Communications to the Editor

Chem. Pharm. Bull.
32(3)1252—1255(1984)

OXIDATION OF TERTIARY AMINES AND SULFIDES BY AN IRON(III)PORPHYRIN-O_2-$Na_2S_2O_4$ SYSTEM AS A MODEL OF CYTOCHROME P-450[1,2]

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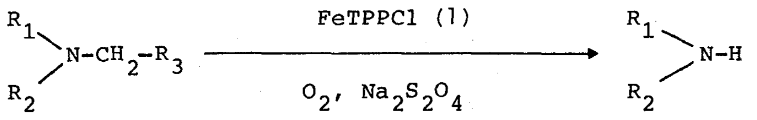
A novel cytochrome P-450 model system using iron(III)porphyrin, O_2 and $Na_2S_2O_4$ was studied. With this system, several tertiary amines and sulfides were oxidized to secondary amines and sulfoxides.

KEYWORDS——oxidation; tertiary amine; oxidative dealkylation; sulfide; sulfoxidation; tetraphenylporphynatoiron(III); cytochrome P-450 model reaction; reductive activation of molecular oxygen; sodium dithionite

An important characteristic of cytochrome P-450 is that it oxidizes a wide variety of xenobiotics in various types of reaction by the reductive activation of molecular oxygen on its iron porphyrin site. Although many leading model reactions, such as the Udenfriend system[4] (Fe^{II}/EDTA/ascorbic acid/O_2), the Viscontini system[5] (Fe^{II}/EDTA/tetrahydropteridine/O_2), etc., were reported more than twenty years ago, only a few reactions using iron porphyrin as a catalyst have been achieved.[6] This is mainly because, in the presence of molecular oxygen, reduced iron porphyrin readily reacts with another reduced iron porphyrin to form a stable and inactive μ-oxo dimer.[7] Therefore, it is important to inhibit the μ-oxo dimer formation when using iron porphyrin as a catalyst for the reductive activation of molecular oxygen. In this communication, we report a cytochrome P-450 type of oxidation of tertiary amines (eq 1) and sulfides (eq 2) using iron porphyrin, O_2 and $Na_2S_2O_4$ in a protic solvent, in which μ-oxo dimer formation is effectively suppressed and molecular oxygen is reductively activated.

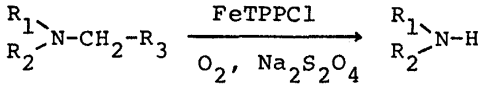


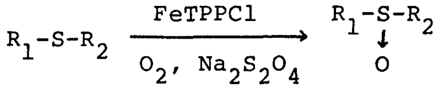
(eq 1)

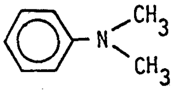
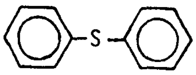
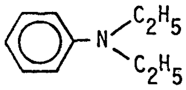
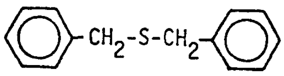
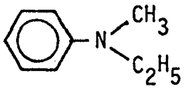
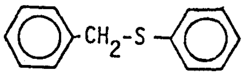
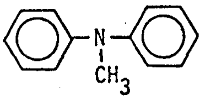
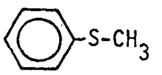
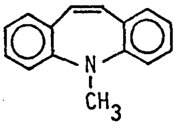
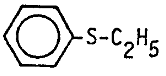
$$R_1-S-R_2 \xrightarrow[O_2,\ Na_2S_2O_4]{FeTPPCl\ (1)} R_1-\underset{\downarrow\atop O}{S}-R_2 \qquad \text{(eq 2)}$$

In a typical experiment, a substrate (amine or sulfide, 1.0 mmol) in 10 ml of a mixed solvent ($CH_2Cl_2:CH_3OH:H_2O=3:6:1$) containing 3% $(CH_3)_4NOH$[8] was vigorously stirred in the air at room temperature in the presence of a catalytic amount of α,β,γ,δ-tetraphenylporphynatoiron(III) chloride(FeTPPCl (1),0.01 mmol) and an excess

Table I. Oxidation of Tertiary Amines and Sulfides Using the FeTPPCl-O_2-$Na_2S_2O_4$ System





Substrate	Yield[a)] (%)	Substrate	Yield[a)] (%)
	800		600
	140		770
	430, 60[b)]		790
	210		600
	170		540

a) Yields are based on FeTPPCl.

b) Yields of N-ethylaniline and N-methylaniline, respectively.

amount of $Na_2S_2O_4$ (500 mg). Under these conditions, oxidation proceeded smoothly within 20 min with no induction period. Thus, tertiary amines were oxidatively dealkylated to secondary amines and organic sulfides were oxidized to sulfoxides. These oxidation products were identified by comparing their retention times in HPLC with those of the authentic compounds and the yields were also determined by HPLC analysis (Table I).

As no appreciable oxidation took place in the absence of FeTPPCl or $Na_2S_2O_4$, these two components are essential for the progress of the reaction. Under argon atmosphere, oxidation was completely depressed and the characteristic electronic absorption spectrum of Fe^{II}TPP (2) was observed. Subsequently, when O_2 was introduced to this solution, oxidation proceeded immediately and the spectrum was converted into that of FeTPPCl and not μ-oxo dimer ($(FeTPP)_2O$ (3)). These results indicate that O_2 was also essential for the progress of the reaction. As shown in Table II, FeTPPCl acted as an effective catalyst in this system, while $FeCl_3$ had no catalytic activity. The good turnover numbers of FeTPPCl are shown in Table II.

