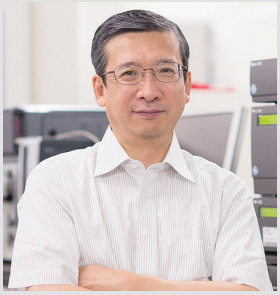
RESEARCH ACTIVITIES
Life and Coordination-Complex Molecular Science

Department of Life and Coordination-Complex Molecular Science is composed of two divisions of biomolecular science, two divisions of coordination-complex molecular science, and one adjunct division. Biomolecular science divisions cover the studies on functions, dynamic structures, and mechanisms for various biomolecules such as sensor proteins, metalloproteins, biological-clock proteins, glycoconjugates, antibodies, and motor proteins. Coordination-complex divisions aim to develop molecular catalysts and functional metal complexes for transformation of organic molecules, and molecular materials with photonic-electronic-magnetic functions and three-dimensional complex structures. Interdisciplinary alliances in this department aim to create new basic concepts for the molecular and energy conversion through the fundamental science conducted at each division.

Bioinorganic Chemistry of Metalloproteins Responsible for Metal Homeostasis and Signal Sensing

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



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Keywords Bioinorganic Chemistry, Metalloproteins, Sensor Protein

Transition metal ions and metalloproteins play crucial roles in meeting the energy demands of the cell by playing roles in intermediary metabolism and in signal transduction processes. Although they are essential for biological function, metal ion bioavailability must be maintained within a certain range in cells due to the inherent toxicity of all metals above a threshold. This threshold varies for individual metal ions. Homeostasis of metal ions requires a balance between the processes of uptake, utilization, storage, and efflux and is achieved by the coordinated activities of a variety of proteins including extracytoplasmic metal carriers, ion channels/pumps/transporters, metal-regulated transcription and translation proteins, and enzymes involved in the biogenesis of metal-containing cofactors/metalloproteins. In order to understand the processes underlying this complex metal homeostasis network, the study of the molecular processes that determine the protein-metal ion recognition, as well as how this event is transduced into a functional output, is required. My research interests are focused on the elucidation of the structure and function relationships of metalloproteins responsible for the regulation of biological homeostasis.

I am also working on gas sensor proteins. Gas molecules such as O_2, NO, CO and ethylene are present in the environment and are endogenously (enzymatically) produced to act as signaling molecules in biological systems. Sensing these gas molecules is the first step in their acting as signaling molecules. Sensor proteins are usually required. Input signals generated by gas sensing have to transduce to output signals that regulate biological functions. This is achieved by biological signal-transduction systems. Recognition of the cognate gas molecules is a general mechanism of functional regulation for gas sensor proteins. This induces conformational changes in proteins that controls their activities for following signal transductions. Interaction between gas molecules and sensor proteins is essential for recognition of gas molecules. Metal-containing prosthetic groups are widely used. In my research group, our research focuses on transition metal-based gas-sensor proteins and the signaling systems working with them.

Selected Publications

- D. Matsui, N. Muraki, K. Chen, T. Mori, A. A. Ingram, K. Oike, H. Gröger, S. Aono and Y. Asano, "Crystal Structural Analysis of Aldoxime Dehydratase from *Bacillus sp.* OxB-1: Importance of Surface Residues in the Optimization for Crystallization," *J. Inorg. Biochem.* **230**, 111770–111779 (2022).
- Y. Ikenoue, Y. Tahara, M. Miyata, T. Nishioka, S. Aono and H. Nakajima, "Use of a Ferritin L134P Mutant for the Facile Conjugation of Prussian Blue in the Apoferritin Cavity," *Inorg. Chem.* **60**, 4693–4704 (2021).
- M. Nishinaga, H. Sugimoto, Y. Nishitani, S. Nagai, S. Nagatoishi, N. Muraki, T. Tosha, K. Tsumoto, S. Aono, Y. Shiro and H. Sawai, "Heme Controls the Structural Rearrangement of Its Sensor Protein Mediating Bacterial Survival," *Commun. Biol.* **4**, 467 (12 pages) (2021).
- N. Muraki, K. Takeda, D. Nam, M. Muraki and S. Aono, "Structural Characterization of Thermoglobin from a Hyperthermophilic Bacterium *Aquifex aeolicus*," *Chem. Lett.* **50**, 603–606 (2021).
- N. Muraki, C. Kitatsuji, Y. Okamoto, T. Uchida, K. Ishimori and S. Aono, "Structural Basis for Heme Transfer Reaction in Heme Uptake Machinery from Corynebacteria," *Chem. Commun.* **55**, 13864–13867 (2019).
- N. Muraki, K. Ishii, S. Uchiyama, S. G. Itoh, H. Okumura and S. Aono, "Structural Characterization of HypX Responsible for CO Biosynthesis in the Maturation of NiFe-Hydrogenase," *Commun. Biol.* **2**, 385 (12 pages) (2019).

1. Complex Formation between [NiFe] Hydrogenase Maturation Factors Responsible for $Fe(CN)_2CO$ Biosynthesis

[NiFe] hydrogenase is a metalloenzyme that catalyzes the oxidation of hydrogen and the reduction of protons reversibly. As its name implies, the metal cluster of [NiFe] hydrogenase is composed of nickel and iron. In the active center of [NiFe] hydrogenase, nickel is ligated by the three cysteine side chains of the protein, while iron is coordinated with two cyanide ions and one carbon monoxide in addition to the cysteine side chains. This intricate metal complex is not spontaneously formed, but is biosynthesized step-by-step in coordination with multiple proteins. The cyanide ions and carbon monoxide are also biosynthesized to form $Fe(CN)_2CO$ complex, which is then incorporated into hydrogenase. We have reported the crystallographic analysis of HypX, which is an enzyme responsible for carbon monoxide biosynthesis during [NiFe] hydrogenase maturation. Additionally, we have showed that the HypC-HypD complex, which acts as a scaffold protein for $Fe(CN)_2CO$ biosynthesis, forms a complex with HypX.

Recently, we have determined the crystal structures of *A. aeolicus* HypC, HypD, and HypE, which are involved in cyanide ion transport (Figure 1 (A), (B), (C)). The crystal structures of these maturation factors show high structural similarity to previously reported structures of corresponding proteins from Archaea. Based on these structure, we propose that the HypCDXE complex will be transiently formed to assemble $Fe(CN)_2CO$ unit (Figure 1 (D)).

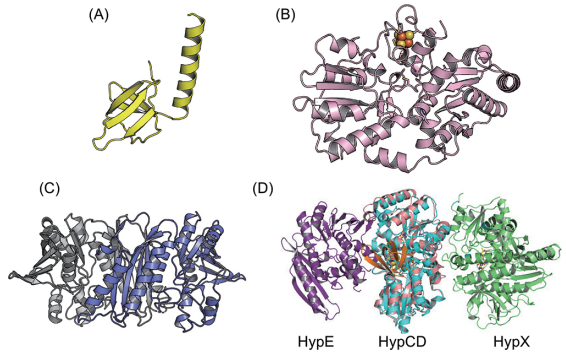


Figure 1. X-ray crystal structures of (A) HypC, (B) HypD, and (C) HypE from *Aquifex aeolicus*, and (D) proposed model of HypCDEX complex.

2. Structural Analysis of Heme-Based Oxygen Sensor Protein HemAT

Recently, it has been reported that gas molecules, including oxygen and nitric oxide, have a role as "signal molecules," and they regulate various physiological functions. In these systems, the regulation of physiological functions is performed when some signal transduction proteins that selectively recognize gas molecules sense external signals. Therefore, signal sensing and signal transduction proteins are essential for regulating physiological functions in response to gas molecules.

