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Kinetic Studies on the Oxoiron(IV) Complex with Tetradentate Aminopyridine Ligand PDP*: Restoration of Catalytic Activity by Reduction with H₂O₂

Marc C. Piquette,*[©] Sergiy V. Kryatov,* and Elena V. Rybak-Akimova[†]

Department of Chemistry, Tufts University, 62 Talbot Avenue, Medford, Massachusetts 02155, United States

Supporting Information

ABSTRACT: Oxoiron(IV) is a common catalytic byproduct observed in the oxidation of alkenes by the combination of H_2O_2 and nonheme iron catalysts including complex 1, Fe^{II}PDP* (where $PDP^* = bis(3,5-dimethyl-4-methoxypyridyl-2-methyl)-(R,R)-2,2'-bi$ pyrrolidine). The oxoiron(IV) species have been proposed to arise by O-O homolysis of the peroxyiron(III) or acylperoxyiron(III) intermediates formed during the presumed Fe^{III}-Fe^V catalytic cycle and have generally been regarded as off-pathway. We generated complex 1^{IV} = O ($\lambda_{max} = 730$ nm, $\varepsilon = 350$ M⁻¹ cm⁻¹) directly from 1 and an oxygen atom donor IBX^{i-Pr} (isopropyl 2-iodoxybenzoate) in acetonitrile in the temperature range from -35 to +25 °C under stopped-flow conditions. Species $1^{IV} = 0$ is metastable (half-life of 2.0



min at +25 °C), and its decay is accelerated in the presence of organic substrates such as thioanisole, alkenes, benzene, and cyclohexane. The reaction with cyclohexane- d_{12} is significantly slower (KIE = 4.9 ± 0.4), suggesting that a hydrogen atom transfer to $1^{\text{IV}}=0$ is the rate limiting step. With benzene- d_{s} , no significant isotope effect is observed (KIE = 1.0 ± 0.2), but UV-vis spectra show the concomitant formation of an intense 580 nm band likely due to the Fe(III)-phenolate chromophore, suggesting an electrophilic attack of $1^{IV}=0$ on the aromatic system of benzene. Treatment of $1^{IV}=0$ with H_2O_2 resulted in rapid decay of its 730 nm visible band ($k = 102.6 \pm 4.6 \text{ M}^{-1} \text{ s}^{-1}$ at $-20 \degree \text{C}$), most likely occurring by a hydrogen atom transfer from H_2O_2 . In the presence of excess H_2O_2 , the oxoiron(IV) is transformed into peroxyiron(III), as seen from the formation of a characteristic 550 nm visible band and geff = 2.22, 2.16, and 1.96 electron paramagnetic resonance (EPR) spectroscopy signals. Reductively formed 1^{III}-OOH was able to re-enter the catalytic cycle of alkene epoxidation by H₂O₂, albeit with lower yields versus those of oxidatively formed (i.e., $1 + H_2O_2$) peroxyiron(III) owing to a loss of ca. 40% active iron. As such, the oxoiron(IV) species can be reintroduced to the catalytic cycle with extra H_2O_{22} acting as an iron reservoir. Alternatively, peroxycarboxylic acids, which have a stronger O-H bond dissociation energy, do not reduce 1^{IV}=O, ensuring that more oxidant is productively employed in substrate oxidation. While this reaction with H_2O_2 may occur for other nonheme oxoiron(IV) complexes, the only previously reported examples are $3^{IV}=0$ and $4^{IV}=0$, which are reduced by hydrogen peroxide 130- and 2900-fold more slowy, respectively (as in Angew. Chemie - Int. Ed. 2012, 51 (22), 5376-5380, DOI: 10.1002/ anie.201200901).

INTRODUCTION

The selective oxidation of unactivated C-H bonds and prochiral alkenes is of the utmost importance for organic synthesis, potentially allowing for the transformation of cheap hydrocarbon feedstocks into commodity chemicals.^{1,2} In nature, iron-containing enzymes, including TauD, TyrH, and cytochrome P450, afford selective C-H and C=C bond oxidation and typically exhibit a formally oxoiron(IV) or oxoiron(V) active oxidant.³⁻⁶ Researchers have developed small-molecule catalysts based on the active sites of these metalloenzymes for the two-fold purpose of harnessing nature's ability to perform challenging oxidations under green conditions and to further understand the mechanisms of these enzymes.^{7,}

Iron complexes with tetradentate aminopyridine ligands like 1 and 2 (Figure 1) are among the best known catalysts to

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activate H_2O_2 (with or without a carboxylic acid cocatalyst) for aromatic hydroxylations,^{9,10} regiospecific aliphatic hydroxylations,^{11–13} and alkene epoxidations.^{14–16} Scheme 1 shows the current mechanistic consensus for the reaction of an iron(II) starting catalytic material with H2O2, where it forms peroxyiron(III) or acylperoxyiron(III) intermediates (in the presence of a carboxylic acid), which are sluggish oxidants by themselves. Heterolytic O–O cleavage of 1^{III} –OOH or 1^{III} – **OOAc** affords the putative active species, formally oxoiron(V), which rapidly oxidizes organic substrates, returning to an iron(III) state.¹⁷⁻²⁰ Oxoiron(IV) species were also observed under catalytically relevant conditions (presumably due to the

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Figure 1. Structure of complex 1 used in this work and complexes 2-4 referenced for comparison. Sol refers to a weakly coordinating solvent molecule, usually CH₃CN.

Scheme 1. Proposed Mechanism of Catalysis for Complexes 1 and 2^{a}



"X = solvent or OAc, depending on the pathway. Following the formation of an iron(III)-peroxo intermediate, it can proceed via a heterolytic pathway forming active $1^{V}=0$ or a homolytic pathway forming $1^{IV}=0$, previously believed to be a catalytic dead end.¹⁹ In this work, we demonstrate additional pathways shown in red, in which $1^{IV}=0$ directly oxidizes organic substrates (slow reactions) or is reduced (quickly) by H_2O_2 , thus returning to the main $Fe^{III}-Fe^V$ catalytic cycle.

O–O bond homolysis, Scheme 1) but generally are considered off-pathway iron sinks. 21,22

Complex 2, $[Fe(BPMEN)(CH_3CN)_2]^{2+}$, was one of the first reported nonheme iron catalysts for the hydroxylation of alkanes and the epoxidation and dihydroxylation of alkenes with H_2O_2 ,^{23–26} and it was later found to also effect aromatic hydroxylation reactions.^{10,27} However, complex 2 is inconvenient for kinetic mechanistic studies, since all of its catalytic intermediates are very short-lived (such as 2^{III}–OOH and 2^{IV}=O) or have never been reliably observed (such as putative 2^V=O).^{10,17,20,28} Therefore, we shifted our attention to complex 1 with ligand PDP*, which has a rigid backbone and additional electron-donating groups (Figure 1), thus affording more stable catalytic intermediates.^{14,15,17,29} Intermediate 1^{IV}=O was cursorily communicated by our group in 2014 from a reaction of iron(II) complex 1 with H₂O₂ and AcOH without added organic substrate, and it was independently generated by the reaction of 1 with an oxygen atom donor IBX^{i-Pr} (isopropyl 2-iodoxybenzoate).¹⁷

Specifically, we decided to focus on the reaction of the oxoiron(IV) species with hydrogen peroxide, since such a process may play an important role in catalytic systems like $1/H_2O_2/substrate$ but has been largely ignored in previous studies. To the extent of our knowledge, there is only one report of the reaction of monomeric nonheme oxoiron(IV) species (derived from complexes 3 and 4, Figure 1) with hydrogen peroxide by Lim, Rohde, and co-workers published in 2012.¹⁸ They generated complexes $3^{IV}=O$ and $4^{IV}=O$ from the iron(II) precursors and PhIO and found both oxoiron(IV) species to oxidize H_2O_2 . For complex $3^{IV}=O$, the reaction proceeded by a clean 2:1 stoichiometry yielding $3^{III}-OOH$ was

generated. We hypothesized that if such mechanistic scheme is also applicable in the case of complex 1 then it may provide a pathway to return the relatively inactive Fe^{IV} intermediate to the $Fe^{III/V}$ active cycle that apparently dominates in the catalytic epoxidation and hydroxylation reactions (Scheme 1).

