Published in final edited form as:

Chem Sci. 2014 January ; 5(1): 372–380. doi:10.1039/C3SC52055B.

Radical Reactivity of the Fe(III)/(II) Tetramesitylporphyrin Couple: Hydrogen Atom Transfer, Oxyl Radical Dissociation, and Catalytic Disproportionation of a Hydroxylamine

Thomas R. Porter and James M. Mayer*

^aDepartment of Chemistry, University of Washington, Seattle, WA 98195-1700

Abstract

The chemistry of low-valent iron porphyrin complexes with oxyl radical reagents has been explored. (*Meso*-tetramesityl porphyrinato) iron(III) hydroxide, (TMP)Fe^{III}(OH) reacts with the hydroxylamine TEMPO–H (1-hydroxy-2,2,6,6-tetramethylpiperidine) to yield the ferrous porphyrin, (TMP)Fe^{II}, together with H₂O and TEMPO. This reaction has a second order rate constant $k_1 = 76 \pm 5 \text{ M}^{-1} \text{ s}^{-1}$ and likely occurs by concerted e^-/H^+ transfer. Hydrazines PhNHNHPh and PhNHNH₂ similarly yield (TMP)Fe^{II}. A subsequent reaction between TEMPO (2,2,6,6-tetramethylpiperdiny) radical and (TMP)Fe^{II} is observed to reversibly form the TEMPO-ligated ferric porphyrin, (TMP)Fe^{III}(TEMPO). A combination of ¹H NMR and optical spectroscopies were used to determine the thermodynamic parameters for TEMPO binding: $K_4(25^\circ\text{C}) = 535 \pm 20 \text{ M}^{-1}$, $\Delta H^\circ_4 = -7.0 \pm 1.5 \text{ kcal mol}^{-1}$, $\Delta S^\circ_4 = -11 \pm 5 \text{ cal mol}^{-1} \text{ K}^{-1}$, $\Delta G^\ddagger_4(235\text{K}) = 21.3 \pm 0.5 \text{ kcal mol}^{-1}$, $\Delta G^\ddagger_{-4}(235\text{K}) = 16.9 \pm 0.5 \text{ kcal mol}^{-1}$. The Fe–O bond is remarkably weak. The stable phenoxyl radical 2,4,6-*t*Bu₃C₆H₂O[•] (ArO[•]) forms a stronger bond to (TMP)Fe^{II} to irreversibly make a similar Fe^{III}(OR) complex. Both (TMP)Fe^{II} and (TMP)Fe^{III}(OH) are catalysts for the disproportionation of excess TEMPO–H to TEMPO and TEMP–H (2,2,6,6-tetramethylpiperidine). The lack of reactivity between (TMP)Fe^{II} and the alkylated TEMPO–H analogue, TEMPO–CH₃, suggests that the disproportionation involves a hydrogen atom transfer step. These results highlight the importance and versatility of the heme Fe^{III/II} couple that is often overshadowed by its higher-valent counterparts.

Introduction

Heme proteins are ubiquitous and have a wide range of functions. In recent years, cytochromes P450 and peroxidases have been a focus of research because of their ability to accomplish difficult oxidative reactions by using high-valent ferryl intermediates (compounds I and II).¹ Other heme enzymes, however, accomplish inner-sphere oxidations and reductions using just the Fe^{III/II} couple.² One example is the autotrophic bacterial multi-heme enzyme hydroxylamine oxidoreductase (HAO),³ which catalyses the oxidation of hydroxylamine to nitrite using just ferric and ferrous oxidation states.⁴ These low-valent odd-electron transformations tend to be underappreciated relative to their high-valent counterparts.

In many cases, the interconversion between heme oxidation states is coupled to proton transfer. Examples range from proton-pumping in cytochrome *c* oxidase⁵ to aliphatic

hydroxylations by cytochromes P450.¹ Reactions involving the transfer of e^- and H^+ are broadly referred to as proton-coupled electron transfer (PCET) processes, and are ubiquitous in chemistry as well as in biochemistry.⁶ The hydroxylamine-to-nitrite process mentioned above is one example. The transfer of one proton and one electron in a single kinetic step is hydrogen atom transfer (HAT), or more generally concerted proton-electron transfer (CPET).⁷ Some enzymes and other catalysts utilize CPET to avoid high energy intermediates, but a variety of pathways are possible for PCET reactions.⁸ While PCET and CPET are frequently invoked pathways for high-valent heme reactions, low-valent heme reactions of this type have received substantially less attention. The non-heme iron lipoxygenase enzymes use the $Fe^{III/II}$ redox couple to remove $H^\bullet$ from fatty acid substrates.⁹

Herein we describe inner sphere redox chemistry of the ferric hydroxide and ferrous states of *meso*-tetramesitylporphyrinato ligated model complexes. Namely, we address three related topics: PCET reactivity, oxyl radical binding to Fe^{II} , and catalytic disproportionation of the hydroxylamine TEMPO-H. Each is presented and discussed in turn below.

Meso-tetramesitylporphyrinato-iron(III) hydroxide, $(TMP)Fe^{III}(OH)$, and related porphyrin complexes have been extensively used as models for heme enzymes by Groves,¹⁰ Balch¹¹, LaMar,^{11b,c} Valentine,¹² Nam¹³ and others. An advantage of this porphyrin ligand is that the steric bulk of the mesityl substituents prevents the formation of μ -oxo dimers, so the ferric hydroxide is readily prepared.^{11b} We first observed that $(TMP)Fe^{III}(OH)$ is readily reduced by the hydroxylamine TEMPO-H to give the ferrous derivative $(TMP)Fe^{II}$, when the reactions are performed and monitored at low concentrations. However, the same reaction gives a different product when performed at higher concentrations, because the TEMPO product reversibly binds to the ferrous heme to form $(TMP)Fe^{III}(TEMPO)$. Reactions with excess TEMPO-H gave yet another set of products, as the iron complexes catalyze the redox disproportionation of TEMPO-H. These results highlight the rich and perhaps underappreciated free-radical chemistry of low-valent heme compounds.

Experimental

Materials

Unless otherwise noted, all chemicals were purchased from Sigma-Aldrich and used without purification. Toluene- d_8 and dichloromethane- d_2 were purchased from Cambridge Isotope Labs, dried over NaK and CaH_2 , respectively, and vacuum distilled. Other solvents were purchased from Fischer and dried using a "Grubbs type" Seca Solvent System installed by GlassContour. TEMPO was purified by sublimation. TEMPO-H,¹⁴ TEMPO- CH_3 ,¹⁵ $tBu_3ArO^\bullet$,¹⁶ $TMPh_2$,¹⁷ $(TMP)Fe^{III}Cl$,¹⁸ and P1-phosphazene $H^+BF_4^-$,¹⁹ were prepared using established literature protocols. All glassware was dried in an oven at 150 °C overnight and pumped into a nitrogen filled glovebox while hot. Celite was dried at 100 °C overnight under vacuum.

