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Water-Soluble Iron Porphyrin Complex-Catalyzed Epoxidation of Olefins with Hydrogen Peroxide and *tert*-Butyl Hydroperoxide in Aqueous Solution

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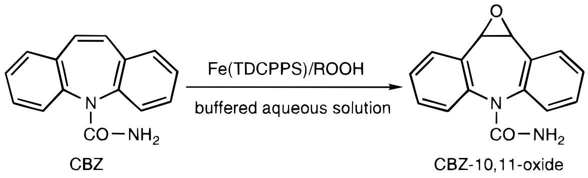
The reactions of iron porphyrin complexes with various oxidizing agents have been extensively studied with the purpose of understanding the nature and structure of reactive intermediates and the mechanism of O−O bond activation occurring in cytochrome P-450 enzymes.[1] In recent years, use of hydroperoxides as terminal oxidants in catalytic oxidations by iron porphyrins has drawn particular attention. Traylor and co-workers first succeeded in using hydrogen peroxide and *tert*-butyl hydroperoxide in the epoxidation of olefins with electronegatively substituted iron porphyrins in hydroxylic solvent systems.[2] We have also shown that an iron porphyrin complex catalyzes the epoxidation of olefins by H_2O_2 in aprotic solvents such as acetonitrile.[3] In aqueous solution, as far as we have been able to discern, epoxidations by iron(III) porphyrin complexes with biologically important oxidants such as H_2O_2 and *t*-BuOOH have not been successful,[4] although elegant kinetic and mechanistic studies of the O−O bond cleavage of hydroperoxides by water-soluble iron porphyrins have been conducted by Bruice and co-workers.[5] In this communication, we report for the first time that a water-soluble iron(III) porphyrin complex catalyzes the epoxidation of olefins by H_2O_2 and *t*-BuOOH in buffered aqueous solutions. A high-valent iron(IV) oxo porphyrin cation radical complex is proposed as a reactive intermediate responsible for the olefin epoxidation, on the basis of the results of stereospecific epoxidation of *cis*-stilbene and isotopically labeled water, $H_2{}^{18}O$, experiments.

Catalytic epoxidations of CBZ (CBZ = carbamazepine)[6,7] with H_2O_2 and *t*-BuOOH were performed in the presence of a water-soluble and non-μ-oxo dimer forming iron(III) porphyrin complex (5,10,15,20-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphinato)-iron(III) [Fe(TDCPPS)],[8] in buffered aqueous solutions.[9] We observed complete conversion of CBZ with a high yield of CBZ-10,11-oxide (above 85% based on CBZ consumed) within 30 min at relatively low pH values (eq 1),[10] and as shown in Figure 1, the conversions of CBZ to the oxide product were found to depend on the pH of the reaction solutions (vide infra).[11] Formation of the oxide product was not detected in the absence of the iron porphyrin complex, and the product yields were not affected whether the reactions were carried out in air or under an inert atmosphere.[12]



(eq 1)

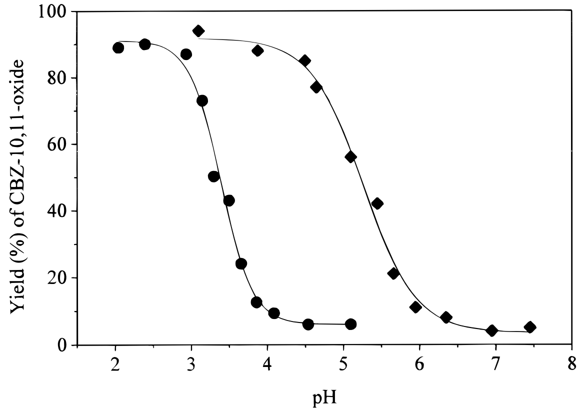


Figure 1. Plot of the percent yield of CBZ-10,11-oxide formed vs pH of reaction solutions for the catalytic epoxidations of CBZ by H_2O_2 (●) and *t*-BuOOH (◆) carried out in the presence of Fe(TDCPPS) in buffered aqueous solutions. The percent yields are calculated on the basis of the CBZ used, and CBZ remained intact at high pH values.

To understand the nature of the epoxidizing intermediate formed in the reactions of H_2O_2 and *t*-BuOOH, we studied the following reactions:[13] (1) stereoselectivity in *cis*-stilbene epoxidation and (2) epoxidation of CBZ in buffered $H_2{}^{18}O$ solution.

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(8) Fe(TDCPPS) was obtained from Mid-Century Chemical.

