

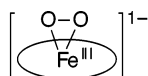
An Iron–Peroxo Porphyrin Complex: New Synthesis and Reactivity Toward a Cu(II) Complex Giving a Heme–Peroxo–Copper Adduct

Eduardo E. Chufán and Kenneth D. Karlin*

Department of Chemistry, The Johns Hopkins University, Charles and 34th Streets, Baltimore, Maryland 21218

Received June 11, 2003; E-mail: karlin@jhu.edu

Ferric peroxo porphyrin complexes



are strong nucleophiles capable of epoxidizing electron-deficient olefins.^{1,2} Such species are postulated as the active oxidant in the cytochrome P450-like aromatase and other enzymes.² [(P)Fe^{III}(O₂²⁻)]⁻ complexes³ were first synthesized by Valentine and co-workers, from reaction of [(P)Fe^{III}-Cl] with potassium superoxide in aprotic solvents.^{4–8} The side-on η²-peroxo high-spin ferric formulation is based on physical-spectroscopic studies,^{9,10} and by analogy to the structurally characterized η²-peroxomanganese complex [(TPP)Mn(O₂²⁻)]⁻.^{11,12}

In cytochrome *c* oxidase (CcO), heme_{a3}-peroxo, heme_{a3}-hydroperoxo or heme_{a3}-(μ-peroxo)-copper¹³ species are likely transients which form following electron transfer from the proximal Cu¹⁺ site to the initially generated heme_{a3}-O₂ adduct (formally a superoxo-iron(III) species).¹⁴ Thus, a viable approach to the understanding of O₂-binding and reductive O–O cleavage at the CcO heme•••Cu active site is to probe reactions between iron–peroxo heme_{a3} synthetic models and Cu_B-site analogue complexes.

In this report, we describe (Scheme 1) (1) a facile method for reduction of a heme–O₂ species [(F₈TPP)Fe^{III}(O₂⁻)(S)] (2),³ generating the ferric peroxo porphyrin complex [(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3) and (2) that this can be subsequently reacted with a ligand–copper(II) complex, affording a heme–peroxo–copper heterobinuclear compound. This distinctive approach to generating heme–

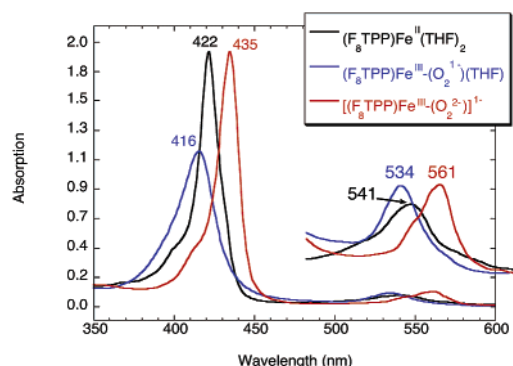


Figure 1. UV–vis spectra of (F₈TPP)Fe^{II}(THF)₂ (1), (F₈TPP)Fe^{III}(O₂⁻)(THF) (2) and [Co^{III}Cp₂][(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3) in THF at 193 K. See text for further discussion.

peroxo and heme–peroxo–copper complexes is of considerable interest since these compounds closely resemble short-lived species relevant to the cytochrome *c* oxidase reaction mechanism.¹⁴

Immediate formation of the iron(III)–superoxo complex [(F₈TPP)Fe^{III}(O₂⁻)(THF)] (2) [λ_{max} = 416 (Soret) and 534 nm]¹⁵ is observed upon bubbling a tetrahydrofuran (THF) solution of [(F₈TPP)Fe^{II}(THF)₂] (1) [λ_{max} = 422 (Soret) and 541 nm] with dioxygen at –80 °C (Scheme 1 and Figure 1). After removal of excess O₂ by vacuum/Ar cycling, addition of 1 equiv of cobaltocene (as a strong outer-sphere reductant)^{16,17} results in the generation of [Co^{III}Cp₂][(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3) based on its characteristic UV–vis spectrum [λ_{max} = 435 (Soret), 540 (sh) and 561 nm].^{10,18} Similar chemistry is observed with CH₂Cl₂/10% CH₃CN (v/v) as solvent, where CH₃CN serves as an axial heme ligand promoting formation of [(F₈TPP)Fe^{III}(O₂⁻)(CH₃CN)].^{15,17}

