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Oxygen Atom Transfer Mediated by an Iron(IV)/Fe(II) Macrocyclic Complex Containing

Pyridine and Tertiary Amine Donors

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Abstract

A new non-heme iron model complex containing a high-spin iron(II) complexed with *N*-methylated pyridine-containing macrocycle was synthesized and crystallographically characterized. The complex generates peroxo- and high-valent iron-oxo intermediates in reactions with tert-butylhydroperoxide and isopropyl 2-iodoxybenzoate, respectively, allowing to gain insight into the formation and reactivity of enzyme-like intermediates related to biological oxygen activation. The formation and reactivity of these intermediate species was investigated by the stopped-flow methodology. The mechanism of oxygen transfer to organic substrates involving reaction of oxoiron(IV) intermediate was elucidated on the basis of spectroscopic and kinetic data. Incorporation of a pyridine ring into the macrocycle increased the reactivity of the Fe^{IV}=O intermediates in comparison with polyamine tetraaza macrocyclic complexes: ferryl (Fe^{IV}=O) species derived from **3** demonstrated electrophilic reactivity in transferring an oxygen atom to substituted triarylphosphines and to olefins (such as cyclooctene). However, iron(III) alkylperoxo intermediate was unreactive with cyclooctene.

Keywords

Non-heme iron, macrocyclic complex, X-ray crystal structure, oxidation, olefin epoxidation, kinetics, reaction mechanisms

1. Introduction

Heme[1, 2] and non-heme[3, 4] iron-containing oxygenase enzymes have invited interest in the enzyme-mediated oxygen atom transfer reaction mechanism. Physical methods, structural biology, and mechanistic enzymology all contribute to the understanding of the active iron center in these enzymes. Peroxoiron(III) species are often cited as mechanistically important intermediates of iron enzymes. Fe^{III}-OOH species has been characterized and proposed as an intermediate of dioxygen activation in heme cytochrome P450 enzyme and non-heme bimolecular such as bleomycin (BLM) [5-7] and superoxide reductase (SOR) [8-13]. On the other hand, oxygen activation with lipoxygenase (LO) proceeds through a well-characterized end-on-coordinated alkylperoxoiron(III) species [14]. Several biomimetic models of the active site of these enzymes have been prepared and mechanistically important intermediates of the catalytic cycles have been spectroscopically characterized [3, 15, 16]. Synthetic model studies have demonstrated that alkylperoxoiron(III) species [17-24] are more stable compared to hydroperoxoiron(III) [25-39], yet the reactivity pathways of these peroxo complexes are often similar.

Further investigation of the peroxoiron(III) intermediates have shown that O–O bond cleavage can occur, yielding high-valent oxoiron(IV) species either via heterolysis or homolysis. Heterolytic two electron cleavage of the O–O bond leads to $(P^{-})Fe^{IV}=O^+$ (is in resonance with $(P^{2-})Fe^{V}=O^+$) in heme such as P450 enzymes[1], whereas one electron homolytic cleavage leads to formation of Fe^{IV}=O species in non-heme systems [40, 41].

Nam et al. have recently provided the first direct spectroscopic evidence that nonheme alkylperoxoiron(III) species are not capable of oxygenating organic substrates such thioanisole, olefin, cyclooctanol, triphenylmethane; instead, the high-valent as oxoiron(IV) complex is the active oxidant [40, 42]. However, a high-spin iron(III) hydroperoxo complex is reactive in oxidations of alkylaromatic compounds with weak CH bonds [43]. The reactivity of iron(III) peroxo species and iron(IV)-oxo species with organic substrates is currently under active investigation in a number of biological [44, 45] and biomimetic [3, 15, 46-51] systems. Isolating and studying the oxoiron(IV) species from peroxoiron(III) is often difficult, and distinguishing between the reactivity of Fe(III)-peroxo vs. Fe(IV)-oxo intermediates in these systems is challenging. On the other hand, such transient iron(IV)-oxo species can be generated by using oxygen atom donors such as iodosylbenzene (PhIO) [52-57], m-chloroperoxybenzoic acid (m-CPBA) [58, 59], peracetic acid (CH₃COOOH) [54, 60], potassium monopersulfate (KHSO₅) [54], NaOX (X = Cl or Br) [61] or O₃ [62, 63]. This has opened an opportunity to understand the reactivity of the key intermediates in oxygen activation and oxygen atom transfer reactions of iron enzymes and biomimetic complexes, thus clarifying the mechanisms of these processes.

Olefin epoxidation is often studied as an example of a practically important oxygen atom transfer process [64]. Biomimetic non-heme iron complexes that participate in stoichiometric or catalytic epoxidations include aminopyridine complexes (e.g. trispicolylamine, TPA) and tetradentate azamacrocycles (e.g. [14]ane]N4 and [15]aneN4)

[40]. Interestingly, both classes of ligands support ferryl intermediates, but only the former complex, (TPA)Fe^{IV}=O, directly transfers its oxygen atom to cyclooctene [60], while Fe^{IV}=O intermediates supported by polyamine macrocycles do not react with olefins directly, but facilitate epoxidations in the presence of excess PhIO [56]. Our laboratory has utilized mononuclear non-heme iron(II) complexes of pyridine-containing macrocycles to investigate their reactivity towards oxygen transfer reactions [65]. Complex 1 showed catalytic reactivity in olefin epoxidation using H_2O_2 as oxidant, whereas complex 2 was less reactive [65]. Moreover, we observed the ligand in 1 and 2 is susceptible to oxidation, limiting the catalyst's efficiency. We thus synthesized an iron(II) complex with *N*-methylated pyridine-containing tetra-azamacrocycle L1 (3,7,11-trimethyl-3,7,11,17-tetra-azabicyclo[11.3.1]heptadeca-1(17),13,15-triene) to prevent the ligand oxidation (Fig. 1).

Herein we report the syntheses, structures, and properties of the iron(II) complexes with ligand L1. *tert*-Butyl hydroperoxide (TBHP) and hydrogen peroxide (H₂O₂), are used as terminal oxidants in the stoichiometric oxidation of substrates (triaryl phosphines or olefins) and in catalytic or stoichiometric olefin epoxidation studies. TBHP and isopropyl 2-iodoxybenzoate were used to generate alkylperoxoiron(III) **3a** and oxoiron(IV) **3b** species, respectively (Scheme 1). The formation and reactivity of these intermediate species was investigated by the stopped-flow methodology. The mechanism of oxygen transfer to organic substrates involving reaction of oxoiron(IV) intermediate was elucidated on the basis of spectroscopic and kinetic data. Incorporation of a pyridine ring into the macrocycle increased the reactivity of the Fe^{IV}=O intermediates in

comparison with polyamine tetraaza macrocyclic complexes: ferryl(IV) species derived from **3** transfer an oxygen atom to olefins (such as cyclooctene). However, iron(III) alkylperoxo intermediate was unreactive with cyclooctene.

2. Experimental

2.1. General considerations

All reagents were obtained from commercial vendors and used without further purification unless noted otherwise. 2,6-Pyridinedicarboxaldehyde [66] and isopropyl 2iodoxybenzoate [67] were prepared following a published procedure. The tetradentate ligand **L1** was synthesized according to previously published procedures [68, 69]. All manipulations of air-sensitive materials were carried out in the MBraun glove box under an atmosphere of additionally purified from oxygen and moisture ultra-high-purity argon. $H_2^{18}O_2$ (90% ¹⁸O-enriched, 2% solution in $H_2^{16}O$) and $H_2^{18}O$ (98% ¹⁸O-enriched) were purchased from Cambridge Isotope Laboratories Inc. Fe(OTf)₂·2CH₃CN (OTf = CF₃SO₃⁻) was prepared from FeCl₂ and CF₃SO₃SiMe₃ in CH₃CN following an unpublished procedure provided by Dr. Miquel Costas and Prof. Lawrence Que. *m*-CPBA was recrystallized from dichloromethane prior to use. The olefin substrates were purified from traces of alkylperoxides by passing through a short column of activated alumina and stored in a glove box. All concentrations intended for the stopped-flow experiments were before mixing, unless otherwise noted.

