PhD thesis offer in bioinorganic chemistry (theory and experiment)

Deciphering the reaction mechanism of CODH,
a key enzyme in CO/CO_2 interconversion

Financing: Labex Arcane (https://arcane.univ-grenoble-alpes.fr)
Doctoral school: Doctoral School of Chemistry and Life Sciences, UGA, Grenoble (https://edcsv.univ-grenoble-alpes.fr)
Place of work: CEA/LCBM, Grenoble, France (https://www.cbm-lab.fr/en)
Directors of thesis: Dr. Ragnar Bjornsson (CEA Grenoble), Dr. Christine Cavazza (CEA Grenoble)
PhD starting date: October 2024

Keywords: Bioinorganic chemistry, computational chemistry, crystallography, metallobiochemistry, metalloenzymes, small-molecule activation, catalysis, multiscale modelling, QM/MM, iron-sulfur clusters

This PhD thesis project will be carried out in collaboration between the computational chemistry and X-rays team (CoMX) and the bioenergy and environment team (BEE) at the laboratory for chemistry and biology of metal laboratory (LCBM) at the CEA (https://www.cbm-lab.fr/en).

The purpose of the project is to uncover the mechanism of how Nature reduces CO_2 and oxidizes CO by the Ni,Fe-dependent CO dehydrogenase, the most proficient catalyst for CO/CO_2 interconversion.

Context and objectives

Carbon monoxide dehydrogenase (CODH) is a vital enzyme of the carbon cycle, being responsible for CO/CO_2 interconversion. The 2-electron reduction of CO_2 to CO is furthermore a key step in chemical carbon recycling, the conversion of the green-house gas CO_2 towards useful carbon-based products. The enzyme catalyzes this reaction in either direction with very small overpotential and fast rates. However, despite decades of biochemical, crystallographic, and spectroscopic work, the enzyme reaction mechanism is still under debate, hindering bioinspired catalyst design from fully reaching its potential. In particular, the nature of the reduced C_{red2} state and how it binds CO_2 and cleaves it to CO and H_2O is unclear and even controversial. There is a disconnect between an experimental X-ray structure of C_{red2} and spectroscopic work with various hypotheses having been suggested to account for the added 2 e-, such as a Ni(0) reduced species, Ni-hydride or a Ni-Fe metal-metal bond.

In this PhD project we will take a fresh new look at this fascinating system through a combined approach of X-ray crystallography, modern multiscale modelling QM/MM techniques and quantum crystallographic refinement. New attempts at acquiring crystal structures of the C_{red2} state and others in both native and mutant forms will be carried out, guided by multiscale modelling.

References

CODH (general):

- Dobbek, H. Mechanism of Ni,Fe-Containing Carbon Monoxide Dehydrogenases *Struct. Bond.* **2019**, *179*, 153-166.
- Drennan C.L. et al. Life on Carbon Monoxide: X-Ray Structure of Rhodospirillum Rubrum Ni-Fe-S Carbon Monoxide Dehydrogenase. *Proc Natl Acad Sci USA*, **2001**, *98*, 11973–11978.
- Jeoung, Dobbek, *Science*, **2007**, *318*, 1461-1464.
- Fesseler et al. How the [NiFe4S4] Cluster of CO Dehydrogenase Activates CO2 and NCO. *Angew. Chem. Int. Ed.* **2015**, *54*, 8560 –8564.
- Kung Y et al. A role for nickel-iron cofactors in biological carbon monoxide and carbon dioxide utilization. *Curr. Opin. Chem. Biol.* **2011**, 15, 276-283.
- Lindahl P. A. Metal-metal bonds in biology, *J. Inorg. Biochem.* **2012**, *106*, 172-178.
- Gong W. et al. Structure of the α2ε2 Ni-Dependent CO Dehydrogenase Component of the Methanosarcina barkeri acetyl-CoA decarbonylase/synthase complex. *Proc Natl Acad Sci USA.* **2008**; 105:9558–9563.

Related work by thesis directors:

- Contaldo U.; Cavazza, C. et al. Efficient Electrochemical CO2/CO Interconversion by an Engineered Carbon Monoxide Dehydrogenase on a Gas-Diffusion Carbon Nanotube-Based Bioelectrode. *ACS Catal.* **2021**, 5808–5817.
- Contaldo U.; Christine Cavazza, et al: A pyrene- triazacyclononane anchor affords high operational stability for CO2RR by a CNT-supported histidine- tagged recombinant CODH, Angew. Chem. Int. Ed., **2022**, *61*, e202117212.
- Alfano, M.; Cavazza, C. Structure, function and biosynthesis of nickel-dependent enzymes. *Protein Science*, **2020**, *29*, 1071-1089.
- Pang, Y.; Bjornsson, R, Understanding the Electronic Structure Basis for N2 Binding to FeMoco: A Systematic Quantum Mechanics/Molecular Mechanics Investigation, *Inorg. Chem.* **2023**, *62*, 5357-5375.
- Benediktsson, B.; Thorhallsson, A. Th.; Bjornsson, R. QM/MM calculations reveal a bridging hydroxo group in a vanadium nitrogenase crystal structure, *Chem. Comm.* **2018**, *54*, 7310-7313.
- Thorhallsson, A. Th.; Benediktsson, B.; Bjornsson, R. A model for dinitrogen binding in the E4 state of nitrogenase, *Chem. Sci.* **2019**, *10*, 11110-11124.

Applicant profile

Candidates should a master's degree in chemistry or biochemistry and should have an interest in bioinorganic chemistry, biochemistry, computational chemistry or inorganic chemistry. Experience in either computational chemistry or crystallography is an advantage.

Candidates should have an interest in multidisciplinary work as the project involves both computational and experimental work. A strong command of English is required.

Apply before April 5th, 2024.

For more information and application

Please contact us with a CV and motivation letter:

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