O_2 acts as a signal molecule in the bacterial chemotaxis regulating system, in which the heme-containing signal transducer protein HemAT (Heme Aerotaxis Transducer protein) works as an oxygen sensor protein. HemAT is mainly composed of two domains, sensor and siganaling domain. Sensor domain and signaling domain of HemAT is homologous to globin structures and the chemotaxis receptor Methyl-accepting Chemotaxis Protein (MCP), respectively.

HemAT forms a complex with the histidine kinase CheA and the conjugation protein CheW. Signal transduction proceeds in the HemAT/CheA/CheW complex upon O_2 sensing by HemAT, which results in the activation of CheA kinase activity. However, the molecular mechanisms of O_2-dependent signal transduction in the HemAT/CheA/CheW complex remain to be elucidated because of a lack of the structural information of HemAT and the HemAT/CheA/CheW complex. To understand the sensing mechanism and signaling mechanism of the HemAT and HemAT/CheA/CheW complex, we tried to solve the structures of HemAT and HemAT/CheA/CheW complex by X-ray crystallography and cryo-electron microscopy (Cryo-EM), respectively. In this year, we have determined the crystal structure of the sensor domain of HemAT from *Bacillus smithii* (Figure 2).

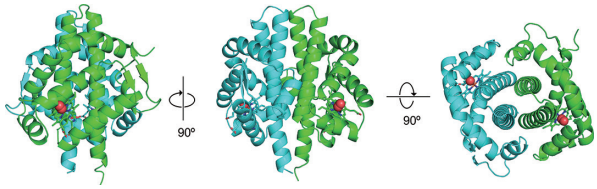


Figure 2. X-ray crystal structure of the sensor domain of HemAT from *Bacillus smithii*.

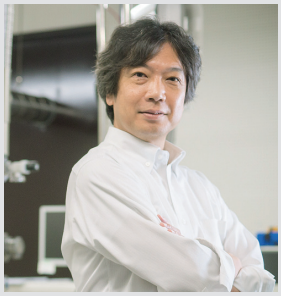
3. Iron Sensing by Sensor Kinase, VgrS, Responsible for Intracellular Iron Homeostasis

Iron is an essential trace element for all organisms. While it is essential, excess intracellular iron can generate reactive oxygen species, leading to oxidative stress and cellular damage. Therefore, iron homeostasis is essential for cells. In *Xanthomonas campestris*, the two-component system, VgrS/VgrR, plays an important role for the regulation of iron homeostasis. The periplasmic sensor domain of histidine kinase VgrS senses extracellular iron ions. However, detailed mechanism for regulating iron homeostasis by VgrS/VgrR has not yet been elucidated. In this work, we examined the structure-function relationships of VgrS.

To determine the stoichiometry of metal ion binding to VgrS sensor domain, ICP analyses was carried out, which revealed that VgrS sensor domain bound 2.5 equivalents Fe(III) or 1 equivalents Mn(II) or Co(II), respectively. The ExxE motif in VgrS seems to be a metal binding site at which Fe(III) binds. To determine the structure of VgrS, we prepared three constructs of the sensor domain of VgrS composed of Met1-Thr100, Met1-Met87, and Met27-Met87, respectively. The single crystal was obtained for the truncated sensor domain composed of Met27-Met87 while two other samples were not crystalized. X-ray crystallographic analysis of this construct is now in progress.

Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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



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Keywords Biomolecule Organization, NMR

Living systems are characterized as dynamic processes of assembly and disassembly of various biomolecules that are self-organized, interacting with the external environment. The omics-based approaches developed in recent decades have provided comprehensive information regarding biomolecules as parts of living organisms. However, fundamental questions still remain unsolved as to how these biomolecules are ordered autonomously to form flexible and robust systems (Figure 1). Biomolecules with complicated, flexible structures are self-organized through weak interactions giving rise to supramolecular complexes that adopt their own dynamic, asymmetric architectures. These processes are coupled with expression of integrated functions in the biomolecular systems.

Toward an integrative understanding of the principles behind the biomolecular ordering processes, we conduct multidisciplinary approaches based on detailed analyses of dynamic structures and interactions of biomolecules at atomic level, in conjunction with the methodologies of molecular and cellular biology along with synthetic and computational technique.

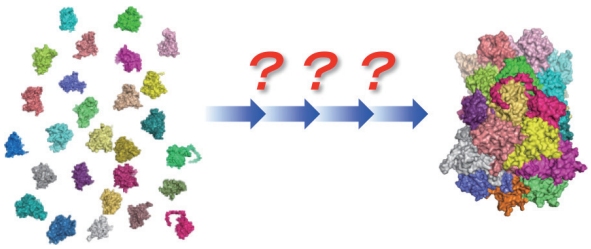

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- K. Kato and H. Yagi, "Current Status and Challenges in Structural Glycobiology," *Trends Carbohydr. Res.* **15**, 38–46 (2023).
- K. Kato, H. Yagi and S. Yanaka, "Four-Dimensional Structures and Molecular Designs of Glycans," *Trends Glycosci. Glycotechnol.* **34**, E85–E90 (2022).
- M. Yagi-Utsumi and K. Kato, "Conformational Variability of Amyloid-β and the Morphological Diversity of Its Aggregates," *Molecules* **27**, 4787 (2022).
- K. Kato, T. Yamaguchi and M. Yagi-Utsumi, "Experimental and Computational Characterization of Dynamic Biomolecular Interaction Systems Involving Glycolipid Glycans," *Glycoconjugate J.* **39**, 219–228 (2022).
- H. Yagi, S. Yanaka and K. Kato, "Structural and Functional Roles of the *N*-Glycans in Therapeutic Antibodies," in *Comprehensive Glycoscience, 2nd edition*, J. Barchi, Ed., Elsevier; Oxford, **vol. 5**, pp. 534–542 (2021).
- S. Yanaka, R. Yogo and K. Kato, "Biophysical Characterization of Dynamic Structures of Immunoglobulin G," *Biophys. Rev.* **12**, 637–645 (2020).

1. Exploring Dynamic Biomolecular Organization: Insights from Amyloid β Assembly and Protein Folding Analyses

Utilizing our structural analysis techniques, we enhanced and developed our collaborative research network both within and outside IMS to investigate the mechanisms governing the dynamic organization of biomolecules. Specifically, our focus was on exploring the dimerization process during the early stages of amyloid β (Aβ) protein oligomerization, a process implicated in the onset of Alzheimer's disease. Through molecular dynamics (MD) simulations and in vitro assays, we uncovered that intramolecular electrostatic interactions between the Arg5 side chain and the carboxyl terminal play a pivotal role in the dimerization of Aβ42 (in partnership with the Okumura group).[1] The Aβ protein is recognized for its interaction with GM1 ganglioside, a glycolipid abundant in neuronal cell membranes, and its role in promoting the formation of amyloid fibrils. Our investigation encompassed a comprehensive three-dimensional structural analysis of the GM1-Aβ complex using solid-state NMR and MD simulations, revealing a distinctive assembly characterized by a double-layered antiparallel β structure.[2] Furthermore, our findings indicate that this specific Aβ assembly does not undergo a transition into amyloid fibrils directly. Instead, it facilitates the conversion of Aβ monomers into amyloid fibrils by presenting a hydrophobic surface composed of β sheets on the GM1 glycan (in collaboration with the Nishimura and Okumura groups).

