

4-15-2014

Computational Study of the Nitric Oxide Autoxidation Mechanism Using Quantum Chemistry Methods

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Abusad, Yazen, "Computational Study of the Nitric Oxide Autoxidation Mechanism Using Quantum Chemistry Methods" (2014). *Collection of Engaged Learning*. 33.
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**Computational Study of the Nitric Oxide Autoxidation Mechanism
Using Quantum Chemistry Methods
Yazen Abusad
Engaged Learning 2014 - Final Report
Mentor: Dr. Peng Tao**

Section 1. Introduction

Nitric oxide (NO) is a critical cell-signaling messenger in the immune, cardiovascular, and nervous systems. It is linked to several diseases, and due to its high reactivity, and toxicity as a free radical, NO possesses a controversial effect on cell viability. The S-nitrosylation of protein thiol groups is a key mechanism in NO redox signal transduction, and lends a mechanistic basis for NO as a cell regulator. Numerous experiments have shown that the rate-limiting step of S-nitrosylation is NO autoxidation, independent of thiol concentration. Due to the transient nature, and structural variety of reactive nitrogen species, very little is known about the mechanisms of either NO autoxidation or S-nitrosylation.

1.1 My project goal

The goal of this study is to use quantum chemistry methods to calculate the reaction mechanisms of the NO autoxidation process to answer some fundamental mechanistic questions of NO cell signaling function. This research will impact cell biology, and make significant contributions to biomedical research and pharmaceutical development.

Section 2. Materials and Methods

2.1 Gaussian

Gaussian 09, which is the latest in the Gaussian series of programs, provides state-of-the-art capabilities for electronic structure modeling. This program also contains every scientific/modeling feature, and does not impose any artificial limitations on calculations other than computing resources and patience. In regards to this project Gaussian is used mainly for calculating the structures, and properties of different molecules.

2.2 SMU High-Performance Computing Facilities

The Center for Scientific Computation provides the main resource for scientific computing collaboration. Membership of the CSC provides access to the large-scale SMU computing cluster. All calculations are submitted through Gaussian, and the SMU computing cluster.

Section 3. Discussion

While working on my project, I analyzed some of the calculations submitted in a recently published article by the Goddard Research group from the California Institute of Technology. What I learned is that dinitrogen tetroxide (N_2O_4) is a reactive species, and possesses what is known as a multi-reference characteristic. This is important, and is something that needs to be taken into consideration when applying computational methods to the overall system. The Goddard group used

several methods none being perfectly consistent with one another. However, they did propose the working method to be the one involving GVB-RCI/cc-pVDZ. The issue with this method is that it can be very expensive when applied to larger systems. Therefore, we are looking for a more affordable alternative that will give us similar results.

3.1 Broken Symmetry

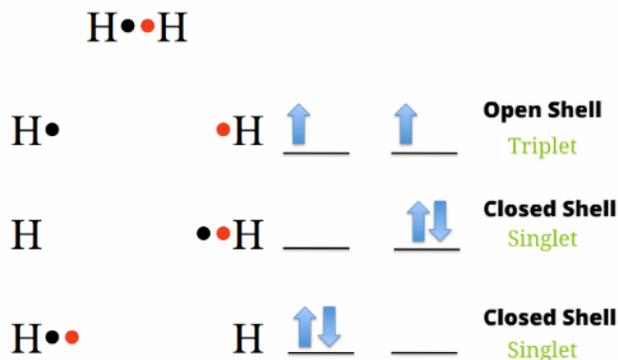
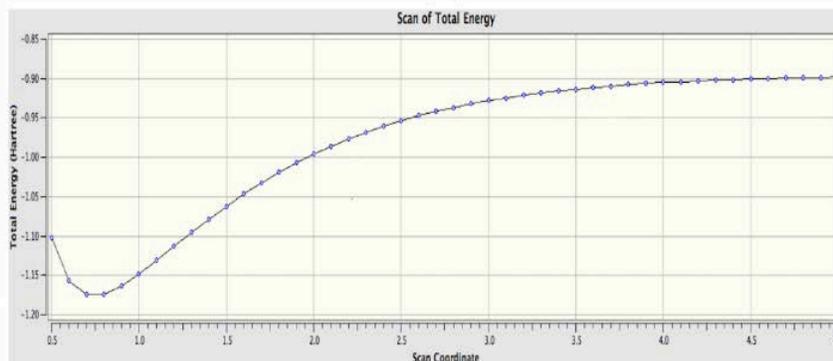


Figure 1: H-H dissociation leads to one of three distinct cases. In the first case each hydrogen atom has one electron, which leads to an open shell or triplet multiplicity. In the bottom two cases both electrons end up on a single hydrogen atom, which leads to a closed shell or singlet multiplicity. The singlet state is higher in energy due to a highly unfavorable separation of charge.

