University of Surrey

Division of Chemistry
School of Biomedical and Molecular Sciences

Synthesis of Novel Platinum Oxadiazoline Complexes with Potential Anti-tumour Activity

Submitted in fulfilment for the degree of Doctor of Philosophy
By
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This is not the beginning of the end....
It is perhaps the end of the beginning.
Adapted from Sir Winston Churchill, 1942.
Novel Platinum and Ruthenium complexes with potential antitumour activity.

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<td>Am</td>
<td>Ammine</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
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<tr>
<td>C</td>
<td>Centigrade</td>
</tr>
<tr>
<td>Cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlated Spectroscopy</td>
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<tr>
<td>Dach</td>
<td>1,4-diaminocyclohexane</td>
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<td>Dichloromethane</td>
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<td>DNA</td>
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<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
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<tr>
<td>Et al.</td>
<td>Et alia</td>
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<td>electronV olt</td>
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<td>FAB^+MAS</td>
<td>Positive ion Fast Atom Bombardment MAss Spectroscopy</td>
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<tr>
<td>GA</td>
<td>Guanine-Adenine</td>
</tr>
<tr>
<td>g cm^{-3}</td>
<td>grams per cubic centimetre</td>
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<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
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<td>Molecular Weight</td>
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<td>Tvp</td>
<td>Triphenylphosphite</td>
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<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<td>Tetramethylsilane</td>
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<td>Ultra violet</td>
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Synthesis of Novel Platinum Oxadiazoline Complexes with Potential Anti-tumour Activity.

Julien Sarju MRSC 

Abstract: In the framework of this project, a series of platinum $\Delta^4$-1,2,4-oxadiazoline complexes was produced. These complexes were tested in vitro for anti-tumour effect and have been found to exhibit anti-tumour activity in ovarian, testicular and colon cell cultures. One complex, JS5, trans-dichlorobis{2-methyl-3-phenyl-5-(4-hydroxyphenyl)-$\Delta^4$-1,2,4-oxadiazoline}platinum(II), \textit{trans-[PtCl$_2$\{N=C(p-HO-C$_6$H$_4$)-O-N(Me)-CH(Ph)\}$_2$]} (product 45), proved to be twice as effective as carboplatin and also showed good activity in carboplatin resistant cell lines. Another complex JS6, \textit{trans-dichloro(4-(2-methoxyethoxy)benzonitrile){2-methyl-3-phenyl-5-(4-(2-methoxyethoxy)phenyl)-$\Delta^4$-1,2,4-oxadiazoline}platinum(II)}, \textit{trans-[PtCl$_2$(p-MeOOC$_2$H$_4$O-C$_6$H$_4$CN){N=C(p-MeOOC$_2$H$_4$O-C$_6$H$_4$)-O-N(Me)-CH(Ph)}]} (product 41), proved to be more effective in carboplatin resistant cell lines than platinum sensitive ones. This suggests a binding mode different to the accepted one exhibited by cisplatin, which is to the N7 nitrogen of guanine. The synthetic strategy employed was the $[2+3]$ cycloaddition of platinum nitrile complexes to nitrones. This method was chosen as it is a straightforward route to the platinum heterocycles, using relatively mild conditions. Also, properties such as solubility of the platinum oxadiazoline in polar solvents can easily be modified by using starting nitrones and platinum nitriles that contain polar substituents. The starting reagents for these compounds are commercially available, simplifying the overall synthesis. In this way the ligand is constructed in the coordination sphere and subtle changes are effected without altering the basic skeleton of the complex.

Nitrones of the type RC$_6$H$_4$CH=NOCH$_3$ (R= OH, CO$_2$H, 2-CH$_3$OC$_2$H$_4$O, N(Me)$_2$, N$_2$(Me)$_3$, and sodium sulphonate salt), were prepared from the corresponding aldehydes via the condensation of an aldehyde with N-methyl-hydroxylamine method. Novel platinum complexes of the type PtX$_2$(RC$_6$H$_4$CN)$_2$, (X= halogen, R = OH, 2-CH$_3$OC$_2$H$_4$O, were also prepared by a modification of the Kharasch route. Both mono and bis $\Delta^4$-1,2,4-oxadiazoline platinum complexes were produced that were more soluble in polar solvents than previously known similar complexes.
Substitution and oxidative addition reactions of the said oxadiazoline platinum complexes were also studied and are discussed. The synthesis of analogous ruthenium complexes was attempted, but ruthenium did not behave in the same way as platinum.

**Keywords:** nitrones, cycloaddition, platinum complexes, anti-tumour.

**Publications**


Synthesis and characterisation of mono and bis oxadiazoline platinum(II) complexes with bromo and iodo ligands, and mono oxadiazoline platinum(IV) complexes. (Article in preparation) Julien Sarju, Gabriele Wagner.


Variable temperature $^1$H NMR spectral studies of the conformational changes of oxadiazoline heterocycles, in the free ligand and in mono and bis oxadiazoline platinum(II) and (IV) complexes. (Article in preparation) Timothy Garland, Julien Sarju, Gabriele Wagner.
1. Introduction.

Since the serendipitous discovery that cisplatin \((\text{cis-dichlorodiammine platinum(II)})\) inhibited the growth of bacteria by Rosenberg and co-workers some 40 years ago\(^1\), research has been unrelenting in an effort to find anti-tumour platinum complexes. Barnett Rosenberg, shown in figure 1, was a biophysicist at the Michigan State University, and also had an interest in electrochemistry, so he had a broad scientific background. He had observed through his microscope that in bacterial cells undergoing mitotic division, the chromatids migrate to the polar regions of the cells. This reminded him of experiments he did as a schoolboy using bar magnets and iron filings. He tried to investigate this by applying an electric current with its associated magnetic field to bacterial soup. He used a platinum electrode which at that time was thought to be chemically inert. He found that the growth of the cells was inhibited, and with further investigation discovered cisplatin, and its tetrachloro platinum(IV) analogue, had been produced at the platinum electrode during the reaction, and that these were responsible for the observed inhibition\(^2,3\).

![Barnett Rosenberg](https://example.com/barnett_roosenberg.jpg)

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Figure 1. Barnett Rosenberg; the founder of platinum chemotherapy.

Bacteria, like cancer cells, are rapidly dividing, and it was thought that if cisplatin inhibited the growth of one it would work for the other too. This was subsequently shown to be the case when Rosenberg’s team carried out experiments on mice bearing
Sarcoma 180 and Leukemia L1210. In the wake of their research cisplatin entered phase 1 clinical trials in 1971 and received approval in 1978 for the treatment of testicular and ovarian cancer. Cisplatin is very effective at treating these cancers, but is also used in combination with other drugs in the treatment of oropharyngeal carcinoma, bronchogenic carcinoma, cervical carcinoma, bladder carcinoma, lymphoma, osteosarcoma, melanoma and neuroblastoma. However, due to the toxicity of cisplatin and the limited range of cancers treatable with it, the search has been on for platinum complexes that:

1. are more selective (i.e. they selectively attack tumours),
2. attack a greater range of tumours,
3. have less severe side effects,
4. are more orally bioavailable.

It is thought that by making the complexes more selective in the tissues they attack, side effects will be reduced as a result. Oral bioavailability is important as patients are less likely to be put off by a treatment not involving intravenous injections, and oral medicine could be administered as out-patient treatment without the need for long stays in hospital. Recent research has produced many water soluble platinum complexes, for example the platinum(IV) complexes of the type \( A_2PtCl_2(OH)_2 \) where \( A \) is a bidentate diamino ligand, made by E.J. Lee and co-workers in Korea in 1999. Whilst these complexes are water soluble, they are too polar to pass through the fatty stomach lining and are thus of no use as oral anti-tumour drugs as they never reach the site of action.

Whilst research has produced many thousands of platinum compounds over the last 40 years, in the main cisplatin analogues, initially only one of these analogues received worldwide approval. This is carboplatin, and its structure and that of cisplatin are shown in figures 2 (b) and 2 (a) below.
Carboplatin is only useful on the same range of tumours as cisplatin; whilst it is slightly less active, it is also far less toxic with a daily dosage of 2000 mg possible, compared to 100 mg for cisplatin\textsuperscript{11, 12}. A third complex, oxaliplatin\textsuperscript{12, 13} (figure 3(a)) has been granted a partial licence in some European countries for certain colorectal cancers, and more recently has been approved for metastatic colon cancer by the FDA in America. A similar complex nedaplatin (figure 3b) has received approval in Japan\textsuperscript{12, 13}.

The reason for this lack of progress is the constraints that were placed on researchers after the discovery of cisplatin's anti-tumour effect. Bearing in mind this was completely accidental, researchers went on to state that to be an effective anti-cancer agent, new platinum complexes should be:

1. Square planar \textit{cis} complexes (\textit{trans} complexes were believed to be inactive as initial tests on transplatin showed it to be inactive and more toxic than cisplatin).
2. Have two leaving groups (preferably anionic) such as chloride in the \textit{cis} position.
3. Have two non-leaving ligands such as amino (preferably primary) in the other \textit{cis} positions.
4. The complexes should be electronically neutral.
These structure activity rules were formalized by Cleare and Hoeschele in 1973\textsuperscript{13,14,15}. Better understanding of the mechanism of binding of platinum, and the chemistry of platinum(II) and platinum(IV) in general has led to a rethink in strategy, and now trans-platinum, platinum(IV) and polynuclear complexes are being studied\textsuperscript{13}.

The purpose of this study is to produce platinum complexes that contain polar as well as non-polar moieties, making them orally bioavailable and able to pass through the stomach lining and other lipophilic tissues. Analogous ruthenium complexes will also be attempted, as similar ruthenium complexes have been shown to possess anti-tumour activity\textsuperscript{16-18}, and also to have anti-bacterial effect, e.g. in the treatment of Chagas' disease\textsuperscript{19}. Ruthenium has the advantage of being available in its two most common oxidation states, ruthenium(II) and ruthenium(III). Ruthenium(III) is more inert towards substitution reactions than ruthenium(II) and allows the possibility of introduction into a biological system of inert complexes. These could be reduced in the reducing environment of the hypoxic tissue of tumours to more active ruthenium(II) complexes\textsuperscript{20}. This may have special significance in the treatment of cancer especially with regards to side effects, as the ruthenium(II) complexes would target cancer tissue DNA and not healthy tissue.
2. Background.

The variety of cancer chemotherapy drugs is large, from the comparatively simple inorganic molecule cisplatin to the large and complex natural products such as vinblastine (figure 4). This was originally extracted from the Madagascan periwinkle plant, but has since been synthesized artificially in the laboratory.

![Figure 4. The structure of the anticancer drug vinblastine.](image)

The mechanisms of action of these drugs are dissimilar; cisplatin binds to DNA and prevents replication whereas vinblastine induces tubulin polymerization. Tubulin is a cytoplasmic protein which is responsible for carrying organelles such as mitochondria around the cell. When tubulin polymerises the cytoplasm becomes turbid and can no longer function properly. Tubulin is important in mitotic cell division and when this is inhibited apoptosis is induced leading to cell death. The present project is primarily concerned with platinum complexes.

2.1 Binding of metallic drugs

Platinum complexes are of importance in cancer treatment as they are able to interact with DNA, which is plentiful in the rapidly growing tissue of tumours. Interaction of platinum and transition metal complexes in general, with DNA impairs its ability to replicate and leads eventually to cell death. Platinum compounds are able to bind to DNA in several different ways, shown in figure 6(a):
1. Intercalation.
2. Outer sphere binding to the helix.
3. Inner sphere binding, either intrastrand or interstrand, to the helix.
4. Strand breakage.

Intercalation was originally proposed by Lerman over 40 years ago. In simple terms a planar molecule bonds by van der Waal's forces between two base pairs of DNA in opposing helices. The molecule can be carried to the site of action by platinum, as a ligand e.g. proflavine (figure 5).

![Figure 5. Proflavine.](image)

This classical view of intercalation requires that the helix is locally extended and unwound. This alters the shape of the double helix and prevents replication and transcription. An alternative view of intercalation that involves bending of the helix was proposed twelve years later in 1973 by Gabbay and co-workers. This is shown in figure 6(b).

![Figure 6(a). The modes of interaction of metal complexes with DNA.](image)
Outer sphere binding is possible because the outside of the helix is negatively charged. This stems from the structure of the backbone, i.e. sugar residues linked by phosphate diester bridges. The phosphate group carries a negative charge. There is the obvious possibility of coulombic attraction of positively charged metal species, phosphate oxygen attraction between the helix and appropriate ligands and also the possibility of hydrogen bonding. Cobalt ammine complexes are amongst the most studied in this area of binding to DNA. Cobalt hexa-ammine and its ethylene diamine analogue carry a 3+ charge, and the inert nature of these species indicates an outer sphere attraction dominated by coulombic forces. The binding of ruthenium ammine complexes has also been found to contain an electrostatic component. An example is [Ru(NH₃)₅(H₂O)]³⁺²⁻. Of most importance to the binding of platinum in the treatment of cancer is inner sphere binding. This is a strong covalent attraction. Most studied are the mixed chloro amines of platinum such as cisplatin. These will be expanded on later, so suffice to say here that complexes such as cisplatin bind to DNA bases. Binding can be of an inter- or intrastrand nature, interstrand binding involves bonding to bases on opposite strands of the double helix. This would prevent the double helix from unraveling. Intrastrand binding occurs on bases of the same strand of the double helix, and although this does not prevent unraveling, it does prevent transcription and replication.

Lastly, strand breakage involves the cleaving of one or two of the helical backbones of the DNA skeleton. It is achieved by highly reactive species known as radicals. As long ago as fifty years this was done as a result of irradiation. The highly reactive hydroxyl radical was the product of irradiation and this breaks either a C-C bond in the sugar skeleton, or a phosphate ester-sugar bond. Damage of this nature prevents...
transcription and replication, and has subsequently been achieved by chemical means, the Ru\(^{3+}\) ion being an example. This is made possible by the Ru\(^{3+}\) / Ru\(^{2+}\) redox reaction in the presence of a reductant, the electron transfer induces radical production and this is in contrast to the binding of platinum\(^{25}\).

### 2.2 Toxicity of Cisplatin

In 1978 cisplatin was approved for use in the treatment of testicular and ovarian cancer, and later on for bladder cancer\(^9\). Cisplatin can also be administered in conjunction with other chemotherapeutic drugs such as bleomycin and 5-fluorouracil, displaying synergic activity. What has been a major obstacle to the widespread use of cisplatin in the past and at present is the presence of major toxic side effects. The dose-limiting nephrotoxicity is of a renal nature, and the damage is permanent. This can range from abnormal urinalyses to fatal renal dysfunction\(^{11,13}\).

Cisplatin binds preferentially with cellular material rich in sulphur, which is in abundance in the tissue of the kidneys. Platinum has a special affinity for sulphur as platinum is a soft acid and prefers soft ligands such as sulphur. This can be partially overcome by re-hydration and the co-administration of a diuretic that flushes the kidneys\(^{26}\). If this problem had not been overcome cisplatin would have been dropped from clinical trials early in its life in 1973. More recently, since 1991, tests have been performed on cisplatin bound to sulphur containing protecting groups. This reduces the amount of binding of cisplatin to kidney tissue\(^{27}\). Safeguarding against kidney damage in this way is at the expense of the anti-tumour activity, and the right balance has to be struck between the benefits of effective anti-tumour action and the risk of renal damage to the patient. In effect, physicians do as much damage as they can without endangering the life of the patient in the short term, in order to achieve the maximum benefit in the long term.

Accumulative dosing of cisplatin can result in significant peripheral neurotoxicity. This improves with time after cessation of cisplatin. It takes the form of reduced sensation, impaired proprioception, and paraesthesiae in the distal extremities\(^{27}\). More rarely motor weakness can occur that can be severe enough to confine the patient to a
wheelchair. From the early nineties to the present, extensive research has been carried out on glutathione and other antioxidants to test their efficacy in reducing the neurotoxicity of cisplatin. The mechanism of platinum’s neurotoxicity is little understood but it is thought that because the damage is peripheral, perhaps platinum acts in cells of the dorsal root ganglia. It should be stressed that clinical research into the use of small peptides such as glutathione for the purpose of reducing the neurotoxicity of cisplatin must be exhaustive, as small peptides may act as tumour growth factors which would be most undesirable.

Ototoxicity is widespread in cisplatin treatment and is known to affect up to 50% of patients. It manifests itself initially by ultra-high frequency hearing loss (9000 – 20 000 Hz), followed by high frequency loss (4000 – 8000 Hz) and finally low frequency (250 – 4000 Hz) impairment.

Less serious is cisplatin’s haematological toxicity. Normal doses of cisplatin produce myelosuppresion and anaemia though this is not serious in the majority of cases and is monitored and treated in a standard manner. Although little is known about the mechanism of this toxicity, suggestions that it is a side effect of renal toxicity have been discredited as carboplatin produces anaemia but is not renally toxic.

Other less serious toxicities are vascular problems, nausea and vomiting, and hair loss. As hair is constantly growing involving rapid cell growth and DNA, it is affected in the same way as rapidly growing cancer tissue, and inhibited. This hair loss is reversible after cessation of cisplatin, which is curious as one would hope that the damage to cancer cells was final. It is difficult to account for this apparent anomaly. One possibility is that as hair is rich in sulphur and presumably hair follicles and the bloodstream flowing to them are too, it is likely that the drug is substituted and the hair loss is an effect of the resulting platinum complex. If the new complex does not bind with DNA in the follicle, then the follicle may survive to grow hair another day when cisplatin treatment is discontinued.
2.3 Tolerance and resistance to cisplatin.

It has been observed that some tumours do not respond to platinum drugs at all, possibly for reasons of pharmacokinetics or tumour architecture, while some respond initially but later on become resistant. The mechanisms of tolerance and resistance are not well understood, but one hypothesis is that platinum initially binds to DNA in tumour cells that are susceptible to attack, leaving behind platinum resistant cancer cells. An example of this is in hypoxic tissue. The tumour cells closest to the blood supply are prone to attack from platinum which has a medium in which to travel within the tumour. Platinum cannot reach the cells further away from the blood supply so these cells are platinum resistant. Another theory is that the cells adapt and the DNA repair mechanism is able to work around the presence of certain levels of DNA damage within the cell.

The various mechanisms of tolerance and resistance fall into two categories, firstly those that result in less of the active drug gaining access to and reacting with the target DNA, and secondly those that increase a cells ability to tolerate certain levels of DNA damage.

2.3.1 Reduced access of the drug to DNA

This could result from alterations in one or any of the following parameters:

1. Drug pharmacokinetics.
2. Tumour vasculature and / or tissue architecture.
3. Extracellular factors which might inactivate the drug within the tumour.
4. Uptake into tumour cells.
5. Intracellular factors which inactivate the drug such as binding to glutathione or metallothioneins.
6. Accessibility of the DNA or of specific regions of the DNA.

