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Engineering the Oxidative Potency of Non-Heme Iron(IV) Oxo Complexes in Water for C–H Oxidation by a *cis* Donor and Variation of the Second Coordination Sphere

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7. The $\nu_{\text{Fe}=0}$ values of 832 ± 2 cm⁻¹ indicate similar Fe^{IV}=0 bond strengths; however, different reactivities toward C–H substrates in water are observed. HAT occurs at rates that differ by 1 order of magnitude with nonclassical KIEs ($k_{\text{H}}/k_{\text{D}} = 30-66$) consistent with hydrogen atom tunneling. Higher KIEs correlate with faster reaction rates as well as a greater thermodynamic stability of the iron(III) resting states. A doubling in rate from pH 7 to pH 2 for substrate C–H oxidation by the most potent complex, that with a *cis*-carboxylate donor, [Fe^{IV}O(Htpena)]²⁺, is



observed. Supramolecular assistance by the first and second coordination spheres in activating the substrate is proposed. The lifetime of this complex in the absence of a C–H substrate is the shortest (at pH 2, 3 h vs up to 1.3 days for the most stable complex), implying that slow water oxidation is a competing background reaction. The iron(IV)=O complex bearing an alcohol moiety in the second coordination sphere displays significantly shorter lifetimes due to a competing selective intramolecular oxidation of the ligand.

INTRODUCTION

Synthetic iron(IV) oxo complexes are models for the active sites of mononuclear non-heme iron enzymes capable of substrate C–H oxidation. Both hydrogen atom transfer (HAT) and oxygen atom transfer (OAT) mechanisms are proposed for these reactions;¹⁻⁷ however, the generation and spectroscopic characterization of the transient iron oxidant and highvalent iron oxo species have been performed predominantly in organic solvents, below room temperature, conditions that are of limited biological relevance.⁸ Studies in water are often hampered by the insolubility of the complexes;⁹ however, pH and especially ligand dissociation are significant¹⁰—and complicating-factors for the stability and reactivity of iron(IV) oxo species and their precursors, not least since iron(III) complexes tend to aggregate through oxo-bridge formation, even at low pH.¹¹ Reactions in water are quite simply more difficult to study in comparison to those in organic solvents, and the reactivity trends of non-heme iron(IV) oxo complexes in an aqueous milieu have yet to be established.

The work of Collins and co-workers with the "first to fourth" generation tetraamido macrocyclic ligand (TAML) high valent iron oxo systems stands out with respect to a focus on working

in water.¹² The precatalyst and resting state for these systems is iron(III), and aggregation by oxo-bridged formation is presumably alleviated due to the already high anionic charge of the ligands and complexes. Reactivity spanning the oxidative destruction of organic water pollutants through C–H activation to water oxidation is tuned by minor structural variations in the planar tetradentate TAML ligands and experimental conditions.^{13–21} Iron complexes of aminopyridyl ligands have also been reported to oxidize water,^{22–26} and while the oxidation of water is sought for in the field of artificial photosynthesis,²⁷ it is a show-stopping competing reaction when organic substrates are the targets for oxidation under aqueous conditions. The crucial O–O bond forming step in water oxidation to O₂ and C–H bond cleaving steps are mechanistically distinct (Scheme 1), and reactivity in one

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Downloaded via UNIV OF CONNECTICUT on May 15, 2021 at 05:24:28 (UTC). See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles Scheme 1. Alternative Pathways: What Are the Supporting



Ligand and Environmental Factors That Determine if the

reaction type does not imply reactivity in the other. Mutual exclusion or possible competition between these reactions might be engineered through a modification of the supporting ligand. In general, the field of non-heme iron modeling is lagging in the rate of attaining a comparable level of maturity in the knowledge of the structure—activity relationship (SAR) in comparison to that which was achieved in the field of noble organometallic catalysts in the last half of the 20th century.

In comparison to the planar anionic Fe-TAML systems, many of the cationic iron(IV) oxo complexes are more reminiscent of the iron(IV) oxo intermediates which play a crucial role in the oxidation of strong C–H bonds catalyzed by non-heme iron-dependent enzymes.^{28–30} Minor variations in the active site environments in this class of enzyme tune the reactivities, allowing for a wide diversity in function.³¹⁻³⁵ A systematic exploration of the comparative potencies of cationic iron oxo models toward C-H bonds-in water-is now timely. Since common features of the mononuclear O2activating non-heme iron enzymes are an Asp/Glu O donor in the first coordination sphere cis to putative O_2 binding sites^{28,36} and hydrogen-bonding motifs in the second coordination sphere, 37-39 systems that can address the influence of these features should be targeted. Influences from the second coordination sphere have been probed for model systems in nonaqueous solvents through the introduction of pendent basic groups⁴⁰⁻⁴⁴ and Lewis acids.⁴⁵⁻ Trends in reactivity, efficiency and selectivity in aqueous solution are not known. To date the supporting ligand influence on the properties of Fe(IV) oxo complexes, predominantly studied in organic solvents, show that trans donors, not unexpectedly, have a significant influence on the spectroscopic properties and reactivity.^{48,49} The *cis* position as part of a chelating ligand to the oxo ligand has been more scantily probed. Notably, it was recently found that (in organic solvent) using a N3O macrocycle analogue of cyclam through replacement of one of the tertiary amine donors with a neutral ether oxygen atom enhances the rate of HAT reactions by 5 orders of magnitude.⁵⁰ In the only SAR study to be carried out in water, Chartarojsiri et al.⁵¹ have shown that an increase in $\nu_{\rm Fe=0}$ correlates with an increase in HAT and OAT rates within a series of iron(IV) oxo complexes supported by pentadentate pentapyridyl ligands, where the para substituent on the pyridyl donor trans to the oxo group is varied (H, CH₃, CF_3).

Our earlier work shows clearly that a biomimetic monodentate carboxylato donor in the *cis* position of nonheme iron peroxides and oxides exerts significant influence on the reactivity of non-heme iron systems in comparison to systems based on analogous neutral N-only donor ligands.^{52–58} One manifestation of this is the difference in the solvents in which peroxide adducts can be detected. (N5)Fe^{III}OOH/R complexes have been characterized predominantly in methanol.^{52,53,55} Equivalent (N4O)Fe^{III}OOH/R complexes oxidize methanol rapidly, precluding the use of this solvent for a determination of comparable spectroscopic data, and intramolecular ligand amine or aryl oxygenation reactions occur.^{56,58} To date spectroscopic data have been gathered for only one biomimetic *cis* carboxylato iron peroxide which is supported by N_iN_iN' -tris(2-pyridylmethyl)ethylenediamine-N'-acetate (tpena).^{43,57-60}

The Rtpen system (Scheme 2), which includes tpena, offers a convenient scaffold for probing the importance of the position *cis* to the oxo ligand. This can be a pyridine 61,62 or carboxvlato^{43,57} donor when $R = CH_2py$ or CH_2COO^- . The potentially hexadentate ligands are hemilabile, and sixcoordinated metal oxo complexes will be bifunctional through pentadenticity and the genesis of the nonchelating methylpyridyl arm or ethyl alcohol arm. This will furnish a stereochemically appropriate proximal acid/base group in the second coordination sphere. A systematic investigation of the Rtpen iron(IV) oxo system-at two pH values in water-using six structurally related non-heme iron(IV) oxo complexes (Scheme 2) differing in the *cis* donor and second coordination sphere is described in the present study. The trans donor (a tertiary amine) is identical in all six complexes, and two of the complexes, $[Fe^{IV}O((H)tpen)]^{2+/3+}$ and $[Fe^{IV}O((H)$ tpena)] $^{+/2+}$, have acidic and basic forms depending on the pH due to the pyridyl group in the second coordination sphere.