In the present work, we report a stopped-flow kinetic study of the reaction between iron(II) complex 1 (Figure 1) and oxygen donor IBX^{i-Pr} that quickly generates metastable species $1^{IV} = 0$. This oxoiron(IV) intermediate is reduced by \dot{H}_2O_2 in a reaction that is 2–3 orders of magnitude faster than analogous processes with $3^{IV}=0$ and $4^{IV}=0$.¹⁸ The reaction of $1^{IV} = O$ with H_2O_2 results in the formation of $1^{III} - OH$, which is converted to 1^{III}-OOH in the presence of excess H_2O_2 . When organic substrates are injected into the resulting solution, fast aromatic hydroxylation (with benzoic acid and benzene) and epoxidation (with cyclohexene and cyclooctene) are observed, thus demonstrating a restoration of catalytic activity (Scheme 1). Complex $1^{IV} = 0$ is also found to quickly oxidize thioanisole (an active oxygen atom acceptor), but its direct reactions with benzene, alkenes, and cyclohexane are found to be relatively slow (compared to the reaction with H_2O_2).

EXPERIMENTAL SECTION

Materials. All reagents were obtained from commercial vendors and used without additional purification unless otherwise specified. All experiments were run in HPLC-grade acetonitrile additionally purified via an Innovative Technology PS-MD-7 solvent purification system. Alkene substrates (cyclohexene and cyclooctene) were filtered through an alumina plug before use. Hydrogen peroxide was taken from a 50 wt % stock solution (Aldrich) and diluted into acetonitrile before use. Peracetic acid was taken from stock solution (ca. 39% in acetic acid (Aldrich)) and diluted into acetonitrile before use; it had a reported ~6% H₂O₂ impurity. mCPBA was purified according to ref 30. Ligand PDP* and its iron(II) complex 1 (as a perchlorate salt) were synthesized as previously reported.¹⁷ Isopropyl 2-iodoxybenzoate (IBX^{i-Pr}) was synthesized according to ref 31. Mentions of "reductively formed" 1^{III} -OOH refer to its formation from 1^{IV} =O and H_2O_2 , while "oxidatively formed" 1^{III} -OOH was made from iron(II) complex 1 and H_2O_2 (all at low temperatures in acetonitrile solutions).

Electron Paramagnetic Resonance Spectroscopy. X-band electron paramagnetic resonance (EPR) spectra were acquired on a Bruker EMX EPR instrument at 120 K, with BVT-3000 temperature controller, ER 081 magnet, and ER 041 X G microwave bridge using the WIN-EPR Acquisition Program version 3.01. Integration and quadratic baseline correction were done with the WIN-EPR 2.11 software. Due to the fleeting nature of catalytic intermediates, they were typically generated in cold baths, either ethylene glycol and dry ice (-17 °C) or acetonitrile and dry ice (-41 °C). Quantification of 1^{III} -OOH was done using 1.6 mL of 0.125 mM $Cu^{II}(ClO_4)_2$ in acetonitrile as an external reference. Subsequently, oxidatively formed 1^{III}-OOH was prepared (-17 $^\circ$ C, 0.4 mL each of 4 mM 1 and 40 mM H_2O_2 , 0.8 mL of acetonitrile) in the same EPR tube, to the same total volume, placed into microwave cavity to the same depth, and run under the same parameters to minimize differences. See Figures S1-S6 for all parameters and spectra. Reductively formed 1^{III} –OOH was generated by mixing 0.4 mL each of 4 mM acetonitrile solutions of IBX^{*i*-Pr} and **1** (for 5 s at -41 °C) to generate **1**^{IV}=**O** followed by the addition of 0.4 mL of 40 mM H_2O_2 in acetonitrile and 0.4 mL of dichloromethane. Adding CH₂Cl₂ allowed for better signal resolution compared to that using pure MeCN solvent, although was not necessary for the formation of 1^{III}-OOH.

Electrospray Ionization-Mass Spectrometry. Electrospray ionization-mass spectrometry (ESI-MS) was carried out using a Finnigan LTQ apparatus. Complex **1**^{IV}=**O** was generated by mixing 1 mM acetonitrile solutions of **1** and IBX^{i-Pr} at 0 °C immediately

before injecting into the instrument. Signals included m/z = 609.2 and 610.3 corresponding to ions $[1^{IV} = O(ClO_4)]^+$ and $[1^{III}(OH)-(ClO_4)]^+$, respectively, with matching isotopic satellites (Figure S7).

Gas Chromatography. GC-MS experiments were run using a SHIMADZU GC-17A gas chromatograph and GCMS-QP5050 gas chromatograph—mass spectrometer equipped with Thermo Scientific TraceGOLD TG-5MS GC column (30 m × 0.25 mm × 0.25 μ m). Data were collected and analyzed with the GCMSsolution version 1.20 software. Some experiments had outputs that were below the GC-MS limit of detection of the above instrument and were instead run with on an Agilent 7890B GC system with FID detector and Agilent Technologies HP-5 column (30 m × 0.320 mm × 0.25 μ m) and analyzed with the OpenLAB CDS software, otherwise following the matching sample preparation protocols.

GC Quantification. Alkene epoxidation products were quantified using the following procedure. Stock solutions (1 M each) of chlorobenzene, alkene, and its corresponding epoxide were prepared. Calibration standards were made by taking the following volumes of the stock solutions and diluting to 1 mL total volume with acetonitrile: 80 μ L of 1 M chlorobenzene and a variable volume of 1 M alkene or epoxide (40, 80, 120, 160, or 200 μ L). Then, a 10 μ L portion of each standard was diluted into 1 mL of acetonitrile and analyzed by GC-MS in triplicate. Integrated areas (subjected to Grubbs test at 95% interval) were used to establish a calibration curve of concentration ratio (analyte/chlorobenzene) versus peak area ratio (analyte/chlorobenzene).

Catalysis experiments with oxidatively formed $1^{\rm III}$ –**OOH** were performed by mixing 0.25 mL each of acetonitrile, 4 mM 1, H₂O₂ (20, 40, 60, 80, 120, or 200 mM), and 0.4 M alkene with a 0.16 M chlorobenzene reference. Reaction mixtures were stirred for 30 min. Afterward, 20 μ L of the reaction mixture was diluted into 1 mL of acetonitrile and subjected to GC-MS analysis in triplicate. With reductively formed $1^{\rm III}$ –**OOH**, an altered procedure was used. Solutions of 1 and IBX^{+Pr} (0.25 mL of 4 mM each in acetonitrile) were mixed for ~3 s, and 0.25 mL of H₂O₂ (20, 40, 60, 80, 120, or 200 mM) and 0.25 mL of 0.4 M olefin with 0.16 M chlorobenzene were added.

To explore the possibility of asymmetric induction in the oxidation of *cis-β*-methylstyrene and thioanisole by $\mathbf{1}^{IV}=\mathbf{0}$, equal volumes of 4 mM **1**, 4 or 40 mM IBX^{*i*-Pr}, 200 mM substrate, and acetonitrile were mixed at room temperature for 30 min and then analyzed by GC-MS using a Chiraldex beta cyclodextrin dimethyl column (30 m × 0.25 mm).

