2021

Synthetic Pathways for Potential Platinum 1,10-Phenanthroline Compounds

Jacob Young
Western Kentucky University, jacobyo94@gmail.com

SYNTHETIC PATHWAYS FOR POTENTIAL PLATINUM 1,10-PHENANTHROLINE COMPOUNDS

A Capstone Experience/Thesis Project Presented in Partial Fulfillment

of the Requirements for the Degree Bachelor of Science

with Mahurin Honors College Graduate Distinction

at Western Kentucky University

By

Jacob M. Young

August 2021

*****

CE/T Committee:

Dr. Kevin Williams, Advisor

Dr. Blairanne Williams

Ms. Cheryl Kirby-Stokes

ABSTRACT

There are extremely important uses for platinum when it comes to the treatment of cancers and dementias. One potential therapeutic combines platinum with a structure known as phenanthroline. This platinum phenanthroline structure is normally extremely water-insoluble, rendering it difficult to study and use in biological systems. The Williams' Biochemistry Laboratory endeavored to find a simpler synthetic pathway for a water-soluble phenanthroline product. While unsuccessful in identifying a product as of yet, many synthetic pathways have been ruled out, and more hypothetical pathways are being formulated for testing.

Among the strategies analyzed are varying solvent, reagents, apparatus, methodology, and temperature in order to coax platinum(II) 1,10-phenanthroline dichloride into solution to promote reaction with more water-soluble compounds. Among potential future hypotheses are the use of harsher solvents and potentially increasing the oxidation state of platinum.

This thesis is dedicated to my family and friends who have encouraged me and helped drive me to success in my undergraduate career.

ACKNOWLEDGEMENTS

I would like to take this opportunity to acknowledge the guidance of both Dr. Kevin and Blairanne Williams, in teaching me the fundamentals of biochemistry as a laboratory science and assisting in my development as a young researcher. I would like to thank my roommates for helping me revise this thesis, my parents for reminding me of the importance of my work, and my sisters for encouraging me to exceed expectations. I would like to thank WKU and the Mahurin Honors College for the opportunity to conduct undergraduate thesis research. Finally, I would like to acknowledge the financial assistance I was provided through the Office of Research and Creative Activity and their Faculty-Undergraduate Student Engagement Grant, which partially funded the materials needed to pursue this line of research.

VITA

EDUCATION

Western Kentucky University, Bowling Green, KY — August 2021
B.S. in Biochemistry, B.S. in Psychological Sciences
Mahurin Honors College Graduate
Honors CE/T: *Analysis of Water-Soluble 1,10-Phenanthroline Compounds*

Saint Xavier High School, Louisville, KY — May 2017

PROFESSIONAL EXPERIENCE

Williams Biochemistry Laboratory, WKU — August 2018–Present
Research Assistant

AWARDS AND HONORS

Magna Cum Laude, WKU, May 2021
Ogden Research Scholar, WKU, 2017-2021
FUSE Grant Recipient, WKU, 2019

PRESENTATIONS

ACS National Conference and Expo, cancelled due to COVID-19 pandemic, April 2020
WKU Student Research Conference, March 2019

CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Introduction to Platinum Compounds

Platinum-based compounds have been used in the treatment of disease and advancement of science since the mid-eighteenth century. One of the important chemical properties of platinum is its ability to coordinate multiple covalent bonds. Platinum (II) can coordinate up to four covalent bonds, whereas the more oxidized version, platinum (IV), can maintain six stable bonds, as seen in satraplatin (Johnstone, Park, & Lippard 2014).

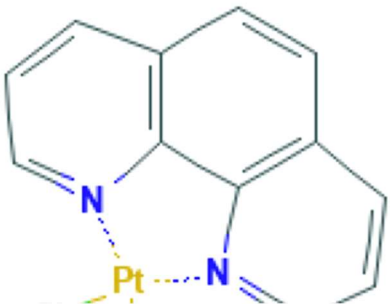
While there are a multitude of compounds containing platinum used in medicine, many unsuccessful candidates struggle with providing adequate bioavailability. Since platinum is a stable heavy metal that coordinates with DNA, it provides considerable cytotoxicity in biologically active systems. Medicinal compounds containing platinum include drugs used in the treatment of cancers such as cisplatin and oxaliplatin. One of the first functions of these drugs was to act as an antineoplastic, preventing or reversing the onset of paraneoplastic syndrome in cancer patients (Johnstone, Park, & Lippard, 2014).

There are other forms of platinum compounds commonly used in scientific study. Platinum compounds frequently used in laboratory settings include tetrachloroplatinate, elemental platinum (II) and platinum (IV), and various catalytic salts. Platinum's modern primary use is as a catalyst for a variety of chemical reactions.

History and Synthesis of Phenanthroline

One family of platinum compounds – those containing or derived from a 1,10-phenanthroline ligand – have been detailed in the scientific literature since Monatsh Blau's discovery in 1898.