2.2. Physical methods

Room temperature UV-visible (UV-vis) spectra were recorded on a Jasco V-570 spectrophotometer. Low-temperature UV-vis spectra were recorded at -40 °C using AP disposable dip probe UV (part No: FA-CTI01-AP2D) purchased from C Technologies, Inc. ESI-MS was performed on a Thermo Finnigan LCQ quadruple field mass spectrometer with electrospray ionization in the positive ion detection mode. NMR spectra were acquired in CDCl₃ at 300K on a Bruker DPX 300 MHz spectrometer; chemical shifts in δ are reported versus tetramethylsilane. The EPR spectra were recorded on a Bruker EMX EPR spectrometer (9.41 GHz) in CH₃CN at 120 K. GC-MS analyses were performed using a Shimadzu QP5050A mass spectrometer connected to Shimadzu GC-17A gas chromatograph equipped with Rtx®-XLB column (length, 30 m; i.d. 0.25 mm; film thickness, 0.25 µm). Helium at a flow rate of 45 cm/s was used as the carrier gas. Injections were made in the splitless mode using an initial column temperature of 50 °C. The temperature was raised at 15 °C/min until 320 °C. Full scan was performed using ionization energy of 70 eV. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside, NY).

2.3. Synthesis of $[Fe^{II}(L1)](OTf)_2(3)$

Fe(OTf)₂·2CH₃CN (440 mg, 1.01 mmol) dissolved in 2.0 mL of dry acetonitrile was added to a solution of **L1** (309 mg, 1.12 mmol) in 2.0 mL of CH₃CN with two drops of dry methanol under an argon atmosphere. When mixing, the solution turned red. A pale yellow solid was obtained after 3 days by crushing the mixture into diethyl ether. Light yellow crystals suitable for X-ray diffraction analysis were obtained by dissolving the solid in CH₃CN followed by adding solution dropwise into diethyl ether. Yield: 64 mg

(43%). ESI(+)–MS (CH₃CN) *m/z*: {[Fe(L1)(CN₃CN)]}²⁺ calcd for 186.6; Found, 186.6;
{[Fe(L1)](OTf)}⁺ calcd for 481.1; Found, 481.3. Anal. Calcd for C₁₈H₂₈N₄FeO₆F₆S₂: C, 34.28; H, 4.48; N, 8.89; Fe, 8.87. Found: C, 34.52; H, 4.43; N, 8.96; Fe, 8.46.

Light green crystals of $[Fe^{II}(L1)](OTf)Cl (4)$ were obtained according to procedure prepared for complex **3** but using a mixture of Fe(OTf)₂·2CH₃CN and FeCl₂ (1:1) instead of pure Fe(OTf)₂·2CH₃CN. ESI(+)–MS (CH₃CN) *m/z*: {[Fe(L1)](Cl)}⁺, calcd for 367.1; Found, 367.4.

2.4. X-ray crystallography

Samples were selected and mounted on a glass fiber in Paratone. The data collections were carried out at a sample temperature of 173 K on a Bruker AXS platform three-circle goniometer with a CCD detector. The first 100 frames were then re-collected at the end of the data collection for monitoring decay. The data were processed utilizing the program *SMART* [70] and *SAINTPLUS* [71] supplied by Bruker AXS. The structures were solved by direct methods (SHELXTL v5.1, Bruker AXS) [72-74] in conjunction with standard difference Fourier techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters. For complex **4**, one chloride ion was found to be disordered. Similarity restraints were applied using the SADI command. Structural parameters for **3** and **4** are given in Table 1. The data were deposited in Cambridge Crystallographic database: CCDC 818640 and 818641.

2.5. Cyclic voltammetry

Cyclic voltammetry experiments were carried out using a CH Instruments electrochemical analysis system (Model 830) using a conventional three-electrode configuration. A glassy carbon electrode (3 mm diameter) was used as working electrode and platinum wires as the counter and reference electrodes. Measurements were performed with 2 mM analyte in CH₃CN at ambient temperature under argon using 0.1 M tetra-*n*-butylammonium hexafluorophosphate as the supporting electrolyte. The range of potentials was scanned at a scan rate of 100 mV s⁻¹. The ferrocenium/ferrocene (Fc⁺/Fc) reference couple was used as an internal standard.

2.6. Measurements of effective magnetic moments in solution

Measurements by Evans method were performed on a Bruker DPX-300 spectrometer at 25 °C [75-77]. A solution of complex **1** (1 mM) in a 0.5 mL of CD₃CN (with 1% tetramethylsilane, TMS) was prepared under an argon atmosphere. The effective magnetic moment (μ_{eff}) was calculated from $\mu_{eff} = 8\chi_g M_w T$, where as the χ_g (cm₃ g⁻¹) is the corrected molar susceptibility derived from $\chi_g = 3\delta v /4\pi v_o CM_w + \chi_o$ [78]. δv is the shift in frequency (Hz) from the value found for the pure solvent, *C* is the concentration of the complex (mol cm⁻³), M_w is the molecular weight of the complex (g mol⁻¹), v_o is the operating frequency of the NMR spectrometer (Hz), and χ_o is the mass susceptibility of the pure solvent (-0.682 × 10⁻⁶ cm³ g⁻¹ for acetonitrile). The 4 $\pi/3$ shape factor is for a cylindrical sample in a superconducting magnet. Then, the number of unpaired electrons per molecule, n, can be easily derived from the magnetic moment using $\mu^2 = g^2 S(S + 1)$,

where *S* is the electronic spin and g the Landé factor. This can be further simplified into n(n + 2) for g = 2 [79].

2.7. Catalysis experiments

Solutions of the iron(II) complexes **3** and **4** were prepared in a glove box under an argon atmosphere (0.8 μ mol, 5% catalyst) in 1.0 mL of CH₃CN. Cyclooctene (25 μ L, 0.016 mmol) was added to the catalyst solution by a syringe. To this mixture was added H₂O₂ (30 wt.% in H₂O) or TBHP (70 wt.% in H₂O) (30 μ L, 0.024 mmol) all at once. The reaction was carried out at room temperature under argon atmosphere for 5 min and analyzed by GC–MS. The ratio of catalyst/substrate/H₂O₂ was 1/20/30. In the ¹⁸O-labeling experiments, H₂¹⁸O₂ or H₂¹⁸O (300 μ L, 0.24 mmol) was added to the catalyst solution following the method described as above.

2.8. Stopped-flow kinetics

Stopped-flow spectrophotometry was performed on a TgK Scientific (formerly, Hi-Tech Scientific, UK) SF-61DX2 cryogenic double-mixing stopped-flow system [80] equipped with J&M TIDAS diode array spectrophotometer (MCS UVNIR 500-3, 200– 1024 nm) [81]. Low temperatures were maintained through the use of a liquid-nitrogencooled ethanol bath equipped with a cryo unit. All flow lines of the instrument were extensively washed with oxygen-free, argon-saturated anhydrous CH_3CN before charging the driving syringes with reactant solutions. CH_3CN solutions of the reagents were prepared in a glove box filled with argon and placed in Hamilton gastight syringes. Kinetic StudioTM [82] and J&M TIDAS software package were used to control the

instrument and collect data. The raw kinetic data were treated with Kinetic StudioTM software from TgK Scientific, and with Spectfit/32 Global Analysis System software from Spectrum Software Associates [83].

3. Results and discussion

Iron(II) complexes with the pyridine-containing macrocycle **L1** were prepared from the appropriate iron(II) salt and the free ligand, and characterized by elemental analysis, mass spectrometry, UV–vis spectrophotometry, and structural determination by singlecrystal X-ray diffraction. Crystallographic information was particularly revealing for comparing the complexes of *N*-alkylated macrocycle with other pyridine-azamacrocyclic (PyMAC) complexes prepared in our group [65, 84, 85].

3.1. X-ray crystallographic analysis

X-ray crystallographic results demonstrated that **3** had an iron(II) ion in a distorted octahedral environment and **4** adopted a square-pyramidal geometry (Fig. 2, 3). The iron(II) center of **3** was essentially four-coordinate, with four nitrogen donors from the 'folded' macrocyclic ligand and two distant oxygen donors from two different weekly bound triflate ions in a relative *cis* orientation completing the coordination sphere. The crystal structure of **3** showed this pyridine-containing macrocycle was folded about the N(2) to N(4) axis, and the apex was occupied by N(3) and located almost perpendicular to the pseudo-planar atom set defined by the metal ion and three remaining nitrogens of the macrocyclic amine. This conformation allowed easier N inversion at N(3), as observed. The coordination sphere of iron in the crystal structure of **4** was also completed

by a 'folded' structure, defined by the four nitrogen donors from the ligand and one chloride anion in the apical site which occupied in a *trans* position to the pyridine N atom, leaving one triflate as a counter ion. Selected bond lengths and angles were listed in Table 2. For **3** and **4**, the values of the N2–Fe1–N4 angles (153.12 (9)° and 152.58 (8)°), N1–Fe1–N3 angles (100.09 (9)° and 101.72 (8)°) were observed, respectively. This geometry has also been found in nickel [69, 86] and copper analogue of **3** and **4** [87].

