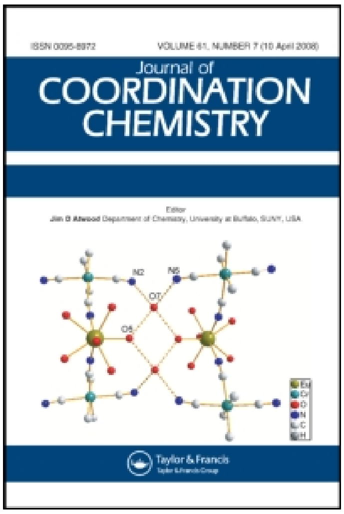

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SHORT COMMUNICATION

Catalytic Action of Iron(II) Phthalocyanine as a Tryptophan-2,3-Dioxygenase Model in Oxygenolysis of 3-Methylindole with Metallophthalocyanines

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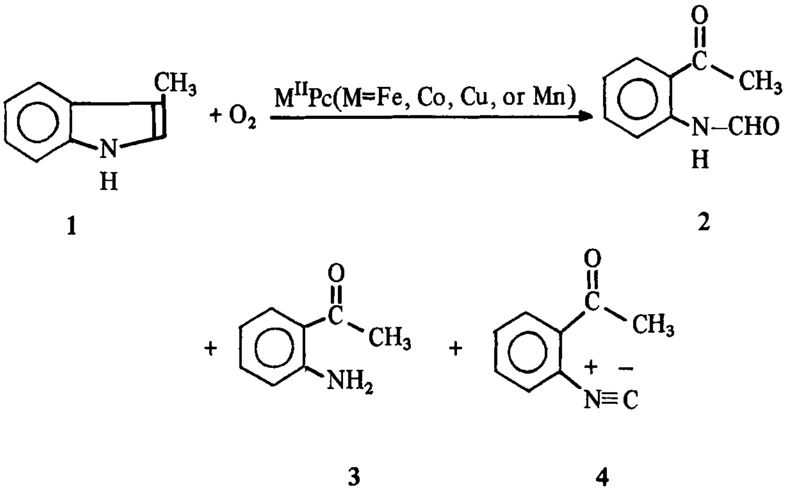
Although the enzyme action of protohaem-containing tryptophan-2,3-dioxygenase has recently been simulated by the oxygenation of 3-substituted indoles to ring-opened keto-amides with bis(salycylidene)ethylenediaminatocobalt(II) (CoSalen),[1–3] cobalt(II) tetraphenylporphyrin (CoTPP),[4,5] manganese(II) phthalocyanine (MnPc),[6] and a copper(I) chloride-pyridine complex (CuCl-Py),[7–9] the catalytic efficiency of iron(II or III) complexes as models of tryptophan-2,3-dioxygenase has hitherto been the subject of limited investigation in the oxygenolysis of indoles related to tryptophan; there is only one report dealing with the oxygenation of indoles to the ring-opened products catalyzed by FeTPP(Py)$_2$.[10] The present paper describes the catalytic action of iron(II) phthalocyanine (Fe^{II}Pc) in the oxidative ring-opening of 3-methylindole with metallophthalocyanines (M^{II}Pc: M = Fe, Co, Cu, and/or Mn) as shown in the following equation.



1 2 3 4

The oxygenolyses of **1** (1.0 mmol) by M^{II}Pc (0.0069–0.1 mmol) under atmospheric oxygen was carried out at room temperature in a solvent (20 cm^3) of dimethylformamide (DMF), dimethylacetamide (DMA), tetrahydrofuran (THF), or dimethylsulfoxide (DMSO) with or without an additive (0.1–1.0 mmol) of pyridine (Py) or imidazole (Im). The amounts of unreacted **1** and the keto-amides (**2** and **3**) were

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TABLE I

Oxygenation of 3-methylindole (**1**) by metallophthalocyanines ($M^{II}Pc$).[a]

$M^{II}Pc$	$1/M^{II}Pc$ (mmol/mmol)	Solvent	Time (h)	Conv. (%)	Yield (%) **2**	Yield (%) **3**	(reacted **1**)/$M^{II}Pc$ (mmol/mmol)	(**2**+**3**)/$M^{II}Pc$ (mmol/mmol)
$Fe^{II}Pc$	10	THF	6	90	11.3	0	9.0	1.1
	10	DMF	6	90	10.1	3.7	9.0	1.4
$Mn^{II}Pc$[c]	144[b]	DMF	2.7	39	3.5	0	56.2	5.0
	144[b]	DMF	2.7	89	11.0	3.0	128.2	20.2
$Co^{II}Pc$	10	THF	12	60	10.6	0	6.0	1.1
	10	DMF	24	19	3.0	0	1.9	0.30
$Cu^{II}Pc$[d]	10	THF	24	40	4.5	0	4.0	0.45

