Attempt at the Synthesis of Quinone Systems Capable of Intramolecular Proton Transfer to Explore Their Redox Properties

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Abstract:

Quinones, which serve important roles in many different biological functions, are known for their electron transfer and hydrogen atom transfer chemistry. The synthesis of hydroquinones with appended bases were attempted with the intention of investigating their electrochemical properties. The cyclic voltammograms of these compounds are expected to reveal information about the mechanism of proton and electron transfers. Specifically, the shape and amount of broadening in the waves may provide markers to whether the mechanism is concerted or stepwise. To this end, the reactions of pyrazole and imidazole with benzoquinone and 1,4-naphthoquinone were attempted. ^{1}H NMR indicated the reactions performed in THF did not lead to a reaction and those performed in 1,4-dioxane led to complex reaction mixtures. Purification by column chromatography was attempted twice. The first attempt was done on the reaction of benzoquinone and imidazole but was did not yield a pure compound. The second attempt was done on the reaction of 1,4-naphthoquinone and pyrazole and indicated a product; however, it did not have the expected spectrometric characteristics and the identity of the product could not be identified.

Introduction:

Quinones serve important roles in many different biological functions. In order to understand how protons and electrons react with quinones is important in understanding their chemistry. Quinones are electron acceptors in electron transport chains found in photosystem enzymes, used in photosynthesis for plants. Quinones also play a role in aerobic respiration where the chemical bonds of energy rich molecules are converted into energy. Hence, the study of quinones is important because of their biological relevance and their inherent reactivity.[1]

Quinones are known for their electron transfer chemistry and their hydrogen atom transfer chemistry. In redox reactions, as one substance loses electrons the other substance accepts them. An atom's oxidation state changes, and there is an electron transfer. The biological activity of the quinones is related to their ability to accept one or two electrons, depending on their chemical structure. In the reduction process, an electron is gained. In the oxidation process, an electron is lost. Therefore, there should be a correlation between changes in the frontier orbitals and redox potentials due to changes in substituents. The electron accepting ability of the quinones can be modified by substituents on the system. Benzoquinone is a six-membered ring containing two ketones. 1,4-Naphthoquinone, a benzannulated benzoquinone, is commonly studied due to its involvement in a variety of medical and biological applications. The donor and acceptor properties of the substituents influence the electronic properties of the quinone system. An investigation of the specific substituent effects will provide information to the mechanisms of the quinones' biological activity.

