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Greener Oxidation and Purification Methods for Mechanochemical  
Porphyrin Synthesis

Hannah Shy

Greener Oxidation and Purification Methods for Mechanochemical Porphyrin Synthesis

Thesis submitted to the Faculty of Barry University in partial fulfillment of the requirements for the completion of the Honors Program

By

Hannah Shy

December 2013

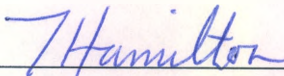
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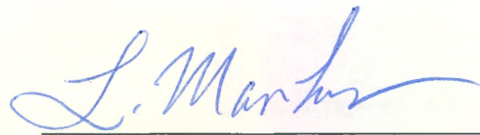


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Greener Oxidation and Purification...Porphyrin Synthesis

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Abstract

Solvent-free chemistry has become popular because of the increased emphasis on waste reduction and lessening cost. Porphyrins are cyclic, organic compounds that have become important in the construction of larger, self-assembled systems. The traditional synthesis of porphyrins consists of an acid-catalyzed condensation of pyrrole and aldehyde to produce a precursor: porphyrinogen, which is then oxidized to become porphyrin. The traditional process is inefficient with yields lower than 30% and requires high-dilution solvent conditions to ensure the proper reaction takes place. We have been successful in developing a solvent-free approach using either a mortar and pestle or a ball mill. Grinding produces the cyclized product, porphyrinogen, which needs to be oxidized. We currently use the traditional method for this step and have focused on developing a green method. Here we present the results of our studies to develop a 100% green methodology for synthesis of these important organic molecules.



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## 1. Introduction

Scientific research has always been driven by results. This mindset has allowed for the invention of influential technology such as the internal combustion engine or the home computer. Researchers were never worried about the amount of energy they were using or the kinds of toxic chemicals being generated. It was not until the 1970's that people became more environmentally conscious. In the United States, this came with the creation of the Environmental Protection Agency, the founding of Earth Day and the passing of the Clean Air and Water Act in Congress.

In the United States approximately 80 percent of our energy comes from fossil fuels. This has caused an increase in the amount of carbon dioxide released into the air. Over 800 pounds of carbon dioxide is released into the air for every one British thermal unit (BTU) of energy used. In the United States alone in 2010, people used 20 quadrillion BTU's of energy. The global energy consumption is only going to increase as developing countries with large populations such as China and India continue to industrialize. One way to help alleviate the strain being put on the environment is to use natural energy sources. One such example is the use of solar panels for solar energy, which is where this research becomes important.

### 1.1 Porphyrins

Porphyrins are naturally-occurring organic structures that play a vital role in the make-up of chlorophyll in plants and hemoglobin in vertebrates, including humans. They are highly symmetrical, aromatic compounds that are used in processes such as metal transportation and catalysis<sup>1</sup>.

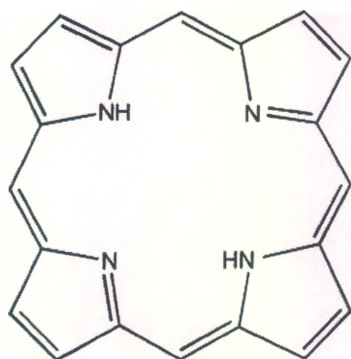


Figure 1: The molecule porphine illustrates the porphyrin backbone.

The optical properties of porphyrins, due to their alternating single and double bonds, make them ideal compounds for light harvesting which is useful in the design of solar panels. In addition, because porphyrins are natural products, synthetic porphyrin structures are useful for studying processes that occur in nature and biological organisms. Porphyrins also present opportunity for fine-tuning optical and electronic properties for specific applications by making small changes to the structure<sup>2</sup>. In the laboratory, porphyrins are made using a four-fold acid-catalyzed condensation reaction between pyrrole and an aldehyde, followed by oxidative aromatization (Figures 2 and 3). The reaction may be done under one of two sets of conditions: 1) the Adler-Longo method or 2) the Lindsey synthesis. The Adler-Longo method (Figure 2) employs a single-step reaction in which condensation and oxidation of the porphyrin occur all at once. It takes place in refluxing propionic acid (141°C) and has afforded preparation of multi-gram quantities of some porphyrins in yields of up to 20%<sup>3</sup>.

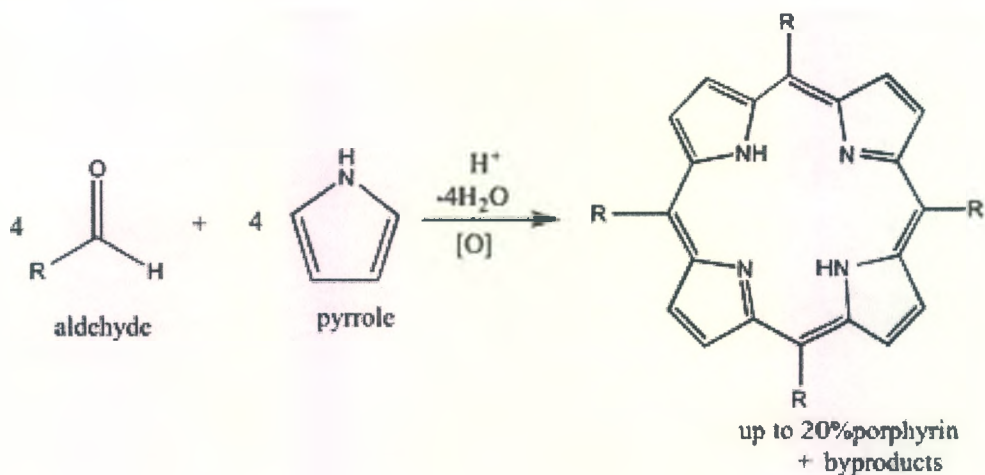


Figure 2: Adler-Longo synthesis of porphyrins: single step four-fold condensation and oxidation reaction of an aldehyde and pyrrole.

A complementary procedure is the Lindsey synthesis: a two-step process during which condensation is done in an anaerobic (oxygen-free) environment using chlorinated solvents, followed by the use of an oxidizer in a second step, to produce the porphyrin. The Lindsey synthesis is ideal for more sensitive aldehydes<sup>4</sup>.

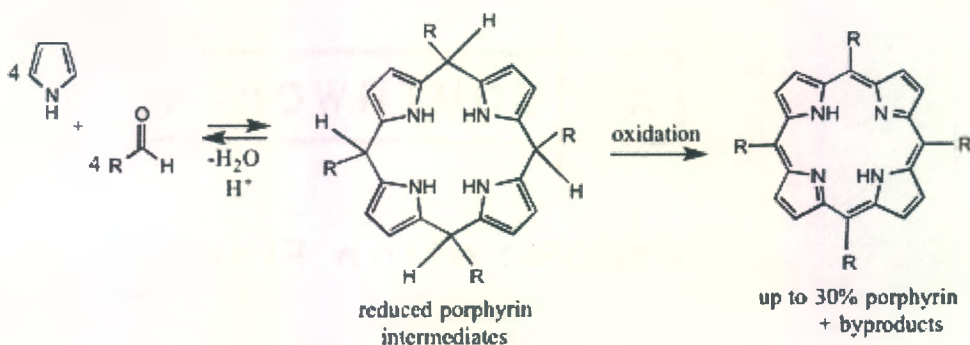


Figure 3: Lindsey synthesis of porphyrins: four-fold condensation of an aldehyde and pyrrole to give cyclized reduced-porphyrin intermediates, followed by addition of an organic oxidizing agent to form a porphyrin.

The major problem with both of these syntheses is the large amount of solvent needed to generate and purify such small yields of porphyrin. Although these methods are the current state-of-the-art in porphyrin production, yields are no higher than 30%. In addition, the large amounts of caustic or toxic solvents such as propionic acid or chloroform required are problematic in an industrial setting. This has hindered large-scale production of porphyrins for mass-produced applications, such as production of solar panels, in spite of the proven efficacy of porphyrins in such applications.