Figure 1

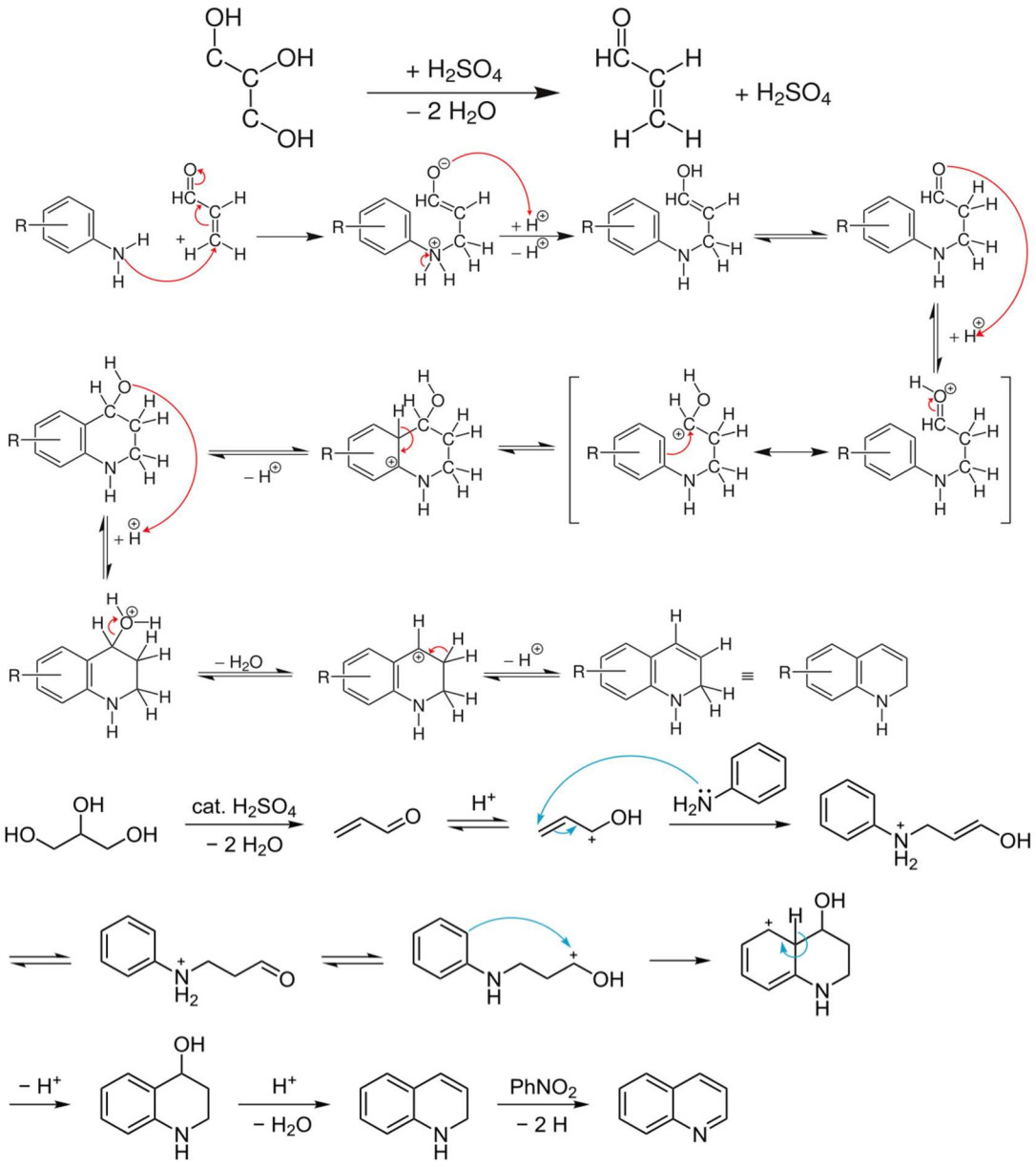


[*Chemical Structure of Platinum (II) 1,10-Phenanthroline*]

A refined synthetic method for synthesis of *o*-phenanthroline was published by Breckenridge and Singer (1947). The synthetic process outlined in the mid 20th century dictates the use of two successive Skraup reactions to synthesize *o*-phenanthroline from glycerol and *o*-phenylenediamine (Halcrow & Kermack, 1946).

The general mechanism for a Skraup synthesis is shown below in **Figure 2:**

Figure 2



[image sourced from Wikipedia article on Skraup reactions. Z.H. Skraup published the general model for quinoline synthesis in 1880 manuscript "Eine Synthese des Chinolins." Note that this model is archetypal and is not the Skraup reaction for phenanthroline.]

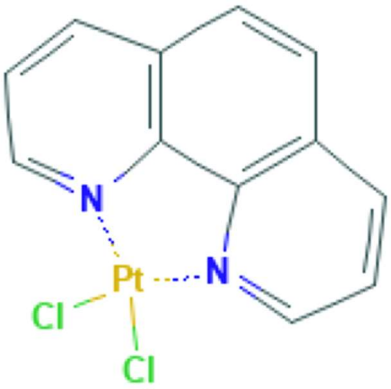
At the conclusion of the Skraup reaction, the *o*-phenanthroline compound can be reacted in hydrochloric acid solution under a nitrogen gas atmosphere with tetrachloroplatinate to

form Platinum (II) 1,10-phenanthroline dichloride (IUPAC preferred name: dichloroplatinum;1,10-phenanthroline) [Pt(II)(phen)](Sun, et al. 2019).

Properties of Phenanthroline Compounds

At the conclusion of a Skraup reaction an aromatic multi-ring structure is formed. In the instance of (phen), there are nitrogen atoms at the 1 and 10 positions of the ring structure. Phenanthroline derived compounds exhibit varying levels of pKa, solubility, and bioactivity. Of particular concern is Pt(II)(phen)Cl_2. There is very limited data available on the compound. **Figure 3** Shows the complex which phenanthroline creates with platinum.

