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The Mechanism of Catalytic O₂ Reduction by Iron Tetraphenylporphyrin

Michael L. Pegis,^{1,3,§} Daniel J. Martin,^{1,§} Catherine F. Wise,^{1,§} Anna C. Brezny,¹ Samantha I. Johnson,^{2‡} Lewis E. Johnson,⁴ Neeraj Kumar,⁵ Simone Raugei,² and James M. Mayer^{1*}

Abstract

The catalytic reduction of O₂ to H₂O is important for energy transduction in both synthetic and natural systems. Herein, we report a kinetic and thermochemical study of O₂ reduction catalyzed by iron tetraphenylporphyrin (Fe(TPP)) in N,N'-dimethylformamide using decamethylferrocene as a soluble reductant and para-toluenesulfonic acid (pTsOH) as the proton source. This work identifies and characterizes catalytic intermediates and their thermochemistry, providing a detailed mechanistic understanding of the system. Specifically, reduction of the ferric porphyrin, $[Fe^{III}(TPP)]^+$ forms the ferrous porphyrin, Fe^{II}(TPP), which binds O₂ reversibly to form the ferricsuperoxide porphyrin complex, $Fe^{III}(TPP)(O_2^{\bullet-})$. The temperature dependence of both the electron transfer and O₂ binding equilibrium constants have been determined. Kinetic studies over a range of concentrations and temperatures show that the catalyst resting state changes during the course of each catalytic run, necessitating the use of global kinetic modeling to extract rate constants and kinetic barriers. The rate-determining step in oxygen reduction is protonation of $Fe^{III}(TPP)(O_2^{\bullet-})$ by pTsOH, which proceeds with a substantial kinetic barrier. Computational studies indicate that this barrier for proton transfer arises from an unfavorable pre-association of the proton donor with the superoxide adduct and a transition state that requires significant desolvation of the proton donor. Together, these results are the first example of oxygen reduction by iron tetraphenylporphyrin where the pre-equilibria between ferric, ferrous, and ferric-superoxide intermediates have been quantified under catalytic conditions. This work gives a generalizable model for the mechanism of iron porphyrin-catalyzed ORR and provides an unusually complete mechanistic study of an ORR reaction. More broadly, this study also highlights the kinetic challenges for proton transfer to catalytic intermediates in organic media.

Introduction

Many diverse biological and energy processes involve the catalytic reduction of dioxygen (O_2) .^{1–5} In nature, cytochrome *c* oxidase reduces O_2 to drive ATP synthesis in cellular respiration,⁶ and cytochromes P450 couple the reduction of O_2 to the oxidations of endogenous and xenobiotic substances in numerous synthetic and metabolic processes.^{7–9} In energy conversion

technologies such as fuel cells, the oxidation of a fuel (dihydrogen, methanol, etc.) is coupled to the oxygen reduction reaction (ORR, eq 1), producing usable electrochemical work for portable and stationary applications.¹⁰ For such approaches to be practical, the ORR must be performed at fast rates and with high selectivity and energy efficiency over thousands of hours of operation. Achieving this goal will have vast implications for the global energy economy.

$$0_2 + 4H^+ + 4e^- \rightarrow 2H_20$$
 (1)

Given the kinetic complexity of the ORR, widespread commercialization of fuel cell technologies requires identification of inexpensive and efficient electrocatalysts capable of delivering 4H⁺ and 4e⁻ to O₂ and cleaving the O=O bond. Numerous research efforts have focused on developing new catalytic systems and improving previously known ORR electrocatalysts.^{3,4,11,12} Given their biological relevance as active sites, iron porphyrins have been widely studied as ORR catalysts under electrocatalytic conditions.^{13,14} Notably, graphiteembedded iron porphyrinic-like materials have been shown to exhibit ORR activity rivaling that of platinum metal in acidic media; however, the exact nature of their active sites remains a continued discussion.⁶⁻⁸

Further improvement of ORR cathodic materials will require an understanding of the catalyst identity and turnover-limiting step(s) in the catalytic cycle. Such a detailed understanding is difficult to achieve for heterogeneous electrode surfaces, where the nature and catalytic activities of specific sites and intermediates are difficult to determine. Studying molecular ORR electrocatalysts that have been physi- or chemisorbed onto electrode surfaces can circumvent some of these complications, especially with the use of *in-situ* spectroscopic characterization.^{18–}

Reaction mechanisms are more easily analyzed in systems with homogeneous molecular catalysts, as these catalysts can be prepared in pure form and are readily examined using standard spectroscopic and kinetic methods for solution species. Optical spectroscopies have been extensively used to study iron porphyrins in the biomimetic context of dioxygen binding^{24–} ²⁶ and the oxidation of organic molecules.^{27,28} However, surprisingly few studies have investigated the *catalytic* reduction of O₂ by iron porphyrins using soluble reductants.¹¹

Nearly 30 years ago, two reports by Fukuzumi described the first mechanistic investigations of O₂ reduction by iron tetraphenylporphyrin (abbreviated herein as Fe(TPP) if the oxidation state and axial ligand(s) are not specified). These studies were performed in acetonitrile (MeCN) using substituted ferrocenes (Fc) as the source of electrons and perchloric acid (HClO₄) as the source of protons.^{29,30} Under these conditions, the rate-determining step was proposed to be outer-sphere electron transfer from the reductant to [Fe^{III}(TPP)]ClO₄, based upon the first-order dependence on [Fc] and the zero-order dependences on [O₂] and [HClO₄]. In this example, the strongly acidic medium with relatively weak reductants resulted in no detectable intermediates within the catalytic cycle.

More recently, kinetic studies examined O_2 reduction catalyzed by Fe^{III}(TPP)CI and other porphyrin derivatives in acidic acetonitrile and *N*,*N*'-dimethylformamide solutions containing decamethylferrocene (Fc*) as a soluble reductant.^{31,32} With excess of this stronger reductant, the rate law for catalysis via Fe^{III}(TPP)CI was zero-order in reductant because electron transfer from Fc* to Fe^{III}(TPP)CI was initially rapid and favorable. Under these conditions, the rate of ORR

catalysis was first order in O_2 , acid, and catalyst.³¹ The same rate law and rate constant were obtained under electrocatalytic conditions. Subsequent studies found this rate law to be general for electrocatalytic O_2 reduction using substituted iron porphyrins³² and in the presence of proton donors of varying acidity (pK_a).³³ The rate law implicates a mechanism of initial reduction of Fe^{III} to Fe^{II}, pre-equilibrium O_2 binding to Fe^{II}, and rate-limiting proton transfer from the acid to the Fe^{III}-superoxo intermediate (**Scheme 1**). However, efforts to decrease the proton transfer barrier by appending proton relays to the iron porphyrins did not result in rate enhancements.³² To obtain direct support for the proposed mechanism and to better understand the factors affecting catalytic rates, a more thorough mechanistic analysis was needed.

Scheme 1. Proposed mechanism for oxygen reduction catalyzed by Fe(TPP), with TPP abbreviated as an oval. Red = Fc^* or electrode.



Herein, we report a much more complete and nuanced analysis of the $4H^+/4e^-$ reduction of O₂ to H₂O catalyzed by iron tetraphenylporphyrin, prepared as the triflate salt ([Fe^{III}(TPP)]OTf).

