

# Computational Study of TTQ Reaction Kinetics

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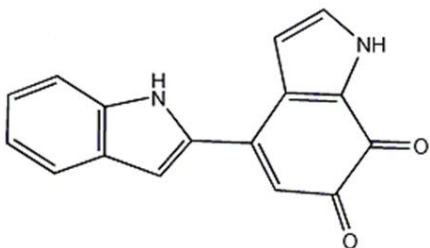
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### 1. Introduction

Computational methods play an important role in the advancement of modern chemistry. Through such methods we gain perspective into chemical phenomena that is experimentally unobservable as well as explore molecular properties without the costliness of lab experimentation. Our goal is to determine to what degree of accuracy we can use computational tools to model a reaction. The ability to do so would be a significant testament to the reputability of computational methods.

We choose to explore the mechanism for the dehydrogenation of methylamine, an electrobiochemical pathway consisting of a series of electron transfer reactions. This reaction was chosen for several reasons, the most significant of which being that portions of this mechanism have been studied before, providing data that will help us to measure the accuracy of our model once it is completed. Also, the individual steps that we believe make up the mechanism are simple enough that they can be constructed in Gaussian without too high a high degree of difficulty.

The oxidation of methylamine is catalyzed by the enzyme methylamine dehydrogenase. We aim to characterize the reaction mechanism for the enzyme, focusing on the cofactor Tryptophan Tryptophyl Quinone (TTQ). TTQ metabolizes methylamine ( $\text{CH}_3\text{NH}_2$ ) into formaldehyde ( $\text{H}_2\text{CO}$ ) plus ammonia ( $\text{NH}_3$ ) by reaction with water over several steps. The reaction takes place entirely in the quinone region of the molecule. We propose to describe the entire mechanism until the elimination of the formaldehyde.



TTQ molecule

## 2. Computational Methods

Using the reaction mechanism that we proposed, we input the molecules from each step of the reaction into the software Gaussian and optimize their geometries using Density Functional Theory (DFT). For each step of the reaction, we also freeze the coordinates of the interacting atoms at increments of .2 angstroms and optimize the intermediate geometries at each increment. Then, for each step in the mechanism, we run transition state calculations to determine reaction barriers.

Because of the volume of computations involved, we chose DFT for the balance it strikes between efficiency and accuracy. DFT provides an appealing alternative to solving the wavefunction of the Schrodinger equation by instead using functionals of spatially dependent electron density to calculate the ground state electronic structure of the molecule. We run our DFT calculations using the B3LYP method and a correlation-consistent basis set, cc-PVDZ, which we have found to be an accurate and computationally affordable combination.

After optimizations are completed, there are several factors that we must account for, namely the zero-point energy and solvent corrections. Frequency calculations must be carried out for each of the optimized geometries in order to account for zero-point and thermal energy contributions to the free energies of reaction. Also, the optimizations performed by Gaussian are in the gas phase and our reaction occurs in a water solvent. We believe that the solvent plays a significant role in the reaction and that it has a stabilizing effect on the TTQ because the polar water molecules delocalize the charge. Because we consider the effect of the solvent to be significant, we run a solvent correction on our optimized geometries in a compatible program called COSMO-RS. This is seen in the graph where the energy is reduced significantly after the solvent correction.

The transition state calculations discussed previously may prove to be a more challenging task than typically encountered because the transition state geometries may rely strongly on solvent corrections.

The DFT-B3LYP method and cc-PVDZ basis set are being used to run all of our initial optimizations on our proposed pathway. Once preliminary testing is completed and we have a better understanding of exactly what the reaction mechanism is, we will do final calculations of all of our geometries using a larger TZVP basis set.

## 3. Results and Discussion of Future Work

Reactions may occur at either of the two C=O groups in TTQ leading to an

"a" reaction series and a "b" reaction series. The "a" mechanism we proposed occurs at the carbonyl group furthest from the five-sided ring while the "b" mechanism occurs at the carbonyl group closest to the five-sided ring. An image of the latter portion of the "a" mechanism is depicted in the Introduction. We compare the two to determine which is more stable. Preliminary results lead us to conclude that the "a" mechanism may in fact be more favorable as depicted in table 1.

At this stage, our results indicate that we may need to test an alternate path for the final six steps of our proposed mechanism. In several of these steps, we are seeing the energy climb from reactants to products and there is no visible transition state. However, once all of the frequency and solvent corrections are completed, we may see more of the desired parabolic energy curve take shape.

Another reason we feel we need to rework the latter portion of our reaction mechanism is because one of our optimizations gave us an unexpected result where the formaldehyde was released several steps sooner than we originally thought possible. We are investigating this possibility to determine whether or not this is indicative of what occurs in the real system. We are also currently exploring the relative energies of protonated versus deprotonated molecules, determining whether one may be more stable than the other. This in turn will tell us how pH dependent our structures are and what the composition of our solution will be in the solvent; i.e. what concentration of each molecule will be present at different pH levels.

This project is ongoing. Though at first glance the reaction appears relatively simple, we find quickly that there are many intermediate reactions, and to computationally model this is a significant undertaking.

Reactant	Product	$\Delta G$ (kcal/mol)
TTQ+MA	21a	4.2
21a	22a+OH <sup>-</sup>	9.1
22a	23a+H <sub>3</sub> O <sup>-</sup>	18.0
23a+H <sub>3</sub> O <sup>+</sup>	24a	-13.4
24a+OH <sup>-</sup>	25a	-25.1
TTQ+MA	21b	4.1
21b	22b+OH <sup>-</sup>	13.0
22b	23b+H <sub>3</sub> O <sup>+</sup>	18.7
23b+H <sub>3</sub> O <sup>+</sup>	24b	-15.4
24b+OH <sup>-</sup>	25b	-29.2