The Fe–O_{triflate} bond lengths in **3** were 2.03(2) and 2.24(2) Å and the Fe–Cl bond length in **4** was 2.29(9) Å. The Fe–N bond length in **3** and **4**, which ranged from (2.07(2) to 2.27(2) Å) and (2.07(2) to 2.20(2) Å), respectively, were in the range expected for typical high-spin iron(II) complexes [88, 89], with the shortest bond length to the pyridine nitrogens 2.07(2) Å in both cases. The Fe–N separation was similar to the reported high-spin **2** (2.06–2.18 Å) [65].

For comparison, the Fe–N bond length (1.89–2.04 Å) for low-spin **2** has been reported previously[65], which was shorter than the iron-nitrogen bond lengths in high-spin **3** and **4**. Low spin complex **1**, bearing the ligand with several primary amine donors in the macrocycle, adopted an octahedral geometry with coordinated CH₃CN in the axial position, whose crystal-field stabilization energy favored low-spin octahedral complexes for a d⁶ configuration. Nevertheless, tetradentate macrocycles of iron(II), nickel(II) and copper(II) complexes [18, 90-93] were often coordinated to additional monodentate anions (Cl⁻, Br⁻, I⁻, N⁻₃, NSC⁻ or NO₂⁻), displaying a strong structural preference for a square-pyramidal geometry. Changes of the coordination geometry of the

metallomacrocycles from the six-coordinate octahedral to a five-coordinate squarepyramidal often resulted in changes from the low-spin to a high-spin configuration of the central metal ion, evidenced by the appropriate changes in their magnetic and spectroscopic properties [18, 94, 95].

3.2. Properties of iron(II) complexes with L1

3.2.1. Magnetic properties of iron(II) complexes in solution

Magnetic susceptibility measurements using Evans' method was performed on **3** and **4** in CD₃CN. The effective magnetic moment values obtained ($\mu_{eff} = 5.2$ B.M.) for complexes **3** and **4** were in the range expected for high-spin d⁶ electronic configuration of the iron(II) centers in mononuclear complexes. The five-coordinate **2** had a typical high-spin configuration ($\mu_{eff} = 5.1$ B.M.), whereas the low-spin **1** definitely showed no splitting of TMS peak (Table 3) [65]. The *N*-methylation of secondary aminogroups caused the iron(II) complex with ligand **L1** to adopt high-spin configuration, while the structurally similar complex **1** with the macrocycle containing non-alkylated secondary aminogroups was low-spin. Meyerstein et al. demonstrated that transforming all the nitrogen donor atoms into tertiary nitrogens elongated the Metal–N bonds.[95] This structural effect has also been observed in **3**, **4** and other reported iron(II) complexes with *N*-methyl substituted TPA and cyclam-acetate [18, 94, 96]. These iron(II) complexes with *N*-methylated ligand all favor the high-spin configuration of the metal center.

3.2.2. Cyclic voltammetry (CV)

Electrochemical characteristics of **3** and **4** derived from cyclic voltammetry are shown in Fig. 4. The CV scan of **3** in CH₃CN showed a well-formed anodic peak $E_{pa} = 0.91$ V assigned to Fe^{III}/Fe^{II} couple. During the cathodic reduction scan two responses were observed: 0.715 V and 0.219 V. The observation of two cathodic processes implies the change in the coordination sphere of iron after oxidation of the iron(II) center; formation of the iron(III) oxo-bridged dimers is a likely possibility. The asymmetry in the wave's shape is also indicative of the deposition upon oxidation of conducting species at the electrode. Other high-spin iron(II) complexes [18, 24] were also oxidized at high potential, but the oxidations were irreversible in these cases. The chloride-coordinated complex 4, however, displayed a quasi-reversible metal-centered redox process Fe^{III}/Fe^{II} $(E_{1/2} = 0.41 \text{ V vs Fc}^+/\text{Fc}, \Delta E_p = 169 \text{ mV})$. The shift on oxidation potential of **4** compared to 3 is consistent with relative stabilization of the Fe(III) upon coordination of the negatively charged chloride ligand. Coordination of chloride also protects the iron(III) species from iorreversible hydrolysis and formation of oxo-bridged dimers or oligomers. The previously reported high-spin 2 ($E_{1/2} = 0.58 - 0.56$ V with $\Delta E_{p1} = 260$ mV and $\Delta E_{p2} =$ 540 mV) also exhibited a quasi-reversible redox process. Furthermore, 2 differed from low-spin 1, as the latter complex showed reversible one electron transfer process at 0.40 V vs Fc^+/Fc (non-coordinating counterions, perchlorate or triflate, were present in 1 and 2) [65]. Therefore, coordination sphere effects on Fe^{III}/Fe^{II} redox potential can be identified by CV scan and reveal the relative reducing strength of iron(II) macrocyclic complexes in a series of PyMACs.

3.2.3. Catalytic and stoichiometric olefin epoxidation

cis-Cyclooctene is commonly used as a suitable substrate for catalyst screening in epoxidations with H_2O_2 in the presence of non-heme iron catalysts [79]. Catalytic epoxidation of cyclooctene with complexes **3** and **4** using H_2O_2 and TBHP as oxidants were examined to explore the effectiveness of the new complexes compared to that of complex **1** and **2**. Table 4 showed epoxide yields and turnover numbers (TON) after 5 min of reaction, carried out under argon atmosphere at room temperature with **1–4** as catalysts.

Complex **3** did not efficiently catalyze olefin epoxidation, and acted as a stoichiometric reagent instead, resulting in only 7% yield of epoxide (1 TON) using H_2O_2 as the oxidant. Other identified side products include diol (ca. 0.25% with respect to cyclooctene) and allylic alcohol (ca. 0.25%). Incorporation of ¹⁸O into the epoxide and one ¹⁸O into *cis*-diol were observed when the reaction was carried out in the presence of $H_2^{18}O_2$. ¹⁶O-epoxide and trace of ¹⁸O of *cis*-diol were detected when the reaction was carried out in the presence of H_2O_2 and $H_2^{18}O$. These observations suggested that the oxygen of epoxide and one oxygen atom of *cis*-diol were exclusively derived from H_2O_2 . One oxygen atom source of diol arose from H_2O . In a control experiment, diol was not obtained from the epoxide and water (in the presence of H_2O or $H_2^{18}O$), indicating that the incorporation of oxygen into diol only took place during the catalytic oxidation of the olefin. Neither **2** nor **3** exhibited a reversible CV wave, which indicated that the small turnover number might be related to poor stability of the oxidized forms of these

complexes. In contrast, low-spin **1**, which exhibited a classic redox wave in the cyclic voltammogram, afforded about 6 TON of epoxide [65]. This suggested that the high-spin iron(II) PyMAC complexes did not efficiently catalyze epoxidation, whereas the low-spin ones were more reactive. It appeared that the weak-field ligands that form high-spin iron(II) complexes did not sufficiently stabilize the oxidized forms of the catalysts (e.g. Fe (III) species) with respect to partial or complete hydrolysis. Indeed, the loss of iron was observed after several redox cycles with complex **3**. Coordinatively saturated complex **4** had no activity in olefin epoxidation using H_2O_2 as the oxidant, presumably because no vacant sites were available for initial coordination of the oxidant. Somewhat higher activity of **3** compared to **4** underscored the importance of the vacant or labile site at the iron centers in hydrogen peroxide activation, and highlights the critical role of the coordination sphere of iron that controlled the catalytic activity of PyMAC complexes.

t-Butylhydroperoxide (TBHP) has also been examined as an oxidant in epoxidation with **3**, and it afforded the same product yield as the one obtained with H_2O_2 as the oxidant (7% epoxide with respect to cyclooctene). This led us to propose that similar activity in both reactions may be attributed to the same intermediate responsible for olefin epoxidation. In search of transient iron-based intermediates, reactions of complex **3** with oxidants were examined by *in situ* spectrophotometry at low temperature. In these exploratory studies, low-temperature spectra were acquired with the dip probe connected to a regular spectrophotometer; in detailed mechanistic studies, low-temperature stopped-flow measurements allowed us to acquire accurate time-resolved spectra.

