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INTERVENTION OF N,N-DIMETHYLANILINIUM CATION RADICAL IN THE POLONONOVSKI TYPE REACTION OF N,N-DIMETHYLANILINE N-OXIDE CATALYZED BY MESO-TETRAPHENYLPORPHINATOIRON/IMIDAZOLE

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Abstract:Meso-tetraphenylporphinatoiron(III)/imidazole catalyzes the Polonovski type reaction of substituted N,N-dimethylaniline N-oxides to give mixtures of N-demethylated and N-deoxygenated products. Effect of substituent on the turnover number and the ratio of the demethylation to the deoxygenation, and other observations suggest that the Polonovski type N-demethylation reaction takes place via the rate determining N,N-dimethylanilinium cation radical formation.

Mechanisms of reactions of N,N-dimethylaniline N-oxide (DMAO) catalyzed by metalloporphyrins have recently been a matter of controversy as model reactions of cytochrome P-450.[1-4] Bruice et al. have reported that metalloporphyrins containing Fe^{III}, Mn^{III} and Cr^{III} catalyze both N-demethylation and N-deoxygenation of DMAO via rate determining heterolytic cleavage of N-O bond of the N-oxide bound to the metalloporphyrins.[2] Meanwhile, Burka et al. have claimed that both Mn^{III} and Cr^{III}-porphyrins do not promote the N-demethylation of DMAO in detectable level.[3] We have found that amines, especially imidazole, in cooperation with meso-tetraphenylporphinatoiron(III) chloride($TPPFe^{III}Cl$) catalyze effectively the Polonovski type reaction of DMAO eventually affording N-demethylated product, N-methylaniline (NMA), and N-deoxygenated product, N,N-dimethylaniline (DMA)(eq.1).[1,4] This paper deals with that the N-demethylation of p-substituted N,N-dimethylaniline N-oxides (DMAO-X) with $TPPFe^{III}$/imidazole proceeds via the rate determining N,N-dimethylanilinium cation radical ($DMA\text{-}X^{+\cdot}$) formation.

The reaction of DMAO-X with $TPPFe^{III}Cl$/imidazole has been carried out in chloroform at 25° C and monitored by thin layer chromatography. When the reaction was completed, the mixture was treated with hydrazine to convert quantitatively the intermediary N-hydroxymethyl-N-methylaniline to NMA by removing formaldehyde[4] and then subjected to gas chromatographic analysis (OV-1, 2m column, 90°C). The results are summarized in Table I together with oxidation potential of DMA-X.[5] The data in Table I reveal that not only the electron-withdrawing substituent, X, retards the reaction of DMAO-X catalyzed by $TPPFe^{III}$/imidazole but also

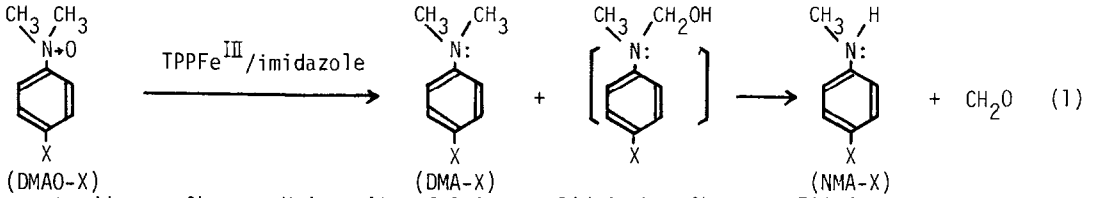

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Table I Reactions of DMA-X with $TPPFe^{III}Cl$/imidazole in Chloroform at 25°C[a)]

X	Reaction time[b)]	Demethylation : Deoxygenation	E_{pa} of DMA-X[c)]
OCH_3	3 min	73 : 27	+ 0.60 volt vs SCE
CH_3	11	67 : 33	+ 0.73
H	30	39 : 61	+ 0.81
Cl	30	31 : 69	+ 0.97
NO_2	1 day[d)]	16 : 84	+ 1.20

