Controlling the Reactivity of Metal Oxo Clusters as Artificial Proteases: from General Perspectives to Potential Applications

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The investigation of protein structure and function in the field of proteomics requires the cleavage of the proteins into the smaller fragments in order to facilitate their analysis by mass spectrometry.[1] For this purpose the natural enzymes are employed, where trypsin represent "golden standard".[2] However, the trypsin tends to produce many short peptide fragments, hampering the analysis of the whole proteome.[2] Furthermore, the stability and activity of natural proteases is very affected by the experimental conditions such as the presence of surfactants, which are of crucial importance for the solubilization of insoluble and membrane proteins. [3] Therefore, new catalysts which are capable of hydrolyzing different water-soluble proteins as well as partially soluble and insoluble proteins in the presence of surfactants, are in urgent need in the field of proteomics and could further impact different fields of medicine and pharmacology. Inspired by reports on the non-covalent, mainly electrostatic interaction between negatively charged polyoxometalates (POMs) and positive surface domains of proteins, our group introduced a conceptual new approach for development of artificial proteases by using polyoxometalates (POMs) as ligands for Lewis acid active metal ions.[4,5] Consequently, the POM does not only act as a ligand for the active metal ion, but due to its three-dimensional shape and negative charge it also induces the selectivity that is necessary for a controlled fragmentation of the polyamide backbone in a wide range of soluble and insoluble proteins.[4,5] Beside POMs, metalorganic framework (MOFs) attracted specific interest due to their high reactivity, stability, and recyclability. However, the previous investigation suggests that protein hydrolysis mainly occurs on the MOF surface, thereby questioning the need for their highly porous 3D nature.[4] Therefore, catalytic activity of water-soluble metal-oxo cluster $[Zr_6O_4(OH)_4(CH_3CO_2)_8(H_2O)_2Cl_3]^+$, which is based on the same hexamer motif found in various MOFs was additionally investigated. The detailed mechanistic study of Zr_6 cluster revealed that hydrolysis is facilitated by dynamic nature of capping ligand, by prompting fast protein/cluster interactions and further leading to the protein unfolding. This work presents the first solution study reporting an in-depth mechanistic investigation of a reaction occurring at the Zr_6 cluster core, which is prevalent in many catalytically active MOF materials.[6]

References:

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