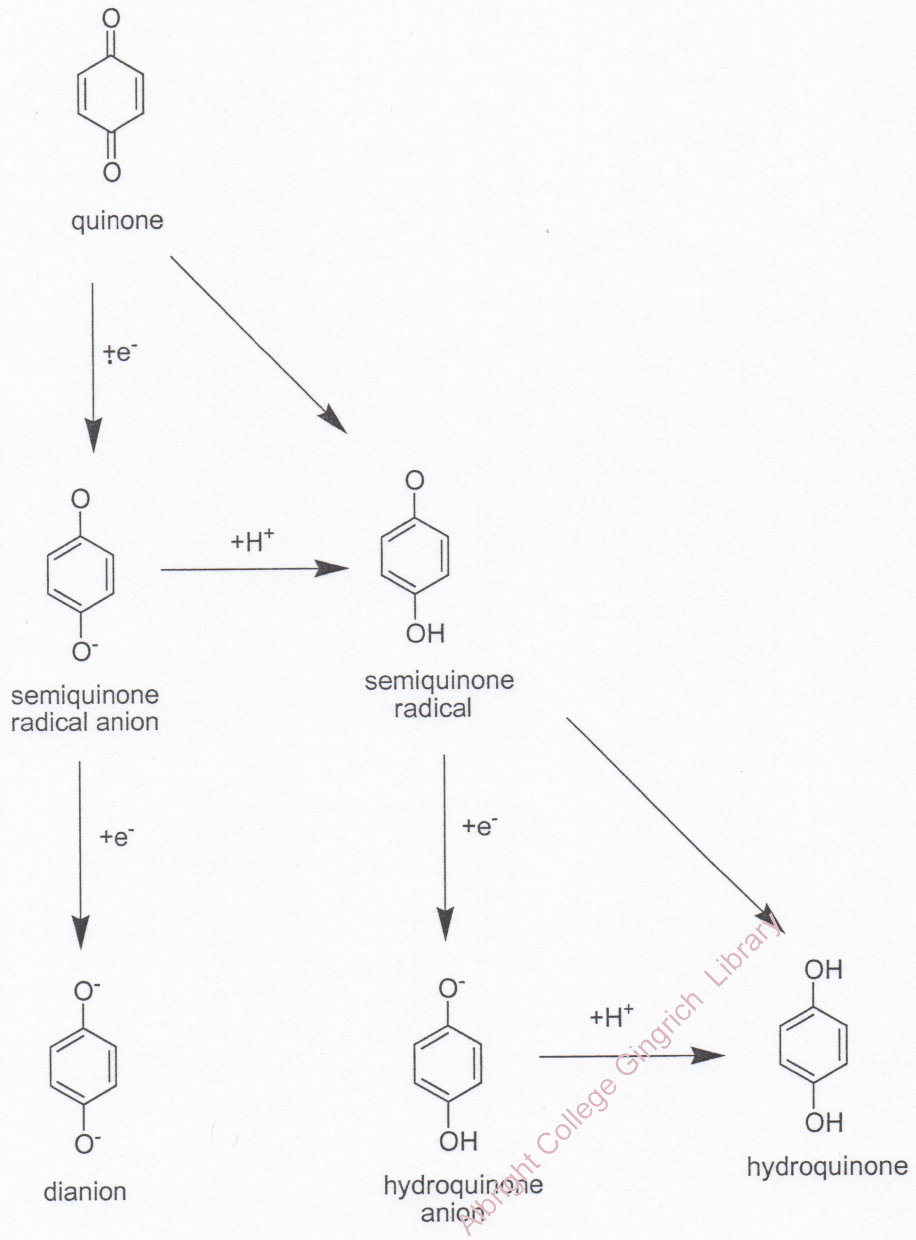
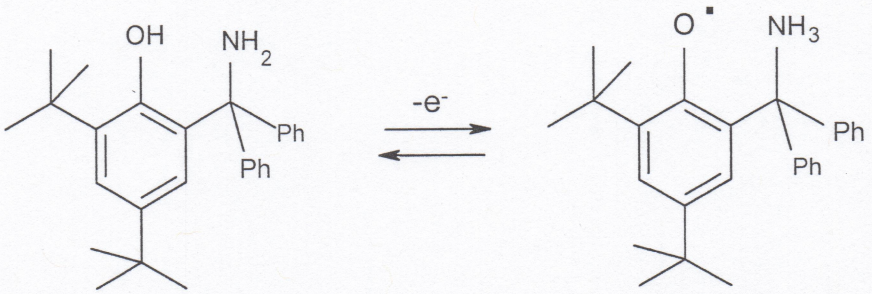


Figure 1. Proton and electron transfer properties of 1,4-benzoquinone

The addition of an electron and a proton to a quinone forms a semiquinone radical. The addition of a proton and an electron to a semiquinone radical forms a hydroquinone. The addition of only an electron to either a quinone or semiquinone radical gives anions. The redox properties of quinones are outlined above (Figure 1).

