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A Mononuclear Nonheme Iron(IV)–Amido Complex Relevant for the Compound II Chemistry of Cytochrome P450

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Abstract

A mononuclear nonheme iron(IV)–amido complex bearing a tetraamido macrocyclic ligand, [(TAML)Fe^{IV}(NHTs)][−] (**1**), was synthesized via a hydrogen atom (H atom) abstraction reaction of an iron(V)–imido complex, [(TAML)Fe^V(NTs)][−] (**2**), and fully characterized using various spectroscopies. We then investigated (1) the p*K*_a of **1**, (2) the reaction of **1** with a carbon-centered radical, and (3) the H atom abstraction reaction of **1**. To the best of our knowledge, the present study reports for the first time the synthesis and chemical properties/reactions of a high-valent iron(IV)–amido complex.

Heme and nonheme iron enzymes as well as their synthetic model compounds catalyze the hydroxylation of alkanes with high efficiency and selectivity.^{1–3} High-valent iron(IV)-oxo porphyrin π -cation radical species (Porp⁺)-Fe^{IV}(O), referred to as compound I (Cpd-I), are the key intermediates responsible for the C–H hydroxylation of substrates in heme systems; a hydrogen atom is abstracted from substrate C–H bonds by Cpd-I (Scheme 1A, reaction *a*), followed by a fast oxygen rebound between the Fe(IV)–OH porphyrin species, referred to as compound II (Cpd-II), and the carbon radical (Scheme 1A, reaction *b*).^{1,4} Since the H atom abstraction by Cpd-I is the rate-determining step (rds) (Scheme 1A, reaction *a*), the O-rebound step has never been observed directly (Scheme 1A, reaction *b*). However, very recently, Goldberg and co-workers reported the first direct O-rebound process, in which an

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11045.
Experimental Section, Tables S1–S3, and Figures S1–S35 (PDF)

The authors declare no competing financial interest.

iron(IV)–hydroxide corrole complex, $[\text{Fe}^{\text{IV}}(\text{OH})]$,⁵ and a nonheme iron(III)–methoxide complex, $[\text{Fe}^{\text{III}}(\text{OCH}_3)]$,⁶ were utilized in reactions with carbon-centered radicals. In the study, they demonstrated the C–O bond formation between Fe–OX (X = H and CH₃) and carbon radicals.^{5,6}

Another interesting subject that has attracted much attention recently is the basicity of the Cpd-II Fe(IV)–OH;^{1b,7,8} the basicity of the Fe(IV)–OH species is an important factor that determines the reactivity of Cpd-I in C–H activation reactions and that the strong electron-donating ability of the thiolate axial ligand increases the basicity of the iron-oxo moiety, influencing the reactivity of Cpd-I in H atom abstraction reactions. Indeed, pK_a s of several Fe(IV)–OH intermediates were determined in heme enzymes,^{7,8} showing that Cpd-II with a high pK_a is more reactive in C–H bond activation reactions.

High-valent iron–imido (Fe=NR) and iron–amido (Fe–NHR) species, which are iron–oxo (Fe=O) and iron–hydroxo (Fe–OH) analogs, respectively, have been proposed as reactive intermediates in nitrogen group transfer reactions.⁹ Very recently, we reported that a high-valent iron(V)–imido complex, $[(\text{TAML})\text{Fe}^{\text{V}}(\text{NTs})]^-$ (**2**) (NTs = tosylimido), is capable of activating C–H bonds of substrates (Scheme 1B).¹⁰ In the amination reactions, an iron(IV)–amido intermediate, $[(\text{TAML})\text{Fe}^{\text{IV}}(\text{NHTs})]^-$ (**1**), is generated as a transient intermediate (Scheme 1B, reaction *a*), as Cpd-II is proposed as a transient intermediate in heme systems (compare Scheme 1A and B). Then, the iron(IV)–amido intermediate is recombined with the carbon radical to yield an aminated product and an iron(III) product (Scheme 1B, reaction *b*). Encouraged by the successful synthesis of the Fe(V)–NTs complex and the reaction of the Fe(V)–NTs complex with alkane C–H bonds,^{10a} we attempted to synthesize an Fe(IV)–NHTs complex as an analog of Cpd-II and investigated the chemical properties/reactions of the Fe(IV)–NHTs complex in various aspects. Herein, we report a novel high-valent iron(IV)–amido complex, $[(\text{TAML})\text{Fe}^{\text{IV}}(\text{NHTs})]^-$ (**1**), which is synthesized via a H atom abstraction reaction of **2** (Scheme 2, reaction *a*). We also report the pK_a determination, nitrogen rebound, and H atom abstraction reactions of the Fe(IV)–NHTs complex (Scheme 2).

