

THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DIVISION OF SCIENCE

THE MOLECULAR MODELING AND CHARACTERIZATION OF ACETAMINOPHEN
USING SPARTAN 5.0 COMPUTATIONAL SOFTWARE

KAYLA JARDINE
SPRING 2015

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Biology
with honors in Biology

Reviewed and approved* by the following:

Lorena Tribe
Associate Professor of Chemistry
Thesis Supervisor

Sandy Feinstein
Associate Professor of English
Honors Adviser

* Signatures are on file in the Schreyer Honors College.

ABSTRACT

In the past few decades, computational chemistry has emerged as a research tool in the pharmaceutical industry. Computational chemistry can be used to model the structure of individual molecules and predict chemical properties, which can be used in the process of drug design. In addition to its predictive capabilities, computational chemistry can also be used to validate experimental results. This research focuses on the use of computational chemistry to characterize and model acetaminophen following an experimental synthesis. Acetaminophen was synthesized in the laboratory and analyzed using Infrared Spectroscopy. Then, the products and reactants of the synthesis were modeled using the Spartan 5.0 software and calculated spectra were obtained for various EDF2 potentials. The calculated spectra converged with the experimental gas phase IR spectra interfaced in the Spartan software. The calculated spectra for acetaminophen were also consistent with IR absorption ranges found in the literature.

TABLE OF CONTENTS

LIST OF FIGURES	iii
LIST OF TABLES	iv
ACKNOWLEDGMENTS	v
Chapter 1 Introduction	1
Background	1
Goals and Objectives.....	6
Synthesis of Acetaminophen.....	7
Structures and Molecular Models	8
Significance of Research.....	11
Chapter 2 Materials and Methods	13
Chapter 3 Results	17
Chapter 4 Discussion	25
Conclusion	30
BIBLIOGRAPHY	31

LIST OF FIGURES

Figure 1. Reactants and products for the synthesis of acetaminophen.....	7
Figure 2. The organic structure of acetaminophen.....	8
Figure 3. A molecular model of the acetaminophen molecule generated using Spartan 5.0 computational software	8
Figure 4. Molecular actions within a molecule that can be demonstrated by computational software.....	9
Figure 5. Molecular models of reactants and products of the acetaminophen synthesis generated by the Spartan 5.0 software.....	15
Figure 6. P-aminophenol IR spectrum.....	17
Figure 7. Acetaminophen standard IR spectrum.....	18
Figure 8. Synthesized acetaminophen IR spectrum	18
Figure 9. Screenshot of Spartan software calculation.....	19
Figure 10. Linear regression of the experimental and calculated IR spectra for acetic anhydride generated by Spartan software	21
Figure 11. Linear regression of the calculated and experimental IR spectra for acetic acid generated by Spartan software	22
Figure 12. Linear regression of the calculated and experimental IR spectra for p-aminophenol generated by Spartan software	23
Figure 13. Linear regression of the calculated and experimental IR spectra for acetaminophen generated by Spartan software	24
Figure 14. Organic structures of p-aminophenol and acetaminophen	26

LIST OF TABLES

Table 1. The mass of the acetaminophen standard, synthesized acetaminophen samples, and KBr used to run IR spectra.....	14
Table 2. IR shift frequency values for reactants and products of acetaminophen synthesis reaction generated by Spartan software	20
Table 3. IR absorption peak ranges based on functional group	27

ACKNOWLEDGMENTS

I would like to thank Dr. Sandy Feinstein for her feedback and constructive criticism during the composition of my thesis. Her persistence and support has kept me focused throughout this process. I would also like to thank Dr. Lorena Tribe for her mentorship throughout my academic career at Penn State Berks and for allowing me to conduct this research project in her lab. With her guidance and teachings, I was able to explore my interest in computational chemistry. Last but not least, I would like to thank my friends and family who have supported me during my academic career at Penn State Berks.

Chapter 1

Introduction

Background

Acetaminophen

Acetaminophen, also known as paracetamol in the United Kingdom, is an active ingredient used in many pain-relieving pharmaceutical preparations. It is considered an antipyretic because of its fever-reducing capabilities and is classified as an analgesic due to its ability to reduce pain. Due to its limited side effects when consumed in recommended doses, acetaminophen is a widely used analgesic. When prescribed by a doctor, acetaminophen may be administered in therapeutic doses to most individuals, including: elderly patients, children, and pregnant women¹. However, overdoses of acetaminophen can be toxic and result in severe liver damage.

Acetaminophen was introduced to the medical community in England in 1893, but was sparingly used as an antipyretic². In 1949, it was determined that acetaminophen was the active metabolite of two established antipyretic drugs: acetanilide and phenacetin^{3,4}. After this discovery, acetaminophen became a popular antipyretic in the United Kingdom, but failed to gain popularity in the United States until the mid 1950's. In 1955, McNeil Laboratories marketed acetaminophen under the name Tylenol, which is now one of the best-selling analgesics on the market.

Even though acetaminophen has been a widely used analgesic since the early 1950's, its exact mechanism of action is still poorly understood⁵. As a result, acetaminophen continues to be

studied in the pharmaceutical industry in order to better understand the biochemical interactions that produce its pharmacological effect. This process is referred to as the pharmacological mechanism of action.

In addition, acetaminophen is used in the pharmaceutical industry to study the efficiency of various analytical methods such as FT-IR spectroscopy and Raman spectroscopy to determine qualitative purity and quantitative quality of manufactured tablets. Quantitative quality refers to the measurement of the amount of acetaminophen present in each tablet compared to the quantity listed by the manufacturer. Qualitative purity refers to the presence of acetaminophen and absence of contaminants present in manufactured tablets.

Acetaminophen Research

The areas of acetaminophen research vary greatly, with topics ranging from pharmacological action to quality control assessment. Acetaminophen is still actively studied in the pharmaceutical industry. Previous studies have indicated that acetaminophen's antipyretic activity results from its inhibition of prostaglandins, especially in the brain^{6,7}. Further elucidation of acetaminophen's action has indicated that the COX gene is involved in the antipyretic activity of acetaminophen. It appears that acetaminophen inhibits prostaglandins by competing for the active site on the COX gene⁸.

Aside from studying the mechanism of action, current research in the pharmaceutical industry aims to measure both qualitative and quantitative quality of commercially manufactured tablets. Unfortunately, current techniques used for qualitative determination and quality control assessment, such as chromatography, are both costly and time-consuming. As a result, more cost-effective and time-efficient methods of analysis, such as Raman spectroscopy, Infrared (IR)

spectroscopy, and Nuclear Magnetic Resonance (NMR) spectroscopy have recently been explored to identify other possible techniques for quantitative and qualitative determination. Previous studies have indicated that Raman spectroscopy and FT-IR spectroscopy can provide an effective method of qualitative determination when assessing acetaminophen concentration in pharmaceutical tablets^{9,10}.

Recent research has indicated that Raman spectroscopy is an adequate method of quantitative quality control for commercial formulations. A study compared experimental quantitative values to the values assigned by the manufacturer of the drug¹¹. With Raman spectroscopy, a discrepancy of 2.5% was found between the experimental quantitative values and the quantitative amount assigned by the manufacturer, which indicated that Raman spectroscopy was a sufficient method of quality control assessment¹¹.

Computational Chemistry

Another area of pharmaceutical research is drug development, specifically structure and ligand based drug design¹². Structure and ligand based drug design uses information about a specific biological target within the body—known as the ligand—to develop a drug that contains the appropriate structure to bind to the ligand. Possible structures and biochemical interactions for a novel drug can be predicted using computational chemistry.

Computational chemistry refers to a relatively new research field that utilizes software to provide models of chemical molecules as well as predict chemical outcomes. The possible chemical properties that can be predicted using computational chemistry include: molecular geometry, energies of molecules, transition states, chemical reactivity, and analytical spectra. The computational approach has become increasingly popular in the last decade as a result of the

advancement of computers. Computational software can be used to validate experimental results based on fundamental processes, but it can also be used as a predictive method for future studies¹³.

A portion of pharmaceutical research is shifting toward theoretical modeling in order to save money on costly lab experiments¹⁴. By using computational chemistry, predictions about the solubility and reactivity of a new drug can be made without conducting wet laboratory experiments. In addition, computational software allows researchers to perform calculations from experimental data that help to determine the most stable crystalline structure and can be used to complement other analytical methods^{13,15}. Therefore, computational chemistry can be a useful resource in drug design based on its capabilities to model chemical reactions and predict chemical properties¹⁶.