[a] $M^{II}Pc$ = 0.1 mmol, **1** = 1.0 mmol, and Solvent = 20 cm^3. [b] $1/Fe^{II}Pc$ = 1.0 mmol/0.0069 mmol = 144 and $1/M^{II}Pc$ = 7.6 mmol/0.053 mmol = 144. [c] Data were taken from ref. 6; The molar ratio of (**2** + **3** + **4**)/$Mn^{II}Pc$ = 27.4 was obtained by the addition of 5% yield of **4**. [d] The solubility in DMF was low.

TABLE II

Effects of solvents and additives on the $Fe^{II}Pc$-catalyzed oxygenation of **1**[a].

1/$Fe^{II}Pc$ (mmol/mmol)	Solvent	Additive (Additive/$Fe^{II}Pc$)	Time (h)	Conv. (%)	Yield (%) **2**	Yield (%) **3**	(reacted **1**)/$Fe^{II}Pc$ (mmol/mmol)	(**2** + **3**)/$Fe^{II}Pc$ (mmol/mmol)	Intensity[b] of esr (g=2.003)
100	THF	none	12	86	8.8	0	86	8.8	0.86
100	DMA	none	24	67	10.8	1.1	67	11.9	1.37
100	DMSO	none	24	9	5.5	0	9	5.5	0.25
100	DMF	none	24	66	7.5	5.3	66	12.8	0.98
20[c]	DMF	none	12	69	12.4	6.9	13.8	3.9	1.41
10[d]	DMF	none	6	90	10.1	3.7	9.0	1.4	3.52
100	DMF	Py(10)	24	50	6.1	4.2	50	10.3	0.31
100	DMF	Py(100)	24	40	6.0	5.9	40	11.9	0
100	DMF	Im(10)	24	34	4.9	2.5	34	7.4	0

[a] $Fe^{II}Pc$ = 0.01 mmol, **1** = 1.0 mmol, and Solvent = 20 cm^3. [b] Signal intensity at g = 2.003 was measured on the basis of the intensity at the third and fourth manganese markers (Mn^{2+} in MgO). [c] $1/fe^{II}Pc$ = 2.0 mmol/0.1 mmol. [d] $1/Fe^{II}Pc$ = 1.0 mmol/0.1 mmol.

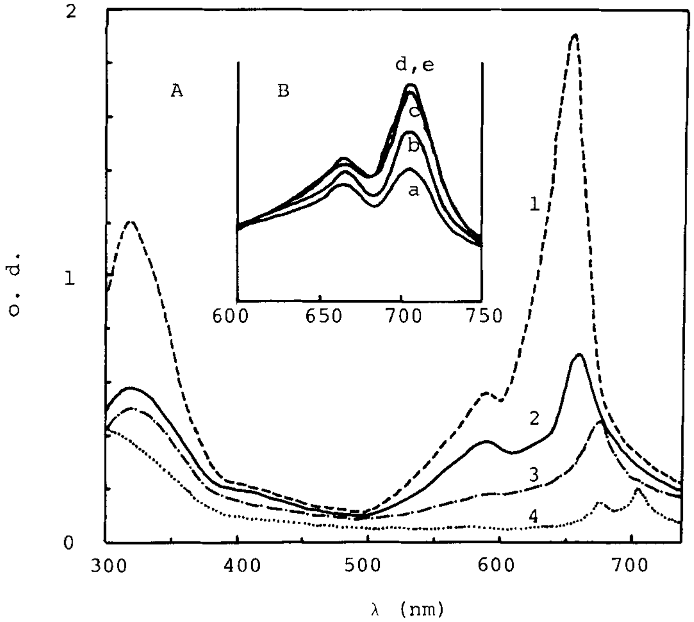


FIGURE 1 Absorption spectra of (A) bis-adduct-complexes of $Fe^{II}Pc(S)_2$ (S = solvent; DMSO (1), DMF (2), DMA (3), and THF (4)) and (B) indole(**1**)-$Fe^{II}Pc$ complex of $PcFe^{II}(S)$ (**1**) or $PcFe^{II}(\mathbf{1})_2$ (molar ratio of 1/$Fe^{II}Pc$ = 0 (a), 1 (b), 5 (c), 10 (d), and 20 (e)).