After working with symmetric N₂O₄, I discovered that as the N--N atoms are closer together a pair of electrons is coupled. However, as the distance between the N--N atoms increases the electrons are no longer paired. This is what computational chemists refer to as broken symmetry. To further investigate the details behind this intriguing concept I choose to experiment with hydrogen (H₂). The reason for working with H₂ is because it is a simple molecule that is fast and easy to work with when performing calculations. As the H-H bond dissociates the electrons separate in one of three ways. In one scenario, each of the individual hydrogen atoms contains a single electron in its valence shell resulting in a system characterized with an overall open shell, and triplet multiplicity. In the latter two scenarios, both electrons occupy the valence shell of a single hydrogen atom leading to an overall closed shell, and singlet multiplicity. This also generates a separation of charge due to H⁺ and H⁻ ions. And gives a more unfavorable state than in the former scenario. Which one of these cases would you expect to be higher in energy? I predicted the singlet state to be higher in energy simply because it would require more energy to keep the ions from attracting with one another. Furthermore, in the triplet state both hydrogen atoms are neutral or in stable forms, and this corresponds to lower energy.

**RB3LYP/6-31G
Singlet**



**UB3LYP/6-31G
Singlet**

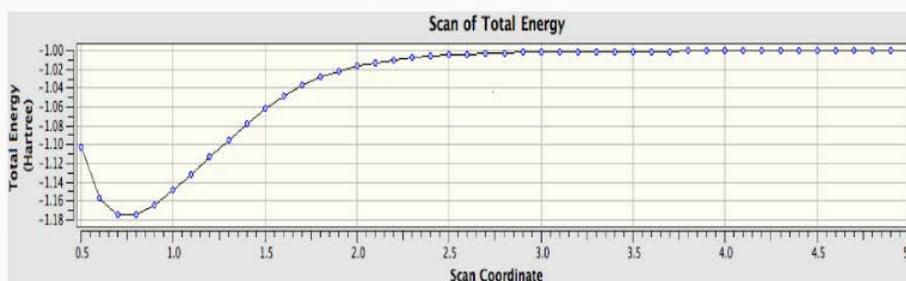


Figure 2: The first curve represents a restricted density functional theory (DFT) with purely the singlet state occurring. The second curve represents an unrestricted DFT with both the singlet and triplet states occurring simultaneously. The first curve gives an energy value of -0.90 hartree, which is greater than energy value of -1.00 obtained for the unrestricted DFT.

To address the energy question of which state is higher in energy I implemented two specific calculations with H_2 , and plotted the results. For the first calculation I used a RB3LYP/6-31G density functional theory (DFT), and for the second calculation I used a UB3LYP/6-31G DFT. The difference between these two density functional theories is that one corresponds to a restricted closed shell, and the other corresponds to an unrestricted open shell. Clearly, the restricted closed shell represents the singlet state whereas the unrestricted open shell represents the triplet state. According to my results, the RB3LYP DFT produced an energy value of -0.90 hartree (-564.8 kcal/mol), and the UB3LYP DFT produced a value of -1.00 hartree (-627.5 kcal/mol). This proves to us that our hypothesis was correct, and indeed the singlet state is greater in energy than the triplet state.