Most of the evidence available from research on resistant cell lines points to 4 and 5 as the main cause of resistance.
2.3.2. Increased repair or tolerance of DNA damage.

It is not understood how DNA damage leads to cell death. At first it would appear obvious that binding of platinum inhibits transcription and replication, but as cells contain extensive enzymatic repair machinery, there may be more to it. It is possible that the cells pre-programmed self-destruct mechanism called apoptosis may come into play in an effort to remove the damaged cell. In short, this means that platinum directly induces the cell to self destruct. It is proposed that in resistant tumours the cells do not have such an efficient apoptotic mechanism and therefore do not die but tolerate the presence of platinum and DNA damage\textsuperscript{31}.

2.4 The chemical nature of cisplatin binding with DNA.

Cisplatin contains two non-exchanging ammonia groups and two leaving chloride ligands. The binding of ammonia to platinum is strong and these groups should not easily be removed \textit{in vivo}. It is reasonable to assume that platinum will bind well with nitrogens containing a lone pair such as amine groups, which are found in DNA. These bonds are strong and covalent in nature and cannot be broken even by the CN\textsuperscript{-} ion. The platinum adducts formed can be isolated by chemical or enzymic means\textsuperscript{13}. Most research points to platinum binding with the N-7 of guanine on one strand of DNA and the guanine of the opposing strand (GG linkage), but guanine to adenine linkages (GA) are also known. The nature of the binding is thought to be mainly interstrand links. Research into this is contradictory and some researchers suggest the binding is of an intrastrand nature. Linkages to purine are also known, and this can lead to a conformational switch of the sugar residues of the bound purine. This is thought to be important in the mechanism of cisplatin’s inhibition of DNA synthesis. It should be noted that the \textit{trans} isomer also forms GG linkages but these do not produce a kink in the DNA like cisplatin and this is considered to be the reason the \textit{trans} isomer has no anti-tumour effect\textsuperscript{32}.

With cisplatin the GG linkages reach a maximum after approximately twelve hours, whereas in the case of the \textit{trans} isomer the maximum is reached after six hours. Three factors could be responsible for this, firstly, cisplatin is slower at forming GG adducts
for steric reasons, secondly, because it is kinetically more stable, or lastly, the DNA repair mechanism is able to act more quickly in the case of the trans isomer. In any case, the trans isomer is cytotoxic like cisplatin.

2.5 The aqueous chemistry of cisplatin

Before cisplatin can bind with DNA it has to arrive at the site of action. Cisplatin is only sparingly soluble in water, and when injected intravenously is prevented from dissociating by the high blood plasma chloride ion concentration of 103 mmol. This hampers any binding that might have occurred between blood proteins and cisplatin. However, as 50% of cisplatin is eliminated from the body within 24 hours, binding of cisplatin in the bloodstream must occur in some way. In the cytoplasm the chloride concentration is only 4 mmol and hydrolysis occurs as shown in the figure 7 below.

\[
\begin{align*}
(\text{Am})_2\text{PtCl}_2 & \quad (\text{Am})_2\text{PtCl}^+ & \quad (\text{Am})_2\text{PtCl}_2^- \\
\text{Am} \cdot \text{Pt} \cdot \text{Cl} & \quad \text{Am} \cdot \text{Pt} \cdot \text{Cl} & \quad \text{Am} \cdot \text{Pt} \cdot \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{Am} \cdot \text{Pt} \cdot \text{H}_2\text{O} & \quad \text{Am} \cdot \text{Pt} \cdot \text{H}_2\text{O}^+ & \quad \text{Am} \cdot \text{Pt} \cdot \text{H}_2\text{O} \\
(\text{iv}) & \quad (\text{v}) & \quad (\text{vi})
\end{align*}
\]

Figure 7. The structures of the hydrolysis products of platinum – amine (Am) complexes, at each stage of hydrolysis.

This mechanism of transport of cisplatin across the cell membrane to its point of action can be either passive or active. Neutral species preferentially cross the membrane by the passive mode, i.e. from a point of high concentration to one of low concentration. Cisplatin can also cross a cell membrane by an active transport mechanism. This is where the drug is carried across the membrane by a carrier within the membrane. The passive mode is thought to be the main route of transport\textsuperscript{33,34}.
2.6. Design of novel platinum anti-tumour drugs

In the last fifteen years or so, research has steered away from the restrictive structure/activity rules which were written in stone in the early 1970s. The main reasons for this are the lack of progress in developing drugs that are an improvement of cisplatin, and a better understanding of the pharmacology of platinum drugs. The driving force behind this is the desire to find chemotherapeutic drugs that are effective on a wider range of cancers, are less toxic, non-tolerant and more orally bioavailable.

Novel research falls into the following categories:

1. Sterically hindered platinum complexes.
2. Platinum(IV) complexes.
3. Trans platinum complexes.
5. Diaminocyclohexane platinum complexes.
6. Platinum compounds with carrier ligands.

2.6.1. Sterically hindered platinum complexes

In recent years, knowledge of the mechanisms of tumour resistance to platinum has improved. Various factors affect the level of tolerance, the major contributing factors being impaired transport of the drug, cytoplasmic detoxification due to increased levels of glutathiones and metallothioneins, improved DNA repair, and DNA tolerance to platinum adducts.

The reasoning behind research into sterically hindered platinum complexes is that it is well known that axial steric hindrance reduces the rate of substitution reactions in square planar complexes. This means that the platinum complex is less susceptible to substitution by glutathione and metallothioneins found in cells. The importance of this is that resistance to the platinum complex is reduced as more of the drug reaches the site of action. With this in mind platinum complexes including ligands such as
substituted pyridines have been designed\textsuperscript{35}. The steric hindrance occurs as the ring bends down from the PtCl\textsubscript{2}N\textsubscript{2} plane and the methyl substituent lies over the platinum, inhibiting axial substitution. Crystal structures have shown this to be the case. An example of this is \textit{cis}-amminedichloro(3-methylpyridine) platinum(II) shown in figure 8. The ring is tilted (rotation about the Pt-N) with respect to the square plane by 48.9\textdegree. In the case of the 2-methylpyridine analogue, the angle is 103\textdegree, and the methyl group lies directly over the platinum square plane.

![Figure 8. \textit{cis}-amminedichloro(3-methylpyridine) platinum(II).](image)

Clinical trials have shown the 2-methylpyridine analogue to be active in cisplatin resistant cell lines. However, the time for DNA platinum adducts to reach a maximum is significantly longer than for cisplatin, and this has implications regarding DNA repair that require more research. This rationale is adopted in the current project.

2.6.2 Platinum(IV) complexes.

Early studies by Rosenberg showed platinum(IV) complexes to have anti-tumour activity. This was largely ignored until fifteen years ago. Research into platinum(IV) has been fuelled by the desire to find anticancer drugs that are orally bioactive. This improves the quality of life of patients as few people enjoy injections, and it opens up the possibility of outpatient treatment. Platinum(IV) compounds are more inert to ligand substitution and it is thought that they are reduced to platinum(II) by both extracellular and intracellular agents prior to binding with DNA. The type of axial ligand determines the rate of reduction of platinum, and consequently the biological activity of the complex. Platinum(IV) opens up all sorts of possibilities of different ligands. An example of a platinum(IV) complex is Iproplatin synthesized by Tobe and co-workers\textsuperscript{13} (figure 9), although clinical trials of this complex were abandoned due to
lack of superior performance. The major obstacle to overcome is gastrointestinal absorbency. The complex has to be sufficiently polar to be water soluble, but also lipophilic enough to pass through the stomach lining.

![Figure 9. Iproplatin.](image)

More recently, research into platinum(IV) complexes has experienced a revival, after a tail off due to the poor performance of Iproplatin. Complexes containing ethylene diamino and carboxy ligands have been produced. Absorbance is poor, between 20% and 37% of administered dose\textsuperscript{13}. Another drawback is gastrointestinal problems caused by the drugs. Carboplatin for example resulted in severe problems and is administered intravenously, like cisplatin. However, the limited success has fuelled research using these types of ligands. Axial carboxy and equatorial amine ligands provide three sites for modification\textsuperscript{13,36}, and this can reduce the rate of reduction from platinum(IV) to platinum(II) in the bloodstream. One of these complexes JM216, was the first orally active platinum complex to be designed\textsuperscript{13}. Its structure is similar to that in figure 10 except that it has axial acetate ligands instead of hydroxide. It is hoped this will enable more drug to reach the target. The activity of the platinum(IV) drugs is necessarily dependent on their platinum(II) analogues.

2.6.3 Trans Platinum complexes

Transplatin is kinetically more reactive than cisplatin and therefore more susceptible to deactivation. This is one reason why it is not active as an anti-tumour complex. This kinetic reactivity may be reduced by the introduction of a ligand that sterically hinders the platinum. Research in this area has produced several complexes that do exhibit anti-tumour activity; in some cases it is greater than their cis counterparts\textsuperscript{13,37,38}. An example of one of these is shown below in figure 10.
trans,trans,trans-aminine(cyclohexylamine)dichlorodihydroxy platinum(IV).

By having a large bulky ligand in a trans position there is also the possibility of forming platinum - DNA adducts of a completely different nature compared to the GG adducts. This is important as one of the main mechanisms of resistance to cisplatin is the tolerance to, and / or removal of platinum - DNA adducts. This has been shown to be the case in a study of platinum iminoether complexes of the type PtCl₂(E-iminoether)₂(EE-trans complex), where platinum DNA mono adducts were isolated. These were formed at the N7 of guanine, and even after 48 hours incubation at 37 °C only mono adducts were formed. This is in contrast to transplatin which forms bifunctional adducts, and demonstrates that some transplatin analogues bind to DNA in a different way. This idea is continued in the next sub-section.

Another important group of platinum(IV) compounds are the imidazole complexes. These are tetrachloro complexes with the imidazole in a trans position to another ligand such as DMSO or to another imidazole. Similar ruthenium complexes have also been developed and display anti-tumour activity. Analogous pyridine and thiazole complexes have also been developed, and all three classes show comparable activity to cisplatin in cisplatin resistant cell lines.
2.6.4. Multinuclear Platinum complexes.

Having bi- and trinuclear platinum complexes opens up the possibility of new binding sites on DNA, and consequently entirely new platinum - DNA adducts. Hopefully these adducts will be resistant to the DNA repair mechanism. These complexes take the form of simple square planar platinum complexes joined by bridging linkers such as aliphatic diamines. An example of this is BBR3464\textsuperscript{13,40} (figure 13) and in preclinical tests it has exhibited a complete lack of cross resistance to cisplatin resistant cell lines\textsuperscript{41}. It is also more potent than cisplatin \textit{in vitro} in an osteosarcoma cell line\textsuperscript{42}. This improvement in potency is due to increased DNA binding and cellular platinum uptake compared to cisplatin.

\[
\begin{align*}
\text{Figure 13. The structure of BBR 3464.}
\end{align*}
\]

The overall 4+ charge on the platinum complex facilitates binding in the minor DNA groove which is negatively charged. The minor groove of DNA is shown in figure 14 below.
2.6.5. Diaminocyclohexane platinum complexes (dach)

Since the first synthesis of this type of complex in the 1970s\textsuperscript{43,44}, many platinum(II) and platinum(IV) complexes of this type have been synthesized, the most famous being oxaliplatin\textsuperscript{12, 13}. They were found to be active in some cisplatin resistant cell lines. The new platinum(IV) complexes are analogues of oxaliplatin with axial carboxyl ligands. Some of the complexes have the amines on the 1 and 2 positions, others on the 1 and 4. A complex of Pt(cis-1,4-dach)Cl\textsubscript{2} (figure 15) exhibited \textit{in vitro} activity in Pt(1,2-dach) resistant cell lines. This could be for structural reasons but very little is understood on how Pt(1,4-dach) overcomes this resistance and more work is required\textsuperscript{13}.

![Figure 15. Pt(cis-1,4-dach)Cl\textsubscript{2}](image-url)
2.6.6. Complexes with biologically active carrier ligands.

Already mentioned in section 2.1 were the platinum proflavine complexes which are intercalators. The theory behind the research is that by attaching ligands to platinum that are known DNA intercalators, the concentration of platinum can be localized in the vicinity of the DNA, rather than being bound to tissue in the kidneys and metallothioneins in the bloodstream. In this way, toxicity can be reduced. Although plenty of research is ongoing in this area, so far the results of the platinum complexes are not an improvement on the carrier ligands alone, although some are an improvement on cisplatin\textsuperscript{13}. Carrier ligands are also used that are not biologically active, such as sugars, amino acids, and polymer backbones. These are used to alter the properties of the platinum complex, such as solubility, absorbance across cell membranes, or the time the complex remains in the system before elimination.

2.6.7. Water soluble complexes

There are two main strategies in this approach, the first is to introduce polar moieties to ligands or to the platinum directly, and secondly to make a hydrosol colloid of an insoluble platinum complex, such as [(+1)-1,2-bis(4-fluorophenyl)ethylenediamine]-dichloro platinum\textsuperscript{13,45}. Both methods have yielded active complexes and an example of the former approach is shown in figure 16.

![Figure 16. A water soluble anionic phosphono carboxylate complex of platinum\textsuperscript{13,46}.

\[ \text{Figure 16. A water soluble anionic phosphono carboxylate complex of platinum}^{13,46}. \]
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<thead>
<tr>
<th>Phase 1</th>
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<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>Approved during phase 1 development (not approved)</td>
<td>Approved during phase 1 development (not approved)</td>
</tr>
<tr>
<td>(parecoxib, tramadol)</td>
<td>(parecoxib, tramadol)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved in Japan for multiple coagulopathy</td>
<td>Approved in Japan for multiple coagulopathy</td>
</tr>
<tr>
<td>(parecoxib, tramadol)</td>
<td>(parecoxib, tramadol)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved in Japan for multiple coagulopathy</td>
<td>Approved in Japan for multiple coagulopathy</td>
</tr>
<tr>
<td>(parecoxib, tramadol)</td>
<td>(parecoxib, tramadol)</td>
</tr>
</tbody>
</table>

**Table 1. The current status of platinum chemotherapy**

<table>
<thead>
<tr>
<th>Compound</th>
<th>T-20905</th>
<th>T-20906</th>
<th>T-20907</th>
<th>T-20908</th>
<th>T-20909</th>
<th>T-20910</th>
<th>T-20911</th>
<th>T-20912</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.7. Ruthenium in chemotherapy

Searching the literature revealed many hits for ruthenium complexes to do with catalysis, but comparatively few for medical applications, though this situation is improving. This may be because research into ruthenium for anti-tumour effect is more recent than for platinum which has been ongoing for forty years. Initially ruthenium complexes were synthesized that were analogues of platinum compounds. As time passes and the research progresses, more publications will undoubtedly appear. Patent issues may delay the publication of results by researchers and pharmaceutical companies alike. The origin of funding and the motivation behind research also play a part. Research into platinum chemistry was common before the discovery of cisplatin’s anti-tumour activity, and platinum chemistry for research’s sake is still a major motivation. Another factor could be the heavy emphasis put on biological testing and anti-tumour effect. Researchers may be reluctant to publish their work if the compounds made are less efficacious than cisplatin and carboplatin.

One of the groups of complexes in the public domain is ruthenium coordinated imidazoles \(^{48,17}\), an example of which is shown in figure 17 below.

![Figure 17. A ruthenium tetrachloro(DMSO)(imidazole) complex.](image)

This complex is very similar to the platinum imidazole complexes shown in figure 12 and both are important in current cancer research. This complex carries a negative charge, and if a protonated imidazole cation (ImH\(^+\)) is used as the counter ion instead of Na\(^+\), the molecule has greater chemical stability. This compound has been proposed
for phase I and II clinical trials. Another benefit of this complex is that it is less toxic than the analogous platinum complex.

Imidazoles are similar to the heterocycles of the present study, oxadiazoles, so it is reasonable to assume if imidazole complexes are active anti-tumour agents, then oxadiazoline complexes might be too. The other main areas of ruthenium chemotherapeutic research are multinuclear ruthenium complexes, and complexes of ethylenediaminetetraacetic acid (EDTA) and phenyl hydroxamic acid. The latter are being investigated by the Royal College of Surgeons in Ireland, and the general structure of them is shown in figure 18. The EDTA is coordinated via the two nitrogens in a cis manner, and by two of the carboxylate groups in a trans manner.

![Figure 18. The structure of a ruthenium(III) hydroxamato complex.](image)

Of growing importance is the use of nitric oxide donors ligated to metal centres, particularly ruthenium. The above complex, figure 18, and figure 19 below are examples of nitric oxide donors. This has a dual effect as nitric oxide inhibits tumour growth and hopefully the ruthenium complex does too. The nitric oxide is released in the reducing conditions of the tumour so it is a type of carrier ligand. Using this approach introduces a dual approach to cancer treatment.

![Figure 19. Ruthenium nitric oxide complex.](image)
Summing up, despite platinum chemotherapy being approved for 28 years, the range of tumours treatable is still fairly limited, and problems of toxicity and tolerance remain. Plenty of scope remains for research into platinum and ruthenium complexes that may circumvent these problems. The present project adopts many of the above approaches to the design of novel platinum complexes, namely, *trans* complexes, sterically hindered complexes, introducing polar moieties, multinuclear complexes, water soluble complexes and ionic complexes. Hopefully complexes that have greater solubility in water, improved anti-cancer activity and reduced tolerance, will be designed.
3.0 A brief overview of platinum chemistry.

The chemistry of platinum can be summarised into three distinct areas;

1. electrochemistry,
2. catalysis,
3. coordination chemistry.

Platinum is a typical transition element, characterised by its high melting point of 1772 °C, high density of 21.45 g/cm³ and variable oxidation state. It is also chemically inert and has good electrical conductivity which is why it has historically been used in electrical circuitry, to make crucibles, and in electrodes. Indeed it was only its use as an electrode that led to the discovery that cisplatin inhibited the growth of bacteria. So platinum was not quite as chemically inert as was thought at the time. Platinum is used in the hydrogen electrode which is the universal standard for measuring half cell potentials.

3.1 Catalytic activity of platinum.

Platinum is well known for its catalytic activity, not least because of its use in the modern exhaust catalytic converter.

\[ \text{Pt/Rh} \quad 2 \text{CO} + 2 \text{NO} \xrightarrow{\text{Pt/Rh}} \text{N}_2 + 2 \text{O} = \text{C} = \text{O} \]

Scheme 1. The conversion of noxious gases in automotive exhausts to more acceptable gases.