Electrochemical studies can reveal much about the electron transfer (and related proton transfer) properties of a system.[2] Electrochemistry studies the electron transfer properties of molecules such as quinones with situations where an oxidation and reduction reaction is separated in space. Cyclic voltammetry is a type of potentiodynamic electrochemical measurement. In cyclic voltammetry, a potential is applied to the system, and the faradaic current, the current due to a redox reaction, response is measured. The current response over a range of potentials is measured, beginning at an initial value and varying the potential in a linear approach up to a pre-defined limiting value. At this potential, referred to as a switching potential, the direction of the potential scan is reversed. The same potential window is scanned in the opposite direction. The species formed by oxidation on the first forward scan can be reduced on the second reverse scan. Because two peaks are associated with a redox reaction, the parameters of a cyclic voltammogram are the peak potential and the peak current. This technique provides a fast method for initial characterization of a redox-active system. Cyclic voltammetry provides an estimate of the redox potential, information about the rate of electron transfer between the electrode and the analyte, and the stability of the analyte in the electrolyzed oxidation states.[3]

The research group of James M. Mayer recently studied phenols with intramolecularly hydrogen bonded bases.[4] The removal of an electron corresponds with the transfer of a proton. The mechanism is shown.



The mechanism was determined to be a concerted proton electron transfer mechanism, as opposed to stepwise electron and proton transfers.[5] Both reactivity and electrochemical measurements were included in the study. The importance of this type of concerted reactivity has only been recently recognized as important. The phenols are structurally similar to quinones, as they both have an oxygen atom on the ring. Additionally, they both transfer a proton from an oxygen atom to a base and an electron from a phenol π system.

One important marker of the concerted mechanism was broad quasireversible cyclic voltammogram. This is indicative of slow electrochemical kinetics associated with the concerted mechanism. In contrast, reversible, fast electron transfer processes have voltammograms with peak differences of 59 mV or slightly larger. The studied phenols gave much larger results of 143 mV, 105 mV, and 100 mV.[4]

We wanted to compare the voltammograms of the phenols with those of structurally similar hydroquinones (as a reduced form) or quinones (as an oxidized form).

It is not known if a quinone system would have broad voltammograms indicative of the concerted mechanism. We decided to examine pyrazole compounds originally reported by Paloma Ballesteros and coworkers to synthesize the hydroquinones, which are the reduced forms of the quinones, and should be able to do similar proton transfer reactions as the previously studied phenols, perhaps with the concerted mechanism.[5,6] On 1,4-benzoquinone, there are four places pyrazole can add. We wanted to isolate one of the pyrazole-susbituted compounds.

In their synthetic paper, this group reacted five pyrazoles with differing nucleophilic character with 1,4-benzoquinone in 1,4-dioxane at 100°C (Figure 2) to synthesize some hydroquinones. While they obtained mixtures of addition compounds, they were able to separate the products. This suggests that the reaction is dependent on the nature of the pyrazole and the solvent being used. Pyrazole gave the mono-adduct as the major product. The 2,3-bis- and 2,5-bis- adducts were also produced as well as traces of the 2,3,5-tris-adduct. The nucleophilic character of the pyrazoles as well as the oxidation potentials of the mono-adducts are important factors to this process. The relative amounts of the products obtained depend upon the reaction time. To have an exclusive mono-adduct product, the reaction mixture proceeded for 61 hours. As we show below, we obtained complex reactions mixtures in much less time, with the exception of one case which occurred for 72 h, and were not able to reproduce their results. The authors only briefly examined the electrochemistry and did not include details about the shape of the voltammograms. The mono- , bis-, and tris- adducts are shown (Figure 2).[6]