3.2.4. Reactions of complex 3 with oxidants

In order to further understand the details of stoichiometric or catalytic oxidations with iron PyMAC's, various oxidants have been examined in reactions with catalytically active complex 3, generating putative intermediates in order to further understand the details of the catalytic mechanisms. Complex 3 in CH₃CN gave a pale yellow solution. The reaction of 3 with TBHP in CH₃CN at -40 °C produced a deep purple intermediate which persisted for several hours at -40 °C, but quickly turned to yellow at room temperature. The visible spectrum of this intermediate was consistent with an iron(III)alkylperoxo species [18, 20-22, 97-101]; somewhat lower observed extinction coefficient may be explained by a less-than-quantitative yield of this intermediate. Treatment of 3 with H₂O₂, *m*-CPBA or isopropyl 2-iodoxybenzoate at -40 °C in CH₃CN generated a transient brownish yellow solution, which also turned to yellow species upon warming up to room temperature. Spectral changes included the growth of the weak near-IR absorption band in the ca. 700-800 nm region, typical of the iron(IV)-oxo intermediates [21, 23, 97, 100, 102, 103]. Low-temperature UV-vis spectra for these transient species are shown in Fig. 5. We then investigated the formation of these transient species and their corresponding reactivity towards oxygen transfer reactions, using stopped-flow methodology.

3.3. Generation and reactivity of high-spin alkylperoxoiron(III) intermediates

In the stopped-flow experiment, treatment of **3** (2 mM) with 15-fold excess of TBHP at -20 °C in CH₃CN resulted in the rapid formation of a purple-colored transient species which exhibited a broad absorption band with a maximum at 530 nm ($\epsilon \approx 500 \text{ M}^{-1} \text{ cm}^{-1}$)

(Fig. 6) due to the charge transfer (LMCT) from the ligand to the high-spin iron(III) center.[104] This assignment was consistent with reported spectroscopy of alkylperoxoiron(III) complexes [18, 20-22, 97-100]. The reaction of TBHP with **3** generating a deep purple species $[Fe^{III}(L1)(OO'Bu)]^{2+}$ **3a** was proposed and the overall process was outlined in the eq (1):

$$\mathbf{3} + \text{TBHP} \xrightarrow{k_1} [\text{Fe}^{\text{III}}(\text{L1})(\text{OO}^t\text{Bu})]^{2+}$$
 (3a) (1)

Under pseudo-first-order conditions, excess TBHP (5–25 fold) was added to the solution of **3** (2 mM) in CH₃CN at –20 °C. Pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} value for the reaction with TBHP (Fig. 7). The pseudo-first-order rate constants were independent of concentrations of **3** and displayed linear dependency on the concentration of TBHP. This led us to propose the rate law in eq (2) and determine the second-order rate constants to be $k_2 = 0.40 \text{ M}^{-1}\text{s}^{-1}$ at –20 °C.

$$-\frac{d[\mathbf{3}]}{dt} = \frac{d[\mathbf{3}\mathbf{a}]}{dt} = k_{\text{obs}}[\mathbf{3}] = k_2[\mathbf{3}][\text{TBHP}] \quad (2)$$

Acquisition of kinetic data for the reaction of **3** (2 mM) with a 10-fold excess of TBHP over a range of temperature (-40 to 0°C) was performed for determining the activation parameters of this process. An Eyring plot of the second-order rate constants was linear for the reaction and yielded the activation parameters of $\Delta H^{\ddagger} = 33.6$ kJ/mol and $\Delta S^{\ddagger} = -107$ J/mol K (Fig. 8). The moderately high activation enthalpy and large, negative activation entropy indicated the [Fe^{III}(L1)(OO'Bu)]²⁺ species **3a** formed in an associative process. Reaction (1) was a multi-step process that included a one-electron

oxidation of Fe(II) into Fe(III) followed by the ligand substitution at the iron(III) center, eventually affording the (L)Fe^{III}-^{*t*}BuOOH species.[105, 106] While the activation parameters for reaction (1) are consistent with the peroxide coordination to Fe(III), the activation parameters for a multi-step process are composite values that likely reflect the contributions from both the one-electron oxidation process and the subsequent ligand binding process.

(L)Fe^{II} + ^tBuOOH →(L)Fe^{III} + ^tBuOO' (L)Fe^{III} + ^tBuOOH → (L)Fe^{III}(OO^tBu) + H

(^tBuOO[•] may abstract a hydrogen atom from the solvent, the ligand, or the substrate)

The purple intermediate **3a** was also characterized by EPR and ESI–MS. An EPR spectrum of a frozen solutions of $[Fe^{III}(L1)(OO'Bu)]^{2+}$ **3a** in CH₃CN was obtained at 120 K (Fig. A.1). The intense purple intermediate exhibiting isotropic signals at *g* = 8.8 and 4.3 indicated a high-spin iron(III) species (*S* = 5/2) with rhombic symmetry [18-23, 101]; the presence of additional high-spin iron(III) signals at g = 4.3 cannot be excluded. The assignment to high-spin iron(III) was distinct from more common low-spin Fe^{III}–OO'Bu (*S* = 1/2) with axial symmetry exhibiting *g* values of 2.28, 2.19 and 1.97 [17, 18, 24]. A sharp signal at *g* = 2.0 possibly arose from organic radical. As reported, low-spin [Fe^{II}(TPA)(CH₃CN)₂]²⁺ and high-spin [Fe^{III}–OO'Bu complexes, respectively [18]. Introduction of methyl substituents to the amine nitrogens of the ligand decreased the ligand-field strength of the macrocycle and generated steric interactions to favor the high-

spin state of the Fe^{III}–OO^{*t*}Bu complexes. Similar spin state changes upon alkylation of macrocyclic nitrogen donors were reported for related iron(III) alkylperoxo complexes [96].

The ESI-MS spectrum was obtained by directly injecting the purple solution of $[Fe^{III}(L1)(OO'Bu)]^{2+}$ **3a** in CH₃CN generated at -40 °C into mass spectrometer (Fig. A.2); main peaks are listed in Table 5. Peaks *m/z* at 174.2, 497 correspond to $[Fe^{IV}(L1)(O)]^{2+}$ and $[Fe^{IV}(L1)(O)(OTf)]^+$, respectively. The oxoiron(IV) species was possibly formed from decay of $[Fe^{III}(L1)(OO'Bu)]^{2+}$ **3a** by O–O bond homolysis. This observation demonstrated that the $(L1)Fe^{III}O-O'Bu$ intermediate underwent the homolytic cleavage of the O–O bond under mass-spectrometric conditions, to yield a high-valent oxoiron(IV) species **3b**. In addition to the evidence of ESI-MS data, a low-intensity near-IR absorption band at 800 nm may also indicate the formation of oxoiron(IV) [107, 108] (Fig. 5). A similar homolytic O–O bond cleavage has been proposed for the alkylperoxoiron(III) species with β-BPMCN and TPA ligands [21, 23], whereas the homolytic LFe^{III}-OO'Bu (iron-oxygen) bond cleavage was observed in other alkylperoxoiron(III) species with 6-Me₃-TPA and Py(ProMe)₂ ligands [22, 98].

The purple $[Fe^{III}(L1)(OO'Bu)]^{2+}$ species **3a** did not react with cyclooctene at low temperature. Therefore, other intermediate(s) must be responsible for olefin epoxidation promoted by **3**. The oxoiron(IV), that can result from a homolytic O–O bond cleavage in LFe^{III} –OO'Bu, was an obvious alternative for a potential reactive oxidant for olefin epoxidation that should be considered. A direct way of generating oxoiron(IV) was required for understanding the reactivity of this key intermediate.

