Darinee Sae-Tang 2009: Quantum Chemical Calculations and ONIOM Studies on Cyclopropane Synthase, Succinate Dehydrogenase and Cyclooxygenase. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 127 pages.

The application of computational calculations to biological systems has become interesting to describe enzyme/ligand interaction. Three enzymes, cyclopropane synthase, succinate dehydrogenase and cyclooxygenase, were investigated using performance of quantum chemical calculations and ONIOM approach. Firstly, the interaction energies of the cofactor in the methylation with the cyclopropane synthase, SAM, SAH, and sinefungin were performed. The important residues are found to be Asp70 and Glu121 in which SAM shows a stronger interaction than sinefungin and SAH, respectively. Moreover, twenty five systematic ONIOM2 calculations were performed for the cyclopropane synthase with various model systems. The SAM cofactor obviously strongly interacts in the cofactor binding site than SAH product as a consequent of the methyl substituent at the sulfur atom resulting in positive charge around sulfur and neighboring atoms in the system. Secondly, the ONIOM calculations of succinate dehydrogenase and 3-NP inhibitor, were investigated and compared with succinate, in the substrate binding site of succinate dehydrogenase flavoprotein subunit.The obtained results showed that the succinate establishes more tight binding than 3-nitropropionate of about 3 times. The individual interaction calculations between 3-NP/succinate, including FAD, and various amino acids indicated that the interaction energy with Arg409 is the main contributor and the flavin derivatives FAD play an important role in the binding pocket of the complex. Finally, the binding energy calculations of flurbiprofen to the binding pocket of cyclooxygenase were performed. Comparison of interaction energies between flurbiprofen with COX-1 and COX-2 binding site was studied. The results showed that the main interaction between flurbiprofen and two COX isozymes are due to Arg120. In addition, selective COX-2 inhibitor, SC558, was also compared and it was found that repulsive interaction plays significant role for specific interaction of this inhibitor to COX-2 inhibition. Taken into account, ONIOM2 method can be useful to describe specific interaction of the inhibitor and helpful for design of specific potent inhibitors.

_____ _____ ___ / ___ / ___

Student's signature Thesis Advisor's signature