Platinum is also used in around thirty industrial processes from the cracking of petroleum to the curing of silicones. It is probably most famous for its use in reductive hydrogenations. Platinum can be used as either homogeneous or heterogeneous catalysts. The catalytic converter is an example of a heterogeneous catalyst where the platinum is mounted on a solid support. This type of catalyst depends on high temperature and surface activity for its catalytic action. Platinum catalysts used for curing silicones such as siloxanes are examples of homogeneous catalysts. They dissolve in the reaction medium so are in the same phase as the reactants. Much lower concentrations of homogeneous platinum catalysts are required to achieve similar
activity compared to heterogeneous catalysts in the production of silicones. More recently platinum nanoclusters have been used to catalyse the polymerisation of siloxanes.

3.2 Coordination chemistry of platinum.

Coordination chemistry involving platinum may be motivated by interest in medicinal chemistry, or just for chemistry’s sake. Chemists may be interested in a certain type of reaction and use platinum to make the reaction possible or make it easier. Platinum has made a significant contribution to organometallic chemistry. The first organometallic compound described was Zeise’s salt in 1830. This was nearly fifty years before the birth of Victor Grignard. The structure of Zeise’s salt is shown in figure 20 below.

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{Pt-Cl} \\
\text{H} \\
\text{H} \\
\end{array}
\]

Figure 20. The structure of Zeise’s salt.

Whilst Zeise’s salt has no commercial value whatsoever, its palladium analogue is extremely important in the conversion of alkenes to carbonyl compounds. This is known as the Wacker process after the German scientist who invented it. The Wacker process was one of the first large scale industrial applications of catalysis, utilizing readily available ethylene and converting it to ethanol via acetaldehyde.

Platinum is important in coordination chemistry because of its ability to bind to both saturated hydrocarbons and unsaturated systems such as arenes and alkenes. It is also able to bond with lone pair donors such as nitrogen, sulphur and phosphorus. Figure 21 (a) below shows the σ bond in Zeise’s salt which involves electron donation from full π orbitals of ethylene to the empty d_{x^2-y^2} orbital of platinum.
Figure 21(a) The main orbitals involved in $\sigma$ bonding in Zeise’s salt, (b) the main orbitals involved in $\pi$ bonding in Zeise’s salt.

Figure 21(b) above shows the $\pi$ bonding of Zeise’s salt which involves back donation from the electrons of the filled $d$ orbital of platinum to the empty antibonding orbitals of ethylene. The $p$ group elements such as nitrogen and sulphur are good $\sigma$ donors through their lone pairs. However the strength of the bond can vary between compounds that contain the same donor element. An example of this is the difference in bond strength of nitriles and amines. This is due to the hybridisation of the nitrogen in each case. In a nitrile the lone pair is a $sp$ hybrid so has 50% $s$ character. This means the lone pair is more tightly bound to the nucleus than in the case of an amine, which has $sp^3$ hybridisation. In this case the lone pair has 75% $p$ character and is not so tightly bound to the nucleus. The amine is able to bind more efficiently with platinum.
3.2.1 The classification of hard and soft acids and bases.

The affinity of a ligand for platinum is governed by its Lewis basicity. Platinum is a soft Lewis acid and preferentially binds with soft Lewis bases\(^5\). Soft Lewis acids are characterised by a large ionic radius, a low positive oxidation state, valence orbitals containing electron pairs and they are readily oxidised. Soft Lewis bases are characterised by a large atoms of intermediate electronegativity (2.5-3.0 on the Pauling scale) and are readily polarised and oxidised. Platinum(II) meets the criteria for a soft Lewis acid while sulphur and phosphorus fall into the soft base category\(^52,55\), depending on oxidation state and particular ligand. Nitrogen is in general classed as intermediate but again this depends on the particular ligand. Table 2 below summarises some of these ligands.

<table>
<thead>
<tr>
<th>Hard Lewis Base</th>
<th>SO(_4^{2-})</th>
<th>PO(_4^{3-})</th>
<th>NO(_3^-)</th>
<th>NH(_3)</th>
<th>R-NH(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate Lewis Base</td>
<td>SO(_3^{2-})</td>
<td>NO(_2^-)</td>
<td>Pyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Lewis Base</td>
<td>CN(^-)</td>
<td>PR(_3)</td>
<td>SR(_2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Classification of various Lewis bases.

In the same way that bases are classified as hard or soft, so are Lewis acids. Pearson classified hard acids as those that formed their strongest complexes with hard bases, and soft acids form their strongest complexes with soft bases\(^56\). This is in agreement with Chatt’s theory of class ‘a’ and ‘b’ metal ions\(^52,57\). This stated that class ‘a’ metals prefer to complex with elements of lower atomic number within a group of the periodic table, whilst class ‘b’ metals prefer to complex with elements of higher atomic number within a group. So for platinum halide complexes the stability decreases from iodine to fluorine. This trend coincides with a reduction in the polarisability of the halogens going up the group, and Pearson used polarisability as a criterion for measuring hardness or softness. So the two theories of Pearson and Chatt are in overall agreement. Both the Gibb’s free energy and enthalpy of formation of divalent tetrahaloplatinate anions become less positive going from chlorine to iodine, indicating an increase in stability moving down the group\(^52\). This is shown below in table 3.
<table>
<thead>
<tr>
<th>Halogen</th>
<th>$\Delta G_{aq}$ (kJ / mol)</th>
<th>$\Delta H_{aq}$ (kJ / mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorine</td>
<td>143.9</td>
<td>159.3</td>
</tr>
<tr>
<td>Bromine</td>
<td>133.1</td>
<td>111.3</td>
</tr>
<tr>
<td>Iodine</td>
<td>77.0</td>
<td>39.7</td>
</tr>
</tbody>
</table>

Table 3. The Gibb’s free energy and enthalpy of formation of divalent tetrahaloplatinate anions in aqueous solution.

Both these theories were devised by experimental observation of the reactions of different metals and anions and then applied to the periodic table as a whole.

### 3.2.2 Substitution reactions of platinum(II) complexes.

This affinity of different ligands for platinum is exploited in substitution reactions to synthesize new complexes. This method is employed in the present project. Platinum nitrile complexes are often used as starting materials for ligand exchange reactions as they are not tightly bound and are easily substituted. Important to these reactions is the rate of exchange of a ligand. Experimental observation of the rate of exchange of ligands on square planar platinum complexes was used to devise a series which is the approximate order of the decreasing labilising ability of ligands. This became known as the trans effect\(^{58}\), and is a measure of the effect a ligand has on the rate of substitution of the ligand trans to it in the square planar complex. From its first conception, the order of the series has evolved to the following\(^{59}\) although it is by no means exhaustive;

$$
\text{C}_2\text{H}_4 \sim \text{NO} \sim \text{CO} \sim \text{CN}^- \sim \text{R}_3\text{Sb} \sim \text{R}_3\text{As} \sim \text{H}^- \sim \text{SC(NH}_3)_2 \sim \text{CH}_3^- \sim \text{C}_6\text{H}_5^- \sim \text{SCN}^- \sim \text{NO}_2^- \sim \text{I}^- \sim \text{Br}^- \sim \text{Cl}^- \sim \text{NH}_3 \sim \text{OH}^- \sim \text{H}_2\text{O}.
$$

The first thing to note is that the end of the series with the greater labilising effect is dominated by good $\pi$ acceptors such as unsaturated systems, arsines and phosphines, and the trans effect is most appropriate when the ligands involved are good $\pi$ acceptors. This is because they withdraw electron density from the platinum and this is translated to the bond trans to the ligand thus weakening it. At the other end of the series are the halogens and ammonia, and according to the trans effect, chlorine should labilise ammonia. This is understood not to be the case in the binding of
cisplatin to DNA, where the chlorines are the leaving groups. Whilst chlorine and ammonia are adjacent in the series, and might be considered to be similar, ammonia is a difficult ligand to remove. This leads on to another effect which is called the trans influence. The difference between the two phenomena is that the trans effect is a kinetic property dealing with the rate of exchange, whereas the trans influence is a thermodynamic property dealing with bond strengths. The two effects are inextricably linked. As the platinum-ammonia bond is stronger than the platinum-chlorine bond the latter is substituted in cisplatin. This also explains why transplatin is more reactive than cisplatin with regard to exchange of the chlorine. In the Cl-Pt-Cl the chlorines are more strongly labilised than in the Cl-Pt-NH₃ of cisplatin.

The main mechanism for the substitution of square planar platinum complexes is thought to be associative. This is outlined in figure 26(b). This assumption is based on indirect evidence such as the rate of substitution decreasing as the degree of substitution of a ligand increases. This means that the ligand’s substituents sterically hinder substitution of the ligand, and the rate is consequently slower.⁶⁰

3.2.3. The oxidation states of platinum.

Platinum exhibits various oxidation states, the most common being 0, +2 and +4. The mean atomic radii have been measured experimentally for these oxidation states in a number of environments including triphenylphosphine and isocyanide, and are identical at 0.131 nanometres. The corresponding palladium atomic radii are the same. This feature is due to the contraction of the ionic radius caused by shielding from the nucleus of the valence d electrons by the 4f subshell of electrons. This is the so called lanthanide contraction effect and is common in second and third transition series. It is worth noting the covalent radii of platinum complexes where the platinum is in 0, +2 or +4 oxidation state, are also identical.⁵²

Ionisation potentials have also been measured and are summarised in table 4 below. Just a glance at the table shows the difficulty in achieving the higher oxidation states of platinum. The transition from tetravalent to pentavalent platinum requires 55 eV. Ionisation potentials are used in the calculation of lattice energies of ionic compounds.
This application is of limited value in platinum chemistry as Born-Haber lattice energies are based purely on coulombic attraction, and take no account of covalent bonding. In platinum complexes there is a major contribution from covalent attraction.

<table>
<thead>
<tr>
<th>Transition</th>
<th>Ionisation potential (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M^0 \rightarrow M^+$</td>
<td>9.0</td>
</tr>
<tr>
<td>$M^0 \rightarrow M^{2+}$</td>
<td>27.56</td>
</tr>
<tr>
<td>$M^0 \rightarrow M^{3+}$</td>
<td>56.06</td>
</tr>
<tr>
<td>$M^0 \rightarrow M^{4+}$</td>
<td>97.16</td>
</tr>
<tr>
<td>$M^0 \rightarrow M^{5+}$</td>
<td>152.16</td>
</tr>
</tbody>
</table>

Table 4. Ionisation potentials of platinum.

More relevant to the stability of platinum complexes in different oxidation states are oxidation-reduction potentials. Three of these relevant to the current project are shown in table 5.

<table>
<thead>
<tr>
<th>Oxidation state change</th>
<th>Equilibrium</th>
<th>Oxidation potential (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt$^0$ $\rightleftharpoons$ Pt$^{II}$</td>
<td>Pt $\rightleftharpoons$ Pt$^{2+}$ + 2e</td>
<td>-1.2</td>
</tr>
<tr>
<td>Pt$^{II}$</td>
<td>Pt + 4Cl$^-$ $\rightleftharpoons$ PtCl$_4^{2-}$ + 2e</td>
<td>-0.75</td>
</tr>
<tr>
<td>Pt$^{IV}$</td>
<td>PtCl$_4^{2-}$ + 2Cl$^-$ $\rightleftharpoons$ PtCl$_6^{2-}$ + 2e</td>
<td>-0.77</td>
</tr>
</tbody>
</table>

Table 5. Selected redox potentials for the common oxidation states of platinum.

Platinum is described as a noble metal as it is not considered reactive, and this is reflected in the negative oxidation potential of the first transition in table 5. The reverse reaction is favourable in aqueous solution, i.e. Pt$^{2+}$ is more likely to be reduced to elemental platinum than platinum being oxidised. This is immediately obvious on inspection of the Nernst equation;

$$\Delta G_m^0 = -nFE^0$$

A negative redox potential will give a positive Gibbs free energy which is unfavourable for a reaction. In fact the Gibbs free energy and enthalpy of formation of the second reaction in table 5 are 143.9 kJ / mol and 159.3 kJ / mol respectively. This
renders the anion unstable in aqueous solution. This is demonstrated by the following equilibrium; the complex ion \([\text{PtCl}_4]^{2-}\) is unstable in aqueous solution and disproportionates to elemental platinum and the platinum(IV) complex ion\(^{62}\). However this is not a spontaneous process and does not occur under mild conditions of room temperature. This is amply demonstrated by the use of aqueous potassium tetrachloroplatinate as a nuclear magnetic resonance spectroscopy (NMR) reference standard, which can be stored and used for years.

\[
2[\text{PtCl}_4]^{2-} \rightarrow \text{Pt}(0) + [\text{PtCl}_2]^{2-} + 2\text{Cl}^-
\]

Scheme 2. The disproportionation of the divalent tetrachloroplatinate anion in aqueous solution.

Platinum(IV) species can be reduced to platinum(II), and platinum(II) oxidised to platinum(IV), by iron(II) and iron(III) respectively. These were originally thought to involve a platinum(III) intermediate\(^{63}\), but this theory was subsequently thrown into doubt by an investigation on the reduction of platinum(IV) by chromium(II) which showed the rate determining step to involve a two electron transfer\(^{64}\). Platinum(IV) is stable with regard to oxidation, which is why there are so few platinum(V) or platinum(VI) species known. This is due to the electronic configuration of the valence orbitals of platinum(IV) species being \(d^6\). The low spin octahedral geometry results in full \(xy, xz\) and \(yz\) orbitals, which is a more stable state than having unpaired electrons which would be the case in the platinum(V) or (VI) oxidation states.

3.2.4 Geometry of platinum complexes with varying oxidation state.

Platinum in different oxidation states displays varying coordination number and structure. The most common are summarised in table 6. By far the most studied platinum (0) complexes are those of phosphines and arsines. They were used as models for the compounds formed when small molecules are chemisorbed onto the metal. This was believed to be at the heart of the metal’s catalytic action. Zerovalent platinum complexes are stabilised by ligands that are both strong \(\sigma\) donors and strong \(\pi\) acceptors. Amongst these are the two aforementioned and nitric oxide, ammonia, isocyanide and cyanide\(^{32}\).
Divalent platinum complexes with a coordination number of four are always square planar in structure. Having square planar geometry leads to the possibility of cis and trans isomers for mixed ligand complexes. An obvious example is cisplatin and transplatin.

<table>
<thead>
<tr>
<th>Oxidation state</th>
<th>Coord. No.</th>
<th>Structure</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>Tetrahedral</td>
<td>[Pt{P(OR)₃}₄]</td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>Planar</td>
<td>[Pt(PPh₃)₃]</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>Linear</td>
<td>[Pt(PPh₃)₂]</td>
</tr>
<tr>
<td>2+</td>
<td>4</td>
<td>Square-planar</td>
<td>[PtCl₂(NH₃)₂]</td>
</tr>
<tr>
<td>2+</td>
<td>4</td>
<td>Tetrahedral</td>
<td>None known</td>
</tr>
<tr>
<td>4+</td>
<td>6</td>
<td>Octahedral</td>
<td>[PtCl₄(NH₃)₂]</td>
</tr>
</tbody>
</table>

Table 6. The common oxidation states, coordination numbers and structures of platinum complexes.

Platinum(IV) complexes exhibit solely octahedral geometry, and like platinum(II) complexes they are diamagnetic as the low spin crystal field splitting renders the $\varepsilon^2$ and $\chi^2 - \gamma^2$ orbitals empty and the electrons of the $\pi$ bonding orbitals all paired. Platinum(II) and platinum(IV) complexes make up the bulk of platinum complexes studied.

Much less common are platinum complexes in oxidation states of one, three, five and six. The reason for the rarity of odd number oxidation states is that they would involve an unpaired valence shell electron which renders the complex unstable. In fact the only reports of univalent platinum complexes are clusters of more than one platinum complex sub-unit. This facilitates the lone electron being paired with a similar electron on another platinum centre resulting in Pt-Pt bond involving an electron pair. Trivalent platinum compounds are also rare. Some reaction intermediates have been claimed to be platinum(III), only to later be discredited. Also claimed are some di-platinum(III) compounds such as Pt₂O₃, but these have later been found to be a combination of platinum(II) and platinum(IV). This is concluded as the complexes are diamagnetic, indicating there are solely electron pairs. Platinum(III) would be paramagnetic because of the unpaired electron. Platinum
triiodide has also been claimed but again is diamagnetic. As the structure has been confirmed as octahedral by X-ray crystallography, it is thought to be Pt(II)Pt(IV)I₆ which is consistent with its observed diamagnetism. Platinum trichloride and tribromide have also been claimed but their dark colours are inconsistent with the claimed oxidation state, e.g. PtCl₂ is yellow green and PtCl₄ is red brown, however the claimed trichloride is black.

Of all the odd number oxidation states of platinum, platinum(V) is most common. The complex ion [PtF₆]⁻ is the most well known pentavalent platinum complex, the bulk of the work being carried out by Bartlett et al. It is found in combination with alkali metals, oxygen and xenon. The alkali metal hexafluoroplatinates have been shown by X-ray diffraction to have the complex anion in an octahedral geometry. They are also readily reduced to platinum(IV), the reaction in water being violent. This is also an indication of how difficult it is to oxidise platinum(IV) complexes, the ionisation potential of Pt (IV) → Pt (V) is 55 eV which is very large. Xenon has a similar first ionisation potential to oxygen, being approximately 12 and 13 eV respectively. As a dioxygenyl hexafluoroplatinate complex had been isolated and confirmed by X-ray diffraction, it was considered by Bartlett et al. that xenon might behave in the same way. The complex Xe⁷⁺[F₆Pt]⁻ and the others mentioned have all been found to be paramagnetic, indicative of the unpaired valence electron of pentavalent platinum. These complexes are by no means easy to prepare and require either high temperatures of 250-300 °C, or high temperatures and high pressure.

The fluoride of platinum is the only hexavalent platinum compound known. It is made by electrically heating a platinum wire in fluorine close to a liquid nitrogen cooled surface. It is a red black solid that melts at 61.3 °C and boils at 69.1 °C. It is thermally unstable decomposing to form fluorine and platinum tetrafluoride. It is also extremely reactive, being a very strong oxidising agent. It has pure octahedral symmetry which is evident in its IR absorption spectrum.