Instrumentation

All 1H NMR spectra were obtained on Bruker 300 and 500 MHz instruments. Variable temperature spectra were acquired on a Bruker 500 MHz instrument. The chemical shifts reported are referenced to TMS using the residual solvent peak. UV-visible absorption spectra were collected with a Hewlett-Packard 8453 diode array spectrometer equipped with a Unisoku USP-203 cryostat. Kinetic measurements were performed on an OLIS RSM-1000 stopped-flow spectrophotometer.

Syntheses

(meso-Tetramesitylporphyrinato) iron(III) hydroxide, (TMP)Fe^{III}(OH)—

(TMP)Fe^{III}(OH) was prepared from (TMP)Fe^{III}Cl as described in the literature.^{11a} The dark green solid product was macerated with a spatula and dried at 60 °C under high vacuum for 24 hours to remove residual water from the product. Disappearance of characteristic upfield water resonance^{11a} at δ -1.2 confirmed that the product was dry. ¹H NMR (300 MHz, toluene-*d*₈) δ : 81.55 (bs, 8H, β -pyrrole), 12.14 (s, 4H, *m*-Ar), 11.18 (s, 4H, *m*-Ar), 3.29 (s, 12H, *p*-CH₃).

(meso-tetramesitylporphyrinato) iron(II), (TMP)Fe^{II}—(TMP)Fe^{III}Cl (217 mg, 0.249 mmol) was treated with equimolar cobaltocene (47.1 mg, 0.249 mmol) in 10 mL of toluene in a nitrogen filled glovebox. The solution was stirred for 30 minutes then filtered through a Celite plug to remove cobaltocenium chloride. The solvent was removed under reduced pressure and a dark red solid was collected (148 mg, 71%). The identity was confirmed by comparison with literature ¹H NMR characterization.^{11c} ¹H NMR (300 MHz, toluene-*d*₈) δ : 11.72 (s, 8H, *m*-Ar), 6.04 (s, 12H, *p*-CH₃), 5.62 (s, 24H, *o*-CH₃), 2.86 (s, 8H, β -pyrrole).

Representative Reaction Procedure

In a typical NMR-scale reaction, equimolar solutions of (TMP)Fe^{II} and TEMPO were prepared in toluene-*d*₈ in the glovebox (4.0 mM). Solutions were added to a J. Young NMR tube and the tube sealed. In a typical optical absorption spectroscopy experiment, equimolar solutions of (TMP)Fe^{II} and TEMPO were prepared in toluene in a nitrogen filled glovebox (80 μ M). Solutions were added to a 1 cm pathlength quartz cuvette fitted with a Kontes valve and sealed. For both optical and NMR experiments, the sample was inverted several times to ensure that complete mixing had occurred prior to obtaining spectra. ¹H NMR data for (TMP)Fe^{III}(TEMPO) and (TMP)Fe^{III}(*t*Bu₃ArO) are given in Table 1.

Results

I. (TMP)Fe^{III}(OH) as a Net Hydrogen Atom Abstractor

The addition of one equivalent of TEMPO-H to a dark green solution of (TMP)Fe^{III}(OH) (80 μ M in toluene) forms a bright red solution over approximately 45 minutes. The UV-visible absorption spectrum of the reaction product displayed a Soret band at 418 nm and Q bands at 445 and 538 nm, in good agreement with the spectrum of the known^{11c} 4-coordinate ferrous porphyrin (TMP)Fe^{II} and with an independently prepared sample (Table 1).²⁰ These data indicate a net hydrogen atom transfer from TEMPO-H to (TMP)Fe^{III}(OH), as shown in eq 1.

Reaction 1 was monitored by stopped-flow spectrophotometry under *pseudo*-first order conditions ([TEMPO-H] = 3.6-14.4 mM, Figure 1 and Supporting Information). The kinetics are first order in both (TMP)Fe^{III}(OH) and TEMPO-H, with $k_1 = 76 \pm 5 \text{ M}^{-1} \text{ s}^{-1}$ at 25° C ($\Delta G^\ddagger_1(25^\circ \text{C}) = 15.0 \pm 0.1 \text{ kcal mol}^{-1}$).

The reactivity of (TMP)Fe^{III}(OH) with other potential hydrogen atom donors has been examined in toluene-*d*₈ at 4.0 mM concentrations. TEMPO-H is a strong H-atom donor because its O-H bond dissociation free energy (BDFE) is only 65.2 kcal mol⁻¹.⁷ The first N-H bond in 1,2-diphenylhydrazine is similar, BDFE = 64.3 ± 1.5 kcal mol⁻¹.⁸ Adding 0.5 equivalents (1 H[•] equivalent) PhNHNHPh to (TMP)Fe^{III}(OH) resulted in a colour change from dark green to deep red and ¹H NMR spectroscopy showed (TMP)Fe^{II} and PhN=NPh had been generated (eq 2). The same reaction was carried out at a lower concentrations (80 μM (TMP)Fe^{III}(OH), 40 μM PhNHNHPh) in toluene and monitored optically. Over approximately 8 hours, the characteristic absorption features of (TMP)Fe^{III}(OH) were replaced with those of (TMP)Fe^{II}. The weaker H-atom donor PhNHNH₂ (BDFE = 67.5 ± 1.5 kcal mol⁻¹)⁸ also reacted with (TMP)Fe^{III}(OH) but only slowly, requiring approximately 24 hours at RT for 4.0 mM (TMP)Fe^{III}(OH) plus 2.0 mM PhNHNH₂²² (eq 3, and Supporting Information). 2,4,6-Tri-*tert*-butyl phenol, with a significantly stronger O-H bond (BDFE = 76.6 kcal mol⁻¹)⁸ did not react with (TMP)Fe^{III}(OH) over 24 hours.

Surprisingly, the reaction between (TMP)Fe^{III}(OH) and TEMPO-H at higher concentrations, 4.0 mM of each reagent, proceeds to a different set of products. Under these conditions, reaction solutions rapidly turn dark brown, rather than the red solution described above for 80 μM solutions. ¹H NMR spectra of this reaction mixture showed the complete consumption of TEMPO-H but some (TMP)Fe^{III}(OH) remained. Peaks were also observed for new organic and Fe^{III} products, which were later assigned to 2,2,6,6-tetramethyl piperidine, TEMP-H, and a (TMP)Fe^{III}-TEMPO complex, as described in the next sections.

II. Reactions of (TMP)Fe^{II} with Oxyl Radicals

Reaction of (TMP)Fe^{II} and TEMPO—Addition of one equivalent of the stable oxyl radical TEMPO to a 80 μM toluene solution of (TMP)Fe^{II} at room temperature showed very little change by UV/Vis absorption spectroscopy. In contrast, carrying out the same reaction at fifty times higher concentrations (4.0 mM in toluene-*d*₈) showed an instantaneous and dramatic colour change from deep red to dark green. The ¹H NMR spectrum of this reaction mixture showed the complete disappearance of (TMP)Fe^{II} and the appearance of a new species with a broad downfield resonance characteristic of the β-pyrrolic signal of a high-spin (TMP)Fe^{III}X species.^{11a} Typically, such C_{4v}-symmetric (TMP)Fe^{III}X complexes have inequivalent *meta*-aryl protons that are resolvable by ¹H NMR spectroscopy, due to hindered rotation about the porphyrin-mesityl bond.^{11a} However, in this case only a single peak was observed, indicating a high-spin [(TMP)Fe^{III}]⁺ complex with effective D_{4h} symmetry on the NMR timescale.