The oxidation of cyclohexane by $1^{IV}=0$ was studied by mixing 0.25 mL each of acetonitrile, 4 mM 1, 4 mM IBX^{*i*-Pr}, and 400 mM cyclohexane at +25 °C for 60 min, and an alcohol/ketone ratio was determined by the ratio of peak areas in GC-FID.

Stopped-Flow Spectroscopy and Data Analysis. Stoppedflow UV-vis-near-IR spectroscopy was carried out using a Hi-Tech Scientific SF-43 cryogenic double-mixing stopped-flow system. Multiwavelength measurements were collected with a TIDAS I diode-array detector. Low temperatures were maintained using a stirred liquid-nitrogen-cooled ethanol bath equipped with a cryostat. All solutions were prepared and handled with air-free techniques. Reactant solutions were prepared in a glovebox under argon and transferred to the stopped-flow instrument in Hamilton Gastight Syringes. The instrument was controlled using TgK Scientific Kinetic Studio version 1.08 software package with J&M TIDAS-DAQ version 2.20 software to collect multiwavelength data. For each experiment, 1000 scans were taken at 2.5-3.0 ms intervals and 60-1000 averages, depending on experiment length. Kinetic traces were fit using the Kinetic Studio KS-1 version 4.0.8 software, by applying appropriate kinetic equations (single or double exponential). An example kinetic fit is provided in Figure S8. Experiments were typically run in triplicate or quadruplicate, with outliers (Grubbs test, 95% interval) removed prior to data averaging. All concentrations reported in stopped-flow experiments refer to the "after mixing" conditions.

RESULTS AND DISCUSSION

Formation of 1^{IV}=O. Mixing acetonitrile solutions of iron(II) complex 1 and oxygen atom donor IBX^{*i*-Pr} (isopropyl 2-iodoxybenzoate)^{10,31} at -35 °C under stopped-flow conditions resulted in the rapid growth of a 730 nm absorption band characteristic of low-spin oxoiron(IV) complex with aminopyridine ligands (Figure 2).^{17,28,32} The identity of the



Figure 2. Formation of 1^{IV} =O from 1 mM 1 and equimolar IBX^{i-Pr} in acetonitrile at -35 °C followed by stopped-flow spectrophotometry. Inset: 730 nm kinetic trace.

730 nm chromophore as $1^{IV}=O$ was confirmed by ESI-MS. Prominent ESI-MS peaks from a freshly prepared mixture of 1 and IBX^{*i*-Pr} in MeCN at 0 °C and analyzed at +40 °C can be attributed to $[(1^{IV}=O)(CIO_4)]^+$ and $[1^{III}(OH)(CIO_4)]^+$ based on the m/z values and isotopic satellite pattern (Figure S7). The observation of the peak attributable to $[1^{III}(OH)-(CIO_4)]^+$ suggests that the most likely fate of the high-valent intermediate is the abstraction of a hydrogen atom from solvent or other organic molecules present in the system, which is supported by other data (*vide infra*).

The growth of the 730 nm band at different ratios of reagents (1 vs IBX^{i-Pr}), including a 1:1 ratio, could be fit well to a single-exponential function (Figures 2 and S8). The plot of observed pseudo-first-order rate constants versus [IBX^{i-Pr}] is a straight line with a significant intercept (Figure S9) indicating the following rate law.

$$\frac{d[\mathbf{1}^{\text{IV}}=\mathbf{O}]}{dt} = k_1[\mathbf{1}] + k_2[\mathbf{1}][\text{IBX}]$$
(1)

Article

At-35 °C, the values of the rate constants are $k_1 = 1.12 \pm 0.05$ s^{-1} and $k_2 = 38 \pm 2 \text{ M}^{-1} \text{ s}^{-1}$ (Figure S9). Such kinetic behavior may suggest two pathways for the reaction of coordinatively saturated complex 1, $[Fe^{II}(PDP^*)(CH_3CN)_2]^{2+}$, with the oxygen donor IBX^{i-Pr}: a dissociative monomolecular pathway controlled by the loss of a solvent molecule and an associative bimolecular pathway that depends on the concentration of both reactants.³³ At higher temperatures, the monomolecular pathway becomes dominant; on the basis of the dependence of rate constant k_1 on temperature in the range from -35 to +22°C (Figure S10), the activation parameters were determined as $\Delta H^{\ddagger} = +49.0 \pm 0.6 \text{ kJ} \cdot \text{mol}^{-1} \text{ and } \Delta S^{\ddagger} = -34.4 \pm 2.3 \text{ J} \cdot \text{mol}^{-1}$ K^{-1} . The relatively small value of ΔH^{\ddagger} and the negative sign of ΔS^{\ddagger} do not agree well with the dissociative nature of the ratelimiting step in this pathway, suggesting that the actual mechanistic picture may be more complicated than described above. Other experimental evidence confirms the mechanistic complexity of the reaction between 1 and IBX^{*i*-Pr}; thus, the reported kinetic parameters should be taken as a first approximation and only serve for rough comparisons in relation to the reactivity of the thus generated $1^{iv} = 0$. The maximum absorbance at 730 nm (attributed to $1^{IV}=0$) is not reached with the use of 1 equiv of IBX^{*i*-Pr}; instead, it gradually increases with the use of 1-3 equiv and plateaus at 4-10 equiv of the oxidant. Moreover, the very fast formation of the 730 nm chromophore is immediately followed by its relatively fast partial decay, where about 15% of the 730 nm optical absorbance is lost (Figure S8). The rate of this partial decay is not influenced significantly by the amount of IBX^{i-Pr} used (Figure S12). At-35 °C, the partial decay has a half-life of 9 s, and after its completion the 730 nm chromophore is stable for at least 30 min. As temperature is increased, both phases in the decay of this chromophore accelerate, and its overall half-life is reduced to just 2 min at +25 °C (Figure S13). The complex kinetic behavior of this system may be caused by the following factors: (1) IBX^{*i*-Pr} (*ortho-i*-PrOOC-C₆H₄-IO₂) has an iodoxy group with two oxygen atoms that can be used for oxidation. (2) Both IBX^{*i*-Pr} and the product of its monodeoxygenation $(ortho-i-PrOOC-C_6H_4-IO)$ can coordinate to iron. (3) Complex $1^{IV}=0$, $[Fe^{IV}(O)(PDP^*)(CH_3CN)]^{2+}$, can exchange the solvent molecule for other ligands present in the system.^{31,34} Notwithstanding these possible complications, we

Table 1. Second-Order Rate	Constants (M ⁻¹	s^{-1} for the	Oxidation of Selected	Organic S	Substrates by	Oxoiron(IV)
Complexes ^a						

complex	thioanisole	cyclohexane	1,4-cyclohexadiene	ref
1 ^{IV} =0	8.7 ± 1.1 (-15 °C) 274 ± 4	0.099 ± 0.011	683 ± 98	this work
3 ^{IV} =0	$0.87 \pm 0.04 \ (0 \ ^{\circ}C)$	6.7×10^{-5}	10.69	36, 39, 40
4 ^{IV} =0	9×10^{-4}	no reaction	0.12	37, 41
(N3PyB)Fe ^{IV} =O	$3.3 \pm 0.09 \times 10^{-2} (-40 \ ^{\circ}\text{C})$	0.3 ± 0.02		40
(N2Py2B)Fe ^{IV} =O	$3.1 \pm 0.11 \times 10^{-1} (-40 \ ^{\circ}\text{C})$	2.9 ± 0.1		40
(N4Py ^{Me2})Fe ^{IV} =O	$1.03 \pm 0.03 (-10 \ ^{\circ}C)$	6.73×10^{-4}	0.78	39
(N2Py2Q)Fe ^{IV} =O	7.4 (−10 °C)	0.029		42
(Me ₂ EBC)Fe ^{IV} =O	0.41 (0 °C)		7.4 (0 °C)	37
(Me ₃ NTB)Fe ^{IV} =O	$2.1 \times 10^4 (-40 \ ^{\circ}C)$	0.25 (-40 °C)	$9.4 \times 10^2 (-40 \ ^{\circ}C)$	38
(TQA)Fe ^{IV} =O		0.37 (-40 °C)		43

^aThe temperature is +25 °C unless specified otherwise.

have sufficient evidence that complex $1^{IV}=0$ forms very quickly from 1 and IBX^{i-Pr} , as suggested by UV-vis spectroscopy and ESI-MS data, and that $1^{IV}=0$ is sufficiently stable in solution to study its reactivity with substrates by the double-mixing stopped-flow technique.

