Selective bridging of protein interfaces via heterobimetallic complexes: a polyhedra case study.

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Proteins are nature's favorite building block as they can support numerous biological processes while exhibiting variable levels of complexities, and as such mimicking their properties has been the focus of extensive research. As a rule of thumb structural and functional complexities exhibited by protein constructs go hand in hand. However, creating elaborate structures from scratch is non-trivial and requires meticulous tailoring of the interacting interfaces. Symmetry is often nature's preferable design strategy that facilitates the formation of macromolecular structures using only a handful of interacting interfaces. Protein cages are considered a lucrative target for the de novo design of proteinaceous structures as they are composed of multiple subunits that engage in several interfaces that are templated by various symmetry axes. As a design strategy for protein-protein interactions (PPIs) we employed the metal-directed protein self-assembly (MDPSA) method where metal-binding ligands are installed on the designated interfaces, leading to the formation of stable supramolecular assemblies in the presence of interacting metals. In this work, a robust cytochrome cb-562 was employed as a building block where two sets of orthogonal ligands were installed into the protein backbone based on the Pearson Hard-Soft Acid-Base (HSAB) classification, in order to differentiate between interfaces and to template the formation of appropriate symmetry axes. One set included native ligands that were used to coordinate Zn(II) ions and stabilize C2 symmetry axis, while a bioinspired hydroxamic acid set was used as a strategic handle to coordinate hard Fe(III) ions, leading to the formation tris-hydroxamate-Fe(III) complexes at the C3 nodes. This strategy proved both successful and flexible as it mediated the formation of two types of nanometer-size protein cages. Moreover, the interfacial metal sites imbued the cages with kinetic lability that manifested in a stimuli-responsive disassembly via various mechanisms.