The two main areas of atomic level computational calculations in chemistry are molecular modeling and quantum mechanics. Both areas can be used to calculate the intermolecular forces that occur between molecules. Intermolecular forces are molecular interactions that can either cause the molecules to repel or attract. These forces include ion-dipole interactions, hydrogen bonding, dipole-dipole interactions, and van der Waals forces. Computational software can help predict these intermolecular forces through parameterization or by using the principles of quantum mechanics¹⁷.

Typically, molecular structures and energies are well represented by molecular mechanics. Molecular mechanics tends to focus on the motions of the nuclei rather than the electrons. By focusing on the motion of the nuclei, the electrons are not explicitly studied at all, assuming they are optimally distributed around the nuclei¹⁷. Therefore, molecular mechanics calculations, or force field calculations, focus on the structure of the molecule rather than the

electronic or spectroscopic properties. One of the most widely used force fields in molecular mechanics is the MMFF potential, which can be especially useful in the study of small molecules, specifically those molecules that are relevant to drugs¹⁸.

In computational chemistry, one of the more advanced techniques for calculating molecular structure is the density functional theory (DFT). This technique focuses on the electron density to calculate the electronic structure of a molecule. These calculations can be used to interpret the behavior of complex systems¹⁷.

Another significant aspect of DFT is the ability to represent molecular orbitals and electron densities. Stylized shapes and colors can be used to indicate the varying electron densities within a molecule. These properties are combined to develop an isodensity surface—a surface of constant total electron density—that is represented graphically by computational software. The isodensity surface can also be used to calculate the electrostatic potential surface, which depicts the distribution in charge over the molecule's surface. This property helps to identify regions in a molecule that may be susceptible to electron attack based on the electron density of the region. This behavior is important when analyzing the pharmacological action of potential drugs¹⁷.

In addition, computational chemistry can be utilized to predict thermodynamic and spectroscopic properties. Computational chemistry can be used to estimate standard enthalpies of formation for molecules with complex three-dimensional structures. Computational methods also allow a scientist to study the effect of solvation on the enthalpy of formation without actually conducting experiments in the laboratory. The ability to predict as much information about the molecule as possible without entering the laboratory can prevent a costly trial and error experimental period, which can ultimately lead to a faster and cheaper drug discovery process¹⁷.

Goals and Objectives

The goal of my research was to synthesize acetaminophen, characterize the product using computational software, and compare the synthesized product to an acetaminophen standard through spectroscopy. The synthetic route used for this experiment was a combination of p-aminophenol and acetic anhydride. My research involved implementing the technique of characterization, which goes beyond the conventional measure of purity such as melting point and introduces the synergy of experimentally obtained IR spectra with computationally generated vibrational frequencies.

Originally, Raman Spectroscopy was to be used in addition to Infrared Spectroscopy to analyze the synthesized acetaminophen. However, Raman Spectroscopy was unavailable. The addition of the Raman component would have been beneficial to the research because it would have provided more insight into the theoretically calculated spectra. In the spectra calculated by the Spartan 5.0 computational software, Infrared Spectroscopy and Raman Spectroscopy are shown in conjunction, since their wavelengths are so similar. Therefore, experimental data for both Raman Spectroscopy and Infrared Spectroscopy would allow a more thorough comparison of the calculated spectra and the experimental spectra to characterize the product.

Synthesis of Acetaminophen

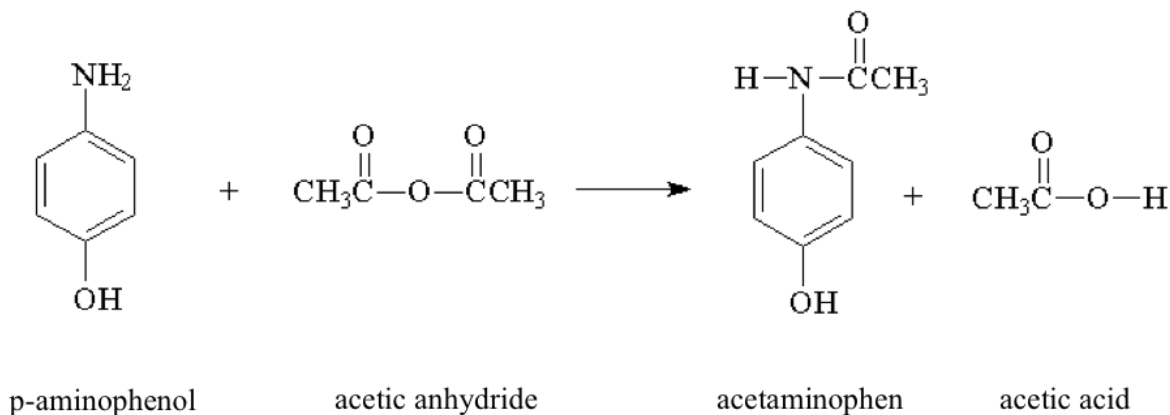


Figure 1. Reactants and products for the synthesis of acetaminophen

The synthesis of acetaminophen has been well studied^{19,20}, and therefore, the focus of this research was not to develop a novel synthesis of acetaminophen. The protocol used for this research is available in the literature²¹. The synthetic route used in this research was the addition of p-aminophenol and acetic anhydride. The products of the reaction are acetaminophen and acetic acid. Figure 1 shows the organic structures for the reactants and products of the acetaminophen synthesis reaction. Upon completion of the reaction, determination of the desired product can be analyzed using melting point and spectroscopic techniques. Indication of impurities can be seen in an experimental melting point that varies from the literature value of the melting point of acetaminophen, 169 °C²². Qualitative determination of the product can also be analyzed by comparing the IR spectrum of the synthesized product to the IR spectrum of an acetaminophen standard.

Structures and Molecular Models

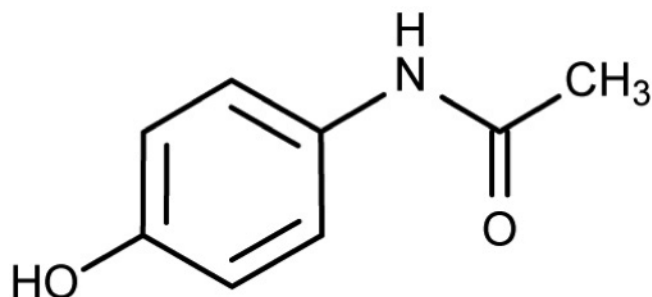


Figure 2. The organic structure of acetaminophen

Acetaminophen is an aromatic compound that includes a hydroxyl functional group as well as an amide. Figure 2 shows the organic structure of the acetaminophen molecule. Certain characteristics of the molecule's reactivity can be predicted based on the functional groups of the organic structure. However, the organic structure can sometimes be complex, making it difficult to visualize the vibrations of a molecule. One of the advantages of computational chemistry is the ability to model a molecule in its most stable form.

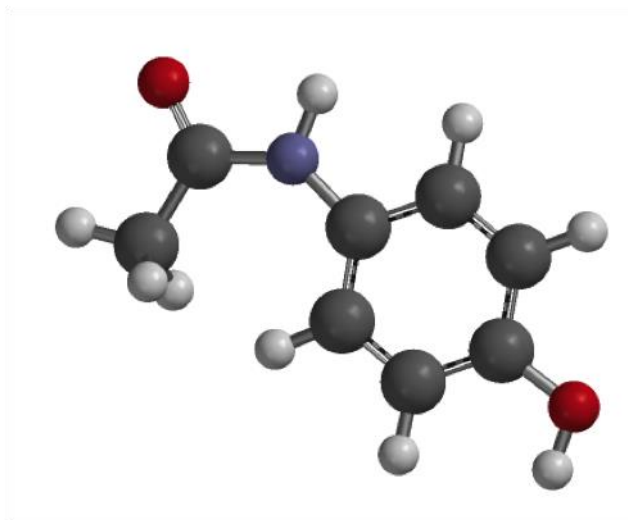


Figure 3. A molecular model of the acetaminophen molecule generated using Spartan 5.0 computational software

Figure 3 exhibits the molecular model of acetaminophen generated from the Spartan 5.0 software. The model was built based on the organic structure depicted in Figure 2. The dark grey spheres represent carbon atoms, the red spheres represent oxygen, the blue sphere represents nitrogen, and the remaining white spheres represent hydrogen atoms. The model has been energy minimized in order to show acetaminophen in its most stable state. In addition to generating models, such as the one shown above, Spartan provides visualization of the vibrational modes that occur between each atom at varying frequencies.