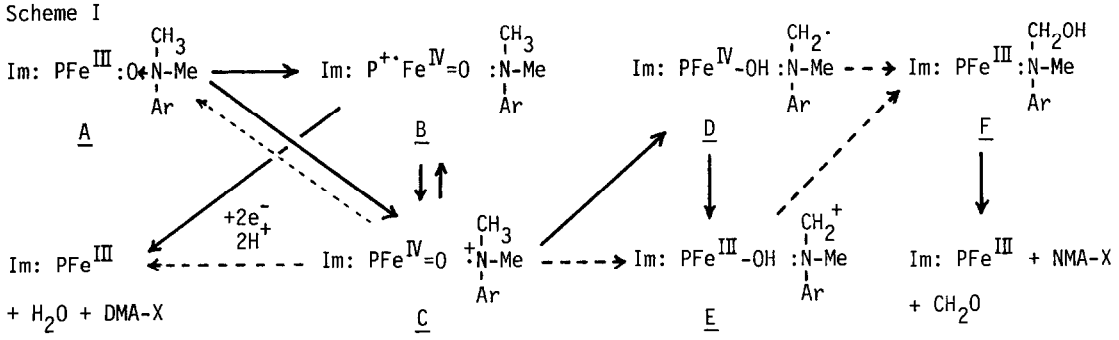
a) Initial concentrations of reactants: $[DMAO-X]_o$=10 mM;$[TPPFe^{III}Cl]_o$=0.1 mM;$[imidazol]_o$=10 mM. b) Time required to complete the reaction. c) Peak potential of the first oxidation peak of cyclic voltammetric curve in CH_3CN (0.1 M Bu_4NClO_4) using Pt electrode. d) Increase of the concentration of the iron catalyst extremely shortens the reaction time to consume $DMAO-NO_2$.

decreases ratio of the N-demethylation to the N-deoxygenation; i.e. the reaction of $DMAO-OCH_3$ is completed within 3 min and gives mainly $NMA-OCH_3$, whereas it takes one day to consume whole $DMAO-NO_2$ under the condition to afford mainly the deoxygenation product.

All conceivable reaction intermediates are illustrated in Scheme I. Since both DMAO-X and imidazole are good ligand to $TPPFe^{III}$ in chloroform, the reaction begins undoubtedly with fast formation of the ternary complex, A.[4)] Then there are two possible modes for the cleavage of the N-O bond of DMAO bound to $TPPFe^{III}$ as an axial ligand, i.e. heterolytic (A→B) and homolytic (A→C) ones. Meanwhile, MINDO/3 MO calculations of heats of formations for $DMA-X^{+\cdot}$, substituted N-methyl-N-phenylaminomethyl radicals and N-methyl-N-phenylmethaniminium cations reveal that both processes of proton abstraction (C→D) and hydrogen atom abstraction (C→E) from $DMA-X^{+\cdot}$ are accelerated by electron-withdrawing substituent on the cation radical, and therefore the C-H bond cleavage processes cannot be the rate determining step of the reaction in eq.1. Thus, the rather nice correlation between significant polar substituent effect on the turnover number and oxidation potential (E_{pa}) reveals that the rate determining step of the reaction in eq.1 involves $DMA-X^{+\cdot}$ formation.[6,7)]

In order to examine whether the $DMA-X^{+\cdot}$ is formed by the single step mechanism involving the rate determining N-O bond homolysis (A ↛ C) or the stepwise mechanism (A→B↛C) involving the fast N-O bond heterolysis and subsequent rate determining single electron transfer (SET) from DMA-X to $TPP^{+\cdot}Fe^{IV}$=O, $DMAO-NO_2$ was treated with TPPFe/imidazole in the presence of $DMA-OCH_3$. If the single step mechanism is responsible for the poor reactivity of $DMAO-NO_2$,

