Nonheme iron hydroxylases and halogenases: How does the protein influence the product distributions?

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Nonheme iron dioxygenases catalyze a range of vital reactions for human health, including the biosynthesis of hydroxyproline, the catabolism of cysteine as well as DNA repair mechanisms.[1] There are many facets to the catalytic reaction mechanism of these enzymes that are still elusive, which is partially due to their high reactivity but also as a result of multiple spin states interfering into the reaction mechanism. In this presentation, I will give an overview of recent computational studies of our group on the mechanism and function of a nonheme iron hydroxylase (prolyl-4-hydroxylase)[2] and a nonheme iron halogenase (hectochlorin biosynthesis protein).[3] In both enzymes the oxidant triggers a regio- and stereospecific reaction mechanism and the calculations were focused on understanding the reactivity patterns and particularly the importance of the secondary structure of the protein to guide the regio- and stereospecific product formation through proper substrate positioning but also through electrostatic interactions.

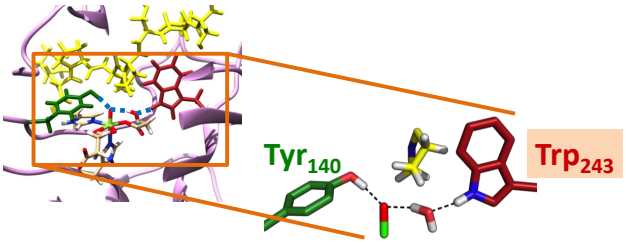

Figure 1. Active site structure of prolyl-4-hydroxylase with key residues affecting substrate positioning and that guide the regio- and stereoselectivity of the reaction.

References

[1] S. P. de Visser and D. Kumar (Eds.) I*ron-containing enzymes: Versatile catalysts of hydroxylation reactions in nature*; Royal Society of Chemistry Publishing, Cambridge (UK), 2011.

[2] A. Timmins, M. Saint-André and S. P. de Visser, *J. Am. Chem. Soc.*, **2017**, *139*, 9855.

[3] A. Timmins, N. J. Fowler, J. Warwicker, G. D. Straganz and S. P. de Visser, *Submitted*.