Figure 3



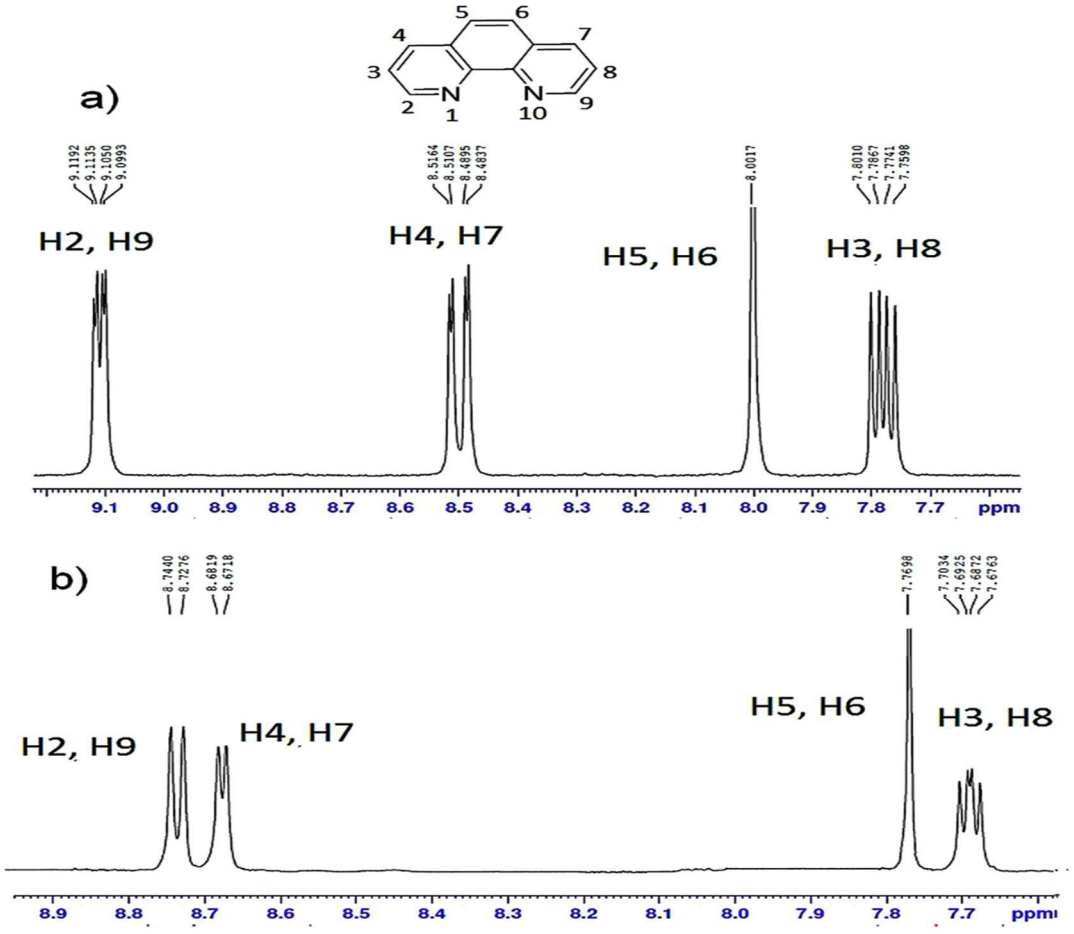
[*dichloroplatinum;1,10-phenanthroline*]

Platinum can then form two other coordinate covalent bonds, either with a bidentate ligand, or with two separate atoms or molecules.

Phenanthroline's appearance on ^1H nuclear magnetic resonance spectroscopy [NMR] shows 4 groups of peaks. **Figure 4** shows standard (phen) spectra (with and

without a platinum complex), along with a labeled diagram assigning each proton to a peak.

Figure 4



[*Standard 1,10-Phenanthroline Peak assignments. Adapted from Sun, et al. 2019.*]

Due to the symmetry of the molecule along the central line of the platinum, there are only four expected peak groups associated with 1,10-phenanthroline. ^{1}H-NMR assists with identification of the compounds synthesized or utilized in experiments.

Solubility and Bioavailability

The platinum coordinated (phen) compound discussed above has no known remarkable solubility in water. Limited efforts have been documented in synthesizing derivative compounds which both include Pt(II)(phen) and also increase the water solubility of the compound. Of particular note are alkoxyacetate compounds synthesized by Sun, et al. (2019), which show considerably increased bioavailability and cytotoxicity when uptake occurs in various tumor cell lines. Their study showed a maximum solubility of 17.5 mg/ml when the coordinated ligand for platinum was alkoxyacetate. While these particular compounds have not been reproduced, it shows important promise for the phenanthroline ligand.

In a review of current literature, no published data has been found for *in vitro* bioavailability of Pt(II)(phen) in mammalian subjects. It is suspected, however, that due to the extreme insolubility of the species, bioavailability would approach zero percent.

Current Research into Phenanthroline

A few studies of note demonstrate the potential of *o*-phenanthroline. Halcrow and Kermack (1946) attempted to derive new antimalarial compounds based on phenanthroline from quinolines. The study demonstrated that the aromatic rings themselves could have substituents added using simple organic chemistry methods. However, these *o*-phenanthroline compounds are distinct from their platinum-coordinated derivatives described earlier. While likewise having low solubility in water, they do not share the same level of cytotoxicity and chelating ability as the Pt(II)(phen) compounds.

Barnham, et al (2008) described how Pt(II)(phen)Cl_2 could potentially be used to prevent aggregation of β-amyloid [Aβ] into insoluble plaques. By binding to histidine

residues in Aβ, Pt(II)(phen) can inhibit essential metal activity and reduce toxicity that the plaques cause in synapses. The Pt(II)(phen)Cl_2 lowers oxidative stress by inhibiting formation of Aβ-Copper(II) complexes which are known to catalyze formation of peroxides [Opazo, et al. 2002]. The (phen) ligand shows higher affinity for Aβ than other neurological proteins *in situ*.

Sun, et al. (2019) utilized structurally similar derivatives of Pt(II)(phen) in order to increase solubility of the phenanthroline. They showed that some of these compounds were cytotoxic and readily taken in by tumor cell lines in culture, yet less potent than the traditional anticancer platinum drugs.

