The Optimization Of Dipyrromethane Synthesis

By: Jonathan Mikael Kenneth Bryant

Submitted to:
Frank LaBanca, Program Director
Newtown High School Applied Science Research Program
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Abstract

Dipyrromethanes are one of the cofactors in the synthesis of porphyrins; porphyrins are aromatic compounds that have very specific yet important applications in biology and chemistry. For example, porphyrins can be used in photophysics and photodynamic therapy in the treatment of cancer. In 1960, MacDonald discovered a the new method of making dipyrromethanes that solved preceding problems of pyrrole redistribution enabling scientists to make porphyrins more readily. This experiment will conduct a more recent variation of this synthesis, a one-step synthesis conducted in water, in the hopes of making a pure aqueous solution of dipyrromethanes. This synthesis of β-free-dipyrromethanes has been shown to be a cheap, non-toxic, and environmentally friendly means of acquiring dipyrromethanes in a one-step procedure using pyrrole and carbonyl compounds. In doing so, this will further provide information which will be used to determine what variables could be changed to yield an even higher percentage of dipyrromethane and, subsequently, porphyrins.

Introduction

Firstly, lets consider what are dipyrromethanes. Dipyrromethanes are actually very beneficial compounds composed of three constituents pyrrole, ketone, and an acid (fig.1). Seemingly useless by themselves, dipyrromethanes are one of the cofactors in the synthesis of porphyrins, which have many uses. Different dipyrromethanes produce different porphyrins. These porphyrins are then used in applications such as photophysics or photodynamic therapy. Photophysics is the usage of porphyrins to determine speeds; different speeds produce different colors, which let scientists know the velocity at which an object is moving. Photodynamic therapy is the use of porphyrins to destroy tumors. Light-sensitive porphyrins are injected into the tumor and then doctors shine a certain wavelength of light destroying the cancerous cells. On a little side note, Dr. Bruchner, of the University of Connecticut, is trying to find of porphyrin that will be sprayed on bees to find out how they fly. Aerodynamically, bees shouldn't be able to fly; normally animals must have slender bodies with large wings in proportion to their bodies, which is clearly not seen in the typical bee.

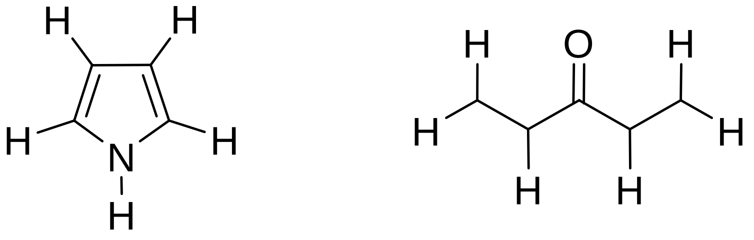

Fig. 1
These are the molecular structures of pyrrole and 3-pentanone (a ketone) respectively.

Dipyrromethane research is a rather new subject thus little information can be acquired about them. With the seemingly unlimited variable changes, dipyrromethane synthesis can be altered in many areas, although not easily. The use of highly reactive constituents pose a problem when synthesizing as slight contamination of an instrument or chemical can leave the product looking entirely black or orange. Maintenance of ones instruments is crucial in dipyrromethane production or the product may be unpredictable. When finally completed with multiple syntheses, there should be many to one variable(s) of dipyrromethane that are viable, which would conclude this project with success. The molecular structure of the final product is shown below in figure 2.

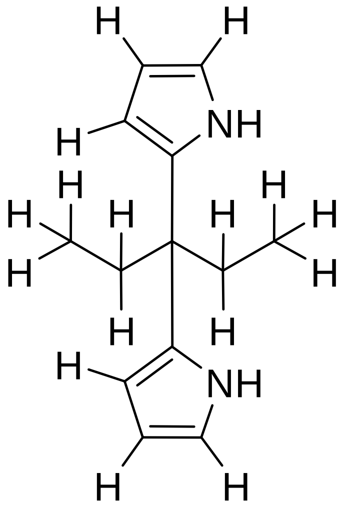

Fig. 2
The molecular structure of dipyrromethane.

