RESEARCH ACTIVITIES VII
Coordination Chemistry Laboratories

Professor Yasuhiro Uozumi and Associate Professor Hiroyuki Kawaguchi joined to laboratories of Synthetic Coordination Chemistry and Functional Coordination Chemistry. Prof. Isao Nishida, Prof. Yasutaka Tanaka took the position of Synthetic Coordination Chemistry from April 1998. Prof. Hiromu Sakurai (Kyoto Pharmacy Univ.) and Assoc. Prof. Yasushi Mizobe (Univ. Tokyo) finished their term as Adjunct Prof. in March 2000 in the Laboratory of Coordination Bond. Their effort during their term is gratefully appreciated. Prof. Takuzo Aida (Univ. Tokyo) and Assoc. Prof. Itaru Hamachi (Kyushu Univ.) continue 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 oxygen 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 (Y. Nishida, *Trends Inorg. Chem.* **5**, 89 (1998)). This idea has been supported by many experimental facts, especially by the work of Sligar *et al.* (*Science* **287**, 1615 (2000)). 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.

VII-A-1 Interaction between a Copper(II) Compound and Protein Investigated in terms of the Capillary Electrophoresis Method

NISHINO, Satoshi; ISHIKAWA, Yoshihiro; NISHIDA, Yuzo

[*Inorg. Chem. Commun.* **2**, 438 (1999)]

Recently there have been a number of reports on peptides which aggregate in ways that may be relevant to their biological activity. The formation of amyloid deposits in Alzheimer's disease and the conversion of PrP^{C} (the normal cellular prion protein) into PrP^{Sc} and its truncated form PrP 27–30, the abnormal disease-causing isoform) in certain human and animal neurodegenerative diseases are typical examples. Very recently we have postulated that a copper(II)-peroxide adduct plays an important role in the formation of PrP^{Sc} protein and its truncated form PrP 27-30. However the mechanism of conversion from PrP^{C} into PrP^{Sc} is unknown at present. In order to elucidate the above problems it seems necessary to obtain detailed information on the interaction between the metal chelaltes and protein, but at present there are few suitable ways to study the interaction between the protein and a small metal chelate. In this paper, we have shown that the capillary electrophoresis method is very useful for studying the interaction in question.

VII-A-2 Contribution of a Metal-Peroxide Adduct to Neurodegeneration is due to its Oxidase Activity

NISHIDA, Yuzo; NISHINO, Satoshi

[*J. Bioscience* **54C**, 1107 (1999)]

Many hypothesis have been developed to explain aging and age-related neurodegenerative diseases, one of he most compelling is the role of oxidative stress to induce changes in protease activity in brains of patients of Alzheimer's disease and prion diseases. At the moment, however, there is no clear answer how protein degradation may be achieved in the brain. We have observed that several metal compounds can degrade proteins in the presence of hydrogen peroxide, and elucidated the reaction scheme based on the new theoretical point for the reactivity of a metal-peroxide adduct with η^1-coordination mode. In this article we have pointed out the importance of a copper(II)-peroxide adduct to promote neurodegenerative diseases such as prion disease and amyotrophic lateral sclerosis through its oxidative protease activity.

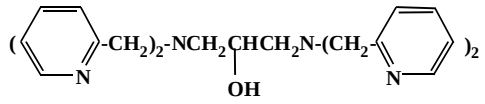
VII-A-3 DNA Promotes the Activation of Oxygen Molecule by Binuclear Cobalt(II) Compounds

NISHIDA, Yuzo; NISHINO, Satoshi; GUO, Li Li; KUNITA, Mami; MATSUSHIMA, Hideaki; TOKII, Tadashi

[*Inorg. Chem. Commun.* **2**, 609 (1999)]

During the past decades there has been an explosion in the research effort directed towards the isolation and evaluation of naturally occurring DNA cleaving agents and towards the design and synthesis of model compounds that can specifically recognize and cut DNA. The potential scope of the utility of these compounds ranges from the creation of synthetic restriction enzymes for use of biologists to the development of chemotherapeutic agents that may be effective against a variety of neoplastic diseases. The

bleomycins (BLM) are family of glycopeptide-derived antibiotics, discovered by Umezawa and co-workers, which have been used clinically against certain malignant lymphomas and squamous cell carcinomas. The therapeutic activity of BLM is generally believed to correlate with the ability of an "active-BLM," which is derived from either Fe(II)-BLM/O_2 or Fe(III)-BLM/H_2O_2 system, to bind to and degrade DNA. This means that Fe-BLM is a dangerous species for the human beings, because it always contains an active oxygen species, although the active bleomycin is quickly bleached when this drug is activated outside of this target(DNA). The most desirable agent for clinical use, should be that the agent cleaves DNA oxidatively through production of an active oxygen species only when it reacts with DNA. In this report we have showed that some binuclear cobalt(II) compounds with H(HPTP)(see below) belong to this type of compounds.



H(HPTP)

VII-A-4 Structure and Function of "Free Iron Ion" in Biological System and Their Model Compounds

NISHIDA, Yuzo

[*Recent Res. Dev. Pure Appl. Chem.* **3**, 103 (1999)]

Iron is as essential participant in many human metabolic processes, but recent studies on neurodegenerative diseases have revealed that free ion, *i.e.*, excess iron ion in the cell, is potentially dangerous, and abnormalities in rain iron metabolism have been described for several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. In this study we have prepared several model compounds for the "free iron(II) ion" in the cell, and discussed origin of the free iron ion formation, and the mechanism of oxygen activation, the cell damage, and cancer process by the free iron ion in biology. We have pointed out that hydrogen peroxide and free iron(III) ion which is captured by a chelate containing peptide-group should be a serious origin for the iron ion toxicity in cells.

VII-A-5 New Insight into Oxidative DNA Cleavage Reaction Catalyzed by Metal Chelates

NISHIDA, Yuzo

[*Recent Res. Dev. Pure Appl. Chem.* **3**, 123 (1999)]

Mechanism of oxidative DNA cleavage reactions catalyzed by a metal compound was re-considered based on the new concept on the chemical reactivity of the metal-peroxide adduct. The fact that chemically inert Co(III)-bleomycin-OOH mediate DNA strand scission only when irradiated at 366 nm light, and the recent results on the steric interaction between the Co(III)-bleomycin-OOH and oligomer investigated by NMR technique has lead to the conclusion that photoirradiation at 366 nm on the Co(III)-bleomycin-OOH induces d-d transition (from t_{2g} orbital to d_{z^2}-orbital) and charge transfer transition (from the ligand orbital to d_{z^2}-orbital), leading to facile O-O heterolysis of the peroxide ion; after this terminal oxygen atom is transferred directly into C(4'-position)-H bond of the sugar moiety, to give the corresponding hydroxylated derivative, leading to strand scission. The results obtained from the model compounds including Fe(III) and Cu(II) all support the above conclusion, and new mechanism for DNA cleavage reaction, which excludes the possible formation of 4'-carbon radical as an intermediate, was proposed for DNA cleavage by the Fe(III)-bleomycin.

VII-A-6 Cleavage of C–N bond of Peptide Group by Copper(II)-peroxide Adduct with η^1-Coordination Mode

NISHINO, Satoshi; KUNITA, Mami; KANI, Yoshiyuki; OHBA, Shigeru; MATSUSHIMA, Hideaki; TOKII, Tadashi; NISHIDA, Yuzo

[*Inorg. Chem. Commun.* **3**, 145 (2000)]

The bioactivation of many peptide hormones and neuropeptides involves oxidative cleavage of carboxy-terminal glycine-extended precursors. The process is catalyzed by the enzyme peptidylglycine α-amidating monooxygenase (PAM), which comprises two subunits. One of these, requires copper ion, ascorbate and molecular oxygen, and facilitates α-hydroxylation of glycine residues. A range of chemical models of PAM has been developed, however the detailed reaction mechanism of cleavage of C-N bond is not clear at present.

Very recently we have reported that some copper(II) compounds exhibit high activity for degrading albumin in the presence of hydrogen peroxide, and postulated that a copper(II)-peroxide adduct may play an important role in the formation of PrP 27-30 and PrP^{Sc}, which are believed to be an abnormal disease-causing isoform of prion protein, and also in conformational change in mutated SOD enzyme observed for ALS patients. In this study we have obtained a clear evidence to support that a copper(II)-peroxide adduct with η^1-Coordination mode can cleave the C-N bond of peptide group and hydroxylate the alkyl group nearby; this may give a new idea to elucidate the reaction mechanism of PAM enzyme.