RESULTS AND DISCUSSION

Iron(II) complexes of metpen,⁵² ettpen,⁵³ bztpen,⁵³ tpen,⁶³ and tpenOH⁵⁵ and an iron(III) complex of Htpena^{43,64} (Scheme 2) were used as the solid-state starting materials for the aqueous species, which were oxidized by cerium ammonium nitrate (CAN) (3 equiv) to generate the complexes [Fe^{IV}O(metpen)]²⁺, [Fe^{IV}O(ettpen)]²⁺, [Fe^{IV}O-(bztpen)]²⁺, [Fe^{IV}O(Htpen)]³⁺, [Fe^{IV}O(tpenOH)]²⁺, and [Fe^{IV}O(Htpena)]²⁺, respectively (Scheme 2c; for an explanation of proton placement in the formulations see Scheme 2b). These reactions occur with a final pH of 2 at room temperature. The iron(II) complexes of the neutral ligands metpen, ettpen, bztpen, and tpen are oxidized according to eqs 1a and 1b. Equation 1b only applies to the iron(III) complexes of tpena and deprotonated tpenOH ([Fe^{III}(tpenO)]²⁺ is spontaneously generated on dissolution of [Fe^{II}Cl(tpenOH)]- (PF_6) under ambient conditions⁵⁸). Given the pK₂ of pyridinium (ca. 5.5) noncoordinated methylpyridine arms in the complexes of tpen and tpena will be protonated at pH 2.^{59,65} Likewise, on the basis of the pK_a values of alcohols vs pyridinium, decoordination and protonation of the alkoxide donor in $[Fe^{III}(tpenO)]^{2+}$ can be anticipated when this complex converts to $[Fe^{IV}O(tpenOH)]^{2+}$.

$$\mathrm{Fe}^{\mathrm{II}} + \mathrm{Ce}^{\mathrm{IV}} + \mathrm{H}_{2}\mathrm{O} \rightarrow \mathrm{Fe}^{\mathrm{III}} - \mathrm{OH} + \mathrm{Ce}^{\mathrm{III}} + \mathrm{H}^{+} \qquad (1a)$$

$$Fe^{III} - OH + Ce^{IV} \rightarrow Fe^{IV} = O + Ce^{III} + H^{+}$$
(1b)

The addition of hypochlorite (CIO^{-}) to aqueous solutions of the precursor complexes also produces iron(IV) oxo complexes (eqs 2a-2d), and in this case the final pH is 7. At this pH, noncoordinated py arms can be expected to dominantly exist as the free base. Again the alcohol arm of tpenOH will be uncoordinated in the iron(IV) oxo complex. It is reasonable to expect that the pH is important for the ensuing reactivity of these iron(IV) oxo complexes and that the Scheme 2. (a) Generic Chemical Structure of the Ligands N-R-N,N',N'-tris(2-pyridylmethyl)ethane-1,2-diamine,^{*a*} (b) Drawing Specifying Protonation Sites in the tpenaH/tpena/ Htpena and tpenOH/tpenO/HtpenO Designations in Complex Formulations, and (c) the Iron(IV) Oxo Complexes at pH 2^{*b*}



 ${}^{a}R$ = methyl, ethyl, or benzyl group in metpen, ettpen, and bztpen, respectively; *N*,*N*,*N'*,*N'*-Tetrakis(2-pyridylmethyl) ethylenediamine = tpen. *N*,*N*,*N'*-Tris(2-pyridylmethyl)ethylenediamine-*N'*-ethanol = tpenOH. *N*,*N*,*N'*-Tris(2-pyridylmethyl)ethylenediamine-*N'*-acetate = tpena. b The pyridiniums in the second coordination spheres are deprotonated at pH 7 and shown in red.

pyridinium H atom donor (pH 2), pyridine H atom acceptor (pH 7), and alcohol (pH 2 and 7) groups in the second coordination spheres might potentially play a role in C-H oxidation reactions by these complexes.

 $2Fe^{II} + ClO^{-} + H_2O \rightarrow 2Fe^{III} - OH + Cl^{-}$ (2a)

$$Fe^{III} - OH + ClO^{-} \rightarrow Fe^{III} - OCl + OH^{-}$$
 (2b)

$$Fe^{III} - OCl \rightarrow Fe^{IV} = O + Cl^{\bullet}$$
 (2c)

 $Fe^{II} + ClO^- \rightarrow Fe^{IV} = O + Cl^-$

(2d)

The X-ray structures of the stable isostructural and isovalent complexes $[V^{IV}O(Htpena)](ClO_4)_2\cdot H_2O,^{43}~[V^{IV}O(tpen)]-(ClO_4)_2, \ and ~[V^{IV}O(tpenOH)](PF_6)_2$ (Figure 1, see the



Figure 1. Crystal structures of the cations in (a) $[V^{IV}O(Htpena)]$ - $(ClO_4)_2(H_2O)_2$ (included for facile comparison, coordinates from ref 43), (b) $[V^{IV}O(tpen)](ClO_4)_2$, and (c) $[V^{IV}O(tpenOH)](PF_6)_2$. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms, except those on the dangling methylpyridyl and ethyl alcohol arms of $[V^{IV}O(Htpena)]^{2+}$ and $[V^{IV}O(tpenOH)]^{2+}$, respectively, are omitted for clarity.

Supporting Information for crystallographic details) exemplify the bifunctionality of the ligand scaffolds and perhaps suggest the most likely isomers of the analogous iron(IV) oxo compounds. Importantly, a tertiary amine donor is trans to the vanadium(IV) oxo moiety in all three structures. Consequently, the V=O distances in these complexes are similar at 1.59(15),⁴³ 1.5943(13), and 1.591(3) Å, respectively. The structures support that, in solution, the second coordination sphere arms (-CH₂pyH⁺, -CH₂py, or -CH₂CH₂OH) are sterically capable of interacting (by an electrophilic interaction or by H-bonding) with the cis Fe^{IV}O moiety and potentially proximal substrates. Equally, they are nucleophiles (in the case of -CH₂pyH⁺, and -CH₂CH₂OH, after deprotonation) and are sterically capable of replacing the oxo ligand to become hexadentate ligands. In the solid state, the pyridinium of $[V^{IV}O(Htpena)]^{2+}$ H-bonds to the noncoordinated carboxyl group of an adjacent complex cation⁴³



Figure 2. ¹H NMR (400 MHz) from 50 to -20 ppm of $[Fe_2O(Htpena)_2](ClO_4)_4$ dissolved in $D_2O(1 \text{ mM})$ and oxidized with CAN (6 equiv) with an inset showing the range from 9 to 8 ppm.

and the disordered alcohol arm of [V^{IV}O(tpenOH)]²⁺ Hbonds to a counteranion, while the free pyridine N of $[V^{IV}O(tpen)]^{2+}$ does not show any significant supramolecular interaction. Interestingly, the complexes achieve the same overall cationic charge in the crystal structures, despite the support of an effectively pentadentate monoanionic (tpena) or neutral (tpen and tpenOH) first coordination sphere because of the charge-compensating ionizable dangling pendant arms. Protonation-or not-of the uncoordinated py arm is, however, likely to be driven by crystal-packing forces since pK_a values of the noncoordinated functional groups are not expected to vary significantly. The N(CH₂py)₂ (N1, N2, N3) tridentate end is consistently facial in all of the known structures of the Rtpen ligands. We note that the arrangement of the remaining tertiary amine and py donors in the pentadentate tpenOH of [V^{IV}O(tpenOH)]²⁺ is opposite to that in $[Fe^{II}Cl(tpenOH)]^{+5}$: i.e., the $Fe^{II}-Cl$ and $V^{IV}=O$ units cannot simply be substituted from one to the other structure.

