A Pseudotetrahedral Terminal Oxoiron(IV) Complex: Mechanistic Promiscuity in C–H Bond Oxidation Reactions

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Dedicated to Professor Wolfgang Kaim on the occasion of his 70th birthday

Abstract: $S=2$ oxoiron(IV) species act as reactive intermediates in the catalytic cycle of nonheme iron oxygenases. The few available synthetic $S=2$ Fe$IV$=O complexes known to date are often limited to trigonal bipyramidal and very rarely to octahedral geometries. Herein we describe the generation and characterization of an $S=2$ pseudotetrahedral Fe$IV$=O complex 2 supported by the sterically demanding 1,4,7-tri-tert-butyl-1,4,7-triazacyclononane ligand. Complex 2 is a very potent oxidant in hydrogen atom abstraction (HAA) reactions with large non-classical deuterium kinetic isotope effects, suggesting hydrogen tunneling contributions. For sterically encumbered substrates, direct HAA is impeded and an alternative oxidative asynchronous proton-coupled electron transfer mechanism prevails, which is unique within the nonheme oxoiron community. The high reactivity and the similar spectroscopic parameters make 2 one of the best electronic and functional models for a biological oxoiron(IV) intermediate of taurine dioxygenase (TauD-J).

Introduction

High-valent oxoiron(IV) intermediates act as the active oxidants in the catalytic cycles of a variety of mononuclear non-heme iron oxygenases.[1] These high-valent species have been characterized by rapid freeze quench methods in few cases[2] and were unambiguously shown by UV/Vis, Mössbauer, and X-ray absorption spectroscopic methods to contain high-spin ($S=2$) iron(IV) centres. However, the available experimental data could not reveal other important structural features, such as the number, identity, and disposition of ligands in the Fe$IV$ coordination sphere. Density functional theoretical (DFT) studies[3] on the taurine:oxoiron(IV) (TauD) system have shown that the spectroscopic properties of the hydrogen-abstracting oxoiron(IV) key intermediate (TauD-J) are consistent with both suggested structural models (Scheme 1), that is, with trigonal bipyramidal (TBP) as well as distorted octahedral ($Oh$) coordinations. Significant synthetic efforts in the past decade have led to the generation of oxoiron(IV) cores in both TBP and $Oh$ geometries (Scheme 1). Although the majority of the synthetic complexes exhibit $S=1$ ground states in the $Oh$ geometry,[4] DFT-studies predicted stabilization of the more reactive[5] $S=2$ oxoiron(IV) units[6] either by enforcing a TBP geometry at the iron(IV) centre[5a,6] or by weakening the equatorial donation in $Oh$ geometry.[5c]

Results and Discussion

In the context of the existing ambiguity related to the coordination number of iron in biological oxoiron(IV) intermediates[1] and the limitation of the synthetic $S=2$ oxoiron(IV) cores to mainly TBP and in rare cases to $Oh$ geometries, we have now sought to identify a tripodal ligand that allows for trapping an Fe$IV$=O core in a geometry different from the known TBP or $Oh$ geometries. Herein we report the synthesis and characterization of the $S=2$ pseudotetrahedral [Fe$IV$(O)(Bu$_3$tacn)]$^{2-}$ (2, Bu$_3$tacn[6] = 1,4,7-tri-tert-butyl-1,4,7-triazacyclononane) complex, which exhibits spectroscopic and reactivity properties distinct from the oxoiron(IV) cores in TBP or $Oh$ geometries. In particular, in direct contrast to the vast majority of previous oxoiron(IV) cores,[5a,6,5c] where the reactivity with substrates containing C–H bonds is controlled by the C–H bond dissociation

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energies (BDE(C=C)), complex 2 demonstrates a mechanistic promiscuity in its C–H oxidation reactions. Sterically less hindered C–H bonds are oxidized via a conventional direct hydrogen atom abstraction (HAA; Scheme 2) mechanism that is characterized by large deuterium kinetic isotope effects (KIEs), which are greater than the semi-classical limit of 7, implying a significant contribution of hydrogen tunnelling.[7]

In contrast, for sterically encumbered substrates, where the direct access to the Fe(IV)=O core is blocked, the C–H oxidation reaction proceeds with a significantly lower KIE and presumably involves a proton-coupled electron transfer (PCET) mechanism along a spectrum of “asynchronicity”[8] in which the transition state for the net H-atom transfer contains more electron transfer character (Scheme 2; Oxidative asynchronous PCET).