3.4. Generation and reactivity of the oxoiron(IV) intermediates

3.4.1. Formation of $[Fe^{IV}(L1)(O)]^{2+}$ (**3b**) in the reaction of **3** with isopropyl 2iodoxybenzoate

In general, the formation of oxoiron(IV) complexes was accompanied by the appearance of the low-energy d-d transition band in the near-IR region, characteristic for the S = 1 oxoiron(IV) center [107, 108]; similar, but weaker near-IR absorption band was also observed for a high-spin (S = 2) $Fe^{IV}=O$ intermediate [109]. The formation of oxoiron(IV) **3b** from the iron(II) PyMAC complex **3** was indicated by an absorption band at ca. 780 nm at low temperature (e.g., -40 °C) using H₂O₂, m-CPBA or isopropyl 2iodoxybenzoate as an oxidant (Fig. 5). The analysis of the UV-vis spectra of these systems identified isopropyl 2-iodoxybenzoate as the most promising oxidant for clean generation of the Fe(IV) species for subsequent reactivity studies. Indeed, the reaction of 1 with H_2O_2 in CH₃CN exhibited a broad, but relatively weak absorption band at *ca*. 800 nm. With *m*-CPBA, the reaction showed a relatively strong absorption band at 780 nm along with a less intense absorption at 550 nm, which can be tentatively assigned to an *m*-CPBA adduct of iron(III) species; formation of two colored intermediates would complicate the interpretation of kinetic data. Finally, the reaction of 3 with isopropyl 2iodoxybenzoate in CH₃CN monitored by a regular benchtop UV-vis spectrophotometer equipped with an immersion probe (dip probe) generated a single species exhibiting an absorption maximum at 780 nm ($\epsilon \approx 50 \text{ M}^{-1} \text{ cm}^{-1}$). This rapid and clean reaction (Scheme 1-(b)) was selected for detailed studies described below.

Mass spectrometry is also consistent with the assignment of the yellow-green intermediate generated in the reaction of 1 with isopropyl 2-iodoxybenzoate as the iron(IV)-oxo species. This intermediate exhibited a peak m/z at 194.6 and 497.1 on ESI-MS, corresponding to $[Fe^{IV}(L1)(O)(CH_3CN)]^{2+}$ and $[Fe^{IV}(L1)(O)(OTf)]^{+}$, respectively (Fig. 9). Additionally, a peak m/z at 497 slowly changed to a high relative abundance peak at m/z = 498 which was assigned to $[Fe^{III}(L1)(OH)(OTf)]^+$, a decomposition product of oxoiron(IV) species. This m/z 498 peak became predominant after 10 min, along with the peak of a free ligand L1 (m/z at 277), suggesting the instability of the iron complex (Fig. A.3). The resulting yellow acetonitrile solution precipitated a rust-colored solid after one day at room temperature. ESI-MS showed the solution in CH₃CN mainly contained the ligand, thus the precipitate was likely to be Fe₂O₃. A similar rust-colored hydrolysis product was also obtained previously in a related system by adding TBHP to high-spin [Fe^{II}(L^{8} py₂)(X_{apical})] (L^{8} py₂ = N,N'-bis(2-pyridylmethyl)-1,5-diazacyclooctane; X = triflate, benzoate or 4-methylbenzenethiolate) in CH₂Cl₂.[22] Relative instability of **3b**, combined with low yield of this species (as determined by low observed intensities of the absorption bands in near-IR region) precluded a more detailed spectroscopic characterization of this intermediate. A related intermediate obtained from 5 and isopropyl 2-iodoxybenzoate also demonstrated UV-vis absorption peak at 705 nm ($\varepsilon =$ 240 M⁻¹ cm⁻¹) and showed ferryl-derived peaks in the mass spectra analogous to the ones observed for **3b**. Moreover, the intermediate obtained from **5** and isopropyl 2iodoxybenzoate was characterized by Mössbauer spectroscopy, which unequivocally showed an iron(IV) oxidation state of the metal center in this intermediate [84]. We

propose that the intermediate **3b** also contains a high-valent Fe(IV)-oxo species. This formulation agrees with distinct UV-vis-NIR signatures of Fe(IV) species (low intensity absorption band in the 700 – 800 nm region), and with mass spectroscopic results clearly showing the peaks for (L)Fe=O intermediate, and is also consistent with the methods of generating this intermediate from the Fe(II) precursor and several oxygen atom donors (Figure 5) and its chemical reactivity discussed in detail below. In brief, a clean oxygen atom transfer to substrates (phosphines or olefins) was observed; ¹⁸O label was transferred to epoxide products in reactions with H₂¹⁸O₂. Reactions of **3b** with PPh₃ yield OPPh₃ and an iron(II) complex **3**. All these reactivity data are consistent with **3b** being being an iron(IV) species containing a transferable oxygen atom. In the absence of direct spectroscopic data (e.g. Mössbauer spectra measured in applied magnetic field), determining the spin state of iron(IV) in **3b** is not possible at present.

Detailed studies of the reactivity of **3b** were performed using an iodine(V) oxidant, isopropyl 2-iodoxybenzoate, as an oxygen atom transfer reagent that cleanly reacted with **3**, forming **3b**. Unlike other commonly used oxidants, such as PhIO or Me₂-PhIO (2,6-dimethyliodosylbenzene) [110], isopropyl 2-iodoxybenzoate was soluble in CH₃CN (*ca*. 100 mM in CH₃CN at 25 °C). Due to the small value of the extinction coefficient of oxoiron(IV) (**3b**), higher concentration of iron and oxidant solutions were needed to obtain good time-resolved spectra for the stopped-flow measurements. Additionally, most kinetic studies were performed at low temperature; thus, oxidants with good solubility in CH₃CN were necessary to achieve the proper stoichiometry of reactants. The reaction of excess isopropyl 2-iodoxybenzoate with **3** was monitored at -40 °C by

stopped-flow spectroscopy and reveals an increase of the oxoiron(IV) species **3b** at 780 nm (Fig. A.4).

A stopped-flow study of the reaction of **3** with isopropyl 2-iodobenzoate showed a two-step process, with a very rapid (*ca.* 20 ms at -40 °C) build-up of an absorption band with $\lambda_{max} = 700$ nm, which quickly converted into a much more stable band with $\lambda_{max} =$ 780 nm (Fig. A.4). This shift of an absorption maximum of the iron(IV) species is likely related to the coordination on the oxidant (isopropyl 2-iodobenzoate) or the product of its partial reduction (an iodine(III) compound) to the initially formed Fe(IV) intermediate (Scheme 2). When Fe(II) complex 3 was the limiting reactant (in reactions with 0.5 moles or less of IOO oxidant per 1 mole of 3), both oxygen atoms of the iodine(V) oxidant were eventually transferred to the iron center (the transfer of the first oxygen atom is very rapid, while the second oxygen atom transfer is somewhat slower). Increasing the concentration of the oxidant resulted in the expected increase in the values of k_{obs} , although limited series of the reactant concentrations could be explored due to low extinction coefficient of **3b**. Detailed kinetic analysis of the reaction between **3** and isopropyl 2-iodoxybenzoate was not performed in this work; instead, the optimal conditions of generating Fe(IV) intermediate were identified in single-mixing kinetic experiments.

3.4.2. Reactions of Oxoiron(IV) 3b with PPh₃

Using experimental conditions that allowed us to generate iron(IV)-oxo intermediate **3b** in single-mixing stopped-flow experiments described above, we investigated the reactivity of this high-valent iron-oxo intermediate with substrates, such as PPh₃ or olefin (cyclooctene). PPh₃ can be oxidized easily by isopropyl 2-iodoxybenzoate. Therefore, less than 1 equivalent of isopropyl 2-iodoxybenzoate was used in the formation of oxoiron(IV) species in order to avoid excess oxidant in subsequent reactions with substrates.

