

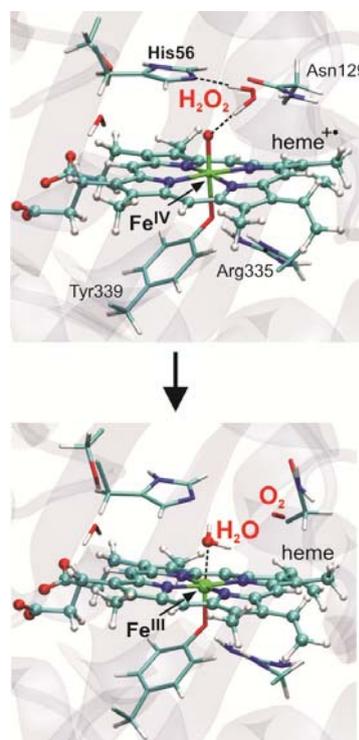
The molecular mechanism of catalase by Car-Parrinello QM/MM metadynamics

Carme Rovira

ICREA / Parc Científic de Barcelona / IQTC

crovira@pcb.ub.es

Catalases are ubiquitous enzymes that prevent cell oxidative damage by degrading hydrogen peroxide to water and oxygen ($2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$) with high efficiency [1]. The enzyme is first oxidized to a high-valent iron intermediate, known as Compound I (Cpd I) which, at difference from other hydroperoxidases, is reduced back to the resting state by further reacting with H_2O_2 . The normal catalase activity is reduced if Cpd I is consumed in a competing side reaction, forming a one-electron reduced species named Cpd I*. By means of hybrid QM/MM metadynamics [2] simulations, we unravel the mechanism of the reduction of Compound I by H_2O_2 in catalase [3,4]. We found that the Cpd I: H_2O_2 complex evolves to a Cpd II-like species through the transfer of a hydrogen atom from the peroxide to the oxoferryl unit. To complete the reaction, two mechanisms may be operative: an *His-mediated* mechanism [2], which involves the distal His as an acid-base catalyst mediating the transfer of a proton (associated with an electron transfer), and a *direct mechanism*, in which a hydrogen atom transfer occurs. Independently of the mechanism, the reaction proceeds by two one-electron transfers rather than one two-electron transfer, as has long been assumed. The calculations provide a detailed view of the atomic and electronic reorganizations during the reaction, and highlight the key role of the distal residues to assist the reaction [3,4]. Calculations of the one-electron reduction potential and proton transfer free energy suggest that the energetics of the oxoferryl protonation is the key factor regulating the propensity to form Cpd I* in catalases and possibly also in other hydroperoxidases [5]. A brief introduction to the Car-Parrinello and metadynamics methods will be provided.



References

- [1] P. Nichols, I. Fita, P. C. Loewen, In *Advanced Inorganic Chemistry*; Sykes, A. G., Mauk, G., Ed.; Academic Press: New York, 2001; pp 51-106.
- [2] A. Laio, M. Parrinello, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12562–12566.
- [3] M. Alfonso-Prieto, A. Borovik, X. Carpena, G. Murshudov, W. Melik-Adamyan, I. Fita, C. Rovira, P. C. Loewen, *J. Am. Chem. Soc.* **2007**, *129*, 4193–4205.
- [4] M. Alfonso-Prieto, X. Biarnés, P. Vidossich, C. Rovira, *J. Am. Chem. Soc.* **2009**, *131*, 11751–11761.
- [5] M. Alfonso-Prieto, H. Oberhofer, M. L. Klein, C. Rovira, J. Blumberger, *J. Am. Chem. Soc.* **2011**, *133*, 4285–4298.