Reactions of 1^w=0 with Thioanisole and Hydrocarbons. The reactivity of $1^{IV}=0$ was studied by pregenerating the intermediate from an equimolar solution of 1 and IBX^{*i*-Pr} in acetonitrile under stopped-flow conditions until the concentration of $1^{IV}=0$ reached maximum, then adding the substrates in a second mix. First, we examined thioanisole (PhSMe), which had commonly been employed in an oxoiron(IV) reactivity studies.^{28,35} Mixing $1^{IV} = 0$ with 10– 100 equiv of PhSMe afforded rapid bleaching of the 730 nm chromophore with a second-order rate constant of 8.7 \pm 1.1 $M^{-1} s^{-1} at -15 °C or 274 \pm 4 M^{-1} s^{-1} at +25 °C (Figure S14).$ These rate constants are considerably faster than those reported for complexes $3^{IV}=O$ (0.87 ± 0.04 M⁻¹ s⁻¹ at 0 °C) and $4^{IV}=O$ (9 × 10⁻⁴ M⁻¹ s⁻¹ at +25 °C).^{36,37} In contrast, Nam reported a trigonal bipyramidal oxoiron(IV) species that oxidized PhSMe with a second-order rate constant as high as 2.1×10^4 M⁻¹ s⁻¹ at -40 °C.³⁸ A comparison of these and some other rate constants is provided in Table 1.36-4

Mixing of $1^{IV} = 0$ with cyclohexene, cyclooctene, or cyclohexane at -15 °C yielded no reaction on the stoppedflow time scale (up to 10 min). However, when the temperature was increased to +25 °C, oxidation of these and some other hydrocarbons was observed. In stopped-flow experiment, mixing of $1^{IV} = 0$ with cyclohexene in acetonitrile solution at +25 °C afforded fast bleaching of the 730 nm chromophore ($k = 5.4 \pm 0.4 \text{ M}^{-1} \text{ s}^{-1}$, Figure S15), far faster than the self-decay of $1^{IV} = 0$ at this temperature. For product analysis, a benchtop room-temperature experiment was carried out, in which a 1 mM acetonitrile solution of 1, equimolar IBX^{i-Pr}, and 50 equiv of cyclohexene were mixed for 30 min, then analyzed by GC-MS. The major oxidation products as analyzed by GC-MS were cyclohexene-3-ol (29.1%), cyclohexene-3-one (49.7%), and epoxycyclohexane (21.2%) (Figure S16).⁴⁴ A hydroperoxide product is also possible from this reaction, and it may decompose to the enone in the GC injector.⁴⁵ To account for this, a control experiment was conducted where excess PPh3 was added to the reaction mixture prior to the GC injection (potentially converting hydroperoxide to alcohol), 46 but the product distribution remained unchanged, thus excluding the formation of cyclohexene hydroperoxide. A similar reactivity of cyclohexene, with a marked preference for allylic oxidation over epoxidation by oxoiron(IV) species, has been reported by Talsi et al. for $2^{IV}=0$, by Paine et al. for a derivative of $3^{IV}=0$, and by Que et al. for the oxoiron(IV) complex of TPA (tris(2pyridylmethyl)-amine).^{39,44,47}

By comparison, oxidation of cyclooctene by $\mathbf{1}^{IV}=\mathbf{O}$ at +25 °C had a second-order rate constant of $1.36 \pm 0.07 \text{ M}^{-1} \text{ s}^{-1}$ (Figure S17), about 4 times slower than that observed for cyclohexene. A benchtop oxidation of cyclooctene by a mixture of 1 and IBX^{*i*-Pr} showed exclusive formation of the epoxide and no appreciable amounts of allylic oxidation products as observed in GC-MS. Therefore, the lower rate constant observed with cyclooctene likely reflects its lessened reactivity for allylic oxidation compared to cyclohexene. It should be noted that oxoiron(IV) complexes capable of alkene epoxidation have been rarely reported.^{20,34,43,48} Our group

reported one such complex, (PyMAC)Fe^{IV}=O (where PyMAC is a tetradentate pyridine containing macrocycle), which epoxidized cyclooctene with a rate constant of 0.45 M⁻¹ s⁻¹ at 0 °C.³⁴ The most reactive oxoiron(IV) complex reported to date, (TQA)Fe^{IV}=O (where TQA = tris(2quinolylmethyl)amine), reacts with cyclooctene with a rate constant of 3.3 M⁻¹ s⁻¹ at -40 °C yielding 80% epoxide.⁴³ Complex 2^{IV}=O was claimed to be competent for alkene epoxidation when promoted by Sc^{III} ions,⁴⁹ as was 3^{IV}=O with triflic acid,⁵⁰ as well as a derivative of 3^{IV}=O.⁵¹

The relatively slow rate of olefin epoxidation compared to the putative oxoiron(V) pathway (Scheme 1), combined with the preference for allylic oxidation in cyclohexene, makes 1^{IV} O a poor choice for catalytic epoxidation. Still, a slower rate may afford a more enantioselective oxidant, so we briefly investigated its potential for the asymmetric epoxidation of *cis*- β -methylstyrene. First, 0.25 mL each of 4 mM 1, 4 mM IBX^{*i*-Pr}, and 200 mM *cis-\beta*-methylstyrene in acetonitrile were mixed at room temperature for 30 min before GC-MS analysis. On the basis of the peak area, both enantiomers of the epoxide were present in nearly equal abundances, indicating no significant asymmetric induction by $1^{IV}=0$. By comparison, putative $1^{V} = 0$ intermediate generated from 1 and H₂O₂ with Sibuprofen acid cocatalyst in the epoxidation of $cis-\beta$ methylstyrene gave 86% ee, making the oxoiron(V) pathway preferable for asymmetric epoxidation.¹⁴ We also carried out the sulfoxidation of thioanisole under analogous conditions, but again, both enantiomers of thioanisole sulfoxide were present in nearly equal amounts showing a lack of enantioselectivity. This is in contrast to successful ee induction in the sulfoxidation of para-methoxythioanisole by complex $[Fe^{IV}(O)(asN4Py)]^{2+}$ (a chiral homologue of complex 3^{IV} O) reported recently by Kaizer and co-workers.⁵⁷

With the oxidation of thioanisole and olefins by $\mathbf{1}^{IV}=\mathbf{O}$ established, we turned our attention to the oxidation of C–H bonds, particularly in comparison to the reported reactivity of $\mathbf{3}^{IV}=\mathbf{O}$ and $\mathbf{4}^{IV}=\mathbf{O}$. A fast reaction was observed from a combination of $\mathbf{1}^{IV}=\mathbf{O}$ and 1,4-cyclohexadiene, which has activated allylic C–H bonds (BDE = 78 kJ·mol⁻¹).⁴¹ In a stopped-flow experiment, 1 mM 1 and IBX^{*i*-Pr} each were mixed at +25 °C for 0.6 s, and then 1,4-cyclohexadiene (10–60 equiv) was added in a second mix. The second-order rate constant for the oxidation of 1,4-cyclohexadiene by $\mathbf{1}^{IV}=\mathbf{O}$ was determined to be 683 ± 98 M⁻¹ s⁻¹ (Figure S18), compared to the reported values of 10.69 M⁻¹ s⁻¹ for $\mathbf{3}^{IV}=\mathbf{O}$ and 0.12 M⁻¹ s⁻¹ for $\mathbf{4}^{IV}=\mathbf{O}$ at +25 °C.

