Spring 5-16-2014

The Reaction of Platinum Triamine Complex with Different DNA and Protein Complexes

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THE REACTION OF A PLATINUM TRIAMINE COMPLEX WITH DIFFERENT DNA AND PROTEIN COMPLEXES

A Capstone Experience/Thesis Project

Presented in Partial Fulfillment of the Requirements for

the Degree of Bachelors of Science with

Honors College Graduate Distinction at Western Kentucky University

By

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*****

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2014

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ABSTRACT

The platinum compound \([Pt(ET_2dien)Cl]\)Cl [Chloro[N,N-diethyl-diethylenetriamine] Platinum(II) Chloride] was synthesized and reacted with N-acetylmethionine (N-AcMet) and guanosine 5’-monophosphate (5’-GMP). Previous experiments show that N-AcMet reacts kinetically faster with the central platinum atom and that 5’-GMP bonds slower yet stronger. When \([Pt(ET_2dien)Cl]\)Cl was reacted with N-AcMet the N-AcMet displaced the chloride ion as expected. When \([Pt(ET_2dien)Cl]\)Cl was reacted with 5’-GMP the 5’-GMP binds to the chloride ion and the reaction is finished. Yet, when 5’-GMP was added in the solution already containing N-AcMet, the N-AcMet was not displaced as predicted. Through \(^1\)H NMR Spectroscopy and Mass Spectrometry we observed that the 5’-GMP also bonds to the central platinum ion displacing one of the nitrogen atoms of the \(ET_2dien\) chelate. Multiple experiments were done adding different ratios of N-AcMet and 5’-GMP and at different stages of the reaction. It was observed that the dominant product is the same, and the reaction is complete in approximately 24 hours. Platinum compounds similar to \(ET_2dien\), but with varying degrees of bulk surrounding the central molecule, have been reacted with N-AcMet and 5’-GMP, yet the formation of an analogous product was not observed.

Keywords: Platinum Compounds, 5’-GMP, N-acetylmethionine, DNA, proteins, NMR
Dedicated to my friends and family for all the support and encouragement they have given me, and also to my professors at WKU for their guidance and advice.
ACKNOWLEDGEMENTS

The support I received from my friends, family, and advisors are what made this project possible. I owe thanks to my family for continually encouraging and believing in me throughout this process. I am grateful to Dr. Kevin Williams, my CE/T advisor, for encouraging me to take on this project. And also for all the time he has spent, advice given, and support he has provided me throughout this project.

I would also like to thank the Honors College for its financial support of my project through an Honors Development Grant. Without their contribution this project would not have been possible.
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CHAPTER 1

INTRODUCTION

Cancer is defined as abnormal cell proliferation. It occurs when abnormal cells divide without control, and these cells also have the ability to invade other tissues. It begins in the cell, which is the basic unit of life, and occurs due to damage of the DNA. It is spread throughout the body through the circulatory and lymphatic systems. Cancer is not one specific disease; it is a multitude of varying diseases each affecting a different type of tissue (Howlader et al., 2013). Due in part to the relatively recent discovery of successful platinum anti-cancer drugs, the death rates for all cancers combined for men and women of all major races and ethnicities is declining (Ahmedin et al., 2013). Yet, despite these advancements there will be an estimated occurrence of 1,660,290 new cases of cancer in the United States in the year 2013 (Howlader et al., 2013).

The anticancer properties of cisplatin were accidentally discovered in the 1970’s by Barnett Rosenberg at Michigan State University. He was investigating if magnetic or electric dipoles were involved in cell growth. When he applied the electromagnetic radiation the cells appeared as very long filaments, instead of short rods. The effect was shown to be due not to the electric field but the platinum electrodes and the electrolysis products that they formed (Kelland, 2007). Since
then it has become one of the leading treatments for cancer. Cisplatin was the first platinum based anticancer drug approved by the FDA and carboplatin was the second. The mechanism of cisplatin’s anticancer properties is due to the fact that it can covalently bond to purine DNA bases. This bonding forms platinum DNA adducts, which then leads to the blockage of the replication and transcription mechanism, and programmed apoptosis.

