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Fast Hydrogen Atom Abstraction by a Hydroxo Iron(III) Porphyrazine

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Abstract

A reactive hydroxoferric porphyrazine complex, $[(PyPz)Fe^{III}(OH)(OH_2)]^{4+}$ (**1**, PyPz = tetramethyl-2,3-pyridino porphyrazine), has been prepared via one-electron oxidation of the corresponding ferrous species $[(PyPz)Fe^{II}(OH_2)_2]^{4+}$ (**2**). Electrochemical analysis revealed a pH-dependent and remarkably high Fe^{III}–OH/Fe^{II}–OH_2 reduction potential of 680 mV vs Ag/AgCl at pH 5.2. Nernstian behavior from pH 2 to pH 8 indicates a one-proton, one-electron interconversion throughout that range. The O–H bond dissociation energy of the Fe^{II}–OH_2 complex was estimated to be 84 kcal mol^{-1}. Accordingly, **1** reacts rapidly with a panel of substrates via C–H hydrogen atom transfer (HAT), reducing **1** to $[(PyPz)Fe^{II}(OH_2)_2]^{4+}$ (**2**). The second-order rate constant for the reaction of $[(PyPz)Fe^{III}(OH)(OH_2)]^{4+}$ with xanthene was 2.22×10^3 M^{-1} s^{-1}, 5–6 orders of magnitude faster than other reported Fe^{III}–OH complexes and faster than many ferryl complexes.

Nature has evolved a variety of remarkably efficient metalloenzymes for the selective oxygenation of even the most unreactive C–H bonds.[1] Copper-containing particulate methane monooxygenases (pMMO), and the nonheme diiron enzymes sMMO and AlkB allow microorganisms to grow on natural gas and petroleum as their sole sources of carbon.[2] Cytochrome P450s are thiolate-ligated heme proteins that use an oxoiron(IV)-porphyrin π-radical cation (compound I) as the active oxidant to functionalize substrates.[3] Nonheme iron proteins such as TauD and SyrB2 break strong C–H bonds using a ferryl species, Fe^{IV}=O.[4] By distinct contrast, lipoxygenases, which are widely distributed in plants, animals and fungi, employ hydroxoiron(III) or manganese(III) as reactive intermediates to activate allylic C–H bonds.[5] These enzymes catalyze the regio- and stereospecific dioxygenation of polyunsaturated fatty acids to afford alkyl hydroperoxides. The use of enz-Fe^{III}–OH as a hydrogen atom transfer (HAT) agent to cleave the substrate C–H bond produces [enz-Fe^{II}–OH_2 ·R]. This strategy avoids the formation of high-valent intermediates and facilitates oxygen capture by the incipient substrate radical, ·R.

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Supporting Information

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UV–vis and NMR spectra spectra, stopped-flow transients, kinetic traces and electrochemical data (PDF)

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Notes

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Heme and nonheme oxoiron(IV) models have been extensively studied as hydrogen abstractors.[4d,6] However, much less is known about the range of reactivity of hydroxometal(III) species, especially hydroxoiron(III). Notable early examples are hydroxoFe^{III}(PY5) complexes described by Stack et al.,[7] and strongly hydrogen bonded terminal hydroxoiron(III) and manganese(III) species reported by Borovik et al.[8] Mayer et al. have examined mechanisms of proton-coupled electron transfer with a hydroxoiron(III) porphyrin complex[9] and recently, Tolman et al. have shown that a copper(III) hydroxide complex was highly reactive in C–H oxygenation reactions.[10] An Fe(III) hydroxide complex described by Kovacs et al.[11] is an unusually weak oxidant and Jackson et al. have described phenol oxidations by mononuclear Mn^{III}–OH complexes.[12] Yet, with the exception of the high-valent Cu(III)–OH complex, the reaction rates of hydrogen atom abstraction by these metal(III) hydroxide species are very slow compared with lipoxygenases.[5f,13]

We describe here the generation and reactions of a cationic hydroxoferric complex, $[(PyPz)Fe^{III}(OH)\ (OH_2)]^{4+}$ (**1**, PyPz = tetramethyl-2,3-pyridino porphyrazine, Scheme 1) that is capable of fast hydrogen atom abstractions from substrates with moderate C–H bond energies (<85 kcal mol^{-1}). The ferric complex is reduced to $[(PyPz)Fe^{II}(OH_2)_2]^{4+}$ (**2**) for which an O–H BDE of 84 kcal mol^{-1} was estimated from the Fe^{III}/Fe^{II} reduction potential. Second-order rate constants for C–H hydrogen atom abstraction by **1** are orders of magnitude faster than other reported ferric complexes.

