A Thermometric Titration Study of Acetaminophen and Sodium Hypochlorite

A project completed in partial fulfillment of the requirements for the Honors Program
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Abstract: Thermometric titrimetry has been used by many scientists as a means of determining the end-point of a reaction in acid-base and oxidation-reduction chemistry. Acetaminophen is an effective method for deterring pain in an individual, therefore, we sought to develop a unique relationship between the weight of sodium hypochlorite added to acetaminophen and the temperature from the heat that evolves from this reaction. One gram of acetaminophen was reacted with varying weights of sodium hypochlorite. As the weight increased, so did the average temperature change; yet, the average change of temperature per gram of bleach decreased, indicating that the temperature evolved from the reaction is dependent on the combined weights of the two reactants. Thus, we have effectively demonstrated an inexpensive and useful means of further determining the quality of acetaminophen via an inexpensive reaction combined with an inexpensive apparatus.

Introduction: Thermometric titrimetry has been utilized as a means of determining a reaction in acid-base and oxidation-reduction chemistry by utilizing the change in temperature evolved as heat to determine the end-point (Zenchelsky, 1960). According to Hume et al., thermometric titrations are able to demonstrate the completion of a reaction by comparing a temperature rise against a controlled release of a given volume of titrant over time, allowing the slope of the curve to help determine the equivalence point (1953). Tyrrell and Beezer illustrate a clarification of the difference conventional and thermometric titrimetry, showing that the determination of the end-point of a reaction does not rely on some qualitative observation, but rather in this case, the quantitative measurement of temperature change against the controlled release of the titrant over time (1968). Thus, thermometric titration does not necessarily end when the reagent is consumed, but until the change in temperature has plateaued.

Furthermore, catalytic end-point titration is a form of thermometric titrimetry in which the reagent undergoes a different reaction once the original titration has finished, marked by a relatively smaller temperature change after the initial (Tyrell and Beezer, 1968). Therefore, there would be an observable, abrupt shift in temperature change to indicate that a new reaction is occurring. Greenhow and Jayaraj demonstrate this phenomenon, explaining that such methods tend to result in a clearly defined inflection point to indicate the conclusion of the reaction (1983). This catalytic end-point reaction can happen in the form of a polymerization reaction in both aqueous and non-aqueous systems. For example, Greenhow and Dajer de Torrijos illustrate such in a non-aqueous system, using the alcohol groups in the titrant to react with acrylonitrile (1979). In addition, it should be noted that, in developing this experiment, we tried to conduct a similar experiment between acetaminophen and ceric ammonium nitrate by dissolving both reagents in water. Acetaminophen, however, would not dissolve, or even be suspended, in water without the use of much stirring and additional heat.

Acetaminophen is an effective method for deterring pain in an individual. Many know it as an over-the-counter pain killer and fever reducer (Mackenzie et al., 2000). As such, it is a very common over-the-counter
preparation and must have strong documentation associated with its quality testing, hence the need for different tests to assure its potency.

Next, not only is it clearly important to determine the presence and quality of acetaminophen, there are many means of determining the presence of this drug. For example, it has been shown that acetaminophen can be determined via the use of carbon nanotubes with modified electrodes (Duan et al., 2007 and Umasankar et al., 2012). Furthermore, acetaminophen can be determined through the use of graphene sheets, again with electrodes (Moghaddam et al., 2015). The concentration of acetaminophen in solution can even be determined through the use of high pressure liquid chromatography (Horvitz and Jatlow, 1977). In addition, to determine the presence of acetaminophen by its mass, mass spectrometry with liquid chromatography has been used as an effective means (An et al., 2011). Indeed, even a thermometric titration of acetaminophen has been carried out with sodium hydroxide (Burgot et al., 1997). The dilemma with these methods, by their very description, is their lack of availability to the common market. That is, many of these materials are not readily available in a store or they are simply expensive. In this study however, Clorox bleach will be used since it has been proven to be inexpensive and as readily available to the public as acetaminophen (Morgan, 1992). Furthermore, it has been demonstrated that the active ingredient of bleach, sodium hypochlorite, will indeed oxidize acetaminophen (Bedner and MacCreahan, 2006). Thus, a thermometric titration between these two reagents is feasible.