The bifunctionality of the ligands tpenaH/tpena/Htpena and tpenOH/tpenO/HtpenO in the iron(IV) oxo complexes (Scheme 2) was investigated with density functional theory (DFT). Using the crystal structures of the V^{IV}O complexes as a starting point, we investigated the feasibility of interchanging either the carboxyl O1 with pyridine nitrogen (N3) in Figure 1a or the pyridine N4 with the (deprotonated) O2 in Figure 1c for the coordination to the iron(IV) oxo unit. Additionally, we also investigated other potential isomers with DFT, but they were generally found to be less stable. The results of these DFT calculations are given in Tables S4 and S5.

The DFT calculations indicate that, for iron(IV) oxo complexes of the HtpenO/tpenOH ligand, the complex with the first coordination sphere comprised of only N donors is the most stable, by more than 50 kJ/mol. This is the structure obtained for the analogue $[V^{IV}O(tpenOH)](PF_6)_2$ (Figure 1c). The situation is more complex for the Htpena/tpenaH ligand, where both free pyridine and free carboxylate arms can

potentially be either protonated or deprotonated. We investigated all variants (i.e., protonated fully N-coordinated $[Fe^{IV}O(tpenaH)]^{2+}$ and O-coordinated $[Fe^{IV}O(Htpena)]^{2+}$ and the corresponding deprotonated systems). The calculations predict that the energy differences between the N4O and N5 coordination are about half of those for the corresponding tpenOH complexes; hence, it could not unequivocally be concluded on the basis of the DFT calculations which of the isomers was the most stable.

The ¹H NMR spectrum of [Fe^{IV}O(Htpena)]²⁺ (generated in situ from $[Fe_2O(Htpena)_2](ClO_4)_4$ and CAN) in D_2O shows narrow and well-defined resonances in the range of -17 to 45ppm (Figure 2). Significantly, one set of pyridyl resonances at 8.7 ppm (d, J = 6.2 Hz, 1H), 8.5 ppm (t, J = 8.1 Hz, 1H), 8.0 ppm (d, J = 7.8 Hz, 1H), and 7.9 ppm (t, J = 6.9 Hz, 1H) (Figure 2 insert) is not paramagnetically shifted, consistent with noncoordination of one pyridyl arm at this pH. The spectrum is reminiscent of that of [Fe^{IV}O(bztpen)]²⁺ recorded in d_3 -MeCN,⁶⁶ where the presence of one isomer was concluded. Thus, the two coordinating pyridyl units are oriented parallel with the Fe=O axis, exactly as in the structures of [V^{IV}O(Htpena)]²⁺ (Figure 1). Solution-state NMR spectroscopy and the crystal structure of the vanadium complex analogue indicate that the relevant solution species is $[Fe^{IV}O(Htpena)]^{2+}$ at pH 2. It is important to note that the iron speciation is not 100% [Fe^{IV}O(Htpena)]²⁺ in the NMR sample that produces the spectrum in Figure 2.43 At pH 2 the remaining iron speciation takes the form of antiferromagnetically coupled iron(III) centers in $[Fe^{III}_{2}O(Htpena)_{2}]^{4+}$. This situation allows for the tractable ¹H NMR spectrum shown. At pH 7 the ¹H NMR spectrum is too broad to allow extracting any useful information (Figure S1). This is due to the fact that the concentration of $[Fe^{IV}O(tpena)]^+$ will be lower at pH 7 than that of $[Fe^{IV}O(Htpena)]^{2+}$ at pH 2, due to the shorter lifetime, and significantly, that the dominant resting state speciation $([Fe^{III}_{2}O(Htpena)_{2}]^{4+} \rightleftharpoons 2[Fe^{III}(OH)(tpena)]^{+} +$

H₂O) is now in the form of the high-spin complex $[Fe^{III}(OH)(tpena)]^+$ (S = 5/2).⁴³ This will broaden the NMR resonances. The UV/vis spectra at pH 2 and pH 7 are the same (*vide infra*); thus, it is likely that the first coordination sphere is the same at both pH values, i.e., N4O coordination sphere for the iron(IV) oxo complexes of Htpena (pH 2) and tpena (pH 7).

The UV/vis absorption and Raman spectra (Figure 3, Figure S2, and Tables 1 and 2) for the series of iron(IV) oxo



Figure 3. (a) UV/vis absorption spectra of $[Fe^{IV}O(tpenOH)]^{2+}$ (blue, λ_{max} , 723 nm), $[Fe^{IV}O(Htpena)]^{2+}$ (green, λ_{max} 730 nm), $[Fe^{IV}O(Htpen)]^{3+}$ (purple, λ_{max} 712 nm), $[Fe^{IV}O(bztpen)]^{2+}$ (black, λ_{max} 722 nm), $[Fe^{IV}O(ettpen)]^{2+}$ (orange, λ_{max} 718 nm), and $[Fe^{IV}O(metpen)]^{2+}$ (red, λ_{max} 714 nm) in water. Conditions: [Fe]= 1.5 mM, 3 equiv of CAN. The dashed line indicates λ = 722 nm. (b) Raman spectra of $[Fe^{IV}O(Htpena)]^{2+}$ generated in H₂O (green) and H₂¹⁸O (gray). Conditions: [Fe] = 4 mM, pH 2, [CAN] 12 mM, λ_{exc} = 785 nm, rt.

complexes are identical at pH 2 and pH 7. The iron(IV) oxo complexes are blue to green with a narrow λ_{max} range of 712– 730 nm and a $\nu_{Fe=O}$ Raman band at 832 ± 2 cm⁻¹, typical for non-heme iron(IV) oxo complexes.⁸ In H₂¹⁸O, the Fe=¹⁸O stretching bands for $[Fe^{IV}O(Htpena)]^{2+}$ and $[Fe^{IV}O((ettpen)]^{2+}$ are shifted to 795 and 796 cm⁻¹ (Figure 3b), respectively, as expected ($\Delta = 36 \text{ cm}^{-1}$ using the two-atom approximation). A change in the *trans* position will typically exert a significant influence on the Fe^{IV}=O bond;^{48,49,67} thus, the lack of variation in the Raman spectroscopic data supports that the *trans* donor, a tertiary amine, remains a constant throughout the series in aqueous solutions and that the crystal structures in Figure 1 are representative. It is especially notable that the variation in the *cis* donor from a negatively charged carboxylato group to softer neutral aromatic N atoms has negligible influence on the Fe^{IV}=O bond strength. The electronic structures, however, differ slightly, with [Fe^{IV}O-(Htpena)]²⁺ exhibiting the most red shifted λ_{max} (by ca. 300 cm⁻¹, 730 nm vs 712–723 nm).

