# Self-Assembling Molecular Systems Based on Coordination Chemistry


## Division of Advanced Molecular Science

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**Education**
1980 B.S. Chiba University
1982 M.S. Chiba University
1987 Ph.D. Tokyo Institute of Technology

**Professional Employment**
1982 Researcher, Sagami Chemical Research Center
1988 Assistant Professor to Associate Professor, Chiba University
1997 Associate Professor, Institute for Molecular Science
1999 Professor, Nagoya University
2002 Professor, The University of Tokyo
2018 Distinguished Professor, Institute for Molecular Science
2019 Distinguished Professor, The University of Tokyo

**Awards**
1994 Progress Award in Synthetic Organic Chemistry, Japan
2000 Division Award of Chemical Society of Japan (Organic Chemistry)
2001 Tokyo Techno Forum 21 Gold Medal
2001 Japan IBM Award
2003 Nagoya Silver Medal
2004 Izatt-Christensen Award
2006 G. W. Wheland Award (Chicago University Lectureship Award)
2010 The Reona Esaki Award
2010 The JSCC Award
2011 3M Lectureship Award (University of British Columbia)
2012 Thomson Reuters Research Front Award 2012
2013 The Chemical Society of Japan (CSJ) Award
2013 Arthur C. Cope Scholar Award (ACS National Award)
2013 Merck-Karl Pfister Visiting Professorship (MIT Lectureship Award)
2014 ISNSCE 2014 Nanoprize
2014 Medal with Purple Ribbon
2014 Fred Basolo Medal (Northwestern University)
2018 Wolf Prize in Chemistry
2019 The Imperial Prize and the Japan Academy Prize
2020 The 73rd Chunichi Cultural Award
2020 Clarivate Citation Laureates (Chemistry)
2020 "Major Results" of Nanotechnology Platform, MEXT

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**Keywords** Self-Assembly, Nano-Space, Coordination Chemistry

We are designing new self-assembled molecular systems based on coordination chemistry, and trying to apply the molecular system to various research fields.

For example, we applied the self-assembled molecular systems to biological studies and the structure elucidation of small molecules (Figures 1 and 2).

Currently, we are focusing on the following two projects:

(1) Protein encapsulation in self-assembled Coordination cages: In this project, we aim to explore the potential of proteins encapsulated within precisely designed molecular capsules (Figure 1). We envision to 1) control the property of protein (*e.g.*, stability, ligand affinity or selectivity), 2) control enzymatic reactivity (*e.g.*, activity or new function), and 3) develop new analytical methodology (coupled with NMR, X-ray, MS or cryoEM *etc.*).

(2) Crystalline sponge (CS) method: The CS is a porous crystal, which can accommodate various kinds of small molecules, and align the accommodated molecules neatly in its inner space. Actually, we can observe the structure of the small molecules neatly aligned in the CS by the X-ray crystallography (Figure 2). The method has a potential to accelerate the various kinds of researches, in which the structure elucidation of novel compounds is required. We target to develop new drug discovery using this method.

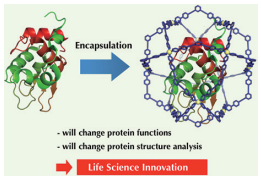


**Figure 1.** Cartoon presentation for the protein encapsulation.

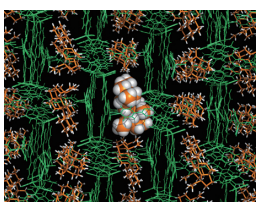

**Figure 2.** One example of the crystalline sponge methode.

## Selected Publications


- Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hitora, K. Takada, S. Matsunaga, K. Rissanen and M. Fujita, "X-Ray Analysis on the Nanogram to Microgram Scale Using Porous Complexes," *Nature* **495**, 461–466 (2013).
- D. Fujita, Y. Ueda, S. Sato, N. Mizuno, T. Kumasaka and M. Fujita, "Self-Assembly of Tetravalent Goldberg Polyhedra from 144 Small Components," *Nature* **540**, 563–566 (2016).

## 1. Protein Stabilization and Refolding in a Gigantic Self-Assembled Cage

Spatial isolation of molecules is often a powerful strategy for regulating their molecular behavior. Biological systems employ such mechanisms well; however, scientists have yet to rival nature, particularly for macromolecular substrates. We demonstrated that the encapsulation of a protein in a molecular cage with an open framework stabilizes the tertiary structure of the protein and improves its enzymatic activity. Particularly, when the three-dimensionally confined enzyme was exposed to an organic solvent, its half-life was prolonged 1,000-fold. Kinetic and spectroscopic analysis of the enzymatic reaction revealed that the key to this stability is the isolated space; this is reminiscent of chaperonins, which use their large internal cavities to assist the folding of client proteins (Figure 3). The single-molecule protein caging affords a new type of protein-based nanobiotechnology that accelerates molecular biology research as well as industrial applications.