Cyclohexane, which has unactivated C–H bonds (BDE = 99.3 kJ·mol⁻¹),⁵³ also accelerated the bleaching of 1^{IV} =O. In an analogous stopped-flow experiment with 25–300 equiv of cyclohexane, a second-order rate constant for the reaction of 1^{IV} =O with cyclohexane was determined as 0.099 ± 0.011 M⁻¹ s⁻¹ (Figure S19), 4 orders of magnitude faster than that for 3^{IV} =O (5.5 × 10⁻⁵ M⁻¹ s⁻¹).⁴⁰ GC analysis of the product mixture confirmed the oxidation of cyclohexane by 1^{IV} =O, but showed little selectivity with an alcohol/ketone ratio of ca. 1:1.4. In a complementary reaction with cyclohexane- d_{12} , the oxidation was markedly slower, with a H/D kinetic isotope effect of 4.9 ± 0.4 (Figure S19). This compares well to the H/D KIE of 4.5 with 3^{IV} =O in the oxidation of cyclohexane reported by van den Berg et al., and it supports a metal-based oxidant with a HAT rate-determining step.⁵⁴

Benzene was also oxidized by 1^{IV} =O, but at the slowest rate among studied hydrocarbons. In stopped-flow, 50–300 equiv

of benzene was added to pregenerated $1^{IV}=0$ in acetonitrile solution at +25 °C, which resulted in the decay of the 730 nm oxoiron(IV) band that proceeded faster than that with no substrate and accelerated in proportion to the amount of added benzene with the second-order rate constant of $0.046 \pm$ $0.007 \text{ M}^{-1} \text{ s}^{-1}$ (Figure S20). As the 730 nm chromophore decayed, subsequent growth of a 580 nm band was observed, suggesting the formation of an Fe(III)-phenolate complex after the hydroxylation of C_6H_6 .¹⁰ Benzene- d_6 reacted with $1^{IV}=0$ with nearly the same rate constant ($0.043 \pm 0.007 \text{ M}^{-1} \text{ s}^{-1}$ at +25 °C, Figure S20), showing a negligible H/D kinetic isotope effect of 1.0 ± 0.2 and suggesting an electrophilic aromatic substitution mechanism.^{9,10}

To the extent of our knowledge, this is the first experimental observation of a direct reaction between a synthetic lowmolecular oxoiron(IV) complex and benzene, although the hydroxylation of aromatic substrates is commonly attributed to the Fe^{IV}=O intermediates in native nonheme iron oxygenases (such as TyrH).⁴ Goldberg and co-workers reported an intramolecular hydroxylation of a pendant phenyl group that was part of a polydentate ligand (a derivative of complex 3) that likely proceeded via an oxoiron(IV) intermediate. Interestingly, when a 2,6-difluorophenyl group was appended instead, the Fe^{IV}=O intermediate was trapped at low temperature, but it effected the hydroxylation of a C-F bond at room temperature.^{55,56} Nam and co-workers observed the hydroxylation of anthracene by complexes $3^{IV}=0$ and (Bn-tpen)Fe^{IV}=O that proceeded smoothly at +25 °C in acetonitrile/dichloromethane (1:1) solutions with rate constants of 0.24 and 0.68(5) M^{-1} s⁻¹, respectively; their computational studies suggested the possibility of benzene hydroxylation by these complexes as well, but no experimental confirmation was reported. 53,54 Banse and co-workers observed hydroxylation of aromatic substrates (including benzene) with the help of a (L_5^2) Fe^{III}-OOH complex, where L_5^2 is a pentadentate analog of ligand 2 with an additional aminopyridine arm; their proposed mechanism included homolysis of the Fe(III)-OOH intermediate to generate a caged oxoiron(IV) + •OH pair, which worked together to afford hydroxylation of regular and deuterated benzenes with small KIE's of 1.05–1.53 in different experiments.⁵⁷

Our group previously reported preliminary experiments showing that the relatively fast self-decomposition of complex $2^{IV}=O$ in acetonitrile solution at +20 °C was not accelerated by added benzene or toluene.¹⁰ However, when we tried to replicate those experiments more recently, we did observe some acceleration of the bleaching of $2^{IV}=O$ in the presence of added benzene.⁵⁸ Complex $1^{IV}=O$ differs from $2^{IV}=O$ by the presence of electron-donating groups in the ligand (Scheme 1). Thus, it is expected that complex $2^{IV}=O$ should be more electrophilic than $1^{IV}=O$. It should be mentioned that complex $2^{IV}=O$ has been only cursorily studied,¹⁰ and more experimental work is necessary to determine its actual reactivity with benzene and other substrates.

The oxidations of cyclohexane, 1,4-cyclohexadiene, and thioanisole by different oxoiron(IV) complexes have been studied extensively, and some kinetic data are summarized in Table 1. Generally, more stable complexes have been found to be less reactive. The most stable oxoiron(IV) complex, $4^{IV}=0$ or *trans*-[Fe^{IV}O(TMC)(MeCN)]²⁺ (where TMC is 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, Figure 1), is also the least reactive and is not able to hydroxylate unactivated C– H bonds.²⁸ The change of the macrocyclic ligand topology in

complex (Me₂EBC)Fe^{IV}=O (where Me₂EBC is 4,11dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane) resulted in enforced *cis*-coordination and higher reactivity (Table 1),³⁷ yet complex (Me₂EBC)Fe^{IV}=O had a rather long halflife of about 5 h at 0 °C and was not able to oxidize unactivated hydrocarbons.

Complex $3^{iv} = 0$ that features a pentadentate ligand N4Py (N,N-bis(2-pyridylmethyl)-N-bis(2-pyridyl)methylamine, Figure 1) is less stable than $4^{IV} = 0$ and also more reactive, able to hydroxylate cyclohexane with a rate constant of 6.7×10^{-5} M⁻¹ s⁻¹ at +25 °C.³⁹ Structural modifications of N4Py aimed at increasing steric bulk resulted in lower ligand field, affording less stable oxoiron(IV) complexes with higher reactivity. Nordlander showed that in replacing one pyridine on 3^{IV} = O with 1-methylbenzimidazole in $(N3PyB)Fe^{IV} = O$, the +25 $^{\circ}$ C cyclohexane oxidation rate constant of 0.30 ± 0.02 M⁻¹ s⁻¹ was 4 orders of magnitude higher than that of the unmodified complex and increased further by replacing a second pyridine with 1-methylbenzimidazole in $(N2Py2B)Fe^{IV}=O$ (Table 1).⁴⁰ The results were less dramatic and mixed for Paine, who replaced two pyridines with 6-methylpyridines in (N4Py^{Me2})⁻ Fe^{IV}=O: The rate constant for the oxidation of cyclohexane was 1 order of magnitude faster than that of unmodified 3^{IV} O, but 1 order of magnitude slower for the oxidation of 1,4cyclohexadiene (Table 1).³⁹ Que reported a variant with two pyridines replaced by quinolines, (N2Py2Q)Fe^{IV}=O, which oxidized cyclohexane with an intermediate rate constant of 0.029 $M^{-1'}$ s⁻¹ at +25 °C (Table 1).⁴² Overall, lower ligand field strength (and longer average Fe-N bond distances) correlated well with $\log k$ values for substrate oxidation for complex 3^{IV} =O and its derivatives.⁴² Such a trend in reactivity of the oxoiron(IV) species was justified by lowering the energy gap from the unreactive S = 1 ground state to the reactive S = 2state as suggested by computational analysis.^{42,59-61}

