Second-Generation Crystalline Sponges: Structural Analysis of Medium-Sized Pharmaceutical Compounds

Division of Advanced Molecular Science

FUJITA, Makoto
Distinguished Professor
[mfujita@ims.ac.jp]

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
2022 Le Grand Prix 2022 de la Fondation de la Maison de la Chimie
2023 Asahi Prize2023
2023 2022 Natta Award (Politecnico di Milano)
2024 Van't Hoff Award
2025 International Honorary Member of American Academy of Arts & Sciences

Member
Research Assistant Professor
MITSUHASHI, Takaaki
Post-Doctoral Fellow
HE, Wei
Secretary
MASUDA, Michiko
NOGAWA, Kyoko

Keywords Self-Assembly, Nano-Space, Coordination Cages

The crystalline sponge (CS) method is a novel technique for X-ray diffraction analysis, in which a porous crystal absorbs and aligns target molecules, thereby eliminating the need for crystallization of the analyte. However, this approach faces significant challenges when analyzing large or highly polar molecules. We are developing a second-generation CS (2G-CS) method that employs coordination cages as CS, leveraging their exceptional guest-binding capability to overcome these limitations. This breakthrough method greatly expands the range of analyzable compounds, now including water-soluble molecules and large amphiphilic pharmaceutical compounds (MW > 1000). We anticipate this method will become a definitive technique for molecular structure determination in both academia and industry.

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).
- M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi and K. Ogura, "Self-Assembly of Ten Molecules into Nanometre-Sized Organic Host Frameworks," *Nature* **378**, 469–471 (1995).

1. Supramolecular Coordination Cages as Crystalline Sponges through a Symmetry Mismatch Strategy[1)]

The self-assembled octahedral M_6L_4 coordination cage **1** exhibits exceptional guest-binding abilities in solution. In the past thirty years, the rich host–guest chemistry of its host–guest complexes was thoroughly investigated and frequently elucidated through crystallographic studies. Motivated by these results, we aimed to convert this cage into a crystalline material that can enhance the current CS method.

Introducing large aromatic "sticker" anions **2** into the cage solution leads to the formation of high-quality crystals, driven by electrostatic interactions between the positively charged cage and the negatively charged anions. The symmetry mismatch between the T_d-symmetric cage and the D_{2h}-symmetric anions resulted in the production of crystals in a low-symmetry space group (P-1), preventing the disorder of guest molecules and leading to the formation of guest-accessible channels in the crystal.

This cage-immobilized crystals were examined for the CS method to determine the structure of guest molecules. Guest molecules can be introduced to the crystal either before or after the cage crystallization. Owing to the versatile molecular recognition with cage, analytes with molecular weights ranging from 200 to 1200 can be captured by the cage thus enabling their structural determination *via* X-ray diffraction analysis. Notably, various large amphiphilic molecules **3**–**6** with significant pharmaceutical interest were examined and successfully determined the molecular structures.

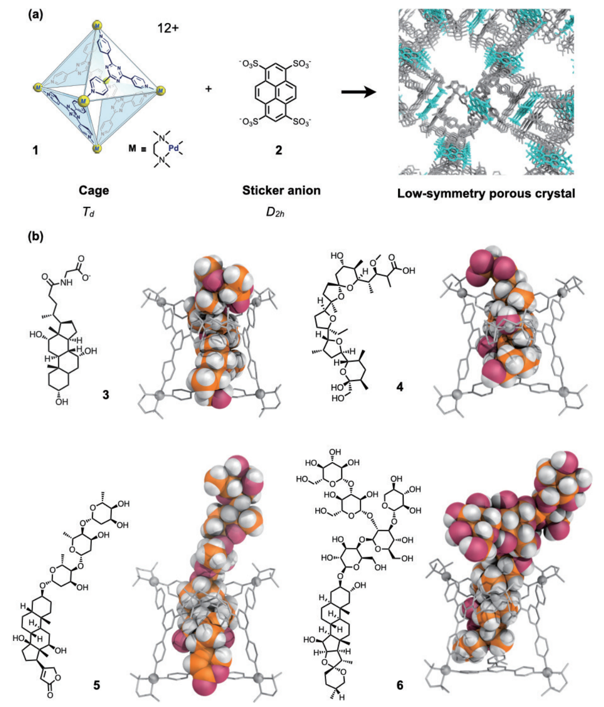

Figure 1. Coordination cages as crystalline sponges for structural analysis of medium-sized pharmaceutical compounds. (a) Symmetry-mismatched pair used for crystallization. (b) Crystal structures of amphiphilic molecules **3**–**6** encapsulated in cage-based crystals.

2. Host–Guest Chemistry in a Capillary Applied to the Facilitation of the Crystalline Sponge Method[2)]

Although conceptually elegant, the traditional CS method requires delicate handling and high experimental skill, limiting its broader applicability. Major challenges include handling trace amounts of analyte and simplifying the workflow.

We addressed these by employing glass capillaries—a convenient tool for transferring, mixing, and storing micro-volumes of liquid. Our optimized protocol involves simply dipping the capillary into a series of bench-stable standard solutions. This process yields sponge crystals encapsulating the target molecule. The resulting in-capillary crystals are comparable in quality to those grown in flasks and can be directly analyzed within the capillary using standard laboratory X-ray diffractometers.

This miniaturized approach reduces the required sample amount from milligrams to micrograms and shortens the analysis time from weeks to days. As a result, the CS method is transformed from a specialized technique into a simple, broadly applicable tool suitable for any chemical laboratory, enabling on-site molecular detection and promoting broader adoption in both academia and industry.

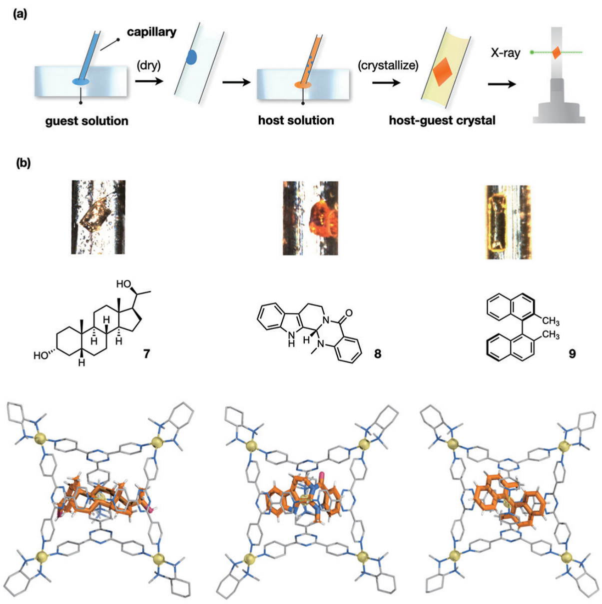

Figure 2. Highly practical CS analysis using glass capillaries. (a) Schematic illustration of the in-capillary workflow. (b) Photographs of guest-encapsulated crystals in capillaries, chemical structures, and X-ray structures of molecules **7**–**9**.

References

1) W. He, Y. Yu, K. Iizuka, H. Takezawa and M. Fujita, *Nat. Chem.* **17**, 1–10 (2025).
2) W. He, H. Takezawa, R. Yakushiji, S. Yoshida, S. Sato and M. Fujita, *Angew. Chem., Int. Ed.* **64**, e202501025 (2025).