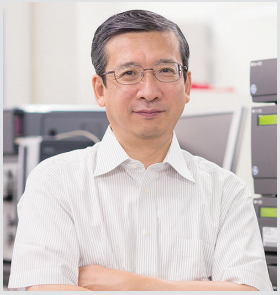
RESEARCH ACTIVITIES
Life and Coordination-Complex Molecular Science

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

- 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).
- A. Pavlou, H. Yoshimura, S. Aono and E. Pinakoulaki, "Protein Dynamics of the Sensor Protein HemAT as Probed by Time-Resolved Step-Scan FTIR Spectroscopy," *Biophys. J.* **114**, 584–591 (2018).
- A. Pavlou, A. Loullis, H. Yoshimura, S. Aono and E. Pinakoulaki, "Probing the Role of the Heme Distal and Proximal Environment in Ligand Dynamics in the Signal Transducer Protein HemAT by Time-Resolved Step-Scan FTIR and Resonance Raman Spectroscopy," *Biochemistry* **56**, 5309–5317 (2017).

1. Structural Characterization of Thermoglobin from a Hyperthermophilic Bacterium *Aquifex aeolicus*

Globins are heme-binding proteins, which show a variety of biological functions such as oxygen transport, oxygen storage, redox catalysis and gas sensing. In bacteria, four distinct globins are identified; single domain hemoglobin (sdHb), truncated hemoglobin (tHb), flavohemoglobin (fHb) and globin-coupled sensor (GCS). Truncated hemoglobins (tHbs) are shorter than the canonical vertebrate hemoglobins by 20–40 residues. Whereas the canonical hemoglobins, sdHb, fHb and GCS are composed of eight α-helices (A–H), that fold into a 3-on-3 α-helical sandwich structure, tHbs form a 2-on-2 α-helical sandwich in which helices B and E lie over helices G and H. The physiological function of some sdHb, tHb, and fHb is proposed to provide resistance to nitrosative stress such as reactive nitrogen species. In this work, the structural characterization of AaTgb was carried out by X-ray crystallography.

We have determined the crystal structure of Y29F-AaTgb in the imidazole-bound form. Y29F-AaTgb shares the structural similarity to known bacterial sdHb structures; *Campylobacter jejuni* Hb (CjHb, 44% sequence identity), *Methylacidiphilum infernorum* Hb known as hell's gate globin I (HGbI, 32% sequence identity) and *Vitreoscilla stercoraria* Hb (VsHb, 43% sequence identity). sdHb was discovered from *Vitreoscilla stercoraria*, which shares approximately 30% amino acid sequence identity with the globin domain of fHb that functions as nitric oxide dioxygenase. Based on the amino acid sequence homology, it is assumed that sdHb also acts as nitric oxide dioxygenase. Indeed, *Campylobacter jejuni* Hb and *Helicobacter pullorum* Hb have been reported to contribute to remove nitric oxide.

The superposition between the Cα atoms of Y29F-AaTgb and CjHb (PDB ID: 2wy4), HGbI (PDB ID: 3s1i) and VsHb (PDB ID: 3vhb) shows a root mean square deviation of 0.89 Å, 1.04 Å and 1.18 Å, respectively. By using a structural homology search in Structure Navigator in PDBj, Y29F-AaTgb has the highest structural homology to the globin domain of nitric oxide dioxygenase from *Rhodothermus marinus* (RmaNOD, UniProt ID: D0MGT2). The superposition between the Cα atoms of Y29F-AaTgb and the globin domain of RmaNOD (PDB ID: 6wk3) shows a root mean square deviation of 0.60 Å with 48% sequence identity. The structural similarity of AaTgb to sdHb and RmaNOD suggests a possibility that AaTgb is also responsible for NO detoxification, though further studies must be required to confirm this hypothesis.

The heme environmental structure of Y29F-AaTgb is shown in Figure 1. In Y29F-AaTgb, the heme iron is coordinated by His82 and imidazole in the proximal and distal side, respectively. The distances between iron and nitrogen atom are 2.17 and 2.13 Å for His82 and imidazole, respectively. ND1 of His82 forms hydrogen bonds with OH of Tyr92 and OE2 of Glu132. These hydrogen bonds will fix the orientation of imidazole ring of His82. These amino acids and hydrogen bonds network in the proximal site are conserved in sdHbs except to HGbI.

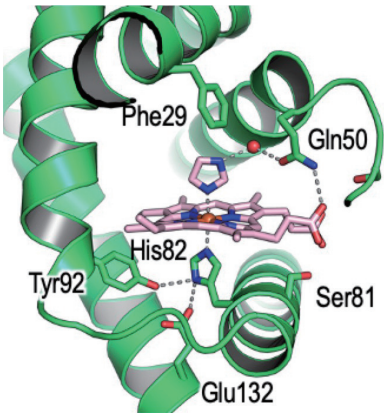


Figure 1. Heme environmental structure of Y29F-AaTgb in the imdazole-bound form. Hydrogen bonds are shown in dashed lines. Nitrogen and oxygen atoms are shown in blue and red, respectively. Red sphere in the heme pocket shows the water molecule W.

Imidazole bound to heme participate in a hydrogen bonding network in the distal heme pocket. A well-defined water molecule (W) present in the distal heme pocket forms hydrogen bonds with imidazole and Gln50. Gln50 forms a hydrogen bond with a propionate group of heme. This hydrogen bonding network will stabilize and fix the orientation of imidazole ligand. On the other hand, Phe29 was 3.41 Å from nitrogen of imidazole and 3.69 Å from the water molecule W.

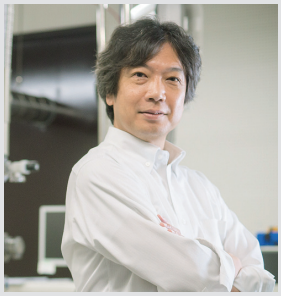
The binding affinity of imidazole (K_d) to the ferric form of AaTgb was 4.1 and 5.7 μM for the wild type and Y29F variant, respectively, which were determined by measuring absorbance changes upon imidazole titration. Similar binding affinity of imidazole will be achieved as a loss of the hydrogen bond between Tyr29 and imidazole in Y29F variant is compensated by the hydrogen bond between the water molecule W and imidazole.