A decrease of ligand denticity from N5 to N4 appears to increase the reactivity of oxoiron(IV) complexes, which may be justified by either a decrease in ligand field stabilization or the appearance of a labile site near the oxo ligand in the LFe^{IV}=O unit (for the cis N4 ligand topology). The most reactive examples of such complexes known to date, (Me₃NTB)Fe^{IV}=O and (TQA)Fe^{IV}=O, feature bulky tripod N4 ligands and oxidize cyclohexane at -40 °C with rate constants of 0.23 and 0.37 M⁻¹ s⁻¹, respectively.^{38,43}

The rate of the reaction between complex $\mathbf{1}^{IV}=\mathbf{O}$ and cyclohexane (0.099 \pm 0.011 M⁻¹ s⁻¹ at +25 °C) reported in this work is roughly in the middle of the range observed for oxoiron(IV) species, and the same can be stated about most other studied substrates taking into account different temperatures used (Table 1). Thus, the reactivity of $\mathbf{1}^{IV}=\mathbf{O}$ with thioanisole, 1,4-cyclohexadiene, alkenes, and cyclohexane is reasonable for a low-spin Fe^{IV}=O complex with a cis- α -coordinated tetradentate aminopyridine ligand. However, the observed hydroxylation of benzene by $\mathbf{1}^{IV}=\mathbf{O}$ is unusual and may deserve a more detailed study, which is beyond the scope of this article.

Reaction of 1^{IV}=0 with H_2O_2. As mentioned in the Introduction, we were particularly interested in the reactivity of $1^{IV}=0$ with H_2O_2 , as it had been frequently employed as the oxidant in catalytic experiments with 1. The O-H bond dissociation energy of 86 kJ·mol⁻¹ for hydrogen peroxide falls between the BDE values of cyclohexane and 1,4-cyclohexadiene described above.⁶² As such, $1^{IV}=0$ was expected to be capable of H-atom abstraction from H_2O_2 . At -35 °C, 1

mM 1 and 1 mM IBX^{i-Pr} in acetonitrile were premixed for 1 s, after which 1–15 equiv of of H_2O_2 was added in a second mixing. Decay of the 730 nm oxoiron(IV) chromophore was rapid (Figures 3 and S21), with a second-order rate constant of



Figure 3. Decay of 1^{IV} =**O** in the presence of 1 equiv of hydrogen peroxide. 1^{IV} =**O** was pregenerated from 1 mM 1 and IBX^{*i*-Pr} for 1 s at -35 °C, and then 1 mM H₂O₂ was added, causing the 730 nm band of 1^{IV} =**O** to rapidly decay. Inset: Kinetic trace at 730 nm.

44.5 \pm 0.8 M⁻¹ s⁻¹ (Figure S22). With only 1 equiv of H₂O₂, the 730 nm band was bleached completely, with no features forming in the visible region following decay of 1^{IV}=O (Figure S23). At higher loadings of H₂O₂, the growth of an intense 550 nm band occurred isosbestically as the 730 nm oxoiron(IV) chromophore decayed (Figure 4). The 550 nm chromophore has previously been connected to peroxyiron-(III) species 1^{III}-OOH, a sluggish oxidant but en route to a highly potent oxoiron(V).¹⁰



Figure 4. Decay of 1^{IV} =O at -15 °C after addition of 10 equiv of H_2O_2 in a second mixing. Nearly isosbestic conversion of the 730 nm band to the 550 nm band resembling 1^{III} -OOH was observed. Inset: 550 nm trace (red) and 730 nm trace (blue).

The identity of this 550 nm chromophore as 1^{III} –OOH was confirmed by EPR spectroscopy: First, 0.4 mL each of 4 mM 1 and 4 mM IBX^{*i*-Pr} in acetonitrile were mixed at -41 °C in a dry ice/acetonitrile bath to generate 1^{IV} =O; after ca. 2 s, 2.5, 5, or 10 equiv of H₂O₂ in 0.4 mL of acetonitrile and 0.4 mL of dichloromethane were added and mixed for ca. 3 s before freezing in liquid nitrogen (Figures 5, S5, S22, and S23). The resulting samples were EPR-active and showed a prominent set of rhombic signals of $g_{eff} = 2.22$, 2.16, and 1.96 consistent with past reports of analogous 2^{III} –OOH and other known low-



Figure 5. Overlay of the 120 K EPR spectra of 1^{III} –**OOH** formed by reductive and oxidative pathways, from 1^{IV} =**O** and **1**, respectively. Orange: reductive, 2.5 equiv of H₂O₂. Red: reductive, 5 equiv of H₂O₂. Blue: reductive, 10 equiv of H₂O₂. Purple: oxidative, 10 equiv of H₂O₂. While possessing the same primary features, the intensity of the oxidatively formed (purple) spectrum is noticeably greater than that of the reductively formed (blue) spectrum, corresponding to ~50% and ~30% iron, respectively. The feature below 2000 G belongs to the unidentified Fe(III) byproduct with $g_{\text{eff}} = 4.3$.

spin peroxyiron(III) complexes.^{10,17,21} These signals compare well to a sample of 1^{III} –OOH generated by the "oxidative" pathway from mixing 0.4 mL each of 4 mM iron(II) complex 1 and 40 mM H₂O₂, diluted with 0.8 mL of acetonitrile for 5 s at -17 °C (Figures 5 and S3). In both the reductively and oxidatively formed samples of 1^{III} –OOH, an intense broad signal at $g_{eff} = 4.3$ was also observed, belonging to an unidentified, unreactive high-spin iron(III) byproduct commonly observed in similar systems.^{63–65} At low H₂O₂ loadings, one more signal was observed with $g_{eff} = 2.42$, likely belonging to iron(III)-hydroxy species 1^{III} –OH.^{18,66}

In quantifying the peroxyiron(III) formed via the two pathways ("reductive" from $\mathbf{1}^{IV}=\mathbf{O}$ and "oxidative" from iron(II) complex 1, with 10 equiv of H_2O_2 each), we saw a considerable difference in the amount of EPR-active iron present in the system. In reference to an acetonitrile solution of 0.125 mM Cu^{II}(ClO₄)₂,⁶⁷ about 50% of the iron formed from the reaction of 1 with 10 equiv of H_2O_2 at -15 °C existed as $\mathbf{1}^{III}-\mathbf{OOH}$, while in the reaction of $\mathbf{1}^{IV}=\mathbf{O}$ with 10 equiv of H_2O_2 at -40 °C, this amount was only ca. 30%, indicating a substantial loss of EPR-active iron by the "reductive" pathway. In both cases, the quantity of the $g_{eff} = 4.3$ species is roughly equivalent at 30 and 27%, respectively, so the loss of EPR-active iron in the $\mathbf{1}^{IV}=\mathbf{O}$ -mediated pathway was due to the formation of some unidentified EPR-silent species, which were also catalytically inactive (*vide infra*).