Summing up, the chemistry of platinum is vast and it has only been possible to lightly scratch the surface. There are still many areas of platinum chemistry that warrant further investigation. The present project deals with a tiny area of platinum chemistry, namely platinum mediated cycloadditions, and this is expanded on in section 4.2.
4.0 Previous work

The synthesis of classic platinum drugs such as cisplatin and carboplatin is a lengthy process of ligand exchange involving several steps, and employing expensive silver reagents. The synthesis of cisplatin is outlined in scheme 3 below.

$$\begin{align*}
\text{K}_2\text{PtCl}_4 & \xrightarrow{\text{NH}_3} \text{H}_2\text{N}^+\text{Pt}^\text{I}^- \xrightarrow{\text{AgNO}_3(\text{aq})} \left[\begin{array}{c}
\text{H}_2\text{N}^-\text{Pt}^\text{OH}^\text{I}^- \\
\text{H}_2\text{N}^-\text{Pt}^\text{OH}^\text{I}^-
\end{array}\right] + \text{AgI} \\
\text{Cl}^- & \xrightarrow{} \text{H}_2\text{N}^-\text{Pt}^\text{Cl}^-
\end{align*}$$

Scheme 3. The outline synthesis of cisplatin.$^75$

The above synthesis begs the question, why not stop the synthesis at the dihydroxy stage? After all it has already been stated in the aqueous chemistry of cisplatin section, that it is thought cisplatin is converted to dihydroxydichloro platinum(II) in the blood stream. The answer to this is that cisplatin and its full synthesis were known decades before any serious understanding of how it worked was postulated. In fact this synthesis was proposed some thirty years before it was discovered that cisplatin had any anti-tumour activity at all. More importantly, although the dihydroxy complex is thought to exist in aqueous solution, it has not been possible to isolate it as a solid.

The idea behind the present project is to construct the ligands directly in the platinum coordination sphere.

This approach has a number of advantages:

1. The stereochemistry surrounding the platinum centre should remain unchanged by the process.
2. It facilitates a modular approach where substituents can be varied, easily building up a large bank of complexes from relatively few components.
3. This allows for a combinatorial chemistry approach.

In the past, the cycloaddition products $\Delta^4$-1,2,4-oxadiazolines have proven difficult to prepare. The 1,3-dipolar cycloaddition of nitrones to nitriles is essentially the only
method of preparing them. This reaction works well with electron deficient nitriles, but normal alkyl substituted nitriles are not reactive enough. Acetonitrile for example, does not react, even at high temperatures or pressures. Microwave irradiation does not induce a reaction. This is why up until recently only a few 1,2,4-oxadiazolines were known, and there was not a method for the enantioselective synthesis of these compounds.

A first improvement was achieved when it became apparent that platinum nitriles underwent cycloaddition with nitrones relatively easily compared to uncoordinated nitriles. Platinum(IV) activates nitriles more strongly than platinum(II), indicating that the metal acts as a Lewis acid and withdraws electron density from the CN triple bond.

![Scheme 4](image)

Scheme 4. Bis cycloaddition of platinum bis benzonitrile to a nitrone.

This effect is so marked that in the case of coordinated cinnamomitrile, cycloaddition occurs exclusively at the CN triple bond instead of the C=C double bond which is the preferred site for cycloaddition in uncoordinated cinnamomitrile. The reaction is also accelerated from days to hours, and the yield improved by microwave irradiation.

The mechanism of the 1,3-dipolar cycloaddition of nitrones to nitriles is thought to follow a classic cycloaddition reaction, i.e. a concerted one step mechanism with the ring bonds being formed simultaneously. A recent theoretical study by G. Wagner into the effect of Lewis acids on the mechanism has shown it is very likely that the metal mediated reaction follows a two step process with an intermediate. The Lewis acid, which is coordinated to the nitrile, does not alter the reactivity of the nitrile, it stabilises the intermediates, transition states and products. This is shown
schematically below in figure 22. For both kinetic and thermodynamic reasons the $\Delta^4$-1,2,4-oxadiazolines are preferred over the $\Delta^4$-1,2,5 regioisomer.$^8$.

![Diagram of reaction mechanism](image)

**Figure 22.** The two step mechanism of the cycloaddition of Lewis acid coordinated nitriles to nitrones.

This reaction is quite general and PtCl$_2$(sulphoxide)(nitrile) complexes for example, undergo cycloaddition equally well (scheme 5)$^{85}$. In addition, if a chiral sulphoxide is used, complexes with two chiral centres can be prepared. If the chiral sulphoxide is enantiomerically pure then two diastereoisomers will result.$^{85}$

![Scheme 5](image)

**Scheme 5.** Outline synthesis of mixed nitrile DMSO platinum complexes.
4.1. Aims of the study.

The previous platinum $\Delta^4$-1,2,4-oxadiazoline complexes produced proved to be only soluble in chlorinated organic solvents and it was not possible to test them for biological activity. They were also far too apolar to be of much use as anti-cancer agents.

In the framework of this project, the main objective is the introduction of more polar oxadiazoline ligands onto the platinum centre. This should make the platinum complexes more soluble in polar and aqueous compatible solvent systems. In this way the previous synthetic methodologies will be improved and extended.

Both mono and bis oxadiazoline platinum complexes will be prepared. An analogous approach will be applied to ruthenium complexes.

The platinum oxadiazoline complexes produced will be biologically tested for anti-tumour effect.

The reactivity of the platinum oxadiazoline complexes will be studied with regard to substitution at the metal centre, and oxidative addition, also at the metal centre. Little is known about the reactivity of this class of compound, and it is intended to elucidate this in a small way.
4.2. General considerations about the synthetic strategy.

For the present study, platinum nitrile complexes were chosen as targets because it is known from previous experiments that nitriles (e.g. benzonitrile and cinnamoniitrile), when coordinated to platinum(IV) or platinum(II), are activated to undergo [2+3] cycloadditions with nitrones. The expected reaction should also occur between more polar platinum nitrile complexes and more polar nitrones.

4.2.1. Preparation of nitrones.

One way of making oxadiazolines more polar is the introduction of polar groups on the phenyl ring of the nitrone. This was achieved using commercially available raw materials such as substituted benzaldehydes. Nitrones are one of the few dipolar reagents that do not need to be used in situ but can be isolated, purified and stored. They can be prepared in many different ways, e.g. by oxidation of $N,N$-dialkyl-hydroxylamines, oxidation of secondary amines or imines, $N$-alkylation of oximes, or condensation of carbonyl compounds or imines with hydroxylamines. These methods are shown in figure 23. The condensation of aldehydes with $N$-methylhydroxylamine, shown in scheme 6, has been shown to be a straightforward route, and was employed in this study.

![Figure 23. Various ways of preparing nitrones.](image)
Scheme 6. The condensation of aldehydes with N-methyl-hydroxylamine.

R = H or Me

4 hrs reflux
NaXO
HONHMeCl
CH2Cl2
MeOH

The reaction conditions in scheme 6 are specific to R = H or Me. Different conditions are required when the substituent is: p-OH, p-COOH, p-MeOCH2CH2O, p-dimethylamino, p-N⁺(Me)₃, m-MeOCH₂CH₂O, o-MeOCH₂CH₂O, o-sodium sulphonate salt, m-OH and m-COOH, see section 8 (experimental section).

In the reaction, solid Na₂CO₃ is applied as a base and methanol is used as co-solvent to dissolve the N-methyl-hydroxylamine-hydrochloride and to facilitate its deprotonation. Unfortunately, it also dissolves other organic compounds, and that is why a two step evaporation-extraction procedure is used to isolate the product. All nitrones were made in this way unless otherwise stated in section 8.

4.2.2. Preparation of platinum nitrile complexes:

In order to produce results that are complementary to the previous studies, new platinum nitrile complexes of the general type [PtX₂(RC₄H₄CN)₂] (R = H, OH, COOH, 2-MeOCH₂CH₂O Me₂N and p-N(CH₃)₃⁺ CH₃SO₄, X = Cl, Br and I) were attempted. The reactions of those platinum nitrile complexes isolated pure, with various nitrones were studied. The method of preparation of platinum(II) complexes was varied to produce mainly cis or mainly trans complexes.

The three routes used were:

1. A variation on the Eysel et al. method⁹ which is an aqueous route starting with potassium tetrachloroplatinate. This is dissolved in water and acetonitrile and left to exchange at room temperature. The initial kinetic product is predominantly cis, but if left longer the thermodynamic trans product is produced as well. For reasons of symmetry and polarity it is believed the trans isomer crystallises out first. The cis isomer has a net
dipole whereas the *trans* does not. The opposing dipole vectors cancel out in the *trans* case, this is shown in figure 24 below. Ligand exchange of acetonitrile with other nitriles, such as benzonitrile, was carried out in chloroform at 60 °C using a ten molar excess of ligand, again producing a mixture of isomers.

![Figure 24. Symmetry and polarity of cis and trans platinum nitrile complexes.](image)

2. To produce a predominantly *trans* product a variation on the Kharasch method of direct ligand attachment to platinum was employed, using platinum dihalide and the desired ligand. A large excess of ligand was used and the platinum dihalide gradually stirred into the free ligand at 110 °C. Temperature was varied depending on the melting point of the ligand, and in some cases toluene was used as solvent.

3. To produce a predominantly *cis* product, direct ligand substitution was carried out at room temperature using the aqueous route, potassium tetrachloroplatinate, and the desired ligand in place of acetonitrile.

It has been mooted that a mixture of *cis*- and *trans*-bis nitrile platinum complexes can be converted to mainly *trans* by heating at 120 °C in the solid state, or in kerosene. This was attempted using the present complexes. Thin layer chromatography (TLC), NMR and IR spectroscopic studies performed before and after were used to determine which signals correspond to each isomer, and whether the method was successful in general. There are various possible mechanisms to explain this transition. The most simplistic is that with an input of energy the square planar *cis* complex assumes a tetrahedral arrangement, and then relaxes back to square planar but with the similar ligands in a *trans* position. This is shown in figure 25.
Figure 25. Solid state mechanism for conversion of a cis platinum to a trans platinum complex.

Another mechanism is that one of the ligands, most likely a nitrile becomes detached, it then attaches to the planar three ligand platinum complex to give a mixture of cis and trans isomers. This is an example of a dissociative mechanism\textsuperscript{52}, shown in figure 26 (a).

Figure 26 (a). Dissociative mechanism for conversion of cis to trans platinum complexes.
Another possibility is an SN$_2$ type mechanism is where the bond between platinum and one benzonitrile ligand weakens as the bond between the incoming benzonitrile forms. The result is a five coordinate intermediate. Observation of figure 26 (b) shows that either a cis or trans isomer could form in contrast to the associative mechanism shown in figure 77. The other possibility is an associative mechanism outlined below in figure 26 (c). This involves a five coordinate intermediate which would require the chlorine in the square plane to labilise the nitrile trans to it. Most probably the transformation is effected by more than one mechanism.

![Figure 26 (b). SN$_2$ type mechanism intermediate.](image)

4.2.3. Cycloaddition of nitrones to platinum nitrile complexes:

The cycloaddition of nitrones to platinum nitrile complexes creates a new centre of chirality which is situated at the N-CHR-N carbon atom in the heterocycle. We can expect the formation of two diastereomeric products, in different ratios. Cycloadditions were initially attempted in an NMR tube which facilitated monitoring the progress of the reaction by proton NMR spectroscopy. If successful they were scaled up. Nitrones and platinum nitriles were dissolved in a suitable deuterated
solvent in the molar ratio of 2:2:1 for bis cycloadditions and 1:1 for mono. The NMR tube was placed in a heating block at 60 °C for up to 10 days for cycloaddition to both nitriles, or left at room temperature for a similar period for mono cycloaddition. Proton NMR spectroscopy was regularly performed to monitor the progress of the reactions. Appearance of a broad singlet at around 5.90 ppm and a doublet at 8.80-9.00 ppm in the proton NMR spectrum is indicative of cycloaddition. This is demonstrated by the proton NMR spectra of a nitrone, and a mono cycloaddition product shown below in figures 27 and 28 respectively. The HC=N proton of the nitrone appears in the aromatic region due in small part to ring current effects and its close proximity to the ring, but mainly to the electronic effect of the H-C=N and its associated magnetic field. After cycloaddition, the double bond is replaced by a H-C-N single bond, which does not have a large magnetic field compared to the double bond, and the proton signal moves out of the aromatic region. The position of the doublet at 9.05 ppm is an effect of the 5dx2 non-bonding orbital of platinum which effectively deshields the two equivalent ortho phenyl protons of the C=N-Ar ring. This is a consequence of the geometry of the molecule and the close proximity of the phenyl rings to the z axis.

Figure. 27. Proton NMR spectrum of N-methyl-C-phenyl nitrone in CDCl3 including an expansion of the aromatic reading.
It is known that *trans*-platinum nitrile complexes can form both mono and bis cycloadducts, whereas their *cis* counterparts can only form mono-adducts. This is thought to be due to the extreme steric hindrance that would result from having two oxadiazoline ligands in a *cis* positions. If the mono oxadiazoline complex is not isolated and further reaction allowed to progress, the complex decomposes. This characteristic can be, and was, used to determine the stereochemistry of starting platinum nitrile complexes, where this could not be achieved by spectroscopic means.

Figure. 28. Proton NMR spectrum of a mono oxadiazoline platinum complex in CDCl₃ with the main aromatic region expanded.
5. Results and discussion

5.1. Production of nitrones.

Nitrones are more formally named benzylidene-methylamine-N-oxides. Nitrones were produced using accepted methods without much to report. The route used was the condensation of an aldehyde with N-methyl-hydroxylamine. This method was chosen over the other methods outlined in the section 4 as it is a direct, one step route to the nitrone. The other methods such as oxidation of imines or alkylation of oximes would require the starting reagents to be made as a separate step. An additional problem with the oximes is that alkylation can occur at the nitrogen forming a nitrone, or the oxygen giving the oxime ether. This is dependent on the configuration of the oxime and reaction conditions. Anti-benzaldoximes yield nitrones while syn-benzaldoximes yield oxime ethers as shown in scheme 7.

![Scheme 7](image.png)

Scheme 7. A mixture of syn and anti oximes yields a mixture of products.

Aldehydes were chosen over ketones as the aim of the project is to make complexes that are more polar and consequently more soluble in polar solvents and aqueous systems. The formyl proton is acidic, and a ketone, lacking this proton, would certainly result in a more lipophilic complex. Unless non-symmetrical ketones were chosen there would be no chiral centre in the resulting oxadiazoline. It is also unlikely that non-symmetrical ketones with a benzene ring containing various different polar substituents would be commercially available, and this would make the overall synthesis more complicated and less cost effective. Another problem with ketones is that the reaction compared to aldehydes is slow, due to the increased steric hindrance at the carbonyl carbon. The water of condensation has to be removed to shift the equilibrium of the reaction to the right hand side. This requires a Dean-Stark apparatus. Also the products of the condensation of ketones are mixed cis and trans isomers. If one was significantly more reactive than the other this could affect the product of cycloaddition and yield. On the other hand, aldehydes only produce one
product which is the isomer with the phenyl group and the oxygen on the same side of the double bond. This is confirmed by Nuclear Overhauser enhancement NMR spectroscopy (NOESY), where no correlation is visible between the N-Me and the ortho phenyl protons. This is shown in figure 29. In short, aldehydes are the first choice of reagent for making nitrones as they are cheap, off the shelf starting materials, and produce one nitrone only. Using aldehydes with a variety of electron withdrawing and donating functionalities facilitates the rapid production of a bank of nitrones with similar but slightly different properties. For example, the pKₐ of benzaldehydes with an hydroxy group show the meta-substituent to contain a less acidic proton than the ortho or para. This is due to the electron withdrawing formyl group which affects the ortho and para positions but not the meta position. In this way a family of platinum oxadiazoline complexes can be produced and studied, and valid comparisons drawn.

\[ \text{O} \quad \text{Me} \quad \text{N} \quad \text{R} \quad \text{H} \quad \leftrightarrow \quad \text{O} \quad \text{Me} \quad \text{N} \quad \text{R} \quad \text{H} \]

Figure 29. Two of the resonance forms of benzylidene-methylamine-N-oxides.

In the left hand structure of figure 29 there is free rotation about the CH-N bond and this eliminates the stereochemistry associated with the right hand structure. Attack comes from both sides and the products are a mixture of geometric isomers. If it was the case that the nitrones existed in two stereoisomeric forms, namely cis and trans, this would still have no effect on the resulting oxadiazoline. According to the proposed two step mechanism⁸⁴ the double bond breaks in the intermediate, again facilitating free rotation and the end result is a mixture of enantiomers.

To produce more polar nitrones, benzaldehydes with polar substituents such as amino, carboxy and hydroxy were chosen. It was hoped that this would impart polarity in the platinum oxadiazoline end products and make them more soluble in a greater range of organic solvents and possibly aqueous systems as well.
The following nitrones were made (product numbers in brackets).

\[
\begin{align*}
\text{HONH}_2\text{MeCl} + \text{R}^+\text{H} & \rightarrow \text{R}^+\text{H} + \text{HONH}_2\text{MeCl} \text{O} \quad \text{(13)} \\
\text{R}=\text{H}(1) \text{ and } \text{para}-\text{OH}(4), \text{COOH}(9), \text{2-MeOC}_2\text{H}_4\text{O}(7), \text{(Me)}_2\text{N}(11), \text{(Me)}_3\text{N}(12), \\
\text{meta}-\text{OH}(3), \text{COOH}(8), \text{2-MeOC}_2\text{H}_4\text{O}(6), \\
\text{Ortho}-\text{OH}(2), \text{2-MeOC}_2\text{H}_4\text{O}(5), \text{SO}_3(10)
\end{align*}
\]

Scheme 8. Production of nitrones.

A dinitrone\(^9\) (13) was also made from the dialdehyde terephthaldehyde with the intention of producing a multinuclear platinum compound. Specific reaction conditions and yields are contained in section 8.

\[
\begin{align*}
\text{HCONH}_2\text{MeCl} + \text{2HONH}_2\text{MeCl} & \rightarrow \text{N}^+\text{Me} \text{O}^{-} \quad \text{(13)} \\
\end{align*}
\]

Scheme 9. Production of a dinitrone.

By using electron withdrawing and donating substituents in \textit{ortho} or \textit{para} positions it was hoped the polarity and subsequent reactivity of the nitrones would be affected one way or the other, and this could be studied. The specific results are discussed in the platinum oxadiazoline section (5.4). Incorporating a positively charged quaternary ammonium ion would introduce a new binding site to the resulting platinum oxadiazoline complex. There is the possibility of binding to the negatively charged phosphate ester bridges of DNA. Having hydroxy-, carboxy- or amino-substituents, containing a proton, facilitates the possibility of hydrogen bonding with nitrogen or oxygen in the DNA.
The major confounding problem making these nitrones was that carboxy and hydroxy groups especially in the para position, made the nitrones so polar they were difficult to isolate from any residual inorganics left after reaction. In the case of para-carboxy nitrone, this was insoluble in anything but water, so not only was isolation of the product impossible, but hydrolysis of the nitrone was extremely likely. Soxhlet extraction for 10 days using DCM only yielded a few milligrams, barely enough for a proton NMR spectrum. The absence of a signal at ~10.0 ppm in the spectrum suggests reaction of the aldehyde had taken place. In the end it was not possible to proceed further with this particular nitrone.

