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Computational Investigation of the Reaction Thermochemistry and Kinetics of TTQ Cofactor

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Abstract

Among the simplest electrobiochemical pathways to characterize experimentally is a series of electron transfer reactions that provide the mechanism for dehydrogenation of methylamine. We describe a computational investigation of the chemical reaction mechanism for the enzyme activity of methylamine dehydrogenase in converting methylamine to ammonia and formaldehyde, focusing on the activity of the cofactor tryptophan tryptophylquinone (TTQ). The free energies, reaction rate constants, and related effects of temperature, pH, and isotopic substitution are being computed for comparison against experimental observations. Electronic structure calculations are carried out by density functional methods shown to be effective in the study of simpler chemical systems involving the dynamics of conjugated pi-electron systems. The reaction energies of several reaction steps have been mapped along selected reaction coordinates, and additional reaction steps are currently being probed to determine the minimum energy path. The COSMO-RS model will then be applied to account for the considerable solvent effects in ion-mediated reaction dynamics, and will allow determination of the influence of pH on the reaction system.

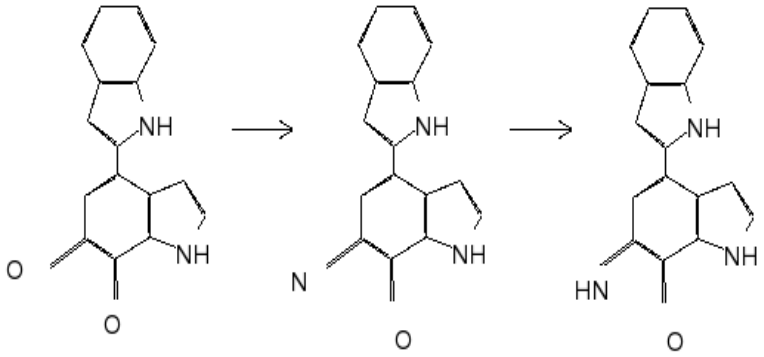

Fig. 1. General scheme for the TTQ metabolic reaction.

Introduction

The purpose of this project is to probe the reaction of TTQ, a non-protein component of the enzyme methylamine hydrogenase, to metabolize methylamine. The enzyme is present in various anaerobic bacteria, and converts methylamine (CH_3NH_2) into formaldehyde (H_2CO) and ammonia (NH_3) by reaction with water, in a reaction of several steps, summarized in Fig. 1. The computational study is focused on the effects of intermolecular interactions upon the energies, rate constants, and molecular structures. The most stable molecular geometries are calculated at the beginning and end of each step in the reaction, to find the reactant and product energies. Starting from these, basic thermodynamic properties such as the ΔH (heat of reaction) and ΔG (free energy of reaction) for the reaction can be calculated. To obtain the reaction rate constants, it is necessary to graph the energy of the reacting molecules as the reaction progresses. The

reaction rate will be determined mainly by the energy of the transition state – the highest energy point along this graph. The higher the energy of the transition state, the slower the reaction. This procedure must be carried out for each reaction step.

Upon completion, we will be able to model all the steps of the complete reaction, including all of the intermediate steps, demonstrating the ability of these computational tools to predict the stability and structures of this biochemical system.

Results

Figure 2 graphs the Hartree-Fock energies during the first step in the metabolic reaction, attachment of the methylamine to the TTQ. The peak energy activation of the molecule corresponds to most unstable part of the reaction step, the transition state of the molecule. The reactant energy corresponds to the energy at scan step 1, and the most stable product structure is associated with the base of the curve in scan step 8. Thus, it takes more energy for the molecule to move back to reactants over the unstable transition state. The energy of activation is the energy required to reach the transition state from the reactant structure.

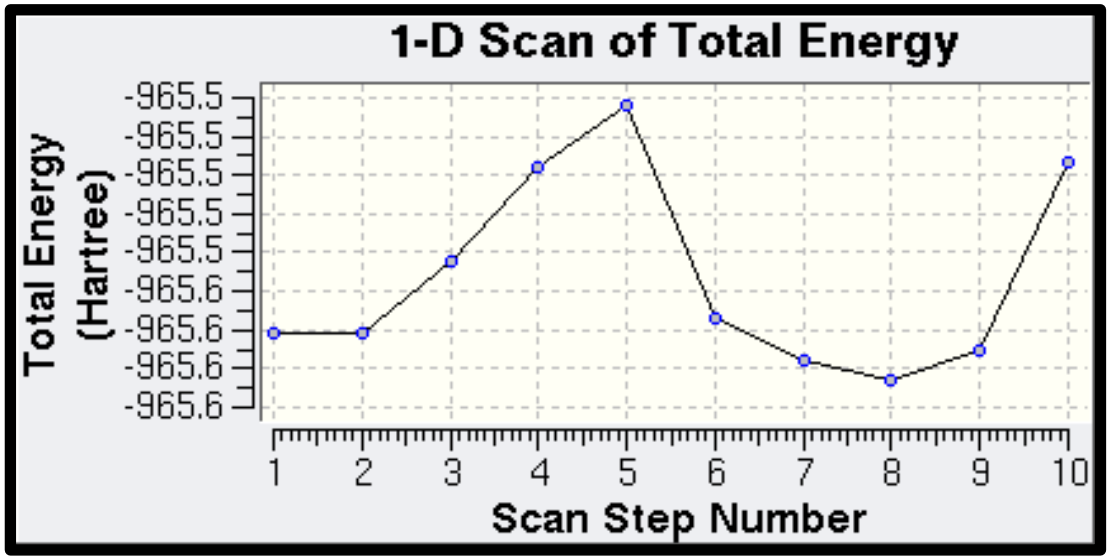

Fig. 2. HF energies evaluated as a function of N-C distance in an early step of the reaction.

Continuing work on this project includes mapping the remaining reaction steps, and optimizing the reactant, product, and chemical intermediate structures at higher levels of theory to improve the energy predictions.

Acknowledgments

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