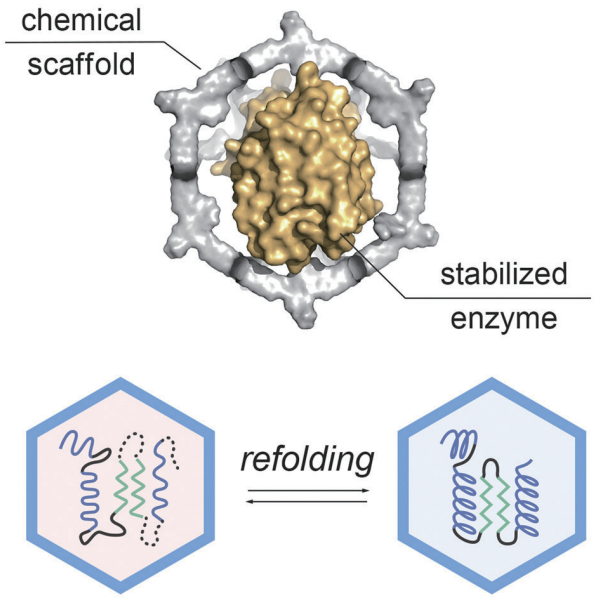


**Figure 3.** Protein refolding in the cage.

## 2. Absolute Configuration Determination from Low *ee* Compounds by the Crystalline Sponge Method

When chiral compounds with low enantiomeric excess (*ee*, R:S = *m*:*n*) were absorbed into the void of the CS, enantiomerically pure [$(R)_m(S)_n$] chiral composites were formed, changing the centrosymmetric space group into non-centrosymmetric one (Figure 4). The absolute configuration of the analyte compounds was elucidated with a reasonable Flack (Parsons) parameter value. This phenomenon is characteristic to the "post-crystallization" in the pre-determined CS crystalline lattice, seldom found in common crystallization where the crystalline lattice is defined by an analyte itself. The results highlight the potential of the CS method for absolute configuration determination of low ee samples, an often encountered situation in asymmetric synthesis studies, which is important for the development of new drugs.

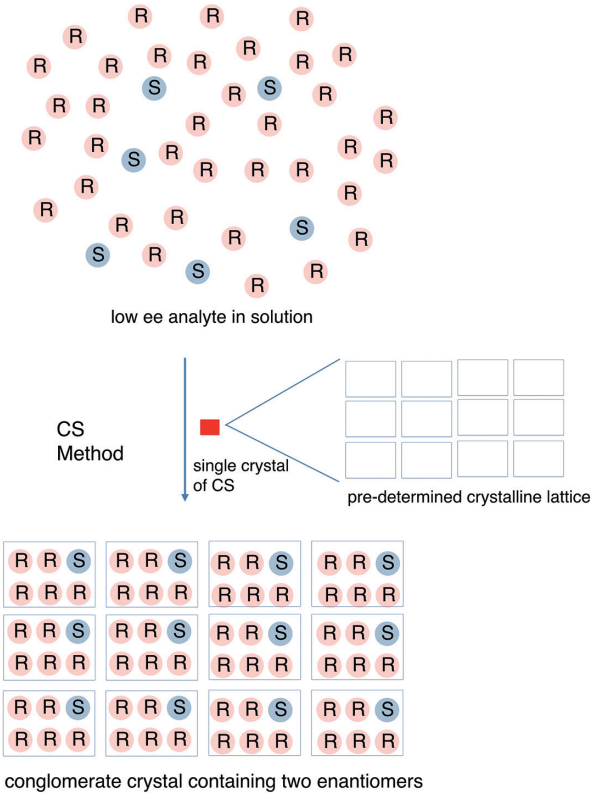


**Figure 4.** CS method was applied to the analysis of chiral compounds with low enantiomeric excess.

### References

1) D. Fujita, R. Suzuki, Y. Fujii, M. Yamada, T. Nakama, A. Matsugami, F. Hayashi, J.-K. Weng, M. Yagi-Utsumi and M. Fujita, *Chem* **7**, (2021), in press.
2) R. Dubey, K. Yan, T. Kikuchi, S. Sairenji, A. Rossen, S. S. Goh, B. L. Feringa and M. Fujita, *Angew. Chem., Int. Ed.* **60**, 11809–11813 (2021).

### Awards

FUJITA, Makoto; Clarivate Citation Laureates (Chemistry) (2020).
MITSUHASHI, Takaaki; FUJITA, Makoto; "Major Results" of Nanotechnology Platform, MEXT (2020).

* carrying out graduate research on Cooperative Education Program of IMS with the University of Tokyo