2. Structural and Functional Analyses of Heme Sensing Transcriptional Regulator PefR

Hemes (iron-porphyrins) are critical for biological processes in all organisms. In this work, structural, functional and spectroscopic analyses of the heme-responsive sensor protein PefR from *Streptococcus agalactiae*, were carried out to elucidate the molecular mechanisms of how heme molecule regulates the functional acitivity of PefR. The crystal structures of apo-PefR, apo-PefR/DNA complex, and heme-bound (holo-) PefR were determined at 2.6, 2.5 Å, and 1.7 Å resolutions, respectively. Structural comparison of the apo-PefR/DNA complex and holo-PefR reveals that conformational change occur around the heme-binding site, which is induced by the coordination of His114 of one subunit to heme followed by the coordination of the N-terminal amino group of the other subunit. Rigid-body motion of the α1 helix in association with heme accommodation alters the relative orientation of the DNA-binding domain in holo-PefR from the apo form, resulting in a conformational change in the DNA-binding domain.

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.

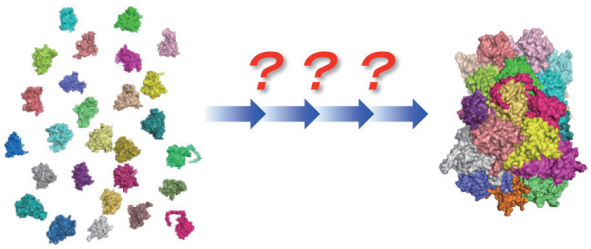

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- 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).
- T. Satoh and K. Kato, "Structural Aspects of ER Glycoprotein Quality-Control System Mediated by Glucose Tagging," in *Glycobiophysics*, Y. Yamaguchi and K. Kato, Eds., Springer Nature; Singapore, pp. 149–169 (2018).
- K. Kato, H. Yagi and T. Yamaguchi, "NMR Characterization of the Dynamic Conformations of Oligosaccharides," in *Modern Magnetic Resonance, 2nd Edition*, G. A. Webb, Ed., Springer International Publishing, pp. 737–754 (2018).
- T. Yamaguchi and K. Kato, "Molecular Dynamics of Gangliosides," in *Gangliosides*, S. Sonnino and A. Prinetti, Eds., Methods in Molecular Biology, Humana Press; New York, **vol. 1804**, pp. 411–417 (2018).
- K. Kato and T. Satoh, "Structural Insights on the Dynamics of Proteasome Formation," *Biophys. Rev.* **10**, 597–604 (2018).

1. Methodological Advancements for Analysis of Conformational Dynamics and Interactions of Biomolecules

During the past year, we have made significant progresses in our methods for investigating conformational dynamics and interactions of biomolecules, especially oligosaccharides and glycoproteins. Oligosaccharides play versatile roles in various biological systems but are difficult to characterize from a structural viewpoint due to their remarkable degrees of freedom in internal motion. Therefore, molecular dynamics simulations have been widely used to delineate the dynamic conformations of oligosaccharides. However, hardly any methods have thus far been available for the comprehensive characterization of simulation-derived conformational ensembles of oligosaccharides. We developed a theoretical approach for comprehensive characterization of oligosaccharide conformational ensembles with conformer classification by free-energy landscape via reproductive kernel Hilbert space.[1] This methodology will open opportunities to explore oligosaccharides' conformational spaces, and more generally, molecules with high degrees of motional freedom.

In addition, we sophisticated our experimental methods for stable-isotope-assisted measurements of nuclear magnetic resonance (NMR) and small-angle neutron scattering (SANS) using immunoglobulin G (IgG) as a model glycoprotein. This enabled us to achieve NMR spectral assignments of the N-linked oligosaccharides as well as polypeptide backbones of the Fc portion of IgG.[2,3] Moreover, we combined inverse contrast-matching SANS method with size exclusion chromatography and thereby successfully observed SANS from the non-deuterated IgG glycoprotein in complex with its binding partners with 75% deuteration, which were unobservable in terms of SANS in D_2O.[4] Furthermore, we revealed residual structure of unfolded ubiquitin by employing a dimethylsulfoxide-quenched hydrogen/deuterium-exchange NMR technique with the use of spin desalting columns.[5]

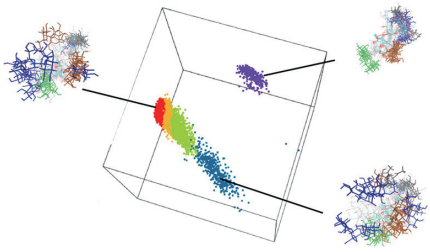

Figure 2. A kernel method for the comprehensive characterization of conformational ensembles of oligosaccharides in association with the conformational free-energy landscape.

2. Integrative Approaches for Characterizing Biomolecular Assembly Systems

We characterized various biomolecular assembling systems using integrative approaches. Cold atmospheric plasma (CAP) has attracted much attention in the fields of biotechnology and medicine owing to its potential utility in clinical applications. Recently accumulating evidence has demonstrated that CAP influences protein structures. However, there remain open questions regarding the molecular mechanisms behind the CAP-induced structural perturbations of biomacromolecules. In view of this situation, we investigated the potential effects of CAP irradiation of amyloid β (Aβ).[6] Based on NMR, mass spectrometry, and kinetics analyses, we demonstrated that the CAP irradiation results in selective oxidation of the methionine residue at position 35 of Aβ, which suppresses amyloid fibril formation. This modification is made by H_2O_2 generated in the plasma-irradiated buffer solution, rather than by the direct action of the plasma.

We also conducted a cryo-electron microscopic study of the proteasome α7 subunit, which self-assembles into a homo-tetradecamer consisting of two layers of α7 heptameric rings.[7] Our observations suggest that the α7 double-ring structure was significantly different from the previously reported crystallographic model and fluctuates considerably in solution.

In addition, we contributed to an IMS Joint Research lead by Dr. Ryo Ohtani (Kyushu University) on two-dimensional coordination polymers as *pseudo-membrane jackets*, which achieve visible phase separation in cell membrane.[8,9] This system opens new avenues for the application of metal complex lipids toward controlling lipid distributions in fluid membranes.