## 1.2 Green Chemistry

Green Chemistry is defined as “the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances”<sup>5</sup>. It adheres to twelve principles that were developed and later published by Paul T. Anastas and John Warner in 1998<sup>6</sup>. Many syntheses use harmful chemicals and complex methods to obtain desired results and these principles help revamp syntheses in ways that achieve sustainability. In recent years, awareness and desirability of Green Chemistry has grown in both industry and academia. In addition to the obvious environmental benefits, Green Chemistry has been proven to save industries both time and money. In contrast to many innovative ideas, Green Chemistry encourages the use of fewer resources to get a desired effect. Industries win because they save money and workers win by benefiting from safer working conditions<sup>7</sup>. The twelve principles of Green Chemistry are as follows<sup>6</sup>:

Table 1: The 12 Principles of Green Chemistry by Paul T. Anastas and John Warner.

<b>12 Principles of Green Chemistry</b>
1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficiency of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc) should be made unnecessary whenever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatisation (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

It can sometimes be difficult to determine if an alternative method is in fact “greener” than the original synthesis. There are several metrics that have been proposed to quantify exactly how “green” a reaction is and to compare the “greenness” of two reactive methodologies. In this work, I will focus on two such metrics: E-factor and Eco-factor<sup>8</sup>. E-factor is a metric that measures how much waste is used for the amount of product produced:

$$\text{E-factor: } \frac{\text{total waste}}{\text{total product}}$$

The EcoScale for determining the Eco-factor is more complex. Every synthesis starts with 100 total points and penalty points are taken away based on how poorly the synthesis adheres to the parameters of the EcoScale. In order to find the EcoScale value for a reaction, all of the penalty points must be added together and subtracted from 100. The larger the final number, the more “green” the synthesis is. It takes the following parameters into consideration:

1. Yield:

- To determine penalty points from the yield the following equation is used:

$$\frac{(100-\% \text{yield})}{2}$$

2. Price of Reaction Components:

- The price is based on the amount of reaction components needed to theoretically produce 10mmol of end product.
- Penalty points should be counted for each reaction component and then added together.

Table 2: Penalty points incurred from the price of reaction components.

Price	Penalty Points
Inexpensive (< \$10)	0
Expensive (> \$10 and < \$50)	3
Very Expensive (> \$50)	5

### 3. Safety:

Table 3: Penalty points incurred from safety hazards for the chemicals used.

Safety Hazard	Penalty Points
N (dangerous to environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10

### 4. Technical Setup:

Table 4: Penalty points incurred from various synthesis setups.

Setup Parameters	Penalty Points
Common setup	0
Instruments for controlled addition of chemicals	1
Unconventional activation technique	2
Pressure equipment > 1atm	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3

### 5. Temperature/ Time:

Table 5: Penalty points incurred from various reaction conditions.

Reaction Conditions	Penalty Points
Room temperature < 1 hr	0
Room temperature < 24 hr	1
Heating < 1hr	2
Heating > 1hr	3
Cooling to 0°C	4
Cooling < 0°C	5



## 6. Workup and Purification:

Table 6: Penalty points incurred from various purification methods.

Purification Method	Penalty Points
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction	3
Classical chromatography	10

This is a good evaluation of the various parameters to compare the “greenness” of different techniques. In this research, we hope to develop a greener synthesis of porphyrins than the current state-of-the-art synthesis employed in academic and industrial laboratories. We hope to do this by synthesizing porphyrins using mechanochemistry<sup>8</sup>.

### 1.3 Mechanochemistry

Mechanochemistry is defined as the “reaction, normally of solids, induced by the input of mechanical energy, such as by grinding either by hand or in ball mills.”<sup>9</sup> It dates as far back as the 4th century BC, but was not used to synthesize organic molecules until the 1980s. Mechanochemistry may be done either by manual grinding or automated grinding using a ball mill. The physical grinding of reagents together is a way of providing energy to a reaction without the use of a solvent, thereby creating a more efficient reaction. In some cases reactions are done in the presence of a few drops of solvent, but solvent is not always necessary for a successful reaction. Although

mechanochemistry is typically used for reactions between solids, our reaction is between two liquids in the presence of a solid acid to generate a solid product<sup>9</sup>. In automated grinding, the reactants are placed inside a steel jar along with two small metal balls that aid in grinding. The jar is placed on the ball mill where it is shaken back and forth. The movement forces the metal balls to hit the inside walls of the jar, mixing the reactants in the process. This produces enough mechanical energy to mix the reactants and cause them to form products.

#### 1.4 Green Purification

Traditional purification of porphyrins involves the use of large amounts of chlorinated solvents, such as chloroform and dichloromethane, mixed with silica in a tall column. There are two purification methods that have potential of providing a “green” alternative to silica columns: sublimation and recrystallization. Sublimation is the physical state change from a solid to a gas without first becoming a liquid. Porphyrins are known to undergo sublimation at temperatures of around 400°C. Two different types of sublimation were attempted: entrainment and traditional.

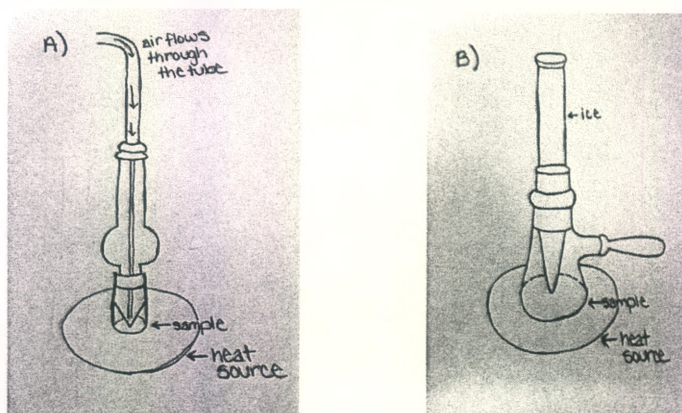


Figure 4: a) Apparatus needed for entrainment sublimation on a small scale. b) Apparatus needed for traditional sublimation on a small scale.

Traditional sublimation uses an ice filled condenser positioned above a heating device, such as a sand bath, to vaporize a product selectively from a mixture including impurities, and deposit the pure product on the surface of the ice filled condenser above. The difference with entrainment sublimation is the use of air or other gas to carry the sample vapors away from the heating source. In both cases, the sample will change state from solid to gas with heat and the pure product will become solid again and settle on either the cold finger in traditional sublimation or the air condenser in entrainment sublimation.

Recrystallization is the dissolution and cooling of a substance in solvent as a way to produce a pure product. The impure product is dissolved in a small amount of a hot solvent. As the resulting solution cools, the solubility of the product decreases. Because of this, the pure product will form crystals while the impurities will remain in solution. The liquid can then be filtered out, leaving only the desired pure product.

Sublimation and recrystallization do not use any kind of chlorinated solvents and the amount of acetic acid used for recrystallization is minuscule compared to the amount of solvent used in a column. The reduction or elimination of solvent is one of the Twelve Principles of Green Chemistry, making it extremely beneficial to the environment<sup>6</sup>. Reducing amounts of solvent also reduces the likelihood of chemical accidents, keeping both the environment and those living in it safer.

### 1.5 Characterization of Porphyrins

Porphyrins can be characterized by both UltraViolet Visible (UV-Vis) and Proton Nuclear Magnetic Resonance (<sup>1</sup>H NMR) Spectroscopy. A sharp, intense peak called a Soret band will appear around 417nm in the UV-Vis spectrum if a porphyrin is present<sup>10</sup>.

