The Substitution Behaviour of Terpy polyglycoxyl and Ruthenium-Platinum Complexes with Biologically Significant Nucleophiles. A Kinetic and Mechanistic study.

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I M. K. Sitati do hereby declare that:

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2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons’ data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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I hereby certify that these statements are correct, and as the candidates’ supervisor I have approved this thesis for submission

Signed: ………………………… Professor D. Jaganyi (Supervisor)   Date: ……………

Pietermaritzburg

June 2014
“Do not brood over your past mistakes and failures as this will only fill your mind with grief, regret and depression. Do not repeat them in the future.”

Swami Sivananda
This work is dedicated to my family for being the firm support that was the springboard to accomplish this piece of work. I will forever be indebted to you. Above all God was the leading light to this accomplishment.
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Abstract

The kinetics of two sets of complexes was investigated under pseudo first order conditions using UV-Visible spectrophotometry as a function of concentration and temperature. The first set consisting 4'-substituted terpy polyglycoxyl complexes reacted with biological relevant N-donor nucleophiles showed that the oxygen on the polyglycoxyl group donates electrons to the Pt-metal resulting in a decrease in reactivity from Pt to Pt(eg). The first carbon-oxygen pendant bond plays a crucial role in regulating the electron density donated because there is insignificant change in the reactivity as the chain length is increased to Pt(deg) and then Pt(tec). The trend in the reactivity slightly increases in general from Pt(eg) to Pt(tet) due to reduction in steric hindrance imposed by the ethylene glycoxy unit on one side of the complex. The reactivity of the nucleophiles is pKa and steric dependent. It can be concluded that reactivity of the metal complexes is mostly electronically controlled while that of the nucleophiles is dependent on the basicity and steric bulk. The obtained kinetic data is supported by the DFT calculations that reveal a less electrophilic Pt(II) metal centre for complexes bearing the 4'-substituent. The temperature dependent studies support an associative mode of activation.

The second set of complexes studied included Ru(III)-Pt(II) complexes with a semi-rigid linker 4’-pyridyl-2,2':6',2”terpyridine (qpy) whose results indicated that increase in the overall charges of the respective complexes is the key reason for the observed increase in the reactivity. Additionally, replacing the cis pyridyl group in Pt1 by Ru(III) polypyridyl to give Pt2 and Pt3 respectively lowers the energy of the LUMO (π*) orbitals. The two qpy groups in the tri-nuclear complex Pt3 only slightly increases the reactivity from that of Pt2 because the qpy groups are in orthogonal positions preventing π-electron communication hence the two Pt(II) centres act independently of each other.

The observed activation parameters for both sets of complexes support an associative mode of substitution. The results of this project elucidate intrinsic, electronic and steric properties of the complexes that might be exploited for medicinal, photophysical or other applications.
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- Shawn for coordinating the deliveries. Hashim Desai for allocation of space in the masters’ office and handling laboratory issues. All technicians and assistants for helping with issues in the laboratory.
List of abbreviations and symbols

5'-GMP  Guanosine-5’-monophosphate
aaa  [Pt(diethylenediamine)OH$_2$]$^{2+}$
aap  [Pt(N-(pyridyl-2-methyl)-1,2-diamino-ethane)OH$_2$]$^{2+}$
apa  [Pt(2,6-bis-aminomethylpyridine)OH$_2$]$^{2+}$
app  [Pt(2,2’-bipyridine)(NH$_3$)OH$_2$]$^{2+}$
BBR3464  [$\{\{trans-PtCl(NH$_3$)$_2\}\}_2\{\mu-trans-Pt(NH$_3$)$_2$(HN$_2$(CH$_2$)$_6$NH$_2$)$_2\}\}$]$^{4+}$
DEDTC  Diethyldithiocarbamate
DNA  Deoxyribonucleic acid
GSH  Glutathione
HET  2-hydroxyethanethiol
HMG  High mobility group
HOMO  Highest occupied molecular orbital
L  Ligand
LUMO  Lowest unoccupied molecular orbital
mM  milliMolar
NER  Nuclear excision repair
pap  [Pt(bis(2-pyridylmethyl)amine)OH$_2$]$^{2+}$
ppp  [Pt(2,2’:6,2’’-terpyridine)OH$_2$]$^{2+}$
pt  [Pt(2,2’:6,2’’-terpyridine)Cl]$^+$
Pt(deg)  [Pt\{4’-diethyleneglycoxyl)- 2,2’:6,2’’-terpyridine)Cl]$^+$
Pt(eg)  [Pt\{4’-ethyleneglycoxyl)- 2,2’:6,2’’-terpyridine)Cl]$^+$
Pt(teg)  [Pt\{4’-triethyleneglycoxyl)- 2,2’:6,2’’-terpyridine)Cl]$^+$
Pt1  [Pt(en)OH$_2$]$^{2+}$
Pt2  [H$_2$O(en)Pt(qpy)Ru(tpy)]$^{4+}$
Pt3  [H$_2$O(en)Pt(qpy)Ru(qpy)Pt(en)OH$_2$]$^{6+}$
qpy  Quarterpyridine (4’-(pyridyl) 2,2’:6,2’’-terpyridine)
RNA  Ribonucleic acid
terpy/tpy  2,2’:6,2’’-terpyridine
TU  Thiourea
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Chapter 1

Platinum complexes and cancer chemotherapy

1.1. Introduction

A large number of platinum complexes have been synthesized and evaluated for potential to cure cancer since the discovery of cisplatin (figure 1.1). Cisplatin, a complex of platinum metal is currently the most widely used for cancer chemotherapy after approval for clinical use in 1978, though cancer chemotherapy remains a subject of keen interest due to the limitations of cisplatin. Cancer occurs when diseased cells grow uncontrollably forming a solid mass known as a tumour. Benign tumours do not invade the normal surrounding tissues while malignant tumours spread to neighbouring tissues or other parts of the body. A primary tumour becomes fatal if it obstructs vessels or a body organ however metastasis is the common cause of death. Cancer accounts for about 13% of deaths worldwide.

1.2 Cisplatin and analogues

\[
\begin{align*}
\text{NH}_3 \\
\text{H}_3\text{N} \quad \text{Pt} \quad \text{Cl} \\
\text{Cl}
\end{align*}
\]

Figure 1.1 Molecular structure of cisplatin.

Due to resistance and toxicity in the administration of cisplatin, a large number of cisplatin analogues were synthesised but only few merited clinical trials including carboplatin, oxaliplatin, nedaplatin, labaplatin (figure 1.2) e.t.c.
Although the cellular distribution of cisplatin and its exact mode of action are not well understood, its interaction with target \textbf{DNA} (deoxyribonucleic acid) is now accepted to be responsible for its anti-cancer activity.\textsuperscript{12}

\section*{1.3 DNA}

It’s a nucleic acid macromolecule containing genetic instructions that allow living organisms to develop and function.\textsuperscript{13} Molecules that can bind and interact with DNA provide access to genetic material which allows them applied as diagnostic probes, reactive agents or therapeutics.\textsuperscript{14} DNA is a long polymer of simple units known as nucleosides each constituting a phosphate group, five carbon sugars (2-deoxyribose sugar) and a cyclic nitrogen containing compound called a base.\textsuperscript{13,15} The phosphate group and sugar are joined by phosphodiester bonds forming the DNA backbone. The bases are attached to the sugar – phosphate backbone to form complete nucleotide. Bases commonly found in DNA are; adenine, quinine, thymine and cytosine. DNA macromolecule consists of double strands which intertwine to form a double helix (figure 1.3).\textsuperscript{15} A nucleotide constitutes a backbone that holds the chain together and a base that interacts with the other strand in the helix.
The strand backbones are closer together on one side of the helix than on the other. The major groove occurs where the backbones are far apart, the minor groove occurs where they are close together (figure 1.3). The grooves twist around the molecule on opposite sides. Certain proteins bind to DNA to alter its structure or to regulate transcription (copying DNA to RNA) or replication (copying DNA to DNA). It is easier for these DNA binding proteins to interact with the bases (the internal parts of the DNA molecule) on the major groove side because the backbones are not in the way. The DNA is the ultimate target in the mechanism of cancer chemotherapy.

1.4 Mechanism of action

The antitumor activity of platinum drugs is ascribed to interaction between the metal complex and DNA, primarily with the genetic DNA located in the nucleus of the cell given that interactions with mitochondrial DNA are less responsible for antitumor activity. Experimental results affirm that there is high accumulation of the drug in the nuclei of cells because the relatively high concentration of chloride ions in the extra cellular fluids (~ 100mM) keeps the drug neutral but after crossing the cell membrane one or both the chloride ions on the platinum drug are displaced by aqua ligands to form the cationic reactive species. The first aquation is relatively rapid due to low chloride ion concentration in the cytosol (~4mM). A two-step ligand exchange then occurs between the labile aqua ligands and the nucleobases of the DNA to form bifunctional adducts. Binding to the DNA primarily occur through N7 atom of the guanine, while the binding to N7 and N1 of adenine and N3 of cytosine occur to a lesser degree. The N7 position is preferred due to stabilising hydrogen bonding interactions and higher basicity. Various bifunctional
adducts result after DNA binding *viz.* intrastrand cross-linking (GpG), interstrand cross-links of the type 1,2-(ApG), crosslinks between two deoxyquanosines separated by a third nucleosite (GnG), intrastrand crosslinks of the type GpG and mono adducts as illustrated in figure 1.4

![Figure 1.4 Models illustrating various DNA-cisplatin adducts.](image)

It is still unknown which are the most important adducts with respect to cytotoxicity, however research has shown that the adducts inhibit DNA replication or transcription but the exact mechanism of toxicity is a subject for further study. Diamino-platinum(II) ($[(\text{NH}_3)_2\text{Pt}]^{2+}$) creates a unique junction between the strands, the distortion impedes DNA processing in the tumour cells. The distortion is characterised by a high mobility group (HMG); an 80 amino acid sequence present in many proteins that bend DNA dramatically. The HMG protein binds to DNA-cisplatin adducts in a 1:1 ratio and protects them from DNA repair enzymes, thus it’s not just the distortion that disrupts DNA functions but additionally the ability to attract HMGs shields against effective repair of the DNA lesions by the nuclear excision repair (NER) machinery. Failure to repair lesions effectively triggers an abortive mitosis resulting in cell death by apoptosis pathway.

### 1.5 Cisplatin resistance

A large number of the cancers have a natural resistance to treatment with the drug and some cancers that respond to the treatment would subsequently acquire resistance. Acquired resistance results from, reduced cellular uptake, increased repair of the lesions, increased tolerance of the cisplatin-DNA lesions, and deactivation by preferential reactions or binding
to thiol containing proteins.\textsuperscript{29} Reduced uptake of the drug prevents it from reaching its ultimate DNA target; deactivation could also occur when the drug reacts with other biomolecules like glutathione and metallothionein in the cytosol hence the drug that reaches the target is insufficient to inhibit tumour growth.\textsuperscript{2} The sulphur coordinated forms of cisplatin are then excreted as conjugates coupled to the multi-drug resistance proteins through the golgi gateway.\textsuperscript{29} However some of the sulphur containing bio-molecules especially the thioethers are under study as chemoprotectors in the platinum based chemotherapy. Pt-S(thiol) compounds are stable hence responsible for toxic side effects, but the bond can be broken in the presence of compounds known as ‘rescue agents’ which are exclusively sulphur-containing compounds such as diethylthiocarbamate(DEDTC), thiourea(TU), thiosulphate, biotim, amifostine among others.\textsuperscript{11,15,30-32} Figure 1.5 summarises uptake of the cancer drug

Figure 1.5 The likely pathways the Pt(II) complex drug may follow after uptake.\textsuperscript{33}

Increased efflux reduces intracellular drug concentration. Cisplatin resistance is also enhanced by the repair of Pt-DNA lesions by nucleotide excision repair protein (NER), the nucleotide repair protein recognizes DNA damage, excises the damaged segments as base pair oligonucleotides which prompts gap filling by DNA polymerase.\textsuperscript{5,34} Reduction in repair efficiency in insensitive tumour cells leads to resistance and drug tolerance. Further,
apoptotic malfunctions caused by mutant genes like the $p^{53}$ proteins sequence can also lead to DNA lesions tolerance.$^{17}$ Continued research has produced more platinum(II) complexes some of which are on clinical trial as possible therapeutic agents.

### 1.6 Subsequent Platinum Anti-cancer complexes.

The development of analogues resulted in a few clinically useful complexes, most of which, cross-resistant to cisplatin.$^{35,36}$ A variety of platinum complexes have been synthesized, which are structurally distinct from cisplatin, and as a result bind to DNA in a fundamentally different manner.$^{37-39}$

#### 1.6.1. Platinum(IV) complexes

Though it has been shown that intravenous hydration has been able to reduce nephrotoxicity, side effects are still a problem in the use of cisplatin.$^{40}$ Intravenous injection and infusions being the only procedures of administration, novel Pt(IV) complexes were developed to overcome this limitation. One important member of this class of compounds is trans-bis(acetate) amine dichloro (cyclohexylamine) platinum(IV) (saraplatin) in figure 1.6 that is in phase (III) clinical trials in Europe and USA for the treatment of ovarian and lung cancers.$^{41}$ Saraplatin is regarded as a pro-drug of cisplatin since it undergoes reduction to yield cisplatin-like species once in the system. It has better activity than cisplatin in several cisplatin sensitive and resistant cell-lines with low nephrotoxicity and neurotoxicity.$^{42}$ Cis-aminodichloro(2-methylpyridine) platinum(II) (ZD0473) undergoing phase (II) trials displays good oral availability and anti-tumour activity.$^{43}$

![Figure 1.6 Selected Pt(IV) complexes](image-url)

Figure 1.6 Selected Pt(IV) complexes
1.6.2.  Trans-Platinum(II) complexes

Some trans complexes have anti-tumour activity with distinct DNA binding modes against the Cleare and Hosche rules.\textsuperscript{44} These discoveries led to the development of more trans-platinum complexes with several of the compounds being characterised and showing favourable cytotoxicity against cancer cells especially the cisplatin-resistant cell lines.\textsuperscript{45} The most notable trans-platinum(II) complexes with remarkable in-vitro anti-tumour activity include those bearing some planar aromatic ligand such as pyridine, N-methylimidazole, benzo-thiazole or quinoline and those carrying an alkylamine or imminoether.\textsuperscript{46-48} Redesigning some trans-complexes slows their reactivity, increases solubility and cytotoxicity and makes them better cancer drugs.\textsuperscript{49-53} Even with gains made in reduction of toxicity and overcoming resistance, there was little difference in cytotoxicity and spectrum of activity with cisplatin analogues because they form similar adducts as cisplatin.\textsuperscript{29} Thus interest shifted to multinuclear platinum(II) complexes (figure 1.6-1.8) that can form a different range of DNA adducts that display unique anti-cancer activity vis-à-vis cisplatin (figure 1.1).

1.6.3  Multinuclear complexes

The first multinuclear platinum complexes were consistent with the traditional structure-activity relationships with examples being the compound with two cisplatin derivatives linked with flexible diamine linker and the other where the chloride groups replaced with malonate as shown in figure 1.7 which has improved water solubility and activity\textsuperscript{54,55}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.7.png}
\caption{Molecular structures of dinuclear Pt(II) complexes cisplatin analogues.}
\end{figure}

Where \(n = 2, 3, 4, 5, 6\)

Subsequent multinuclear complexes were designed with either single or double bridge, mono-functional or multi-functional platinum centres and flexible or rigid linkers in an
attempt to improve cytotoxicity, increase charge and solubility as illustrated in the figure 1.8. \textsuperscript{56-66}

Figure 1.8 Molecular structures of some doubly and singularly bridged multinuclear Pt(II) complexes bearing the 4,4’-dipyrazolylmethane (dpzm) ligand

From the many multi-nuclear complexes synthesised and tested, tri-nuclear complex \textit{BBR3464}, figure 1.9 was the first to enter clinical trials because it’s more active than cisplatin in all cell lines tested.\textsuperscript{67} Based on the clinical trials, \textit{BBR3464} will be much needed to treat non-small lung cancer, gastric cancer, ovarian cancer, small-cell lung cancer plus and not limited to pancreatic cancer.\textsuperscript{68}

Figure 1.9 Molecular structure of tri-nuclear Pt(II)complex (\textit{BBR3464})

Studies of multi-nuclear complexes reveal that chain length and linker flexibility, hydrogen bonding potential of the linker, charge and geometry of leaving group to the linker are the key factors that dictate their design and potential for cancer therapy.\textsuperscript{69-80}

1.7 Current research on platinum (II) terpyridine complexes.

Platinum(II) terpyridine complexes ([Ptx(tpy)L]\textsuperscript{n+} where x is a substituent on the terpyridine ligand and L is the ligand in the fourth coordination site\textsuperscript{81,82} were first synthesised in 1934.\textsuperscript{81}
These complexes have versatile chemical benefits in biological and other fields and are important to account for ligand substitution reactions in square-planar $d^8$ metal complexes.\textsuperscript{81} Platinum(II) complexes including terpyridine and 1,10-phenanthroline have elicited a lot of interest currently due to their capacity to selectively bind to DNA\textsuperscript{83} and inhibit telomerase activity. Pt(II) terpy complexes have been shown to have interactions with bio-molecules such as DNA and proteins hence the focus on them in the bioinorganic field.\textsuperscript{82,84}

First evidence to their DNA binding was shown by Lippard and co-workers when they studied the interactions of the complex [Pt(terpy)(HET)]\textsuperscript{+} (HET=2-hydroxyethanethiol) with calf thymus DNA in 1974.\textsuperscript{84} McFayden et al.\textsuperscript{85} discovery that free terpy ligands do not intercalate to DNA at physiological pH illustrated the vital role of platinum in these reactions. Mechanistic studies on Pt(II) terpy complexes have been done with different variations on the basic terpy structure either by the addition of substituents onto the chelate or by adjusting the chelate itself to investigate the different effects that steric and electronics play on the reaction kinetics. These investigations were envisaged to explain the substitution mechanism and behaviour of square planar $d^8$ transition metal complexes.\textsuperscript{86-91}

The importance of the three joined pyridine rings in a planar configuration to the reaction kinetics of Pt(II) terpy as demonstrated by Van Eldik et al.\textsuperscript{86} cannot be overemphasised. Their studies on the aqua substitution reactions on complexes in figure 1.10 with thiourea nucleophiles show for instance that the rate of substitution with thiourea increases by a factor of 4 by just the addition of a single pyridine ring in going from aaa to aap, a further increase in the reaction rate by a factor of 4 on the addition of a second pyridine ring to pap and yet another increase by 4 orders on going from aaa to ppp.\textsuperscript{86} This was explained to be mainly due to the increase of the electrophilicity of the metal centre as a result of increased electron back-donation to the ligand orbitals. Electronic communication between the $\pi$-acceptor ligands increases on going from aaa to ppp. The $\pi$-acceptor effects on their own (i.e in the cis or trans position) may have only a minor influence on the rate of the substitution reactions when there is no direct electronic communication.
Studies by Jaganyi et al.\textsuperscript{88} revealed that substituents on the terpy have different effects on the overall reactivity of the complex; Computational studies with complexes containing either electron-donating or electron-withdrawing groups in 4, 4′, 4″ positions showed electron-donating groups decrease the positive charge on the metal centre, as well as increasing the HOMO-LUMO gap of the ground state, making the complex less reactive while electron-withdrawing groups increase the positive charge on the metal centre and decreases the HOMO-LUMO gap of the ground state, enhancing the reactivity of the complex. From their observations they further concluded that substituents in both the \textit{cis} and \textit{trans}-positions affect reactivity with overall \textit{trans}-influence greater than \textit{trans}-effect and overall \(\pi\) \textit{cis}-effect being greater than overall \(\pi\) \textit{trans}-effect.\textsuperscript{88,92-94} This study involves the reaction of Pt(II) complexes with nucleophiles of biological significance \textit{viz.} azoles and bio-molecules, as such it is important to review their chemistry.

1.8 Azoles

The structure of azoles resembles that of DNA nucleic bases, thus, studies of reactions of Pt(II) complexes with azoles mimics the reaction of these complexes with the DNA base pairs\textsuperscript{95}. Furthermore, imidazole derivatives have been shown to exhibit antineoplastic properties\textsuperscript{96} (ability to prevent the development of neoplasm which can cause tumours). Substitution of azoles with platinum complexes is anticipated to throw more light on the designing of platinum-based cancer drugs. The coordination chemistry of five-membered
azole rings to transition metal is of interest because most reactions in biological systems involve the coordination of some form of azole to a metal centre. Histidine, an amino acid which is essentially an imidazole derivative, forms an important fragment of many biological systems by binding to hemeproteins. Its coordination to metal complexes varies with pH as illustrated in figure 1.11.

\[
\begin{align*}
\text{NH} & \quad \text{pK}_a = 6.5 \\
\text{N} & \quad \text{pK}_a = 14 \\
\text{NH} & \\
\text{N} & \\
\text{N} & \\
\text{+} & \\
\text{-H}^+ & \\
\text{+H}^+ & \\
\end{align*}
\]

Figure 1.11 pH dependent tautomers of Histidine.

Hemeproteins consist of the iron(II) complex of protoporphyrin IX with an axially bound histidine responsible for the uptake, storage and transport of oxygen. Haemoglobin and myoglobin are hemeproteins responsible for oxygen transport and storage respectively. Since azoles form a part of hemeproteins they are part of the life-giving reactions in biological systems. Azoles also form building blocks for the synthesis of higher complexes because they are good ligands and can serve to bridge complexes. Apart from the azoles, substitution reaction using L-methione, guanosine-5’-monophosphate and reduced glutathione were investigated.

1.9 Other biologically relevant molecules

1.9.1 L-methionine

L-methionine is thioether containing an essential amino acid having two acid dissociation constants, pK$_{\text{COOH}}$ = 2.13 and pK$_{\text{NH3}^+}$ = 9.2. Based on its pKa values, the carboxylate group is protonated to an extent of about 50 % at pH 2 where our reactions were studied resulting in an overall charge of +1. The residual 50 % exist in the form of zwitterions as shown in figure 1.12. The zwitterion is the one that coordinates to the metal complexes. Even if the positively charged species interacts with the Pt(II) complex, it will deprotonate...
as a result of significant drop in the pKa value upon coordination to the metal centre giving the product complex with same charge as the starting complex. At pH 7.4 the zwitterionic form is predominantly present in solution and interacts with the platinum(II) compound.

Figure 1.12 The zwitterionic form of L-methionine at pH 2

1.9.2 L-glutathione

The tripeptide glutathione is an ubiquitous thiol found in the cells of microorganisms, fungi, and plant and animal tissues, with intracellular concentrations varying between 0.1 and 10 mM consisting of the three amino acids glutamic acid, cysteine and glycine. It has several cellular functions, including but not limited to working as an antioxidant to protect cells against reactive oxygen species, UV radiation, and heavy metals such as mercury, cadmium, and lead. It is also applied in the biological detoxification processes as it’s a known fact that formation of a complex between a heavy metal ion and GSH is the key step in detoxification. Its presence in significant concentrations in cytoplasm predisposes it to react with platinum compounds before they can reach the DNA, or after they bind to DNA. The role of glutathione in the presence of cisplatin was studied in detail revealing that glutathione can be used to reserve the drug since it readily binds on it lowering toxicity and other negative effects of the chemotherapy. Glutathione exists as a zwitterions at pH 2 as shown in figure 1.13.

