Application of QM/MM Methods to probe reaction mechanisms

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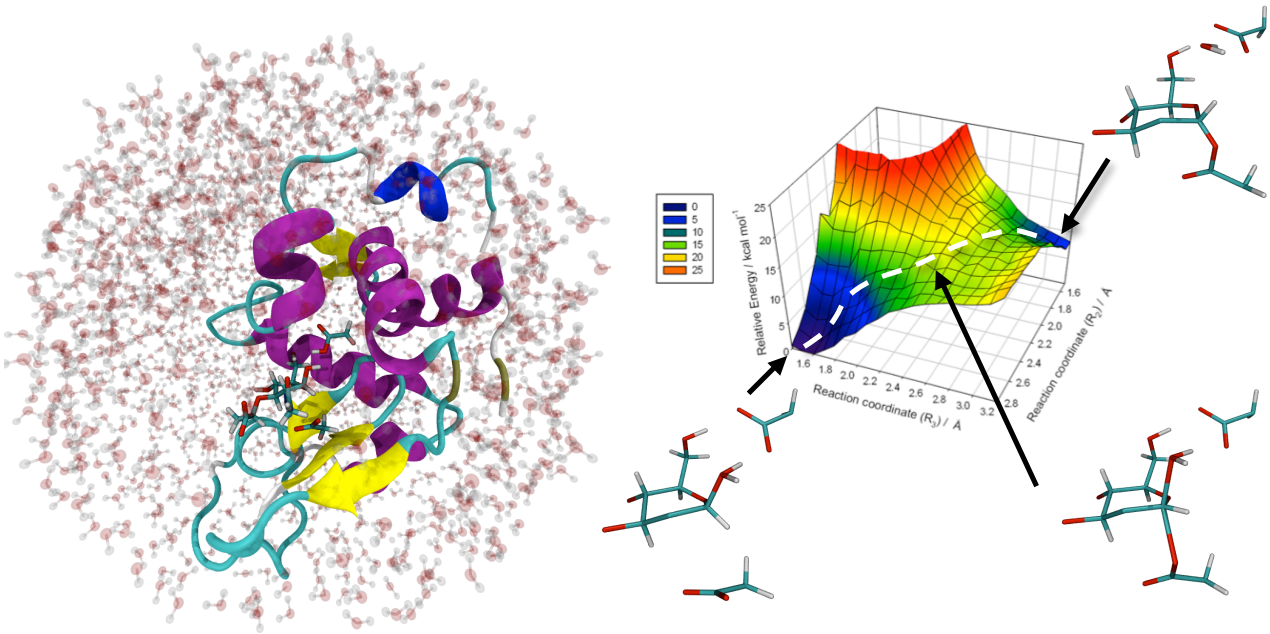
QM/MM (Quantum Mechanics/ Molecular Mechanics) methods are increasingly important in analyzing and predicting enzyme activity. QM/MM methods allow a detailed atomic level investigation of reactions in enzymes by coupling quantum chemical calculations on the active site with a simpler, empirical 'molecular mechanics' treatment of the rest of the protein. This has the significant advantage of probing possible reaction mechanisms in enzymes with quantum methods of potentially high accuracy, while retaining the ability to produce results for large, solvated enzymes, on reasonable time scales and at relatively small computational expense [1].

An example of QM/MM analysis of the effects of mutations, and investigations of alternative substrates, is provided by HEWL (Hen Egg White Lysozyme). GPU (Graphics Processing Unit) aided, long timescale MD (Molecular Dynamics) simulations were performed on the enzyme system allowing suitable 'reactive frames' to be generated for the reaction. QM/MM calculations where then used to determine the nature of the catalytic intermediate formed during the enzyme-catalyzed reaction [2]. Reactions of mutant enzymes and alternative (fluorinated) substrates were then modeled, for comparisons with experimental studies: such modifications were necessary for the experimental trapping of a reaction intermediate [3]. QM/MM calculations compared the reactions with the wild-type and native substrate, and analyzed the changes caused by these modifications, testing the conclusions drawn from mutant enzymes and non-natural substrates.



[1] Ranaghan K.E., Mulholland A.J., *Int. Rev. Phys. Chem.,* 2010, **29,** 65-133.
[2] Bowman A.L., Grant I.M., Mulholland A.J., *Chem. Commun*., 2008, **37**, 4425-4427.
[3] Vocadlo D.J., Davies G.J., Laine R., Withers S.G., *Nature*, 2001, **412**, 835- 838.