Other reduced-porphyrin products can also be indicated by various peaks at longer wavelengths than the Soret band<sup>11</sup>. They are present on the UV- Vis spectrum when oxidation has not fully occurred. Porphyrinogens have an excess of six hydrogen atoms attached to nitrogen atoms and methine bridges, as shown in the following figure.

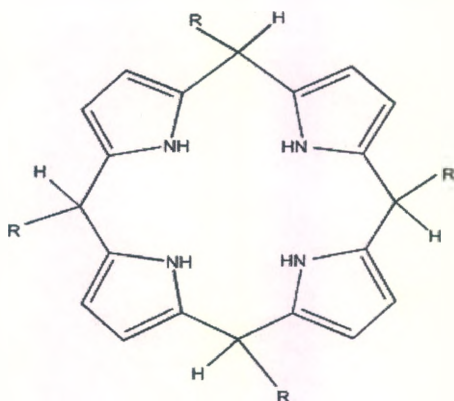


Figure 5: Porphyrinogen contains six more hydrogen atoms than a porphyrin. These can be removed in a stepwise manner, giving five other “reduced porphyrins”.

Oxidation occurs when these hydrogens are removed. Porphyrinogen itself does not absorb in the visible region, but some of the other “reduced porphyrins” do. Stages of oxidation correspond with the removal of each hydrogen atom. Each resulting molecule has been characterized and can be seen on a UV- Vis spectrum. The molecule does not become a porphyrin until all six hydrogens have been removed to give an aromatic cycle.

Proton NMR is another useful tool for characterization. The highly shielded protons attached to the nitrogen atoms on the inside of the porphyrin ring of the final aromatic product produce a singlet far upfield on the <sup>1</sup>H NMR spectrum. These singlets can be seen between -2 and -3ppm<sup>10</sup>. In my project, I used UV- Vis spectroscopy to confirm presence of a porphyrin and obtain a rough idea of the yield throughout our experiments.

## 1.6 Previous Work

Our group has found that equal molar quantities of pyrrole and an aldehyde (both liquids) will react upon grinding in the presence of toluenesulfonic acid to give a pink solid, which the UV-Vis spectrum reveals is a mixture of reduced porphyrin precursors. After oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 50mL of chloroform, a porphyrin is produced and shows a Soret band at 417nm. After purification by column chromatography, yields are close to 30%, similar to those from the Adler-Longo or Lindsey syntheses. This discovery shows it is possible to eliminate solvent from condensation of pyrrole and an aldehyde in a mechanochemical reaction and still produce similar results to those obtained with a solvent in the first step, providing for a “greener” synthesis. However, both the oxidative aromatization and purification steps remain less environmentally friendly.

Initially, the pink solid product from step 1 was left out in air and tested by UV-Vis spectroscopy for presence of porphyrin after one week, then after two weeks of air-oxidation. Oxidation in air seems the most “green” method for oxidation. However, the yield suffers. Although oxidation does occur, many other byproducts are also produced. Over time it was hoped that the amount of oxidized porphyrin would increase. However, results show that only a very small yield of porphyrin can be obtained this way. The porphyrin precursors revert to reactants if not oxidized soon enough after production, as seen in the UV-Vis spectrum. The following figure shows this behavior:

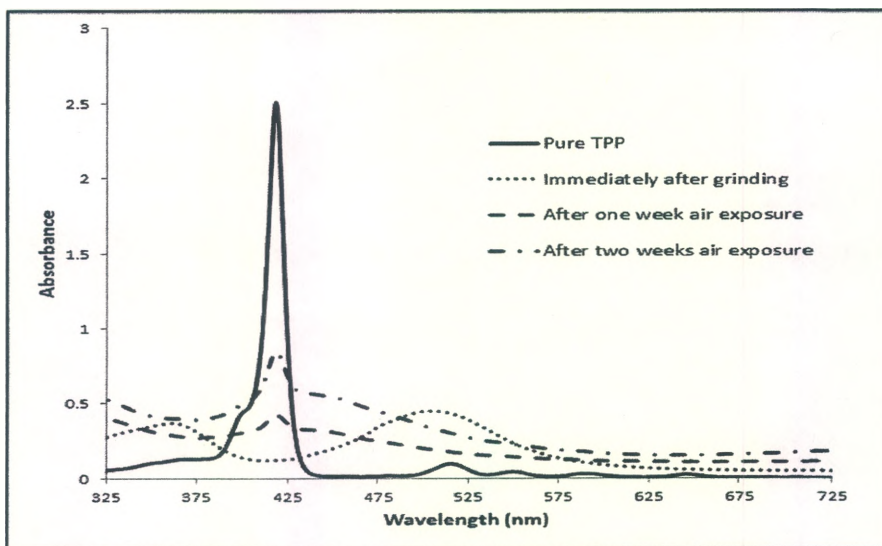


Figure 6: UV-Vis spectrum of TPP during various stages of oxidation.

### 1.7 Statement of Research

I plan to use Green Chemistry principles to find greener methodologies for 1) oxidative aromatization of reduced porphyrin intermediates to porphyrin and 2) purification of porphyrin from the final reaction mixture. I will use tetraphenylporphyrin (TPP) as a model compound. I propose to do this by introducing grinding for the oxidation step using several oxidizing agents and varying conditions such as grinding time and introduction of auxiliary grinding agents. Various non-chromatographic purification methods, such as sublimation and recrystallization will also be tested.

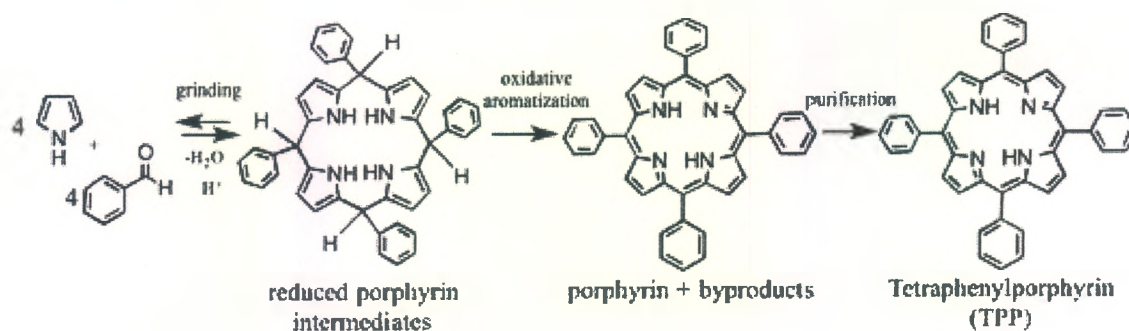


Figure 7: Full reaction scheme for the greener synthesis of tetraphenylporphyrin.

If successful, we will have developed an entire “green” synthesis of these important molecules.

### 1.8 Contribution to Society

The twentieth century brought much scientific and technological advancement that improved our quality of life. However, these advancements often came at a great environmental cost. Since these times, we have become more socially conscious. Global concerns about the environment have led chemists to propose and think about Green Chemistry when designing new chemical syntheses. Now, chemists can find alternative ways to produce the same technology that are less harmful to the environment. In the case of chemical research, desire to reach the end product by any means possible has traditionally directed the research process. The environment has now become more important to everyone and all sorts of measures have been taken with this in consideration. The most important motive behind green chemistry has been based on issues concerning the well-being and sustainable future of society, not just the advancement of science. Although in the past this has not been a concerning issue, in this particular case, value-conscious scholarship has been the primary motive.

Green Chemistry is now playing an important role in the way scientists perform their research. Although it is relatively new, it has already begun to have a positive impact on both science and the environment. By doing things such as using less toxic solvents, using renewable materials and designing safer chemicals, scientists have been able to perform their research effectively and more consciously. In addition, Green Chemistry syntheses have less of an impact on our already fragile environment<sup>12</sup>.