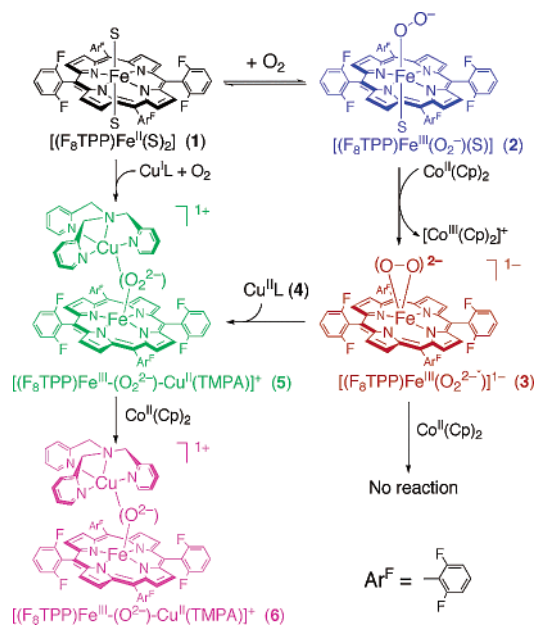
A number of lines of evidence further support the formulation given for [Co^{III}Cp₂][(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3):

(1) The presence of the cobaltocenium ([Co^{III}Cp₂]⁺) as the counterion is evident by the occurrence of a characteristic new UV band at 262 nm,¹⁹ and a 6.7 ppm signal in the ¹H NMR spectrum (CH₂Cl₂/10% CH₃CN, –80 °C).¹⁶

(2) EPR spectra of [Co^{III}Cp₂][(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3) (Figure 2) show a strong marker signal at *g* = 4.2, typical for rhombic [(P)Fe^{III}(O₂²⁻)]⁻ complexes^{10,18} and η²-peroxo–nonheme iron species.^{20,21} With excess Co^{III}Cp₂, which eliminates high-spin iron(III) heme impurities (such as (F₈TPP)Fe–OH, *g* ≈ 7.0), the additional characteristic *g* = 8.7 signal is also observed.^{10,20,21}

(3) [(F₈TPP)Fe^{III}(O₂⁻)(THF)] (2) is characterized by its typical ¹H-NMR diamagnetic spectrum, (δ_{pyrrole} = 8.5 ppm, THF-*d*₈ solvent).¹⁵ Addition of Co^{III}Cp₂ leads to a downfield shifting of the pyrrole resonance to 90 ppm.¹⁷ The complex shows Curie behavior (–80 to –40 °C) and extrapolation to room temperature leads to an assignment of this signal occurring at 68 ppm for [Co^{III}Cp₂][(F₈TPP)Fe^{III}(O₂²⁻)]⁻ (3),¹⁷ close to published values for other [(P)Fe^{III}(O₂²⁻)]⁻ complexes.^{22,23}

Scheme 1



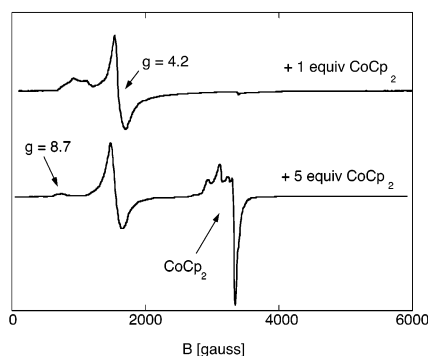


Figure 2. X-band EPR spectra of $[\text{Co}^{\text{III}}\text{Cp}_2][(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^-$ (**3**) generated with 1 equiv of cobaltocene (upper spectrum) and with an excess of cobaltocene (lower spectrum) in $\text{CH}_2\text{Cl}_2/10\%$ CH_3CN : temperature, 5 K; time constant 20.48 ms; sweep width 6000 G.

(4) The peroxidic nature of **3** is demonstrated by its protonation using hydrochloric acid, leading to the formation of $(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}\text{-Cl}$ and hydrogen peroxide (>70% yield).^{17,24}

