Physics Colloquium

Michigan Technological University

Thursday, February 25, 2008
4:00 - 5:00 pm
Room 139, Fisher Hall

Effects of Protein Dynamics on Enzyme Catalysis: Studies of Dihydrofolate Dehydrogenase

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Abstract: The correlation of protein dynamics to enzyme catalysis is an intriguing question that has attracted extensive experimental and computational studies. The hydride transfer reaction between the cofactor NADPH and 7,8-dihydrofolate catalyzed by dihydrofolate reductase (DHFR) is a prototypical example, which exhibits remarkable rate variations when residues as far as 19 angstroms away from the active site are mutated. Theoretical and experimental studies indicate that amino acid mutations, including M42 and G121, both remote from the active site, affect the dynamics of the protein and the reaction rate of the enzymatic process. It has been proposed that these residues are involved in a network of hydrogen bonding interactions that directly influence the chemical activity in the active site. Furthermore, recent measurements of intrinsic kinetic isotope effects for the hydride transfer reaction catalyzed by the wild-type and mutant DHFR at different temperatures (L. Wang, N. M. Goodey, S. J. Benkovic, A. Kohen, Proc. Nat. Acad. Sci. 2006, 103, 15753) suggest that the double mutation of G121V and M42W causes changes in the protein dynamics that requires donor-acceptor distance fluctuations in the hydride transfer, whereas such fluctuations are not essential in the wild-type enzyme. In this paper, we describe a combined quantum mechanical and molecular mechanical (QM/MM) simulation study of the wild-type and the double mutant DHFR and determine the primary and secondary intrinsic kinetic isotope effects using a path integral method with bisection sampling at different temperatures. We compare the computed temperature dependence of kinetic isotope effects with experiments and analyze dynamical factors that contribute to the overall change in the observed free energy barrier.

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