The ferrous complex **2** was prepared by heating pyridine-2,3-dicarboxylic acid with urea and ferrous chloride with ammonium heptamolybdate as a catalyst, followed by *N*-methylation with methyl *p*-toluenesulfonate as previously described.[14] Complex **2** showed an appropriate molecular ion in the ESI MS (Figure S1) and sharp peaks in the ^1H NMR with similar chemical shifts to those of Zn^{II}PyPz (Figure S2).[15] The EPR spectrum of **2** showed no signals (Figure S3). On the basis of these results, air-stable complex **2** is formulated as a diamagnetic, low-spin ferrous complex $[(PyPz)Fe^{II}(OH_2)_2]^{4+}$.[16] Titration of **2**, as monitored by UV–vis spectroscopy (Figure S4), showed two successive deprotonations of axial water with pK_{a1} = 8.0 and pK_{a2} = 10.1, indicative of diaqua, aqua-hydroxo and dihydroxo coordination of iron(II).[6i,17]

Cyclic voltammetry of **2** afforded a pH-dependent redox potential with a slope of −69 mV/pH in the Pourbaix diagram between pH 2.2 and 7.7 (Figure S5), close to the expected −59 mV/pH for ideal Nernstian behavior.[11,18] Further, the $E_{pa} - E_{pc}$ difference at pH 2.2 decreased as the scan rate decreased, with a ΔE of 68 mV at 2 mV/s (Figure S6 and Table S1). This behavior is indicative of the transfer one proton per electron and that the ferric complex **1** has one hydroxo and one aqua axial ligand over this entire pH range. The redox potential of Fe(III/II)PyPz is 680 mV vs Ag/AgCl at pH 5.2, unusually high for a Fe^{III}/Fe^{II} couple, explaining the stability of **2** in air.

The ferrous complex **2** could be oxidized to complex **1** either by bulk electrolysis at 1 V (vs Ag/AgCl) or by adding one equivalent of *t*-butyl hydroperoxide, as monitored by UV–vis spectroscopy at pH 2.2 (Figure S7). The EPR spectrum of complex **1** (g = 2.49, 2.21, 1.89) indicates that **1** can be formulated as a low-spin ferric complex $[(PyPz)Fe^{III}(OH)\ (OH_2)]^{4+}$ (Figure S3).[19]

The strength of the O–H bond in transition metal complexes is of considerable importance in determining the driving force for hydrogen atom abstraction.[20] Because the redox potential of **1**/**2** is pH-dependent, the *D*(O–H) of **2** could be calculated using the modified form of the Bordwell eq (eq 1):

$$D(\mathrm{O-H}) = 23.06E_{1/2} + 1.37\mathrm{pH} + C\ \mathrm{kcal/mol} \quad (1)$$

where $E_{1/2}$ is the oxidation potential of **2** (referenced to NHE, Ag/AgCl + 220 mV) at a given pH and C is the solvent-dependent energy of formation and solvation of H in H_2O, which equals to 55.8 kcal mol^{-1}.[20b,21] With the exceptionally high Fe^{III}/Fe^{II} redox potential of the **1**/**2** couple, *D*(O–H) in **2** is calculated to be 84 ± 2 kcal mol^{-1}, suggesting that **1** should be capable of oxidizing C–H substrates with moderate C–H bond strengths.

Indeed, the decay of (PyPz)Fe^{III}–OH to (PyPz)Fe^{II}–OH_2 was greatly accelerated by added substrates. The kinetics monitored at 453 nm by stopped-flow spectrophotometry for a panel of C–H substrates were very well fit by single exponentials over a range of substrate concentrations as expected for a pseudo-first order reduction of **1** to **2** (Figure 1). The second-order rate constant for xanthene oxidation was remarkably fast; k = 2216 ± 28 M^{-1} s^{-1}. For xanthene-d_2, the value was 109.7 ± 0.6 M^{-1} s^{-1}, indicative of a very large substrate kinetic isotope effect (KIE) of 20.2 ± 0.3. Clearly, cleavage of the C–H bond is the rate-determining step. Conversely, the solvent isotope effect was negligible (Figure 1B).[6h]

A correlation of the reduction of **1** by a panel of five substrates is plotted versus the C–H BDE in Figure 2. A linear Brønsted–Evans–Polanyi (BEP) relationship was found with a slope of −0.35, indicating a homolytic hydrogen atom transfer with an early transition state.[6e,20c,22] Similar results were obtained in phosphate buffer/acetonitrile solution at both acidic (Figure S8–12) and near-neutral pH (Figure S13–15), with very little pH sensitivity up to pH 7.2 (Figure S16).