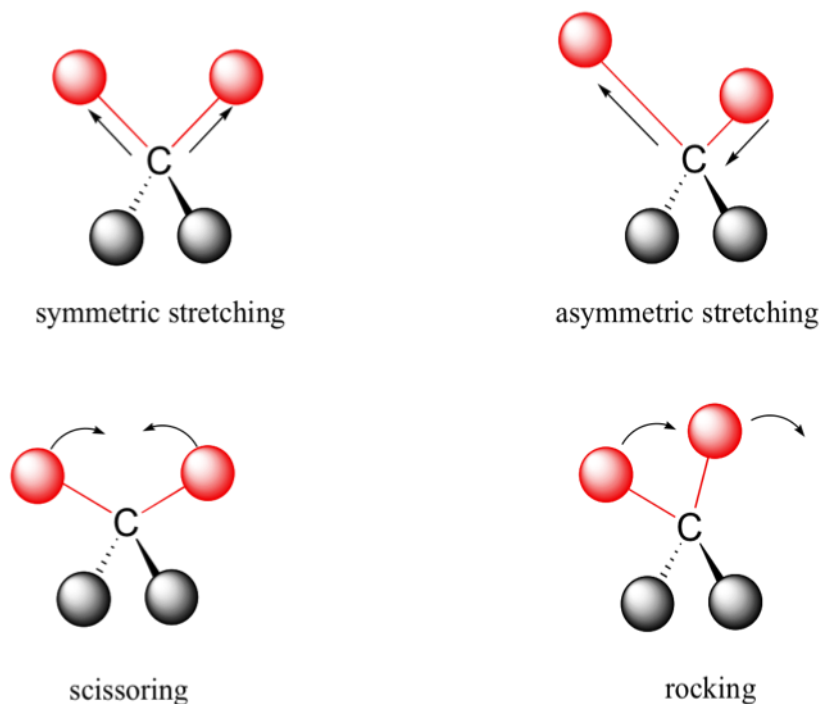


Figure 4. Molecular actions within a molecule that can be demonstrated by computational software

Figure 4 displays the different molecular actions that can be demonstrated by the Spartan software. The action labeled scissoring on the diagram can also be referred to as a “bend.” Also, stretching may occur in the absence of symmetry, in which case it cannot be labeled as either

symmetric or asymmetric. Each peak present in an IR spectrum corresponds to one of the vibrational actions shown above. Computational software models these vibrational actions that occur at each peak. For example, a peak that appears at 3484 cm^{-1} on an IR spectrum may correspond to an N-H stretch that can be modeled using computational software.

Significance of Research

As computational chemistry continues to emerge as a useful technique in the scientific community, an introductory study using computational methods to enhance the comprehension of the obtained product offers a potential advancement from previous techniques used in chemistry to analyze experimental products. In the absence of computational chemistry, acetaminophen can only be determined by experimental measures such as melting point and analytical techniques such as spectroscopy. With the use of computational chemistry, experimental results can be validated through the modeling of the molecular interactions of acetaminophen, and the experimental product can be characterized based on the combination of experimental data and computational methods.

In previous studies, the presence of acetaminophen was analyzed using FT-IR spectroscopy⁹ and Raman spectroscopy¹⁰, and the purity of acetaminophen was determined using melting point²³. Other studies have implemented computational chemistry to predict or validate experimental results²⁴. However, the combination of experimental analysis and computational software to characterize acetaminophen has not yet been explored.

In addition, computational chemistry can be utilized as a diagnostic resource in chemistry laboratory courses. Introducing computational chemistry in the undergraduate laboratory setting can improve comprehension of molecular-level phenomenon through visualization^{25,26} and provide an example of how computational chemistry can be utilized in industry. As the pharmaceutical industry continues to shift toward the use of theoretical modeling and

computational chemistry, the use of computational chemistry in a laboratory setting can offer students useful skills that can later be employed in graduate school and industry.

Chapter 2

Materials and Methods

Synthesis

Acetaminophen was synthesized according to Katz's method²¹ by adding p-aminophenol, water, and phosphoric acid to an Erlenmeyer flask. The flask was placed in warm water for 10 minutes. Then, the flask was transferred to an ice bath for 30 minutes to form crystals. The crystals were recovered using a filtration apparatus and allowed to dry. Once the crystals had dried, both the crude acetaminophen and water were added to a beaker, and the solution was heated. The beaker was then placed in an ice bath for 20 minutes to allow crystals to reform. The purified acetaminophen was collected using a filtration apparatus and the crystals were allowed to dry. The synthesis was conducted twice in order to compare results.

Analysis

An IR spectrum for the synthesized acetaminophen was measured. The samples were ground and mixed with KBr in a 1:100 ratio in order to run the IR. A KBr "blank" was also used to run the IR. Table 1 contains the mass values for the samples and KBr used to run each IR. An IR spectrum for an analytical grade acetaminophen standard was also measured for comparison.

Table 1. The mass of the acetaminophen standard, synthesized acetaminophen samples, and KBr used to run IR spectra

Sample	Sample Mass (g)	KBr Mass (g)
Blank	—	0.3175
Acetaminophen Standard	0.0286	0.3086
Synthesized Acetaminophen Trial #1	0.0307	0.3340
Synthesized Acetaminophen Trial #2	0.0265	0.3186

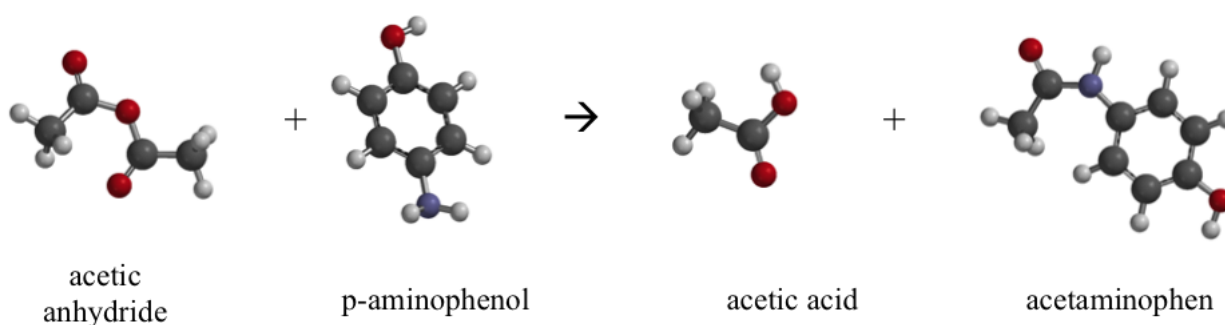


Figure 5. Molecular models of reactants and products of the acetaminophen synthesis generated by the Spartan 5.0 software

Spartan 5.0 software was used to model the products and the reactants for the synthesis of acetaminophen. Figure 5 shows the reactants and products generated by the Spartan software. Each molecule was built by choosing the appropriate atoms, fragments, and hybridizations. These molecular components were chosen from the “build” menu of the software package. The molecules were energy minimized with molecular mechanics using the MMFF potentials²⁷. The infrared vibrational frequencies were then determined with full electronic structure calculations using Density Functional Theory^{28,29} with the EDF2 potentials³⁰ at the 6-31G* level³¹. A theoretical IR spectrum was calculated for each reactant and product. The theoretical IR spectrum for acetaminophen was compared to the IR spectrum for the experimentally synthesized acetaminophen and analytical acetaminophen standard.

A second set of calculations was run for acetic acid and acetic anhydride with the EDF2 potentials at the 6-311++G** level³¹. A calculated spectra was attempted for the acetaminophen and p-aminophenol for the 6-311++G** potential but the calculation could not be completed due

to a limitation in the calculating capabilities of the computers available during the time of the research. It is possible that the calculations could be performed using a more advanced computer system, but no such system was available during this research. For this reason, a 6-311G** potential³¹ and 6-311+G** potential³¹ were used for p-aminophenol and a 6-311+G** potential was used for acetaminophen.

Spartan software also interfaces the NIST Chemistry WebBook to provide experimental IR spectra in the software package. The calculated spectra for the two different theoretical potentials for each respective molecule were compared to the experimental IR Spectra available in Spartan using linear regression.

Chapter 3

Results

Experimental IR Spectra and Boiling Point

The IR spectra of the synthesized acetaminophen, an acetaminophen standard, and p-aminophenol were obtained experimentally. Figure 6 shows the IR spectrum of p-aminophenol, Figure 7 shows the IR spectrum of the acetaminophen standard, and Figure 8 shows the IR spectrum of the experimentally synthesized acetaminophen. The boiling point for the synthesized acetaminophen was 165 °C, which was close to the literature value of 169 °C²².