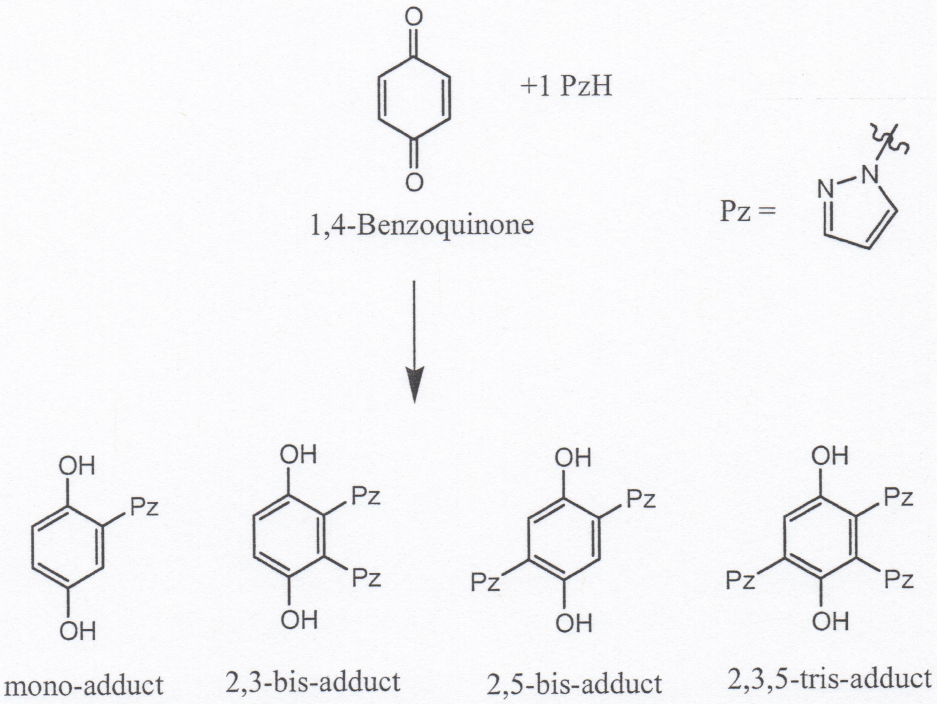


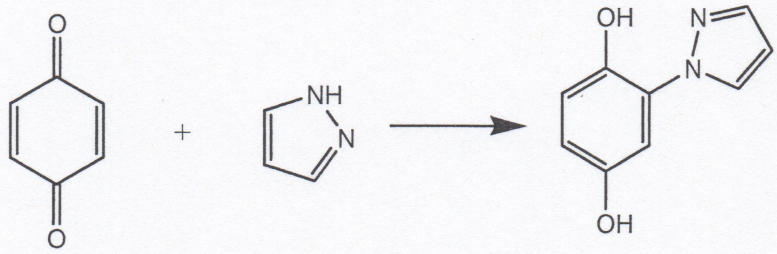
Figure 2. Products of the Reaction of 1,4-Benzoquinone with Pyrazole

We wanted to also synthesize a similar system with an imidazole attached in place of the pyrazole where the proton is not hydrogen bonded to compare its chemistry. The chemistry may vary when the proton is not in the hydrogen bonded system.

Results:

We attempted the reaction of pyrazole with 1,4-benzoquinone in two solvents: tetrahydrofuran (THF) and 1,4-dioxane, as shown below. Although the literature reaction was performed in 1,4-dioxane, we decided to attempt the reaction with THF as it is more readily available. The reaction was refluxed for 1 h. Analysis of the product mixture by TLC indicated that only starting materials remained; the reaction must require a higher

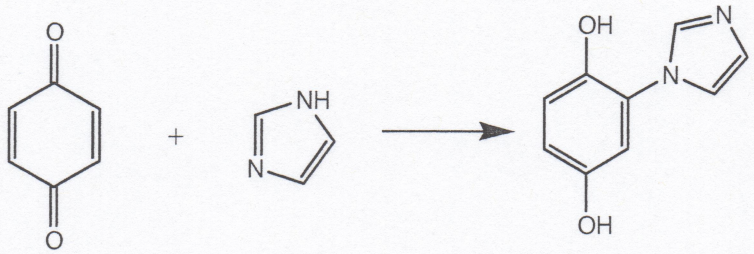
temperature than the boiling point of THF (66°C) to proceed. The potential mono-adduct of the reaction of 1,4-benzoquinone and pyrazole is shown below.