Figure 1.13 The zwitterionic form of L-glutathione at pH 2
1.9.3 Guanosine-5´-monophosphate

Guanosine-5´-monophosphate is a DNA model molecule which consists of a phosphate and sugar (2´-ribose) moiety connected to the nucleobase guanine. It includes N-donor atoms and is a model for binding to a nucleobase. Figure 1.14 shows structures of 5´-GMP with changing pH that includes atom numbering and pKa values. It is known that the N7-site of 5´-GMP is strongly favoured for binding to metal centres.\textsuperscript{114-116}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Resonance structures of 5´-GMP at pH 2.}
\end{figure}

From the pKa\textsubscript{(N7)} value of 2.48\textsuperscript{116}, 65 – 75 % of the 5´-GMP is protonated at N7 at pH 2 and therefore without charge while 25 – 35 % of 5´-GMP carry negative charge as they possess a singly deprotonated phosphate group. The non-protonated N7 of the negatively charged 5´-GMP is the one that reacts with the platinum centre with the acid–base equilibrium rapidly generating non-protonated N7.\textsuperscript{117}

1.10 Aims of the study

Reedijk\textsuperscript{118-120} underscores the importance of mechanistic studies as key to the design of new anticancer drugs with improved antitumor activities. Reactivity of the drug determines whether it reaches the target DNA molecule amid side reactions, lifetime in the body and of greatest importance the antitumor activity of the drug. The substitution reactions of platinum complexes with appropriate model nucleophiles have gained a lot of popularity today\textsuperscript{121} with the hope of striking a platinum therapeutic drug of improved efficacy. To contribute to this pool of knowledge, we investigated the thermodynamic and kinetic properties of two sets of complexes. The first set of complexes that was studied, comprises of mononuclear Pt(II) terpy complexes (Pt(eg), Pt(deg), Pt(teg)) with a 4´-substituted polyglycoxyl pendant (figure 1.15). These were reacted with azole nucleophiles (imidazole, pyrazole, methylimidazole, 1, 2, 4-triazole and 1, 2-dimethylimidazole). Since the final target of the anticancer drugs is the N7 guanine of DNA, understanding substitution reactions of Pt(II)
complexes with heterocyclic nitrogen donors with similar binding sites to that of guanine and other biologically relevant ligands like histidine is useful to understanding the mechanism of action of these drugs with DNA.

![Structural formulae of the platinum (II) terpyridine complexes studied.](image1)

Figure 1.15 Structural formulae of the platinum (II) terpyridine complexes studied.

The second set of complexes were designed to determine the role of replacing the cis pyridyl group in **Pt1** with a (tpy)Ru(qpy) to give **Pt2** and then with Ru(qpy)$_2$ to form **Pt3** (figure 1.16) on the thermodynamic and kinetic properties of these complexes. They were reacted with biological nucleophiles L-methionine, glutathione and guanosine-5’-monophosphate never done before for this set of complexes. The sulphur containing nucleophiles (L-met and GSH) are good models for reactions involving sulfur-containing biomolecules which commonly take place in biological systems and are therefore available for competition reactions with Pt-based drugs while 5’-GMP is a model for DNA. The complexes were synthesised by standard procedures and reacted with the nucleophiles in aqueous lithium triflate medium at pH 2. Experimental data is supplemented by modelled DFT-calculations of the Pt(II) complexes to facilitate explanation of the observed trend in the reactivity.

![Structural formulae the Ru(III)-Pt(II) polypyridyl complexes studied](image2)

Figure 1.16 Structural formulae the Ru(III)-Pt(II) polypyridyl complexes studied
1.11 References


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List of abbreviations and symbols

$\eta_{pt}/\eta_{pt}^0$  Nucleophilicity constant/Standard nucleophilicity const

A  Associative
D  Dissociative
I  Interchange
IA  Associative activation
ID  Dissociative activation
ks  Rate constant for attack by solvent
ky  Rate constant for entering nucleophile
L  Ligand
MeOH  Methanol
MO  Molecular orbital
py  pyridine
TS  Transition state
X  Leaving group unless stated otherwise
Y  Incoming group unless stated otherwise
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Chapter 2

Substitution Reactions

2.1 Introduction

Substitution reactions involve bond breaking and subsequent bond formation and in the process a ligand from the environment replaces a ligand on a coordination shell.\(^1,2\) Bond breaking according to Ingold and Hughes\(^3,4\) can be categorised as homolytic or heterolytic based on electron distribution. Homolytic bond breaking involves dividing the bonding electron pair evenly between the products such that each species gets an electron as illustrated by equation 2.1. Heterolytic bond breaking on the other hand could either be nucleophilic heterolysis where the electrons of the bond leave with the leaving group (equation 2.2) or electrophilic heterolysis where the electrons of the bond remain with the reaction centre (equation 2.3).\(^5\)

\[
\begin{align*}
A:B &\rightarrow A + B & \text{Homolysis} & (2.1) \\
A:B &\rightarrow A^+ + :B^- & \text{Nucleophilic heterolysis} & (2.2) \\
A:B &\rightarrow A^- + B^+ & \text{Electrophilic heterolysis} & (2.3)
\end{align*}
\]

Where, \(A = \text{reaction centre, } B = \text{leaving group and } : \text{ represent bonding electron pair.}\)

Ingold and Hughes classification is sufficient for describing substitutions on carbon centres, but limited in the area of inorganic reaction mechanisms.\(^1\)

2.2 Inorganic substitution reactions

Inorganic reactions are divided into electrophilic substitution (SE) or nucleophilic substitutions (SN), and the latter could be represented by \(SN_1\) or \(SN_2\) depending on the molecularity of the rate determining step of the mechanism.\(^2\) Most substitution reaction pathways are based on \(SN_1\) or \(SN_2\) mechanisms.\(^2\) Investigations in the substitution reactions involving transition metal complexes in other solvents other than water revealed that the order of a reaction is not a reliable ground of molecularity and that often substitution occurs within a preformed aggregate.\(^1\) Langford and Gray,\(^6\) applied the operational approach to classify inorganic substitution reactions based on the concepts of stoichiometric mechanism and
intimate mechanisms.\textsuperscript{7} The stoichiometric mechanism is determined from the kinetic behaviour and classified as,\textsuperscript{7-10}

2.2.1. **Dissociative mechanism (D):**

The intermediate consists of a species with reduced coordination number because the bonds between the leaving group and the metal first breaks before the formation of the bond between the metal and the entering ligand. The mechanism is similar to SN\textsubscript{1} pathways. The bond breaking step is the rate-determining step hence rate of reaction depends on the nature of the leaving group.\textsuperscript{11,12} The energy reaction profile is shown in figure 2.2 d.

2.2.2. **Associative mechanism (A):**

An intermediate of increased coordination number is formed because formation of the bond between the entering group and the metal, M-Y, occurs simultaneously with the breaking of the bond to the leaving group, M-X. The mechanism is similar to SN\textsubscript{2} reactions. Given that bond formation is the rate determining step, the rate of reaction is dependent on the entering group.\textsuperscript{12-15} The energy reaction profile is shown in figure 2.2 a.

2.2.3. **Interchange Mechanism (I):**

Concerns reactions where bond breaking between the metal and the leaving group and bond forming between the metal and entering group proceed simultaneously which is why no distinguishable intermediate is detected because of the rapidly exchanging activated complex. The interchange mechanisms can be further sub-divided into two groups based on which of the two mechanisms (D or A) is more favoured by the interchange transition state;\textsuperscript{1,7,9}

2.2.3.1. **Dissociative activated interchange mechanism (I\textsubscript{D}):**

Involves transition state that constitutes a very weak bond between the metal centre and the entering group because the leaving group is in the primary coordination sphere and the entering group is bound to the metal centre from the secondary coordination sphere (figure 2.1 a).\textsuperscript{12,15} The entering group has a minor effect on the reaction rate but the reaction is more sensitive to the nature of the leaving group i.e. bond breaking is more important than bond formation.
2.2.3.2. **Associatively activated interchange mechanism (IA):**

Its transition state consists of a weak bond between the metal centre and the leaving group. The rate is more sensitive to the changes in the entering group because it’s in the primary coordination sphere and the leaving group is in the secondary coordination sphere (figure 2.1 b). Bond formation is superior to bond breaking. Most substitution reactions proceed by the associatively activated mechanism\(^7,9\) as illustrated by figure 2.1.

Where \(Y = \text{entering group}, \ L = \text{leaving group} \) and \(Y = \text{entering group}\)

Figure 2.1  Diagrams to illustrate a (a) dissociatively activated and (b) associatively activated intimate mechanism.\(^7,9\)

A summarised energy profile diagram showing the different modes of substitution is presented in figure 2.2.

Figure 2.2  Gibbs free energy diagrams showing D, A, and I mechanisms.\(^9\)
2.3. **Substitution reactions of the square planar complexes**

Square planar complexes are metal complexes where the metal ion contains eight electrons in the $d$-orbital that include Au(III), Ni(II), Ir(I), Pt(II), Rh(I) and Pd(II) which are invariably spin paired.$^{16,17}$ Square planar Pt(II) complexes are the most studied because platinum is easily available and has moderate reactivity allowing study by conventional sampling techniques.$^{18}$ The bias towards the Pt(II) complexes was renewed and sustained after the discovery of antitumor activity of cisplatin.$^{17}$ The rest of the square planar complexes viz. Ir(I) and Rh(I) have too rapid substitution reactions while Pd(II) is about five times more reactive than Pt(II) analogues.$^{19}$ Au(III)$^{20,21}$ complexes also show substitution by associative mechanism.

Since substitution reactions of all square planar complexes are similar, the reaction behaviour of Pt(II) complexes is similar to that of the other square planar complexes. Substitution reactions of square planar complexes proceed readily via the associative mechanism because $d$-block elements are stable with eighteen-electron valence shell and since four coordinate $d^8$ metal complexes have sixteen-electron valence shells, the five coordinate transition state is energetically more feasible as it leads to stable eighteen-electron system.$^1$ This is confirmed by voluminous data in literature on kinetic and thermodynamic studies of Pt(II) complexes.$^7,10$

Based on steric and electronic reasons, the reactions in these systems would proceed most readily by an increase in the coordination number after inclusion of the entering ligand. The metal is open to attack above and below the plane, as there is no ligand perpendicular to the plane to obstruct it. Further, these low spin $d^8$ systems have a vacant $p_z$ orbital of relatively low energy to accommodate the pair of electrons donated by the entering ligand.$^{21,22}$

Reactions of cis- and trans-PtK$_2$LX with Y to yield PtK$_2$LY as shown in scheme 2.1 have been studied and reveal that the cis and trans conformations yield cis and trans products respectively.$^{22}$ The retention of configuration originates from a mechanism with precise stereo-specificity which excludes the dissociative mechanism where the three coordinated species assume a nearly regular planar structure with angles nearly 120$^\circ$ with equal chance to form the cis or trans isomer irrespective of whether Y enters PtK$_2$ LX adjacent to L or
opposite to L as illustrated by scheme 2.3. Stereo-specific displacement best assumes a nucleophilic attack via a trigonal bi-pyramidal intermediate illustrated in scheme 2.1

Where, Y = nucleophile, X = leaving group and K and L = non-labile ligands

Scheme 2.1 Stereo-specific substitution reactions of square planar complexes.

The observation illustrated by scheme 2.1 is evidence that substitution reactions of square planar complexes involve a bimolecular displacement mechanism although studies have revealed some dissociative character in square planar complexes.\textsuperscript{23-26}

### 2.3.1 Mechanism of reaction of square planar complexes

Reactions of square planar complexes are best described in terms of bimolecular displacement mechanism.\textsuperscript{22} It is important to note that kinetic studies are carried out in solvents, for the reactions represented by equation 2.4.\textsuperscript{5,22,27}

\[
[ML_3X] + Y \rightleftharpoons [ML_3Y] + X
\]  \hspace{1cm} (2.4)

Where, $M = \text{metal ion}$, $L = \text{non-labile ligand}$, $X = \text{leaving group}$ and $Y = \text{the nucleophile}$.

The rate law can be described as,

\[
\text{Rate} = k_1 + k_2[ML_3X]Y
\]  \hspace{1cm} (2.5)

$k_1$ and $k_2$ are $1^{\text{st}}$ and $2^{\text{nd}}$ order rate constants respectively.
Applying pseudo-first-order conditions with at least ten-fold excess of nucleophile (Y), the experimental first-order rate constant \( (k_{\text{obs}}) \) and the rate constant of the respective complex relate according to equation 2.6 known as the typical rate law for square planar complexes.

\[
    k_{\text{obs}} = k_1 + k_2 [Y]
\]  

(2.6)

A plot of \( k_{\text{obs}} \) against \([Y]\) is linear with the slope equal to \( k_2 \) and the intercept equal to \( k_1 \) as illustrate by the sample plot in figure 2.3 where [Nu] represents [Y] which is concentration of L- methionine and glutathione nucleophiles.

Figure 2.3 Plots of \( k_{\text{obs}} \) verses [Nu] for the reaction of Pt1 with L-methionine and glutathione nucleophiles done in this thesis.28

Values of \( k_1 \) will normally be constant for different nucleophiles reacting with same metal complex, but \( k_2 \) values vary with nature of the entering nucleophile, Y. A positive intercept may not necessarily be attributed to \( k_1 \) but might represent the rate constant for the reverse reaction as shown in equation 2.4.29,30 Coordinating solvents19 commonly used like methanol or water usually present in large excess may be responsible for the \( k_1 \) term (solvosis pathway) if the reverse reaction is negligible.8,10 Slow displacement of \( X \) by solvent is represented by \( k_1 \), but solvent is rapidly displaced by nucleophile, \( Y \) thus \( k_2 \) stands for direct displacement of \( X \) by \( Y \) as illustrated by scheme 2.2.
2.4 Factors affecting the rate of substitution reactions

The rate at which substitution reactions of square planar complexes proceeds is dependent on a number of factors.\textsuperscript{21,31,32}

2.4.1 Effect of the non-labile ligand

Reactions of square planar complexes follow the associative pathway involving a trigonal bipyramidal transition state intermediate, in which the entering group, the leaving group and the trans-ligand are in the trigonal plane while the other two cis-ligands are out-of-plane.\textsuperscript{22,32} The trans-ligand is able to exert a significant effect on the leaving group and consequently on the rate of substitution and this effect is called the trans-effect. The ligands cis- to the leaving group also exert an effect on the substitution reaction though less significant. This effect initially observed by Alfred Werner\textsuperscript{33,34} was applied in 1926 when Chernayev and coworkers\textsuperscript{35} initiated the idea of trans-effect to explain reactions of Pt(II) complexes. They reported that negatively charged ligands like chloride ions have higher labilizing effect on leaving groups trans to them than a leaving group cis to it, and overall the labilizing effect is greater than exhibited by a non π-bonding neutral ligand like ammonia. The trans effect is illustrated by substitution reactions of Pt(II) complexes in equations 2.7-2.14. The phenomenon of trans effect has been applied in the synthesis of desired Pt(II) complex isomers.
In equation 2.7, the *cis* isomer of Pt(NH$_3$)$_2$Cl$_2$ is synthesised successfully due to the chloride ion having a larger trans directing influence than ammonia enabling the second ammonia to coordinate to the *cis* position confirming that the least reactive chloride group in PtNH$_3$Cl$_3$ is that opposite the ammonia group. In the second stage of the reaction represented by equation 2.8, the chloride ion replaces the most labile ammonia in Pt(NH$_3$)$_3$Cl$^+$ which is apparently the one opposite the chloride ion. From the observations in equations 2.7 and 2.8, the synthesis of *cis*- and *trans*- isomers of [Pt(NH$_3$)(NO$_2$)$_2$]Cl$_3$ can be achieved by reversing the order of the incoming nucleophiles.

Equation 2.10 shows that the trans-directing effect of the nitrite group is superior to that of chloride because the incoming ammonia molecule coordinates trans to the nitrite. Further examples to emphasize the idea of trans-effect appear in equations 2.11- 2.14.²²
First chloride ion entered the complex and then labilised the ammonia ligand $trans$ to it causing the second chloride ion to substitute the ammonia group showing that the chloride ion has a greater $trans$-labilizing effect than either pyridine or ammonia. Isomers of $[\text{Pt(Py)(NH}_3\text{(Cl)(Br)}]^2$ were synthesised as shown by the subsequent equations.

\begin{align*}
\text{Cl}^- & \quad \text{Br}^- \\
\text{Cl}\text{Pt-NH}_3 & \quad \text{Cl}\text{Pt-NH}_3 \\
\text{Cl} & \quad \text{Cl}
\end{align*}

(2.12)

\begin{align*}
\text{Cl}^- & \quad \text{Br}^- \\
\text{Cl}\text{Pt-Py} & \quad \text{Cl}\text{Pt-Py} \\
\text{Cl} & \quad \text{Cl}
\end{align*}

(2.13)

\begin{align*}
\text{Cl}^- & \quad \text{Br}^- \\
\text{Cl}\text{Pt-Py} & \quad \text{Cl}\text{Pt-Py} \\
\text{NH}_3 & \quad \text{NH}_3
\end{align*}

(2.14)

The reactions already illustrated and many others indicated that strength of the metal-leaving group bond and the labilizing influence of the $trans$-group play important roles in substitution reactions. Ligands can be arranged in order of decreasing labizing strength as in the series;$^7$

$CO, CN^-, C_2H_4 > PR_3, H > CH_3 > SC(NH_2)_2 > C_6H_5, N_2O, I, SCN > Br, Cl > py, NH_3, OH, H_2O$

Effects at the ground state and transition state both play a role in understanding the $trans$ effect and its role in increasing the rate of reactions. It is interesting to note that kinetically,
this effect can be large to a factor of $10^6$ or higher in rates between complexes containing good $\text{trans}$-labilizing ligand to those containing weak $\text{trans}$ labilizing ligand. Arguably, it is the most dramatic on the substitution reactions rates in metal complexes. Basolo and Pearson\textsuperscript{22} defined the $\text{trans}$-effect as the "effect of a coordinated group upon the rate of substitution reactions of ligands opposite to it in a metal complex". Possibly the best explanation takes to account both the $\sigma$-donating and $\pi$-accepting capabilities of the ligand; Strong $\sigma$-donation from a ligand, results in a weaker $\text{trans}$-bond (high ground state $\text{trans}$-influence), increasing the rate of substitution.

When charge is delocalized in the transition state, the species is stabilized which increases the rate. Strong $\pi$-acceptors typically facilitate this kind of stabilization leading to high $\text{trans}$-effects.\textsuperscript{37,38} $\text{Trans}$-effect gives information about $\text{trans}$-ligand on the ground state and transition state. The effect of $\text{trans}$-ligand to ground state properties like bond lengths is called $\text{trans}$-influence while $\text{trans}$-effect is the influence of the $\text{trans}$-ligand to the transition state complex.\textsuperscript{9,39} A good $\pi$-accepter stabilises the five coordinate transition state because it accepts electrons donated from the filled $\pi$-orbitals of the metal $(d_{xy}, d_{xz}, d_{yz})$ to its empty $p$-orbitals or the $p$-orbitals of the leaving group.\textsuperscript{22}

The metal-ligand bond is strengthened by the back donation if the ligand is a good $\pi$-acceptor and as a result the increase in the electron density due to increased coordination number on the metal centre in the transition state is reduced effectively lowering activation energy while increasing the reaction rate. $\sigma$-donation is a ground state stabilization of metal-leaving group bond since in the transition state, the leaving group and $\text{trans}$ ligand don’t directly share the same $p$-orbitals. A number of studies have been keen to account for $\text{trans}$ effect\textsuperscript{35,40,41} with the $\pi$-bonding and the polarisation theories being the most common.\textsuperscript{42}

\subsection{2.4.1.1 The polarization theory}
Postulated by Grinberg\textsuperscript{43}, the polarization theory explains that the primary charge on the Pt(II) induces a dipole in the $\text{trans}$-ligand, which then induces a dipole in the metal as shown in figure 2.4. The dipole induced in the metal then repels the negative charge in the leaving group causing the metal-leaving group bond to stretch and weaken. There is indeed a link between the $\text{trans}$-influence of the $\text{trans}$-ligand and its polarisability e.g. $\text{H}^- \sim \Gamma^- > \text{Cl}^-$.\textsuperscript{22} Objections to the electrostatic theory argue that the induced dipole on Pt(II) should depend
inversely to the distance from the *trans*-ligand which should depend on the net charge of the ligand more strongly than on its induced dipole moment.\(^{22}\) On the basis of this contrary view, Cl\(^-\) would have greater *trans*-effect than I\(^-\) which is not true. This is however clarified by taking into account covalent bonding because highly polarizing ligands will also form more covalent bonds to Pt(II).

---

Where, \(T = \text{trans-ligand}\) and \(X = \text{leaving group}\)

Figure 2.4 Induced dipole moments along T-Pt-X\(^{22}\)

### 2.4.1.2 The π-bonding theory

Pauling\(^{44}\) first introduced the idea of π-bonding to account for the short Ni-C bond distance within the Ni(C0)\(_4\) complex and the large stability of the cyanide complexes of transition metals as compared to non-transition metals. The existence and significance of such double bonding are now generally recognized and involves ligands capable of forming π-bonds like C\(_2\)H\(_4\), CO and PR\(_3\) due to their strong π-acceptor abilities making them strong *trans*-directors.\(^{22}\) A σ-bond is formed between the ligand and metal by the donation of a pair of electrons from the ligand to the metal centre and the π-bond by the overlap of a filled \(d\)-orbital of the platinum centre and a vacant orbital of the ligand. In the ground state, it would appear that the removal of electrons from the metal by the π-bonding actually strengthens instead of weakening the metal leaving group bond but Chatt *et al.*\(^{45}\) and Orgel\(^{46,47}\) proposed π-bonding stabilization of the trigonal bi-pyramidal intermediate in the transition state to explain the *trans* effect. Chatt *et al.*\(^{45}\) emphasised that decrease in electron density from Pt(II) centre in the transition state by π-bonding of the *trans*-ligand enhances addition of incoming group as activation energy is lowered. π-bonding according to Orgel\(^{46,47}\) reduces the electron density on Pt(II) along the metal-leaving group and metal-incoming group directions which leads to a retention of configuration which is referred to as the π-*trans* effect\(^{22}\) as illustrated in figure 2.5.
2.4.2 The Molecular orbital theory

The molecular orbital theory best explains *trans*-effect by considering both the σ-donation and π-accepting capacities of the *trans*-ligand. Consider a simple molecular orbital (MO) diagram of [PtCl\textsubscript{4}]\(^{2-}\) as shown in figure 2.6.

Figure 2.5 π-back donation of charge from the filled *d* orbitals of Pt(II) to the empty orbitals of the *trans* ligand.\(^{22}\)

Figure 2.6 A simple MO diagram of [PtCl\textsubscript{4}]\(^{2-}\) \(^{22,49}\)
The σ-bonding orbitals are the most stable followed by the π-bonding molecular orbitals, all mainly located on the four chlorines.\textsuperscript{22,49} Next orbitals relatively stable are anti-bonding orbitals, $\pi_x^*, \pi_y^*, \pi_z^*$, $\sigma_x^*$, and $\pi_{xy}^*$ while $\sigma_{xy}^*$ are relatively unstable from the 5$d$ atomic orbitals of Pt(II).\textsuperscript{22,49} Anti-bonding σ orbitals $\sigma_x^*, \sigma_y^*, \sigma_z^*$ are at high energy.\textsuperscript{49} Orbitals $\pi_x^*$, $\pi_y^*$, and $\pi_{xy}^*$ are the only ones with the correct orientation for π-bonding in square planar complexes.\textsuperscript{23} On formation of the trigonal bipyrimidal intermediate after addition of $Y$ (equation 2.4), $\pi_x^*$, $\pi_y^*$, $\pi_{xy}^*$ and $\pi_{x^2-y^2}^*$ are now in the strategic orientation for π interactions and are shared in π-bonding with the ligands, $L$, $X$ and $Y$ (equation 2.4) in the trigonal plane.\textsuperscript{22}

The trans-ligand can thus greatly stabilize the transition state if it is capable of bonding to the π*-orbitals and delocalize the electronic charge to lower the energy. The transition state is stabilized as there are more filled π-orbitals than in the ground state the reason why a good trans π-acceptor ligand will lower the activation energy of the substitution reaction. According to Langford and Gray\textsuperscript{11} in the ground state of a square planar complex, there is only one $p$-orbital $p_z$ used to bond $L$–Pt–$X$, addition of the entering group, causes $X$ to move out of the $x$-axis into the trigonal plane which has two $p$-orbitals, $p_x$ and $p_y$ increasing the number of orbitals available for bonding.

