A QM/MM study on the key catalytic intermediate states of alternative oxidase in Trypanosoma (TAO)

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Alternative oxidase (AOX) is a membrane-bound ubiquinol oxidase which has diiron centers [1]. It catalyzes the reoxidation of reduced ubiquinone produced by ATP production in protozoan parasite Trypanosoma, which is a cause of a lethal infection called sleeping sickness. AOX in Trypanosoma (trypanosome alternative oxidase: TAO) is considered as an optimal drug target of sleeping sickness, and its crystal structure was revealed in 2013[2]. In this study, based on quantum mechanical/molecular mechanical (QM/MM) calculations, we investigated on the five catalytic intermediate states of TAO. These states are (1) oxodiiron (resting), (2) differrous, (3) superoxo, (4) hydroperoxo, and (5) peroxodiiron. For the superoxo state, we searched stable O_2 binding states, because in the X-ray structure, the O_2 molecule binds to the iron center in the side-on type, which is quite unique among all the Fe-O_2 binding states. We found, however, that end-on type structures are more stable on the contrary to the X-ray structure. Calculated spin densities showed that the O_2 molecule is close to a free O_2 form ($^3O_2$) and weakly binds to the iron center. QM/MM optimized structures for other key intermediate states are also discussed.

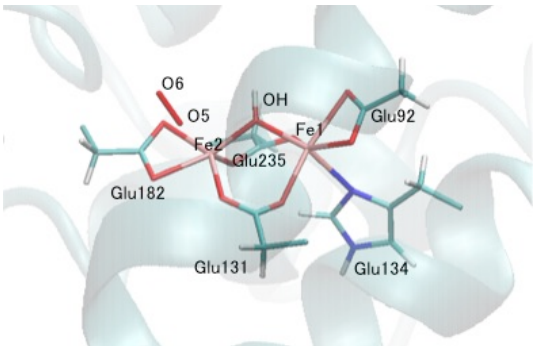

Figure 1: The active site of trypanosome alternative oxidase (TAO)

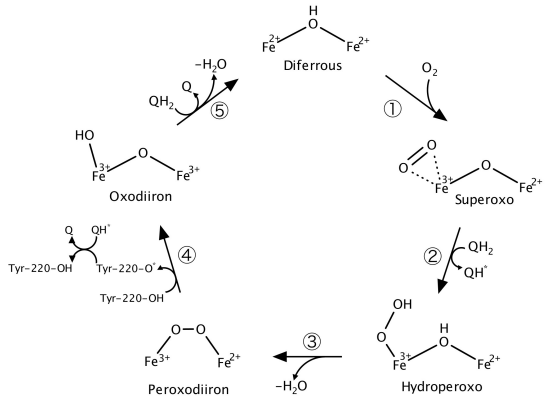

Figure 2: Proposed reaction mechanism of TAO

[1] A.L. Moore *et al*. *Annu. Rev. Plant Biol.* **64**, 637 (2013).
[2] T. Shiba *et al*. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 4580 (2013).