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The ferrous and ferric-superoxide porphyrin species are identified and observed as catalytic intermediates for the first time, and their temperature-dependent speciation is reported. This includes measurements of the equilibrium constants for electron transfer from Fc* to $[Fe^{III}(TPP)]OTf$ and for O₂ binding to Fe^{II}(TPP). These shifting equilibria and speciation play a critical and previously unappreciated role in the kinetics of catalysis, as the catalyst resting state varies among three different species during the course of the reaction. The temperaturedependence of these equilibria combined with measurements of catalytic rates and catalyst speciation by optical stopped-flow and electrochemical methods provide an unusually rich dataset. Modelling these results gives a detailed view of the catalytic mechanism under different conditions. The model gives the activation parameters for protonation of the ferric-superoxo intermediate, the rate-determining step in the catalytic cycle. These results are used in conjunction with computational modeling to analyze the underlying factors limiting proton transfer to the ferric-superoxide intermediate. Such a detailed mechanistic understanding provides critical insight into iron porphyrin-catalyzed oxygen reduction and should enable further improvement of catalytic systems.

$$O_2 + 4pTsOH + 4Fc^* \xrightarrow{[Fe(TPP)]OTf} 2H_2O + 4pTsO^- + 4Fc^{*+}$$
 (2)

Experimental

Materials

Iron tetraphenylporphyrin chloride, Fe^{III}(TPP)Cl, was synthesized by the metalation of *meso*-tetraphenylporphyrin with iron(II) chloride in refluxing DMF as previously reported³² (see

SI, **Figure S1-S2**). [Fe^{III}(TPP)]OTf was generated *in situ* from Fe(TPP)Cl and TIOTf in acidified DMF (see SI, **Figure S3-S4**). Fe^{II}(TPP) was prepared from the well-known reduction of Fe^{III}(TPP)Cl by Zn/Hg amalgam and was recrystallized from toluene/THF mixtures.^{34,35} This compound was also prepared using modified literature procedures (see SI, **Figure S7-S8**). All solvents and electrolytes were purchased at high purity and purified as needed, as further described in Section 1.2 of the SI.

Optical Equilibrium and Kinetic Measurements

Equilibrium measurements were performed by optical spectroscopy using a temperaturecontrolled Unisoku Unispeks cryostat. Equilibrium constants for electron transfer were made by fitting the UV-vis spectra of DMF solutions containing 0.1 M [*n*-Bu₄N][PF₆] and equimolar (100 μ M) amounts of [Fe^{III}(TPP)]OTf, Fe^{II}(TPP), Fc^{*}, and Fc^{*+} between 213 K and 293 K. Likewise, equilibrium constants for O₂ binding were made by fitting the UV-vis spectra of O₂-saturated DMF solutions initially containing 0.1 M [*n*-Bu₄N][PF₆] and 60 μ M Fe^{II}(TPP) between 213 K and 238 K. Both sets of equilibria data were analyzed using van 't Hoff plots to yield enthalpic and entropic parameters. See Sections 2-3 of the SI for complete details.

Stopped-flow kinetics measurements were performed by mixing N₂-saturated DMF solutions of Fc* in one syringe with air-saturated DMF solutions containing [Fe^{III}(TPP)]OTf and *p*TsOH in a second syringe. The reaction progress was monitored by following the appearance of Fc*+ over time. Experiments were performed at various [*p*TsOH], [catalyst], and temperature (253 – 303 K). Changes in catalyst speciation over time were determined by fitting optical spectra to linear combinations of three catalyst species: [Fe^{III}(TPP)]OTf, Fe^{II}(TPP), and Fe^{III}(TPP)(O₂*-). The concentration time courses were modeled to obtain thermodynamic and kinetic parameters. See

Section 5-6 of the SI for complete details.

Kinetic Modeling

The time course data from the stopped-flow catalytic experiments were fit to a multi-step kinetic model in the program COPASI.³⁶ The thermodynamic parameters (ΔH° and ΔS°) for electron transfer and O₂ binding, as well as the activation parameters (ΔH^{\dagger} and ΔS^{\dagger}) for proton transfer, were optimized in order to minimize the sum of squared deviations between the experimental concentrations and fitted time course concentrations. See Section 6 of the SI for complete details.

Computational Modeling

The present density functional theory (DFT) calculations build on previously reported work.³² Stationary points were optimized using the PBE exchange and correlation functional.³⁷ The Stuttgart/Dresden basis set with relativistic effective core potential (SDD) was used for the Fe center, and the 6-31G** basis set^{38,39} was used for all atoms except sulfur. Diffuse functions and additional polarization functions (6-31++G(2df,2pd)) were used on sulfur in order to capture the sulfur–oxygen bonding correctly. Justification for this can be found in Section 8 of the SI. Single point solvation energies in DMF were modeled using the SMD continuum solvent.⁴⁰ Harmonic vibrational frequencies, calculated at the same level of theory, were used to estimate zero-point energy (ZPE) and the thermal contributions free energies. Free energies are referred to the standard state concentration of 1 M for the solute and 12.9 M for the solvent DMF at *T* = 298 K. See Section 8 of the SI for complete details.

Results

I. Electron Transfer Equilibrium

The proposed mechanism involves initial reduction of $[Fe^{III}(TPP)]OTf$ to $Fe^{II}(TPP)$ by decamethylferrocene (Fc*). Qualitatively, addition of excess Fc* to $[Fe^{III}(TPP)]OTf$ results in the predominant formation of Fe^{II}(TPP) (**Figure S9-S10**). Adding Fc*+ to this solution reoxidizes some Fe^{III}(TPP) and confirms the equilibrium nature of this ET process (eq 3; **Figure S11**). Equilibrium constants in DMF were measured by preparing solutions containing the four species and 0.1 M $[n-Bu_4N][PF_6]$, to make the conditions similar to those used in the electrocatalytic and optical measurements. After correcting for dilution, analysis of the optical spectra gave the ratio of $[Fe^{III}(TPP)]OTf$ to Fe^{II}(TPP) (see SI).

$$Fc^{*} + Fe^{III}(TPP)^{+} \rightleftharpoons Fc^{*+} + Fe^{II}(TPP)$$
(3)

$$K_{\rm ET} = \frac{[{\rm Fc}^{*+}][{\rm Fe}^{\rm II}({\rm TPP})]}{[{\rm Fc}^{*}][[{\rm Fe}^{\rm III}({\rm TPP})]^{+}]}$$
(4)

Following eq 4 and knowing the concentrations of all four species, K_{ET} was determined at 293 K to be 0.16 ± 0.03. This K_{ET} could also be determined from electrochemical measurements: $E_{1/2}$ (Fe^{III}(TPP)⁺/Fe^{II}(TPP)) = -0.538 V vs. Fc⁺/Fc (*vide infra*) and $E_{1/2}$ (Fc^{*+}/Fc^{*}) = -0.484 V vs. Fc⁺/Fc in DMF³¹ containing 0.1 M [*n*-Bu₄N][PF₆]. The 0.054 V difference in reduction potentials gives K_{ET} = 0.12 (SI Section 2.2), very close to the K_{ET} = 0.16 from optical measurements. The optical measurements were repeated at temperatures between 213 and 293 K to investigate the temperature dependence of K_{ET} (Figure 1a). The resulting van 't Hoff plot yielded the enthalpy and entropy for the electron transfer from Fc^{*} to [Fe^{III}(TPP)]OTf: $\Delta H^{\circ}_{\text{ET}}$ = 2.8 ± 0.1 kcal mol⁻¹ and $\Delta S^{\circ}_{\text{ET}}$ = 6 ± 2 cal mol⁻¹ K⁻¹ (Figure 1b).

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Figure 1. a) Spectra of a DMF solution containing 100 μ M [Fe^{III}(TPP)]OTf, Fe^{II}(TPP), Fc^{*}, and Fc^{*+} and 0.1 M [*n*-Bu₄N][PF₆] in the Q-band region at temperatures between 293 K and 213 K. **b)** van 't Hoff analysis of In(K_{ET}) derived from the data in a).

