

# Ferric chloride-catalyzed activation of hydrogen peroxide for the demethylation of *N,N*-dimethylaniline, the epoxidation of olefins, and the oxidative cleavage of vicinal diols in acetonitrile: A reaction mimic for cytochrome P-450

(Lewis acid)

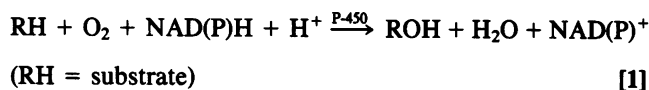
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Communicated by Thomas C. Bruice, November 12, 1986 (received for review February 5, 1986)

**ABSTRACT** In dry acetonitrile, anhydrous  $\text{Fe}^{\text{III}}\text{Cl}_3$  catalyzes the demethylation of *N,N*-dimethylaniline, the epoxidation of olefins, and the oxidative cleavage of 1-phenyl-1,2-ethanediol (and other 1,2-diols) by hydrogen peroxide. For each class of substrate the products closely parallel those that result from their enzymatic oxidation by cytochrome P-450. Because of (i) the close congruence of products, (ii) the catalytic nature of the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{H}_2\text{O}_2$  reaction mimic, and (iii) the similarity of the dipolar aprotic solvent (acetonitrile) to the proteinaceous lipid matrix of the biomembrane, the form of the reactive intermediate may be the same in each case. A mechanism is proposed in which an initial Lewis acid-base interaction of  $\text{Fe}^{\text{III}}\text{Cl}_3$  with  $\text{H}_2\text{O}_2$  generates a highly electrophilic  $\text{Fe}^{\text{III}}$ -oxene species as the reactive intermediate. This is in contrast to the prevailing view that cytochrome P-450 acts as a redox catalyst to generate an  $\text{Fe}^{\text{V}}$ -oxo species or an  $\text{Fe}^{\text{IV}}$ -oxo cation radical as the reactive intermediate.

The cytochrome P-450 enzymes catalyze a wide variety of substrate transformations (1), including monooxygenation via oxygen atom transfer (Eq. 1).



These proteins consist of a single polypeptide chain (45–50 kDa) that contains an iron(III) protoporphyrin IX prosthetic group. The resting state of the enzyme is low spin, with a thiolate of cysteine in one axial position and a water molecule in the other (2). The metal center is surrounded by hydrophobic protein residues, which provide an essentially nonaqueous matrix at the active site.

The exact sequence and nature of the electron-transfer steps that are involved in cytochrome P-450 and its facilitation of oxygen-atom transfer have not been elucidated. However, *in vivo* cytochrome P-450 utilizes molecular oxygen, which the system reduces by two equivalents to the peroxy level prior to transfer of an oxygen atom to substrate during the catalytic cycle. The fact that cytochrome P-450 can utilize hydrogen peroxide, alkyl hydroperoxides, or peroxy acids as a source of oxygen atoms for substrate monooxygenation (a process termed the "peroxide shunt") (3) supports the idea of a peroxide intermediate in the redox cycle for  $\text{O}_2$  reduction in cytochrome P-450. This discovery provided the basis for a series of model studies with a variety of synthetic iron(III) porphyrins in conjunction with peroxides or peroxy acids (4, 5). Such systems are able to mimic the many sub-

strate transformations that are catalyzed by cytochrome P-450 (including hydroxylation of aromatic and aliphatic hydrocarbons, epoxidation of olefins, dehydrogenation, and demethylation of amines). On the basis of such studies, mechanisms for the P-450-catalyzed oxygen-atom transfer have been proposed. These involve an active intermediate that usually is formulated as an iron(IV)-oxo porphyrin cation radical [ $+\cdot\text{PorFe}^{\text{IV}}=\text{O}$ ], which monooxygenates the substrate and dissociates to regenerate the iron(III) form of the enzyme.