We also pursued an analysis of protein folding processes using NMR techniques. Using hydrogen/deuterium exchange NMR spectroscopy, we captured residual structural information in proteins denatured by 6 M guanidinium chloride (in collaboration with Dr. Kunihiro Kuwajima of the University of Tokyo),[3] and by capturing proteins within the cavity of spherical self-assembling complexes, we were able to observe hysteresis behavior in the folding and refolding processes of proteins (in collaboration with Dr. Makoto Fujita of the University of Tokyo and IMS).[4]

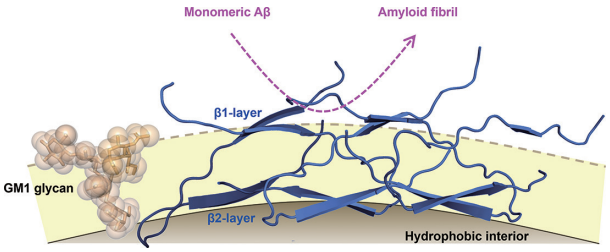

Figure 2. Schematic drawing of Aβ assemblage on GM1-containing membrane which catalytically promotes amyloid fibrillization. The distance between β1- and β2-layers of the assemblage is almost the same as the GM1 glycan dimension. The β1-layer provides a catalytic hydrophobic surface evoking fibril formation in GM1-sugar clusters.

2. Exploration, Design, and Control of Higher-Order Functions Arising from Multidomain Proteins

Multidomain proteins can manifest intricate functions through cooperative interactions and allosteric regulation, achieved by spatial rearrangements of their constituent domains. Our study delved into the potential of utilizing multidomain proteins as a foundation for Förster resonance energy transfer (FRET) biosensors, with a specific focus on protein disulfide isomerase (PDI) and Lys48-linked ubiquitin (Ub) chains as model cases.

The substrate-recognition domains of PDI undergoes redox-dependent conformational changes. Both experimental and computational approaches were employed to characterize FRET efficiency across various redox states of these domains fused with fluorescent proteins as the FRET acceptor and donor. In vitro and in vivo assessments revealed heightened FRET efficiency of this biosensor in the oxidized form of PDI, underscoring domain reorganization and its responsiveness to intracellular redox environments.[5]

On a different note, the conformational flexibility of Lys48-linked diUb presented a distinctive framework for engineering Ub-based biosensors, enabling the detection of environmental conditions like temperature and pH, as well as the recognition of binding molecules. The present findings emphasized the sensitivity of the open-closed conformational equilibrium of diUb to modifications at position 48 of the distal Ub unit, offering a means to manipulate its conformational distribution.[6]

Furthermore, our investigation into the impact of serum proteins on the functionality of therapeutic antibodies revealed that the human serum albumin (HSA) and the Fab region of serum immunoglobulin G (IgG) non-competitively inhibit antibody-dependent cellular cytotoxicity mediated by the interaction of Fcγ receptor III (FcγRIII) with rituximab, an anti-CD20 mouse/human-chimeric IgG1.[7] Stable-isotope- assisted NMR data demonstrated the interaction of HSA with the Fab and Fc regions of rituximab, as well as the extracellular domain of FcγRIII. These findings suggest the significance of considering interactions with serum proteins in the design and application of therapeutic antibodies.

References

1) S. G. Itoh *et al.*, *ACS Chem. Neurosci.* **22**, 3139–3151 (2022).
2) M. Yagi-Utsumi *et al.*, *ACS Chem. Neurosci.* **14**, 2648–2657 (2023).
3) S. Yanaka *et al.*, *Protein Sci.* **32**, e4569 (2023).
4) T. Nakama *et al.*, *Chem. Sci.* **14**, 2910–2914 (2023).
5) M. Yagi-Utsumi *et al.*, *Int. J. Mol. Sci.* **24**, 12865 (2023).
6) M. Hiranyakorn *et al.*, *Int. J. Mol. Sci.* **24**, 6075 (2023).
7) S. Yanaka *et al.*, *Front. Immunol.* **14**, 1090898 (2023).

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Operation and Design Principles of Biological Molecular Machines

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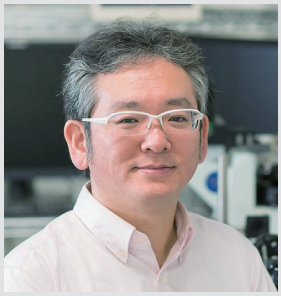

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Keywords Molecular Motors, Single-Molecule Analysis, Protein Engineering

Activity of life is supported by various molecular machines made of proteins. Protein molecular machines are tiny, but show very high performance, and are superior to man-made machines in many aspects. One of the representatives of protein molecular machines is linear and rotary molecular motors (Figure 1). Molecular motors generate the mechanical forces that drive their unidirectional motions from the energy of chemical reaction or the electrochemical potential across the cell membrane. We unveil operational principles of molecular motors with advanced single-molecule functional analysis. With the help of site-saturation mutagenesis and robot-based automation, we also engineer non-natural molecular motors to understand their design principles.

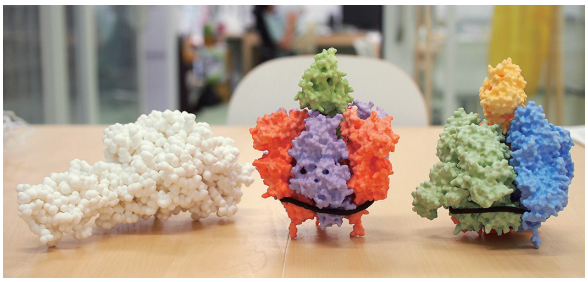

Figure 1. Protein molecular machines. (Left) A linear molecular motor chitinase A. (Center and Right) Rotary molecular motors F_1-ATPase and V_1-ATPase, respectively.

Selected Publications

- T. Kosugi, T. Iida, M. Tanabe, R. Iino and N. Koga, "Design of Allosteric Sites into Rotary Motor V_1-ATPase by Restoring Lost Function of Pseudo-Active Sites," *Nat. Chem.* (2023). DOI: 10.1038/s41557-023-01256-4
- A. Otomo, T. Iida, Y. Okuni, H. Ueno, T. Murata and R. Iino, "Direct Observation of Stepping Rotation of V-ATPase Reveals Rigid Component in Coupling between V_o and V_1 Motors," *Proc. Natl. Acad. Sci. U. S. A.* **119**, e2210204119 (2022).
- A. Nakamura, N. Kobayashi, N. Koga and R. Iino, "Positive Charge Introduction on the Surface of Thermostabilized PET Hydrolase Facilitates PET Binding and Degradation," *ACS Catal.* **11**, 8550–8564 (2021).
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- T. Iida, Y. Minagawa, H. Ueno, F. Kawai, T. Murata and R. Iino, "Single-Molecule Analysis Reveals Rotational Substeps and Chemo-Mechanical Coupling Scheme of *Enterococcus hirae* V_1-ATPase," *J. Biol. Chem.* **294**, 17017–17030 (2019).
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- A. Nakamura, K. Okazaki, T. Furuta, M. Sakurai and R. Iino, "Processive Chitinase is Brownian Monorail Operated by Fast Catalysis after Peeling Rail from Crystalline Chitin," *Nat. Commun.* **9**, 3814 (2018).

1. Six States of *Enterococcus hirae* V-Type ATPase Reveals Non-Uniform Rotor Rotation during Turnover[1)]

The vacuolar-type ATPase from *Enterococcus hirae* (EhV-ATPase) is a thus-far unique adaptation of V-ATPases, as it performs Na^+ transport and demonstrates an off-axis rotor assembly (Figure 2). Recent single molecule studies of the isolated V_1 domain have indicated that there are subpauses within the three major states of the pseudo three-fold symmetric rotary enzyme. However, there was no structural evidence for these. Herein we activate the EhV-ATPase complex with ATP and identified multiple structures consisting of a total of six states of this complex by using cryo-electron microscopy. The orientations of the rotor complex during turnover, especially in the intermediates, are not as perfectly uniform as expected (Figure 3 and 4). The densities in the nucleotide binding pockets in the V_1 domain indicate the different catalytic conditions for the six conformations. The off-axis rotor and its' interactions with the stator a-subunit during rotation suggests that this non-uniform rotor rotation is performed through the entire complex.

