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IMPORTANCE OF AXIAL LIGAND IN MESO-TETRAPHENYLPORPHINATOIRON(III) PROMOTED N-O AND O-O BONDS CLEAVAGES

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Abstract: Amines, especially imidazole, were found to be essential in the meso-tetraphenylporphinatoiron(III) promoted demethylation of N,N-dimethylaniline N-oxide through the Polonovski type reaction and in the cumene hydroperoxide dependent oxidative demethylation of N,N-dimethylaniline in dichloromethane. When benzenethiol was used instead of these amines, deoxygenation of N,N-dimethylaniline N-oxide took place very readily.

Earlier, Terayama reported that incubation of 4-dimethylaminoazobenzene N-oxide with myoglobin or hemin afforded a mixture of N-demethylated and deoxygenated products.[1] Meanwhile, Ziegler et al. found that a hepatic microsomal hemoprotein catalyzes the demethylation of N,N-dimethylaniline N-oxide (DMAO).[2] Actually the purified liver microsomal cytochrome P-450 catalyzes the demethylation of DMAO.[3,4] Recently, the reaction of DMAO with metalloporphyrins have been proposed to be good models of cytochrome P-450 reaction.[3,5,6] We have shown that the meso-tetraphenylporphinatoiron(III) chloride ($TPPFe^{III}Cl$) promoted oxygenation of sulfides in which imidazole is an essential component.[7] This paper deals with that amines, especially imidazole, play an essential role in the $TPPFe^{III}$ promoted cleavage of N-O bond in DMAO and that of O-O bond of cumene hydroperoxide.

When DMAO was treated with $TPPFe^{III}Cl$ in dichloromethane at room temperature, no measurable reaction took place. In the presence of imidazole, however, the reaction proceeded readily at room temperature eventually affording a mixture of demethylated product, N-methylaniline (NMA), and deoxygenated product, N,N-dimethylaniline (DMA)(Eq. 1). When the reaction mixture was analyzed by high pressure liquid chromatograph (HPLC) equipped with YANACO GEL 1 m column monitoring by UV at 245 nm, three peaks appeared, while gas chromatography (GC) of the same reaction mixture gave only two peaks due to NMA (peak A) and DMA (peak C)(Fig. 1). After treating the reaction mixture with hydrazine, the unknown peak B on HPLC chart disappeared, while the height of peak A (NMA) increased. These observations may suggest that the unknown peak, B, on the HPLC chart is due to N-hydroxymethyl-N-methylaniline, which was postulated as an intermediate of the enzymatic oxidative demethylation of DMA by Ziegler et al.[8]

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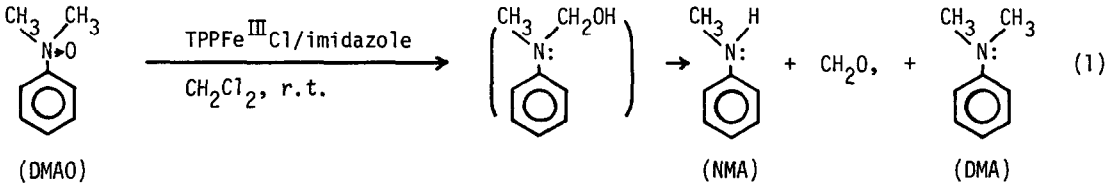


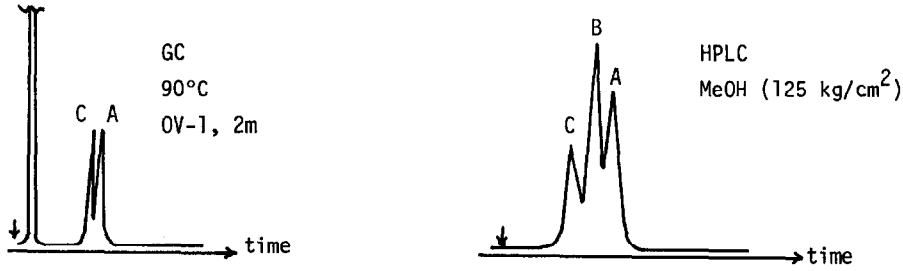


Fig. 1. HPLC and GC Charts of the Reaction Mixture of DMAO with TPPFe^{III}Cl/imidazole.

Table 1 summarizes experimental results of the reaction of DMAO with TPPFe^{III}Cl/base under various conditions. Inspection of the data reveals that only catalytic amounts of TPPFe^{III} promotes the reaction quite efficiently. When the amount of imidazole was reduced to 20% of DMAO, no measurable retardation of the reaction was observed, indicating that imidazole also acts as a catalyst. The catalytic ability of the amine decreases in the order of imidazole > 1,4-diazabicyclo[2,2,2]octane(DABCO) > pyridine. This order is not consistent with that of the binding abilities of the bases to TPPFe^{III}Cl, i.e. DABCO > imidazole > pyridine, which is the order of their basicities.[9]