Para-hydroxy, meta-carboxy and meta-hydroxy substituted nitrones, could be isolated in low yield of 30% by slow recrystallisation from methanol in the freezer. The yields improving the longer the crude products were left in the freezer. In the case of the para-hydroxy nitrone, the procedure was improved by using ethanol instead of DCM as solvent for the synthesis. The higher reflux temperature meant that not only was more energy imparted to the system, but also the starting aldehyde was completely soluble in the reaction mixture. The reaction proceeded faster and went to completion resulting in a higher yield, the product still being recrystallised from methanol.

The synthesis of the ortho-hydroxy substituted nitrone was trouble free; the starting aldehyde and corresponding nitrone being soluble in DCM, which was used to extract the product from the crude after vacuum evaporation. This particular nitrone had been used within the group to make a platinum(IV) oxadiazoline complex, so it was deemed a suitable candidate for cycloaddition with platinum(II) nitrile complexes. Hydroxy-substituted nitrones have been reported in the past, but the age of the publications (circa 1965) meant there was no detailed characterisation.

To overcome the problem of solubility in the hydroxy-substituted nitrones, it seemed we had gone from one extreme to the other, it was decided to functionalize the hydroxy groups with an alkylation that would result in glycol ether substituents. 2-bromo-(1-methylethyl ether) was used to alkylate p-hydroxybenzaldehyde following a thermal Williamson ether synthesis using methanol as solvent. Methanol was used instead of DMF as it was considered the product would only be extracted from DMF using an aqueous work up with some difficulty. Glycol ethers are known
to be soluble in a wide range of solvents including water. The reaction was slow (10 days) and the yield poor (40%), but this was greatly improved with the use of microwave irradiation. This is described separately in the section on alkylation, 5.2. The microwave procedure was extended to meta- and ortho-hydroxybenzaldehydes with similarly good results.

\[
\begin{align*}
\text{H} & \quad \text{C} \\
\text{O} & \quad \text{H} \\
\text{C} & \quad \text{MeOH} \\
\text{K}_2\text{CO}_3 & \quad \text{Microwave}
\end{align*}
\]

Scheme 10. Microwave synthesis of formyl phenyl ethers. \(X=\text{Br or Cl} \).

Nitrones were produced from all three glycol ether substituted benzaldehydes in high yield without difficulty using ethanol as solvent.

A nitrone was made from para-dimethylaminobenzaldehyde without problem but it was considered cycloaddition with platinum nitrile complexes would be confounded by competition for the platinum coordination site between the amino and nitrile nitrogens. In an attempt to overcome this problem it was decided to methylate the nitrone using dimethyl sulphate. It was considered that if the powerful methylating agent methyl iodide was used it might methylate in other positions, or the iodide may interfere with the platinum by way of exchange with chloride. Initially the methylation was attempted using methanol as solvent but this was unsuccessful. The result was a mixture of products including the aldehyde, possibly an acetal or hemiacetal and some starting material. All attempts to methylate the nitrone were unsuccessful, and this is described in section 5.2. Finally methylation of the dimethylaminobenzaldehyde was attempted and after many failures the optimum conditions of no solvent other than a fourfold excess of dimethyl sulphate, 70 °C for one hour and a nitrogen atmosphere were discovered. A nitrone was successfully made from the product of this reaction.
R= CHO or CN.

Scheme 11. Production of a quaternary amine.

The reactions of the nitrones with platinum complexes are described in section 5.4, 'Production of platinum oxadiazoline complexes', only to mention here that the nitrones with electron withdrawing groups did not undergo cycloaddition giving the desired product, whereas the nitrones with electron rich hydroxy groups especially in meta and para positions did. However the reaction of these was slower than for the unsubstituted nitrone.
5.2. The O-alkylation of phenols and the methylation of tertiary amines

Apart from the work on platinum directly concerned with the main aims of the project, two things arose from initial work on nitrones and nitriles. Firstly, introduction of an hydroxy group on the phenyl ring of nitrones or nitriles greatly reduces their solubility in chlorinated solvents. In the case of nitrones, acetone can be used as solvent, but with platinum nitriles the hydroxy group renders them only partially soluble in acetone. Their solubility in methanol is better, but this is not the solvent of choice for platinum coordinated cycloadditions as it can reduce the platinum(II) to platinum (0), being oxidized to formic acid in the process. Good solubility is important during these reactions in achieving the correct stoichiometric mix. A substituent that would make the precursors more soluble in a wide range of organic solvents was required. It was decided that an alkylation on the hydroxy group resulting in a glycol ether substituent would be promising as such compounds are known in the coatings industry as coalescent solvents and are compatible with a wide range of solvents. Initially a thermal Williamson ether synthesis was used but the reaction time was long (96 hours), and the yield low (40%). Clearly what was required was an improvement on the Williamson ether synthesis with regards to reaction time, yield and work up procedure. Microwave irradiation was employed for a series of alkylations on the ortho-, meta- and para-hydroxy groups of substituted benzaldehydes and benzonitriles, with excellent results.

The second matter worthy of note is that a rapid method of quaternisation of a tertiary amine had been developed. This was carried out to eliminate competition from the nitrogen of the tertiary amine for coordination to platinum rather than the nitrogen of the nitrile group. Being a more expedient method than the accepted one of using an alkyl halide and refluxing DMF, it was decided to spend some time alongside the main project to try and extend this work.
5.2.1 Rapid microwave assisted synthesis of phenyl ethers under mildly basic and water free conditions.

The major confounding problem with the cycloadditions attempted in year one was the poor solubility of the hydroxy-substituted platinum nitrile complexes. This was a two-fold problem, either the platinum nitriles were poorly soluble meaning the nitrene was always in excess and only bis products were produced, or secondly, if mixed solvent systems incorporating methanol were used, there was a competing reaction which reduced the platinum complex to elemental platinum. This had the result of either a reduced yield of cycloaddition product, or no cycloaddition at all.

A Williamson ether synthesis had been successfully used to functionalise the hydroxy group on one of the nitrones used, and it was decided to extend this approach to the hydroxy-substituted benzonitrile platinum complexes. Utilising 2-bromo-(1-methylethyl ether) as alkylating agent results in a glycol ether substituent, and as already explained, this should impart greater solubility in a wider range of solvents to the compounds.

Due to the long reaction time and poor yield in the previous thermal reaction (8.2.1.14, 40%, 96 hours), microwave irradiation was employed to improve the yield and reaction time. The results were encouraging and a significant improvement in the Williamson ether synthesis has been developed where pure products in high yield can be made in less than an hour from start to finish. The reactions were optimized with regard to yield by varying reaction time and temperature, and bromo- and chloro-substituted alkylating agents were used for comparison. Initially, microwave irradiation was used for only 1 minute and TLC was used to monitor the progress of the reaction. The time was then increased to five minutes with successive increments of five minutes. When the TLC looked promising the reaction was worked up. This procedure was repeated until the optimum conditions were reached. For both the formyl and cyano phenols, the para-substituted phenol was optimized and the optimum conditions applied to the ortho- and meta-substituted phenols. The microwave reactor works by setting the required temperature and microwave absorbency settings (high or normal). A large initial pulse swiftly brings the reaction
up to the required temperature, and further smaller pulses maintain the temperature. The reactor monitors temperature and pressure in the reaction vessel.

5.2.1.1. Discussion and results.

Microwave irradiation was first used in organic synthesis in 1986\textsuperscript{96,97}, and since then its use has become widespread\textsuperscript{98-101}. It is generally used where thermal reactions work but are slow, or produce low yields, and microwave irradiation significantly speeds up the reaction. This is thought to be due to the so called microwave effect. Polar moieties in the substrates and solvents are good absorbers of microwaves and this produces hot spots. It is thought this is what increases the rate. With the present compounds it could just as likely be due to the high temperatures and pressures associated with the reactions. The use of microwave irradiation in synthesis, lends itself to combinatorial chemistry and automated processes employing high throughput schemes\textsuperscript{102-104}, and is thus attractive to commercially driven researchers.

Ethers are typically prepared using the classical Williamson ether synthesis from an alkyl halide and an alkoxide or phenoxide salt. To date, most microwave methods developed for the preparation of aliphatic ethers involve a large excess of either of the strong bases potassium or sodium hydroxide\textsuperscript{105-107}.

Phenols, being more acidic than aliphatic alcohols, require a much milder base such as potassium or sodium carbonate to effect reaction. The use of potassium carbonate has been occasionally reported in thermal synthesis, although these reactions have required long reaction times (up to 72 hours)\textsuperscript{108-110}. It is therefore surprising that almost all reaction schemes previously described for alkylation of phenols under microwave irradiation employ a large excess of sodium or potassium hydroxide\textsuperscript{111}, often in an aqueous medium\textsuperscript{112-115}. This could lead to side reactions such as degradation of the alkylating reagent to the corresponding alcohol as the hydroxide ion is both basic and considerably nucleophilic. These reactions are therefore very often run as a two-step process, initially forming the phenoxide salt by stirring the phenol with base, and subsequent addition of the alkyl halide. This can also lead to unwanted side reactions of sensitive functional groups present in the substrates such
as hydrolysis of nitrile groups. As a consequence, only substrates that do not contain any functional groups prone to hydrolysis or reaction with bases have been used. Other schemes employ solvents with a high boiling point that can be difficult to remove such as DMF or glycols\textsuperscript{116,117}, and this can cause problems if the reaction product is not compatible with an aqueous work-up, due to considerable solubility in water. In many cases phase transfer catalysts have been employed to effect reaction\textsuperscript{118}. This can lead to contamination of the product or the need for more sophisticated and time consuming work-up procedures. With commercial considerations in mind this must increase process costs. In general, the previous methods have taken the thermal reaction mixtures and applied microwaves to them, rather than tailoring the reaction to suit microwave irradiation. Very often domestic microwave ovens have been used which are more powerful than bespoke microwave reactors, and they require moderators such as sand or silica. The present method is by far the quickest and simplest method for the alkylation of phenols to date.

In an attempt to extend the application range of microwave-assisted methods to more sensitive substrates and partially water-soluble products bearing glycol ether side chains, it has been found that phenols can be alkylated under microwave conditions in the presence of a stoichiometric amount of mild base namely potassium carbonate, and methanol as solvent, in non-aqueous conditions and without the need of a phase transfer catalyst. This is a true ‘one pot’ synthesis.

\[
\begin{align*}
\text{R} \quad \text{OH} + \quad \text{X-} \quad \text{O} - \quad \text{K}_2\text{CO}_3 \quad \text{MeOH} \quad \text{Microwave} \\
\text{O} \quad \text{R} 
\end{align*}
\]

Scheme 12. Microwave assisted Williamson ether synthesis using substituted phenols.

The reaction conditions which are given in Table 7 are favourably mild, have short reaction times and high yields. The method is useful for differing areas of chemistry, as the target compounds chosen for this work are frequently used as precursors of pharmaceutically relevant compounds\textsuperscript{119-122}, liquid crystalline compounds\textsuperscript{123,124} or polymer materials\textsuperscript{125,126}.
Recently a paper on microwave-assisted methylation of phenols suggested the use of excess potassium carbonate (K$_2$CO$_3$) in refluxing acetone$^{128}$. However, at the high temperatures required with the alkylating agents used in the present study, acetone undergoes a competing aldol reaction with the aromatic aldehydes which are among the substrates. Thus, microwave heating of a mixture of 4-hydroxybenzaldehyde and 0.6 equivalents of K$_2$CO$_3$ in acetone at 140 °C for 30 min produced 24% of E-4-(4-hydroxyphenyl)-3-buten-2-one. Acetone is therefore not the solvent of choice for the present work. This is shown in the reaction scheme below.

\[
\begin{align*}
\text{C}=\text{O} + \text{HO-CHO} & \xrightarrow{\text{MW}} \text{H}_3\text{C}-\text{C}-\text{C}(\text{OH})\text{H} \\
\text{K}_2\text{CO}_3 & \xrightarrow{\text{K}_2\text{CO}_3} \text{H}_3\text{C}-\text{C}-\text{C}(\text{OH})\text{H} - \text{H}_2\text{O}
\end{align*}
\]

Scheme 13. The competing aldol condensation reaction when acetone is used as solvent.
Methanol, in contrast, can be used without being alkylated. This is consistent with previous reports on unsuccessful attempts to alkylate aliphatic alcohols in the presence of carbonate as a base. The use of this weak base in only stoichiometric amounts further assures the mildest possible conditions and the method lends itself to schemes using base sensitive substrates.

2-bromo-(1-methylethyl ether) was used in close to equimolar ratio (1.2 equivalents), whereas the less reactive 2-chloro-(1-methylethyl ether) required a threefold excess and higher reaction temperatures to achieve comparable results. The chloro-alkylating agent also required longer reaction times when used with hydroxybenzaldehydes. Despite the chloro-alkylating agent requiring a threefold excess, this would still be attractive from the commercial viewpoint as the chloro-compound is considerably cheaper than the corresponding bromo-compound.

The hydroxybenzonitriles were slightly less reactive than the corresponding hydroxybenzaldehydes, and required longer times and higher temperatures with both alkylating agents. However, there seems to be no straightforward relationship between the reactivity and the pKa values. This is plausible because the reactivity depends on a delicate balance between the ease of deprotonation of the phenol and the nucleophilicity of the resulting phenoxide. Electron withdrawing substituents in the 2- or 4- position facilitate deprotonation, as reflected in a lower pKa value. On the other hand the nucleophilicity of the phenoxide oxygen atom is decreased due to delocalisation of its negative charge into the aromatic ring.

The work-up procedure was designed avoiding water from which the products would have been extracted with difficulty, and with some loss of yield, and only processes that are easily carried out by automated systems were applied. After evaporation of the solvent from the crude reaction mixture, hexane was used to selectively extract the product from the inorganic salts. Residual phenolic starting material is not released from the inorganic solid under these conditions. The hexane can also be recycled and reused. In all cases, the product was obtained in high yield and purity within one hour. Due to a previous report on the use of a mixture of NaF and K₂CO₃ as base for the alkylation of less sensitive substrates, the synthesis of the target compounds was
attempted using solvent free conditions and K₂CO₃ as solid support. However, this led to a significant reduction in both yield and purity of the products, compared to the analogous reaction in methanol. Substituting methanol with ethanol which is cheaper and less toxic led to drastically reduced yields. This is presumably due to the lower solubility of the K₂CO₃ in ethanol (MeOH, 16500 ppm, EtOH, 904 ppm).

Using thermal conditions, 3- and 4-(2-methoxyethoxy)benzaldehyde have been previously synthesised from 2-chloro-(1-methylethyl ether) and the corresponding hydroxybenzaldehydes, using K₂CO₃ in refluxing DMF resulting in yields of 60 to 75%. However, no detailed information concerning the reaction conditions, reaction times and work-up procedure was disclosed. Reaction of potassium 4-formylphenoxide with 2-bromo-(1-methylethyl ether) in ethanol in a sealed tube required a reaction time of 3 hours at 160-170 °C, resulting in a 50% yield of product. 2-(2-methoxyethoxy)benzonitrile was also previously prepared under similarly harsh conditions. In the present study it was found that the thermal reaction in refluxing methanol as solvent and otherwise equivalent conditions to the ones used for the microwave experiments required 96 hours of reaction time and yielded 40% of 4-(2-methoxyethoxy)benzaldehyde. In the reaction with 4-hydroxybenzonitrile, less than 1% of 4-(2-methoxyethoxy)benzonitrile was obtained under these conditions.

Subsequently, the same reaction has been attempted using 3,4-dihydroxybenzonitrile as substrate and the optimum conditions for nitriles. Initial results gave a yield of 40% of the desired di-glycol ether product (20), the remainder being starting material and mixed phenoxides with a glycol ether group in either the meta or para position. This would suggest the second alkylation is significantly more difficult to achieve than the first one. Column chromatography was required to purify this product, so the work-up procedure is not as straight forward as the reaction using mono substituted substrates. Attempts to improve this yield were unsuccessful. The present study is a significant improvement on Williamson ether syntheses to date.
5.2.1.2. Conclusions.

In conclusion, a simple and rapid method of microwave-assisted alkylation of phenols using stoichiometric amounts of K$_2$CO$_3$ as a mild, cheap and environmentally compatible base has been developed. Both reaction and workup procedure are easy to perform and potentially suited for automated synthesis in high-throughput schemes and combinatorial chemistry. The reaction can be run as a true one step reaction, without the need for pre-formation of the phenoxide salt prior to addition of the halo compound, and without risk of degradation of the alkylating agent. The mild reaction conditions are compatible with functional groups that are sensitive towards strong bases or hydrolysis. The non-aqueous work-up allows for partially water-soluble products being obtained in high yield, without any loss due to incomplete extraction. Overall, only a minimum of reagents is used, and there is no need for a phase transfer catalyst that complicates the work-up procedure. Bearing this in mind; the process is also economically and environmentally acceptable.

5.2.2. Quaternisation of tertiary amines.

5.2.2.1. The methylation of tertiary amino substituted aromatic aldehydes and nitriles.

A simple method for the quaternisation of tertiary amino-substituted benzaldehyde and benzonitrile has been developed that used no solvent apart from the methylating agent dimethyl sulphate.

The reaction using (4-dimethylaminobenzaldehyde) was attempted as a first step to making the quaternary ammonium substituted nitrone, as all attempts to methylate the dimethylamino nitrogen on the nitrone had failed. Dimethyl sulphate was chosen as the methylating agent for two reasons, firstly, the counter ion would not interfere with platinum whereas an iodide from methyl iodide would, and secondly, a stronger methylating agent such as methyl iodide might methylate the aldehyde oxygen. The second reaction (4-dimethylaminobenzonitrile) was carried out to eliminate
competition from the amino nitrogen for the coordination site on platinum leaving it free for the nitrile nitrogen.

The method employs a fourfold excess of the alkylating agent as solvent, mild conditions of one hour heating at 70 °C under a nitrogen atmosphere. Excess of dimethyl sulphate is removed with diethyl ether and the product easily purified by washing with successive portions of diethyl ether and DCM. The products are produced in high yield of 70%. For these substrates this is a significant improvement on the usual method of quaternisation which involves a lengthy reflux using DMF, and an aqueous work up from which the products may well be difficult to remove\textsuperscript{134}.

5.2.2.2. Attempted methylation of tertiary amino substituted imine and nitrone.

It was decided to extend this work and have another attempt at methylation the nitrone \textsuperscript{[11]}, and also a corresponding imine. The imine \textsuperscript{[23]} was made from aniline and 4-dimethylaminobenzaldehyde\textsuperscript{135} as described in the experimental section, 8.

Results:
The various attempts listed below to methylate the imine and the nitrone were unsuccessful.

