

Communications to the Editor

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OXYGEN ACTIVATION AND OLEFIN OXYGENATION
BY IRON(III)PORPHYRIN AS A MODEL OF CYTOCHROME P-450¹⁾

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Tetraphenylporphinatoiron(III) catalyzed the reductive activation of molecular oxygen in the presence of NaBH_4 and Me_4NOH . Several olefins were oxidized with this system and oxidized products were isolated in high yields.

KEYWORDS — olefin; oxidation; tetraphenylporphinatoiron(III); cytochrome P-450 model reaction; reductive oxygen activation; sodium borohydride; tetramethylammonium hydroxide






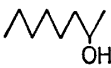






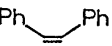




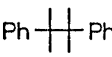


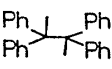


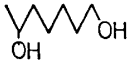
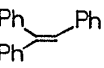




Cytochrome P-450 oxidizes a wide variety of xenobiotics by the reductive activation of the molecular oxygen on its iron porphyrin site. Although many model reactions of this enzyme have been reported, using previously activated oxygen sources such as iodosobenzene or alkylhydroperoxide, only a few reactions involving reductive activation of molecular oxygen with iron porphyrin have been achieved.²⁾ This is mainly because reduced iron porphyrin rapidly reacts with molecular oxygen to form the stable and inactive μ -oxo dimer. We now report a cytochrome P-450 type oxygenation of olefins using iron porphyrin, O_2 , and NaBH_4 in the presence of Me_4NOH . In this system, formation of the μ -oxo dimer was suppressed and oxidized products were isolated in high yields.

In a typical experiment, the substrate olefin (2.0 or 3.0 mmol) and a catalytic amount of tetraphenylporphinatoiron(III) chloride ($\text{Fe}^{\text{III}}\text{TPPCl}$ 0.005 mmol) were dissolved in a mixed solvent (benzene:methanol=4:5) containing Me_4NOH (1.0 mmol). The mixture was stirred in air at room temperature in the presence of an excess of NaBH_4 (200 mg). Under these conditions, the reaction proceeded with no induction period. After completion of the reaction, products were isolated by silica gel column chromatography, and their structures were determined by analysis of the ^1H -NMR and IR spectra (Table I).

Since reaction products were not detectable in the absence of $\text{Fe}^{\text{III}}\text{TPPCl}$, NaBH_4 or O_2 , these three components were essential for the progress of the reaction. The very large turnover number (528 with styrene as a substrate) showed that $\text{Fe}^{\text{III}}\text{TPPCl}$ acted as an effective catalyst in this system, while FeCl_3 had no catalytic activity.

The effect of adding Me_4NOH in this system was critical. Without Me_4NOH ,

Table I. Oxidation of Several Olefins in the FeTPPCl - O₂ - NaBH₄ - Me₄NOH System

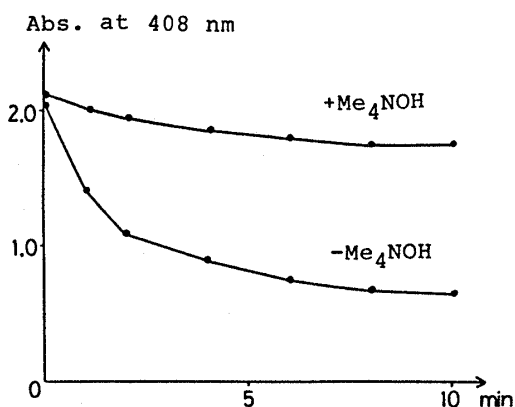
Substrate	Product
1 	 88 %
2 	 67 %
3 	 66 %
4 	 61 %  15 %
5 	 7.5 %  45 %
6 	 22 %  40 %
7 	 40 %  41 %
8 	 33 %  42 %
9 	 38 %  4.4 %
10 	 65 %  60 %
11 	 78 %