References

1) T. Watanabe *et al.*, *Phys. Chem. Chem. Phys.* **23**, 9753–9760 (2021).
2) H. Yagi *et al.*, *Biomolecules* **10**, 1482 (2020).
3) S. Yanaka *et al.*, *Biomol. NMR Assignments* **15**, 187–192 (2021).
4) N. Sato *et al.*, *J. Biochem.* **169**, 701–708 (2021).
5) M. Yagi-Utsumi *et al.*, *Biophys. J.* **119**, 2029–2038 (2020).
6) M. Yagi-Utsumi *et al.*, *Int. J. Mol. Sci.* **22**, 3116 (2021).
7) C. Song *et al.*, *Int. J. Mol. Sci.* **22**, 4519 (2021).
8) R. Ohtani *et al.*, *Angew. Chem., Int. Ed.* **61**, 13603–13608 (2021).
9) R. Ohtani *et al.*, *Angew. Chem., Int. Ed.* **59**, 17931–17937 (2020).

Awards

YAGI-UTSUMI, Maho; 10th Young Researcher Award, National Institutes of Natural Sciences (2021).
YANAKA, Saeko; Award for Young Scientists, the Division of Physical Sciences of the Pharmaceutical Society of Japan (2021).
UMEZAWA, Fumiko; Young Scientist Award, Japanese Biochemical Society Chubu Branch (2021).
SAITO, Taiki; the Young Scientist Award, the 16th Forum of the Glycoscience Base for Chubu (2021).

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Operation and Design Principles of Biological Molecular Machines

Department of Life and Coordination-Complex Molecular Science
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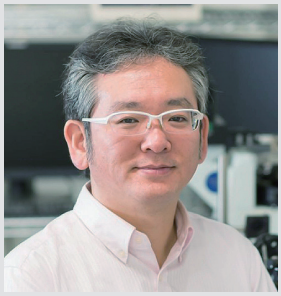

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Keywords Molecular Motors, Single-Molecule Analysis, Protein Engineering

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 mechanical forces and torques that drive their unidirectional motions from the energy of chemical reaction or the electrochemical potential across the cell membrane.

We unveil operation 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.

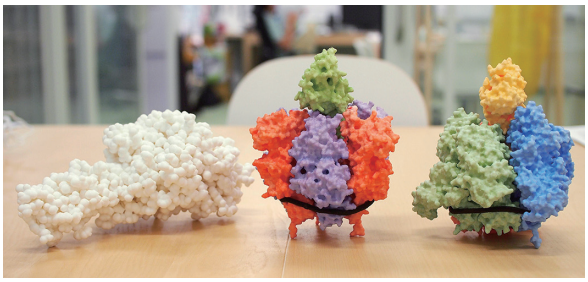

Figure 1. Protein molecular machines. (Left) A linear molecular motor chitinase A. (Center and Right) Rotary molecular motors F_1-ATPase and V_1-ATPase, respectively.

Selected Publications

- A. Visootsat, A. Nakamura, P. Vignon, H. Watanabe, T. Uchihashi and R. Iino, "Single-Molecule Imaging Analysis Reveals the Mechanism of a High-Catalytic-Activity Mutant of Chitinase A from *Serratia marcescens*," *J. Biol. Chem.* **295**, 1915–1925 (2020).
- J. Ando, T. Shima, R. Kanazawa, R. Shimo-Kon, A. Nakamura, M. Yamamoto, T. Kon and R. Iino, "Small Stepping Motion of Processive Dynein Revealed by Load-Free High-Speed Single-Particle Tracking," *Sci. Rep.* **10**, 1080 (2020).
- J. Ando, A. Nakamura, M. Yamamoto, C. Song, K. Murata and R. Iino, "Multicolor High-Speed Tracking of Single Biomolecules with Silver, Gold, Silver-Gold Alloy Nanoparticles," *ACS Photonics* **6**, 2870–2883 (2019).
- 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).
- J. Ando, A. Nakamura, A. Visootsat, M. Yamamoto, C. Song, K. Murata and R. Iino, "Single-Nanoparticle Tracking with Angstrom Localization Precision and Microsecond Time Resolution," *Biophys. J.* **115**, 2413–2427 (2018).
- 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).
- A. Nakamura, T. Tasaki, Y. Okuni, C. Song, K. Murata, T. Kozai, M. Hara, H. Sugimoto, K. Suzuki, T. Watanabe, T. Uchihashi, H. Noji and R. Iino, "Rate Constants, Processivity, and Productive Binding Ratio of Chitinase A Revealed by Single-Molecule Analysis," *Phys. Chem. Chem. Phys.* **20**, 3010–3018 (2018).

1. Domain Architecture Divergence Leads to Functional Divergence in Binding and Catalytic Domains of Bacterial and Fungal Cellobiohydrolases[1)]

Cellobiohydrolases directly convert crystalline cellulose into cellobiose and are of biotechnological interest to achieve efficient biomass utilization. As a result, much research in the field has focused on identifying cellobiohydrolases that are very fast. Cellobiohydrolase A from the bacterium *Cellulomonas fimi* (CfCel6B) and cellobiohydrolase II from the fungus *Trichoderma reesei* (TrCel6A) have similar catalytic domains (CDs) and show similar hydrolytic activity. However, TrCel6A and CfCel6B have different cellulose-binding domains (CBDs) and linkers: TrCel6A has a glycosylated peptide linker, whereas CfCel6B's linker consists of three fibronectin type 3 domains. We previously found that TrCel6A's linker plays an important role in increasing the binding rate constant to crystalline cellulose. However, it was not clear whether CfCel6B's linker has similar function. Here we analyze kinetic parameters of CfCel6B using single-molecule fluorescence imaging to compare CfCel6B and TrCel6A. We find that CBD is important for initial binding of CfCel6B, but the contribution of the linker to the binding rate constant or to the dissociation rate constant is minor. The crystal structure of the CfCel6B CD showed longer loops at the entrance and exit of the substrate-binding tunnel compared with TrCel6A CD, which results in higher processivity. Furthermore, CfCel6B CD showed not only fast surface diffusion but also slow processive movement, which is not observed in TrCel6A CD. Combined with the results of a phylogenetic tree analysis, we propose that bacterial cellobiohydrolases are designed to degrade crystalline cellulose using high-affinity CBD and high-processivity CD.