Combination of equimolar amounts of the previously reported \( \text{Bu}_4\text{tacn} \) ligand[6–9] and \( \text{Fe}^{II}(\text{OTf})_2(\text{CH}_3\text{CN})_2 \) in \( \text{CH}_2\text{Cl}_2 \) afforded \( \text{Fe}^{II}(\text{tBu}_3\text{tacn})(\text{OTf}) \)(OTf) (Figure S1; Tables S1,S2) exhibited a distorted tetrahedral geometry (N-Fe-N angles of 86.5–88.3°) with 2-\( \text{H} \) oxidation reactions. Sterically less hindered C–H oxidation reactions would result in the formation of a 

**Scheme 1.** Left: Proposed structures of \( S = 2 \) TauD-J based on DFT studies;[2] middle: selected examples of \( S = 1 \) and \( S = 2 \) oxoiron(IV) cores in \( TBP \) and \( O \) geometries; right: A pseudotetrahedral \( S = 2 \) oxoiron(IV) complex 2 reported in this work; in the inset is shown the DFT calculated structure of 2 in the \( S = 2 \) state.

Iodosobenzene (PhiIO)[12] yielded a transient species 2 (Figure 1A; half-life at \(-70^\circ \text{C} = 20 \text{ min} \)) with electronic absorption features centered at \( \lambda_{\text{max}} = 356 \text{ nm} \) (\( \epsilon = 7500 \text{ M}^{-1}\text{cm}^{-1} \)) and \( 780 \text{ nm} \) (\( \epsilon = 150 \text{ M}^{-1}\text{cm}^{-1} \)). Notably, the presence of a well-defined strong absorption band in the near-UV region is typical of \( S = 2 \) oxoiron(IV) cores (Table S4);[3a–d] in 2 this band at \( \lambda_{\text{max}} = 356 \text{ nm} \) is slightly red-shifted (Table 1) relative to that of TauD-J (\( \lambda_{\text{max}} = 318 \text{ nm} \)).[14] The \( S = 2 \) spin state of 2 was additionally corroborated by the Evans[13] NMR method (Figure S3) at \(-90^\circ \text{C} \) which yielded the magnetic moment \( \mu_{\text{eff}} = 4.50 \mu_\text{B} \) (theoretical value for \( S = 2 \): 4.90 \( \mu_\text{B} \)). An electron spray ionization mass spectrum (Figure S4) of 2 exhibited...
Resonance Raman spectroscopy revealed a v(Fe=O) stretching mode at 802 cm$^{-1}$ in 2 (Figure 1A, inset) that shifted to 767 cm$^{-1}$ upon $^{18}$O-labelling. The observed v(Fe=O) mode has one of the lowest energies reported to date for oxoiron(IV) cores. This may be attributed to the high spin mode has one of the lowest energies reported to date for the pre-edge region of oxoiron(IV) complexes. This may be rationalized in terms of a splitting of the $a_2$ orbitals by spin polarization in the $S=2$ oxoiron(IV) core.\cite{5a,5b}