In the ground state there were only one $p$-orbital bonding two ligands but in the transition state there are two orbitals bonding three ligands, leading to increased stability of the transition state which means that good σ-bonding ligands which can donate into the extra $p$-orbitals can stabilize the σ-structure in the transition state.\textsuperscript{22} The effect is known as the σ-trans effect.\textsuperscript{11} Ground state stability of a complex can be affected by σ-bonding in that at ground state, the trans-ligand and the leaving group share the same $p_z$ orbital as shown in figure 2.7, with a strong σ-donor trans-ligand, such as H\textsuperscript{−} and CH\textsubscript{3}• more electron density will be donated to the shared $p$-orbital strengthening the L–Pt bond and weakening the Pt–X bond which increases the rate of the reaction.\textsuperscript{22}
Figure 2.7  Representation of L-Pt-X bonding using $\sigma_x$ MO; in (a) the strength of the $\sigma$-bonds are almost equal but stronger for the stronger $\sigma$-donor L in (b)

2.4.3 Effect of incoming group

The associative mechanism of reaction is sensitive to the nature of incoming nucleophile such that the rate of reaction is a manifestation of the reactivity (nucleophilicity) of the respective nucleophile.\textsuperscript{14} Considering a standard reaction 2.15;

$$trans - [Pt(py_2)Cl_2] + L^- \rightarrow trans - [Pt(Py_2)(L)Cl]^{val} + Cl^{-1} \quad (2.15)$$

The rate of the reaction will be given by equation 2.16

$$Rate = k_s[Pt(py_2)Cl_2] + k_l[L^-][Pt(py_2)(L)Cl] \quad (2.16)$$

Where, $py = pyridyl$ group, $L =$ entering nucleophile, $k_l =$ rate constant for the entering nucleophile and $k_s =$ rate constant for attack by solvent on the complex

The nucleophilicity of a nucleophile is given by equation 2.17,

$$\eta_{pt} = \log\left(\frac{k_l}{k_s}\right) \quad (2.17)$$

Most reactive nucleophiles are “soft” (species that are large, have low charge and are strongly polarisable) which accounts for sulphur being a better donor than oxygen.\textsuperscript{14,33,34,50,51} For Pt(II) complexes, plots of $\log k_l$ verses $\eta_{pt}$ were observed to be linear according to equation 2.18 which gives the linear free energy relationship.\textsuperscript{22}

$$\log k_l = s\eta_{pt} + \log k_s \quad (2.18)$$
Where $k_L$ is second order rate constant for the nucleophile, $L$, $s$ is nucleophilic discrimination factor (slope) and $\log k_s$ is the intrinsic reactivity of the complex (y-intercept).

The nucleophilic discrimination factor is specific for a complex and measures the sensitivity of the metal centre to the nucleophilicity of the entering nucleophile. A large value of the slope means the reaction is more sensitive to the changes in the nucleophilic nature. The y-intercept gives the rate constant for the weakest nucleophile measured in a solvent; a low value of $k_s$ signifies that the complex is more sensitive to changes in the nucleophile.

Ligands with capacity to form dative $\pi$-bonding with Pt(II) in the transition state exhibit high values of $s$ (low values of $k_s$) which allows addition of electrons from the nucleophiles to the metal centre facilitating the entering group to participate in the transition state. There are exceptions from the general trend illustrated by table 2.1 for certain nucleophiles like $NO_2^-$, $SeCN^-$ among others because of other factors including effective charge of the metal centre and shape and size of nucleophile.

2.4.4 Nature of the cis Ligand

A ligand cis to the leaving group has generally less electronic effect on the reaction than when in the trans-position; however it will be more sensitive to steric hindrance in the cis-position. Steric hindrance magnifies when the tri-gonal bi-pyramidal complex is formed in the transition state because the trans-ligand is in the equatorial plane $120^\circ$ from the incoming and leaving groups while the axial cis-ligand is separated from the groups by only $90^\circ$ which lowers the rate of substitution the reaction. It has been shown that trans-activating ligand is a poor cis-activator. There is contrary data however on this cis and trans-behaviour as illustrated by the reaction in equation 2.19.

$$cis - [Pr(PEt_3)_2 LCI] + py \rightarrow cis - [Pr(PEt_3)_2 Lpy] + Cl^-$$

The effect of the ligands, L; CH$_3^-$, C$_6$H$_5^-$ and Cl$^-$, on the reaction and order is same for cis and trans-complexes as shown in table 2.2.
Table 2.1 Effect of cis ligand, L, on the rate of reaction in equation 2.19

<table>
<thead>
<tr>
<th>L</th>
<th>$k_f (10^{12})/s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>1.7</td>
</tr>
<tr>
<td>C$_6$H$_5^-</td>
<td>3.8</td>
</tr>
<tr>
<td>CH$_3^-$</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Observations indicate that varying basicity of amines in the cis position affects reactivity significantly with the least reactive amine forming the most reactive complex to be substituted. When the trans-activator is weak, the cis-activator may have greater influence on the rate. When the trans-activator is weak, the cis-activator may have greater influence on the rate. Generally, cis-effect is small and the order variable unless steric factors play a role.

2.4.5 Nature of the leaving group

Effect of a leaving group is not very easy to account for because it’s very closely connected with the nature of the incoming nucleophile and the trans-ligand. If a reaction is dissociative, the bond between the leaving ligand and the metal complex breaks in the transition state consequently there is a large dependence on the nature of the leaving group. But for an associative reaction, effect of the leaving group depends on the extent to which bond breaking occurs in the transition state which is variable. Effect of the leaving group has been investigated for the reaction shown in the equation 2.20,

$$[Pt(dien)X]^+ + py \rightarrow [Pt(dien)py] + X^-$$  \hspace{1cm} (2.20)

The rate of substitution of X follows the order:\[NO_3^- > H_2O > Cl^- > Br^- > I^- > N_3^- > SCN^- > NO_2^- > CN^-]$

Leaving groups exert considerable influence to the rates of substitution which indicate that even associative modes of substitution encounter considerable bond breaking between metal and leaving group in the transition state which depends on the type of the reaction. The bond breaking doesn’t automatically lead to dissociative process but only requires bond breaking to make a comparable contribution to bond formation between metal and incoming group. Leaving groups high in the trans-effect series (strongly binding) are hard to replace consequently lead to a slower rate of substitution.
2.4.6 Steric effect
Steric hindrance could be caused by either bulky incoming ligand or bulky spectator ligand. Its worthy noting the fact that the transition state in an associative mode of substitution produces species with increased coordination number hence increased steric hindrance. Bulky non-labile ligands in the cis position significantly slow down the rate of reaction.

2.4.7 Effect of the solvent
Solvents may play a key role on the rate of a substitution reaction in square planar complexes with the effect of solvent increasing with increase in the coordination ability of the solvent. In the case where the solvent coordinates, the rate law will include a reaction path attributed to solvent attack. The effect of solvent has been determined by investigating the chloride exchange reaction represented by equation 2.21 whose data is shown in table 2.2.

\[
\text{trans} - [\text{Pt}(\text{py})_2 \text{Cl}_2]^{[36]\text{Cl}} \rightarrow \text{trans} - [\text{Pt}(\text{py})_2 \text{Cl}(^{36}\text{Cl})]+\text{Cl}^- \quad (2.21)
\]

Table 2.2 The effect of solvent on the chloride exchange reactions of equation 2.21.

<table>
<thead>
<tr>
<th>Coordinating solvents</th>
<th>Weakly coordinating solvents</th>
<th>(K M^1 s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>CCl₄</td>
<td>10000</td>
</tr>
<tr>
<td>H₂O</td>
<td>C₆H₆</td>
<td>100</td>
</tr>
<tr>
<td>CH₃NO₂</td>
<td>i-BuOH</td>
<td>0.1</td>
</tr>
<tr>
<td>EtOH</td>
<td>EtOAc</td>
<td>0.01</td>
</tr>
<tr>
<td>PrOH</td>
<td>(CH₃)CO</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>DMF</td>
<td>0.001</td>
</tr>
</tbody>
</table>

First column consists of solvents with good coordinating capacity where the rates depend on the nucleophilicity of the solvent (\(k_S \gg k_{Cl}[^{36}\text{Cl}]\)). In the third column the solvents have low coordination capacity hence reactions proceed only by attack by incoming nucleophile (\(k_{Cl}[^{36}\text{Cl}] \gg k_S\)). In the non-polar solvents, the rates are highest probably because the chloride is not solvated making it more reactive although in general the extent of solvation is uncertain. For coordinating solvents, \(k_2\) values go in the order:

\[
\text{DMSO} > \text{CH}_3\text{NO}_2 \sim \text{H}_2\text{O} > \text{ROH}
\]
The significance of the order for coordinating solvents is that Pt-solvent bond formation is more important than bond breaking in the transition state because if solvating the leaving group was the sole role of the solvent then water will be superior to DMSO in solvent effects, however, DMSO is a more efficient nucleophile because sulphur is a better nucleophile than oxygen.\textsuperscript{57,58}

2.5 Evidence of the dissociative pathway for the substitution reactions of square planar Pt(II) complexes.

Though rare, the dissociative mode of substitution in square planar complexes may occur if the metal complex is sterically hindered preventing axial approach by nucleophile, the nucleophile is weak so that the solvotic pathway is dominant or there is a sufficiently strong trans σ-donor which weakens the metal-leaving group bond enhancing bond breaking.\textsuperscript{25} Complexes with strong σ-donor atoms like sulphur, carbon or phosphorus in the cis-position are observed to undergo the dissociative pathway during substitution reactions.\textsuperscript{24-26,59} The strong σ-donor atoms stabilize the 14-electron three coordinate intermediate. Complexes whose nature is cis-[Pt(Me)\textsubscript{2}R\textsubscript{2}] or cis-[Pt(ph)\textsubscript{2}R\textsubscript{2}] (where R=DMSO or thioether) were found to exhibit dissociative mode of substitution. However, ligands with strong π-acceptor capacities like CO accept electrons from the metal centre making it more electrophilic facilitating the associative pathway.\textsuperscript{59} One hallmark of the dissociative mechanism of substitution is its non-stereo selectivity possibly because the T-shaped 14 electron three coordinate intermediate species has long life enough to allow intermolecular rearrangements of ‘cis-like’ form to a trans-like’ form so that addition of nucleophile results in isomeration to give non-stereo specific products as shown in scheme 2.3. These mechanisms have small solvent effects.\textsuperscript{24} With weak nucleophiles, the solvolytic pathway predominates a shortcoming for the dissociative mechanism of substitution.

![Scheme 2.3 Non-stereospecific substitution in dissociative mechanism of a Pt(II) square planar complex as a result of intermolecular rearrangement.](image-url)
2.6 References

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List of abbreviations and symbols

Å  Angstrom
A  Arrhenius pre-exponential factor (M$^{-1}$s$^{-1}$)
e  Exponential
$E_a$  Activation energy (Jmol$^{-1}$)
eq  Equilibrium
h  Plank’s constant (6.626 x 10$^{-34}$Js$^{-1}$)
IR  Infrared
K  Kelvin
$k_1, k_{-1}$  Rate constants
$k_b$  Boltzman’s constant (1.38 x 10$^{-23}$JK$^{-1}$)
k$_{exp}$  Experimental pseudo first-order rate constant
$k_{obs}$  Observed pseudo first-order rate constant
M  moldm$^{-3}$
mgmL$^{-1}$  Milligrams per millilitre
Nu  Nucleophile
R  Universal gas constant (8.3145JK$^{-1}$mol$^{-1}$)
s  Nucleophilic discrimination factor
T  Absolute temperature (K) unless stated otherwise
t  Time
UV  Ultraviolet
VIS  Visible
$\Delta G^\neq$  Gibbs free energy of activation
$\Delta H^\neq$  Activation enthalpy
$\Delta S^\neq$  Activation entropy
$\varepsilon$  Molar absorptivity co-efficient
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Chapter 3

Kinetic theory and associated techniques

3.1 Introduction

The reaction rate can be defined as the amount of reactant converted into product per unit time or amount of product formed per unit time. The amount is expressed in terms of the concentrations of the stoichiometric reactants or products making it independent of the size of the sample but dependent on the molecular collisions. The study of reaction rates constitutes kinetics. Kinetics is divided into physical kinetics and chemical kinetics where chemical kinetics deals with the rate of chemical reactions which covers a whole spectrum of reactions from those that proceed very fast to those which are exceedingly slow to the extent that they are unnoticed and thermodynamics concerned with enthalpy and entropy among other quantities which depend only on initial and final states of a system. Chemical kinetics deals with how fast a chemical reaction occurs where measurements are made under dynamic conditions in which the concentrations of the reactants and products are changing as a function of time which lead to the determination of the reaction rate.

Kinetics not only explains a reaction and its parameters but also enlightens us on the factors that influence the rate of reactions. Data from chemical kinetics using a range of factors allows for the prediction of how fast a reaction would proceed under hypothetical conditions. Secondly the data provide some of the information needed to determine the mechanism of a reaction. Kinetic methods allow many more chemical reactions to be applied for analytical purposes because it can make use of reactions that are too slow for thermodynamic studies. The factors that influence the rate of a reaction include those that can be controlled viz. temperature, concentration, pressure, available surface area, solvent properties and presence of catalysts plus other factors inherent to the process like identity of the chemical reagents or the set thermodynamic conditions which must all be taken into account to appreciate the kinetics of a given process. The factors affecting the rate of reactions are briefly discussed in sub-sections 3.1.1-3.1.4.

3.1.1 Concentration

The higher the concentration of reagents the higher the number of reactant particles which increases the number of effective collisions increasing the rate of a reaction.
3.1.2 Solvent Properties
Solvents can directly affect a reaction by acting as a reactant or may form a solvent cage around the molecule consequently changing the kinetics of a reaction. Coordinating solvents slow down the rate with nucleophile as the solvent path predominates while weakly coordinating solvent have negligible effect on the reaction.

3.1.3 Intensity of absorbed radiation
For photosensitive reactions, exposure of a sample to white light will alter the rate at which the reaction proceeds. This could be due to the change in the nature of the reagents.

3.1.4 Physical conditions
Physical conditions including factors like temperature and pressure which are normally kept constant for a given kinetic measurement.

Change in the concentration of reactants or/and products with time is investigated in the study of kinetics. Since concentration cannot be measured directly, absorbance which is proportional to concentration is monitored during kinetic studies. This chapter presents a summary of the relevant rate laws and the experimental techniques applied in kinetic measurements.

3.2 Rate laws
Rate of a reaction is the change in the concentration of reactant or product as a function of time whose unit is mol dm$^{-3}$ s$^{-1}$ (Ms$^{-1}$). Consider a chemical reaction represented by equation 3.1,

$$aA + bB \rightarrow cC + dD$$

where $a$, $b$, $c$ and $d$ represent the stoichiometry of the reaction and $A$, $B$, $C$ and $D$ represent formulae of chemical compounds.

The general rate law for a reaction is represented by equation 3.2,

$$Rate = \frac{-d[\text{reactant}]}{dt} = \frac{d[\text{product}]}{dt}$$
The negative sign in equation 3.2 shows that the concentration of the reactant reduces with time. With appropriate signs in the rate law, the rate itself is always a positive number. The rate law includes the concentration of all species that affect the rate.\(^{14}\)

The rate law according to equation 3.2 if re-written to include reagents gives equation 3.3,

\[
Rate = -\frac{1}{a} \frac{d[A]}{dt} = -\frac{1}{b} \frac{d[B]}{dt} = \frac{1}{c} \frac{d[C]}{dt} = \frac{1}{d} \frac{d[D]}{dt}
\]  

(3.3)

In general the rate law may be written as;

\[
Rate = -k \prod_i [A_i]^{\alpha_i} [X_j]^{\beta_j}
\]  

(3.4)

\(A_i\) is reactants, \(k\) is rate constant, \(X_j\) is other species such as catalysts that may affect the rate and \(\alpha\) and \(\beta\) are rate orders with respect to reagents, \(A\) and \(B\) respectively determined experimentally.

The order of a reaction is defined as:\(^{15}\)

\[
Order \ of \ reaction = \sum \alpha_i
\]  

(3.5)

While the unit for the rate of a reaction is mol dm\(^{-3}\)s\(^{-1}\), the unit for the rate constant, \(k\), depends on the reaction order.\(^{11}\) The order of a reaction is not always related to the stiochiometry of the reaction hence it is determined experimentally.

### 3.3 Integrated rate laws

#### 3.3.1 Irreversible first-order reactions

Most of the reactions fall under the category of first order or are studied under conditions that approximate first-order conditions. For a first-order reaction, the rate is directly proportional to a single reactant concentration thus the kinetics follow a rate law with the reaction order being unity.\(^{16}\) The rate constant for the forward reaction is much greater than that for the reverse reaction. A first-order reaction can be simplified by the relation 3.6.

\[
A \xrightarrow{k_1} B
\]  

(3.6)
The rate law for the reaction represented by 3.6 will be given by equation 3.7.

\[
Rate = -\frac{d[A]}{dt} = k_i[A],
\]  

(3.7)

Rearranging equation 3.7 forms equation 3.8.

\[
-\frac{d[A]}{[A]} = k_i dt
\]  

(3.8)

Integrating equation 3.8 from time \( t = 0 \) to \( t = t \) during which concentration changes from \([A]_0 \) to \([A] \), proceeds from equations 3.9 to 3.10.

\[
\int_{[A]_0}^{[A]} \frac{d[A]}{[A]} = -k \int_{0}^{t} dt
\]  

(3.9)

\[
\ln \frac{[A]}{[A]_0} = -kt
\]  

(3.10)

Equation 3.10 simplifies to equation 3.11.

\[
\ln[A] = -kt + \ln[A]_0
\]  

(3.11)

Equation 3.11 can be simplified further to equation 3.12.

\[
[A] = [A]_0 e^{-kt}
\]  

(3.12)

\([A]_0 \) and \([A] \) are concentrations of \( A \) at time \( t = 0 \) and \( t = t \) respectively.

From equation 3.10 which is consistent with the equation of a straight line \( y = mx + c \), a plot of \( \ln[A] \) versus \( t \) gives a straight line graph whose slope and intercept are equivalent to the rate constant, \(-k\), and \( \ln[A]_0 \) respectively. Physical parameters proportional to concentration...
viz. absorbance, pressure, conductivity or volume directly apply in the determination of the rate constant for first-order reactions.\textsuperscript{10-12}

3.3.2 Reversible first-order reactions

A reaction that doesn’t proceed to completion but establish equilibrium where some of the product formed is converted back into starting material is described as reversible (equation 3.13).\textsuperscript{11,12}

\[
A \xrightleftharpoons[k_{-1}]{k_1} B
\]

(3.13)

Where, \( k_1 \) and \( k_{-1} \) are rate constants for the forward and reverse reactions respectively.

The rate law for this reaction is given by equation 3.14,

\[
Rate = \frac{d[B]}{dt} = -\frac{d[A]}{dt} = k_1[A] - k_{-1}[B]
\]

(3.14)

At \( t = 0 \), \( [B]_0 = 0 \) and \( [A] = [A]_0 \) thus \( [A]_0 \), \([A]_r\) and \([B]_r\) are related by equation 3.15,

\[
[B]_r = [A]_0 - [A]_r
\]

(3.15)

Substituting for \([B]_r\) in equation 3.14 gives equation 3.16,

\[
-k_1[A] - k_{-1}([A]_0 - [A]_r)
\]

(3.16)

At equilibrium the net reaction is zero, hence equation 3.16 reduces to equation 3.17,

\[
-k_1[A] = 0
\]

(3.17)

Applying equations 3.16 and 3.17 to equation 3.14 leads to equation 3.18,
\[ k_1[A]_{eq} = k_{-1}[B]_{eq} = k_{-1}([A]_0 - [A]_{eq}) \] (3.18)

Equation 3.18 can be rearranged to form equation 3.19,

\[ [A]_t = \frac{k_i + k_k}{k_{-1}}[A]_{eq} \] (3.19)

Substituting equation 3.19 in 3.16 forms equation 3.20,

\[ \frac{-d[A]}{dt} = (k_i + k_k)[A] - (k_i + k_k)[A]_{eq} \] (3.20)

Rearranging equation 3.20 gives equation 3.21,

\[ \frac{d[A]}{([A]_t - [A]_{eq})} = -(k_i + k_k)dt \] (3.21)

Integrating equation 3.21 as shown in equation 3.22 gives equation 3.23,

\[ \int_{[A]_t}^{[A]} \frac{d[A]}{([A]_t - [A]_{eq})} = -(k_i + k_k) \int_0^t dt \] (3.22)

Then,

\[ \ln \left( \frac{[A]_t - [A]_{eq}}{[A]_0 - [A]_{eq}} \right) = - (k_i + k_k) t \] (3.23)

Rearranging equation 3.23 gives equation 3.24,

\[ \ln([A]_t - [A]_{eq}) = - (k_i + k_k) t + \ln([A]_0 - [A]_{eq}) \] (3.24)
Using equation 3.24 which is in the form, \( y = mx + c \), a plot of \( \ln([A]_t - [A]_{eq}) \) against, \( t \), gives a straight line with the slope equal to \( -(k_1 + k_{-1}) \). To determine \( k_1 \) and \( k_{-1} \), the equilibrium constant, \( K_{eq} \), must be evaluated.

