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A Highly Reactive Oxoiron(IV) Complex Supported by a Bioinspired N₃O Macrocylic Ligand

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Abstract

The sluggish oxidants, $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) and $[\text{Fe}^{\text{IV}}(\text{O})(d_{12}\text{-TMCN})(\text{OTf})]^+$ (**3d**; $d_{12}\text{-TMCN}$ = 1,4,7,11-tetra-*d*₃-methyl-1,4,7,11-tetraazacyclotetradecane), are transformed into a highly reactive oxidant, $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCO})(\text{OTf})]^+$ (**1**; TMCO = 4,8,12-trimethyl-1-oxa-4,8,12-triazacyclotetradecane), upon replacement of a -NMe donor in the TMC and TMCN ligands by an O-atom. A rate enhancement of 5 – 6 orders of magnitude in both H-atom and O-atom transfer reactions is observed upon oxygen incorporation into the macrocyclic ligand and can be explained based upon the higher electrophilicity of the iron center and the higher availability of the more reactive *S* = 2 state in **1**. This rationalizes nature's preference for using O-rich ligand environments for the hydroxylation of strong C-H bonds in enzymatic reactions.

Graphical Abstract

The drastically enhanced reactivity of an oxoiron(IV) center in an N₃O environment relative to an N₄ environment explains nature's preference for using oxygen rich ligand environment for the hydroxylation of strong C-H bonds.

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Supporting information for this article is given via a link at the end of the document.

Keywords

Oxoiron(IV) Complex; Oxygen-Based Ligands; Spin State Effect; Hydrogen Atom Transfer; Oxygen Atom Transfer

High-valent oxoiron(IV) ($\text{Fe}^{\text{IV}}=\text{O}$) species have been identified as key reactive intermediates in the activation of dioxygen and the oxygenation of organic substrates by mononuclear nonheme iron enzymes.^[1] The $\text{Fe}^{\text{IV}}=\text{O}$ moiety is always found in the quintet ($S = 2$) spin state, which is predicted by DFT calculations^[2] to be more reactive in H-atom transfer (HAT) than the corresponding triplet ($S = 1$) spin state. The biological $\text{Fe}^{\text{IV}}=\text{O}$ oxidants all contain at least two weak-field O-based ligands (either carboxylate or water) *cis* to the oxo donor (Scheme 1A),^[3] which can play a significant role in the stabilization of the $S = 2$ state by modulating the energy gap between the Fe $d(xy)$ and $d(x^2-y^2)$ orbitals. A related species is also proposed to be the oxidant formed in the reactions of N_2O with coordinately unsaturated iron(II) centers in carboxylate-based metal–organic frameworks capable of catalyzing ethane hydroxylation.^[4] While no direct spectroscopic evidence is currently available, DFT studies suggest that this intermediate is an $S = 2$ $\text{Fe}^{\text{IV}}=\text{O}$ species possessing an O-rich ligand environment.

The reactivity of $\text{Fe}^{\text{IV}}=\text{O}$ complexes with weak-field O-rich ligand environments are, therefore, of particular interest. Successful synthesis and characterization of such compounds has been limited by their high reactivity and instability under ambient conditions. For example, the short half-life of 20 s at 25 °C of the $S = 2$ $[\text{Fe}^{\text{IV}}(\text{O})(\text{H}_2\text{O})_5]^{2+}$ complex^[5] has inhibited a detailed investigation of its spectroscopic and reactivity properties. On the other hand, employment of strong-field pyridine and tertiary amine donors^[1a–b,6] or carbene donors^[7] has led to the isolation and characterization of several well-characterized $S = 1$ $\text{Fe}^{\text{IV}}=\text{O}$ model complexes with high stability and low reactivity. Efforts to stabilize the more reactive $S = 2$ state by replacing one or more N-donors with weak carboxylate ligands^[8] have previously resulted in only a small enhancement (5 – 10 folds) in the HAT abilities of the complexes. In fact, no $\text{Fe}^{\text{IV}}=\text{O}$ complexes supported by O-based ligands that are able to oxidize substrates containing C–H bonds with a bond dissociation energy (BDE) $> 80 \text{ kcal mol}^{-1}$ are presently known. This is surprising,

considering nature's preference for employing $\text{Fe}^{\text{IV}}=\text{O}$ complexes with O-rich ligand environments to oxidize strong C-H bonds.