1. Mild conditions, room temperature with stirring under nitrogen for times varying from 30 minutes to 4 hours using excess dimethyl sulphate as solvent.
2. 60 °C, stirring under nitrogen 30 minutes to 12 hours using excess dimethyl sulphate as solvent.
3. 90 °C, stirring under nitrogen 30 minutes to 12 hours using excess dimethyl sulphate as solvent.
4. 140 °C, stirring under nitrogen for 10-90 minutes.
5. Using a stoichiometric amount of dimethyl sulphate and acetonitrile as solvent at room temperature to reflux temperature.
6. Using a stoichiometric amount of dimethyl sulphate and methanol as solvent at room temperature to reflux temperature for varying times up to 3 days.
7. All the above without using nitrogen.
All these conditions were used in an attempt to methylate 4-dimethylaminobenzaldehyde, resulting in no reaction for the mild conditions and acetal formation for the extreme ones, before the successful solventless synthesis under nitrogen was attempted. In the case of 4-dimethylaminobenzonitrile, only the successful method was used as this was subsequent work.

Results for methylation of 4-dimethylaminophenylnitrore.

These fall into three areas:
1. Using the mildest conditions there was no significant reaction at all judging from the proton NMR spectra.
2. At more moderate conditions an oil was produced which based on the proton NMR spectrum could be a mixture of starting nitrore, the corresponding aldehyde with the nitrore cleaved, possibly some of the desired product, and possibly some nitrore methylated on the oxygen of the nitrore.
3. At the more extreme conditions there was also a mixture of products the most likely being an acetal.

Results for the methylation of the imine (23) of aniline and 4-dimethylaminobenzaldehyde.

Again, at the mild to moderate conditions there was no significant reaction. At the more extreme conditions there was a mixture of products (yellow oil), the proton NMR spectrum of which could not be interpreted with any accuracy, only to say that the major product was not the desired one.

Conclusions

Methylation of the dimethylamino nitrogen on para-substituted dimethylaminobenzene derivatives is difficult to carry out but can be achieved when the substituents are formyl or nitrile, however, when they are an imine or nitrore functionality, methylation is not possible.
5.3 Platinum nitrile complexes

\[
\begin{align*}
\text{H}_2\text{O} / \text{RT} & \quad \text{CHCl}_3 / 60 \degree \text{C} \\
\text{K}_2\text{PtCl}_4 + \text{MeCN} & \rightarrow \text{PtCl}_2(\text{MeCN})_2 + \text{RCN} & \rightarrow \text{PtCl}_2(\text{RCN})_2
\end{align*}
\]


5.3.1. The production of bis benzonitrile platinum(II) complexes.

Bis(benzonitrile) platinum(II) complexes were first described in 1907, when Hofmann and Bugge\textsuperscript{136}, and Ramberg\textsuperscript{137}, synthesized dichlorobis(benzonitrile) platinum(II) from potassium tetrachloroplatinate using an aqueous ligand exchange method. In 1938 Kharasch and co-workers synthesized the analogous palladium compound with a far superior yield by direct ligand attachment starting from palladium dichloride\textsuperscript{92}. They mention that the method employed had been successfully applied previously to platinum dichloride but the work was unpublished. Whilst Hartley’s review of the older literature introduces some doubt as to what method produces which isomer\textsuperscript{92,52}, more recent publications such as Uchiyama and co-workers\textsuperscript{138} accept that all methods described to date produce varying mixtures of cis and trans isomers. These have been separated by column chromatography, and the crystal structure of each has been published\textsuperscript{91}.

It is impossible to distinguish cis and trans isomers of dichlorobis(benzonitrile) platinum(II) from the proton NMR spectra, if one has pure separated samples. It is slightly easier from the spectrum of a mixture of isomers as the two sets of signals are not perfectly superimposed. In the \textsuperscript{13}C NMR spectra there are slight differences between the signals of cis and trans isomers. The most obvious is the signal of the CN carbon which is at 116.8 and 115.3 ppm for trans and cis isomers respectively\textsuperscript{138}.

IR spectroscopy has also been used to identify isomers. The cis isomer should show two nitrile stretches at 2285 and 2290 cm\textsuperscript{-1} due to coupling whereas the trans isomer only exhibits one stretch at 2286 cm\textsuperscript{-1} \textsuperscript{91,115}. In the present study the findings were not
so clear cut. The trans isomer shows a nitrile stretch at 2287 cm$^{-1}$ and the cis isomer at 2285 cm$^{-1}$. However, a 1/1 mixture of the two showed only one stretch at 2286 cm$^{-1}$. Also cited are the Pt-Cl and Pt-N stretches in the 100-400 cm$^{-1}$ region, and the out of plane C-H stretches in the 500-1000 cm$^{-1}$ region$^{91,139}$. In the cis complex there should only be one stretch at 162 cm$^{-1}$, whereas with the trans complex there should be one at 158 cm$^{-1}$ and two stretches at 356 cm$^{-1}$ and 394 cm$^{-1}$. With the instrument used in the present study the region below 350 cm$^{-1}$ cannot be measured, and the region between 350 and 400 cm$^{-1}$ contains so many absorptions that positive conclusions could not be drawn. Again, in the 500-1000 cm$^{-1}$ region it is suggested that for the cis complex many of the stretches should be split, however this was only exhibited by one complex made in the present study, which is believed to be a mixture of cis and trans isomers. For these reasons it is not accepted that IR spectroscopy is a reliable technique for distinguishing these isomers. It should be stressed that many of the reports, Walton$^{139}$ for example, predate the widespread use of multinuclear NMR spectroscopy, and pressure would have been on the scientists to assign complexes with the techniques available to them.

A method that can definitely distinguish the two isomers is $^{195}$Pt NMR spectroscopy. Rochon and co-workers$^{140}$ found that the cis isomer has a signal at -2288 ppm whereas the trans isomer has one at -2350 ppm. They explain the lower signal of the trans isomer in terms of increased shielding. The trans isomer has less efficient platinum to nitrogen back donation, presumably because the trans ligands have to share an orbital, either the zx or zy, whereas the cis ligands receive electron density from both these orbitals.

To date, the structure of dichlorobis(benzonitrile) platinum(II) has been well elucidated. Complexes involving other halide ions such as bromide and iodide have been reported but often they have been used as precursors to make something else$^{141,142}$, or for IR or Raman spectroscopic studies$^{91,138,139}$. Detailed characterisation has not been reported and the stereochemistry of them is ambiguous. In the present study diido- and dibromobis(benzonitrile) platinum(II) complexes are characterized for the first time. It is believed trans complexes were made exclusively but this is more difficult to ascertain when there is no cis complex to compare them with. It is known from previous research that trans platinum benzonitrile complexes undergo bis
cycloaddition in contrast to cis complexes where mono cycloadducts are the sole products. This criterion has been used to assign the stereochemistry of platinum nitrile complexes where no other spectroscopic technique could identify them.

Platinum nitrile complexes of the type in figure 30 were produced, and are described more specifically in table 8 shown below.

<table>
<thead>
<tr>
<th>Complex no.</th>
<th>X</th>
<th>R</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Cl</td>
<td>H</td>
<td>52, 91, 92, 137, 138, 139</td>
</tr>
<tr>
<td>25</td>
<td>Cl</td>
<td>o-OH</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Cl</td>
<td>m-OH</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Cl</td>
<td>p-OH</td>
<td>140 cis complex only</td>
</tr>
<tr>
<td>28</td>
<td>Cl</td>
<td>m-2-MeOC_2H_4O</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Cl</td>
<td>p-2-MeOC_2H_4O</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Cl</td>
<td>m,p-di(2-MeOC_2H_4O)</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Br</td>
<td>H</td>
<td>52, 91, 138, 139, 141, 142</td>
</tr>
<tr>
<td>32</td>
<td>Br</td>
<td>m-OH</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Br</td>
<td>p-OH</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>I</td>
<td>H</td>
<td>91, 141</td>
</tr>
<tr>
<td>35</td>
<td>Cl</td>
<td>p-N(Me)_2 *</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Cl</td>
<td>m,p-di-OH</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Cl</td>
<td>p-NO_2</td>
<td></td>
</tr>
</tbody>
</table>

* considered to be coordinated via the amino nitrogen

Table 8. Summary of the platinum(II) nitrile complexes produced.

Figure 30. The structure of cis and trans platinum(II) nitrile complexes.
The three methods of production described in section 4.2.2 were used resulting in varying mixtures of cis and trans isomers when \( X = \text{Cl} \). This is consistent with the literature\(^{138}\). To make complexes that are mainly trans in configuration, specific conditions had to be used and these are described in section 8. Contrary to previously described methods\(^{91}\), when \( X = \text{Br} \), solely trans isomers were produced in the present study. The same was found when \( X = \text{I} \), but nothing conclusive about the stereochemistry of this complex has been described previously in the literature. In the first instance aromatic nitriles bearing polar substituents such as hydroxy, carboxy and dimethylamino were chosen as ligands. Exchange in chloroform at 60 °C, typically for 48 hours using a 10 molar excess of ligand and starting with dichlorobis(acetonitrile) platinum(II) was carried out (method 1).

### 5.3.1.1 Coordination of hydroxy-substituted benzonitrile.

The first three platinum complexes made using method 1 were the para-, meta- and ortho-hydroxy substituted nitrile compounds. Coordination became increasingly difficult moving from para to meta to ortho. Meta-substituents have no electronic effect on the nitrile group unlike para- and ortho-substituents, which explains the difficulty in coordinating the meta-hydroxybenzonitrile compared to its isomers. There are also increasing steric effects of the hydroxy group going from meta to ortho. The ortho-substituted product is unstable in solid and solution (deuterated acetone), the free ligand being liberated. This was noticeable in the complex turning from bright yellow to darker orange, and an odour characteristic of the free ligand.

The initial kinetic product is generally the cis isomer which is more polar and has less symmetry than the trans isomer, so is less likely to crystallise out. The thermodynamic trans product is more symmetrical and less polar and though it is produced second, may well be the first to precipitate out. It was found that occasionally ligand exchange using para-hydroxybenzonitrile produced the trans isomer in large enough amounts to undergo bis cycloaddition, the cis isomer characteristically can only undergo mono cycloaddition. However, in the majority of cases, the product of this method of ligand exchange was predominantly the cis isomer.
X-ray crystallography would indisputably be able to assign cis and trans isomerism, however the trans isomers once precipitated were not soluble enough to grow decent crystals. Also in the case of mixtures of cis and trans isomers many crystals would have to be scanned to estimate the composition. Poor solubility is also a problem for \(^{195}\)Pt NMR spectroscopy, and experiment times ran to days rather than hours. And of course two isomers are required for comparison. In contrast to para-hydroxybenzonitrile, meta-hydroxybenzonitrile produced mainly a trans platinum complex. It was able to undergo both mono and bis cycloaddition. This lends weight to the theory that the difficulty in coordination of this ligand is one of steric rather than electronic influence.

![Figure 31. cis and trans isomers of PtCl\(_2\)(m-OH-C\(_6\)H\(_4\)-CN)\(_2\)](image)

Whilst figure 31 does not immediately demonstrate any excessive steric hindrance in the cis isomer, it does show, in conjunction with figures 26 (b) and (c), that the substitution of the second ligand would be made easier by approach from the side which results in a trans complex.

Exchange was also attempted using 3,4-dihydroxybenzonitrile but this proved more difficult than would have been expected compared to the two mono hydroxy-substituted ligands. Ten days at 90 °C using 4 / 1 toluene / chloroform as solvent gave a poor yield. IR spectroscopy suggested that the bulk of the product was possibly a species with one acetonitrile ligand and one di-hydroxybenzonitrile ligand, the broad absorption at 2341 cm\(^{-1}\) being roughly intermediate of the two. \(^{195}\)Pt NMR spectroscopy gave the major signal at -2303 ppm compared to -2339 ppm for the para-hydroxy nitrile complex, and -2369 ppm for the corresponding meta complex. Analysis of the analogous glycol ether substituted complexes showed the disubstituted
complex to have an almost identical signal to the para-substituted complex, at -2315 and -2313 ppm respectively. The discrepancy further suggests that the product obtained from 3,4-dihydroxybenzonitrile was not the intended complex. It was not particularly soluble in chloroform or acetone, so recrystallisation and crystallography were not possible, and the complex showed no evidence of cycloaddition. Possibly the insolvability of the product of the first substitution meant it immediately precipitated and the second substitution was rendered impossible.

5.3.1.2. Coordination to glycol ether substituted benzonitriles.

Platinum nitrile complexes$^{52,85}$, and their platinum oxadiazoline counterparts$^{85}$ are notoriously insoluble in all but chlorinated organic solvents. It was hoped that the introduction of an hydroxy group would impart solubility to the platinum oxadiazoline end products in more polar solvents. Unfortunately, this rendered the para-hydroxy nitrile complex only partially soluble in acetone and methanol, and in dimethyl sulphoxide, it rapidly exchanged. Methanol is best avoided in platinum chemistry as it is oxidised by platinum(II) which in turn is reduced. This poor solubility would inevitably lead to problems with the cycloaddition reactions with regard to stoichiometry, so it was decided to functionalise the hydroxy group in a similar way to the functionalisation of hydroxybenzaldehydes in section 5.1 and 5.2, i.e. with a glycol ether substituent. This is still a polar group but unlike hydroxy is aprotic. It was hoped this would make the products soluble in a wider range of solvents. This was carried out on the three hydroxybenzonitriles using microwave irradiation as described in the previous section and illustrated in the scheme below. The 3,4-dihydroxybenzonitrile ligand was treated in the same way.

![Scheme 15. Microwave synthesis of cyano-substituted phenyl ethers. X= Br or Cl.](image)
Ligand exchange using dichlorobis(acetonitrile) platinum(II) and all four glycol ether derived ligands was attempted. This proved to be much more difficult than the hydroxy-compounds and took 10 days at 90 °C, and 2 weeks for the di-substituted compound. Products were isolated and characterised for all of these except the ortho-substituted complex which was either unstable or did not coordinate in the first place. There is undoubtedly steric hindrance of the glycol ether group with either or both the platinum centre and the other ligand. It was considered that with such large side-chains only the trans complexes would be possible and this was borne out in the cycloaddition reactions, where in the case of the para-substituted platinum complex both mono and bis products were produced.

5.3.1.3. Coordination of carboxy-substituted benzonitrile.

Attempts to coordinate para-carboxybenzonitrile to platinum using method 1 were thwarted by the insolubility of the free ligand in chloroform. DMF was used instead but it was impossible to isolate a product using either solvent extraction or aqueous work up. Ligand exchange using water and potassium tetrachloroplatinate was carried out without work up in order to determine the $^{195}$Pt NMR signal. However the signal, at -2034.2 ppm, was not where it was expected and it is thought that the most likely outcome was that the nitrile had been hydrolysed to an amide, or that only one ligand had exchanged resulting in a [PtCl$_3$ligand]$^+$ charged species. This will be expanded on later in the chapter. Exchange was also attempted using THF and dichlorobis(acetonitrile) platinum(II), but the results were erratic and non-reproducible. The product isolated, although having a consistent proton NMR spectrum, did not undergo cycloaddition. The only reliable conclusion to be drawn from it was that THF is not a suitable solvent for exchanges in platinum chemistry.

5.3.1.4. Coordination of para-dimethylaminobenzonitrile.

Coordination of para-dimethylaminobenzonitrile was attempted but IR absorption spectroscopy showed that the amino nitrogen is likely to have coordinated to platinum rather than the nitrile nitrogen. This was indicated by the nitrile stretch being at around 2235 cm$^{-1}$ which is typical of the uncoordinated nitrile, rather than at 2280-
2290 cm\(^{-1}\) which is where a coordinated aromatic nitrile appears. Comparison of the \(^{195}\)Pt NMR spectrum with known amines\(^{140}\) supports the assumption. Rochon found that primary and secondary amines coordinated to platinum have signals at -2230 ppm and -2180 ppm respectively. Extrapolating for the tertiary amine gives a signal of approximately -2130 ppm, which is in rough agreement with 2124.7 ppm which is the signal found for the present complex. The tertiary amine was methylated as described in section 5.2. Coordination of the quaternary ammonium salt 4-(Me)\(_3\)N^+\(^+\)C\(_6\)H\(_4\)CNMeSO\(_4\)^{-} was attempted but it was not possible to separate the product, if any, from the starting materials for reasons of solubility. It was inconclusive from proton NMR spectroscopy if exchange had taken place, but in the IR spectrum a small absorption was visible at 2295 cm\(^{-1}\) which is in the right region for a platinum coordinated nitrile. The positive charge on the quaternary ammonium nitrogen is strongly electron withdrawing, and would draw in towards the nitrogen the lone pair on the \textit{para}-nitrile substituent. This would make coordination to platinum more difficult.

5.3.2 Coordination employing direct ligand attachment starting with platinum dichloride\(^{92,52}\) (method 2).

\[
\text{PtCl}_2 + 2\text{RCN} \rightarrow \text{PtCl}_2(\text{RCN})_2
\]

Scheme 16. Ligand attachment method of producing bis nitrile platinum (II) complexes at temperatures varying from 85 - 160 °C depending on the ligand.
A full description of the complexes produced is given in tables 8 and 21.

5.3.2.1. Coordination with benzonitrile varying the halide ion.

Platinum chloride, bromide and iodide were employed using benzonitrile at 110 °C and Kharasch’s method\(^{92,52}\) (method 2). The literature regarding the configuration of the products is contradictory. According to Hartley\(^{52}\), who refers only to the bromo- and chloro-compounds, the complexes formed are \textit{cis} in configuration. However Uchiyama and co-workers claim a mixture of isomers depending on temperature\(^{138}\).
To date, the situation regarding the chloro complexes is clear. All methods produce
varying mixtures of cis and trans isomers. The present study found that in the case of the latter two halides only trans products were produced contrary to previous findings, and it is hoped this will be confirmed by X-ray crystallography. Whilst cis-iodo platinum complexes are common, it is easy to accept that at the high temperatures used in the present project, the thermodynamic trans product will be made in preference to the kinetic cis product.

In the case of the chloride it was clear from TLC that there were two products presumed cis and trans, and these were separable using column chromatography, the trans product running first. It was also found that with the chloride, increasing the time of reaction increased the proportion of trans isomer produced. This is demonstrated in figure 32 below.

