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Artificial methanol dehydrogenases towards the sustainable production of formaldehyde

The increasing pressure on fossil resources calls for the development of new and sustainable solutions for the production of fuels, chemicals and value-added products. Formaldehyde is one of the main building blocks currently used in industry, with a production of 30 megatons per year.[1] It is obtained by the high temperature (300-400°C) gas phase oxidation of methanol in high-energy processes. In Nature, methanol dehydrogenases (MDHs) catalyse methanol oxidation under ambient conditions. Recently, lanthanide-dependent MDHs were identified and questioned our understanding of the parameters governing the catalysis.[2] The use of enzymes as catalysts is limited by their purification and isolation, and the need for cofactors for the reaction to proceed. Small artificial enzymes represent a powerful tool to develop catalysts combining a modular water-soluble peptide scaffold that can be synthesized by solid phase peptide synthesis, and a three-dimensional chiral structure to reproduce the active site environment.[3]

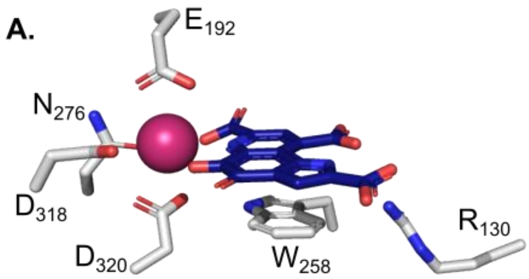

Figure – Active site of a lanthanide (La^{3+}) methanol dehydrogenase (PDB: 6O6C)

The aim of this project is to synthesize and study artificial lanthanide MDHs containing a PQQ cofactor and a lanthanide ion in its active site (Figure 1). The project is divided into three parts:

1) Solid phase peptide synthesis of 6 scaffolds
2) Characterizations of the scaffold structure and stability (NMR, circular dichroism)
3) Determination of the affinity for Ln^{3+} ions and/or PQQ (luminescence, UV-vis)

The rationally designed enzymes thus obtained will help identify the more suited peptidic scaffold – i.e. with a good affinity for Ln- and PQQ-binding, and well-folded. This will be a crucial step before moving forward to studying the catalytic oxidation of methanol under ambient conditions and help identified key parameters governing the catalysis.

The technical and scientific environments in Toulouse are fully appropriate to realize this project. The student will be trained on advanced spectroscopic techniques such as paramagnetic NMR, steady-state and time-resolved emission spectroscopies, circular dichroism, or kinetic monitoring of the aggregation process using multiplate fluorimeters.

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[1] (a) Heim *et al.*, *Green Chem.* **2017**, *19*, 2347-2355; (b) Desmon *et al.*, *ACS Catal.* **2019**, *9*, 9575-9588
[2] Daumann, *Angew. Chem. Int. Ed.* **2019**, *58*, 2-10
[3] (a) Schwizer *et al.*, *Chem. Rev.* **2018**, *118*, 142-231; (b) Lombardi *et al.*, *Acc. Chem. Res.* **2019**, *52*, 1148-1159; (c) Pinter *et al.*, *Angew. Chem. Int. Ed.* **2020**, *59*, 7678-7699