The mechanism of oxygen activation of L-arginine by nitric oxide synthase enzymes, a theoretical study

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In this presentation results of a series of density functional theory (DFT) and quantum mechanical/molecular mechanics (QM/MM) studies on the first catalytic cycle of Nitric Oxide Synthase (NOS) are discussed. NOS enzymes are key enzymes for human health that catalyze the formation of NO from L-arginine in the brain. The studies address the key steps in the catalytic cycle whereby the substrate (L-arginine) is hydroxylated to $N^{ω}$-hydroxo-arginine. Earlier studies suggested a mechanism similar to that obtained for the cytochromes P450; however, our calculations find an alternative low energy pathway whereby the bound L-arginine substrate has two important functions in the catalytic cycle, namely first as a proton donor and later as the substrate in the reaction mechanism. The work predicts that in NOS enzymes arginine binds to the active site in its protonated form, but is deprotonated during the oxygen activation process in the catalytic cycle by either the dioxo dianion species or the hydroperoxo-iron complex. The actual hydroxylation reaction starts with an initial electron transfer from the substrate to the iron(IV)oxo species followed by a concerted hydrogen abstraction/radical rebound to from the substrate. This is the first example of an enzyme where the reduced iron(IV)oxo species is able to participate in a reaction mechanism.