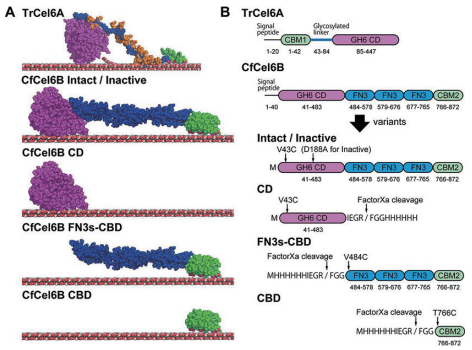

Figure 2. Structures of TrCel6 and CfCel6B. A, model structures of Intact TrCel6A, CfCel6B, and CfCel6B domain constructs used in this study. TrCel6A structure is the same as in the previous report. For CfCel6B, structure of CD is X-ray crystal structure (PDB code 7CBD), and FN3s and CBD are modeled by SWISS-MODEL server. Figures were prepared by PyMOL. B, detailed descriptions of domain compositions for each construct. Positions of mutation sites, histidine tags, and FaXa cleavage sites and estimated amino acid numbers for each domain are shown.

2. Combined Approach to Engineer a Highly Active Mutant of Processive Chitinase Hydrolyzing Crystalline Chitin[2)]

Serratia marcescens chitinase A (SmChiA) processively hydrolyzes recalcitrant biomass crystalline chitin under mild conditions. Here, we combined multiple sequence alignment, site-saturation mutagenesis, and automated protein purification and activity measurement with liquid-handling robot to reduce the number of mutation trials and shorten the screening time for hydrolytic activity improvement of SmChiA. The amino acid residues, which are not conserved in the alignment and are close to the aromatic residues along the substrate-binding sites in the crystal structure, were selected for site-saturation mutagenesis. Using the previously identified highly active F232W/F396W mutant as a template, we identified the F232W/F396W/S538V mutant, which shows further improved hydrolytic activity just by trying eight different sites. Importantly, valine was not found in the multiple sequence alignment at Ser538 site of SmChiA. Our combined approach allows engineering of highly active enzyme mutants, which cannot be identified only by the introduction of predominant amino acid residues in the multiple sequence alignment.

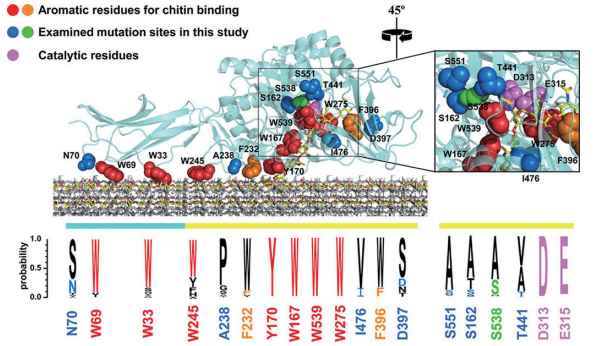

Figure 3. Model structure of SmChiA bound to crystalline chitin, important residues for binding and catalysis, and residues mutated in this study. (Top) A crystal structure of SmChiA (PDB entry 1CTN; ribbon model) aligned with the crystalline chitin chains (stick model). Amino acid residues responsible for binding to chitin (red and orange), catalytic residues (pink), and examined mutation sites (blue and green) are highlighted with sphere models. An expanded image around the catalytic site (transparent box in the left structure) is also shown in the right-hand-side box with 45° turn from the left structure. The cyan and yellow bars under the structure indicate the binding and catalytic domains, respectively. (Bottom) Result of multiple sequence alignment for amino acid residues highlighted in the top. The residues of SmChiA are shown in the same color as the top.

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Award

OTOMO, Akihiro; Best Presentation Award, 2020 Annual Meeting of the Biophysical Society of Japan Chubu Branch Meeting (2020).

Development of Heterogeneous Catalysis toward Ideal Chemical Processes

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Keywords Transition Metal Catalysis, Green Chemistry, Organic Synthesis

Our research interests lie in the development of transition metal-catalyzed reaction systems toward ideal (highly efficient, selective, green, safe, simple, etc.) organic transformations. In particular, we have recently been developing the heterogeneous aquacatalytic systems, continuous flow catalytic systems, and super active catalysts working at ppm-ppb loading levels. Thus, for example, a variety of palladium catalysts were designed and prepared promoting carbon–carbon bond forming reactions at ppm-ppb loading levels (Figure 1).

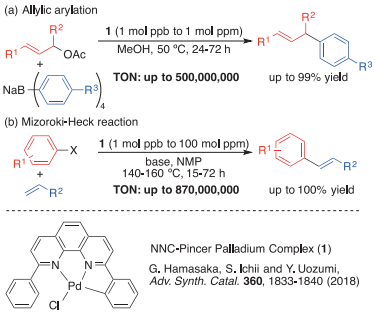

Figure 1. Typical Examples of Pd-Catalyzed Carbon–Carbon Bond Forming Reactions with ppm-ppb Loading Levels of an NNC-Pincer Pd Complexes.

Selected Publications

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- Y. M. A. Yamada, S. M. Sarkar and Y. Uozumi, "Self-Assembled Poly(imidazole-palladium): Highly Active, Reusable Catalyst at Parts per Million to Parts per Billion Levels," *J. Am. Chem. Soc.* **134**, 3190–3198 (2012).
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1. C–H Arylation of Thiophenes with Aryl Bromides by a Parts-per-Million Loading of a Palladium NNC-Pincer Complex[1)]

A palladium NNC-pincer complex efficiently catalyzed the direct arylation of thiophene derivatives with extremely low palladium loadings of the order of parts per million. Thus, the reaction of various thiophenes with aryl bromides in the presence of 25–100 mol ppm of chlorido[(2-phenyl-κ-C ^{2})-9-phenyl-1,10-phenanthroline-κ^2-*N*,*N*']palladium(II) NNC-pincer complex, K_2CO_3, and pivalic acid in *N*,*N*-dimethylacetamide afforded the corresponding 2- or 5-arylated thiophenes in good to excellent yields. A combination of the present C–H arylation and Hiyama coupling with the same NNC-pincer complex provides an efficient synthesis of unsymmetrical 2,5-thiophenes with catalyst loadings at mol ppm levels.