The iron(IV) oxo complexes at pH 2 show differences in their ability to oxidize water-soluble alcohols (Table 1). The substrates 1-phenylethanol, benzyl alcohol, cyclohexanol, and isopropanol have C-H bond dissociation energies (BDEs) of 85, 88, 93, and 95 kcal mol⁻¹, respectively, for the C–H bonds of the alcohol carbon atom.⁶⁸ Pseudo-first-order rate constants, k_{obs} , and second-order rate constants, k_2 , for substrate oxidation were determined from the decay in NIR absorbance (Figures S3-S9). The only products, determined by gas chromatography, were acetophenone, benzaldehyde, cyclohexanone, and acetone, respectively. For all complexes, k_2 values for the oxidation of cyclohexanol fall within 1 order of magnitude of that of [Fe^{IV}O(Htpena)]²⁺, which is significantly the most reactive $(43 \text{ mM}^{-1} \text{ s}^{-1})$. At pH 2 the rates of oxidation for the individual substrates are similar for $[Fe^{IV}O(metpen)]^{2+}$, $[Fe^{IV}O(ettpen)]^{2+}$, and $[Fe^{IV}O(Htpen)]^{3+}$, and these are slow in comparison to those for $[Fe^{IV}O(bztpen)]^{2+}$, $[Fe^{IV}O(tpenOH)]^{2+}$, and $[Fe^{IV}O(bztpen)]^{2+}$, $[Fe^{IV}O(tpenOH)]^{2+}$, and $[Fe^{IV}O(bztpen)]^{2+}$, $[Fe^{IV}O(tpenOH)]^{2+}$, $[Fe^{IV}O(tpenOH$ (Htpena)]²⁺. The rate constants for benzyl alcohol oxidation for all of the complexes, apart from that generated from the tpenOH ligand, are less spread at pH 7 (Table 2). Notably, however, benzyl alcohol oxidation is 2.5 times slower when it is catalyzed by $[Fe^{IV}O(tpena)]^+(pH 7)$ vs $[Fe^{IV}O(Htpena)]^{2+}$ (pH 2). $[Fe^{IV}O(Htpena)]^{2+}$, generated electrochemically in water (pH 4), showed k_2 values for oxidation of benzyl alcohol, isopropanol, and cyclohexanol of 2.1, 16×10^{-3} , and 47×10^{-3} M⁻¹ s⁻¹, respectively,⁵⁹ similar to those seen here at pH 2. Given the pK_a of propanoic acid is 4.88, it can be expected that in both cases the speciation is $[Fe^{IV}O(Htpena)]^{2+}$. Hence, the reactivity of the complexes in water is intrinsic and independent of the method of preparation (chemical or electrochemical).

Tunneling effects can be a major contributor to the reaction rates and selectivity in H atom transfer from C-H bonds as a consequence of the hydrogen atom's low mass.^{69–71} High KIEs are characteristic of tunneling mechanisms and have been reported for the HAT reactions performed by enzymatic iron(IV) oxo intermediates: 37 in the α -ketoglutarate-dependent dioxygenases (TauD "J")⁷² and 50-100 for methane monooxygenase.⁷³ The KIEs (Table 1) for [Fe^{IV}O-(metpen)]²⁺, [Fe^{IV}O(ettpen)]²⁺, and [Fe^{IV}O-(Htpen)]³⁺(generated using CAN) in the oxidation of benzyl alcohol were ca. 30, while [Fe^{IV}O(bztpen)]²⁺, [Fe^{IV}O-(tpenOH)]²⁺, and [Fe^{IV}O(Htpena)]²⁺ show KIEs of ca. 63 and their $k_{2}{}'$ values (where $k_{2}{}'$ is k_{2} divided by the number of equivalent substrate C-H bonds that can be attacked) correlate with the bond dissociation energies of the substrates (Figure 4). Hence, the data we report here are consistent with C-H bond cleavage as the rate-determining step, as expected for HAT reactions.

For comparison, nonclassical, but lower, $k_{\rm H}/k_{\rm D}$ KIE values (10–30) were noted for non-heme iron(IV) oxo (S = 1) complexes prepared in organic solvents.^{48,74–77} Klein et al. have reported a KIE of 80 (–20 °C, 9,10-dihydroanthracene, in methanol) for a tetramethylcyclam iron(IV) oxo complex with a thiolate donor *trans* to the oxo, significantly higher than that when acetonitrile occupies this position (KIE = 10, 25 °C). The large KIE was attributed to tunnelling.⁷⁸ The

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Table 1. Spectroscopic Characterization, Half-Life for Spontaneous Decrease in Absorbance at λ_{max} ($t_{1/2}$), k_2 , and Kinetic Isotope Effect ($k_{\rm H}/k_{\rm D}$) of Iron(IV) Oxo Complexes in Water Generated by the Addition of 3 equiv of CAN to the Precursors (pH 2, 22 °C)^{*a*}

	λ _{max} (nm)	$\nu_{\rm Fe=0} {b \choose 1^8 {\rm O-H_2O}} {cm^{-1}}$	t _{1/2}	k_2 (CyOH) (10 ³ M ⁻¹ s ⁻¹)	$k_2((CH_3)_2CHOH)$ (10 ³ M ⁻¹ s ⁻¹)	$k_2 (PhCH(OH) \ CH_3) \ (10^3 M^{-1} s^{-1})$	$k_2(\text{PhCH}_2\text{OH}) \ (10^3 \text{ M}^{-1} \text{ s}^{-1})$	k_2 (PhCD ₂ OH) (10 ³ M ⁻¹ s ⁻¹)	$k_{ m H}/k_{ m D}$
[Fe ^{IV} O(Htpen)] ³⁺	712	833	1.1 days	5	-	-	510	19	27
$[Fe^{IV}O(metpen)]^{2+}$	714	831	1.3 days	7	-	-	630	16	39
$[Fe^{IV}O(ettpen)]^{2+}$	718	833 (796)	1.3 days	6	-	-	470	19	25
$[Fe^{IV}O(bztpen)]^{2+}$	722	831	1.1 days	19	5	950	1120	19	60
[Fe ^{IV} O(tpenOH)] ^{2+,c}	723	832	80 s	30	5	630	990	16	62
$[Fe^{IV}O(Htpena)]^{2+}$	730 ⁴³	831 (795)	3 h	43	17	1870	1980	30	66

^{*a*}Legend: –, data not available. ^{*b*} λ_{exc} 785 nm. ^{*c*}The competing ligand oxidation of $[Fe^{IV}O(tpenOH)]^{2+}$ has been taken into account in the determination of C–H rate constants.