As part of our continuing efforts to uncover the structure-reactivity relationship of non-heme oxometal complexes, we report herein the synthesis and characterization of an $S = 1$ $\text{Fe}^{\text{IV}}=\text{O}$ complex $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCO})(\text{OTf})]^+$ (**1**) (Scheme 1; TMCO = 4,8,12-trimethyl-1-oxa-4,8,12-triazacyclotetradecane),^[9] bearing a weak-field N_3O macrocyclic ligand in place of the popular N_4 -donor TMC-based ligands. **1** exhibits spectroscopic properties distinct from $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ (TMC=1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)^[10] and $[\text{Fe}^{\text{IV}}(\text{O})(d_{12}\text{-TMCN})(\text{OTf})]^+$ (**3d**; $d_{12}\text{-TMCN}$ =1,4,7,11-tetra-*d*₃-methyl-1,4,7,11-tetraazacyclotetradecane), and, remarkably, 5 – 6 orders of magnitude higher reactivity in HAT and O-atom transfer (OAT) reactions.

Combination of the tetradentate TMCO ligand (Figure S1) with $\text{Fe}(\text{OTf})_2(\text{CH}_3\text{CN})_2$ yielded the expected iron(II) complex $[\text{Fe}^{\text{II}}(\text{TMCO})(\text{CH}_3\text{CN})(\text{OTf})](\text{OTf})$ (**2**). The X-ray structure of **2** (Figure 1 left and Table S1) displays a 6-coordinate geometry with axially bound triflate and CH_3CN ligands. Notably, the macrocyclic ring exhibits a configuration, where all the methyl-groups point *cis* to CH_3CN , with iron-ligand bond lengths (Table S2) typical of a high-spin iron(II) ion. Consistent with this spin-state assignment, the zero-field Mössbauer spectrum of **2** (Figure S2) revealed a single doublet with an isomer-shift (δ) of 1.17 mm/s and a large quadrupole splitting ($E_Q = 3.32$ mm/s). In addition, the ^1H , ^2D and ^{19}F NMR spectra of **2** in CH_2Cl_2 display paramagnetically shifted peaks (Figure S3), indicative of coordination of both triflate anions and retention of the pseudo- C_s symmetric solid-state structure in solution.

The reaction of **2** with 1.5 equiv of 2-(*tert*-butylsulfonyl)iodosylbenzene ($t\text{BuSO}_2\text{C}_6\text{H}_4\text{IO}$)^[11] in anhydrous CH_2Cl_2 at -90°C led to the immediate formation of a pale green intermediate **1** ($t_{1/2} = 1.5$ h; -50°C) with absorption maxima λ_{max} (ϵ_{max}) centered at 390 nm ($>3000\text{ M}^{-1}\text{ cm}^{-1}$), 585 nm ($200\text{ M}^{-1}\text{ cm}^{-1}$), 848 nm ($150\text{ M}^{-1}\text{ cm}^{-1}$) and 1026 nm ($150\text{ M}^{-1}\text{ cm}^{-1}$) (Figure 1, right). The electrospray ionization mass spectrum (ESI-MS) of **1** (Figure S4) exhibited a signal at $m/z = 464.1$, which shifted by two-mass units when $t\text{BuSO}_2\text{C}_6\text{H}_4\text{I}^{18}\text{O}$ was used as an oxidant, possessing a mass and isotope distribution pattern consistent with a $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCO})(\text{OTf})]^+$ formulation. The presence of the $\text{Fe}=\text{O}$ unit in **1** was confirmed by EXAFS analysis that yields a best-fit plot (Figure S5 and Table S3) with an O/N scatterer at $1.64\text{ \AA}$ (assigned to the $\text{Fe}=\text{O}$ unit) and a further shell of 5 O/N scatterers at $2.10\text{ \AA}$ (corresponding to the N/O donors of TMCO and OTf^- ligands). The Fe K-edge X-ray absorption spectrum of **1** (Figure 2A) reveals an edge energy of 7124.3 eV (versus 7121.5 eV for **2**) and a broad pre-edge peak assigned to $1s \rightarrow 3d$ transitions at 7114.2 eV with an area of 45 units (Table S4). Furthermore, the ^1H , ^2D and ^{19}F NMR spectra of **1** (Figure S6) indicate that a single C_s -symmetric iron(IV) species is present, in which one of the OTf^- anions is coordinated to the metal centre. The spectra are consistent with retention of the geometry of the starting complex **2** and led us to formulate **1** as $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCO})(\text{OTf})]^+$.

