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Parallel Worlds Meet at Designed Interfaces with a Vast Number of Potential Frameworks

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Chemistry is the language of linking atoms and molecules to make structures we find alluring and fascinating to study. It is therefore not surprising that some of the most memorable discoveries in chemistry deal with expression of control over putting together matter in precise ways. This is beautifully illustrated by the original synthesis of vitamin B12, polymers, catenanes, and dendrimers. However, throughout most of the 20th century, the "rational", controlled synthesis of structures by linking large molecular building blocks into two-dimensional (2D) and three-dimensional (3D) extended forms remained a challenge because of the difficulties encountered in organizing such objects into crystals. There is no doubt that the recent methods developed for linking metal clusters with organic "struts" or just organic molecules together to make reticular frameworks have significantly changed this landscape and indeed extended the precision of chemistry into two and three dimensions.[1] This is a world in which our creations and the precision with which we carry out their synthesis translate into useful pharmaceuticals, household products, energy storage materials, and the like.

Parallel to this synthetic world is a world derived from biomolecules, where the assembly of extended, ordered structures is less developed. In attempting to address this challenge, we take inspiration from nature with examples such as bones, shells, and collagen, and the way their proteins form long-range ordered laminar structures between sheets of inorganic minerals. This is a useful approach because the interface can be considered as a platform onto which one can "pin down" proteins with the precision chemists are used to practicing. The potential exists for the interface to cause the proteins to adopt structures different from those they assume alone.

However, the structures of most protein−inorganic interfaces are still unknown at the molecular level, and the principles of mineral-bound protein assembly have not been delineated. Considering a 2D interface between a protein surface and a layered inorganic crystal lattice, the following questions arise: how the two systems bind to each other chemically to pay for the entropy loss in bringing them into the proximity of each other and how we can deploy multiple interactions that work together to reduce multiple thermodynamic possibilities into a well-defined state.

The De Yoreo and Baker groups show in a recent report exquisite, compelling examples of how these issues can be fruitfully addressed by designing a protein−mineral interface through spatial matching of the protein binding functionality.[2] The *de novo* protein in this work has helical repeating domains engineered with glutamates on one side. The position and arrangement of these carboxylate residues were deliberately controlled such that they are superimposed onto the K^+ sublattice on muscovite mica (001). The multivalent electrostatic interaction established through lattice matching allows for the docking of discrete proteins on the mica surface and their predefined alignment along the direction of K^+ packing; this is being directly observed by atomic force microscopy. In media with higher K^+ concentrations, the coverage and the order of proteins increased and yielded 2D liquid crystal phases. The authors further installed protein−protein interactions along with the protein−mica binding to build extended, ordered structures supported by the mica surface. An end-to-end interaction joins protein monomers into single-protein thick wires of micrometers in length. Alternatively, a C_3 protein interface introduces a three-connected center for protein assembly into a honeycomb lattice, whose metrics can be systematically modulated by the number of repeating units in the protein monomer. Both of these extended architectures are orientationally constrained by the mica substrate and cannot form in most cases without its guidance.

The protein−mineral interface developed in this work not only provides ordered structures but also may very well be pointing to a new concept in protein chemistry. Let us think of the materials reported as being constructed from two sets of structural scaffolds: the polypeptide backbone of the protein and the inorganic lattice. The former is soft, flexible, and structurally diverse and can be computationally programmed and functionalized "on demand", while the latter is robust yet less variable. When chemical interactions are introduced at the interface, both scaffolds dictate the resulting protein structure. If the protein backbone is optimized for accommodating any geometrical requirements imposed by the inorganic lattice as was done in this work, the protein is set in the state of lowest internal energy and could be stabilized against external stress under which the free protein would be destroyed in solution. However, let us imagine that the protein backbone is slightly varied such that the binding to the interface is still allowed but now with a strained protein, which might present new chemistry. Along this line, the surface becomes a "ligand" capable of manipulating the protein in ways that are otherwise not possible.[3]