Since,

\[
\frac{d[A]}{dt} = 0 = k_1[A]_e - k_{-1}[B]_e, \quad \text{thus,}
\]

\[
K_{eq} = \frac{[B]_e}{[A]_e} = \frac{k_1}{k_{-1}} \quad (3.25)
\]

The experimentally observed rate constant becomes;

\[
k_{obs} = (k_1 + k_{-1}) \quad (3.26)
\]

To treat first-order reversible reactions, \([A]_{eq}\) must be measured accurately.\(^{10,12,15}\)

### 3.3.3 Consecutive first-order reactions

Also known as series reactions, the product formed after the first reaction becomes the reactant for subsequent reactions. Ligand substitution reactions normally don’t stop after one substitution but proceed to form a more highly substituted complex.\(^{10,11}\) Consider a simple consecutive reaction represented in equation 3.27,

\[
A \xrightarrow{k_1} B \xrightarrow{k_2} C \quad (3.27)
\]

The rate law for the process is derived as follows,

\[
-\frac{d[A]}{dt} = k_1[A] \quad (3.28)
\]

\[
\frac{d[B]}{dt} = k_1[A] - k_2[B] \quad (3.29)
\]
\[ \frac{d[C]}{dt} = k_r[B] \]  
(3.30)

At time \( t = 0 \), \( [A] = [A]_0 \) while \( [B]_0 = [C]_0 = 0 \) and after a time, \( t \),
\[ [A]_t = [A]_0 + [B]_t + [C]_t \]  
(3.31)

Integrating equation 3.27 gives equation 3.32,
\[ [A]_t = [A]_0 e^{-k_r t} \]  
(3.32)

Equation 3.32 is substituted in equation 3.29 to give 3.33,
\[ \frac{d[B]}{dt} = k_1[A]e^{-k_2 t} - k_2[B]_t \]  
(3.33)

By integrating factor method, equation 3.33 is multiplied by the integrating factor, \( e^{-k_2 t} \), followed by rearrangement to give;
\[ \frac{d[B]e^{k_2 t}}{dt} = k_1[A]_0 e^{(k_2-k_1)t} - k_2[B]_t e^{k_2 t} \]  
(3.34)

With the initial conditions, \( t = 0, [B]_0 = 0 \) the product rule is applied to equation 3.34 and subsequent integration proceeds as follows to give equation 3.35,
\[ \int_0^t \frac{d[B]e^{k_2 t}}{dt} dt = k_1[A]_0 \int_0^t e^{(k_2-k_1)t} dt, \]
\[ [B] = k_1[A]_0 \frac{e^{(k_2-k_1)t}}{e^{k_2 t}}, \]
\[ [B] = \frac{[A]k_1}{k_2 - k_1} \left[ e^{k_1t} - e^{k_2t} \right] \quad (3.35) \]

The mass law is applied to equation 3.35 to give equation 3.36;

\[ [C]_t = [A]_0 \left( 1 - \frac{k_2}{k_2 - k_1} e^{-k_2t} + \frac{k_1}{k_2 - k_1} e^{-k_1t} \right) \quad (3.36) \]

For the \textit{steady state approximation} (an assumption used for consecutive reactions), \([B]\) is assumed to be very small and doesn’t change during the reaction thus, \(k_1 < k_2^{11}\) based on this assumption, equation 3.29 gives equation 3.37,

\[ \frac{d[B]}{dt} = k_1[A]_t - k_2[B]_t \approx 0 \quad (3.37) \]

This rearranges to equation 3.38,

\[ [B]_t = \frac{k_1}{k_2} [A]_t \quad (3.38) \]

Substituting equation 3.32 into 3.38 gives equation 3.39,

\[ [B]_t = \frac{k_1}{k_2} [A] e^{-k_1t} \quad (3.39) \]

Making \([C]\), the subject of the formula in equation 3.31 gives: \([C] = [A]_0 - [A]_t - [B]_t\), which when substituted with equations 3.32 and 3.39 gives equation 3.40,

\[ [C]_t = [A]_0 \left[ 1 - e^{-k_1t} - \frac{k_1}{k_2} e^{-k_1t} \right] \approx [A]_0 [1 - e^{-k_1t}] \quad (3.40) \]
3.3.4 Irreversible Second –Order reactions

Second-order reactions include two types first, that in which the rate of the reaction is second order with respect to only one of the reactants and the second type is where the reaction is first-order with respect to two different reactants that forms our topic of discussion in this section. Consider a second order reaction represented by equation 3.41.

\[ A + B \xrightarrow{k} C \]  

(3.41)

The rate law for reaction 3.41 is given by equation 3.42,

\[ \text{Rate} = k[A][B] \]  

(3.42)

The rate law can be represented by equation 3.43,

\[ \text{Rate} = \frac{d[C]}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_2[A][B] \]  

(3.43)

If at \( t = 0 \), \([A] = [A]_0 \) and \([B] = [B]_0 \), and letting \( x \) be the amount of the reactants reacted after time, \( t \), then concentration of \([A]\) and \([B]\) at time, \( t \), will be, \([A]_t = ([A]_0 - x)\) and \([B]_t = ([B]_0 - x)\) respectively.

The rate after time, \( t \), is therefore given by equation 3.44,

\[ -\frac{d[A]}{dt} = k_2([A]_0 - x)([B]_0 - x) \]  

(3.44)

Given that \( \frac{dx}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} \), equation 3.44 can be represented by equation 3.45,

\[ \frac{dx}{dt} = k_2([A]_0 - x)([B]_0 - x) \]  

(3.45)

When variables are separated, the new form of equation 3.45 is given by equation 3.46,
\[
\frac{dx}{([A]_0 - x)([B]_0 - x)} = k_2 dt
\]

(3.46)

Integrating equation 3.46 between the limits \(x = 0\) to \(x = x\) and \(t = 0\) to \(t = t\) respectively gives equation 3.47,

\[
\int_0^x \frac{dx}{([A]_0 - x)([B]_0 - x)} = k_2 \int_0^t dt
\]

(3.47)

Equation 3.47 solves to equation 3.48,

\[
\frac{1}{[A]_0 - [B]_0} \ln \frac{[B]_0 ([A]_0 - x)}{[A]_0 ([B]_0 - x)} = k_2 t
\]

(3.48)

Since \(([A]_0 - x) = [A]_0\) and \(([B]_0 - x) = [B]_0\), equation 3.48 changes to equation 3.49,

\[
\frac{1}{[A]_0 - [B]_0} \ln \frac{[B]_0 [A]_t}{[A]_0 [B]_t} = k_2 t
\]

(3.49)

For the second-order rate constant, \(k_2\), to be calculated, \([A]_0\), \([B]_0\), \([A]_t\) and \([B]_t\) must be determined first as its implied in equation 3.49 which is cumbersome.\(^{11,12}\) The rate law is thus commonly simplified by running reactions under pseudo-first-order conditions by having either concentration of \(A\) or \(B\) in excess (at least 10 fold) e.g. if \([B]_0 >> [A]_0\) then concentration of \(B\) remains relatively constant as the reaction proceeds. With the assumption that the reaction is first-order with respect to \(A\), then equation 3.43 converts to equation 3.50,

\[
-\frac{d[A]}{dt} = (k_2[B]_0)[A]_t,
\]

\[
-\frac{d[A]}{dt} = k_{obs}[A]_t
\]

(3.50)

Where \(k_{obs}\) is the observed rate constant whose unit is per second\((s^{-1})\)
With the integrated form of equation 3.50, a graph of \( \ln[A] \) versus time, \( t \), is a straight line with the slope equal to \( k_{\text{obs}} \). With several concentrations of \( B \) investigated each in large excess, respective values of \( k_{\text{obs}} \) are obtained which when plotted against \( [B]_0 \) according to equation 3.51 give a straight line graph with slope equal to the second-order rate constant, \( k_2 \) (\( \text{M}^{-1}\text{s}^{-1} \)).

\[
k_{\text{obs}} = k_2[B]_0 \tag{3.51}
\]

### 3.3.5 Reversible Second-order Reactions

Some second order reactions may not proceed to completion resulting to equilibrium state as illustrated by equation 3.52,

\[
A + B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \tag{3.52}
\]

The forward reaction is second order while the reverse reaction is first order meaning that the reaction is multi-order hence complex. The reaction is simplified by having pseudo first-order conditions for the forward reaction where \([B]_0 \gg [A]_0\) which makes it resemble a reversible first-order reaction with rate given as, \(^{11,12}\)

\[
-k_2[A] - k_{-2}[C] = \frac{d[B]}{dt} \tag{3.53}
\]

The rate of formation of \( C \) is given by equation 3.54,

\[
Rate = k_2[A][B]_t - k_{-2}[C]_t \tag{3.54}
\]

Given the stoichiometry of the reaction is 1:1:1 and no product at time, \( t = 0 \), then after time, \( t \), the masses remaining will be given by equations 3.55 and 3.56,

\[
[A]_t = ([A]_0 - [C]_t) \tag{3.55}
\]
\([B]_t = ([B]_0 - [C]_t) \quad (3.56)\)

At equilibrium, the mass balances will be given by equations 3.57 and 3.58,

\([A]_{eq} = ([A]_0 - [C]_{eq}) \quad (3.57)\)

\([B]_{eq} = ([B]_0 - [C]_{eq}) \quad (3.58)\)

The forward and reverse reactions are equal and opposite represented by equation 3.59,

\[- \frac{d[A]}{dt} = k_2 [A]_{eq} [B]_{eq} - k_{-2} [C]_{eq} = 0 \text{, thus,} \]

\[k_2 [A]_{eq} [B]_{eq} = k_{-2} [C]_{eq} \quad (3.59)\]

Substituting for \([C]_{eq}\) gives equation 3.60,

\[k_2 [A]_{eq} [B]_{eq} = k_{-2} ([A]_0 - [A]_{eq}) \quad (3.60)\]

With this, the rate works out to equation 3.61,

\[k_{-2} [A]_0 = k_2 [A]_{eq} [B]_{eq} + k_{-2} [A]_{eq} \text{ and} \]

\[[C]_t = ([A]_0 - [A]_t) \text{ Then,} \]

\[- \frac{d[A]}{dt} = k_2 [A]_t [B]_t - k_{-2} ([A]_0 - [A]_t) = k_2 [A]_t [B]_t - k_{-2} [A]_0 + k_{-2} [A]_t \]

\[= k_2 [A]_t [B]_t - k_2 [A]_{eq} [B]_{eq} - k_{-2} [A]_{eq} + k_{-2} [A]_t \quad (3.61)\]
Substituting for \([B]\) and \([B]_{eq}\) according to equations 3.56 and 3.58 and making the approximation that, \(k_2[A]_0[A] \approx k_2[A]_{eq}[A]_0\) and \(k_2[A]^2 \approx k_2[A]_{eq}^2\) gives equation 3.62,

\[- \frac{d[A]}{dt} = k_2[A]_0[B]_0 - k_2[A]_{eq}[B]_0 - k_{-2}[A]_{eq} + k_{-2}[A], \tag{3.62}\]

Factorizing equation 3.62 gives equation 3.63,

\[- \frac{d[A]}{dt} = (k_2[B]_0 + k_{-2})\left([A]_0 - [A]_{eq}\right) \tag{3.63}\]

Separating the variables and subsequent integration gives leads to equation 3.64,

\[
\int_{[A]_0}^{[A]} \frac{d[A]}{[A]_0 - [A]_{eq}} = -(k_2[B]_0 + k_{-2}) \int_0^t dt.
\]

\[
\ln\left(\frac{[A]_0 - [A]_{eq}}{[A]_0 - [A]_{eq}}\right) = -(k_2[B]_0 + k_{-2})t = k_{obs}t \tag{3.64}\]

Where \(k_{obs} = k_2[B]_0 + k_{-2}\)

A graph of \(k_{obs}\) verses \([B]_0\) is a straight line whose slope is \(k_2\) and intercept equivalent to \(k_{-2}\).

The ratio of \(k_2 : k_{-2}\) gives equilibrium constant that can be measured thermodynamically.\(^{17}\)

Generally pseudo-first-order reactions are applied in the study of substitution reactions of square planar complexes.

### 3.4 Activation parameters

A rate law helps discern a reaction mechanism, however to obtain further information on the enthalpies of a reaction, the temperature dependence of the rate constant is often analysed which leads to the determination of the activation parameters.\(^{11,12,18}\) This may also involve, for more complex rate laws, a study of concentration dependence of the rate at various temperatures, to determine the temperature dependence of different species in the rate law.
Experimental data for the rate constants can be analyzed according to the Arrhenius equation or transition state theory (absolute reaction rate theory) as follows.\textsuperscript{11}

### 3.4.1 The Arrhenius equation

Equation 3.65 proposed by Svante Arrhenius in 1889,\textsuperscript{19} states the relationship between temperature and rate constants.

\[
k = Ae^{-\frac{E_a}{RT}} \quad (3.65)
\]

Taking natural logarithm of the Arrhenius equation gives equation 3.66,

\[
\ln k = \ln A - \frac{E_a}{R} \cdot \frac{1}{T} \quad (3.66)
\]

Where: \(A\) is Arrhenius pre-exponential factor (\(M^{-1}s^{-1}\)), \(E_a\) is Arrhenius activation energy (\(Jmol^{-1}\)), \(R\) is Gas constant (8.315JK\(^{-1}\)mol\(^{-1}\)) and \(T\) is Absolute temperature (K)

When appropriate experiments are done at different temperatures determining the respective rate constants, \(k\), then a plot of \(\ln k\) verses \(\frac{1}{T}\) gives a straight line graph whose slope is equal to \(-\frac{E_a}{T}\) from which \(E_a\) can be determined. The rate constant is expected to increase with temperature.\textsuperscript{3,12,15,20} The Arrhenius equation comes in handy for complex systems where the determined rate constant, \(k\), is thought to be a composite of specific rate constants.\textsuperscript{12}

### 3.4.2 The Transition-state Theory

The transition-state theory originally known as the theory of absolute reaction states by H. Eyring, M. Evans and M. Polanyi in 1936\textsuperscript{12,21,22} was developed for simple dissociation processes in gaseous phase. It’s based on the assumption that most reactions proceed via a pre-equilibrium mechanism as illustrated by equation 3.67,
The reaction rate can be expressed by equation 3.68,

$$\frac{d[A]}{dt} = k_2[A--B]^*$$  \hspace{1cm} (3.68)

Since $K^e$ is given by equation 3.69,

$$K^e = \frac{[A--B]^*}{[A-B]}$$  \hspace{1cm} (3.69)

Equation 3.68 forms equation 3.70 after substituting for $[A----B]^*$.

$$\frac{d[A]}{dt} = k_2K^e[A-B] = \frac{k_b T}{h} K^e[A-B]$$  \hspace{1cm} (3.70)

Where $k_b$ is Boltzmann’s constant ($1.38 \times 10^{-23} \text{JK}^{-1}$) and $h$ is Planck’s constant ($6.626 \times 10^{-34} \text{Js}^{-1}$).

The experimental rate constant can be incorporated in equation 3.70 to give equation 3.71,

$$\frac{d[A]}{dt} = k_{\text{exp}}[A-B]$$  \hspace{1cm} (3.71)

Where the experimental rate constant is given by equation 3.72,

$$k_{\text{exp}} = \frac{k_b T}{h} K^e$$  \hspace{1cm} (3.72)

Given that Gibbs free energy of activation, $\Delta G^e$, is given by equation 3.73,
\[ \Delta G^* = -RT \ln K^* , \]
\[ = \Delta H^* - T \Delta S^* \quad (3.73) \]

Substituting for \( K^* \) in equation 3.73 gives equation 3.74,

\[ k_{exp} = \frac{k_b T}{h} e^{\frac{-\Delta G^*}{RT}} \quad (3.74) \]

Given that,

\[ -RT \ln K^* = \Delta H^* - T \Delta S^* \text{, where} \]
\[ K^* = e^{\frac{-\Delta H^*}{RT}} e^{\frac{\Delta S^*}{R}} \text{.} \]

Equation 3.72 could also give equation 3.75,

\[ k_{exp} = \frac{k_b T}{h} e^{\left(\frac{-\Delta H^*}{RT}\right)} e^{\left(\frac{\Delta S^*}{R}\right)} \quad (3.75) \]

Rearranging, applying logarithms, linearization and simplifying equation 3.75 gives equation 3.76,

\[ \ln \left( \frac{k_{exp}}{T} \right) = -\frac{\Delta H^*}{R} \frac{1}{T} + \left[ \ln \left( \frac{k_b}{h} \right) + \frac{\Delta S^*}{R} \right] \quad (3.76) \]

From the values of the constants \( k_b \) and \( h \) the value of \( \ln \left( \frac{k_b}{h} \right) \) is given as 23.8 hence equation 3.76 will eventually form equation 3.77,

\[ \ln \left( \frac{k_{exp}}{T} \right) = -\frac{\Delta H^*}{R} \frac{1}{T} + \left[ 23.8 + \frac{\Delta S^*}{R} \right] \quad (3.77) \]
A plot of \( \ln \left( \frac{k_{\text{exp}}}{T} \right) \) verses \( \frac{1}{T} \) gives a graph known as Erying plot, of slope \( \frac{\Delta H^*}{R} \) and an intercept equal to \( 23.8 + \frac{\Delta S^*}{R} \) from which the enthalpy, \( \Delta H^* \), of activation and entropy, \( \Delta S^* \), of activation can be determined respectively.\textsuperscript{12,15,23,24}

3.5 Experimental kinetic techniques

Kinetics of most chemical reactions in solutions has been studied in detail. There exists different methods for measuring reaction rates the choice of a method depends on whether the reaction of interest is fast or slow. The best technique to study chemical kinetics must involve mixing reactants in a time negligible to the time scale of the reaction, measure a variable that is proportional to concentration of reactants or products as a function of time and accurately measure and control temperature or pressure at which a reaction proceeds.\textsuperscript{25} A slow reaction can be studied by conventional methods of analysis to determine the concentration of a reactant or product as a function of time but most reactions are too rapid so that the reaction has to be stopped while the measurement is done (quenching) or a technique that ensures continuous measurement of concentration as the reaction proceeds must be applied.\textsuperscript{4}

Quenching is made possible by lowering temperature to slow the reaction to allow a measurement to be taken which is very slow and time-consuming hence more convenient to monitor the progress of a reaction continuously by spectrophotometry, conductometry, potentiometry or some other instrumental technique. With increasing availability of laboratory instrumentation, many kinetic studies have been studied by monitoring a physical property of a reaction mixture with time.\textsuperscript{4} There are many techniques available for kinetic studies viz. pulse methods, infrared spectroscopy (IR) and nuclear magnetic resonance spectroscopy (NMR). UV/Visible absorption spectroscopy and stopped-flow analysis are the techniques applied in this study hence ones discussed in the proceeding sections.

3.5.1 UV/Visible Spectrophotometry

In a UV/Visible spectrophotometer, light from a continuous light source is passed through a monochromator (a prism, grating or even a filter) which allows a single wavelength. The selected wavelength with an intensity, \( I_o \), strikes a sample in a cell called a cuvette of length, \( l \), and emerges with reduced intensity, \( I \), since the sample absorbs some light.\textsuperscript{4} A double-beam
spectrophotometer facilitates light to pass alternately through the sample and reference cuvettes with pure solvent. Having a reference cuvette with pure solvent is important as it compensates for absorption due to the cuvette and solvent or light scattering. A double-beam spectrophotometer, as shown in figure 1, alternates between cuvettes by using a chopper which is a motor that rotates a mirror into and out of the light path. When the chopper is not deflecting the beam, light passes through the sample and the detector measures the intensity; however, when the chopper deflects the beam through the reference cuvette, the detector reads the reference value i.e. the beam is chopped several times per second.

![Figure 3.1 A schematic diagram of a UV-Visible spectrophotometer.](image)

Transmittance, T, measured by a spectrophotometer is defined as the fraction of light passing through the sample given by equation 3.78,

\[
T = \frac{I}{I_o}
\]  

\[(3.78)\]
Where $I_o$ is intensity of incident radiation and $I$ is intensity of transmitted radiation

Absorbance, a more useful quantity because its directly related to concentration is given by equation 3.79,

$$A = \log \frac{I_o}{I} = -\log T$$

(3.79)

Absorbance is proportional to concentration hence more useful when expressed by by Beer’s law in equation 3.80,

$$A = \varepsilon CL$$

(3.80)

Where $A$ is optical absorbance (dimentionless), $\varepsilon$ is molar absorptivity ($M^{-1}cm^{-1}$), $C$ is concentration of the absorbing species (M) and $L$ is path length(cm)

Consider a simple first-order reaction illustrated by equation 3.81,

$$X \xrightarrow{k_i} Y$$

(3.81)

Absorbance after a time, $t$, will be given by equation 3.82,

$$A_t = \varepsilon_X[X] + \varepsilon_Y[Y]$$

(3.82)

Where $A_t$ is absorbance at time $t$ and $\varepsilon_X, \varepsilon_Y$ represent molar absorptivity of $X$ and $Y$ respectively

At the end of the reaction, the absorbance is given by equation 3.83,

$$A_\infty = \varepsilon_X[X]_0 + \varepsilon_Y[Y]_0$$

(3.83)

Where $A_\infty$ = absorbance at infinity
Kinetic analysis of a reaction represented by equation 3.81, can be done by the relation in equation 3.84,

$$\ln \left( \frac{[X]_0}{[Y]_0} \right) = \ln \left( \frac{A_0 - A_{\infty}}{A_i - A_{\infty}} \right) = k_t t$$

(3.84)

An example of the reaction profile obtained from the UV/Visible spectrophotometer for the substitution of chloride from $[\text{Pt}\{4'\text{-ethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl}]^+$ by imidazole (studied in chapter 3) at 298K is shown in figure 3.2. The reaction was monitored from 200-800nm wavelength.

![UV-Visible spectrum for the reaction of Imidazole (20 fold) with $[\text{Pt}\{4'\text{-ethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl}]^+$ in methanol at 298K. (inset is the respective kinetic trace)](image)

Figure 3.2 UV-Visible spectrum for the reaction of Imidazole (20 fold) with $[\text{Pt}\{4'\text{-ethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl}]^+$ in methanol at 298K. (inset is the respective kinetic trace)

### 3.5.2 Flow methods

Many reactions happen too quickly hence impossible to monitor by standard absorption spectroscopy. The commonly applied method to monitor these rapid reactions is stopped-flow mixing which involves mixing reagents rapidly and stopping the flow of the mixed solution suddenly allowing the progress of the reaction to be analysed near the mixer.$^9,11,19$

The working of the stopped-flow apparatus is illustrated in figure 3.3
Drive syringes are filled separately with the different reagents then the drive mechanism, which is usually piston driven, is activated causing the drive syringe plungers to go forward rapidly.\textsuperscript{19,27} The reagents then move into the mixer where there is rapid mixing within 0.001 s and the solution passes into the observation cell.\textsuperscript{19,27} The reaction solution then passes into the stop syringe until the stop syringe fills causing the plunger to strike the stop block instantly ceasing the flow, but leaving a recently mixed plug of solution in the observation cell.\textsuperscript{19,27}

The mixed solution is stationary in the observation cell allowing a recording device like an oscilloscope to take readings. The method of detection is UV/visible spectrophotometry. Once the recording device starts, the intensity of light transmitted through the observation chamber at a specific wavelength changes as the reaction proceeds to completion.\textsuperscript{19,27} A photomultiplier converts transmitted light into electric current interpreted by a computer as an absorption versus time spectrum which is analysed normally.\textsuperscript{19,27} The stopped-flow analysis is a simple technique with some advantages as it allows very rapid first order reaction constants to be measured, $k \approx 40 \text{ s}^{-1}$, easy to analyse which allows small ($\approx 0.2 \text{ ml}$) volumes of solutions to be used and permits the use of a number of different monitoring methods in conjunction with this technique.\textsuperscript{19}
3.6 References

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List of abbreviations

Å Angstrom
COD Cyclooctadiene
DFT Density functional theory
DIm 1,2-dimethylimidazole
eV Electronvolt
HF Hartree-Fock
HOMO Highest occupied molecular orbital
Im Imidazole
$k_2, k_2$ Rate constants
$k_{obs}$ Observed pseudo first-order constant
LUMO Lowest unoccupied molecular orbital
MIm 1-methylimidazole
NBO Natural bond order
NMR Nuclear magnetic resonance
Pt [Pt(2,2':6,2''-terpyridine)Cl]$^+$
Pt(deg) [Pt{4'-diethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl]$^+$
Pt(eg) [Pt{4'-ethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl]$^+$
Pt(teg) [Pt{4'-triethyleneglycoxyl)- 2,2':6,2''-terpyridine)Cl]$^+$
Pz Pyrazole
R Universal gas constant (8.3145JK$^{-1}$mol$^{-1}$)
T Absolute temperature (K) unless stated otherwise
terpy/tpy 2,2':6,2''-terpyridine
tpy(deg) 4'-[2-(2-Hydroxyethoxy)ethoxy]-2,2':6,2''-terpyridine
tpy(eg) 4'-[2-(2-Hydroxyethoxy)]-2,2':6,2''-terpyridine
tpy(teg) 4'-{2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy]-2,2':6,2''-terpyridine
Tz Triazole
UV Ultraviolet
VIS Visible
$\Delta G^\ne$ Gibbs free energy of activation
$\Delta H^\ne$ Activation enthalpy
$\Delta S^\ne$ Activation entropy
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Chapter 4

The role of ethylene polyglycoxyl pendant units on the terpy based Platinum(II) complexes. A kinetic and mechanistic study.