Conditions: FeTPPCl, 0.005 mmol; substrate, 2.0 or 3.0mmol; NaBH₄, 200 mg; solvent, benzene:methanol:10% Me₄NOH in MeOH=4:4:1 (9.0 ml); room temperature in the presence of air, overnight. Yields are based on substrates.

rapid decomposition of the catalyst took place (Fig. 1), and the product yield was poor.³⁾ Furthermore, the VIS spectrum (Fig. 2,b), which was obtained by adding Me₄NOH to a solution of Fe^{III}TPPCl, was converted to the characteristic spectrum of Fe^{II}TPP by reduction with NaBH₄ under an argon atmosphere (Fig. 2,c). Application of O₂ to the solution resulted in recovery of the initial spectrum (Fig. 2,d), not conversion to that of the μ -oxo dimer. This result also indicates that Fe^{II}TPP acts as a catalyst.

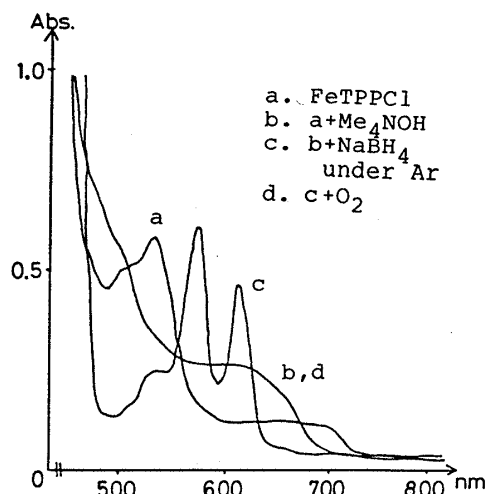
Epoxides were not detected among the expected products, though styrene oxide or cyclohexene oxide was hardly reduced to corresponding alcohol in this system. When the amount of NaBH₄ was decreased, acetophenone was detected by GLC among the oxidation products of styrene.⁴⁾ These results indicate that the alcohols are probably formed not through epoxides but via ketones. Recently, Lieber and Guengerich reported that hydrogen atom migration and formation of carbonyl products could occur in the catalytic cycle of olefin oxidation by cytochrome P-450.⁵⁾ In this model system,

Fig. 1. Time Course of the Decomposition of FeTPP in the Presence or Absence of Me_4NOH



Conditions: $\text{FeTPP}\cdot\text{Cl}$, 1.5×10^{-5} M;
solvent, benzene:methanol=3:7 (10 ml);
 NaBH_4 , 5.0 mg, styrene, 100 mg.

Fig. 2. VIS Spectra of FeTPP



Conditions: $\text{FeTPP}\cdot\text{Cl}$, 0.5×10^{-4} M
solvent, benzene:methanol=1:1.

hydrogen atom migration was proved by using NaBD_4 in a deuterated solvent (CH_3OD).⁶⁾ The active oxidizing species⁷⁾ (Scheme 1,(1)) reacts with olefin to form a reactive intermediate (Chart 1,(2)), and then nucleophilic attack by deuteride may occur to produce alcohol directly (path A), or hydrogen atom migration may occur to produce the carbonyl compound followed by the reduction with NaBD_4 (path B); thus path B results in substitution by deuterium at the benzyl position. The formation of 1-phenylethanol⁸⁾ from styrene in the above system indicated that hydrogen atom migration (path B) occurred to the extent of 72% and deuterium attack (path A) to the extent of 28%⁹⁾ based on ^1H -NMR spectral measurement. Similarly, in the case of 1-phenyl-1-propanol, produced