Other benefits of Green Chemistry include the potential cost savings by universities and companies and safer working and living conditions. Not only are most solvents harmful to the environment, they can also be very expensive and toxic to people exposed to them. By finding ways to eliminate them from chemical syntheses, the overall cost of the reaction can be significantly reduced. Unlike many other reforms in science that may cost money, the incorporation of Green Chemistry can actually reduce chemical costs. In addition, using less toxic chemicals provides safer conditions for the scientists working in chemical plants and the people who live near them<sup>12</sup>. By eliminating solvent and complicated procedures wherever possible, companies can also reduce the costs of safety training and waste disposal.

I plan to incorporate multiple Green Chemistry principles into the synthesis of porphyrins. This research will further the advancement of Green Chemistry as well as provide a safer, more effective way in which to perform this particular synthesis. If successful, this could open the door to improvements in many other chemical and biological processes. In addition, this research can be implemented in teaching labs at the undergraduate level. Students can learn this method of porphyrin synthesis to compare with more traditional methods, thereby exposing future chemists to Green Chemistry principles such as the use of safer solvents or waste reduction.



## 2. Experimental Procedure

### 2.1 Chemicals

All chemicals used were purchased from Sigma Aldrich and not altered from their purchased state, unless otherwise noted. Benzaldehyde and pyrrole were purified by distillation every two weeks, or whenever discoloration appeared. The starting purities of each compound can be seen in the following table:

Table 7: The starting purity of each chemical used in our experiments<sup>13</sup>.

Chemical	Purity
Benzaldehyde	> 99%
Pyrrole	98%
Toluenesulfonic Acid	98%
Iodobenzene Diacetate (IBD)	98%
Hydroxy(tosyloxy)iodobenzene (HTIB)	96%
Manganese (III) Acetate	97%
Sodium Percarbonate	99%
Sodium Perborate	97%
Ruthenium (III) Chloride	99%
Oxone <sup>®</sup>	98%
Sodium Ethoxide	95%
Nitric Acid	70%
Molecular Iodine	>99%

### 2.2 Equipment

Many instruments were vital in our research. A Retsch Mixer Mill MM 200 was used for mechanical grinding of reactants with each other and various oxidizing agents. Two stainless steel grinding jars of 10mL volume and four stainless steel balls of 5mm diameter were also used in the grinding process. A Perkin Elmer Lambda 850 UV/ Vis Spectrophotometer was used to measure absorption spectroscopy within the UV/ Visible range. The UV/ Vis Spectrophotometer measured from 200-800nm at 1nm intervals. The

samples were placed in quartz cuvettes 1cm in width. A thermocouple [BK Tool Kit 2706A] was used to measure the temperature in the sand bath during sublimation. It measures temperatures upwards of 500°C.

## 2.3 Procedures

### 2.3.1 Synthesis of Reduced-Porphyrin Precursors

A 1:1 molar ratio of benzaldehyde (0.380g, 3.73mmol) and pyrrole (0.259g, 3.73mmol) were combined with toluenesulfonic acid (0.026g, 0.151mmol) in one of the metal grinding jars (stainless steel, 10mL volume) of the ball mill along with two stainless steel balls (5mm diameter) to produce a pink powder. The initial grinding time for condensation was 20 minutes at a frequency of 25 Hz.

Manual grinding was done using an agate mortar and pestle. Pyrrole (0.259g, 3.73mmol) and toluenesulfonic acid (0.026g, 0.151mmol) were added to the mortar and were ground together until the acid was completely dissolved. Benzaldehyde (0.380g, 3.73mmol) was added and the new mixture was ground for approximately six minutes or until a dry pink solid formed.

### 2.3.2 Mechanochemical Oxidative Aromatization

An oxidizer (Figure 9) was added to the pink powder at either a 1:1.1 or 1:1.5 molar ratio with the benzaldehyde and pyrrole and returned to the ball mill. The initial grinding time was 20 minutes at a frequency of 25Hz. For manual grinding, the oxidizer was added in a 1 to 1.1 ratio with the pyrrole and benzaldehyde and ground for about 10 minutes changing the solid from a pink to a purple color. Each sample was tested for porphyrin content at a concentration of  $(3.00 \pm 0.01) \times 10^{-6}$  g/mL in chloroform using a UV- Vis spectrophotometer.

Following a procedure from Mphahlele, oxidation was performed using molecular iodine in methanol<sup>14</sup>. Manual grinding methods were used to produce the pink solid. Once the pink solid was produced, one of two methods was followed. In the first method, the pink solid was dissolved in 50mL of methanol along with 1.89g of I<sub>2</sub> and refluxed for 8 hours. That mixture was then washed with 50mL of deionized H<sub>2</sub>O and the organic layer was extracted with 25mL of chloroform three times. The organic layers were combined and washed with 50mL of 10% sodium thiosulfate solution then placed on a rotary evaporator until only solid remained.

In the second method, the pink powder was dissolved in 50mL of methanol and cooled to 0°C. Once cool, a solution of 1.89g I<sub>2</sub> in 10mL methanol and a solution of 0.836g of KOH in 10mL methanol were added to the mixture. The mixture was stirred for 1 hour, washed with 50mL of deionized H<sub>2</sub>O and the organic layer was extracted with 25mL of chloroform three times. The organic layers were combined, washed with 50mL of saturated sodium chloride solution and placed on a rotary evaporator until the solid was completely dry.

### 2.3.3 Green Purification

Both sublimation and recrystallization techniques were tested. In sublimation, a small amount of our crude TPP product was placed inside the flask. The apparatus was placed on a sand bath and heated to 400°C. The heating process continued until the pure product could be seen on the condenser.

In recrystallization, a small amount of crude TPP product was placed in the bottom of a round bottom flask. Enough chloroform was added to allow the entire

product to dissolve. The flask was then placed inside a refrigerator until the pure product was recrystallized.

#### 2.4 Preparation of Samples for UV-Vis

In order to determine the percentage of pure TPP in each reaction mixture after oxidation, each UV-Vis spectrum was recorded using a  $(3.00 \pm 0.01) \times 10^{-6}$  g/mL concentration of sample in chloroform. It could then be compared to a known spectrum of pure TPP at the same concentration. This is possible because of Beer's Law, which defines the direct dependence of absorbance on concentration of a solution. A set concentration was found by first measuring out  $(3.00 \pm 0.01) \times 10^{-2}$  g of pure TPP and dissolving it in 10.00mL of chloroform. A diluted solution was then created by extracting 1.00mL of the existing solution with an Eppendorf pipet and diluting to 10.00mL with chloroform. This was done three times until the final concentration was reached. The absorbance level of pure TPP at 417nm was 1.056 for the final concentration of  $(3.00 \pm 0.01) \times 10^{-6}$  g/mL; this was used as a standard for all other UV-Vis spectra of samples at the same concentration.

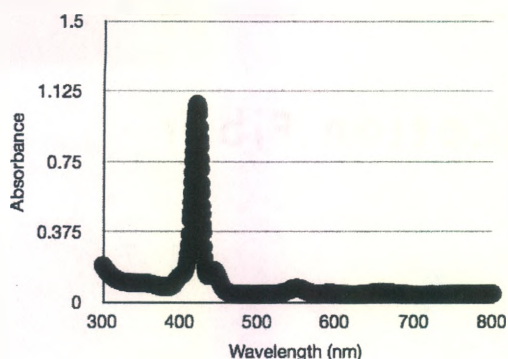


Figure 8: The UV-Vis spectrum of pure TPP at a concentration of  $(3.00 \pm 0.01) \times 10^{-6}$  g/mL.