Double-mixing stopped-flow experiments were performed to gain mechanistic insight into the reactivity of $[Fe^{IV}(L1)(O)]^{2+}$ **3b** with substrates. In the first mixing step, solutions of **3** (16 mM) and 0.3 equiv isopropyl 2-iodoxybenzoate in CH₃CN were combined at – 20 °C and incubated for 500 s to ensure maximum formation of oxoiron(IV). Then, a solution of PPh₃ in CH₃CN was added in the second mixing. Changes in absorbance at λ = 780 nm are monitored. As shown in Fig. 10, when 3 equiv PPh₃ (48 mM) was added to the oxoiron(IV) solution, the reaction proceeds rapidly. It was completed within seconds at –20 °C, yielding Ph₃PO quantitatively, which was confirmed by GC–MS. This implies a fast oxygen atom transfer in the process. ESI–MS of this resulting solution shows a predominant peak *m/z* at 481 indicating that the $[Fe^{IV}(L1)(O)]^{2+}$ species **3b** was converted back to the starting complex **3** (Fig. A.5). These results, taken together, indicate a fast oxygen atom transfer in the process. Moreover, generation of $[Fe^{IV}(L1)(O)]^{2+}$ (**3b**) and its decay upon addition of PPh₃ can be repeated several times and monitored by regular

spectrophotometry with an immersion probe (Fig. A.6), suggesting that the oxo transfer could afford several catalytic cycles.

Acquisition of kinetic data for the reaction of **3b** with 3 equiv of PPh₃ over a temperature range from -30 to 0 °C allowed us to determine activation parameters. An Arrhenius plot was linear for the reaction (Fig. 11), and yielded rather high activation energy ($E_a^{\ddagger} = 53 \text{ kJ/mol}$); this values exceeds the activation energy of cyclooctene epoxidation discussed below. It can be concluded that the oxygen atom transfer from oxoiron(IV) in **3b** to PPh₃ is a high-barrier process.

3.4.3. Reactions of oxoiron(IV) 3b with cyclooctene

The pre-mixed solution containing $[Fe^{IV}(L1)(O)]^{2+}$ **3b** was generated in the stoppedflow mixing cell as described above. The reaction of excess cyclooctene with **3b** was monitored at 20 °C under pseudo-first-order conditions by the stopped-flow spectrophotometry and revealed a smooth decay of the oxoiron(IV) species. In a control reaction, in which **3b** was mixed with CH₃CN, little change in optical absorbance at 780 nm was observed (Fig. 12-a). The pseudo-first-order fitting of the kinetic data in the reaction of **3b** with cyclooctene allowed us to determine k_{obs} values which increase linearly with cyclooctene concentration, yielding the second-order rate constant $k_2 =$ 0.032 M⁻¹ s⁻¹ at 20 °C (Fig. 12-b); the proposed mixed second-order rate law is shown in eq (3). This rate law was consistent with a bimolecular reaction pathway depicted in equation (4); epoxide products were quantitated by GC–MS in separate benchtop experiments. A plot of the temperature dependence (25 to 35 °C; experimental difficulties

did not allow us to perform the measurements over broader temperature range) for the reaction of $[Fe^{IV}(L1)(O)]^{2+}$ **3b** with 60 equiv cyclooctene in CH₃CN fits the linear form of the Eyring equation, giving the activation parameters of $\Delta H^{\ddagger} = 60$ kJ/mol and $\Delta S^{\ddagger} = -69$ J/mol K ($R^2 = 0.9993$) (Fig. 12-c). Thus, an oxygen atom transfer to cyclooctene from oxoiron(IV) is an associative process characterized by a large negative activation entropy.

$$-\frac{d[\mathbf{3b}]}{dt} = \frac{d[\mathbf{3c}]}{dt} = k_{\text{obs}}[\mathbf{3b}] = k_2[\mathbf{3b}][\text{cyclooctene}]$$
(3)

$$(L1)Fe^{IV}=O (3b) + (L1)Fe^{III} - (L1)Fe^{III} + O (4)$$

The ability of iron(IV) oxo intermediate **3b** to transfer an oxygen atom to cyclooctene under anaerobic conditions determined in kinetic experiments was mirrored by the formation of cyclooctene epoxide in benchtop experiments. The organic oxidation products were analyzed by gas chromatography – mass-spectrometry (GC–MS). For example, mixing 1 mole of **3** with 0.3 moles of isopropyl 2-iodoxybenzoate at room temperature, followed by the addition of 20 moles of cyclooctene afforded 0.3 moles of epoxide (0.3 turnovers with respect to iron complex; 50% yield with respect to limiting reactant of isopropyl 2-iodoxybenzoate). Low concentration of the oxidant and its rapid (within seconds) consumption in the initial reaction with **3** ensured the absence of excess isopropyl iodoxybenzoate in the process of cyclooctene eoxidation. It required about 15 min to reach the maximum yield of epoxide in this stoichiometric reaction of cyclooctene and isopropyl 2-iodoxybenzoate in the presence of **3**. This time scale was comparable to the decay time of **3b** in the presence of cyclooctene substrate. Additionally, no diol was

produced, providing indirect evidence that the diol formation needed H_2O (and/or H_2O_2) during the epoxidation/dihydroxylation reaction. These experiments demonstrate that an iron(IV) oxo intermediate **3b** is a competent oxo-transfer reactant in cyclooctene epoxidation. This behavior is similar to the previously reported reactivity of ferryl intermediates supported by aminopyridine ligands (such as TPA [60]), but differs from the lack of reactivity of iron(IV) species bound to polyamine macrocycles [64]. It is becoming increasingly clear that the reactivity of high-valent iron-oxo species can be altered by the exact structure of the first coordination sphere of the metal [15, 40, 41, 111]. More electron donating tetraaza macrocycles stabilized ferryl species and rendered them unreactive; more electron-withdrawing ligands bearing several pyridine rings decreased the stability of high-valent iron-oxo intermediates and increased the reactivity of these species with oxygen atom acceptors. The ligand L1 bears one pyridine rings and three tertiary amine donors, and its ability to support reactive iron(IV)-oxo intermediates falls between the reactivities of the ligands with several pyridine donors and those with several amine donors.

The ability of complex **3** to support a high-valent iron(IV)-oxo intermediate that reacts (albeit slowly) with cyclooctene did not lead to high catalytic activity of this complex in epoxidations. Unfortunately, upon addition of cyclooctene to $[(L1)Fe^{IV}=O]^{2+}$ (**3b**), this iron(IV)-oxo intermediate did not convert back to the iron(II) precursor **3**. Instead, **3b** decomposed into an as-of-yet uncharacterized iron(III) complex (that presumably results from comproportionation of the iron(IV) species **3b** and the iron(II) complex **3** and the free ligand **L1**, that was detected by ESI–MS. This indicated that the low turnover

numbers and efficiency of epoxidation with 3 was due to the iron dissociation from the macrocycle. In contrast, as we have described above, several catalytic cycles can be observed with stronger reducing agents, such as PPh₃, as can be estimated from the fast observed rate of reaction between **3b** and triarylphosphine substrate. Low catalytic activity of the N-methylated iron macrocyclic complexes compared to their nonmethylated secondary amine precursors parallels the observations previously reported in the literature. For example, Nam and Valentine [112] discovered catalytic activity of iron(II) cyclam complex in epoxidation of olefins with hydrogen peroxide, while analogous iron complex with tetramethylcyclam (TMC) was inactive. Interestingly, tetramethylcyclam supported a relatively stable, crystallographically characterized ferryl(IV) complex[52, 64]. Iron complex with tetramethylcyclam also supports a side-on peroxo adduct that does not act as an active oxidant, and an end-on hydroperoxo species that displays both nucleophilic and electrophilic reactivity with substrates, and generates an iron(IV)-oxo species via hemolytic O-O bond cleavage [43]. It can be concluded that the ability of the polydentate ligand to stabilize iron(IV)-oxo intermediates is insufficient for designing highly reactive catalysts of oxygen atom transfer to olefin substrates; the reactivity of the iron(IV)-oxo intermediates is the key. The presence of secondary aminogroups in the immediate vicinity of the redox center appears to facilitate an oxygen atom transfer to substrates; [84] similar second-sphere effects may increase the reactivity of iron(IV) intermediates in non-heme iron enzymes [113, 114].

As we mentioned earlier, **4** did not promote olefin epoxidation with hydrogen peroxide or TBHP. It is possible that the oxoiron(IV) intermediate cannot be formed because of the

strong coordination of Cl⁻ to the iron center. Additionally, ESI–MS of the reaction of **4** with H_2O_2 shows peak m/z at 367 and 277, corresponding to $\{[Fe(L1)](Cl)\}^+$ and ligand **L1**, respectively. This suggests that the iron dissociated from the ligand upon oxidation. On the other hand, the weakly bound triflate anions can be displaced by acetonitrile molecule in solution to form the oxoiron(IV) intermediate in reactions with strong oxygen atom donors. The presence of vacant or labile coordination cites at iron centers is critical for catalytic efficiency of oxidative metalloenzymes and their models [115].

