QUANTUM MECHANICS/MOLECULAR MECHANICS STUDIES OF ENZYMATIC REACTION MECHANISMS.

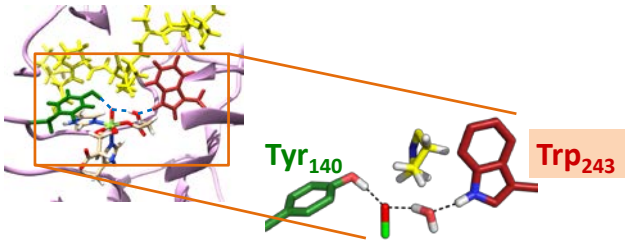
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Metalloenzymes perform vital functions for human health including the biosynthesis and biodegradation of compounds. There are two main types of iron containing oxygenases, namely the heme and nonheme enzymes, but details of their reaction mechanisms and the factors that determine the product formations remain unknown. Our group has extensively investigated heme and nonheme iron oxygenases using computational modelling and established factors related to the oxidant and the protein that influence reaction patterns, bifurcations and product ratios of several enzyme classes.

A lot of the work in the group has focused on the cytochrome P450s, which are heme based monoxygenases and involved in drug metabolism reactions in the liver [1]. In this presentation, I will give an overview of work of our group in the field on establishing the mechanisms of aliphatic and aromatic hydroxylation processes that determine drug metabolic reactions in the liver. In addition, some recent work on biotechnological P450 peroxygenases will be presented whereby long chain fatty acids are converted into terminal olefins [2].

Finally, the presentation will cover recent work on nonheme iron hydroxylases (prolyl-4-hydroxylase) [3] and a nonheme iron halogenases (hectochlorin biosynthesis protein). Both enzymes contain a nonheme iron active center that is bound to the protein through interactions with two histidine side chains and in addition have an anionic ligand: aspartate in the hydroxylases and halide in the halogenases. We performed detailed computational studies on the mechanisms leading to products and by-products for wildtype as well as mutants. The work highlights 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.



1. S. P. de Visser, M. J. Stillman, *Int. J. Mol. Sci*. **2016**, *17*, 519–544.
2. A. S. Faponle, M. G. Quesne, S. P. de Visser, *Chem. Eur. J*. **2016**, *22*, 5478–5483.
3. A. Timmins, M. Saint-André, S. P. de Visser, *J. Am. Chem. Soc*. **2017**, *139*, 9855–9866.