### 3. Results and Discussion

#### 3.1 Solid Mechanochemical Oxidizing Agents

In the Lindsey porphyrin synthesis, where oxidation is separated from condensation, the oxidation step uses a gentle organic oxidizer like 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to oxidize the cyclized porphyrin precursor. This oxidation is done in 50mL chloroform with 2.117g DDQ for a sample of 0.259mL of pyrrole and 0.380mL of benzaldehyde (a 3:1 molar ratio of DDQ to benzaldehyde and pyrrole). The solution is mixed on a magnetic stir plate for a minimum of 30 minutes. The porphyrin is then separated from the resulting mixture using silica gel column chromatography with ethyl acetate/ hexanes (1:9) as the mobile phase. Solvent is removed from the final product using a rotary evaporator. The product is characterized using UV-Vis and/or Proton NMR spectroscopy<sup>4</sup>.

In order to “green” the oxidation step in porphyrin synthesis, we substituted oxidizing agents that needed chlorinated solvents with oxidizing agents that we hoped would perform oxidative aromatization mechanochemically, without a solvent. When selecting potential mechanochemical oxidizing agents, we looked for those that had already proven successful in oxidative aromatization, either in the solid state, in a “green” solvent, like methanol, or in other solvents. In addition, we looked for chemicals that were relatively non-toxic and easy to produce in the lab, making them less expensive. Every oxidizer selected fits at least one of these criteria.

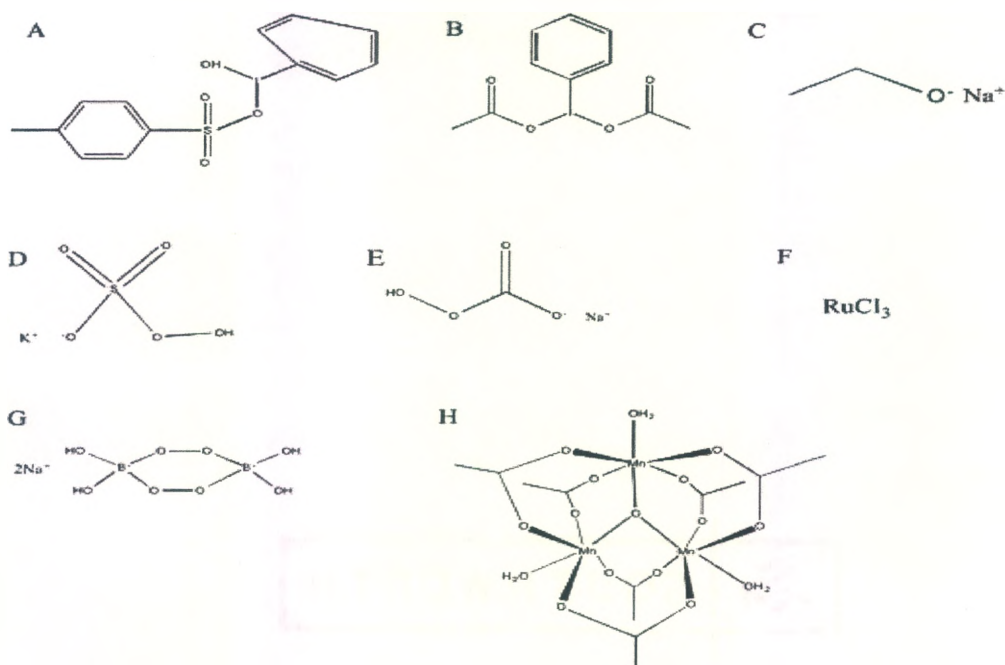


Figure 9: Chemical structures of oxidizers used: a) Hydroxy(tosyloxy)iodobenzene (HTIB); b) Iodobenzene Diacetate (IBD); c) Sodium Ethoxide; d) Potassium Peroxymonosulfate (Oxone<sup>®</sup>); e) Sodium Percarbonate; f) Ruthenium (III) Chloride; g) Sodium Perborate; h) Manganese (III) Acetate.

The majority of these oxidizing agents were chosen for their proven ability to oxidize non-aromatic structures into aromatic structures in previous solution-based reactions<sup>14-16</sup>. Sodium Perborate and Sodium Percarbonate were chosen because they are relatively nontoxic, inexpensive oxidizers found in household cleaning agents and bleaches. Oxone<sup>®</sup> was tested because of its past success in the mechanochemical oxidation of sulfur compounds<sup>17</sup>, as well as the oxidation of amines<sup>18</sup>, alcohols<sup>19</sup>, aldehydes<sup>20</sup> and ketones<sup>21</sup>. However, mechanochemical oxidative aromatization of a porphyrin or similar molecule has never been reported in literature.

As a starting point, in order to test the effectiveness of each oxidizing agent the grinding time of the oxidation step was set for 20 minutes after the initial porphyrin

precursor was made by also grinding for 20 minutes. Each sample was tested qualitatively for the presence of porphyrin, indicated by a sharp peak at 417nm in the UV-Vis spectrum. For our control experiment, the porphyrin precursor was made and left in air for 20 minutes.

Table 8: Initial results for oxidizing agents, indicated by the presence of a Soret band.

Oxidizing Agent	Soret Band (Y/N)
Control	No
Iodobenzene Diacetate (IBD)	Yes
Hydroxy(tosyloxy)iodobenzene (HTIB)	Yes
Manganese (III) Acetate	Yes
Sodium Percarbonate	Yes*
Sodium Perborate	Yes
Ruthenium (III) Chloride	Yes
Oxone <sup>®</sup>	No
Sodium Ethoxide	Yes*

\*These reaction mixtures exhibited the sharpest Soret bands, compared to peaks for unoxidized materials in their spectrum.

From here, other factors were varied, in hopes of improving yield. These included changes in grinding method, the addition of grinding agents and grinding times. In addition, a set concentration was introduced to gain quantitative data on the yield.

### 3.2 Grinding Methods

The first change made was to switch from automated to manual grinding. With manual grinding, the reaction takes place in a mortar and pestle out in the open making it easy for us to see what is happening with the reaction. As opposed to automated grinding, there is no chance that grinding could be hindered if the metal balls became stuck in the solution. This was done in order to see the difference; automated grinding is much more practical for large-scale syntheses. The two best oxidizers from the initial attempts,

Sodium Perborate and Sodium Ethoxide, were selected for manual grinding. In addition, Oxone<sup>®</sup> was chosen even though it did not show the presence of a Soret band upon automated grinding. Due to its previous success as a mechanochemical oxidizer, we hoped it would eventually be successful with some variation of reaction conditions. The results can be seen in the following table and UV-Vis spectra:

Table 9: Percent yields from manual and automated grinding

Oxidizer	Manual ( $\pm 0.01$ )	Automated ( $\pm 0.01$ )
Sodium Perborate	7.29%	8.28%
Sodium Ethoxide	8.97%	6.91%
Oxone <sup>®</sup>	6.16%	0%

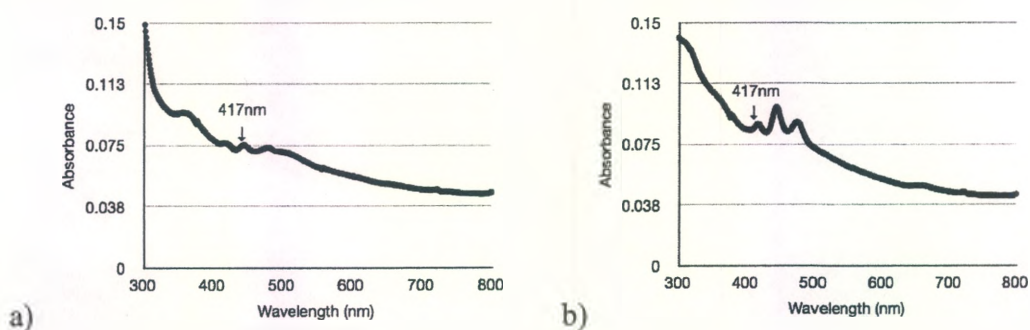


Figure 10: UV- Vis spectra with Sodium Perborate as the oxidizing agent using a) manual grinding and b) automated grinding.