The mononuclear iron(V)–imido complex $[(\text{TAML})\text{Fe}^{\text{V}}(\text{NTs})]^-$ (**2**) was synthesized according to the literature procedures.¹⁰ Upon addition of 1 equiv of TEMPOH (=2,2,6,6-tetramethylpiperidin-1-ol) or excess amounts of 9,10-dihydroanthracene (DHA) or 1,4-cyclohexadiene (CHD) to **2** in CH₃CN (MeCN) at –40 °C, the color of the reaction solution changed from dark green to purple (Supporting Information (SI), Experimental Section). The purple intermediate (**1**) was metastable ($t_{1/2} \approx 3$ h) at –40 °C, allowing us to characterize it using various spectroscopies, such as UV–vis, cold spray time-of-flight mass spectrometry (CSI-MS), electron paramagnetic resonance (EPR), Mössbauer, and X-ray absorption spectroscopy/extended X-ray absorption fine structure (XAS/EXAFS). The UV–vis spectrum of **1** exhibited two distinct absorption bands at 526 ($\epsilon = 6100 \text{ M}^{-1} \text{ cm}^{-1}$) and 690 nm ($\epsilon = 3600 \text{ M}^{-1} \text{ cm}^{-1}$) (Figure 1a; Figures S1–S3). CSI-MS of **1** in negative mode exhibited a prominent ion peak at m/z of 596.1, with mass and isotope distribution patterns corresponding to $[(\text{TAML})\text{Fe}(\text{NHTs})]^-$ (calculated m/z of 596.1) (Figure 1a, inset). When **1** was generated using ¹⁵N-labeled **2**, $[(\text{TAML})\text{Fe}^{\text{V}}(^{15}\text{NTs})]^-$, one-mass-unit shift from 596.1 to 597.1 was observed (Figure 1a, inset; Figures S4 and S5, inset). This result demonstrates

that **1** contains one NHTs group. The X-band EPR spectrum of **1** was silent when **1** was generated using DHA or CHD (Figure S6). However, when **1** was generated using TEMPOH, the EPR spectrum of the reaction solution showed signals at $g \sim 2.0$ from TEMPO[•] (Figure S7).

1 was also analyzed with Mössbauer spectroscopy (Figure 1b). The spectrum recorded at 80 K without applied magnetic field is constituted by a quadrupole doublet accounting for 97% of the sample iron, with hyperfine parameters consistent with an $S=1$ Fe(IV) species. This assignment was confirmed by experiments at 4.5 K at 0 and 7 T (Figure S8). A global simulation of all spectra resulted in the following parameters: $\delta = -0.00$ mm s⁻¹, $E_Q = 3.33$ mm s⁻¹, and $D = 15$ cm⁻¹ (Table S1), which match with those reported for other Fe(IV) complexes of related ligands.¹¹

Fe K-edge XAS was performed on solutions of **1** and **2**, and the data are presented in Figure 2a. The data show that the rising edge of **1** is ~ 1 eV lower in energy relative to **2**. A comparison of the pre-edge region is present in the inset of Figure 2a, which shows that the pre-edge energy position of **1** has shifted to lower energy by ~ 0.5 eV (7112.9 eV in **2** to 7112.4 eV in **1**), and the intensity has decreased significantly in **1** relative to **2**. This lowering of pre-edge energy position and decrease in intensity suggest a change in the Fe–N axial interaction on going from **2** to **1**.^{10b,12,13} Fe K-edge EXAFS data for **1** and **2** were measured and analyzed for local structure determination. A comparison is shown in Figure 2b, and fits to the data of **1** are shown in Figure S9 and Table S2. The best fits to the data for **1** reveal a first shell devoid of a short Fe–N interaction and consistent with either four or five Fe–N interactions at 1.89 Å (Table S2), suggesting elongation of the Fe–N relative to **2**. These data are supported by TD-DFT simulations of the Fe K-edge pre-edge region on the triplet ground state structure of a five-coordinate **1** and comparing that to that of **2**. The TD-DFT calculations (Figure S10) reveal an excellent agreement with the Fe K-pre-edge data, supporting the five-coordinate EXAFS fit. Based on the spectroscopic characterization and the density functional theory (DFT) calculations (see Figure S11 for the DFT-optimized structure; Table S3), **1** can be assigned as an $S=1$ iron(IV)–amido complex with a single Fe–N bond, [(TAML)Fe^{IV}(NHTs)]⁻.

