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A Conversation with Makoto Fujita

Mark Peplow

His "crystalline sponge" is helping researchers figure out the architecture of organic molecules.

X-ray crystallography is one of the best tools to determine a molecule's structure. But it's not much use when your cherished compound is a greasy smear that resolutely fails to crystallize.

In 2013, Makoto Fujita of the University of Tokyo unveiled a method that offered hope to researchers struggling with stubborn samples. It relies on a metal organic framework (MOF), a highly porous lattice of metal-based nodes connected by organic ligands. When organic molecules soak into these pores, the crystal lattice of the MOF holds them in an oriented way as though they were crystallized, allowing their structure to be probed by X-ray analysis.

Although this "crystalline sponge" technique had some early missteps, Fujita's team has refined the method, and it is winning supporters. Mark Peplow checked in with Fujita for a progress update.

How did you develop the crystalline sponge?

More than 10 years ago, we found that we could use solvents to draw organic molecules into the pores of a particular MOF and trap them. Initially, we thought it was a common phenomenon for all MOFs, but then we realized that most cannot accept these guest molecules very efficiently because there are not enough binding units in the pores.

Our crystalline sponges have large hydrophobic cavities with many hydrogen-bonding sites and pi-stacking sites, so common organic molecules are effectively bound, ordered, and concentrated, up to 100% occupancy.

A small crystal of the crystalline sponge is dipped in a solution of the target compound. The solvent is slowly evaporated, and the guest molecules are pulled from this saturated solution into the pores of the crystalline sponge. Once the sample is prepared, the X-ray analysis is the same as for a normal crystal.

Courtesy Makoto Fujita

What reaction did you get after you unveiled the technique?

We received a great deal of feedback; we were very surprised. We heard from industry and academia, including the natural product and X-ray crystallography communities.

At the beginning, the quality was not fantastic. This wasn't due to poor X-ray crystallography; it's because the soaking process is very critical. Some compounds diffuse in a few minutes while others take weeks, and all the conditions must be optimized for each guest.

In our 2013 paper we did not optimize all the steps, which was why the structures weren't very good. Now that we have optimized all the steps, the X-ray data quality is comparable to conventional crystallography.

In February, we published our updated technique in *IUCrJ*, a journal of the International Union of Crystallography. I think it proves that the crystallography community has approved our method.

How widely is the technique used now?

We have started collaborations with more than 10 research groups in different countries, and we're analyzing compounds for them. In the past few months we've published many collaborative papers, mostly on the absolute structure determination of natural products and on assigning stereochemistry. We also have a chiral crystalline sponge, which allows us to determine the absolute chirality of a guest molecule.

Published: May 13, 2016

DOI: 10.1021/acscentsci.6b00136
ACS Cent. Sci. 2016, 2, 268–269

It's not an easy technique. There's no universal procedure, so for each guest the researchers have to optimize the conditions—the temperature, the solvent—and although the principle is simple, you have to be experienced. But this is common in chemistry: Many protocols, like chromatography techniques, need to be set up for a given compound.

One great advantage is that we only need very small quantities of sample. We can easily obtain a structure with 50 ng, and by using a crystal that is 20 μm wide we reduced the amount of guest to just 5 ng. At the moment that's our limit, our champion record.

Are you working with industry?

Pharmaceutical companies have to analyze metabolites derived from drugs. So when they collect micrograms of metabolites from patients' blood, they need an efficient method to determine their structure. We're working with several major pharmaceutical companies, including Merck and Pfizer.

Food and fragrance companies are also interested in our method, because they deal with volatile compounds that are very difficult to crystallize. And we are working with the major X-ray equipment companies, Rigaku in Japan and Bruker in the U.S. They expect our method to increase the market for X-ray crystallography.

Can researchers buy the crystalline sponge from reagent suppliers?

Nonexperts should not use the method, as we found at the beginning, because their success rate would be much lower than in our group. So at least for the next few years, until the method becomes a lot more convenient, we won't commercialize the crystalline sponge because it could cause a lot of confusion.

But our government is funding us to make the method more widely applicable in industry and academia. One idea is to set up a company to analyze researchers' compounds. In the next few years we need to test lots and lots of samples to perfect the technique, and the company could start business after that.

Mark Peplow is a freelance contributor to Chemical & Engineering News, the weekly newsmagazine of the American Chemical Society. Center Stage interviews are edited for length and clarity.

DOI: 10.1021/acscentsci.6b00136
ACS Cent. Sci. 2016, 2, 268−269