determined spectrophotometrically after separating them from the reaction mixtures by means of thin-layer chromatography on silica gel (Merck F 254; $R_f = 0.67$ (**1**), 0.43 (**2**), and 0.55 (**3**) in ether:n-heptane:benzene = 1:1:1); $\lambda_{max}(\varepsilon) = 282$ (4590) for **1**, 259 (12400) and 318 (4450) for **2**, and 256 (6120) and 366 nm (4640 mol^{-1} dm^2) for **3** in CH_3OH. The negligibly small amount of **4** was not determined for the simplicity of quantitative analysis of products.

The present oxygenolysis of **1** did not proceed in the absence of $M^{II}Pc$ (M = Fe, Co, Cu, or Mn), indicating that $M^{II}Pc$ was acting as a catalyst in the reaction. The catalytic efficiency of $M^{II}Pc$ for the present reaction, which reflected in the molar ratio of (reacted **1**)/$M^{II}Pc$ or (**2** + **3**)/M^{II} in Table I, followed the order of $Mn^{II}Pc > Fe^{II}Pc >$ **2** + **3**)/$Fe^{II}Pc$ = 5.0) was smaller than that of $Mn^{II}Pc$ ((reacted **1**)/$Mn^{II}Pc$ = 128.2 or (**2** + **3**)/$Mn^{II}Pc$ = 20.2) in the oxygenation of **1** under the identical molar ratio of **1**/$Mn^{II}Pc$ = 144, the highest isolated yield of **2** (10–11%) obtained with $Fe^{II}Pc$ and that (11%) obtained with $Mn^{II}Pc$ were of the same order. Therefore, $Fe^{II}Pc$ is useful as a model of tryptophan-2,3-dioxygenase, because the catalytic efficiency of $Mn^{II}Pc$ for the oxygenolysis of **1** is higher than that of other models such as CoTPP and CoSalen.[5] However, the catalytic activity of $Fe^{II}Pc$ was directly influenced by the reaction conditions (Table II). With respect to the molar ratio of (reacted **1**)/$Fe^{II}Pc$ (or (**2** + **3**)/$Fe^{II}Pc$) and the reaction time in Table II, the apparent catalytic activity of $Fe^{II}Pc$ decreased with increasing dielectric constant (ε) of the present weakly basic solvents (S), THF (ε = 7.58) > DMF (36.71) ~DMA (37.78) > DMSO (46.68). The elevation of solvent basicity (in the order of THF < DMF DMA < DMSO) promoted the formation of a bis-adduct of $PcFe^{II}(S)_2$ (λ_{max} = 655 nm)[11] *via* the coordination of S to $Fe^{II}Pc$ (Fig. 1A), but the generation of $PcFe^{II}(S)$ (**1**) or $PcFe^{II}(\mathbf{1})_2$ by the reaction of

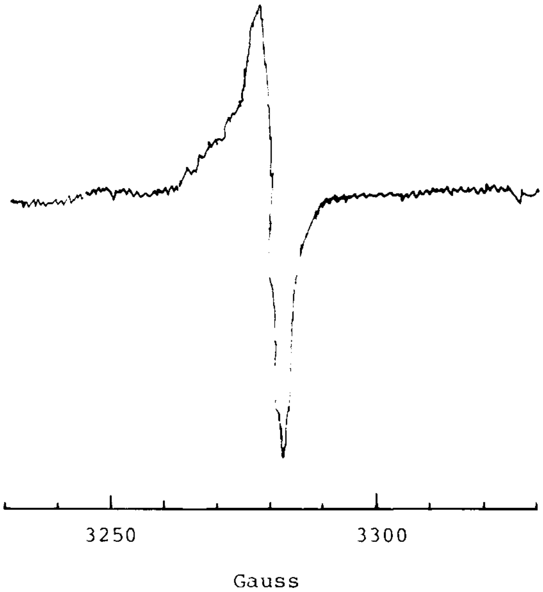


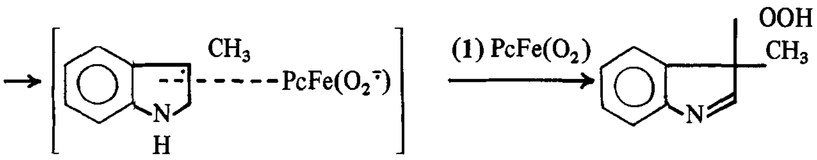
FIGURE 2 Typical example of the esr signal ($g = 2.003$) of the complex obtained by the reaction of Fe^{II}Pc (8.79×10^{-3} mmol) and **1** (0.879 mmol) in DMF (10 cm^3) by bubbling O_2 for 0.5 h.

