Theoretical Studies of Naphthoquinone Reactivity towards Amino Group

Project Description/Research Objective

The objective of the research project is to use computational methods to gain a better understanding on how three naphthoquinones are likely to react towards a protein. The three naphthoquinones investigated are 2-hydroxy-1,4-naphthoquinone (HNQ), 1,2-naphthoquinone (ONQ), and 1,4-naphthoquinone (PNQ) as seen in Figure 1.

![Naphthoquinone molecules](image)

**Figure 1:** Naphthoquinone molecules to be examined in research 1) 2-hydroxy-1,4-naphthoquinone 2) 1,2-naphthoquinone 3) 1,4-naphthoquinone

In the computations, a methylamine molecule, CH$_3$NH$_2$, will be utilized as a model of a lysine amino acid from a protein since they have the same amino functional group. A previous study has shown that there is no significant change in reactivity with increasing alkyl side chain in the model used.\textsuperscript{1} For the reaction, the main focus is to examine the first step that involves the transfer of hydrogen from the methylamine to one of the double bonded oxygens on the naphthoquinones, and there are many different pathways for this reaction to occur. The different pathways are due to the possibility of hydrogen transfering through 1,2-addition or 1,4-addition at each unique double bonded oxygen. Therefore, HNQ and ONQ will have 4 possible reaction pathways while PNQ will have 2 reaction pathways. There are three major stages along a reaction pathway: the reactants, the saddle point, and the products. An example of one possible pathway is presented in Figure 2. Each of these parts will have to be characterized by the calculated lowest energy state that will further determine the rate of the reaction, how fast the reactants
are transforming into products. Of these three stages, the saddle points, commonly known as transition states, are the most crucial part as they determine the activation energy, the minimum amount of energy needed for a reactant to become a product. Therefore, the majority of the research will focus heavily on identifying and characterizing the saddle points for the hydrogen transfer mentioned earlier.

![Figure 2](image_url)

**Figure 2.** 1,2-addition of methylamine towards carbon 1 of 2-hydroxy-1,4-naphthoquinone

To investigate the various different pathways for the reaction to occur, a chemistry computational program called Gaussian is utilized. The data will be collected, analyzed, and presented at the Southeastern Regional Meeting of the American Chemical Society, Inc. (SERMACS) in the Fall of 2018.

**Project Significance**

Quinones are a class of organic compounds containing a six-membered unsaturated cyclic compound with two carbonyl groups. Quinones are known to be involved in the redox chemistry of many living organisms, such as the plastoquinone in the electron transport chain of photosynthesis and ubiquinone in aerobic respiration.² Therefore, quinones play an important role in our everyday lives. However, there are also quinones that could be toxic to the body, such as polycyclic aromatic hydrocarbon quinones or PAH-quinones. PAH-quinones are abundant in environmental contaminants and are easily absorbed into the human body which make them a prevalent topic of study.³ Inside the body, quinones can react with cellular proteins and nucleic acids through redox cycling, adduct formation, and protein aggregation.⁴ Adduct formation occurs when the quinones bind to the nucleophilic sites of proteins which causes a structural change, thus changing the function.⁵ Redox cycling of PAH-quinones
produce reactive molecules that can cause oxidative damage. Lastly, protein aggregation occurs when the quinones cause protein-crosslinking to make chains of protein aggregates.\(^4\)

There have been many experimental studies that investigated the toxicity of these PAH-quinone. For instance, studies were carried out with 1,4-benzoquinone (PBQ) which displayed how the quinone led to RNase structure changes, and these studies were complemented by theoretical studies that examined how the reactions were occurring.\(^1\)\(^4\)\(^6\)\(^7\) To add on to this field of study, our laboratory is carrying out research on the naphthoquinones, HNQ, PNQ, and ONQ, and how two proteins, lysozymes and ribonuclease, are being modified by them. Therefore, to complement the experimental study of naphthoquinones being done in our lab, I am currently carrying out this research project to computationally investigate the reaction pathways.

**Research Design and Methods**

For this theoretical study, the three naphthoquinones, HNQ, PNQ, and ONQ, will be reacting with methylamine. As stated previously, the methylamine can be utilized instead of an amino acid of a protein since there is not much change in the calculated reactivity.\(^1\) To characterize the reactant states, reactant complexes will be examined where the quinones, methylamine, and two water molecules are placed in close proximity without allowing chemical bonding between these molecules. There are many conformations, and we will utilize the lowest energy conformation we find to calculate reaction energetics. For the products, different conformations will also be examined where we will change the position of the methyl and hydrogen on the methylamine, and we will also change the location of the OH’s formed in the product. There will be around 20 different conformations to be considered for each pathway. For the saddle point, we will be examining the hydrogen transfer through two water molecules since it is the water solvent that gives the lowest energy pathway when compared with other solvents in prior calculations.\(^1\) All possible conformations of the saddle point will be examined where factors like the hydrogen position on the waters, methyl and H position on methylamine, and location of the hydrogen transfer will be changed to determine the different possible conformations.
For this research project, all calculations will be done using a chemistry computation program called Gaussian 09. The theoretical calculations will be performed using Hybrid Density Functional Theory (HDFT) of MPW1K, in conjunction with the 6-31+G(d,p) basis set which give good results for saddle point geometries. From these calculations, the optimized structures will be compared with one another and only the lowest energy structures which will be utilized to create the final reaction pathways.

**Budget Justification**

To carry out this research, I am requesting a total budget of $900 to be put towards a visualization software and traveling expenses. $400 of this amount will be utilized for transportation, registration, lodging, and meals for attending SERMACS in Fall 2018 to present my research. In addition to travel expenses, about $100 will be allocated to supplies, including printing the poster for the conference. Most importantly, about $400 will be used to purchase two copies of Chemcraft, one copy for my advisor and another for me. Chemcraft is a Gaussian visualization software, and it is essential that I get it to get an accurate visualization of what was calculated from the Gaussian software.

**Student Merit and Need**

During this past summer, I was part of the Undergraduate Research Program in the Chemistry Department where I began to learn how to do research. During the summer, I learned a lot on how to carry out quantum chemistry computations using the Gaussian software and to interpret the results I got from it. However, the research is not complete. Over the past two semesters, I have continued to do research and have become more well-versed in using Gaussian. In addition, I have completed Physical Chemistry I in the fall, and I will complete Physical Chemistry II in this spring semester which I believe is very important in understanding computational chemistry. After taking these classes, I will have the knowledge necessary to better understand and interpret the results of my research. By completing this research, I believe that I will have expanded my scientific comprehension and my ability to think critically on complicated problems. By the end, the goal is to finalize this research into an Honors Thesis.
Professionally, I hope to go to medical school to become a doctor. Although research looks good on an application, I believe that performing research will also help me learn to apply what I know and allow me to think critically which I believe to be necessary skills for a doctor. Overall, I believe that completing this research will further me as a scientist and help me in my professional goals.

References