4.1 Abstract

The rate of Chloride substitution from \([\text{Pt}\{(4’-ethylglycoxyl)-2,2’:6’,2’’-terpyridine}\}\text{Cl}][\text{CF}_3\text{SO}_3], \text{Pt(eg)} \), \([\text{Pt}\{(4’-diethylglycoxyl)-2,2’:6’,2’’-terpyridine}\}\text{Cl}][\text{CF}_3\text{SO}_3], \text{Pt(deg)} \) and \([\text{Pt}\{(4’-triethylglycoxyl)-2,2’:6’,2’’-terpyridine}\}\text{Cl}][\text{CF}_3\text{SO}_3], \text{Pt(teg)} \) by a series of biological nitrogen donor nucleophiles, \text{viz.} pyrazole (\text{Pz}), triazole (\text{Tz}), imidazole (\text{Im}), 1-methylimidazole (\text{MIm}) and 1,2-dimethylimidazole (\text{DIm}) under pseudo-first-order conditions in methanol using UV/Visible spectrophotometry were investigated. The analysis of kinetic trend on the candidate complexes show that the first carbon-oxygen pendant bond plays a crucial role in regulating the electron density donated by the polyethyleneglycoxyl fragment. This is reflected in the significant reduction in reactivity from \text{Pt} to \text{Pt(eg)} followed by insignificant change in the reactivity as the chain length is increased. The trend in the reactivity slightly increases from \text{Pt(eg)} to \text{Pt(teg)} as the length of the polyethyleneglycoxyl is increased. This is attributed to reduction in steric hindrance imposed by the ethyleneglycoxyl unit. The reactivity of the nucleophiles is in line with the basicity and the steric hinderance.

The obtained kinetic data is supported by the DFT calculations that reveal a less electrophilic Pt(II) metal centre for complexes bearing the 4’-substituent. The temperature dependent studies support an associative mode of activation where bond formation in the transition state is favoured.
4.2 Introduction

The voluminous number of Pt(II) complexes synthesized in the preceding decades informs of continuing research with the focus on tuning reactivity and other properties of Pt(II) complexes with a view to widen the biological spectrum of cisplatin. Among the many synthesised compounds is 2,2’:6″,2″-terpyridine (tpy) whose derivatives are known to be good models for DNA intercalation. 2,2’:6″,2″-terpyridine (tpy) first synthesised by Morgan in 1932 readily reacts with Mn+ octahedral metal ions to give [M(tpy)2]n+ complexes. For [M(tpy)Cl]+ only the chloride ligand is labile due to the stable π-conjugated terpy ligand backbone, thus π-conjugation explains the greater reactivity of platinum(II) terpyridine complexes relative to the less conjugated Platinum(II) ethylenediamine. DNA-cisplatin adducts replication result to different strands of DNA with mutations leading to resistance which has elicited unmatched interest in substitution reactions of Pt(II) centre with nucleosides and other related compounds lately unlike earlier research that focused on knowing the mechanism of ligand substitution and binding mode of complexes with sulphur and nitrogen donor nucleophiles.

Research has shown that increasing the number of pyridine rings on the platinum (II) ethylenediamine increases its lability because the π-acceptor ability of subsequent complexes is enhanced. The π-back-bonding of the terpy ligand enables the additional electron density from the incoming nucleophile to the π-acceptor orbitals of the pyridine groups to be stabilized in the transition state compared to the ground state, a significant property of the terpy complexes. Recent attention has been paid to the mechanistic investigations into the substitution behaviour of platinum(II) terpy complexes with regard to the electronic tuning and the reactivity of the metal centre by changing the structure of the ligand. Constable and Housecroft have reported a variety of terpy ligands containing different functional groups at the 4’-position. Inclusion of these substituents alters the electronic as well as steric properties of the complexes. It is reported that different electron-withdrawing and donating groups change the electronic properties of the ruthenium complexes. Lowe et al. reported alteration of the electronic property of the terpy ligand on addition of substituents at the 4’ position. A check in literature reveals that lability of the chloride ligand depends on the strength of π-back-bonding properties of the spectator terpy ligand backbone. Substitution kinetics of [Pd(bpma)(H2O)]2+, [Pd(dien)(H2O)]2+ and [Pd(dien)Cl]+ (bpma-bis(2-pyridylmethyl)amine and dien-diethylenetriamine) with azoles were reported by Bugarcic et
al.. Pitteri et al. also reported on the kinetics of reversible displacement of the chloride from [Pt(terpy)Cl] by some pyridines and heterocyclic compounds.27-29

From a bioinorganic standpoint, azoles are essential given that the ligand histidine that binds to haemoproteins through its imidazole group is responsible for uptake of oxygen and electron transfer via cytochromes in plants and animals,29 hence the need to probe the substitution behaviour of azole nucleophiles.30,31 Furthermore, coordination chemists have a keen interest in imidazole and its derivatives because information on their ability to coordinate to metal complexes is linked to that of proton affinities in gaseous phase, aqueous solutions, aprotic solvents and hydrogen binding abilities.32-36

Data concerning the role of the π-acceptor ligands in the substitution reactions of square-planar platinum(II) complexes and the influence exerted by the substituents on the ancillary terpy ligand on the reactivity of these types of complexes37,38 in the literature has no mention on the effect on the reaction of [Pt(terpy)Cl]⁺ with polyglycoxyl at the 4’-position. It’s on this basis that we extended the research to explore the effect the polyglycoxyl substituents at the 4’-position on the terpy ligand system will have on the rate of chloride substitution using azoles as the incoming nucleophiles. DFT calculations were used to aid in the interpretation of kinetic results. It is envisaged that this paper will throw more light on the mechanism and kinetics of these complexes with azoles given their relevance in biological systems. The structural formulae of the platinum complexes investigated and the respective azole nucleophiles are shown in schemes 4.1 and 4.2 respectively.
**4.3 Experimental**

The Pt(II) complexes were synthesised in our group according to modified literature procedures. The chemical analysis, UV-VIS spectra and $^1$H NMR spectra data were in good agreement with those obtained in previous preparations. The purity of the ligands was confirmed by $^1$H NMR and mass spectroscopy. The $^1$H NMR spectra obtained are similar in the aromatic region for the ligands. The identity and the purity of the final complexes were confirmed by using $^1$H NMR, $^{13}$C NMR, $^{195}$Pt NMR, elemental analyses, IR and mass spectroscopy. Similarly the $^1$H NMR spectra of the complexes obtained show similarity in the aromatic region. Presence of a peak at about -2700 ppm on the $^{195}$Pt NMR spectra confirms the Pt(NNN) coordination. Representative $^1$H NMR, $^{13}$C NMR, $^{195}$Pt NMR, IR and mass spectra are given in figures SI 4.1-4.19 in the supporting information. The peak due to
the OH proton is not seen in any of the $^1$H NMR spectra due to the proton exchange with the methanol solvent.\textsuperscript{45(c)} IR spectra of the complexes show distinct broad bands at around 3200 to 3300 cm\textsuperscript{-1} due to the O-H stretches along with the C-H peaks at around 3000 cm\textsuperscript{-1}.\textsuperscript{45(d-f)}

4.3.1 Materials
Methanol bought from Merck was distilled over magnesium\textsuperscript{44(b)} prior to use for kinetic analysis. Dimethylsulfoxide (99.9\%) from Aldrich was used without any further purification. Ethylene glycol (99.8\%), diethylene glycol (99\%) and triethylene glycol (99\%) were bought from Sigma Aldrich. The ligand, 4'-chloro,2,2':6',2''-terpyridine (97\%), tetraethylene glycol (99\%), and the platinum salt, potassium tetrachloroplatinate(II) (99.9\%) were bought from Aldrich. All other chemicals were purchased from Sigma Aldrich and were used without further purification.

4.3.2 Synthesis of Ligands
The syntheses of ligands were carried out by literature procedures.\textsuperscript{39} To a suspension of KOH in dry DMSO at 50 °C was added the ethylene glycol and its respective polymer (n = 2, 3, 4) in excess to avoid the formation of the di-terpyridine ligand.\textsuperscript{39(c)} After stirring for 30 minutes, 4'-chloro-2,2':6',2''-terpyridine was added and the reaction mixture stirred for 20 hours at this temperature. Upon cooling to room temperature, the reacting mixture was treated with deionised water and filtered. The crude product was extracted from the filtrate in dichloromethane (3 x 30 mL) dried over anhydrous magnesium sulfate and the solvent removed. 4'-[2-(2-Hydroxyethoxy)ethoxy]-2,2':6',2''-terpyridine (tpy(eg)) and 4'-[2-(2-Hydroxyethoxy)ethoxy]-2,2':6',2''-terpyridine (tpy(deg)) gave a white paste and a white powder respectively. The respective crude products were purified in THF to give white solids. 4'-[2-(2-Hydroxyethoxy)ethoxy]ethoxy-2,2':6',2''-terpyridine (tpy(teg)) yielded pale yellow oil, pure enough for platination.

**tpy(eg)**
Yield: 250 mg, (70\%), off white paste. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$/ ppm: 8.63 (d, 2H, 6 6''), 8.55 (2H, d, 3 3''), 7.99 (2H, s, 3' 5''), 7.79 (dt, 2H, 4 4''), 7.29 (dt, 2H, 5 5''), 4.23 (t, 2H, CH2), 3.97 (t, 2H, CH2). $^{13}$C NMR (77 MHz, CDCl$_3$), $\delta$ / ppm: 61.1, 69.6, 107.6, 121.5, 123.8, 136.9, 148.9, 155.6, 157.2, 167.1. TOF MS-ES$^+$, m/z: 316.1062, (M + Na)$^+$. 
tpy(deg)
Yield: 190 mg, (80%), white powder. $^1$H NMR (400 MHz, CDCl$_3$) δ/ ppm: 8.69 (d, 2H, 6 6''), 8.62 (d, 2H, 3 3''), 8.13 (s, 2H, 3' 5''), 7.87 (t, 2H, 4 4''), 7.35 (t, 2H, 5 5''), 4.46 (t, 2H, CH2), 3.94 (t, 2H, CH2), 3.77 (t, 2H, CH2), 3.69 (t, 2H, CH2). $^{13}$C NMR (77MHz, CDCl$_3$), δ / ppm: 61.7, 68.1, 69.9, 72.8, 108.3, 121.6, 124.0, 137.1, 148.9, 155.7, 156.7, 167.3. Anal. Calc. for C$_{19}$H$_{19}$N$_3$O$_3$: C, 67.64; H, 5.68; N, 12.46; Found: C, 68.00; H, 5.81; N, 11.97. TOF MS-ES$^+$, m/z: 360.1324, (M + Na)$^+$. 

tpy(teg)
Yield: 175 mg, colourless oil (70%). $^1$H NMR (400 MHz, CDCl$_3$) δ/ ppm: 8.66 (d, 2H, 6 6''), 8.59 (d, 2H, 3 3''), 8.03 (s, 2H, 3' 5''), 7.83 (t, 2H, 4 4''), 7.31 (t, 2H, 5 5''), 4.40 (t, 2H, CH2), 3.92 (t, 2H, CH2), 3.73 (m, 4H, CH2), 3.69 (t, 2H, CH2), 3.60 (t, 2H, CH2). $^{13}$C NMR (77 MHz, CDCl$_3$), δ / ppm: 61.7, 67.9, 69.8, 70.4, 71.0, 72.9, 107.8, 121.4, 123.9, 136.9, 148.9, 155.9, 157.0, 167.1. TOF MS-ES$^+$, m/z: 404.1580, (M + Na)$^+$. 

4.3.3 Synthesis of Platinum(II) Complexes
The syntheses of the complexes was carried out using the following procedure: To a stirred solution of [Pt(COD)Cl$_2$]$^{60(a)}$ in dry methanol at room temperature, a suspension of the appropriate ligand in dry methanol was added at 55 °C. The reaction mixture was stirred for 24 hours at the same temperature, after which the solution was cooled and filtered. When the bright yellow filtrate was concentrated under vacuo, the desired compound precipitated as pale yellow solid. The compound was filtered, washed with chloroform (20 mL), cold methanol (1 x 5 mL), diethylether (2 x 15 mL) and dried and stored in a desiccator.

Pt(eg)
Yield: 35 mg, (55%), pale yellow powder. $^1$H NMR (400 MHz, CD$_3$OH) δ/ ppm: 10.23 (2H, d, 6 6''), 9.79 (2H, d, 3 3''), 9.78 (t, 2H, 4 4''), 9.39 (2H, s, 3' 5''), 9.20 (t, 2H, 5 5''), 5.88 (t, 2H, CH2), 5.44 (t, 2H, CH2). $^{195}$Pt NMR (CD$_3$OH) δ/ ppm: -2715. IR (4000-650 cm$^{-1}$) υ: 3237 (O-H), 3062 (C-H stretch), 1607 (C=H, pyridine), 1476 – 1423 (C-H stretch), 1222.43 (C-O), 788 (C-H stretch). Anal. Calc. for C$_{17}$H$_{15}$Cl$_2$N$_3$O$_2$: C, 36.51; H, 2.70; N, 7.51; Found: C, 36.38; H, 3.20; N, 7.92. TOF MS-ES$^+$, m/z: 524.0482, (M + 1)$^+$. 

4
Pt(deg)
Yield: 46 mg, (64%), crystalline yellow powder. $^1$H NMR (400 MHz, CD$_3$OH) δ/ ppm: 9.76 (d, 2H, 6 6’’), 9.67 (d, 4H, 3 3’’), 9.65 (t, 2H, 4 4’’), 9.17 (s, 2H, 3 5’’), 9.07 (t, 2H, 5 5’’), 5.87 (t, 2H, CH2), 5.38 (t, 2H, CH2), 5.21 (t, 2H, CH2), 5.11 (t, 2H, CH2). $^{13}$C NMR (77 MHz, CD$_3$OH), δ / ppm: 62.66, 69.93, 72.01, 74.07, 112.07, 126.95, 130.28, 142.73, 152.27, 156.70, 159.58, 170.89. $^{195}$Pt NMR (CD$_3$OH) δ/ ppm: -2705. IR (4000-650 cm$^{-1}$) $\nu$: 3338 (O-H), 3071 (C-H stretch), 1607 (C=H, pyridine), 1476 - 1430(C-H stretch), 1219 (C-O), 773(C-H stretch). Anal. Calc. for C$_{19}$H$_{21}$Cl$_2$N$_3$O$_4$: C, 37.73; H, 3.41; N, 6.76; Found: C, 37.35; H, 3.75; N, 6.34. TOF MS-ES$^+$, m/z: 568.0847, (M + 1)$^+$.

Pt(teg)
Yield: 38 mg, dark orange powder (60%). $^1$H NMR (400 MHz, CD$_3$OH) δ/ ppm: 9.98 (dd, 2H, 6 6’’), 9.73 (s, 2H, 3 5’’), 9.71 (d, 2H, 3 3’’), 9.29 (t, 2H, 4 4’’), 9.13 (t, 2H, 5 5’’), 5.90 (t, 2H, CH2), 5.40 (t, 2H, CH2), 5.22 (m, 2H, CH2), 5.14 (t, 2H, CH2), 5.11 (t, 2H, CH2), 5.04 (t, 2H, CH2). $^{195}$Pt NMR (CD$_3$OH) δ/ ppm: -2708. IR (4000-650 cm$^{-1}$) $\nu$: 3332 (O-H), 3071 (C-H stretch), 1607 (C=H, pyridine), 1448 – 1429 (C-H stretch), 1220 (C-O), 774 (C-H stretch). Anal. Calc. for C$_{21}$H$_{23}$Cl$_2$N$_3$O$_4$: C, 38.96; H, 3.58; N, 6.49; Found: C, 38.48; H, 3.41; N, 6.32. TOF MS-ES$^+$, m/z: 612.1027, (M + 1)$^+$.

4.3.4 Chemicals and solutions
Solutions of chloro-complexes were prepared by dissolving known amount of the complex in methanol solution of constant ionic strength ($I$=0.01M, (0.009M LiCF$_3$SO$_3$ + 0.001M LiCl)). Solutions of Pt(eg), Pt(deg) and Pt(teg) were dissolved to give platinum concentrations of $5.00 \times 10^{-5}$ M each. The 0.01 M ionic strength solution used to prepare complex and nucleophile solutions was made up of required amounts of LiCF$_3$SO$_3$ (0.009M) and LiCl (0.001M) dissolved in dry methanol since CF$_3$SO$_3^-$ does not coordinate to Pt(II). Lithium chloride was added to suppress spontaneous solvolytic reactions. Nucleophile solutions were prepared by dissolving a known amount of the required nucleophile in 50 mL of methanol solution of constant ionic strength to afford a concentration of ca. 100 times that of the metal complex. Subsequent dilutions of the stock solution were done to afford a series of standards of 80, 60, 40 and 20 times that of the platinum complex.
4.3.5 Physical measurements and instrumentation

Kinetic measurements were done using a Varian Carry 100 Bio UV-VIS spectrophotometer with an attached Varian Peltier temperature control unit with online kinetics application. All the UV-VIS spectrophotometric measurements were thermostatically controlled to within ± 0.1 °C. All kinetic measurements were performed under pseudo-first-order conditions \textit{i.e.}, at least 10 fold excess of nucleophile concentration was used. The spectral changes resulting from mixing of complex and ligand solutions were recorded over the wavelength range of 200 - 800 nm and a suitable wavelength at which kinetic measurements could be performed was determined. Reactions were initiated by mixing equal volumes of metal complex and azole solutions in a tandem cuvette on the UV-visible spectrophotometer and the rate of complex formation was followed by monitoring the decrease in absorbance at 310 nm. All the kinetic measurements are reproducible within the limits of error of ± 0.5%. The quoted values are the average of three runs under identical experimental conditions. Figure 4.1 shows an absorbance spectrum for the reaction of $\text{Pt(eg)}$ and $\text{Im}$ at 298 K and \textit{inset} is a kinetic trace obtained for the same reaction at 298 K. Other kinetic traces were presented in the supplementary information figures SI 4.17-4.22. Data for $\text{Pt}^{60}$ was incorporated for comparison purposes.
The observed *pseudo* first-order rate constants, $k_{obs}$, were obtained from kinetic traces applying the online non-linear least-squares fit using equation 1

$$A_t = A_0 + (A_0 - A_\infty)e^{-kt_{obs}} \quad (1)$$

Where; $A_0$ is initial absorbance of the mixture, $A_t$ is absorbance of the reaction mixture at time, $t$ and $A_\infty$ is final absorbance. Second order rate constant, $k_2$, for the forward reaction and the solvolytic rate constant, $k_{-2}$, for each one of the Pt(II) complexes with a respective nucleophile were obtained from the slope and intercept respectively of the graph of $k_{obs}$ verses nucleophile concentration drawn from graphical analysis software package, Origin 7.5® from the relationship illustrated by equation 4.2

$$k_{obs} = k_2[Nu] + k_{-2} \approx k_2[Nu] \quad (4.2)$$

A typical plot of $k_{obs}$ verses $[Nu]$ is shown by figure 4.2 for the substitution reactions of Pt(eg) with Im, Pz and Tz. Other concentration dependence plots are presented in the
supplementary information figures SI 4.20, 4.22 and 4.24. Data for the concentration dependence is presented in supplementary information tables SI 4.1-4.3.

Figure 4.2  Concentration dependence plots to determine $k_2$ and $k_{-2}$ from the reaction of \textbf{Pt(deg)} with \textbf{Im}, \textbf{Pz} and \textbf{Tz} at 298K.

The temperature dependence of the rate constants were studied over the temperature range of 20-40° C in increments of 5° C. Graphs of $\ln \left( \frac{k_2}{T} \right)$ verses $\frac{1}{T}$ were plotted using Origin 7.5® from which activation parameters, enthalpy of activation, $\Delta H^\neq$ and entropy of activation, $\Delta S^\neq$ were obtained by applying the slope and the intercept respectively to the Eyring equation 3 where the letters represent their usual meaning.

$$\ln \frac{k_2}{T} = \left( \frac{\Delta H^\neq}{R} \right) \frac{1}{T} + \left( 23.8 + \frac{\Delta S^\neq}{R} \right) \hspace{1cm} (3)$$

A typical Eyring plot is shown in figure 4.3 for the reaction of \textbf{Pt(eg)} with \textbf{MIm}, \textbf{DIm} and \textbf{Tz}. Other Eyring plots are presented in the supplementary information figures SI 4.21, 4.23 and 4.25. Respective data for Eyring plots is presented in the supplementary information tables SI 4.4-4.6.
4.3.6 Computational details

To gain further insight on the structural and electronic differences among the complexes in this study, computational calculations were done at the DFT level of theory that has been applied by other researchers.\textsuperscript{47-50} DFT calculation data in systems that contain transition metals have shown better agreement with experimental data than that obtained from Hartree–Fock (HF) calculations.\textsuperscript{51} The LANL2DZ basis set was employed in the current case because it is known to provide reliable results in systems of this nature.\textsuperscript{50,52-55} Singlet states were used due to the low electronic spin of Pt(II) complexes. The frontier molecular orbitals of the complexes were generated in Gauss view 5.0 applying the same level of theory. The Gaussian09 suite of programs was used for all DFT computations.\textsuperscript{56} A summary of the DFT calculated frontier HOMO and LUMO molecular orbitals of the complexes in the study are shown in table 4.1 while the data processed for the complexes is included in table 4.2.

Figure 4.3 Eyring plots for the reaction of \textit{Pt(eg)} with \textit{MIm}, \textit{DIm} and \textit{Tz}
Table 4.1  DFT-calculated frontier molecular orbitals of the investigated Pt(II) complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Lowest energy structure</th>
<th>Map</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HOMO</td>
</tr>
<tr>
<td>Pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt(eg)</td>
<td></td>
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<tr>
<td>Pt(deg)</td>
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<td></td>
</tr>
<tr>
<td>Pt(tec)</td>
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</tr>
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</table>
Table 4.2  Computational data of the complexes investigated

<table>
<thead>
<tr>
<th>Property</th>
<th>Pt</th>
<th>Pt(eg)</th>
<th>Pt(deg)</th>
<th>Pt(tec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bond lengths (Å)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Trans N-Pt</td>
<td>1.961</td>
<td>1.960</td>
<td>1.960</td>
<td>1.960</td>
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<tr>
<td>Cis N-Pt</td>
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<tr>
<td>Pt-Cl</td>
<td>2.443</td>
<td>2.444</td>
<td>2.444</td>
<td>2.442</td>
</tr>
<tr>
<td>C7 – O21, x, (Å)</td>
<td>-</td>
<td>1.369</td>
<td>1.369</td>
<td>1.369</td>
</tr>
<tr>
<td><strong>Angles (°)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bite</td>
<td>161.90</td>
<td>161.69</td>
<td>161.70</td>
<td>161.71</td>
</tr>
<tr>
<td>Trans N-Pt-Cl</td>
<td>179.99</td>
<td>179.76</td>
<td>179.77</td>
<td>179.81</td>
</tr>
<tr>
<td>Angle of elevation ,a, of the ethylene glycoxy pendant. (°)</td>
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<td>36.44</td>
<td>19.38</td>
</tr>
<tr>
<td>C7 O21 C22, a, (°)</td>
<td>-</td>
<td>120.2</td>
<td>120.5</td>
<td>120.7</td>
</tr>
<tr>
<td><strong>Energy (eV)</strong></td>
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<td></td>
</tr>
<tr>
<td>LUMO</td>
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<td>-3.23</td>
<td>-3.23</td>
<td>-3.23</td>
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<tr>
<td>HOMO</td>
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<td>-6.89</td>
<td>-6.89</td>
<td>-6.89</td>
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<td>ΔE_{LUMO-HOMO}</td>
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<td><strong>NBO Charges</strong></td>
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<tr>
<td>Pt$^+$</td>
<td>0.605</td>
<td>0.591</td>
<td>0.591</td>
<td>0.590</td>
</tr>
<tr>
<td>N(trans)</td>
<td>-0.453</td>
<td>-0.471</td>
<td>-0.470</td>
<td>-0.471</td>
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<tr>
<td>Dipole moment (D)</td>
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<td>11.51</td>
<td>10.72</td>
<td>6.83</td>
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<tr>
<td>Electronic chemical potential (µ)</td>
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<td>-5.06</td>
<td>-5.06</td>
<td>-5.06</td>
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<tr>
<td>Electrophilicity index (ω)</td>
<td>7.31</td>
<td>6.94</td>
<td>6.97</td>
<td>7.00</td>
</tr>
<tr>
<td>Chemical hardness (η)</td>
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<td>1.83</td>
<td>1.83</td>
<td>1.83</td>
</tr>
<tr>
<td><strong>Point group</strong></td>
<td>C₁</td>
<td>C₁</td>
<td>C₁</td>
<td>C₁</td>
</tr>
</tbody>
</table>
\[ \alpha = 120.7^\circ, \ a = 19.38^\circ \ x = 1.369\text{Å} \]

Figure 4.4  DFT calculated angles around the oxygen atoms on the polyglycoxy group of Pt (teg)

### 4.3.7 Kinetic analysis

Substitution of the coordinated chloride from Pt(eg), Pt(deg) and Pt(teg) by the azole nucleophiles *viz* imidazole, 1,2-dimethylimidazole, pyrazole, 1,2,4-triazole and 1-methylimidazole was investigated. UV-visible spectrophotometry was used to track the progress of the reaction. All the kinetic traces were described by single exponentials with the *pseudo* first order rate constants calculated from the traces plotted against the concentration of incoming nucleophiles giving straight lines with negligible intercepts (figure 4.2). Values of second order rate constant, \(k_2\), representing direct attack of by nucleophile according to equation 4.2 are shown in table 4.3. Solvolytic rate constants, \(k_{-2}\), values are infinitesimal (averagely \(10^5\) times less than \(k_2\)) showing that the reaction proceeds predominantly by the direct attack by nucleophile. The proposed mechanism of substitution for the studied complexes can be represented by scheme 4.3.
Scheme 4.3 Proposed mechanism of substitution for the studied complexes.