VII-A-7 Important role of Proton in Activation of Oxygen Molecule in Heme-Containing Oxygenases

NISHIDA, Yuzo

[*Inorg. Chem. Commun.* **3**, 310 (2000)]

Peroxoiron(III) complexes are increasingly being considered as potential intermediates in oxidation reactions catalyzed by both non-heme and heme-

centers. In cytochrome P-450 and heme-oxygenase, a hydroperoxide adduct of Fe(III) with η^1-coordination mode has been considered to be an important intermediate but detailed electronic property and reactivity of the peroxide adduct are less known at present. In recent years, Density Functional Theory (DFT) has emerged as an accurate alternative first-principles approach to quantum mechanical molecular investigations. DFT currently accounts for approximately 90% of all quantum chemical calculations being performed, not only because of its proven chemical accuracy, but also of its relatively cheap computational expense. In this study we have investigated the electronic property of the peroxide adduct of the heme compounds in terms of DFT.

DFT (density-functional theory) calculations have revealed that the position of proton of a hydroperoxide adduct of Fe(III)-porphyrin compound influences greatly the electron density on the oxygen atoms of the peroxide ion, suggesting that the position of proton in the hydroperoxo-iron(III) compound plays an important role in controlling the electronic interaction between the hydroperoxide adduct and porphyrin system (OOH-π interaction). These are very useful to consider the reaction mechanism of the both cytochrome P450 and heme-oxygenase.

VII-B Electronic Structure and Reactivity of Metal Cluster Complexes

Dimetal complexes with metal-metal bond have been a subject of wide interest in these three decades. Meta-metal single- or mulltiple bonds show different reactivitties and properties from those in organic compounds. The reported dimetal complexes were mainly 4d metal complexes. Enhanced metal-metal and metal-ligand interactions are expected for 5d metal cluster compounds. However, rather fewer examples of 5d metal complexes, especially dimetal complexes of iridium(II), have been explored. We have been interested in development of chemistry of Ir_2^{4+} and Ir_2^{5+} complexes.

VII-B-1 A One-Step Synthesis of an Ir(II) Dinuclear Complex. Preparation, Structures and Properties of Bis(μ-acetato)dichlorodicarbonyldiiridium(II) Complexes

EBIHARA, Masahiro; KANEMATSU, Naohiro[1]; KAWAMURA, Takashi[1]
([1]Gifu Univ.)

[*J. Chem. Soc., Dalton Trans.* 4413 (1999)]

A bis(μ-acetato)dicarbonyldichlorodiiridium(II) complex, $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2]$ **1**, was prepared by the one-step reaction of H_2IrCl_6 with $MeCO_2Li$ under O_2 in a mixture of acetic acid and acetic anhydride. Dissolution of **1** into various ligating solvents gave $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2L_2]$ (L = MeCN: **2**, dmso: **3**, py: **4**, 4-isopropylpyridine: **5**). X-ray structure determinations of **2**, **3** and **4** gave the Ir–Ir distances of 2.569(1), 2.5980(5) and 2.5918(5) Å, respectively, which are in the range of the reported Ir(II)–Ir(II) single-bond distances. CV of **2**, **4** and **5** exhibited a one-electron quasi-reversible oxidation wave at $E_{1/2}$ of 1.30, 0.97 and 0.94 V vs Fc^+/Fc, respectively. Complex **3** gave no CV response in the potential window of dmso.

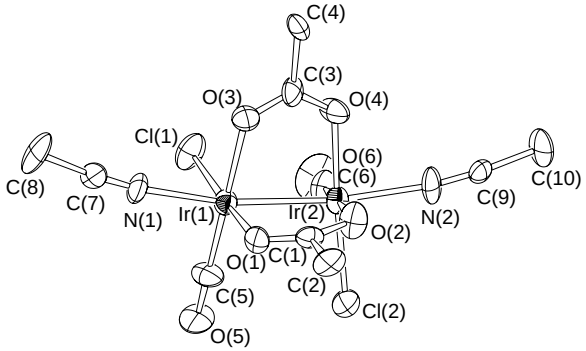


Figure 1. Structure of $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2(CH_3CN)_2]$.

VII-B-2 Preparation and Structure of Bis(μ-acetato)dichlorodicarbonyldiiridium(II) Complexes with group 15 ligands, $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2L_2]$ (L = PPh_3, PCy_3, $P(OPh)_3$, $AsPh_3$, $SbPh_3$), and ESR and DFT Studies of Electronic Structure of Their Cationic Radicals

EBIHARA, Masahiro; KANEMATSU, Naohiro[1]; KAWAMURA, Takashi[1]
([1]Gifu Univ.)

Bis(μ-acetato)dichlorodicarbonyldiiridium(II) complex with group 15 compounds as the axial ligands, $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2L_2]$ (L = PPh_3 **6**, PCy_3 **7**, $P(OPh)_3$ **8**, $AsPh_3$ **9**, $SbPh_3$ **10**) were synthesized. The Ir–Ir distances (2.6936(7) Å of **7**, 2.6458(8) Å of **8**, 2.6207(9) Å of **9** and 2.6200(9) Å of **10**) were longer than those of the complexes with axial MeCN, py or dmso. The complexes had a chemically reversible one-electron oxidation wave of which $E_{1/2}$ (*vs.* Fc^+–Fc) values were between 0.22 of **7** and 0.75 V of **8** depending on their axial ligands. Electrolytic or radiolytic oxidation of **6, 7** and **9** gave their cationic radicals. The ESR spectra of $\mathbf{6}^{+\bullet}$, $\mathbf{7}^{+\bullet}$ and $\mathbf{9}^{+\bullet}$ at 77 K were pseudo-axially symmetric with g tensors of $g_\perp$ = 2.15 and $g_\parallel$ = 1.96, 2.18 and 1.95, and 2.20 and 1.96, respectively. Their hyperfine coupling splitting indicates that their odd electron is delocalized equivalently onto the two axial phosphorous or arsenic atoms. The odd electron densities were estimated form the hyperfine coupling tensors as $\rho \approx 0.1$ on the P atom of $\mathbf{6}^{+\bullet}$ and $\mathbf{7}^{+\bullet}$ and $\rho \approx 0.15$ on the As atom of $\mathbf{9}^{+\bullet}$. These ESR results indicate that their SOMO is the σ_{IrIr} orbital with the σ_{IrP}*/σ_{IrAs}* character. DFT calculations for the model complexes, $[Ir_2(\mu\text{-}O_2CH)_2Cl_2(CO)_2(PH_3)_2]^{+\bullet}$ and $[Ir_2(\mu\text{-}O_2CH)_2Cl_2(CO)_2(AsH_3)_2]^{+\bullet}$, gave an electronic structure consistent with the ESR results. A similar DFT calculation of $[Ir_2(\mu\text{-}O_2CH)_2Cl_2(CO)_2(py)_2]^{+\bullet}$ gave a result that its odd electron is accommodated in the orbital with σ_{IrIr}, σ^*_{IrN} and π_{IrCr}* character. This calculated result, however, is not consistent with the previously reported results of the ESR study of $[Ir_2(\mu\text{-}O_2CMe)_2Cl_2(CO)_2(py)_2]^{+\bullet}$ showing that the odd electron occupies the δ_{IrIr}* orbital.

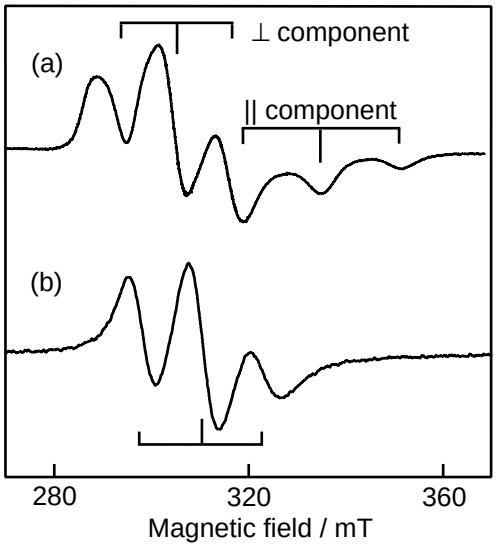


Figure 1. X-Band ESR spectrum of complex $\mathbf{6}^{+\bullet}$ (a) in frozen solution at 77 K and (b) in fluid solution at 273 K.

VII-C Research on the Relationship between Structure of Vanadyl Complex and Insulin-Mimetic Activity

The number of people suffering from diabetes mellitus (DM), one of the life-style related disease, has risen to approximately 14 million, including the figure of potential patients in Japan. DM is classified mainly into two types; insulin-dependent DM (IDDM: type 1) is associated with absolute insulin deficiency and non-insulin dependent DM (NIDDM: type 2) is with relative insulin deficiency. Although NIDDM is treated with several types of synthetic medicines, IDDM is given daily insulin injections to normalize the high blood glucose levels. Vanadium ions and complexes have been found to be active to normalize the high blood glucose level in not only experimental animals but the patients with both type of DM. Then we have developed several types of vanadyl complexes in VO^{2+} state and evaluated their in vitro and in vivo insulinomimetic activities to know the relationship between structure of vanadyl complexes and their insulinomimetic activities.

