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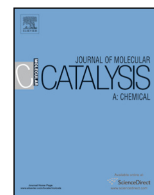

Catalysis without a headache: Modification of ibuprofen for the design of artificial metalloenzyme for sulfide oxidation

Laurianne Rondot, Elodie Girgenti, Frédéric Oddon, Caroline Marchi-Delapierre, Adeline Jorge-Robin, Stéphane Ménage*

Univ. Grenoble Alpes CNRS, UMR 5249, CEA-Grenoble, DSV/iRTSV, Laboratoire de Chimie et Biologie des Métaux, 17, Avenue des Martyrs, 38054 Grenoble, France

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ABSTRACT

A new artificial oxidase has been developed for selective transformation of thioanisole. The catalytic activity of an iron inorganic complex, **FeL**$_{ibu}$, embedded in a transport protein NikA has been investigated in aqueous media. High efficiency (up to 1367 t), frequency 459 TON min^{-1} and selectivity (up to 69%) make this easy to use catalytic system an asset for a sustainable chemistry.

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1. Introduction

Selective catalytic oxidations represent still a challenge for modern chemistry, and their importance has been highlighted by the Nobel Prize attribution to Noyori, Sharpless and Knowles in 2001 [1–4]. These processes, requiring generally a metal, are used for a wide range of applications from fine chemistry (drug synthesis, for example) to petroleum industry (valuation of carbon centered molecules usually considered as wastes). However, a large number of them have to be reassessed in light of environmental considerations. For example, toxic metals –like osmium- or strong oxidant—such as MnO_4– that led to toxic industrial wastes or even harsh reaction conditions—high pressure and temperature or chlorinated solvents-urged chemists to search for new leads in oxidation catalysis.

Nature conducts many redox reactions, from respiration to photosynthesis. These bioprocesses, resulting of million years of evolution, perfectly fit with the principles of green chemistry. An enzymatic reaction usually takes place in water at room temperature, uses safe metals like iron and copper and the naturally occurring oxidant dioxygen for metal based catalytic oxidations. However, the enzymatic capacity is lowered by the low stability of enzymes out of their natural environment or even outside of the cells.

There is then a new bioinspired approach that combines biocatalysis and metal based chemical catalysis, based on the design of artificial enzymes. Their interest relies on their use under mild and ecological conditions, associated to a gain of stability or even to the design of new catalytic activities [5–7]. The construction of these new biohybrids consists of the insertion of a metal complex (usually with catalytic properties in organic solvent) into a protein scaffold. Then, the (enantio) selectivity and the reactivity can be associated from different part of the hybrid, the protein and the metal complex, respectively. The infinite combination of associations between metal complexes and proteins makes this approach very attractive, especially because protein scaffolds can be selected for their stability and potential binding site for substrates and the metal complexes for their broad scope of reactivity [8–10].

There are a few main approaches to attaching synthetic catalysts to protein scaffolds: covalent attaching, dative anchoring (direct coordination to the metal center) and supramolecular anchoring (with biotin-avidin (Avi) being the most commonly employed). These strategies can be described more precisely in the field of

* Corresponding author.
E-mail address: stephane.menage@cea.fr (S. Ménage).

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sulfide oxidation. First, an achiral Mn(III) salen complex, containing two methanethiosulfonate substituents, has been attached by a dual point covalent link into the cavity of an apo myoglobin mutant, in which two cysteine residues replace residues Tyr103 and Leu72 [11]. Enantioselective sulfoxidation of thioanisole by H_2O_2 was obtained with up to 51% *ee* whereas a single point attachment resulted in only 12% *ee* with a rate under 0.4 TON min^{-1} and a maximum TON of 40. The second strategy consists of the fixation of an inorganic complex into a cavity *via* metal binding to an amino acid residue [12]. Mn and Cr Schiff base complexes have been stabilized into the cavity of apo myoglobin (wild type or mutants) by coordinating Cr(III) or Mn(III) atoms to the His93 nitrogen and *via* non-covalent interactions between the ligand and the surrounding peptide chains. The sulfoxidation of thioanisole was also enantioselective with *ee* values between 5 and 32% and rates up to 2 TON min^{-1}. Finally, in a third strategy, the ligand is tightly bound to the protein cavity thanks to supramolecular interactions between the ligand and the amino acid residues. The seminal work by Wilson et al. evidenced the biotin/avidin technology in which a ligand was substituted with a biotin molecule [13]. Recently, this technology, named "Trojan horse", was illustrated by the sulfoxidation of thioanisole by H_2O_2 using a Mnsalen complex embedded into wild type or S112D mutant streptavidin [14].