Of interest is a drastic effect of the reaction media. Oxidation proceeded only in a homogeneous protic solvent such as CH_2Cl_2-CH_3OH-H_2O (3:6:1), benzene-CH_3OH-H_2O (3:7:1) etc., but proceeded hardly at all in a bi-layer solvent such as CH_2Cl_2-H_2O and benzene-H_2O (bi-layer system), in which reduced porphyrin (2) was

Table II. Catalytic Effects of FeTPPCl in the Reductive Activation System of O_2

Substrate	Catalyst	$\frac{\text{Substrate}}{\text{Catalyst}}$	Turn over number of catalyst
N,N-Dimethylaniline,			
10 mM	FeTPPCl, 1.0 mM	10	2
100 mM	FeTPPCl, 1.0 mM	100	8
100 mM	FeTPPCl, 0.2 mM	500	24
100 mM	FeTPPCl, 0.05 mM	2000	56
100 mM	$FeCl_3$, 1.0 mM	100	0.1 >
Diphenyl sulfide,			
20 mM	FeTPPCl, 1.0 mM	20	2.8
100 mM	FeTPPCl, 1.0 mM	100	6
100 mM	FeTPPCl, 0.2 mM	500	17
250 mM	FeTPPCl, 0.1 mM	2500	39
100 mM	$FeCl_3$, 1.0 mM	100	0.1 >

readily converted into μ-oxo dimer (3) via the bi-nuclear oxidation process (Chart 1, path a). As to the decomposition of the reduced porphyrin-O_2 complex (4), it has already been revealed that μ-oxo dimer formation is markedly depressed in a protic solvent.[7] Therefore, it can be concluded that these solvent effects are closely related to the generation of an active oxidizing intermediate and the subsequent oxidation of substrates (Chart 1, path b). Since no characteristic absorption spectrum of an active intermediate was observed, it seems that the active oxidizing species which formed in this reaction system had a short lifetime and a high reactivity.

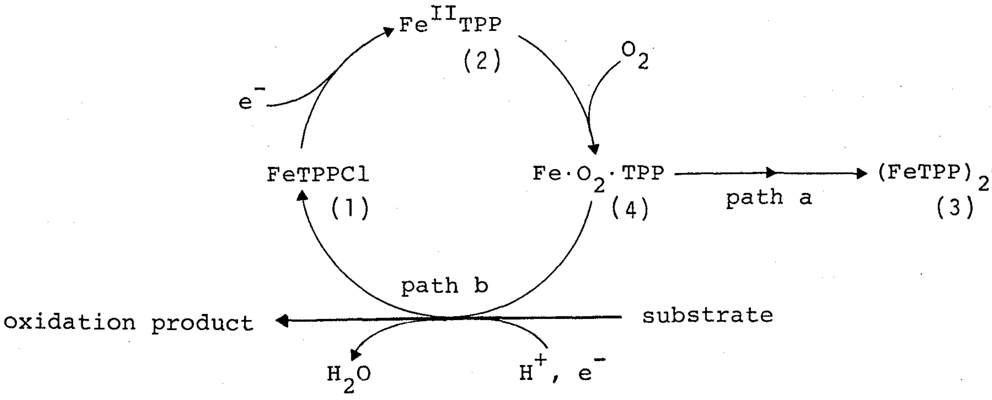


Chart 1

In a preliminary experiment, the reactivities of several *p*-substituted N,N-dimethylanilines and *p*-substituted phenylmethylsulfides were effectively influenced by the electronic effects of the substituents and the order of the relative oxidation rates was in accord with the electron donating effects of the substituents.[9] These results suggest that the present oxidizing species is electrophilic. As the methyl group was readily eliminated rather than the ethyl group in the dealkylation of tertiary amines (see Table I), it appears that the more acidic hydrogen atom of the N-alkyl groups is dissociated as proton in this oxidation. These tendencies resemble those of the other cytochrome P-450 type oxidations using iron porphyrin and oxidants such as iodoso aromatics10) and peroxides.11)

The identification of the active oxidizing species and further developments of this system are now in progress .

ACKNOWLEDGEMENT The present work was supported in part by a Grant-in Aid for Scientic Research from the Ministry of Education, Science and Culture, Japan, (# 57123114), which is gratefully acknowledged.

REFERENCES AND NOTES

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8) Oxidation also proceeded in the absence of $(CH_3)_4NOH$ but a small amount of base increased the yields.
9) The relative reactivities of *p*-substituted compounds towards the present system were estimated from a series of competition experiments. The order of oxidation rates ($k_{substituted}$) of *p*-substituted N,N-dimethylanilines is

$$k_{CH_3} > k_H > k_{Cl} > k_{NO_2}$$

and that of *p*-substituted phenyl methyl sulfides is

$$k_{CH_3O} > k_{CH_3} > k_H > k_{Cl}.$$

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(Received January 19, 1984)