The Reaction Mechanism of the Enzyme Salicylate Dioxygenase Revealed by QM/MM Simulations

Salicylate 1,2-Dioxygenase (SDO) is the first enzyme discovered to catalyze the oxidative cleavage of a monohydroxylated aromatic compound, salicylate, in contrast to the well-known electron-rich substrates. We have investigated the mechanism of dioxygen activation in SDO by QM/MM calculations. Our study reveals that the non-heme Fe^III^ center in SDO activates salicylate and O_2 synergistically by a strong covalent interaction to facilitate the reductive cleavage of O_2. A covalent Salicylate-Fe^III^-O_2 complex is the reactive oxygen species in this case, where the electronic structure is best described as between the two limiting cases, Fe^III^-O_2 and Fe^III^-O_2^- with partial electron transfer from the activated salicylate to O_2 via the Fe center. Thus, SDO employs a synergistic strategy of ‘substrate activation’ and ‘oxygen activation’ to carry out the catalytic reaction, which is unprecedented in the family of iron dioxygenases. Moreover, O_2 activation in SDO happens without the assistance of a proton source. Our study essentially opens up a new window in the mechanism of O_2 activation.