ELECTROCHEMICAL ANALYSIS OF OXIDATION OF PRIMARY AMINES TO KETONES WITH 3,5-DI-TERT-BUTYL-1,2-BENZOQUINONE

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ELECTROCHEMICAL ANALYSIS OF OXIDATION OF PRIMARY AMINES TO KETONES WITH 3,5-DI-TERT-BUTYL-1,2-BENZOQUINONE

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University of Missouri-Kansas City, 2022

ABSTRACT

Electrochemical techniques have been used extensively to study electrode reactions and the coupled chemical-electrochemical reactions. Moreover, the concentration of redox active species in many of the redox reactions can be measured electrochemically, that enables the study of the chemical redox reactions by electrochemical techniques. This area of research in electrochemistry is unexplored and there are only few examples in literature. In this thesis we demonstrated the capability of electrochemical techniques for study of oxidation reaction of amines to ketones by 3,5-di-tert-butyl-1,2-benzoquinone (DTQ). The concentration profiles of quinone and aminocatechol, as the redox active components of reaction, were monitored in the course of reaction by chronoamperometric and voltammetric techniques. Using microelectrodes, instead of traditional disk electrodes, allowed access to the bulk concentrations of electroactive species with minimizing the effect of electrode reactions and diffusion layer.

The first chapter of this thesis discusses the importance of a class of electroactive compounds known as quinones and their role in some biologically and chemically related redox reactions. Followed by a comparison of the characteristics of microelectrodes versus traditional electrodes as well as interpretation of voltammograms that will appear throughout this work. Chapter two describes fabrication of microelectrodes that were used for this study and the

detailed experimental reaction conditions. In chapter three the oxidation reactions of three amines including: 3-penthylamine, cyclohexylamine, and 1-penthylamine with DTQ were explored and studied by voltammetric and chronoamperometric monitoring of DTQ and aminocatechol. This study provides insight into the intermediate compounds that are formed in the course of reaction, as well as providing a method of determining the rate of reaction of DTQ and a given amine.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Science and Engineering, have examined a thesis titled "Electrochemical Analysis of Oxidation of Primary Amines to Ketones with 3,5-Di-Tert-Butyl-1,2Benzoquinone," presented by Matthew Ray Mumau, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

1.1. INTRODUCTION AND BACKGROUND

1.1 Redox Reaction and o-Quinone based Co-factors for Amine Oxidation

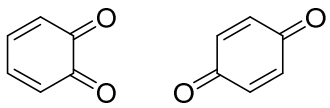
Oxidation reactions serve as a cornerstone of organic chemistry, providing a pathway to a variety of functional groups that allow for further functionalization for starting materials used in synthesis. Many typical oxidation reactions are carried out with stoichiometric amounts of transition metal-based oxidants. However, increased attention has been placed on using organocatalytic methods that offer more mild and selective processes.[1]

A class of organo-catalysts, enzymes, offer a list of desirable characteristics. Enzymes provide a high level of selectivity while operating in mild conditions in addition to high rates of catalytic turnover. Furthermore, there exists a broad range of enzymes that perform oxidation reactions. Enzymes can catalyze oxidation processes encompassing hydroxylation and dihydroxylation of both aliphatic and aromatic -H bonds, epoxidation, heteroatom oxidation including sulfoxidation and amine oxidation, Baeyer-Villiger oxidation of ketones to lactones, and halohydrin formation from alkenes.[1]

Understanding enzymatic processes *in vitro* and *in vivo* allows for a more complete knowledge of the many redox reactions that are essential to any currently known form of life.[2] Electron transfer mediated by proteins is an essential step for biological energy conversion processes from photosynthesis to respiration. There are several types of nitrogen containing compounds which undergo oxidation in biological systems. These include aliphatic and aromatic primary, secondary, and tertiary amines.

Moderate amounts of biological amines are essential for normal physiological and psychological function. For instance, many neurotransmitters are amines, including dopamine,

serotonin, histamine, epinephrine, and norepinephrine. These compounds play a key role in governing processes all throughout the body but are most known for regulating thought processes. An imbalance of any neurotransmitter can cause a profound effect on the individual's cognitive function.[3] The proper balances of amines in biological tissue is in part, maintained by a class of enzymes or amine oxidases known as quinoproteins or sometimes called quinoenzymes. Quinoproteins are enzymes whose catalytic mechanism involves a quinone-containing group at their active sites.[4] These quinone groups that are tightly bound to the enzyme are known as a type of cofactor. Quinones, such as *ortho*-quinone and *para*-quinone (Error! Reference source not found.), are important redox-active organic molecules that have applications in diverse redox processes, including in oxidation reactions for organic synthesis, as electron carriers, antioxidants, and cofactors in biological processes.



ortho-quinone *para*-quinone

Figure 1.1. Structures of ortho-quinone and para-quinone

compounds. Several quinoenzymes classes are known, including copper amine oxidase, methylamine dehydrogenase, and methanol and glucose dehydrogenases which contain cofactors trihydroxyphenylalanine (TPQ), tryptophan tryptophylquinone (TTQ) and pyrroloquinoline quinone (PQQ) respectively (Error! Reference source not found.). TPQ-containing enzymes and TTQ-containing enzymes have been shown to be involved in oxidative deamination of amines.[5]

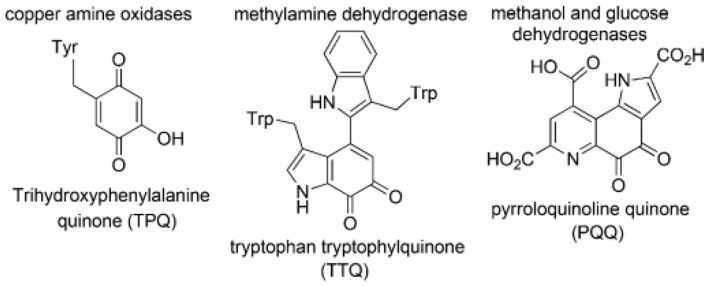


Figure 1.2. Structures of cofactors TPQ, TTQ, and PQQ. Adopted form reference 6.

Pyrroloquinoline quinone (PQQ) was the first of the *ortho*-quinone cofactors to be identified.[7] It is well known that free PQQ works as a catalyst for amine oxidation.[5] The catalytic aerobic oxidation of primary amines to ketones and aldehydes was achieved by Itoh and co-workers under aqueous micellar conditions by using a 1:10 ratio of PQQ: hexadecyltrimethylammonium bromide under ambient air at room temperature.[6,8]

Quinones feature three accessible oxidation states, fully oxidized quinone, one-electron-reduced semiquinone, and two-electron- reduced hydroquinone as shown in Error! Reference source not found..[6] The transition between oxidative states of quinones is facilitated by the addition or removal of an electron and hydrogen atom.

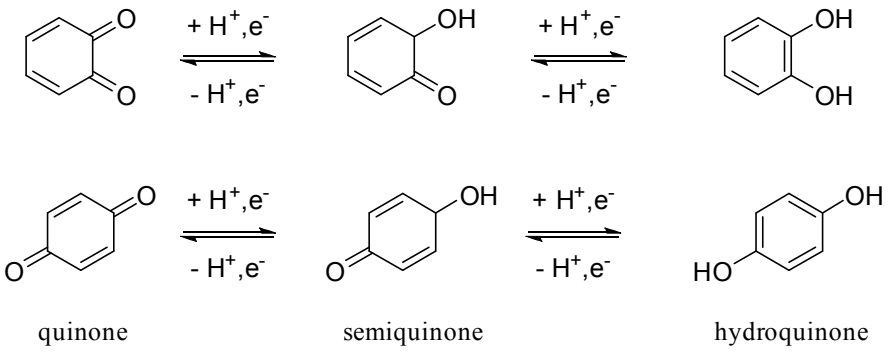


Figure 1.3. Scheme showing all oxidation states for ortho-quinone and para-quinone

1.2 Electrochemical Techniques for Detection Electroactive Chemicals

Detection of the addition or removal of electrons from a quinone based molecule allows for detection of the quinone derivative utilizing electrochemical techniques.

Cyclic voltammetry (CV) is the most widely used technique for acquiring qualitative information about electrochemical reactions. CV is often the first experiment performed in an electroanalytical study of an electroactive species as it offers rapid location of redox potentials and evaluation on the effect of environment on the electroactive species.[9] CV consists of scanning the potential of a working electrode in a linear fashion. A working electrode is an electrical conductor that is typically made of platinum, gold, mercury, or glassy carbon. Using an external power source, such as a potentiostat, potential (also known as voltage) can be applied to the electrode to adjust the amount of energy of the electrons in the electrode.

When the electrons in the electrode are of higher energy than that of the LUMO in the electroactive compound, electrons are transferred from the electrode to the electroactive compound. The energy difference between the and the LUMO of the analyte and the electrode is what causes the transfer of electrons. [10] The description electron transfer from electrode to the LUMO of an analyte is known as the process of reduction. The reverse process of an electrode having a potential lower than that of the HOMO of analyte would initiate the electron transfer from the electroactive compound to the electrode, also known oxidation of the compound.

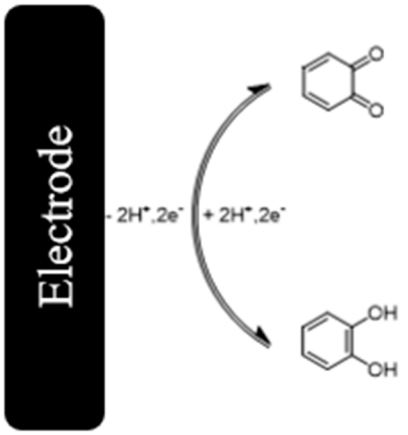


Figure 1.4. Electron transfer at electrode surface of quinone and hydroquinone

During the potential scan, a potentiostat measures the resulting current from the applied potential. The resulting current vs potential plot is known as a cyclic voltammogram as seen in Error! Reference source not found..[11]

Figure 1.5. Archetypical reversible CV of electroactive compound. Adopted form reference 11.