Scheme I



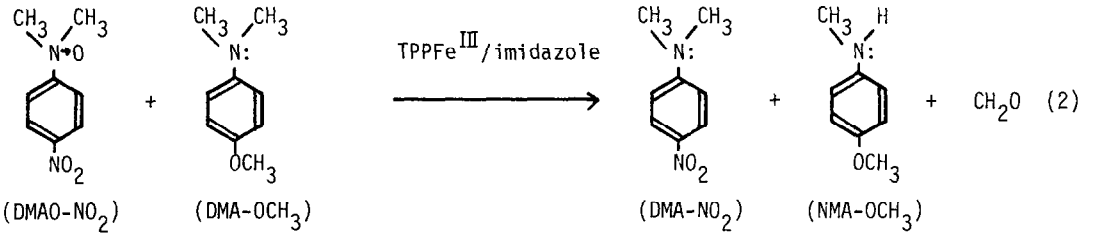


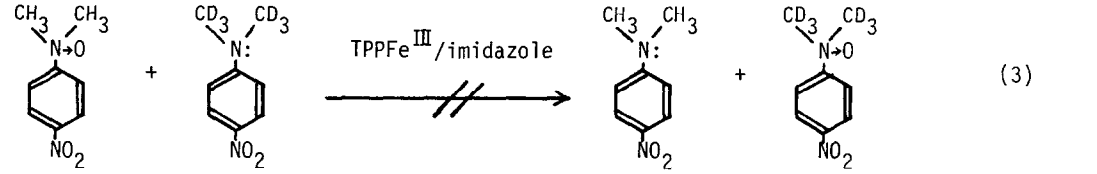
Table II Reactions of DMAO-NO_2 with TPPFe^{III}Cl under Various Conditions in $CHCl_3$ at 25°C[a)]

Run	[Imidazole]$_o$	[DMA-OCH_3]$_o$	Reaction time	Conversion	Demethylation : Deoxygenation
1	0 mM	0 mM	30 min	~0 %	
2	10	0	30	11	
3	10	0	1 (day)	100	16 : 84
4	0	12	30	0.4	
5	10	12	30	100	0 : 100
6	10	20	3	69	0 : 100
7	10	20	20	100	0 : 100

a) Initial concentrations: [DMAO]$_o$=10 mM; [TPPFe^{III}Cl]$_o$=0.1 mM.

the presence of DMA-OCH_3 should not change the rate of the reaction catalyzed by TPPFe^{III}/imidazole. Whereas, if the stepwise mechanism is valid, the presence of DMA-OCH_3 should accelerate the reaction of DMAO-NO_2, since DMA-OCH_3, an excellent electron donor, gives an electron to the iron oxenoid and undergoes eventually oxidative N-demethylation instead of the N-demethylation of DMA-NO_2 (eq.2). Experimental results are summarized in Table II. In the presence of DMA-OCH_3, DMAO-NO_2 has been consumed extremely fast (runs 5-7) affording exclusively deoxygenated product, DMA-NO_2. Under the condition, DMA-OCH_3 was found to undergo the oxidative N-demethylation. Imidazole is again essential[4)] in this reaction as shown in runs 4 and 5 in Table II. When a solution containing DMAO-NO_2 (10 mM) and N,N-bis(trideuteromethyl)-p-nitroaniline (20 mM) was treated with TPPFe^{III}Cl (1 or 0.1 mM) and imidazole (10 mM) in chloroform at 25°C. The unreacted N-oxide was recovered after a partial reaction and reduced to DMA-NO_2, which was then subjected to mass spectroscopic analysis. Even after 95 % of the N-oxide has been consumed, no excess deuterium has been introduced into the remaining N-oxide at all (eq.3), clearly revealing that the N-O bond cleavage of DMAO-NO_2 is irreversible.

Thus, the Polonovski type N-demethylation of DMAO-NO_2 catalyzed with TPPFe^{III}/imidazole has been shown to take place by the stepwise mechanism through the initial fast irreversible N-O bond heterolysis followed by the rate determining SET process of B→C. However, very low E_{pa}



of DMA-OCH_3 (0.60 V vs SCE in CH_3CN) and the extremely high reactivity of DMAO-OCH_3 toward $TPPFe^{III}$/imidazole suggest that DMAO-OCH_3 bound to the iron catalyst affords directly DMA-$OCH_3^{+\cdot}$; i.e. the mode of the N-O bond cleavage of DMAO-X bound to $TPPFe^{III}$/imidazole may vary from heterolytic to homolytic, depending on the polar nature of the substituent, X.