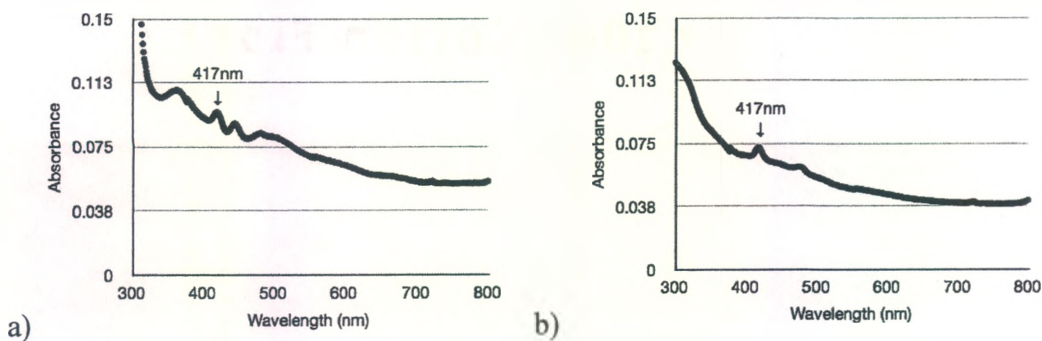


Figure 11: a) UV- Vis spectra with Sodium Ethoxide as the oxidizing agent using a) manual grinding and b) automated grinding.



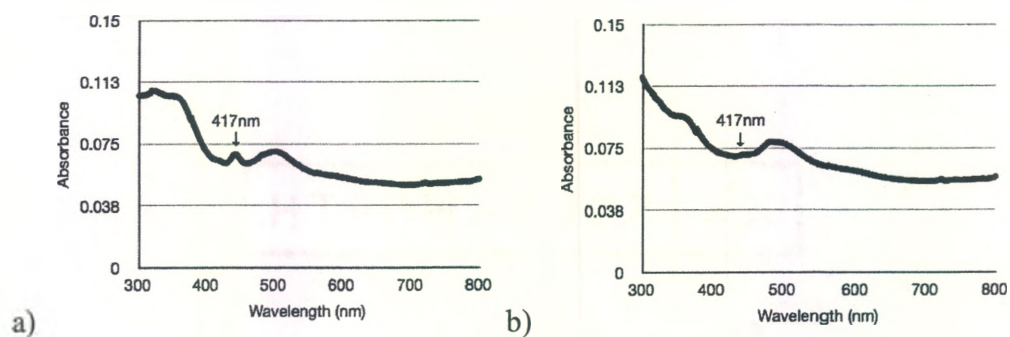


Figure 12: a) UV- Vis spectra with Oxone<sup>®</sup> as the oxidizing agent using a) manual grinding and b) automated grinding.

Based on the increases in percent yield, the switch from automated to manual grinding resulted in a slight improvement for both Sodium Ethoxide and Oxone<sup>®</sup>, but not for Sodium Perborate. The most success was with Oxone<sup>®</sup>; where there initially was no Soret band in the 400-420nm range, the switch to manual grinding resulted in a small band at 417nm. Both Sodium Perborate and Sodium Ethoxide also showed small bands at both 443nm in addition to the Soret bands at 417nm. The band at 443 nm is a sign that although some oxidation did take place, the precursor did not lose all six hydrogens, to make a porphyrin. Even though there was a decrease in yield upon going from automated to manual grinding for Sodium Perborate, the UV- Vis spectrum for automated grinding showed a more prominent peak at 443nm than at 417nm, indicating oxidation did not fully take place. Although this method resulted in improvements in yield, other changes were made to the synthesis in order to further increase yields.

### 3.2.1 Nitric Acid as an Oxidizer

Nitric acid was tested as another possible oxidizer, both by manual and automated grinding<sup>14</sup>. Nitric Acid, although corrosive, is not toxic and can easily be neutralized and removed from a final product without causing environmental harm. After using manual grinding to produce the pink solid, six drops of nitric acid were added and the mixture

was ground for about 10 minutes. This resulted in a very small Soret band at 417nm in addition to another band at 443nm.

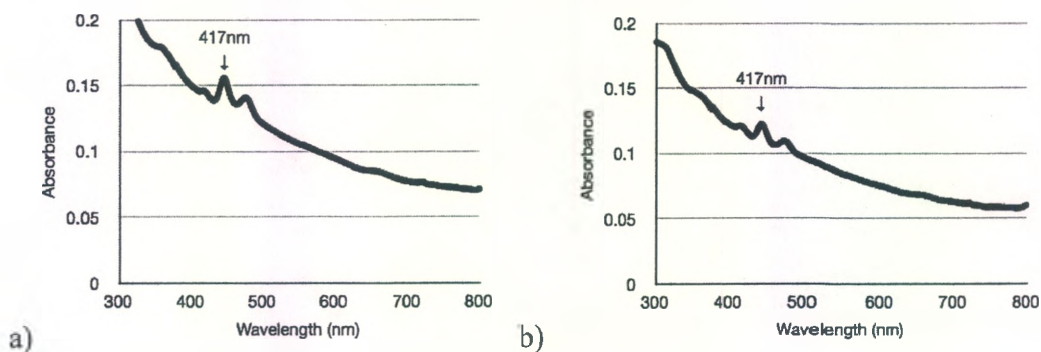


Figure 13: a) UV- Vis spectra with Nitric Acid as the oxidizing agent using a) manual grinding and b) automated grinding.

The band at 443nm indicates that oxidation has not been completed. For automated grinding, both the condensation and oxidation steps were carried out for 20 minutes in the ball mill. Nearly identical results were found from both manual and automated grinding producing yields at 13.8% and 11.5% respectively. However, the nitric acid corroded the inside of the grinding jars. Even though the overall TPP yield improved, the change was not significant enough to make up for the difficulty in handling of nitric acid in comparison with the other oxidizing agents.

In an attempt to overcome some of the difficulties, the pink solid from condensation was exposed to nitric acid vapors instead of put back into the ball mill. The powder was placed in an open vial which was placed inside a closed jar containing a small amount of nitric acid at the bottom. The jar was sealed and left for two hours. This did not produce any desirable results. In contrast, the UV-Vis spectrum showed no signs that any type of oxidation had taken place.

### 3.3 Use of Grinding Agents

In some cases, a grinding agent was added to the reaction to aid with the grinding process by reducing the stickiness of, increasing friction of and removing water from the reaction. We tested three grinding agents: sodium chloride, silica and magnesium sulfate, with the hopes they would help drive the reaction forward by removing the water produced from the reaction between benzaldehyde and pyrrole and alleviate the “stickiness” of the reaction mixture (facilitating grinding). The most success came with either Oxone<sup>®</sup> or Sodium Ethoxide as oxidizing agents with a set grinding time of 20 minutes for each step. The following tables show these results.

Table 10: Percent yields using grinding agents with Oxone<sup>®</sup> or Sodium Ethoxide.

Grinding Agent	Oxone <sup>®</sup> (±0.01)	Sodium Ethoxide (±0.01)
None	0%	8.18%
Silica	5.31%	5.18%
Sodium Chloride	4.69%	0%
Magnesium Sulfate	0%	9.29%

The following UV-Vis spectra show the most successful of the experiments from

Table 10:

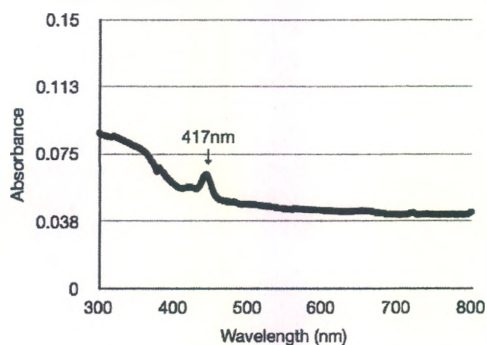


Figure 14: UV using Oxone<sup>®</sup> with silica as the grinding agent.

