HYDROXYLATION AND EPOXIDATION REACTIONS CATALYZED BY SYNTHETIC METALLOPORPHYRINATES: MODELS RELATED TO THE ACTIVE OXYGEN SPECIES OF CYTOCHROME P-450

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Summary

Iodosylbenzene has been found to react with catalytic amounts of synthetic metalloporphyrinates to give epoxides and alcohols from olefins and alkanes. Tetraphenylporphinatoiron(III) chloride (TPPFeCl) catalyzed the epoxidation of cis-stilbene to cis-stilbene oxide whereas the *trans* isomer was unreactive. Dioctyl protoporphyrin IX reacted with iodosylbenzene to give significant oxidation of the side chain alkyl groups. The distribution of products is interpreted to be the result of an intramolecular oxygen transfer reaction.

Treatment of tetra-ortho-tolylporphinatoiron(III) chloride (TTPFeCl) with iodosylbenzene afforded a reactive intermediate which degraded the porphyrin in the absence of an oxidizable substrate. Similar oxidation of tetraphenylporphinatochromium(III) chloride with iodosylbenzene gave a stable intermediate which has been characterized as an oxochromium(V) complex.

Introduction

The activation of molecular oxygen by the biological oxygenases has attracted attention because of the high selectivity commonly observed in these enzymic reactions and the mild conditions under which the transformations occur. Cytochrome P-450, the heme-containing monooxygenase responsible for drug detoxification and steroid hydroxylation [1], is particularly interesting in this regard because much is known regarding the details of the catalytic cycle [2].

As outlined in Scheme I, the resting state of cytochrome P-450 is the Fe^{3+} state [3]. Binding of a substrate molecule and reduction of iron leads

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to an Fe^{2+}-substrate complex which binds molecular oxygen in a manner similar to hemoglobin [4]. Subsequent steps in the cycle involve a second, one-electron reduction to give what would be equivalent to an Fe^{3+}-peroxo complex. The details of the later stages of oxygen activation and transfer have been presumed to involve O–O bond cleavage and the generation of a transient iron–oxo [5] intermediate, formally iron(V) [2a]. This complex could react with hydrocarbons in a manner reminiscent of reactions of chromate and permanganate to give epoxides and alcohols [6].

Scheme 1
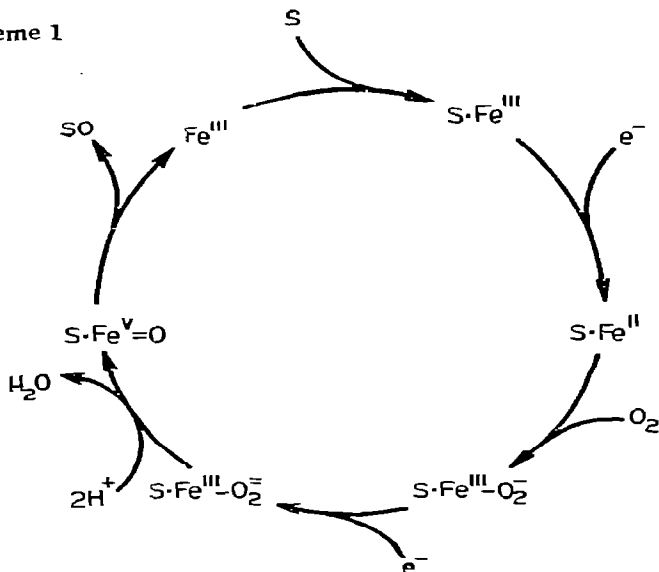
One difficulty with this mechanism is the lack of a simple chemical precedent for the formation of an oxometalloporphyrinate by such a peroxy bond heterolysis and the lack of any information regarding the chemistry of such species (eqn. (1)) [7, 8].

(1)
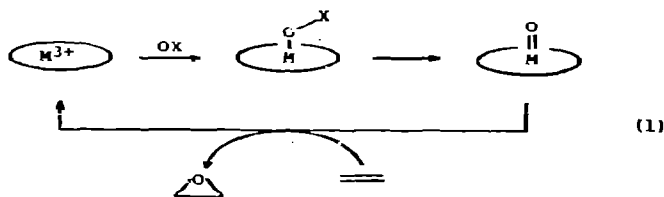
Recently, we reported that just such a reaction occurred in the reaction of iodosylbenzene with hydrocarbons in the presence of tetraphenyl-porphinatoiron(III) chloride (TPPFeCl) [9]. Under these conditions olefins were epoxidized in good yield and alkanes were hydroxylated to give alcohols (Table 1).