The zero field Mössbauer spectrum of **1** recorded at 4.2 K exhibits a doublet representing ca. 90% of the iron with $E_Q = 1.58\text{ mm s}^{-1}$ and $\delta = 0.13\text{ mm s}^{-1}$ (Figure 2B); the remaining

10% of the signal corresponds to unreacted **2**. Applied magnetic fields, B , elicit magnetic hyperfine interactions (Figure S7) with parameters typical of $S = 1$ $\text{Fe}^{\text{IV}}=\text{O}$ complexes. Within resolution, the zero-field splitting (ZFS) tensor, described by the parameters D and E , was found to be axial ($D = 35 (\pm 3) \text{ cm}^{-1}$; $E/D = 0.0(+0.05)$). Notably, the D value of **1** is significantly higher than that reported for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ and all other oxoiron(IV) complexes (Table 1 and Table S4); this may point to a more accessible $S = 2$ excited state in **1**.^[1]

The oxidative reactivity of **1** was examined in the oxidation of hydrocarbons with C–H BDEs of 77 – 99.3 kcal mol⁻¹ (Table S5 and Figure S8). The experimentally determined (see SI for details) second-order rate constants, k_2 , were then adjusted for reaction stoichiometry to yield k_2' based on the number of equivalent target C–H bonds of substrates; the k_2' values were correlated with the BDEs of the substrates (Figure 3 left and Table S4). This observation is consistent with the rate-determining step of the reaction being C–H bond cleavage, as is expected in HAT reactions. Furthermore, a deuterium kinetic isotope effect (KIE) of 24.8 was obtained when ethylbenzene- d_{10} was used as a substrate (Figure 3 right). Such a large KIE value implies a tunneling mechanism in H-atom abstraction, as is frequently proposed in C–H bond oxidation reactions of $\text{Fe}^{\text{IV}}=\text{O}$ species.^[1,6] Product analysis of the reaction mixture for cyclohexane reaction revealed the formation of cyclohexanol (35% yield), cyclohexanone (5%) and high-spin iron(III) (>90% yield; Figure S9) products. Thus, **1** performs HAT in an oxygen non-rebound mechanism,^[12] as proposed earlier for other nonheme $\text{Fe}^{\text{IV}}=\text{O}$ complexes.

Comparison of the HAT reactivities of **1** and other oxoiron(IV) complexes (Tables 1 and S4) shows that the rate of cyclohexane oxidation by **1** at -40°C ($0.01 \text{ M}^{-1} \text{ s}^{-1}$) is only an order of magnitude lower than that of the two most reactive complexes reported to date; namely, the $S = 2$ $[\text{Fe}^{\text{IV}}(\text{O})(\text{TQA})(\text{CH}_3\text{CN})]^{2+}$ ($0.37 \text{ M}^{-1} \text{ s}^{-1}$)^[13] and $S = 1$ $[\text{Fe}^{\text{IV}}(\text{O})(\text{Me}_3\text{NTB})(\text{CH}_3\text{CN})]^{2+}$ ($0.25 \text{ M}^{-1} \text{ s}^{-1}$)^[14] complexes. In particular, the closely related $S = 1$ $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ complex does not react at all with cyclohexane even at 25°C . Furthermore, comparison of the OAT abilities of **1** (Table S4, Figure S10) and $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ towards thioanisole (PhSMe) shows that the former reacts five-orders of magnitude faster than the latter at -40°C .^[15]

The TMCN ligand differs from TMC not only in being a N_3O rather than a N_4 macrocycle, but also in having the two propylene (and also the two ethylene) spacers *adjacent*, rather than *alternating* with respect to one another (Scheme 1). A comparison of the reactivity of **1** with that of the $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$ (**3**; TMCN = 1,4,7,11-tetramethyl-1,4,7,11-tetraazacyclotetradecane) is, therefore, warranted for a proper analysis of the effect of N- vs O-donors in an otherwise identical ligand environment.

