[Chem. Pharm. Bull. 29(5)1489—1492(1981)]

Oxidative Dealkylation of Tertiary Amines by Iron(III) Porphyrin-Iodosoxylene System as a Model of Cytochrome P-450[1]

The oxidative dealkylation of several tertiary amines with 2-iodoso-*m*-xylene catalyzed by chloro-$\alpha,\beta,\gamma,\delta$-tetraphenylporphinatoiron(III) (Fe(III)TPPCl, **3**) was examined. N,N-Dimethylaniline (**2**) was smoothly dealkylated to N-methylaniline (**4**) in mild conditions and **3** was ascertained to act as an effective catalyst in this system. N,N-Diethylaniline and N,N-dimethylbenzylamine were similarly dealkylated.

When the oxidation of **2** was carried out in the presence of methanol, N-methoxymethyl-N-methylaniline was predominantly formed and the formation of **4** was suppressed. This result suggests that the reactive cationic species, iminium ion, is formed in this reaction. The possible mechanism of this biomimetic dealkylation is also discussed.

Keywords——chloro-$\alpha,\beta,\gamma,\delta$-tetraphenylporphinatoiron(III); 2-iodoso-*m*-xylene; oxidative dealkylation; catalytic oxidation; cytochrome P-450 model system; N,N-dimethylaniline; iminium ion; N-methoxymethyl-N-methylaniline

The cytochrome P-450 enzymes containing a protoporphyrin-IX group catalyze the mono-oxygenation and the oxidative dealkylation of a wide variety of organic compounds. These enzymes are known to cleave the oxygen-oxygen bond of molecular oxygen by two electron uptakes followed by the elimination of one oxygen atom as water. The other oxygen atom which is left on the iron as a carben like oxene, $[FeO]^{3+}$, is thought to be the key oxidizing species.[2] Indeed, it has been demonstrated that a cytochrome P-450-iodosobenzene system can catalyze several oxidations in the absence of NADPH and O_2.[3] Recently, Groves *et al.*[4] and Chang *et al.*[5] reported that several chloroporphinatoiron(III) compounds were capable of catalyzing oxygen transfer from iodosoaromatics to saturated and unsaturated hydrocarbons, and suggested the possible intermediary role of a $[FeO]^{3+}$ complex in these reactions.

The oxidative dealkylation of amine which is catalyzed by cytochrome P-450 is important since many valuable drugs and pharmacologically active compounds contain nitrogen.[6] In this communication, we report the biomimetic dealkylation of several tertiary amines with 2-iodoso-*m*-xylene (**1**)[7] catalyzed by synthetic iron(III) porphyrin and related reactions.

To the demethylation of N,N-dimethylaniline (**2**), a suspension of **1** (100 μmol) in 50 ml of anhydrous methylene chloride[8] containing **2** (1 mmol) and chloro-$\alpha,\beta,\gamma,\delta$-tetraphenylporphinatoiron(III) (Fe(III)TPPCl, **3**)[9] (5 μmol, ratio of **3** to **1** was 0.05) was stirred under argon at 0°. The reaction was followed by gas chromatography (GC). The formation of N-methylaniline (**4**) was completed within 30 minutes (Fig. 1) and the yield of **4** was 71% based on **1**.[10] Formaldehyde was also detected with Nash reagent.[11]

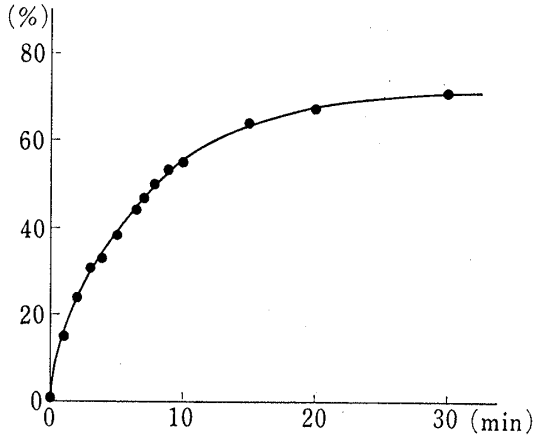

Fig. 1. Time Course of the Formation of N-Methylaniline (**4**)