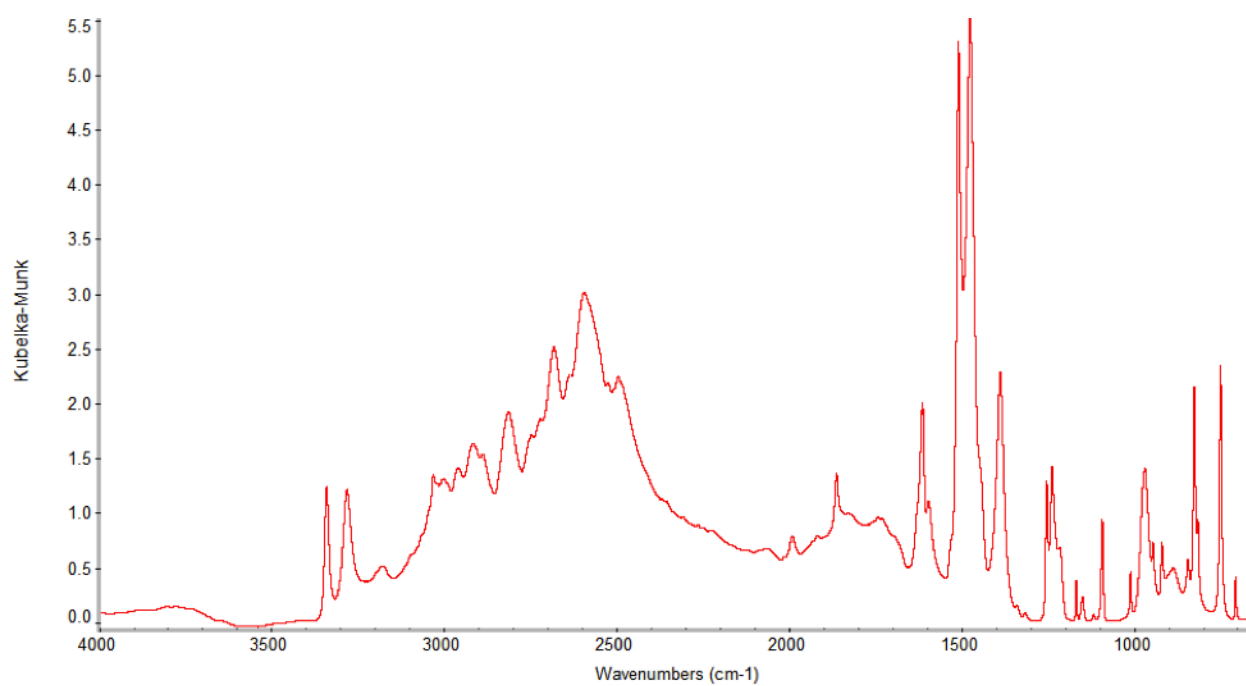


Figure 6. P-aminophenol IR spectrum

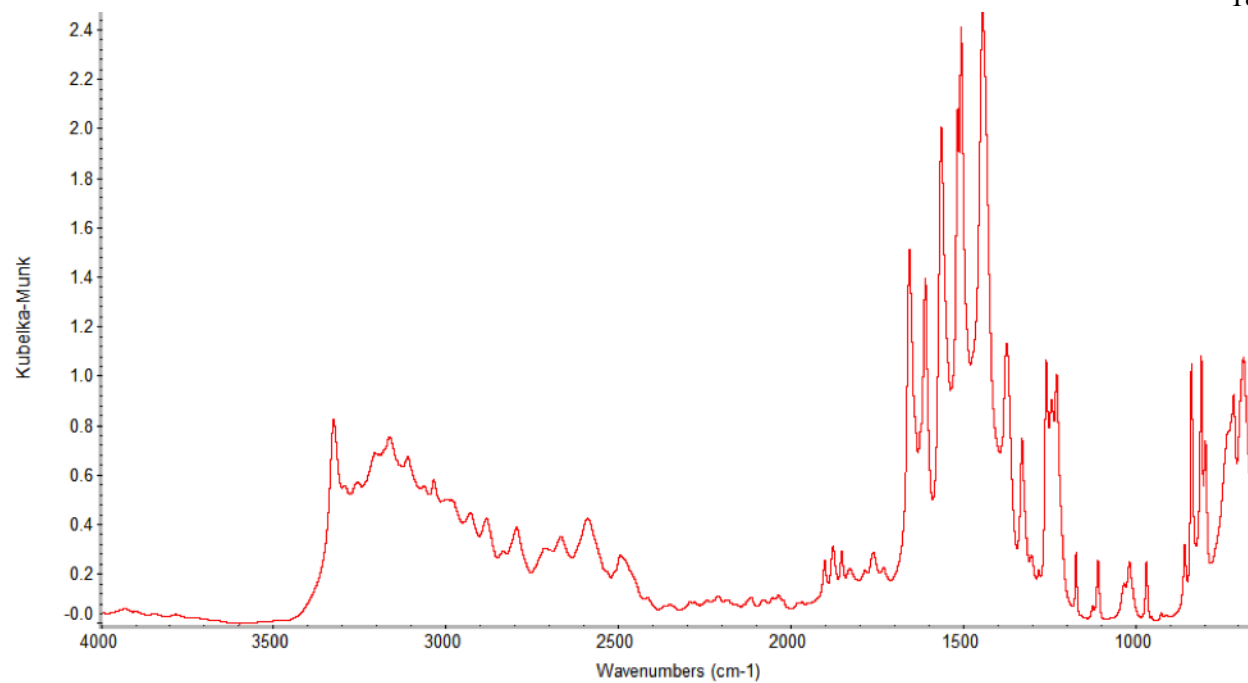


Figure 7. Acetaminophen standard IR spectrum

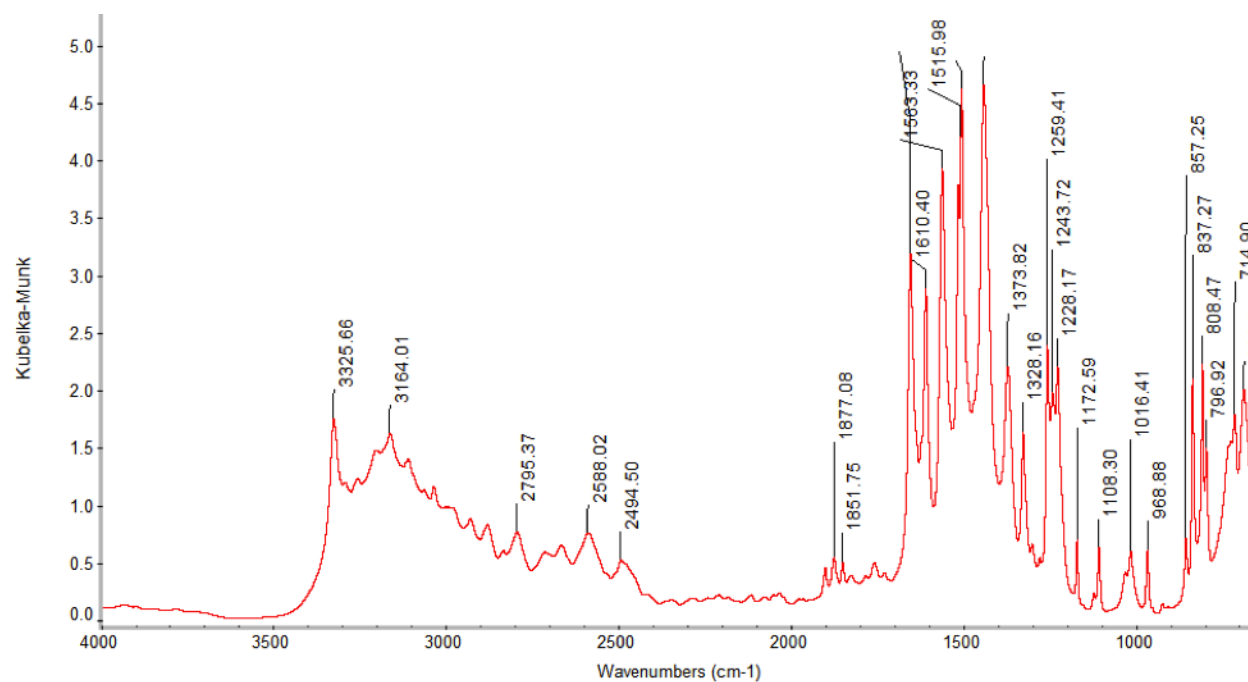


Figure 8. Synthesized acetaminophen IR spectrum

Theoretical Calculations

Following each calculation using the Spartan 5.0 software, an IR spectrum was generated, as well as a list of the corresponding peak for the calculated spectrum. Figure 9 shows a screenshot of the output of the calculation performed. The list of peaks corresponding to the IR spectrum is shown on the right. The predicted motion of the molecule was displayed using the molecular model on the left side of the screen. A calculated spectrum was generated for all of the reactants and products of the acetaminophen synthesis. The most notable peaks from each reactant and product are shown in Table 2. The molecular motion assigned to each peak is also shown in Table 2.