We then investigated the pK_a of Fe(IV)–N(H)Ts by the spectroscopic titration with bases in MeCN at -40 °C (Scheme 2, reaction *b*). When **1** was reacted with pyridine ($pK_a = 12.3$)¹⁴ and 2-aminopyridine ($pK_a = 14.3$),¹⁴ we did not observe any spectral changes in the reactions. However, addition of **1** equiv of 4-dimethylaminopyridine (4-DMAPy, $pK_a = 17.6$)¹⁴ or 4-aminopyridine (4-APy, $pK_a = 17.2$)¹⁴ to **1** resulted in the fast disappearance of the peaks at 526 and 690 nm due to **1** with the formation of a new species (**3**) (Figures S12 and S13). Interestingly, addition of 1 equiv of HOTf to the solution of **3** regenerated **1** (Figure S14) (Scheme 2, reaction *b*). Thus, the results of the acid–base reaction indicate that addition of base to **1** generates a deprotonated species, [(TAML)Fe^{IV}(NTs)]²⁻ (**3**), and **3** is converted back to **1** upon protonation (Scheme 2, reaction *b*). Since **3** is not stable ($t_{1/2} \approx 550$ s at -40 °C) (Figure S15) due to disproportionation to [(TAML)Fe^V(NTs)]⁻ and [Fe^{III}(TAML)]⁻ (Figure S16), we were not able to provide strong spectroscopic evidence for **3** except the UV–vis and EPR data. Indeed, such disproportionation reaction of Fe(IV) to Fe(V) and Fe(III) is well documented in iron(IV)–oxo porphyrin chemistry.¹⁵

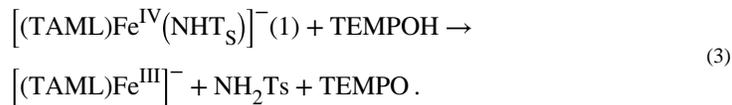
Then, the K values of the deprotonation of **1** with 4-DMAPy and 4-APy were determined by fitting of the titration data (see SI, Experimental Section and Figures S17–S20). The pK_a of **1** was then determined to be 15.7(1) with the K values and the pK_a s of 4-DMAPy and 4-APy (eq 1). In addition, with the determined pK_a value of **1**, the BDE value of Fe–N(H)Ts in **1** was also determined to be 79.3 kcal mol⁻¹ from the E_{red} value (vs Fc+/Fc) of **2** using eq 2,¹⁶ where E_{red} (vs Fc+/Fc) of **2** = -0.07 V (Figure S21). **1** is less basic with the lower BDE than those of L^{mes}Fe^{III}-N(H)Ad⁺, an iron(III)-amido with $pK_a = 37$ and BDE = 88(5) kcal mol⁻¹, which may result from several factors including the nature of the amide substituent, Fe oxidation state, and charge of the complex.¹⁷