There has been a reasonable amount of data published which demonstrates Pt(II)(phen) based compounds as potential targeted therapeutics for complex medical ailments such as cancers and Alzheimer's disease. However, the extreme insolubility of stock compounds creates a severe inability to utilize findings presented in the literature for the advancement of therapeutics. By understanding the implications of a relatively easily synthesized yet soluble compound, one can easily understand the need to develop and properly characterize such a compound. Various methods have been employed to attempt this feat, and to analyze and characterize any resulting compound which may be created.

EXPERIMENTAL

General Considerations

Among much of the general operating theory of this project in the Williams' Biochemistry Laboratory is that if Pt(II)(phen)Cl_2 can undergo a displacement reaction with silver oxalate [Ag_2(ox), ox = $C_2O_4^{-2}$] to create Pt(II)(phen)(ox) and a silver chloride precipitate, the oxalate product would likely be appropriately water-soluble. The most difficult task has been identifying an appropriate anhydrous solvent which can pull the Pt(II)(phen) compound into solution without creating solvation products or creating an environment too harsh to isolate the desired product.

In order to identify an appropriate solvent, a qualitative solubility survey was conducted. A few milligrams of commercially available Pt(II)(phen)Cl_2 were dissolved in four milliliters each of deionized (DI) water, acetone, chloroform, dichloromethane (DCM), and methanol. After 24 hours of stirring in microvials, the DCM and acetonitrile appeared to best pull the phenanthroline compound into solution. However, after another 48 hours without stirring, all compounds appeared to settle back as precipitates. While none of these compounds were analyzed using spectroscopic methods to verify that the compound had failed to go into solution, this qualitative study demonstrated the difficulty which would be present throughout all experiments conducted.

As a precursor to discussing individual experiments, **Table 1** below shows each reagent, solvent, and notes of the reaction sequence which have been attempted for

Pt(II)(phen). **Table 2** shows each reagent, solvent, and notes of the reaction sequence which have been attempted for platinum (II) neocuproine dichloride [Pt(II)(neo)], which is sterically and chemically similar to 1,10-phenanthroline. Each experiment will be discussed in depth.

Table 1: Summary of Platinum (II) 1,10-Phenanthroline Dichloride Reactions

Reagent	Solvent	Notes
Silver Oxalate	DI Water	Yellow resulting solution. Light orange precipitate after drying.
Histidine	DMSO-d_6/D_2O	Quick exergonic reaction.
N-Acetyl-L-Methionine	DMSO-d_6/D_2O	
Silver Oxalate	DMF	Green-yellow solution. NMR characterized using both D_2O and DMSO-d_6.
Silver Oxalate	DCM	Concentrated under vacuum. Crystals knocked out with diethyl ether.
Silver Nitrate	DCM	Concentrated under vacuum. Crystals knocked out with diethyl ether.

Table 2: Summary of Platinum (II) Neocuproine Dichloride Reactions

Reagent	Solvent	Notes
Histidine	DMSO-d_6/D_2O	Exergonic reaction.
N-Acetyl-L-Methionine	DMSO-d_6/D_2O	Neocuproine compound reluctant to enter solution.
Silver Oxalate	DMSO	Unremarkable.
Silver Oxalate	DI Water	Unremarkable.

Stock Synthesis Reactions

Two compounds utilized throughout multiple experiments were synthesized in house. The synthetic strategy of $Ag_2(ox)$ and Pt(II)(neo)Cl_2 are explained below.

Silver Oxalate: Although stock bottles of the reagent are available for purchase, it was more cost effective to synthesize the compound as needed in the lab. To synthesize $Ag_2(ox)$, 250 mg of silver nitrate was combined with 125 mg of anhydrous oxalic acid with 50 mL of DI water in an amber bottle. The solution was stirred overnight, and vacuum filtered. The final product was a white, powdery precipitate. The product was stored in an Eppendorf tubule in complete darkness to prevent unwanted photoreactions.

Platinum (II) Neocuproine Dichloride: The synthesis of the (neo) compound consisted of two consecutive reactions. First, 1.25 g of potassium tetrachloroplatinate were dissolved in 10 mL of DI water. Once dissolved, 639 mL of DMSO was added. After stirring for just under a day, yellow crystals were observed, and the original red color of the tetrachloroplatinate was no longer present. This yellow precipitate was gravity filtered and dried overnight. This resulting compound, not characterized by NMR, is believed to be $Pt(II)(DMSO)Cl_2$.

The DMSO compound was used to synthesize the (neo) compound. First, 315 mg of the DMSO compound and 156 mg of pure (neo) were brought into solution using 80 mL of ethanol. This solution was refluxed for one day. After reflux, the resulting solution was rotary evaporated, and the resulting solid was dissolved in dichloromethane. This new solution was then run through a silica gel column, and a yellow solution was collected and dried. This final compound is characterized as $Pt(II)(neo)Cl_2$.