From the ^1H and ^2D NMR spectra of $[\text{Fe}^{\text{II}}(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$, it was discovered that the chemically equivalent methyl groups (and ethylene and propylene units) of TMCN are magnetically inequivalent (Figure S11). This indicates that these two methyl substituents point in different directions and results in the complex being C_1 symmetric. The zero-field Mössbauer spectrum of $[\text{Fe}^{\text{II}}(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$ (Figure S12) revealed a single doublet with $\delta = 1.20 \text{ mm s}^{-1}$ and $E_Q = 2.90 \text{ mm s}^{-1}$ typical of a high-spin iron(II) ion.

The reaction of $[\text{Fe}^{\text{II}}(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$ with $t\text{BuSO}_2\text{C}_6\text{H}_4\text{IO}$ in CH_3CN at -40°C revealed the formation of a transient intermediate **3**, whose fast decay prevented its isolation. The instability of **3** can be presumably attributed to its self-decay via intramolecular attack of a ligand methyl C–H bond (*cis* to the oxo group) by the $\text{Fe}=\text{O}$ unit (see DFT calculation below). With an assumption that a large KIE would be involved for such a self-decay mechanism, the perdeuterated d_{12} -TMCN ligand was synthesized in an effort to stabilize the corresponding complex $[\text{Fe}^{\text{IV}}(\text{O})(d_{12}\text{-TMCN})(\text{OTf})]^+$ (**3d**). Indeed, the reaction of $[\text{Fe}^{\text{II}}(d_{12}\text{-TMCN})(\text{CH}_3\text{CN})]^{2+}$ with $\text{C}_6\text{H}_4\text{IO}$ in CH_3CN at 0°C led to a clean conversion to **3d** ($t_{1/2} = \sim 8$ min at 0°C), as confirmed by NMR (Figure S13), UV-Vis (Figure S14; $\lambda_{\text{max}} = 820$ nm; $\epsilon = 300 \text{ M}^{-1} \text{ cm}^{-1}$) and ESI-MS (Figure S15). The oxidative reactivity of **3d**, when tested in intermolecular HAT and OAT reactions, shows it to be a sluggish oxidant similar to $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ (Tables 1 and S4).

The electrochemistry of **1**, $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$, and **3d** was then investigated as a means to gain insight into the observed reactivity and provide a more quantitative basis for the influence of the TMCO, TMC and d_{12} -TMCN ligands, respectively, on the $\text{Fe}^{\text{IV}}=\text{O}$ center (Figure S16). Cyclic voltammetry (CV) of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ has previously revealed an $\text{Fe}^{\text{IV/III}}$ potential of $+0.39$ V vs. SCE in CH_3CN .^[16] A comparable $\text{Fe}^{\text{IV/III}}$ potential of $+0.37$ V has been determined for **3d** in CH_3CN . In contrast, a large positive shift of the $\text{Fe}^{\text{IV/III}}$ potential to $+0.90$ V was observed for **1** in trifluoroethanol, which justifies the much higher HAT and OAT capabilities of **1** relative to $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ and **3d**.

DFT calculations (Figure S17; Table S6) for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCO})(\text{CH}_3\text{CN})]^{2+}$ (**1-CH₃CN**) and $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ provided further insight into their differing reactivity. For both complexes, a ground-state (GS) with a triplet ($S = 1$) spin quantum number and a low-lying quintet ($S = 2$) spin state were predicted. In $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$, the $S = 2$ state is 5 kcal mol^{-1} higher in energy than the $S = 1$ GS, but for **1-CH₃CN**, this spin-state splitting is reduced to only 1 kcal mol^{-1} . Free energies, which has been shown^[17] to better rationalize the different reactivities of the oxoiron(IV) complexes than electronic energies, have also been determined for **1-CH₃CN** and $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ in the temperature range $10 - 370$ K (Tables S7, S8). While the $S = 1$ state is preferred for $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ at all temperatures, the $S = 2$ state is the predicted GS at the experimental temperature of 223 K for reactivity studies. The reaction profile for HAT from cyclohexane by **1-CH₃CN** and $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ in the $S = 1$ and $S = 2$ spin states is displayed in Figure S18. The obtained barriers (Table S6) are consistent with the experimental findings, with a large reduction of the barrier upon going from $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$ to **1-CH₃CN** in both the $S = 1$ and $S = 2$ spin states; this together with the higher accessibility of the more reactive $S = 2$ spin state for **1** may rationalize its enhanced oxidative reactivity relative to $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMC})(\text{CH}_3\text{CN})]^{2+}$.