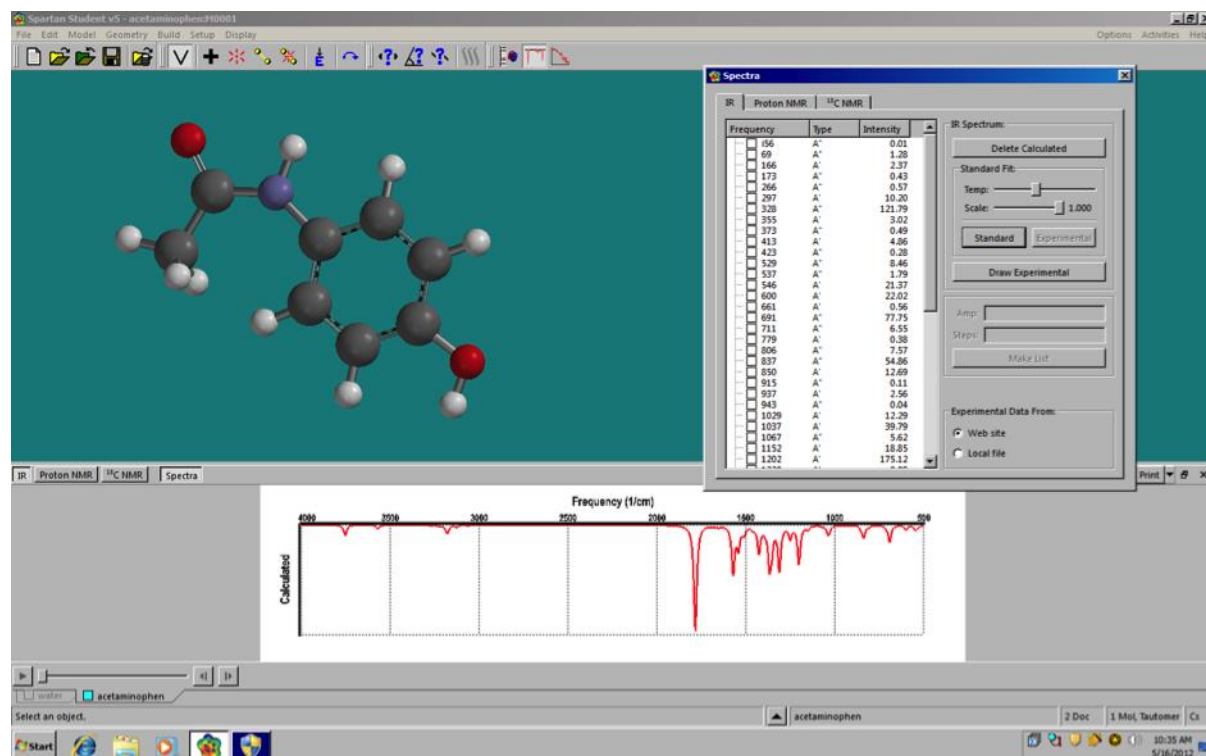


Figure 9. Screenshot of Spartan software calculation

Table 2. IR shift frequency values for reactants and products of acetaminophen synthesis reaction generated by Spartan software

P-aminophenol	Acetic anhydride	Acetaminophen	Acetic acid	Assignment
	757		838	C-O bend C-C-O stretch C-O stretch
	920			
1279	1210	1271	1179 1273	C-OH bend C-O stretch C-O stretch C-O-H stretch C-N Stretch
1516		1345 1511 1519		C-O-H bend C-N stretch C-N stretch N-C=O stretch
	1791 1826	1725	1831	C=O stretch C=O stretch C=O stretch C=O stretch
3412 3506 3633		3484 3624	3607	N-H stretch N-H stretch N-H stretch O-H stretch O-H stretch O-H stretch

Two different potentials were used to obtain calculated IR spectra for each of the reactants and products. These calculated IR spectra were compared to the experimental IR spectra interfaced in Spartan. Figure 10 shows the linear regressions used to compare the experimental and calculated values of acetic anhydride for two different potentials: 6-31G* and 6-311++G**. The R^2 value for the trend line corresponding to 6-31G* was 0.99385 and the R^2 value for the trend line corresponding to 6-311++G** was 0.99492. An ideal value for an R^2

value is 1.00. The R^2 value for the 6-31++G** trend line was slightly closer to 1.00 than the R^2 value for the 6-31G* trend line.

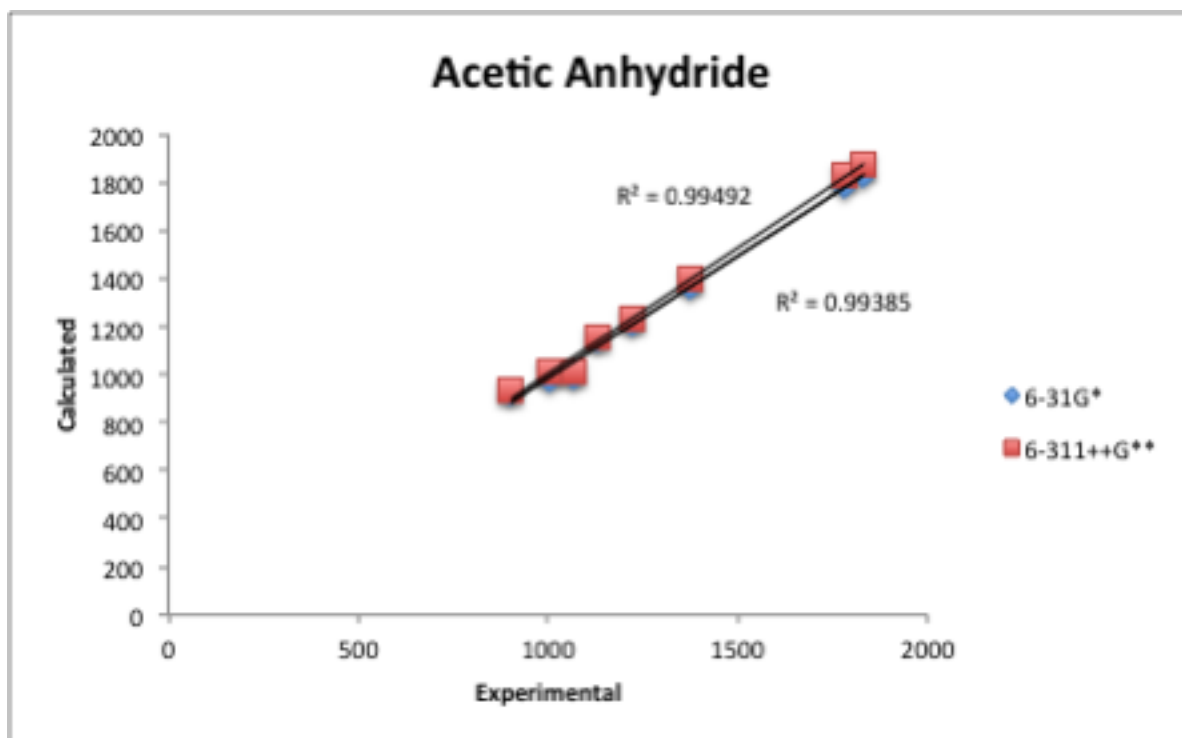


Figure 10. Linear regression of the experimental and calculated IR spectra for acetic anhydride generated by Spartan software

A linear regression was also calculated for acetic acid, which was a product of the synthesis. Figure 11 shows the linear regression comparison of the experimental and calculated Spartan values for acetic acid for two different potentials. The two potentials compared in the linear regression of acetic acid were 6-31G* and 6-311++G**. The R^2 value for the trend line corresponding to 6-31G* was 0.99545 and the R^2 value for the trend line corresponding to 6-31++G** was 0.99749. The R^2 value for the 6-31++G** trend line was slightly closer to 1.00 than the R^2 value for the 6-31G* trend line.