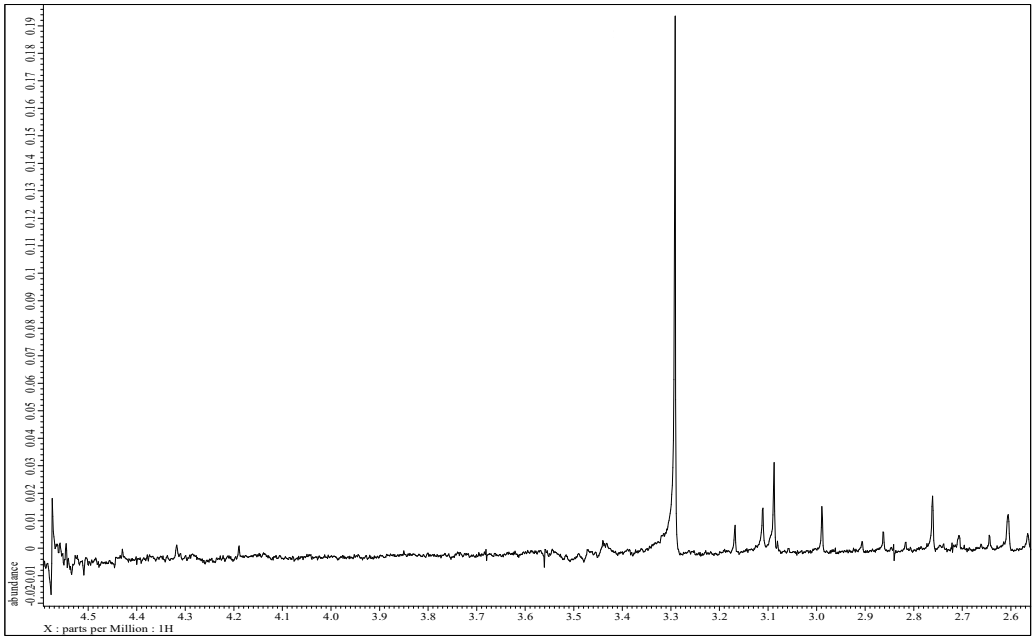
Silver Oxalate Reactions

There are four reactions which utilized silver oxalate as a reagent: three (phen) and one (neo). No reactions produced confirmed water-soluble products, but one produced a potential success which could not be confirmed by NMR.

In the first two phenanthroline reactions, one used DI water as the solvent, and the other used N,N-dimethyl formamide (DMF). The DI water reaction was allowed to stir overnight in an amber bottle, and then was gravity filtered, and the resulting solution was rotary evaporated. This produced the expected failed reaction, although a minor color change in the precipitate from light yellow to light orange was recorded. NMR data did not show evidence of any of the expected compounds (reactants or products), and therefore the reaction was considered unsuccessful.

The reaction utilizing DMF, Ag_2(ox), and (phen) marked the strongest anhydrous solvent used as of yet. A sickly green-yellow color precipitate was formed after the solution was allowed to stir overnight. The resultant compound was characterized by NMR in both dimethyl sulfoxide-d_6 (DMSO-d_6) and deuterium oxide (D_2O).

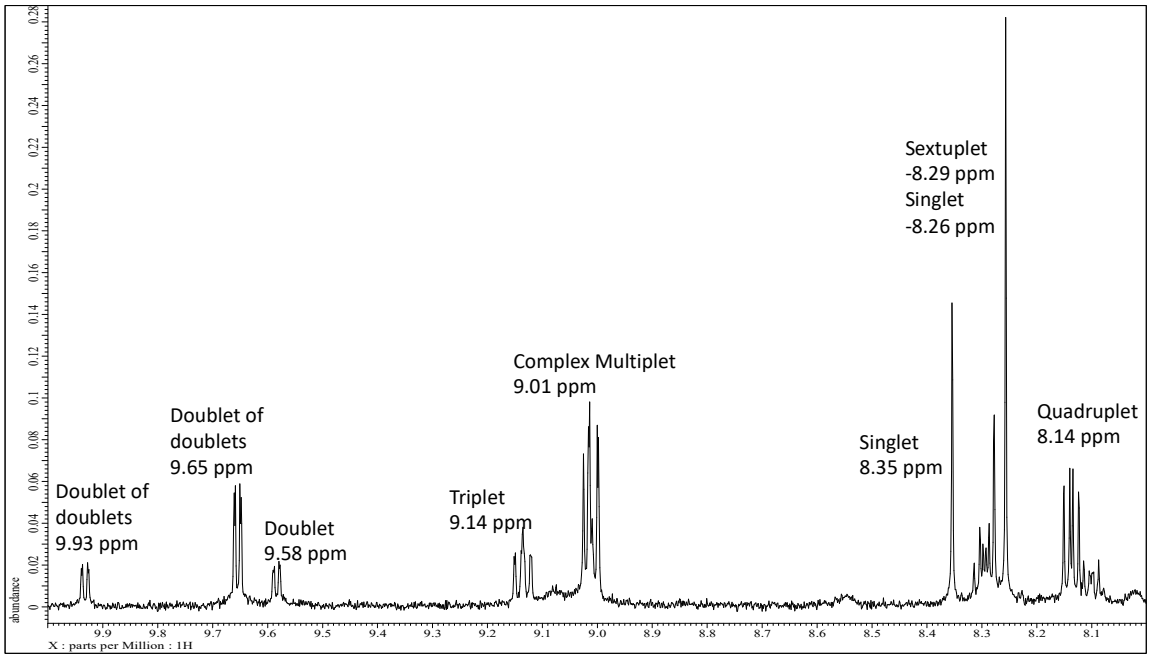
Figure 5: ^{1}H NMR of Silver Oxalate and Platinum (II) 1,10-Phenanthroline in D_2O



[*This spectra shows the result of reaction between silver oxalate and platinum(II) 1,10-phenanthroline with DMF as the solvent. Product dissolved in D_2O.*]

The NMR data presented shows a variety of peaks set between 2.6-3.1 ppm. These shifts are not expected in phenanthroline compounds. Since silver oxalate does not contain any additional deuterated protons, it is unclear what compound is present, and whether it has any significance in the data.