At first, it would seem that a more powerful oxidizing agent, such as ceric ammonium nitrate, would be most effective and useful for this study. It has been shown, however, that it is possible for ceric ammonium nitrate to interact effectively with both functional groups of acetaminophen, the imine group and the phenol group, eliminating the piece-wise means that lays the foundation of this project (Hwu and King, 2001). In addition, while it and acetaminophen are able to dissolve in sulfuric acid, it is possible for reagents such as sodium hypochlorite to interact with their solvents. So, such a reaction in sulfuric acid would generate additional heat that would need to be factored out. Furthermore, while it would seem apparent in the literature that ceric ammonium nitrate would be readily able to oxidize a common molecule like acetaminophen; but when reacted with citric acid, no heat was generated (Sharma et al., 2011). Therefore, it would be useful to utilize an effective, well-known, and affordable oxidizing agent that has been shown to only oxidize at one point of acetaminophen, that is, the phenol group; hence, sodium hypochlorite, the active component of bleach, being our choice of reagent (Bedner and MacCreahan, 2006).

The aim of this study is to prove a unique relationship between the weight of sodium hypochlorite added to acetaminophen, and the temperature (heat) that evolves from this reaction.

**Methods:** 1g±0.02 of ammonium chloride was weighed into a beaker. Next, using stoichiometry, one mole equivalent (±0.02g) of sodium hypochlorite in bleach was weighed (assuming 6% NaOCl by weight of bleach solution) in a separate beaker. The thermometer was placed into the beaker of ammonium chloride such that the tip was in the bottom center of the beaker (see Figure 1). Then, the bleach was completely poured into the
beaker of ammonium chloride and the solution was stirred. Temperature was recorded against time using Vernier Graphical Analysis software. The maximum and minimum temperatures were recorded to obtain the total temperature difference for each trial. This process was repeated five times. An average temperature difference was determined. Next, the average temperature change was divided by the weight of bleach used. The same apparatus was used for the next combinations of a gram of a certain chemical and a mole equivalent of sodium hypochlorite, with five trials per combination. The chemicals reacted with bleach were conducted in a similar way using the following order of chemicals: urea, paracetin, phenol, starch, a generic-brand acetaminophen pill, and acetaminophen. For the acetaminophen, the only exception, the various weights of bleach were used: 0.5 mol equivalent, 1mol equivalent, 10g (approximately 1.2mol equivalent), 1.5mol equivalent, and 2 mol equivalent.

![Figure 1: The apparatus](image)

**Results:** Table 1 shows the average temperature change as well as the average temperature change for each gram of bleach added when combined with 1g of Ammonium chloride, Urea, Phenol, Phenacetin, a generic pill, and corn starch. The generic pill and starch were included in order to determine the possible effects of common binders on this titration. Since the values determined were both far less than the values obtained for all the substances, the effects of corn starch, and similarly other binders, seem to hold less impact.

<table>
<thead>
<tr>
<th>Substance Used (1g substance used)</th>
<th>Mean Net Temperature Change (°C)</th>
<th>Mean Net Temperature Change per gram bleach added (°C/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenacetin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen pill</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: 1g Substance Used versus Mean Net Temperature Change (°C) and Mean Net Temperature Change per g of bleach added(°C/g)
<table>
<thead>
<tr>
<th>Substance</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium Chloride</td>
<td>23.68</td>
<td>1.02</td>
</tr>
<tr>
<td>Urea</td>
<td>33.58</td>
<td>1.63</td>
</tr>
<tr>
<td>Phenol</td>
<td>21.87</td>
<td>1.66</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>21.35</td>
<td>3.08</td>
</tr>
<tr>
<td>Tylenol Pill</td>
<td>27.79</td>
<td>3.73</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>0.4326</td>
<td>0.0600</td>
</tr>
</tbody>
</table>