When using CV to detect quinone containing compounds, the starting potential is set according to the oxidation state of the starting material. In the case of the full oxidized quinone, the starting potential must be above the redox potential of quinone. Potential is the swept in the negative going direction. Meaning the scanning direction starts in higher potentials and decreases to lower potentials. This is to allow for reduction of quinone molecules at the electrode surface. This reduction, or gaining of electrons by the quinone, is responsible for the cathodic current (shown as negative current in Error! Reference source not found.) in the voltammogram. Once the potential is sufficiently passed the reduction potential, as in there is a drop in current, the scanning direction is reversed and is now a positive going scan. Meaning the scan starts in lower potentials and potential is increased. Reduction of the quinone continues during the initial phase of the reverse scan but is then ceased when the electrode's

potential is above the redox potential. At which point, oxidation of the reduced species, hydroquinone, which was generated in the initial sweep is oxidized back to the original quinone material. This oxidation or loss of electrons by the hydroquinone is responsible for the anodic current (shown as positive current in **Figure 1.5**) seen in the voltammogram. The individual one-electron processes from quinone to semiquinone or from hydroquinone to semiquinone normally occur with no resolution of the semiquinone intermediate. However, the semiquinone intermediate can be observed with the used of aprotic solvents.[12]

In the fully oxidized form, the electrochemically generated quinones easily undergo reduction. This attributes to their ability to act as oxidizing and dehydrogenating agents. This feature allows quinones to undergo nucleophilic attack by many electron donating compounds. This allows for C-C, C-S, C-N, and C-P bond formation depending on the nucleophile initiating the attack on the quinone.[13] Nematollahi and co-workers, demonstrate the effects of electrochemical nitration of electrochemically generated *o*-benzoquinones in the presence of nitrite ions as nucleophiles in aqueous solution. The resulting CV (Error! Reference source not ound.) indicate the reaction of *o*-benzoquinones in with nitrite ions to form the corresponding nitrocatechols.[14]

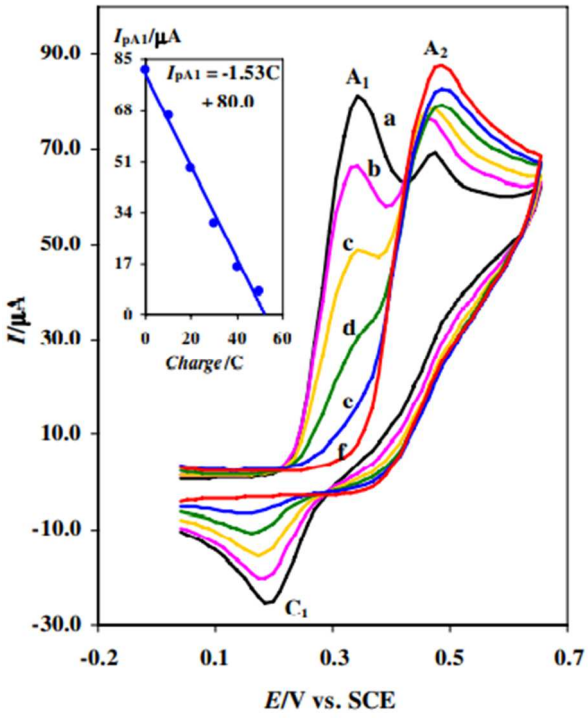


Figure 1.6. CV of catechol in the presence of equimolar nitrite ion, at glassy carbon electrode during controlled potential coulometry at 0.25 V vs SCE. After consumption of: (a) 0, (b) 10, (c) 20, (d) 30, (e) 40, and (f) 50 Q. Adopted form reference 14.

The CV of catechol was recorded during controlled potential coulometry, meaning that *o*-benzoquinones is being electrochemically produced by oxidation of catechol at the electrode surface, generating the anodic peak (A_1). Subsequently a cathodic peak (C_1) on the reverse scan is correspondent to the reduction of the electrochemically generated *o*-benzoquinone. In the presence of nitrite ions, the decrease and disappearance of peaks A_1 and C_1 and the formation of peak A_2 are indicative of an electrochemical-chemical pathway known as EC mechanism. The electrochemical step (E), oxidation of catechol to *o*-benzoquinone. Followed by the chemical step (C), *o*-benzoquinone is removed by chemical reaction with the nitrite ion. This is supported by the evidence of the disappearance of A_1 and C_1, the concentration of *o*-benzoquinone is decreasing by removal via nitrite ions. Paralleled with appearance of A_2, the increase in concentration of nitrocatechol.[13,14]

1.3 Disc Electrode vs Microelectrode

The characteristic peaks in a cyclic voltammogram are caused by the formation of a diffusion layer near the electrode surface. With a traditional electrode (or macroelectrode), electrically generated compounds form the diffusion layer. A CV recorded with a macroelectrode results in a peak current followed by a diffusion tail. Since as the diffusion layer of the generated compounds increases, the further the analyte must travel to get to the electrode surface to undergo electron transfer, thus a decay in current.[11] When the potential of the electrode extends beyond the necessary redox potential of the initial compound, it is possible for the newly generated compounds to undergo further electron transfer.[15]

The increasing interest in microelectrodes has led to the use of carbon fiber as choice material for making electrodes. Electrodes with a surface less than 25 μm are commonly referred to as microelectrodes. Microelectrodes may appear simply as smaller versions of their macroelectrode counterpart, but due to their small size, offer an array of advantages of traditional electrodes. These advantages include analysis of very small sample volumes and measurements of local concentration profiles such as monitoring neurochemical events in extra cellar spaces in living tissue.[9,16] The use of nanoscopic electrodes has allowed for studies of in-vivo probing and real-time monitoring of neurochemical events after cellular stimulation.[15]

Another consequence of their size, microelectrodes do not exhibit the same diffusion characteristics as traditional disc electrodes. With the electrode significantly smaller than the diffusion layer, the produced compounds simply diffuse into the bulk solution. The difference in mode of diffusion for a macroelectrode and a microelectrode can be seen in Error! Reference source not found..[11]

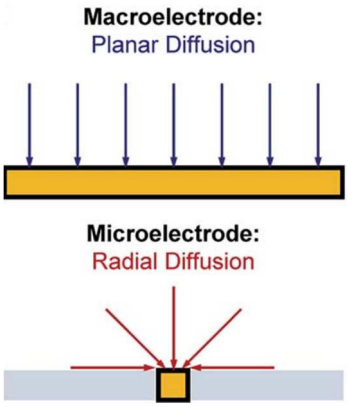


Figure 1.7. The different modes of mass transfer for macroelectrode and microelectrode. Adopted form reference 11.

The difference in mode of diffusion between macroelectrode and microelectrode causes a significant difference in the profile of the voltammogram when CV is recorded. **Figure** 1.7. The different modes **of mass transfer for macroelectrode and microelectrode** shows the stark difference in voltammograms from that of a macroelectrode and of a microelectrode in the same chemical environment. In contrast to macroelectrodes, the constant flux of bulk solution to the surface of microelectrodes results in a steady-state response with a limiting

current which is determined by the rate of refreshment of bulk solution to the electrode surface to undergo electron transfer.

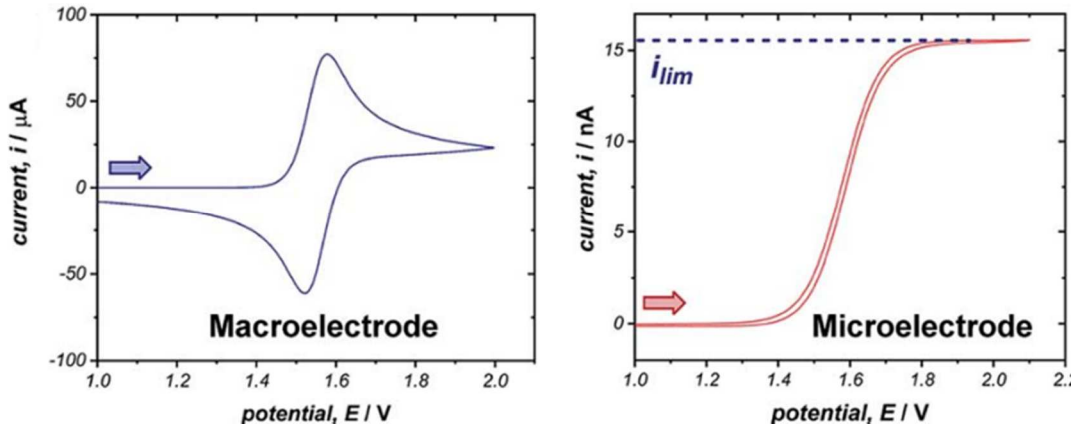


Figure 1.8. CV comparison between macroelectrode and microelectrode. Adopted form reference 11.

Another clear difference is the lack of peaks with the microelectrode. This is also caused by the radial diffusion of electrogenerated compounds diffuse away from the electrode. Essentially, there is no diffusion layer of electrogenerated compounds to interfere with the approach of fresh reactant, hence no decay in current is observed. Additionally, since the generated species has diffused into solution, they are not present to undergo electron transfer when the potential scan is reversed. Therefore, there is no peak current observed in the reverse scan either.

This phenomenon does come with its limitations. The rate at which the potential changes (also known as scan rate) must be less than the rate of diffusion. Otherwise, if the scan rate is too large, the rate of electron transfer is faster than diffusion and peak shaped voltammogram will be observed instead of the desired s-shaped voltammogram.[11] Finding an optimal scan rate for a given microelectrode to avoid peak shaped voltammograms can be

easily found by method of guess and check with a known redox active compound and adjusting the scan rate of the potentiostat being used until the desired shape is achieved.

Consequently, this allows for monitoring of species present in the bulk solution without interference of molecules generated at the electrode surface. Additionally, molecules generated at the electrode surface are not present to undergo further electron transfer nor are they present to undergo electron transfer when the potential is swept in the opposite direction. This gives the advantage of giving more simplistic voltammograms while eliminating the need for a cyclic sweep of potential at the electrode surface due to the lack of information gained in the reverse scan direction. Further simplifying voltammograms by using linear sweep voltammetry (LSV) in lieu of CV.

