HOW DOES CATALASE RELEASE NITRIC OXIDE? PREDICTING REACTION MECHANISMS VIA A COMPUTATIONAL STRUCTURE ACTIVITY RELATIONSHIP STUDY

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Hydroxyurea, the only FDA approved treatment of sickle cell disease, is believed to increase pharmacological nitric oxide (NO) levels as its primary mechanism of action. Despite this fundamental understanding, specific details are still undetermined. Interaction of hydroxyurea with human catalase Compound I is known to produce NO, which is essential in the treatment of sickle cell disease. Presently, we combine virtual screening with an energy decomposition analysis to examine atomic level details. This methodology allows us to investigate substrate binding modes of hydroxyurea analogs to catalase Compound I and the structural changes of the enzyme-substrate complex. Two major binding poses provide insight into the reaction mechanisms that result in NO production from hydroxyurea analogs. Furthermore, we learn that reactive intermediates are stabilized by the distal residues His75, Asn144, Gln168, and oxoferryl-heme. This identification could lead to substrate design that targets effective NO production.