



Review

Coordination complexes and biomolecules: A wise wedding for catalysis upgrade



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Dedicated to the memory of our colleague and friend Dr Guy Lavigne (deceased April 23th 2015).

Abbreviations: A, adenine; Bipyridine, 2-Pyridin-2-ylpyridine; BPMCN, N ;N'-bis(2-pyridylmethyl)-N ;N'-dimethyl-trans-1 ;2-diaminocyclohexane; BPMEN, N ;N'-dimethyl-N ;N'-bis-(pyridin-2-ylmethyl)-1 ;2-diaminoethane; C, cytosine; Conv., conversion; Cp, cyclopentadienyl; Cyt, cytochrome; DNA, deoxyribonucleic acid; EDTA, 2-(2-[bis(carboxymethyl)amino]ethyl)(carboxymethyl)aminoacetic acid; ee, enantiomeric excess; er, enantiomeric ratio; G, guanine; h, hour; His, histidine; min, minute; NAD, nicotinamide adenine nucleotide; Nika, periplasmic nickel-binding protein; phenanthroline, 1 ;10-phenanthroline; Ref, reference; salen, 2 ;2'-ethylenebis(nitrilomethylidene)diphenol; salophen, N ;N'-bis(3 ;5-di-tert-butylsalicylidene)-1 ;2-diaminobenzene; St-DNA, Salmon testes deoxyribonucleic acid; SWOT, Strength weakness, opportunities and threats; T, thymine; terpyridine, 2 ;6-bis(2-pyridyl)pyridine; TO, turnover; TON, turnover number; WT, wild-type.

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ABSTRACT

Artificial metalloenzymes, with their high selectivity and specificity combined with a wide scope of reactivity and substrates, constitute an original approach for catalyst development. Different strategies have been proposed for their elaboration, proceeding from modification of natural enzymes using bioengineering methods to *de novo* protein design. Another bio-inspired methodology for the development of hybrid catalysts consists in the incorporation of coordination complexes into biomolecules, with the aim to upgrade their catalytic abilities. In these systems, the reaction performed by the naked catalyst is modulated by the well-defined structure of the host biomolecule. This conveys added value to the catalyst, such as enantioselectivity or chemoselectivity. DNA, apo-enzymes, proteins and peptides have been engaged in this approach, affording a wide diversity of reactivities and substrates. The resulting systems can then be improved by combined chemical and bioengineering optimization, allowing access to powerful catalysts. Because this approach can virtually be applied to any biomolecule or coordination complex, the elaboration of bio-based hybrid catalysts seems promising for advance in catalysis.

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1. Introduction

Over the last 15 years, the three Nobel Prizes associated with organic synthesis have been awarded to Knowles, Noyori and Sharpless for metal-catalyzed asymmetric hydrogenation and oxidation in 2001, Chauvin, Grubbs and Schrock for the work on olefin metathesis, based on the use of ruthenium, molybdenum and tungsten complexes as catalysts, and in 2005 Heck, Negishi and Suzuki for palladium catalysed cross coupling in 2010.

This exemplifies the importance of coordination complexes (noted as such in the present review to define a metallic centre bound to synthetic ligands) in organic synthesis. From a general view, coordination catalysis utilises a large selection of metallic ions, ligands and substrates to achieve a large set of reactivities.

The reactivity of a coordination complex is mainly based on the tuning of its redox properties, substrate accessibility and/or Lewis acidity of its metallic centre. This is achieved by modulating the donor/acceptor character of the ligands, and by controlling their geometry and arrangement around the metallic centre. For instance, steric hindrance can be used to induce substrate selectivity. Chemists excel at developing very sophisticated ligands that confer to the complexes the desired properties. But this has several bottlenecks, among which the multi-step synthesis of the targeted ligands which potentially represents a significant economical concern and might hamper its accessibility.

By observing metalloenzymes, it appears that the first, second and outer coordination spheres play a crucial role in tuning the reactivity of the metallic centre. Indeed within enzymes, the reactivity is not only driven by steric control of the metal site by the ligands (proteic and/or non-proteic) but also *via* remote interactions (H bonding, electrostatic, stacking *etc.*) that guide the substrate into the active site, position it to ease the reaction, and help the release of the products.

In other words, the strength of enzymes resides in the combination of inner and outer sphere effects, which confers rate enhancement, specificity and selectivity to the enzyme. Moreover the mobility, dynamics and/or conformational changes of the proteic chain can help to adopt the most suitable geometry for the active site. All of this makes enzymes very powerful catalysts, but only considering a single reactivity and substrate. Chemists thus developed synthetic analogues of enzymes active sites, to better understand the structure-properties relationships. The ultimate goal would be to select the crucial parameters for powerful catalysis, getting rid of the less pertinent ones. Such mimics (structural, functional or both) were thus developed for hydrogenases [1–4], superoxide dismutases [5–9], photosynthetic system [10,11], oxygenases [12] *etc.* These systems go from the simplest, using very usual metallic ions and ligands [13] to the most sophisticated ones

[14–16]. Even though models of metalloenzymes are very helpful for investigation purposes, these models are often poor catalysts (with respect to their loadings).

To overcome these two drawbacks, namely the cost and time consuming production of the ligands involved in the coordination catalysts while achieving the very high selectivity of enzymes, chemists have recently developed two convergent strategies: (i) Protein re-design, based on their knowledge of the natural systems and (ii) *de novo* design of biomolecules, seeking for perfectly defined metal ion environment. In the first approach, shown in Fig. 1 artificial metalloenzymes are re-designed by modification of the native metal ion (panel B) or of the ligands (panel C) using bioengineering. In the second approach, depicted in the panel D of Fig. 1, host cavities are rationally formed from scratch.

This review covers an alternative approach, which cannot be classified into those previously defined categories. It relies on the insertion of a simple coordination catalyst into a host biomolecule (Fig. 1, panel A). The guest coordination complex already possesses its own reactivity, which is modulated by the environment provided by the host biomolecule. The appealing nature of this approach is that it truly takes advantage of the knowledge of the two fields (biochemistry and coordination chemistry driven catalysis). The coordination complex can be chosen among the wide library of catalysts, according to the desired reactivity, and can be tuned easily. Obviously the chosen system should be able to operate under condition compatible with biomolecules (*i.e.* solvent and temperature compatibility). On the other hand, biomolecules can be engineered to host the complex in the most suitable way. This strategy is exemplified by a Cu(bipy) complex, into a host biomolecule, namely DNA, proteins and peptides, which is anticipated to confer selectivity properties to the guest complex.

Therefore, this review will focus on highlighting how a coordination complex could have its activity upgraded by its interaction with a biomolecule. Using selected examples, we are trying to exemplify this concept and to highlight the different methodologies used. We may try to foresee the opened perspectives and future development of this approach.

2. The artificial metalloenzyme approach

Before covering the main topic of this review, *i.e.* incorporation of coordination complexes into biomolecules (Panel A Fig. 1), we will give a concise overview of the other approaches (Panels B–D). They all share the same ultimate goal: development of systems able to catalyse synthetically relevant reactions with the exquisite rates and selectivities of enzymes, and with an extended set of substrates. This goal seems very ambitious, and the path to this target appears still long and tough. Still, huge progresses have been made in the

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