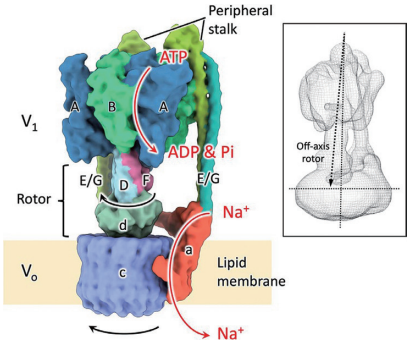

Figure 2. Schematic drawing of the EhV-ATPase. A-, B-, D-, E-, F-, G- and d-subunits form the V_1 domain, while a- and c-subunits form the V_o domain. The a-subunit and c-ring are embedded in lipid membrane. The rotation of the D/F/d rotor shaft and c-ring proceeds clockwise when viewed from V_1 to V_o domains, as indicated. Turnover is driven by the entry of ATP into a binding pocket at the interface of each A/B dimer, the hydrolysis reaction drives conformational changes which cause the rotation of the rotor. Inset shows the off-axis rotor.

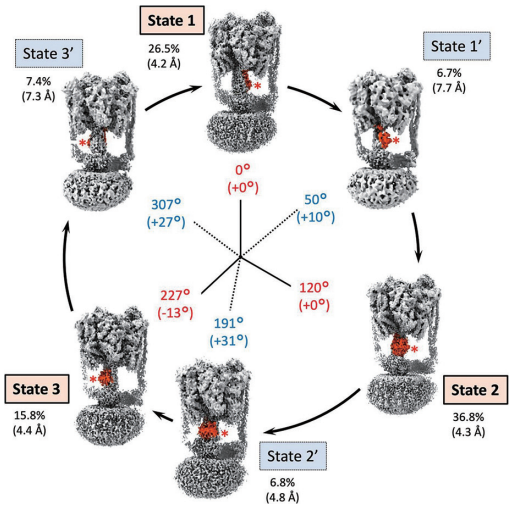

Figure 3 (top right). The six state structures of EhV-ATPase isolated. The F-subunit position is highlighted in red for easier identification of orientation of the rotor. Starting in State 1 at "12 o'clock" on the circle and proceeding clockwise when turnover is viewed from the V_1 to V_o domains. The six state structures are defined as State 1, State 1', State 2, State 2', State 3, and State 3' with comparisons to the other V-ATPases. Total rotation of the rotor at F subunit is labelled in red for the major states and blue for the intermediate states internally of the circle. The gaps from the orientations based on the single-molecule imaging studies (120° major pauses, and 40/80° subpauses in the major pauses) are in brackets. Relative percentages of the total final particles used and their resolutions (brackets) for each reconstruction are indicated externally of the circle. The cryo-EM maps of EhV-ATPase are aligned according to the orientation of the F-subunit.

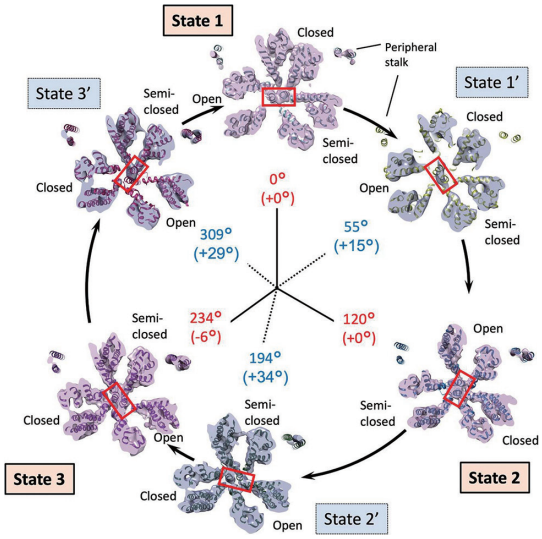

Figure 4. V_1 domain cross-section view of the six states. The figure is laid out as shown in Figure 3 viewed from the V_1 to V_o domains. The rotor D subunit is boxed in red, demonstrating the positions of a pair of the longest helices. The catalytic conformations of the A/B subunit in V_1 domain are indicated with "Open," "Closed," and "Semi-closed." The positions of peripheral stalk are labelled.

Reference

1) R. N. Burton-Smith, C. Song, H. Ueno, T. Murata, R. Iino and K. Murata, *Commun. Biol.* **6**, 755 (2023).

Award

HARASHIMA, Takanori; Best Presentation Award, 2022 Annual Meeting of the Biophysical Society of Japan Chubu Branch (2023).

* IMS International Internship Program

Development of Novel Catalytic Organic Transformations

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Keywords Transition Metal Catalysis, Green Chemistry, Photocatalysis

Our research interests lie in the development of catalytic reaction systems toward ideal (highly efficient, selective, green, safe, simple, etc.) organic transformations. In particular, development of a wide variety of the heterogeneous aquacatalytic systems, continuous flow catalytic systems, and super active catalysts working at ppm-ppb loading levels, have been achieved. Furthermore, we have recently been developing a novel photocatalysis where, for example, the carbonyl groups underwent two successive one-electron reduction to generate carbinol anion species achieving electrophilic carbonyl substitution.

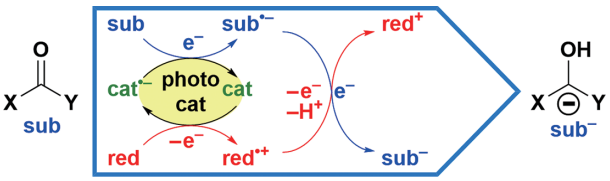

Figure 1. The outlined concept of photocatalytic reductive activation of substrate through two successive one-electron transfer process (*e.g.* carbonyl reduction to carbinol anion).

Selected Publications

- S. Okumura and Y. Uozumi, "Photocatalytic Carbinol Cation/Anion Umpolung: Direct Addition of Aromatic Aldehydes and Ketones to Carbon Dioxide," *Org. Lett.* **23**, 7194–7198 (2021).
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- Y. M. A. Yamada, T. Arakawa, H. Hocke and Y. Uozumi, "A Nanoplatinum Catalyst for Aerobic Oxidation of Alcohols in Water," *Angew. Chem., Int. Ed.* **46**, 704–706 (2007).

1. Umpoled Carbonyl Chemistry

Carbonyl chemistry is dominated by nucleophilic additions in which a carbonyl compound (an aldehyde or ketone) serves as an electrophilic carbinol cation synthon to form a secondary or tertiary alcohol product [Figure 2(a)]. In contrast to the well-investigated conventional chemistry of carbonyl compounds, their umpoled nucleophilic reactivity has been less-well explored [Figure 2(b)]. Symmetrization of the carbonyl reactivity, which would permit carbonyl compounds to react as nucleophilic carbinol anions (i.e., carbinol cation/anion umpolung), could open a new avenue in synthetic organic chemistry.

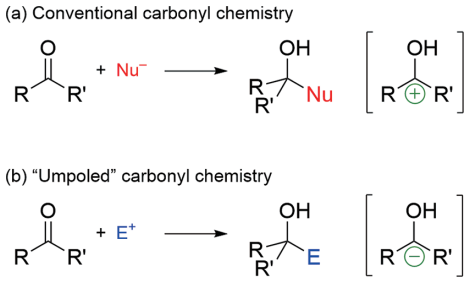

Figure 2. Carbonyl Reactivity: Conventional *vs*. Umpoled.

In previous report, we have developed a novel photocatalytic carboxylation of aromatic aldehydes and ketones to give mandelic acid derivatives [Figure 3(a)]. In this reaction, nucleophilic carbinol anion species were generated under visible light that subsequently reacted with carbon dioxide. Here, in 2023, we developed photocatalytic cross-pinacol coupling between two different carbonyl compounds to afford the unsymmetric 1,2-diols, where the resulting carbinol anions reacted with second carbonyl compounds [Figure 3(b)]. We also achieved the photocatalytic 1,4-addition of carbonyl compounds with electron-deficient olefins to give the corresponding γ-substituted alcohols [Figure 3(c)].

