Synthesis and Analysis of Acetaminophen in an Undergraduate Laboratory

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Abstract

Acetaminophen, commonly known as Tylenol, was synthesized and analyzed using computational chemistry techniques along with spectroscopy to assess the purity of the compound. The analytical techniques and synthesis of acetaminophen provided students with a connection between well known over-the-counter medication and the experience of producing then characterizing that compound and the introduction to computational chemistry, which is a growing field of chemistry.

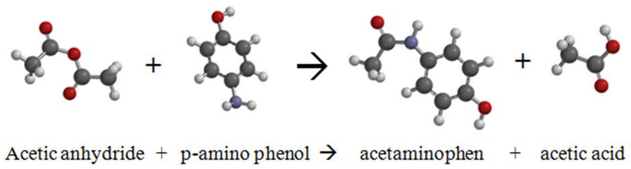

Figure 1. Synthesis of acetaminophen with models made in Spartan

Introduction

Acetaminophen, also known as paracetamol, is widely used as an antipyretic and analgesic. Its use is popular as a minor pain reliver in the United States and goes by the brand name Tylenol.[1] Acetaminophen is usefully experimentally when studying the effectiveness of Infrared and Raman spectroscopy in both qualitative and quantitate determinations.[2] In the undergraduate laboratory, acetaminophen is useful in that it is stable and easy to synthesize. The general synthesis in undergraduate laboratories of acetaminophen is p-aminophenol reacting with acetic anhydride in the presence of an acid (sulfuric or phosphoric) to produce acetaminophen and acetic acid as shown in figure 1, usually followed by water recrystallization.

Students in this lab can expect to learn how to synthesize and purify a compound then characterize it using various analytical techniques such as percent yield, melting point, and IR and Raman spectroscopy. An introduction to computational modeling is displayed in this lab where students will be able to explore how to use the program Spartan to digitally produce and analyze a compound.

The experiment was developed by a team of undergraduate students and their instructor in a second-semester chemistry laboratory as part of a Peer-Developed and Peer-Led (PDPL) [3] laboratory format.

Methods

Solid acetaminophen was synthesized using acetic anhydride and *p*-amino phenol with liquid acetic acid as a byproduct. The acetaminophen crystals were purified by being dissolved in hot water then allowed to recrystallize. Of the recrystallized acetaminophen, percent yield, melting point, IR and Raman spectra were obtained. The melting point was found by using Mel-Temp II (Laboratory Devices, Holliston, MA 01746-6402 melting point apparatus. Nicolet 6700 FT-IR (Thermo Fisher Scientific, Madison, WI 53711-4495) was used to determine the IR spectra of the product. For the Raman Spectra, B&W Tek I-Raman Plus spectrometer equipped with 532nm excitation system and a 20x objective was used to obtain spectra.

Methods (cont.)

A computational model of acetaminophen was developed using a computational software Spartan. Model was energy minimized using MMFF potential. Expected IR and Raman spectra for the model were obtained by using Density Functional Theory with the B3LYP-D3 density functional at the 6-311+G(2d,p) level.

Results

Analysis of the recrystallized acetaminophen product through melting point gave melting point ranges that were mostly slightly under, as seen in table 2, and still comparable with the expected literature value melting point of acetaminophen at 169 °C. However, this could still indicate some impurity in the product.

Trial	mass/g	mass/g	mass/g	mass/g	% yield
	p-amino phenol	crude product	recrystallized product	expected product	
1	1.5005	1.951	0.8018	2.0782	38.58
2	1.5002	1.0402	0.5043	2.0778	24.27
3	1.513	1.3917	0.4325	2.0956	20.64
4	1.5007	1.5944	0.4916	2.0785	23.65
5	1.5125	0.6348	0.2548	2.0949	12.16
6	1.5092	1.4628	1.4139	2.0903	67.64
7	1.503	1.0466	0.6292	2.0817	30.22
8	1.5017	1.0138	0.6214	2.0799	29.88
9	1.5012	0.8812	0.4905	2.0792	23.59
10	1.51	1.57	0.9	2.0914	43.03
11	1.503	0.9263	0.402802	2.0817	19.35
12	1.5022	1.7133	1.0722	2.0806	51.53

Table 1. Masses of reactants, the recrystallized product, expected mass based on mass of reactants and percent yield for each student trial

Trial	mp/°C	
	onset	end
1	160	162
2	163	165
3	173	173
4	164	164
5	135	145
6	155	160
7	181	181
8	157	160
9	164	164
10	164	167
11	164	166
12	161	162

Table 2. Melting points of the recrystallized product for each of the student trials

Expected IR and Experimental IR: In figure 2, the IR spectra for a standard acetaminophen sample and experimental acetaminophen are compared. The peaks for the experimental are very similar to that of the expected IR indicating that acetaminophen was produced with some amount of purity.