The lack of interference of electrochemically generated species at the electrode surface allows for the detection of concentration fluctuation of electroactive compounds in solution. An increase or decrease in current at the redox potential of an electroactive compound corresponds to an increase or decrease in concentration of the analyte in solution. Applying this concept to a chemical reaction involving electroactive compounds provides information of the rate of consumption of an electroactive reagent or the rate of formation of an electroactive product.

This concept has been shown in a study conducted by Amatore and Pflüger. Where microelectrodes were utilized to study the mechanism and rates of oxidative addition of substituted iodobenzenes to tertrakis(triphenylphosphine)palladium (0). It was shown that monitoring the current plateau (also known as i_{lim}, as seen in **Figure 1.8**) of the palladium complex while scanning the potential towards and passing the oxidative potential was found to be a suitable method for following concentration changes as seen in Error! Reference source

not found.. This is due to the fact that the products, $ArPdI(PPh_3)_2$ and triphenylphospine, are not electroactive in the same potential range.[17]

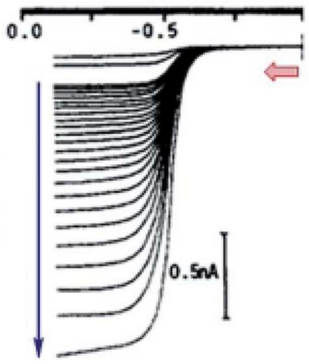


Figure 1.9. Change in current from concentration changes of palladium complex. Adopted form reference 17.

1.4 Amine Oxidation by Quinone Derivative.

In this project, a synthetic approach for oxidative deamination of primary amines by utilizing the efficiency of the bio mimic process of transamination using a quinone derivative. The reaction kinetics of 3,5-di-tert-butyl-1,2-benzoquinone (DTQ) with various primary amines is studied with the use of microelectrodes to observe changes in concentration of DTQ and electroactive products. DTQ readily undergoes reduction at the electrode surface to form 3,5-di-*tert*-butyl-catechol (DTC) as shown in Error! Reference source not found..

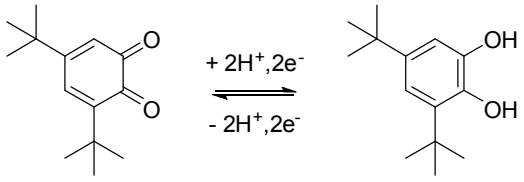


Figure 1.10. Reversible redox process of DTQ and DTC

In an earlier work shown by E. J. Corey and K. Achiwa, DTQ has been shown to be an extremely effective reagent for the conversion of primary amines to ketones under very mild conditions.[18] Normally, primary amines react with quinones to give an amino hydroquinone among other things. The success of DTQ with deamination of amines comes from its structural design. The tert-butyl groups protect the ring from nucleophilic attack from the amine. Directing the amine to the C_1-carbonyl of the aromatic ring, thereby favoring the formation of the Schiff base. Deprotonation of the Schiff base to for the required intermediate then thermodynamically favors the 1,5-prototropic rearrangement to form the desired isomeric Schiff base. Aqueous acid hydrolysis of the desired Schiff base yields the desired ketone and the electroactive compound 2-amino-4,6-di-tert-butylphenol (ADB) when using branched primary amines.[18,19] In the case of unbranched primary amine, deamination of the amine does not occur, and the resulting oxazole adduct is produced instead.[18]

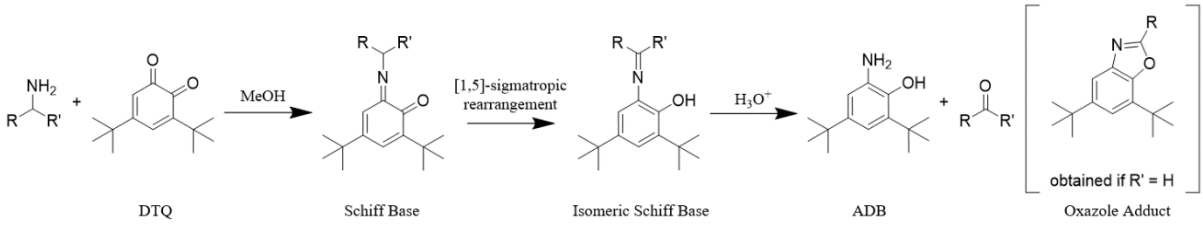


Figure 1.11. Reaction scheme of deamination of amine by DTQ. Adopted form reference 6.

Utilizing a microelectrode and an automated LSV program, it is possible to observe the reduction peak of DTQ and the oxidation peak of ADB within a single potential scan. Many LSVs can be taken during the reaction to provide a clear representation of the reaction kinetics for DTQ by monitoring the decay of current produced by DTQ. As DTQ undergoes nucleophilic attack by the amine, there is less DTQ able to be reduced by the electrode, therefore the reduction current produced by DTQ lowers over time as the reaction progresses. The structural differences in amines can be showcased to have an effect on rate of reaction as

well as final product formation. In the case of branched primary amines, the oxidation current of ADB is observed to increase over time as the reduction current produced by DTQ decreases with time. This method offers the advantage of detecting similarly structured compounds and intermediates by sweeping a user-controlled range of potentials at a speed set by the user. Offering a large variety of possible reactions that can be monitored using this method.

CHAPTER 2

EXPERIMENTAL

2.1 General Details

All solvents and chemicals were attained from commercial suppliers and used without any purification. Voltammertric experiments were conducted utilizing a Metrohm Autolab PGSTAT204. For non-aqueous mechanistic studies, a 10 mL Pine electrochemical cell was utilized and equipped with an Ag/Ag^+ (internal solution 0.01 M $AgNO_3$, 0.1 M tetrabutylammonium hexafluorophosphate in MeCN) reference electrode and a Pt wire counter electrode. A glassy carbon (GC) disk (2 mm) as the working electrode was used for cyclic voltammetric (CV) experiments and a polyolefin carbon fiber (11 μm) working micro-electrode was used for linear sweep voltammetric (LSV) experiments. Carbon fiber micro-electrode (CFME) were made in house by inserting a carbon fiber into a glass capillary tube. The end of the capillary tube was heated using a flame to seal the glass around the carbon fiber. 36 AWG wire was coated in conductive epoxy which was inserted in the open end of the capillary tube. Heat shrink tubing was place over the wire and capillary tube to create a more robust connection. A crimp snap pin was soldered to the exposed end of the wire to allow for connection to the potentiostat (**Figure 2.1)**.

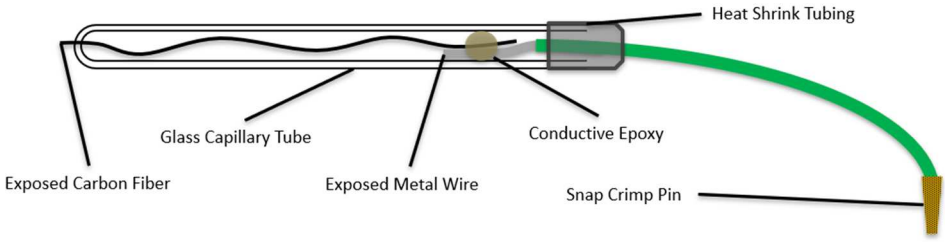


Figure 2.1. Diagram of CFME construction used in LSV experiments.

Due to the nature of the size of the CFME, electromagnetic background noise caused significant interference in early tests. This was remedied by placing the electrochemical cell and electrical leads in a Faraday cage and disconnecting any surrounding unused equipment.

2.2 Experimental Procedures

2.2.1 Sample Preparation

For mechanistic studies in solution phase, each trial was prepared fresh by dissolving the desired amount of 3,5-di-tert-butyl-1,2-benzoquinone, and desired supporting electrolyte in 9 mL of methanol (MeOH). The solution was then purged with ultra-high purity nitrogen gas to remove any dissolved molecular oxygen. CV and LSV analysis were then performed on the sample to record initial reduction and/or oxidation current/s of 3,5-di-tert-butyl-1,2-benzoquinone. The desired amine was prepared by weighing the desired amount and dissolving in 0.5 mL of MeOH in a separate container. The amine was transferred to the electrochemical cell containing the benzoquinone solution. The container was promptly rinsed with an additional 0.5 mL of MeOH which was also transferred to the electrochemical cell. The solution was briefly mixed using a magnetic stir bar before the automated LSV program was started. The reaction mixture was left unagitated during the entirety of the reaction. The reaction was considered complete when there was no longer a reduction current of the benzoquinone during a LSV, meaning there was no longer benzoquinone present in solution. At which point, a CV was recorded using a GC electrode.

The solutions of benzoquinone, amines, supporting electrolytes are:

- 9 mL 3,5-di-tert-butyl-1,2-benzoquinone (0.0441 g, 0.2 mmol) in MeOH
- 9 mL 1-butyl-3-methylimidazolium acetate (BMIA) (0.1982 g, 1.0 mmol) in MeOH

- 9 mL lithium perchlorate ($LiClO_4$) (0.1064 g, 1.0 mmol) in MeOH
- 9 mL TBAPF6 (0.3874 g, 1.0 mmol) in MeOH
- 0.5 mL cyclohexylamine (0.0198 g, 0.2 mmol) in MeOH
- 0.5 mL 1-pentylamine (0.0174 g, 0.2 mmol) in MeOH
- 0.5 mL 3-pentylamine (0.0174 g, 0.2 mmol) in MeOH
- 0.5 mL diethylamine (0.0146 g, 2 mmol) in MeOH

Hydrolysis of the final product was carried out by diluting 3.0 mL of the benzoquinone and amine reaction mixture in 3.0 mL of tetrahydrofuran and 1.0 mL of D.I. water. CV and LSV were recorded after addition of solvents. A small amount of acid was added (30 μL 1M oxalic acid or 220 μL 1.5 M perchloric acid) by hand, using an adjustable micropipette, to facilitate hydrolysis of the intermediate species. LSVs were recorded over time to monitor the concentration of the final product. After 2 hours, CV was recorded.

