

P024 Atomic description of enzyme catalysed hydrogen tunnelling: two case studies

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It is widely accepted that quantum mechanical tunnelling can significantly influence the rate of hydrogen transfer in many enzyme-catalysed reactions. More controversial at present is the role enzyme dynamical effects play. Two systems, hyperthermophilic dihydrofolate reductase (TmDHFR) and morphinone reductase (MR), have been chosen to investigate the role of environmentally coupled hydrogen tunnelling. In both cases, the computational studies – using a combined QM/MM method in conjunction with EA-VTST/MT – qualitatively reproduced the experimental hydrogen transfer rate and kinetic isotope effects (KIEs) and allowed us to obtain an atomic description of tunnelling dynamics, a level of detail not possible solely based on experimental measurements. In TmDHFR, 50-80 % of hydrogen (hydride) transfer was calculated to occur by tunnelling at 5-65 °C. Structural and dynamical analysis indicated the catalytic power of TmDHFR was correlated with motions between domains as well as within and between its two subunits. In contrast to TmDHFR, hydrogen (hydride) transfer catalysed by MR was dominated by tunnelling – 99 % of the reaction proceeds via tunnelling with 1° H/D KIE of 15.3 and exalted 2° KIE of 1.20 at 25 °C. This dominant tunnelling contribution likely arises from pre-organisation of the active site and participation of the heavy atom motions in the substrate and cofactor.