

Tuanjai Somboon 2011: Hybrid Quantum Mechanical/Molecular Mechanical Studies on the Reaction Mechanism of *cis,cis*-Muconate Lactonizing Enzymes. Master of Science (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 80 pages.

Muconate lactonizing enzymes (MLEs) derived from *Mycobacterium smegmatis* and *Pseudomonas fluorescens* share ~76% identity and have a very similar arrangement of catalytic residues in their respective active site. MLEs catalyze the conversion of *cis,cis*-muconate to the same achiral product, muconolactone. However, studies in deuterated solvent surprisingly show that the cyclo-isomerization proceeds along stereochemically distinct mechanistic routes. The theoretical calculation performed here have helped to confirm the identity of the basic residues involved in the MLE reaction originally proposed by Sakai et al through indirect means from an analysis of the products produced in experiments performed in deuterated solvents. The results show that although the basic Lys residues located on the 6<sup>th</sup> strand in both MLEs are almost equally well positioned to accept a proton, however, it is the base located on the 2<sup>nd</sup> strand that is thermodynamically and kinetically more favorable, as well as giving the optimized QM/MM product closest to the original X-ray structure.

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Thesis Advisor's signature