TABLE 1

Hydrocarbon oxidation with TPPFeCl and iodosylbenzene

Substrate	Products	Yield (%)*
		55
	OH	15
		74
		82
	No reaction	—
	OH	8
adamantane	1-adamantanol	12
	2-adamantanol	1

*Yields based on iodosylbenzene consumed. Preliminary results indicate that the lower yields with the less reactive hydrocarbons were due to competing destruction of the catalyst.

This reaction showed an unusual specificity for *cis*-olefins. Thus, a mixture of *cis*- and *trans*-stilbene afforded an 82% yield of *cis*-stilbene oxide while the *trans*-stilbene was recovered unreacted. Similarly, *cis*-2-butene was found to be six times more reactive than *trans*-2-butene. *Cis,trans,trans*-cyclododecatriene, which can be formed in large quantities by the cyclo-trimerization of butadiene [10], is also readily epoxidized by iodosyl benzene/TPPFeCl. The 2:1 mixture of *trans*- and *cis*-epoxide indicates that the two types of double bonds are of about equal reactivity. This result contrasts markedly with the reaction of *cis,trans,trans*-cyclododecatriene with reagents such as *m*-chloroperoxybenzoic acid which gives 98% *trans*-epoxide [11].

The origin of this unusual selectivity is unclear at this time but is clearly related to the steric environment of the porphyrin. If tetra-*o*-tolylporphinato-iron(III) chloride (TTPFeCl) is used instead of TPPFeCl in this reaction with *cis,trans,trans*-cyclododecatriene, the ratio of *cis*- to *trans*-epoxide is 1.3:1 [12]. A reasonable explanation of this effect is that the oxygen transfer from

iodine to the double bond occurs at the metal center of the porphyrin and that the *trans*-olefins have difficulty approaching this site in a manner conducive to oxygen transfer. One likely geometry is indicated in **1**.

1
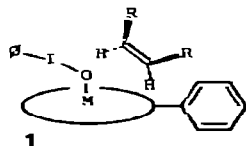
Another indication that the active oxygen in this reaction is derived from the locus of the iron in the catalyst was the distribution of oxidation products obtained from the reaction of chlorodioctylprotoporphyrin(IX) (**2**) with iodosyl benzene.

Cleavage of the side chain octyl groups and analysis of the products indicated that a family of octane diols had been produced in significant yield (Table 2). The distribution of these isomers indicated that nearly 60% of the new hydroxyl groups had been incorporated into the middle of the octyl chain at carbons 4 and 5. A similar oxidation of octyl acetate showed no such specificity. Molecular models indicate that an intramolecular reaction of the octyl side chain with oxygen bound at the iron would readily explain this selectivity (Scheme II).

TABLE 2

Intermolecular *vs.* intramolecular oxidation of octyl esters

	Octanediol isomers					
	1,2	1,3	1,4	1,5	1,6	1,7
Octyl acetate	<2	17	15	21	22	24
2	<2	15	28	30	13	14

Scheme 2
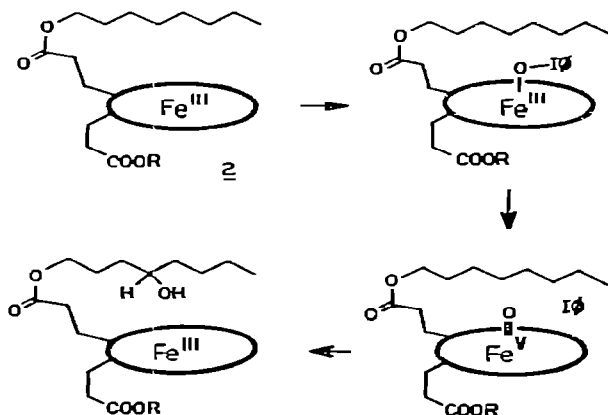
Iodosyl benzene and its derivatives have been shown to be effective substitutes for oxygen and NADPH in the oxidation reactions catalyzed by cytochrome P-450 [13]. It was therefore of interest to explore whether this reaction could provide a route to reactive oxo-metalloporphyrin intermediates.

