Direct evidence for an iron(IV)-oxo porphyrin π-cation radical as an active oxidant in catalytic oxygenation reactions†

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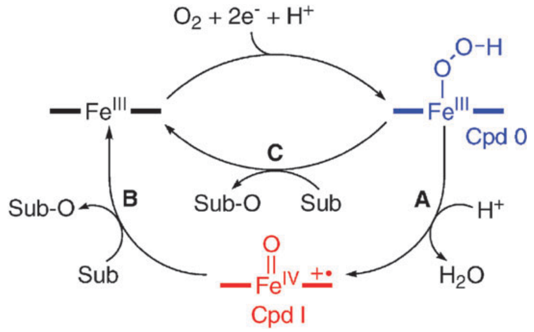
A high-valent iron(IV)-oxo porphyrin π-cation radical is an active oxidant in the catalytic oxygenation of organic substrates by an iron(III) porphyrin complex and peracids, whereas an iron(III)-oxidant porphyrin adduct is a sluggish oxidant in iron porphyrin model reactions.

Elucidation of the nature of reactive intermediates in the catalytic cycle of dioxygen activation and oxygen atom transfer reactions by cytochromes P450 (CYP 450) has been a subject of intense research in the bioinorganic and biological chemistry communities.[1] It has been believed for a long time that high-valent iron(IV)-oxo porphyrin π-cation radicals, so called Compound I (Cpd I), are generated *via* O–O bond heterolysis of ferric-hydroperoxo porphyrins, so called Compound 0 (Cpd 0), and are the active oxidants that effect the oxygenation of organic substrates (Scheme 1, pathways A and B). Although Cpd I has been poorly characterized in enzymatic reactions, probably due to a high reactivity and instability in nature,[2] a number of synthetic iron(IV)-oxo porphyrin π-cation radicals have been prepared and investigated in various oxygenation reactions, including alkane hydroxylation and olefin epoxidation.[1a,3] Thus, there is no doubt that Cpd I is a strong oxidant capable of oxygenating various organic substrates.

Very recently, the involvement of Cpd 0 as a "second electrophilic oxidant" has been proposed in CYP 450-catalyzed oxygenation of alkanes, olefins, sulfides and *N*,*N*-dialkylanilines (Scheme 1, pathway C).[4] The primary evidence for the second electrophilic oxidant derives from site-directed mutagenesis studies, in which different products and/or product distributions were observed in the reactions of CYP 450 and their mutants.[5] Since mutant enzymes exhibit reactivity patterns different from those of wild type enzymes, Cpd 0 has been invoked as an alternative intermediate in the oxygenation reactions by mutant enzymes.[4a,5] The multiple oxidants hypothesis has also been proposed in iron porphyrin models, mainly from competitive olefin epoxidation and alkane hydroxylation reactions.[4b,6] In competitive oxygenation reactions, product ratios were different, depending on reaction conditions such as iron porphyrin catalysts used and their axial ligands, oxidants (*e.g.*, peracids and iodosylarenes), and solvents (*e.g.*, CH_2Cl_2 and toluene), speculating that the different selectivities in the competitive reactions result from the participation of multiple oxidants.[6] In contrast, we have shown very recently that iron(IV)-oxo porphyrin π-cation radicals can exhibit diverse reactivity patterns under different circumstances, leading us to postulate that the different product distributions observed in iron porphyrin-catalyzed competitive reactions do not arise from the involvement of multiple oxidizing species but from *one* iron-oxo oxidant under different conditions.[7] Similarly, computational studies by Shaik *et al.* concluded that the reactivity of Cpd I generally involves two-state reactivity (TSR), a low-spin doublet state and a high-spin quartet state, thereby showing diverse reactivity patterns by high-valent iron-oxo intermediates.[8]

As alluded to above, the argument on multiple oxidants hypothesis remains elusive in the oxygenation reactions by CYP 450 and their model compounds. In order to resolve such an intriguing, current controversy, we need to identify reactive oxidant(s) directly in the course of catalytic oxygenation reactions. We now report direct experimental evidence that a high-valent iron(IV)-oxo porphyrin π-cation radical is an active oxidant in the oxygenation of organic substrates by an iron(III) porphyrin complex and *m*-chloroperbenzoic acid (*m*-CPBA) under catalytic turnover conditions.

