

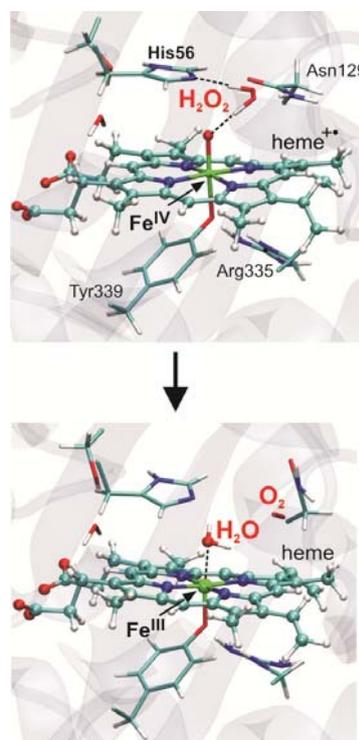
# The molecular mechanism of catalase by Car-Parrinello QM/MM metadynamics

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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  $\text{H}_2\text{O}_2$ . 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  $\text{H}_2\text{O}_2$  in catalase [3,4]. We found that the Cpd I: $\text{H}_2\text{O}_2$  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

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