



Fitting Proteins into Metal Organic Frameworks

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Proteins are no longer just ingredients for biologists: Proteinaceous materials are gradually stepping into the spotlight as highly functional next generation materials, despite the fact that “material science” has previously mainly been explored by chemists. In the September 16th issue of *Journal of American Chemical Society*, Tezcan and co-workers report an interesting methodology to prepare a novel three-dimensional (3D) protein crystalline material utilizing the metal organic framework (MOF) approach (Figure 1).¹ This work has the potential to be a milestone for the next decade, as these proteinaceous MOFs may overcome several major drawbacks of conventional proteinaceous materials.

Obviously, the most attractive feature to using protein building blocks to forge 3D porous materials is the wide variety of structures and functions that inherently exist in proteins, particularly catalysis, electron transfer, and molecular recognition. Emulating protein function with synthetic molecules remains a daunting challenge, and thus, fabricating materials with proteins incorporated has so far best provided the benefit of proteins’ stunning functions. There have already been several successful attempts to directly exploit some porous protein single crystals as materials toward specific purposes.² These more typical protein crystals rely structurally on weak surface intermolecular interactions, meaning they are unstable. Poor mechanical strength is an unavoidable limitation to the scope of their application. When the crystallization conditions were optimized, the authors obtained the world’s first proteinaceous MOF crystal, and a rare rationally designed crystal structure.

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The methodology reported is a promising approach to surmount the aforementioned problems. Stated simply, MOFs are infinite organized structures composed of metal ions/clusters (nodes) and organic linkers (struts) bound to each other in a

The combined powers of MOFs and protein-based materials were tethered (Tezcan and co-workers in a recent JACS Communication).

3D network. Tezcan and co-workers successfully built a 3D crystalline protein stack not by relying on the protein’s original interfacial interactions but rather by rationally designing artificial metal coordinative interactions in a similar manner to MOF. They employed human heavy-chain ferritin, a globular protein complex consisting of 24 protein subunits, as the key base structure for the nodes. Taking advantage of ferritin’s intrinsic symmetry, the authors could anchor eight zinc ions on its surface through coordination to three newly installed histidine residues. The zinc-decorated ferritin provided a huge metal cluster (node) for building the MOF. After checking that the zinc ions were properly arranged at the designated positions, several bidentate organic linkers (struts) were tested to interconnect the ferritin-based nodes. When the crystallization conditions were optimized, the authors obtained the world’s first proteinaceous MOF crystal, and a rare rationally designed crystal structure. Each structure was confirmed by single crystal X-ray crystallographic analysis. The mutant ferritins gave face-centered cubic (fcc) crystals under conventional crystallization conditions. However, in the presence of the organic struts, the ferritin provided 0.5 mm body-centered cubic (bcc) crystals in less than 24 h. The expertly designed interactions between the hydroxamate struts and zinc ions on the ferritin surface overrode the native inter-protein interactions which then dominate the course of the crystallization. This result implies that we can rationally control the strength, structure, and stability of fabricated crystals.

As previously mentioned, proteinaceous MOFs have the potential to open up a number of novel applications. Ferritin itself has been recognized as a promising platform for various nanoparticle fabrications,^{3,4} so this scaffold in particular could

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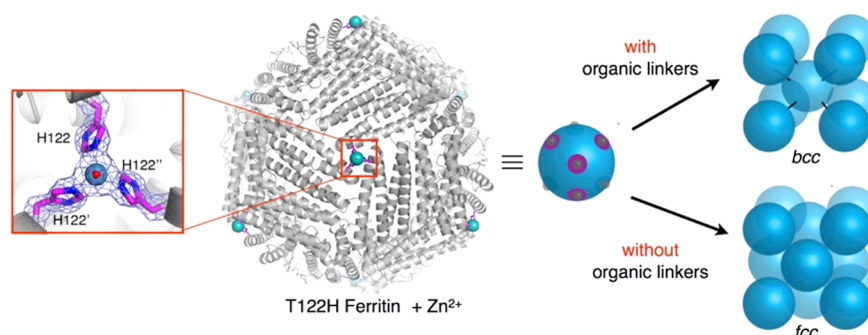


Figure 1. Preparation of the proteinaceous MOF. Zn^{2+} immobilized T122H ferritin itself assembles into fcc packing but, upon complexation with organic linkers, gives a bcc crystal as expected from the metal–ligand geometries. Adapted with permission from ref 1.

be used to precisely situate particles by controlling the density and packing manner providing materials with astonishing properties. Alternatively, the leveraging of the biocompatibility of proteins could improve the suitability of MOFs for drug carriers and for other *in vivo* applications. MOFs have received increasing attention for drug delivery in recent years, owing to their high loading capacity and versatile functionality,^{5,6} and proteinaceous MOF would provide both flexible tuning of properties and biocompatibility. Finally, a new protein crystallization methodology could emerge from this report, as the rapid crystallization rate suggests that metal-mediated interprotein interactions could aid and accelerate the formation of diffraction-worthy crystals. Ferritin itself has been recognized as a promising platform for various nanoparticle fabrications, so this scaffold in particular could be used to precisely situate particles by controlling the density and packing manner providing materials with astonishing properties.

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The idea to integrate proteins with MOFs has already existed, but it has been achieved only by protein enclathration within the large cavity of MOFs or porous cages.^{7–10} These materials, due to their limited absorption, uncontrolled orientation, and insufficient characterization of proteins, do not compare with Tezcan's well-defined proteinaceous MOFs. Of course, we must caution that the present report alone is not enough to fulfill the promise of a bright future, because the reported technology has yet to be applied to other general

proteins. However, we believe further efforts to explore the field of protein–metal–organic composites will promote additional stories.

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