Mechanisms of oxygen activation in biology

About the project or challenge area: Life in an aerobic environment requires activation of O_2. But activation of O_2 is thermodynamically unfavourable and requires electrons, which metalloenzymes can provide to control oxidative metabolism in biology. The catalytic capability of oxygen-activating iron enzymes is truly enormous and offers huge future potential for biocatalysis and biotechnology applications. The process works because, unlike other metals, a redox-active transition metal can change oxidation state and in doing so can push electron density onto a dioxygen (O_2) ligand (thereby "activating" the oxygen). In the presence of a suitable reductase, this leads to rapid cleavage of the O-O bond and the formation of a high-valent state, Fig. 1. It is this formation of high oxidation states that drives all metal-catalysed biological activation. In the case of iron, a high valent ferryl species is always used, Fig. 1. These ferryl intermediates provide the oxidative power for biological oxidations catalyzed by both non-heme and heme iron-containing enzymes. This project focuses characterizing the latter category.

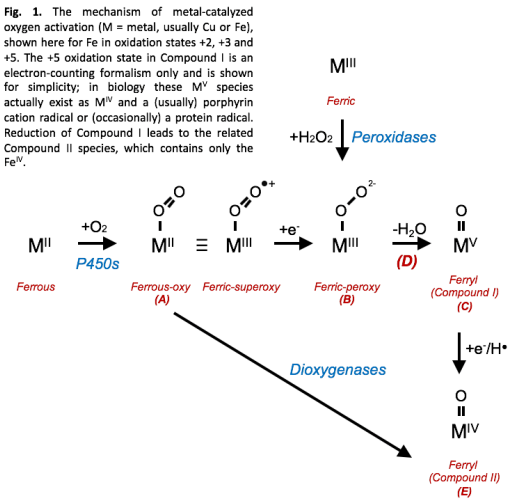
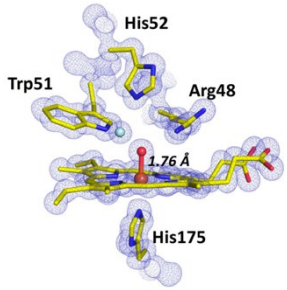


Fig. 1. The mechanism of metal-catalyzed oxygen activation (M = metal, usually Cu or Fe), shown here for Fe in oxidation states +2, +3 and +5. The +5 oxidation state in Compound I is an electron-counting formalism only and is shown for simplicity; in biology these M^V species actually exist as M^{IV} and a (usually) porphyrin cation radical or (occasionally) a protein radical. Reduction of Compound I leads to the related Compound II species, which contains only the Fe^{IV}.



Why choose this opportunity? There have many attempts to study the mechanisms of O-O bond cleavage in heme enzymes. But none of the previous methods can actually *visualise* the O-O bond cleavage steps – they can only access intermediates if they are stable enough, formed quantitatively and on the correct timescales. This means that a true visualisation of the O-O bond breaking steps has not been possible. In this proposal, we intend to shift the debate from the static – looking at static intermediates at single points in time – to the dynamic – visualising bond breaking and bond making events in real time. Serial femotosecond crystallography (as a collaboration with Prof A Orville, Diamond) provides a way forward because it allow us to access short lived intermediates formed during the O_2 activation event and on timescales that have not been previously accessible – in essence, building a molecular movie of catalysis. Since all heme enzymes use the same chemistry for O_2 activation, Fig. 1, the results generated will be generically relevant across all heme enzymes and will therefore be of wide impact. There are opportunities to work with structural biologists and beam line scientists around the world, who are interested in the dynamics of heme catalysis. You will participate with others in the group in external conferences (on-line), giving you an opportunity interact with other scientists outside of Bristol and to present your work to a wider audience. You will learn a range of techniques in chemical biology, enzymology, molecular biology and structural biology.

Full training will be provided for all aspects of this project. You will be embedded in the Prof Raven's research group, who will provide support. In addition, you will be assigned a mentor for the duration of your project, who will provide extra support and help you to identify any additional training needs or opportunities.

About you: You will have skills and knowledge in chemistry, chemical biology or biochemistry. You will be prepared to work well in a team, and be able to manage your time efficiently. These skills are desirable but not essential.

Bench fees: A bench fee of £7.5 k is required.

How to apply: Applications are accepted throughout the Academic Year, and you should complete the online application form for Chemistry (MSc by Research).

Supervisor: Your supervisor for this project will be Your supervisor for this project will be Professor Emma Raven in the School of Chemistry. You can contact her at +44 (0) 117 928 7657 or email emma.raven@bristol.ac.uk.

Find out more about your prospective research program: Published work from the Raven lab below gives more information. *Science,* **2014***, 345*, 193-197 (DOI: 10.1126/science.1254398); *Proc. Natl. Acad. Sci USA* **2021**, 118 (22) 118 No. 22 e2104008118 (DOI: 10.1073/pnas.2104008118); Moody, P. C. E., Raven, E., *Acc Chem Res* **2018,** *51*, 427-435; *ACIE* **2020**, *60,* 1