1,4-benzoquinone pyrazole mono-adduct

The reaction of pyrazole and 1,4-benzoquinone was then attempted in 1,4-dioxane. 1,4-Dioxane has a boiling point of 101.1°C and therefore the reaction was able to reach a higher temperature. After the reaction refluxed for 1 h, the solvent was removed by rotary evaporation, and the product analyzed by ^{1}H NMR and GC/MS. The ^{1}H NMR indicated that there was a complex reaction mixture with multiple products. The GC/MS was performed to analyze the mixture and see if the diagnostic fragment ion had the correct molecular weight of 176 g/mol. There was only one peak that was analyzed; therefore we had 100% peak area. The largest molecular ion in the mixture had an m/z of 109 g/mol which is inconsistent with the product. (See Appendix A).

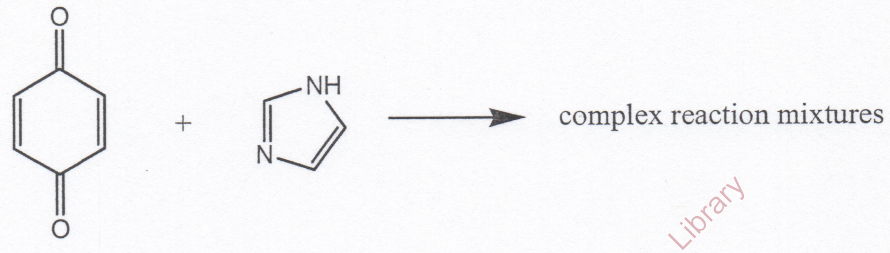
The reaction of imidazole and 1,4-benzoquinone done in 1,4-dioxane is shown below.



1,4-benzoquinone imidazole mono-adduct

It was observed that an insoluble product formed immediately upon mixing the starting materials in the reaction flask. The reaction was refluxed for 1 h, and the solvent removed by rotary evaporation. After examining the ^{1}H NMR, it was evident that this reaction also gave a complex reaction mixture. However, a spot was indicated on a TLC plate eluted with methanol. These TLC conditions indicate that the product was more polar than originally expected, and required a more polar solvent was to dissolve it. This was also indicated since the DMSO was required for the NMR solvent, and chloroform could not be used. We attempted a chromatography column on this product, eluting with methanol. However, we were not able to separate the product mixture. After TLC analysis, we were unable to isolate a pure compound.

The complex mixtures in these reactions are most likely due to varying numbers of additions of imidazole to 1,4-benzoquinone.



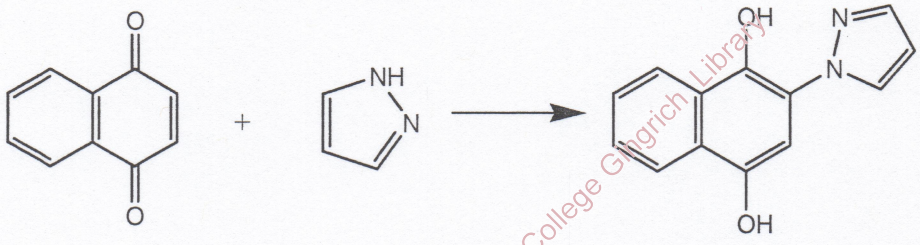
1,4-benzoquinone imidazole

In attempt to effect only addition of one pyrazole, we tried the reaction again, over a longer period of time while continuously, slowly adding imidazole to excess 1,4-benzoquinone; since the 1,4-benzoquinone is in excess. This was expected to produce only the mono-adduct since it would be at a higher concentration than any other reactant. The reaction was refluxed for 24 h. After removing the solvent by rotary evaporation, the product mixture was washed with chloroform to remove any excess 1,4-benzoquinone

and imidazole. This was done because the products above were not soluble in chloroform. This was expected to give a more pure product. Analysis was not done in dimethylsulfoxide (DMSO).