The formation, stability and reactivity of $[(TMP)^{+\bullet}\text{-}Fe^{IV}{=}O]^+$ (**1**) (TMP = *meso*-tetramesitylporphyrin) were examined in a solvent mixture of CH_3CN and CH_2Cl_2 (1 : 1) at −40 °C. Addition of 4 equiv. of *m*-CPBA (0.8 mM, diluted in 50 μL of CH_3CN–CH_2Cl_2 (1 : 1)) to a reaction solution containing Fe(TMP)(Cl) (0.2 mM) afforded the formation of a green-colored solution, showing the characteristic UV-Vis spectrum of **1** (Fig. 1(a)).[9] The intermediate **1** was stable ($t_{1/2}$ = ~0.5 h) enough to investigate its reactivity in olefin



Scheme 1 Two intermediates, Cpd 0 and Cpd I, proposed in the catalytic oxygenation of organic substrates by CYP 450.

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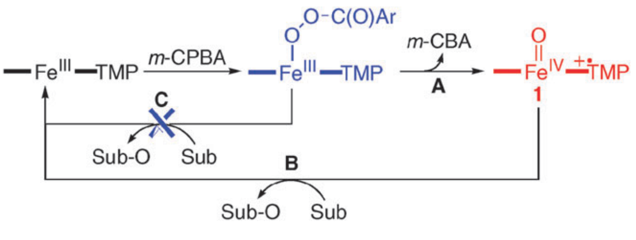
epoxidation with cyclohexene, aromatic ring oxidation with anthracene, C–H bond activation with dihydroanthracene, and alcohol oxidation with benzyl alcohol. Upon addition of substrates to **1**, the intermediate reverted back to the starting $[Fe^{III}(TMP)]^+$ complex (Fig. 1(b)) for the reaction of dihydroanthracene, which is representative of the spectra of all other substrates), and pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} values. Plotting the pseudo-first-order rate constants against the concentration of substrates led us to determine second-order rate constants at −40 °C for the reactions of cyclohexene (k_2 = 5.0(5) × 10^{-1} M^{-1} s^{-1}), anthracene (k_2 = 1.1(3) M^{-1} s^{-1}), dihydroanthracene (k_2 = 6.6(4) M^{-1} s^{-1}), and benzyl alcohol (k_2 = 7.1(4) × 10^{-2} M^{-1} s^{-1}) (ESI,† Fig. S1), indicating that the relative reactivities of the substrates are in the order of dihydroanthracene > anthracene > cyclohexene > benzyl alcohol.

The reaction of Fe(TMP)Cl with *m*-CPBA was then carried out in the presence of substrates under the conditions described above. When *m*-CPBA (4 equiv. to the iron catalyst) was added to a reaction solution containing Fe(TMP)(Cl) (0.2 mM) and substrates, such as cyclohexene, anthracene, dihydroanthracene and benzyl alcohol, in a solvent mixture of CH_3CN and CH_2Cl_2 (1 : 1) at −40 °C, we observed the formation of **1** (Fig. 1(c)), followed by its disappearance with rates identical to those observed in the reaction of **1** and the substrates (*vide supra*) (Fig. 1(d)).[10] When the catalytic reactions were carried out at room temperature, we observed the same reactivity patterns (ESI,‡ Fig. S2 for the reactions of dihydroanthracene and benzyl alcohol).‡ These results demonstrate unambiguously that **1**, which is formed *via* O–O bond heterolysis of Fe^{III}(Por)(*m*-CPBA) (Scheme 2, pathway A),[9b,e] is an active oxidant that is responsible for the oxygenation of organic substrates at low- and room-temperatures (Scheme 2, pathway B). Further, the present results imply that an iron(III) porphyrin-oxidant adduct, Fe^{III}(Por)(*m*-CPBA), is a sluggish oxidant in oxygenation reactions (Scheme 2, pathway C).[11] In line with this conclusion, we have shown very recently that mononuclear nonheme iron(III)-hydroperoxo and -alkylperoxo species are sluggish oxidants in the oxygenation of sulfides and olefins and that the oxidizing power of the intermediates cannot compete with that of nonheme iron(IV)-oxo complexes.[12] Furthermore, the participation of $[(TMP)Fe^{V}{=}O]^+$, which is an isomer of **1**, was not observed in the reactions of Fe(TMP)Cl and *m*-CPBA at low and room temperatures.[13]