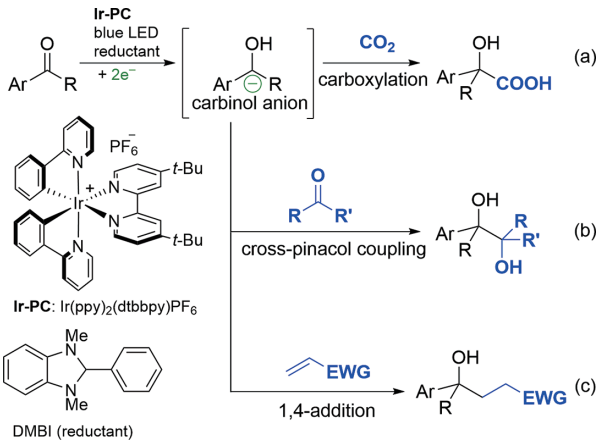

Figure 3. Photocatalytic Eelectrophilic Substitution of Carbonyls: (a) carboxylation, (b) cross-pinacol coupling, (c) 1,4-addition.

1-1. Cross-Pinacol Coupling[1)]

We have developed the first photocatalytic cross-pinacol coupling between two different carbonyl compounds, promoted by a CO_2 additive. The cross-pinacol coupling took place with a various combination of two aldehydes, two ketones, or an aldehyde and a ketone in the presence of an iridium photocatalyst and 1,3-dimethyl-2-phenyl-2,3-dihydro-1*H*-benzimidazole (DMBI) as a reductant under visible-light irradiation to afford the corresponding unsymmetric vicinal 1,2-diols in up to 91% yield [Figure 3(b)]. In the coupling reaction, an umpoled carbinol anions are generated in situ through successive one-electron reduction and the resulting anions attack the more-electron-rich carbonyl compounds serving as electrophiles. CV and DFT calculations revealed that the CO_2 additive plays a key role in the second reduction to suppress undesired dimerization.

1-2. Conjugate Addition of Carbonyls to Electron-Deficient Olefins[2)]

A 1,4-addition reaction of aromatic aldehydes and ketones to electron-deficient olefins was achieved under photocatalytic conditions [Figure 3(c)]. In the reaction, an umpoled carbinol anion generated in situ through two successive one-electron reductions of the carbonyl compound reacted nucleophilically with the electron-deficient olefin. Various electron-deficient aromatic aldehydes and ketones successfully underwent the reaction to afford the corresponding γ-functionalized alcohols.

2. Transition Metal Catalysis Forming C–H, C–C, C–N, C–S Bonds[3,4)]

We have developed transition metal-catalyzed C–H, C–C, C–N, C–S bond forming reactions. A phenylboronic ester-activated aryl iodide-selective Buchwald−Hartwig-type C–N bond forming reaction using $Ni(acac)_2$ catalyst was developed. This reaction does not proceed in the absence of phenylboronic ester.[3)] C–S bond formation was achieved in the reaction of 2,2'-dithiobis(benzenamine)s with various aldehydes in the presence of CuOAc catalyst under air without any additives to afford the corresponding benzothiazoles.[4)] We recently developed in-water C–H bond forming catalysis with PS-PEG supported palladium nanoparticles using tetrahydroxydiboron ($B_2(OH)_4$) as a water-compatible reducing agent.

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Design and Synthesis of Chiral Organic Molecules for Asymmetric Synthesis

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The field of molecular catalysis has been an attractive area of research for realizing efficient and new transformations in the synthesis of functional molecules. The design of chiral molecular catalysts has been recognized as one of the most valuable strategies; therefore, a great deal of effort has been dedicated to the developments. In general, "metals" have been frequently used as the activation centers, and conformationally rigid catalyst frameworks have been preferably components for the catalyst design. To develop a new type of molecular catalysis, we have focused on the use of non-metal elements as activation centers and have incorporated non-covalent interactions as organizing forces in the molecular design of catalysts. This approach had not received much attention until recently. We hope that our approach will open a new frontier in chiral organic molecules to chiral molecular science from chiral molecular chemistry.

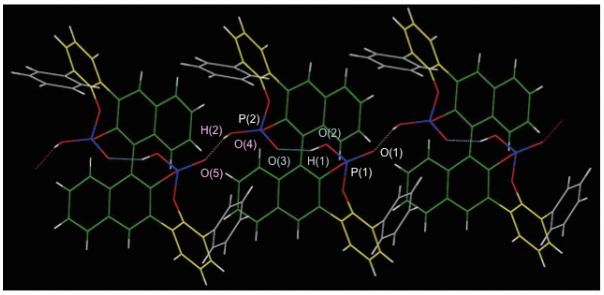

Figure 1. Hydrogen bonding network in chiral bis-phosphoric acid catalyst derived from (*R*)-3,3'-di(2-hydroxy-3 -arylphenyl)binaphthol. Hydrogen bond acts as activation unit for the substrate in asymmetric reaction space and controls atropisomeric behavior in naphthyl–phenyl axis.

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- T. P. Yoon and E. N. Jacobsen, *Science* **299**, 1691–1693 (2003).
- N. Momiyama and H. Yamamoto, "Brønsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis," *J. Am. Chem. Soc.* **127**, 1080–1081 (2005).
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- N. Momiyama, H. Tabuse, H. Noda, M. Yamanaka, T. Fujinami, K. Yamanishi, A. Izumiseki, K. Funayama, F. Egawa, S. Okada, H. Adachi and M. Terada, "Molecular Design of a Chiral Brønsted Acid with Two Different Acidic Sites: Regio-, Diastereo-, and Enantioselective Hetero-Diels–Alder Reaction of Azopyridinecarboxylate with Amidodienes Catalyzed by Chiral Carboxylic Acid–Monophosphoric Acid," *J. Am. Chem. Soc.* **138**, 11353–11359 (2016).
- S. Oishi, T. Fujinami, Y. Masui, T. Suuki, M. Kato, N. Ohtsuka and N. Momiyama, "Three-Center-Four-Electron Halogen Bond Enables Non-Metallic Complex Catalysis for Mukaiyama-Mannich-Type Reaction," *iScience* **25**, 105220 (2022).

1. Design of Hydrogen Bond-Based Molecular Catalysts

Allylation of imines with allylic metal reagents has been one of the most valuable tools to synthesize enantioenriched homoallylic amines. Due to the inherent nature of allylic metal reagent, however, regioselectivity has been a long-standing subject in this area. To develop the synthetic reaction for enantioenriched linear homoallylic amines, we discovered chirality transferred formal 1,3-rearrangement of ene-aldimines in the presence of Brønsted acid, and developed it as synthetic method for variety of enantioenriched linear homoallylic amines.[1] Furthermore, we studied details of reaction mechanism and succeeded catalytic asymmetric version of this rearrangement.[2] On the basis of our discovery, catalytic asymmetric version of this reaction was developed.[3] To the best our knowledge, our discovery is the first example of catalytic asymmetric methylene migration.

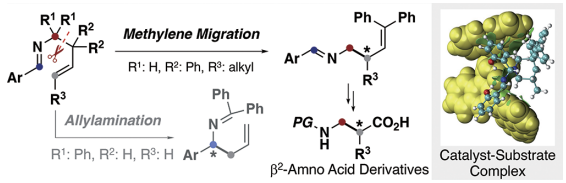

Figure 2. Asymmetric counteranion-directed catalysis *via* OH···O, CH···O, CH···π, π···π interactions.

