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First Direct Evidence for Stereospecific Olefin Epoxidation and Alkane Hydroxylation by an Oxoiron(IV) Porphyrin Complex

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High-valent oxoiron(IV) porphyrins have been frequently invoked as the key oxidants in the catalytic cycle of heme-containing enzymes.[1] Especially, oxoiron(IV) porphyrin π-cation radicals, referred to as compound I, are believed to carry out oxygen atom transfer reactions in the catalytic oxidation of organic substrates by cytochromes P450 and iron porphyrin models.[2] Indeed, it has been demonstrated that in situ-generated oxoiron(IV) porphyrin π-cation radicals oxygenate olefins and alkanes to the corresponding epoxides and alcohols efficiently and stereoselectively.[3] In contrast, oxoiron(IV) porphyrins, referred to as compound II, have been considered to be such poor oxidants that they can only oxygenate triphenylphosphine to triphenylphosphine oxide until Groves and co-workers reported that an oxoiron(IV) porphyrin complex, (TMP)-Fe^{IV}═O (TMP = tetramesitylporphinato dianion), is able to oxidize olefins.[4,5] However, the (TMP)Fe^{IV}═O complex reacts with olefins with a selectivity which is very different from that observed for $(TMP)^{+\bullet}Fe^{IV}$═O, an oxoiron(IV) porphyrin π-cation radical complex.[5] Moreover, there is no report yet that oxoiron(IV) porphyrins are able to activate C−H bonds of alkanes, thereby yielding alcohol products. In this Communication, we report that an oxoiron(IV) porphyrin complex bearing electron-deficient porphyrin ligand oxygenates olefins and alkanes with reactivities similar to those found in oxoiron(IV) porphyrin π-cation radicals. To the best of our knowledge, this study provides the first example of an oxoiron(IV) porphyrin complex that conducts two-electron oxidations of olefins to epoxides and of alkanes to alcohols with a high stereoselectivity.

Treatment of an iron(III) porphyrin complex, Fe(TPFPP)Cl (TPFPP = *meso*-tetrakis(pentafluorophenyl)porphinato dianion) **1**, with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of a small amount of H_2O in a solvent mixture of CH_3CN and CH_2Cl_2 at 25 °C resulted in the formation of an oxoiron(IV) porphyrin complex, (TPFPP)Fe^{IV}═O **2** (Supporting Information, Figure S1 for UV−vis spectra of **1** and **2**).[6] Titration experiments show that the complete conversion of **1** to **2** required 4 equiv of *m*-CPBA (Supporting Information, Figure S2 for UV−vis spectral changes upon the addition of different amounts of *m*-CPBA). In addition, the stability of **2** was found to depend significantly on the amounts of H_2O present in reaction solutions (Supporting Information, Figure S3).[7] Therefore, **2** was prepared by reacting **1** with 4 equiv of *m*-CPBA in the presence of H_2O and directly used in reactivity studies. When olefins were added to a reaction solution containing **2**, the intermediate **2** reverted back to an iron(III) porphyrin complex with clear isosbestic points at 476, 524, and 566 nm (Supporting Information, Figure S4).[8] Product analysis of the reaction mixture revealed that epoxides were yielded as major products (Table 1A), demonstrating that **2** is capable of oxygenating olefins to the corresponding epoxide products. In the case of cyclohexene, cyclohexene oxide was yielded as a major product, and the formation of allylic oxidation products such as cyclohexenol and cyclohexenone was not observed. In the epoxidation of *cis*- and *trans*-stilbenes, *cis*- and *trans*-stilbene oxides were yielded, respectively, and the formation of isomerized epoxide products and benzaldehyde was not detected, indicating that the epoxidation of olefins by **2** is highly stereospecific. Table 1 also shows that the reaction rates of **2** toward olefins were in the order of cyclohexene > *trans*-stilbene > cyclooctene > *cis*-stilbene.[9]

Table 1. Epoxidation of Olefins and Hydroxylation of Alkanes by **2**[a,b]

substrate	products	yields (%)[c]	$k_{obs} \times 10^3$ s^{-1} [d]
	A. Epoxidation of Olefins		
cyclooctene	cyclooctene oxide	43 ± 5	3.5 ± 0.3
cyclohexene	cyclohexene oxide	35 ± 4	12 ± 2
cis-stilbene	*cis*-stilbene oxide	17 ± 3	2.1 ± 0.2
trans-stilbene	*trans*-stilbene oxide	21 ± 4	6.9 ± 0.5
	B. Hydroxylation of Alkanes		
triphenylmethane	triphenylmethanol	39 ± 4	6.4 ± 0.5
adamantane	1-adamantanol	33 ± 4	1.8 ± 0.2
	2-adamantanol	3 ± 1	
	2-adamantanone	1 ± 1	
cis-1,2-dimethyl-cyclohexane	(1*R*,2*R* or 1*S*,2*S*)-1,2-dimethylcyclohexanol	29 ± 4	1.6 ± 0.2