The solution properties of synthetic metalloporphyrins have required the use of halogenated hydrocarbons or methanol for most model studies. However, the redox properties of complexed metal ions and the delicate balance of the ligand-metal interactions that are associated with metal ion catalyses are extremely sensitive to the immediate solution environment (6), and thus the choice of a model solvent is a critical consideration. We believe that the solution matrix of the active site of cytochrome P-450 is best modeled by dipolar aprotic solvents such as acetonitrile.

This prompted an earlier study (7), in which we demonstrated that the combination of  $\text{Fe}^{\text{III}}\text{Cl}_3$  and  $\text{H}_2\text{O}_2$  in dry acetonitrile (MeCN) efficiently epoxidizes olefins and monooxygenates alkanes, alcohols, ethers, aldehydes, thioethers, and sulfoxides. We now report that  $\text{Fe}^{\text{III}}\text{Cl}_3$  catalyzes  $\text{H}_2\text{O}_2$  to epoxidize olefins, to demethylate *N,N*-dimethylaniline ( $\text{PhNMe}_2$ ), and to cleave  $\alpha$ -diols to give aldehydes. These substrate conversions are analogous to those catalyzed by cytochrome P-450. A mechanism is proposed in which an initial Lewis-acid-induced activation of  $\text{H}_2\text{O}_2$  by  $\text{Fe}^{\text{III}}\text{Cl}_3$  occurs to form an electrophilic  $\text{Fe}(\text{III})$ -oxene reactive intermediate.

## MATERIALS AND METHODS

Burdick and Jackson "distilled in glass" acetonitrile (0.004%  $\text{H}_2\text{O}$ ) was dried by passage through a column of Woelm N Super I alumina. Anhydrous  $\text{Fe}^{\text{III}}\text{Cl}_3$  (Aldrich) was used as received. Pure  $\text{H}_2\text{O}_2$  (assay 98%) was prepared from 50% (wt/wt)  $\text{H}_2\text{O}_2$  (J. T. Baker Chemical, Phillipsburg, NJ). Careful removal of water from 10 ml of 50%  $\text{H}_2\text{O}_2$  at  $0^\circ\text{C}$  under high vacuum gave 2.5–3 ml of pure hydrogen peroxide. This was quickly dissolved in dry acetonitrile (25 ml) to make an approximately 1 M solution, which was assayed by permanganate titration (the presence of acetonitrile did not interfere). The acetonitrile solution of  $\text{H}_2\text{O}_2$  was stable at  $0^\circ\text{C}$ ; its assay did not change over a period of 1 month. Other reagents and substrates were analytical grade or highest purity available and were used without further purification.

**Hazard Warning!** Pure  $\text{H}_2\text{O}_2$  is an exceptional oxidant. Trace quantities of reduced transition metals can initiate its

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Abbreviations: Por, porphyrin; NHE, normal hydrogen electrode.  
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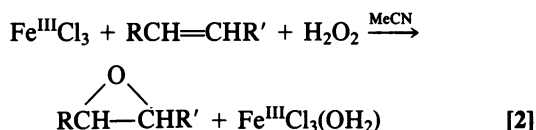
violent decomposition and oxidation of organic materials. Exercise extreme care, use adequate safety protection, and work with small quantities during the course of its purification, storage, and use.

In a typical experiment, 0.1 mmol of  $\text{Fe}^{\text{III}}\text{Cl}_3$  (1 M in  $\text{CH}_3\text{CN}$ ) was added slowly over 1 min to a mixture of 1.0 mmol of substrate and 3.0 mmol of  $\text{H}_2\text{O}_2$  [1 M  $\text{H}_2\text{O}_2$  (98%) in  $\text{MeCN}$ ]. The reaction mixture was held at  $-10^\circ\text{C}$  with stirring for various reaction times, after which the product solution was added to 50 ml of  $\text{NaCl}$ -saturated  $\text{H}_2\text{O}$ . This was then extracted with 20 ml of diethyl ether and the latter was analyzed by use of capillary gas chromatography, GC-MS, and HPLC.

