TUNNELING RATES IN THE ENZYME GLUTAMATE MUTASE: THE INSTANTON METHOD APPLIED TO LARGE SYSTEMS

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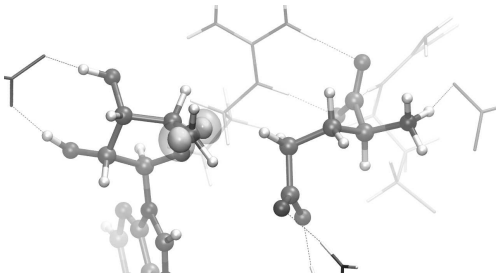

Reactive part of glutamate mutase

Glutamate mutase is an adenosylcobalamin-dependent enzyme catalyzing a radical reaction with two different types of reaction steps. The first are proton transfers, whereas the second includes a carbon-skeleton rearrangement. We investigated this system with QM/MM calculations based on density functional theory verified by MP2. The enzyme was found to provide enantioselectivity in the carbon-skeleton rearrangement step which is aided by an acid-base reaction with nearby aminoacid glutamate 171 reducing the barrier. The enzyme significantly lowers the barriers for the proton transfers.
The experimentally found kinetic isotope effects ranging from 10 to 50 for adenosylcobalamin-dependent enzymes suggest proton tunneling. We use an improved path-integral-based instanton approach to figure out how the enzyme modulates these effects. The instanton is a first order saddle point in the space of closed Feynman paths between the product and the reactant. We compared mode-following to Hessian-based transition state search algorithms and to the dimer method. This enabled us for the first time to locate instantons in systems with several hundred degrees of freedom. The methods were tested on the H addition to benzene as a simple model for the astrochemically relevant chemisorption to polycyclic aromatic hydrocarbon [1] and on other small test systems. Finally, we calculated kinetic isotope effects in glutamate mutase.

[1] T. P. M. Goumans and Johannes Kästner, *Angew. Chem. Int. Ed.* accepted (2010)

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