RESEARCH ACTIVITIES VII
Coordination Chemistry Laboratories

Prof. Mitsuhiko Shionoya and Dr. Kentaro Tanaka in laboratory of Complex Catalysis moved to Faculty of Science, Tokyo University in April 1999. Prof. Makoto Fujita and Dr. Takahiro Kusukawa in laboratory of Functional Coordination Chemistry also moved to Faculty of Engineering, Nagoya University in April 1999. Prof. Yuzo Nishida, Prof. Masahiro Ebihara, Dr. Tomohiro Ozawa and Dr. Hiroyuki Kawaguchi continued the position of Synthetic Coordination Chemistry from April 1998. Prof. Ginya Adachi (Osaka University) and Assoc. Prof. Hiromi Tobita (Tohoku University) finished their term as Adjunct Prof. in March 1999 in the Laboratory of Coordination Bond. Their effort during their term is gratefully appreciated. Prof. Hiromu Sakurai (Kyoto pharmacy University) and Assoc. Prof. Yuji Mizobe (Tokyo University) continued their position as Adjunct Prof. of Laboratory of Complex Catalysis. Prof. Takuzo Aida (Tokyo University) and Assoc. Prof. Itaru Hamachi (Kyushu University) took the position of the laboratory of Coordination Bond.

VII-A New Insight into Mechanism of Oxygen Activation in Biological Oxygenases

One of the remaining frontiers in organic chemistry is the direct functionalization of saturated hydrocarbons. The catalytic cycle that oxidizes a hydrocarbon R-H to an alcohol R-OH employing cytochrome P-450 and methane monooxygenase is a well-established process, however no reasonable mechanism for dioxygen activation and for formation of the R-OH is available at present. Recently the present author has proposed a new idea that elucidates many biological oxygenation reactions including monooxygenases and dioxygenases comprehensively. In this new concept, the importance of electrophilic nature of a metal-peroxide adduct and the role of the substrate as an electron donor to the peroxide adduct were emphasized. This idea suggests that formation of a high-valent iron-oxo species, which has been frequently pointed out by the previous authors, occurs most likely when the metal-peroxide intermediate is activated through electronic interaction with both the substrate and the peripheral organic group; the latter two act as an electron donor to the peroxide adduct (see Figure 1: Y. Nishida, *Trends Inorg. Chem.* **5**, 89 (1998)). We are now continuing the study on the reactivity of the metal-peroxide adducts in order to ascertain that my idea is applicable to other reactions, such as degradation of DNA and proteins by the metal-peroxide adducts.

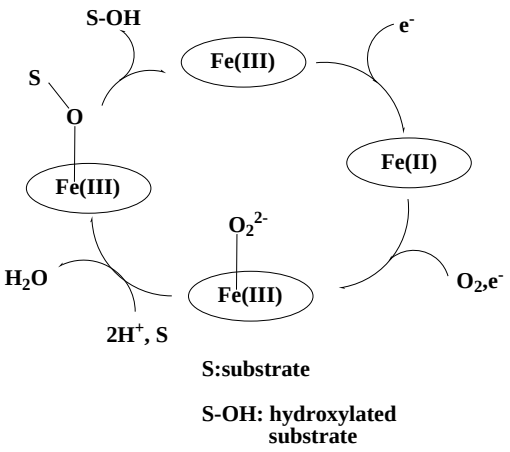


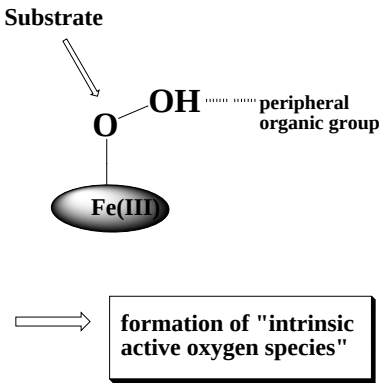
Figure 1. Nishida's mechanism for hydroxylation reaction catalyzed by cytochrome P-450

VII-A-1 Important Role of Substrate in Activation of Dioxygen in Biological Oxygenases

NISHIDA, Yuzo

[*Trends Inorg. Chem.* **5**, 89 (1998)]

In this paper, I have discussed the reaction mechanism of monooxygenases and dioxygenases based on the results obtained for the model systems. Monooxygenases and dioxygenases activate peroxide ion and dioxygen molecule, respectively, and in both cases the substrate plays an important role in the activation of the oxygen species, generating an "intrinsic active oxygen species." (see the Scheme shown below)



My idea is completely different from those of the previous papers; in the latter cases it has been believed that the active oxygen species generates from the reaction between oxygen and the metal enzymes, and then it reacts with a substrate. According to our scheme,

the oxygen atom of the peroxide adduct which is coordinate to the iron(III), is inserted to the substrate in P-450 reaction (see the figure above). On the contrary, terminal oxygen atom of the peroxide adduct is inserted to the porphyrin ring in Heme-oxygenase; in the latter case the substrate is identical to the peripheral group. Thus, it seems quite likely that oxygen atom, which interacts strongly with the substrate is transferred to the organic group, and that electronic interaction between the orbitals of a metal-peroxide and substrate induces heterolytic cleavage of O-O bond, and the electron transfer is not necessary in this process.

