V-F Bioinorganic Studies on Structures and Functions of Non-heme Metalloenzymes Using Model Complexes

Metal-containing enzymes have been widely distributed in both plants and animals and have been related to metabolic processes such as hydroxylation, oxygen transport, oxidative catalysis, electron transfer, and so on. In this project the structures and functions for the metal complexes are studied as a model of several metallo-enzymes by using some physico-chemical methods.

V-F-1 Electron Transfer Reaction Induced by Self-Assembly of Biguanidato and Violurato Complexes through Triple Hydrogen-Bond

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Hydrogen bond, which is one of the non-covalent interactions, plays an important role for controlling supramolecular synthesis through metal-induced self-assembly of organic compounds as well as covalent- and coordinate-bonds. The 1:1 mixture of [Co(bg)$_3$] and [Co(va)$_3$] complexes containing biguanidado (bg) and violuric acid (va) ligands, which enable formation of ADA–DAD style hydrogen bonding, respectively, gave a three-dimensional network structure constructed with triple hydrogen bonding interaction accompanying interligand proton transfer equilibrium. Internal void in this structure formed by the aggregation of the polar functions of bg and va may capture water molecule through the bonding. Moreover, an interesting electron transfer reaction, Cu(II) + Mn(III) $\rightarrow$ Cu(I) + Mn(IV), was observed in the 1:1 mixture system consisting of square planar [Cu(va)$_2$] and octahedral [Mn(enbg)(OH)-(H$_2$O)] complexes, when the linear tape structure was generated through the interligand hydrogen bonding between va ligand and ethylenebisbiguanidado (enbg). Oxidation of Mn(III) to Mn(IV) by Cu(II) supported by the reduction potential of the complexes might be occurred through the bonding of Mn–O–Cu, which was accurately generated by the two-dimensional assembly of this linear tape.

V-F-2 A Novel Diiron Complex as a Functional Model for Hemerythrin

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Diiron(II) complexes with a novel dinucleating polypyridine ligand, *N*,*N*,*N*',*N*'-tetrakis(6-pivalamido-2-pyridylmethyl)-1,3-diaminopropan-2-ol (HTPPDO), were synthesized as functional models of hemerythrin. Structural characterization of the complexes, [Fe$^{II}_2$(Htppdo)(PhCOO)](ClO$_4$)$_3$ (**1**), [Fe$^{II}_2$(Htppdo)(*p*-Cl-PhCOO)](ClO$_4$)$_3$ (**2**), [Fe$^{II}_2$(Htppdo)(*p*-Cl-PhCOO)]-(BF$_4$)$_3$ (**2'**) and [Fe$^{II}_2$(tppdo)(*p*-Cl-PhCOO)](ClO$_4$)$_2$ (**3**), were accomplished by electronic absorption, and IR spectroscopic, electrochemical, and X-ray diffraction methods. The crystal structures of **1** and **2'** revealed that the two iron atoms are asymmetrically coordinated with HTPPDO and bridging benzoate. One of the iron centers (Fe(1)) has a seven-coordinate capped octahedral geometry comprised of an N$_3$O$_4$ donor set which includes the propanol oxygen of HTPPDO. The other iron center (Fe(2)) forms an octahedron with an N$_3$O$_3$ donor set and one vacant site. The two iron atoms are bridged by benzoate (**1**) or *p*-chlorobenzoate (**2**). On the other hand, Fe atoms of complex **3** are both symmetrically coordinated with N$_3$O$_4$ donors and two bridging ligands; benzoate and the propanolate of TPPDO. Reactions of these complexes with dioxygen were followed by electronic absorption, resonance Raman and ESR spectroscopies. Reversible dioxygen-binding was demonstrated by observation of an intense LMCT band for O_2^{2-} to Fe(III) at 610 (**1**) and 606 nm (**2**) upon exposure of dioxygen to acetone solutions of **1** and **2** prepared under an anaerobic conditions at –50 °C. The resonance Raman spectra of the dioxygen adduct of **1** exhibited two peaks assignable to the ν(O–O) stretching mode at 873 and 887 cm^{-1}, which shifted to 825 and 839 cm^{-1} upon binding of $^{18}O_2$. ESR spectra of all dioxygen adducts were silent. These findings suggest that dioxygen coordinates to the diiron atoms as a peroxo anion in a μ-1,2 mode. Complex **3** exhibited irreversible dioxygen binding. These results indicate that the reversible binding of dioxygen is governed by the hydrophobicity of the dioxygen-binding environment rather than the iron redox potentials.