Cisplatin interacts and binds with DNA based on the Hard Soft Acid Base (HSAB) theory. This theory states that hard acids and hard bases will react fastest with and bind strongest to each other; while soft acids and soft bases react fastest and strongest with each other. Elements categorized as hard are small in size, have a high charge, are weakly polarizable, and have a high electronegativity. Soft elements are large in size, have low charge, are strongly polarizable, and have a low electronegativity. Platinum is considered a soft acid, and sulfur is considered a soft base. Polarizability in this case is defined as the degree to which a molecule or ion is easily distorted by interaction with another molecule or ion. Electrons of easily polarizable molecules are easily distorted by interactions with other molecules or ions (Meissler, Tarr, 2011). The HSAB theory states that these two soft acids will prefer to react with one another. This theory explains why cisplatin and other platinum containing cancer drugs bind to the N-7 position of guanine bases. The nitrogen atom of the guanine molecule is in this case considered a soft base, and therefore reacts with platinum which is a soft acid. This N-7 atom is also the most nucleophilic site on guanine, and it is also free to bond with different compounds due the fact that it does not bind to any DNA bases on the opposite strand. Cisplatin
generally binds to two adjacent guanine bases on the same strand of DNA and forms a 1,2-intrastrand cross-link. It can occasionally be found forming adducts with adjacent guanine and adenine molecules, and rarely with two adjacent adenine molecules on the same strand. It forms a monofunctional adduct, which closes by binding to the N-7 position of an adjacent purine and forms a cross link. Protein folding into the tertiary structure involves the formation of disulfide bonds. Two amino acids contain sulfur: cysteine and methionine. N-acetylmethionine contains sulfur and therefore is a primary protein target for this platinum compounds and mediates its ability to gain entrance into a cell.

The fact that cells can develop resistance during the duration of the treatment drove further research in the area of anticancer drugs (Kelland, 2007). This expanse in research led to the creation of oxaliplatin, satraplatin, and picoplatin. Oxaliplatin has been found to be most effective at treating colorectal cancers, satraplatin is used experimentally for treating prostate cancers, and picoplatin was designed to overcome resistance and accurately treats colorectal cancer (Kelland, 2007). Of the previously listed anticancer drugs only oxaliplatin is currently approved by the FDA. Current chemotherapy drugs affect cancers cells, yet they also interact with normal, healthy cells in the body. The reaction with the non-cancerous cells in the body is what causes chemotherapy drugs to be considered toxic (Sandlin et al., 2010). Continued research is focused on creating a more accurate and less toxic forms of cancer treatment. The current drugs available today are accompanied with undesirable side effects such as nephrotoxicity, ototoxicity, neurotoxicity, and
emesis. These harsh and damaging side effects are what drive research in this area today.

The structure of cisplatin shows an equal distribution around the central platinum atom, with an ammonia and chloride attached on each side. Previous experiments have studied how different amounts of bulk on the platinum compound effect the reaction with N-acetylmethionine and guanosine 5’-monophosphate (5’-GMP). The platinum compound $[\text{Pt(dien)}(\text{D}_2\text{O})]^2+$ which has no bulk on either side reacted faster with N-acetylmethionine. $\text{Me}_5\text{dien}[\text{N,N,N',N',N''-}$
pentamethyldiethylenetriamine) which has bulk on both sides reacted faster with 5’GMP. (Sandlin, et al., 2010). The current project is concerned with discovering how having a large nitrogen containing ligand on one side of Chloro[N,N-diethylidiethylenetriamine] Platinum(II) Chloride (Et₂dien) will affect the reaction with N-acetylmethionine and 5’-GMP. It was originally hypothesized that N-acetylmethionine would displace the chlorine molecule and bond to Et₂dien at a very fast rate. Then the N-acetylmethionine would be displaced by 5’-GMP, which binds more strongly to platinum but at a slower rate. The data indicates that this is not the case.
CHAPTER 2

MATERIALS AND METHODS

Synthesis of Pt Compounds: The platinum compound was made from a multistep synthesis process. 300 mg of $K_2PtCl_4$ was dissolved in 30mL of $H_2O$. Then 1 mL of N,N-diethyl diethylenetriamine was added. Concentrated HCl was added to adjust the solution to pH of 3. This solution was refluxed for 24 hours. The yellow solution that resulted was gravity filtered and dried on the rotary evaporator with a starting temperature of 30 °C. The temperature was raised to 35 degrees Celsius. 4 mL of concentrated solution resulted and was then refrigerated for 24 hours. A yellow precipitate formed. This yellow precipitate was vacuum filtered and ethanol was added to remove as much product as possible. The solution was then dried for three days. The sample was then dissolved in 3.5 mL of $H_2O$, heated, filtered, and then refrigerated. When removed from the refrigerator a yellow solid had formed. 53.7 mg of [Chloro[N,N-diethyl diethylenetriamine] Platinum(II) Chloride] was synthesized.