Results

Treatment of TPPFeCl or TTPFeCl with iodosyl benzene was found to lead rapidly to a spectral intermediate (3) [14, 15]. In the absence of a substrate the Soret band of 3 diminished in a few minutes indicating degradation of the porphyrin (Fig. 1). In the presence of cis-stilbene, however, the
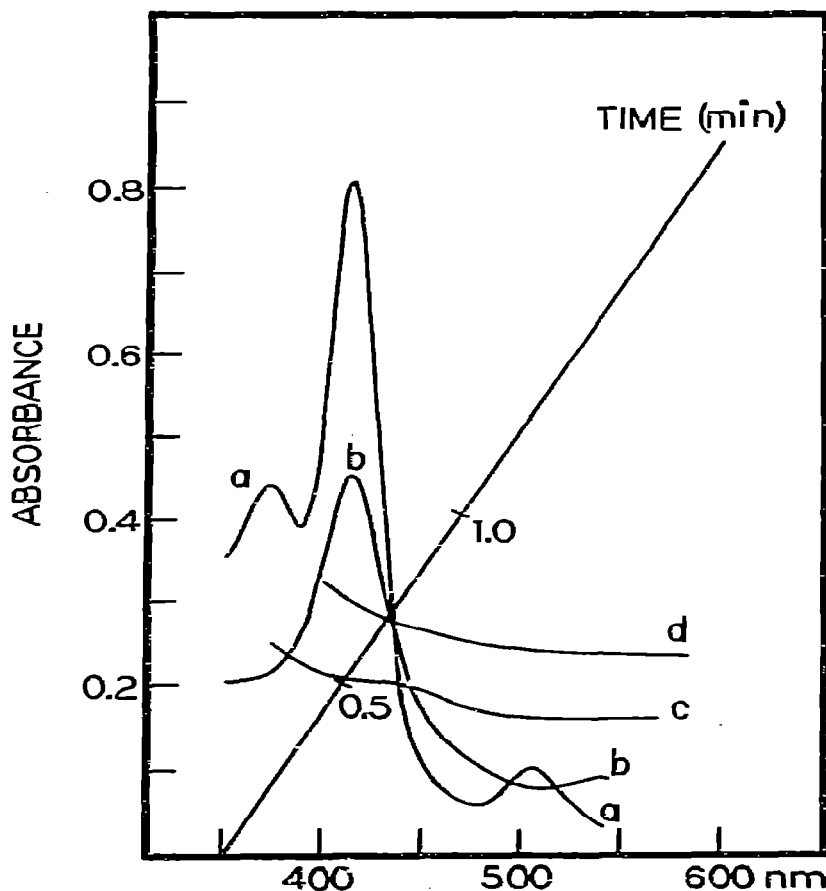

Fig. 1. Visible spectrum of TTPFe(III)Cl and iodosylbenzene in methylene chloride; scan a, time = 0; scan b, time = 13 s; scan c, time = 25 s; scan d, time = 35 s.

spectrum of the intermediate decayed with time back to the spectrum of the starting catalyst, and analysis of the reaction mixture revealed the presence of *cis*-stilbene oxide. It is apparent that the catalyst is protected from self-oxidation by the presence of the substrate.

While the structure of this intermediate is not yet clear, two possibilities are an iodosyl benzene complex of the iron(III)–porphyrin (4) and an iron–oxo intermediate equivalent to iron(V) (5).

Tetraphenylporphinatochromium(III) chloride (TPPCrCl) also has been found to catalyze the epoxidation and hydroxylation of simple olefins as well as the oxidation of alcohols to ketones [16] (Table 3). Treatment of

TABLE 3

Oxidations catalyzed by Cr(III)TPPCl–iodosylbenzene

Substrate	Products	Yield (%)*
		66
		99**
		65
		23
		17
		28
$\phi\text{-CH}_2\text{OH}$	$\phi\text{-CHO}$	56

*Yields are based on iodosylbenzene. No other organic products were produced.
**Contained 3% endo-epoxide.

TPPCrCl with one equivalent of iodosyl benzene in methylene chloride gave a red intermediate (6) which was stable at room temperature for several hours. Treatment of this intermediate with excess cyclohexanol caused the regeneration of TPPCrCl and oxidation of the alcohol to cyclohexanone. Similarly, addition of norbornylene to solutions of 6 gave norbornylene oxide in 99% yield.

The infrared spectrum of 6 determined in methylene chloride showed a band at $1\,026\ cm^{-1}$ which shifted to $982\ cm^{-1}$ when iodosyl benzene–^{18}O was used to generate 6. This band has been assigned to a Cr=O stretching frequency in 6 [17]. Also apparent in this spectrum were sharp bands at $1\,018$ and $999\ cm^{-1}$ which are characteristic of iodobenzene.

The red intermediate, 6, could also be generated by the reaction of TPPCrCl with m-chlorobenzoic acid at $-78\ ^\circ C$ or by the reaction of sodium hypochlorite at room temperature. The visible spectra of TPPCrCl and 6 are compared in Fig. 2.

