Quantum Mechanical/Molecular Mechanical Simulations of Hydride Transfer Reactions in Quinone Reductase

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Flavin is a tricyclic 7, 8, 10-substituted isoalloxazine ring that acts as an electron mediatory cofactor in many classes of enzymes including quinone oxidoreductases. In NRH:quinone oxidoreductase 2 (NQO2), the flavin is known to mediate hydride (two electron one-proton equivalent) transfers utilizing a so called ping pong kinetics mechanism in which one substrate binds the active site and donates the hydride to the flavin. The oxidized substrate is then released followed by binding of the second one (at the same active site pocket) which accepts the hydride from the flavin. We are using quantum mechanical/molecular mechanical (QM/MM) simulations to explore the energetics of the ping-pong kinetics in NQO2. In cell, NQO2 catalyze the conversion of prodrug into drug and understanding the energetics involved in this ping pong kinetics will aid in drug design. The QM/MM setup, methods, and some results will be presented.