Dipyrromethane synthesis is achieved by combining pyrroles, ketones, and acids. The first step in this procedure involves the combination of these three chemicals. The reaction then starts off with the acid's hydrogen ions attaching to the ketone double bonded oxygen leaving it with a single bond; this is called protonation. This is a direct result of hydrogen ions' affinity for electron rich oxygen. This compound now has a tertiary carbon that is electron deficient. A pyrrole ring, which is electron rich, now attaches itself to the tertiary carbon and restructures the bond arrangement because nitrogen is electron rich. It then quickly rearranges itself internally to form a stable compound. The acid's hydrogen ion then protonates attaching itself to the compound's hydroxide. The compound then loses H$_2$0 resulting in another tertiary carbon. An electron rich pyrrole ring then once again attaches itself to the tertiary carbon. The compound then rearranges its bonds to form the final product. This reaction can be seen visually below in figure 1.

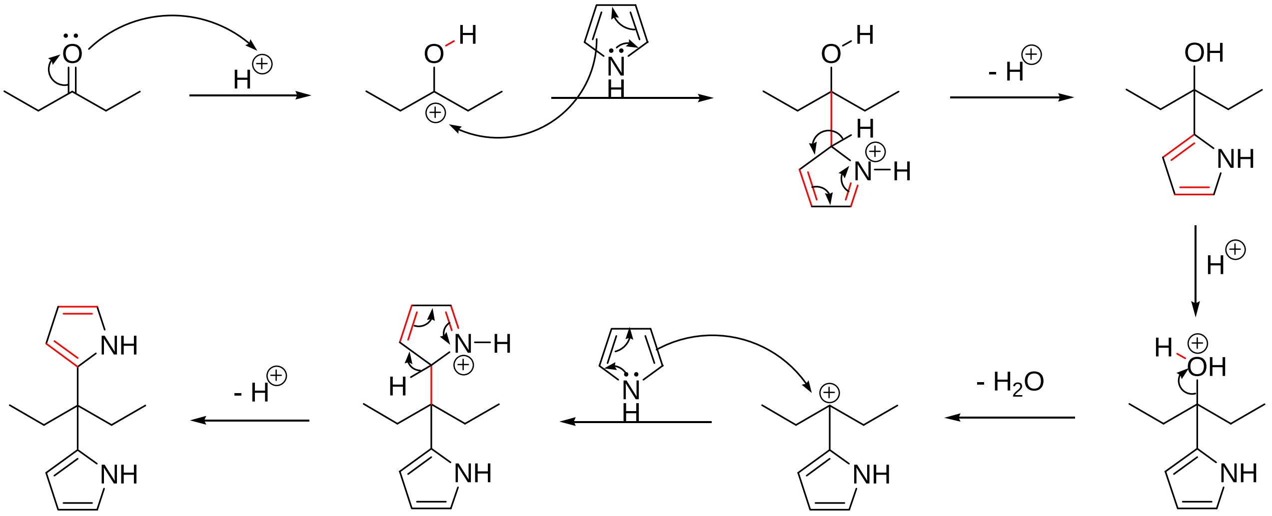

Fig. 3
The chemical process that takes place in dipyrromethane synthesis.

Materials & Procedure

Dipyrromethane Synthesis (Control)

Materials

Chemical / Consumables	Supplies	Equipment
1mL pyrrole 0.1mL 37% aq HCl 3mL 3-pentanone 20ml distilled water	3-neck flask 2 20mL glass burette 1cm magnetic stirring bar Condenser Separatory burette Pipette Test tube 25mL glass bowl Tubing Thermometer Graduated cylinder Micropipette	Power converter Magnetic stirrer Access to water supply Heater Support stand Support rod Burette clamp Dome-shaped heater (for flask)

Procedure

Set up the magnetic stirrer in a hood that has access to both electricity and water. Place the heater on top of the magnetic stirrer and plug the heater into the power converter. Set up the support stand and rod behind the magnet stirrer. Place the 3-neck flask into the heater and add the condenser into the middle neck along with the separatory burette on the left of it. Use the clamp to hold the condenser in place making sure everything can stand by itself. Place the magnetic stirring bar into the flask and turn on the magnetic stirrer to a slow and steady speed. Pour 20mL of distilled water into the flask and adjust the power as needed to bring the temperature of the water to a boil. Measure and pour 3mL of 3-pentanone into the water using a glass burette. Add 0.1mL of 37% aqueous hydrochloric acid using the micropipette followed by the dropwise addition of 1mL pyrrole. Reflux for 30 to 45 minutes. Pour the solution into a test tube and let it cool to 40^{o}C - 50^{o}C. Transfer the upper layer into the 25mL glass bowl using a pipette and let it cool to room temperature.