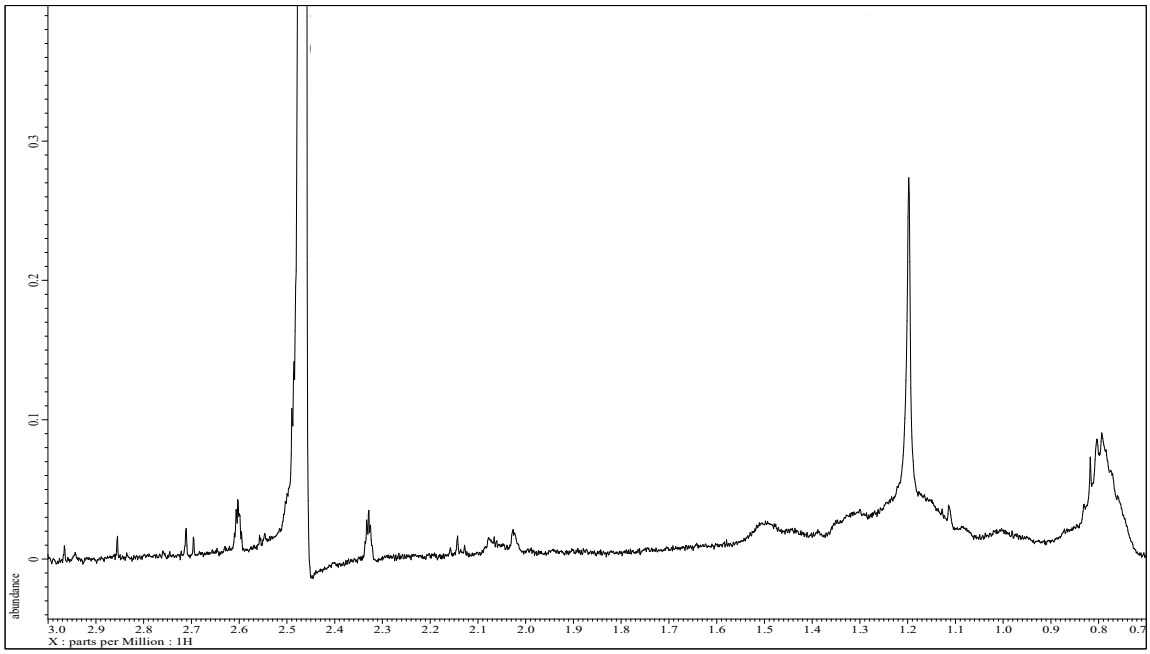
Figure 6: ^{1}H NMR of Silver Oxalate and Platinum (II) 1,10-Phenanthroline in DMSO (8.0-10.0 ppm)



[*This spectra shows the upfield shifts in the reaction between silver oxalate and platinum(II) 1,10-phenanthroline with DMF as the solvent. Product dissolved in DMSO.*]

The data depicted shows peaks consistent with (phen) shielded by the addition of more electronegative atoms, such as oxygen on the (ox). All of the peaks exist in the 8.0-10.0 ppm range in the NMR, suggesting aromaticity.

Figure 7: ^{1}H NMR of Silver Oxalate and Platinum (II) 1,10-Phenanthroline in DMSO (0.7-3.0 ppm)



[*This spectra shows the downfield shift in the reaction between silver oxalate and platinum(II) 1,10-phenanthroline with DMF as the solvent. Product dissolved in DMSO.*]

The NMR data presented shows a variety of peaks set between 0.7-3.0 ppm. These shifts are not expected in (phen) compounds. Since $Ag_2(ox)$ does not contain any additional deuterated protons, it is unclear what compound is present, and whether it has any significance in the data. The large peaks at 1.2 ppm and 2.5 ppm may be a residual solvent such as acetone or water.

The final unsuccessful trials with silver oxalate were with (neo) rather than (phen). This reaction in both DI water and DMSO (following the same procedure as for phenanthroline) yielded no considerable products, and no identifiable products could be identified on NMR.

There was one trial with Ag_2(ox) and (phen) which has yielded inconclusive results, yet the most likely result is the lack of meaningful reaction. In this reaction, the reagents were allowed to stir overnight in dichloromethane. The resulting solution was concentrated from 50 mL to 15 mL by rotary vacuum. Then, 5 mL of diethyl ether was added, and a sandy yellow precipitate was drawn out of solution. This precipitate was gravity filtered, dried overnight, and analyzed via NMR using D_2O. The NMR data showed no indications of any compounds present in solution and is not included due to its lack of remarkability. However, it was observed that the physical characteristics of the resultant compound were noticeably different to the original phenanthroline, and the compound appeared to go into solution under vortex but would quickly settle when unagitated.

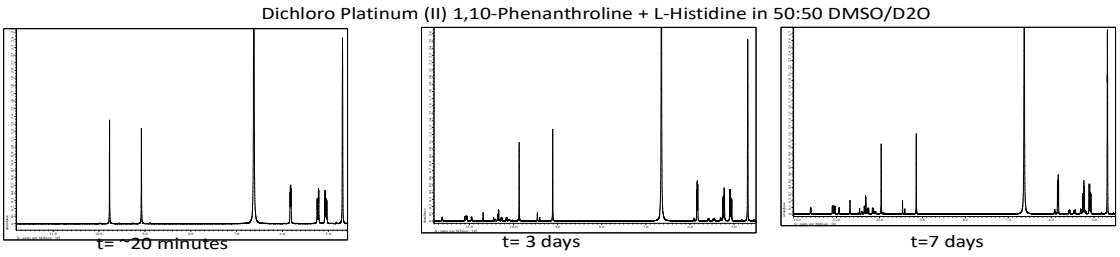
Silver Nitrate Reactions

There were a few reactions conducted with silver nitrate, each involving (phen). Of particular note was a reaction scheme which paralleled the (phen), (ox), and DCM pathway. The method followed for each was identical, with the only alteration being the use of silver nitrate instead of silver oxalate. The NMR data once more lacked any significant signals. The observation of the resultant compound in preparation for NMR showed the yellow product being pulled into solution, and the entire solution becoming colorless. It is not confirmed if this product was the intended one, but it is reasonable to conclude that not enough product was drawn fully into solution to yield significant results.