VII-C-1 Stereospecific and Structure-Dependent Insulin-Mimetic Oxovanadium(IV) Complexes with N,N'-Ethylene-bis-amino Acids

KAWABE, Kenji[1]; TADOKORO, Makoto[1]; ICHIMURA, Akio[1]; KOJIMA, Yoshitane[1]; TAKINO, Toshikazu[2]; SAKURAI, Hiromu[3]
([1]Osaka City Univ.; [2]Kyoto Pharm. Univ.; [3]IMS and Kyoto Pharm. Univ.)

[*J. Am. Chem. Soc.* **121**, 7937 (1999)]

The structure-insulinomimetic activity relationship of the tetradentate oxovanadium(IV) complexes with N,N'-ethylene-bis-amino acid (XeX) was examined. The complexes [VO(XeX)(H_2O)], where X = G (Gly), mG or Gm (N-methylglycine), L- and D-A (Ala), L- and D-V (Val), L- and D-M (Met), and L- and D-P (Pro), were prepared and structurally characterized by X-ray analysis and CD spectra. The insulin-mimetic activity of the complexes was evaluated in an *in vitro* system in terms of IC_{50} value due to FFA release from isolated rat adipocytes. The *in vitro* insulin-like activities of the complexes were found to depend on the absolute configuration of the complexes and the complexes which contain achiral amino acids or D-amino acids were found to have higher insulin-mimetic activities than the corresponding L-isomers. In addition, the insulin-like activities of the complexes were found to depend on the acid dissociation constants of the amino acids as the ligands, partition coefficients and redox potentials of them.

VII-C-2 A New Type of Orally Active Insulin-Mimetic Vanadyl Complex: Bis(1-oxy-2-pyridinethiolate)oxovanadium(IV) with VO(S_2O_2) Coordination Mode

SAKURAI, Hiromu[1]; SANO, Hiromi[2]; TAKINO, Toshikazu[2]; YASUI, Hiroyuki[2]
([1]IMS and Kyoto Pharm. Univ.; [2]Kyoto Pharm. Univ.)

[*Chem. Lett.* 913 (1999)]

A new purple vanadyl complex, bis(1-oxy-2-pyridinethiolato)oxovanadium(IV), VO(OPT), with VO(S_2O_2) coordination mode, was prepared by mixing 2-mercaptopyridine-N-oxide or 1-hydroxy-2-pyridine-thione and $VOSO_4$, and characterized by UV, IR and EPR spectra, magnetic susceptibility and partition coefficient. Based on the higher *in vitro* insulin-mimetic activity of VO(OPT) (IC_{50} = 0.19 mM) than that of $VOSO_4$ (IC_{50} = 0.9 mM), the complex was found to be a potent agent for treating insulin-dependent diabetes mellitus in rats when given by daily intravenous injection or oral administration.

VII-C-3 Evidence for the Improvement of Noninsulin-Dependent Diabetes Mellitus in KKA^y Mice with Daily Oral Administration of Bis(6-methylpicolinato)oxovanadium(IV) Complex

FUJISAWA, Yae[1]; SAKURAI, Hiromu[2]
([1]Kyoto Pharm. Univ., [2]IMS and Kyoto Pharm. Univ.)

[*Chem. Pharm. Bull.* **47**, 1668 (1999)]

A vanadyl complex, bis(6-methylpicolinato)oxo-vanadium(IV), VO(6MPA), with VO(N_2O_2) coordination mode, was found to exhibit a normoglycemic effect on KKA^y mice with hereditary noninsulin-dependent diabetes mellitus with daily oral administration.

VII-C-4 In vivo Coordination Structural Changes of a Potent Insulin-Mimetic Agent, Bis(picolinato)oxovanadium(IV), Studied by Electron Spin-Echo Envelope Modulation Spectroscopy

FUKUI, Koichi[1]; FUJISAWA, Yae[2]; OHYA-NISHIGUCHI, Hiroaki[1]; KAMADA, Hitoshi[1]; SAKURAI, Hiromu[3]
([1]Inst. Life Support Techn., Yamagata Technopolis Found.; [2]Kyoto Pharm. Univ.; [3]IMS and Kyoto Pharm. Univ.)

[*J. Inorg. Biochem.* **77**, 215 (1999)]

Bis(picolinato)oxovanadium(IV) [$VO(pic)_2$] is one of the most potent insulin-mimetic vanadium complexes. To probe coordination structural changes of this complex in vivo and provide insights into the origin of its high potency, an electron spin-echo envelope modulation (ESEEM) study was performed on organs (kidney, liver and bone) of $VO(pic)_2$- and $VOSO_4$-treated rats. Kidney and liver samples from both types of rats exhibited a ^{14}N ESEEM signal that could be attributed to equatorially coordinating amine nitrogen.

The relative intensity of the amine signal was larger for the organs of the rat treated with the less potent $VOSO_4$, suggesting that this amine coordination inhibits the insulin-mimetic activity. The spectra of kidney and liver from the $VO(pic)_2$-treated rat contained a weak signal due to the picolinato imine nitrogen. This suggests that some picolinato species (including both the bis-picolinato and a partially decomposed monopicolinato species) still exist in the organs as a minor species, where the proportions of the picolinato species to the total amount of the EPR-detectable $V^{IV}O$ species are estimated as 8–16% in the kidney and 12–24% in the liver. The picolinato ligand presumably serves to prevent VO^{2+} from being converted into the inactive amine-coordinated species. Bone samples from both types of rats exhibited an ESEEM signal due to ^{31}P nuclei. The VO^{2+} in bone is therefore most likely incorporated into the hydroxyapatite $Ca_{10}(PO_4)_6(OH)$ matrix, which is consistent with the hypothesis that the bone-accumulated VO^{2+} is gradually released and transported to other organs as is Ca^{2+}. No ^{14}N signals were observed, even in the bone samples of the $VO(pic)_2$-treated rats, indicating that vanadium uptake by bone requieres complete decomposition of the complex.

VII-C-5 Role of Vanadium in Treating Diabetes

SAKURAI, Hiromu[1]; FUJISAWA, Yae[2]; FUJIMOTO, Seiki[2]; YASUI, Hiroyuki[2]; TAKINO, Toshikazu[2]
([1]IMS and Kyoto Pharm. Univ.; [2]Kyoto Pharm. Univ.)

[*J. Trace Elem. Exp. Med.* **12**, 393 (1999)]

Since insulin-dependent diabetes mellitus (IDDM), which causes many severe secondary complications, is characterized by hyperglyceria due to absolute deficiency of insulin, the diseases is controlled by daily injection of insulin. Therefore, the development of insulin replacements or mimetics upon oral administration is an important investigation. Recent studies indicate that vanadium, which is proposed to be one of essential trace elements in animals and humans, relates to both glucose and lipid metabolisms, and the metal in turn shows insulin-mimetic effect. Thus several types of vanadium complex have been proposed to be insulin mimetics. In 1990, we proposed first vanadyl-cysteinate complex, which normalized the blood glucose level of IDDM rats on oral administration. On the other hand, simple vanadium compounds such as vanadyl sulfate and sodium vanadate have been reported to be useful to treat human non-insulin-dependent diabetes mellitus (NIDDM). Based on the observations, we have developed several types of vanadyl complexes with different coordination modes such as $VO(O_4)$, $VO(N_4)$, $VO(S_4)$, $VO(O_2N_2)$, $VO(S_2N_2)$ and $VO(O_2S_2)$, and found that vanadyle-methylpicolinate complex with long acting character and low toxicity is the most effective to treat IDDM as well as NIDDM rats, when administered orally. The mechanism was also studied with respect to the pharmacokinetic analysis and vanadium distribution in animals.

VII-C-6 Ternary Complex Formation between VO(IV)-picolinic Acid or VO(IV)-6-Methyl-picolinic Acid and Small Blood Serum Bioligands

KISS, Erzsébet[1]; GARRIBBA, Eugenio[2]; MICERA, Giovanni[2]; KISS, Tamás[3]; SAKURAI, Hiromu[4]
([1]Kossuth Univ.; [2]Univ. Sassari.; [3]Jozsef Attila Univ.; [4]IMS and Kyoto Pharm. Univ.)