^1H NMR spectra of similar reactions with 0.5 or 2 equivalents of TEMPO were surprising because in both cases no $(\text{TMP})\text{Fe}^{\text{II}}$ was identifiable in solution and each reaction appeared to have cleanly generated a different D_{4h} -symmetric $[(\text{TMP})\text{Fe}^{\text{III}}]^+$ complex. These results suggested an equilibrium reaction in which $(\text{TMP})\text{Fe}^{\text{II}}$ and TEMPO are in rapid equilibrium with a C_{4v} symmetric adduct, $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$ (eq 4). In the rapid exchange limit, the observed chemical shifts are the weighted average of all the species present, so different shifts are observed with different reagent ratios.²³ This interpretation was confirmed by ^1H NMR spectra of $(\text{TMP})\text{Fe}^{\text{II}}$ plus sub-stoichiometric TEMPO at -80°C , which displayed distinguishable resonances for $(\text{TMP})\text{Fe}^{\text{II}}$ and the C_{4v} -symmetric $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$. Thus at ambient temperatures, TEMPO must be rapidly dissociating from $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$ and re-binding to $(\text{TMP})\text{Fe}^{\text{II}}$, a process that would give the apparent D_{4h} symmetry observed. The coalescence temperature of $\sim 235\text{ K}$ and the chemical shift difference of $\sim 500\text{ Hz}$, provide estimates of the dissociation rate constant of $k_{-4}(235\text{ K}) = 1100 \pm 200\text{ s}^{-1}$ and a barrier $\Delta G^\ddagger_{-4}(235\text{ K}) = 16.9 \pm 0.5\text{ kcal mol}^{-1}$ (both at 235 K ; see Supporting Information).

An oximato-iron(III) adduct, $\text{R}=\text{N}-\text{O}-\text{Fe}^{\text{III}}(\text{TMP})$, closely related to $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$, has been similarly prepared from the fluorenone oxime and $(\text{TMP})\text{Fe}^{\text{III}}\text{OH}$ (eq 5).^{10j} While this product is stable, and was structurally characterized, slow dissociation of the fluorenyl oxyimyl radical was indicated and radical formation was facilitated by the addition of CO.

To study the TEMPO dissociation equilibrium (eq 4), multiple 4.0 mM samples of $(\text{TMP})\text{Fe}^{\text{II}}$ in $\text{toluene-}d_8$ were prepared with various concentration of TEMPO. Their ^1H NMR spectra at 25°C showed peaks with positions that changed as a function of TEMPO concentration (Figure 2). Plotting the porphyrin chemical shifts *vs.* $[\text{TEMPO}]$ showed smooth curves that were extrapolated to high $[\text{TEMPO}]$ to give the chemical shifts of pure $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$ (Figures S4). Reasonable estimates of these chemical shifts could be made for *m*-H, *p*-CH₃, and β -pyrrolic peaks (Table 1) but was not possible for the *o*-CH₃ peak because significant broadening of this signal was observed even at low concentrations of TEMPO. Taking the observed chemical shifts of each sample as the weighted average of the shifts of $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$ and $(\text{TMP})\text{Fe}^{\text{II}}$ in solution and assuming mass balance, a plot of the $[(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})]/[(\text{TMP})\text{Fe}^{\text{II}}]$ ratio *vs.* the concentration of free TEMPO in solution gives the equilibrium constant. K_4 was calculated using the β -pyrrolic, *m*-aryl, and *p*-CH₃ resonances to give a value of $520 \pm 25\text{ M}^{-1}$ (see Supporting Information).

The TEMPO binding equilibrium was also studied by optical spectroscopy, using $80\text{ }\mu\text{M}$ $(\text{TMP})\text{Fe}^{\text{II}}$ and one equivalent of TEMPO in toluene, at temperatures from 25°C to -90°C . As the temperature decreased, the Q band associated with $(\text{TMP})\text{Fe}^{\text{II}}$ at 538 nm began to disappear and a new Q band assigned to $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$ at 565 nm grew in. Equilibrium constants were obtained at each temperature from the absorbance at three different wavelengths (487 , 538 , and 565 nm), assuming mass balance for the iron species and that the extinction coefficients in Table 1 are independent of temperature (and ignoring the very small absorbance due to free TEMPO). The value obtained at 25°C , $K_4(25^\circ\text{C})_{\text{optical}} = 550 \pm 25\text{ M}^{-1}$, is in good agreement with that obtained by NMR measurements,

and together those give a consensus value of $535 \pm 20 \text{ M}^{-1}$. This K_4 is consistent with the differences observed in the above experiments, that the TEMPO adduct is mostly formed at NMR concentrations but mostly dissociated at the lower concentrations used for optical studies..

A van't Hoff analysis of TEMPO binding gives $\Delta H^\circ_4 = -7.0 \pm 1.5 \text{ kcal mol}^{-1}$ and $\Delta S^\circ_4 = -11 \pm 5 \text{ cal K}^{-1} \text{ mol}^{-1}$ (Figure 3 and Supporting Information). The Fe–O bond in (TMP)Fe^{III}(TEMPO) is remarkably weak, with a bond dissociation enthalpy (BDE) of only 7 kcal mol^{-1} (a BDFE of only 4 kcal mol^{-1}). Combining $K_4(235 \text{ K}) = 1.3 \times 10^4 \text{ M}^{-1}$ with the dissociation rate constant ($k_{-4}(235 \text{ K})$) gives the rate constant for TEMPO addition $k_4(235 \text{ K}) = K_4 k_{-4} = (1.4 \pm 0.5) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ and $\Delta G^\ddagger_4(235 \text{ K}) = 21.3 \pm 0.5 \text{ kcal mol}^{-1}$.

Reaction of (TMP)Fe^{II} and ^tBu₃ArO•—To explore the same type of reactivity with another stable organic radical, (TMP)Fe^{II} was reacted with the 2,4,6-tri-*tert*-butyl phenoxy radical, ^tBu₃ArO•. ¹H NMR spectra of 1:1 mixtures of (TMP)Fe^{II} plus ^tBu₃ArO• in toluene-*d*₈ have a broad downfield β-pyrrolic resonance at 89 ppm (Table 3), indicating the oxidation of iron(II) to iron(III).^{11a} Interestingly, two resonances are observed for the *m*-aryl protons, as is typical for (TMP)Fe^{III}X species with C_{4v} symmetry. These data indicate that ^tBu₃ArO• is bound to the iron centre: (TMP)Fe^{III}(^tBu₃ArO). The pair of *m*-aryl resonances shows that dissociation of the aryloxy radical is slow on the NMR timescale, so that the two sides of the porphyrin ring are inequivalent. This slow exchange is also indicated by ¹H NMR spectra of solutions with (TMP)Fe^{II} with 0.5 equivalents of ^tBu₃ArO•, which show separated signals for (TMP)Fe^{III}(^tBu₃ArO) and (TMP)Fe^{II} at 25° C.