The reaction of (PyPz)Fe^{III}–OH with xanthene was examined in greater detail. A KIE of 20.2 at 293 K is significantly greater than the semiclassical limit of 7. Analyzing Arrhenius plots for xanthene and xanthene-d_2 oxidation by **1** gave $E_a(D) - E_a(H)$ = 2.5 ± 0.4 kcal mol^{-1} and $A(H)/A(D)$ = 0.28 ± 0.14 (Figure S17). These results meet all three Kreevoy criteria for hydrogen tunneling: a KIE significantly larger than 6.4 at 20 °C; an activation energy difference greater than 1.2 kcal mol^{-1}; and a ratio of pre-exponential factors less than 0.7.[23] This large KIE of 20.2 is much greater than those reported for other synthetic ferric hydroxide complexes, and closer to the colossal KIE of ~80 found for lipoxygenases.[7d,24]

An Eyring analysis of the temperature dependence of the rate constants gave remarkably small enthalpies of activation; $\Delta H^{\ddagger}$ = 6.1 ± 0.3 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −23.7 ± 1.1 cal mol^{-1} K^{-1} for xanthene and $\Delta H^{\ddagger}$ = 6.8 ± 0.3 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −27.2 ± 0.8 cal mol^{-1} K^{-1} for 9,10-dihydroanthracene (DHA) (Figure S18). Accordingly, C–H scission occurs under entropy control with $T\Delta S^{\ddagger} > \Delta H^{\ddagger}$. Notably, the enthalpy barrier for lipoxygenase is only 2 kcal mol^{-1}, resulting in the very fast rate of the enzyme.[25]

The unusually high reactivity of this hydroxoferric porphyrazine complex (**1**) prompts a comparison of C–H bond cleavage rates with other hydroxometal(III) and oxoiron(IV) complexes, as well as organic radicals. Figure 3 shows such a comparison for DHA oxidation at 25 °C by various complexes versus the *D*(O–H) values associated with the oxidants.[6a,c,h,k,7,10a,b,18,26] For calibration, the dashed line passes through rates with known *D*(O–H) for permanganate, the *t*-butylperoxyl radical and the *t*-butoxyl radical (not shown).[26a–d,27] Although the O–H BDE associated with **1**/**2** is only a few kcal mol^{-1} stronger than other synthetic hydroxo-manganese(III) and iron(III) complexes, the rate of **1**/**2** is 5 to 6 orders of magnitude faster. Moreover, this rate is 50–100-fold faster than typical ferryl complexes and comparable to that of the PINO radical, *t*-butylperoxy radical and a hydroxocopper(III) complex.[10b,26e] Much faster rates of DHA oxidation have been reported for oxoiron(IV) porphyrin cation radicals[6e,h] and for a high-spin ferryl species.[26j]

What factors contribute to the high HAT reactivity of (PyPz)Fe^{III}–OH (**1**)? Certainly, part of the acceleration derives from the unusually high Fe^{III}/Fe^{II} redox potential. We note that the Fe^{IV}–OH (compound II) of the heme-thiolate peroxygenase APO is also highly reactive toward C–H bond scission despite its modest (0.84 V vs NHE) reduction potential.[6i] On the other hand, oxoFe^{IV}-4-TMPyP, a cationic porphyrin similar to **1** with four methylpyridinium positive charges, oxidizes xanthene at a rate more than 1 order of magnitude slower than the hydroxoferric species **1**.[28] A small reorganization energy for reduction of **1** to **2** might derive from the low-spin configuration of both species and the rather rigid porphyrazine ring system. The significant hydrogen tunneling contributes a factor of ~3. These factors suggest that some iron hydroxides may have intrinsically lower reorganization energies than corresponding ferryl species, reflecting less drastic bond-order changes. The possibility of a disproportionation of the ferric complex **1** to generate a reactive ferryl species is highly unlikely given the near-perfect fit of the kinetic data to a single exponential (R^2 = 0.9997) over six half-lives of reaction and the tight isosbestic point at 407 nm (Figure 1A). Disproportionation processes should be second-order in Fe^{III}–OH (Figure S19).