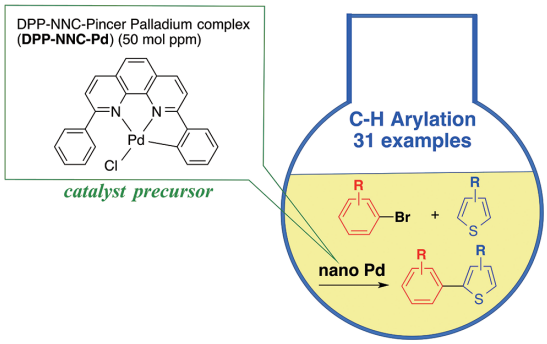

Figure 2. C–H Arylation of Thiophenes with Aryl Bromides by a Parts-per-Million Loading of a Palladium NNC-Pincer Complex.

2. A Convoluted Polyvinylpyridine-Palladium Catalyst for Suzuki-Miyaura Coupling and C–H Arylation[2)]

The development of highly active and reusable supported catalysts for Suzuki-Miyaura coupling and catalytic C–H arylation is important for fundamental and applied chemistry, with these reactions being used to produce medical compounds and functional materials. We found that a mesoporous composite made of a linear poly(4-vinylpyridine) and tetrachloropalladate acted as a dual-mode catalyst for a variety of cross-coupling reactions, with both Pd nanoparticles and a Pd complex catalyst being observed under different conditions. The polyvinylpyridine-palladium composite was readily prepared via the molecular convolution of poly(4-vinylpyridine) and sodium tetrachloropalladate to provide a hardly soluble polymer-metal composite. The Suzuki-Miyaura coupling and the C–H arylation of aryl chlorides and bromides with arylboronic acids, thiophenes, furans, benzene, and anisole proceeded in the presence of 0.004 mol% (40 mol ppm) to 1 mol% Pd to afford the corresponding coupling products in high yields. Furthermore, the catalyst was reused without an appreciable loss of activity. Pharmaceutical compounds and functional materials were synthesized via the coupling reactions. N_2 gas adsorption/desorption analysis indicated that the catalyst had a mesoporous nature, which played a crucial role in the catalysis. In the Suzuki-Miyaura couplings, in situ generated palladium nanoparticles in the polymer matrix were catalytically active, while a polymeric Pd(II) complex was crucial in the C–H arylations. These catalytic species were investigated via XAFS, XPS, far-infrared absorption, and Raman spectroscopies, as well as DFT calculations.

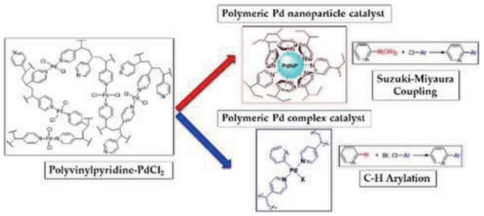

Figure 3. Polyvinylpyridine-Palladium Catalyst for Suzuki-Miyaura Coupling and C–H Arylation.

3. Synthesis of α-Tertiary Amines by the Ruthenium-Catalyzed Regioselective Allylic Amination of Tertiary Allylic Esters[3)]

We demonstrated a ruthenium-catalyzed regioselective allylic amination of tertiary allylic esters with various amines using [Cp*Ru(CH$_3$CN)$_3$][PF$_6$]/5,5′-dimethyl-2,2′-bipyridine (5,5′-diMe-2,2′-bpy) and related ruthenium catalytic systems, and successfully obtained a diverse range of α-tertiary amines as single regioisomers. The present ruthenium catalytic system was effective for reactions with various types of amines.

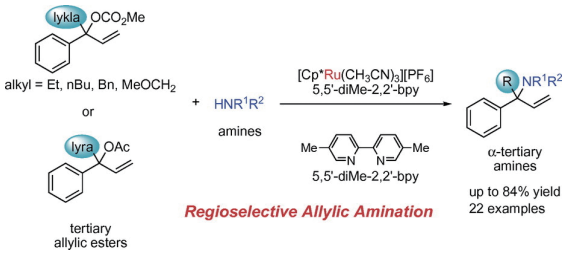

Figure 4. Ruthenium-catalyzed Regioselective Allylic Amination of Tertiary Allylic Esters.

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Design and Synthesis of Chiral Organic Molecules for Asymmetric Synthesis

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Keywords Synthetic Chemistry, Molecular Catalyst, Non-Covalent Interaction

The field of molecular catalysis has been an attractive area of research to realize efficient and new transformations in the synthesis of functional molecules. The design of ligands and 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, "metal" has been frequently used as the activation center, and conformationally rigid catalyst framework has been preferably components for the catalyst design. To develop new type of molecular catalysis, we have focused on the use of hydrogen and halogen atom as activation unit, and have utilized non-covalent interactions as organizing forces of catalyst framework in the molecular design of catalyst, which had not received much attention until recently. We hope that our approach will open the new frontier in chiral organic molecules from chiral molecular chemistry to chiral molecular science.

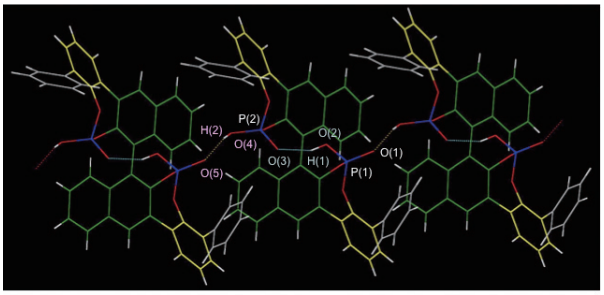

Figure 1. Hydrogen bonding network in chiral bis-phosphoric acid catalyst derived from (*R*)-3,3'-di(2-hydroxy-3 -arylphenyl)binaphthol. Hydrogen bond acts as activation unit for the substrate in asymmetric reaction space and controls atropisomeric behavior in naphthyl–phenyl axis.