Amino Acid Reactions

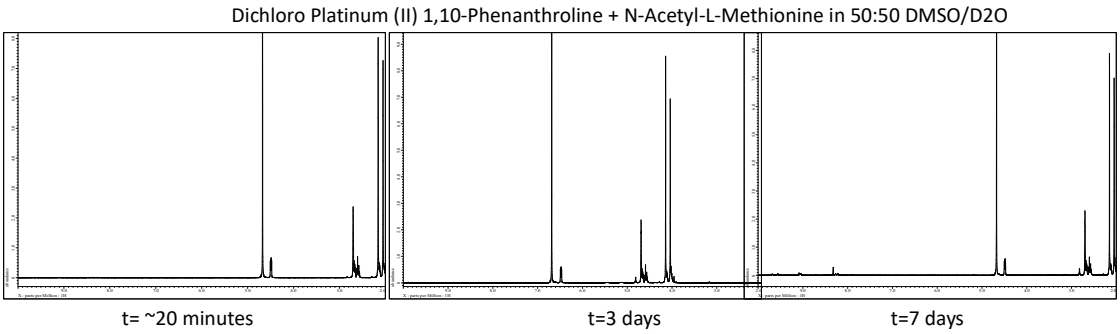
A few non-synthetic reactions were conducted to examine the interactions of the phenanthroline and neocuproine compounds with methionine [Met] and N-acetyl-L-histidine [His]. These reactions are important in confirming whether the (neo) and (phen) ligands have potential to be biologically active. All four series of reactions were conducted in microscale in 80:20 DMSO-d_6/D_2O. All four produced heat at the addition of D_2O, as the process of bringing amino acids into solution is an exergonic process. The NMR data of all four reactions was collected at multiple time points for comparison and compared with the NMR spectra of the stock compounds; at all readings, the instrument was calibrated for the DMSO-d_6 signal.

Figure 8: ^{1}H NMR for Platinum (II) 1,10-Phenanthroline Dichloride and L-Histidine in 50:50 DMSO-d_6/D_2O



[*The above spectra shows the spectra collected at three different time points for a reaction between Pt(II)(phen)Cl_2 and (His).*]

Figure 9: ^{1}H NMR for Platinum (II) 1,10-Phenanthroline Dichloride and N-Acetyl-L-Methionine in 50:50 DMSO-d_6/D_2O



[*The above spectra shows the spectra collected at three different time points for a reaction between Pt(II)(phen)Cl_2 and (Met).*]

Both of the above spectra demonstrate a general shift in chemical pattern over time in sealed systems. This suggests that there is a product after three and seven days which was not present initially. Most importantly, this NMR data suggests that the (phen) compound is bioactive with histidine and methionine, as suggested by Barnham et al. (2008).

DISCUSSION

Discussion of Results

One may analyze the results and forget to consider the implications of non-affirmative results. Of note, there are multiple synthetic pathways that have been ruled out as feasible in creation of a viable water-soluble (phen) or (neo) compound. From these unsuccessful syntheses, one can extrapolate other potential non-starting points, better streamlining the research into synthesis of a final, usable compound. For instance, since the qualitative solubility study mentioned earlier yielded similar results for all six solvents utilized (DI water, acetonitrile, acetone, chloroform, dichloromethane, methanol), it can be reasonable assumed (although not empirically ruled out) that the unused solvents would produce similar reactions, or lack thereof.

Experiments conducted also verify the potential bioactivity of (phen) and (neo), exhibited by the reactions with (His) and (Met). This confirmed reactivity further emphasizes the need for research into water-soluble and bioavailable compounds. If these compounds can be synthesized, then studies can be undertaken which utilize living biological models, such as mice and potentially humans.

Hypothetical Approaches for Future Work

There are a few theoretical approaches which can be considered as potential synthetic pathways for future research. Of these, there are two primary concepts two examine: using a wider variety of solvents and increasing the oxidation state of the platinum.

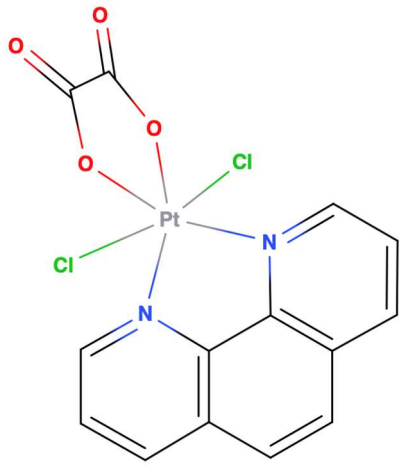
Change the Solvent: There are a variety of harsher solvents and processes which can be utilized to force the highly insoluble (phen) into solution. Among these strategies include the use of polar aprotic solvents which better facilitate the creation of polar compounds. Since water best dissolves polar compounds, polar aprotic solvents like DMF, DMSO, and tetrahydrofuran (THF) can help facilitate creation or preservation of net-dipole moments in newly synthesized compounds, producing net polarity. Some of these solvents may contain residual water, which can be pulled out of the solution using molecular sieves.

Some of these stronger solvents may require the use of different methods to isolate a product than simple filtration or evaporation. Many of these methods are still relatively basic isolation techniques, such as extraction using immiscible aqueous and organic phase solvents. Alternatively, if the product remains in solution and is not precipitated out, it might be possible to produce hydrochloride salts by adding hydrochloric acid and ether.