**Figure 2:** Time (s) vs temperature (ºC) of 1g acetaminophen and 0.5 mole equivalent of bleach (4.1g)

**Figure 3:** Time (s) vs temperature (ºC) of 1g acetaminophen and 1.0 mole equivalent of bleach (8.21g)
Figures 2-5 show the temperature curves of the thermometric titrations of 1g acetaminophen with 0.5, 1.0, 1.5, and 2.0 mole equivalents, respectively, of bleach. The curves of each reaction are observably similar. The point of inflection (that is, where the curve of each reaction plateaus) is indicative of the end-point of the reaction. Between Figures 2-5, each of them share a similar, almost sigmoidal curve structure, but the peak temperature is greater as more bleach is added.

Next, Table 2 and Figures 6 and 7 serve to compare the weights of bleach used with 1g of acetaminophen with their respective average temperature changes and their changes relative to the amount of
each gram of bleach added. Each of the following weights added were calculated mole ratios, except for 10 grams of bleach added. This weight was arbitrarily chosen.

Table 2: Weight of bleach added versus Mean Net Temperature Change (ºC) and Mean Net Temperature Change per g of bleach added(ºC/g)

<table>
<thead>
<tr>
<th>Weight of Bleach Used to 1g Acetaminophen (g)</th>
<th>Mean Net Temperature Change (ºC)</th>
<th>Mean Net Temperature Change per gram bleach added (ºC/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>22.84</td>
<td>5.57</td>
</tr>
<tr>
<td>8.21</td>
<td>28.77</td>
<td>3.50</td>
</tr>
<tr>
<td>10</td>
<td>28.76</td>
<td>2.88</td>
</tr>
<tr>
<td>12.31</td>
<td>30.78</td>
<td>2.50</td>
</tr>
<tr>
<td>16.41</td>
<td>33.07</td>
<td>2.02</td>
</tr>
</tbody>
</table>

In Figure 6, it shows the average temperature change against the weight of bleach used. The average change in temperature between 4.1 and 8.21 grams, as well as between 10 and 12.31 grams and 16.41 grams, were statistically significant (p<0.05) using two-tailed tests, as indicated by the asterisks. This figure demonstrates a
proportional increase in the average change in temperature as more bleach is added to the same 1g of acetaminophen.

Figure 7: Weight of bleach used (g) versus mean temperature change per gram of bleach (°C/g), asterisks above each bar indicate p-value < 0.05, marking statistical significance

Figure 7 compares the average temperature change per gram of bleach against the weight of bleach used. The average change in temperature for every gram of bleach added was statistically significant (p < 0.05) using two-tailed t-tests. The asterisks serve the same purpose as it was used in Figure 6. This figure demonstrates a steadily decreasing average change in temperature per gram of bleach as more bleach is added to the same 1g of acetaminophen.

**Discussion:** First, in proving that the apparatus works, 1 gram of each of the substances listed in Table 1 were combined with a mole equivalent weight of bleach. By demonstrating an observable and quantifiable difference in temperature, the apparatus was verified to work. Furthermore, the average change in temperature per gram of bleach added was measured to further observe the difference when utilizing chemicals that progressively begin to resemble the structure of acetaminophen. The closer the chemical began to structurally resemble acetaminophen, and the larger the molecule became with the addition of said functional groups, the greater the increase in average net temperature per gram of bleach added.

Having determined that the apparatus is effective as a means of conducting a thermometric titration of chemicals progressively more structurally similar to acetaminophen, it has been shown that the next step is to compare the thermometric titrations of combinations of 1g of acetaminophen and varying mole equivalent ratios
of bleach. In addition, the pill and the starch used help to demonstrate the irrelevance of any binders or similar molecules in the pill that contribute to the pill’s additional weight.