(TMP)Fe^{III}(^tBu₃ArO) reacts with excess distilled, degassed water to cleanly form (TMP)Fe^{III}(OH) and ^tBu₃ArOH, by ¹H NMR spectroscopy (eq 6). This reaction is consistent with the inability of (TMP)Fe^{III}(OH) to abstract a hydrogen atom from ^tBu₃ArOH that was mentioned above. This reaction is also essentially the reverse of reactions 4 and 5.

III. The Catalytic Disproportionation of TEMPO–H by (TMP)Fe^{II}

In a reaction originally formulated as a control experiment, one equivalent of TEMPO–H was added to 4.0 mM toluene-*d*₈ solution of (TMP)Fe^{II}. No reaction was expected as both of these reagents typically act as reductants. To our surprise, the solution slowly turned from deep red to green. After 24 hours, the ¹H NMR spectrum indicated the presence of (TMP)Fe^{III}(OH), a (TMP)Fe^{II} / (TMP)Fe^{III}(TEMPO) equilibrium mixture, and a set of resonances for 2,2,6,6-tetramethylpiperidine (TEMP–H), in a 1:1:1 ratio (eq 7, Figure S9). The piperidine product was identified by GC/MS and by comparison of its ¹H NMR signals to an authentic sample. The chemical shifts for (TMP)Fe^{II} + TEMPO / (TMP)Fe^{III}(TEMPO) are sensitive to the position of the equilibrium, so these shifts indicate the concentration of TEMPO. The concentration of TEMPO was determined to be half of the initial concentration of TEMPO–H, indicating the overall product stoichiometry of 1:1:1:1 as indicated in eq 7. When 2 equivalents of TEMPO–H were used, (TMP)Fe^{II} was completely converted to (TMP)Fe^{III}(OH), one equivalent of TEMP–H and presumably one equivalent of NMR silent TEMPO (eq 8).

Since the (TMP)Fe^{III}(OH) product could be reduced by additional TEMPO-H back to (TMP)Fe^{II} (eq 1 above), reactions 6 and 1 indicate that the disproportionation of TEMPO-H should be catalytic in iron, using either (TMP)Fe^{II} or (TMP)Fe^{III}(OH). To test this, 12 equivalents of TEMPO-H were added to a toluene-*d*₈ solution of (TMP)Fe^{III}(OH). After 24 hours, ¹H NMR spectra showed the presence of 4 equivalents of TEMPO-H and a broad upfield water resonance, and the (TMP)Fe^{III}(OH) was unchanged, consistent with the expected stoichiometry (eq 9).

Over 100 turnovers of TEMPO-H disproportionation was observed in benzene-*d*₆ over 9 hours with 0.08 mM (TMP)Fe^{II} loading and 33 mM TEMPO-H. The disappearance of TEMPO-H resonances matches the growth of TEMP-H resonances in a 3:1 ratio with nearly quantitative yield (~96% mass balance), determined by ¹H NMR with a hexamethylbenzene internal standard (Figure 5A). The reaction is substantially inhibited by the addition of excess TEMPO (Figure 5B), presumably due to the equilibrium reaction of TEMPO with (TMP)Fe^{II} previously described (eq 4).

To probe the mechanism of the catalytic disproportionation, the reactivity of the methoxyamine TEMPO-CH₃ was explored. No reaction was observed between TEMPO-CH₃ and (TMP)Fe^{II} or (TMP)Fe^{III}(OH), even after heating at 75° C for 48 h. Since TEMPO-H reduces itself in reaction 8, we also tested whether TEMPO-CH₃ could be reduced by TEMPO-H, PhNHNHPh, or ^tBu₃ArOH in the presence of (TMP)Fe^{II}. However, no products derived from TEMPO-CH₃ were observed.

Discussion

I. Net H-atom transfer to (TMP)Fe^{III}(OH); the “Effective BDFE” of (TMP)Fe^{II} + H₂O

(TMP)Fe^{III}(OH) reacts with TEMPO-H, PhNHNHPh and PhNHNH₂ by net hydrogen atom transfer to give (TMP)Fe^{II}, water and the oxidized donor (TEMPO, PhN=NPh or [PhN=NH]). The TEMPO-H reaction (eq 1, repeated here) is quantitative and therefore provides thermochemical information (independent of the mechanism of the reaction, which is discussed below).

Reaction 1 shows that the effective O-H BDFE of the (TMP)Fe^{II} + H₂O combination should be comparable to or greater than the O-H BDFE of TEMPO-H (65.2 kcal mol⁻¹).⁷ The effective BDFE is defined in 10; the term *effective* is used because equation 10 is not a simple bond homolysis. It encompasses both the (unfavourable) binding of H₂O to (TMP)Fe^{II} and the cleavage of the (TMP)Fe^{II}(HO-H) bond. Because the reduced product, (TMP)Fe^{II} + H₂O, is two molecules, the thermochemical analysis of eq 1 is not as simple as a typical H-atom transfer reaction X + HY → XH + Y, for which K_{eq} has no units. The experimental execution of eq 1 was done at 80 μM concentrations, and these low concentrations will entropically favour the products (3 species vs. 2), as compared with 1 M standard state. This provides an extra driving force under the reaction conditions, so the effective BDFE of (TMP)Fe^{II} + H₂O could be slightly lower than the BDFE of TEMPO-H

and reaction would still proceed to completion. We conclude that the BDFE of [(TMP)Fe^{II} + H₂O] = 64 kcal mol⁻¹.

To complement this lower limit, a firm upper limit is provided by the downhill reaction of (TMP)Fe^{III}(^tBu₃ArO) with H₂O to form (TMP)Fe^{III}(OH) + ^tBu₃ArOH (eq 6). Equations 10-12 sum to equation 6, as shown below. Reaction 12, the dissociation of aryloxy from Fe^{II}, was shown above to be very unfavourable. Therefore, the effective BDFE of (TMP)Fe^{II} + H₂O must be substantially less than the BDFE of 2,4,6-tri-*tert*-butyl phenol, BDFE = 76.6 kcal mol⁻¹.⁸

The conclusion that 64 = BDFE[(TMP)Fe^{II} + H₂O] << 76.6 is consistent with the reactions of (TMP)Fe^{III}(OH) with hydrazines. 1,2-Diphenylhydrazine, in which the first N–H bond (BDFE = 64.3 ± 1.5 kcal mol⁻¹) is likely even weaker than that in TEMPO–H and phenylhydrazine, in which the first N–H bond is slightly stronger (BDFE = 67.5 ± 1.5 kcal mol⁻¹).⁸ There are clearly kinetic as well as thermodynamic effects in play, because PhNHNHPh reacts more slowly than TEMPO–H even though its XH bond is likely weaker. These data suggest an effective BDFE of 67 ± 3 kcal mol⁻¹.

The mechanism of H⁺ and e⁻ transfer from TEMPO–H to (TMP)Fe^{III}(OH) could occur by (i) concerted proton-electron transfer (called CPET or H-atom transfer), (ii) initial proton transfer then electron transfer (PT/ET), (iii) initial electron transfer then proton transfer (ET/PT), or (iv) an initial protolytic ligand-exchange mechanism (see below).

