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Mapping the vibrational transition-state conformational change in enzymes for drug design

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About a quarter of the current registered pharmaceutical drugs are enzyme inhibitors. Many of them are the enzyme transition-state (TS) analogues that are designed largely on the basis of the crystal structure of the stable "frozen" TS analogues or the "still" TS structures from the kinetic studies. Recent decade has, however, witnessed much of the role of the enzyme dynamics in catalysis. Protein vibrations with different time scales have been proposed to assist various processes of the complex enzymatic reactions, including the bond-formation and - cleavage in the active site. The latter suggests a vibrational TS structure on the reaction coordinate, coupled with the local fast motions of enzyme. While study of the vibrational TS that involves the fast fluctuations of the reaction distance is still in its infancy, it would be worthy to consider the concept in design of what may come to be more effective inhibitors and more successful drugs. E.g., a successful inhibitor may be that can also interrupt the TS/enzyme coupled vibrations. In this paper, we present a method to gain the different TS structures at different donor-acceptor distance (DAD) in both solution and enzymatic H-transfer reactions. We use secondary (2°) kinetic isotope effect (KIE) as a structural descriptor. We determine the 2° KIEs and thus TS structures for hydride- and deuteride-tunneling processes that have different DADs. Information about the DAD-dependent TS structures in enzymes would help track the path of the vibrational TS conformational changes. This information would be useful for drug design.

Biography

Yun Lu received his PhD degree in Organic Chemistry from Nankai University, China in 1996. He did his post-doctoral work in Utah State University with professor Vernon D Parker and Wayne State University with professor Martin Newcomb. His research focuses in the field of physical organic chemistry studying the mechanism of organic reactions and the transition state structures. He is now a professor in the department of chemistry at Southern Illinois University Edwardsville, USA. He has published nearly 50 papers in reputed journals.

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