Perfluorinated aryls have emerged as an exquisite class of motifs in the design of molecular catalysts, and their electronic and steric alterations lead to notable changes in the chemical yields and the stereoselectivities. We developed the perfluoaryls-incorporated chiral mono-phosphoric acids as chiral Brønsted acid catalysts that can deliver high yields and stereoselectivities in the reactions of imines with unactivated alkenes. We have described the first example of a diastereo- and enantioselective [4+2] cycloaddition reaction of *N*-benzoyl imines, as well as the enantioselective three-component imino–ene reaction using aldehydes and $FmocNH_2$.[4]

We have developed (*R*)-3,3'-di(2-hydroxy- 3-arylphenyl) binaphthol derived chiral bis-phosphoric acid which efficiently catalyzed enantioselective Diels–Alder reaction of acroleins with amidodienes.[5,6] We demonstrated that two phosphoric acid groups with individually different acidities can play distinct roles in catalyst behavior through hydrogen bonding interactions. Therefore, we developed a Brønsted acid with two different acidic sites, aryl phosphinic acid-phosphoric acid.[7] Furthermore, molecular design of a chiral Brønsted acid with two different acidic sites, chiral carboxylic acid–cyclic mono-phosphoric acid, was identified as a new and effective concept in asymmetric hetero-Diels–Alder reaction of 2-azopyridinoester with amidodienes.[8]

2. Design of Halogen Bond-Based Molecular Catalysts

Halogen bonds are attractive non-covalent interactions between terminal halogen atoms in compounds of the type R—X (X = Cl, Br, I) and Lewis bases LBs. It has been known that strong halogen bonds are realized when "R" is highly electronegative substituents such as perfluorinated alkyl or aryl substituents. On the basis of electrophilic feature for halogen atom, we have examined it to develop catalysis with halogen bond for carbon–carbon bond forming reactions.[9,10,11]

We found that the three-center-four-electron halogen bond become a new driving force for catalysis.[9] By integrating halogen(I) (X^+: I^+ or Br^+), the bis-pyridyl ligand *NN*, and a non-nucleophilic counter anion Y, we developed non-metallic complex catalysts, [*N*···X···*N*]Ys, that exhibited outstanding activity and facilitated the Mukaiyama–Mannich-type reaction of *N*-heteroaromatics with parts-per-million-level catalyst loading. NMR titration experiments, CSI-MS, computations, and UV-vis spectroscopic studies suggest that the robust catalytic activity of [*N*···X···*N*]Y can be attributed to the unique ability of the 3c4e X-bond for binding chloride: i) the covalent nature transforms the $[N\cdots X\cdots N]^+$ complexation to sp^2 CH as a hydrogen-bonding donor site, and ii) the noncovalent property allows for the dissociation of $[N\cdots X\cdots N]^+$ for the formation of $[Cl\cdots X\cdots Cl]^-$. This study introduces the application of 3c4e X-bonds in catalysis *via* halogen(I) complexes.

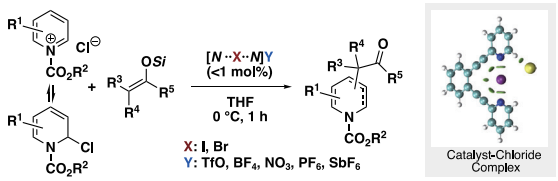

Figure 3. Three-center-four-electron halogen bond enables non-metallic complex catalysis for Mukaiyama–Mannich-type reaction.

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Creation of Novel Photonic-Electronic-Magnetic Functions Based on Molecules with Open-Shell Electronic Structures

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Keywords Radical, Open-Shell Electronic States, Photonic-Electronic-Magnetic Properties

The molecules with open-shell electronic states can exhibit unique properties, which are difficult to achieve for conventional closed-shell molecules. Our group develops new open-shell organic molecules (= radicals) and metal complexes to create novel photonic-electronic-magnetic functions.

While conventional closed-shell luminescent molecules have been extensively studied as promising components for organic light-emitting devices, the luminescent properties of radicals have been much less studied because of their rarity and low chemical (photo-)stability. We have developed highly photostable luminescent organic radicals, PyBTM and its analogues, and investigated photofunctions attributed to their open-shell electronic states. We have discovered that (i) PyBTM-doped molecular crystals exhibit photoluminescence at RT with φ_{em} = 89%, which is exceptionally high in radicals, (ii) radical-doped crystals and radical-based coordination polymers exhibit drastic changes in the emission spectra by applying a magnetic field. These are the first demonstrations of magnetoluminescence in radicals, and are attributed to interplay between the spin and the luminescence. Our studies provide novel and unique concepts in molecular photonics, electronics, and spintronics, and also bring innovative ideas in the development of light-emitting devices.

Our group focuses on strongly-interacted spins in molecular crystals. The anisotropic assembly of open-shell molecules in crystalline states enables unique molecular materials with exotic electrical and magnetic properties, such as superconductors, ferromagnets, and quantum spin liquids.

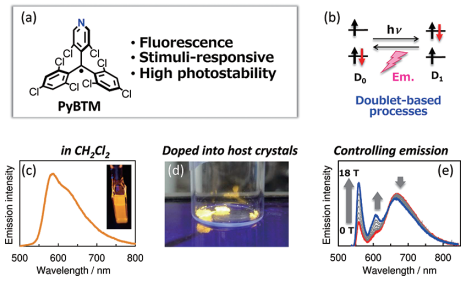

Figure 1. (a) Molecular structure of PyBTM and its characteristics. (b) Schematic photoexcitation-emission processes. (c) Emission in CH_2Cl_2. (d) Emission of PyBTM-doped molecular crystals. (e) Controlling emission by magnetic field.

Selected Publications

- S. Kimura, M. Uejima, W. Ota, T. Sato, S. Kusaka, R. Matsuda, H. Nishihara and T. Kusamoto, "An Open-Shell, Luminescent, Two-Dimensional Coordination Polymer with a Honeycomb Lattice and Triangular Organic Radical," *J. Am. Chem. Soc.* **143**, 4329–4338 (2021).
- S. Kimura, T. Kusamoto, S. Kimura, K. Kato, Y. Teki and H. Nishihara, "Magnetoluminescence in a Photostable, Brightly Luminescent Organic Radical in a Rigid Environment," *Angew. Chem., Int. Ed.* **57**, 12711–12715 (2018).
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1. Development of Two-Dimensional Kagome-Honeycomb Lattice Coordination Polymer Based on Triangular Radical

Two-dimensional (2D) open-shell coordination polymers (CPs) with honeycomb, Kagome, and Kagome-honeycomb hybrid lattices have attracted growing interest because of the exotic electronic structures and physical properties attributed to the structural topology. Employing organic radicals as building blocks is a promising approach to producing open-shell CPs, where structural topology and efficient electronic and magnetic interaction between the radical ligands and the metal ions enable peculiar electrical, magnetic, and photonic properties. Recently, we have prepared a highly-crystalline 2D honeycomb lattice CP, trisZn, via coordination of a triangular-shaped organic radical tris(3,5-dichloro-4-pyridyl)methyl radical (trisPyM) to Zn ions (Figure 2).[1] TrisZn demonstrated magnetoluminescence (MagLum) below 20 K.[2] This is the first example showing MagLum of pure (*i.e.*, non-doped) radical compounds.

Employing magnetic ions such as Cu^{II} (S = 1/2) and Ni^{II} (S = 1) instead of the nonmagnetic Zn^{II} is expected to enable Kagome-honeycomb hybrid lattices, where the magnetic ions and trisPyMs construct Kagome and honeycomb lattices, respectively. We prepared Cu^{II} and Ni^{II} Kagome-honeycomb hybrid lattices. Magnetic investigations indicated the emergence of long-range magnetic order and metamagnet-like behavior at low temperatures in these materials. Efficient magnetic couplings between the magnetic ions and the radicals extended onto two dimensions were expected to induce strong magnetic anisotropy.