II. Oxygen Binding Equilibrium

To test the hypothesis that O_2 binding follows the initial reduction of $[Fe^{III}(TPP)]OTf$, a genuine $Fe^{II}(TPP)$ sample was prepared and exposed to O_2 at low temperatures in DMF. The addition of 1 atm O_2 to DMF solutions of $Fe^{II}(TPP)$ at 213 K resulted in the quantitative conversion of $Fe^{II}(TPP)$ to a new species with Q-band absorbance features at 542 and 580 nm, characteristic of a ferric tetra-arylporphyrin superoxide complex, $Fe^{III}(TPP)(O_2^{\bullet-})$.^{41,42} The chemically-generated $Fe^{III}(TPP)(O_2^{\bullet-})$ complex was relatively stable (~30 minutes) at 213 K but decomposed quickly at temperatures above 238 K to the well-known μ -oxo dimer, $[Fe^{III}(TPP)]_2O$.⁴²

The stoichiometry of O₂ binding was measured by titrating a DMF solution of Fe^{II}(TPP) at 213 K with a room temperature DMF solution containing 1 atm O₂ (3.1 mM [O₂]).⁴³ With substoichiometric concentrations of O₂, the Q-bands of Fe^{II}(TPP) incrementally shifted to those of Fe^{III}(TPP)(O₂^{•-}) (**Figure 2a**). At 213 K, slightly more than one equivalent of O₂ was necessary to reach the end point of the titration, after which no additional changes occurred in the spectra (**Figure S13** and **S15**).

The reversibility of O₂ binding to Fe^{II}(TPP) was investigated by sparging a solution of the generated Fe^{III}(TPP)(O₂^{•-}) adduct with argon at 213 K. A spectrum collected after 5 minutes of sparging closely matched the initial anaerobic spectrum of Fe^{II}(TPP) with some residual contributions from remaining Fe^{III}(TPP)(O₂^{•-}) (**Figure S16**). That Fe^{II}(TPP) could be formed from Fe^{III}(TPP)(O₂^{•-}) proved O₂ binding reversibility and enabled us to measure equilibrium constants (eq 5).

$$K_{O_2}(M^{-1}) = \frac{\left[Fe^{III}(TPP)(O_2^{\bullet^-})\right]}{\left[Fe^{II}(TPP)\right][O_2]}$$
(5)

The equilibrium constants for O₂ binding to Fe^{II}(TPP) (K_{O_2} , eq 5) were measured at various temperatures. With excess O₂, a solution of Fe^{III}(TPP)(O₂^{•-}) was prepared at 213 K and incrementally warmed to 238 K. Upon warming, the initial spectrum gradually changed to contain Q-bands of both Fe^{III}(TPP)(O₂^{•-}) and Fe^{II}(TPP) (**Figure S17**). The UV-vis spectrum at each temperature was fit to a linear combination of independently measured Fe^{III}(TPP)(O₂^{•-}) and Fe^{II}(TPP) spectra (see SI Section 3.3). The concentrations of Fe^{III}(TPP), Fe^{III}(TPP)(O₂^{•-}), and of dissolved O₂ from mass balance were then used to calculate K_{O_2} at each temperature (eq 5). At

213 K, the free energy of formation for Fe^{III}(TPP)(O₂⁻⁻) is exergonic, $\Delta G^{\circ}_{O2} = -3.68$ kcal mol⁻¹. The slope and intercept of the resulting van 't Hoff plot (**Figure 2b**) yielded the enthalpy and entropy for the binding of O₂ to form Fe^{III}(TPP)(O₂^{•-}): $\Delta H^{\circ}_{O2} = -10.5 \pm 0.7$ kcal mol⁻¹ and $\Delta S^{\circ}_{O2} = -32 \pm 3$ cal mol⁻¹ K⁻¹. By extrapolating the van 't Hoff plot to 298 K , the equilibrium constant for O₂ binding at room temperature was determined to be ca. 5 M⁻¹. A T-test gave a 95% confidence interval for this extrapolated value at 298 K to be between 0.21 M⁻¹ and 110 M⁻¹ (see SI for details).⁴⁴



Figure 2. **a)** Optical spectra (corrected for dilution) of a titration at 213 K of a DMF solution containing 50 μ M Fe^{II}(TPP) and 0.1 M [*n*-Bu₄N][PF₆] with DMF containing dissolved O₂. **b)** van 't Hoff analysis of O₂ binding to Fe^{II}(TPP) (K_{O_2} in M⁻¹).

Our previous studies have shown that the rate of ORR catalyzed by iron tetraarylporphyrins exhibits first-order dependences on the concentrations of catalyst, O₂, and acid.³² In order to verify that the same rate law applies to the system studied here, we investigated the kinetics of ORR catalyzed by [Fe^{III}(TPP)]OTf using cyclic voltammetry.

In anaerobic DMF solutions containing [Fe^{III}(TPP)]OTf and 0.1 M [*n*-Bu₄N][PF₆], a chemically reversible, diffusion-controlled reduction was observed at –0.538 V vs. Fc⁺/Fc (**Figure 3a** (black trace), **Figure S20**). This wave is diagnostic of the reduction of [Fe^{III}(TPP)]⁺ to Fe^{II}(TPP), as previously reported by Savéant⁴⁵ and later by our group.^{32,33} Addition of *p*TsOH did not affect $E_{1/2}$ (Fe^{III}(TPP)⁺/Fe^{II}(TPP)) (**Figure S21**), in contrast to what has been observed for Fe(TPP) in the presence of chloride salts.³¹ These results are consistent the preferred binding of DMF solvent over triflate, in both Fe(III) and Fe(II) redox states, as previously observed.^{32,45} For simplicity, we exclude explicit solvent molecules from the abbreviated formulas and continue to abbreviate these redox states as [Fe^{III}(TPP)]OTf and Fe^{II}(TPP).

When DMF solutions containing [Fe^{III}(TPP)]OTf, *p*TsOH, and [*n*-Bu₄N][PF₆] were sparged with 1 atm air (0.7 mM O₂ in DMF),⁴³ the voltammograms displayed significant current enhancements (>10x) centered above $E_{1/2}$ (Fe^{III}/Fe^{III}) (**Figure 3a**, red trace). The magnitude of this irreversible current was linear with the square root of the scan rate, which suggests that the catalytic current arises from an electrogenerated, homogeneous catalyst.³¹ Rotating ring-disk electrochemistry (RRDE) was used to quantify the amount of H₂O₂ produced during turnover. The RRDE measurements demonstrated that catalysis is selective for the 4H⁺/4*e*⁻ reduction of O₂ to water and produces ~1.5% H₂O₂ (*n*_{cat} = 3.9) under these conditions (**Figure S50-S51**).

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Figure 3. a) Electrochemical response of 0.3 mM [Fe^{III}(TPP)]OTf in the presence of 1 M *p*TsOH and 1.6 mM O₂ (green), 0.7 mM O₂ (red, air sparged), and 0 mM O₂ (black, N₂ sparge) at 298 K. **b**) Dependence of k_{obs} from FOWA on [*p*TsOH] at different O₂ concentrations. All CVs were taken in the presence of 0.1 M [*n*-Bu₄N][PF₆] electrolyte.