The stepwise ET/PT and PT/ET paths are unlikely based on thermochemical arguments. TEMPO–H is a poor one-electron reductant, *E* = 0.71 V in MeCN,⁸ while (TMP)Fe^{III}(OH) is reported to be quite difficult to reduce, *E*_{1/2} = -1.23 V in dichloromethane (all potentials vs. Cp₂Fe^{+/0}).²¹ While the differences in solvent preclude a completely quantitative comparison, the rough estimate is that ET is nearly 2 V or 45 kcal mol⁻¹ endoergic. This value is substantially higher than the observed kinetic barrier for reaction 1, Δ*G*[‡] = 15.0 ± 0.1 kcal mol⁻¹, even considering the uncertainties involved. Thus it is unlikely the reaction of (TMP)Fe^{III}(OH) with TEMPO–H proceeds through an ET/PT mechanism. In a similar vein, initial PT is unlikely because TEMPO–H is a *very* weak acid (p*K*_a in MeCN of 41⁸), and (TMP)Fe^{III}(OH) is not very basic. (TMP)Fe^{III}(OH) is not protonated in CD₂Cl₂ by 20 equivalents of the weak acid *tert*-butylimino-tris(pyrolidino)phosphorane hydrofluoroborate, P1-phosphazeneH⁺BF₄⁻, which has a p*K*_a in MeCN of 28.42²⁴ (See Supporting Information). The ET/PT and PT/ET mechanisms are particularly unlikely in toluene solution because the formation of charged intermediates is even more difficult in this low-polarity solvent. The results are thus consistent with a mechanism of H-atom transfer (concerted H⁺ and e⁻ transfer), which is very common for TEMPO–H.

However, a protolytic ligand-exchange mechanism is also possible. This path would involve TEMPO–H substituting for the OH ligand on (TMP)Fe^{III}(OH) with proton transfer to form water and (TMP)Fe^{III}(TEMPO), which subsequently dissociates TEMPO. Such a protolytic pathway is likely followed by the closely related fluorene oxime reaction^{10j} shown in eq 5 above. The displacement of ArOH from (TMP)Fe^{III}(OAr) by water (eq 6) has to be hydrolytic because the HAT pathway is precluded by the high water O–H BDFE. This mechanism has been studied for exchange of phenolate ligands in (TMP)Fe(OAr) with carboxylic acids and alcohols.²⁵ The alcohol exchange reactions are quite slow, with rate constants $\sim 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ at 60 °C, and are slower for less nucleophilic and more crowded alcohols.

Based on these precedents, we tentatively favour an HAT mechanism for the TEMPO–H reaction rather than a hydrolytic one. TEMPO–H is a crowded molecule, yet it reacts with (TMP)Fe(OH) many orders of magnitude faster than alcohols react with (TMP)Fe(OPh). TEMPO–H has a very low acidity ($\text{p}K_{\text{a}}$ 31^{8a} in DMSO, vs. 16.2 for fluorenone oxime²⁶) making it less likely to participate in protolytic reactions. Finally, the qualitative rate comparison observed here, $k(\text{TEMPOH}) > k(\text{PhNHNHPh}) \gg k(\text{PhNHNH}_2)$, is more consistent with a hydrogen atom transfer mechanism based on the X–H bond strengths, but clearly do not parallel the $\text{p}K_{\text{a}}$ values: TEMPO–H, 31 > PhNHNH₂, 28.8 > PhNHNHPh, 26.2 (in DMSO^{8a}). The very weak O–H bond in TEMPO–H (BDE $\sim 70 \text{ kcal mol}^{-1}$) biases its reactivity toward HAT as opposed to the fluorene oxime (BDEs ~ 70 vs. $\sim 82 \text{ kcal mol}^{-1}$ ²⁷). These mechanistic arguments are, however, suggestive rather than definitive.

II. Binding of stable oxyl radicals to (TMP)Fe^{II}

The binding of the oxyl radicals TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) and *t*Bu₃ArO• 3 (2,4,6-tri-*tert*-butyl phenoxyl radical) to (TMP)Fe^{II} is reminiscent of the much-studied reversible binding of O₂ to ferrous hemes.²⁸ The product (TMP)Fe^{III}(OR) complexes are well described as high-spin Fe^{III} species based on their ¹H NMR spectra.^{11a} The binding of TEMPO is reversible, with $K_4 = 535 \pm 20 \text{ M}^{-1}$ from both NMR and optical studies. A van't Hoff analysis gives the TEMPO-iron bond dissociation enthalpy as only $-\Delta H^\circ_4 = 7.0 \pm 1.5 \text{ kcal mol}^{-1}$. This is a very weak bond (the Fe–O homolytic bond dissociation *free* energy (BDFE) is $3.7 \pm 0.1 \text{ kcal mol}^{-1}$). To our knowledge, these are the first measurements of such Fe–O homolytic bond energies, other than for the binding of O₂.

The $(1.4 \pm 0.5) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ and 1100 s^{-1} rate constants for TEMPO association and dissociation are near the middle of the ranges of related values for O₂ binding to natural and synthetic hemes. These vary from 10^4 to almost $10^9 \text{ M}^{-1} \text{ s}^{-1}$ for k_{on} , and from 2 to 10^5 s^{-1} for k_{off} .²⁸

Related redox coordination chemistry of TEMPO with transition metal complexes has received significant attention, for instance in the area of living radical polymerizations.²⁹ Waymouth and co-workers have shown that TEMPO reversibly binds Ti(III) sandwich complexes in an η^1 fashion through the TEMPO oxygen.³⁰ With Cp₂Ti^{IV}Cl(TEMPO), for instance, Ti–O bond homolysis occurs at 60 °C in the presence of CCl₄ to afford Cp₂Ti^{IV}Cl₂, TEMPO, and •CCl₃. The Ti–O BDE of Cp₂Ti^{IV}Cl(TEMPO) was determined to be approximately 27 kcal mol^{-1} .^{30c}

The reaction between (TMP)Fe^{II} and TEMPO bears a particularly close resemblance to the reactivity of (TMP)Rh^{II} with TEMPO reported by de Bruin and co-workers.³¹ The Rh complex makes a somewhat stronger bond, $\Delta H^\circ_{\text{Rh-TEMPO}} = 14.7 \pm 1.4 \text{ kcal mol}^{-1}$. The higher bond energy for Rh^{III}–TEMPO is reasonable considering that second row transition metals typically form stronger bonds than first row metals, and that Rh^{II} is generally a less favourable oxidation state than Fe^{II}.