(9) In a typical reaction, oxidant (4 mM H_2O_2 and 10 mM *t*-BuOOH, introduced as 1 M H_2O_2 and *t*-BuOOH solutions in water) was added to a reaction solution containing Fe(TDCPPS) (0.04 mM) and CBZ (1 mM, introduced as a 0.1 M solution in methanol) in buffered aqueous solution (5 mL). Reactions at pH 2−3 were performed in formate buffer (0.1 M), at pH 4−5 in acetate buffer (0.1 M), and at pH 6−7 in phosphate (0.1 M), and the pH of the reaction solutions was adjusted by adding either HCl (3 N) or NaOH (3 N) solutions whenever necessary. The reaction mixture was stirred in air for 30 min at 25 °C and then analyzed by an *Orom Vintage 2000* HPLC equipped with a variable-wavelength UV-200 detector. CBZ and its epoxide derivative were separated on a Waters Symmetry C18 column, 5 μM, eluted by a mixture of methanol/water, 60:40 (v/v), with retention times of 4.8 and 3.5 min, respectively. Detection was made at 215 nm. Calculation of the conversions of CBZ and the yields of CBZ-10,11-oxide was determined on the corresponding calibration curves of CBZ and the authentic CBZ-10,11-oxide prepared by a literature method.[6]

(10) Failure to observe olefin epoxidations by water-soluble iron porphyrin complexes with H_2O_2 and *t*-BuOOH in water, reported previously by Bruice et al.,[4] might be due to the reactions being studied at pH 7.0 (see Figure 1).

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(12) Deoxygenated water was prepared by three freeze−pump−thaw cycles, and the epoxidation reaction was performed under an argon atmosphere.

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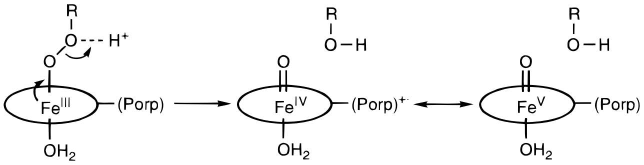
Table 1. Percentages of ^{18}O-Incorporation from $H_2{}^{18}O$ into CBZ-10,11-oxide Formed in the Epoxidation of CBZ by H_2O_2, *t*-BuOOH, and $KHSO_5$ in the Presence of Fe(TDCPPS)[a,b]

oxidants	pH	^{18}O (%) in solvent water	^{18}O (%) in CBZ-10,11-oxide	yield (%) of oxide product[c]
H_2O_2	2.7	81	52 ± 4	93
t-BuOOH	2.7	79	51 ± 4	89
$KHSO_5$	2.7	79	56 ± 5	90

[a] Reactions were run in a buffered solution (0.1 M formate consisted of 200 μL of $H_2{}^{18}O$ (95% ^{18}O enrichment, Aldrich Chemical Co.) and 40 μL of $H_2{}^{16}O$) containing Fe(TDCPPS) (0.1mM) and CBZ (0.4 mM, introduced as a 0.1 M solution in methanol). Oxidant (1.6 mM H_2O_2, 4 mM *t*-BuOOH, and 0.5 mM $KHSO_5$) was added to the reaction solution, and the solution was stirred for 30 min at room temperature. The reaction solution was taken to dryness using a Speed-Vac. Then, CH_3CN (300 μL) was added to the residue, followed by filtration. The filtrate was analyzed with a VG70-VSEQ mass spectrometer (VG Analytical) by using the electronic impact method at 70 eV. ^{16}O and ^{18}O compositions in CBZ-10,11-oxide were determined by the relative abundances of mass peaks at $m/z = 252$ for ^{16}O and $m/z = 254$ for ^{18}O. All reactions were performed in duplicate, and the data reported represent the average of these reactions. [b] A control reaction for the stability of CBZ-10,11-oxide, performed by stirring CBZ-10,11-oxide (0.45 mM) in the presence of Fe(TDCPPS) (0.1mM) in 0.1 M formate buffer solution (pH 2.7, 200 μL of $H_2{}^{18}O$ and 20 μL of $H_2{}^{16}O$), showed that the oxygen of CBZ-10,11-oxide did not exchange with labeled water under the reaction conditions. Another control reaction for the oxygen exchange between $KHSO_5$ and $H_2{}^{18}O$ was also carried out as follows: $KHSO_5$ (1 mM) in a buffered solution (pH 2.7, 0.1 M formate consisted of 200 μL of $H_2{}^{18}O$ and 40 μL of $H_2{}^{16}O$) was stirred for 30 min at room temperature. The solution was dried using a Speed-Vac. Subsequently, $H_2{}^{16}O$ (200 μL) and CBZ (0.4 mM, introduced as a 0.1 M solution in methanol) was added. Then, the CBZ epoxidation was initiated by adding Fe(TDCPPS) (0.1mM). After 30 min of stirring, the percentage of ^{18}O in CBZ-10,11-oxide was analyzed by the procedures described above. The oxide product did not contain ^{18}O, indicating that oxygen exchange between $KHSO_5$ and $H_2{}^{18}O$ did not occur during the preincubation time.[17] [c] CBZ disappeared completely and the yield of the oxide porduct is based on the amount of CBZ consumed.