To clarify the catalytic effect of **3**, this demethylation was examined under various conditions (Table I). The yield of **4** increased with the amount of **3** and went up to 85% when the ratio of **3** to **1** was 0.5 (run No 1). When the ratios were even 0.02 and 0.005 (run No 3 and 4), this demethylation proceeded and the yields of **4** were 52% and 26%, respectively. However, in the absence of **1** or **3**, this reaction scarcely proceeded (run No 5 and 6). These results ascertain that **3** acts as an effective catalyst in this reaction.[12] Control experiments used other iron ca-

Table I. Reactions of N,N–Dimethylaniline and 2-Iodoso-*m*-xylene under Various Conditions

Run No[a]	2-Iodoso-*m*-xylene (1)	Iron catalyst	Ratio of iron catalyst to 1	Yield of N-methylaniline[b] (%)	Turnover number of 3
1	10 μmol	Fe(III)TPPCl (3), 5 μmol	0.5	85[c]	1.7
2	10 μmol	Fe(III)TPPCl (3), 0.5 μmol	0.05	77[c]	15
3	10 μmol	Fe(III)TPPCl (3), 0.2 μmol	0.02	52[c]	26
4	10 μmol	Fe(III)TPPCl (3), 0.05 μmol	0.005	26[c]	52
5	10 μmol	—	—	1.7	—
6	—	Fe(III)TPPCl (3), 0.5 μmol	—	0.6	—
7	10 μmol	$Fe(II)Cl_2$,[d] 0.5 μmol	—	1.1	—
8	10 μmol	$Fe(III)Cl_3$,[d] 0.5 μmol	—	0.6	—
9	10 μmol	Fe(III)acetylacetonate, 0.5 μmol	—	1.4	—

a) All reactions used 100 μmol of **2** and were carried out at 0° for 30 minutes in absolute methylene chloride under argon.
b) Yields were determined by GC analysis and based on **1**.
c) The mean yield on repeated runs.
d) These catalysts were only slightly soluble in methylene chloride.

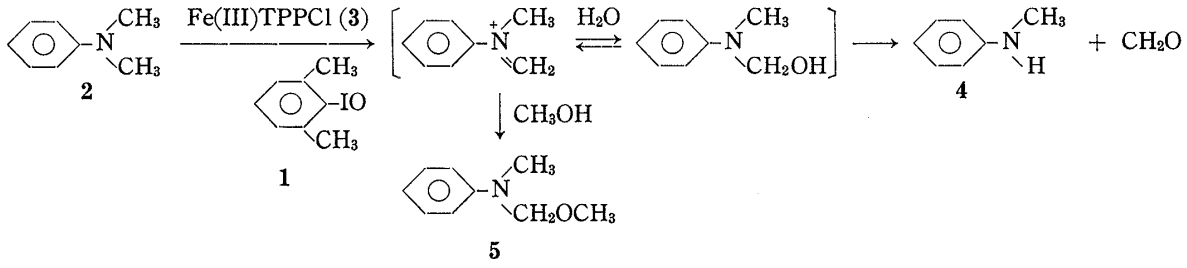

Chart 1

talysts are also summarized in Table I.

Similarly, when N,N-diethylaniline was oxidized by the above system (the reaction conditions were identical with that of run No 1), N-ethylaniline was afforded in 40% yield. And in the oxidation of N,N-dimethylbenzylamine, benzaldehyde was afforded in 93% yield.