Calculations were also performed for the complex $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$, for which one of the *N*-methyl groups was predicted to be *syn* to the $\text{Fe}=\text{O}$ unit (consistent with experiment) in its most stable configuration (Figure S17C). The barrier for self-decay of $[\text{Fe}^{\text{IV}}(\text{O})(\text{TMCN})(\text{CH}_3\text{CN})]^{2+}$ by an intramolecular HAT from the *syn* methyl group is $13 -$

14 kcal mol⁻¹ lower than the oxidation barrier for cyclohexane (Figure S18), explaining the inherent instability of [Fe^{IV}(O)(TMCN)(CH₃CN)]²⁺.

In summary, we have generated a highly reactive oxoiron(IV) complex **1** by weakening the ligand field about the Fe^{IV}=O unit via introduction of an O-atom into the N4 macrocycle of the TMC or TMCN ligands. The Fe^{IV}=O center goes from being a sluggish oxidant (within an N4 macrocycle) to being an extremely reactive species (in an N₃O environment) that can hydroxylate alkanes with C-H bonds as strong as 99.3 kcal mol⁻¹. Furthermore, a dramatic enhancement of the rate of OAT to PhSMe by five-orders of magnitude was observed upon swapping to the N₃O coordination sphere. Complex **1** represents the only example of a highly reactive Fe^{IV}=O complex supported by an O-containing ligand system, and explains nature's preference for using O-rich ligand environment for the hydroxylation of strong C-H bonds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Left: X-ray crystal structure of **2**. Right: UV-Absorption spectra of **1** (black) and **2** (gray) in CH_2Cl_2 at -90°C . The inset shows the expansion of the 500 – 900 nm region.

Figure 2.

A) Normalized Fe K-edge X-ray absorption spectra of **1** (solid line) and **2** (dashed line) in a CH₃CH₂CN/CH₂Cl₂ solvent mixture (10% CH₂Cl₂ by volume); B) The zero field Mössbauer spectrum of **1** recorded at 4.2 K. The solid line is the simulation of the experimental spectrum (black dots) representing >95% of the absorption. The major component (90%; black shaded area) corresponds to **1**; the minor component (10 %; gray shaded area) corresponds to unreacted **2**.

Figure 3.

Left: Plot of $\log k_2'$ vs C-H BDE of substrates for **1**. **Right:** Plot of the pseudo-first-order rate constants, k_{obs} (s^{-1}), against substrate concentrations to determine second-order rate constants, k_2 , and C-H kinetic isotope effect (KIE) value for the reaction of **1** with ethylbenzene.

Scheme 1.

Structures of biological (A) and bioinspired (B) oxoiron(IV) complexes.

Table 1

A comparison of the redox potentials, zero-field splitting and second-order rate constants (k_2) with C₆H₁₂ and PhSMe for **1**, **3d** and [Fe^{IV}(O)(TMC)(CH₃CN)]²⁺

Complex	D [cm ⁻¹]	$E(\text{Fe}^{\text{IV/III}})$ vs SCE	$k_2^{[a]}(\text{C}_6\text{H}_{12})$ [M ⁻¹ s ⁻¹]	$k_2^{[a]}(\text{PhSMe})$ [M ⁻¹ s ⁻¹]
1	35±3	0.90	1×10^{-2}	2.5×10^2
3d	-	0.37	no reaction	4.0×10^{-3}
[Fe ^{IV} (O)(TMC)(CH ₃ CN)] ²⁺ [1a]	26.95 ± 0.15	0.39	no reaction	1.3×10^{-3}

[a] @ -40 °C