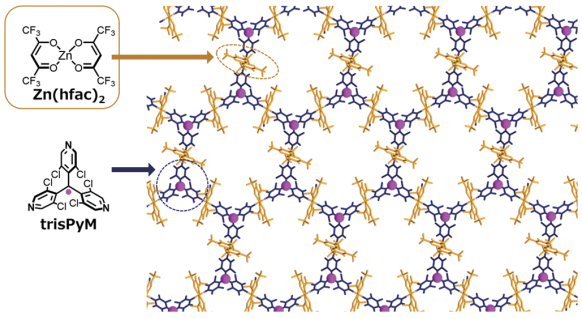

Figure 2. Crystal structure of trisZn and the chemical structure of the components.

2. Single-Molecule Magnetoluminescence from a Luminescent Diradical

Luminescent radicals attract increasing interest as a new class of materials that enable unique photofunctions not found in conventional closed-shell molecules due to their open-shell electronic structure. Particularly promising are photofunctions resulting from the correlation between the radical's spin and luminescence, such as MagLum, in which an external magnetic field reversibly controls the luminescence. Developing such photofunctions and elucidating their mechanisms would establish fundamental understandings that could be a basis for future spin-photonics and photo-spintronics. However, previous observations of MagLum in radicals have been limited to systems where radicals are randomly doped in host crystals or periodically arranged within the crystal lattices of the coordination polymer through metal complexation. This study shows that a diradical with covalently-linked two radical units within a single molecular skeleton can exhibit MagLum as a single-molecular property (Figure 3).[3] This enables the detailed elucidation of the requirements for and mechanisms of MagLum in assembled radicals and can aid the rational design of MagLum-active radicals based on synthetic chemistry.

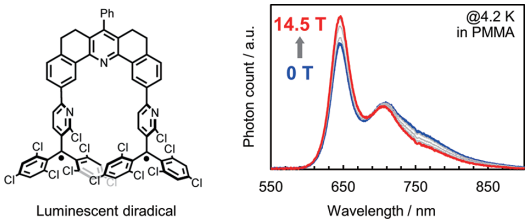

Figure 3. Chemical structure and magnetoluminescence at 4.2 K of a luminescent diradical.

References

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Design and Synthesis of Three-Dimensional Organic Structures

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Education
2005 B.S. The University of Tokyo
2007 M.S. The University of Tokyo
2009 Ph.D. The University of Tokyo

Professional Employment
2009 Assistant Professor, Nagoya University
2013 Designated Associate Professor, Nagoya University
2013 Group Leader and Project Coordinator, JST ERATO Itami Molecular Nanocarbon Project (until 2020)
2020 Associate Professor, Institute for Molecular Science
Associate Professor, The Graduate University for Advanced Studies

Award
2013 RSC PCCP Prize
2014 Akasaki Award
2017 Chemical Society of Japan Award for Young Chemists
2018 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
The Young Scientists' Prize
2019 Nozoe Memorial Award for Young Organic Chemists
2021 Chemist Award BCA

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Keywords π-Conjugated Molecules, Molecular Topology, 3D Network Polymer

Aromatic compounds are potentially useful as functional electronic materials. However, the controlled synthesis and assembly of three-dimensional complex molecules are still very difficult, especially for the crystal engineering of organic molecules. This group aims to create novel topological and reticular organic structures by using synthetic organic chemistry and geometric insights.

To achieve our purpose, this group will start electron-diffraction crystallography (MicroED) for the rapid structure determination of organic compounds. While X-ray crystallography is a general and reliable method for structure determination, it requires ~0.1 mm single crystals and making such crystal sometimes needs tremendous times and efforts. Since electron beam have much higher diffraction intensity than X-ray, structural analysis can be performed even with ultra-small crystals (1 μm or less). There are many fields such as covalent organic crystals with a three-dimensional structure and molecules with complex molecular topologies, where structural analysis has not been sufficiently developed.

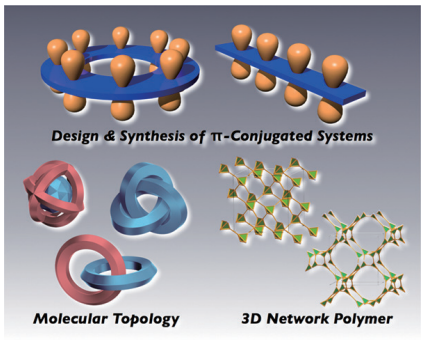


Figure 1. Design and synthesis of π-conjugated organic molecules (top); Development of novel molecular topology (bottom left); Construction of three-dimensional network polymers (bottom right).

Selected Publications

- M. Nagase, S. Nakano and Y. Segawa, "Synthesis of Penta- and Hexa(3,4-thienylene): Size-Dependent Structural Properties of Cyclic Oligothiophenes," *Chem. Commun.* **59**, 11129–11132 (2023).
- Y. Segawa, "Nonplanar Aromatic Hydrocarbons: Design and Synthesis of Highly Strained Structures," *Bull. Chem. Soc. Jpn.* **95**, 1600–1610 (2022).
- Y. Segawa, T. Watanabe, K. Yamanoue, M. Kuwayama, K. Watanabe, J. Pirillo, Y. Hijikata and K. Itami, "Synthesis of a Möbius Carbon Nanobelt," *Nat. Synth.* **1**, 535–541 (2022).
- K. Kato, K. Takaba, S. Maki-Yonekura, N. Mitoma, Y. Nakanishi, T. Nishihara, T. Hatakeyama, T. Kawada, Y. Hijikata, J. Pirillo, L. T. Scott, K. Yonekura, Y. Segawa and K. Itami, "Double-Helix Supramolecular Nanofibers Assembled from Negatively Curved Nanographenes," *J. Am. Chem. Soc.* **143**, 5465–5469 (2021).
- K. Y. Cheung, K. Watanabe, Y. Segawa and K. Itami, "Synthesis of a Zigzag Carbon Nanobelt," *Nat. Chem.* **13**, 255–259 (2021).
- Y. Segawa, M. Kuwayama, Y. Hijikata, M. Fushimi, T. Nishihara, J. Pirillo, J. Shirasaki, N. Kubota and K. Itami, "Topological Molecular Nanocarbons: All-Benzene Catenane and Trefoil Knot," *Science* **365**, 272–276 (2019).
- G. Povie, Y. Segawa, T. Nishihara, Y. Miyauchi and K. Itami, "Synthesis of a Carbon Nanobelt," *Science* **356**, 172–175 (2017).

1. Synthesis of Cyclic ß-Thiophenes

Macrocyclic polyaromatic molecules are interesting materials that exhibit a wide variety of electronic and optical properties derived from their structures, but they are often synthetically challenging because of the ring strain associated with their macrocyclic structures. In this study, we have succeeded in synthesizing 3,4-pentathienylene (**5T**) and 3,4-hexathienylene (**6T**), in which all five and six thiophenes are linked at the 3,4-positions (β-positions), using Ni-catalyzed borylation, Pd-catalyzed cross-coupling and Ni-mediated homocoupling reactions (Figure 2).[1)]

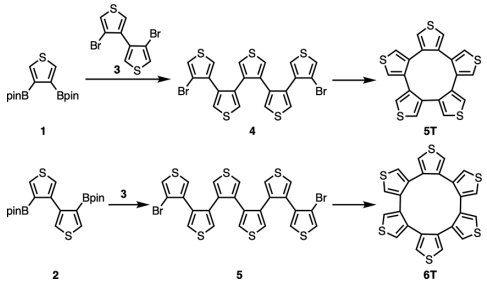


Figure 2. Synthesis of penta(3,4-thienylene) (**5T**) and hexa(3,4-thienylene) (**6T**).