The pseudo-first order rate constant k_{obs} for ORR was quantified using foot-of-the-wave analysis (FOWA, equation 7),⁴⁶ where n_{cat} = 3.9 (determined by RRDE, see above). FOWA allows the determination of catalytic rate constants under conditions where the concentrations of the substrates in the reaction-diffusion layer (O₂ and *p*TsOH in this case) are essentially identical to the bulk solution concentrations (see SI).⁴⁶ The linearity of the foot-of-the-wave plots (**Figure S22**) indicated that the reaction was first order in catalyst. Additionally, k_{obs} was linearly dependent on both [O₂] and [*p*TsOH] (**Figure 3**), indicating the third-order rate law in equations 6 and 8. The quotient of k_{obs} and the reactant concentrations then afforded the third order rate constant k_{cat} . Considering the upper and lower bounds for σ in eq 7 (see SI), k_{cat} ranged from (3.2-6.4) × 10⁵ $M^{-2} s^{-1}$.

$$rate = n_{cat}k_{obs}[Fe(TPP)]$$
(6)

$$\frac{i_c}{i_p} = \frac{2.24n_{cat}^{\sigma} \sqrt{\frac{RT}{Fv}} k_{obs}}{1 + \exp\left[\frac{F}{RT}(E - E_{1/2})\right]}$$
(7)

$$k_{\rm obs} = k_{\rm cat} [O_2] [p \text{TsOH}] \tag{8}$$

IV. Optical Kinetics

The kinetics of Fe(TPP)-catalyzed ORR were also studied by optical spectroscopy, over a range of temperatures. These experiments were performed in DMF using pTsOH as the proton source and Fc* as the soluble reductant. During optical measurements, all solutions also contained 0.1 M [n-Bu₄N][PF₆] to mirror the electrochemical conditions. In a typical experiment, a solution of air-saturated DMF (0.7 mM O₂) containing [Fe^{III}(TPP)]OTf (60 μ M) and pTsOH (50 mM) was rapidly mixed in a stopped-flow instrument with an equal volume of an anaerobic DMF solution of Fc* (6 mM, higher concentrations were limited by solubility), with all concentrations being halved upon mixing (see SI). After mixing, optical spectra showed the growth of a broad absorbance feature between 600-700 nm, diagnostic of decamethylferrocenium (Fc*+) formation, along with various changes in the porphyrin Q-band region (Figures 4a and S24, discussed further below). Control experiments performed under identical conditions but in the absence of [Fe^{III}(TPP)]OTf catalyst formed a much smaller amount of Fc^{*+} over the same time course (~10%) (Figure 4b). The small amount of Fc* auto-oxidation likely results from unfavorable pre-equilibrium electron transfer with O_2 followed by irreversible chemical reactions of $O_2^{-.47}$ When *p*TsOD was substituted for *p*TsOH, the rate of Fc^{*+} formation did not change (KIE \approx 1, see Figure S25).



Figure 4. a) Spectral changes measured for the reaction of O₂ (0.33 mM) with *p*TsOH (50 mM) and Fc* (3 mM), catalyzed by [Fe^{III}(TPP)]OTf (30 μ M) over a 30 second reaction at 298 K. **b)** Rate of Fc*+ formation over the course of the first 10 s of reaction (**a**) (black trace), compared to the same reaction conducted in the absence of added [Fe^{III}(TPP)]OTf catalyst (purple trace). Concentrations of Fc*+ were calculated at 700 nm after removal of the absorbance contributions from [Fe^{III}(TPP)]OTf (see SI, Section 5.3).

The kinetics of the Fe(TPP)-catalyzed ORR were examined by stopped-flow methods at temperatures between 253 and 303 K. In these experiments, the air-saturated syringe was prepared at room temperature so that the initial concentration of dissolved O_2 remained constant for all catalytic runs. Notably, as shown in **Figure 5**, the spectrum collected 1 s after mixing was temperature dependent. At 253 K, absorbance features at 542 and 580 nm were immediately present (**Figure 5a**). These features match those of the independently prepared ferric superoxide, Fe^{III}(TPP)($O_2^{\bullet-}$), described above. However, at temperatures above 273 K, the initial spectrum resembled a mixture of Fe^{III}(TPP) and Fe^{III}(TPP)($O_2^{\bullet-}$) (**Figure 5b**). At all temperatures, the initial traces decayed with the formation of [Fe^{IIII}(TPP)]OTf and Fc^{*+}.



Figure 5. a) Spectral changes after stopped-flow mixing of $[Fe^{III}(TPP)]OTf (30 \mu M)$, *p*TsOH (35 mM), Fc* (3 mM), and O₂ (0.33 mM) at 253 K. Black trace = initial spectra after mixing (1 s) Red trace = final spectra after mixing (50 s). **b)** Same conditions as (**a**), at 303 K. Black trace = initial spectra after mixing (1 s) Red trace = final spectra after mixing (20 s).

The temperature dependence of the initial stopped-flow kinetic traces reflects the temperature-dependent equilibrium constant for O_2 binding. The initial spectra showed exclusively $Fe^{III}(TPP)(O_2^{\bullet-})$ at low temperatures and a mixture of $Fe^{II}(TPP)$ and $Fe^{III}(TPP)(O_2^{\bullet-})$ at higher temperatures, consistent with the independent O_2 binding measurements described above. While the electron transfer equilibrium also shows a temperature dependence, ΔG_{ET} only changes by ~ 0.3 kcal mol⁻¹ across this temperature range. Thus, the observed spectral differences are dominated by the difference in O_2 -binding favorability between the two temperatures. Additionally, the observation of $Fe^{II}(TPP)$ or $Fe^{III}(TPP)(O_2^{\bullet-})$ as the initial catalyst resting state also

supports the proposed mechanism in which the rate of ORR is limited by protonation of $Fe^{III}(TPP)(O_2^{\bullet-})$ rather than initial electron transfer or O_2 binding (**Scheme 1**).

Over the course of the stopped-flow kinetics runs, the speciation of the iron catalyst changed, with [Fe^{III}(TPP)]OTf becoming the predominant species at the end of the reaction (when limiting O_2 is completely consumed). The changes in catalyst speciation reflect the positions of the time- and temperature-dependent equilibria between [Fe^{III}(TPP)]OTf, Fe^{II}(TPP), and $Fe^{III}(TPP)(O_2^{\bullet-})$ during catalytic turnover, as discussed in more detail in the next section. In the absence of a constant catalyst resting state, the rate law for Fc*+ formation needs to be defined with respect to total amount of catalyst in solution, [Fe(TPP)]_{total}. The resulting rate law (eq 9) includes the two pre-equilibria ($K_{\rm ET}$ and $K_{\rm O_2}$) and the turnover-limiting protonation step, $k_{\rm PT}$. The complexity of this rate law arises from the uphill electron transfer equilibrium between Fc* and [Fe^{III}(TPP)]OTf (K_{ET} < 1). As such, even with a large excess of Fc^{*} (e.g. >40:1 ratio of [Fc^{*}]:[O₂]), the growth of the oxidized product Fc*+ shifts the initial electron transfer reaction away from the formation of catalytically active Fe^{II}(TPP), as demonstrated independently in Section I above. The complexity of this rate law and the inability to find experimental conditions under which it simplifies have precluded simple fitting and the determination of a simple reaction order in [Fc*] (see SI).

$$\frac{d[Fc^{*+}]}{dt} = \frac{n_{cat}K_{ET}K_{O_2}k_{PT}[Fe(TPP)]_{total}[O_2][Fc^{*}][pTsOH]}{K_{ET}[Fc^{*}](1 + K_{O_2}[O_2]) + [Fc^{*+}]}$$
(9)

Longer time-scale catalytic experiments were conducted by combining a large excess of Fc* (10 mM) and *p*TsOH (260 mM) relative to [Fe^{III}(TPP)]OTf (1 μ M) and stirring the solution in ambient air. Over 15 minutes, significantly larger amounts of Fc^{*+} were produced than an

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identical experiment conducted in the absence of [Fe^{III}(TPP)]OTf. Iodometric titrations of the resulting solution were used to quantify the amount of H₂O₂ produced during the catalyzed reaction and revealed that ~15% H₂O₂ ($n_{cat} = 3.7 e^{-}/O_2$, **Figure S51**) was formed under such conditions, in good agreement with the selectivity values obtained electrochemically ($n_{cat} \approx 3.9 e^{-}/O_2$).³¹ These results demonstrate that the catalyst remains active for ORR for at least 15 minutes and permit a rough estimation of the catalyst turnover number over 15 minutes, TON = 2000 moles O₂ consumed per mole catalyst, **Figure S26**.