The stock solutions of acid are:

- 10 mL oxalic acid (0.9003 g, 10 mmol) in D.I. water
- 10 ml perchloric acid (2.153 g, 15.14 mmol) in D.I. water

2.2.2 Voltammetric Analysis

For voltammetric analysis performed using LSV, the potential of the working electrode was swept from -1v to 1v. This was to capture the reduction current of benzoquinone and the oxidation current of the formed species as well as any intermediate products.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Oxidation of 3-Pentylamine

The reversibility of an electron transfer process can be determined through study of DTQ via cyclic voltammetry. Furthermore, by the facile reaction conditions required by DTQ to facilitate deamination of primary amines to ketones.

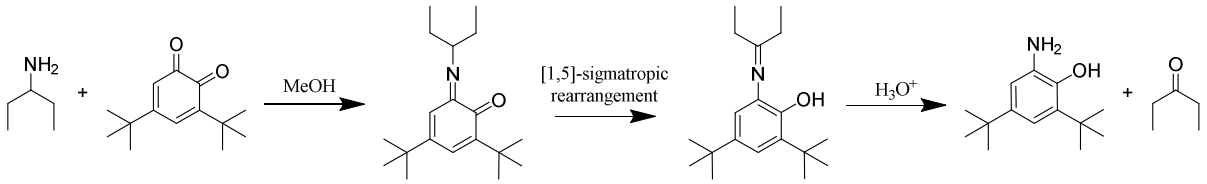


Figure 3.1. Reaction of DTQ and 3-pentylamine.

Our study was initiated with voltammetric study of redox activity of 3,5-di-*tert*-butyl-1,2-benzoquinone (DTQ). **Figure 3.2**. shows the cyclic voltammogram (CV) of DTQ in methanol solution, with tetrabutylammonium hexafluorophosphate ($TBA^+PF_6^-$) as supporting electrolyte. The CV shows a cathodic peak in negative going scan for two electron reduction of DTQ to its catechol form, 3,5-di-*tert*-butylcatechol (DTC). By switching the potential to positive going scan the electrochemically generated DTC oxidizes to DTQ and consequently an anodic peak for this oxidation process is observed (Error! Reference source not found..).

his CV was recorded using a traditional glassy carbon electrode; thus, we observe the classic peak shaped voltammogram.

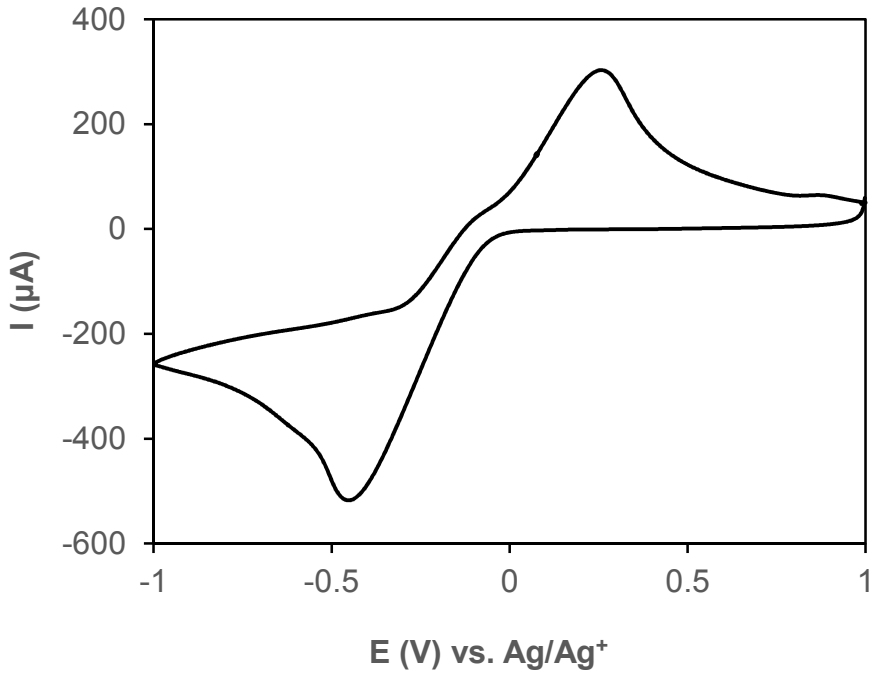


Figure 3.2. Cyclic voltammogram of DTQ (20 mM) in $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 100 mVs^{-1}.

The CV was recorded of the same conditions as seen in F**igure 3.2** using a microelectrode. The resulting CV can be observed in F**igure 3.3**. As discussed previously in section 1.3. The S-shaped voltammogram is observed with the use of microelectrode as a result of the reduction of DTQ to DTC that diffuses into the bulk solution. Since the positive going scan does not provide any more meaningful information compared to that of the negative going scan, only LSV was recorded. Omitting the positive going scan allows for more rapid scans of negative going scans without any loss of information while providing more rapid results of changes in concentration of species with oxidation potentials in the more positive ranges. Since there is not cycle of negative and positive direction, instead there is only one direction present

a time. These voltammograms are referred to as linear sweep voltammograms (LSV). An LSV of DTQ can be seen in **Figure 3.3**.

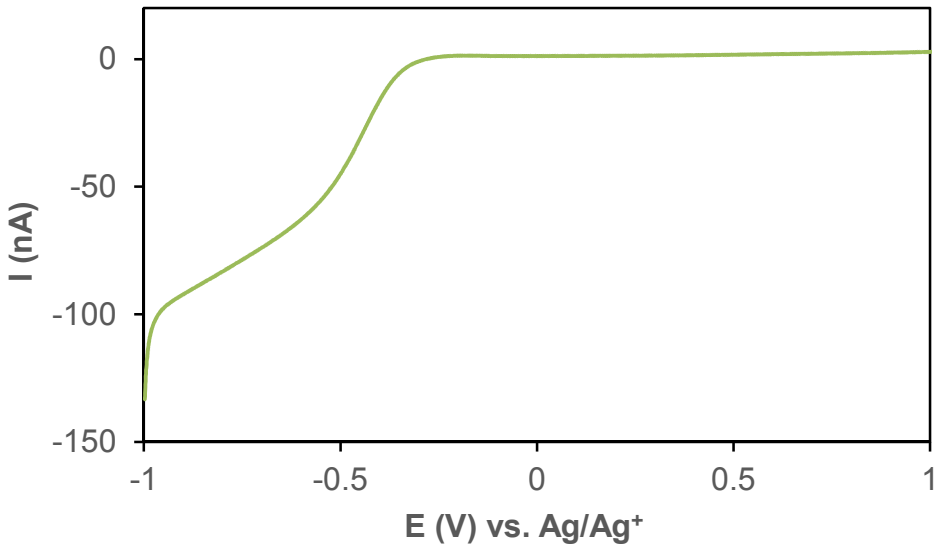


Figure 3.3. Negative going LSV of DTQ (20 mM) in $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 100 mVs^{-1}.

However, when monitoring electroactive species formation in solution with higher oxidation potentials than DTQ, it is desirable to scan in a positive going direction. This allows for the electrode to approach the oxidation potential of the compound, giving a more well-defined current peak. Additionally, this approach strategy allows for detection of similarly structured intermediates that would otherwise not be detected with negative going scans, where the starting potential of the electrode is higher than the oxidation potentials. This would oxidize all developing compounds and provide less useful information. **Figure 3.4** shows the resulting LSVs taken over the course of reaction of adding 3-pentylamine to DTQ. The quinone reduction current is gradually depleted with time. Additionally, the oxidative (positive) current for ADB increases over time. This showcases microelectrode capabilities of monitoring concentration of multiple compounds within a single LSV scan. LSV time intervals can be

seen in **Figure 3.4**. Initial scans are recorded at a much higher frequency than the later scans. The meaning for this is to capture the significant change of concentration during the beginning of the reaction, while taking fewer towards the end of reaction due to a decrease in the reaction speed. This method was used for all LSV experiments to allow for further analysis of rates of reaction that will be discussed more throughout this work.

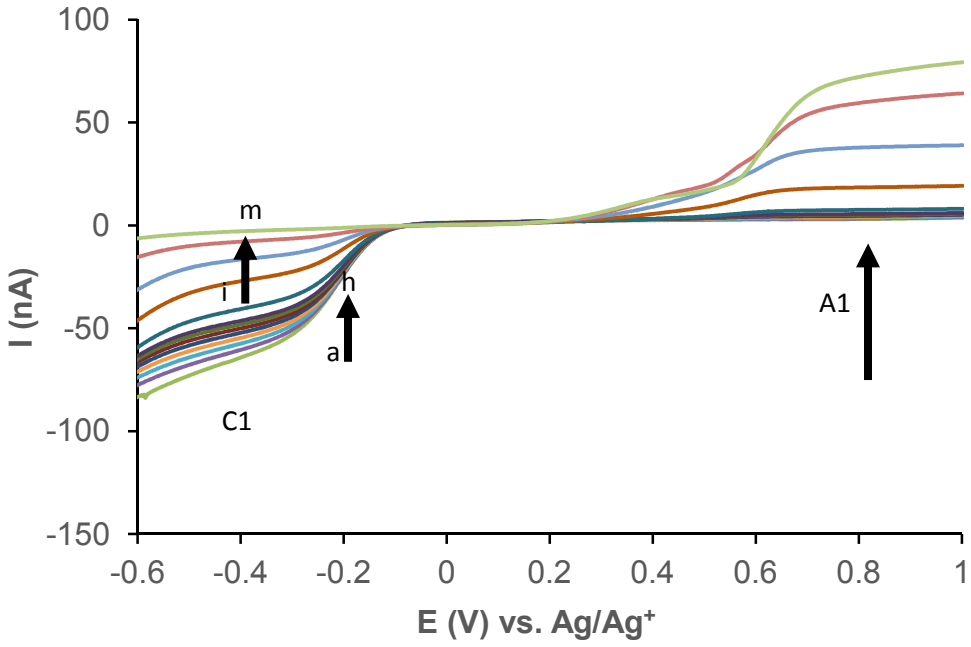


Figure 3.4. LSV of reaction of DTQ (20 mM) and 3-pentylamine (20 mM) with $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 100 mVs^{-1} over time. Scans a – h time intervals 5, 25, 45, 65,85,105, 125, 145 seconds respectively. With scans i-m at time intervals 530, 1015,1980, and 3905 seconds respectively.