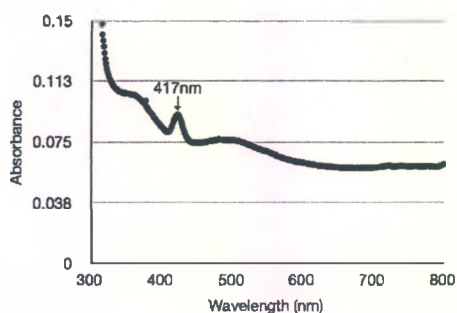


Figure 15: UV using Sodium Ethoxide with magnesium sulfate as the grinding agent.

Table 10 shows that silica was the most successful grinding agent for Oxone<sup>®</sup> and magnesium sulfate was the most successful grinding agent for Sodium Ethoxide. A significant change can be seen with Oxone<sup>®</sup>; the use of silica allowed for oxidation even though no oxidation occurred without a grinding agent present. Sodium Ethoxide also showed a significant improvement. The next change made was the grinding time for each step.

### 3.4 Grinding Times

Using automated grinding, grinding time was varied for both the first step (condensation) and the second step (oxidation). First, time for oxidation was kept at a constant 40 minutes while time for condensation was varied from 20 to 60 minutes.

Table 11: Percent yields for changes in grinding time of condensation.

Step 1 Grinding Time	Oxone <sup>®</sup> ( $\pm 0.01$ )	Sodium Ethoxide ( $\pm 0.01$ )
20 minutes	0%	0%
40 minutes	5.13%	5.22%
60 minutes	7.12%	5.44%

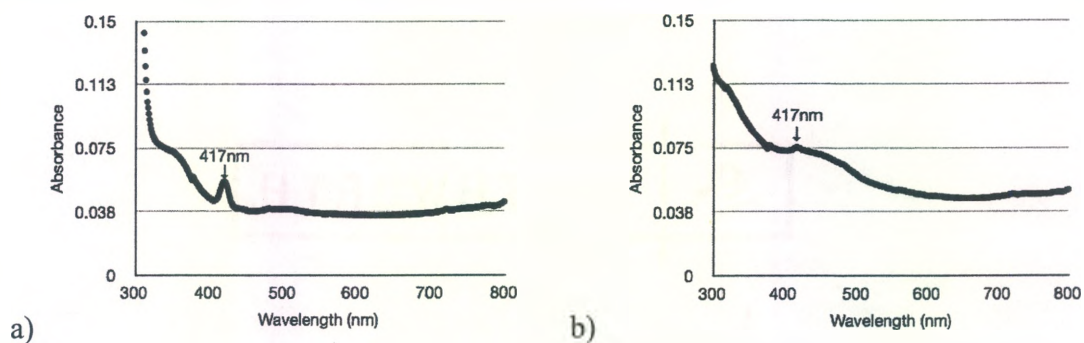


Figure 16: UV- Vis spectra with a grinding time of 60 minutes for condensation and 40 minutes for oxidation using a) Sodium Ethoxide as the oxidizing agent and b) Oxone<sup>®</sup> as the oxidizing agent.

The percent yield increased with the increase in grinding time for step 1 for both Oxone<sup>®</sup> and Sodium Ethoxide. Although the percent yield is higher with Oxone<sup>®</sup> as the oxidizing agent, the UV-Vis spectrum using Sodium Ethoxide shows a more definitive Soret band at 417nm than that using Oxone<sup>®</sup>. This method did not turn out to be as successful as expected. The increase in grinding time did not lead to significantly larger yields. This ends up being less “green” because of the energy used by the ball mill for those extended periods of time.

Next, we used a constant grinding time of 30 minutes for condensation, then grinding for oxidation over the course of eight hours in 30 minute intervals. For each grinding time change, a UV-Vis spectrum was taken of the sample after each time to verify the presence of porphyrin. This was done both with and without grinding agents and a final absorbance was not measured until after the eight hours had passed.

Table 12: Percent yields of Oxone<sup>®</sup> and Sodium Ethoxide after grinding time of eight hours for oxidation.

Grinding Agent	Oxone <sup>®</sup> (±0.01)	Sodium Ethoxide (±0.01)
None	8.06%	6.65%
Silica	0%	7.01%
Sodium Chloride	0%	4.98%
Magnesium Sulfate	0%	5.48%

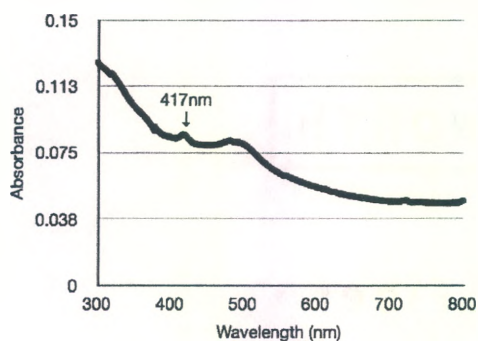


Figure 17: UV of Oxone<sup>®</sup> with no grinding agent present and eight hours of oxidation.

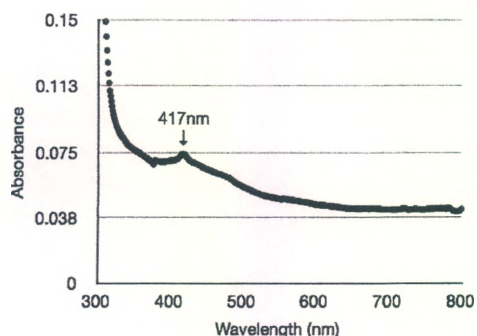


Figure 18: UV of Sodium Ethoxide with silica as a grinding agent and eight hours of oxidation.

Oxone<sup>®</sup> and Sodium Ethoxide reacted very differently with the addition of grinding agents under the conditions named above. Sodium Ethoxide produced percent yields that were about the same with and without the presence of a grinding agent. Oxone<sup>®</sup> on the other hand, showed a small Soret band at 417nm without a grinding agent. When a grinding agent was used, the appearance of the Soret band was inconsistent. It

kept disappearing and reappearing each time a new UV- Vis spectrum was taken. In addition, the yields obtained were no better than the yields when other changes were made to the synthesis. Just like the other change with grinding time, a synthesis with an extremely long grinding time like these ones leads to a less “green” synthesis than when other variables of the synthesis are changed.

### 3.5 Molecular Iodine as an Oxidizer

Molecular iodine in methanol was tested as an oxidizing agent. This is similar to a synthesis with DDQ as an oxidizing agent with chloroform as the solvent. In both cases large amounts of solvent and extensive purification methods must be used to obtain a final pure product.

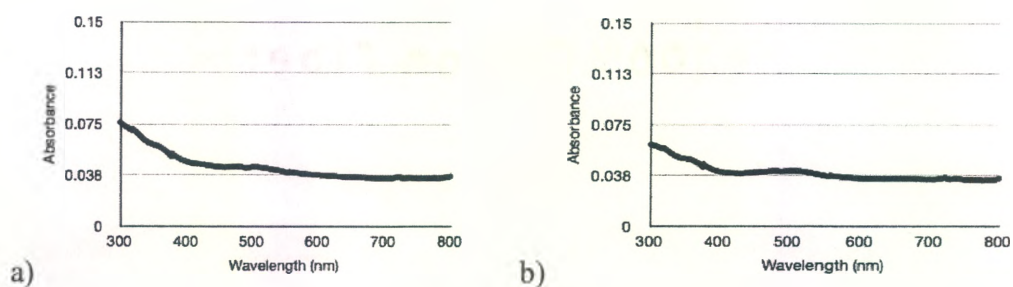


Figure 19: a) UV of method 1 using molecular iodine as the oxidizer. b) UV of method 2 using molecular iodine as the oxidizer.

