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MANGANESE PHTHALOCYANINE AS A MODEL OF TRYPTOPHAN-2,3-DIOXYGENASE

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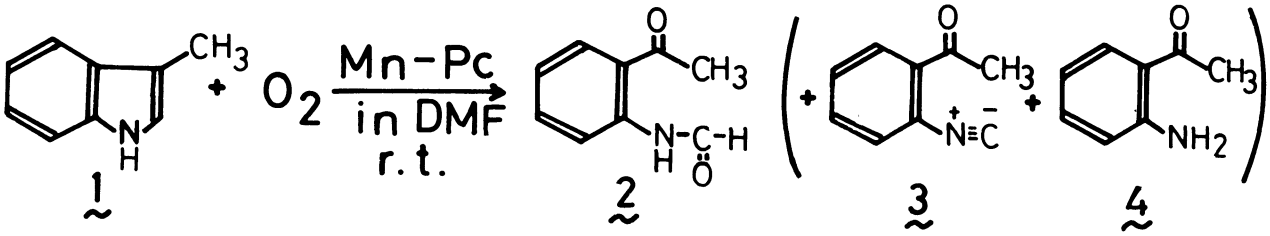
High catalytic activity of manganese phthalocyanine, as a model of tryptophan-2,3-dioxygenase, for the oxygenation of 3-methylindole was demonstrated. The substrate specificity for the oxygenation of indole derivatives is markedly different from that by singlet oxygen or radical autoxidation. A reaction mechanism is proposed taking the intimate correlation between the substrate specificity and the electronic spectra of the catalyst—substrate mixture into account.

Considering the participation of dioxygen complex in heme-containing dioxygenase,[1,2] one would expect a metal dioxygen complex to be active for catalytic oxygenation in an oxygenase model system. Nishinaga reported the oxygenation of 3-substituted indoles catalyzed by Co(salen) as a model of heme-containing enzyme, tryptophan-2,3-dioxygenase.[3] However, the molar ratio of the catalyst required amounts to a quarter of substrate. After his report, Dufour-Ricroch and Gaudemer reported the catalyzed oxygenation of indole derivatives by Co-tetraphenylporphine with an improved activity.[4] Although the dioxygen complexes of Co(salen) and Co-tetraphenylporphine are known,[5,6] their occurrence in the oxygenation reaction has not been clarified. Recently we found that manganese phthalocyanine (Mn-Pc) binds oxygen in N,N-dimethylformamide (DMF) to form an adduct of Mn^{3+}-Pc·O_2^-·(DMF).[7] In this letter, we report its high catalytic activity for the oxygenation of skatole (3-methylindole) 1, a tryptophan analogue, to form 2-formamidoacetophenone 2 and its unique substrate specificity for the oxygenation of indole derivatives, and propose a reaction mechanism including the formation of the ternary complex of Mn-Pc, O_2, and skatole.

The DMF solution (30 ml) of Mn-Pc (30 mg) in a glass reaction vessel connected to a vacuum line was stirred under O_2 ($\sim$40 cmHg) before the reaction, in order to make the complex of Mn-Pc dissolved well. The reaction was started by adding skatole dissolved in DMF (1 g / 20 ml) contained in a side arm attached to the vessel to the solution at room temperature under the same pressure of O_2. Note that the molar ratio of skatole to Mn-Pc was 144. In 160 min. the reaction was completed, where the amount of oxygen consumed was equivalent to 81 % of that of the added skatole as determined by manometric measurement. After the solvent was evaporated, the products were separated by a silica gel column. The main product



1 2 3 4

(about 60 % of the products) was 2-formamidoacetophenone 2 (isolated yield 11 %, m. p. 75—78°C, Lit. 78—79°C,[8] 79—80°C,[3]), whose structure was confirmed by NMR and mass spectroscopies. The NMR spectrum of 2 [δ = 2.63 (3H), δ = 6.98—8.78 (6H)] was consistent with that reported by Nishinaga.[3] Two other compounds were also detected as minor products. One of them exhibited a sharp and strong IR absorption band at 2140 cm^{-1}, this indicating the formula of 3 (isolated yield 5 %), which was also confirmed by means of mass spectroscopic analysis. The other minor product is considered to have the formula 4 (isolated yield 3 %) because of its parent mass peak m/e = 135. These minor products 3 and 4 are considered to be produced by way of 2. The amount of recovered reactant 1 was 11 %. Although the total isolated amount of the reactant and products was rather low, any other products were not detected with silica gel thin layer chromatography. The reaction did not proceed in the absence of Mn-Pc, showing that Mn-Pc was acting as a catalyst in this reaction.

The substrate specificity for the Mn-Pc catalyzed oxygenation of indole derivatives was examined. In the case of 2,3-dimethylindole also, the stoichiometric amount of O_2 was consumed in 200 min. under the same conditions as described above, the main product being 2-acetamidoacetophenone (isolated yield 47 %). However, the

reaction did not proceed at all with such substrates as indole, 1-methylindole, 2-methylindole, 1,2-dimethylindole, and 1,3-dimethylindole at room temperature. Therefore, in order to be oxygenated catalytically by Mn-Pc, it is required for indole derivatives to possess 3-methyl group and N-H group. This specificity is different from that in the photosensitized oxygenation by singlet oxygen[9] or radical autoxidation of indole derivatives,[10] suggesting the reactivity of metal coordinate dioxygen different from that of singlet oxygen or radical oxygen species in autoxidation. As for the Mn-Pc catalyzed oxygenation of tryptophan, oxygen consumption was observed, but the rate was very slow compared with skatole or 2,3-dimethylindole, probably due to the low solubility of tryptophan in DMF.

The changes in electronic absorption spectrum during the Mn-Pc catalyzed oxygenation of skatole were studied. On addition of skatole to Mn^{3+}-Pc$\cdot O_2^-\cdot$(DMF) complex under O_2, the absorption band at 710 nm due to dioxygen complex of Mn-Pc decreased and disappeared in the course of the reaction, during which any new prominent absorption band in visible region was not observed. In the absence of O_2, the electronic absorption band of Mn-Pc in skatole—DMF appeared at 672 nm, which was the same as that of Mn-Pc in DMF. Therefore, the spectrum change of Mn-Pc in the presence of O_2 implies that skatole reacts with Mn^{3+}-Pc$\cdot O_2^-$, forming a ternary complex of Mn-Pc, O_2, and skatole.

Similar spectrum change was also obtained on addition of reactive 2,3-dimethylindole to Mn^{3+}-Pc$\cdot O_2^-\cdot$(DMF). However, the addition of inactive indole derivatives mentioned above to Mn^{3+}-Pc$\cdot O_2^-\cdot$(DMF) induced no significant spectrum changes, the 710 nm band being stable for a long time. Only the indole derivatives which form ternary complexes with Mn-Pc and O_2 are reactive for Mn-Pc catalyzed oxygenation.

Taking both the results described above and the fact that the rate of Mn-Pc catalyzed oxygenation of skatole was of second order as to the amount of catalyst (Mn-Pc) into consideration, we propose the next reaction mechanism: Skatole activated by Mn^{3+}-Pc$\cdot O_2^-$ reacts with the oxygen in other ternary complex, producing 2-formamidoacetophenone. This mechanism suggests the importance of activation of tryptophan, besides the activation of oxygen, by tryptophan-2,3-dioxygenase as was previously proposed.[11] Detailed studies on the reaction mechanism are now in progress.

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