## RESULTS

Table 1 summarizes the reactivities and products from the slow addition of  $\text{Fe}^{\text{III}}\text{Cl}_3$  to a binary mixture of  $\text{H}_2\text{O}_2$  and *N,N*-dimethylaniline, an olefin, or a 1,2-diol in dry acetonitrile. (Under the reaction conditions all substrates were unreactive in the presence of either  $\text{Fe}^{\text{III}}\text{Cl}_3$  or  $\text{H}_2\text{O}_2$  alone.) The oxidation state of the  $\text{Fe}^{\text{III}}\text{Cl}_3$  catalyst is conserved in all the experiments on the basis of electrochemical measurements [in dry acetonitrile the characteristic reduction potential for the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{Fe}^{\text{II}}\text{Cl}_3$  couple is +0.46 V vs. the normal hydrogen electrode (NHE)] and redox titrations, prior to and after each experiment. In the absence of substrate, the combination of  $\text{Fe}^{\text{III}}\text{Cl}_3$  with  $\text{H}_2\text{O}_2$  results in its rapid conversion to  $\text{O}_2$  and  $\text{H}_2\text{O}$ .

As with cytochrome P-450, the  $\text{Fe}^{\text{III}}\text{Cl}_3$  system catalyzes  $\text{H}_2\text{O}_2$  to epoxidize olefins.

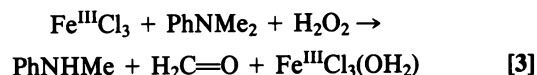


The conversion of norbornene is stereospecific to the *exo*-epoxide. For *cis*-stilbene, the *cis*-to-*trans* epoxide ratio is 2:1, but when the  $\text{H}_2\text{O}_2$ -to-substrate ratio is increased to 6:1, the *cis*-to-*trans* epoxide ratio increases to 4:1. Substitution of  $[\text{Fe}^{\text{III}}(\text{H}_2\text{O})_6](\text{ClO}_4)_3$  for  $\text{Fe}^{\text{III}}\text{Cl}_3$  decreases the overall conversion efficiency for *cis*-stilbene by a factor of 9 and yields no epoxide ( $\text{PhCHO}$  is the major product). Addition of one equivalent of tetrabutylammonium chloride ( $\text{Bu}_4\text{NCl}$ ) to the *cis*-stilbene/ $\text{H}_2\text{O}_2$  mixture prior to  $\text{Fe}^{\text{III}}\text{Cl}_3$  addition results in a decrease in conversion efficiency by a factor of 3. [Addition of one equivalent of  $\text{Bu}_4\text{NCl}$  to a solution of  $\text{Fe}^{\text{III}}\text{Cl}_3$  causes its reduction potential to shift from +0.46 V

( $\text{Fe}^{\text{III}}\text{Cl}_3/\text{Fe}^{\text{II}}\text{Cl}_3$ ) to +0.34 V vs. NHE (characteristic of the  $\text{Fe}^{\text{III}}\text{Cl}_4^-/\text{Fe}^{\text{II}}\text{Cl}_3^- + \text{Cl}^-$  couple).]

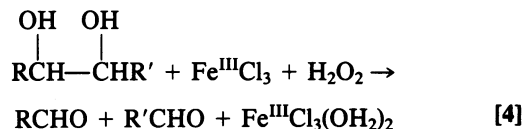
Substitution of *m*-chloroperbenzoic acid in place of  $\text{H}_2\text{O}_2$  results in the analogous epoxide products. Careful competition experiments in the presence and absence of  $\text{Fe}^{\text{III}}\text{Cl}_3$  have demonstrated that it accelerates the epoxidation process. Attempts to utilize iodosylbenzene and pentafluoroiodosylbenzene with  $\text{Fe}^{\text{III}}\text{Cl}_3$  produced a wide variety of products. Many of these derived from the attack on substrate by chlorine atoms, presumably from the direct oxidation of chloride ion by iodosylbenzene. However, catalytic olefin epoxidations have been observed in acetonitrile through the use of iodosylbenzene in conjunction with simple non-chloride-ligated iron(III) salts (8).

