Structure-Function Relationship of Metalloproteins

Department of Life and Coordination-Complex Molecular Science
Division of Biomolecular Functions

FUJII, Hiroshi	Associate Professor
KURAHASHI, Takuya	Assistant Professor
CONG, Zhiqi	IMS Fellow
OHTSUKI, Akimichi	Post-Doctoral Fellow
WANG, Chunlan	Graduate Student
TANIZAWA, Misako	Secretary

Metalloproteins are a class of biologically important macromolecules, which have various functions such as oxygen transport, electron transfer, oxidation, and oxygenation. These diverse functions of metalloproteins have been thought to depend on the ligands from amino acid, coordination structures, and protein structures in immediate vicinity of metal ions. In this project, we are studying the relationship between the electronic structures of the metal active sites and reactivity of metalloproteins.

1. Formation of Iron(III) *Meso*-Chloro-Isoporphyrin as a Reactive Chlorinating Agent from Oxoiron(IV) Porphyrin π-Cation Radical[1)]

Oxoiron(IV) porphyrin π-cation radicals are generally known to function as key reactive intermediates in a variety of oxidation reactions catalyzed by heme enzymes such as cytochrome P450. The oxoiron(IV) porphyrin π-cation radical complex has several isoelectronic forms which are two oxidation state equivalents higher than that of the iron(III) porphyrin complex. Isoporphyrins, tautomers of porphyrins with a saturated *meso* carbon, were originally postulated by Woodward, and its metal complex was first reported by Dolphin *et al.*, who prepared a zinc(II) 5'-methoxy-5,10,15,20-tetraphenylisoporphyrin complex by nucleophilic attack of methanol on zinc(II) 5,10,15,20-tetraphenylporhyrin π-dication complex. Since then, iron(III) isoporphyrin complexes, particularly *meso*-tetraaryl derivatives, have been synthesized chemically and electrochemically. However, to our surprise, atom transfer reactions of isoporphyrin complexes to substrates, such as oxygenation and halogenation reactions, have not been studied well. In this study, we show that an oxoiron(IV) porphyrin π-cation radical complex can be converted to iron(III) *meso*-chloro-isoporphyrin complex in the presence of trifluoroacetic acid (TFA) and chloride ion. The formation of the isoporphyrin complex would be due to protonations of the oxo ligand of oxoiron(IV) porphyrin π-cation radical species. More importantly, this study shows that the iron(III) *meso*-chloro-isoporphyrin complex is a reactive reagent for chlorination of aromatic compounds and olefins.

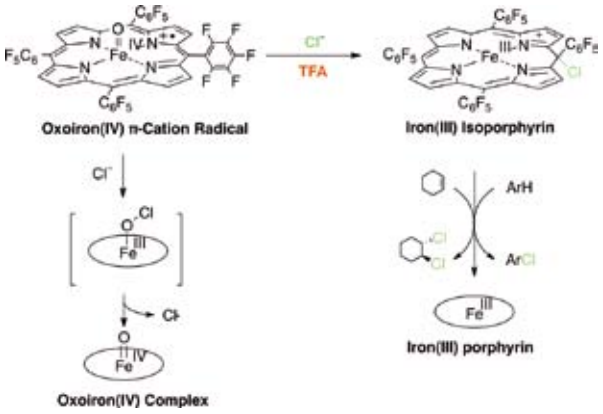

Figure 1. Reaction of oxoiron(IV) porphyrin π-cation radical complex with chloride ion in the presence and absence of proton.

2. The Effect of the Axial Ligand on the Reactivity of the Oxoiron(IV) Porphyrin π-Cation Radical Complex: Higher Stabilization of the Product State Relative to the Reactant State[2)]

The proximal heme axial ligand plays an important role in tuning the reactivity of oxoiron(IV) porphyrin π-cation radical species (compound I) in enzymatic and catalytic oxygenation reactions. To reveal an essence of the axial ligand effect on the reactivity, we investigated from a thermodynamic viewpoint. Compound I model complexes, $(TMP^{+\bullet})Fe^{IV}O(L)$ (where TMP is 5,10,15,20-tetramesitylporphyrin and $TMP^{+\bullet}$ is its π-cation radical), can be provided with altered reactivity by changing the identity of the axial ligand, but the reactivity is not correlated with spectroscopic data (ν(Fe=O), redox potential, and so on) of $(TMP^{+\bullet})Fe^{IV}O(L)$. Surprisingly, a clear correlation was found between the reactivity of $(TMP^{+\bullet})$