Table 2. Spectroscopic Data, $t_{1/2}$, and k_2 for Iron(IV) Oxo Complexes in Water Generated with 3 equiv of ClO⁻ to the Precursors (pH 7, 22 °C)^{*a*}

	λ_{\max} (nm)	$\nu_{\rm Fe=0}^{b} (\rm cm^{-1})$	$t_{1/2}$	$k_2(\text{CyOH}) [10^3 \text{ M}^{-1} \text{ s}^{-1}]$	k_2 (PhCH ₂ OH) [10 ³ M ⁻¹ s ⁻¹]
$[Fe^{IV}O(tpen)]^{2+}$	712	832	1.5 h	_	550
[Fe ^{IV} O(metpen)] ²⁺	714	832	4.5 h	_	600
[Fe ^{IV} O(ettpen)] ²⁺	718	833	1.5 h	_	580
[Fe ^{IV} O(bztpen)] ²⁺	722	830	1.5 h	16	890
[Fe ^{IV} O(tpenOH)] ²⁺	723	np	60 s	#	#
[Fe ^{IV} O(tpena)] ⁺	730	831	1.5 h	20	780

^{*a*}Legend: np, not possible due to short $t_{1/2i}$ –, not performed; #, experiment not possible due to competing regioselective oxidation of the ligand to tpena under these conditions (see text). ^{*b*} λ_{exc} 785 nm.



Figure 4. (left) Plot of k_{obs} against substrate concentration of benzyl alcohol to determine k_2 and KIE. (right) Plot of log k_2' vs C–H BDEs of substrates. Color code: black, $[Fe^{IV}O(bztpen)]^{2+}$; blue, $[Fe^{IV}O(tpenOH)]^{2+}$; green, $[Fe^{IV}O(Htpena)]^{2+}$.

different donors in these cases, however, clearly attenuate the Fe=O bond; Fe–O distances are 1.65 and 1.70 Å for the *trans* MeCN and thiolate complexes, respectively.^{79,80} The latter distance is the longest recorded for an S = 1 iron(IV) oxo complex.⁸ Given that it is the *cis* donor we vary, the expectation for the present series is that the length of the Fe=O bonds, which all show the same $\nu_{\text{Fe}=O}$ values, are close to the 1.67 Å found for [Fe^{IV}O(bztpen)]^{2+.81} The structures of the vanadyl complexes (Figure 1) illustrate that little variation is expected with V=O distances of 1.593 ± 0.002 Å.

To understand the observed reactivity in more detail, we also calculated the energy difference ΔE_{Q-T} (Q = quintet, T = triplet), as this parameter is often invoked in discussions of (two-state) reactivity in HAT reactions.^{82–84} We note that previous studies (in organic solvents) have found that a decreasing spin-state splitting ΔE_{Q-T} (spanning -6 to +20 kJ/mol with the B3LYP functional) for a series of 11

 $[Fe^{IV}O(TMC)(X)]^{+/2+}$ complexes correlated with increasing k_2 (and decreasing free energy of activation ΔG^*), in line with the two-state-reactivity (TSR) model.⁷⁷ We here focus on specific isomers of the iron(IV) oxo complexes of tpenOH/ HtpenO and tpenaH/tpena/Htpena (chosen on the basis of ligand conformations found in crystal structures of the vanadium(IV) oxo complexes and spectroscopic indications). For these complexes, calculations were performed for both S =1 and S = 2 spin states; we only discuss B3LYP results here, but TPSS was also investigated. The two functionals in almost all cases agree that the most stable spin state is the S = 1 state (the exception is [Fe^{IV}O(HtpenO)]²⁺). This result is consistent with the prediction that can be based on the spectrochemical series. Thus, a carboxylate donor is also expected to be a weaker ligand than pyridine; hence, higher spin states will favored.

For $[Fe^{IV}O(tpenOH)]^{2+}$ and $[Fe^{IV}O(Htpena)]^{2+}$ the calculations are consistent with the TSR model where a lower ΔE_{Q-T} correlates with a larger k_2 . An interesting observation is that N4O coordination generally lowers ΔE_{Q-T} . Pérez and co-workers have reported that the iron(IV) oxo complex of an ether-substituted cyclam (N3O) also results in a lower ΔE_{Q-T} relative to that of the cyclam (N4) analogue;⁷⁶ thus, changing the *cis* donor appears to provide a route to control ΔE_{Q-T} . This is important information for the rational design of complexes for specific HAT reactivity. We also note that ΔE_{Q-T} for $[Fe^{IV}O(tpena)]^{2+}$ is larger than that of its protonated congener and this seems to be reflected in the k_2 value measured at pH 7 (Table 2), which is approximately half that measured at pH 2.

Other parameters besides ΔE_{Q-T} are most likely also important in determining the reactivity of the complexes, particularly at different pH values. Supramolecular interactions immediately prior to substrate oxidation will depend on pH, the second coordination sphere, and possible water involvement. At pH 2 we have now established that the Htpenasupported iron(IV) oxo complex possesses biomimetic *first* (*carboxylate O*) and second coordination (*carbonyl/pyridinium*) sphere moieties that will potentially assist H atom/proton movements. A DFT structure optimization on the adduct between [Fe^{IV}O(Htpena)]²⁺ and cyclohexanol visualizes these features (Figure 5). The protonated pyridyl arm steers the



Figure 5. Optimized structure of the cyclohexanol $[Fe^{IV}O-(Htpena)]^{2+}$ adduct (B3LYP). H atoms participating in hydrogen bonding are shown in green.

substrate to the Fe^{IV}O moiety, and the H atom that will be removed in the HAT to Fe^{IV}O is proximate to the O atoms of both the coordinated carboxylate and oxo group. Hydrogen bonding between a C–H substrate (methanol) in water and a ruthenium(IV) oxo complex has previously been experimentally confirmed as the driving force for adduct formation.⁸⁵

With half-lives of 80 s and 3 h at pH 2 for $[Fe^{IV}O(tpenOH)]^{2+}$ and $[Fe^{IV}O(Htpena)]^{2+}$, respectively, the stabilities of these complexes in water in the absence of C– H substrates are significantly shorter in comparison to the four complexes formed using the neutral N5 ligands, for which the

half-lives are over 1 day (Table 1 and Figure 6a). All of the complexes decay relatively more quickly at pH 7.

In the case of $[Fe^{IV}O(tpenOH)]^{2+}$ at both pH 2 and 7, the shorter lifetime in both the presence and absence of C–H substrates is due to an intramolecular ligand C–H oxidation (Figure 6b). Signals corresponding to those observed for the iron complexes of tpena⁴³ appear in the ESI mass spectra of $[Fe^{IV}O(tpenOH)]^{2+}$ mixed with CAN or ClO⁻ (Figure S10). Thus, the alcohol group of tpenOH is converted to a carboxylate group and hence the ligand Htpena is generated in situ. ¹⁸O labeling (Na¹⁸OCl in H₂¹⁸O) shows that this peak appropriately shifts 2 mass units, consistent with a single ¹⁸O-labeled tpena (Figure S10). Thus in water, as its iron complex, tpenOH is susceptible to regioselective oxidation by oxidants, and under catalytic conditions, the C–H oxidation of external substrates competes with this selective intramolecular oxidation of the ligand scaffold.