The oxidation of N-methylcarbazole (**6**), which was known to be metabolized to N-hydroxymethylcarbazole (**7**) by cytochrome P-450,[13] was also examined by our model system, and **7** was detected as a main product (17%).[14]

When the oxidative demethylation of **2** was carried in the presence of methanol, a product other than **4** was detected and the yield of **4** fell to 4.6%. This new product was identified as N-methoxymethyl-N-methylaniline (**5**, 63% yield) with GC-mass spectrometry and high-performance liquid chromatography (HPLC) by an authentic sample.[15] These results suggest that demethylation proceeds *via* a carbinolamine intermediate, which is in equilibrium with an iminium ion, and that the reactive iminium ion species[16] is able to be attacked by methanol (if present) to form methoxymethylamine[17] (Chart 1).

One possible mechanism in the formation of iminium ion is through a radical cation[18] (two one-electron transfers *via* a radical cation intermediate, mechanism A) which has precedence in the electrochemical oxidation of tertiary amine[19] and iron catalyzed dealkylation of tertiary amine oxide in acidic condition.[20] In this mechanism, it will require that a nonbonded electron of the amine nitrogen is first transferred to the $[FeO]^{3+}$ to afford the amine radical cation and $[FeO]^{2+}$. This radical cation facilely renders the much more acidic α proton of the amine. The radical generated by proton loss is coupled with $[FeO]^{2+}$ and one electron is subsequently transferred to $[FeO]^{2+}$ to afford an iminium ion and $[FeO]^{+}$ which is finally oxidized to $[FeO]^{3+}$ by **1** (Chart 2). This mechanism is plausible because $[FeO]^{3+}$ is thought to be effective electron acceptor in this system.[21]

