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Perspective

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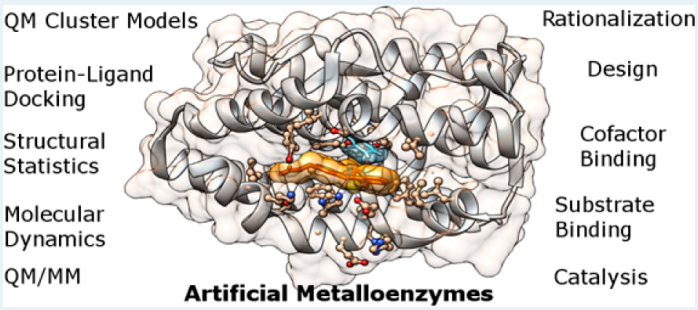
Toward the Computational Design of Artificial Metalloenzymes: From Protein–Ligand Docking to Multiscale Approaches

Victor Muñoz Robles, Elisabeth Ortega-Carrasco, Lur Alonso-Cotchico, Jaime Rodriguez-Guerra, Agustí Lledós, and Jean-Didier Maréchal*

Departament de Química, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Barcelona, Spain

ABSTRACT: The development of artificial enzymes aims at expanding the scope of biocatalysis. Over recent years, artificial metalloenzymes based on the insertion of homogeneous catalysts in biomolecules have received an increasing amount of attention. Rational or pseudorational design of these composites is a challenging task because of the complexity of the identification of efficient complementarities among the cofactor, the substrate, and the biological partner. Molecular modeling represents an interesting alternative to help in this task. However, little attention has been paid to this field so far. In this manuscript, we aim at reviewing our efforts in developing strategies efficient to computationally drive the design of artificial metalloenzymes. From protein–ligand dockings to multiscale approaches, we intend to demonstrate that modeling could be useful at the different steps of the design. This Perspective ultimately aims at providing computational chemists with illustration of the applications of their tools for artificial metalloenzymes and convincing enzyme designers of the capabilities, qualitative and quantitative, of computational methodologies.



KEYWORDS: *artificial metalloenzymes, biocatalysis, molecular modeling, multiscale approaches, protein–ligand dockings*

INTRODUCTION

Biocatalysis consists of the industrial application of enzymes for the manufacturing of chemical compounds. It is one of the cornerstones for green and sustainable chemistry because enzymes are by nature biodegradable, biocompatible, and easily renewable.[1] Despite being widespread in current industries, most biocatalysts are based on naturally occurring enzymes that, despite their variety, cover only a narrow spectrum of the needs of chemical industries.

During the past century, homogeneous catalysis has been the most prolific chemical field in discovering new chemical reactivities. The award of two recent Nobel Prizes of Chemistry (Chauvin, Grubbs, and Schrock in 2005; Heck, Negishi, and Suzuki in 2010) appears particularly illustrative. However, the transition metal complexes that sustain homogeneous catalysis are in their majority functional under nonenvironmentally friendly conditions, which include apolar solvents and low or high temperatures, among others. Moreover, control over substrate and regio- and enantiospecificities is generally challenging in these complexes; conversely, they are properties inherent to enzymatic activities.

With one-third of naturally occurring biocatalysts containing metal ions, metalloenzymes have been the focus of attention of enzyme designers. One possible framework consists of mutating residues that coordinate the metal in the native biomolecule or simply switch the metal by another. Such approaches have led to interesting outcomes in recent years, although modulating the activity of these scaffolds resides mainly in the biochemical space afforded by the 20 amino acids available in Nature.[2−5]

Another framework consists of physically merging homogeneous catalysts within a biomolecular host. Conceptually mimicking natural hemoenzymes, this strategy is increasingly applied to the development of biocatalysts absent from the biological realm.[6] In the resulting hybrids, also called artificial metalloenzymes, the cofactor (synthetic in this case) provides most of the catalytic specificity of the system. The protein environment protects the homogeneous catalyst from the solvent and generates an asymmetric second coordination sphere that dictates substrate, regio- and enantioselectivities, and specificities (Figure 1). Today, numerous systems developed using this concept have already been reported and include reactivities such as hydration of ketone,[7] transfer hydrogenation,[8] and sulfoxidation.[9] Strategies used to incorporate the cofactor inside the protein include pure host–guest interactions, "Trojan horse" insertion in which the cofactor is covalently bound to the natural ligand of a protein, or covalent anchoring in which peripheral substitutents of the organometallic catalyst chemically bind to the host.[10] A nonexhaustive list of artificial metalloenzymes with their catalytic activities can be found in Table 1.

The successful development of artificial metalloenzymes stands on the quality of the molecular partnership between

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