In the monooxygenases such as cytochrome P-450 and methane monooxygenase, at first a metal peroxide forms via two electron transfer reduction, and heterolysis of the O-O bond of the metal-peroxide occurs in the presence of substrate and also peripheral organic moiety near the metal ion, and one oxygen atom is incorporated into the substrate.

In the dioxygenases, the metal ion plays a role to bring the substrate near to oxygen molecule and to promote the electron transfer from the substrate to oxygen, giving a C-OOH bond formation. In this case, since the activation of oxygen molecule occurs, O-O bond cleavage does not occur. The substrate in the dioxygenases are generally oxidizable than those in the monooxygenases.

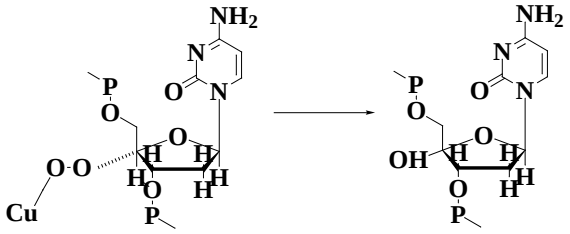
In the case of phenylalanine hydroxylase and tyrosine hydroxylase, which are one of the mono-oxygenases, dioxygenase reaction proceeds in the first step, and in the next step, monooxygenase, does. In the first step the substrate is pterin, and in the second step, amino acid, such as phenylalanine or tyrosine.

VII-A-2 Structural Variety of Copper(II)-Peroxide Adducts and its Relevance to DNA Cleavage

NISHINO, Satoshi; KOBAYASHI, Teruyuki; KUNITA, Mami; ITO, Sayo; NISHIDA, Yuzo

[*J. Bioscience* **54C**, 94 (1999)]

The reactivity of copper(II) compounds with several tetradentate ligands towards some spin-trapping reagents was studied in the presence of hydrogen peroxide. The compounds used in this study are roughly divided into two groups based on the reactivity towards 2,2,6,6-tetramethy-4-piperidinol (and also 2,2,6,6-tetramethyl-4-piperidone), which are trapping agents for singlet oxygen, $^1O_2(^1\Delta_g)$. The A-group compounds exhibited a high activity to form the corresponding nitrone radical, which was detected by ESR spectrometry, but the corresponding activity of the B-group compounds was very low. The A-group compounds defined as above exhibited high activity for cleavage of DNA (super-coiled Form I DNA in the presence of hydrogen peroxide, yielding DNA Form II (relaxed circular) or Form III (linear duplex) under our experimental conditions. On the other hand, the B-group compounds effected complete degradation of the DNA (double-strand scission) under he same experimental conditions; formation of Form II or Form III DNA is negligible. Two different DNA cleavage patterns observed for A- and B-group compounds were elucidated by different structural properties of the copper(II)-peroxide adducts, which is controlled by the interaction through both DNA and the peripheral group of the ligand system. Based on these results, it was assumed that double-strand break by Cu(bdpg)/H_2O_2 system(one of the B-group compound) may proceed via formation of 4'-OH as shown in Scheme.

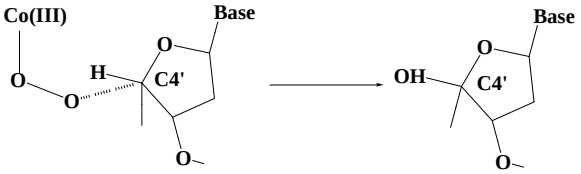


VII-A-3 Mechanism of DNA Cleavage due to Green Cobalt(III)-Bleomycin Hydroperoxide Irradiated by Visible Light

NISHIDA, Yuzo; KUNITA, Mami; NISHINO, Satoshi

[*Inorg. Chem. Commun.* **2**, 156 (1999)]

The origin of the DNA cleavage reaction due to green cobalt(III)-bleomycin hydroperoxide irradiated by visible light (366 nm) was developed on the molecular orbital theory. The importance of the activation of the peroxide ion by transferring an electron from the occupied orbital to σ*-orbital of the peroxide ion was pointed out. We have proposed that the irradiation of the system by the light (366 nm) induces a direct hydroxylation reaction at the 4' position associated with a concerted heterolytic O-O cleavage reaction (*i.e.*, insertion of an atomic oxygen into the C-H bond) without formation of a C4' radica l(see the Scheme shown below). This consideration is quite consistent with the observed results, and a study on the reaction mechanism of hydroxylation by heme-oxygenase, and our previous theoretical consideration.