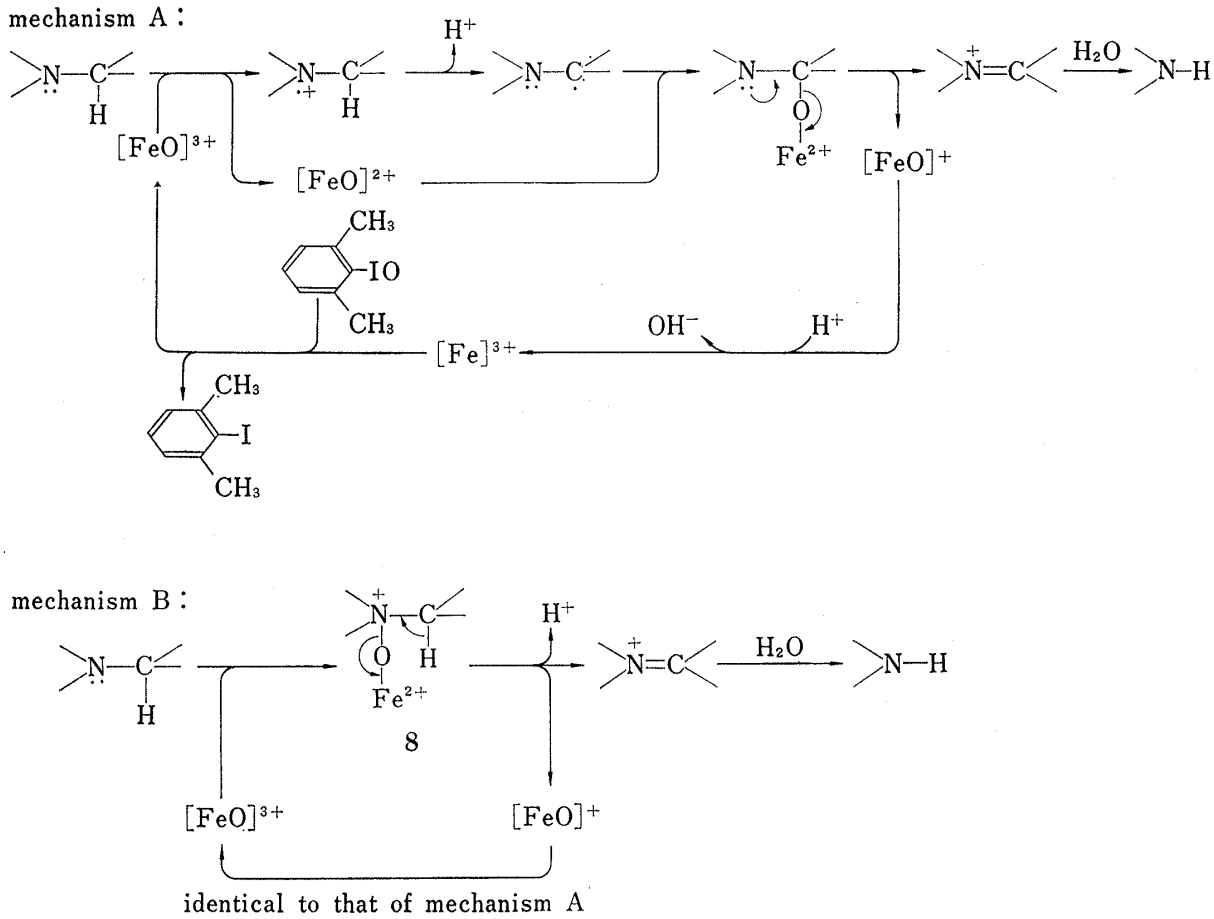

Chart 2

Another mechanism is an ionic one (two-electrons transfer followed by a proton release, mechanism B). In the first step, a lone pair of the amine nitrogen coordinates to the electron deficient $[FeO]^{3+}$ to form the complex (**8**). This complex liberates the α proton of the amine in concert with the heterolytic cleavage of $N^+—O$ bond[22] to form an iminium ion and $[FeO]^+$, and then $[FeO]^{3+}$ is regenerated.

Further experiments are in progress to decide which of these two mechanisms, if either, best accomodate the data.

References and Notes

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10) 2-Iodo-*m*-xylene was also detected but aniline was not detected in this reaction.

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12) Oae *et al.* recently reported a similar demethylation of **2** by the use of cumene hydroperoxide in the presence of **3**, Abstracts of the 14th Oxidation Symposium, Yokohama, November, 1980, p. 170.
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21) The participation of amine oxide in the dealkylation process can be excluded, because amine oxide was not detected in these reactions in the presence or absence of **3**.
22) If the N^+-O bond of **8** is homolytically cleaved, amine radical cation and $[FeO]^{2+}$ is formed. The same intermediate (**8**), therefore, may be formed in mechanism A.

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Received March 24, 1981

[Chem. Pharm. Bull. 29(5)1492—1494(1981)]

Foliaspongin, an Antiinflammatory Bishomosesterterpene from the Marine Sponge *Phyllospongia foliascens* (PALLAS)

An antiinflammatory bishomosesterterpene named foliaspongin has been isolated from the Okinawan marine sponge *Phyllospongia foliascens* (PALLAS) and the structure (**1**) of a new scalarane-type has been proposed on the basis of chemical and physicochemical evidence.

Keywords——marine sponge; *Phyllospongia foliascens*; scalarane-type bishomosesterterpene; foliaspongin; CI-MS; ^{1}H NMR; ^{13}C-NMR; UV

Scalarane-type sesterterpenes have been revealed to occur in some species of marine sponge by several groups in recent years.[1-3] As a continuing study in search of bioactive substances from marine natural products,[4,5] we have been investigating chemical constituents of the marine sponge *Phyllospongia foliascens* (PALLAS) (order Ketatosa),[6] collected in Okinawa Prefecture. Recently, we isolated from this sponge a new scalarane-type bishomosesterterpene named foliaspongin which showed an antiinflammatory activity. This paper deals with evidence supporting the structure (**1**).

The MeOH extract of the fresh sponge (28 kg) was partitioned into an EtOAc-water mixture and chromatographic purification of the EtOAc soluble portion furnished foliaspongin (**1**) (120 mg), $C_{32}H_{52}O_6 \cdot H_2O$,[7] mp 186—189° (MeOH), $[\alpha]_D$ +44° ($CHCl_3$), CI(NH_3)-Mass: *m/z*