A similar reactivity of oxoiron(IV) species with H_2O_2 was reported previously by Lim and Rohde based on complexes 3 and 4 (Figure 1).¹⁸ They started by oxidizing the iron(II) precursors with PhIO to make acetonitrile solutions of $3^{IV}=O$ and $4^{IV}=O$, respectively. Subsequent addition of 0.5 equiv of H_2O_2 to $3^{IV}=O$ yielded a hydroxyiron(III) species with $g_{eff} =$ 2.40, 2.14, 1.94, further supporting the identification of our observed $g_{eff} =$ 2.42 shoulder peak as $1^{III}-OH$ (*vide supra*). With 50 equiv of H_2O_2 , a rhombic EPR signature of g = 2.20, 2.14, and 1.97 with a visible band of $\lambda_{max} =$ 536 nm was observed, attributed to $3^{III}-OOH$.¹⁸ Their proposed mecha-

Table 2. Kinetic Parameters for the Reactions of Oxoiron(IV) Species with H_2O_2

oxoiron(IV)	second-order rate constant of HAT with $\rm H_2O_{2^{\prime}}$ –20 $^{\circ}\rm C$	activation enthalpy	activation entropy	ref
1 ^{IV} =0	$102.6 \pm 4.6 \text{ M}^{-1} \text{ s}^{-1}$	$22.6 \pm 1.3 \text{ kJ} \cdot \text{mol}^{-1}$	$-151 \pm 5 \text{ J} \cdot \text{mol}^{-1} \text{ k}^{-1}$	this work
3 ^{IV} =0	$0.80 \pm 0.02 \ \mathrm{M^{-1} \ s^{-1}}$	$30.8 \pm 0.7 \text{ kJ} \cdot \text{mol}^{-1}$	$-158 \pm 2 \text{ J} \cdot \text{mol}^{-1} \text{ k}^{-1}$	18
4 ^{IV} =0	$0.035 \text{ M}^{-1} \text{ s}^{-1}$	not reported	not reported	18

nism involved a 2:1 stoichiometric reaction of Fe^{IV} with H₂O₂, in which one oxoiron(IV) unit abstracted hydrogen from H₂O₂ yielding hydroxyiron(III) and a superoxy radical HO₂•, from which another oxoiron(IV) unit quickly abstracted the remaining H atom, ultimately yielding two hydroxyiron(III) units and a molecule of O₂.¹⁸ At higher peroxide loadings, 3^{III} -OH was readily transformed into 3^{III} -OOH by labile ligand substitution (Scheme 1).

In the reaction of H_2O_2 and $1^{IV}=O$, we likewise observed O_2 gas evolution (in benchtop experiments) and a 2:1 stoichiometry (in stopped-flow experiments, Figure S25). Taken together with the consistency of our EPR and UV-vis measurements, the mechanism of oxoiron(IV) reduction by H_2O_2 proposed by Lim and co-workers is likely to occur with $1^{IV}=O$ as well, but with much greater rate constants compared to $3^{IV}=O$ and $4^{IV}=O$ (Table 2). We also want to note that the putative oxoiron(V) active species in catalysis, which is far more effective for HAT and OAT reactions than $1^{IV}=O$, should also be able to quickly abstract hydrogen from H_2O_2 , leading to unproductive and unaccounted H_2O_2 consumption. This may explain why catalysts such as 1 and 2 required very gradual syringe-pump addition of H_2O_2 for optimal results.^{14,26}

A common thread in the oxidation of different substrates by oxoiron(IV) species is that 1^{IV} =O affords rate constants 2–3 orders of magnitude greater than those reported for more stable complexes 3^{IV} =O and 4^{IV} =O (Tables 1 and 2). At -20 °C, the rate constant for hydrogen abstraction from H₂O₂ by 1^{IV} =O is 103 ± 5 M^{-1} s⁻¹, which is 130 times greater than that reported by Lim and Rohde for 3^{IV} =O and 2900 times greater than that for 4^{IV} =O (Table 2).

To study the influence of temperature in the range from -35to -10 °C, we generated $1^{IV}=0$ under stopped-flow conditions by premixing 1 mM acetonitrile solutions of 1 and IBX^{i-Pr} until the maximum formation of oxoiron(IV) intermediate and then added H_2O_2 (20 equiv) in a second mixing. From this, we determined an activation enthalpy of +22.6 \pm 1.3 kJ·mol⁻¹ (Figure S24), somewhat lower than that reported for $3^{IV}=0$ in the same reaction (+30.8 ± 0.7 kJ· mol^{-1}), which may account for the higher reactivity of $1^{IV}=0$. The activation entropies for this reaction by $3^{IV}=0$ and $1^{IV}=$ O are quite similar at -158 ± 2 and -151 ± 5 J·mol⁻¹K⁻¹, respectively, indicative of a common, associative ratedetermining step.¹⁸ In surveying the literature, we could not find any other detailed kinetic studies of nonheme oxoiron(IV) reactivity with H_2O_2 , except in the case of dimeric iron(IV) species reported previously by our group,⁶⁸ which is beyond the scope of the current investigation focused on mononuclear iron complexes.

As $1^{V}=0$ was quite capable of hydrogen abstraction from H_2O_2 , the oxidant commonly used in catalysis with 1, a natural extension of this work was to look at other oxidants which have been applied in catalysis-peroxycarboxylic acids. These species, including mCPBA and peracetic acid, can epoxidize alkenes by themselves, but the reaction is greatly accelerated and becomes stereoselective in the presence of catalysts like 1.69,70 In a -15 °C stopped-flow experiment, 1 mM 1 and

IBX^{*i*-Pr} were mixed for 1 s to generate $1^{IV} = 0$, and then 1–20 equiv of mCPBA was added. While with H₂O₂, decay of the 730 nm oxoiron(IV) band took only seconds, no decay of the 730 nm chromophore was observed with mCPBA over a 5 min period. An analogous experiment with commercial peracetic acid solution did result in depletion of the 730 nm band. However, an important consideration is the presence of hydrogen peroxide in commercial solutions of peracetic acid. This peracid exists as an equilibrium mixture with H₂O₂ and acetic acid, so the residual H₂O₂ present may in fact be the source of $1^{IV} = 0$ consumption. In support of this hypothesis, we noted that in the experiment with 1 equiv of peracetic acid (~0.33 equiv of H_2O_2), the 730 nm band did not decay completely, whereas at all higher concentrations it did. Earlier, we established a 2:1 stoichiometry for the reaction of $1^{IV}=0$ with H_2O_2 (vide supra), so this observation supports the idea that the peracid is merely a spectator. This may be owed to the higher O-H bond dissociation energy of peracetic acid (90.4 kJ·mol⁻¹),⁷¹ which renders it less capable or incapable of reacting with $1^{IV}=0$. Assuming that only H_2O_2 present in commercial peracetic acid solution reacted with $1^{IV} = 0$ (while CH₃CO₂H and CH₃CO₃H were merely spectators), we calculated a second-order rate constant of 53.0 \pm 8.7 M⁻¹ s^{-1} at -35 °C (Figure S27), in reasonable agreement with the value obtained for the reaction of $1^{IV}=0$ with pure H₂O₂ (44.5 \pm 0.8 M⁻¹ s⁻¹ at -35 °C). In a control experiment, no reaction between **1**^{IV}=**O** and acetic acid (O–H BDE 104.7 \pm $0.8 \text{ kJ} \cdot \text{mol}^{-1})^{72}$ was observed under stopped-flow double mixing conditions at -35 or +25 °C. Likewise, experiments with mCPBA demonstrated no reaction with $1^{IV} = 0$, showing that peroxycarboxylic acids are not suitable substrates for 1^{IV} **O**. This may lend favor to peracids over H_2O_2 in catalytic oxidations of organic substrates, as one avenue of inefficient oxidant consumption is avoided, allowing more oxidant to partake in the substrate oxidation.