V-F-3 A Substrate-specific α-Hydoxylation of Dipeptides Mediated upon a Co(III)-terpyridine Complex: A Functional Model for Peptidylglycine α-Hydroxylating Monooxygenase

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A substrate-specific α-hydroxylation of dipeptides has been found out as a functional model for peptidylglycine α-hydroxylating monooxygenase (PHM), in the reaction of the Co(III) ternary complexes containing terpyridine and dipeptide ligands under aerobic and slightly alkaline conditions.

V-F-4 Site-Selective Recognition of Amino Acids by Co(III) Complexes Containing a (N)(O)$_3$-Type Tripodal Tetradentate Ligand

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The bis-*N*,*N*-carboxymethy-(*S*)-phenylalaninato carbonato cobalt(III) complex, [Co(bcmpa)(CO$_3$)]$^{2-}$, has been prepared as a simple model that enables the recognition of an amino acid (Haa) whose coordination behaviours in solution have been characterized by electronic absorption (AB), circular dichroism (CD) and ^{1}H-NMR spectroscopies. The reaction of the K$_2$[Co-(bcmpa)(CO$_3$)] complex with amino acids (Haa) has predominantly afforded the [Co(bcmpa)(aa)] complex in the *trans*(*N*)-configuration mode, rather than in the *cis*(*N*)-form. By using amino acid derivatives with bulky substituents at their amino or carboxylate sites under a neutral condition, the reactions have been demonstrated to be initiated by coordination of the amino nitrogen site. Interestingly, the *cis*(*N*)-complex, which is isolated as a minor product, isomerizes to the *trans*(*N*)-form in the presence of active charcoal under pH 7 in an aqueous solution. The site-selective coordination of Haa to the [Co(bcmpa)(CO$_3$)]$^{2-}$ complex and the stereoselective isomerization of the [Co(bcmpa)(aa)]$^-$ complex have been explained to be regulated by weak non-covalent interactions within the ligands, whose origin has been discussed based on a detailed examination of the crystal structures of the *trans*(*N*)- and *cis*(*N*)-K[Co(bcmpa)(aa)] complexes.

V-F-5 Crystal Structure and Redox Behavior of a Novel Siderophore Model System: A Trihydroxamato-iron(III) Complex with Intra- and Interstrand Hydrogen Bonding Networks

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An iron(III) complex of a novel tripodal tris-hydroxamate with intramolecular hydrogen-bonding networks (**1**), tris[2-{(N-acetyl-N-hydroxy)glycylamino}ethyl]amine (TAHGA), has been synthesized as a siderophore model, whose crystal structure revealed the formation of the intra- and interstrand hydrogen bonding networks. Formation of the strong hydrogen bonding networks has also been demonstrated in a DMSO solution using the corresponding gallium(III) complex by ^{1}H-NMR spectroscopy. The amide proton peak of Ga(III)-TAHGA was quite independent on temperature in the range of 303–323 K, indicating that the amide hydrogens of the Ga(III)-TAHGA complex are well shielded from the outer sphere and are tightly protected from hydrolysis of the complex. The redox behavior of **1** in an aqueous solution exhibited higher potential (–230 mV *vs.* NHE) for its larger pM value (25.1) compared with those for natural siderophores reported hitherto, indicating that the hydrogen-bonds with the coordinating aminohydroxyl oxygens cause to lower the potential of metal ion. It is suggested that the inter- and intrastrand hydrogen-bonding interactions play an important role for not only tight holding of the iron(III) atom and its shielding from the outer sphere but also control of the redox potential of the central metal ion.