Synthesis of Platinum N-AcMet Solution: The following solutions were made in different ratios. For the 1:1 N-AcMet platinum reaction 4.3 mg of the platinum compound and 1.9 mg of N-AcMet were combined in 1.0 mL of $D_2O$. For the 2:1 N-AcMet platinum reaction 4.3 mg of the platinum compound and 3.8 mg of N-AcMet
were combined in 1.0 mL of D$_2$O. The pH of these reactions stayed consistently around 2.

**Synthesis of Platinum 5’-GMP Solutions:** The following solutions were made in different ratios. For the 1:1 5’-GMP platinum reaction 4.3 mg of the platinum compound and 4.1 mg of 5’-GMP were combined in 1.0 mL of D$_2$O. In the 2:1 5’-GMP platinum reaction 8.2 mg of 5’-GMP and 4.3 mg of the platinum compound were combined in 1.0 mL of D$_2$O. The pH 1:1 ratio reaction was 5.55 and the pH of the 2:1 reaction was 6.33 after the course of four days. On the fourth day the pH of each reaction was lowered to 3.7.

**Synthesis of Platinum N-AcMet and 5’-GMP solution:** 4.3 mg of the platinum compound and 1.9 mg of N-AcMet were combined in 1.0 mL of D$_2$O. 4.1 mg of 5’-GMP were added at varying stages throughout the reaction.

**NMR Spectroscopy:** The reactions of the platinum compound and DNA protein complexes were analyzed using $^1$H NMR spectroscopy. The data was attained on a JEOL Eclipse 500 MHz NMR instrument. Through analysis of the spectra obtained via NMR spectroscopy were able to discern the displacement and binding that occurred around the central platinum atom of $Et_2$dien.

**Liquid Chromatography-Mass Spectrometry:** The samples were diluted by 100: 1 concentration; 10 µL of solutions were added to 1000 µL of distilled water. The samples were then analyzed by liquid chromatography/mass spectrometry. Ionization was operated in a positive mode ion, the ion spray used was 5200 V and the orifice voltage applied was 10 V. The data was attained on a Varian LC/MS 500
Ion Trap. Using a mass-to-charge ratio this instrument enables us to be able to distinguish the various products in our reaction from each other. The experiment parameters used positive ion mode. When ionizable groups picked up an extra protein that is seen as the M+1 peak, fragments were also visible. Fragments occurred when an ionizable group picks up a sodium ion instead of a hydrogen, if a water molecule is lost, and when the HCl is lost no charge difference is seen just a change in mass.
CHAPTER 3