Magnetic susceptibility data for 6 obtained by the Evans method [18] indicated a value of 2.05 BM, close to the spin only magnetic susceptibility of 1.73 BM expected for a chromium(V) complex. Decomposition of 6 with cyclohexanol caused the magnetic susceptibility to increase to 3.8 BM, consistent with the regeneration of TPPCrCl.

The red intermediate 6 was found to exchange its oxo ligand with water. Addition of $H_2{}^{18}O$ (95% ^{18}O) to a methylene chloride solution of 6 at room temperature caused the disappearance of the Cr=^{O} band at $1\,026\ cm^{-1}$ and the appearance of a Cr=^{18}O band at $982\ cm^{-1}$. Addition of
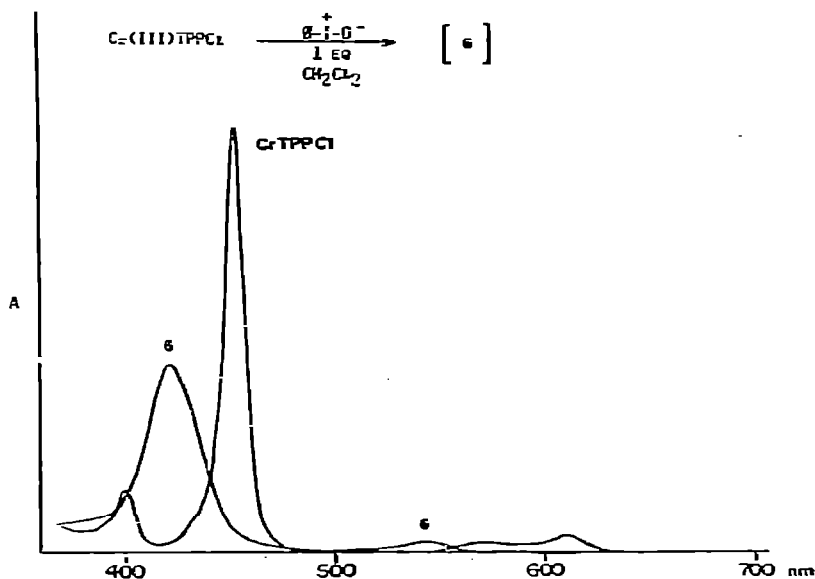

Fig. 2. Visible spectra of Cr(III)TPPCl and 6.

norbornylene to this exchanged solution of $6-{}^{18}O$ led to the production of norbornylene oxide with 94% incorporation of ^{18}O into the epoxy oxygen.

Taken together, the results favor a two-electron oxidation of the TPPCrCl by iodosyl benzene with discrete oxygen transfer from iodine to chromium. The resulting oxochromium(V) intermediate (6) can exchange its oxo-ligand with added water or react with olefins to produce epoxides and alcohols (Scheme 3).

Scheme 3
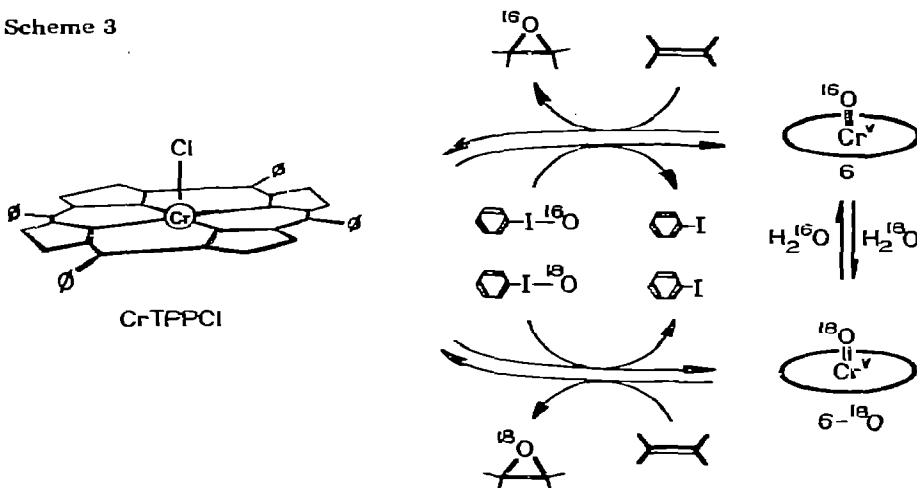
Although other oxo-metalloporphyrin species have been characterized [19], these results present the first indication that such a species can be formed by the reaction of peroxides or peroxide mimics such as iodosyl benzene. Further, the results indicate that such a species is competent to carry out the hydrocarbon oxidations characteristic of cytochrome P-450.

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