In the next reaction of pyrazole and 1,4-naphthoquinone done in THF, 1,4-naphthoquinone was used because there is less opportunity for the pyrazole group to continue adding. Because there are only two places it may add in this case, we hoped that 1,4-naphthoquinone would give a more pure product. The reaction was refluxed for 1 h, and the solvent was removed by rotary evaporation. Again, the ^{1}H NMR indicated the reaction did not go to completion, most likely because the temperature was not high enough.

The mono adduct of the reaction of pyrazole with 1,4-naphthoquinone done in 1,4-dioxane is shown below. The reaction was refluxed for 12 h and the solvent was removed by rotary evaporation. We added an additional 20 mL of 1,4-dioxane to the mixture. The reaction was refluxed for 72 h.



naphthoquinone pyrazole mono-adduct

The ^{1}H NMR showed a product is present. Flash column chromatography with 5/1 v/v hexanes/ethyl acetate was done on this product to purify it. The ^{1}H NMR indicated a relatively pure product was obtained.

The identity of the product, however, was not clear. The GC/MS done on this mixture indicates the largest molecular ion has an m/z of 168. The theoretical weight of the product is 226 g/mol. (See Appendix B). The ^{13}C NMR shows nine peaks; theoretically there should be 13 peaks. The IR indicates the following functional groups: OH, C=N, C–O, as indicated by peaks at ~2921 (wide peak), ~1594 and ~1051 cm^{-1}, respectively. We have been unable to determine the identity of this product from the spectral data. Notably, there are fewer ^{13}C NMR peaks than there should be, and the formula weight is not diagnostic of the expected product or fragment components.

Conclusion:

In an effort to synthesize compounds for electrochemical studies, we attempted the reactions of imidazole and pyrazole with 1,4-benzoquinone and 1,4-naphthoquinone. The reactions done in THF led to no reaction, most likely due to too low reaction temperatures. ^{1}H NMR showed that the reactions done in 1,4-dioxane led to complex reaction mixture. Purification of these proved to be very difficult. The reaction of 1,4-naphthoquinone and pyrazole led to a reaction product that did not have the expected spectrometric characteristics. Unfortunately, we have been unable to recognize the identity of the product.

Experimental Section:

Pyrazole, 1,4-benzoquinone, 1,4-naphthoquinone, 1,4-dioxane, and tetrahydrofuran were purchased form Acros. Imidazole was purchased form Fisher Biotech. Hexanes and ethyl acetate were purchased from Pharmco.

Proton NMR spectra use in characterization of product studies was recorded on a Varian Unity INOVA-300 spectrometer operating at 300 MHz and Varian Unity INOVA-200 spectrometer operating at 200 MHz. Carbon-13 NMR spectra were recorded on a Varian Unity INOVA-300 spectrometer operating at 75 MHz. GC/MS use was recorded on a Hewlett Packard 5970 Series Mass Selective Detector and Hewlett Packard Gas Chromatograph. Infared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer.

1. Attempt at Reaction of Pyrazole and 1,4-Benzoquinone in THF

To 1,4-benzoquinone (0.50 g, 0.00463 mol) were added two equivalents of pyrazole (0.63 g, 0.00925 mol). The mixture was warmed to ~70°C in THF (10 mL). The mixture was stirred under reflux for 1 h, cooled to room temperature, and rotary evaporated. ^{1}H NMR was done in $CDCl_3$ and indicated a complex reaction mixture. GC/MS indicated the most abundant product to have a weight of 109 g/mol.

2. Attempt at Reaction of Pyrazole and 1,4-Benzoquinine in 1,4-Dioxane

To 1,4-benzoquinone (0.50 g, 0.00463 mol) were added two equivalents of pyrazole (0.63 g, 0.00925 mol). The mixture was warmed to ~102°C in 1,4-dioxane (10 mL). The mixture was stirred under reflux for 1 h, cooled to room temperature, and rotary evaporated. TLC was done using 1/1 v/v hexanes/ethyl acetate. ^{1}H NMR was done in $CDCl_3$ and indicated a complex reaction mixture.