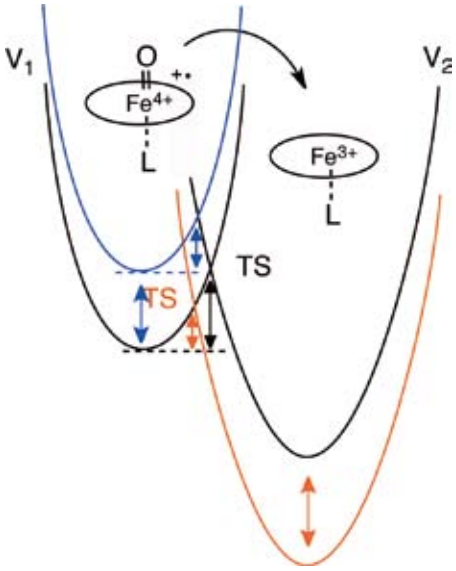

Figure 2. Curve crossing diagram of potential-energy surfaces of the reactant, $(TMP^{+\bullet})Fe^{IV}O(L)$, and product, $(TMP)Fe^{III}(L)$, states. Blue line; Change of stability of $(TMP^{+\bullet})Fe^{IV}O(L)$ and red line; change of stability of $(TMP)Fe^{III}(L)$.

$Fe^{IV}O(L)$ and the Fe^{II}/Fe^{III} redox potential of $(TMP)Fe^{III}L$, the final reaction product. This suggests that the thermodynamic stability of $(TMP)Fe^{III}L$ is involved in the mechanism of the axial ligand effect. Axial ligand-exchange experiments and theoretical calculations demonstrate a linear free-energy relationship, in which the axial ligand modulates the reaction free energy by changing the thermodynamic stability of (TMP) $Fe^{III}(L)$ to a greater extent than $(TMP^{+\bullet})Fe^{IV}O(L)$. The linear free energy relationship could be found for a wide range of anionic axial ligand and for various types of reactions, such as epoxidation, demethylation, and hydrogen abstraction reactions. An essence of the axial ligand effect is neither the electron donor ability of the axial ligand nor the electron affinity of compound I, but the binding ability of the axial ligand (the stabilization by the axial ligand). An axial ligand that binds more strongly makes $(TMP)Fe^{III}(L)$ more stable and $(TMP^{+\bullet})Fe^{IV}O(L)$ more reactive. All results indicate that the axial ligand controls the reactivity of compound I (the stability of the transition state) by the stability of the ground state of the final reaction product and not by compound I itself.

3. Oxidation of Chloride Ion and Subsequent Chlorination of Organic Compounds by Oxoiron(IV) Porphyrin π-Cation Radical Complexes[3)]

Enantioselective transition-metal-catalyzed oxygenation reactions have received much attention because of the demand for organic synthesis strategies and their biological relevance with respect to metalloenzymes. Terminal oxidants such as peroxides, iodosylarenes, and peracids have been utilized as an oxygen source for these oxygenation reactions. Since the terminal oxidants must be stable for easy handling, the primary role of the transition-metal catalyst is to activate a stabilized oxidant and to generate a transient species that remains active enough to transfer an oxygen atom to a substrate. The activation of a terminal oxidant is initiated by binding to the metal complex to form a terminal oxidant adduct of the metal complex. Recently, evidence has been mounting in support of the proposal that the terminal oxidant adduct of a metal complex is not only a precursor to a reactive high valent metal-oxo species, but also itself may serve as a reactive species for an oxygenation reaction. Although terminal oxidant adducts of metal complexes are unstable and reactive compounds in most cases, metal complex adducts with hydrogen peroxide, alkylperoxides, and *m*-CPBA have been isolated and structurally characterized. In contrast to these successful reports, and much to our surprise, there have been no examples of structural characterization of any iodosylarene adducts of metal complexes, although they have emerged as useful oxidants for various organic reactions. The most intensive spectroscopic study was performed by Hill *et al.*, who thoroughly investigated an iodosylbenzene adduct of a manganese porphyrin complex with ^{1}H NMR, IR and ^{127}I Mössbauer spectroscopy. However, the nature of the bonding interaction between iodosylbenzene and the metal ion remains unclear. Here, we report on the preparation and X-ray crystal structure of an iodosylarene adduct of a manganese(IV) salen complex bearing a *trans*-cyclohexane-1,2-diamine linkage as chiral unit.

Figure 3. Synthesis and structural characterization of bis-iodosylmesitylene adduct of manganese(IV) salen complex.

References

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Award

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