V-F-6 Characterization of an NH-π Interaction in Co(III) Ternary Complexes with Aromatic Amino Acids

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The NH-π interaction has been detected in the crystal structures of Co(III) ternary complexes with N,N-bis(carboxymethyl)-(S)-phenylalanine (BCMPA) and aromatic amino acids including: (S)-phenylalanine ((S)-Phe), (R)-phenylalanine ((R)-Phe), and (S)-tryptophan ((S)-Trp)). Additionally, this interaction has been characterized in solution for Co(III) ternary complexes with BCMPA or NTA (NTA = nitrilotriacetic acid) and several amino acids (AA) by means of electronic absorption, circular dichroism (CD), and ^{1}H NMR spectroscopies. The CD intensities of the Co(III) complexes with aromatic amino acids measured in the d-d region ($\sim 20.5 \times 10^3$ cm^{-1}) are significantly decreased in ethanol solutions relative to water. Analogous complexes with aliphatic amino acids do not exhibit this solvent effect. The ^{1}H NMR spectra of the Co(III) complexes with aromatic amino acids in DMSO-d$_6$ exhibit up-field shifts of the N–H peaks compared with those with aliphatic amino acids, which suggest a shielding effect due to the aromaticity. The up-shift values coincide with those experimentally evaluated from the crystal structures. The magnitude in the upper field shifts agrees well with Hammett’s rule, indicating that the increase of π-electron densities on the aromatic rings exerts a larger shielding effect for the NH protons. In ligand-substitution reactions of the carbonatocobalt(III) complexes with amino acids, the yields of those with aromatic amino acids are higher than the yields obtained for complexes with aliphatic amino acids. This observation is discussed in connection with the important contribution of the NH-π interaction as one of the promotion factors in the reaction.

V-F-7 Reverse Reactivity in Hydroxylation of Adamantane and Epoxidation of Cyclohexene Catalyzed by the Mononuclear Ruthenium-oxo Complexes with 6-Substituted Tripodal Polypyridine Ligands

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The electronic character of the ruthenium complexes with tripodal polypyridine ligands, which is controlled by the substituted groups at pyridine 6-position, gives rise to differences in the reactivity for the ruthenium catalyzed hydroxylation of adamantane and epoxidation of cyclohexene with PhIO as an oxidant; Ru complexes containing electron-withdrawing groups (**1**, **3**, and **5**) promote the epoxidation, while those containing electron-donating groups (**2**, **4**, and **6**) promote the hydroxylation.

V-F-8 A Structural Model of the Ferrichrome Type Siderophore: Chiral Preference Induced by Intramolecular Hydrogen Bonding Networks in Ferric Trihydroxamate

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Tris[2-{(N-acetyl-N-hydroxy)-D-alanylamino}-ethyl]amine (*R*-TAAE) has been synthesized as a chiral trihydroxamate artificial siderophore with hydrogen bonding networks, whose crystal structure of the iron(III) complex revealed Λ configuration induced by interstrand hydrogen bonding networks and steric repulsion by optically active amino acid residues.

V-F-9 Crystal Structure and Solution Behavior of the Iron(III) Complex of the Artificial Trihydroxamate Siderophore with Tris(3-aminopropyl)amine Backbone

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Microorganisms produce low molecular weight compounds called siderophores for an uptake of iron. The iron(III)-siderophore complexes are very stable and the ligand backbones as well as the iron(III)-binding groups are important for the stabilization of iron(III) complexes. Although many tripodal artificial siderophore analogues have been synthesized as ferrichrome and enterobactin analogues, tris(3-aminopropyl)amine (TRPN) has not been much employed as tripodal anchor and the details are little examined. Here, we report the synthesis of newly designed tris[{3-(N-acetyl-N-hydroxy)-glycylamino}-propyl]amine (TAGP) as a trihydroxamate artificial siderophore with TRPN anchor and the crystal structure and solution behaviors of its iron(III) complex. The crystal structure of iron(III)-TAGP complex is the first report on the trihydroxamate artificial siderophore with TRPN anchor which is very similar to the calculated lowest energy conformation of the iron(III) complex of the trishydroxamate with triscarboxylate anchor previously reported. However, the solution behaviors of these iron(III) complexes are quite different from. TAGP forms the 1:1 tris(hydroxamato)-iron(III) complex in pH 2–8, while, the ferrichrome analogue with triscarboxylate anchor forms polymeric and polynuclear iron(III) complexes, despite the higher conformational similarity between these iron(III) complexes. Interestingly, the former promotes the growth of the siderophore-auxotrophic bacterium, while the latter does not. These results suggest that the TRPN tripodal anchors are quite important not only for the stabilization of iron(III) complexes in strong acidic pH but also for the biological activity.