3.2 Spin Contamination

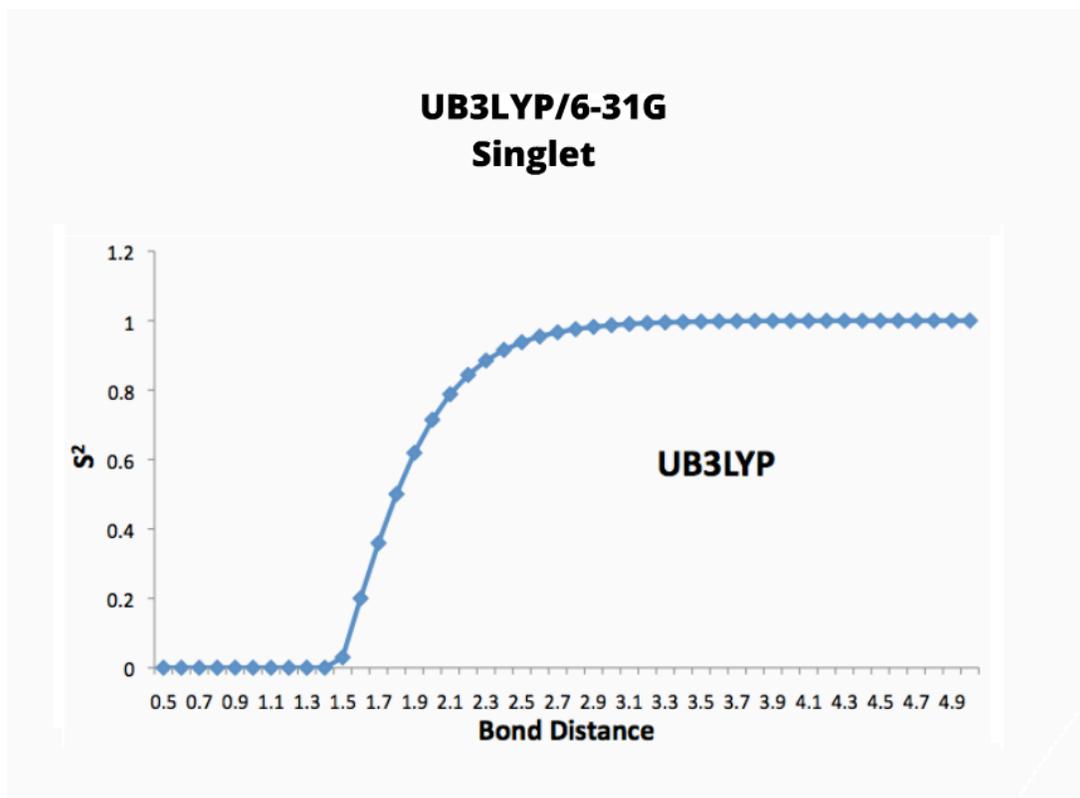


Figure 3: This diagram shows correlation between S^2 values and bond distance of the unrestricted open shell (UB3LYP) DFT with singlet state specificity. Because the curve deviates at 1.5 Angstroms, and levels out with S^2 values of 1 we see that the system experiences spin contamination.

After performing calculations, I further analyzed the UB3LYP DFT, and generated a plot to illustrate the S^2 values vs. bond distance. This helped me realize that the system experiences spin contamination. Spin contamination is the terminology used to describe systems with artificial mixing of different electron spin states. The eigenvalues of S^2 are $S(S+1)$ where S can take the values 0 (singlet), 1 (triplet), and so forth. The letter S in this case simply denotes spin. As the two hydrogen atoms are closer together (small bond distance), we would expect to see S^2 values of 0 indicating the singlet state. As the hydrogen atoms grow apart from each other (large bond distance), we would expect to see S^2 values of 2 indicating the triplet state. However, because the curve deviates at about 1.5 Angstroms, and eventually levels out to give S^2 values of 1 we automatically can see that the system experiences spin contamination. This means that both the singlet and triplet states are occurring simultaneously. The average of 0 and 2 is 1, and this explains why the curve levels out at this S^2 value.

Section 4. Project Results

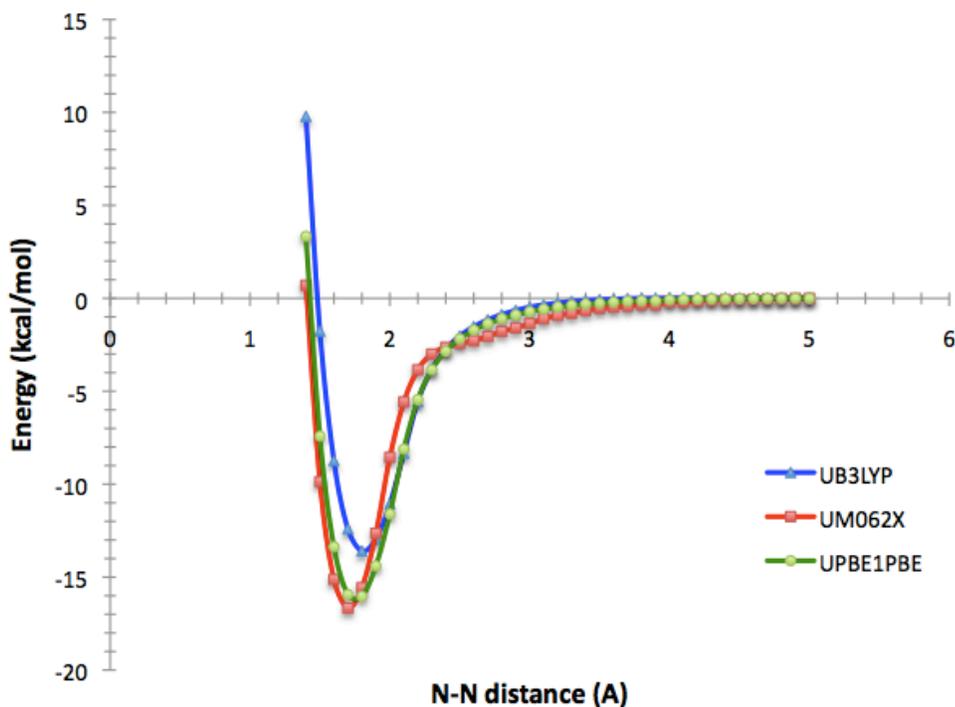


Figure 4

With my new acquired knowledge about broken symmetry, and spin contamination I tested two relatively new density functional theories with symmetric N_2O_4 . The first DFT is M06-2X, which is a global hybrid functional. The second is PBE1PBE, which is a global functional. After performing both calculations I plotted the results, and analyzed the curves. Because both curves are steeper than the curve for UB3LYP we automatically conclude that both of the newly tested methods are unreliable. Ideally, we are looking for a DFT that will give us a shallower curve than UB3LYP.

Section 5. Conclusion

The results of my Engaged Learning project can hopefully lead to the development of a more informative and efficient future for the mechanism behind nitric oxide autoxidation. The outcome of this project constitutes a positive contribution to larger global pharmaceutical development, biomedical research, and cell biology.

Section 6. References

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