The oxidative reactivity of 2 (Figures S9–S18; Table S6) has been investigated with several substrates in oxygen atom transfer (OAT) and HAA reactions and the second order rate constants derived from these studies in CH$_3$CN are compared with three of the most reactive high-valent Fe-oxo intermediates reported to date (namely the [(TQA)FeIV(O)(CH$_3$CN)]$^{2+}$ (TQA = tris(2-quinolylmethyl)amine),[\textsuperscript{14,15}] [(Me$_3$NTB)FeIV(O)]$^{2+}$ (Me$_3$NTB = tris(N-methyl-benzimidazol-2-yl)methyl)amine)[\textsuperscript{16}] and [(TMCO)FeIV(O)(CH$_3$CN)]$^{2+}$ (TMCO = 4,8,12-trimethyl-1-oxa-4,8,12-triaza-cyclooctadecane)[\textsuperscript{17}] complexes (Table 2). In reactions with ethylenebenzene, 1,4-cyclohexadiene (1,4-CHD), and toluene, 2 is a stronger oxidant than [(TMCO)FeIV(O)(CH$_3$CN)]$^{2+}$, but comparable to [(TQA)FeIV(O)(CH$_3$CN)]$^{2+}$ and [(Me$_3$NTB)FeIV(O)]$^{2+}$. Interestingly, the reactivity trend is reversed in reactions with 9,10-dihyrdroanthracene (DHA), where 2 exhibits the least reactivity. Furthermore, when the logarithms of the statistically corrected second order rate constants ($k_2$) were plotted vs. the BDE values of the substrates (Figure 2A, Figure S2A, Table 2), the linear correlation typically observed for oxoiron(IV) cores is found to be not valid for 2. While the respective log($k_2$) values associated with 2 for the oxidation of 1,4-CHD, 1,3-cyclohexadiene (1,3-CHD), ethylenebenzene, cyclohexene and toluene fall on a line (Figure 2A, black points), xanthene, DHA, indene and fluorene substrates (Figure 2A, inset) deviate from this pattern and exhibit significantly lower rates than predicted by the linear relationship. Particularly interesting is the large rate difference of two orders of magnitude for DHA and 1,4-CHD, which are known to have small difference in BDE$^{\text{C-H}}$ values.\cite{30} Furthermore, large deuterium KIEs of 7 (Figure S9), 12 (Figure S10), and 53 (Figure 2C, Figure S11) were
recorded for toluene, 1,4-CHD, and ethylbenzene reactions, respectively, suggesting a HAA mechanism with significant contribution of hydrogen-tunneling, as is frequently proposed in C–H bond activation reactions of FeIV=O species.[7]

In contrast, significantly reduced KIEs of 1.2 (Figure 2D, Figure S12) and 2.1 (Figure S13) were determined for DHA and xanthene, respectively, thereby pointing to a change of mechanism. Further mechanistic insights were obtained by plotting the rate constants against the pKₐ and the ionization energies (IE) of the substrates. The log(kᵢ) vs. IE plot (Figure 2B, Figure S20B) revealed that for reactions of 2 with xanthene, DHA, indene and fluorene the rate decreased linearly with increasing IE, whereas the rates for 1,4-CHD, 1,3-CHD, ethylbenzene, cyclohexene and toluene remained constant. Furthermore, no linear trend was observed in xanthene, DHA, indene and fluorene the rate decreased linearly. Furthermore, no linear trend was observed in xanthene, DHA, indene and fluorene the rate decreased linearly.

**Conclusion**

Taken together the results presented herein unequivocally validate the formation of a terminal oxoiron(IV) complex 2 in a pseudotetrahedral geometry. The computational and experimental analyses are consistent with the presence of an S = 2 FeIV=O core in 2. Complex 2 represents the only example of a high-spin complex with metal-ligand multiple bond character in a pseudotetrahedral geometry; notably, a pseudotetrahedral oxoiron(IV) complex has been very recently demonstrated to possess an S = 0 state in the gas-phase.[19] The absorption spectrum, Mössbauer ΔE₀– Fe K-edge energy, and the (Fe=O) mode of 2 (Table 1) bear very close resemblance to the corresponding spectroscopic properties of TauD-J. 2 also exhibits the distinct high-reactivity features known from the strongly oxidizing iron-oxo cores in biology and accordingly possesses one of the most reactive oxoiron(IV) cores that have been synthesized to date. Furthermore, a large KIE of 53 has been determined for the reaction of 2 with ethylbenzene, which compares well with the KIE of 57[3] determined for the oxidation of taurine by TauD-J. The uniqueness of 2 within the non-heme oxoiron family is, however, emphasized in its ability to oxidize sterically hindered C–H bonds by an IE-driven asynchronous PCET mechanism. Although limited examples of C–H oxidation by a basicity controlled PCET mechanism (Scheme 2) are known,[8,20] evidence of oxidative PCET mechanism has stayed elusive prior to this study. In conclusion, the high reactivity and the similar spectroscopic parameters of 2 and TauD-J make 2 one of the best structural, electronic and functional models for TauD-J.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords**: bioinorganic chemistry · enzyme models · high-valent iron · hydrogen atom abstraction · electron transfer

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