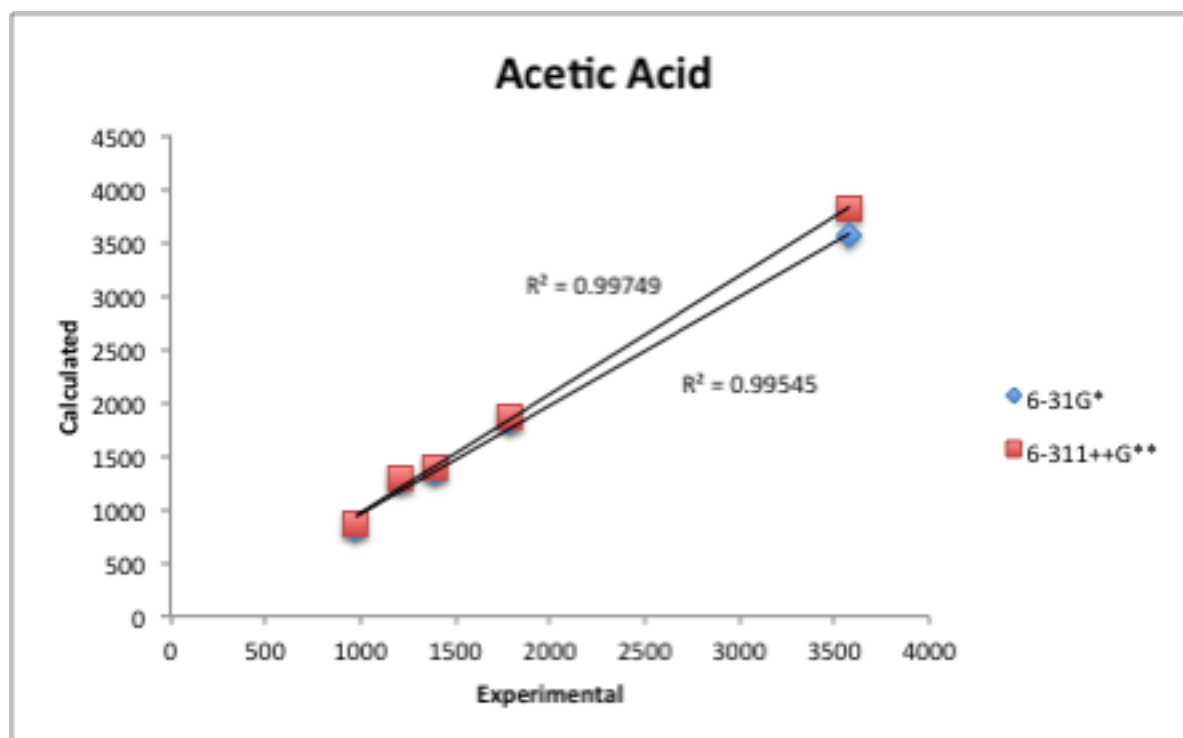


Figure 11. Linear regression of the calculated and experimental IR spectra for acetic acid generated by Spartan software

Figure 12 shows the linear regression comparison for the calculated and experimental values from Spartan for p-aminophenol. The theoretical spectra were calculated for three other potentials. The three potentials used were 6-31G*, 6-311G**, and 6-311+G**. The R^2 value for the 6-31G* trend line was 0.99868, the R^2 value for the 6-311G** trend line was 0.99859, and the R^2 value for the 6-311+G** trend line was 0.99836. The R^2 value was almost the same for all three potentials and the three R^2 values were all very close to 1.00.

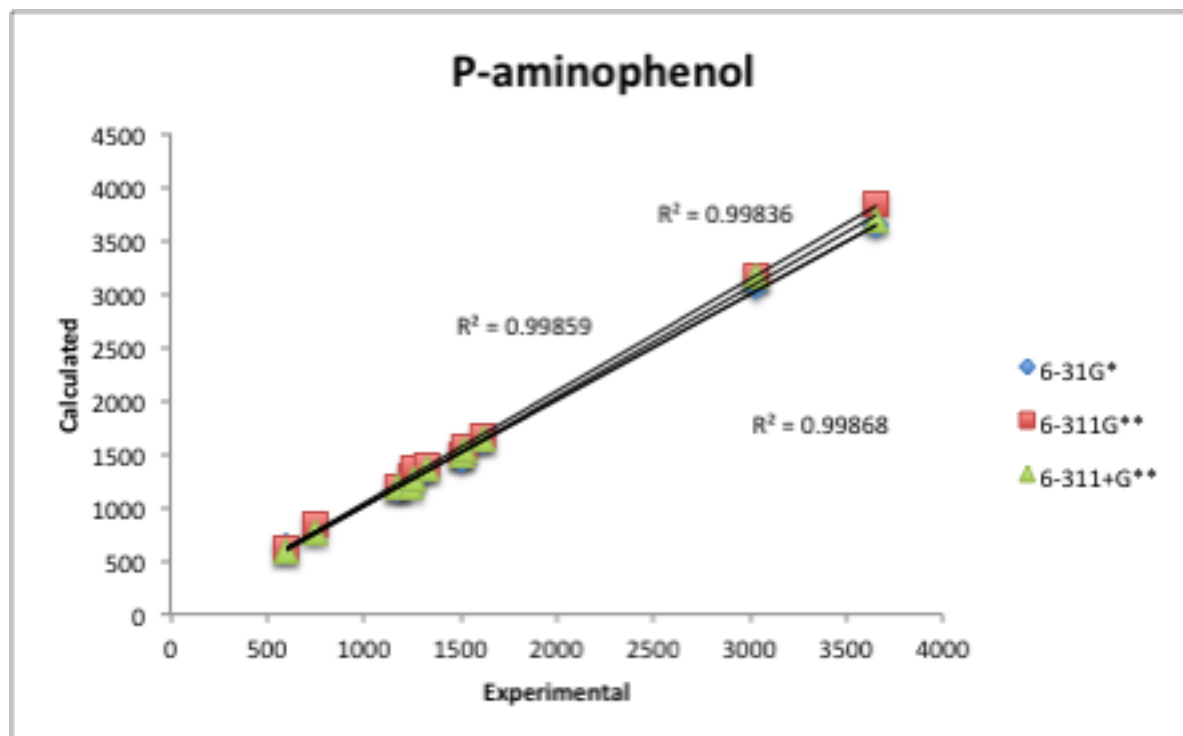


Figure 12. Linear regression of the calculated and experimental IR spectra for p-aminophenol generated by Spartan software

Figure 13 shows the linear regression comparing the experimental spectrum and calculated spectrum from Spartan for acetaminophen for two different potentials. The two potentials used were 6-31G* and 6-311+G**. The R^2 value for the 6-31G* trend line was 0.99976 and the R^2 value for the 6-311+G** trend line was 0.99906. The R^2 values for the two potentials were almost identical and both R^2 values were very close to 1.00.

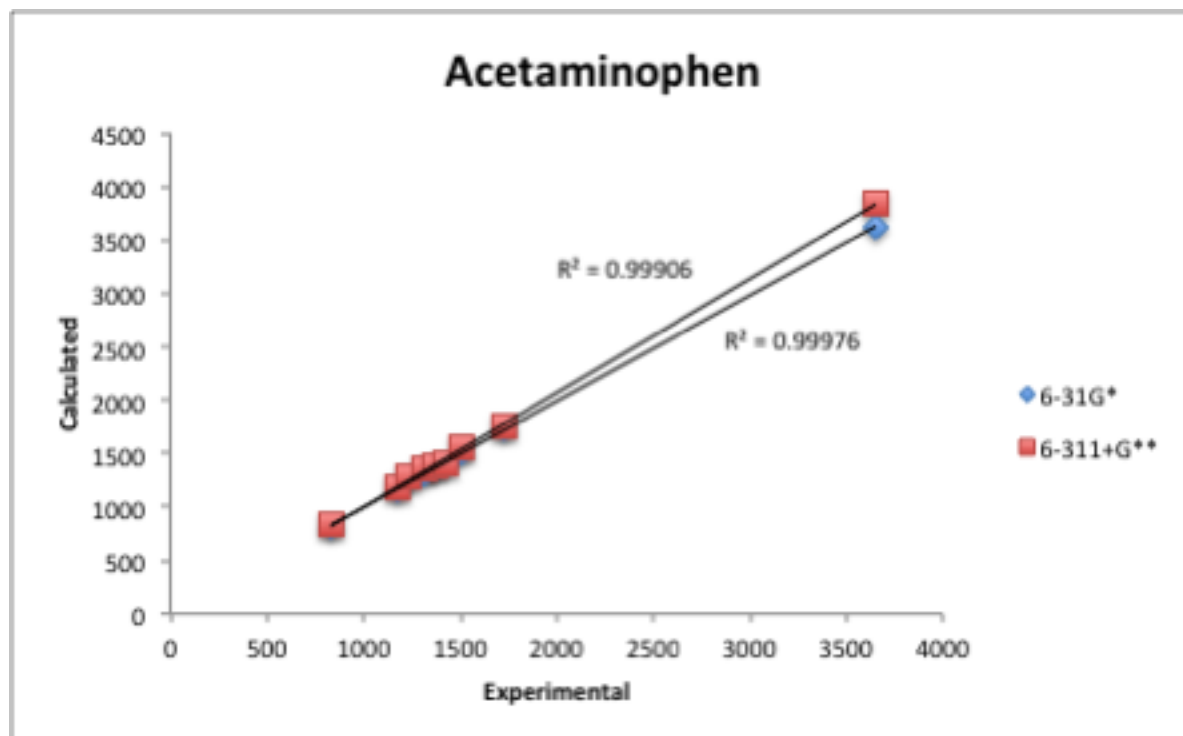


Figure 13. Linear regression of the calculated and experimental IR spectra for acetaminophen generated by Spartan software