[*J. Inorg. Chem.* **78**, 97 (2000)]

In order to assess the role of the low molecular mass bioligands of blood serum in vanadium binding, a study was made of the interactions of the complexes formed in the VO(IV)-picolinic acid and VO(IV)-6-methyl-picolinic acid systems with various low molecular mass constituents of blood serum, such as oxalate, lactate, citrate and phosphate. The speciation of VO(IV) in these ternary systems and also in the binary VO(IV)-picolinic acid and VO(IV)-6-methylpicolinic acid systems was studied by pH-potentiometry at 25 °C and at an ionic strength I = 0.2 M (KCl). The binding modes of the complexes formed were determined by spectral (electronic absorption and EPR) methods. Picolinic acid and 6-methylpicokinic acid were found to form mono and bis complexes through the pyridine nitrogen and carboxylate oxygen, but the presence of the methyl group in 6-methylpicolinic acid surprisingly decreases the stability of its complexes significantly. The results obtained on the ternary systems reveal that mixed ligand complex formation is favoured in these systems, especially with citrate, and must therefore be taken into account in the speciation description of VO(IV) in blood serum.

VII-D-7 An Orally Active Antidiabetic Vanadyl Complex, Bis(1-oxy-2-pyridinethiolato)oxo-vanadium (IV), with $VO(S_2O_2)$ Coordination Mode; *In vitro* and *In vivo* Evaluation in Rats

SAKURAI, Hiromu[1]; SANO, Hiromi[2]; TAKINO, Toshikazu[2]; YASUI, Hiroyuki[2]
([1]IMS and Kyoto Pharm. Univ.; [2]Kyoto Pharm. Univ.)

[*J. Inorg. Biochem.* **80**, 99 (2000)]

According to Pearson's HSAB (hard and soft acids and bases) rule, the vanadyl ion is classified as a hard acid. However, vanadyl-cysteine methyl ester and dithiocarbamate complexes with $VO(S_2O_2)$ and $VO(S_4)$ coordination modes, respectively, that contain bonds with a combination of hard acid (VO^{2+}) and soft base (sulfur) have been found to form stable complexes and exhibit insulin-mimetic activities in *in vitro* and *in vivo* evalutions. Based on such observations, a purple bis(1-oxy-2-pyridinethiolato)oxovanadium(IV) (VO(OPT)) complex with $VO(S_2O_2)$ coordination mode was prepared and found to have a strong insulin-mimetic activity in *in vitro* evalution, which followed *in vivo* effectiveness on intraperitoneal injection and oral administration. Then, we examined the real-time ESR analysis of vanadyl species in the blood of live rats given VO(OPT) by use of the blood circulation

monitoring-ESR method. The clearance of vanadyl species from the blood in terms of half-life ($t_{i/2}$) was determined as 15 min in VO(OPT)-treated rats, while $t_{i/2}$ of $VOSO_4$-treated rats was 5 min, indicating the long-term acting character of VO(OPT). On the basis of the results, VO(OPT) with $VO(S_2O_2)$ coordination mode is proposed to be a potent orally active insulin-mimetic complex in treating insulin-dependent diabetes mellitus in experimental animals.

VII-C-8 Interaction of Vanadyl Complexes with Biological Systems: Structure-Insulinomimetic Activity Relationship of Vanadyl-Picolinate Complexes

SAKURAI, Hiromu[1]; TAMURA, Asuka[2]; TAKINO, Toshikazu[2]; OZUTSUMI, Kazuhiko[3]; KAWABE, Kenji[4]; KOJIMA, Yoshitane[4]
([1]IMS and Kyoto Pharm. Univ.; [2]Kyoto Pharm. Univ.; [3]Ritsumeikan Univ.; [4]Osaka City Univ.)

[*Inorg. React. Mechan.* **2**, 69 (2000)]

Since bis(picolinato)oxovanadium(IV), ($VO(PA)_2$), complex was found in 1995 to have good insulinomimetic activities, the structure-activity relationship was examined to develop more active complexes. By introducing an electron-donating group such as methyl group into the picolinate ligand, bis(3- and 6-methylpicolinate)oxovanadium(IV) ($VO(3MPA)_2$ and $VO(6MPA)_2$) were prepared. By introducing an electron-withdrawing group such as a halogen atom into the ligand, bis(5-iodo- and 4-choloro-picolinato)oxovanadium(IV) ($VO(5IPA)_2$ and $VO(4ClPA)_2$) were prepared. The structure of the complexes was characterized by EXAFS, ESR, IR and absorption spectra.

In vitro insulionmimetic activity of the complexes were in the order of $VO(5IPA)_2 > VO(6MPA)_2 > VO(PA)_2 > VO(3MPA)_2 > VO(4ClPA)_2$. Among four best complexes, both $VO(5IPA)_2$ and $VO(3MPA)_2$ were found to be potent agents to treat the hyperglycemia of streptozotocin (STZ)-induced diabetic rats. On the basis of the results, introduction of halogen atom or methyl group into the picolinate ligand was indicated to be a useful method to design more active insulinomimetic complexes.

VII-C-9 Synthesis of New Vanadyl Complexes of Hydroxyazine-Type Heterocycles and Their Insulin-Mimetic Activities

KATOH, Akira[1]; TAGUCHI, Kazutoshi[1]; OKADA, Hiroko[1]; HARATA, Manabu[1]; FUJISAWA, Yae[2]; TAKINO, Toshikazu[2]; SAKURAI, Hiromu[3]
([1]Seikei Univ.; [2]Kyoto Pharm Univ.; [3]IMS and Kyoto Pharm. Univ.)

[*Chem. Lett.* 866 (2000)]

Four kinds of vanadyl complexes of hydroxyazine-type heterocycles were synthesized. Bis(1,2-dihydro-4,6-dimethyl-2-oxo-1-pyrimidinolato)-and bis(1,2-dihydro-2-oxo-3,5,6-trimethyl-1-pyrimidinolato)-oxovanadium(IV) complexes showed higher insulin-mimetic activity than vanadyl sulfate as a positive control.

VII-C-10 Speciation of Insulin-Mimetic VO(IV)-Containing Drugs in Blood Serum

KISS, Tamás[1]; KISS, Erzsébet[2]; GARRIBBA, Eugenio[3]; SAKURAI, Hiromu[4]
([1]Jozsef Attila Univ.; [2]Kossuth Univ.; [3]Univ. Sassari.; [4]IMS and Kyoto Pharm. Univ.)

[*J. Inorg. Biochem.* **80**, 65 (2000)]

The biospeciations of three potential insulin-mimetic VO(IV) compounds, $VO(maltolate)_2$, $VO(picolinate)_2$ and $VO(6\text{-}Me\text{-}picolinate)_2$, in blood serum were assessed via modelling calculations, using the stability constants reported in the literature for the binary insulin-mimetic complexes and their ternary complexes formed with the most important low molecular mass binders in the serum: oxalic acid, citric acid and phosphate. The binding capabilities of two high molecular mass serum proteins, albumin and transferrin, were also taken into account.

VII-D Syntheses of Transition Metal-Sulfur Clusters and Development of Their Catalysis

This project focuses on the development of the new, relilable synthetic pathways affording the transition metal-sulfur clusters with the tailored core structures in high yield, and also on the determination of the detailed structures of the novel clusters prepared in this study by the X-ray crystallography. Activation of the small molecules will be attempted by the use of polynuclear homo- or hetero-metallic site in these clusters to exploit the new catalytic reactions that are inaccessible by the mononuclear complex catalyst.

VII-D-1 Syntheses of a Dinuclear Ir Complex Containing Bridging Tetraselenide Ligands $[(C_5Me_5)Ir(\mu\text{–}Se_4)_2Ir(C_5Me_5)]$ and its Conversion into $Ir_2Pd_2Se_3$ and $Ir_2Pd_3Se_5$ Clusters

NAGAO, Shoken[1]; SEINO, Hidetake[1]; MIZOBE, Yasushi[2]; HIDAI, Masanobu[1]
([1]Univ. Tokyo; [2]Univ. Tokyo and IMS)

[*Chem. Commun.* 207 (2000)]

Treatment of $[Cp^*IrCl(\mu\text{–}Cl)_2IrCp^*Cl]$ (Cp^* = η^5–C_5Me_5) with Li_2Se_4 gave a tetraselenide-bridged diiridium complex $[Cp^*Ir(\mu\text{–}Se_4)_2IrCp^*]$, which reacted further with two equivalents of $[Pd(PPh_3)_4]$ to afford a mixture of bimetallic tetra- and penta-nuclear selenido clusters $[(Cp^*Ir)_2\{Pd(PPh_3)\}_2(\mu_3\text{–}Se)_2(\mu_2\text{–}Se)]$ and $[(Cp^*Ir)_2\{Pd(PPh_3)\}_3(\mu_3\text{–}Se)_3(\mu_3\text{–}Se_2)]$.