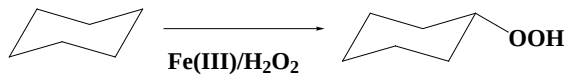


VII-A-4 Selective Dioxygenation of Cyclohexane Catalyzed by Hydrogen Peroxide and Dinuclear Iron(III) Complexes with μ-Alkoxo Bridge

NISHINO, Satoshi; HOSOMI, Hiroyuki; OHBA, Shigeru; MATSUSHIMA, Hideaki; TOKII, Tadashi; NISHIDA, Yuzo

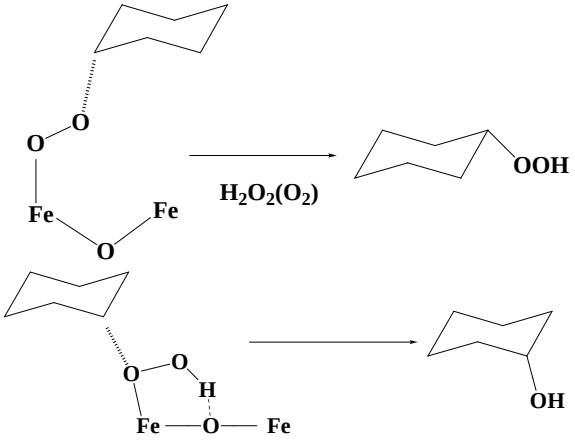
[*J. Chem. Soc., Dalton Trans.* 1509 (1999)]

Several dinuclear iron(III) complexes with μ-alkoxo bridge gave predominantly cyclohexyl hydroperoxide in the reaction with cyclohexane and hydrogen peroxide



and similar results were observed when linear n-alkanes, such as n-nonane and n-octane, were used instead of cyclohexane.

These facts clearly indicate that the Fish's mechanism for the hydroxylation of cyclohexane by Fe(III)/H_2O_2 system is wrong. We have proposed new mechanism for the functionalization of alkanes by Fe(III)/H_2O_2 system; the active species which catalyze dioxygenation and monooxygenation are different from each other, and theoretical elucidation was also provided to our conclusion.

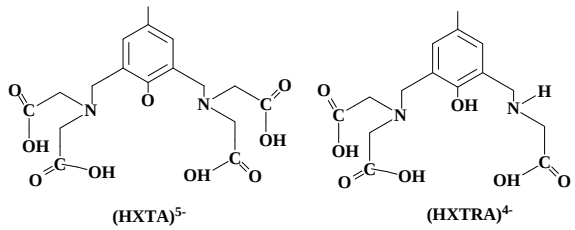


VII-A-5 Interaction between the Peroxide Ion and Acetate Moiety of the Ligand System in a Cobalt(II) Complex with a Binucleating Ligand

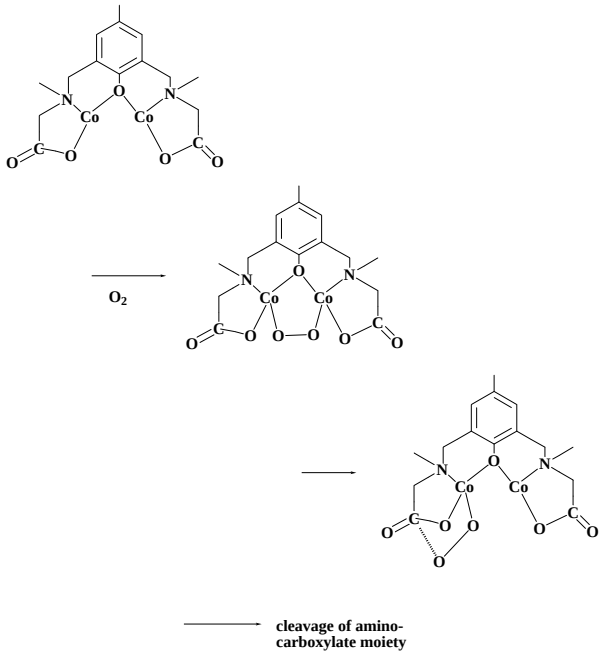
SASAKI, Yumiko; KOBAYASHI, Teruyuki; MASUDA, Hideki; EINAGA, Hisahiko; OHBA, Shigeru; NISHIDA, Yuzo

[*Inorg. Chem. Commun.* **2**, 244 (1999)]

We have found that reaction between $Na_3H_2(HXTA)$ and $Na_3Co(CO_3)_3$ in an aqueous solution gave a binuclear cobalt(III) complex, $Na_2Co_2(HXTRA)$, where in $(HXTRA)^{4-}$ ligand one of the four acetato arms of the original $(HXTA)^{5-}$ ligand is lost.