V. Kinetic Modeling

The constantly evolving catalyst speciation during ORR by Fe(TPP), observed by stoppedflow measurements, required us to use a complete kinetic model to fit the data. As described in this section, the model revealed the thermodynamic parameters for the ET and O₂-binding preequilibria and the kinetic parameters for the turnover-limiting step.

Fitting the optical data to a kinetic model first required the concentration of each catalyst species at every time point to be determined. These concentrations were obtained using Beer's Law and a system of linear equations that considered absorbance contributions from $[Fe^{III}(TPP)]OTf$, $Fe^{III}(TPP)$, $Fe^{III}(TPP)(O_2^{\bullet-})$, and Fc^{*+} . Absorbance contributions from Fc* were negligible in the wavelength region of interest and could be ignored (see SI Section 5.3).

Global modeling of all the room temperature stopped-flow kinetic runs was performed with the software COPASI³⁶ using the kinetic model in **Scheme 2** and the corresponding rate law (eq 9 above). The only parameters input into the model were the fast rate constants ($10^7 M^{-1} s^{-1}$) for (1) electron transfer from Fc* to Fe^{III}(TPP)⁺ and (2) O₂-binding to Fe^{II}(TPP). This was done to

ensure that these steps were fast pre-equilibria, as observed experimentally (see above). Step 4 was included to account for mass balance in the reaction and was set to a fast enough rate to be kinetically invisible.

Scheme 2. Kinetic model and parameters used for global fitting of the stopped-flow kinetic data, to and obtain ΔH°_{ET} , ΔS°_{ET} , ΔH°_{O2} , ΔS°_{O2} , ΔH^{\ddagger}_{PT} , and ΔS^{\ddagger}_{PT} .

1.
$$[Fe^{III}(TPP)]^{+} + Fc^{*} \leftrightarrow \frac{k_{ET}}{k_{-ET}} Fe^{II}(TPP) + Fc^{*+}$$

$$k_{ET} = 10^{7} M^{-1} s^{-1}; \quad K_{ET} = k_{ET}/k_{-ET}; \quad K_{ET} = \exp \left[\left(\frac{\Delta H^{\circ} - T\Delta S^{\circ}}{RT}\right)\right]$$
2.
$$Fe^{II}(TPP) + O_{2} \leftrightarrow \frac{k_{O_{2}}}{k_{-O_{2}}} Fe^{III}(TPP)(O_{2}^{-1})$$

$$k_{O_{2}} = 10^{7} M^{-1} s^{-1}; \quad K_{O_{2}} = k_{O_{2}}/k_{-O_{2}}; \quad K_{O_{2}} = \exp \left[\left(\frac{\Delta H^{\circ} - T\Delta S^{\circ}}{RT}\right)\right]$$
3.
$$Fe^{III}(TPP)(O_{2}^{-1}) + \rho TSOH \leftrightarrow \frac{k_{PT}}{h} Fe^{III}(TPP)(O_{2}H^{*})]^{*} + \rho TSO^{-1}$$

$$k_{PT} = \frac{k_{B}T}{h} \exp \left[\left(\frac{\Delta H^{\pm} - T\Delta S^{\pm}}{RT}\right)\right]$$
4.
$$[Fe^{III}(TPP)(O_{2}H^{*})]^{*} + 3\rho TSOH + 3Fc^{*}$$

$$k_{fast} \mapsto [Fe^{III}(TPP)]^{*} + 3\rho TSO^{-1} + 3Fc^{*+} + 2H_{2}O$$

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Table 1. Results of COPASI global fitting of stopped flow optical kinetic results and comparison with experimental values.^{*a*}

Reaction	Parameter ^b	Model	Experimental ^c
	К _{ЕТ} (298 К)	0.055(7)	0.18(3)
$Fc^* + Fe^{II}(TPP)^+ \rightleftharpoons$ $Fc^{*+} + Fe^{II}(TPP)$	∆H° _{ET}	2.9(1)	2.8(1)
	ΔS° _{ET}	4.1(4)	6(2)
	К ₀₂ (250 К, М⁻¹) ^d	(2.7 - 6.4) × 10 ⁴	$(0.205 - 11.5) \times 10^2$
$Fe^{III}(TPP) + O_2 \rightleftharpoons$ $Fe^{III}(TPP)(O_2^{\bullet-})$	∆H° _{O2}	-9.5(1)	-10.5(7) ^e
	Δ S° _{O2}	-16.9(4)	–32 (3) ^e
$Fe^{III}(TPP)(O_2^{\bullet-}) + nTsOH \rightarrow$	<i>к</i> _{РТ} (298 К)	1.5(3) $ imes 10^3$ M ⁻¹ s ⁻¹	$2.0(9)^{f}$ $\times 10^{5} \text{ M}^{-1} \text{ s}^{-1}$
$Fe^{III}(TPP)(O_2H^{\bullet})^+ + pTsO^-$	ΔH^{\ddagger}_{PT}	12.0(1)	-
	ΔS^{+}_{PT}	-3.1(2)	-
$Fe^{II}(TPP) + O_2 + pTsOH →$ $Fe^{III}(TPP)(O_2H^{\bullet})^+ + pTsO^{-g}$	k_{cat} (298 K, M ⁻² s ⁻¹) = $K_{0_2}k_{PT}$	(2-20) × 10 ^{5 h}	(3.2–6.4) × 10 ^{5 i}

^a Optimized values from COPASI analysis of data at 253-303 K, 50-100 mM pTsOH, 30–50 µM Fe(TPP). COPASI values and experimental equilibrium parameters are given with the uncertainty in parentheses representing one standard deviation. ^b ΔH° and ΔH^{\ddagger} values in kcal mol⁻¹; ΔS° and ΔS^{\dagger} values in cal K⁻¹ mol⁻¹. ^c Direct experimental measurements of equilibrium parameters from optical spectra and van 't Hoff analyses (Sections T and 11). ^d Values extrapolated from thermodynamic parameters from kinetic data (Model) or lower-temperature equilibrium measurements (Experimental). ^e The 95% confidence limits from a T-test are for K_{0_2} at 298 K: 0.21 to 110 M⁻¹; for ΔH°_{02} : -9.6 to -11.8 kcal mol⁻¹; and for ΔS_{02} : -28 to -38 cal K⁻¹ mol⁻¹, SI Section 3.4). ^f Calculated as $k_{cat(echem)}/K_{O_2(experimental)}$, where K_{O_2} was defined as the mean value, 5 M⁻¹. ^g Chemical steps involved in defining the catalytic rate constant, k_{cat} , determined electrochemically. ^h Calculated as K_{0_2} (model) × k_{PT} (model). ⁱ Calculated from footof-the-wave analysis, vide infra.