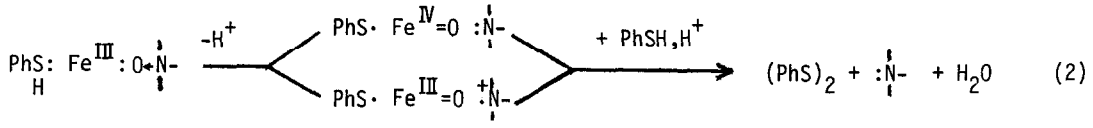
There are two conceivable roles of imidazole. First, imidazole activates the iron to initiate the N-O bond cleavage of DMAO as an axial ligand as has been observed in the catalytic activities of various hemoproteins, each of which has its own axial ligand controlling the reactivity of the heme for its specific role.[10,11] Similar activations with the axial ligand have been known for metal complex catalysts. Carter, Rillema and Basolo showed that the basicity of the axial ligand of N,N-ethylenebis(benzoylacetiminato)cobalt(II) determines the dioxygen binding ability of the cobalt(II) complex through controlling the oxidation potential of the cobalt(II).[12] Chin, Balch and LaMar found that N-methylimidazole adds to the peroxo-dimer of *meso*-tetra-m-tolylporphinatoiron(III) as the axial ligand and cleaves O-O bond to afford porphyrin ferryl FeO^{2+}- N-methylimidazole complex.[13] Recently, Powell, Pai and Bruice claimed that a halide ion is essential as the axial ligand of *meso*-tetraphenylporphinatomanganese(III) promoting the reaction of p-cyano-N,N-dimethylaniline N-oxide with olefins.[5c] Second, imidazole also acts as a base to abstract a proton from N,N-dimethylanilinium cation radical formed in the reaction.[14]

The fifth ligand of the heme involved in cytochrome P-450 is known to be thiol of the cysteine residue of the apoprotein.[11] In order to simulate cytochrome P-450 promoted demethylation of DMAO, thiophenol was added to the mixture of TPPFe^{III}Cl and DMAO in dichloro-

Table I. Products of $TPPFe^{III}$ Promoted Reactions of N,N-Dimethylaniline N-Oxide[a)]

$[DMAO]_0$	$[TPPFe^{III}Cl]_0$	$[Base]_0$	Reaction time	NMA	DMA
40 mM	4 mM	0 mM	60 min	0 %	0 %
40	4	40 (imidazole)	15	50	42
40	4	20 (")	15	39	42
40	4	4 (")	15	30	37
40	4	0.8(")	15	54	31
40	0.4	4 (")	15	59	37
40	4	40 (pyridine)	60[b)]	39	21
40	4	40 (DABCO)	30[b)]	28	16
5	0.5	10 (benzenethiol)	1	0	100

a) Reactions were carried out in CH_2Cl_2 at 25°C in the dark. b) Starting DMAO still remains.



(2)

methane. Then the reaction was found to be completed within a minite to afford DMA and diphenyl disulfide quantitatively, but no NMA was detected (bottom row of Table I). This observation suggests that thiophenol is quite potent ligand to initiate N-O bond fission of DMAO bound to the iron; however, the reaction gives only the deoxygenation product probably through either pathway in Eq. 2. One essential difference between cytochrome P-450 and $TPPFe^{III}$/PhSH system is as follows. Since the thiol group which is the fifth ligand to the heme is fixed at the correct position in the active site of the enzyme and protected by surrounding apoenzyme, it cannot interact directly each other. In the model system, however, the thiol group is naked and can react with the second thiol to promote the reaction in Eq. 2 eventually giving the disulfide. Only when electrons are supplied from cytochrome P-450 reductase, cytochrome P-450 is known to catalyze exclusively the deoxygenation of DMAO[15)]

On the other hand, cytochrome P-450 and horse radish peroxidase are known to catalyze peroxide dependent oxidative dealkylation of amines.[16)] In order to mimic the reaction, DMA was treated with cumene hydroperoxide in the presence of $TPPFe^{III}Cl$ in dichloromethane, no demethylation took place. However, when imidazole was added to the mixture, demethylation of DMA started immediately at room temperature. The result of the control experiment shown in the top row of Table II reveals that cumene hydroperoxide does not oxidize DMA to give DMAO under the condition of the reaction of Eq. 3. Consequently, the oxidative demethylation of DMA does not take place via the reaction of DMAO which is formed by the oxidation with the hydroperoxide but proceeds via the direct oxidation of DMA with the active species generated by the reaction between $TPPFe^{III}$/imidazole and the hydroperoxide. Here again imidazole may act not

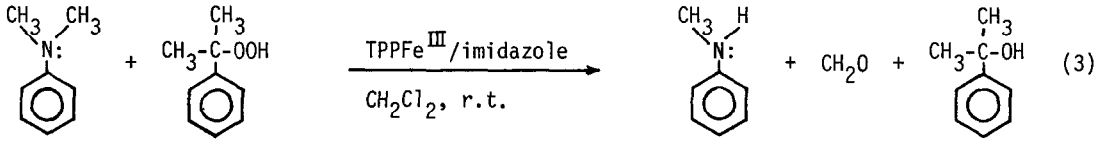


Table II. TPPFe^{III} Catalyzed Oxidative Demethylation of DMA with Cumene Hydroperoxide.[a)]

$[DMA]_0$	$[TPPFe^{III}Cl]_0$	$[Imidazole]_0$	$[Cumyl\text{-}OOH]_0$	Yield of NMA
20 mM	0 mM	20 mM	40 mM	0 % b)
20	2	0	40	0 b)
20	2	20	40	58.3 c)
20	2	20	20	23.6

a) Reactions were carried out in CH_2Cl_2 at room temperature under argon in the dark.
b) Starting DMA was recovered quantitatively. c) 37.5 % of the starting DMA was recovered.

only as a base to abstract a proton from the hydroperoxide to increase its binding ability of the iron but also as the axial ligand of the iron to activate it cleaving O-O bond of the hydroperoxide as horse radish peroxidase in which imidazole plays as the axial ligand of the heme and promotes the oxidative demethylation of DMA.[10,16b)]

Thus, imidazole plays as an axial ligand of TPPFe and controls the chemical reactivity of TPPFe, the catalyst, to cleave both N-O and O-O bonds. Further study on detailed mechanisms of these reactions is now underway in this laboratory.

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