$$pK_{a,(1)} = -\log K + pK_{a,(4-X-py)} \quad (1)$$

$$\text{BDE} = 1.37pK_{a,(1)} + 23.06E_{red} + 59.4 \quad (2)$$

With the spectroscopically well characterized **1** and **2**, we investigated the H atom abstraction reaction of **2** (Scheme 1B, reaction *a*) and the N-rebound reaction of **1** (Scheme 1B, reaction *b*); triphenylmethane (Ph₃CH) was used as a substrate. First, the reaction of **2** with Ph₃CH yielded [Fe^{III}(TAML)]⁻ and Ph₃C-NHTs (Figures S22–S24). The second-order rate constant of the reaction of **2** with Ph₃CH was determined at different temperatures and then extrapolated to -40 °C (Figures S25–S27),¹⁸ in which the second-order rate constant was determined to be 7.5 × 10⁻⁵ M⁻¹ s⁻¹ at -40 °C (Scheme 1B, reaction *a*). Then, we examined the N-rebound reaction of **1** with triphenylmethyl radical (Ph₃C[•]) (Scheme 1B, reaction *b*; also see Scheme 2, reaction *c*). Addition of (Ph₃C)₂, which is in equilibrium with Ph₃C[•],¹⁹ to a deaerated MeCN solution of **1** at -40 °C under an Ar atmosphere afforded the Ph₃C-NHTs and [Fe^{III}(TAML)]⁻ products in ~90% yield (Figures S28 and S29). The rate constant of the N-rebound reaction between **1** and Ph₃C at -40 °C was estimated to be larger than 2.4 × 10³ M⁻¹ s⁻¹ from the first-order rate constant (7.2 × 10⁻³ s⁻¹) in Figure S30, inset, and the maximum concentration of [Ph₃C[•]] (<3 × 10⁻⁶ M) in the equilibrium with (Ph₃C)₂.²⁰ Thus, by comparing the rate constants of the H atom abstraction of Ph₃CH by **2** (7.5 × 10⁻⁵ M⁻¹ s⁻¹) and the N-rebound reaction between **1** and Ph₃C[•] (2.4 × 10³ M⁻¹ s⁻¹), we can conclude that the N-rebound reaction (Scheme 1B, reaction *b*) is more than 3.2 × 10⁷ times faster than the H atom abstraction reaction (Scheme 1B, reaction *a*).

Finally, the reaction of **1** with TEMPOH (BDE of O–H = 70.6 kcal mol⁻¹)^{16c} was investigated (Scheme 2, reaction *d*). Addition of TEMPOH to **1** in MeCN at -40 °C resulted in the disappearance of **1** (Figure S31). The second-order rate constant (K_2) was determined to be 1.6 × 10² M⁻¹ s⁻¹ at -40 °C (Figure S32). Product analysis revealed the formation of NH₂Ts and TEMPO[•] with the yields of ~95% and ~86%, respectively, as the organic products (Figures S33 and S34) and the formation of [Fe^{III}(TAML)]⁻ as the decay product of **1** (Figure S35); the overall reaction stoichiometry is shown in eq 3.



In summary, we have reported the synthesis and characterization of a mononuclear nonheme iron(IV)–amido complex, $[(\text{TAML})\text{Fe}^{\text{IV}}(\text{NHT}_s)]^-$ (**1**). We have also reported the chemical properties and reactions of the iron(IV)–amido complex, such as the pK_a and BDE values and the N-rebound and H atom abstraction reactions.

Supplementary Material

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ACKNOWLEDGMENTS

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- (20). The concentration of Ph_3C^\bullet during the reaction was too small to be detected, being estimated to be smaller than 3×10^{-6} M from A (<0.001) based on the ϵ value at 514 nm due to Ph_3C^\bullet (SI, Experimental Section). The reaction of **1** with Ph_3C^\bullet was much faster than the formation of Ph_3C^\bullet from the dimer (SI, Figure S30). $\cdot^{-6}_3 \cdot^{\bullet}_3 \cdot^{\bullet}_3$

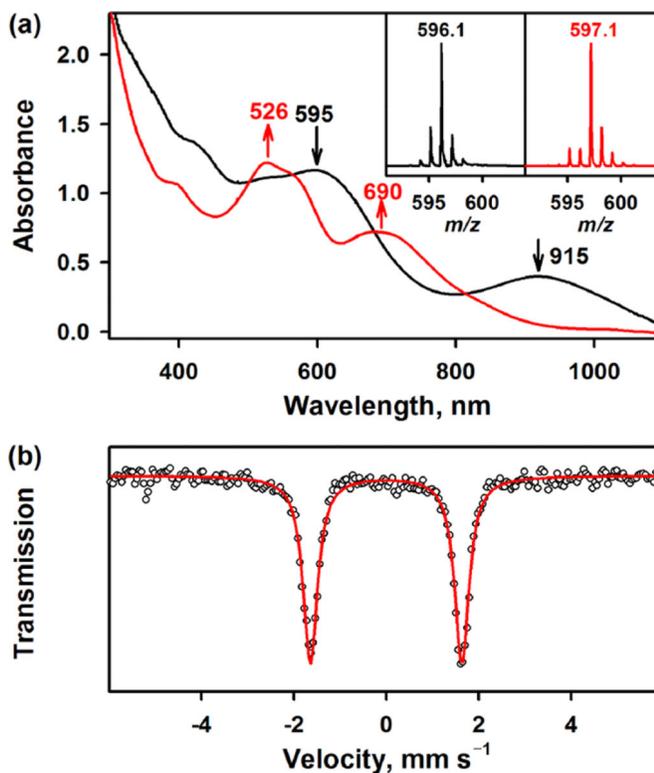


Figure 1.