The model used in **Scheme 2** attempted to optimize both the simulated rate of decamethylferrocenium formation ($d[Fc^{*+}]/dt$) and the catalyst speciation to the experimental data by varying the thermodynamic parameters for electron transfer (ΔH°_{ET} and ΔS°_{ET} , step 1),

the thermodynamic parameters for O₂ binding ((ΔH°_{O2} and ΔS°_{O2} , step 2) and the activation parameters for proton transfer (ΔH^{t}_{PT} and ΔS^{t}_{PT} , step 3). The six parameters were optimized to fit all stopped flow data simultaneously—including experiments between 253 and 303 K with varied concentrations of substrate (50–100 mM pTsOH) and catalyst (30–50 μ M [Fe(TPP)]_{total}). The experiments have some uncertainty in the catalyst speciation with time due to the overlapping absorbance features, low concentrations of the different Fe(TPP) species, and the uncertainties in the experimental ε values (in part due to high air sensitivity at low concentrations and instability of the materials). Therefore, we sought a model that fit the general trends in catalyst speciation rather than the exact concentration profiles (Figure 6). The fits are good for the [Fc*+] time courses and agree with the general trends of catalyst speciation. Notably, the model fits well to changes in initial [Fe^{III}(TPP)] and [Fe^{III}(TPP)($O_2^{\bullet-}$)] concentrations across a variety of temperatures and is representative of the temperature-dependent O_2 binding equilibrium. Across the whole temperature range, the model also correctly predicts that [Fe^{III}(TPP)]OTf is the predominant catalyst species at the end of the reaction, even when excess Fc* is used.

The accuracy of the model is evidenced by the remarkable agreement with experimental data for both the thermodynamic and kinetic parameters (**Table 1**). The modeled values for ΔH°_{ET} , ΔH°_{O2} and ΔS°_{ET} very closely match the directly determined experimental values from Sections I and II above. The modeled value for ΔS°_{O2} is somewhat less negative than the experimental value, which is similar to typical entropies for O₂ binding in polar organic solvents.⁴⁸ The inconsistencies between modeled and experimental ΔS°_{O2} could be due to an unrecognized catalyst complex in the spectral fitting. Although we cannot rule out such a contribution, we believe the higher than

expected modeled ΔS°_{O2} may instead be related to the lower than expected ΔS^{\dagger}_{PT} , which would
usually be a positive value for a bimolecular reaction. Thus, the ΔG^{\dagger}_{PT} of 11 kcal mol ⁻¹ at 298 K
derived from the modeled may be an underestimation. At room temperature, the model predicts
$ln(k_{PT})$ to be between 7.1-7.5 and $ln(K_{0_2})$ to be between 5.3-7.5. Under electrochemical
conditions, where k_{cat} is the product of K_{0_2} and k_{PT} , the model predicts k_{cat} to be between 2-20 ×
10 ⁵ M ⁻² s ⁻¹ , which is within error of the experimental k_{cat} value of (3.2–6.4) \times 10 ⁵ M ⁻² s ⁻¹ . This
agreement in rate constants at 298 K could also be suggestive of a balancing of errors in the
modeled ΔS°_{O2} and ΔS^{\dagger}_{PT} . Although ΔS°_{O2} and ΔS^{\dagger}_{PT} are not significantly correlated according to
the COPASI statistical analysis, there is evidence that these parameters are not all known
completely independently from one another. We can achieve similarly strong fits of the data with
different parameter values when they are tightly constrained the to the experimental results (see
SI, Section 6).



Figure 6. Data (points) and fits (lines) for three stopped-flow ORR time courses (0.3 μ M Fe(TPP), 50 mM *p*TsOH, 0.33 mM O₂, 3 mM Fc*, varied temperatures: **a)** 253 K, **b)** 283 K, **c)** 303 K. For each temperature column, the top figure shows the Fc*+ concentrations with an expansion for the Fe(TPP) speciation below.

VI. Computational Analysis of the Barrier for protonation of $Fe^{III}(TPP)(O_2^{\bullet-})$ by *p*TsOH:

For the ORR by Fe(TPP) in DMF with [DMF-H]OTf as the acid, prior DFT and experimental studies identified protonation of Fe^{III}(TPP)($O_2^{\bullet-}$) as the rate-limiting step.^{11,32} This section extends that computational analysis to evaluate the thermochemistry and kinetics of protonation of Fe^{III}(TPP)($O_2^{\bullet-}$) by *p*TsOH, the acid used in this study.

The thermochemistry and kinetics of $Fe^{III}(TPP)(O_2^{\bullet-})$ protonation are dictated by interactions between the proton source, solvent, and the superoxide adduct.³² As such, DFT analysis was performed to quantify the energetics of interactions between explicit ρ TsOH, pTsO⁻, and DMF molecules in DMF solvent. Calculations show that the free energy of the pTsOH+++DMF pair is stabilized by 1.6 kcal mol⁻¹ relative to its constituent parts (separate pTsOH and DMF molecules). Formation of the [pTsOH+++pTsO]⁻ homoconjugate is even more stable, favored by 5.9 kcal mol⁻¹ relative to separate pTsOH and pTsO⁻ molecules; however, the experimental conditions ([DMF] >>> [pTsO⁻]) favor the pTsOH++++DMF heteroconjugate. Therefore, the thermochemistry and kinetics of proton transfer to Fe^{III}(TPP)(O₂+-) were investigated using pTsOH++++DMF as the proton donor.

The computed free energy profiles for protonation of Fe^{III}(TPP)(O₂^{•-}) (**1**) by *p*TsOH•••DMF are shown in **Figure 7a**, wherein all energetics are referenced to **1**. The free energy profile for protonation by *p*TsOH•••DMF first features the formation of a pre-association complex, **2**, in which the acid approaches Fe^{III}(TPP)(O₂^{•-}) (**1**). Formation of **2** involves solvent reorganization and the establishment of a three-center site and has an overall energetic penalty of 8.5 kcal mol⁻¹. This energetic cost results from unfavorable entropic ($-T\Delta S = 10.7$ kcal mol⁻¹ at 298 K) and

solvation terms (7.8 kcal mol⁻¹) that are only partially balanced by being electronically favorable (–9.9 kcal mol⁻¹). Proton transfer then yields the perhydroxyl (**3**) species, which was calculated to be 9.8 kcal mol⁻¹ uphill from **1**. This result indicates that the proton transfer is unfavorable and is consistent with the experimental data.



Figure 7. a) Computed free energy profile for association (K_{assc}) and protonation of Fe^{III}(TPP)(O₂^{•-}) by the *p*TsOH•••DMF heteroconjugate pair. **b)** Optimized structure for the proton transfer transition state (k_{PT}) and the corresponding O-H bond lengths for the proton transfer donor (*p*TsOH), solvent (DMF), and acceptor Fe^{III}(TPP)(O₂^{•-}). All distances in Ångstroms.

To further understand the kinetics of proton transfer, the barrier for protonation from the heteroconjugated pair *p*TsOH•••DMF was sought. As shown in **Figure 7**, the transition state (**TS***) involves proton transfer from the pre-association complex (**2**) and has an overall barrier of 22.0 kcal mol⁻¹ relative to Fe^{III}(TPP)($O_2^{\bullet-}$). This calculated barrier is an upper bound, as it does not compensate for the errors in computing sulfonate group energetics. Taking into account these errors as discussed in the SI, the estimated lower bound of this barrier is about 17.0 kcal mol⁻¹. The energetic contributions for the energy change between **2** and **TS*** show that the transition state energy is enthalpically driven. Additionally, at the transition state, the proton is closer to

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the acceptor $Fe^{III}(TPP)(O_2^{\bullet-})$ than the donor *p*TsOH•••DMF, as evidenced by the O-H bond lengths in the optimized structure (**Figure 7b**). The kinetic isotope effect for this transition state was calculated using *p*TsOD•••DMF as the proton donor, affording a KIE of 0.94 (see section 8 SI).