Figure 6 and Figure 7 serve to summarize Figures 2 through 5, as well as to illustrate the difference between the amount of temperature change observed and the amount of bleach added. The curves illustrated in Figures 2 through 5 coincide with the expected results of a thermometric titration as established in previous literature (Zenchelsky, 1960). Furthermore, using the point of inflection where the temperature curve plateaus, it is possible to determine the conclusion of reaction, indicating that this rudimentary apparatus is able to generate standard thermometric titration curves between these two substances (Hume et al., 1953). Since the active group of acetaminophen in this titration is likely the phenol group, and a thermometric titration of acetaminophen with a similar reagent has been conducted, it seems apparent that these methods produced results that coincide with the literature (Bedner and MacCreahan, 2006; Potter and Hinson, 1987; and Burgot et al., 1997).

Indeed, while adding more bleach to a given amount of acetaminophen yielded a greater increase in temperature, the change in temperature per gram of bleach added decreased. Knowing the ingredients of bleach, it can be inferred that, while more of the contents of the bleach ingredients are interacting with acetaminophen, less of the individual molecules of sodium hypochlorite, the primary active ingredient, are interacting with acetaminophen just as has been demonstrated in a thermometric titration with a similar reagent, sodium hydroxide (Burgot et al., 1997). Furthermore, to assume the other ingredients of bleach were playing a minor role would still justify these values as the heat generated from a reaction purely between sodium hypochlorite and acetaminophen would generate heat that would then be dissipated throughout the rest of the liquid. A greater amount of bleach would decrease the overall change in temperature per amount of bleach added. Thus, this reaction would demonstrate abiding by Newton’s Law of Cooling (Vollmer, 2009).

Therefore, in a similar manner to the literature, one could use this project as a basis of comparison. That is, if one were to assume their product of acetaminophen was correct and they wished to test the purity using this method, it would be justified that excess product formed would higher than normal results, and vice-versa for lower yields (Burgot et al., 1997). In industry, therefore, this project would help to explain the purity of acetaminophen once a batch of pills has been made. Thus, this experiment shows that thermometric titrations can be a cheap alternative means of determining quality of product, a useful point for pharmaceutical endeavors.

This project allows for several opportunities to gain further insight. First, and most obvious, would be to improve the results for this reaction. This could be done via similar methods with either slight alterations to the methods or via increased trials to improve data, just as was demonstrated between the reaction of acetaminophen with sodium hydroxide compared to another study that utilized horseradish peroxidase to achieve similar oxidative ends (Potter and Hinson, 1987 and Bedner and MacCreahan, 2006). Second, this project further demonstrates that thermometric titration can act as a means of quality control. Therefore, one project could contain similar, smaller projects using other chemicals with oxidative-reductive properties to obtain values in the same fashion. For example, ceric ammonium nitrate is such an effective oxidizing agent
that it would be of interest to determine if there would be any difference when using a reagent that could interact with both of the key functional groups of acetaminophen, both the imine and the phenol. Thus, it is possible for future thermometric titration experiments to be carried out using these two reagents (Hwu and King, 2001). In addition, it has been demonstrated that ceric ammonium sulfate -where cerium (IV) is still the oxidizing agent- can be used in thermometric titrimetry to determine ascorbic acid. It would be of interest to carry out a similar reaction between acetaminophen and ceric ammonium nitrate or ceric ammonium sulfate (Mayers and Taylor, 1987).

One of the drawbacks to this experiment was that the assumption in determining stoichiometric weight relationships, that all acetaminophen would react completely and solely with sodium hypochlorite, giving the other ingredients a minor role in the reaction. Furthermore, there was statistical significance between the change in temperature between 1 mole ratio of bleach added and 10 grams exactly, but not between 10 grams and 1.5 mole ratio. Another study, probably with more trials would be needed to clarify this finding. Finally, it is important to note that these methods, much like spectrophotometry or carbon-nanotube electrodes, cannot act as a final determinant of a chemical; but rather can act as a supplemental proof of quality of product (Souri et al., 2015 and Umasankar et al., 2015).

**Literature Cited:**