### 4.4 Results and discussion

Table 4.3 Rate constants and activation parameters for Pt(II) complexes with the azole nucleophiles.

<table>
<thead>
<tr>
<th>Complex + Nu</th>
<th>$k_2$ (M$^{-1}$s$^{-1}$)</th>
<th>$\Delta H^\circ$ (Kj mol$^{-1}$)</th>
<th>$\Delta S^\circ$ (JK$^{-1}$mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt$^*$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazole</td>
<td>3.98 ± 0.05</td>
<td>41 ± 3</td>
<td>-96 ± 10</td>
</tr>
<tr>
<td>Pyrazole</td>
<td>2.25 ± 0.11</td>
<td>42 ± 1</td>
<td>-96 ± 5</td>
</tr>
<tr>
<td>1-methylimidazole</td>
<td>3.84 ± 0.04</td>
<td>42 ± 2</td>
<td>-91 ± 5</td>
</tr>
<tr>
<td>1,2-dimethylimidazole</td>
<td>1.62 ± 0.04</td>
<td>46 ± 1</td>
<td>-88 ± 3</td>
</tr>
<tr>
<td>1,2,4-triazole</td>
<td>1.04 ± 0.07</td>
<td>40 ± 2</td>
<td>-107 ± 6</td>
</tr>
<tr>
<td>Pt(eg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.610 ± 0.01</td>
<td>64 ± 3</td>
<td>-33 ± 10</td>
</tr>
<tr>
<td>Pyrazole</td>
<td>0.209 ± 0.004</td>
<td>59 ± 2</td>
<td>-55 ± 6</td>
</tr>
<tr>
<td>1-methylimidazole</td>
<td>0.734 ± 0.11</td>
<td>54 ± 1</td>
<td>-64 ± 3</td>
</tr>
<tr>
<td>1,2-dimethylimidazole</td>
<td>0.269 ± 0.004</td>
<td>67 ± 3</td>
<td>-31 ± 9</td>
</tr>
<tr>
<td>1,2,4-triazole</td>
<td>0.180 ± 0.01</td>
<td>71 ± 1</td>
<td>-21 ± 3</td>
</tr>
<tr>
<td>Pt(deg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.611 ± 0.01</td>
<td>69 ± 3</td>
<td>-16 ± 10</td>
</tr>
<tr>
<td>Pyrazole</td>
<td>0.226 ± 0.01</td>
<td>59 ± 1</td>
<td>-57 ± 3</td>
</tr>
<tr>
<td>1-methylimidazole</td>
<td>0.740 ± 0.02</td>
<td>57 ± 1</td>
<td>-56 ± 3</td>
</tr>
<tr>
<td>1,2-dimethylimidazole</td>
<td>0.284 ± 0.01</td>
<td>61 ± 3</td>
<td>-49 ± 9</td>
</tr>
<tr>
<td>1,2,4-triazole</td>
<td>0.185 ± 0.004</td>
<td>62 ± 1</td>
<td>-50 ± 5</td>
</tr>
<tr>
<td>Pt(teg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.612 ± 0.02</td>
<td>62 ± 1</td>
<td>-40 ± 4</td>
</tr>
<tr>
<td>Pyrazole</td>
<td>0.242 ± 0.01</td>
<td>58 ± 2</td>
<td>-59 ± 5</td>
</tr>
<tr>
<td>1-methylimidazole</td>
<td>0.760 ± 0.02</td>
<td>65 ± 2</td>
<td>-28 ± 5</td>
</tr>
<tr>
<td>1,2-dimethylimidazole</td>
<td>0.293 ± 0.01</td>
<td>55 ± 1</td>
<td>-69 ± 3</td>
</tr>
<tr>
<td>1,2,4-triazole</td>
<td>0.158 ± 0.004</td>
<td>63 ± 2</td>
<td>-47 ± 5</td>
</tr>
</tbody>
</table>

(*) data extracted from Ref. 60 (b)

The data in table 4.3 indicate higher reactivity for Pt$^*$ complex than Pt(eg), Pt(deg) and Pt(teg). There is about six fold drop in the reactivity for most studied nucleophiles when the ethylene glycoxy unit is added in the 4’-position revealing that the substituent donate
electron-density towards the terpy system. The lone pair of electrons on the first oxygen atom (O21 figure 4.4) is in close proximity to the extended π-conjugation of the terpyridyl unit allowing greater delocalization into the pyridyl rings. Donation of electron density towards the Pt(II) centre is also reflected in the raised LUMO energy of Pt(eg) (-3.23 eV) compared to that of Pt (-3.35 eV) (table 4.2) which makes it harder for π-back donation for Pt(eg). The higher enthalpy of activation of Pt(eg) (table 4.3) also lends credence to its lower reactivity arising from the effects of electron donation hence higher energy is now needed to form the transition state complex. The π-donation along with σ-electron donation increases the negative charge on the trans nitrogen atom (table 4.2) of Pt(eg) compared to Pt and thus lowers the charge on the Pt(II) centre from 0.605 to 0.591 as well as the electrophilicity of the complex which changes from 7.31 to 6.94 revealing that there is electron flow towards the metal centre which can be accounted for in terms of trans-effect.

The C7- O21 (figure 4.4) bond length (1.369Å) (table 4.2) is shorter than the other C-O bonds (range 1.456 - 1.467Å) also reported elsewhere, further, α (figure 4.4) angles of about 120° indicate that the oxygen atom (figure 4.4) has sp² character and hence proves delocalization of the lone pair of electron into the π-system of the terpy. The donation of electron-density to the terpyridyl rings reduces the π-accepter capabilities of terpy bearing the polyglycoxyl substituents causing the platinum centre and the whole complex to be less electropositive hence less reactive. The dipole moments of the Pt(II) complexes (table 4.2) corroborate the fact that the terpy unit of Pt has highest extended π-withdrawing character hence most electropositive platinum centre. The substituent in the 4’-position on Pt(eg) being inclined at an angle of 120° introduces steric hindrance on one side of this complex unlike in Pt without any substituent. The inclined pendant hinders nucleophiles approaching the complex from the axial position an additional contribution to the reduction in the reactivity.

The reactivity remains fairly constant on addition of other substituents with more ethylene glycoxyl units in the 4’-position (table 4.3) for the studied complexes. A similar trend is observed for all the other incoming nucleophiles. One would have expected the reactivity to decrease due to increase in electron donation as the chain length increases but from DFT calculations, the charges on Pt(II) centre and on the trans nitrogen atom remain constant for Pt(eg), Pt(deg) and Pt(teg) indicating that there is no further electronic effects as the ethylene glycoxy unit grows beyond the first glycol unit. Even the global electrophilicity indices show insignificant increase with increase in the length of the pendant (table 4.2). It
can then be concluded that after the first glycol unit, both electronic and steric hindrance have minimal or no influence on the reactivity of the complexes. This is despite the angles of inclination, \( a \), for \( \text{Pt(eg)} \), \( \text{Pt(deg)} \) and \( \text{Pt(teg)} \) decreasing from 37.55°, 36.44° and 19.38° respectively (table 4.2). Very weak intra-molecular hydrogen bonding interactions between the lone pairs of electrons on the oxygen atoms and neighbouring hydrogen atoms as shown in figure 4.5. \(^{58(c)}\)

\[ \text{Attractioin between lone pairs of electrons and adjacent hydrogen atoms} \]

![Figure 4.5 Hydrogen bonding interactions in the polyglycoxyl pendant](image)

While the predominant factor remains electron donation to the terpyridyl ring, the stabilization by hydrogen bonding actually seems to play a significant role as increase in chain length of the glycol unit from \( \text{Pt(eg)} \) to \( \text{Pt(deg)} \) and \( \text{Pt(teg)} \) resulted in increase in \( k_2 \) values for all the nucleophiles.

It’s worth noting that while the electron density in the chain increases with the increase in the chain length of the appended group; the donation of electron density towards the Pt atom becomes less effective as the chain length of the pendant increases. \(^{59}\) The geometry of the platinum centres remains distorted square-planar with bite angles of 160 – 161° (table 4.2), a slight deviation from planarity typical of Pt(II) square planar complexes. \(^{60}\) Table 4.2 has a summary of calculated bond lengths, energies of frontier molecular orbitals and electron density surrounding the Pt(II) centre for each of the Pt(II) complexes. It can be observed that the introduction of the ethylene glycoxyl units has negligible influence on the structural differences which was also observed by others working with similar compounds. \(^{60}\) There is decrease in the positive charge (electrophilicity) on the Pt(II) centre on introduction of the polyglycoxyl units as already observed due to electron donation hence decrease in reactivity an effect previously noted in similar complexes. \(^{61,62}\) The DFT-calculated ground-state
orbitals in table 4.1 show that the addition of the glycoxyl units causes the electron density of the HOMO to be centred above and below the Pt(II) metal centre and towards the glycoxyl substituent along the trans axis causing a less electrophilic metal centre, an effect reported by other researchers as well. The electrophilicity index changes from Pt(7.31), to Pt(eg)(6.94), Pt(deg)(6.97) and Pt(teg)(7.00) (table 4.2) an indication Pt is the strongest electrophile compared to the rest of the nucleophiles.

The trend in the reactivity of the nucleophiles investigated is Im > Py > Tz also observed in other reports. The decrease in the reactivity correlates with their basicities; 7.00, 2.52 and 2.19 respectively though the trend is non-linear because Tz is unique as a result of its tautomerism even though the 1H form is predominant. The reactivity of the other set of nucleophiles follows the order; MIm > Im > DIm having basicities of 7.30, 7.00 and 7.85 respectively. The reactivity doesn’t correlate with the basicities because steric hindrance brought about by the presence of methyl groups on DIm comes into play. The overall trend in reactivity for the nucleophiles is MIm > Im > DIm > Py > Tz consistent with their respective basicities except for DIm because of its steric bulk.

The observed trend agrees with previous studies on [Pd(terpy)Cl]⁺ and [Pt(terpy)Cl]⁺ complexes with pyridines and [Pt(terpy)Cl]⁺ complex with five membered N-donor heterocyclic ligands. The magnitude of steric effects is attributed to the free rotation of the ligand around the Pt-N(azole) bond. In the associative mode of reaction, the Pt-N(azole) bond is well formed and Pt-Cl bond weakened at the transition state, the trigonal bipyramidal intermediate contains pyridine rings on either side of the terpy in axial positions where the pyridyl protons sterically interact with α-methyl protons of the incoming nucleophiles which impede free rotation of the just formed Pt-N(azole) bond effectively retarding the reaction. The effects of bulky azoles affect the energy of both ground state and transition state complexes hence the observed reaction rate (table 4.3). Steric hindrance due to interaction between α-substituted methyl with solvent that causes charge dispersion through hydrogen bonding with solvent reducing basicity of the nucleophile in solution could have played a role in the slow reaction of DIm. The higher reactivity of MIm is due to the inductive effects of the methyl group attached to N1 of the imidazole ring that results in the donation of electrons from the methyl group to N3 making it more basic. Since the methyl in MIm is further from the pyridyl rings on the terpy, steric congestion in the transition state is unlikely.
or minimal. For DIm, steric effects prevail over inductive effects of the methyl groups,\textsuperscript{69,72} accounting for the difference in reactivities.

The intercepts were insignificantly small indicating that the reverse reactions are very slow or absent the reason being that the Pt-N(azole) bond formed is stabilized by the $\pi$-back-bonding with the Pt(II) centre.\textsuperscript{27} Values of enthalpy of activation, $\Delta H^\ddagger$, are relatively low while those of entropy of activation, $\Delta S^\ddagger$, are large and negative confirming an associative mode of substitution typical of Pt(II) square planar complexes.\textsuperscript{73-76}
4.5 Conclusions

This study clearly reveals that electron donation towards the terpy chelate by the 4’-substituted polyglycoxyl units decreases the \( \pi \)-accepter ability of the chelate making the platinum centre of these complexes less electrophilic retarding their ligand substitutions reactions when compared to that of Pt. The electron donation is only effective up to the first oxygen atom (O21 figure 4.4) beyond which no significant electronic effect affect the Pt(II) centre. The overall decrease in reactivity from Pt to Pt(eg) mostly due to the electronic effect and to a minimal extent the steric factor. The reactivity of the nucleophiles is controlled by the basicity and steric hindrance, with the more basic nucleophiles being more reactive but steric factors come into play for the bulky nucleophiles.
4.6 References


68. B. Pitteri and M. Bortoluzzi, *polyhedron*, 2006, **25**, 2698
4.7 Supplementary Information

NMR, IR and mass spectra for ligands and complexes. Additionally, observed pseudo-first order rate constants, $k_{\text{obs}}$, at different concentrations and temperatures, concentration and temperature dependence plots for Pt(eg), Pt(deg) and Pt(tec) and UV-visible kinetic traces.

Figure SI 4.1 $^1$H NMR spectrum of tpy(eg) in CDCl$_3$. 
Figure SI 4.2 $^3\text{C}$ Spectrum of $\text{tpy(eg)}$ in CDCl$_3$.

Figure SI 4.3 $^1\text{H}$ NMR and $^{195}\text{Pt}$ NMR spectra of $\text{Pt(eg)}$
Figure SI 4.4  $^1$H NMR spectrum of tpy(deg) in CDCl$_3$.

Figure SI 4.5  $^{13}$C NMR spectrum of tpy(deg) in CDCl$_3$. 
Figure SI 4.6 \( ^1\text{H} \) NMR and \( ^{195}\text{Pt} \) NMR spectra of \textbf{Pt(deg)}.

Figure SI 4.7 \( ^{13}\text{C} \) NMR spectrum of \textbf{Pt(deg)}
Figure SI 4.8  $^1$H NMR spectrum of tpy(teg) in CDCl$_3$.

Figure SI 4.9  $^{13}$C NMR spectrum of tpy(teg) in CDCl$_3$. 
Figure SI 4.10 $^1$HNMR and $^{195}$Pt NMR spectra of of Pt(teg).

Figure SI 4.11 Low resolution ESI mass spectrum of tpy(eg).
Figure SI 4.12  Low resolution ESI mass spectrum of tpy(deg).

Figure SI 4.13  Low resolution ESI mass spectrum of tpy(teg).
Figure SI 4.14  Low resolution ESI mass spectrum of Pt(eg).

Figure SI 4.15  Low resolution ESI mass spectrum of Pt(deg).
Figure SI 4.16  Low resolution ESI mass spectrum of Pt(teg).

Figure SI 4.17  IR Spectrum of Pt(eg).
Figure SI 4.18  IR Spectrum of Pt(deg).

Figure SI 4.19  IR Spectrum of Pt(teg).
Table SI 4.1  Average observed rate constants, $k_{\text{obs}}/\text{s}^{-1}$, for the substitution of chloride from $\text{Pt(eg)}$ by azole nucleophiles in methanolic solution at 298K

<table>
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<tr>
<th>[Nu]/M</th>
<th>$k_{\text{obs}}/\text{s}^{-1}$ X10^4</th>
<th>[Nu]/M</th>
<th>$k_{\text{obs}}/\text{s}^{-1}$ X10^4</th>
<th>[Nu]/M</th>
<th>$k_{\text{obs}}/\text{s}^{-1}$ X10^4</th>
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Table SI 4.2  Average observed rate constants, $k_{\text{obs}}/\text{s}^{-1}$, for the substitution of chloride from $\text{Pt(deg)}$ by azole nucleophiles in methanolic solution at 298K

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<th>[Nu]/M</th>
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Table SI 4.3  Average observed rate constants, $k_{\text{obs}}/\text{s}^{-1}$, for the substitution of chloride from $\text{Pt(eg)}$ by azole nucleophiles in methanolic solution at 298K

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<th>[Nu]/M</th>
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Table SI 4.4 Temperature dependence of $k_2$/M$^{-1}$s$^{-1}$ for the substitution of chloride from Pt(eg) by azole nucleophiles at 60 fold excess [metal complex] in methanolic solution at 298K.

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<th>$\text{Pz} (\lambda=310\text{nm})$</th>
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Table SI 4.5 Temperature dependence of $k_2$/M$^{-1}$s$^{-1}$ for the substitution of chloride from Pt(deg) by azole nucleophiles at 60 fold excess [metal complex] at 298K.

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<th>$\text{DIm} (\lambda=310\text{nm})$</th>
<th>$\text{Pz} (\lambda=310\text{nm})$</th>
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Table SI 4.6 Temperature dependence of $k_2$/M$^{-1}$s$^{-1}$ for the substitution of chloride from Pt(tec) by azole nucleophiles at 60 fold excess [metal complex] in methanolic solution at 298K.

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Figure SI 4.20 Concentration dependence plots for the chloride substitution on Pt(eg) in methanol solution at 298K

Figure SI 4.21 Eyring plots for the reactions of Pt(eg) with the azole nucleophiles at different temperatures in the range 20-40°C
Figure SI 4.22 Concentration dependence plots of for the chloride substitution on Pt(deg) in methanol solution at 298K

Figure SI 4.23 Eyring plots for the reactions of Pt(deg) with the azole nucleophiles at different temperatures in the range 20-40°C
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Figure SI 4.29  The kinetic trace for the reaction of \textbf{Pt(deg)} with 60 folds \textbf{Tz} in methanol at 293K
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List of abbreviations

- LUMO: Lowest unoccupied molecular orbital
- HOMO: Highest occupied molecular orbital
- DNA: Deoxyribonucleic acid
- 5'-GMP: Guanosine-5'-monophosphate
- DEDTC: Diethyldithiocarbamate
- DFT: Density functional theory
- GSH: Glutathione
- $k_2$: Rate constants
- $k_{obs}$: Observed pseudo first-order constant
- mM: Millimolar
- NBO: Natural bond order
- Nu: Nucleophile
- [Nu]: Nucleophile concentration
- Pt1: $[\text{Pt(en)OH}_2]^{2+}$
- Pt2: $[\text{H}_2\text{O}(\text{en})\text{Pt(qpy)Ru(tpy)})]^{4+}$
- Pt3: $[\text{H}_2\text{O}(\text{en})\text{Pt(qpy)Ru(qpy)Pt(en)OH}_2]^{6+}$
- Pt1-Cl: $[\text{Pt(en)Cl}]^{+}$
- Pt2-Cl: $[\text{Cl(en)Pt(qpy)Ru(tpy)})]^{3+}$
- Pt3-Cl: $[\text{Cl(en)Pt(qpy)Ru(qpy)Pt(en)Cl}]^{4+}$
- py: Pyridine
- qpy: Quarterpyridine (4’-(pyridyl) 2,2’:6,2’’-terpyridine)
- T: Absolute temperature (K) unless stated otherwise
- terpy/tpy: 2,2’:6,2’’-terpyridine
- TU: Thiourea
- UV: Ultraviolet
- $\Delta H^\ddagger$: Activation enthalpy
- $\Delta S^\ddagger$: Activation entropy
- L-met: L-methionine
- en: Ethylenediamine
- NMR: Nuclear magnetic resonance
- MLCT: Metal to ligand charge transfer
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Chapter 5

The role of Ruthenium Polypyridyl fragment on the reactivity of ethylene Pt(II) aqua units with biological nucleophiles.

5.1 Abstract

Thermodynamic and kinetic study of Ru(II)-Pt(II) complexes with a semi-rigid linker 4’-pyridyl-2,2’:6’,2’’terpyridine (qpy) with biological nucleophiles was carried out under pseudo first-order conditions as a function of concentration and temperature using UV-visible spectrophotometer. The reactions proceeded via a single step following first-order kinetics with the pseudo first-order rate constant obeying the rate law; \( k_{\text{obs}} = k_2 [\text{Nu}] \). The study revealed that increase in the overall charges of the respective complexes is the key reason for the observed increase in the reactivity. Additionally, replacing the cis pyridyl group in Pt1 by Ru(III) polypyridyl to give Pt2 and Pt3 respectively lowers the energy of the LUMO (\( \pi^* \)) orbitals and HOMO-LUMO energy gap which influences the reactivity to some extent. The two qpy groups in the trinuclear complex Pt3 only slightly increases the reactivity from that of Pt2 because the qpy groups are in orthogonal positions preventing \( \pi \)-electron communication hence the two Pt(II) centres act independently of each other. The marginal increase in reactivity is due to increased charge and extension of the \( \pi \)-surface. The observed activation parameters support an associative mode of substitution.
5.2 Introduction

For the last two decades, platinum based chemotherapeutic regiments have been the mainstay in the treatment of cancer, diabetes and alzheimer’s among others. The discovery of the anti-tumour activity of cisplatin elicited further research efforts towards more effective and wide-spectra drugs for the cure of cancer. To this effect thousands of platinum complexes have been synthesised and evaluated for anti-tumour activity, though only few have entered clinical use. Cisplatin is responsible for the cure of over 90% of testicular cancer cases and plays a vital role in the treatment of other forms of cancer.