The reaction of $[\text{Co}^{\text{III}}\text{Cp}_2][(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^-$ (**3**) toward the pentacoordinated copper(II) complex $[\text{Cu}^{\text{II}}(\text{TMPA})(\text{CH}_3\text{CN})](\text{ClO}_4)_2$ (**4**)^{25,26} (which has a labile CH_3CN ligand) is suggestive of nucleophilic behavior of **3** (Scheme 1), otherwise known for $[(\text{P})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^-$ complexes.^{1,2} When **4** was added to a solution of **3** generated in THF at -95°C , heme- μ -peroxo-copper complex $[(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}-(\text{O}_2^{2-})-\text{Cu}^{\text{II}}(\text{TMPA})](\text{ClO}_4)$ (**5**) is obtained;¹⁷ a solid form was isolated by precipitation with heptane.²⁷ Redissolution (-80°C) showed that the solid retains the unique UV-vis and ^1H NMR spectroscopic features known for **5**,¹⁷ which was previously only generated by oxygenation of a 1:1 mixture of reduced complexes $(\text{F}_8\text{TPP})\text{Fe}^{\text{II}}$ and $[\text{Cu}^{\text{I}}(\text{TMPA})(\text{CH}_3\text{CN})](\text{ClO}_4)$, Scheme 1.^{12,28–30}

It is noteworthy that excess $\text{Co}^{\text{II}}\text{Cp}_2$ ($E^\circ \approx -1.3$ V vs Fc^+/Fc)¹⁶ does not react with the η^2 -peroxo complex $[(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^-$ (**3**); however, it does reduce the μ -peroxo complex $[(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}-(\text{O}_2^{2-})-\text{Cu}^{\text{II}}(\text{TMPA})]^+$ (**5**) (CH_3CN , -40°C), yielding the corresponding μ -oxo species $[(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}-(\text{O}^{2-})-\text{Cu}^{\text{II}}(\text{TMPA})]^+$ (**6**) [UV-vis: $\lambda_{\text{max}} = 433$ (Soret) and 555 nm] (Scheme 1).²⁸ This inertness toward reductants has also been observed for the η^2 -peroxo complex $[(\text{EDTA})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^{3-}$ and is indicative that the O–O bond is not activated for reductive cleavage.²⁰ The details of this peroxo-to-oxo conversion (**5** to **6**) are unclear and require further study; coordination by copper(II) as an electrophile in **5** probably assists the O–O bond “activation”.

In summary, we have developed a rather simple method to generate an important peroxo-heme species via O_2 chemistry and chemical reduction with cobaltocene. This peroxo-heme species reacts with a copper(II) complex, yielding a heme-peroxo-copper adduct which resembles a suggested transient in the reaction mechanism of CcO .¹⁴ This reactivity methodology opens avenues for future investigation whereby $[\text{Co}^{\text{III}}\text{Cp}_2][(\text{F}_8\text{TPP})\text{Fe}^{\text{III}}(\text{O}_2^{2-})]^-$ (**3**) can be reacted with copper(I) complexes (which can serve as both a copper source and a reducing equivalent),²⁹ and possibly additional proton or electron sources,³¹ in an attempt to understand reductive cleavage of an O–O bond in a heme-Cu environment.

Acknowledgment. We thank Professor Joan Valentine (UCLA) for encouraging the approach employed in this report, i.e. reactivity of species like **3** with copper complexes. We thank the National

Institutes of Health (K.D.K., GM60353), CONICET-Argentina, and Universidad Nac. de San Luis-Argentina (E.E.C.) for research support.