Purification Procedure (Control)

Materials

Chemical / Consumables	Supplies	Equipment
Silicone gel Dipyrromethane solution 10mL dichloromethane 1mL pyrrole 1mL 3-pentanone 1mL 37% aq HCl	Open ended glass burettes Chromatography paper 250mL beaker Cotton wool 25mL glass bowl	Access to pressurized air Ultraviolet lamp

Procedure

Place a bit of cotton wool in the end of the thinner opening on the glass burette making sure it is tightly packed. Pour silicone gel into the burette until approximately half full. Pour ~3mL of dichloromethane onto your dipyrromethane crystals making sure it all dissolves. Pour this into the burette so it rests on top of the silicone gel. Apply pressurized air on the top of the burette forcing the solution to pass through the silicone gel. Occasionally put a drop of solution from the receiving end on chromatography paper while allowing the rest to go into a 25mL glass bowl. Mark the initial spot where the droplet was placed and then put these chromatography papers in a 250mL beaker filled with ~7mL of dichloromethane. Let five minutes or so go by until chromatography papers have developed. Let them dry and put them under the ultraviolet lamp. Drop 1mL of pyrrole, 3-pentanone, and 37% aq HCl on three separate chromatography strips. Mark the initial spot and develop the same way the other were developed. Contrast the marks left on the chromatography paper under the ultraviolet light. If marks are seen at the same height of one of the impurities (pyrrole, HCl, or 3-pentanone) filter your solution once more through the silicone gel. Repeat procedure as necessary.

Results

After several attempts to synthesize dipyrromethane the results were as follows:

Dipyrromethane Synthesis Variable Chart

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
Ketone or Aldehyde	3-Pentanone	3-Pentanone	3-Pentanone	3-Pentanone	Benzaldehyde	Benzaldehyde
Acid	37% aq HCl	37% aq HCl	37% aq HCl	37% aq HCl	37% aq HCl	37% aq HCl
Temperature of Water	68°C	85°C	97°C	92°C	83°C	60°C
Time Refluxed (minutes)	45	45	30	60	60	420

Analysis After Purification Method

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
Impure		X	X	X	X	X
Pure	X					

After analyzing the following solutions it is believed that the first run (the control) was the most successful in creating pure dipyrromethane. The following runs were of no success as they contained to many contaminants and/or impurities after purification to be considered as optimized synthesis variables; such impurities consist of pyrrole and ketone/aldehyde. It was noted that most impure substances have a top layer color of dark brown or orange; white is considered to be the color sought after. While refluxing for an increased amount of time should theoretically better purify the solution proved false in these series of experiments as it only took 45 minutes of refluxing for the first run which proved to have a low impurity level. Other noteworthy aspects of these series of syntheses are that lower temperatures seem to have better results. This is interesting because normally more heat provides a better catalyst in chemical reactions. Further research will be done to explain these conflicting ideas.

Conclusion

Further experimentation of different chemicals will be considered, as this project is not yet conclusive. Ongoing research will be circumscribed around the field of organic chemistry enabling one to work with more viable chemicals. Major concerns for future experimentation will be emphasized on different acids, ketones, aldehydes and cleanliness. Pyrrole, being a highly reactive chemical, produces highly unpredictable outcomes when coming in contact with the slightest amount of contamination; this might include prolonged light exposure, reused burettes, and minuscule chemical remnants on glass. Dipyrromethane syntheses will continue until each variable is isolated at its optimum efficiency. As of now, there are no viable substitutes to chemicals used in the one-step synthesis proposed by Sobre and his colleagues.

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