In contrast to [Fe^{IV}O(tpenOH)]²⁺, [Fe^{IV}O(Htpena)]²⁺ is robust in aqueous solvent: e.g., it can be stoichiometrically regenerated on the addition of further oxidant. The shorter lifetime for [Fe^{IV}O(Htpena)]²⁺ in comparison to the complexes of the N-only ligands in the absence of C-H substrates is proposed to be due to competing water oxidation. This is consistent with previous work using electroactivation to generate the iron(IV) oxo complexes of tpena/Htpena. Rate constants of 1.2×10^{-3} and 4×10^{-4} M⁻¹ s⁻¹ were deduced respectively for the decay of $[Fe^{IV}O(tpena)]^+$ at pH 6–7 and [Fe^{IV}O(Htpena)]²⁺ pH 3-4 in buffered water.⁶⁰ This was ascribed to slow water oxidation. While our work shows that [Fe^{IV}O(Htpena)]²⁺ is the most potent aqueous iron(IV) oxo complex for C-H oxidation in the present series, slow background water oxidation might marginally compromise this activity, when C-H substrates are limited.

CONCLUSIONS

Finding the optimal conditions and robust catalysts for the selective oxidation of organic substrates in water without suppression due to competing water oxidation by high-valent iron complexes is a task with high priority for green chemistry applications. The intrinsic reactivities of a series of closely structurally analogous iron(IV) oxo complexes have been ascertained using bifunctional ligands where the differences lie in the *cis* position (py or COO⁻) and the second coordination sphere (none, a pyridinium/pyridine at pH 2/7 or an alcohol at pH 2 and 7). This series, studied in water alone, has uncovered some biorelevant SARs. In stark contrast to iron(IV) oxo complexes in which the trans effect has been explored, differences in reactivities are not accompanied by a correlation with measurable spectroscopic parameters. The change of a cis equatorial donor from a neutral pyridine to an anionic carboxylate causes only a marginal change in the λ_{max} value by a few nanometers at pH 2 and 7 and has no effect on the Fe^{iv}=O bond stretching frequency. However, the rate constants for HAT during C-H oxidation vary by 1 order of magnitude with a clear trend for faster reactions and enhanced hydrogen atom tunneling, in the complex with a cis carboxylato in comparison to complexes based on solely N donors in the first coordination sphere. Electronic changes have been linked to reactivity trends, and a formally spin forbidden transition of the conversion of a S = 1 Fe^{IV}=O complex to the corresponding S = 5/2 Fe^{III} complex has been proposed to transverse a spin-crossover process from S = 1 to $\hat{S} = 2$ prior to the HAT and has been coined TSR.^{47,75,77,84,86,87} DFT

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Figure 6. (a) Absorbance at $\lambda_{max}(NIR)$ over time showing the decay of iron(IV) oxo species: $[Fe^{IV}O(tpenOH)]^{2+}$ (blue), $[Fe^{IV}O(Htpena)]^{2+}$ (green), $[Fe^{IV}O(Htpen)]^{3+}$ (purple), $[Fe^{IV}O(ettpen)]^{2+}$ (orange), $[Fe^{IV}O(metpen)]^{2+}$ (red), and $[Fe^{IV}O(bztpen)]^{2+}$ (black). Conditions: [Fe] = 1.5 mM, 3 equiv of CAN. At the right is an expansion of the blue plot for $[Fe^{IV}O(tpenOH)]^{2+}$. (b) Conversion of $[Fe^{II}(tpenO)]^{2+}$ to $[Fe^{III}(tpena)]^{2+}$.

calculations show that O coordination lowers the energy difference between the triplet and quintet states for the iron(IV) oxo complexes of Htpena/tpenaH and HtpenO/ tpenOH in comparison to complexes of N5 ligands, making the more reactive S = 2 spin state more accessible. This advantage is supplemented by high thermodynamic stability of the iron(III) states for the complexes of the monoanionic N5O ligands compared to the iron complexes of the neutral Rtpen ligands.⁵⁸ In MeCN, the E°(Fe^{III}/Fe^{II}) value for the tpenasupported system is approximately 350 mV lower than its tpen counterpart⁵⁸ (and other systems based on neutral N-only donor ligands which otherwise dominate the field of modeling non-heme iron). With this work we have now demonstrated greater reactivity, in water, for HAT to iron(IV)oxo complexes from alcohol substrates when a carboxylate donor is cis to the oxo group.

The pH and the presence of H-bond donors and acceptors in the first and second coordination spheres will be important in water. Ultimately our study of eight closely related iron(IV) oxo complexes, $[Fe^{IV}O(metpen)]^{2+}$, $[Fe^{IV}O(ettpen)]^{2+}$, $[Fe^{IV}O(bztpen)]^{2+}$, $[Fe^{IV}O(Htpen)]^{3+}$, $[Fe^{IV}O(tpenOH)]^{2+}$, $[Fe^{IV}O(Htpena)]^{2+}$, $[Fe^{IV}O(tpen)]^{2+}$, and $[Fe^{IV}O(tpena)]^{+}$, shows that subtle structural differences in the first and second coordination spheres tune their individual reactivity, producing large differences by orders of magnitude in reactivity-exactly as seen in nature for the non-heme enzymes. [Fe^{IV}O-(Htpena)]²⁺ (pH 2) shows k_2 values for C–H HAT from alcohols which are twice those for [Fe^{IV}O(tpena)]⁺ (pH 7). The modeling suggests favorable substrate C-H association with both the cis carboxylate O donor and noncoordinated carbonyl and the Fe=O group, with the pendant pyridinium in the second coordination sphere furnishing a H atom donor for the O atom acceptor of the alcohol substrate. This type of interaction can be translated directly to non-heme enzymes themselves because either an Asp or Glu donor is cis to the oxo site and interactions with surrounding amino acids steer the substrate selectivity. The enhanced reactivity and tunneling effects for the complex with a cis-carboxylate donor parallels

Nature's preference for incorporating a Asp/Glu O donor in the first coordination sphere *cis* to the putative O_2 binding site of the O_2 -activating non-heme iron enzymes and the hemilabile pendant arms of the potentially hexadendate ligands furnish biomimetic second coordination spheres that clearly influence the reactivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c03441.

Experimental section, computational details, extended DFT results including relative free energies and calculated spectroscopic and structural parameters, kinetic data for reactivity studies toward C–H bonds, and crystallographic and structural details for CCDC 1971388 and 2017382 (PDF)

Accession Codes

CCDC 1971388 and 2017382 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Shan, X.; Que, L. J. Inorg. Biochem. 2006, 100, 421-433.
- (2) Nam, W. Acc. Chem. Res. 2007, 40, 522-531.
- (3) Hohenberger, J.; Ray, K.; Meyer, K. Nat. Commun. 2012, 3, 720.
- (4) Bryliakov, K. P.; Talsi, E. P. Coord. Chem. Rev. 2014, 276, 73-96.
- (5) Nam, W. Acc. Chem. Res. 2015, 48, 2415–2423.
- (6) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L. Chem. Rev. 2004, 104, 939–986.
- (7) Olivo, G.; Cussó, O.; Borrell, M.; Costas, M. JBIC, J. Biol. Inorg. Chem. 2017, 22, 425–452.
- (8) McDonald, A. R.; Que, L. Coord. Chem. Rev. 2013, 257, 414–428.

(9) Sastri, C. V.; Sook Seo, M.; Joo Park, M.; Mook Kim, K.; Nam, W. Chem. Commun. 2005, 1405–1407.