RESULTS

Reaction of $[Pt(Et_2dien)Cl]Cl$ and 5\textsuperscript{'-}GMP: The $[Pt(Et_2dien)Cl]Cl$ sample was prepared, and the identity and purity was confirmed by $^1$H NMR spectroscopy (Figure 4). All platinum solutions were made as a 10mM solution, using 1.0 mL of D\textsubscript{2}O and 4.3 mg of$[Pt(Et_2dien)Cl]Cl$. The reaction of $[Pt(Et_2dien)Cl]Cl$ with 5\textsuperscript{'-}GMP at both 1:1 and 2:1 ratios, meaning there were two 5\textsuperscript{'-}GMP molecules per every $[Pt(Et_2dien)Cl]Cl$, yielded the same product. The 5\textsuperscript{'-}GMP molecule displaced the chloride atom on $[Pt(Et_2dien)Cl]Cl$ and a mono product was formed (Figure 5). The tall, sharp singlet at 8.0 ppm and 5.75 ppm represent the unreacted 5\textsuperscript{'}GMP in solution. Over time peaks at 8.4 ppm, 5.7, and 5.85 ppm grew, and those peaks represent the mono product described above. As time passed, and the reaction occurred, the peaks representing the unreacted 5\textsuperscript{'}-GMP became shorter, and the peaks representing the mono product grew taller leading us to predict that the formation of this product was occurring. No further reaction occurred as the peaks did not change after the formation of the mono product had drawn to completion.
Figure 5: Shows the NMR spectra of $[Pt(Et_2\text{dien})Cl]Cl$. 
Figure 6: Left column shows the NMR spectra of the Platinum 5’-GMP 1:1 ratio reaction. The right column shows the NMR spectra of the Platinum 5’-GMP 1:2 ratio. The comparison of these spectra shows that the same product is formed in both reactions. The 5’-GMP displaces the chloride and binds to the platinum and the reaction is over.
**Reaction of \([Pt(Et_2dien)Cl]\)Cl with N-AcMet:** The addition of N-AcMet with \([Pt(Et_2dien)Cl]\)Cl led to the formation of both a mono product and bis product. The reaction with a 1:1 ratio of \(Et_2dien\) to N-AcMet leads to the formation of the mono product, \([Pt(Et_2dien)(N-AcMet)]^+\). The N-AcMet binds to the platinum atom of the \([Pt(Et_2dien)Cl]\)Cl molecule and displaces the chloride atom. This reaction proceeds relatively fast and is usually finished in approximately 2 hours as can be seen in Figure 7. The mono product appears as a sharp singlet at 1.9 ppm using, and a broader singlet at 2.2 ppm. In the 2:1 ratio of N-AcMet to \([Pt(Et_2dien)Cl]\)Cl reaction, meaning that there was one \([Pt(Et_2dien)Cl]\)Cl molecule for every N-AcMet, both the mono and bis \(([Pt(Et_2dien)(N-AcMet)_2])\) products are formed. The mono product forms when the chloride is displaced, yet a second N-AcMet displaces one of the nitrogen atoms of the Et_2dien chelate. There is only one coordination site available on \([Pt(Et_2dien)Cl]\)Cl the N-AcMet comes in first and binds, therefore when the second N-AcMet binds it must be displacing something other what is already bound at the at the primary binding site, where the chloride was originally bound. This addition of a second N-AcMet allows the formation of the bis product to occur. This addition of the second N-AcMet occurs at a slower rate than the addition of the first. Figure 7 shows that the formation of the bis product has begun to occur in the same two hour time frame, yet the reaction has not drawn to completion, therefore this reaction occurs slower than the formation of the mono product. The bis product occurs as a multiple singlets due to stereochemistry located near 2.4 ppm.
Figure 7: Left column shows the NMR spectra of the 1:1 \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl N-AcMet}\) ratio reaction over time and the formation of the monoproduct. The right column shows the NMR spectra of the 1:2 \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl N-AcMet}\) ratio reaction and the formation of the bis product.
Reaction of $[Pt(Et_2dien)Cl]Cl$ N-AcMet and 5'-GMP: In this reaction the N-AcMet reacts faster with $[Pt(Et_2dien)Cl]Cl$ and replaces the chloride ion forming the same mono product as is seen in Figure 6 at 1.9 and 2.2 ppm in the 1:1 $[Pt(Et_2dien)Cl]Cl$ and N-AcMet reaction described above ($[Pt(Et_2dien)(N\text{-AcMet})^+]$). Yet, 5'-GMP comes
in and displaces the nitrogen atom of the [Pt(Et$_2$dien)Cl]Cl chelate; this forms the N-AcMet 5′-GMP product, [Pt(Et$_2$dien)(N-AcMet)(5′-GMP)].