Human Serum Albumin (HSA) possesses binding sites for a wide range of drugs that have been extensively studied by X-ray crystallography and ^{1}H NMR. The protein binds a variety of endogenous ligands including acidic non esterified fatty acids, bilirubin, hemin, thyroxin, ibuprofen and lipophilic compounds at any sites [15]. Six different binding sites have been structurally characterized: two primary sites located in subdomains IIA and IIIA called drug site 1 and drug site 2, respectively, and four other sites with lower binding affinities located in subdomains IIIB, IIA-IIB, IB together with the cleft of the protein. Our group has been involved in the design of artificial enzymes using supramolecular interactions to anchor Mn(III) salen complexes into HSA. The hybrid containing a salen ligand substituted by sulphonato groups catalyzes the exclusive formation of thioanisole using NaOCl as the oxidant with an efficiency of 20 TON min^{-1} [16]. Moreover, this hybrid demonstrated an improved stability protecting the active center during the catalytic process (up to 1200 TONs). The rather large number of binding sites in HSA made it difficult to model the position of salen complexes and they were only placed thanks to competitive binding experiments [16]. To circumvent this problem, we have decided to test the Trojan horse strategy using ibuprofen, 2-[4-(2-méthylpropyl) phenyl]propionic acid, as the HSA ligand/recognition molecule. The ibuprofen binds to drug site 2, IIIA domain, with high affinity and IIA-IIB subdomain of HSA with low affinity. Its orientation into the cavities IIA-IIB or IIIA indicates a large exposition of the carboxylate function toward the protein surface, making it then the best position to connect the inorganic catalyst, without dramatically affecting the binding. Since we already have demonstrated the efficiency of Mnsalen complexes embedded into HSA, we decided to switch to a variant of our iron catalysts, known to provide high selectivity and stability when embedded into NikA as protein host [17].

The most common reactants or substrates in industrial context are alcohols, sulfides, alkenes and alkanes. Among them, sulfides present a great interest as their products, sulfoxides, have renowned bioactivity and their chiral version are accessible targets based on controlled oxygen transfer [18]. One can cite omeprazole, a popular proton pump inhibitor used in the treatment of peptic ulcers and gastro-oesophageal reflux disease. [19,20]

Here we highlight the Trojan horse strategy as an "easy to use" method for sulfide catalysis in aqueous medium and we provide new assets for this strategy of design by the robustness (up to 1367 TONs and selectivity (up to 69%) of such hybrids.

2. Experimental

2.1. Reagents and material

All reagents were purchased from commercial sources and were used as received unless otherwise noted. Solvents were dried and degassed before use

2.2. Physical methods

UV–Vis absorption spectra were recorded on a Varian Cary1Bio, with a quartz cell of 10 mm path length. The concentration of the sample was 30 − 190 μM

Circular Dichroism measurements were performed on a JASCO J-815 spectropolarimeter equipped with a thermostated cell holder, using a quartz cell of either 10 mm or 1 mm path length. Spectra were recorded at 25 °C over the 500–250 nm wavelength range at 0.5 nm intervals. Each spectrum is the average of 5 scans. 50 mM Phosphate buffer, pH 7.4 was used for all the samples.

Fluorescence spectra were recorded on a JASCO FP-8500 spectrofluorometer. All spectra were recorded at 25 °C using a quartz cell of 10 mm path length. Spectra were recorded over the wavelength range 500–300 nm after excitation of the samples at 278 nm. 50 mM Phosphate buffer, pH 7.4 was used for all the samples.

X band EPR spectra (9 GHz) were obtained on a Bruker EMX spectrometer equipped with an Oxford ESR 910 cryostat for low temperature studies. The microwave frequency was calibrated with a frequency counter and the magnetic field with an NMR gaussmeter.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts (in ppm) are referenced against solvent peaks.

Gas chromatography was performed on a PerkinElmer Autosystem instrument or a PE Clarus 500 with a FID detector, using an Optima 17 (0.25 μm × 30 m) column. Injector and detector temperatures were 250 °C and 280 °C, respectively. The oven temperature program was as following: 100 °C for 4 min followed by a gradient of 25 °C/min over a period of 13 min.

2.3. Synthesis of L_{ibu}

$\mathbf{L}_{ibu}$ has been synthesized in three steps starting from *N,N'*-bis(2-pyridylmethyl)-*N*-methyl-1,2-ethanediamine (BPHMEN) itself synthesized using the method reported by Baffert et al. [21]

Step 1: BPHMEN (1 g, 4 mmol) and K_2CO_3 (0.608 g, 1.1 eq.) were dissolved in 25 mL of CH_3CN. Then, 2 mL of 3-chloropropoxytetrahydropyran (1.66 g, 3 eq.) were added dropwise at room temperature. The mixture was refluxed under stirring during 48 h under argon, concentrated under reduced pressure and dissolved in CH_2Cl_2 to be washed with $NaHCO_3$ 10% and brine. After drying on Na_2SO_4 and evaporation under reduced pressure, the product was purified by silica gel chromatography eluded with acetone:cyclohexane:triethylamine = 12:12:1 (R_f = 0.38) to give a yellow oil (m = 0.736 g, Y = 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.45 (d, 2H, J = 4.5 Hz); 7.56 (t, 2H, J = 7.8 Hz); 7.40 (dd, 2H, J_1 = 7.8 and J_2 = 25.2 Hz); 7.07 (br, 2H); 4.49 (s, 1H); 3.73 (m, 4H); 3.63 (s, 2H); 3.39 (m, 2H); 2.63 (m, 6H); 2.20 (s, 3H); 1.75 (t, 2H, J = 6.6 Hz); 1.44 (br, 4H).

Step 2: Recovering of the alcohol functionality was obtained by adding dropwise at room temperature 0.102 mL of 37% HCl to the previously obtained oil in 30 mL absolute EtOH. The mixture was stirred during 4 h at 60 °C and concentrated under reduced pressure. The oily residue was dissolved into water and washed with CH_2Cl_2 (3 times). The aqueous phase was then basified with NaOH 1 M and extracted with CH_2Cl_2. The latter organic phase was dried on Na_2SO_4, filtered and concentrated under reduced pressure to

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