After the completion of the reaction, CV is recorded to provide a more complete narrative of the electroactive species in solution.

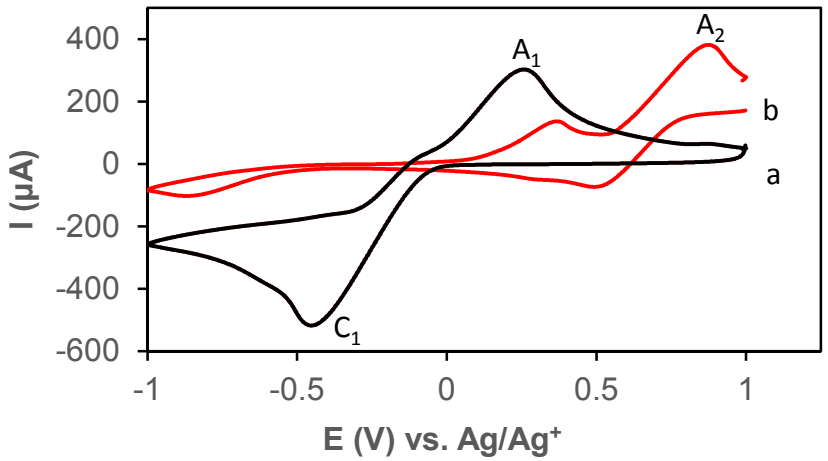


Figure 3.5. CV of DTQ (20 mM) in the absence (a) and after reaction with 3-pentylamine (20 mM) (b) in $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 100 mVs^{-1}.

The formation of peak A2 is a result of formation of ADB as ADB is the only other compound that is electroactive in this potential range. The co-product of the reaction, 3-pentanone, and other ketone containing compounds do not undergo oxidation in this potential range. **Figure 3.6** illustrates the lack of any current from CV of the ketone containing compound, acetone. Furthermore, the oxidation peak observed in **Figure 3.5** is not from oxidation of the amine in solution. **Figure 3.7** shows the CV for a methanol solution of cyclohexylamine. There is positive current being produced from the oxidation of the trace amount of water present in the reaction and negative current from the reduction of oxygen dissolved in solution. However, the characteristics of peak A2 in **Figure 3.5** are not present thus the amine and ketone in solution are not interfering with the CV response.

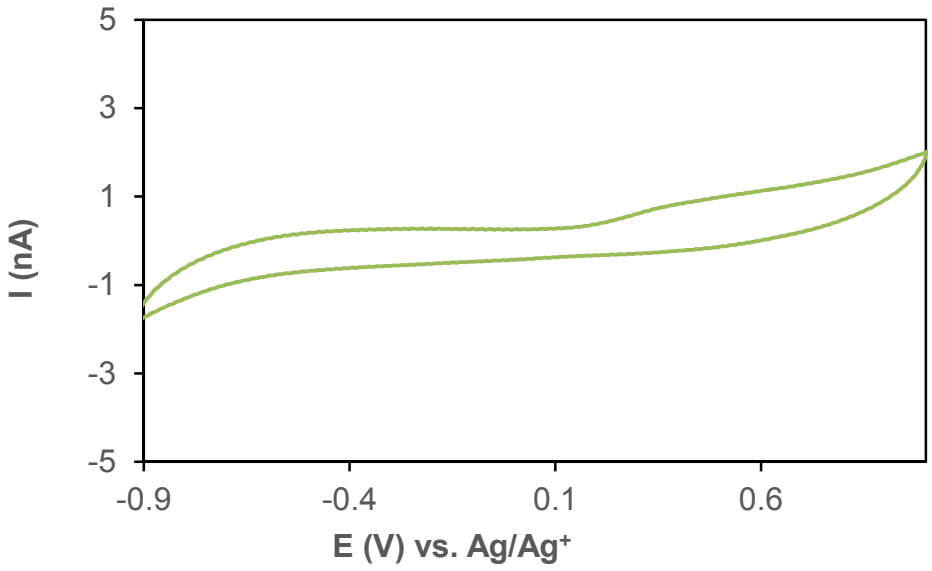


Figure 3.6. CV of $TBA^{+}PF_6^{-}$ (20 mM) in acetone with microelectrode. Scan rate: 100 mV/s-1.

A similar but more dramatic current can be seen in **Figure 3.6**. Although acetone and cyclohexylamine are not electro inactive, there still exists small traces of compounds electroactive in this potential range. The two most noteworthy compounds are oxygen and water. The reduction current in **Figure 3.6** and **Figure 3.7** is produced by the reduction of dissolved oxygen in solution. While the oxidation current produced is from oxidation of the water dissolved in solution.

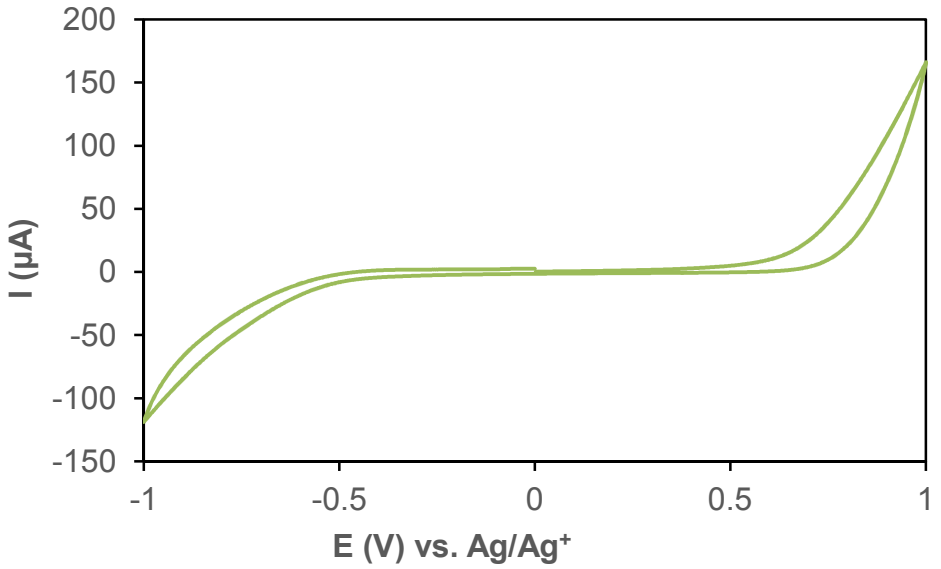


Figure 3.7. CV of cyclohexylamine (20 mM) with $TBA^{+}PF_6^{-}$ (100 mM) supporting electrolyte in methanol solution with glassy carbon electrode. Scan rate: 100 mV/s^{-1}.

After completion of the reaction of DTQ and 3-pentylamine, Corey deemed necessary for the addition of THF and water to ensure solubility of the product while adding a small amount of acid to facilitate the hydrolysis of the ketone from the isomeric Schiff base. After addition of acid, the peak oxidation current shifts to more positive potentials as seen in **Figure 3.8**. This finding is in agreement with the results from previous studies. Where cyclic voltammetry of authentic samples of ADB, verified via NMR, were found to be similar to that of DTC, except in acidic media. The anodic peak was shifted positively due to the protonation of the amine group on ADB.[19] This is in agreement with what was found in this study.

The LSV shown in **Figure 3.4** of the reaction of DTQ and 3-pentylamine. The most notable characteristics of peak A1 and C1 have been previously described. However, the shoulder to peak A1 does cause interest. When considering peak C1, the current follows a well-defined path leading from C1. Each LSV starts at a different peak high due to the change in concentration of DTQ but inevitably converge to the same path. This is not the case for peak

A1. To make this distinction more apparent, plotting the derivative of each LSV, highlights the points of inflection of the original LSV. The derivative of **Figure 3.4** can be seen in F**igure 3.8**.

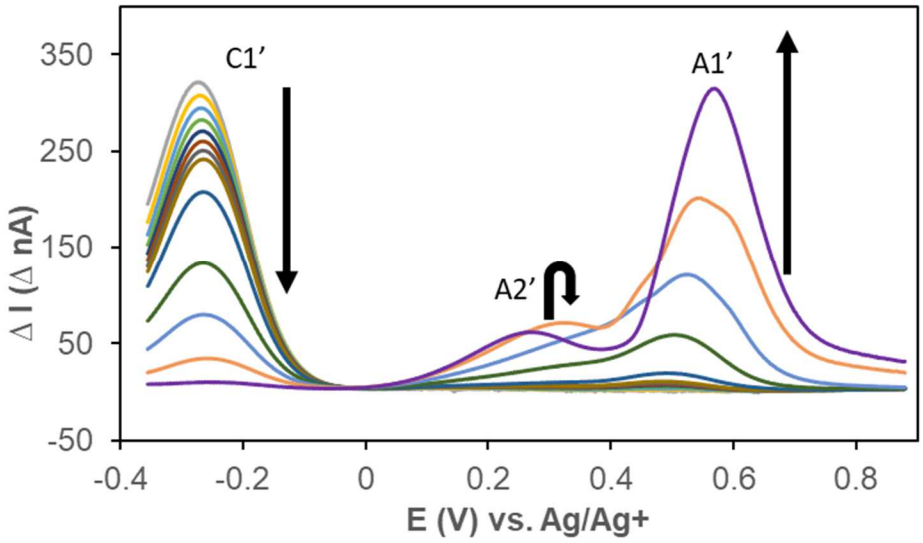


Figure 3.8. Derivative of LSV of DTQ (20 mM) and 3-pentylamine (20 mM) reaction progression with $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 100 mVs^{-1}.

C1' and A1' are a result of the change in peak high of peaks C1 and A1 respectively. Corresponding the consumption of DTQ and ADB as described previously. Furthermore, the previously mentioned shoulder on peak A1 is now more obvious, which will now be referred to as peak A2'. This elusive peak is seen to slowly increase in height during the reaction but inevitably decreases in height by the end of the reaction. Additionally, the peak height is of much less intensity than that of C1' and A1'. This suggests that there exists an electroactive compound that is only present during the reaction that does not persist for the entirety of the reaction. In other words, there is an electroactive intermediate species that undergoes oxidation at approximately 0.3 V. A possible explanation for this peak is the oxidation of the isomeric Schiff base to the initial Schiff base.