[a] Reactions were run at least in triplicate under argon. [b] In general, **2** (2 mM) was prepared by adding 4 equiv of *m*-CPBA (8 mM, in 20 μL of CH_3CN) to a reaction solution containing **1** (2 mM) and H_2O (15 μL) in a solvent mixture (0.5 mL) of CH_3CN and CH_2Cl_2 (3:1) in a 0.1-cm UV cell at 25 °C. Substrate (0.2 M, in 20 μL of CH_2Cl_2) was then injected into the UV cell, and spectral changes of **2** were directly monitored by a UV−vis spectrophotometer. Product analyses were performed with GC/GC-MS or HPLC, and product yields were determined by comparison against standard curves prepared with authentic samples. [c] Yields were calculated on the basis of the amount of **2**. [d] Pseudo-first-order rate constants for the reduction of **2** to $[Fe^{III}(TPFPP)]^+$ upon the addition of 100 equiv of substrate were determined by monitoring the absorbance change at 547 nm.

Isotope labeling studies were then performed with $H_2{}^{18}O$ and $^{18}O_2$, to understand the nature of oxidizing species and the origin of oxygen atoms in epoxide products (see Supporting Information for experimental details). When the cyclooctene epoxidation was carried out with **2** in the presence of $H_2{}^{18}O$, we found that ~30% of the oxygen in cyclooctene oxide derived from the labeled water (Scheme 1A) and the degree of ^{18}O incorporated into the epoxide product increased linearly with the increase of the amounts of $H_2{}^{18}O$ in the reaction mixture (Supporting Information, Figure S6).[10] Furthermore, a significant increase of ^{18}O-incorporation was also observed when **2** was incubated in reaction solution containing $H_2{}^{18}O$ prior to the addition of cyclooctene (Supporting Information, Figure S7). The cyclooctene epoxidation by **2** was then carried out under $^{18}O_2$ atmosphere, to ensure that O_2 does not play a significant role in the olefin epoxidation. In this reaction, only a trace amount of ^{18}O was incorporated from $^{18}O_2$ into the epoxide product (Scheme

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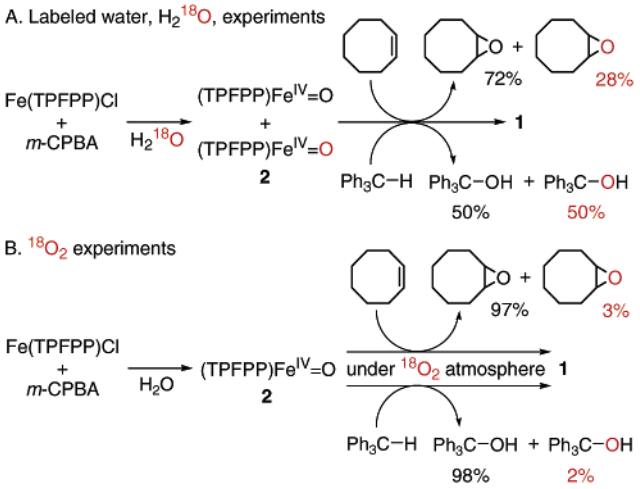
Scheme 1. Isotope Labeling Studies



1B). On the basis of the results described above, we conclude that the oxygen atom in the epoxide product did not derive from O_2 but from **2**.[11]