With the strong evidence that **1** is an active oxidant, we have investigated ^{18}O-labeled water experiments in the oxygenation of cyclohexene by Fe(TMP)Cl and *m*-CPBA in a solvent



Scheme 2 High-valent iron(IV)-oxo porphyrin π-cation radical, **1**, as an active oxidant in the oxygenation of organic substrates by Fe(TMP)Cl and *m*-CPBA under catalytic turnover conditions.

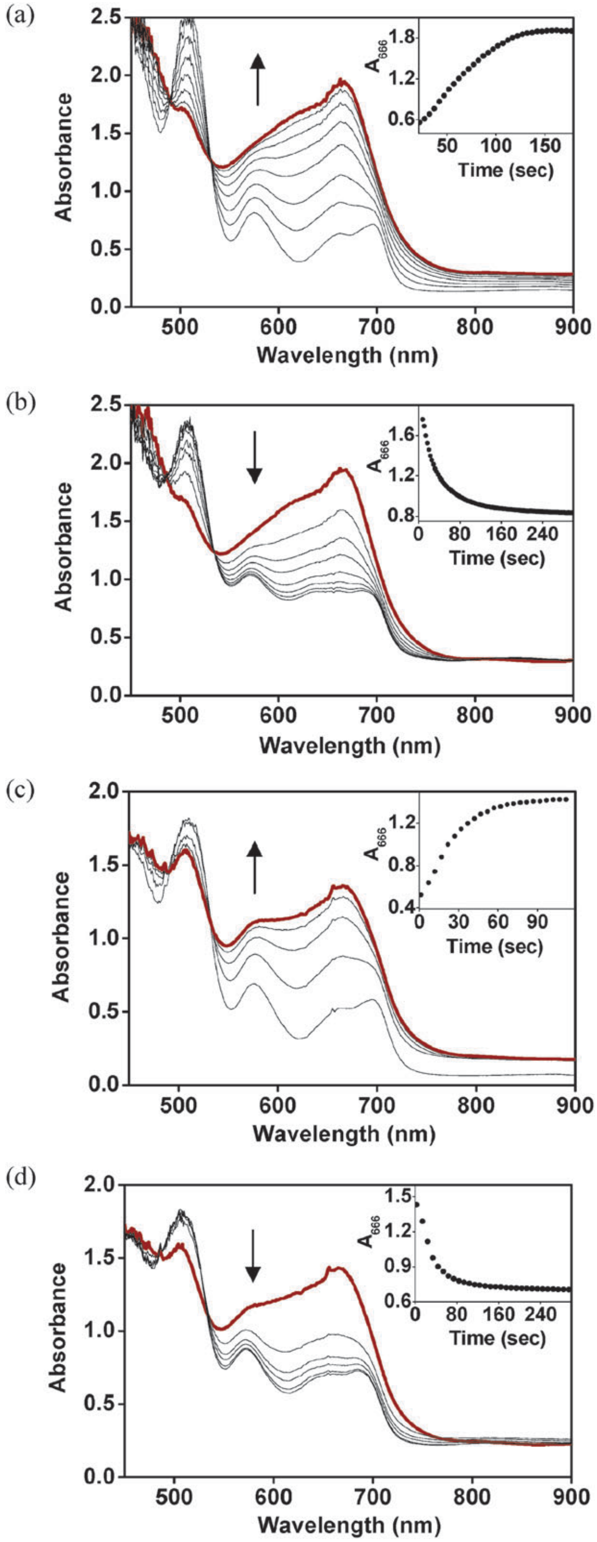
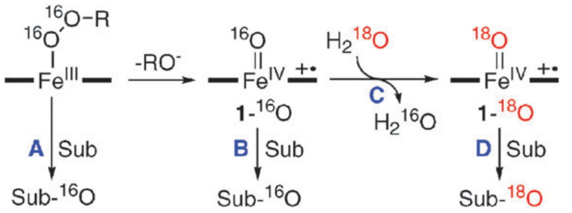