Chapter 4

Discussion

The IR spectrum obtained for the synthesized acetaminophen was consistent with the IR spectrum for the acetaminophen standard, as shown in Figure 7 and Figure 8. This convergence of experimental results indicated that the desired product—acetaminophen—was formed. However, the acetaminophen experimental IR spectrum was shifted compared to the calculated spectrum generated by Spartan. The experimental IR spectrum for the synthesized acetaminophen also contained more peaks than the calculated spectrum generated by Spartan. The experimental IR spectrum from the p-aminophenol was also shifted compared to the calculated IR spectrum. The difference between the two experimental and calculated spectra indicate the possibility that a shift factor needed to be used to account for the discrepancy. However, recent research indicated that a benefit of the EDF2 potential was that no such factor should need to be applied¹⁹.

To resolve the discrepancy between the experimental IR spectrum for the synthesized acetaminophen and the calculated IR spectrum, an experimental spectrum interfaced by the Spartan software was compared to the calculated spectrum. The experimental spectrum interfaced by the Spartan software appeared more consistent with the calculated spectrum, but did not appear to be consistent with the experimental IR spectrum for the synthesized acetaminophen. Upon further investigation, it was determined that the interfaced experimental spectrum for Spartan was for the gas phase of acetaminophen, whereas the IR spectrum for the

synthesized acetaminophen was for the solid state. The NIST Chemistry WebBook, which was the database interfaced in the Spartan software, also contained an experimental IR spectrum for the solid-state acetaminophen. The solid-state experimental spectrum was consistent with the IR spectrum for the synthesized acetaminophen, which further supported that acetaminophen was the product of the synthesis reaction.

Since the experimental IR spectrum for the synthesized acetaminophen could not be directly compared to the calculated IR spectrum, the theoretical spectrum for all of the reactants and products was analyzed independently. Table 2 shows the most notable peaks for the reactants and products, as well as the molecular motion associated with each peak.

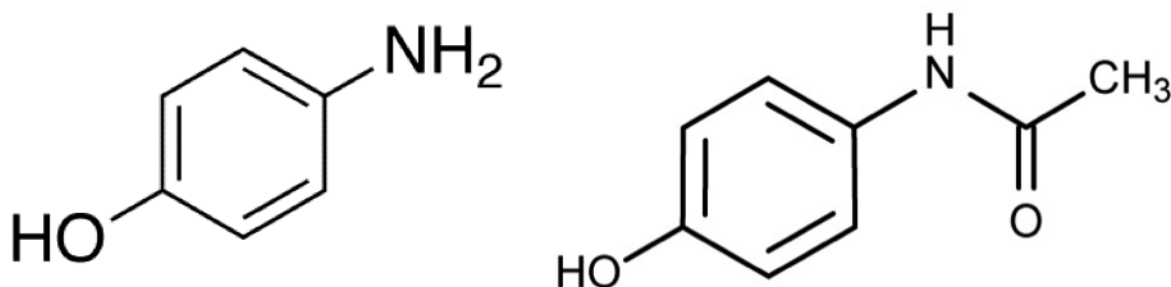


Figure 14. Organic structures of p-aminophenol and acetaminophen

The structure of acetaminophen is more closely related to p-aminophenol than acetic acid or acetic anhydride. The structures of the two compounds are shown in Figure 14. The difference between the two structures is that acetaminophen contains an amide functional group, whereas p-aminophenol only contains an amino functional group. The different peaks in the theoretical spectra found in Table 2 represent the difference in the structures. In the calculated

spectra, a peak at 1725 cm^{-1} indicated a C=O stretch for the acetaminophen molecule. This peak was consistent with the carbonyl compound absorption range of 1670 cm^{-1} to 1780 cm^{-1} found in the literature, which are shown in Table 3³². The theoretical acetaminophen spectra also contained a peak at 3484 cm^{-1} that corresponded to an N-H stretch. This value was consistent with the literature absorption range of 3300 cm^{-1} to 3500 cm^{-1} that indicates an N-H bond of an amine functional group³². The theoretical spectra for p-aminophenol contained two N-H stretch peaks at 3412 cm^{-1} and 3506 cm^{-1} , which were also consistent with the literature range. The two peaks in the amine absorption range were consistent with the expected results for p-aminophenol, since there are two N-H bonds.

Table 3. IR absorption peak ranges based on functional group

Functional Group	Absorption (cm^{-1})	Intensity	Functional Group	Absorption (cm^{-1})	Intensity
Alkane			Amine		
C-H	2850-2960	Medium	N-H	3300-3500	Medium
Alkene			C-N	1030-1230	Medium
=C-H	3020-3100	Medium	Carbonyl compound		
C=C	1640-1680	Medium	C=O	1670-1780	Strong
Alkyne			Carboxylic acid		
≡C-H	3300	Strong	O-H	2500-3100	Strong, broad
C≡C	2100-2260	Medium	Nitrile		
Alkyl halide			C=N	2210-2260	Medium
C-Cl	600-800	Strong	Nitro		
C-Br	500-600	Strong	NO ₂	1540	Strong
Alcohol					
O-H	3400-3650	Strong, broad			
C-O	1050-1150	Strong			
Arene					
C-H	3030	Weak			
Aromatic ring	1660-2000	Weak			
	1450-1600	Medium			

The potential used for the calculated spectra in Table 2 was 6-31G* because it was the lowest basis set used for each compound. The other basis sets used in the linear regression plots were 6-311G**, 6-311+G**, and 6-311++G**. In Figure 10, a linear regression was used to show how the 6-31G* basis set and the 6-311++G** basis set compared to the experimental IR spectra interfaced in Spartan for acetic anhydride. The R^2 value for the 6-311++G** basis set trend line was closer to 1.00, which indicated that it was a better fit to the experimental spectrum. Similarly, the R^2 value for the 6-311++G** basis set trend line was also closer to 1.00 for acetic acid as shown in Figure 11. These results indicate that 6-311++G** basis set provides more accurate calculated spectra compared to the 6-31G* basis set.

On the other hand, when the higher potentials were compared to the 6-31G* basis set for p-aminophenol and acetaminophen, the R^2 values were almost identical. As shown in Figure 12, the trend lines for the 6-31G* basis set, the 6-311G** basis set, and the 6-311+G** basis set yielded almost the exact same R^2 value, which indicated that all three basis sets were consistent with the experimental spectrum. The R^2 value for the 6-31G* trend line and the 6-311+G** trend line for acetaminophen were also almost the same, as shown in Figure 13. Overall, the results of the linear regression analysis seemed to show that for smaller molecules such as acetic acid and acetic anhydride, a higher level basis set was a more accurate fit to the experimental data, but for larger molecules like p-aminophenol and acetaminophen, the higher level basis set did not deviate much from the 6-31G* basis set.

As stated earlier, a theoretical spectra for the 6-311++G** basis set was attempted for both p-aminophenol and acetaminophen, but the calculations could not be completed on the computers available during the time of the research. Basis sets are a set of functions that are combined through quantum calculations to create molecular orbitals³³. The basis sets used in

this research were 6-31G*, 6-311G**, 6-311+G**, and 6-311++G**. These basis sets fall under a category called split-valence basis sets, which were designed by John Pople's research group. The general notation for these basis sets is X-YZg, where X represents the core atomic orbital basis function and Y and Z represent the valence orbitals. In other words, the more letters, plus signs, and asterisks that follow the hyphen in the basis set name represent the various orbitals that an electron can travel to³³. Since each orbital is associated with at least one type of Gaussian function, the calculations can become extremely complex. For this reason, the 6-311++G** calculation could not be performed on the computers available on campus for larger molecules such as acetaminophen and p-aminophenol. It is possible that the calculations could be performed with a more advanced computer system, but such an advanced computer system is not always available to students.

Conclusion

Acetaminophen can be modeled using Spartan 5.0 computational software. The IR spectra calculated by Spartan can also be compared to spectra found in the literature. However, at the present time, the IR spectra calculated by Spartan software available to students cannot be directly compared to experimentally obtained solid-state IR spectra. When using computational software in the laboratory setting, it is important to account for the phase of the compound being studied. As shown in the IR spectra, the IR spectrum of the gas phase of acetaminophen differs from the solid state IR spectrum. This discrepancy indicates that researchers should either change the phase of the compound being studied, or study the spectra independently.