Discussion

I. The mechanism of ORR catalysis by Fe(TPP)

The results of the spectroscopic, electrochemical, and computational experiments described above support the mechanism illustrated in **Scheme 1**. In this mechanism, Fc* or an electrode rapidly reduce [Fe^{III}(TPP)]OTf to the ferrous porphyrin, Fe^{II}(TPP). Fe^{II}(TPP) then binds O_2 reversibly (K_{O_2}) to form the ferric superoxide, Fe^{III}(TPP)($O_2^{\bullet-}$). The rate-determining step is protonation of Fe^{III}(TPP)($O_2^{\bullet-}$) (k_{PT}) to form the perhydroxyl-iron(III) complex, [Fe^{III}(TPP)(O_2H^{\bullet})]⁺. The perhydroxyl complex is rapidly reduced and protonated under the catalytic conditions to produce two equivalents of H₂O and restart the catalytic cycle. The evidence in support of this mechanism is discussed below.

Reduction of [Fe^{III}(TPP)]OTf to Fe^{II}(TPP), the first step in the proposed catalytic cycle, was found to be a fast pre-equilibrium between [Fe^{III}(TPP)]OTf and the reductant in both electrochemical and spectroscopic measurements. The cyclic voltammograms during electrocatalytic O₂ reduction fit well to a mechanism in which rapid pre-equilibrium electron transfer from the electrode ([Fe^{III}(TPP)]⁺ + $e^- \rightleftharpoons$ Fe^{II}(TPP)) is followed by a rate limiting catalytic step, k_{obs} (an EC' mechanism). With Fc* as a chemical reductant, this pre-equilibrium is

thermodynamically uphill at standard state ($\Delta G^{\circ}_{ET} = +1.01(8)$ kcal mol⁻¹). Spectroscopic studies of the reduction of [Fe^{III}(TPP)]OTf by Fc* at different temperatures have yielded the ΔH°_{ET} and ΔS°_{ET} for this equilibrium (Results Section I). Those values are consistent with the electrochemically measured difference in reduction potentials between [Fe(TPP)]^{+/0} and Fc^{*+/0} at ambient temperatures. In the room temperature stopped-flow kinetics, the initial spectra show almost complete reduction of [Fe^{III}(TPP)]OTf only because the starting concentration of Fc^{*+} is very small ~0 mM and the [Fc*]/Fc^{*+} ratio is very large. As catalysis progresses, however, the ratio of Fc* to Fc^{*+} decreases, quickly shifting this equilibrium so that [Fe^{III}(TPP)]⁺ is the resting state of the catalyst for much, if not most, of the reaction (**Figures 6** and **S34-S49**).

Spectroscopic experiments have also quantified the rapid pre-equilibrium O_2 binding to Fe^{II}(TPP), which is proposed to follow initial electron transfer. The distinct optical spectrum of the superoxide complex Fe^{III}(TPP)($O_2^{\bullet-}$) enabled measurements of the equilibrium constants for binding (K_{O_2}) at low temperatures in the absence of reductant and acid. Low temperatures are required to avoid the decomposition of Fe^{III}(TPP)($O_2^{\bullet-}$) to the well-known μ -oxo dimer.⁴² The measured $\Delta H^o{}_{O2}$ and $\Delta S^o{}_{O2}$ could then be used to predict values of K_{O_2} at the higher temperatures of catalysis. The μ -oxo dimer is not formed under the catalytic conditions because of the presence of strong acid, as indicated reaction of independently prepared μ -oxo dimer with *p*TsOH (see SI, Section 5.4) and by prior reports.^{49,50} Consistent with these equilibrium measurements, Fe^{III}(TPP)($O_2^{\bullet-}$) is observed as the predominant initial catalyst resting state in catalytic stopped-flow experiments at low temperatures (e.g. 253 K). Under such conditions, [Fe^{III}(TPP)]OTf is completely converted to Fe^{III}(TPP)($O_2^{\bullet-}$) within 0.1 s (Figure S29). As the reaction proceeds, both [O_2] and the ratio of Fc*:Fc*+ decrease, leading to a change in resting state from reduced

porphyrin intermediates to [Fe^{III}(TPP)]⁺ (Figures 6 and S34-S49).

The kinetics of the *electro*catalysis are not complicated by the shifts in the pre-equilibrium reduction or O_2 -binding steps observed in the stopped flow data. The catalytic voltammograms are fit using FOWA, which yields rate constants for reactions catalyzed by the reduced Fe^{II}(TPP) catalyst resting state. Additionally, because the current is analyzed at the 'foot' of the wave, the concentration of substrates in the reaction-diffusion layer is the same as the bulk solution (true pseudo-first order conditions). For these reasons, the electrocatalytic kinetics yield a simple third order rate law, as previously reported,³¹ obtained by removing the K_{ET} , [Fc*], and [Fc*+] terms from the complex rate law required for the stopped-flow data (eq 9). Despite the complex rate law using Fc* as a chemical reductant, the similarities between the k_{cat} values obtained electrochemically and chemically confirm that electron transfer kinetics are not involved in the rate limiting steps and remain a fast pre-equilibrium step under all conditions. Furthermore, the first order dependence on O_2 , *p*TsOH and [Fe(TPP)] exclude bimolecular pathways that involve peroxo (Fe- O_2 .Fe) or μ -oxo (Fe-O-Fe) dimeric intermediates, pathways that are observed in the absence of strong acids.^{51–54}

Catalytic turnover requires the addition of four protons and three more electrons to $Fe^{III}(TPP)(O_2^{\bullet-})$, ultimately forming water and $[Fe^{III}(TPP)]OTf$. A number of initial steps could be imagined for this transformation, but only those which have an acid dependence were considered since the rate of the ORR is first order in [*p*TsOH]. Within that constraint, the two possible pathways for the reaction of the superoxide complex involve *i*.) proton transfer (PT) from *p*TsOH to form perhydroxyl or *ii*.) concerted proton-coupled electron transfer (CPET) with *p*TsOH and a reductant to give a hydroperoxo complex. While option *ii*. should be thermodynamically

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advantageous, it is formally a termolecular CPET reaction and thus is kinetically challenging in the absence of a favorable pre-association with the proton donor.^{55,56} As DFT calculations show that pre-association of *p*TsOH with Fe^{III}(TPP)($O_2^{\bullet-}$) is uphill by 8.5 kcal mol⁻¹ (**Figure 7**), pathway *ii*. is unlikely, and rate-limiting proton transfer from *p*TsOH to Fe^{III}(TPP)($O_2^{\bullet-}$) is the more plausible mechanism. Previous studies of ORR by Fe(TPP) under different conditions – using HClO₄ as the acid and in the presence of excess chloride – found a zero order dependence of turnover frequency on the concentration of Fc^{*}.³¹ In the model used successfully here (**Scheme 2**), the concentration of the electron donor appears only in the first pre-equilibrium. The rate determining step cannot be CPET because that would require a molecule of reductant.

The strongest support for the proposed mechanism is the close agreement between the equilibrium parameters determined by COPASI-fits to the stopped flow data and the directly measured equilibrium values of $\Delta H^{\circ}_{ET}/\Delta S^{\circ}_{ET}$ and $\Delta H^{\circ}_{O2}/\Delta S^{\circ}_{O2}$. In addition, the idealized third-order rate constant predicted by the COPASI-fit, (2-20) × 10⁵ M⁻² s⁻¹, is in excellent agreement with the value determined by electrocatalysis, $k_{cat} = (3.2 - 6.4) \times 10^5$ M⁻² s⁻¹.