In terms of structure design, the inorganic lattice is directing the distribution of protein functionalities in space, thereby enriching the landscape of structures awaiting assembly. The "blueprint" for such structures may eventually be taken from the parallel world of reticular chemistry (Figures 1 and 2), where for example, a 2D honeycomb structure can be decorated [a term describing the placement of multiple vertices on a vertex without changing its underlying

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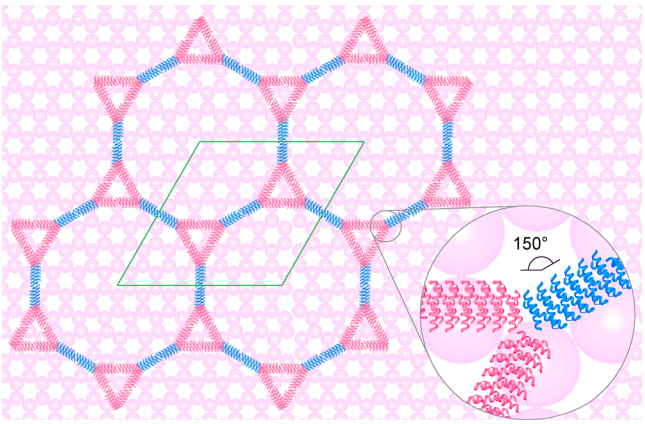

Figure 1. Decorated honeycomb lattice constructed by rod-shaped proteins through their end-to-end intermolecular interactions. The trimetric interface is designed in a way that proteins of the same type (red) are aligned at an angle of 60° while those of different types (red and blue) are aligned at an angle of 150°. The resultant three-connected node further extends over the 2D plane, generating triangles (red) linked by rods (blue), which could be guided by the symmetry of the underlying inorganic scaffold (pink).

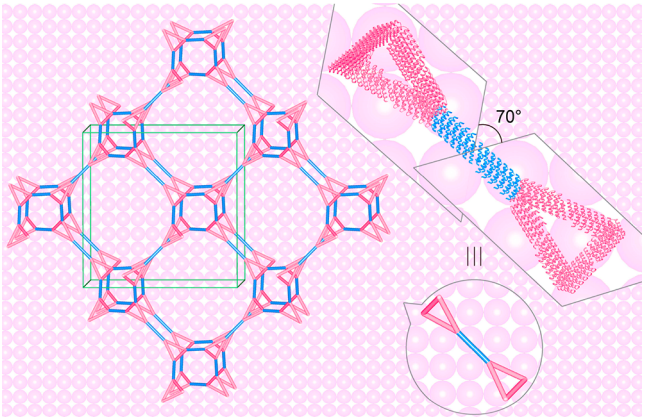

Figure 2. Decorated **srs** net formed by linking triangles (red) with rods (blue), where a torsion angle of 70° between neighboring triangles is imposed for their extension into 3D space instead of 2D space. The molecular structure at the trimeric interface remains the same as that in Figure 1, but the protein colored blue is redesigned such that its two ends are rotated around the long axis to satisfy the geometrical requirement. The reticulation of such structure could be guided by an inorganic square grid lattice (pink).

connectivity (Figure 1)] to form its augmented structure.[1] Alternatively, as one learns how to control the dihedral angles between the vertices in these protein structures, it is possible to turn the triangular vertices (in the honeycomb) with respect to each other and form a 3D extended arrangement (Figure 2). Here, again the decoration could be applied. It is worth noting that there is a handful of regular and quasi-regular 2D forms that can be targeted for protein assembly, and just on the basis of triangular vertices, there are no fewer than 1000 3D forms available for design with an almost infinite number possible when considering shapes other than the triangle.[1,4,5] In other words, the world of synthetic reticular crystals has gone through the journey that we are now embarking on with proteins, continuing the chemists' tradition of making beautiful and, in the fullness of time what we might find to be, useful objects.

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