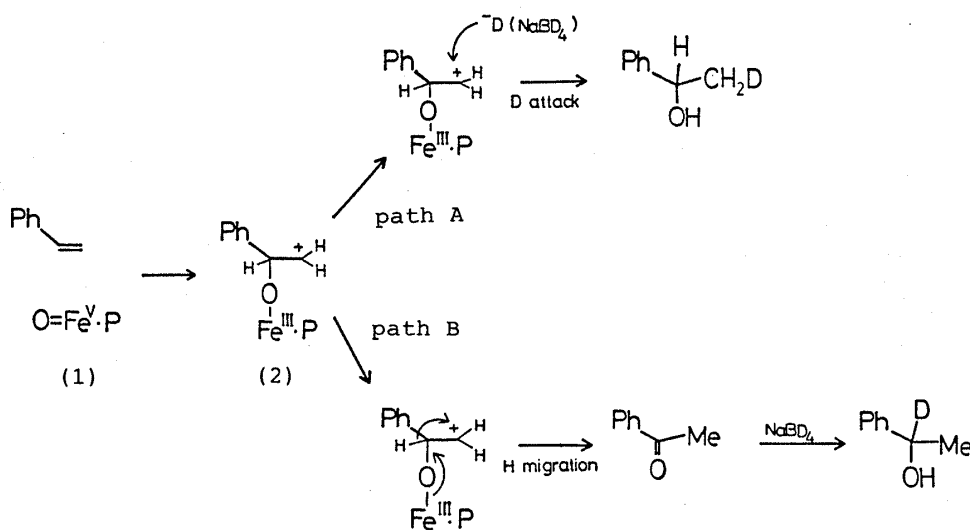


Chart 1

from (E)-1-phenylpropene, migration (path B) occurred to the extent of 50%. On the other hand, 2-phenylpropene has no migrating hydrogen, and indeed, only the deuterium attack (path A) was observed.¹⁰⁾ Thus, if there is a migrating hydrogen on the olefin, both path A and path B could occur in the alcohol formation.

Coupled products were also obtained from 1,1-disubstituted olefins (Table I, 7,8) and cleavage products from 2-substituted olefins (Table I, 4,5,6,9,10,11) in this model system. Detailed studies on the reaction mechanism of the formation of such products are in progress.

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REFERENCES AND NOTES

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- 2) Hydroxylation of aniline by a hemin-thiol-O₂ system was reported by H. Sakurai, *Chem. Pharm. Bull.*, 28, 3437, (1980). Similar cytochrome P-450 model reactions using MnTPP were reported. I. Tabushi and N. Koga, *J. Am. Chem. Soc.*, 101, 6456, (1979). I. Tabushi and A. Yazaki, *ibid.* 103, 7391, (1981). M. Perree-Fauvet and A. Gaudemer, *J. Chem. Soc., Chem. Commun.* 874 (1981). M. Fotecave and D. Mansuy, *Tetrahedron*, 40, 4297, (1984). Another system was based on rhodium porphyrin. Y. Aoyama, T. Watanabe, H. Onda and H. Ogoshi, *Tetrahedron Lett.*, 24, 1183, (1983).
- 3) The yield of 1-phenylethanol produced from styrene was only 11% under the same conditions as in Table I but without Me₄NOH.
- 4) GLC conditions: column, polyethylene glycol-6000 10% (2.6 mm X 2 m); inj. temp., 190°C; column temp., 170°C.
- 5) D. C. Lieber and F. P. Guengerich, *Biochemistry*, 22, 5482, (1983).
- 6) The Me₄NOH used was also converted to Me₄NOD previously.
- 7) Formally described as O=Fe^V.P which is postulated in the cytochrome P-450 system, though it was not characterized in this system.
- 8) The ratio of aromatic and benzyl protons was 5:0.28 (calculated from ¹H-NMR data), which indicated that the benzyl proton was 72% substituted by deuterium.
- 9) Oxidation of 1-phenylethanol to acetophenone did not take place, because the ratio of aromatic, benzyl, and methyl proton was unchanged during the reaction when 1-phenylethanol was used as the starting material.
- 10) The ratio of aromatic and methyl protons of 2-phenyl-2-propanol formed was 5:4.8 (approximately 5:5).

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