Protein Dynamics and Enzyme Catalysis: Insights from Simulation

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Enzymes exhibit complex dynamics and conformational changes associated with their catalytic cycles. Debates in biochemistry centre on the possible functional roles of these motions. Simulations have an important part to play in resolving these challenging issues. Classical molecular dynamics simulations can identify functionally relevant motions on the nanosecond timescale: for example, simulations of human scavenger decapping enzyme have identified a cooperative periodic opening and closing of the dimer. For modelling enzyme-catalysed reaction mechanisms, combined quantum mechanics/molecular mechanics (QM/MM) methods are a good approach. QM/MM calculations can now be carried out with high-level *ab initio* methods capable of high accuracy. Calculated activation energies for some enzyme reactions, such as those catalysed by chorismate mutase and p-hydroxybenzoate hydroxylase, agree well with experiment, indicating that dynamical effects on the rate are relatively small. Quantum tunnelling can be a significant factor, e.g. in the key proton transfer step of aromatic amine dehydrogenase. Semiempirical QM/MM VTST/SCT calculations show that quantum tunnelling is dominant in the reaction, and can give calculated KIEs in good agreement with experiment. Simulations indicate that long-range coupled motion of the protein is apparently not involved in 'driving' tunnelling in this case. Complex conformational effects are observed in some enzymes: for example, hydrolysis of the 'sleep inducer' oleamide in fatty acid amide hydrolase appears to involve a minor conformation of the protein. QM/MM modelling of citrate synthase has suggested an unusual mechanism involving arginine acting as an acid; this mechanism also suggests a means of coupling chemical and conformational changes in this enzyme.