(10) Bautz, J.; Bukowski, M. R.; Kerscher, M.; Stubna, A.; Comba, P.; Lienke, A.; Münck, E.; Que, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 5681–5684.

- (11) Kurtz, D. M. Chem. Rev. 1990, 90, 585-606.
- (12) Collins, T. J.; Ryabov, A. D. Chem. Rev. 2017, 117, 9140-9162.

(13) Ellis, W. C.; McDaniel, N. D.; Bernhard, S.; Collins, T. J. J. Am. Chem. Soc. 2010, 132, 10990-10991.

(14) Ghosh, A.; Mitchell, D. A.; Chanda, A.; Ryabov, A. D.; Popescu, D. L.; Upham, E. C.; Collins, G. J.; Collins, T. J. J. Am. Chem. Soc. **2008**, 130, 15116–15126. (15) Kundu, S.; Chanda, A.; Espinosa-Marvan, L.; Khetan, S. K.; Collins, T. J. Catal. Sci. Technol. 2012, 2, 1165.

- (16) Gupta, S. S.; Stadler, M.; Noser, C. A.; Ghosh, A.; Steinhoff, B.; Lenoir, D.; Horwitz, C. P.; Schramm, K.-W.; Collins, T. J. *Science* **2002**, *296*, 326–328.
- (17) Tang, L. L.; DeNardo, M. A.; Schuler, C. J.; Mills, M. R.; Gayathri, C.; Gil, R. R.; Kanda, R.; Collins, T. J. J. Am. Chem. Soc. 2017, 139, 879–887.

(18) Kundu, S.; Chanda, A.; Thompson, J. V. K.; Diabes, G.; Khetan, S. K.; Ryabov, A. D.; Collins, T. J. *Catal. Sci. Technol.* **2015**, *5*, 1775–1782.

(19) Beach, E. S.; Malecky, R. T.; Gil, R. R.; Horwitz, C. P.; Collins, T. J. Catal. Sci. Technol. 2011, 1, 437.

- (20) Chanda, A.; Khetan, S. K.; Banerjee, D.; Ghosh, A.; Collins, T. J. J. Am. Chem. Soc. **2006**, 128, 12058–12059.
- (21) Shen, L. Q.; Beach, E. S.; Xiang, Y.; Tshudy, D. J.; Khanina, N.; Horwitz, C. P.; Bier, M. E.; Collins, T. J. *Environ. Sci. Technol.* **2011**, 45, 7882–7887.
- (22) Parent, A. R.; Nakazono, T.; Lin, S.; Utsunomiya, S.; Sakai, K. Dalton Trans. 2014, 43, 12501–12513.
- (23) Codolà, Z.; Gómez, L.; Kleespies, S. T.; Que, L.; Costas, M.; Lloret-Fillol, J. Nat. Commun. 2015, 6, 5865.
- (24) Yang, B.; Yang, Q.-Q.; Jiang, X.; Chen, B.; Tung, C.-H.; Wu, L.-Z. Chem. Commun. 2017, 53, 9063–9066.
- (25) Fillol, J. L.; Codolà, Z.; Garcia-Bosch, I.; Gómez, L.; Pla, J. J.; Costas, M. *Nat. Chem.* **2011**, *3*, 807–813.
- (26) Wickramasinghe, L. D.; Zhou, R.; Zong, R.; Vo, P.; Gagnon, K. J.; Thummel, R. P. J. Am. Chem. Soc. **2015**, 137, 13260–13263.
- (27) Gamba, I.; Codolà, Z.; Lloret-Fillol, J.; Costas, M. *Coord. Chem. Rev.* **2017**, 334, 2–24.
- (28) Kovaleva, E. G.; Lipscomb, J. D. Nat. Chem. Biol. 2008, 4, 186–193.
- (29) Solomon, E. I.; Goudarzi, S.; Sutherlin, K. D. Biochemistry 2016, 55, 6363-6374.
- (30) Kal, S.; Que, L. JBIC, J. Biol. Inorg. Chem. 2017, 22, 339–365.
 (31) Wang, Y.; Li, J.; Liu, A. JBIC, J. Biol. Inorg. Chem. 2017, 22, 395–405.
- (32) Neidig, M. L.; Solomon, E. I. Chem. Commun. 2005, 5843-5863.
- (33) Nakashima, Y.; Mori, T.; Nakamura, H.; Awakawa, T.;
- Hoshino, S.; Senda, M.; Senda, T.; Abe, I. Nat. Commun. 2018, 9, 104. (34) Wallar, B. J.; Lipscomb, J. D. Biochemistry 2001, 40, 2220-
- 2233. (35) McCusker, K. P.; Klinman, J. P. J. Am. Chem. Soc. 2010, 132, 5114–5120.
- (36) Koehntop, K. D.; Emerson, J. P.; Que, L. JBIC, J. Biol. Inorg. Chem. 2005, 10, 87–93.
- (37) Shook, R. L.; Borovik, A. S. Inorg. Chem. 2010, 49, 3646–3660.
 (38) Cook, S. A.; Hill, E. A.; Borovik, A. S. Biochemistry 2015, 54, 4167–4180.
- (39) Saban, E.; Chen, Y.-H.; Hangasky, J. A.; Taabazuing, C. Y.; Holmes, B. E.; Knapp, M. J. *Biochemistry* **2011**, *50*, 4733–4740.
- (40) Borovik, A. S. Acc. Chem. Res. 2005, 38, 54–61.
- (41) Cook, S. A.; Borovik, A. S. Acc. Chem. Res. 2015, 48, 2407-2414.

(42) Lacy, D. C.; Gupta, R.; Stone, K. L.; Greaves, J.; Ziller, J. W.; Hendrich, M. P.; Borovik, A. S. J. Am. Chem. Soc. **2010**, 132, 12188– 12190.

(43) Vad, M. S.; Lennartson, A.; Nielsen, A.; Harmer, J.; McGrady, J. E.; Frandsen, C.; Mørup, S.; McKenzie, C. J. *Chem. Commun.* **2012**, 48, 10880–10882.

(44) Cheaib, K.; Mubarak, M. Q. E.; Sénéchal-David, K.; Herrero, C.; Guillot, R.; Clémancey, M.; Latour, J.-M.; de Visser, S. P.; Mahy, J.-P.; Banse, F.; Avenier, F. Angew. Chem., Int. Ed. 2019, 58, 854–858. (45) Fukuzumi, S.; Morimoto, Y.; Kotani, H.; Naumov, P.; Lee, Y.-

M.; Nam, W. Nat. Chem. 2010, 2, 756–759.

(46) Fukuzumi, S.; Ohkubo, K.; Lee, Y.-M.; Nam, W. Chem. - Eur. J. 2015, 21, 17548–17559.

(47) Draksharapu, A.; Rasheed, W.; Klein, J. E. M. N.; Que, L. Angew. Chem., Int. Ed. 2017, 56, 9091–9095.

(48) Sastri, C. V.; Lee, J.; Oh, K.; Lee, Y. J.; Lee, J.; Jackson, T. A.; Ray, K.; Hirao, H.; Shin, W.; Halfen, J. A.; Kim, J.; Que, L.; Shaik, S.; Nam, W. Proc. Natl. Acad. Sci. U. S. A. 2007, 104, 19181–19186.