As shown in the results above, no Soret band could be seen at 417nm. Even though methanol is a better solvent, the yields are far worse than any obtained using DDQ in chloroform. Because of this, different methods were used to try and create a more successful and “green” synthesis.

### 3.6 Benzaldehyde as an Oxidizer

In addition to the oxidizing agents listed above, benzaldehyde was also used as an oxidizer. Two different techniques were tested: 1) an additional amount of benzaldehyde

added as the oxidizing agent with a 3:1 molar ratio to the initial amounts of benzaldehyde and pyrrole and 2) a 10:1 initial molar ratio of benzaldehyde to pyrrole in a one-step reaction. The first set of reaction conditions had grinding times of 20 minutes for both the condensation and oxidation steps of the reaction. The second set of reaction conditions underwent grinding for 60 minutes in an attempt to allow both condensation and oxidation to occur with an excess of benzaldehyde.

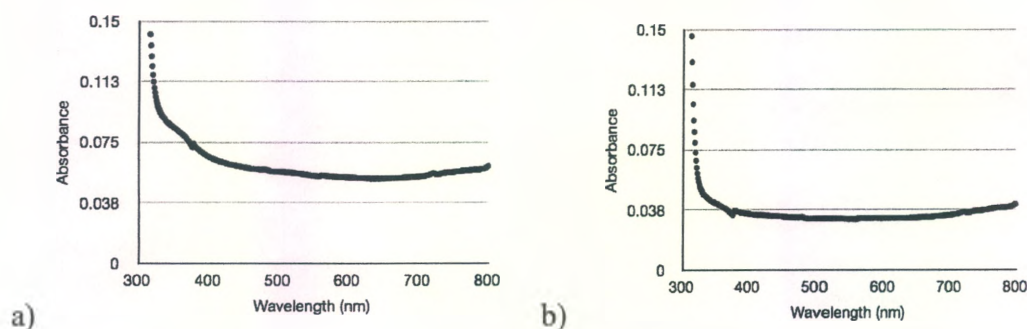


Figure 20: a) Two step synthesis of porphyrin with benzaldehyde as the oxidizer. b) One step synthesis of porphyrin with benzaldehyde as the oxidizer.

As shown from the UV-Vis spectra above, the use of benzaldehyde as an oxidizing agent was not successful. In each case, no Soret band could be seen at 417nm.

### 3.7 Green Purification Techniques

Sublimation and recrystallization techniques were attempted as an alternative to column chromatography. Recrystallization was done using a small amount of acetic acid. In addition, we hoped the acetic acid would also aid in the oxidation process. However, this method of purification did not prove successful. The pure product never recrystallized in the acetic acid. Despite the lengthy amount of time it was left to recrystallize, the solution remained a dark brown liquid and no crystals ever formed.

Although there was not much success with traditional sublimation at a small scale, there was some success with small scale entrainment sublimation. Trace amounts



of a purple substance appeared on the condenser after prolonged heating in a sand bath. However, not enough product was recovered to get a sample big enough for a UV-Vis spectrum. In addition, product was only sublimed when heated in the sand bath at 400°C for several hours.

### 3.8 EcoScale Metrics

The “greenness” of various syntheses could be calculated using the parameters of the EcoScale<sup>9</sup>. Calculations were done to compare 1) the traditional Lindsey synthesis, 2) a mechanochemical synthesis with DDQ as the oxidizer and 3) a mechanochemical synthesis with Sodium Ethoxide as the oxidizer. The results are shown in the following tables:

Table 13: EcoScale metrics for the Lindsey Synthesis.

Category	Penalty Points
Yield	35
Price of reaction components	37
Safety	60
Technical setup	1
Temperature/ time	3
Workup and purification	10
Total	146
Eco-factor	-46
E-factor	2783.7

Eco-factor for the Lindsey synthesis was calculated assuming a maximum percent yield of 30%. This synthesis has an EcoScale number of -46, meaning it is extremely hazardous to the environment. Most of the penalty points are a result of the safety hazards from auxiliary chemicals used during each step of the synthesis. In addition, this synthesis has an E-factor of 2783.7, meaning the amount of waste is very high when

compared to the amount of product produced. The elimination of some of these chemicals could result in an improvement even if the final yield were not as high.

Table 14: EcoScale metrics for mechanochemical condensation, followed by oxidation with DDQ.

Category	Penalty Points
Yield	37.5
Price of reaction components	32
Safety	50
Technical setup	1
Temperature/ time	3
Workup and purification	10
Total	133.5
Eco-factor	-33.5
E-factor	1681.96

This synthesis was done using solvent free mechanochemistry for the condensation of benzaldehyde and pyrrole. The oxidation was done in solution with DDQ as an oxidizer, and purification by column chromatography. Both the oxidation and purification for this synthesis therefore, are the same as the Lindsey synthesis. Based on the improvement from 146 to 133.5 penalty points, it is clear that by removing solvent from step one has made the reaction more “green” even though the percent yield decreased from 30% to 25% with the change. In addition, there was an E-factor improvement of over 1000, indicating a decrease in waste produced for the reaction. However, despite the improvement, this synthesis still has a negative Eco-factor.

Table 15: EcoScale metrics for mechanochemical condensation, followed by oxidation with Sodium Ethoxide.

Category	Penalty Points
Yield	45.36
Price of reaction components	15
Safety	30
Technical setup	0
Temperature/ time	0
Workup and purification	3
Total	93.36
Eco-factor	6.64
E-factor	19.7

This synthesis was done using solvent free mechanochemistry in two steps with Sodium Ethoxide as the oxidizing agent in addition to silica as a grinding agent. This is a significant improvement from oxidation with DDQ and an even greater improvement over the Lindsey synthesis. Removing solvent from both condensation and oxidation steps improved the number of penalty points from 133.5 with DDQ to 93.36 with Sodium Ethoxide, despite the decrease in percent yield from 25% to 9.29%. In addition, the E-factor decreased from 1681.96 to 19.7, which can be attributed to the switch in purification method. Of the three methods for porphyrin synthesis compared, this is the only one with a positive Eco-Factor.

#### 4. Conclusion

Our results show that solvent-free mechanochemical oxidative aromatization can be done with some success. Most of the oxidizing agents tested produced tetraphenylporphyrin, but some were more successful than others. Oxone<sup>®</sup> and Sodium Ethoxide were the most successful oxidizing agents. Changes to grinding time, grinding method and the addition of grinding agents did produce slightly better yields, but were also inconsistent. In addition, the EcoScale proved that our changes resulted in a “greener” and more environmentally friendly synthesis.

Further experimentation should be done to find a “green” oxidation method that will produce better results. The highest percent yield obtained was still only about half of the typical percent yields of both the Adler-Longo and Lindsey syntheses. Future work should involve: 1) using new oxidizing agents and 2) large scale entrainment sublimation. Ferrate, 30% hydrogen peroxide and 30% hydrogen peroxide with surfactant are potential oxidizing agents. Performing grinding in an oxygen atmosphere is another possibility, however, special equipment would be required to introduce this into grinding jars. Once more success is found for oxidation, “green” purification techniques should also be tested more thoroughly. Although a small scale sublimation produced traces of tetraphenylporphyrin, sublimation on a larger scale, using a tube furnace, should produce a large enough sample of porphyrin that could then be tested for purity by UV- Vis spectroscopy.

We have already had success in improving the “green-ness” of porphyrin synthesis with the changes made to porphyrin synthesis thus far. Green Chemistry principles including: 1) elimination of waste and auxiliary substances, 2) use of less

caustic materials and 3) minimizing potential chemical accidents were all successfully employed in my research. This is just another step towards a complete green synthesis of porphyrins which could later be implemented on a larger scale both in industry and in academia.

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