X-ray crystallographic analysis confirmed the C_2 and D_2 symmetries of **5T** and **6T**, respectively (Figure 3). Interestingly, the ^{1}H NMR spectra of the two molecules were very different: **5T** had a single singlet, whereas three different signals were observed for **6T**, and these remained unchanged at both low and high temperatures (Figure 3).

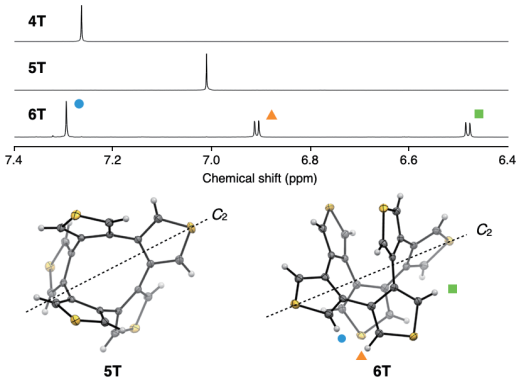


Figure 3. ^{1}H NMR spectra of **4T**–**6T** in CD_2Cl_2, and X-ray structures of **5T** and **6T** with thermal ellipsoids at 50% probability.

The isomerization barriers of **5T** and **6T** calculated by DFT method were 5.0 kcal/mol and 26.5 kcal/mol, respectively, and the difference in isomerization rate was the reason for the difference in NMR spectra (Figure 4). The synthesized **5T** and **6T** are useful as a platform for the synthesis of novel polycyclic π-conjugated compounds utilizing the macrocyclic nonplanar structures and the active α-positions.

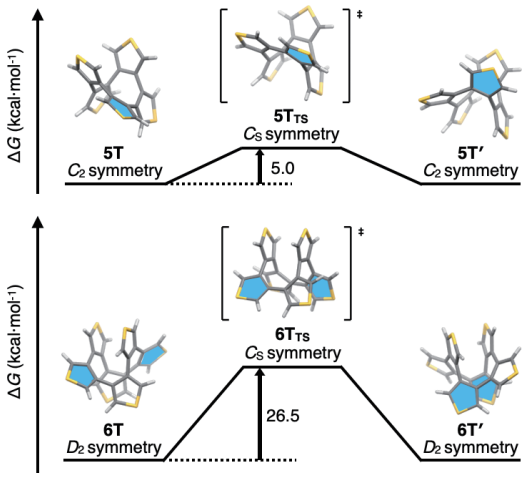
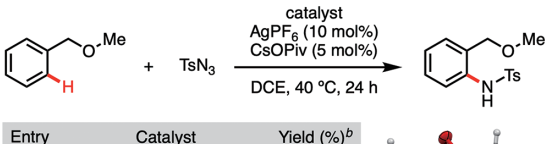


Figure 4. Energy diagrams for the enantiomerization of **5T** and **6T**.

2. An Electron-Deficient Cp^E Iridium(III) Catalyst for Ether-Directed C–H Amidation

The synthesis, characterization, and catalytic performance of an iridium(III) catalyst with an electron-deficient cyclopentadienyl ligand ($[CpEIrI_2]_2$) are reported.[2)] The $[CpEIrI_2]_2$ catalyst was synthesized by the complexation of a precursor of the CpE ligand with $[Ir(cod)OAc]_2$ followed by oxidation, desilylation, and removal of the COD ligand. The electron-deficient $[CpEIrI_2]_2$ enabled C–H amidation reactions assisted by a weakly coordinating ether directing group. Experimental mechanistic studies and DFT calculations suggested that the high catalytic performance of $[CpEIrI_2]_2$ is due to its electron-deficient nature, which accelerates both C–H activation and Ir(V)-nitrenoid formation.



Entry	Catalyst	Yield (%)[b]
1	$[Cp^EIrI_2]_2$ **1** (2.5 mol%)	> 95
2	$[Cp^{A1}IrI_2]_2$ (2.5 mol%)	< 5
3	$[Cp^*IrCl_2]_2$ (2.5 mol%)	9
4	$[Cp^ERhCl_2]_2$ (2.5 mol%)	N.R.
5	$[Cp^{A1}RhCl_2]_2$ (2.5 mol%)	N.R.
6	$[Cp^*RhCl_2]_2$ (2.5 mol%)	N.R.
7	$Cp^*Co(CO)I_2$ (5 mol%)	N.R.
8	none	N.R.

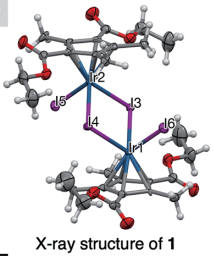


Figure 5. Optimized reaction conditions and control experiments for the Ir-catalyzed ether-directed C–H amidation reaction.

References

1) M. Nagase, S. Nakano and Y. Segawa, *Chem. Commun.* **59**, 11129–11132 (2023).

2) E. Tomita, M. Kojima, Y. Nagashima, K. Tanaka, H. Sugiyama, Y. Segawa, A. Furukawa, K. Maenaka, S. Maeda, T. Yoshino and S. Matsunaga, *Angew. Chem., Int. Ed.* **62**, e202301259 (2023).

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Visiting Professors

Visiting Professor
KAMIYA, Yukiko *(from Kobe Pharmaceutical University)*

Expand the Artificial Nucleic Acid World Based on the Studies of Molecular Science

Nucleic acids (DNA and RNA) are essential biopolymers that carry genetic information in all living organisms. On the other hand, various artificial nucleic acids (XNAs) such as ribose-modified or non-ribose type nucleic acids having nucleic acid recognition ability have been developed. One of our motivation of XNA study is development of nucleic acid drugs. Another big motivation is addressing the fundamental question why nature selected ribose as backbone of genetic materials. Our group has focused on amino acid-type artificial nucleic acids and we are studying on characterization of their molecular recognition properties, design of unique structures, and development of molecular tools and drugs that target RNA as applications. In recent study we successfully established a preparation scheme for full-XNA oligonucleotides possessing artificial nucleobases. The artificial oligonucleotides are currently being applied in in vitro and in vivo study to test whether they function in the biological system.

Visiting Professor
SATO, Sota *(from The University of Tokyo)*

Integrated Molecular Structure Analysis Through Industry-Academia Collaboration

Elucidating molecular structures is crucial in various fields of molecular science, regardless of academia or industry. In addition to NMR and mass spectrometry, X-ray/electron diffraction is a powerful analytical technique that can directly determine atomic positions, enabling clear determination of three-dimensional structures. We are actively pursuing the “crystalline sponge method” as one of core technologies, which eliminates the need for the crystallization process and completes sample preparation by simply soaking the target molecules into crystalline sponge, allowing structural analysis even with minute sample amounts. Furthermore, we are extensively deriving technological advancements and building collaborative relationships with numerous companies and institutions to promote research aimed at creating new industries. Recently, we have been dedicated to fostering future talent who will support the scientific community in Japan and the world. We organized mock lectures and research experiences for high school students in collaboration with corporate researchers, aiming to nurture the next generation of scientists.

Visiting Professor
TOYABE, Shoichi *(from Tohoku University)*

Optimal Control of Biological Molecular Motors—What Is the Most Efficient Way to Control Motors?

ATP synthase plays a central role in cellular energetics by synthesizing most of the ATP molecules required by cells. ATP synthase consists of two coupled motors, F_1 and F_o. F_1 has the ATP-synthesizing activity and catalyzes ATP synthesis using the mechanical driving force rovided by F_o. We assume that nature has optimized F_o and F_1 to rotate F_1 efficiently. However, we do not know in detail how F_o rotates F_1. Instead, we should be able to know what is the most efficient way to rotate F_1 based on physical theory. We use optimal transport theory to find the optimal way to rotate F_1 with the least amount of work, and practice the obtained optimal protocol by single molecule experiments. We have not found the optimal protocol. However, we have at least found that rotation by trapping torque at constant speed requires less work than rotation by constant torque at the same speed.