The binding of platinum complexes to S-containing bio-molecules in the cell before reaching target DNA molecule produces toxic effects though a certain amount of the Pt drug eventually binds to N-donor biomolecules (amino acids or DNA) a mechanism which is now accepted to be responsible for the anti-cancer activity. The interactions with mitochondrial DNA are less responsible for the anti-tumour activity of the platinum complexes. Different modes of binding exist but binding to DNA primarily occurs through the N7 atom of guanine. The concentration of the thiols including glutathione (GSH) and L-cysteine in intracellular liquid is about 10 mM, it is assumed that most of the Platinum drug binds to sulphur before it reaches the DNA. The resulting Pt–S(thioether) bond may be broken in the presence of DNA, i.e. the N7 atom of guanosine-5'-monophosphate (5'-GMP) can substitute the S-donor. For these reasons the S-bound Pt(II) complexes are Pt-reservoirs in the body. On the other hand, Pt(II) complexes can bind to sulphur from thiol molecules with the resulting Pt–S(thiol) bond being very stable and compounds of this type are responsible for the occurrence of toxic side effects and resistance during the use of Pt(II) complexes as anti-tumour agents. However the Pt–S(thiol) bond can be broken in the presence of “rescue agents”, which are exclusively S-containing compounds, such as diethylthiocarbamate (DEDTC), thiourea (TU), thiosulfate, glutathione(GSH), cysteine, biotin and amifostine. Pt(IV) complexes being slower in reaction than Pt(II) complexes can act as precursors and undergo reduction within the body to form active Pt(II) species.

On the other hand ruthenium complexes have been suitable candidates to fill the shortcomings of platinum based drugs as exhibited by cisplatin. Ruthenium complexes are very promising; given the fact that they overcome cisplatin resistant cell-lines with a low general toxicity and have found their way into the clinic, where their properties are exploited for many
The wide range of accessible oxidation states of ruthenium under physiological conditions makes this metal unique amongst the platinum group. For instance Ru(II) and Ru(III) show antitumor activity and chemical toxicity different from those of platinum. Their tendency to selectively bind bio-molecules partly accounts for their low toxicity. Selectivity is enhanced due to the complexes binding to transferin and albumen that are usually supplied to cancerous and other diseased cell with great demand for iron which exposes the complexes to the target cells. A lot of ruthenium complex groups have been synthesized namely; amino-chlorido, ruthenium polyamino carboxylate, organoruthenium and photoreactive ruthenium complexes.

It is therefore instructive that a combination of different metal centres provides a hybrid of properties which are advantageous for instance, platinum-ruthenium hetero-dinuclear complexes have the capacity to select and sequentially react with particular DNA sequences due to their unique interactions facilitating unique DNA modification. In addition, the presence of non-binding metal centres in hetero-dinuclear metallic complexes considered has shown to increase the overall cationic charge thus enhancing their water solubility. Furthermore, they also photo react with DNA through a light absorbing ruthenium metal centre which transfers the energy to the binding metal centre thus enhancing its reactivity. These advantageous effects that results from hetero-dinuclear complexes inspired us to do a mechanistic investigation on the Pt(II)–Ru(III) complexes.

Two of the complexes used in this study consist of a bis(terpyridyl)-ruthenium(III) moiety, and one or two platinum-ethylenediamine centres, which coordinate to the fourth pyridine ligand of quarterpyridine and the third complex has a pyridyl coordinating to the platinum-ethylenediamine centre. The hetero-polynuclear ruthenium-platinum complexes has short and semi-rigid linking ligand 4’-pyridyl-2,2’;6’,2’’-terpyridine (quaterpyridine or qpy) which presents a tridentate coordination site, and coordinate to a second metal via the fourth pyridine appended at the 4’-position of the terpyridine. The non-coordinated pyridyl groups of the bis(quaterpyridine) ruthenium complex have been shown to react with a range of electrophiles. The bis(terpyridyl)-ruthenium(III) moiety, a constituent of two of the complexes can photo-react with DNA and subsequent energy transfer activates the platinum unit, which can coordinate to DNA.
We used biologically relevant nucleophiles viz. guanosine 5'-monophosphate (5'-GMP), L-methionine (L-Met) and reduced glutathione (GSH) for the kinetic investigation. The nucleophiles were selected based on the difference in nucleophilicity, steric hindrance, binding properties and biological relevance. The reactions were studied in aqueous solution using UV-visible spectrophotometric techniques. It is envisaged that this paper will throw more light on the mechanisms of interaction of the platinum(II) complexes with N- and S-donor ligands, give a better understanding on mechanistic competition between S- and N-donor ligands and reveal the role of the ruthenium polypyridyl fragment on the reactivity of the Pt(II) metal centre. The molecular structures of the studied complexes and nucleophiles are shown in scheme 5.1.

**Complexes**

![Pt1](image1)

![Pt2](image2)

![Pt3](image3)

**Nucleophiles**

![GSH](image4)

![5'-GMP](image5)

![L-met](image6)

Scheme 5.1 Structural formulae of the biological nucleophiles and the Pt(II) complexes.\(^{86,87}\)
5.3 Experimental

5.3.1 Synthesis

The complexes; [Pt(en)OH$_2$], [H$_2$O(en)PtqtpyRutpy] and [H$_2$O(en)PtqtpyRuqtpyPt(en)OH$_2$] were prepared according to the literature methods.$^{88(a),89}$ Chemical analysis, UV-visible and $^1$H NMR spectral data were in good agreement with those obtained in previous preparations.$^{88}$ Experimental procedures for 0.1 M Ru(III) solution,$^{88(a)}$ the Ru complexes, [Ru(tpy)Cl$_3$],$^{88(b)}$ and [Ru(qpy)Cl$_3$],$^{88(a)}$ are summarized under Supporting Information (experimental SI). The details of the characterisation and spectroscopic data for ligands and complexes are included in the experimental section and also under Supporting Information figures 5.1- 5.14. Due to the poor solubility$^{89(d)}$ and the paramagnetic nature of [Ru(tpy)Cl$_3$]$^{88(b)}$ and [Ru(qpy)Cl$_3$],$^{88(a)}$ the two precursors were used as synthesized.$^{85}$

5.3.2 Materials

Buffer standards of pH 4.0, 7.0 and 10.0 were bought from Merck. ruthenium(III)chloride trihydrate (99%),1,5-cyclooctadiene and 4’-chloro-2,2’:6’,2” terpyridine (99%) were purchased from Aldrich. All other chemicals were purchased from Sigma Aldrich and used as received. For preparation of all aqueous solutions, ultra-pure water was used. The ruthenium precursors; [Ru(tpy)Cl$_3$],$^{88(b)}$ [Ru(qpy)Cl$_3$]$^{88(a)}$ and 0.1 M Ru(III) solution$^{88(a)}$ were synthesized as described in literature.

5.3.3 Synthesis of Ligand and Ruthenium Moieties

5.3.3.1 4’-pyridyl-2,2’:6’,2”-terpyridine (qpy)

The ligand, 4’-pyridyl-2,2’:6’,2”-terpyridine (qpy) was synthesized as in literature.$^{88(c)}$ 2-acetylpypyridine (5 g, 4.13 mol), was added to a suspension of NaOH in polyethylene glycol (PEG 300) (35 mL) and the reaction mixture was stirred for 10 minutes at 0 °C. 4-pyridine carboxaldehyde (2.21 g, 2.06 mol) was added to the suspension and left at 0°C for 2 hours. The reaction mixture was stirred manually in every 15 minutes due to the high viscosity of the reaction mixture. After this time, excess NH$_4$OAc (10 g) was added and the suspension was heated at 100 °C for 2 hours. Brown precipitate was formed from the initially formed red solution. Water (75 mL) was added to the precipitate. The precipitate was filtered, washed with more water (50 mL) followed by cold ethanol (10 mL). The ligand was recrystallized from ethanol. Yield: 0.509 g, (70%), Colourless needles. $^1$H NMR (400 MHz, CDCl$_3$) δ/ ppm:

- 8.79 (2H, m, 2’’’ 6’’’),
- 8.77 (2H, s, 3’ 5’),
- 8.74 (2H, br dm, 6 6’’),
- 8.67 (2H, dd, 3 3’’),
- 7.90
(2H, td, 4 4’’), 7.80 (2H, dd, 3’’’ 5’’’’), 7.39 (2H, ddd, 5, 5’’’). TOF MS-ES+, m/z: 333.1114, (M+Na)+.

5.3.3.2 Ru(qpy)(tpy)Cl₂

This ruthenium moiety was synthesized by a slight modification of the literature method. To a filtered solution of AgBF₄ (240 mg; 1.232 mmol) in acetone (15 mL), [Ru(tpy)Cl₃] (40 mg; 0.080 mmol) was added. The reaction mixture was refluxed for 18 hours in the dark after which the precipitated AgCl was removed by filtration. The filtrate was concentrated to 1 mL in vacuo. Into the resulting green oil the ligand qpy (43 mg, 0.148mmol) was added and the mixture was refluxed for 2 hours in DMF (20 mL) which reduced Ru(III) to Ru(II). The reaction mixture was filtered and concentrated in vacuo to (1.0 mL) which gave red oil. A saturated solution of LiCl (2 mL) in EtOH was added to the red oil. A precipitate was formed on adding the oil to acetone (200 mL). The precipitate obtained was purified by column chromatography on neutral alumina using CH₃CN: EtOH (50: 50) as the eluent. The first red band was collected and was lyophilised with diethylether. Recrystallization of the precipitate with a mixture of MeOH and diethylether yielded a relatively pure product. Yield: 35 mg, 0.0489 mmol (61%), Dark red powder. ¹H NMR (400 MHz, DMSO-d₆) δ/ ppm: 9.58 (2H, s, I3’ 5’’), 9.12 (2H, d, I33”), 9.10 (2H, s, II3’ 5’’), 8.99 (2H, d, I2’’’’ 6’’’’), 8.85 (2H, d, II3 3’), 8.56 (2H, t, II4”), 8.45 (2H, d, I3’’’’, 5’’’”), 8.09 (2H, t, 144”), 8.03 (2H, t, II4 4”), 7.52 (2H, d, II6 6’’), 7.46 (2H, d, I6 6’”), 7.30 (2H, t, I5 5’”), 7.25 (2H, t, II5 5’’). TOF MS-ES+, m/z: 366.5616, (M²+).


5.3.3.3 [Ru(qpy)₂]Cl₂

The ruthenium moiety was synthesized by a slight modification of the literature method. To a filtered solution of AgBF₄ (350 mg; 1.798 mmol) in acetone (20 mL), [Ru(qpy)Cl₃] (68.9 mg; 0.133 mmol) was added. The reaction mixture was refluxed for 18 hours in the dark after which the precipitated AgCl was removed by filtration. The filtrate was concentrated to 1 mL in vacuo. To the resulting green oil, the ligand qpy (46 mg, 0.147 mmol) was added and the mixture was refluxed for 2 hours in DMF (25 mL) which reduced Ru(III) to Ru(II). The reaction mixture was cooled to room temperature and filtered. The red filtrate was reduced to 1 mL to afford red oil. A saturated solution of LiCl (6 mL) in EtOH was then added to the red oil. A precipitate was formed on adding acetone (400 mL). The precipitate was purified by column chromatography on neutral alumina using acetone: MeOH: EtOH (3: 6: 1) as the
eluent. The first red band was collected and lyophilized with diethylether gave a relatively pure product. Yield: 50 mg, (46 %), Dark maroon powder. $^1$H NMR (400 MHz, DMSO$_{d_6}$) $\delta$/ ppm: 9.61 (2H, s, 3’ 5’), 9.12 (2H, d, 2”’ 6”’), 9.00 (2H, d, 3”’), 8.45 (2H, d, 3”’ 5”’), 8.09 (2H, t, 4”’), 7.57 (2H, d, 6 6’’), 7.29 (2H, t, 5 5’’). TOF MS-ES$^+$, m/z: 361.1088, (M$^2$+).


5.3.3.4 **Pt(en)Cl$_2$**

The platinum complex precursor was synthesized following a literature procedure.$^{89(b)}$ Into an aqueous solution of K$_2$PtCl$_4$ (125 mg, 0.300 mmol), an aqueous solution of ethane-1,2-diamine (0.018, 0.300 mmol) was added drop wise. The pH of the solution was brought to 6. The reaction mixture was stirred at 313 K. During the reaction, the pH of the solution was maintained between 5- 6 using 0.1 M NaOH. The reaction was stopped when the pH of the solution no longer changed. The yellow precipitate which formed was filtered, washed with water and ethanol and dried. Yield: 0. 068 g, (70%), yellow powder. $^1$HNMR (400 MHz, DMF) $\delta$/ ppm: 5.54 (4H, br , NH), 2.79 (4H, br), 195 Pt (-3298).

5.3.4 **Synthesis of Platinum(II) Complexes**

The platinum complexes, Pt1-Cl, Pt2-Cl and Pt3-Cl were synthesized following a similar approach reported in literature.$^{88(a)}$

5.3.4.1 **Pt1-Cl**

The compound was synthesized by a slight modification of the literature method.$^{88(a)}$ To a stirred solution of [Pt(en)Cl$_2$] (42 mg; 0.126 mmol) in 10 mL of DMF at 310 K, silver nitrate (AgNO$_3$) (21 mg, 0.126 mmol) in dimethylformamide (DMF) (5 mL) was added drop wise. The reaction mixture was stirred for 24 hours at 313 K. After filtration of silver chloride (AgCl) precipitate using a 0.45 $\mu$m nylon membrane filter (Millipore), pyridine (0.010 mL, 0.126 mmol) was added to the filtrate and the mixture was stirred for another 18 hours. The reaction mixture was filtered and co-evaporated using EtOH/MeOH (v: v = 50:50) (20 mL) to remove DMF. The precipitate was dissolved in MeOH. The product was precipitated by slow diffusion of diethyl ether. Yield: 0. 032 g, (60%), off-white crystalline powder. $^1$H NMR (400 MHz, DMF) $\delta$/ ppm: 8.62 (2H, dd , $J$= 6.9, 1.4), 7.89 (1H, tt, $J$= 7.8, 1.5), 7.40 (2H, br), 6.04 (2H, br), 5.65 (2H, br), 3.01 (2H, t), 2.92 (2H, br), 195Pt NMR (500 MHz, DMF) $\delta$/ ppm: -2501. TOF MS-ES$^+$, m/z: 369.0449, (M$^+$). Anal. Calc. For C$_{7}$H$_{13}$ClN$_4$O$_3$Pt: C 19.47, N 12.98, H 2.96. Found: C 19.21, N 12.51, H 2.98.
The purity and the identity of the complexes were confirmed by $^1$H NMR, $^{195}$Pt NMR, mass spectroscopy and elemental analyses. The $^{195}$Pt NMR of all the complexes exhibited a characteristic signal at about -2500 ppm, typical to platinum coordinated to NNN chelate and a chloride. Due to the high charge and complexity of the complexes, the mass spectra obtained show characteristic fragmentations.

5.3.4.2 Pt2-Cl

Yield: 28 mg (15 %), Dark red powder. $^1$H NMR (400 MHz, D$_2$O) δ/ ppm: 9.11 (2H, s, I3 ' 5''), 9.00 (2H, d, I2''' 6''''), 8.78 (2H, d, I3' 5''), 8.61 (2H, d, I3 3'''), 8.50 (2H, d, II3 3'''), 8.42 (2H, t, II4''), 8.25 (2H, d, I3''' 5'''''), 7.93 (2H, t, I4 4'''), 7.89 (2H, t, II4 4'''), 7.45 (2H, d, II6 6'''), 7.35 (2H, d, I6 6''), 7.17 (2H, t, I5 5''), 7.11 (2H, t, II5 5''), 2.73 (2H, br, b), 2.66 (2H, br, c), $^{195}$Pt NMR (500 MHz, D$_2$O) δ/ ppm: -2530. TOF MS-ES$^+$, m/z: 322.5963, (for water substituted M$^{4+}$). Anal. Calc. For C$_{37}$H$_{33}$ClN$_{12}$O$_9$ PtRu·4H$_2$O: C 37.24, N 14.08 , H 3.46. Found: C 36.81, N 13.76, H 3.01.

5.3.4.3 Pt3-Cl

Yield: 0.035 g, (22 %), dark red powder. $^1$H NMR (400 MHz, D$_2$O) δ/ ppm: 9.13 (2H, s, I3' 5''), 9.01 (2H, d, I2''' 6'''''), 8.62 (2H, d, I3 3'''''), 8.25 (2H, d, I3''' 5''''), 7.93 (2H, t, I4 4'''''), 7.45 (2H, d, I6 6'''''), 7.17 (2H, t, I5 5'''''), 2.80 (2H, br, b), 2.73 (2H, br c) $^{195}$Pt NMR (500 MHz, D$_2$O) δ/ ppm: -2532. TOF MS-ES$^+$, m/z: 2901.0024, (for water substituted M$^{6+}$-H$_2$O). Anal. Calc. For C$_{44}$H$_{44}$C$_{12}$N$_{16}$O$_{12}$ PtRu·5H$_2$O: C 32.90, N 13.95, H 3.64. Found: C 32.69, N 13.98, H 3.31.

5.3.5 Preparation of Aqua Complexes

The desired solutions for kinetic studies of aqua complexes (Pt1, Pt2 and Pt3) were Prepared according to the literature procedure which is summarized in scheme 5.2. To a stirred solution of the Pt(II) compound (Pt1-Cl, Pt2-Cl and Pt3-Cl) (0.4 mmol) in 0.01 M triflic acid (CF$_3$SO$_3$H) (40 mL) was added silver triflate (AgSO$_3$CF$_3$) (equal amounts for mono chloro complexes, (Pt1-Cl and Pt2-Cl) and 2 equivalents for the di-chloro complex, (Pt3-Cl)). The mixture was stirred for 24 hours at 50° C in the dark. The precipitated silver chloride was removed by filtration using a 0.45 μm nylon membrane filter (Millipore). The filtrate was made up to 100 mL using 0.01 M CF$_3$SO$_3$H which had an ionic strength of 0.02 M adjusted with LiSO$_3$CF$_3$. For all kinetic studies, the pH of the solution was kept at pH 2, ionic strength
of 0.02 M adjusted with lithium triflate (LiSO$_3$CF$_3$). A pH of 2 was chosen to prevent the formation of the hydroxo species which are inert.$^{89(c)}$

$$\text{[PtL(Cl)$_x$]}^{n+} + x\text{AgCF$_3$SO}_3 \xrightarrow{24\text{hours reflux}} \text{[PtL(H$_2$O)$_x$]}^{(n+1)+} + x\text{AgCl}$$

Where; $L = \text{py(en)}$ for Pt$_1$-Cl, tpyRu(qpy)en for Pt$_2$-Cl and Pt(en)$_2$(qpy)Ru for Pt$_3$-Cl, $x = 1$ for Pt$_1$-Cl and Pt$_2$-Cl and 2 for Pt$_3$-Cl, $n = 1$ for Pt$_1$-Cl, 3 for Pt$_2$-Cl and 5 for Pt$_3$-Cl

Scheme 5.2 Aquation of the complexes

5.3.6 Chemical solutions

The nucleophiles quanosine-5-monophosphate sodium salt hydrate ($5'$-GMP), L-methionine (L-met), and reduced glutathione (GSH) were obtained from Sigma-Aldrich and used as received. Nucleophile stock solutions were prepared shortly before use by dissolving the chemicals in the aqua solvent. All other chemicals were of analytical reagent grade and ultra-pure water was used in preparation of all solutions. Since methanesulfonate ions do not coordinate to Pt(II) and Ru(III) in aqueous solution,$^{90}$ the kinetics of ligand substitution reaction were studied in 0.01M lithium methanesulfonate.

5.3.7 Instrumentation

$^1$H NMR were recorded on either a Bruker Avance DPX 400 or 500 MHz spectrometer, at 303 K using Si(CH$_3$)$_4$ as the reference for the chemical shifts. $^{195}$Pt NMR were done on a 500 MHz spectrometer ($^{195}$Pt, 107.5 MHz) and chemical shifts externally referenced to K$_2$[PtCl$_6$]. Low resolution electron spray ionization (ESI$^+$) mass spectra were recorded on a TOF Micromass spectrometer. Elemental analyses were performed by a Thermal Scientific Flash 2000. UV-visible spectra and kinetic measurements were done on varian Cary 100 Bio UV-visible spectrophotometer with an attached varian in thermostated 1.00 cm quartz suprasil cells the temperature was controlled throughout all kinetic experiments to ± 0.1°C.

5.3.8 Kinetic measurements

Spectral changes resulting from mixing complexes and nucleophile solutions respectively were recorded over the wavelength range of 200-800nm to establish a suitable wavelength at which kinetic measurements could be performed. Respective values of wavelength for the corresponding complexes are presented in supporting information table 5.1. The ligand substitution reactions were studied for the nucleophiles: GSH, L-met, and $5'$-GMP. Reactions
were initiated by mixing equal volumes of the metal complex and ligand thermo-stated solutions in the UV-visible Spectrophotometric cell and the rate of complex formation was followed by monitoring the decrease in absorbance or otherwise. All kinetic measurements were performed under pseudo-first-order conditions with at least a 10-fold excess of the entering nucleophile being used. The values of reported pseudo-first-order rate constants are the average of three kinetic measurements. Kinetic runs were performed at pH 2 to ensure the aqua species is the one reacting based on the pKa values. The pH of the solution was adjusted by adding minute amounts of 0.01M triflic acid to the solution to lower the pH to the require value. A sample of the UV-visible spectrum for the reaction of Pt3 with L-met is shown in figure 5.1 (inset is the respective kinetic trace at 310nm).

![UV-visible spectrum of Pt3 and L-met](image)

Figure 5.1  UV-visible spectrum of Pt3 (3.432 x 10^{-5}M) and L-met (200 fold) in 0.02M LiCF3SO3 at 298K

Other kinetic traces are presented in supporting information figures SI 5.24-5.41. In all cases, substitution reactions fitted to a single exponential equation. Observed pseudo first order constant, $k_{obs}$, values changed linearly with nucleophile concentrations with plots having small but noticeable intercepts; an indication that $k_2 \approx 0$. This means that the back reaction for the studied reactions is negligible; implying that substitution of the attached nucleophile is not effective.
\[ k_{\text{obs}} = k_2 [\text{Nu}] + k_{-2} [\text{Nu}] \approx k_2 [\text{Nu}] \]  

(5.1)

The proposed reaction mechanism therefore is as presented in equation 5.2.

\[ \text{PtL(OH}_2\text{)}_x + x\text{Nu} \xrightarrow{k_2} \text{PtL(Nu)}_x + x\text{H}_2\text{O} \]  

(5.2)

Where; \(X = 1\) for \(\text{Pt}1\) and \(\text{Pt}2\) and \(2\) for \(\text{Pt}3\), \(\text{Nu} = \text{GSH, L-met or GMP}\) and \(L = \text{py(en)}\) for \(\text{Pt}1\) tpyRuqpy(en) for \(\text{Pt}2\) and \(\text{Pt(en)2(qpy)}_2\text{Ru}\) for \(\text{Pt}3\)

A sample of concentration dependence plots is shown in figure 5.2. Other concentration dependent plots are presented in supporting information figures SI 5.15-5.20. Tables showing respective values of nucleophile concentration and \(k_{\text{obs}}\) are presented in tables SI 5.2-5.4.

Figure 5.2 Concentration dependence plots for the substitution of aqua ligand in \(\text{Pt}2\) with GSH and L-met nucleophiles.