In a manner that parallels cytochrome P-450, the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{H}_2\text{O}_2/\text{MeCN}$  system demethylates *N,N*-dimethylaniline to form *N*-methylaniline and formaldehyde (Eq. 3).



The same reactivity has been observed by use of an Fe(III) porphyrin/iodosylbenzene system and has been rationalized in terms of an "oxygen rebound" mechanism (9). For the latter an initial formation of an  $\text{Fe}^{\text{IV}}$ -oxo porphyrin cation radical has been proposed, which abstracts a hydrogen atom from the methyl group of *N,N*-dimethylaniline to generate the *N*-methylene radical and a "crypto-hydroxyl" metal center. These recombine to form the observed products and regenerate the Fe(III) porphyrin center.

Finally, the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{H}_2\text{O}_2/\text{MeCN}$  system also oxidatively cleaves 1,2-diols.



The efficient oxidative cleavage of both  $\text{PhCH}(\text{OH})\text{CH}_2\text{OH}$  and  $\text{PhCMe}(\text{OH})\text{CMe}(\text{OH})\text{Ph}$  by the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{H}_2\text{O}_2/\text{MeCN}$  system (Table 1) closely parallels the results from a recent study (10) in which  $\text{Cr}^{\text{III}}\text{Ph}_4\text{PorCl}$  was used as the cytochrome-P-450 model, 4-CNPhNMe<sub>2</sub>O as the O atom transfer agent, and  $\text{PhCH}(\text{OH})\text{CH}_2\text{OH}$  as the model substrate for cholesterol side-chain cleavage.

## DISCUSSION

Preliminary kinetic studies have demonstrated that the reaction of the  $\text{Fe}^{\text{III}}\text{Cl}_3/\text{H}_2\text{O}_2$  system with substrate is first order

Table 1. Products and conversion efficiencies for the  $\text{Fe}^{\text{III}}\text{Cl}_3$ -catalyzed epoxidation of olefins, demethylation of  $\text{PhNMe}_2$ , and oxidative cleavage of 1,2-diols by  $\text{H}_2\text{O}_2$  in dry acetonitrile

Substrate (RH)	Reaction time, min	Reaction conversion efficiency, %*	Catalyst turnover number†	Products (yield)
<b>Olefins</b>				
Norbornene	10	52	5	<i>exo</i> -Epoxide (80%), other nonepoxide products (20%)
Cyclohexene	30	37	4	Epoxide (64%), dicyclohexyldioxane (13%)
1,4-Cyclohexadiene	20	39	4	Benzene (76%), epoxide (17%)
<i>cis</i> -Stilbene	20	63	6	$\text{PhCHO}$ (50%), epoxides (50%) ( <i>cis</i> -to- <i>trans</i> epoxide ratio, 2.5:1)
<b>Dimethylaniline</b>				
$\text{PhNMe}_2$	20	39	4	$\text{PhNHMe}$ (95%), $\text{PhN}(\text{CHO})\text{Me}$ (5%)
<b>1,2-Diols</b>				
$\text{PhCH}(\text{OH})\text{CH}_2\text{OH}$	30	43	4	$[\text{PhCHO} + \text{CH}_2\text{O}]$ (66%),‡ $\text{PhC}(\text{O})\text{CHO}$ (19%), $[\text{PhCH}(\text{OH})\text{CHO} + \text{PhC}(\text{O})\text{CH}_2\text{OH}]$ (15%)
$\text{PhCMe}(\text{OH})\text{CMe}(\text{OH})\text{Ph}$	30	30	3	$\text{PhC}(\text{O})\text{Me}$ (100%)

\*Percentage of substrate converted to products.

†Millimoles of RH converted per mmol of  $\text{Fe}^{\text{III}}\text{Cl}_3$  added.

‡For the reaction conditions  $\text{PhCHO}$  was inert.

