Computational Chemistry of the Pseudomonic and Monic Acids

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Introduction

The drug Mupirocin has shown positive effects against both Gram-negative and Gram-positive bacteria with varying levels of success. It has been shown to be effective against Methicillin-Resistant Staphylococcus Aureas (MRSA) as a topical treatment in high concentrations. Further research into the structure and electrostatic potentials of the monic acids will allow for greater understanding of these mechanisms through which this compound works. Mupirocin is comprised of pseudomonic acids. The monic acids are structurally similar to the pseudomonic acids and thus function as an effective model compound to better understand the chemical characteristics of the drug. This work presents results of DFT (B3LYP) calculations with an accurate basis set on monic acid A and related species with focus on optimal geometries, IR and Raman spectra and electrostatic potentials to identify the differences between the monic and pseudomonic acids with an eye towards potential antibacterial treatments.

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Materials and methods

All theoretical calculations reported here were obtained using Gaussian 09 Rev C.01 optimized for SSE4-enabled AMD64 processors on a Linux box with 2 AMD Opteron 6136 chips under Red Hat 6.3. DFT calculations used the B3LYP functional, with the basis set 6-311+G(d,p) being the most efficient in terms of time cost versus accuracy. Under these parameters Geometry Optimization, Vibrational Frequency, and Molecular Orbital calculations were performed. Both gas phase and aqueous phase calculations were performed. With this basis, DFT (B3LYP) vibrational frequencies were scaled by a factor of 0.9688 (J. Merrick et al.).

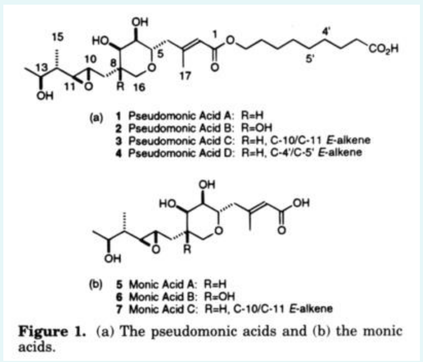

Figure 1: The Monic Acids. The pseudomonic acids have a fatty acid chain coming off of the ester group in the molecule. Pseudomonic acids C and D, as well as monic acid D, replace the epoxide group with an alkene.

Results

We present the results of DFT(B3LYP) calculations on of the Monic Acids using an accurate basis set, including a report of optimized geometries, electrostatic potentials, and calculated IR and Raman spectra.

Optimized Geometries

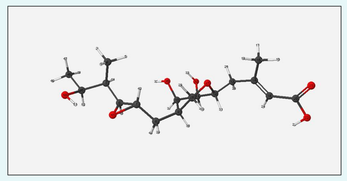

Figure 2: Monic Acid A

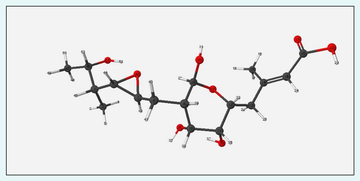

Figure 3: Monic Acid B

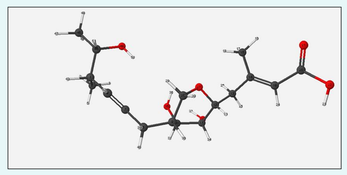

Figure 4: Monic Acid C

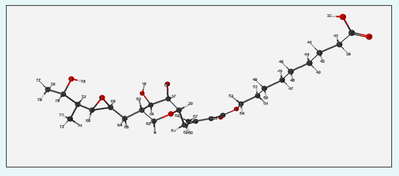

Figure 5: Pseudomonic Acid A

Molecular Orbitals

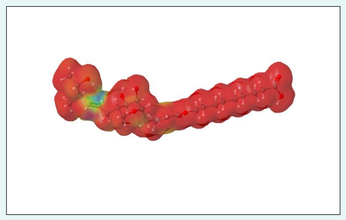

Figure 6: Highest Occupied Molecular Orbital (HOMO) for Pseudomonic Acid C

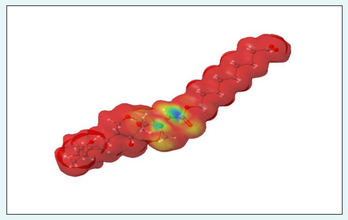

Figure 7: Lowest Unoccupied Molecular Orbital (LUMO) for Pseudomonic Acid C

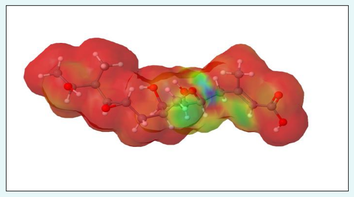

Figure 8: Highest Occupied Molecular Orbital (HOMO) for Monic Acid A

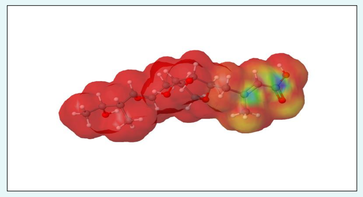

Figure 9: Lowest Unoccupied Molecular Orbital (LUMO) for Monic Acid A

IR and Raman

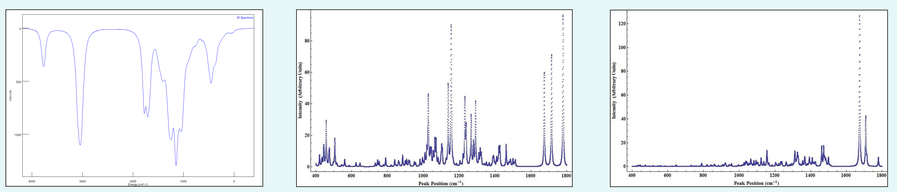

Figure 9: From Left to Right: IR Transmittance Spectra, IR Absorbance Spectra and Raman Spectra of Pseudomonic Acid A

Conclusions

This research is a starting point for further research into the monic acids. Pseudomonic acid was brought to our attention as an ACS molecule of thew eek last spring. This project was undertaken with almost no information in the literature about the structure and function of pseudomonic acid with regards to its effectiveness as an antibacterial agent. Theoretical molecular orbital calculations and the resulting structures provide a starting point towards understanding the mechanism of any chemical interaction. This will prove useful in further investigation of the interactions between the components of mupirocin and bacterial compounds. Prior research has indicated that mupirocin inhibits bacterial isolecuyl tRNA synthetase (Class and DeShong). Future work will investigate the interactions between the monic acids and various solvents to deduce the most effective drug delivery system

References

Merrick, J. P., Moran, D., & Radom, L. (2007). An evaluation of harmonic vibrational frequency scale factors. *The journal of physical chemistry. A*, *111*(45), 11683–700.

Class, Y. J., & DeShong, P. (1995). The Pseudomonic Acids. *Chemical Reviews*, *95*(6), 1843–1857. doi:10.1021/cr00038a005

Acknowledgments

Dr. Liz Atkison

Kevin Romero

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