

**P012** QM/MM study of the sulfoxidation reaction of cytochrome P450

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Cytochrome P450s are ubiquitous enzymes involved in key biochemical processes. Their primary oxidant has never been isolated experimentally, but there is indirect evidence suggesting that it is the oxo-iron species (Compound I). However, recent experimental studies have cast this into doubt based on the sulfoxidation by P450<sub>BM3</sub> implicating the ferric-hydroperoxide species, also known as Compound 0, as the more likely oxidant.

We have performed a quantum mechanical/molecular mechanical (QM/MM) study on the sulfoxidation of dimethylsulfide (DMS) by both Compound I and Compound 0 that includes the full enzyme and solvent environment. The study focused on the elucidation of the primary oxidant involved in the reaction and in particular on the oxidative capabilities of Compound I and Compound 0. The sulfoxidation reaction involves a direct oxygen atom transfer from Compound I via a transition state leading to the dimethylsulfoxide (DMSO) product. By contrast, significantly higher reaction barriers were obtained for Compound 0, which implies that Compound 0 cannot act as an oxidant side-by-side with Compound I. The experimentally observed rate constants are more likely to be the result of two-state-reactivity patterns of competing doublet and quartet spin state surfaces of Compound I.