(49) Jackson, T. A.; Rohde, J.-U.; Seo, M. S.; Sastri, C. V.; DeHont,
 R.; Stubna, A.; Ohta, T.; Kitagawa, T.; Münck, E.; Nam, W.; Oue, L. J.

Am. Chem. Soc. 2008, 130, 12394–12407. (50) Engelmann, X.; Malik, D. D.; Corona, T.; Warm, K.; Farquhar,

E. R.; Swart, M.; Nam, W.; Ray, K. Angew. Chem. **2019**, 131, 4052–4056.

(51) Chantarojsiri, T.; Sun, Y.; Long, J. R.; Chang, C. J. Inorg. Chem. 2015, 54, 5879–5887.

(52) Bernal, I.; Jensen, I. M.; Jensen, K. B.; McKenzie, C. J.; Toftlund, H.; Tuchagues, J.-P. J. Chem. Soc., Dalton Trans. 1995, 3667-3675.

(53) Jensen, K. B.; McKenzie, C. J.; Nielsen, L. P.; Zacho Pedersen, J.; Svendsen, H. M. Chem. Commun. 1999, 1313–1314.

(54) Horner, O.; Jeandey, C.; Oddou, J.-L.; Bonville, P.; McKenzie, C.; Latour, J.-M. *Eur. J. Inorg. Chem.* **2002**, 2002, 3278–3283.

(55) Hazell, A.; McKenzie, C. J.; Nielsen, L. P.; Schindler, S.; Weitzer, M. J. Chem. Soc., Dalton Trans. 2002, 310.

(56) Nielsen, A.; Larsen, F. B.; Bond, A. D.; McKenzie, C. J. Angew. Chem., Int. Ed. 2006, 45, 1602–1606.

(57) Wegeberg, C.; Lauritsen, F. R.; Frandsen, C.; Mørup, S.;

Browne, W. R.; McKenzie, C. J. *Chem. - Eur. J.* **2018**, *24*, 5134–5145. (58) Wegeberg, C.; Browne, W. R.; McKenzie, C. J. *Inorg. Chem.* **2019**, *58*, 8983–8994.

(59) de Sousa, D. P.; Miller, C. J.; Chang, Y.; Waite, T. D.; McKenzie, C. J. Inorg. Chem. 2017, 56, 14936-14947.

(60) Wegeberg, C.; Browne, W. R.; McKenzie, C. J. ACS Catal. 2018, 8, 9980-9991.

(61) Martinho, M.; Banse, F.; Bartoli, J.-F.; Mattioli, T. A.; Battioni, P.; Horner, O.; Bourcier, S.; Girerd, J.-J. *Inorg. Chem.* **2005**, *44*, 9592–9596.

(62) Simaan, A. j.; Döpner, S.; Banse, F.; Bourcier, S.; Bouchoux, G.; Boussac, A.; Hildebrandt, P.; Girerd, J.-J. *Eur. J. Inorg. Chem.* **2000**, 2000, 1627–1633.

(63) Chang, H. R.; McCusker, J. K.; Toftlund, H.; Wilson, S. R.; Trautwein, A. X.; Winkler, H.; Hendrickson, D. N. J. Am. Chem. Soc. **1990**, 112, 6814–6827.

(64) Lennartson, A.; McKenzie, C. J. Angew. Chem., Int. Ed. 2012, 51, 6767-6770.

(65) Bordwell, F. G. Acc. Chem. Res. 1988, 21, 456-463.

(66) Klinker, E. J.; Kaizer, J.; Brennessel, W. W.; Woodrum, N. L.; Cramer, C. J.; Que, L. Angew. Chem., Int. Ed. 2005, 44, 3690-3694.

(67) Rohde, J.-U.; Stubna, A.; Bominaar, E. L.; Münck, E.; Nam, W.; Que, L. Inorg. Chem. **2006**, 45, 6435–6445.

(68) Luo, Y.-R. Comprehensive handbook of chemical bond energies; CRC Press: Boca Raton, FL, 2007.

(69) Ley, D.; Gerbig, D.; Schreiner, P. R. Org. Biomol. Chem. 2012, 10, 3781–3790.

(70) McMahon, R. J. Science 2003, 299, 833-834.

(71) Nagel, Z. D.; Klinman, J. P. Nat. Chem. Biol. 2009, 5, 543-550.

(72) Price, J. C.; Barr, E. W.; Glass, T. E.; Krebs, C.; Bollinger, J. M.

J. Am. Chem. Soc. 2003, 125, 13008–13009.

(73) Nesheim, J. C.; Lipscomb, J. D. *Biochemistry* **1996**, *35*, 10240–10247.

(74) Park, J.; Lee, Y.-M.; Nam, W.; Fukuzumi, S. J. Am. Chem. Soc. **2013**, 135, 5052–5061.

(75) Klinker, E. J.; Shaik, S.; Hirao, H.; Que, L. Angew. Chem., Int. Ed. 2009, 48, 1291–1295.

(76) Monte Pérez, I.; Engelmann, X.; Lee, Y.-M.; Yoo, M.; Kumaran, E.; Farquhar, E. R.; Bill, E.; England, J.; Nam, W.; Swart, M.; Ray, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 14384–14388.

(77) Bigelow, J. O.; England, J.; Klein, J. E. M. N.; Farquhar, E. R.; Frisch, J. R.; Martinho, M.; Mandal, D.; Münck, E.; Shaik, S.; Que, L. *Inorg. Chem.* **2017**, *56*, 3287–3301. (78) Klein, J. E. M. N.; Mandal, D.; Ching, W.-M.; Mallick, D.; Que, L.; Shaik, S. J. Am. Chem. Soc. **2017**, 139, 18705–18713.

(79) Rohde, J.-U.; In, J.-H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que, L. *Science* **2003**, 299, 1037–1039.

(80) Bukowski, M. R.; Koehntop, K. D.; Stubna, A.; Bominaar, E. L.; Halfen, J. A.; Münck, E.; Nam, W.; Que, L. *Science* **2005**, *310*, 1000–1002.

(81) Rohde, J.-U.; Torelli, S.; Shan, X.; Lim, M. H.; Klinker, E. J.; Kaizer, J.; Chen, K.; Nam, W.; Que, L. J. Am. Chem. Soc. **2004**, *126*, 16750–16761.

(82) Schröder, D.; Shaik, S.; Schwarz, H. Acc. Chem. Res. 2000, 33, 139–145.

(83) Shaik, S.; Hirao, H.; Kumar, D. Acc. Chem. Res. 2007, 40, 532–542.

(84) Hirao, H.; Que, L.; Nam, W.; Shaik, S. Chem. - Eur. J. 2008, 14, 1740–1756.

(85) Ishizuka, T.; Ohzu, S.; Kotani, H.; Shiota, Y.; Yoshizawa, K.; Kojima, T. *Chem. Sci.* **2014**, *5*, 1429–1436.

(86) Mandal, D.; Mallick, D.; Shaik, S. Acc. Chem. Res. 2018, 51, 107–117.

(87) Janardanan, D.; Wang, Y.; Schyman, P.; Que, L.; Shaik, S. Angew. Chem., Int. Ed. 2010, 49, 3342–3345.