VII-D-2 Preparation of Sulfido-Bridged Di- or Trinuclear Pyrrolylimido and Diazoalkane Complexes Derived from a Tungsten Dinitrogen Complex

SEINO, Hidetake[1]; MIZOBE, Yasushi[2]; HIDAI, Masanobu[1]
([1]Univ. Tokyo; [2]Univ. Tokyo and IMS)

[*Bull. Chem. Soc. Jpn.* **s**, 631 (2000)]

Tungsten pyrrolylimido and diazoalkane complexes, *cis,mer*-$[WCl_2(NNC_4H_4)(PMe_2Ph)_3]$ and *cis,mer*-$[WCl_2(NN{=}CRR')(PMe_2Ph)_3]$, which are readily derived from the dinitrogen complex *cis*-$[W(N_2)_2(PMe_2Ph)_4]$, reacted with $[PPh_4][WS_4]$ to give the sulfide-bridged di- or trinuclear pyrrolylimido and diazoalkane complexes, $[PPh_4][WCl(NNC_4H_4)(PMe_2Ph)_2(\mu\text{–}S)_2WS_2]$ (**1**) and $[PPh_4][WCl(NN{=}CRR')(PMe_2Ph)_2(\mu\text{–}S)_2WS_2]$ (**2**; R = R' = Me (**2a**); R = Me, R' = Ph), or $[\{WCl(NNC_4H_4)(PMe_2Ph)_2(\mu\text{–}S)_2\}_2W]$ (**3**) and $[\{WCl(NN{=}CMePh)(PMe_2Ph)_2(\mu\text{–}S)_2\}_2W]$. Treatment of **1** or **2a** with tetraalkylthiuram disulfide resulted in the formation of sulfide-dithiocarbamate complexes: $[W(NNC_4H_4)(PMe_2Ph)(S_2CNR_2)(\mu\text{–}S)_2WS(S_2CNR_2)]$ (R = Et, Pr) and $[W(NN{=}CMe_2)(PMe_2Ph)(S_2CNEt_2)(\mu\text{–}S)_2WS(S_2CNEt_2)]$. On the other hand, replacement of two PMe_2Ph ligands in **1** and **2** by $Ph_2PCH_2CH_2PPh_2$ (dppe) afforded $[PPh_4][WCl(NNC_4H_4)(dppe)(\mu\text{–}S)_2WS_2]$ and $[PPh_4][WCl(NN{=}CRR')(dppe)(\mu\text{–}S)_2WS_2]$ (R = R' = Me; R = Me, R' = Ph (**3**)), where **3** has been shown to react further with $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) to give a bimetallic trinuclear complex $[WCl(NN{=}CMePh)(dppe)(\mu\text{–}S)_2W(\mu\text{–}S)_2Rh(cod)]$.

VII-E Reductive Activation of Carbon Monoxide derived from Carbon Dioxide and Oxidative Activation of Hydroxy- and Oxo-Groups Derived from Water

An electrophilic attack of CO_2 to coordinatively unsaturated low valent metal complexes affords M-η^1-CO_2 complexes, which are easily converted to M-CO ones in both protic and aprotic media. Accordingly, organic synthesis through M-CO complexes derived from CO_2 is highly desired from the development of a new C1 resources. A major problem of the reduction of CO_2 using homogeneous catalysis is reductive cleavages of M-CO bonds under reductive conditions. Because of accumulation of too many electrons in the central metals. Ligand localized redox reactions rather than metal centered ones as electron sources would avoid unfavorable CO evolution in the reduction of CO_2. A flexible ligand which has an ability to change the bonding modes among monodentate, bidentate and bridging form to connect metals and carbonyl carbon of M-CO bonds would meet the requirements of smooth M-η^1-CO_2 formation and depression of reductive cleavage of M-CO bond under reductive conditions.

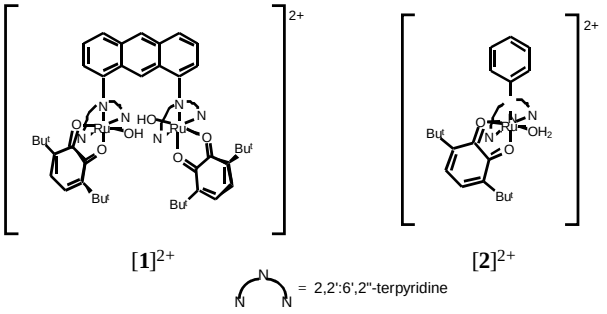
Acids or bases generated in industrial process are not utilized as resources and just wasted after neutralization. Proton gradient (Δp) between inside and outside of a cell is depicted as the sum of electric activity ($\Delta\psi$) and chemical activity (ΔpH) components. $\Delta p = \Delta\psi - Z\Delta$pH ($Z = 2.303RT/F$) Proton gradient is equivalent to the neutralization energy because the neutralization reaction takes place to form water if the separating membrane is removed. Thus, neutralization energy results from the formation of water. Biological system effectively creates and consumes neutralization energy in various reactions. Acids and bases, therefore, have potential energy sources, which are provided by chemical bondings (chemical energy). Along this line, we tried to convert the neutral energy to electronic energy by using ruthenium-aqua complexes.

VII-E-1 Oxidation of Hydrocarbon by Mono- and Dinuclear Ruthenium Quinone Complexes via Hydrogen Atom Abstraction

WADA, Tohru; TSUGE, Kiyoshi; TANAKA, Koji

[*Chem. Lett.* 910 (2000)]

Deprotonation and two-electron oxidation of dinuclear $[Ru^{II}_2(OH)_2(3,6\text{-}Bu^t_2Q)_2(btpyan)]^{2+}$ (Bu^t_2Q = 3,6-di(*tert*-butyl)-1,2-quinone, btpyan = 1,8-bis-(2,2':6',2"-terpyridyl)anthracene, $[\mathbf{1}]^{2+}$) was converted to bis(ruthenium-oxo) complex $[Ru^{II}_2(O)_2(3,6\text{-}Bu^t_2Q)_2$-$(btpyan)]^{2+}$, which oxidized 1,3-cychrohexadiene, 1,2-dihydronaphtalene to corresponding aromatics in higher yields (90%, 94%) in the presence of $AgClO_4$ and Bu^tOK. An analogous mononuclear $[Ru^{II}(OH_2)(3,6\text{-}Bu^t_2Q)(Ph\text{-}terpy)]^{2+}$ (Ph-terpy = 4'-phenyl-2,2':6',2"-terpyridine, $[\mathbf{2}]^{2+}$) was converted to the ruthenium-hydroxo complex $[Ru^{II}(OH)(3,6\text{-}Bu^t_2Q)(Ph\text{-}terpy)]^{2+}$ under similar condoitions, but displayed the low activity for the oxidation compared with the dinuclear complex $[\mathbf{1}]^{2+}$. On the other hand, 9,10-dihydroanthracene was converted to anthracene by $[\mathbf{2}]^{2+}$ in 42% yield, while it was not oxidized by $[\mathbf{1}]^2$ due to the steric hindrance.



$[\mathbf{1}]^{2+}$ $[\mathbf{2}]^{2+}$

VII-E-2 Electrochemical Water-Oxidation to Dioxygen Catalyzed by Oxidized Form of Bis(ruthenium-hydroxo) Complex in H_2O

WADA, Tohru; TSUGE, Kiyoshi; TANAKA, Koji

[*Angew. Chem., Int. Ed. Engl.* **39**, 1479 (2000)]

Much attention has been paid to oxidation of water to dioxygen by homogeneous catalysts. Of particular interest are di- and tetranuclear complex derived from transition metals, since extended X-ray absorption fine structure studies indicated that the O_2-evolving center (OEC) in Photosystem II is composed of a tetranuclear Mn cluster with di-μ-oxo dimeric Mn units. The cyclic voltammetry of $[Ru(OH)(Q)Ru(OH)(Q)]^{2+}$ showed two redox couples at $E_{1/2}$ = 0.43 V and 0.35 V in MeOH. After $[Ru(OH)(Q)Ru(OH)(Q)]^{2+}$ was converted to $[Ru(O)(SQ)Ru(O)(SQ)]^0$ by an addition of 2.0 equiv of *t*BuOK to the MeOH solution, the redox process of the resultant oxo complex displayed also two nearly reversible redox couples at $E_{1/2}$ = 0.40 V and 0.30 V (eq. 1).

$$[Ru(Q)(O)Ru(Q)(O)]^{2+} \underset{0.40\ V}{\overset{e^-}{\rightleftharpoons}} [Ru(Q)(O)Ru(SQ)(O)]^{+} \underset{0.30\ V}{\overset{e^-}{\rightleftharpoons}} [Ru(SQ)(O)Ru(SQ)(O)]^{0} \quad (1)$$