In summary, we have found that the hydroxoferric porphyrazine complex, [(PyPz)Fe^{III}(OH)(OH$_2$)]$^{4+}$ (**1**), is unusually reactive toward hydrogen abstraction from benzylic C–H substrates. The reactions occur through a hydrogen atom transfer mechanism, which is supported by the large KIE and a linear relationship between substrate C–H BDE and log *k*. A (PyPz)Fe^{II}–OH$_2$ O–H BDE of 84 kcal mol^{-1} is estimated from the redox potential of (PyPz)Fe^{III}–OH/(PyPz)Fe^{II}–OH$_2$ and the pK_a of the axial aqua ligand of (PyPz)Fe^{II}. The shallow BEP slope (−0.35) indicates an early transition state for C–H scission and the low activation enthalpies ($\Delta H^{\ddagger}$ = 6.1–6.8 kcal/mol) show that the reaction is entropy controlled ($T\Delta S^{\ddagger} > \Delta H^{\ddagger}$), suggesting a small reorganization energy for this process. These findings provide new insights into the reactivity of Fe^{III}–OH species and suggest that M–OH oxidants may have untapped potential in the context of C–H activation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. We have used BDE values instead of BDFE to facilitate comparisons with other systems. Entropic effects due to electronic reorganization should be small because both 1 and 2 are low-spin. The aqueous BDFE for 2 would be ~2 kcal/mol larger, reflecting the difference between C_H and C_G in eq 1 (cf. references [10c], [11] and [20b]).

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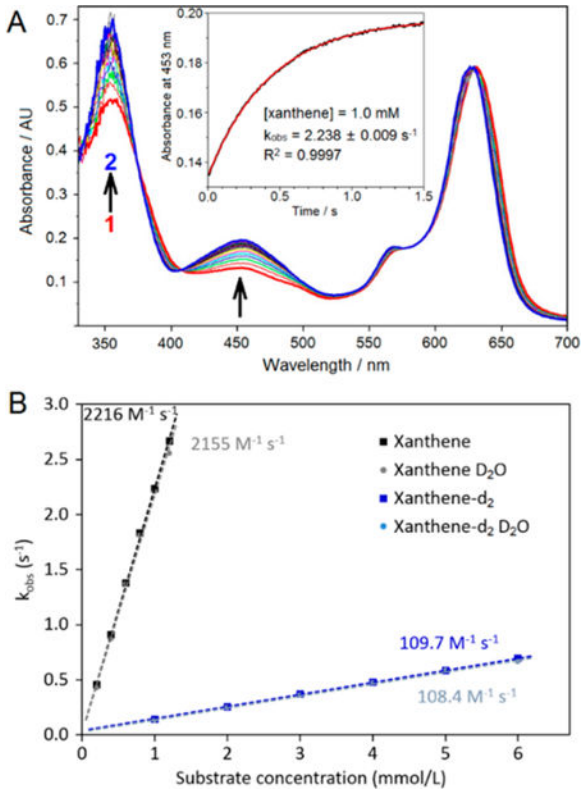


Figure 1.

(A) Single-mixing, stopped-flow UV–vis spectra obtained upon mixing 1.0 mM xanthene with 70 μM (PyPz)Fe^{III}–OH (**1**) in 50:50 (v/v) 6 mM $HClO_4$ water/acetonitrile solution (pH 2.2) at 20.0 °C over 1.5 s. Inset: changes in absorbance at 453 nm vs time (black line). Single exponential fitting (red line) resulted in a pseudo-first-order rate constant of 2.238 ± 0.009 s^{-1} (R^2 = 0.9997). (B) Observed pseudo-first-order rate constants plotted vs xanthene concentration: xanthene in H_2O: 2216 ± 28 M^{-1} s^{-1} (R^2 = 0.9992) (black). Xanthene-d_2 in H_2O: 109.7 ± 0.6 M^{-1} s^{-1} (R^2 = 0.9998), substrate KIE = 20.2 ± 0.3 (blue). Xanthene in D_2O: 2155 ± 62 M^{-1} s^{-1} (R^2 = 0.996), solvent KIE = 1.03 ± 0.04 (gray). Xanthene-d_2 in D_2O: 108.4 ± 2.8 M^{-1} s^{-1} (R^2 = 0.997), combined substrate-solvent KIE = 20.4 ± 0.6 (light blue).