Supporting Information Available: Synthetic and spectroscopic (UV-vis and ^1H -NMR) details, pp S1–S14, with Figures S1–S8 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Sisemore, M. F.; Burstyn, J. N.; Valentine, J. S. *Angew. Chem., Int. Ed.* **1996**, *35*, 206–208.
- Wertz, D. L.; Valentine, J. S. *Struct. Bonding (Berlin)* **2000**, *97*, 37–60.
- Abbreviations used: P = porphyrinate; S = solvent; F_8TPP = tetrakis-(2,6-difluoro-phenyl)porphyrinate; TPP = tetra(phenyl)porphyrinate; Cp = cyclopentadienyl; TMPA = tris(2-pyridyl-methyl)amine.
- McCandlish, E.; Miksztal, A. R.; Nappa, M.; Sprenger, A. Q.; Valentine, J. S.; Stong, J. D.; Spiro, T. G. *J. Am. Chem. Soc.* **1980**, *102*, 4268–4271.
- $[(\text{P})\text{Fe}(\text{O}_2)]^-$ can also be obtained either by electrochemical⁶ or chemical [aluminum hydride reagent]⁷ reduction of a porphyrin ferrous dioxygen, or by addition of dioxygen to an iron(I) porphyrin.⁸
- Welborn, C. H.; Dolphin, D.; James, B. R. *J. Am. Chem. Soc.* **1981**, *103*, 2869–2871.
- Schappacher, M.; Weiss, R.; Montiel-Montoya, R.; Trautwein, A.; Tabard, A. *J. Am. Chem. Soc.* **1985**, *107*, 3736–378.
- Reed, C. A. In *Electrochemical and Spectrochemical Studies of Biological Redox Components*; K. M. Kadish, Ed.; American Chemical Society: Washington, DC, 1982; p 333.
- Friant, P.; Goulon, J.; Fischer, J.; Ricard, L.; Schappacher, M.; Weiss, R.; Momenteau, M. *Nouv. J. Chim.* **1985**, *9*, 33–40.
- Burstyn, J. N.; Roe, J. A.; Miksztal, A. R.; Shaevitz, B. A.; Lang, G.; Valentine, J. S. *J. Am. Chem. Soc.* **1988**, *110*, 1382–1388.
- VanAtta, R. B.; Strouse, C. E.; Hanson, L. K.; Valentine, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 1425–1434.
- The structure of a heme- O_2 -Cu assembly with η^2 -peroxo-heme moiety (and η^1 -ligation to Cu) has recently been described. See Chishiro, T.; Shimazaki, Y.; Tani, F.; Tachi, Y.; Naruta, Y.; Karasawa, S.; Hayami, S.; Maeda, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2788–2791.
- Yoshikawa, S.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yamashita, E.; Inoue, N.; Yao, M.; Jei-Fei, M.; Libeu, C. P.; Mizushima, T.; Yamaguchi, H.; Tomizaki, T.; Tsukihara, T. *Science* **1998**, *280*, 1723–1729.
- Proshlyakov, D. A.; Pressler, M. A.; Babcock, G. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8020–8025.
- Ghiladi, R. A.; Kretzer, R. M.; Guzei, I.; Rheingold, A. L.; Neuhold, Y.-M.; Hatwell, K. R.; Zuberbühler, A. D.; Karlin, K. D. *Inorg. Chem.* **2001**, *40*, 5754–5767.
- Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877–910.
- See Supporting Information.
- Selke, M.; Sisemore, M. F.; Valentine, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 2008–2012.
- Sheats, J. E. *J. Organomet. Chem. Libr.* **1979**, *7*, 461–521.
- Neese, F.; Solomon, E. I. *J. Am. Chem. Soc.* **1998**, *120*, 12829–12848.
- Roelfes, G.; Vrajmasu, V.; Chen, K.; Ho, R. Y. N.; Rohde, J.-U.; Zondervan, C.; la Crois, R. M.; Schudde, E. P.; Lutz, M.; Spek, A. L.; Hage, R.; Feringa, B. L.; Muenck, E.; Que, L., Jr. *Inorg. Chem.* **2003**, *42*, 2639–2653.
- Shirazi, A.; Goff, H. M. *J. Am. Chem. Soc.* **1982**, *104*, 6318–6322.
- Selke, M.; Valentine, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 2652–2653.
- Vibrational spectroscopic characterization of peroxide **3** has been thwarted by its thermal instability (IR) or photodecomposition (resonance Raman).
- Fox, S.; Nanthakumar, A.; Wikström, M.; Karlin, K. D.; Blackburn, N. J. *J. Am. Chem. Soc.* **1996**, *118*, 24–34.
- While we have observed no problems, perchlorate salts are potentially explosive and should be handled with great care.
- $[\text{Co}^{\text{III}}\text{Cp}_2](\text{ClO}_4)_2$ also coprecipitates, as evidenced by a 262-nm UV absorption¹⁹ and 5.6-ppm signal in the ^1H NMR spectrum.¹⁶
- Ghiladi, R. A.; Hatwell, K. R.; Karlin, K. D.; Huang, H.-w.; Moeenne-Loccoz, P.; Krebs, C.; Huynh, B. H.; Marzilli, L. A.; Cotter, R. J.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 6183–6184.
- Tolman and co-workers report a related methodology, wherein a copper(I) complex is added to another side-on dioxygen-Cu complex; this leads to a bis- μ -oxo dicopper(III) product. See *J. Am. Chem. Soc.* **2002**, *124*, 10660.
- Compounds **3** and **5** do not epoxidize menadione, the former presumably due to its thermal instability or its similarity to the behavior of $[(\text{F}_2\text{O})\text{TPP}]\text{Fe}(\text{O}_2)^-$ (ref 230).
- Kamaraj, K.; Kim, E.; Galliker, B.; Zakharov, L. N.; Rheingold, A. L.; Zuberbühler, A. D.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 6028–6029.

JA036632D