This study also indicates a weakness in computational chemistry software. As computational chemistry packages continue to improve to better represent experimental data, this study can indicate areas of discrepancy in the data. This study could lead to further investigation of the computational chemistry software and improve methods for matching computational calculations to experimental data.

In addition, this experiment can serve as the basis for future undergraduate studies utilizing computational software. It is important to note that the software used for this study was a computational software package available to students. However, the package did not contain the option to show solid-state IR spectra, which is the spectral method most often used by undergraduate students. The results of this study may encourage computational software companies to include solid-state IR calculations in student software packages in order to better represent the results of undergraduate laboratory studies.

BIBLIOGRAPHY

1. Fukahara K, Ohno A, Ando Y, Yamoto T, Okuda H. (2011). A ¹H NMR-based metabolomics approach for mechanistic insight into acetaminophen-induced hepatotoxicity. *Drug Metabolism and Pharmacokinetics*. 26(4): 399-406.
2. Mehring von. (1893). Beitrage zu Kenntniss der antipyretica. *Ther Monatschrift*. 7: 577-579.
3. Brodie B, Axelrod A. (1948). The estimation of acetanilide and its metabolic products, aniline, n-acetyl-p-aminophenol and p-aminophenol (free and total conjugated) in biological fluids and tissues. *Journal of Pharmacology and Experimental Therapeutics*. 94: 22-28.
4. Brodie B, Axelrod A. (1949). The fate of acetophenetidin (phenacetin) in man and methods for the estimation of acetophenetidin and its metabolites in biological material. *Journal of Pharmacology and Experimental Therapeutics*. 97: 58-67.
5. Prescott, L. (2000). Paracetamol: past, present, and future. *American Journal of Therapeutics*. 7(2): 143-148.
6. Vane J. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature - New Biology*. 231: 232-235.
7. Harvey C, Milton A. (1975). Proceedings: endogenous pyrogen fever, prostaglandin release and prostaglandin synthetase inhibitors. *Journal of Physiology*. 250: 18-20.
8. Botting, R. (2000). Mechanism of action of acetaminophen: is there a cyclooxygenase 3? *Clinical Infectious Disease*. 31: S202-S210.
9. Komsta L, Czarnik-Matusiewicz H, Szostak R, Gumienicek A, Pietras R, Skibinski R, and Inglot T. (2011). Chemometric detection of acetaminophen in pharmaceuticals by Infrared Spectroscopy combined with pattern recognition techniques: comparison of attenuated total reflectance-FTIR and Raman Spectroscopy. *Journal of the Association of Official Analytical Chemists International*. 91: 743-749.
10. Szostak R, and Mazurek S. (2002). Quantitative determination of acetylsalicylic acid and acetaminophen in tablets by FT-Raman spectroscopy. *Analyst*. 127: 144-148.

11. Borio V, Vinha R, Nicolau R, de Oliveira H, de Lima C, and Silveira L. (2012). Quantitative evaluation of acetaminophen in oral solutions by dispersive Raman spectroscopy for quality control. *Spectroscopy: An International Journal*. 27(4): 215-228.
12. Aparoy P, Reddy K, and Reddanna P. (2012). Structure and ligand based drug design strategies in the development of novel 5-LOX inhibitors. *Current Medicinal Chemistry*. 19(22): 3763-3778.
13. van de Streek J. (2014). Computational pharmaceutical materials science. *Journal of Cheminformatics*. 6(S1): 1.
14. Kortagere S, Lill M, and Kerrigan J. (2012). Role of computational methods in pharmaceutical sciences. *Methods in Molecular Biology*. 929: 21.
15. Price S. (2003). The computational prediction of pharmaceutical crystal structures and polymorphism. *Advanced Drug Delivery Reviews*. 56: 301-319.
16. Singer E. (2011). Drug discovery with computational chemistry. *MIT Technology Review*.
17. Atkins P, de Paula J. (2010). *Physical Chemistry*. 9th Edition.
18. Tosco P, Stiefl N, and Landrum G. (2014). Bringing the MMFF force field to the RDKit: implementation and validation. *Journal of Cheminformatics*. 6: 37.
19. Dittert L, Caldwell H, Adams H, Irwin G, and Swintosky J. (2006). Acetaminophen prodrugs I. Synthesis, physicochemical properties, and analgesic activity. *Journal of Pharmaceutical Sciences*. 57(5): 774-780.
20. Bhattacharya A, Purohit V, Suarez V, Tichkule R, Parmer G, and Rinaldi F. (2006). One-step reductive amidation of nitro arenes: application in the synthesis of acetaminophen. *Tetrahedron Letters*. 47(11): 1861-1864.
21. Katz D. (1996). Synthesis of aspirin and acetaminophen. www.chymist.com/aspirin.pdf. Last accessed 1/30/2015.
22. Pub Chem. U.S. National library of medicine. www.pubchem.ncbi.nlm.nih.gov/compound/acetaminophen. Last accessed 4/3/2015.
23. Sacchetti M. (2006). Thermodynamic analysis of DSC data for acetaminophen polymorphs. *Journal of Thermal Analysis and Calorimetry*. 63(2): 345-350.
24. Jaleel A, Rakhila M, and Parameswaran G. (2010). Comparison between investigational IR and crystallographic data with computational chemistry tools as validation of the methods. *Advances in Physical Chemistry*. 2010: 1-5.

25. Levy D. (2013). How dynamic visualization technology can support molecular reasoning. *Journal of Science Education and Technology*. 22: 702-717.
26. Chiu J, Linn M. (2014). Supporting knowledge integration in chemistry with visualization-enhanced inquiry unit. *Journal of Science Education and Technology*. 23: 37-58.
27. Halgren T. (1996). Merck molecular force field. I. Base, form, scope, parameterization, and performance of MMFF94. *Journal of Computational Chemistry*. 17: 490-519.
28. Hohenberg P, and Kohn W. (1964). Inhomogeneous electron gas. *Physical Review*. 136: 864-871.
29. Kohn W, Sham L. (1965). Self-consistent equation including exchange and correlation effects. *Physical Review*. 140: 1133-1138.
30. Yin C, Georg M, and Gill P. (2004). EDF2: A density functional for predicting vibrational frequencies. *Australian Journal of Chemistry*. 57: 365-370.
31. Krishnan R, Binkley J, Seeger R, and Pople J. (1980). Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *Journal of Chemical Physics*. 72: 650.
32. McMurry J. (2012). *Organic Chemistry*. 8th Edition.
33. Ditchfield R, Hehre W, and Pople J. (1971). Self-consistent molecular-orbital methods. IX. An extended Gaussian-type basis for molecular-orbital studies of organic molecules. *Journal of Chemical Physics*. 54(2): 724-72.

ACADEMIC VITA

Kayla Jardine
kyj5088@psu.edu

Education

Schuylkill Valley High School	August 2007-June 2011
Clemson University	August 2011-December 2011
Penn State Berks	January 2012-May 2015
<i>B.S. Biology, Genetic & Developmental Biology Option</i>	
<i>Honors in Biology</i>	
<i>Minor in Chemistry</i>	
Schreyer Honors Thesis: The Molecular Modeling and Characterization Of Acetaminophen Using Spartan 5.0 Computational Software	

Honors and Awards

<i>Schuylkill Valley High School</i> – Salutatorian	June 2011
<i>Penn State Berks</i> – Dean’s List	January 2012-May 2015
<i>Penn State Berks</i> – Student Marshal	May 2015
<i>Penn State Berks Academic Award for Organic Chemistry</i>	April 2013
<i>Penn State Berks Academic Award for Biology</i>	April 2014
<i>Boscov Award</i>	August 2013-May 2015

Clubs

<i>Penn State Berks Pre-Medical Society</i> – Co-President	August 2013-May 2015
<i>Honors Club</i>	August 2012-May 2015
<i>Berks Chemical Society</i>	August 2012-May 2014

Presentations

<i>American Chemical Society Annual Conference, Indianapolis</i>	October 2013
The synthesis, analysis and modeling of acetaminophen: a student led laboratory	
<i>78th Annual ISC Conference at Albright College, Reading</i>	April 2014
The synthesis, analysis and modeling of acetaminophen: thesis work in progress	

Positions on Campus

<i>CHEM 110 Supplemental Instructor</i>	August 2012-May 2015
<i>CHEM 112 Supplemental Instructor</i>	January 2014-May 2015
<i>Penn State Berks Learning Center Tutor</i>	August 2013-May 2015