It is of particular interest that the rate determining step for the reaction of DMAO-CN catalyzed by $TPPFe^{III}Cl$ alone was reported to be the slow N-O bond heterolysis by Bruice and coworkers[2d] after we finished this work, though electron withdrawing abilities of NO_2 and CN are similar. This difference in the rate determining steps between our system and theirs may be due to the stronger catalytic effect of imidazole than Cl^- as the fifth ligand to $TPPFe^{III}$ as reported in our previous paper. An increase of electron donating ablity of the fifth ligand to $TPPFe^{III}$ increases the ability of the iron catalyst to cleave N-O bond of DMAO in the order of Cl^- < pyridine < 1,4-diazabicyclo[2,2,2]octane < imidazole < thiophenol.[1,4] In our system, since the N-O bond cleavage of DMAO-NO_2 bound to the $TPPFe^{III}$/imidazole is facilitated by the imidazole, the unfavorable SET process from DMA-NO_2 (E_{pa}=1.20 V) became the slowest step in the whole reaction. The data in Table II show how imidazole is effective than Cl^- to promote the reaction.

The mechanism of the processes of C → F is not yet conclusive and now under investigation.

References and Footnotes

1) a) Fujiwara, S., Takata, T., Fujimori, K., and Oae, S. (1980) 41th Ann. Meeting of Chem. Soc. Jpn., Abstr. II, p. 893, April.
   b) Fujimori, K., Takata, T., Fujiwara, S., and Oae, S. (1981) 8th Intern. Congress of Heterocyclic Chem., Abstr. p. 193, at Graz.
2) a) Shannon, P. and Bruice, T. C. (1981) J. Am. Chem. Soc., 103, 4580-4582.
   b) Nee, M. W. and Bruice, T. C. (1982) J. Am. Chem. Soc., 104, 6123-6125.
   c) Powell, M. F., Pai, E. F., and Bruice, T. C. (1984) J. Am. Chem. Soc., 106, 3277-3285.
   d) Dicken, C. M., Lu, F.-L., Nee, M. W., and Bruice, T. C. (1985) J. Am. Chem. Soc., 107, 5776-5789.
3) Burka, L. F., Guengerich, F. P., Willard, R. J., and McDonald, T. L. (1985) J. Am. Chem. Soc., 107, 2549-2551.
4) Fujimori, K., Fujiwara, S., Takata, T., and Oae, S., Tetrahedron Lett., in press.
5) We have not yet made effort to search other possible minor products in the reaction of DMAO-X with TPPFe(III)/imidazole system, since the products, NMA-X and DMA-X, accounted for over 80 %. Bruice et al. have reported very recently detailed analysis of minor products of the reaction of DMAO-CN with TPPFe(III)Cl (ref. 2d).
6) The other possible mechanistic path involving hydride transfer from DMA-X to $TPP^{+\cdot}Fe(IV)=O$ can be ruled out, since the Fe(IV)=O species is believed to be a biradical (ref. 8). Since our MO calculations suggest that the process of B → D is very slightly affected by the change of polarity of the substituent, X, the mechanism which involves the rate determining hydrogen atom abstraction from DMA-X by $TPP^{+\cdot}Fe(IV)=O$ (A → B ↛ D) cannot explain the significant polar substituent effect on the turn over number. Detailed data of MO calculations will be reported later.
7) This mechanism is in keeping with that proposed for the Polonovski type reaction of DMAO-X catalyzed with phenobarbital induced rabbit liver microsomal cytochrome P-450, which involves DMA-$X^{+\cdot}$.[a,b]
   a) Fujimori, K., Yaguchi, M., Iyanagi, T., and Oae, S. (1984) 1st Symposium on Biomimetic Chem., Abst. pp. 105-108, at Fukuoka, May.
   b) Fujimori, K., Kobayashi, K., Sagisaka, K., Kikuchi, O, Furukawa, N., Iyanagi, T., and Oae, S. (1985) 2nd. Symposium on Biomimetic Chem., Abst. pp. 101-104, at Tokyo, June.
8) Groves, G. T. and Submarian, D. V. (1984) J. Am. Chem. Soc., 106, 2177-2181.

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