(III)-hydroperoxo complexes resulted in the formation of Br\textsuperscript{−} with rate constants that were three orders of magnitude higher than those for reactions with the corresponding iron(IV)-oxo complexes. DFT studies confirmed the reaction processes and showed that the nonheme iron(III)-hydroperoxo species is a potential oxidant. The origin of the reactivity differences between heme and nonheme iron(III)-hydroperoxo was assigned to differences in spin states, whereby the nonheme iron(III)-hydroperoxo complex has a high-spin ground state, whereas it is low-spin for the heme-based iron(III)-hydroperoxo complex, thereby making the former species more reactive. These studies have thus highlighted critical differences between heme and nonheme iron(III)-hydroperoxo versus iron(IV)-oxo intermediates, where the heme iron(III)-hydroperoxo species was found to be a sluggish oxidant [24–27].

5. Conclusion

In recent years, considerable new insights into the intrinsic properties of nonheme metal–oxygen complexes have been gained through a combination of experimental and computational techniques. Thus, short-lived catalytic cycle intermediates, such as the iron(IV)-oxo, iron(III)-superxo, iron(III)-peroxo, and iron(III)-hydroperoxo species, were synthesized and spectroscopically characterized using biomimetic nonheme ligand systems. The most successful set of data to date has come from the nonheme iron system with the TMC ligand [9,150–152]. A range of different structures were stabilized and characterized and detailed reactivity patterns with a selection of substrate types were investigated. A clear picture is now starting to emerge surrounding the activity of enzymatic catalytic cycle intermediates and the potency of oxidants. The TMC ligand system with its tetradeinate coordination also enabled studies of the influences/effects of axial ligands on the spectroscopic properties and reactivity of Fe\textsuperscript{IV}=O intermediates.

Furthermore, comparisons between heme and nonheme iron systems have been made and remarkable differences have been discovered. In particular, studies of biomimetic porphyrin complexes, where Cpd I was found to be the only viable oxidant in oxygen atom transfer reactions, have suggested the existence of a single active oxidant in heme enzymes, such as the cytochromes...
P450. By contrast, recent evidence from nonheme iron based super-oxo and hydroperoxo complexes revealed reactive patterns that are considerably different from those of their heme analogues with occasionally higher reactivities for these intermediates than for the corresponding iron(IV)-oxo complexes. Future studies into the differences and comparisons of heme and nonheme iron oxygenases are expected to give further insights into the chemistry of these important enzymes.

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References