The computational conclusions qualitatively agree with experimental results and show that proton transfer is the turnover-limiting step. The barrier extracted from the COPASI fits, $\Delta G^{\dagger}_{PT} \cong 11$ kcal mol⁻¹, is significant but smaller than the computed barrier. As noted above, the modeled ΔG^{\dagger}_{PT} may be low due to an underestimation of the ΔS^{\dagger}_{PT} , which would bring the experimental and computed values into closer agreement. We note that the complexity of the COPASI kinetic modeling and the challenges of computing sulfonate groups make close agreement between experiment and theory unlikely. Still, good agreement between theory and experiment was obtained for the change in barrier heights upon changing the acid from *p*TsOH to [DMF-H]⁺. The same value for this Brønsted $\alpha = \Delta\Delta G^{\dagger}_{PT} / \Delta\Delta G^{\circ}_{PT} = 0.3$ was obtained from both experiment and theory.^{21,22}

In this system, both the computational and experimental results highlight the challenges of proton delivery to the iron-dioxygen adduct. Even when using a relatively strong proton donor like *p*TsOH ($pK_a = 2.3$ in DMF), protonation of Fe^{III}(TPP)($O_2^{\bullet-}$) is computed to be uphill by >5 kcal mol⁻¹. This shows the poor basicity of Fe^{III}(TPP)($O_2^{\bullet-}$), which has an estimated pK_a of –1.7 in DMF.³²

Beyond the endoergic nature of the proton transfer step, the computations and experiments implicate a significant *kinetic* barrier for protonation of Fe^{III}(TPP)(O₂•-). The computational results shown in **Figure 7** allow k_{PT} to be expressed as the product of preassociation (K_{assc} , **Figure 7a**) and a unimolecular proton transfer step. The computed preassociation free energy of +8.6 kcal mol⁻¹ is due to the unfavorable entropy ($-T\Delta S = 10.7$ kcal mol⁻¹) and partial desolvation penalty for *p*TsOH••••DMF (7.8 kcal mol⁻¹) are only partially offset by the hydrogen bonding between the superoxide moiety and *p*TsOH ($\Delta E = -9.9$ kcal mol⁻¹). Overall, this unfavorable interaction contributed almost 50% to the overall reaction barrier height from Fe^{III}(TPP)(O₂•-) determined computationally. These results are consistent with the first order dependence of k_{obs} on the [*p*TsOH] determined electrochemically (**Figure 3b**), which further buttress that pre-association of the proton donor to Fe^{III}(TPP)(O₂•-) is unfavorable.

From the preassociated adduct, the transition state is achieved from a decrease in the O-H-O dihedral angle in the *p*TsOH•••DMF adduct, yielding a species where the proton is shared Page 31 of 40

between the *p*TsO⁻, DMF, and Fe^{III}(TPP)(O₂^{•-}) oxygen atoms (Figure 7b). These results are consistent with a previous computational study that examined [DMF-H]⁺ as the proton source.³² The calculated barrier for proton transfer to Fe^{III}(TPP)(O₂^{•-}) is smaller with the stronger acid [DMF-H]⁺, as expected. Still, even with the stronger, cationic acid, pre-association is again unfavorable by >6 kcal mol⁻¹. As with *p*TsOH••••DMF, there is a significant desolvation penalty for the [DMF-H]⁺•••DMF proton donor that is not offset by hydrogen bonding to the Fe^{III}(TPP)(O₂^{•-}) intermediate.

A surprising feature of this ORR mechanism is that the slow, turnover-limiting step is proton transfer from one oxygen atom to another. The proton donor is para-toluenesulfonic acid, *p*TsOH, and the oxygen acceptor is the superoxide complex, $Fe^{III}(TPP)(O_2^{\bullet-})$. Proton transfers between oxygen atoms are typically fast, although that is not always the case.^{57–60} Physical organic studies of proton transfer reactions have discussed pre-association, non-synchronicity, and other factors to explain slow PT rate constants, particularly for carbon acids.^{57,59,61,62} Taken together, these results suggest that barriers to proton transfer can be an important component of ORR catalysis in DMF and perhaps other polar organic solvents. Given that pre-association dynamics have been shown to play a major role in the catalytic rates of the reduction of H⁺ to H₂ by nickel phosphine-amine complexes,^{32,63} our results suggest that pre-association for proton transfer to $Fe^{III}(TPP)(O_2^{\bullet-})$ may be more facile in media where the proton donor preferentially interacts with the $Fe^{III}(TPP)(O_2^{\bullet-})$ adduct over the solvent. These conditions may be realized by working with strong proton donors in solvents with dielectric constants lower than DMF or MeCN (e.g. THF, CH_2Cl_2). More broadly, using the medium to target preassociation dynamics could be a general approach for improving PCET reactions that are limited by proton transfer steps,

particularly for reactions with containing nonpolar adducts, such as the ORR.

Conclusions

[Fe^{III}(TPP)]OTf is a rapid catalyst and electrocatalyst for the oxygen reduction reaction (ORR). This report describes a detailed mechanistic study of the catalytic chemical reduction of O_2 with decamethylferrocene (Fc^{*}) and p-toluene sulfonic acid (pTsOH) in DMF, forming Fc^{*+}, pTsO⁻ and (predominantly) water. The various results indicate a mechanism initiated by preequilibrium electron transfer to form $Fe^{II}(TPP)$, followed by O₂ binding to form the superoxide complex Fe^{III}(TPP)($O_2^{\bullet-}$) in a second pre-equilibrium step. Both of these equilibria were studied independently as a function of temperature, and their equilibrium constants and enthalpies and entropies are reported. Stopped-flow optical monitoring of the reaction kinetics showed that the resting state of the iron catalyst varies substantially during the reactions and with temperature and reaction conditions. The complexity of the kinetics required global analysis of a large set of kinetic runs under different conditions using the COPASI software. This analysis gave an independent measure of the thermodynamic parameters for the pre-equilibria. The agreement between these kinetic-fit values and the directly measured equilibrium parameters provides very strong evidence for the proposed mechanism. In addition, parallel electrochemical kinetics showed complementary kinetic behavior and rate constants, further supporting the proposed mechanism.

The turnover-limiting step in catalysis is the protonation of $Fe^{III}(TPP)(O_2^{\bullet-})$. Computational studies of this step showed that there is substantial energetic cost to assemble the pre-

association complex of the acid and $Fe^{III}(TPP)(O_2^{\bullet-})$ and that there is a substantial barrier to proton transfer within this complex. This study is a rare example of a mechanistic investigation of the ORR that directly observes and quantifies the pre-equilibria and rate-determining steps of three catalytic intermediates. The ability to correlate thermodynamic, chemical kinetic, electrochemical kinetic, and computational data provide an unusual level of detail about a multistep proton-coupled electron transfer catalytic process. In particular, the results highlight the importance of improving proton transfer dynamics during catalytic transformations involving nonpolar small molecule adducts in organic solvents.

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Author Information Notes

- ¹ Department of Chemistry, Yale University, PO Box 208107, New Haven, Connecticut 06520-8107, United States
- ² Center for Molecular Electrocatalysis, Pacific Northwest National Laboratory, P.O. Box 999 (K2-57), Richland, Washington 99352, United States
- ³ Current Address: Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts, 02139, United States
- ⁴ Department of Chemistry, University of Washington, Box 351700 Seattle, WA 98195-1700
- ⁵ Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National Laboratory, Richland, WA 99352, United States
- [§] These authors contributed equally.
- [‡] Lead computationalist.
- * Corresponding Author, james.mayer@yale.edu

Associated Content: The Supporting Information for this manuscript, including full experimental details and procedures, spectroscopic characterization, and kinetic and computational methods is available free of charge on the ACS Publication website at http://pubs.acs.org.

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