The reactivity of **2** was then examined in alkane hydroxylation reactions (see Table 1B). In the hydroxylation of triphenylmethane by **2**, triphenylmethanol was yielded as the only detected product. When the triphenylmethane hydroxylation was carried out in the presence of $H_2{}^{18}O$, 50% of the oxygen atom in the triphenylmethanol product derived from the labeled water (Scheme 1A). Furthermore, when the triphenylmethane hydroxylation was carried out under $^{18}O_2$ atmosphere, less than 2% ^{18}O was incorporated into the triphenylmethanol product (Scheme 1B). The results of the isotope labeling studies demonstrate clearly that the oxygen in the triphenylmethanol product derives from **2** and that O_2 does not play a significant role in the alkane hydroxylation. In the hydroxylation of adamantane, a high degree of selectivity for tertiary C−H bonds over secondary C−H bonds was observed (i.e., a 3°/2° ratio of ∼25, normalized on a per-hydrogen basis). Such a high 3°/2° ratio has been observed in the catalytic hydroxylation of adamantane by iron complexes of porphyrin and non-porphyrin ligands.[12,13] Most significantly, the alkane hydroxylation by **2** was found to be highly stereospecific. In the hydroxylation of *cis*-1,2-dimethylcyclohexane,[3b,13,14] (1*R*,2*R* or 1*S*,2*S*)-1,2-dimethylcyclohexanol, the tertiary alcohol with the methyl groups cis to each other, was the only detected product, and the formation of (1*R*,2*S* or 1*S*,2*R*)-1,2-dimethylcyclohexanol, the epimer with the methyl groups trans to each other, was not observed at all. This result demonstrates unambiguously that an oxoiron(IV) porphyrin complex hydroxylates alkanes stereospecifically. The same stereospecificity was also observed in the hydroxylation of the tertiary C−H bond of *cis*-decalin (data not shown).[12a] Finally, it should be noted that the oxidizing power of **2** is not as strong as its oxoiron(IV) porphyrin π-cation radical species, (TPFPP)$^{+\bullet}Fe^{IV}$=O,[6a] so that **2** cannot activate alkanes with stronger C−H bonds such as cyclohexane even at 25 °C.[15,16]

In conclusion, we have demonstrated here that an oxoiron(IV) porphyrin complex is able to conduct two-electron oxidations of olefins to epoxides and of alkanes to alcohols with reactivity patterns similar to those found in oxoiron(IV) porphyrin π-cation radicals. Such a finding in iron porphyrin models suggests that oxoiron(IV) porphyrins in cytochromes P450 and recently isolated nonheme oxoiron(IV) complexes[17] may be able to effect olefin epoxidation and alkane hydroxylation. Furthermore, the present results lead us to propose that this oxoiron(IV) porphyrin complex is a "third electrophilic oxidant" that may be involved in oxygen atom transfer reactions by cytochromes P450.[18] Studies designed to synthesize oxoiron(IV) porphyrins with greater oxidative reactivities and to elucidate mechanisms of oxygen atom transfer from the oxoiron(IV) porphyrin complex to olefins and alkanes are currently underway in this laboratory.

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Supporting Information Available: Text containing experimental details for isotope labeling studies and Figures S1−S7 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The formation of an iron(III) porphyrin complex may be the result of a facile oxidation of an iron(II) porphyrin complex, a product formed upon the oxygen atom transfer from **2** to organic substrates, by another oxoiron(IV) porphyrin molecule: see ref 4.
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(15) We have shown previously that **1** associated with *m*-CPBA hydroxylates alkanes including cyclohexane at −40 °C under catalytic reaction conditions and suggested an acylperoxo-iron porphyrin as a reactive species (see ref 6a). In the reactions, the yields of alcohol products were high, and only trace amounts of ^{18}O were incorporated from $H_2{}^{18}O$ into the products when the reactions were carried out in the presence of $H_2{}^{18}O$. In contrast, alkane hydroxylations by **2** did not occur at −40 °C, and the ^{18}O-incorporation from $H_2{}^{18}O$ into oxygenated products was high at room temperature. These different reactivity patterns indicate that the hydroxylating intermediate generated in the reaction of **1** and *m*-CPBA under catalytic conditions at −40 °C is different from **2**.
(16) A (TPFPP)$^{+\bullet}Fe^{IV}$=O complex, prepared in the reaction of **1**−CF_3SO_3 (2 mM) with 1.2 equiv of *m*-CPBA at −40 °C, hydroxylates cyclohexane with $k_{obs} = 9.6 \times 10^{-2}$ s^{-1}, yielding cyclohexexanol (37%) as a major product. The low reactivity of **2**, as compared to the (TPFPP)$^{+\bullet}Fe^{IV}$=O complex, was also observed in the hydroxylation of *cis*-1,2-dimetyhlcyclohexane, in which the (TPFPP)$^{+\bullet}Fe^{IV}$=O complex disappeared immediately upon the addition of the substrate at −40 °C and yielded 55% of alcohol product, whereas **2** was stable in the presence of the substrate at −40 °C and yielded no alcohol product under the identical conditions.
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