Figure 9 shows the NMR spectra for the N-AcMet 5′-GMP Product. This spectrum shows the formation of peaks between 2.0 ppm and 3.5 ppm, which are not seen in the spectra of the other two reactions.
Figure 10: Shows the mass spectrometry results. Peak at m/z = 544 is mono product with methionine; peak at m/z=907 is N-AcMet/GMP product.
CHAPTER 4

DISCUSSION

The purpose of this experiment was to see what effect having a large nitrogen containing ligand around the central platinum atom would have on have the compounds ability to react with N-AcMet and 5'-GMP. We synthesized the \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl}\) and reacted it individually with N-AcMet, 5'-GMP, and a mixture of N-AcMet and 5'-GMP. The results obtained from a 1:1 reaction of \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl}\) and 5'-GMP showed the displacement of the chloride ion by 5'-GMP and the formation of a monoproduct as was predicted. The results obtained from a 1:1 reaction of \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl}\) and N-AcMet showed again the displacement of the chloride ion and the formation of a monoproduct as was predicted. When we reacted \([Pt(\text{Et}_2\text{dien})\text{Cl}]\text{Cl}, 5'\text{-GMP}, \text{and N-AcMet}\) the results indicated the formation of new product we had not expected. We predicted that the N-AcMet would react faster and displace the chloride ion as was seen in the 1:1 \(\text{Et}_2\text{dien}\) and N-AcMet reaction. Then the 5'-GMP which reacts slower, yet binds stronger to the central platinum ion would then come in displace the N-AcMet. Similar reactivity has been previously observed for \([\text{Pt(dien)}\text{Cl}]\text{Cl}\) (Barnham et al., 1994, Djuran et al., 1991).
The product that formed from the reaction of all three indicated that the 5’-GMP and N-AcMet were both bound to the central platinum atom and it was the nitrogen ligand was displaced. By comparison, [Pt(Me₅dien)(NO₃)]⁺, which has significant steric clashes with N-AcMet and thus reacts faster with 5’-GMP, does not show a displacement of a portion of the Me₅dien ligand when 5’-GMP is added after the N-AcMet is able to react. This led us to perform the 1:2 [Pt(Et₂dien)Cl]Cl to N-AcMet, and 1:2 [Pt(Et₂dien)Cl]Cl 5’-GMP reactions to see if the formation of this product was unique to this platinum compound, or was linked to the reagents used and order they were presented. We found that when a second equivalent of N-AcMet is added to [Pt(Et₂dien)Cl]Cl, a second product is eventually observed after the formation of some [Pt(Et₂dien)(N-AcMet)]⁺ occurs. We believe two N-AcMet molecules are coordinating to the platinum, with the second N-AcMet replacing one of the nitrogen atoms of Et₂dien in the coordination sphere.

We think that when N-AcMet binds to the central platinum atom the steric strain is so large that the when 5’-GMP, or another N-AcMet is present the nitrogen containing ligand is knocked off and either the 5’-GMP, or in the 2:1 N-AcMet N-AcMet bind where the nitrogen ligand was. This formation must be more stable than the original conformation, to cause the nitrogen containing ligand to dissociate from the central platinum atom. The formation of either the N-AcMet bis product or the Platinum N-AcMet 5’-GMP product with the large nitrogen ligand hanging from the side leads us to believe that this compound may have anticancer properties, with the large nitrogen ligand being able to block DNA transcription and replication enzymes. Phenanthriplatin, cis-Pt(NH₃)₂(phenanthridine)Cl, has been shown to...
have significant anticancer activity due in part to the large phenanthridine ligand attached to the platinum atom (Park et al. 2012). This platinum complex binds to DNA and blocks transcription, leading to cytotoxicity in a number of cancer cell lines at lower doses than cisplatin. The Et₂dien complex has a similar size to phanenthriplatin, and thus we plan to test the cytotoxicity of this compound in the near future.

**Figure 11**

![Figure 11: Shows the reaction scheme for the [Pt(Et₂dien)Cl]Cl and N-AcMet 1:1 reaction; it shows the formation of the mono product.](image)
Figure 12: Shows the 1:2 ratio reaction scheme of $[Pt(Et_2dien)Cl]Cl$ and N-AcMet, and the formation of the bis product.

Figure 13: Shows the product of the 1:1 reaction of $[Pt(Et_2dien)Cl]Cl$ and 5'-GMP. The same product is seen in the 1:2 ratio reaction as well.
Figure 14: Shows the formation of the Pt N-AcMet-5'-GMP product and the displacement of the nitrogen containing ligand. [Pt(Et$_2$dien)Cl]Cl is first reacted with N-AcMet, and then with 5-GMP as can be seen above.
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