3. Attempt at Reaction of Imidazole and 1,4-Benzoquinine in 1,4-Dioxane

To 1,4-benzoquinone (0.50 g, 0.00463 mol) were added two equivalents of imidazole (0.63 g, 0.00925 mol). The mixture was warmed to 100°C in 1,4-dioxane (10 mL). The mixture was stirred under reflux for 2 h, cooled to room temperature, and rotary evaporated. TLC was done using methanol. ^{1}H NMR was done in DMSO and showed definite starting materials present in a complex reaction mixture. A chromatography column, eluted with methanol, was unable to separate the product mixture.

To 1,4-dioxane (3 mL) was added 1,4-benzoquinone (0.50 g, 0.00463 mol). Separately to 1,4-dioxane (3 mL) were added two equivalents of imidazole (0.63 g, 0.00925 mol). Together both mixtures were warmed to 100°C. The mixture was stirred under reflux for 5 h, cooled to room temperature, and vacuum filtered. TLC was done twice using methanol and 1/1 v/v hexanes/ethyl acetate. ^{1}H NMR was done in DMSO and showed a complex reaction mixture.

To 1,4-benzoquinone (2.50 g, 0.02313 mol) was added imidazole (0.63 g, 0.00925 mol) over 1 h. The mixture was warmed to 100°C in 1,4-dioxane (10 mL). The mixture was stirred under reflux for 48 h, cooled to room temperature, and rotary evaporated. TLC was done twice using methanol and 5/1 v/v hexanes/ethyl acetate. ^{1}H NMR was done in DMSO and showed only starting materials present. The product was dissolved in chloroform to remove traces of imidazole and 1,4-benzoquinone and vacuum filtered. Again, the ^{1}H NMR showed only starting materials.

4. Attempt at Reaction of Pyrazole and 1,4-Naphthoquinone in THF

To 1,4- naphthoquinone (0.50 g, 0.00316 mol) was added one equivalent of pyrazole (0.23 g, 0.00316 mol). The mixture was warmed to 70°C in THF (10 mL). The mixture was stirred under reflux for 7 h, cooled to room temperature, and rotary evaporated. ^{1}H NMR was done in DMSO and indicated a complex reaction mixture.

5. Attempt at Reaction of Pyrazole and 1,4-Naphthoquinone in 1,4-Dioxane

To 1,4- naphthoquinone (0.50 g, 0.00316 mol) was added one equivalent of pyrazole (0.23 g, 0.00316 mol). The mixture was warmed to 100°C in 1,4-dioxane (10 mL). The mixture was stirred under reflux for 11 h, cooled to room temperature, and rotary evaporated. ^{1}H NMR was done in $CDCl_3$ and indicated a possible new product. Additional 1,4-dioxane (20 mL) was added to the mixture and stirred under reflux for an additional 72 h. Again, ^{1}H NMR was done in $CDCl_3$ and indicated a possible new product. ^{13}C NMR was done in $CDCl_3$ and indicated 9 distinct peaks. A chromatography column using nitrogen gas pressure on silica (5/1 v/v hexanes/ethyl acetate) was able to separate the mixture and gave 0.9012 g of the compound: IR (neat) 3600-2200, 1594, 1523, 1411, 1316, 1051, 956, 847, 753 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$); GCMS (EI) *m/z* 168.

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Appendices: Oven and Detector Conditions for GC/MS Analysis

Appendix A:

Injector temperature: 200°C

Detector temperature: 280°C

Initial temperature: 40°C

Initial time: 6 minutes

Ramp rate: 10°C/minute

Final temperature: 270°C

Final time: 5 minutes

Appendix B:

Injector temperature: 200°C

Detector temperature: 280°C

Initial temperature: 70°C

Initial time: 6 minutes

Ramp rate: 10°C/minute

Final temperature: 260°C

Final time: 8 minutes