

Coupled binuclear copper (CBC) enzymes is an important family of redox active metalloenzymes. They catalyze various chemical transformations, typically oxidation reactions. Using hybrid quantum and molecular mechanical calculations (QM/MM), we computationally characterized initial steps in the reaction mechanism of two CBC enzymes: catechol oxidases and *o*-aminophenol oxidases. Catechol oxidases were represented by the polyphenol oxidase 6 (PPO6), and *Ipomoea batatas* catechol oxidase (IBCO). The *o*-aminophenol oxidases were represented by the NspF, a protein named after its gene code. By comparing the computed data with the previous work on tyrosinase (Ty), we attempted to answer the question why both NspF and Ty can hydroxylate phenols whereas catechol oxidases cannot. Our preliminary results indicate that there is a significant difference in the energy of the rate-determining transition state corresponding to the attack of the activated oxyl radical along with the phenol binding to the active site. The computed energy for the second transition state is lower for NspF in comparison with PPO6 and IBCO. Our work may help to understand the chemoselectivity of CBC enzymes, identify the second-sphere residues that are responsible for the diverse reactivities and potentially open new ways to design the CBC enzymes or the biomimetic systems.