Fig. 1 UV-Vis spectral changes of **1** (colored solid line) under stoichiometric (a and b) and catalytic (c and d) conditions. (a) Formation of **1** in the reaction of Fe(TMP)Cl (0.2 mM) and *m*-CPBA (0.8 mM) at −40 °C, (b) disappearance of **1** upon addition of dihydroanthracene (20 equiv, 2 mM) to a reaction solution of **1**, (c) formation of **1** in the catalytic oxygenation of dihydroanthracene (10 equiv, 2 mM) by Fe(TMP)Cl (0.2 mM) and *m*-CPBA (0.8 mM) at −40 °C, and (d) disappearance of **1** in the catalytic reaction. Inset shows absorbance traces monitored at 666 nm.



Scheme 3 Proposed mechanism illustrating the source of oxygen in oxygenated products in labeled water experiments.

mixture of CH_3CN and CH_2Cl_2 under catalytic turnover conditions.§ Interestingly, only a small amount of ^{18}O (∼10%) was incorporated from $H_2{}^{18}O$ into cyclohexene oxide. It has been shown previously that addition of a mixture of olefin and $H_2{}^{18}O$ to iron-oxo intermediates afforded ^{18}O-labeled epoxide products, indicating that iron-oxo species readily exchange their oxygen with $H_2{}^{18}O$ prior to oxo transfer to organic substrates (Scheme 3, pathway B *vs.* pathways C and D).[15] Thus, the observation of the small ^{18}O-incorporation from $H_2{}^{18}O$ into the products may imply the involvement of Fe^{III}(Por)(*m*-CPBA) as an oxidant in the catalytic oxygenation reactions (Scheme 3, pathway A).[16] However, it should be noted that the oxygen exchange of **1**-^{16}O with $H_2{}^{18}O$ (Scheme 3, pathway C) competes with the oxo transfer from **1**-^{16}O to substrates (Scheme 3, pathway B) and the extent of ^{18}O-incorporation varies depending on the ease of oxygen exchange between **1**-^{16}O and $H_2{}^{18}O$.[14a] Indeed, when we carried out the identical reaction in a solvent mixture of CH_3OH, CH_3CN and CH_2Cl_2,§ the amount of ^{18}O found in cyclohexene oxide increased from 10% to 49%, demonstrating that the ^{18}O-incorporation from $H_2{}^{18}O$ into oxygenated products depends on conditions such as the catalyst and solvent.[15]

In conclusion, the nature of reactive intermediates has been often proposed by analyzing products in competitive oxygenation and labeled water experiments in iron porphyrin model studies. Although the formation and reactivity of **1** has been well established previously,[9a] the present study provides direct experimental evidence that an iron(IV)-oxo porphyrin π-cation radical is generated as an active oxidant in the catalytic oxygenation of organic substrates by an iron(III) porphyrin complex and *m*-CPBA.[10] We have also demonstrated that oxygen exchange between iron-oxo species and $H_2{}^{18}O$ can occur slowly under certain catalytic turnover conditions. The present results provide important clues to resolve the long-standing dichotomy in understanding the nature of active oxidant(s) in iron porphyrin model reactions.

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Notes and references

‡ The major products formed in the oxidation of cyclohexene, anthracene, dihydroanthracene and benzyl alcohol were cyclohexene oxide, anthraquinone, anthracene and benzaldehyde, respectively, and the product yields were high (*e.g.*, >60%) in all of the reactions.

§ Reaction conditions were as follows: *m*-CPBA (4 mM) was added to a reaction solution containing Fe(TMP)Cl (1 mM), cyclohexene (50 mM) and $H_2{}^{18}O$ (500 mM) in a solvent mixture of CH_3CN and CH_2Cl_2 (1 : 1) or in a solvent mixture of CH_3OH, CH_3CN and CH_2Cl_2 (2 : 1.5 : 1.5) at 10 °C.

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