4. Conclusions

In conclusion, we have synthesized a high-spin iron(II) complex **3** with *N*-methylated pyridine-containing macrocycle. Introduction of methyl groups on the amine nitrogen of the macrocycle, which suppresses ligand oxidation, alters the properties of the complexes in several ways. For example, *N*-alkylation exerts a significant effect on the spin state of the iron(II) center, favoring the high-spin configuration of the metal center. It also elongates the Fe–N bonds and decreases the thermodynamic stability of iron(II) and iron(III) complexes [95]. Often, *N*-alkylation results in the higher Fe^{III}/Fe^{II} redox potentials [95]. Ligand stability under oxidative conditions allowed us to generate iron-peroxo and –oxo intermediates (**3a** and **3b**, respectively) that mimic proposed intermediates in the catalytic cycles of non-heme iron oxidative enzymes. Alkylperoxo iron(III) species (**3a**) that resulted from the reaction of the Fe(II) precursor with t-butyl hydroperoxide (TBHP), does not react with cyclooctene; instead, it undergoes homolytic O–O bond cleavage to yield high-valent iron species of a non-heme mononuclear high-

spin alkylperoxoiron(III) 3a and oxoiron(IV) (3b). A similar hemolytic O-O bond cleavage of the iron(III)-hydroperoxo species was recently observed for irontetramethylcyclam (TMC) [43], although this Fe^{III}(TMC)-OOH intermediate also displayed the ability to oxidize carbonyl compounds (nucleophilic reactivity) and to abstract a hydrogen atom from alkylaromatic compounds with weak CH bonds (electrophilic reactivity). Comparisons of our new complex 3 to analogous alkylated macrocycles lacking a pyridine ring underscores the importance of subtle changes of the ligand structure on the reactivity of various iron-peroxo and iron-oxo intermediates. Isopropyl 2-iodoxybenzoate, a thermally stable compound of iodine(V), is found to be another good oxidant to efficiently and cleanly generate ferryl species [116]. Oxoiron(IV) intermediate **3b** is capable of epoxidizing cyclooctene by transferring the oxygen atom to the substrate at a slow rate with a single turnover. However, this intermediate can turn over multiple times in PPh₃ oxidation at a fast rate. Similar (but low) catalytic turnovers are obtained using TBHP and H₂O₂ in cyclooctene epoxidation, which suggests that a common intermediate (such as ferryl(IV) species) may be involved in the oxygen atom transfer mechanism. Hydrolytic decomposition of the iron macrocycle (iron leakage) suppresses multiple catalytic turnovers in oxygen atom transfer to challenging substrates. Non-heme iron enzymes modulate and enhance the reactivity of the iron(IV)-oxo intermediate by varying the electronic structure and hydrogen bonding patterns in the first and second coordination sphere of the metal center. Preorganized structures of non-heme iron enzymes also stabilize the complexes and prevent iron leakage.

This study demonstrates the importance of the macrocyclic ligand design structure and the effects of coordinating anions in understanding oxygen transfer reactions in biomimetic non-heme iron enzyme models. The availability of labile coordination sites at iron is also important for redox reactivity of the macrocycles: weakly-binding triflate anions of **3** can be replaced by solvent molecules and/or oxidant molecules, while stronger bound chloride anions of **4** suppress the reactivity of iron(II) complex with hydrogen peroxide. Vacant or labile sites are critically important for oxygen-activating non-iron enzymes [44, 117].

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Table 1. Crystallographic data, experimental conditions, and refinement details forcomplexes 3 and 4

		L.
crystal data	3	4
chemical formula	$C_{18}H_{28}N_4FeO_6F_6S_2$	C ₁₇ H ₂₈ N ₄ FeClO ₃ F ₃ S
Fw	630.41	516.79
crystal system	monoclinic	orthorhombic
space group	$P2_{1}/c$	Pbca
a(Å)	9.3613(10)	14.6240(3)
b (Å)	32.349(3)	13.2933(3)
<i>c</i> (Å)	9.0847(9)	23.0235(5)
β (deg)	114.894(2)	90
volume ($Å^3$)	2495.5(4)	4475.80(17)
Z	4	8
$D_{c} (g cm^{-3})$	1.678	1.534
crystal size (mm ³)	0.20 imes 0.15 imes 0.12	0.28 imes 0.27 imes 0.25
abs coeff (mm^{-1})	0.859	0.937
no. reflns collected	19370	41044
no. indep collected	5891	5435
$R_1^a [I > 2\sigma(I)]$	0.0584	0.0437
$w R_2^{b}$ (all data)	0.1777	0.1132
$\operatorname{GOF}(F^2)$	1.244	1.053
diff peaks (e·Å ⁻³)	1.405, -0.723	0.661, -0.582
$a \overline{\mathbf{R}_1} = \Sigma F_0 - F_c $	$ \Sigma F_0 $. $wR_2 = [\Sigma]w$	$\overline{v(F_0^2 - F_c^2)^2}$ where $w = 1/\sigma^2 (F_0^2)^2$
$+(aP)^{2}+bP$.		
()		

	3	4
Fe(1) - N(1)	2.074(2)	2.079(2)
Fe(1) - N(2)	2.243(2)	2.197(2)
Fe(1) - N(3)	2.277(2)	2.120(2)
Fe(1) - N(4)	2.235(2)	2.202(2)
Fe(1) - O(1)	2.242(2)	
Fe(1) - O(4)	2.035(2)	
Fe(1) - Cl(1)		2.2998(7)
N(1) - Fe(1) - N(2)	76.53(9)	77.11(8)
N(1) - Fe(1) - N(3)	100.09(9)	101.72(8)
N(1) - Fe(1) - N(4)	76.73(9)	77.64(8)
N(1) - Fe(1) - O(1)	89.05(8)	
N(1) - Fe(1) - O(4)	169.67(9)	7
N(2) - Fe(1) - N(3)	91.88(9)	97.60(9)
N(2) - Fe(1) - N(4)	153.12(9)	152.58(8)
N(2) - Fe(1) - O(1)	85.78(8)	
N(2) - Fe(1) - O(4)	106.33(9)	
N(3) - Fe(1) - N(4)	90.19(9)	97.83(9)
N(3) - Fe(1) - O(1)	169.78(8)	
N(3) - Fe(1) - O(4)	89.81(9)	
N(4) - Fe(1) - O(1)	96.40(8)	
N(4) - Fe(1) - O(4)	100.47(9)	
O(1) - Fe(1) - O(4)	81.33(8)	
N(1) - Fe(1) - Cl(1)		152.82(6)
N(2) - Fe(1) - Cl(1)		98.44(6)
N(3) - Fe(1) - Cl(1)		105.44(6)
N(4) - Fe(1) - Cl(1)		99.11(6)

Table 2. Selected bond lengths (Å) and angles (deg) for ${\bf 3}$ and ${\bf 4}$

Table 3. 1H NMR shifts of the internal standard (TMS), magnetic susceptibility, and effective magnetic moments of iron(II) complexes at 25 °C in measurements using Evans method

complex	δv (Hz)	$\chi_{g} \times 10^{6} (\text{cm}^{3} \text{ g}^{-1})$	$\mu_{\rm eff}$ (B.M.)	spin state
1	0	0	0	low-spin
2	147.9	16.8	5.2	high-spin
3	149.7	18.2	5.2	high-spin
4	149.3	22.2	5.2	high-spin
		2CO MA		

Table 4. Cyclooctene Epoxidation Reaction with H₂O₂ or TBHP



a yield of epoxide with the respect to olefin.

^bmmol of epoxide per mmol of catalyst.

^{*c*}TBHP produces the epoxide from cycloctene in about 3% yield using the defined condition without catalyst.

 d Catalyst / Substrate / $H_{2}O_{2} = 1 / 20 / 30$.

S

m/z		m/z	
202.7	$[Fe^{III}(L1)(O'Bu)]^{2+}$ $[Fe^{III}(L1)(O'Bu)(OTf)]^{+}$	174.7	$[Fe^{III}(L1)(OH)]^{2+}$
554		498	$[Fe^{III}(L1)(OH)(OTf)]^{+}$
174.2	$[Fe^{IV}(L1)(O)]^{2+}$	348	$[Fe^{III}(L1)(OH)-H]^+$ or
497	$[Fe^{IV}(L1)(O)(OTf)]^{+}$		$[Fe^{IV}(L1)(O)-H]^+$

Table 5. ESI–MS of the solution of **3** with 5 equiv of TBHP in CH_3CN .