![Figure 32. The yield of trans-PtCl₂(PhCN)₂ produced by thermal route with relation to time at 110 °C based on six experiments.](image)

Reactions were worked up at various times (six experiments) ranging from ten minutes to two hours, and the isomers separated by column chromatography. All reactions were carried out at 110 °C. The yields were calculated from the theoretical maximum yield from a known amount of starting material. A line of best fit was applied so figure 32 is designed to show the trend for the optimisation of the production of the trans isomer. It is not intended as a plot to calculate a rate constant, so results have not been averaged and error bars indicate estimated weighing error and
residual solvent of +/− 1% and −1% respectively. Whilst at first glance, the figure appears to show an attractive mathematical relationship between yield and time, unfortunately this is not the whole story. Platinum dichloride is a polymeric compound with a repeating square planar PtCl₂ unit. Different batches may vary in the length of the polymer chain and the trans isomer may take longer to form and the yields be lower. Generally the yield of trans isomer increased with time up to about 90 minutes. The cis isomer however was isolated in some cases but in others the second product off the column was unstable in solution and turned from a dirty yellow to green to black in a few hours. Recrystallisation for X-ray analysis was therefore not possible. Little could be learned about the structure from proton NMR and IR spectroscopy, or MS-FAB spectrometry, save that there is possibly evidence of nitrile functionality at 2300 cm⁻¹ in the IR spectrum. The ¹⁹⁵Pt NMR spectrum was more illuminating; the main signal is at -2343 ppm which is roughly in agreement with Rochon’s finding at -2350 ppm for the trans isomer. There is also a smaller signal at -2288 ppm which corresponds to Rochon’s cis complex¹⁴⁰. This would suggest that in the main, the unknown complex possesses similar stereochemistry to trans-dichlorobis(benzonitrile) platinum(II). It was thought this was most likely a polymeric platinum nitrile complex. Uchiyama et al.¹³⁸ found that the proportion of trans to cis isomer is increased with increasing temperature. The present study found this to be true but only for short reaction times of a few minutes. With increasing time, at 160 °C, a second product of unknown structure but similar to the one just mentioned is produced. Figure 33 below shows a possible dimeric structure of the unknown complex.

![Figure 33. Possible structure of a dimeric platinum nitrile complex.](image)

Dimeric platinum and palladium complexes are not uncommon²⁴,⁵². Because of the unwanted product formed at higher temperatures, it is believed that the method of the present study at 110 °C is a more reliable method for making the trans complex than that of Uchiyama. Although it takes longer, better yields are achieved.
Platinum bromide gave the same high yield under similar conditions but IR and proton NMR spectroscopy, TLC, and reactivity pointed strongly to only one product, the trans isomer being formed. In the case of platinum iodide it was difficult to see any reaction taking place because of the strong deep red colour of the starting material. However precipitation with petroleum ether, filtration and extraction of the residue with DCM did yield an orange / red solid. Spectroscopy confirmed the product, which was not particularly stable and reverted back to a deep red colour with evolution of an intense almond smell characteristic of benzonitrile. Cycloadditions were carried out immediately with the iodide complex and confirmed its trans configuration. The failure to isolate cis benzonitrile complexes with bromide and iodide ligands is consistent with the increasing size of the halide moving down the group, introducing the possibility of steric hindrance. There may also be a small contribution due to the increasing trans effect from chloride to iodide\(^{24, 52}\). In the cis complexes the benzonitrile would be increasingly labilised going from chloride to iodide weakening the platinum-nitrogen \(\sigma\) bond. This would make the complexes inherently unstable in the case of bromide and iodide. This must lead to the more stable thermodynamic trans complexes being produced. The cis-dibromobis(benzonitrile) platinum(II) complex has been previously claimed and characterised using I.R. spectroscopy by Walton\(^{139}\). However, subsequent attempts by Walton to repeat the synthesis resulted in a trans complex, much to his frustration\(^{144, 145}\). Eysel and co-workers claimed the cis-iodo complex \(^{91}\), which has also been reported without characterisation as a precursor to other platinum complexes\(^{141}\). The fact that in Dhara's synthesis of cisplatin (scheme 3) the cis-iodo complex is exclusively produced by reaction of ammonia with potassium tetraiodoplatinate, which is why the starting reagent is chosen, may appear contradictory when comparing the analogous benzonitrile complexes. However it is the strong trans effect of the iodo ligands that have orbitals energetically similar to platinum that allow back bonding from platinum to iodine and stabilise diamminediiodo platinum(II). The ammonia ligands have a strong trans influence, which means the platinum-nitrogen bond is strong and the molecule is further stabilised. In the benzonitrile complex the platinum-nitrogen bond is not strong so having iodo ligands in trans position would destabilise it.
One of the aims of the project was to produce more polar complexes, and consequently ones more soluble in polar solvents. Changing the halide from chloride to bromide certainly achieved this in the nitrile complexes, and it was hoped this would be reflected in the corresponding oxadiazoline complexes. *trans*-dichlorobis(benzonitrile) platinum(II) is only sparingly soluble in acetone, whereas *trans*-dibromobis(benzonitrile) platinum(II) is very soluble in acetone. From a medical point of view, as bromine is found in the body in trace quantities, 260 mg in a 56 kg body, it was not considered that platinum bromide complexes would be inappropriate. It would inevitably exchange with chloride which is present in the bloodstream in much larger concentrations, and be readily excreted by the kidneys.

5.3.2.2. Coordination with hydroxybenzonitriles using a hot melt system (method 2).

*Para*-hydroxybenzonitrile and *meta*-hydroxybenzonitrile were coordinated to platinum dichloride and dibromide. The melting points of the free ligands are 115 °C and 85 °C respectively, and in the latter case the ligand rapidly vaporises due to its high vapour pressure, and condenses further up the reaction vessel. Care has to taken to keep the temperature just high enough to keep the ligand molten. Addition of a small amount of toluene is also helpful in this respect and it also dissolves some of the platinum dichloride. However, there is a lower energy input than in the benzonitrile or *para*-hydroxybenzonitrile reactions.

In the case of *meta*-hydroxybenzonitrile a mainly *trans* product is formed from platinum dichloride, and solely *trans* from platinum dibromide. This adds to the evidence from method one exchanges, that formation of the product is controlled by steric effects. Using *para*-hydroxybenzonitrile and platinum bromide results in a *trans* isomer, similar to the corresponding benzonitrile reaction. However when it is coordinated to platinum dichloride a mixture of products results and this varies with different batches of the platinum dichloride, and reaction conditions.
In some cases four aromatic systems are visible in the proton NMR spectrum. Apart from the *cis* and *trans* isomer, the other signals are thought, again, to be polymeric, possibly dimeric, platinum compounds. A dimeric complex is more likely as the form of the proton NMR spectrum is too simple to be polymeric.

Whilst mass spectrometry data should be treated with caution, because reactions can occur during the process, there is some evidence to support the presence of dimeric species. The structure of one possible complex shown in figure 34, has formula $\text{Pt}_2\text{Cl}_4\text{N}_2\text{O}_2\text{C}_{14}\text{H}_{10}$, and formula weight 770.21 g. In the MS-FAB spectrum there is a peak for $M-\text{OH}$ at 753, and $M-\text{OH}-\text{HCl}$ at 717. There is also a small peak for $[\text{PtCl}(p-\text{OH-}\text{C}_6\text{H}_4-\text{CN})_2]^+\text{Cl}^-$ at 623, and a large one at 588 for the positive ion $[\text{PtCl}(p-\text{OH-}\text{C}_6\text{H}_4-\text{CN})_2]^+$. These are shown in figure 35.

![Figure 34. Proposed structure of the dimeric platinum species suspected to be one of the products of the Kharasch method of the reaction of platinum dichloride and para-hydroxybenzonitrile.](image-url)
Figure 35. The MS-FAB spectrum of the products of the Kharasch method of the reaction of platinum dichloride and para-hydroxybenzonitrile.

The unknown species are a confounding problem with regard to cycloaddition as unlike the dichlorobis(benzonitrile) platinum(II) complex, the platinum hydroxy-substituted nitrile cannot be purified by column chromatography. The solubility is poor in chlorinated solvents or mixtures, and if dissolved in an excess of acetone or mixtures incorporating acetone, the mixture of products runs off the column together. If methanol is used the compounds turn green on the column. The poor solubility also rules out recrystallisation. Preparative TLC can be used to separate small amounts of the complex and this was performed in order to carry out IR analysis. However it was unclear whether the mixture had separated or decomposed on the plate. The first spot to run was free ligand with an absorbance at 2225 cm\(^{-1}\). The second was a mixture of free and coordinated ligand with absorptions at 2225 and 2284 cm\(^{-1}\). There is no information in the literature to confirm this particular complex but it is consistent with known similar complexes. The third spot had a weak absorbance at 2285 cm\(^{-1}\). As the last two absorptions are so close it is not possible to tell if these are the same complex or cis and trans isomers. What is for certain is that it was not an efficient way of separating the isomers. With the meta-hydroxy substituted complex the impurity was to a lesser extent, but there was a visible difference in the IR absorption spectrum, with signals at 2307 and 2300 cm\(^{-1}\). In the \(^{195}\)pt spectrum a broad signal with two peaks was seen at -2368 and -2372 ppm. The problems incurred during the cycloaddition
reactions are discussed in section 5.4, and the characterisation of one of the impurities in section 8.9.3.

This problem was partially overcome by heating the mixed products in toluene / acetone, 4/1, and a ten molar excess of free ligand, for 30 hours. This reduced the number of aromatic systems visible to two, with one in large excess, hopefully the trans isomer. However this was found not to be the case and it was thought that the impurity was a poly nuclear platinum nitrile complex, similar to the result found for the reaction of benzonitrile with platinum dichloride. It was not possible to overcome this problem using this method, but an almost pure complex was eventually made by a modification of method 1, starting from dichlorobis(acetonitrile) platinum(II) and a mixture of toluene / chloroform in 4/1 ratio as solvent. This was stirred for 45 hours at 85 °C. The use of toluene at this temperature removes acetonitrile from the system and shifts the equilibrium to the right, i.e. towards the desired product. The high temperature also favours production of a trans complex. Starting from a mononuclear platinum complex also eliminates the polymeric impurity problem.

5.3.3 Aqueous ligand exchange using potassium tetrachloroplatinate (method 3).

\[
\begin{align*}
\text{H}_2\text{O} / \text{RT} \\
\text{PtCl}_2(\text{MeCN})_2 + 2\text{RCN} & \rightarrow \text{PtCl}_2(\text{RCN})_2 + \text{MeCN}
\end{align*}
\]


A variation of the Hoffman and Bugge method\textsuperscript{136}, which is the same method used by Walton\textsuperscript{139} and Eysel \textit{et al}.\textsuperscript{91} was employed in the present study. The exact method is described in the experimental section, only to mention that for bromide complexes, potassium bromide was dissolved in water in a ten fold excess compared to potassium tetrachloroplatinate, as well as a ten fold excess of the free ligand. This facilitates exchange of bromide for chloride as well as free ligand for halide on the platinum centre.
For chloride complexes, ortho-, meta- and para-hydroxybenzonitrile were used and products although discolourised pale green, crystallised out. This discolouration may well be due to the liberation of elemental platinum. The tetrachloroplatinate anion is unstable in halide media, according to the following equation:

\[ 2[\text{PtCl}_4]^- \rightleftharpoons \text{Pt}(0) + [\text{PtCl}_6]^{2-} + 2\text{Cl}^- \]

However for the chloride complexes halide media was not employed. The low yield compared to the previous two methods may be due to the reaction not going to completion, i.e. the first product formed \([\text{PtCl}_3(\text{PhCN})]^+\text{Cl}^-\) may be unstable in aqueous solution. Another possibility is that under the reaction conditions the hydroxy groups are prone to oxidation and elemental platinum is produced by reduction of platinum(II). In the case of bromo complexes (meta- and para-hydroxybenzonitrile, and benzonitrile) there was no crystallisation although the solutions turned varying shades of yellow. The products were isolated by evaporation and solvent extraction. There was no spectroscopic evidence to support coordination of meta-hydroxybenzonitrile (in the case of bromo). The bromo complexes of benzonitrile and para-hydroxybenzonitrile were identical according to analysis with the trans complexes made by the previous hot melt method. The yields for bromo complexes, like the chloro complexes, were greatly reduced compared to the previous two methods of production, but there was enough for a thorough spectroscopic analysis.

No iodo platinum complexes were isolated by this method.

Considering the dibromobis(benzonitrile) platinum(II) made by method three, a trans complex was produced, rather than a cis complex as previously reported by Walton. Infrared spectroscopy had been used by Walton as the sole method of characterisation. He refers to absorptions in the 500 - 1000 cm\(^{-1}\) region, which correspond to the out of plane C-H stretches of the phenyl ring, stating that a cis complex would inhibit free rotation of the aromatic ring, resulting in two sets of stretches for the C-H bonds. In the present study this was not evident even for cis-dichlorobis(benzonitrile) platinum(II) where the isomers had been separated by chromatography. Although the CN stretch differs by two wave numbers, 2285 and 2287 respectively, for cis and trans isomers, in the mixture of the two isomers only one CN stretch is evident. The pattern described by Walton was observed on one occasion using meta-hydroxybenzonitrile as ligand. As it has already been established that this produces a
mixture of cis and trans isomers even under mild conditions, it is suggested that the IR pattern is a result of conformational differences of the aromatic rings resulting from steric hindrance of the hydroxy groups in the cis isomer. It was concluded therefore that IR spectroscopy alone is not a good technique for definitely assigning cis and trans isomers.

5.3.4 The effect of a strongly electron withdrawing substituent on coordination.

Because of the lack of positive results using a carboxy-substituted benzonitrile, it was decided to try a nitro-substituted benzonitrile. It was thought the solubility of this would lend itself to the process. To investigate this effect platinum dichloride, potassium tetrachloroplatinate and para-nitrobenzonitrile were used employing methods 2 and 3, which should produce in the main, trans and cis isomers respectively. In both cases coordination was difficult taking ten days to produce complexes with about 10% yield. The para-substituent withdraws electron density from the ring and must deactivate the CN bond by drawing the lone pair of nitrogen in towards the nucleus. The lone pair electrons which are sp hybrids and point away from the nitrogen and so are not able to be delocalised, as shown in figure 36.

Figure 36. Electron withdrawing effect of a nitro-substituent on a nitrile group.

Using the aqueous method there was more than one product which could be due to exchange of hydroxide for chloride, or hydrolysis of the nitrile group. It may also be due to exchange of only one chloride with a nitrile ligand resulting in a negatively charged platinum species. The $^{195}$Pt NMR signal is consistent with similar previously reported findings$^{140}$. Due to the difficulties encountered it was decided not to proceed with the cycloadditions, but to obtain $^{195}$Pt NMR spectra of the platinum nitriles and this is discussed below in section 5.3.6. It was concluded that nitrile ligands with strongly electron withdrawing substituents are not suitable candidates for coordination to platinum.
5.3.5. Conversion of cis to trans isomers of platinum nitriles.

The Kukushkin method\textsuperscript{92} of heating the cis or a mixture of cis and trans isomers in the solid state at 100 °C for 10 days was used. The nitrile complexes used were dichlorobis(benzenitrile) platinum(II), and its ortho-, meta- and para-hydroxy substituted analogues. In addition the para-hydroxy substituted complex was heated under reflux for 10 days in toluene. The products which were a green-grey colour were extracted with a suitable solvent, acetone for the hydroxy-substituted complexes and DCM for the benzonitrile complex. Proton NMR and IR spectroscopy were carried out to illuminate any changes and cycloaddition was attempted. The findings did not support Kukushkin's conclusions\textsuperscript{93} that the cis isomer is easily converted to the trans isomer by this method, though he offers little evidence to support his assumption. The IR spectroscopy data taken alone initially supports the claim of cis to trans conversion. There is a change in position of the CN absorption, most marked for the ortho-hydroxybenzonitrile complex, from 2280 to 2288 cm\(^{-1}\). However the free ligand was evolved and could be seen condensed on the sides of the reaction vessel. This was also evident but to a lesser extent with the meta-hydroxybenzonitrile complex. In the meta- and para-hydroxy nitrile complexes absorptions at 2232 cm\(^{-1}\) and 2234 cm\(^{-1}\) respectively were visible signifying the presence of free ligand. All three crude products were only sparingly soluble in appropriate solvents and the yields after extraction were low, below 20%. The proton NMR spectra showed the presence of an aromatic system in all cases but this only shows what is in solution and tells nothing about coordination to platinum. Cycloaddition was either unsuccessful or in such a small amount that work-up was not viable.

It was concluded that the Kukushkin method is not suitable for the conversion of cis to trans isomers for the nitrile complexes of this study, and that the most likely result is that some of the ligand is evolved, the remainder being a polymeric complex of platinum mixed with some starting platinum nitrile. Using both the mildest and most extreme reaction conditions, solely trans-dibromo bis nitrile platinum complexes are produced. The selected IR data for this method and the other three described methods are summarised in table 9 below.
<table>
<thead>
<tr>
<th>Complex</th>
<th>Method</th>
<th>IR, % proportions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wave number (cm⁻¹)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[PtCl₂(m-HO-C₆H₄-CN)₂]</td>
<td>1</td>
<td>2306 (50) 2295 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2286</td>
</tr>
<tr>
<td>[PtCl₂(p-HO-C₆H₄-CN)₂]</td>
<td>1</td>
<td>2286</td>
</tr>
<tr>
<td>[PtCl₂(m-HO-C₆H₄-CN)₂]</td>
<td>2</td>
<td>2295 (50) 2307 (50)</td>
</tr>
<tr>
<td>[PtCl₂(p-HO-C₆H₄-CN)₂]</td>
<td>2</td>
<td>2287</td>
</tr>
<tr>
<td>[PtCl₂(m-HO-C₆H₄-CN)₂]</td>
<td>3</td>
<td>2292</td>
</tr>
<tr>
<td>[PtCl₂(p-HO-C₆H₄-CN)₂]</td>
<td>3</td>
<td>2286</td>
</tr>
<tr>
<td>[PtCl₂(o-HO-C₆H₄-CN)₂] cisor trans</td>
<td>3</td>
<td>2280</td>
</tr>
<tr>
<td>[PtCl₂(o-HO-C₆H₄-CN)₂] cisor trans</td>
<td>cis&gt;trans</td>
<td>2288 (90)</td>
</tr>
<tr>
<td>[PtCl₂(p-HO-C₆H₄-CN)₂] cisor trans</td>
<td>cis&gt;trans</td>
<td>2295 (90) 2234 (10)</td>
</tr>
<tr>
<td>[PtCl₂(o-HO-C₆H₄-CN)₂] cisor trans</td>
<td>cis&gt;trans</td>
<td>2287 (99) 2234 (1)</td>
</tr>
<tr>
<td>[PtCl₂(NeCN)₂] cisor and trans</td>
<td>1</td>
<td>2360 (55) 2334 (45)</td>
</tr>
<tr>
<td>[PtCl₂(PhCN)₂] cisor and trans</td>
<td>1</td>
<td>2286</td>
</tr>
<tr>
<td>[PtCl₂(PhCN)₂] cisor and trans</td>
<td>2</td>
<td>2286</td>
</tr>
<tr>
<td>cis-[PtCl₂(PhCN)₂]</td>
<td>2</td>
<td>2285 [lit. 2285 sharp, 2290 shoulder¹³⁹], 2284 [lit. 2284⁹¹]</td>
</tr>
<tr>
<td>trans-[PtCl₂(PhCN)₂]</td>
<td>2</td>
<td>2287 [lit. 2286⁹¹]</td>
</tr>
<tr>
<td>trans-[PtBr₂(PhCN)₂]</td>
<td>2</td>
<td>2288</td>
</tr>
<tr>
<td>trans-[PtBr₂(PhCN)₂]</td>
<td>3</td>
<td>2288</td>
</tr>
<tr>
<td>cis-[PtBr₂(PhCN)₂]</td>
<td>Walton</td>
<td>Lit. 2285¹³⁹</td>
</tr>
<tr>
<td>trans-[PtI₂(PhCN)₂]</td>
<td>2</td>
<td>2288 [lit. 2285(cis)⁹¹]</td>
</tr>
</tbody>
</table>

Table 9. Selected IR absorptions of platinum nitrile complexes (the numbers in round brackets represent the relative size of the absorptions subjectively estimated).
5.3.6. Study of $^{195}$Pt NMR spectral data of platinum nitrile complexes.