Oxidize the Platinum: Perhaps one of the more novel methods is to alter the oxidation state of the platinum from platinum(II) to platinum(IV). This strategy is derived from the synthetic method used in the creation of satraplatin. Platinum (IV) octahedral compounds are kinetically inert and act as prodrugs rather than directly as bioactive compounds. According to Karmakar et al. (2019), the synthesis of a six-coordinate platinum(IV) complex arises from oxidative addition of ligands. Oxidative addition of platinum from 4-coordination to 5-or-6-coordination has its most difficult step in the activation of the platinum(II) into accepting more covalent bonds (Rendina & Puddephatt, 1997). Once activated, the platinum can relatively readily accept extra ligands through S_N2, concerted,

and homolytic bond addition mechanisms. A potential product of a successful reaction of this form may appear as **Figure 10:**

Figure 10



[*dichlorooxaloplatinum; 1,10-phenanthroline*]

To lower potential cytotoxicity and to increase the molecules bioactivity, the two chloride ions would be cleaved from the molecule, leaving just the (phen)(ox) ligand to act on the proteins. This would result in the original desired product through an indirect synthetic pathway which takes advantage of platinum's multivalent capabilities. It is anticipated that polarity of the overall compound would be considerable enough to dissolve in water.

CONCLUSION

Platinum and phenanthroline related research has been a promising area of medical science for over fifty years. Among the common pitfalls of the research into these areas is the lack of solubility and bioavailability of the readily synthesized compounds, leaving much of the research findings inapplicable to humans for the time being. The research of the Williams' Biochemistry Laboratory attempted to remedy some of these pitfalls and create compounds which could be utilized in living biological systems to further research applications. While a compound has not at this point been synthesized, it is reasonably believed that there are compounds which can be created, and multiple potential methods have been identified, ruled out, or hypothesized. Platinum (II) 1,10-phenanthroline remains a stubborn yet promising compound.

REFERENCES

Barnham, K.J. & Kenche, V.B. & Ciccotosto, G.D. & Smith, D.P. & Tew, D.J. & Liu, X. & Perez, K. & Cranston, G.A. & Johanssen, T.J. & Volitakis, I. & Bush, A.I. & Masters, C.L. & White, A.R. & Smith, J.P. & Cherny, R.A. & Cappai, R. (2008). Platinum-based inhibitors of amyloid-β as therapeutic agents for Alzheimer's disease. *Proceedings of the National Academy of Sciences*, 105(19):6812-6818. doi: 10.1073/pnas.0800712105.

Breckenridge, J.G. & Singer, S.A.G. (1947). The preparation of 1,10-phenanthroline from *o*-phenylenediamine. *Canadian Journal of Resesarch*, 25:583-584.

Denmark, S.E. & Venkatraman, S. (2006). On the mechanism of the Skraup-Doebner-von Miller quinoline synthesis. *The Journal of Organic Chemistry*, 71(4):1668-1676. doi: 10.1021/jo052410h.

Desoize, B. & Madoulet, C. (2002). Particular aspects of platinum compounds used at present in cancer treatment. *Critical Reviews in Oncology/Hematology*, 42(3):317-325. doi: 10.1016/s1040-8428(01)00219-0.

Fanizzi, F.P. & Natile, G. & Lanfranchi, M. & Tiripicchio, A. & Laschi, F. & Zanello, P. (1996). Steric crowding and redox reactivity in platinum(II) and platinum (IV) complexes containing substituted 1,10-phenanthrolines. *Inorganic Chemistry*, 35(11):3173-3182.

Halcrow, B. & Kermack, H. (1946). Attempts to find new antimalarials, part XXIV: derivatives of *o*-phenanthroline (7:8:3':2'-pyridoquinoline). *Journal of the Chemical Society,* 155-157. doi: 10.1039/JR9460000155.

Johnstone, T.C. & Park, G.Y. & Lippard, S.J. (2014). Understanding and improving platinum anticancer drugs – phenanthriplatin. *Anticancer Research*, 34(1): 471-476.

Karmakar, S. & Poetsch, I. & Kowol, C.R. & Heffeter, P. & Gibson, D. (2019). Synthesis and cytotoxicity of water-soluble dual- and triple-action satraplatin derivatives: replacement of equatorial chlorides of satraplatin by acetates. *Inorganic Chemistry,* 58:16676-16688. doi: 10.1021/acs.inorgchem.9b02796.

Opazo, C. & Huang, X. & Cherny, R.A. & Moir, R.D. & Roher, A.E. & White, A.R. & Cappai, R. & Masters, C.L. & Tanzi, R.E. & Inestrosa, N.C. & Bush, A.I. (2002). Metalloenzyme-like activity of Alzheimer's disease β-amyloid: Cu-dependent catalytic conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H_2O_2. *Journal of Biological Chemistry*, 277:40302-40308. doi: 10.1074/jbc.M206428200.

Rendina, L.M. & Puddephatt, R.J. (1997). Oxidative addition reactions of organoplatinum(II) complexes with nitrogen-donor ligands. *Chemical Reviews,* 97(6):1735-1754. doi:10.1021/cr9704671.

Sun, Y. & Wei, H. & Zhang, Q. & Zhao, X. (2019). Platinum(II) complexes with 1,10-phenanthroline and hydrophilic alkoxyacetate ligands as potential antitumor agents. *Chemistry and Biodiversity*, 16; e1800373. doi: 10.1002/cbdv.201800373

Wikipedia: The Free Encyclopedia. *Skraup Reaction*. Last edited 24 September 2020. Retrieved 2 November 2020.