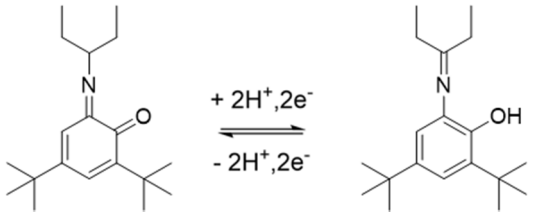


Figure 3.9. Oxidation and reduction of Schiff base and isomeric Schiff base.

The formation of these products has been rigorously verified in previous studies. These verification methods include comparing isolated products from the reaction by infrared and NMR spectra, melting point and mixture melting point, and gas chromatography retention times with authentic reference samples.[18] Furthermore, the isomeric Schiff base has been previously synthesized and compared against authentic reference samples using spectroscopic and chromatographic methods. These tests corroborate with identification of methods of the products formed by reaction of DTQ and various primary amines, thus strongly suggesting the structure of the intermediate compound.[19] Therefore, such characterization was omitted from this study to avoid unnecessary redundancy.

The mechanism of the reaction of DTQ and an amine, is first initiated with a nucleophilic attack on the C_1-carbonyl. The pi electrons of the carbonyl migrate to the associated oxygen. The negative charge on the oxygen atom removes a proton from the attacking amine to for a phenol group. The electron lone pair on the nitrogen collapse to form a double bond with the C_1 carbon it previously attacked. This is followed by the release of the oxygen from the original carbonyl group. This oxygen then removes an additional proton from the incoming amine, thus turning the removed oxygen atom into water and the remaining structure as the previously mentioned Schiff base, also known as quinone imine. As previously mentioned, it is thermodynamically favorable to for the [1,5]-sigma tropic rearrangement to spontaneously to occur. Where the remaining carbonyl group accepts the proton off the alpha

carbon to the nitrogen of the original amine structure. This is followed by the migration of the pi electrons in the carbonyl bond to the carbon ring, restoring aromaticity. This pushes the pi electrons in the C-N bond of the Schiff base to the alpha carbon in the alkyl chain, thus forming the isomeric Schiff base.[19]

There has been no supporting evidence of the mechanism regarding the hydrolysis of the ketone from the isomeric Schiff base upon the addition of acid.

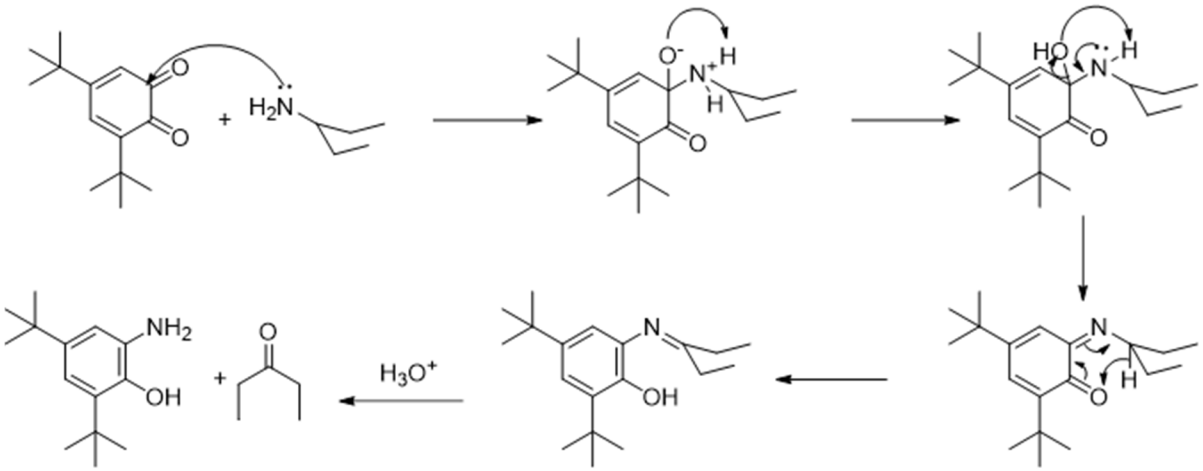


Figure 3.10. Mechanism of reaction of DTQ and 3-pentylamine.

DTQ reaction with 3-pentylamine is quite rapid. With the lifespan of the intermediate isomeric Schiff base being very short. In attempt to lengthen the life span of this molecule, the use of lithium perchlorate ($Li^+ClO_4^-$) as the supporting electrolyte was incorporated into our study. The idea behind using $Li^+ClO_4^-$ was slow down the reaction process by interfering with the rearrangement of the isomeric Schiff base. The intent was to use a small metal cation, such as Li^+, in which the lone pairs on the nitrogen and oxygen would temporarily coordinate with. A depiction of this can be seen in **Figure 3.9**.

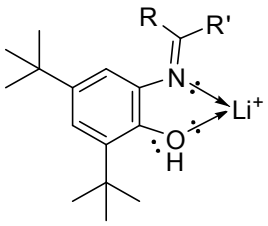


Figure 3.11. Electron lone pairs on isomeric Schiff base coordinating with Li+ ion in solution.

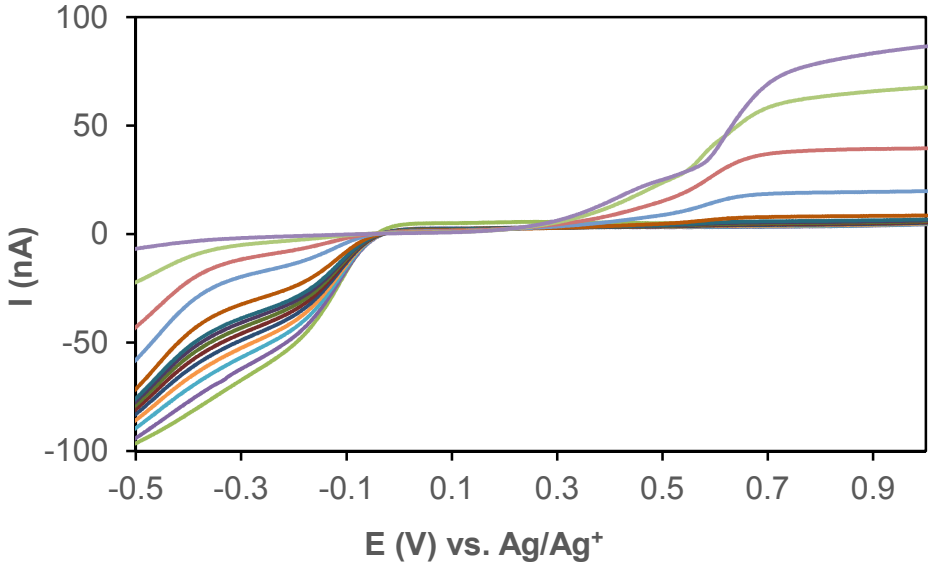


Figure 3.12. LSV progression of DTQ (20 mM) reaction with 3-pentylamine (20 mM) with lithium perchlorate (100 mM) as supporting electrolyte. Scan rate: 100 mV/s^{-1}.

3.2 Oxidation of Cyclohexylamine

The study of DTQ with amines was continued with the study of reaction of DTQ and cyclohexylamine. The interest of this amine, though it is structurally similar to 3-pentylamine, cyclohexylamine contains a cyclohexyl group attached to the nitrogen as seen in **Figure 3.13**. The purpose of this experiment was to observe any effects caused by the difference in structure between the two alkyl substituents.

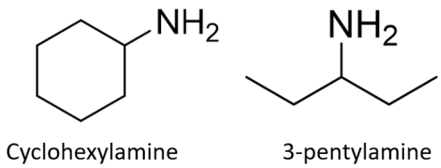


Figure 3.13. Structures of cyclohexylamine and 3-pentylamine.

The pattern that is observed for LSV of DTQ by addition of cyclohexylamine (**Figure 3.14**) is similar to 3-pentylamine (**Figure 3.5** or **Figure 3.12**): where the reduction peak intensity decreases as a result of consumption of DTQ by cyclohexylamine while simultaneously, the oxidation current increases as a result of the formation of Schiff bases and ADB. The most notable difference was the rate of decay of reduction current of DTQ. In other words, the rate of consumption or reaction of DTQ with cyclohexylamine.

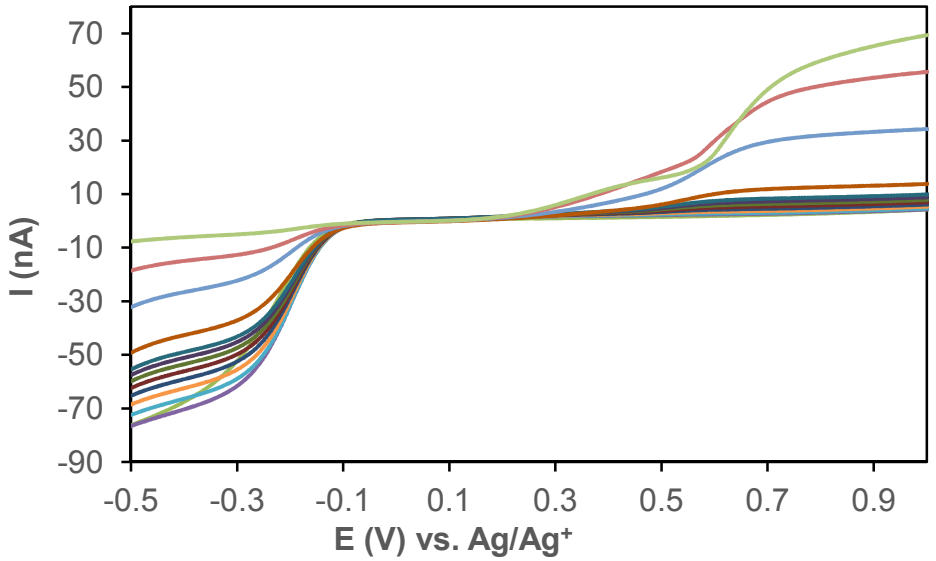


Figure 3.14. LSV of DTQ (20 mM) during reaction with cyclohexylamine (20 mM) with $TBAPF_6$ (100 mM) as supporting electrolyte. Scan rate: 100 mV/s^{-1}.