This may be attributed to the oxidative degradation of one acetato arm of $(HXTA)^{5-}$ ligand due to an electrophilic peroxide-cobalt(III) species with end-on type, as illustrated in Scheme.



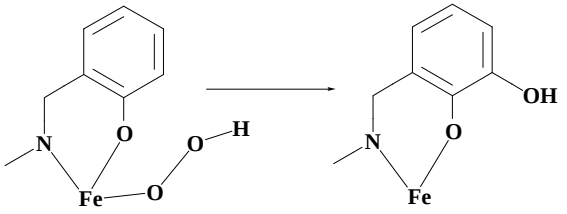
VII-A-6 Electrospray Mass Spectrometry of Peroxide Adduct of Monomeric Fe(III) Complex Containing Phenol Group

OKUTSU, Wataru; ITO, Sayo; NISHIDA, Yuzo

[*Inorg. Chem. Commun.* **2**, 308 (1999)]

Peroxoiron(III) complexes are increasingly being considered as potential intermediates in oxidation catalyzed by both non-heme and heme iron centers. In 1994, Sam *et al.* reported that an "activated bleomycin" is a monomeric iron(III)-peroxide adduct with end-on type, however evidence for the formation of a monomeric iron(III)-peroxide adduct with end-on type is scarce, and their reactivity is unknown at present. In our previous paper, we have reported the preparation, crystal structure determinations of the monomeric iron(III) compounds with ligands containing phenol group, and proposed that the phenol group plays an important role in formation of a peroxide adduct, and in activation of he peroxide ion.

In this study we have confirmed the formation of a peroxide adduct of the monomeric iron(III) complex with end-on type in terms of the electrospray mass spectrometry, and discussed the activation of the peroxide ion and hydroxylation of phenol ring(see Scheme) based on these facts.

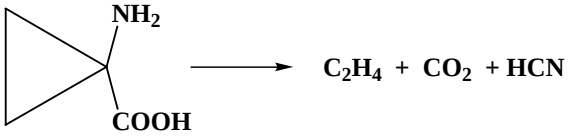


VII-A-7 High Activity of Binuclear Cobalt(II) Complex for Ethylene Evolution from 1-Aminocyclopropane-1-carboxylic Acid in the presence of Hydrogen Peroxide

KOBAYASHI, Teruyuki; SASAKI, Yumiko; AKAMATSU, Tetsuya; ISHII, Toshihiro; MASUDA, Hideki; EINAGA, Hisahiko; NISHIDA, Yuzo

[*Z. Naturforsch., C: Biosci.* **54**, 534 (1999)]

The binuclear Co(II) and Mn(II) complexes with H_5-(HXTA), where H_5(HXTA) represents *N,N*'-(2-hydroxy-5-methyl-1,3-xylylene)bis(*N*-carboxylmethyglycine) induced a strong ethylene evolution from 1-aminocyclopropane-1-carboxylic acid (ACC) in the presence of hydrogen peroxide (see Scheme), whereas the activities of the corresponding Fe(III), Ni(II) and V(III) compounds were found negligible.



ACC

Based on the spectroscopic and mass-spectral data it is proposed that a peroxide adduct of binuclear Co(II) (and Mn(II)) complex with η^1-coordination mode interacts with ACC, which is chelated to a binuclear cobalt(II) complex leading to facile oxidative degradation of ACC and to evolution of ethylene.

VII-A-8 Oxygenation of Nucleosides by Peroxide Adduct of Binuclear Iron(III) Complex with a μ-Oxo Bridge

ITO, Sayo; SASAKI, Yumiko; TAKAHASHI, Yasuyuki; OHBA, Shigeru; NISHIDA, Yuzo

[*Z. Naturforsch., C: Biosci.* **54**, 554 (1999)]

The (μ-oxo)(μ-carbonato)diiron(III) complex with H_2(tfda) (H_2(tfda) = 2-aminomethyltetrahydrofuran-*N,N*-diacetic acid) exhibited high activity for hydroxylation of 2'-deoxyguanosine in the presence of hydrogen peroxide, giving 8-hydroxydeoxyguanosine, but its hydroxylation activity towards other nucleosides, such as 2'-deoxyadenosine, adenosine, or thymidine was found negligible. In the case of the Fe(III)-(eda) complex (H_2(eda) = 2-methoxyethylamine-*N,N*-diacetic acid), hydroxylation reaction occurred mainly at the sugar site, converting 2'-dexoyguanosine to guanosine (see the Scheme). Based on the spectroscopic and structural properties of these iron(III) compounds, it seems most likely that an intrinsic active species for hydroxylation should be an electrophilic peroxide adduct of the (μ-oxo)diiron(III) core with η^1-coordination mode, while the contribution of OH• to the hydroxylation reaction of nucleosides is ruled out.