The complex on ITO electrode exhibited a broad redox couple centered at +0.40 V (*vs.* Ag/AgCl), and an irreversible anodic wave at +1.20 V, which is associated with two-electron oxidations of $[Ru(OH)(Q)Ru(OH)$-$(Q)]^{2+}$ and $[Ru(O)(Q)Ru(O)(Q)]^{2+}$ affording $[Ru(OH)$-$(Q)Ru(OH)(Q)]^{4+}$ and $[Ru(O)(Q)Ru(O)(Q)]^{4+}$, respectively. A strong anodic current at potential more positive than +1.5 V is apparently caused by the oxidation of water to dioxygen. Indeed, when controlled-potential electrolysis of the bis(ruthenium-hydroxo) complex modified on ITO electrode at 1.70 V

(*vs.* Ag/AgCl) in water (pH 4.0), 1.1 ml of O_2 was evolved after 20.2 C passed in the electrolysis. The current efficiency for O_2 evolution was 95% and the turnover number was 500 based on the complex. The current density of the electrode was 0.12 mA/cm^2 in the initial stage. The current gradually decreased with decrement of pH in the aqueous phase and almost stopped at pH 1.2. The current density of the electrode for the oxidation of water recovered, when the pH of water was readjusted to 4.0 by an addition of aqueous KOH to the aqueous phase. The oxidation of water by the bis(ruthenium-hydroxo) complex modified ITO finally evolved 15.0 ml of O_2 (turnover 6730), before the evolution completely stopped in 40 h.

VII-E-3 Selective Production of Acetone in Electrochemical Reduction of CO_2 Catalyzed by Ru-naphthyridine Complex

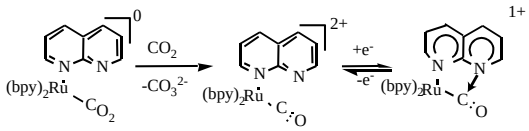
MIZUKAWA, Tetsunori; TSUGE, Kiyoshi; NAKAJIMA, Hiroshi; TANAKA, Koji

[*Angew. Chem., Int. Ed. Engl.* **111**, 373 (1999)]

Carbon dioxide is smoothly converted to CO on metals by oxide transfer from M–CO_2 to CO_2, while reductive cleavage of the resultant metal–CO bond (eq. 1) is the major problem in utilization of CO_2 as a C1 resource. Acylation of the metal–CO complexes

$$[M–\eta^1–CO_2]^0 \xrightarrow[-CO_3^{2-}]{CO_2} [M–CO]^{2+} \xrightarrow{2e^-} [M]^0 + CO \quad (1)$$

derived from CO_2 under reductive conditions, therefore, would provide new methodologies for utilization of CO_2 as a staring material in organic synthesis. One and two-electron reductions of $[Ru(bpy)_2(napy)(CO)](PF_6)_2$ (napy = 1,8-naphthyridine-κ*N*) take place in napy localized orbitals, which induce nucleophilic attack of the free nitrogen of κ^1-napy to the carbonyl carbon (eq. 2). Electron transfer from the reduced form of napy to the CO group in the metallacycle enables reductive activation of the CO group without the



(2)

metal–CO bond cleavage and gives rise to electrophilic attack of $(CH_3)_4N^+$ to the carbonyl carbon. As a result, $CH_3C(O)CH_3$ and CO_3^{2-} were catalytically produced in the electrochemical reduction of $[Ru(bpy)(napy–\kappa N)_2(CO)_2](PF_6)_2$ in the presence of in CO_2-saturated DMSO when $(CH_3)_4NBF_4$ was used as an electrolyte (eq. 3).

$$2CO_2 + 4e^- + 2(CH_3)_4N^+ \rightarrow CH_3C(O)CH_3 + CO_3^{2-} + 2(CH_3)_3N \quad (3)$$

VII-E-4 Energy Conversion from Proton Gradient to Electricity Based on Characteristic Redox Behavior of an Aqua Ruthenium Complex

TSUGE, Kiyoshi; KURIHARA, M.; TANAKA, Koji

[*Bull. Chem. Soc. Jpn.* **73**, 607 (2000)]

A ruthenium aqua complex with a quinone ligand $[Ru(trpy)(dbq)(H_2O)]^{2+}$ (trpy = 2,2':6,2"-terpyridine, dbq = 3,5-di-*t*-butyl-1,2-benzoquinone) $[Ru(q)(H_2O)]^{2+}$) was prepared. Its electrochemical properties and electronic absorption spectra were measured in the presence of a base in acetone. The detailed analysis of those measurements revealed that the addition of base caused not only the deprotonation but also the reduction of $[Ru(q)(H_2O)]^{2+}$. The redox reactions coupled with acid-base reactions were demonstrated from the large difference in redox properties of aqua and hydroxo complexes. Taking advantage of unique redox reactions induced by the acid-base equilibrium between aqua and hydroxo complexes, we have succeeded in construction of the first energy transducer which converts the proton gradient to electricity. A similar ruthenium aqua complex with a bipyridine ligand, $[Ru(trpy)(bpy)(H_2O)]^{2+}$, also reversibly dissociates a proton of the aqua ligand. However, it has no ability to convert the proton gradient to electricity due to the lack of a suitable molecular orbital, which can accommodate electrons on the electron-rich hydroxo ligand.

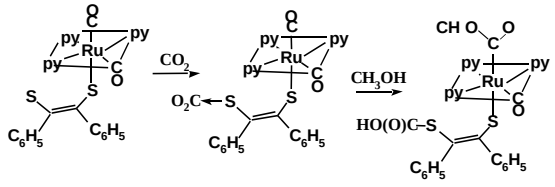
$$[M(Q)(H_2O)]^{2+} + OH^- \rightleftharpoons [M(S)(OH)]^+ + H_2O \quad (1)$$

VII-E-5 Double Addition of CO_2 and CH_3OH to Ruthenium Carbonyl Complex with Novel Mono-dentate Dithiolene

SUGIMOTO, Hideki; TSUGE, Kiyoshi; TANAKA, Koji

[*Chem. Lett.* 1007 (1999)]

The reaction of $[Ru(CO)_2Cl(terpy)]PF_6$ and Na_2mnt in CH_3OH gave a yellow complex (**1a**) with mono-dentate mnt $[Ru(CO)_2(terpy\text{-}\kappa^3N,N',N'')(mnt\text{-}\kappa S)]$ and with bidentate mnt $[Ru(CO)_2(terpy\text{-}\kappa^2N,N')(mnt\text{-}\kappa^2S,S')]$. On the other hand, the reaction between $[Ru(CO)_2Cl(terpy)]^+$ and $Cs_2S_2C_2Ph_2$ in CH_3OH under aerobic conditions gave a complex (**2**) with thio-carboxylic acid and methoxy carbonyl groups rather than the expected $[Ru(CO)_2(SSC_2Ph_2\text{-}\kappa^1S)(terpy\text{-}\kappa^3N,N',N'')]$ (**1**). The most characteristic feature of **2** is that the carbonyl and the uncoordinate thiolate of **1** are changed to methoxy carbonyl and thio-carboxylato units, respectively. Although it is not clear that the carboxylato moiety of **2** exists as protonated or deprotonated form by X-ray analysis, the former is deduced from the elemental analysis and the charge balance of **2**. Unprecedented double addition of CO_2 and methanol to thiolate and carbonyl ligands located far from each other is apparently caused by the long-range π–π interaction between basic $Ph_2C_2SS^{2-}$ and acidic carbonyl units through d-orbitals of the rutheniurn atom.



VII-E-6 Structural and Spectroscopic Characterization of Ruthenium(II) Complexes with Methyl, Formyl and Acetyl Groups as Model Species in Multi-Step CO_2 Reduction

OOYAMA, Dai; TOMON, Takashi; TSUGE, Kiyoshi; TANAKA, Koji

The molecular structures of Ru(II) complexes with methyl, formyl and acetyl groups $[Ru(bpy)_2(CO)L]^+$ (L = CH_3, C(O)H and $C(O)CH_3$) were examined from the view point of active species in multi-step reduction of CO_2 on Ru. The methyl complex was prepared by the reaction of $[Ru(bpy)_2(OH_2)_2]^{2+}$ with trimethylsilyl acetylene and fully characterized by infrared, Raman, ^{13}C NMR and single-crystal X-ray crystallography. Disorder of the Ru–CO and Ru–C(O)H bonds in the crystal structure of the formyl complex made it difficult to determine the bond parameters of the two groups accurately, but the molecular structure of the analogous acetyl complex, which was obtained by the reaction of $[Ru(bpy)_2(CO_3)]$ with propiolic acid, was determined by X-ray analysis. The ruthenium-carbonyl (Ru–C–O) bond angles of the methyl and acetyl complex with 174(1) and 175.5(5)°, respectively, are in the ranges of those of previously characterized $[Ru(bpy)_2(CO)L]^{n+}$ (L = CO_2, C(O)OH, CO and CH_2OH). On the other hand, the Ru–CH_3 and Ru–$C(O)CH_3$ bond distances showed unusual relationship against the stretching frequency in the raman spectra.