The entropy for the association of TEMPO to (TMP)Rh^{II} was reported as $\Delta S^\circ = -30.6 \pm 4.6$ cal mol⁻¹ K⁻¹, much more negative than the analogous value reported here for (TMP)Fe^{III}(TEMPO), -11 ± 5 cal mol⁻¹ K⁻¹. Only a small part of this difference is due to the entropy of the spin multiplicity change. The entropy of the electron spin states is given by $S^\circ = R \ln(2S+1)$, where R is the ideal gas constant and S is the spin multiplicity of the system. So in the binding of (TMP)Rh^{II} and TEMPO, both $S = 1/2$, to give the diamagnetic, $S = 0$ (TMP)Rh^{III}(TEMPO) complex, spin accounts for a positive entropy change of ~ 3 cal mol⁻¹ K⁻¹. The reaction of intermediate spin $S = 1$ (TMP)Fe^{II} 11c with $S = 1/2$ TEMPO results in the formation of a high-spin $S = 5/2$ (TMP)Fe^{III}(TEMPO) complex has an associated entropy change of only ~ -1 cal mol⁻¹ K⁻¹. Thus the differences in the spin entropy of the two systems accounts for only ~ 4 cal mol⁻¹ K⁻¹ of the 20 cal mol⁻¹ K⁻¹ measured difference, suggesting that there must be significant difference in the structural and vibrational change upon TEMPO coordination between the rhodium and iron compounds.

The ^tBu₃ArO• radical binds significantly more strongly to (TMP)Fe^{II} than TEMPO. From one perspective this is surprising because of the high degree of steric bulk on both the iron porphyrin as well as the phenoxide. ^tBu₃ArO• would seem to be slightly more bulky than TEMPO, having *t*-butyl groups bound to the carbons β to the oxyl centre while TEMPO has two methyl groups in those positions. The stronger bond in (TMP)Fe^{III}(^tBu₃ArO) is likely due primarily to ^tBu₃ArO• being a less stabilized radical than TEMPO, as evidenced by the O–H bond being 11.5 kcal mol⁻¹ stronger in ^tBu₃ArO–H vs. TEMPO–H. If the ^tBu₃ArO and TEMPO ligands were rigidly held between the mesityl substituents, the (TMP)Fe^{III}(OR) compounds would have C_{2v} symmetry with inequivalent β-pyrrolic signals, but these resonances are broad and cannot be resolved.

III. Catalytic disproportionation of TEMPO–H

(TMP)Fe^{III}(OH) catalyses the disproportionation of TEMPO–H to TEMPO, TEMP–H and water (eq 9). Over 100 turnovers have been observed with no sign of catalyst degradation. Catalysis is fast initially, but slows over time. The chemistry reported above suggests that the catalytic cycle likely proceeds in a ping-pong fashion, as depicted in Scheme 2. The substrate oxidation part presumably proceeds by PCET from TEMPO–H to (TMP)Fe^{III}(OH). Then the slowing of the catalysis is due to the reversible binding of the TEMPO product to (TMP)Fe^{II}, removing it from the catalytic cycle.

The substrate reduction side, (TMP)Fe^{II} + 2 TEMPO–H → (TMP)Fe^{III}(OH) + TEMPO + TEMP–H, has also been observed in stoichiometric reactions. The mechanism, however, remains obscure, especially how the N–O bond is cleaved. The lack of reactivity between (TMP)Fe^{II} and TEMPO–CH₃ argues against a pathway in which TEMPO–R transfers OR (R = H or CH₃) to (TMP)Fe^{II} to form the tetramethylpiperdiny radical. The N–O homolytic bond strength of TEMPO–CH₃ should be weaker than that of TEMPO–H (because CH₃ is more electron donating than H), so OR transfer should be more facile for TEMPO–CH₃ than for TEMPO–H. Although sterics could conceivably play a role, the strong binding of the bulky phenoxyl radical ^tBu₃ArO to (TMP)Fe^{II} suggests that attack of TEMPO–CH₃ should not be precluded. Reduction of TEMPO–H does not occur by outer-sphere electron transfer from (TMP)Fe^{II}, because TEMPO–H is unreactive with the much stronger reductant cobaltocene (over 24 h in toluene-*d*₈).

The disproportionation of TEMPO–H by (TMP)Fe^{III}(OH) is potentially related to the biochemical conversion of hydroxylamine to nitrite by the multi-heme enzyme hydroxylamine oxidoreductase (HAO).³ This complicated enzyme has inspired a number of different studies into the reactivity of hydroxylamine with both heme³² and non-heme³³

transition metal complexes. For instance, two equivalents hydroxylamine react with (TPP)Fe^{III}Cl in MeOH/CHCl₃ to give NH₄Cl, water, and (TPP)FeNO.^{32a,b} Water soluble iron porphyrin complexes catalyse the disproportionation of hydroxylamine to high yields of NH₃ (the reduced product) and a mixture of N₂ and N₂O as the oxidized products.^{32c} The mechanism is not well understood in either case, but there is some evidence for a pre-equilibrium formation of (porphyrin)Fe^{III}(NH₂OH)₂⁺, and the possibility of radical pathways has been discussed.^{32a,b} NH₂OMe is catalytically decomposed to 1/3 NH₃, 1/3 N₂ and MeOH by aquapentacyanoferrate in aqueous buffer.³³ A mechanism of •NH₂ abstraction by iron(II) to yield a •OCH₃ radical was suggested based on studies with the radical trap DMPO, although such an N–O cleavage is not indicated by the chemistry reported here (and spin adducts of DMPO can also be generated via non-radical mechanisms in the presence of ferric ions³⁴).

TEMPO–H may be considered a simpler surrogate for hydroxylamine. Its oxidation stops at the stable TEMPO radical, while removal of H• from hydroxylamine starts a cascade to 1/2 N₂ and H₂O.³⁵ The bond strength of the NH₂O–H bond in water is only 7.4 kcal mol^{–1} stronger than that of TEMPO–H.⁷ So the results reported here indicate that hydrogen atom transfer from NH₂OH to (heme)Fe^{III}(OH) is a reasonable step in the catalytic cycle of HAO and related enzymes.

Conclusions

Described here are a number of inner-sphere reactions of the (TMP)Fe^{III/II} redox couple (TMP = *meso*-tetramesitylporphyrinato). (TMP)Fe^{III}(OH) reacts with compounds with very weak OH and NH bonds, TEMPO–H, PhNHNHPh and PhNHNH₂, with transfer of a proton to the hydroxide ligand and an electron to the iron centre. This is a convenient way to generate (TMP)Fe^{II}. The data are consistent with either a pathway involving hydrogen atom transfer (concerted H⁺ + e[–] transfer), or by initial hydrolytic conversion of (TMP)Fe^{III}(OH) + TEMPO–H to (TMP)Fe^{III}–(TEMPO) + H₂O followed by TEMPO dissociation. The thermochemical data rule out pathways involving initial electron or proton transfer. Analysis of the reactivity with different hydrogen atom transfer reagents gives an estimate of 67 ± 3 kcal mol^{–1} for the effective bond dissociation free energy (BDFE) of (TMP)Fe^{II} + H₂O → (TMP)Fe^{III}(OH) + H•.

The ferrous porphyrin (TMP)Fe^{II} homolytically binds oxyl radicals to generate (TMP)Fe^{III}–OR complexes. With TEMPO, this reaction is rapid and reversible on the NMR timescale at room temperature but is slower at low temperatures. This is, to our knowledge, the first reported case of a (porphyrin)Fe^{III}–TEMPO complex. Equilibrium studies show that the Fe–O bond is remarkably weak, with a bond dissociation enthalpy is only 7.0 ± 1.5 kcal mol^{–1} (the BDFE is 4 kcal mol^{–1}).