We then compared the reactivity patterns obtained in these reactions to those of *m*-chloroperoxybenzoic acid (MCPBA) and $KHSO_5$ reactions, since it has been shown previously that high-valent iron(IV) oxo porphyrin cation radicals are generated in the latter reactions.[4b,11a] In the *cis*-stilbene epoxidations, *cis*-stilbene disappeared completely under the reaction conditions[14] and *cis*-stilbene oxide was formed predominantly with only a trace amount of *trans*-stilbene oxide formation in all the reactions of H_2O_2, *t*-BuOOH, MCPBA, and $KHSO_5$,[15] leading us to rule out the involvement of peroxyl radicals ($ROO^{\bullet}$) and oxoiron(IV) porphyrin [$(Porp)Fe^{IV}{=}O$] as epoxidizing agents since these species should oxidize *cis*-stilbene nonstereospecifically.[16] More significantly, when the CBZ epoxidation was carried out with the oxidants such as H_2O_2, *t*-BuOOH, and $KHSO_5$ in buffered $H_2{}^{18}O$ solution,[6,7] we observed more than 50% ^{18}O-incorporation from the solvent $H_2{}^{18}O$ (80% ^{18}O enriched) into the oxide product (Table 1). It has been proposed previously by Meunier et al. that metal−oxo species exchange their oxygen atoms with labeled water via a "redox tautomerism" mechanism in aqueous solution.[6,11a]

Scheme 1



Therefore, the results of the labeled-water experiments clearly demonstrate that the reactive intermediate generated in the reactions of Fe(TDCPPS) with H_2O_2 and *t*-BuOOH as well as with $KHSO_5$ is a high-valent iron(IV) oxo porphyrin cation radical complex.[18] On the basis of the results discussed above, we are now able to conclude unambiguously that the reactions of a water-soluble iron porphyrin complex with H_2O_2 and *t*-BuOOH generate a high-valent iron(IV) oxo porphyrin cation radical intermediate at low pH values in aqueous solution.

It is of interest to observe that the yields of the oxide product formed in the epoxidation reactions depend significantly on the pH of the reaction solutions and that the pH ranges for giving the oxide product vary with the kinds of oxidants used (see Figure 1).[19] These results indicate that the generation of the high-valent iron(IV) oxo porphyrin cation radical intermediate in the reactions of H_2O_2 and *t*-BuOOH is affected by the acidity of the reaction solutions.[20] We propose at this moment that the importance of pH of the reaction solutions is attributed to the O−O bond cleavage mechanism (i.e., heterolysis vs homolysis). Heterolysis is facilitated by the presence of proton at low pHs that helps to stabilize the charge-separated heterolytic transition state (Scheme 1).[21] However, other possible mechanisms[22] cannot be ruled out at this time. More detailed mechanistic studies for elucidating the pH dependence of the epoxidation reactions in aqueous solution are currently under investigation in this laboratory.

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(13) These reactions were carried out at pH 2.7, since the olefin epoxidation by H_2O_2 takes place only at low pHs and reactivity comparisons with other oxidants such as *t*-BuOOH, MCPBA, and $KHSO_5$ should be investigated at the same pH.

(14) Reactions were run in a solvent mixture (5 mL) of formate buffer (pH 2.7, 3.2 mL)/CH_3OH (1.0 mL)/CH_3CN (0.8 mL) in order to make the reaction mixture homogeneous. In the reactions, oxidant (4 mM H_2O_2, 10 mM *t*-BuOOH, 1.2 mM MCPBA, and 1.2 mM $KHSO_5$, introduced as 1 M H_2O_2, 1 M *t*-BuOOH, and 0.1 M $KHSO_5$ solutions in water and 0.1 M MCPBA solution in methanol) was added to a reaction solution containing Fe(TDCPPS) (0.04 mM) and *cis*-stilbene (1 mM) in buffered solution. The reaction mixture was stirred for 30 min at 25 °C and then analyzed by HPLC. Products were separated on a Waters Symmetry C18 column, 5 μM, eluted by a mixture of methanol/water, 80:20 (v/v), and detection was made at 215 or 254 nm.

(15) The yields of *cis*-stilbene oxide formed in the reactions of H_2O_2, *t*-BuOOH, MCPBA, and $KHSO_5$ were 75, 63, 81, and 69% based on the substrate consumed, respectively, and the yields of *trans*-stilbene oxide were less than 2% in all the reactions.

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(19) The pH effect in metalloporphyrin-catalyzed oxidation reactions with $KHSO_5$ in aqueous solution has also been observed; however, no clear explanation has been provided for such a phenomenon. See ref 11.

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(22) Other possible mechanisms that we are considering to interpret the pH effect are (1) the generation of $(Porp)^{\bullet+}Fe^{IV}{=}O$ by a facile $1e^-$ oxidation of $(Porp)Fe^{IV}{-}OH$ with $RO^{\bullet}$ "in the cage" at low pHs[5a] and (2) the effect of the nature of the axial ligand bound to the metal center (i.e., (Porp)-$Fe^{III}(X)_2$, where X represents either H_2O or HO^- depending on the pH of the solution) on the heterolytic vs homolytic O−O bond cleavage of $(Porp)Fe^{III}{-}OOR$ species.[23]

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