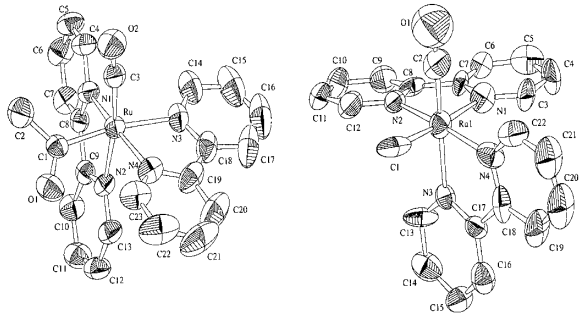


Figure 1. Molecular Structures of $[Ru(bpy)_2(CO)(C(O)CH_3)]^+$ and $[Ru(bpy)_2(CO)(CH_3)]^+$.

VII-F Synthesis of Transition-Metal Chalcogenido Complexes and Their Cluster-Forming Reactions

Transition-metal chalcogenido aggregates are of well-documented importance in biological systems and industrial processes such as hydrodesulfurization. A wide variety of metal chalcogenido clusters have been synthesized, in which the tetrathiometalato anions have been widely used as a building block. In this project, we are focusing on preparation of chalcogenido/chalcogenolato complexes as a precursor for cluster syntheses and their cluster-forming reactions.

VII-F-1 Synthesis of Bis{(2-dimthylphenylphosphino)ethane-1-thiolato}bis(tert-butylthiolato)molybdenum(IV) and Its Cluster-Forming Reactions with $FeCl_2$ and CuBr

ARIKAWA, Yasuhiro[1]; KAWAGUCHI, Hiroyuki; KASHIWABARA, Kazuo[1]; TATSUMI, Kazuyuki[1]
([1]Nagoya Univ.)

[*Inorg. Chem.* **38**, 4549 (1999)]

The Mo(IV) complex $Mo(dmsp)(S^tBu)_2$ (**1**) was readily prepared by the reaction of $Mo(S^tBu)_4$ with 2 equiv of $HSCH_2CH_2PMe_2$ (Hdmsp). The X-ray analysis of **1** reveals a distorted octahedral geometry with a *cis*-disposition of two ^{t}BuS ligands. Treatment of **1** with $FeCl_2$ and CuBr led to the formation of heterometallic clusters, $[Mo(O)(dmsp)_2]_2FeCl_2$ (**2**) and $[MoBr(dmsp)_2(\mu_3\text{-}S)Cu_2]_2(\mu_2\text{-}S^tBu)_2$ (**3**), respectively. The oxo ligand in **2** is most probably derived from adventitious H_2O contained in hygroscopic $FeCl_2$. In the structure of **2**, an $FeCl_2$ unit bridges two square-pyramidal $Mo(O)(dmsp)_2$ fragments through interactions between iron and sulfur atoms of dmsp. The formation of **3** involves C–S bond cleavage of one ^{t}BuS ligand of **1** and rearrangement of ligands between the Mo and Cu sites, resulting in the structure consisting of two $MoCu_2BrS(dmsp)_2$ units and two ^{t}BuS bridges.

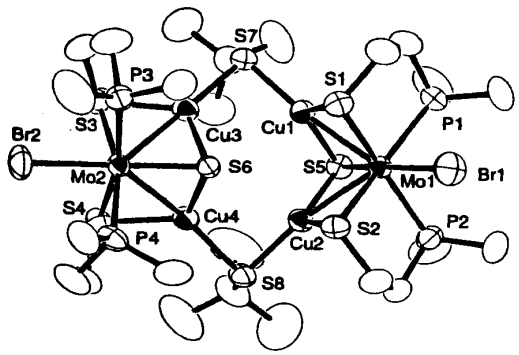


Figure 1. Structure of **3**.

VII-F-2 Synthesis and Structure of a Triply-Fused Incomplete-Cubane Cluster $[\{(\eta^5\text{-}C_5Me_5)WS_3\}_3Cu_7(MeCN)_9](PF_6)_4$ and a 2D Polymer $[(\eta^5\text{-}C_5Me_5)WS_3Cu_3(MeCN)(pz)]PF_6$ (pz = pyrazine)

LANG, Jian-Ping[1]; KAWAGUCHI, Hiroyuki; TATSUMI, Kazuyuki[1]
([1]Nagoya Univ.)

[*Chem. Commun.* 2315 (1999)]

The reaction of $(PPh_4)[Cp^*W(S)_3]$ with 3 equiv of $[Cu(MeCN)_4](PF_6)$ in MeCN yielded a triply-fused incomplete-cubane cluster $[\{(\eta^5\text{-}C_5Me_5)WS_3\}_3Cu_7(MeCN)_9](PF_6)_4$ (**1**). Furthermore, we constructed a 2D polymeric structure $[(\eta^5\text{-}C_5Me_5)WS_3Cu_3(MeCN)(pz)]PF_6$ (**2**) by treating **1** with pyrazine in the presence of LiCl. The $W_3S_9Cu_7$ framework of **1** is broken during the reaction with LiCl and pyrazine, providing a WS_3Cu_3 incomplete-cubane cluster as a building block of the stacked sheet structure of **2**.

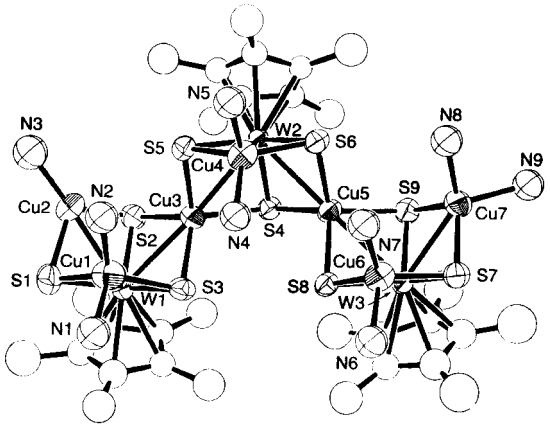


Figure 1. Structure of **1**.

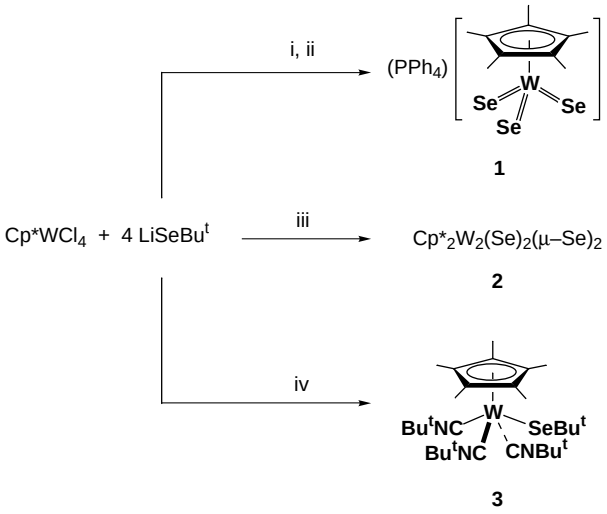
VII-F-3 Synthesis and Structures of the Halfsandwich W(VI) Triselenido and W(II) Selenolato Complexes

KAWAGUCHI, Hiroyuki; TATSUMI, Kazuyuki[1]
([1]Nagoya Univ.)

[*Chem. Commun.* 1299 (2000)]

The reaction of Cp^*WCl_4 with $LiSe^tBu$ at room temperature gave rise to a mixture of *syn*- and *anti*-$Cp^*_2W_2(\mu\text{-}Se)_2(Se)_2$ (**1**), in which C–Se bond cleavage took place. When the similar reaction was carried out in the presence of ^{t}BuNC, the W(II) selenolato complex $Cp^*W(Se^tBu)(CN^tBu)_3$ (**2**) was formed. The structure of **2** was confirmed by X-ray analysis. While two of the isocyanides are nearly linear [C–N–C = 175.8(8)°, 164.3(7)°], the other contains essentially an sp^2-type nitrogen atom [N–C–N, 128.7(6)°] amongst the smallest of the known bent isocyanides (122–156°). In another experiment, a freshly prepared $Cp^*WCl_4/LiSe^tBu$ mixture was quickly transferred into Li_2Se_2 in THF. Cation exchange with PPh_4Br in CH_3CN provided $(PPh_4)[Cp^*W(Se)_3]$ (**3**) concomitant with a mixture of *syn*- and *anti*-**1**. The anion part of **3** has a three-legged piano-stool structure. The average W–Se distance

(2.322 Å) of **3** is similar to that of $(PPh_4)_2[WSe_4]$.