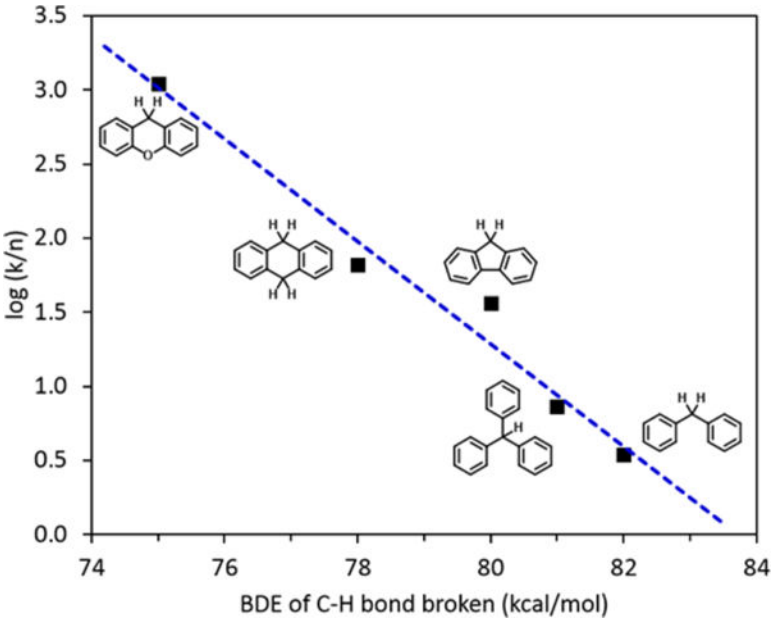


Figure 2.

Plot of log(k/n) vs substrate BDE, where k is the second-order rate constant and n is the number of equivalent C–H bonds that are broken in the reaction. Conditions: T = 20.0 °C, 50:50 (v/v) 6 mM $HClO_4$ water/acetonitrile solution (pH 2.2). Slope = −0.35 ± 0.04 (R^2 = 0.961).

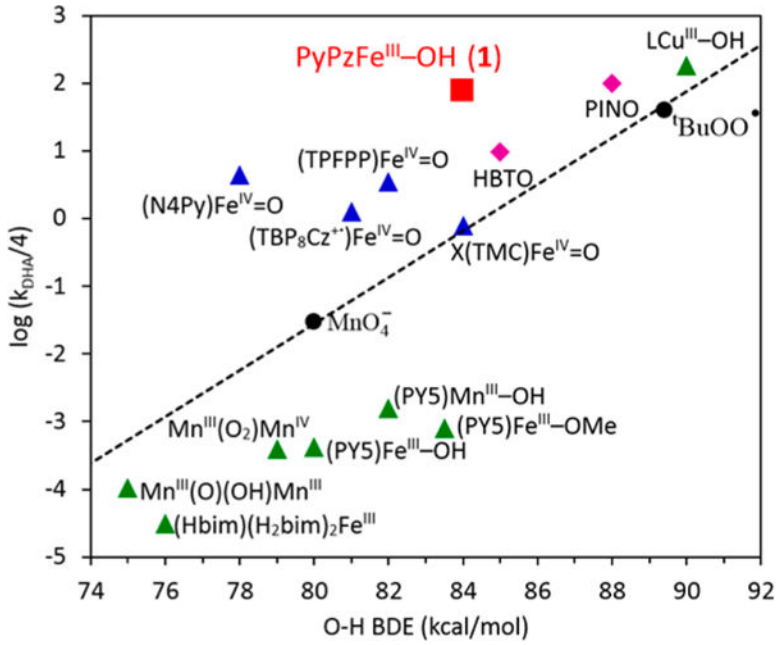
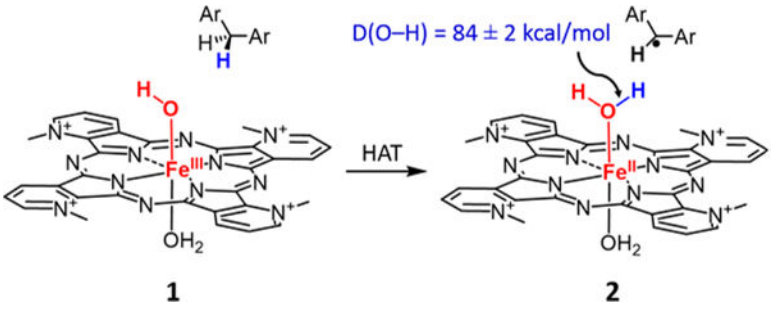


Figure 3.

Plot of log *k* for DHA oxidation and the O–H BDE formed by a variety of oxidants at 298 K. Rates were either measured directly or extrapolated to this temperature from experimentally determined activation parameters (Table S2). The black dashed line was drawn through the points of two oxygen radicals and permanganate as a reference. The red square is (PyPz)Fe^{III}–OH (**1**). Green triangles are reported metal(III) complexes. Blue triangles are reported Fe(IV)=O complexes. Magenta diamonds are organic oxy-radicals. An N–H bond is formed instead of O–H bond in $Fe^{III}(Hbim)(H_2bim)_2$. Data points of HBTO and PINO radicals are estimated from fluorene oxidation rates.



Scheme 1.

Conversion of $[(PyPz)Fe^{III}(OH)\ (OH_2)]^{4+}$ (1) to $[(PyPz)Fe^{II}(OH_2)_2]^{4+}$ (2) via HAT