As stopped-flow UV-vis and EPR data confirmed, $1^{IV}=0$ in the presence of excess H_2O_2 is ultimately converted to 1^{III} -OOH, which has been previously assigned as a precursor to the putative active oxidant $1^{V} = 0$ in catalysis.¹⁹ As such, reacting $1^{IV} = 0$ with extra H_2O_2 (the reductive pathway) should afford a resurgence of catalytic activity comparable to that obtained via oxidation of 1 with H_2O_2 (oxidative pathway). To check this hypothesis experimentally, we studied the hydroxylation of benzoic acid. Benzoic acid is known to undergo rapid aromatic hydroxylation at the ortho position with similar oxidizing systems, resulting in an intense 570 nm iron(III)-salicylate absorption band.²⁷ In a stopped-flow experiment at -15 °C, 1 mM each 1 and IBX^{*i*-Pr} were premixed for 1 s to generate 1^{IV} = O, and then 3-10 equiv of H_2O_2 and 2 equiv of benzoic acid were added in a second mixing. The resulting spectra revealed the expected consumption of $\mathbf{1}^{\text{IV}} = \mathbf{0}$ on reaction with H_2O_2 , followed by fast growth of the iron(III)-salicylate product, with slightly offset kinetic traces indicative of two successive processes (Figure 6). This behavior is similar to our prior observations for the reaction of oxidatively formed 2^{III}-OOH²⁷ and the current observation with oxidatively formed



Figure 6. Oxidation of benzoic acid by the reductively formed Fe^{III} – **OOH.** 1^{IV} =**O** was generated by mixing 1 and IBX^{*i*.Pr} for 1 s at -15 °C, and then adding 2 equiv of benzoic acid and 5 equiv of H₂O₂ in a second mixing. Inset: 730 nm (blue) and 570 nm (red) traces.

I^{III}−**OOH** (Figure S28). Using the established ε(max) ≈ 2300 M⁻¹ cm⁻¹ for the (BPMEN)Fe^{III}-salicylate complexes,²⁷ we estimated iron(III)-salicylate yields of 79% for the oxidative pathway and 57% for the reductive pathway. It should be noted that less than stoichiometric yields arise from tight binding of the salicylate to Fe^{III} in the product, preventing multiple turnovers from occurring,^{10,73} in addition to some iron being lost unproductively (e.g., to the *g* = 4.3 species (*vide supra*)). As a control, we attempted benzoic acid oxidation by **I**^{IV}=**O** in the absence of H₂O₂ at +25 °C under stopped-flow conditions, but no accumulation of the 580 nm iron(III)-salicylate species was observed, indicating the negligible oxidation of benzoic acid by **1**^{IV}=**O**.

Substoichiometric hydroxylation of benzene exposed to 1^{III} -OOH (based on the growth of a 580 nm band attributed to the iron(III)-phenolate) was observed for both oxidative and reductive pathways in stopped-flow experiments. For the oxidative pathway, 1 mM 1, 10 mM H₂O₂, and 300 mM benzene were mixed at +25 °C, with the 580 nm chromophore of Fe(III)-phenolate forming with a pseudo-first-order rate constant of 0.127 s^{-1} . By the same procedure, but pregenerating 1^{IV}=0 with 1 mM IBX^{i-Pr} for 0.6 s prior to adding H_2O_2 and benzene, the iron(III)-phenolate species appeared with $k_{obs} = 0.0543 \text{ s}^{-1}$, about 58% slower. Still, these reactions proceeded faster than the comparable reaction of $1^{\text{IV}}=0$ with benzene in the absence of H_2O_2 ($k_{\text{obs}} = 0.0281$ s^{-1} at the same benzene concentration). It should be noted that 1^{III}-OOH is not expected to directly hydroxylate benzene in an acetonitrile solution and that the reaction likely proceeds via the $1^{V} = 0$ intermediate.¹⁰

While a resurgence of oxidative activity was observed on reduction of $1^{IV} = 0$ with excess H_2O_2 , it was noted during EPR studies that ca. 40% less active iron was present via the reductive pathway as compared to the oxidative pathway. As such, we expected to see a corresponding difference in catalytic activity between the two pathways. 1^{IV}=O reacted with cyclohexene relatively slowly at +25 °C yielding primarily allylic oxidation products and only about 20% of epoxide. When $1^{IV} = 0$ (generated from equimolar amounts of 1 and IBX^{i-Pr} in a benchtop experiment) was further mixed with H_2O_2 (50 equiv of vs Fe) and then with cyclohexene (50 equiv), analysis of the products showed predominant (>80% yield) formation of epoxide (Figure S29), as expected for the iron(III)-iron(V) catalytic cycle in Scheme 1.47 Similar observations were made in experiments with cyclooctene (100 equiv): The yield of epoxide was greater for the oxidative pathway (mixing of 1, H_2O_2 , and alkene) than that for the reductive pathway (generation of $1^{IV}=O$ first, followed by the addition of H_2O_2 and alkene), with the discrepancy becoming more apparent at higher loadings (Figure 7). While the



Figure 7. Catalytic cyclooctene epoxidation after formation of $\mathbf{1}^{III}$ –**OOH**, either oxidatively (from $\mathbf{1}^{II}$ and H_2O_2) or reductively (from $\mathbf{1}^{IV}$ =**O** and H_2O_2). Despite the same concentration of H_2O_2 , the oxidatively formed pathway consistently yielded greater amounts of epoxide, with the difference becoming most prominent at higher concentrations. Bottom: Slope of epoxide formation vs H_2O_2 concentration. Oxidative slope: 0.47 \pm 0.025; reductive slope: 0.24 \pm 0.01. The slope for the reductive process is smaller by 51%, likely reflective of the loss of active iron during the reduction of oxoiron(IV).

restoration of catalytic activity in alkene epoxidation was observed on reaction of $1^{IV}=0$ with H_2O_2 , the loss of active iron during reduction makes this pathway less efficient than oxidative generation of peroxyiron(III) from the iron(II) catalyst.

CONCLUSIONS

In summary, we have demonstrated that nonheme oxoiron(IV) complex $1^{IV}=O$ is a potent oxidizing agent able to directly hydroxylate unactivated C–H bonds in substrates such as cyclohexane and benzene and epoxidize alkenes, but the rates of these hydrocarbon oxidation reactions are relatively slow. More relevant to mechanistic studies of the stereoselective catalytic system $1/H_2O_2/alkenes$ (Scheme 1) is the ability of $1^{IV}=O$ to quickly oxidize H_2O_2 , which had previously only been studied kinetically for $3^{IV}=O$ and $4^{IV}=O$. Following reduction with hydrogen peroxide, $1^{III}=O$ is converted to $1^{III}-OOH$, which further converts to $1^{III}-OOH$ with excess

 H_2O_{22} , allowing fast catalytic oxidation of hydrocarbon substrates to resume via the stereoselective peroxoiron(III)oxoiron(V) pathway. However, about 40% of the active iron is lost on treatment of the oxoiron(IV) with H_2O_{22} , making it a less efficient use of catalyst compared to oxidative generation of peroxyiron(III) from iron(II) complex 1 and H_2O_2 . The reductive pathway can be avoided by use of peracids instead of H_2O_{22} , which may afford higher oxidative yields as a result. The ability of the oxoiron(IV) in this, and likely other nonheme ligand systems, to act as a reservoir for the more active iron(III)-iron(V) pathway during catalysis should be considered in future kinetic studies, as well as the possibility of the reduction of oxoiron(V) by H_2O_{22} , which may serve as a source of unproductive oxidant consumption.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.9b02269.

Additional experimental details, EPR spectra and their quantification, ESI-MS and GC-MS spectra, additional stopped-flow UV-vis spectra, kinetic fittings, Eyring plots, and second-order rate constant calculations (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: marc.piquette@tufts.edu (M.C.P.).

*E-mail: sergiy.kryatov@tufts.edu (S.V.K.).

ORCID [©]

Marc C. Piquette: 0000-0002-8782-5878

Notes

The authors declare no competing financial interest. [†]Elena V. Rybak-Akimova died on March 11, 2018.

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