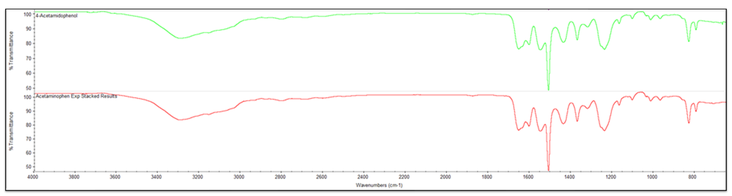

Figure 2. Expected IR on top in green from reference acetaminophen (Acros Organics, Product #102330050, CAS No: 103-90-2) and Experimental IR on bottom in Red from recrystallized product

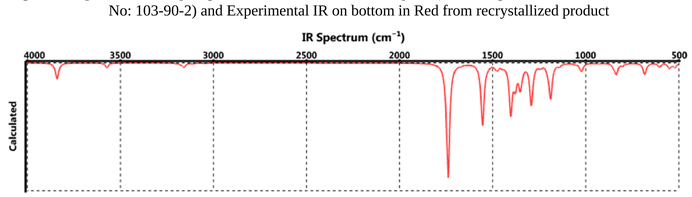

Figure 3. IR spectra produced in the Spartan computational software using the acetaminophen model displayed in figure 1

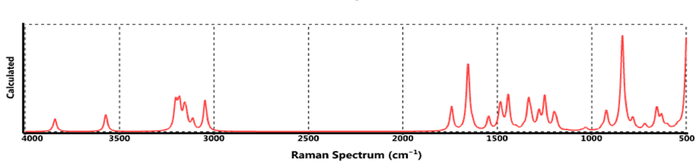

Figure 4. Raman spectra produced in the Spartan computational software using the acetaminophen model displayed in figure 1

Results (cont.)

Expected Raman and Experimental Raman: In figure 5, the Raman spectra for a standard acetaminophen sample and experimental acetaminophen are compared. Good correlation between the two other than some fluorescence between 2000 and 2500 cm^{-1}, which indicated some impurity in the product which was due to some *p*-aminophenol contaminating the product, which the Raman for it is shown in figure 5 to display its effect on the product. The impurity in the product is related to the lower melting point.

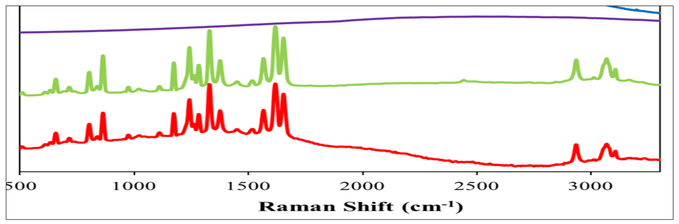

Figure 5. Raman for *p*-aminophenol is on top in purple Expected Raman on middle in green from reference acetaminophen (Acros Organics, Product #102330050, CAS No: 103-90-2), Experimental Raman is on bottom in red from the recrystallized product

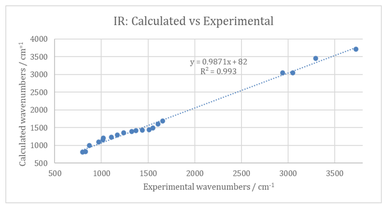

Figure 6. Correlation between experimental IR in figure 2 to computational IR in figure 3

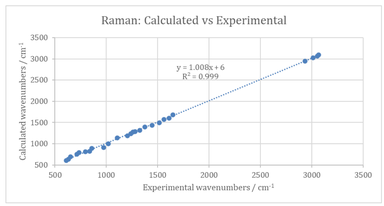

Figure 7. Correlation between experimental Raman in figure 5 to computational IR in figure 4

Conclusions

This laboratory experiment provided students with the opportunity to synthesize a well-known compound, analyze it using a variety different analysis techniques and allowed a glimpse into computational chemistry, which is a growing field of chemistry. The analysis of the product was performed using both experimental analytical techniques and computational calculation. The IR from the experimental product was similar to both standard spectra as seen in figure 2 and computational spectra as seen in figure 3. IR spectra in the computational software allowed students to see the molecule vibrating at different peaks to understand the motion of the molecule at said peaks. The Raman spectra provided an additional way to detect impurities in product. Students were able to use these new techniques and equipment to relate chemistry to daily life. Some of this research has been submitted to the Journal of Chemical Education for publication.[4]

References

1. Prescott, L. Paracetamol: past, present, and future. American Journal of Therapeutics. 2000 7(2), 143-148.
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3. Tribe, L.; Kostka, K. Peer-Developed and Peer-Led Labs in General Chemistry. J. Chem. Educ. 2007, 84, 1031.
4. Pasquarella, K; Jardine, K; Hill, K; Jones, E; Elia, R; Gibbs, G; Sonntag, M; Tribe, L. Synthesis and characterization of acetaminophen: An experimental and theoretical laboratory for the undergraduate curriculum. J. Chem. Educ. 2021 Submitted for publication.