Modulating the Reactivity of Biological Thiols and the Mechanism of Reaction with H_2O_2 by Hydrogen Bonding in Their Local Environments

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We examine in a comparative way the reactivity of several thiols of biological relevance (namely free cysteines in a dipeptide and in two human proteins: serum albumin and two variants of Peroxiredoxin 5, WT and T44V) which have been shown to display quite different efficiencies in reducing hydrogen peroxide (H_2O_2) through a chemical process leading to sulfenic acid derivatives (RSOH). Such reaction has received considerable attention after the recognition of its involvement in catalysis and regulation, being the corresponding mechanism not completely understood yet, in particular the way each protein environment modulates the reactivity of the thiol and the nature of the outcome of the process. To address these topics we have used a combination of state-of-art molecular dynamics simulations and electronic structure calculations conducted both by employing DFT coupled with a continuum PCM representation of environments of variable polarity and ONIOM(DFT:AMBER) methods.

We have thus characterized the structure and dynamics of the environment of each particular thiol, both in absence/presence of H_2O_2, determining that the nature of local hydrogen bonding interactions is the main factor responsible for tuning Cys pKa and nucleophilicty while destabilizing and properly positioning the peroxide for the reaction. In all the cases a S_N2 TS is involved, followed by one/two proton-transfers starting at post-TS bifurcation points in the reaction path, in vicinity to valley-ridge inflections connecting with RSOH/RSO^- interconversion.

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