PcFe^{II}(S)$_2$ and 3-methylindole (**1**) occurs easily in more weakly basic solvents such as THF (Fig. 1B). The enhancement of the PcFe^{II}(S) (**1**) (or PcFe^{II}(**1**)$_2$) formation encourages the reaction of PcFe^{II}(S) (**1**) (or PcFe^{II}(**1**)$_2$) and O_2 so as to generate a ternary oxygen-adduct-complex of (**1**)PcFe(O_2), which is a key intermediate for the present reaction, as well as (**1**)PcFe(O_2).[6] in the Mn^{II}Pc-catalyzed oxygenolysis of **1**. Therefore, the present PcFe^{II}-catalyzed oxygenolysis of **1** might proceed in more weakly basic solvents (THF > DMF~DMA > DMSO). The extent of the formation of the ternary (**1**), PcFe(O_2), complex under the different reaction conditions was estimated by the relative intensity of the esr spectrum of (**1**)PcFe(O_2), at $g = 2.003$ (Fig. 2 and Table II); this esr signal at $g = 2.003$ cannot be obtained from PcFe^{II}(**1**)$_2$ (or PcFe^{II}(S) (**1**)) produced by the reaction of Fe^{II}Pc and **1** in the absence of O_S or from the dimeric dioxygen bridged PcFe-O_2-FePc (or μ-oxy PcFe-O-FePc) complex[11,12] generated by the reaction of Fe^{II}Pc and O_2 in the absence of **1**. Therefore, the esr spectrum ($g = 2.003$) obtained by the reaction of Fe^{II}Pc and **1** in the presence of O_2 is assigned to be that of (**1**)PcFe(O_2) ((a) a super exchange signal of (1)Fe^{III}Pc(O_2^-), (b) a Fe^{II} (high spin)-signal of (**1**)Fe^{III}Pc($O_2^{\cdot}$), or (c) a signal of the indole radical in (**1**$\cdot$)Fe^{II}Pc($O_2^{\cdot}$)).[13] It is also noted from Table II that the decrease of the molar ratio of **1**Fe^{II}Pc in DMF in the range of **1**/Fe^{II}Pc = 10–100 accelerated the reaction rate by encouraging the formation of the ternary (**1**)PcFe(O_2) complex through the suppression of the PcFe^{II}(**1**)$_2$ formation. In this respect, the addition of strongly basic pyridine (Py) and imidazole (Im) into the reaction system retarded the oxygenolysis of **1** through the predominant formation of PcFe^{II}(Py)$_2$ or PcFe^{II}(Im)$_2$ instead of (**1**)PcFe(O_2).

Thus, Fe^{II}Pc catalyzed the oxygenation of **1** to the ring-opened products (**2**, **3** and/or **4**) efficiently in the weakly basic solvents through the formation of the ternary complex of (**1**)PcFe(O_2) as follows.

$$Fe^{II}Pc + S \rightarrow PcFe^{II}(S)_2 \xrightarrow{\mathbf{1}} (\mathbf{1})\,PcFe^{II}(S) \xrightarrow{O_2} (\mathbf{1})\,PcFe(O_2)$$

$$(\text{or } PcFe^{II}(\mathbf{1})_2)$$



$$\longrightarrow \mathbf{2} \text{ or } \mathbf{3} \text{ (and/or } \mathbf{4})$$

where the formation of the 3-methylindolenyl radical is promoted by the electron transfer from **1** to O_2 on the ternary (**1**)$PcFe(O_2)$ complex, as suggested previously,[10] and where the intermolecular reaction of (**1**)$PcFe(O_2)$ is also expectable in the present reaction as well as in the $Mn^{II}Pc$-catalyzed oxygenation of **1**.[6]

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