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- N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, "Design of Chiral Bis-Phosphoric Acid Catalyst Derived from (*R*)-3,3'-Di(2-hydroxy-3-arylphenyl)binaphthol: Catalytic Enantioselective Diels–Alder Reaction of α,β-Unsaturated Aldehydes with Amidodienes," *J. Am. Chem. Soc.* **133**, 19294–19297 (2011).
- 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).

1. Brønsted Acid Catalyzed Asymmetric Rearrangement: Asymmetric Synthesis of Linear Homoallylic Amines

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 this study, 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.

2. Design of Chiral Brønsted Acid Catalyst

Chiral Brønsted acid catalysis has been recognized as one of the useful tools in asymmetric synthesis. We have contributed to this area by focusing on the use of perfluoroaryls and C_1-symmetric design.

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 deriver 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]

3. Design of Catalysis with Halogen Bond for Carbon–Carbon Bond Forming Reactions

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. We recently developed synthetic methodology for perfluorinated aryl compounds and applied it for the development of chiral Brønsted acid catalysts. On the basis of our achievements, we have examined it to develop catalysis with halogen bond for carbon–carbon bond forming reactions.[9]

We found that perfluorinated iodoaryls are able to catalyze the allylation reaction to *N*-activated heteroaromatics. On the basis of this discovery, a quantitative approach was studied using 4-substituted perfluorinated iodobenzene.[10] Examination of the electrostatic potential surfaces showed that substituent R groups significantly affected the charge density of iodine, fluorine, and carbon on the benzene ring. ^{19}F NMR titrations were used to determine the binding constants *K* for chloride, and their catalytic activities were evaluated in the allylation reaction. We revealed that the log *K* and product yields were linearly correlated, and that they were dependent on the Hammett substituent parameter, σ_{meta}. This linear correlation provided a quantitative predictive model for both the binding constant and the reaction yield. Concomitantly, this efficiently permitted the development of a highly active anion-binding catalyst, namely 4-CNC_6F_4I. The catalytic activity of 4-CNC_6F_4I was established in the allylation and crotylation of silatrane reagents to *N*-activated isoquinolines.

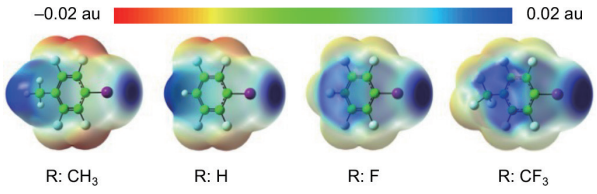

Figure 2. Molecular electrostatic potential surfaces of 4-RC_6F_4I (R: CH_3, H, F, and CF_3) at the M06-2X-D3/6-311+G(d,p)-SDD level of theory.

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2) N. Momiyama, Y. Honda, T. Suzuki and C. Jongwohan, *Asian J. Org. Chem.* **10**, 2205–2212 (2021). [Invitation only] doi: 10.1002/ajoc.202100302
3) N. Momiyama *et al.*, submitted.
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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 its 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.

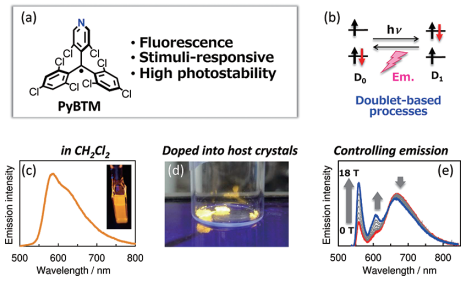

Figure 1. (a) Molecular structure of PyBTM and its characteristics. (b) Schematic photoexcitation-emission processes. (c) Emission in CH_2Cl_2. (d) Emission of PyBTM-doped molecular crystals. (e) Controlling emission by magnetic field.

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).
- Y. Hattori, T. Kusamoto and H. Nishihara, "Enhanced Luminescent Properties of an Open-Shell (3,5-Dichloro-4-pyridyl)bis(2,4,6-trichlorophenyl)methyl Radical by Coordination to Gold," *Angew. Chem., Int. Ed.* **54**, 3731–3734 (2015).
- Y. Hattori, T. Kusamoto and H. Nishihara, "Luminescence, Stability, and Proton Response of an Open-Shell (3,5-Dichloro-4-pyridyl)bis(2,4,6-trichlorophenyl)methyl Radical," *Angew. Chem., Int. Ed.* **53**, 11845–11848 (2014).

1. An Open-Shell, Luminescent, Two-Dimensional Coordination Polymer with a Honeycomb Lattice Based on Triangular Radical

Two-dimensional (2D) open-shell coordination polymers (CPs) with honeycomb lattices have attracted growing interest because of the exotic electronic structures and physical properties derived from their structural topology. Employing organic radicals as building blocks is a promising approach to produce open-shell CPs. However, radical-based CPs with honeycomb lattices reported generally have low chemical stability or poor crystallinity. Accordingly, high crystallinity and persistence are in strong demand in this class of compounds. In this study, we developed a novel triangular organic radical tris(3,5-dichloro-4-pyridyl)methyl radical (trisPyM) possessing three pyridyl groups.[1] trisPyM demonstrates photoluminescence (λ_{em} = 700 nm, φ_{em} = 0.85%, τ = 3.0 ns in dichloromethane) and high photostability with its half-life upon UV irradiation 10000 times that of TTM, a conventional luminescent radical. Complexation of trisPyM with $Zn^{II}(hfac)_2$ afforded single crystals of a novel 2D CP, trisZn, possessing a honeycomb lattice with graphene-like spin topology (Figure 2). The coordination structure of trisZn is stable under evacuation at 60 °C. trisZn exhibits photoluminescence below 79 K at λ_{em} = 695 nm. Importantly, trisZn displays magnetoluminescence below 20 K.[2] This is the first example showing magnetoluminescence as pure (*i.e.*, non-doped) radical compounds. Our results indicate that trisPyM can be a promising building block in the construction of a new class of 2D honeycomb CPs with spin-correlated novel photofunctions.