Figure Legends

Fig. 1. Structure of the ligand and iron(II) complexes used in this work.

Fig. 2. ORTEP diagram of the complex cation of **3** with thermal ellipsoids at 30% probability from a single crystal X-ray diffraction study. Hydrogen atoms are omitted for clarity.

Fig. 3. ORTEP diagram of the complex cation of **4** with thermal ellipsoids at 30% probability from a single crystal X-ray diffraction study. Hydrogen atoms are omitted for clarity.

Fig. 4. Cyclic voltammograms for complexes 3 (up) and 4 (down) (2 mM) in CH₃CN.

Fig. 5. UV–vis spectra of the reaction of **3** (\approx 2 mM) with oxidants in CH₃CN at –40 °C, acquired on a benchtop spectrophotometer equipped with an immersion (dip) probe. Black solid line, gray solid line, red dashed line, blue dotted line, and green dashed-dotted line represent solution of **3** alone, and the reactions of **3** with TBHP ($\lambda_{max} = 530$ nm, $\epsilon \approx 500 \text{ M}^{-1} \text{ cm}^{-1}$), H₂O₂ ($\lambda_{max} \approx 780 \text{ nm}$, $\epsilon \approx 50 \text{ M}^{-1} \text{ cm}^{-1}$), m-CPBA ($\lambda_{max} \approx 780 \text{ nm}$, $\epsilon \approx 50 \text{ M}^{-1} \text{ cm}^{-1}$), and isopropyl 2-iodoxybenzoate ($\lambda_{max} = 780 \text{ nm}$, $\epsilon \approx 50 \text{ M}^{-1} \text{ cm}^{-1}$) in CH₃CN, respectively. Inset: expansion of the selected traces in the 700–900 nm spectral region.

Fig. 6. Time-resolved spectral changes obtained upon mixing complex **3** (2 mM) with TBHP (30 mM) in CH₃CN over 400 s at -20 °C, monitored by stopped-flow spectrophotometry. Inset: time course of the reaction monitored at 530 nm.

Fig. 7. Determination of second-order rate constant by plotting k_{obs} against the concentration of TBHP for the reaction of **3a** with 5–25 equiv TBHP (0.01–0.05 M) (before mixing).

Fig. 8. Eyring plot for the reaction of **3** with 10 equiv. TBHP in CH₃CN (-40 to 0 °C); the second-order rate constant for the formation of $[Fe^{III}(L1)(OO^tBu)]^{2+}$ (**3a**) was measured upon mixing **3** (2 mM) with TBHP (20 mM) in CH₃CN.

Fig. 9. ESI–MS of the solution of 3 mixed with one equiv of isopropyl 2-iodoxybenzoate in CH_3CN at 25 °C.

Fig. 10. Time course of double mixing the $[Fe^{IV}(L1)(O)]^{2+}$ **3b** (generated by mixing **3** (16 mM) with 0.3 equiv isopropyl 2-iodoxybenzoate in CH₃CN in 500 s age time) with 3 equiv PPh₃ (48 mM) in CH₃CN over 10 s at -20 °C monitored at 780 nm. Inset: double mixing $[Fe^{IV}(L1)(O)]^{2+}$ **3b** with CH₃CN as a control experiment to ensure the self-decay of **3b** has a minor change within 10 s.

Fig. 11. Arrhenius plot (-30 to 0 °C) for the reaction of **3b** (generated by mixing **3** (16 mM) with 0.3 equiv isopropyl 2-iodoxybenzoate in CH_3CN and incubating for 100 s) with PPh₃ (3 equiv, 48 mM) in CH_3CN .

Fig. 12. Fig. 12. (a) Time-resolved spectral changes upon mixing $[Fe^{IV}(L1)(O)]^{2+}$, **3b** (generated by the reaction of **3** (16 mM) with 0.3 equiv isopropyl 2-iodoxybenzoate in CH₃CN over 200 s) with 20 equiv cyclooctene (0.32 M); in CH₃CN at 20 °C. Inset: time course of the reaction monitored at 780 nm (red solid line) and a control experiment (self-decay of **3b** double-mixed with CH₃CN, blue dashed line). (b) Determination of second-order rate constant by plotting k_{obs} against cyclootene concentration (0.32–0.96 M before

mixing). (c) Eyring plot (25 to 35 °C) for the reaction of **3b** with 60 equiv cyclooctene (0.96 M) in CH₃CN.

Scheme 1. Key iron-containing compounds and intermediates supported by L1 investigated in the present study. The coordinating triflate anions in iron(II) complex 1 can be substituted for acetonitrile molecules in CH_3CN solutions.

Scheme 2. Proposed sequence of reaction steps in the formation of the iron(IV) species from 3 and isopropyl iodoxybenzoate.

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Fig. 2. ORTEP diagram of the complex cation of **3** with thermal ellipsoids at 30% probability from a single crystal X-ray diffraction study. Hydrogen atoms are omitted for clarity.

R R R



Fig. 3. ORTEP diagram of the complex cation of **4** with thermal ellipsoids at 30% probability from a single crystal X-ray diffraction study. Hydrogen atoms are omitted for clarity.





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Fig. 8. Eyring plot for the reaction of **3** with 10 equiv. TBHP in CH₃CN (-40 to 0 °C); the second-order rate constant for the formation of $[Fe^{III}(L1)(OO^{t}Bu)]^{2+}$ (**3a**) was measured upon mixing **3** (2 mM) with TBHP (20 mM) in CH₃CN.





Fig. 9. ESI–MS of the solution of 3 mixed with one equiv of isopropyl 2-iodoxybenzoate

in CH₃CN at 25 $^{\circ}$ C.



Fig. 10. Time course of double mixing the $[Fe^{IV}(L1)(O)]^{2+}$ **3b** (generated by mixing **3** (16 mM) with 0.3 equiv isopropyl 2-iodoxybenzoate in CH₃CN in 500 s age time) with 3 equiv PPh₃ (48 mM) in CH₃CN over 10 s at -20 °C monitored at 780 nm. Inset: double mixing $[Fe^{IV}(L1)(O)]^{2+}$ **3b** with CH₃CN as a control experiment to ensure the self-decay of **3b** has a minor change within 10 s.



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(a)



(c)



Fig. 12. (a) Time-resolved spectral changes upon mixing $[Fe^{IV}(L1)(O)]^{2+}$, **3b** (generated by the reaction of **3** (16 mM) with 0.3 equiv isopropyl 2-iodoxybenzoate in CH₃CN over 200 s) with 20 equiv cyclooctene (0.32 M); in CH₃CN at 20 °C. Inset: time course of the reaction monitored at 780 nm (red solid line) and a control experiment (self-decay of **3b** double-mixed with CH₃CN, blue dashed line). (b) Determination of second-order rate constant by plotting k_{obs} against cyclootene concentration (0.32–0.96 M before mixing). (c) Eyring plot (25 to 35 °C) for the reaction of **3b** with 60 equiv cyclooctene (0.96 M) in CH₃CN.



Scheme 1. Key iron-containing compounds and intermediates supported by L1 investigated in the present study. The coordinating triflate anions in iron(II) complex 1 can be substituted for acetonitrile molecules in CH_3CN solutions.



Scheme 2. Proposed sequence of reaction steps in the formation of the iron(IV) species from **3** and isopropyl iodoxybenzoate.



Graphical Abstract

Ferryl (Fe^{IV}=O) species derived from **3** demonstrated electrophilic reactivity in transferring an oxygen atom to substituted triarylphosphines and to olefins (such as cyclooctene); however, iron(III) alkylperoxo intermediate was unreactive with cyclooctene



Highlights

N-methylated pyridine azamacrocycle (PyMAC) folds upon binding iron(II), forming a high-spin complex. Reaction with *t*-Buhydroperoxide yields an alkylperoxo intermediate that does not oxidize substrates. Reaction with iodine(V) yields an electrophilic Fe(IV)=O intermediate that epoxidizes olefins. Kinetic parameters for these reactions were determined by the low-temperature stopped-flow method.

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