To derive the rate of reaction between amines and DTQ we can analyze the peak (or plateau) current for the resulted CVs (or LSVs). By use of LSV, the current plateau is recorded with each voltammogram. By plotting the current at the time, the potential of the electrode passes the oxidation potential of a compound during the scan. A current vs time plot can be

made to determine the rate of reaction. This is made possible due to the plateau current being proportional to the concentration of the electroactive compound. The concentration can be determined by the ratio of current at the plateau current during the reaction with the initial current generated by the initial concentration of DTQ. In our study, 20 mM DTQ was used in each experiment. Therefore, the concentration of DTQ during the reaction is the ratio of the plateau current at any given time and the current produced by DTQ in the absence of amine. Using this technique, the rate of reactions between different amines with DTQ can be compared.

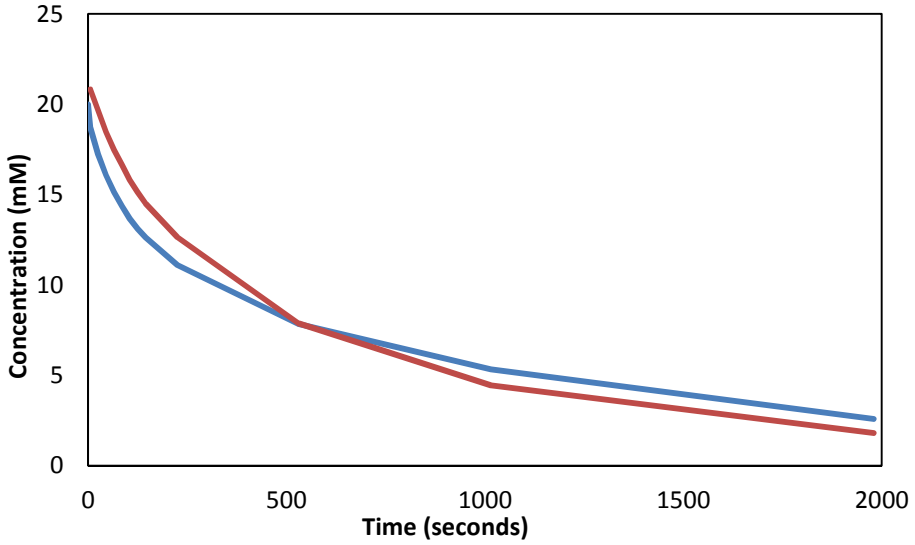


Figure 3.15. Rate of consumption of DTQ (20 mM) and cyclohexylamine (20 mM) (red trace). Rate of consumption of DTQ (20 mM) and 3-pentylamine (20 mM) blue trace). Concentration of DTQ derived from plateau current at -0.4 V from F**igure 3.14** and **Figure 3.12** respectively.

Figure 3.15 highlights the faster initial consumption of DTQ by 3-pentylamine in comparison of cyclohexylamine. The effect of steric hinderance in the rate of reaction resulted in additional experiments with a secondary amine, diethylamine. The rate of reaction with the more sterically hindered amine showed to dramatically decrease the rate of reaction when in the presence of DTQ. Thus, showing a very slow reaction for diethylamine.

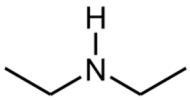


Figure 3.16. Chemical structure of diethylamine.

The effect of the steric bulk around the amine on the rate of reaction with DTQ can be seen in **Figure 3.17**. The rate of reaction for diethylamine can be compared to the rates of reaction for the two previously mentioned amines.

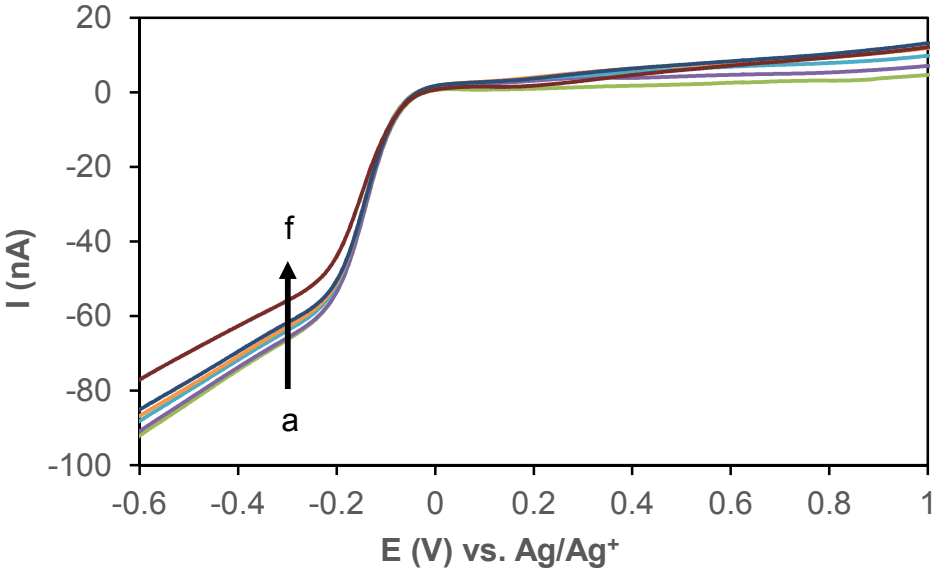


Figure 3.17. LSV progression of DTQ (20 mM) and diethylamine (20 mM) with $TBA^{+}PF_6^{-}$ (100 mM). Scan rate 20 mVs^{-1} . With time intervals of traces a-f as 6, 612, 1824, 3642, 5460, and 16200 seconds respectively.

The rate of reaction for diethylamine can be compared to that of the previosly studied amines with the technique that was decribed for **Figure 3.15**. Comparing the rate of consumption of DTQ by the studied amines can be seen in **Figure 3.18**.

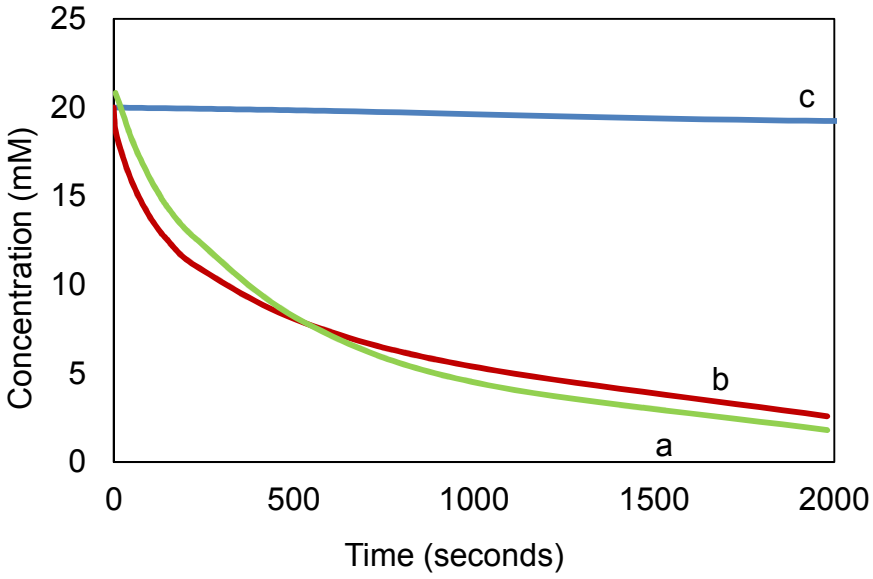


Figure 3.18. Rate of consumption of DTQ in the presence of a) cyclohexylamine b) 3-pentylamine and c) diethylamine.

3.3 Oxidation of Amines with Adjacent CH_2 Groups: 1-Pentylamine

Based on the literature (as discussed in chapter one), when the amine is adjacent to a methylene group based on the following reaction there is a good chance for a cyclization reaction and formation a heterocyclic compound instead of releasing aldehyde and aminocatechol.[6]

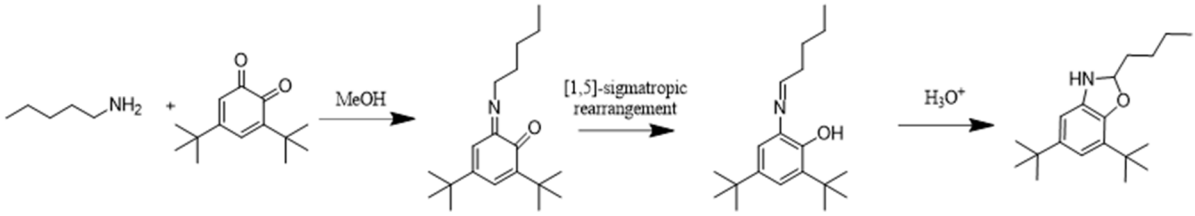


Figure 3.19. Reaction of DTQ and 1-pentylamine

The LSV recording of DTQ and 1-pentylamine progressed in a similar manner to the amines previously discussed. **Figure 3.20** shows the LSV of reaction between DTQ and 1-pentylamine. Showing the characteristic decay of reduction current from the consumption of DTQ and the growth of oxidation current of an electroactive product.