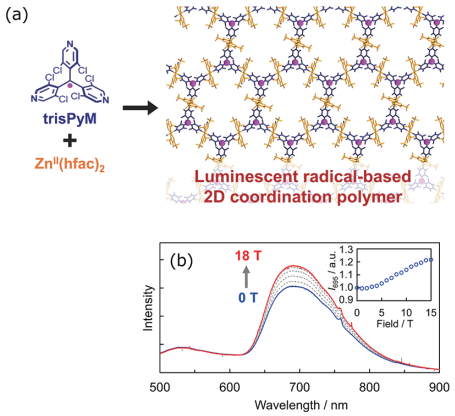

Figure 2. (a) Chemical structure of trisPyM and crystal structure of trisZn. (b) Emission spectra of trisZn at 4.2 K under a magnetic field.

2. Solid-State Room-Temperature Near-Infrared Photoluminescence of a Stable Organic Radical

Luminescent organic radicals have been shown to demonstrate unique emission properties in solvents or in host materials. On the other hand, the luminescent properties of radicals in the fully aggregated pure solid state have rarely been investigated, especially at room temperature. In this study, a novel luminescent radical with a 3-pyridyl moiety, the (2,4-dichloro-3-pyridyl)bis(2,4,6-trichlorophenyl)methyl radical (metaPyBTM) was prepared and the optical properties were investigated in detail.[3] metaPyBTM exhibits distinct near-infrared photoluminescence in its crystalline state at room temperature, in spite of the fact that the electronic structure and photophysical properties in solution are similar to those of the analogues radicals. The solid-state luminescence properties of metaPyBTM are modulated strongly by temperature and the degree of aggregation. metaPyBTM in the moderately aggregated state displays magnetic-field responsive luminescence, magnetoluminescence, whereas no magnetic field effect was detected in the emission spectrum of purely crystalline metaPyBTM. These results suggest that controlling the manner of interactions between radicals is an important factor for achieving magnetoluminescence.

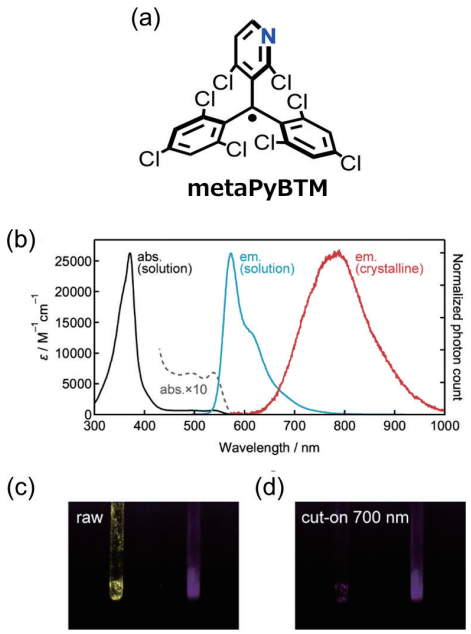

Figure 3. (a) Chemical structure of metaPyBTM. (b) Absorption and emission spectra of metaPyBTM in dichloromethane (black, pale-blue) and in crystalline state (red). (c,d) Vis-NIR photographs of pure metaPyBTM (right) and metaPyBTM-doped αH-metaPyBTM crystals under UV light at λ = 365 nm with (d) and without (c) a longpass filter (cut-on: 700 nm). Photos were taken by BIZWORKS Yubaflex digital camera.

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Design and Synthesis of Three-Dimensional Organic Structures

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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.

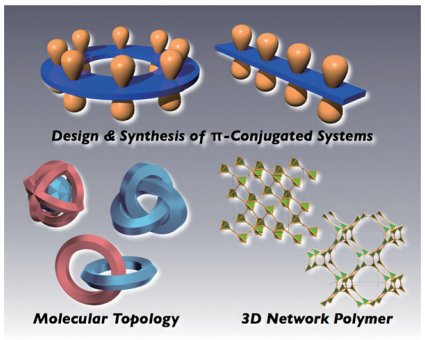

Figure 1. Design and synthesis of π-conjugated organic molecules (top); Development of novel molecular topology (bottom left); Construction of three-dimensional network polymers (bottom right).

Selected Publications

- 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. Saito, K. Yamanoue, Y. Segawa and K. Itami, "Selective Transformation of Strychnine and 1,2-Disubstituted Benzenes by C–H Borylation," *Chem* **6**, 985–993 (2020).
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- 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).
- Y. Segawa and D. W. Stephan, "Metal-Free Hydrogenation Catalysis of Polycyclic Aromatic Hydrocarbons," *Chem. Commun.* **48**, 11963–11965 (2012).

1. Double-Helix Supramolecular Nanofibers Assembled from Negatively Curved Nanographenes

The layered structures of graphite and related nanographene molecules play a key role in their physical and electronic properties. The well-ordered molecular alignment of nanographenes and its structural determination are of interest in order to gain insight into a variety of carbon materials. It is well known that the one-dimensional (1D) assembly of planar nanographenes can be achieved by introducing suitable peripheral substituents that tune solubility. The 1D assembly of bowl-shaped nanographenes was also achieved by convex-concave π-π stacking along with non-covalent interactions. However, the stacking modes of negatively curved nanographenes remain unclear, owing to the lack of suitable nanographene molecules.

We developed the synthesis and 1D self-assembly of a newly designed nanographene **1-H** ($C_{68}H_{28}$), a negatively curved nanographene with 12 carbon atoms fewer than WNG (Figure 2a).[1] Serendipitously, we discovered that **1-H** self-assembles in various organic solvents and works as a highly efficient gelator that forms organic gels at concentrations of <1 wt% (Figure 2b). Transmission electron microscopy (TEM) and atomic force microscopy (AFM) measurements confirm that **1-H** forms fibers with diameters of ~2.8 nm. The presence of efficient π-π interactions in the fiber structures is supported by a bathochromic shift in the fluorescence spectrum of the gel state relative to that of dilute solutions of **1-H**. Finally, using three-dimensional electron diffraction crystallography, the double-helix π-π stacking mode of **1-H** in the supramolecular nanofiber was revealed (Figure 2c).