Both (TMP)Fe^{II} and (TMP)Fe^{III}(OH) catalyse the disproportionation of the hydroxylamine TEMPO–H to 2/3 TEMPO + 1/3 TEMPO–H (2,2,6,6-tetramethylpiperidine). This type of catalytic disproportionation has been observed with hydroxylamine and metal porphyrins but no radical intermediates have been directly observed. The results reported here suggest that the previously reported reactions of hydroxylamine with metal porphyrins may involve hydrogen atom transfer.

In discussions of substrate transformations by heme cofactors, the conversation is often dominated by high-valent intermediates, and the chemistry of lower valent heme species can be overlooked. The results reported here serve to highlight both the rich inner-sphere chemistry of the lesser-explored Fe^{III/II} couple as well as the critical role that PCET can play in these systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge financial support from the U.S. National Institute of Health (GM50422) and the University of Washington Department of Chemistry. We thank Dr. Alexander Fox for useful discussions.

Notes and references

1. Meunier B, de Visser SP, Shaik S. *Chem. Rev.* 2004; 9:3947. [PubMed: 15352783]
2. Guengerich FP. *Chem. Res. Toxicol.* 2000; 14:611. [PubMed: 11409933]
3. Igarashi N, Moriyama H, Fujiwara T, Fukumori Y, Tanaka N. *Nature Struc. Biol.* 1997; 4:276.
4. Fernandez ML, Estrin DA, Bari SE. *J. Inorg. Biochem.* 2008; 102:1523. [PubMed: 18336913]
5. Kaila VRI, Verkhovsky MI, Wilkstrom M. *Chem. Rev.* 2010; 110:7062. [PubMed: 21053971]
6. Mayer JM. *Annu. Rev. Phys. Chem.* 2004; 55:363. [PubMed: 15117257]
7. Constantin C, Evans DH, Robert M, Saveant J-M, Singh PS. *J. Am. Chem. Soc.* 2005; 127:12490. [PubMed: 16144387]
- 8 (a). Warren JJ, Tronic TA, Mayer JM. *Chem. Rev.* 2010; 110:6961. [PubMed: 20925411] (b) BDFE values in toluene are assumed to be the same as those reported in benzene. (c) BDFE values in DMSO were taken from reference 8a and converted to BDFE values in toluene using Abraham's model. See supporting information for more details.
- 9 (a). Haeggström JZ, Funk CD. *Chem. Rev.* 2011; 111:5866. [PubMed: 21936577] (b) Meyer MP, Klinman JP. *J. Am. Chem. Soc.* 2011; 133:430. [PubMed: 21192631] (c) Fukuzumi S. *Helv. Chim. Acta.* 2006; 89:2425.
- 10 (a). Haushalter RC, Nakamura M, Nemo TE, Evans BJ, Groves JT. *J. Am. Chem. Soc.* 1981; 103:2884. (b) Nemo TE, Groves JT. *J. Am. Chem. Soc.* 1983; 105:5786. (c) Nemo TE, Groves JT. *J. Am. Chem. Soc.* 1983; 105:6243. (d) Quinn R, McMurry JT, Nakamura M, Lang G, Boso B, Groves JT. *J. Am. Chem. Soc.* 1985; 107:354. (e) Gilbert JA, Groves JT. *Inorg. Chem.* 1986; 25:123. (f) Watanabe Y, Groves JT. *J. Am. Chem. Soc.* 1986; 108:7834. [PubMed: 22283296] (g) Watanabe Y, Groves JT. *J. Am. Chem. Soc.* 1988; 110:8443. (h) Gross Z, Stern MK, Groves JT. *Inorg. Chem.* 1994; 33:5065. (i) Groves, JT.; Han, YZ. *Cytochrome P450: Structure, Mechanism, and Biochemistry*. 3rd edition. P. R. Ortiz de Montello; Plenum, New York: 2004. p. 1-34. (j) Wang CC-Y, Ho DM, Groves JT. *J. Am. Chem. Soc.* 1999; 121:12094.
- 11 (a). Chen R-J, Latos-Gra y ski L, Balch AL. *Inorg. Chem.* 1982; 21:2412. (b) Latos-Gra y ski L, Chen R-J, La Mar GN, Balch AL. *J. Am. Chem. Soc.* 1982; 104:5992. (c) Chan Y-W, Chen R-J, La Mar GN, Latos-Gra y ski L, Renner MW, Balch AL. *J. Am. Chem. Soc.* 1984; 106:7779. (d) Latos-Gra y ski L, Renner MW, Balch AL. *J. Am. Chem. Soc.* 1985; 107:2983. (e) Arasasingham RD, Cornman CR, Balch AL. *J. Am. Chem. Soc.* 1989; 111:7800.
- 12 (a). Sisemore MF, Selke M, Burstyn JN, Valentine JS. *Inorg. Chem.* 1997; 36:979. [PubMed: 11669659] (b) Selke M, Valentine JS. *J. Am. Chem. Soc.* 1998; 120:2652. (c) Wertz DL, Valentine JS. *Struct. Bonding.* 2000; 97:37. (d) Wertz DL, Sisemore MF, Driscoll J, Valentine JS. *J. Am. Chem. Soc.* 1998; 120:5331.
- 13 (a). Lim MH, Oh S-Y, Nam W. *Inorg. Chem.* 2000; 39:5572. [PubMed: 11154575] (b) Kamachi T, Kuono T, Nam W, Yoshikawa K. *J. Inorg. Biochem.* 2006; 100:751. [PubMed: 16516298] (c) Han A-R, Jeong YJ, Kang Y, Lee JY, Seo MS, Nam W. *Chem. Comm.* 2008:1076. [PubMed: 18292895] (d) Kang Y, Chen H, Jeong YJ, Lai W, Bae EH, Shaik S, Nam W. *Chem. Eur. J.* 2009; 15:10039. [PubMed: 19697378] (e) Nam W. *Acc. Chem. Res.* 2007; 40:522. [PubMed: 17469792]
14. Mader EA, Davidson ER, Mayer JM. *J. Am. Chem. Soc.* 2007; 129:5153. [PubMed: 17402735]
15. Whitesides GM, Newirth TL. *J. Org. Chem.* 1975; 40:3448.
16. Manner VW, Markle TF, Freudenthal JH, Roth JP, Mayer JM. *Chem. Comm.* 2008; 44:256. [PubMed: 18092105]