(a) UV-vis spectra of [Fe^V(NTs)(TAML)]⁻ (**2**, black line) and [Fe^{IV}(NHTs)(TAML)]⁻ (**1**, red line). **1** was synthesized by reacting **2** (0.20 mM) with 1.0 equiv of TEMPOH (0.20 mM) in MeCN at -40 °C. Insets show CSI-MS spectra with the isotopic distribution patterns of the peaks at m/z 596.1 for **1**-¹⁴NHTs (left panel) and at m/z 597.1 for **1**-¹⁵NTs (right panel). (b) Mössbauer spectra (black circles) with fits (red line) for **1** recorded at 80 K and 0 T. The solid line is a calculated spectrum with the following parameters: $\delta = -0.01$ mm s⁻¹ and $E_Q = 3.28$ mm s⁻¹.

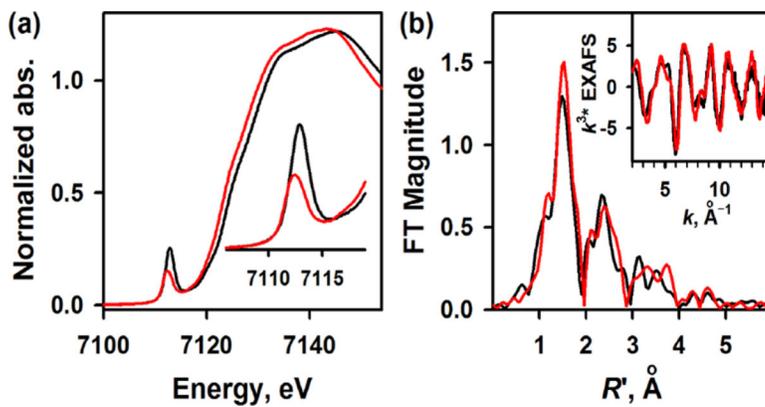
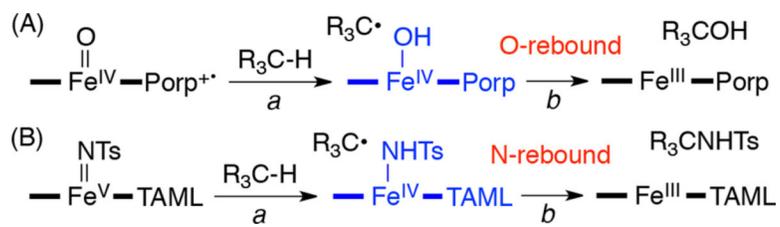
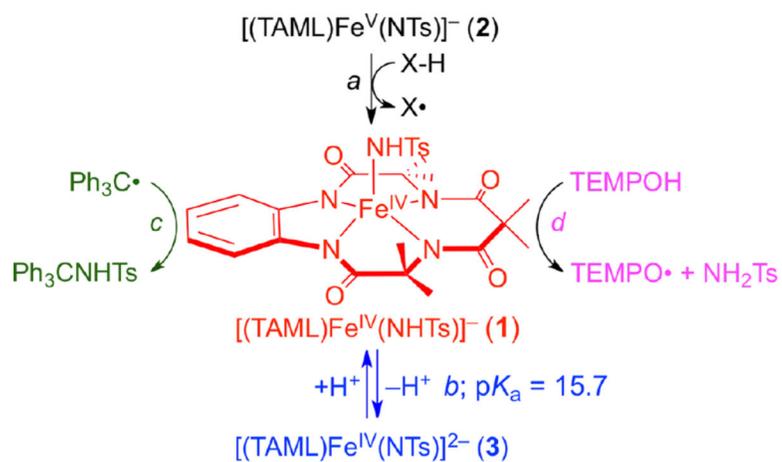


Figure 2.

(a) Normalized Fe K-edge XAS data for **1** (red) and **2** (black). The inset shows the expanded pre-edge region. (b) Non-phase-shift-corrected Fourier transform (FT) data for **1** (red) and **2** (black). The inset shows the EXAFS data.



Scheme 1.
C–H Bond Activation Reactions of Cpd-I and Fe(V)–Imido Complex

**Scheme 2.**

Schematic Representation for the Synthesis and Reactions of $[(\text{TAML})\text{Fe}^{\text{IV}}(\text{NHTs})]^-$