Based on this discovery and its revelation of a new guiding principle in supramolecular self-assembly, we expect that a number of negatively curved nanographenes can be developed for new applications in materials science and biology. Moreover, this work not only reports the discovery of an all-sp^2-carbon supramolecular π-organogelator with negative curvature, but it also showcases the power of 3D electron diffraction crystallography for the structural determination of submicrometer-sized hydrocarbon molecular assemblies.

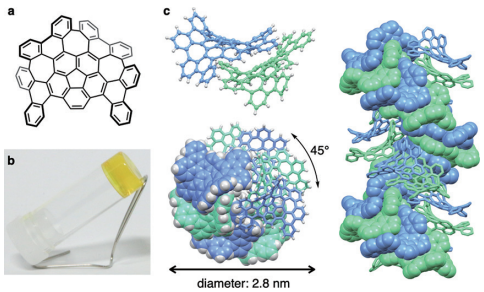

Figure 2. The negatively curved nanographene (**1-H**) that forms double-helix nanofibers. (a) Chemical structure of **1-H**. (b) Photo of organogel made of dichloromethane with 0.3 wt% of **1-H**. (c) The double-helix packing structure of **1-H** revealed by microcrystal electron diffraction crystallography (MicroED).

2. Theoretical Studies on the Strain Energy of Helicene-Containing Carbon Nanobelts

Carbon nanobelts (CNBs), the sidewall segment molecules of carbon nanotubes (CNTs), have attracted growing attention owing to their radial π-conjugation, strain-induced reactivity and potential applications in template CNT synthesis. Various CNB structures have been proposed and investigated by both theoretical and synthetic organic chemists. Recently, our group synthesized armchair-type (*n*,*n*)CNB (**A**$_n$, Figure 3a) and a zigzag-type (18,0)CNB. Apart from these known CNBs, other CNBs with more complex structures can also be designed by cutting the CNTs differently. CNBs with helicene structures (**B**$_n$–**E**$_n$, Figure 3b) are the representative examples of these complex structures, and the structural properties of such unexplored CNBs have been of interest.

To estimate the feasibility of synthesizing strained belt-shaped compounds, the calculation of strain energy (SE) is effective. While homodesmotic reaction method using reference molecules is generally used for strained molecules, we previously found that conventional homodesmotic reactions using small reference molecules could not be applied to CNBs.

Here we have successfully estimated the strain energies of CNBs containing helicene moieties.[2] Through the calculation of CNB **B**$_n$, we revealed that our previously reported method is not applicable to helicene-containing CNBs. The newly developed method, combining the conventional homodesmotic reactions and linear regression analysis, was successful for the determination of the strain energies of CNBs **B**$_n$ and **C**$_n$ that have helicene moieties in their side chains. By changing the reference molecules, the strain energies of CNBs with helicene structures in the main chains (**D**$_n$ and **E**$_n$) were also determined.

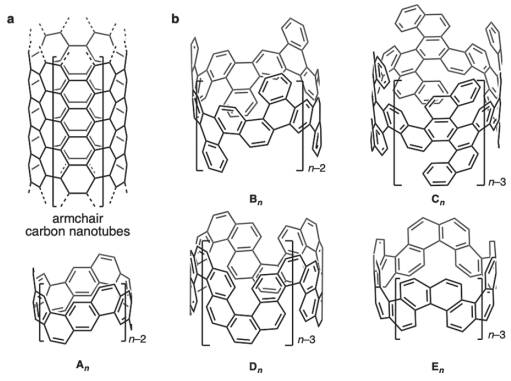

Figure 3. (a) Structures of armchair CNTs and CNBs (**A**$_n$). (b) CNBs containing helicene structures (**B**$_n$–**E**$_n$).

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Visiting Professors

Visiting Professor
FUKAZAWA, Aiko *(from Kyoto University)*

Renaissance of Nonbenzenoid π-Conjugated Systems toward Functional Materials

The work of our group has focused on exploring functional organic compounds with unusual with superb optical and/or electronic properties, based on the molecular designs of novel π-conjugated scaffolds as well as unusual functional groups. In particular, we have recently proposed a rational design of stable yet unusual π-conjugated systems based on the characteristics of nonbenzenoid hydrocarbons, *i.e.*, dehydroannulenes, non-alternant hydrocarbons, and fulvalenes, by annulation of weakly aromatic (hetero)arenes. In this year, we have succeeded in synthesizing several thiophene-fused antiaromatic π-systems that exhibit high thermal stability even without bearing bulky substituents while retaining pronounced antiaromatic character. Moreover, we have recently succeeded in synthesizing the fulvalene-based π-conjugated oligomers that exhibit exceptional electron-accepting character as well as the robustness toward multi-electron reduction.

Visiting Professor
WATANABE, Rikiya *(from RIKEN)*

Single Molecule Physiology

Our study aims to understand cellular functions using a bottom-up approach from the single molecule level. To achieve this, we are attempting to elucidate the mechanism by which individual biomolecules or their networks function in a precise manner, by developing novel single-molecule techniques using multidisciplinary approaches, including biophysics, bioMEMS, and chemical biology. In addition, we are developing a methodology to investigate correlations between genetic mutations, dysfunctions, and diseases with single molecule sensitivity, which would provide new insights for biological as well as pharmaceutical studies. Notably, last year, we developed a novel technology that can identify new coronavirus, SARS-CoV-2, at the single molecule level, enabling the world's fastest quantitative detection for early diagnosis.

Visiting Associate Professor
UEDA, Akira *(from Kumamoto University)*

Development of Purely Organic Molecular Materials with Three-Dimensional Electronic Structure

Design and synthesis of novel molecular materials have been a central issue for the development of molecular science. Our group has recently succeeded in the development of a new type of molecular conductor crystal composed of a zwitterionic neutral radical with a partially charge-transferred structure. Single crystal X-ray analysis reveals that this material has a peculiar electronic structure where two-dimensional conducting layers are electronically coupled to each other through the intramolecular interaction of the partially charge-transferred zwitterionic neutral radical. Therefore, one can say that this material has a three-dimensional-like electronic structure different from one- or two-dimensional ones in the conventional molecular conductors. Interestingly, the low-temperature structural analysis and physical property measurements suggest that this material undergoes a phase transition from the charge-uniform state to a three-dimensionally charge-ordered state.