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Review

Artificial metalloenzymes as selective catalysts in aqueous media

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Contents

Abstract

The fusion of homogeneous and enzymatic catalysis has recently drawn attention due to reported novel activities and high selectivities. The incorporation of metal-catalysts into proteins combines the advantages of both catalytic strategies. Herein we summarize recent approaches of artificial metalloenzymes applied to catalysis. The discussion includes different strategies of anchoring and screening for improved selectivity.

Keywords: Asymmetric catalysis; Artificial metalloenzymes; Hybrid catalysts; Designed evolution; Redox reactions; Hydrolysis; C–C bond formation; DNA-cleavage

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1. Introduction

Nature has provided us with a vast number of enzymes having evolved over millions of years. Starting from amino acid building blocks, complex proteins evolved to perform a variety of catalytic tasks. The scope of amino acid catalysis is limited and thus nature incorporated cofactors and/or metal-ions. It is estimated that around one third of all enzymes are metalloproteins and that some of the most difficult biological transformations are mediated by these [1]. Many enzymes show an intrinsic promiscuity [2,3] for different types of reactions whereas other activities are obtained with only small changes of the active site or the chiral environment [4]. In metalloenzymes, the diversity of promiscuous activity is increased by the variety of metallic ions that can be incorporated in the active site to catalyze a wide range of chemical transformations [5–7]. Our increased understanding of chemical and enzymatic catalysis, especially since the advent of genetic engineering and recombinant technology, has led to attempt the development of new enzymes and catalysts with modified activities, specificities and activities [4,8–10]. Only 50 years ago, the first hybrid catalyst showed promising selectivities by applying Pd on silk [11]. Optically active amines and amino acids were obtained from the corresponding alkenes by hydrogenation. Interestingly, it took 20 more years to develop the first homogeneous artificial metalloenzyme for hydrogenation [12]. Artificial metalloenzymes, as reviewed here, are hybrid catalysts resulting from the introduction of a metal-complex with catalytic activity into macromolecular hosts, such as a protein, DNA or an antibody, which provide a well-defined second coordination sphere and thus induce the selectivity of the reaction (Fig. 1). Several reviews on artificial enzymes have been recently published [1,13–25].

Herein we summarize the most recent advances in the field of artificial metalloenzymes for regio- and stereoselective catalysis with an emphasis on the reaction types implemented thus far which include redox reactions, C–C bond formation, hydrolysis and DNA-cleavage. First, the general anchoring strategies are presented, followed by a detailed description of the different reaction types. For hydrogenation reactions using the biotin–(strept)avidin technology two complementary optimization protocols are described in more detail.

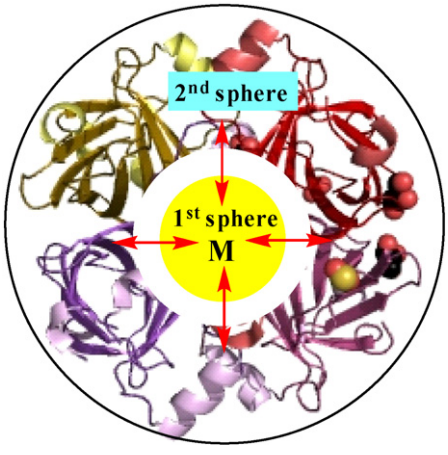

Fig. 1. Characteristics of artificial metalloenzymes: The metal–ligand complex (M) is anchored to the biomolecule host and provides the 1st coordination sphere whereas the host provides the 2nd.

2. Classification of artificial metalloenzymes

2.1. Reaction types

Artificial metalloenzymes differ from each other in three important ways which are summarized in Table 1: (a) the metal-complex, (b) the biomolecule host, and (c) the anchoring strategy.

2.2. Anchoring strategy

Many different approaches for the incorporation of the artificial catalytic moiety with the macromolecular host have been applied [1,13–24,53]: (a) supramolecular anchoring, (b) dative anchoring, and (c) covalent anchoring. Many experiments utilize the metal and the protein in a "black box" without precise knowledge of the artificial coenzyme's localization [54,87–96]. Most of these are assumed to have a supramolecular affinity for the protein whereas others are assumed to have a dative anchoring of, e.g. cysteine-residues complexed to the metal. Several examples of in vivo evolution of designed proteins for artificial metal catalysts via immunization and formation of antibodies have been reported [97]. For catalysis, the metal-complex is incorporated via supramolecular interactions with the isolated immunoglobin.

2.2.1. Supramolecular anchoring

In the context of supramolecular anchoring [22] of metal cofactors within a host protein, the transport proteins serum albumin – especially from bovine (BSA) – play a key role. These display a remarkable ability to bind a variety of hydrophobic guests tightly, including fatty acid, steroids, thyroxine, porphyrins, etc. A variety of enantioselective transformations were performed with these proteins, including sulfoxidation [89–91,98], epoxidation [93–95], reduction [87,88], and Diels–Alder cycloaddition reactions [96].

In the 1970s, Whitesides [12] pioneered the concept of introducing a homogeneous catalyst within a protein environment to guide enantioselectivity (Figs. 2, 3a). Whereas Knowles' innovative approach for organometallic catalysis consisted of providing

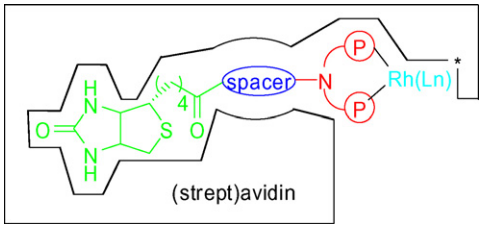

Fig. 2. Biotin–(strept)avidin technology: artificial metalloenzymes [Rh(L_n)(biotin-ligand)]⊂streptavidin for enantioselective catalysis based on the anchoring of a catalytically active metal fragment within a host protein via a ligand, a spacer and biotin.