Slopes of the concentration dependence plots represented the second order rate constants, \(k_2\), at 25°C for the direct attack pathway summarised in table 5.3. The temperature dependence of the second order rate constants studied over the temperature range of 20-40°C in intervals of 5°C enabled the calculation of thermodynamic activation parameters; enthalpy of activation, \(\Delta H^\circ\) and entropy of activation, \(\Delta S^\circ\) by applying the Eyring equation whose values are summarised in table 5.3. Representative Eyring plots are shown in figure 5.3 while the rest
of the plots are presented in supporting information figures SI 5.21-5.23. Respective values of $\ln(k_2/T)$ and $T^{-1}/K^{-1}$ are presented in tables SI 5.5-5.7

$$\ln(k_2/T)$$

Figure 5.3 Eyring plots for the reaction of the complexes with L-met in the range of 20 - 40°C

5.3.9 Computational modelling

Density functional theory (DFT) was performed using Gaussian 09 suite of programs at the DFT B3LYP/LanL2DZ level of theory.\textsuperscript{91} Pt(II) have low electronic spin hence the DFT calculations of the complexes were done at singlet state. Table 5.1 shows minimum energy structures and frontier molecular orbitals of the studied complexes. A Summary of bond lengths, bond angles, DFT-calculated NBO charges, HOMO and LUMO energies plus other parameters obtained from the modelled structures of the platinum-ruthenium complexes are presented in table 5.2.
Table 5.1  DFT calculated minimum energy structures and frontier molecular orbitals (HOMO and LUMO) of the studied complexes

<table>
<thead>
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<th>Structures</th>
<th>HOMO Map</th>
<th>LUMO Map</th>
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<tbody>
<tr>
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<td><img src="image2" alt="Pt1 LUMO Map" /></td>
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<tr>
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<td><img src="image5" alt="Pt3 HOMO Map" /></td>
<td><img src="image6" alt="Pt3 LUMO Map" /></td>
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</tbody>
</table>

Complexes **Pt1** and **Pt2** have both $C_1$ symmetry while **Pt3** has $C_2$ symmetry. DFT calculations (table 5.2) reveal slightly distorted square planar structures around the Pt (II) centres typical of Pt (NNN) centres.\(^9\) As expected, the ruthenium centre takes up distorted octahedral coordination geometry with $\text{trans}$ angles ranging from 158° to 180° (table 5.2) common in octahedral complexes.\(^9\),\(^9\) Bond lengths (table 5.2) are comparable to corresponding bond lengths of other Ru(II) complexes containing tridentate 2,2:2',2''-terpyridine ligands.\(^9\),\(^9\) The DFT calculated structures in table 5.1 show that the 4'-'pyridyl group on the qpy is out of the plane with the terpy ligand backbone bonded to Ru(II) expected to reduce anticipated steric strain when the hydrogens on the 4'-pyridyl group and those on the central pyridine interact an observation reported in previous studies.\(^9\),\(^9\)
Table 5.2  Summary of DFT calculated data for the studied complexes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pt1</th>
<th>Pt2</th>
<th>Pt3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bond lengths (Å)</strong></td>
<td></td>
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<tr>
<td>Pt-OH₂</td>
<td>2.110</td>
<td>2.111</td>
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<tr>
<td><strong>Bond angles (°)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N&lt;sub&gt;cis&lt;/sub&gt;-Pt-N&lt;sub&gt;cis&lt;/sub&gt;</td>
<td>177.51</td>
<td>177.95</td>
<td>178.16</td>
</tr>
<tr>
<td>OH₂-Pt-N&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>174.51</td>
<td>175.36</td>
<td>174.99</td>
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<tr>
<td><strong>NBO charges</strong></td>
<td></td>
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<tr>
<td>Pt</td>
<td>0.736</td>
<td>0.740</td>
<td>0.742</td>
</tr>
<tr>
<td>Ru</td>
<td>-</td>
<td>0.315</td>
<td>0.320</td>
</tr>
<tr>
<td>N&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>-0.831</td>
<td>-0.837</td>
<td>-0.812</td>
</tr>
<tr>
<td>N&lt;sub&gt;cis(py)&lt;/sub&gt;</td>
<td>-0.516</td>
<td>-0.510</td>
<td>-0.510</td>
</tr>
<tr>
<td>N&lt;sub&gt;cis(NH₂)&lt;/sub&gt;</td>
<td>-0.837</td>
<td>-0.812</td>
<td>-0.812</td>
</tr>
<tr>
<td><strong>Orbital energy (eV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMO</td>
<td>-7.00</td>
<td>-6.30</td>
<td>-6.40</td>
</tr>
<tr>
<td>LUMO</td>
<td>-2.11</td>
<td>-3.16</td>
<td>-3.25</td>
</tr>
<tr>
<td>ΔE&lt;sub&gt;HOMO-LUMO&lt;/sub&gt;</td>
<td>4.89</td>
<td>3.14</td>
<td>3.15</td>
</tr>
<tr>
<td>η/eV</td>
<td>2.44</td>
<td>1.57</td>
<td>1.58</td>
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<tr>
<td>µ/eV</td>
<td>-4.56</td>
<td>-4.73</td>
<td>-4.83</td>
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<td>ω/eV</td>
<td>4.25</td>
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</tr>
<tr>
<td><strong>Point group</strong></td>
<td>C₁</td>
<td>C₂</td>
<td>C₂</td>
</tr>
</tbody>
</table>

<sup>µ</sup> - Chemical potential, η – Chemical hardness and ω – global electrophilicity index

Figure 5.4 shows the different nitrogen atoms referred to in table 5.2

![Structural formular](image)

Figure 5.4  Structural formular of Pt2 showing the different N-atoms around the Pt(II) centre.

Due to steric interactions between the pyridyl and trans-amino protons in Pt₁, the pyridyl group lies in a plane almost perpendicular (87.93°) to the plane containing Pt and N atoms reducing π-back bonding between Pt(II) centre and the cis pyridyl entity hence lower electrophilicity of the platinum centre. DFT calculated HOMO electron density of Pt₁ lies
predominantly on the Pt(II) centre while that for Pt2 and Pt3 complexes lies on the Ru(II) centre and sparsely distributed on the pyridyl ligands but none on the Pt(II) centre resulting Pt2 and Pt3 being slightly electrophilic than Pt1. The LUMO electron density in table 5.1 comprises MLCT (Metal-to-ligand charge transfer) which is concentrated on the pyridyl group in Pt1 and on the qpy ligand in the case of Pt2 and Pt3 complexes. The incorporation of Ru(II) moiety narrows the HOMO-LUMO energy gap as is evident from the DFT calculations in table 5.2. The $k_2$ values for Pt2 and Pt3 are close indicating that the doubling of the ligand qpy doesn’t cause a significant effect to the rate of reaction because the qpy-tpy and qpy-qpy ligands in Pt2 and Pt3 respectively are oriented in planes perpendicular (89.58°) to each other hence no π communication that should have led to extended π-conjugation. 

5.4 Results and discussion

To investigate the impact of the ruthenium polypyridyl ligands on the reactivity of the platinum centre and the competition between the S- and N-ligands, ligand substitution reactions of the metal complexes with the chosen nucleophiles; GMP, L-met and GSH were studied. The experiment on the dependence of reactions on nucleophile concentrations and temperature resulted in rate constants and activation parameters enthalpy of activation, $\Delta H^\ddagger$, and entropy of activation, $\Delta S^\ddagger$, for the displacement of coordinated water as shown in table 5.3.

<table>
<thead>
<tr>
<th>Complex +[Nu]</th>
<th>$k_2$ (M$^{-1}$ s$^{-1}$)</th>
<th>$k_3$ (s$^{-1}$)</th>
<th>$\Delta H_2^\ddagger$ (kJ mol$^{-1}$)</th>
<th>$\Delta S_2^\ddagger$ (JK$^{-1}$mol$^{-1}$)</th>
<th>K/(M$^{-1}$)(k$3$/$k2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1 GMP</td>
<td>0.050 ± 0.001</td>
<td>(6.39 ± 0.2) x 10$^{-6}$</td>
<td>50 ± 1</td>
<td>-91 ± 3</td>
<td>7825</td>
</tr>
<tr>
<td>L-met</td>
<td>0.034 ± 0.001</td>
<td>(-7.76 ± 5.1) x 10$^{-6}$</td>
<td>72 ± 1</td>
<td>-32 ± 3</td>
<td>4381</td>
</tr>
<tr>
<td>GSH</td>
<td>0.005 ± 0.0001</td>
<td>(2.63 ± 0.1) x 10$^{-5}$</td>
<td>77 ± 1</td>
<td>-26 ± 3</td>
<td>190</td>
</tr>
<tr>
<td>Pt2 GMP</td>
<td>0.059 ± 0.002</td>
<td>(3.36 ± 0.2) x 10$^{-5}$</td>
<td>68 ± 1</td>
<td>-36 ± 4</td>
<td>1756</td>
</tr>
<tr>
<td>L-met</td>
<td>0.058 ± 0.002</td>
<td>(5.32 ± 0.3) x 10$^{-5}$</td>
<td>62 ± 1</td>
<td>-58 ± 3</td>
<td>1090</td>
</tr>
<tr>
<td>GSH</td>
<td>0.008 ± 0.0001</td>
<td>(1.10 ± 0.1) x 10$^{-5}$</td>
<td>75 ± 1</td>
<td>-23 ± 3</td>
<td>727</td>
</tr>
<tr>
<td>Pt3 GMP</td>
<td>0.057 ± 0.002</td>
<td>(4.16 ± 0.1) x 10$^{-5}$</td>
<td>64 ± 1</td>
<td>-47 ± 3</td>
<td>1370</td>
</tr>
<tr>
<td>L-met</td>
<td>0.065 ± 0.002</td>
<td>(2.64 ± 0.4) x 10$^{-5}$</td>
<td>43 ± 1</td>
<td>-122 ± 4</td>
<td>2462</td>
</tr>
<tr>
<td>GSH</td>
<td>0.010 ± 0.0001</td>
<td>(1.77 ± 0.1) x 10$^{-5}$</td>
<td>62 ± 1</td>
<td>-66 ± 3</td>
<td>565</td>
</tr>
</tbody>
</table>

The substitution reactions of the Pt(II) complexes with the biological nucleophiles studied as a function of nucleophile concentration at 25° C on the UV-visible spectrophotometer showed
only one reaction step in all cases. The hetero-dinuclear complex \textbf{Pt3}, is symmetrical as observed from the DFT calculated structures with the platinum nuclei far apart (22.31\AA) which makes them act independent of each other an observation reported in other studies for dinuclear complexes.\textsuperscript{98} To confirm the simultaneous substitution on \textbf{Pt3}, the complex was subjected to \textsuperscript{195}Pt NMR spectroscopy at 303 K with excess GSH in deuterated water, and the results are displayed by the NMR arrays in figure 5.5.

![NMR Arrays](image)

Where \textbf{A} is the platinum signal due to the starting complex while \textbf{B} platinum signals corresponding to the formation of PtN\textsubscript{3}S core.

Figure 5.5 \textsuperscript{195}Pt NMR arrays of \textbf{Pt-CI} with excess GSH.

Prior to addition of the nucleophile a signal is observed at $\delta \approx -2530$ ppm\textsuperscript{88} due to the starting complex \textbf{Pt3}. A new signal is observed up-field at $\delta \approx -3020$ ppm confirming the formation of PtN\textsubscript{3}S core.\textsuperscript{99} The \textsuperscript{195}Pt NMR results confirm that the aqua ligands in \textbf{Pt3} are substituted simultaneously. Since there was no shift in the Pt peak after a further 48 hrs, it can be concluded that no dechelation is induced by the substituted S-donor nucleophile, an observation similar to that done with thiourea nucleophiles.\textsuperscript{100}

From the $k_2$ values in table 5.3, the replacement of the pyridyl of Pt(en)py in \textbf{Pt1} with tpy(Ru)qpy to form \textbf{Pt2} through the 4’- pyridine of the qpy increases slightly the reactivity of the Pt(II) centre with the studied nucleophiles. The rate constants, $k_2$, for the reaction of \textbf{Pt1}, \textbf{Pt2} and \textbf{Pt3} with L-met are 0.034M\textsuperscript{-1}s\textsuperscript{-1}, 0.058M\textsuperscript{-1}s\textsuperscript{-1} and 0.065M\textsuperscript{-1}s\textsuperscript{-1} respectively. Using \textbf{Pt1} as reference the ratio is 1: 1.7: 1.9 respectively. The trend for the reaction of the Pt(II) complexes with the rest of the nucleophiles also indicate that the reactivity increases in the order \textbf{Pt1} < \textbf{Pt2} < \textbf{Pt3} for most studied nucleophiles. The increase in overall charge of the complexes \textbf{Pt1}(+2) and \textbf{Pt2}(+4) due to addition of the tpy(Ru)qpy(+2) increases the overall electrophilicity of the complex as shown by the global electrophilicity index, $\omega$, in table 5.2 resulting in enhancing reactivity from \textbf{Pt1} to \textbf{Pt3}. Additionally, the tridentate coordination of
the qpy to ruthenium enhances the electronic transitions from the Pt(II) metal centre towards the pyridyl group due to lowering of the energy of the LUMO \( \pi^* \) orbitals.\textsuperscript{101,101,102}

The slight increase in Pt-N\(_{\text{cis}(\text{py})}\) bond length from Pt\(_1\) (2.051 Å) to Pt\(_2\) (2.057 Å) (table 5.2) is attributed to pulling of \( \sigma \)-bonding electrons towards the qpy linker, contributing to the slight increase in the positive charge on the Pt(II) metal centre in both Pt\(_2\) and Pt\(_3\). This shows that the introduction of the qpy ligand enhances to a slight extent electronic transition (MLCT) of the Pt(II) centre.

The introduction of Ru(III) terpyridyl complex results in the narrowing of the HOMO-LUMO energy gap from Pt\(_1\) (4.89 eV) to Pt\(_2\) (3.14 eV) \( \approx \) Pt\(_3\) (3.15 eV) making it easier to transfer electrons from the ground state HOMO to the empty LUMO (\( \pi^* \)).\textsuperscript{94,96,101,102} This also accounts for the slight increase in reactivity. Pt\(_3\) is only slightly more reactive than Pt\(_2\) despite the increase in the overall charge. This is because the linker, qpy(Ru)qpy does not allow \( \pi \)-communication between the back-to-back coordinated qpy ligands that would have increased the reactivity. This means that the observed reactivity is independent of each side of the qpy since they are aligned orthogonal to each other at the Ru(III) metal centre. Thus the higher overall charge of Pt\(_3\) (+6) account for the slight increase in the observed reactivity of Pt\(_3\). The chemical hardness of the complexes decreases from Pt\(_1\) to Pt\(_3\) (table 5.2) showing that stability of the complexes reduces respectively hence the observed increase in reactivity (table 5.2).\textsuperscript{103-105} The trend in reactivity is in agreement with the \( pK_a \)\(_1\) values viz. 3.01, 3.61, and 5.53 for Pt\(_1\), Pt\(_3\) and Pt\(_3\) respectively.\textsuperscript{100}

Reactivity of the nucleophiles follows the order GMP \( > \) L-met \( > \) GSH for most of the studied complexes. Based on the structures of the nucleophiles, one would expect GMP to be the least reactive because of its bulkiness, however its unexpected reactivity points to the existence of an anchimeric effect. This feature arises from hydrogen bonding interactions between the keto group of the base and the amine protons of the ethylene diamine ligand (figure 5.6)\textsuperscript{106} during the transition state with a net reduction in activation energy of substitution. This neighbouring group participation has been observed by other researchers\textsuperscript{107} and is well known in organic reactions.\textsuperscript{108}
L-met is more reactive than GSH in agreement with previously published results.\textsuperscript{109,110} This is attributed to the presence of a methyl group on the sulphur donor atom which through a positive inductive effect increases the nucleophilicity of the atom.\textsuperscript{109,110} It can therefore be concluded that the reactivity of the nucleophiles at pH 2 is largely affected by their charge, electronic, steric factors and anchimeric effects. The stability constants ($K = k_2/k_2$) for the platinum complexes listed in table 3 indicate that the products are very stable based on the large values.\textsuperscript{107} Relatively low values of the enthalpy of activation ($\Delta H^\ddagger$) and the large and negative entropy of activation ($\Delta S^\ddagger$) support the associative mechanism typical of square planar complexes.\textsuperscript{111}
5.5 Conclusion

This study has shown that the replacement of the pyridyl group by tpy(Ru)qpy results in the lowering of the energy of the anti-bonding LUMO orbital and the net HOMO-LUMO energy gap. DFT calculation has shown that qpy ligands lie orthogonal at the Ru(III) centre eliminating any possibility of π-communication between the ligands hence between the metal centres. The net result of this is that the two Pt(II) centres in Pt3 act independently of each other. In general the reactivity of these complexes is influenced by both the electronic as well as steric effects. The dominant factor is the increase in the overall cationic charge from Pt1 to Pt3. The trend in pKa values are in line with the observed trend in reactivity. The higher reactivity of Pt3 is mainly due to the increase in the charge which increases the overall electrophilicity of the complex. 19\textsuperscript{5}Pt NMR confirmed simultaneous substitution of the two aqua ligands in Pt3. The anchimeric effects of GMP make the nucleophile slightly more reactive than others in the studied complexes. The observed activation parameters support an associative mode of substitution.
5.6 References


7586.


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5.7 Supplementary Information

Support information (ESI) available. Selected mass and NMR spectra, kinetic traces and data corresponding to concentration dependence plots and Eyring plots and wavelengths for kinetic measurements for Pt1, Pt2 and Pt3 are presented.

Figure SI 5.1  
$^1$H NMR spectrum of 4’-(4’’-pyridyl)2,2’:6’,2’’-terpyridine in CDCl$_3$. 

[Image of NMR spectrum]
Figure SI 5.2 $^1$H NMR and $^{195}$Pt NMR spectra of Pt(en)Cl$_2$ in DMF-$d^7$.

Figure SI 5.3 $^1$H NMR and $^{195}$Pt NMR spectrum of Pt1-Cl in DMF-$d^7$. 
Figure SI 5.4 $^1$H NMR spectrum of Ru(qpy)(tpy)Cl$_2$.

Figure SI 5.5 $^1$H NMR spectrum of Pt2-Cl. Inset is the signal due to the alkyl protons.
Figure SI 5.6 $^{195}$Pt NMR spectrum of Pt2-Cl.

Figure SI 5.7 $^1$HNMR spectrum of [Ru(qpy)$_2$]Cl$_2$. 
Figure SI 5.8  $^1$H NMR and $^{195}$Pt NMR spectra of Pt3-Cl. Insets are the signals due to the alkyl protons and due to Pt.
Figure SI 5.9  High resolution ESI mass spectrum of qpy.
**Figure SI 5.10**  
High resolution ESI mass spectrum of \textbf{Pt1-Cl}.
Figure SI 5.11  Low resolution ESI mass spectrum of [Ru(qpy)(tpy)Cl$_2$].
Figure SI 5.12  Low resolution ESI mass spectrum of **Pt2-Cl**.
Figure SI 5.13  Low resolution ESI mass spectrum of [Ru(qpy)₂Cl₂].
Experimental SI

Preparation of about 0.1 M Ruthenium(III) Solution
RuCl₃·3H₂O (~1.5 g, 5.7 mmol) was refluxed in a mixture (70 mL) of a 1 M HCl and EtOH (v:v = 1:1) for 3 hours. The mixture was cooled and filtered then the filtrate reduced in vacuo to 10 mL. An aqueous solution of 1 M HCl was used to dilute the solution to the required acidified ~ 0.1 M Ru(III) solution.

[Ru(tpy)Cl₃]
Equal amounts of RuCl₃·3H₂O (~150 mg, 0.574 mmol) and terpyridine were refluxed in absolute EtOH (125 mL) for 3 hours. The resulting reaction mixture was cooled to room temperature and the precipitate was filtered, washed with cold absolute EtOH (5 mL)
followed by copious amount of ethylether and dried in vacuo. Yield: 191 mg, 433 mmol, (76 %), brown precipitate.

\[ \text{[Ru(qpy)Cl}_3 \] \]

The ruthenium moiety was synthesized following the literature procedure. The ligand qpy (100 mg; 0.323 mmol) was refluxed in MeOH (25 mL) until it dissolved. To this solution, a 0.1 M Ru(III) solution (3.25 mL; 0.33 mmol) was added drop-wisely. The reaction mixture was refluxed for 1.5 hours. The precipitated crude product was filtered hot. The filtrated was cooled to 253 K, which resulted in the precipitation of a relatively pure product. The product was filtered and dried. Yield: 84 mg, 0.162 mmol (49%).

Table SI 5.1 Summary of the selected wavelengths (nm) used in kinetic measurements

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Reaction step</th>
<th>Wavelength (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5'-GMP</td>
<td>1</td>
<td>302 318 320</td>
</tr>
<tr>
<td>GSH</td>
<td>1</td>
<td>280 254 255</td>
</tr>
<tr>
<td>L-met</td>
<td>1</td>
<td>253 307 310</td>
</tr>
</tbody>
</table>

Table SI 5.2 Average observed rate constants, \( k_{\text{obs}}/\text{s}^{-1} \), for the substitution of aqua from Pt1 by biological nucleophiles at 298K

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>[Nu]/M</th>
<th>( k_{\text{obs}}/\text{s}^{-1} \times 10^{-6} )</th>
<th>[Nu]/M</th>
<th>( k_{\text{obs}}/\text{s}^{-1} \times 10^{-5} )</th>
<th>[Nu]/M</th>
<th>( k_{\text{obs}}/\text{s}^{-1} \times 10^{-5} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP</td>
<td>0.00005</td>
<td>9.04122</td>
<td>0.002</td>
<td>5.73867</td>
<td>0.002</td>
<td>3.58854</td>
</tr>
<tr>
<td>L-met</td>
<td>0.00010</td>
<td>11.21200</td>
<td>0.004</td>
<td>13.05160</td>
<td>0.004</td>
<td>4.73328</td>
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<tr>
<td>GSH</td>
<td>0.00015</td>
<td>13.62436</td>
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<td>0.00020</td>
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<td>33.38418</td>
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<td>7.71892</td>
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</table>
Table SI 5.3  Average observed rate constants, $k_{obs}/s^{-1}$, for the substitution of aqua from Pt2 by biological nucleophiles at 298K

<table>
<thead>
<tr>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-5}$</th>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-5}$</th>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-5}$</th>
</tr>
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<td>0.0002</td>
<td>4.5206</td>
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<td>0.0008</td>
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<td>0.0010</td>
<td>9.3060</td>
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</table>

Table SI 5.4  Average observed rate constants, $k_{obs}/s^{-1}$, for the substitution of aqua from Pt3 by biological nucleophiles at 298K

<table>
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<tr>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-4}$</th>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-4}$</th>
<th>[Nu]/M</th>
<th>$k_{obs}/s^{-1} \times 10^{-4}$</th>
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<tr>
<td>0.00017</td>
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<td>0.00069</td>
<td>8.0329</td>
<td>0.00086</td>
<td>9.1443</td>
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</tbody>
</table>

Table SI 5.5  Temperature dependence of $k_2/M^{-1}s^{-1}$ for the substitution of aqua from Pt1 by biological nucleophiles at 298K

<table>
<thead>
<tr>
<th>$T^{-1}/K^{-1}$</th>
<th>ln($k_2/T$)</th>
<th>$T^{-1}/K^{-1}$</th>
<th>ln($k_2/T$)</th>
<th>$T^{-1}/K^{-1}$</th>
<th>ln($k_2/T$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.003413</td>
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<td>0.003249</td>
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<td>0.003195</td>
<td>-6.44595</td>
<td>0.003195</td>
<td>-7.65702</td>
<td>0.003195</td>
<td>-9.08925</td>
</tr>
</tbody>
</table>
Table SI 5.6  Temperature dependence of $k_2/M$ s$^{-1}$ for the substitution of aqua from Pt2 by biological nucleophiles at 298K

<table>
<thead>
<tr>
<th></th>
<th>GMP</th>
<th>L-met</th>
<th>GSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T^{-1}/K^{-1}$</td>
<td>ln($k_2/T$)</td>
<td>$T^{-1}/K^{-1}$</td>
<td>ln($k_2/T$)</td>
</tr>
<tr>
<td>0.003413</td>
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<td>-6.98736</td>
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</table>

Table SI 5.7  Temperature dependence of $k_2/M$ s$^{-1}$ for the substitution of aqua from Pt3 by biological nucleophiles at 298K

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<th>L-met</th>
<th>GSH</th>
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Figure SI 5.15  Concentration dependence plots of L-met and GSH nucleophiles for the aqua substitution on Pt1 at 298K

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