17. Wagner RW, Lindsey JS. *J. Org. Chem.* 1989; 54:828.
18. Jiao J, Schmidt I, Taniguchi M, Lindsey JS, Bocian DF. *Langmuir*. 2008; 24:12047. [PubMed: 18823081]
19. Willaredt J, Schlemper H, Keller M, Schmitt D, Fritz H, Schwesinger R. *Chem. Ber.* 1994; 127:2435.
20. The conclusion that the product is 4-coordinate (TMP)Fe^{II} rather than a 5-coordinate aquo complex is based on ¹H NMR spectra. We observe the same spectrum for (TMP)Fe^{II} generated from (TMP)Fe^{III}Cl under rigorously moisture free conditions with cobaltocene and for (TMP)Fe^{II} + H₂O generated from (TMP)Fe^{III}(OH) + 0.5 eq PhNHNHPh (eq 2). Furthermore, alcohols, ethers, and H₂O are known to be poor ligands for ferrous porphyrins (i.e. *K*_{eq} for THF binding to (TPP)Fe^{II} in C₆H₆ = ~5 M⁻¹): Mashiko T, Dolphin D, Wilkinson G. Chapter 21. *Comprehensive Coordination Chemistry* (1st edition). 1987:813. Pergamon Press New York
- 21 (a). Swistak C, Mu XH, Kadish KM. *Inorg. Chem.* 1987; 26:4360. (b) Converted from the reported *E*_{1/2} = -0.86 V vs SCE in CH₂Cl₂.
22. PhN=NH is bracketed since it is unstable to decomposition and is not observed by ¹H NMR. See Huang P-K, Kosower EM. *J. Am. Chem. Soc.* 1968; 90:2367.
23. Sandström, J. *Dynamic NMR Spectroscopy*. 1st edition. Academic Press; New York: 1982.
24. Kaljurand I, Kütt A, Sooväli L, Rodima T, Mäemets V, Leito I, Koppel IA. *J. Org. Chem.* 2005; 70:1019. [PubMed: 15675863]
25. Nee MW, Smith JRL. *J. Chem. Soc. Dalton Trans.* 1999:3373.
26. Bordwell FG. *Acc. Chem. Res.* 1988; 21:456.
27. Luo, Y-R. *Comprehensive Handbook of Chemical Bond Energies*. CRC Press; Boca Raton, FL: 2007.
28. Collman JP, Boulatov R, Sunderland CJ, Fu L. *Chem. Rev.* 2004; 104:561. [PubMed: 14871135]
29. Benoit D, Chaplinski V, Bradslau R, Hawker C. *J. Am. Chem. Soc.* 1999; 121:3904.
- 30 (a). Mahanthappa MK, Huang K, Cole AP, Waymouth RM. *Chem. Comm.* 2002:502. [PubMed: 12120561] (b) Huang K, Waymouth RM. *J. Am. Chem. Soc.* 2002; 124:8200. [PubMed: 12105895] (c) Huang K, Han JH, Cole AP, Musgrave CB, Waymouth RM. *J. Am. Chem. Soc.* 2005; 127:3807. [PubMed: 15771515]
31. Chan KS, Li XZ, Dzik WI, de Bruin B. *J. Am. Chem. Soc.* 2008; 130:2051. [PubMed: 18205361]
- 32 (a). Choi IK, Liu Y, Wei Z, Ryan MD. *Inorg. Chem.* 1997; 36:3113. [PubMed: 11669965] (b) Bari SE, Amorebieta VT, Gutiérrez MM, Olabe JA, Doctorovich F. *J. Inorg. Biochem.* 2010; 104:30. [PubMed: 19879651] (c) Alluisetti GE, Almaraz AE, Amorebieta VT, Doctorovich F, Olabe J. *J. Am. Chem. Soc.* 2004; 126:13432. [PubMed: 15479100]
33. Gutiérrez MM, Olabe JA, Amorebieta VT. *Inorg. Chem.* 2011; 50:8817. [PubMed: 21859073]
- 34 (a). Rangelova K, Mason RP. *Magn. Reson. Chem.* 2011; 49:152. [PubMed: 21246623] (b) Eberson L. *J. Chem. Soc. Perkin. Trans. II.* 1994; 171(c) Makino K, Hagiwara T, Hagi A, Nishi M, Murakami A. *Biochem. Biophys. Res. Commun.* 1990; 172:1073. [PubMed: 2173913] (d) Leinisch F, Rangelova K, DeRose EF, Jiang J, R. P. Mason, *Chem. Res. Toxicol.* 2011; 24:2217.
35. Lind J, Merényi G. *J. Phys. Chem. A.* 2006; 110:192. [PubMed: 16392855]

Figure 1.
Kinetic profile for the reaction of (TMP)Fe^{III}(OH) (80 μ M) with TEMPO-H (4.0 mM).

Figure 2. ^1H NMR spectra of 4.0 mM $(\text{TMP})\text{Fe}^{\text{II}}$ with 0 to 26.6 mM of TEMPO in $\text{toluene-}d_8$ on a 500 MHz spectrometer at 25°C . The dotted box at left shows the shift of the *meta*-aryl protons, and the box at the right shows the shift of the *p*- CH_3 groups, indicating the equilibrium formation of $(\text{TMP})\text{Fe}^{\text{III}}(\text{TEMPO})$. The broad, downfield β -pyrrolic peaks are not shown.

Figure 3.

A. Optical spectra of (TMP)Fe^{II} (80 μM) and one equivalent of TEMPO in toluene at temperatures ranging from 25° C to -90° C. **B.** van't Hoff plot of ln(K₄) vs. 1/T.

Figure 5.

Kinetic traces for the disproportionation of TEMPO-H catalysed by (TMP)Fe^{II} in toluene-*d*₈. Concentrations were determined by ¹H NMR using a hexamethylbenzene internal standard. **A.** The disappearance of TEMPO-H (x) (initial concentration = 33 mM) and the appearance of TEMP-H (O) vs. time in the presence of 0.08 mM (TMP)Fe^{II}. **B.** The disappearance of TEMPO-H (initial concentration = 4 mM) vs. time with 0.04 mM (TMP)Fe^{II} in the absence (x) or presence (●) of 20 mM TEMPO added at *t* = 0.

Scheme 2.

Proposed reaction cycle for the catalytic disproportionation of TEMPO-H by $(\text{TMP})\text{Fe}^{\text{III}}(\text{OH})$.

Table 1Spectroscopic features of (TMP)Fe species in toluene.^a

Compound	¹ H NMR chemical shifts				Q_1 absorbance
	<i>m</i> -H	<i>o</i> -CH ₃	<i>P</i> -CH ₃	β -pyr	$\lambda_{\max}(\epsilon)$
(TMP)Fe ^{II} at -80° C ^{10c}	11.72	5.62	6.04	2.86	538 (11.6)
	14.70	7.79	8.39	-1.44	
(TMP)Fe ^{III} (TEMPO) at -80° C	11.06,	n.o.	3.26	81.0	
	14.24, 13.19	n.o.	3.96	124	565 (8.7) ^b
(TMP)Fe ^{III} (^t Bu ₃ ArO)	13.76, 12.67	5.35	3.30	89.50	---
(TMP)Fe ^{III} (OH)	12.14, 11.18	n.o.	3.29	81.5	580 (7.5) ²¹

^aValues at 25° C unless otherwise noted. NMR spectra in toluene-d₈, with chemical shifts in ppm; n.o. = not observed. Optical spectra: $\lambda_{\max}$ in nm, ϵ in cm⁻¹ M⁻¹ × 10⁻³.

^bat -80° C.