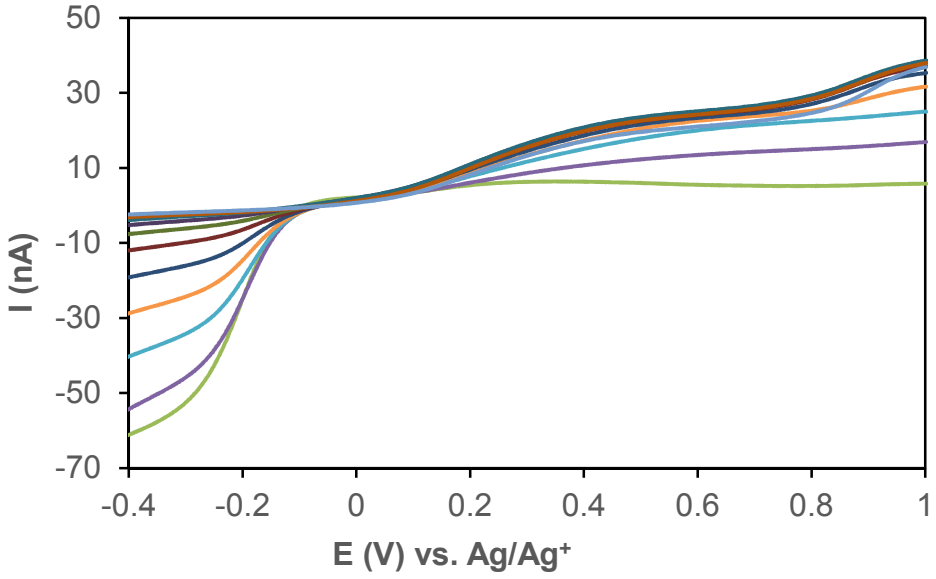


Figure 3.20. LSV progression of DTQ (20 mM) and 1-pentylamine (20 mM) reaction with TBAPF6 (100 mM) as supporting electrolyte. Scan rate: 100 mV/s^{-1}.

With the addition of cosolvents and oxalic acid, the remaining Schiff base undergoes cyclization to form 5,7-di-tert-buty-2,3-dihydro-2-pentylbenzoxazole (DDP). This can be seen by the peak shift in **Figure 3.19**.

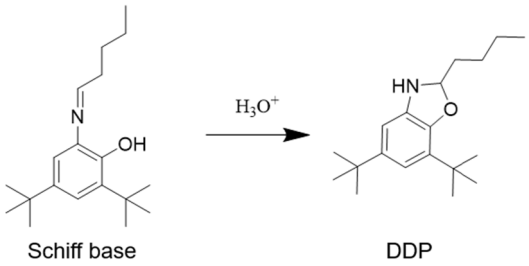


Figure 3.21. Cyclization of Schiff base to form DDP

The Schiff base is consumed upon addition of acid; therefore, the remaining oxidation current is a result of DDP in solution as all other electroactive compounds had been depleted. The decay of the oxidation current of DDP suggests that it is structurally unstable in its electroactive form.

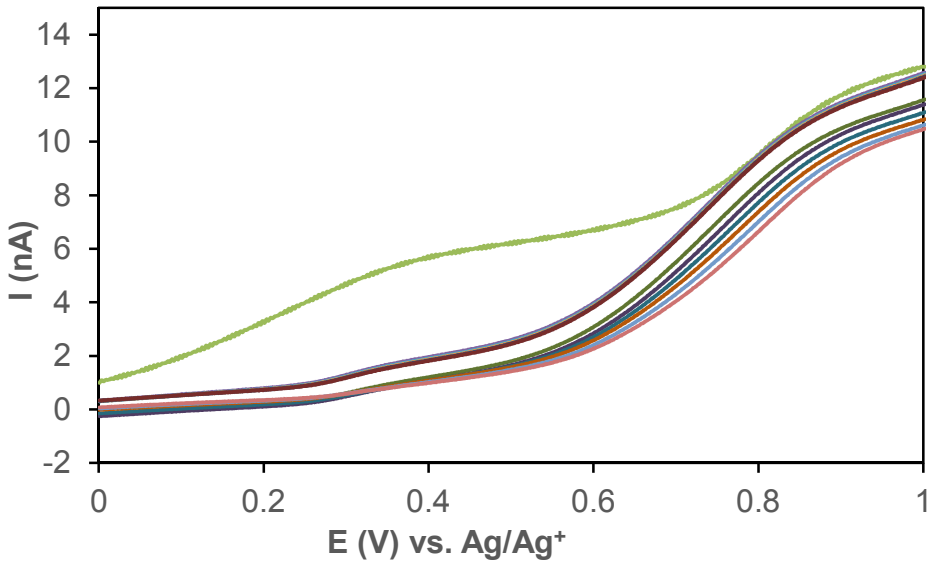


Figure 3.22. LSV progression of acid hydrolysis of reaction of DTQ and 1-pentylamine

Besides the lack of ability to form carbonyl compounds and the ability to form an oxazole product; 1-pentylamine rate of reaction wit DTQ was recorded to be significantly faster than any other amine previously mentioned in this chapter. A comparison of the rates of reaction of 3-pentylamine, 1-pentylamine, cyclohexylamine, and diethylamine can be seen in **Figure 3.22.**

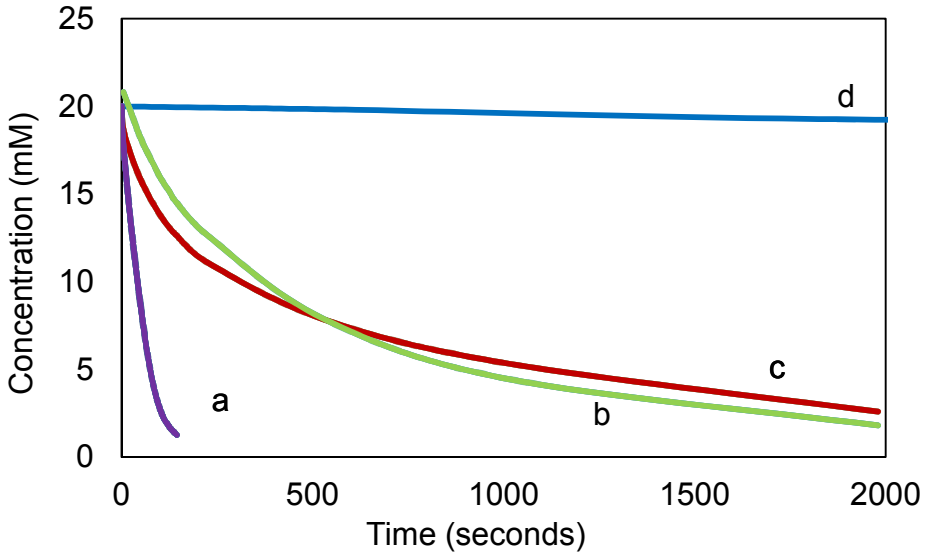


Figure 3.23. Rate of consumption of DTQ in the presence of a) 1-pentylamine b)3-pentylamine c) cyclohexylamine and d) diethylamine.

Further investigation of reaction rates was done with a technique known as chronoamperometry (CA). During the CA experiments, the potential of the working electrode was held at a constant potential of -0.5 volts. This is done to allow constant monitoring of the reduction current produced by DTQ while being consumed by an amine. The current was measured prior to the addition of amine to establish relation between the known starting concentration of DTQ and the observed current produced by the applied potential. This allows for monitoring the change of concentration of DTQ during the reaction as current is proportional to concentration. **Figure 3.24a** shows the resulting amperogram produced during an equimolar reaction of DTQ and 3-pentylamine.

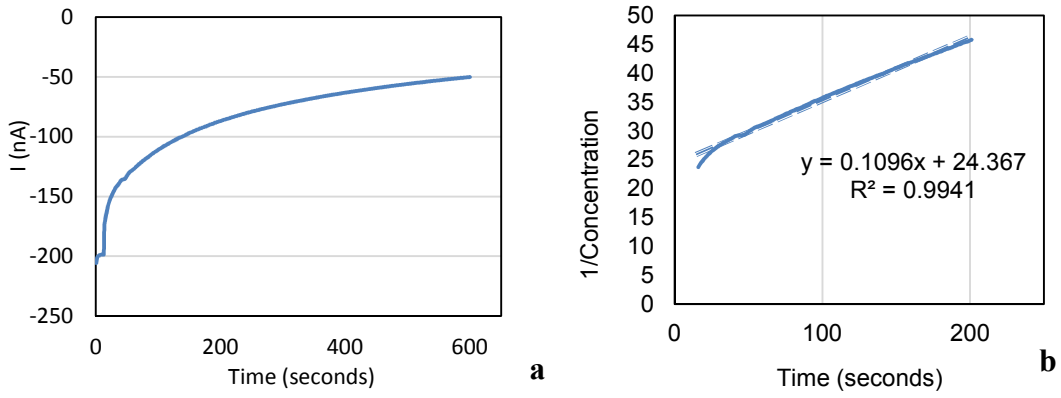


Figure 3.24 a) Amperogram of DTQ (50 mM) and 3-pentylamine (50 mM) with TBAPF6 as supporting electrolyte (10 mM). **b)** Plot of the inverse of concentration of DTQ during reaction with 3-pentylamine with equation providing rate constant for the reaction.

The concentration profile was constructed with the method previously mentioned for earlier figures. **Figure 3.24b** was constructed using the method of initial rates resulting concentration profile for the reaction as the reaction of DTQ and 3-pentylamine. The linear line in this plot confirms the reaction is second order overall. Equation of the trend line provides the rate constant for the reaction as the slope of the line. The rate constants for

cyclohexylamine and 1-pentylamine were calculated in the same manner as above. The rate constants for all primary amines studied in this work can be found in **Figure 3.25.**

Amine	Rate Constant
Cyclohexylamine	0.098 $M*s^{-1}$
3-pentylamine	0.110 $M*s^{-1}$
1-pentylamine	0.372 $M*s^{-1}$

Figure 3.25. Experimentally determined rate constants for studied primary amines.

CONCLUSION AND OUTLOOK

The results described in this thesis show the successful utilization of microelectrodes to monitor the reaction process of the electroactive compound 3,5-di-tert-butly-1,2-benzoquinone (DTQ) with a variety of amines. Microelectrodes were used to monitor the current produced by DTQ and any other electroactive compounds. Giving insight to the structures of intermediate compounds formed during the reactions. Additionally, the current produced by the oxidation and reduction of compounds of interest can be monitored at their oxidation/reduction potential over time. This allows for comparison of different amines structural effects on the rate of reaction with DTQ. This concept can be used to explore many different electroactive reagents and their interactions with a wide array of substrates.

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VITA

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