Scheme 1. *Reagents and conditions*: i, Li_2Se_2, THF; ii, PPh_4Br, CH_3CN; iii, 30 min, –78 °C, THF; iv, Bu^tNC, THF.

VII-G Artificial Photoreaction systems on a Protein Surface

New methodologies are developed which one can construct an artificial photoreaction systems on a protein matrix. Using the protein-based photosystems, we aim to investigate characteristics for electron transfer phenomena in a protein matrix. Furthermore, based on these results, we would like to design and semisynthesize an efficient photoreaction system such as an artificial photoreaction center.

VII-G-1 Direct Observation of the Ferric-Porphyrin Cation Radical as an Intermediate in the Photo-Triggered Oxidation of Ferric- to Ferryl-Heme Tethered to $Ru(bpy)_3$ in Reconstituted Myoglobin

HAMACHI, Itaru[1,2]; TSUKIJI, Shinya[1]; SHINKAI, Seiji[1]; OISHI, Shigero[3]
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[*J. Am. Chem. Soc.* **121**, 5500 (1999)]

Using semisynthetic myoglobins ($Ru(bpy)_3$–Mbs) with covalently-appended $Ru(bpy)_3$ (bpy = 2,2'-bipyridine), an oxidized-Mb is photo-produced through intramolecular electron abstraction reaction as a key step. UV-visible spectra, electron paramagnetic resonance measurements and reactivity tests identify the photo-oxidized Mb as a ferryl-species (*i.e.* Fe^{4+}–heme). By circular dichroism (CD) spectroscopy, high performance liquid chromatography (HPLC) and SDS polyacrylamide gel electrophoresis (SDS-PAGE), the photo-oxidation proceeds without the damage of the protein structure. Significantly, we report the first direct observation of ferryl-Mb photogeneration via the intermediate porphyrin cation radical. As a consequence of this observation and proposed mechanism, the rate constants for each step can be clearly determined. The photo-excited $Ru^{2+}(bpy)_3$ is oxidatively quenched by $[Co(NH_3)_5Cl]^{2+}$, a sacrificial acceptor, to produce $Ru^{3+}(bpy)_3$ which then proceeds to abstract an electron from the porphyrin ring with a first order rate constant of $7.1 \times 10^5\ s^{-1}$, in the first step. The electron transfer is followed by iron(III) oxidation by the porphyrin radical with concurrent deprotonation (a first order rate constant of $4.0 \times 10^4\ s^{-1}$ at pH 7.5, and $2.0 \times 10^5\ s^{-1}$ at pH 9.0) in the second step. Consistent with this mechanism, it is demonstrated that the rate of the fast step of the porphyrin radical generation is independent of pH, whereas the slower step of ferryl-heme formation is dependent on pH. Simulation of the detailed pH dependence of the kinetics clearly shows that the deprotonation-protonation equilibrium of the protein matrix can control the ferryl-heme generation in a heme pocket of Mb.

VII-G-2 Construction of Artificial Photosynthetic Reaction Centers on a Protein Surface: Vectorial, Multistep, and Proton-Coupled Electron Transfer for Long-Lived Charge Separation

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Artificial photosynthetic reaction centers have been constructed on a protein surface by cofactor reconstitution, which mimic the function of photosynthetic organisms to convert light energy to chemical potential in the form of long-lived charge-separated states. They feature a ruthenium tris(2,2'-bipyridine) moiety as the sensitizer, which is mechanically linked (*i.e.* in catenane-type) with a cyclobis(paraquat-*p*-phenylene) unit (BXV^{4+}, acceptor) and covalently linked with a protoheme or Zn-protoporphyrin (donor) located in the myoglobin pocket. Reconstitution of apo-myoglobin (Mb) with **1** and **2** affords the two Mb-based artificial triads, Mb-$(Fe^{III}OH_2)$–Ru^{2+}–BXV^{4+} and Mb(Zn)–Ru^{2+}–BXV^{4+}. Laser flash photolysis of the $Ru(bpy)_3$ moiety of Mb$(Fe^{III}OH_2)$–Ru^{2+}–BXV^{4+} in an aqueous solution yields an initial charge-separated state, Mb$(Fe^{III}$-$OH_2)$–Ru^{3+}–$BXV^{3+\bullet}$, via noncovalent electron transfer, followed by dark electron transfer to generate an intermediate consisting of porphyrin cation radical, Mb-$(Fe^{III\bullet}(OH_2)$–Ru^{2+}–$BXV^{3+\bullet}$. Mb$(Fe^{III\bullet}(OH_2)$–Ru^{2+}–$BXV^{3+\bullet}$ thus generated is subsequently converted, via a proton-coupled process and with a quantum yield of 0.005, into the final charge-separated state, Mb$(Fe^{IV}$=O)–Ru^{2+}–$BXV^{3+\bullet}$, which bears an energy more than 1 eV above the ground state and a lifetime (τ > 2 ms) comparable to that of natural photosynthetic reaction center. By analogy with a related system reported previously, it was considered that back ET from $BXV^{3+\bullet}$ to Mb$(Fe^{IV}$=O) might be coupled to the protonation of Mb$(Fe^{IV}$=O) and governed by the slow interconversion between the metal-oxo form and the proton-activated species, rendering the CS state Mb$(Fe^{IV}$=O)–Ru^{2+}–$BXV^{3+\bullet}$ specially long-lived. Control experiments clearly demonstrated that partial incorporation of the triads into the protein matrix plays a crucial role in regulating the electron transfer pathway and stabilizing the charge separation state.

VII-G-3 Direct Comparison of Electron Transfer Properties of Two Distinct Semisynthetic Triads with Non-Protein Based Triad: Unambiguous Experimental Evidences on Protein Matrix Effects

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In order to understand the roles of protein matrix in electron transfer (ET) within biological systems, a heme-based donor (Zn-heme: ZnPP)-sensitizer ($Ru^{2+}(bpy)_3$)-acceptor (cyclic viologen: BXV^{4+}) triad **1**

was used as a probe molecule. Two semisynthetic systems, Cyt-b_{562}(**1**) and Mb(**1**), in which the triad is incorporated into cytochrome b_{562} (Cyt-b_{562}) or into myoglobin (Mb), were constructed by cofactor reconstitution. These two semisynthetic proteins were compared with the triad itself (*i.e.* without protein matrix) using absorption spectroscopy, steady state emission and excitation studies, laser flash photolysis experiments, and molecular modelling. Photoexcitation of the ZnPP moiety of Cyt-b_{562}(**1**) or Mb(**1**) leads to a direct ET from the triplet state of ZnPP state (^{3}ZnPP) to BXV^{4+} to generate a final charge separated (CS) state, Cyt-b_{562}(Zn^+)–Ru^{2+}–$BXV^{3+\bullet}$ or Mb(Zn^+)–Ru^{2+}–$BXV^{3+\bullet}$. On the other hand, direct ET from the excited ZnPP moiety to the BXV^{4+} moiety is also involved in **1** in the absence of the protein matrix, but the excited state of ZnPP involved is not ^{3}ZnPP, but the singlet excited state (^{1}ZnPP) in this pathway. When the $Ru^{2+}(bpy)_3$ moiety of Cyt-b_{562}(**1**) or Mb(**1**) is excited, a stepwise ET relay occurs with the ion-pair, Cyt-b_{562}(Zn)–Ru^{3+}–$BXV^{3+\bullet}$ or Mb(Zn)–Ru^{3+}–$BXV^{3+\bullet}$, as an intermediate, leading to the same final CS state as that generated in the direct ET pathway. The lifetimes of the corresponding final CS states were determined to be 300 ns for **1** in the absence of the protein matrix, 600–900 ns for Cyt-b_{562}(**1**) and 1.1–18 μs for Mb(**1**), the values of which are greatly affected by the protein matrix. Molecular modeling study of the three systems consistently explained the differences of their photophysical behavior.

VII-G-4 Cyclodextrin-Appended Myoglobin as a Tool for Construction of a Donor-Sensitizer-Acceptor Triad on a Protein Surface

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A protein-based and noncovalently-linked donor-sensitizer-acceptor triad has been prepared by self-assembly via mechanical linkage and hydrophobic interaction, and its photoinduced electron transfer properties has been studied. Cyclodextrin(CD)-appended hemes are successfully reconstituted with apo-myoglobin to yield CD-appended myoglobins. Upon addition of viologen-connected ruthenium tris(bipyridine) bearing adamantane unit, a donor-sensitizer-acceptor triad is formed on a protein surface, which shows a stepwise, vectrial electron transfer reaction by visible light irradiation. Clearly, this is a novel type of supramolecular photoreaction system.