$^{195}$Pt NMR spectroscopy data were collected for the platinum nitrile complexes as part of the characterisation. However some interesting trends emerged which warrant closer examination.

5.3.6.1 The effect of halide ligand on the $^{195}$Pt NMR spectroscopic signal.

From mixed chloro bromo complexes of platinum(II) and platinum(IV) a linear correlation is the result of plotting $^{195}$Pt NMR signal against composition, as shown in figure 37. This suggests that the main mode of bonding of these ligands is one of $\sigma$, with little contribution from $\pi$ bonding. The data in table 10 are the published findings of Kerrison and Sadler\textsuperscript{146} who recorded the $^{195}$Pt NMR signals of the complex ions PtCl\textsubscript{6}\textsuperscript{2-} and PtCl\textsubscript{6}\textsuperscript{2-}, and ions with successive replacements of chlorine by bromine, ending up with PtBr\textsubscript{4}\textsuperscript{2-} and PtBr\textsubscript{5}\textsuperscript{2-}.

<table>
<thead>
<tr>
<th>Pt(IV) complex</th>
<th>$\Delta$ (ppm)</th>
<th>Pt(II) complex</th>
<th>$\Delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PtCl\textsubscript{6}\textsuperscript{2-}</td>
<td>0</td>
<td>PtCl\textsubscript{4}\textsuperscript{2-}</td>
<td>1631</td>
</tr>
<tr>
<td>2 PtCl\textsubscript{5}Br\textsuperscript{2-}</td>
<td>286.8</td>
<td>PtCl\textsubscript{3}Br\textsuperscript{2-}</td>
<td>1858</td>
</tr>
<tr>
<td>3 trans-PtCl\textsubscript{4}Br\textsubscript{2}\textsuperscript{2-}</td>
<td>585.1</td>
<td>trans-PtCl\textsubscript{3}Br\textsubscript{2}\textsuperscript{2-}</td>
<td>2101</td>
</tr>
<tr>
<td>4 fac-PtCl\textsubscript{3}Br\textsubscript{2}\textsuperscript{2-}</td>
<td>892.7</td>
<td>PtClBr\textsubscript{3}\textsuperscript{2-}</td>
<td>2380</td>
</tr>
<tr>
<td>5 trans-PtCl\textsubscript{2}Br\textsubscript{4}\textsuperscript{2-}</td>
<td>1215.9</td>
<td>PtBr\textsubscript{4}\textsuperscript{2-}</td>
<td>2676</td>
</tr>
<tr>
<td>6 PtClBr\textsubscript{3}\textsuperscript{2-}</td>
<td>1547.6</td>
<td>PtBr\textsubscript{5}\textsuperscript{2-}</td>
<td>1894</td>
</tr>
</tbody>
</table>

Table 10. $^{195}$Pt signals for Pt (II) and Pt (IV) chloro / bromo complex ions. (ref. Na\textsubscript{2}PtCl\textsubscript{6})
Mixed halide complex ions of Pt(II) and Pt(IV)

Figure 37. Plots of $^{195}$Pt NMR signal against ion for mixed bromo / chloro Pt (II) and Pt (IV) complex ions based on the data in table 10.

Whilst the plots are not perfect straight lines, any significant $\pi$ back bonding would result in an appreciable deviation from the straight line. This becomes obvious on scrutiny of $^{195}$Pt NMR signals of complexes that contain known $\pi$ acceptor ligands such as phosphines and arsines. Using the results of Goggin and co-workers on platinum phosphine and arsine complexes, figure 38(a) and (b) have been generated which are plots of $^{195}$Pt NMR signal against complex varying the halide ligands (a), and the relative numbers of phosphine and chloride ligands (b). Contrasting figures 38(a and b) with figures 37, shows a strong deviation from straight line in the case of figure 38(a and b).

Figure 38(a). Plot of $^{195}$Pt NMR signals of platinum phosphine and arsine complexes, $\text{trans-PtX}_2\text{L}_2$, varying halide. X is 1=Cl, 2=Br, 3=I.
Figure 38(b). Plot of $^{195}$Pt NMR signals of platinum chloride phosphine complexes, varying the relative numbers of each ligand. $1 = [\text{PtCl}_2\text{PMe}_3]^{-}$, $2 = \text{trans-PtCl}_2(\text{PMe}_3)_2$, $3 = [\text{PtCl}(\text{PMe}_3)_3]^{+}$.

5.3.6.2. The effect of ring substitution on the $^{195}$Pt NMR signal of platinum nitrile complexes.

Table 11 below contains selected $^{195}$Pt NMR signals of the platinum nitrile complexes made in the present study.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Solvent</th>
<th>$\delta$ (ppm) $trans$</th>
<th>$\delta$ (ppm) $cis$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{PtCl}_3(\text{PhCN})_3]$</td>
<td>CDCl$_3$</td>
<td>-3935</td>
<td>NA</td>
</tr>
<tr>
<td>$[\text{PtBr}_2(\text{PhCN})_2]$</td>
<td>CDCl$_3$</td>
<td>-2860</td>
<td>NA</td>
</tr>
<tr>
<td>$[\text{PtBr}_2(p-HO-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2833</td>
<td>NA</td>
</tr>
<tr>
<td>$[\text{PtBr}_2(m-HO-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2873</td>
<td>NA</td>
</tr>
<tr>
<td>$[\text{PtCl}_2(\text{PhCN})_2]$</td>
<td>CDCl$_3$</td>
<td>-2345 (lit. -2350$^{140}$)</td>
<td>-2285 (lit. -2288$^{140}$)</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-2375 (acetone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$d_6$-acetone</td>
<td>-2335</td>
<td>-2245</td>
</tr>
<tr>
<td>$[\text{PtCl}_2(p-HO-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2362</td>
<td>-2272</td>
</tr>
<tr>
<td>$[\text{PtCl}_2(m-HO-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2333</td>
<td></td>
</tr>
<tr>
<td>$[\text{PtCl}_2(o-HO-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2313</td>
<td></td>
</tr>
<tr>
<td>$[\text{PtCl}_2(p-MeO-C_6H_4-CN)_2]$</td>
<td>CDCl$_3$</td>
<td>-2346</td>
<td></td>
</tr>
<tr>
<td>$[\text{PtCl}_2(m-MeO-C_6H_4-CN)_2]$</td>
<td>CDCl$_3$</td>
<td>-2313</td>
<td></td>
</tr>
<tr>
<td>$[\text{PtCl}_2(p-NO}_2-C_6H_4-CN)_2]$</td>
<td>$d_6$-acetone</td>
<td>-2355, 2305 n.b.</td>
<td>-2270</td>
</tr>
</tbody>
</table>

Table 11. The $^{195}$Pt NMR signals of selected platinum nitrile complexes

* Product not isolated so the structure is uncertain.
n.b. uncertain as to whether the difference between these signals is a solvent effect or if the complex is a mixed ligand complex, possibly \([\text{PtCl}_2(\text{MeCN})(p-\text{NO}_2-\text{C}_6\text{H}_4-\text{CN})]\).

It is easy to see that for bromo complexes, the para-hydroxy substituent has a greater effect on the signal, compared to the unsubstituted nitrile complex, than the meta-substituent. This is because ortho- and para-substituents have a direct electronic polarizing effect\(^{91,140}\) on the nitrile group which is not the case with the meta-substituent. The signals of the meta-substituted nitrile complexes are closer to that of the benzonitrile complex as a result. This trend is not so obvious in the case of the chloro complexes. This may be due to the solvent used for the NMR experiments, acetone for the hydroxy-substituted complexes and chloroform for the benzonitrile complex meaning like is not being compared with like. To circumvent this problem the \(^{155}\text{Pt}\) NMR spectrum was carried out on dichlorobis(benzonitrile) platinum(II) using deuterated acetone. This took some time due to the poor solubility of the complex in this solvent but the result was enlightening. There is a significant shift from -2245 ppm to -2275 ppm. Comparison of the signals of the hydroxy-substituted complexes now fit the pattern well. The signal of the para-hydroxy complex is very close to that of the ortho complex which is to be expected, as both have a similar electronic effect on the platinum nitrogen bond, and the signal of the meta-substituted complex is closer to the bis benzonitrile platinum complex.

In the case of the strongly electron withdrawing para-nitro substituent, the greatest effect on the NMR signal is exhibited. It is difficult to rationalize this as it would be expected to have an opposite effect to a complex with an electron donating effect. However factors such as the choice of solvent and the way the complex is solvated can affect the position of the signal.

![Figure 39. The electronic effect of a strongly electron withdrawing ring substituent on the platinum centre.](image-url)
Examination of the resonance structure of the nitro-substituted complex shows electron density being withdrawn from the platinum, see figure 39. This slight deshielding would explain the shift downfield. Applying the same criteria to the hydroxy-substituted complex should therefore result in a shift upfield as the platinum nucleus has greater electron density surrounding it. One explanation is that intermolecular hydrogen bonding of the hydroxy proton to the acetone solvent and to chlorine and hydroxy oxygen, has a deshielding effect on platinum resulting in a slight shift downfield.

X-ray crystallography data is rare for platinum nitrile complexes of this type, but considering the Pt-N bond lengths of cis-[PtCl₂(p-OH-C₆H₄CN)₂]¹⁴⁰ and cis-[PtCl₂(C₆H₅CN)₂]⁹¹, the hydroxy-substituted complex has a slightly shorter bond length, 197.6 pm compared to 201.0 pm. This suggests a stronger bond for the former complex consistent with the electron donating effect of the hydroxy-substituent. However this extra electron density is small compared to the shielding the platinum nucleus already experiences from its own electrons and therefore there is no apparent shielding exhibited by the ¹⁹⁵Pt NMR signal of the hydroxy-substituted complex compared to the bis benzonitrile complex. In fact the opposite is observed with a small downfield shift.

5.3.6.3. The monitoring of aqueous ligand exchange using ¹⁹⁵Pt NMR spectroscopy.

In order to throw some light on the mechanism of aqueous exchange an NMR experiment was conducted using deuterium oxide, potassium tetrachloroplatinate and meta-hydroxybenzonitrile at room temperature. ¹⁹⁵Pt NMR spectra were acquired regularly for fourteen days. After two days the colour had changed from red to orange and a significant signal was detected at -2022 ppm. This is consistent with Rochon’s findings¹⁴⁰ for [PtCl₃nitrile]. The signal took longer to acquire as the days passed and a yellow crystalline deposit built up in the NMR tube. The crystals were filtered and the solution extracted with excess DCM. ¹⁹⁵Pt NMR analysis was carried out on each part. The solid was found to be mainly a trans complex with some cis complex. The DCM extract was mainly cis complex, with only a small signal corresponding to the
trans isomer, and the aqueous phase contained the complex with the signal at -2022 ppm. MS-FAB' showed the aqueous layer to contain 420.5 [PtCl$_3$(3-OH-C$_6$H$_4$CN)]$^-$, and the MS-FAB$^+$ showed 459.65 K$^+$ [PtCl$_3$(3-OH-C$_6$H$_4$CN)]$^+$. This confirms that one chloride is exchanged first and the species is present for many days. It is known that the rate of exchange of ligands on platinum(II) complexes is slow$^{24,52}$. A similar result is also found for the aqueous reaction using para-nitrobenzonitrile. In this case the predominant species present is [PtCl$_3$(4-NO$_2$-C$_6$H$_4$CN)]$. This reflects the strong electron withdrawing effect of the nitro group which renders the nitrogen a poorer $\sigma$ donor. The ionic mono nitrile complex is also stabilised in aqueous solution.

The same experiment was carried out using para-hydroxybenzonitrile yielding similar results. The first signal to appear was at -1991 ppm, again consistent with Rochon’s findings$^{140}$, with subsequent signals appearing corresponding to mainly cis, and a small amount of trans isomers. The main difference with this reaction was the speed of it. $^{155}$Pt NMR spectroscopy showed the major species present after four days were bis para-hydroxybenzonitrile complexes, with only a small signal for the mono benzonitrile complex. In the case of the meta-hydroxybenzonitrile experiment, there was still a significant signal for the mono complex after seven days. This is consistent with the para-substituted benzonitrile being more electron rich than the meta-substituted benzonitrile, facilitating $\sigma$ donation of the para-substituted nitrile. The mild conditions of the reactions mean the cis isomer is expected for the bis complex. In the case of meta-hydroxybenzonitrile there is the possibility of steric hindrance, and the slower rate suggests an associative mechanism. This is consistent with published data$^{52}$.

Summing up, for complexes that are structurally fairly simple, the chemistry of platinum(II) nitrile complexes is far from simplistic. It appears that the similarity of chloride and nitrile ligand with regard to trans effect, means mixtures of cis and trans isomers are produced with differing reaction conditions. In the case of bromide and iodide complexes the increasing trans effect should result in cis complexes under mild conditions, but trans complexes were produced under all conditions. The increasing size of the ions may play a part in this. Whilst more time could have been devoted to
this subject it was not the main aim of the project, so it was decided to move on with the complexes produced. The products are summarised in table 12 below.

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>PROD. No.</th>
<th>START. MAT.</th>
<th>METHOD</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCl₂(PhCN)₂</td>
<td>24</td>
<td>K₂PtCl₄</td>
<td>1</td>
<td>mainly cis product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PtCl₂</td>
<td>2</td>
<td>mainly trans product</td>
</tr>
<tr>
<td>PtCl₂(o-OH-C₆H₄-CN)₂</td>
<td>25</td>
<td>K₂PtCl₄</td>
<td>1</td>
<td>unstable product</td>
</tr>
<tr>
<td>PtCl₂(m-OH-C₆H₄-CN)₂</td>
<td>26</td>
<td>K₂PtCl₄</td>
<td>1</td>
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<tr>
<td></td>
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<td>PtCl₂</td>
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<td>mainly trans product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K₂PtCl₄</td>
<td>3</td>
<td>mainly trans, low yield</td>
</tr>
<tr>
<td>PtCl₂(p-OH-C₆H₄-CN)₂</td>
<td>27</td>
<td>K₂PtCl₄</td>
<td>1</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>PtCl₂</td>
<td>2</td>
<td>high yield mainly trans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K₂PtCl₄</td>
<td>3</td>
<td>low yield cis product</td>
</tr>
<tr>
<td>PtCl₂(p-Me₃N^-C₆H₄-CN)₃</td>
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<td>K₂PtCl₄</td>
<td>1</td>
<td>no product isolated</td>
</tr>
<tr>
<td>PtCl₂(m-MeO-C₂H₅-O-H-C₆H₄-CN)₂</td>
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<tr>
<td></td>
<td></td>
<td>PtCl₂</td>
<td>2</td>
<td>mainly trans product</td>
</tr>
<tr>
<td>PtCl₂(p-MeO-C₂H₅-O-H-C₆H₄-CN)₂</td>
<td>n/a</td>
<td>K₂PtCl₄</td>
<td>1</td>
<td>no product</td>
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<tr>
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<td>trans product</td>
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<tr>
<td>PtBr₂(PhCN)₂</td>
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<td>high yield trans product</td>
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<tr>
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<td></td>
<td>K₂PtCl₄</td>
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<td>low yield trans product</td>
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<tr>
<td>PtBr₂(o-MH-C₆H₄-CN)₂</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>PtBr₂</td>
<td>2</td>
<td>high yield trans product</td>
</tr>
<tr>
<td>PtBr₂(p-OH-C₆H₄-CN)₂</td>
<td>33</td>
<td>K₂PtCl₄</td>
<td>3</td>
<td>low yield trans product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PtBr₂</td>
<td>2</td>
<td>high yield trans product</td>
</tr>
<tr>
<td>PtCl₂(PhCN)₂</td>
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<td>PtI₂</td>
<td>2</td>
<td>low yield unstable trans product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>no product</td>
</tr>
<tr>
<td>PtCl₂(p-Me₂N-C₆H₄-CN)₂</td>
<td>35</td>
<td>K₂PtCl₄</td>
<td>1</td>
<td>low yield, coordination via Me₂N</td>
</tr>
<tr>
<td>PtCl₂(m,p-di-OH-C₆H₄-CN)₂</td>
<td>36</td>
<td>K₂PtCl₄</td>
<td>1</td>
<td>Poor yield</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K₂PtCl₄</td>
<td>3</td>
<td>no pure product isolated</td>
</tr>
<tr>
<td>PtCl₂(p-NO₂-C₆H₄-CN)₂</td>
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<td>K₂PtCl₄</td>
<td>1</td>
<td>low yield, used for characterisation only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PtCl₂</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. A summary of the platinum nitriles produced and methods used.
5.4. Cycloadditions reactions.

5.4.1. Mono oxadiazoline platinum(II) complexes.

Mono cycloaddition products, rather than bis complexes, were initially chosen as targets for biologically active compounds as it was considered that these would be more reactive with regard to substitution reactions than their bis counterparts, and therefore more likely to bind to DNA.

The Pt-NC- part of the complex is linear so the platinum is not axially hindered by it unless there are bulky substituents on the ring of benzonitrile. In contrast, bis oxadiazoline platinum(II) complexes have considerable axial hindrance as can be seen in the simulated structure below (figure 40). Unfortunately, to date there are no X-ray structures of *trans*-platinum mono cycloadducts for comparison.

![Figure 40. Space filling representation (Molekel) of [PtCl_2(oxa)_2] showing axial steric hindrance.](image)

For these reasons it was considered that bis oxadiazoline platinum complexes would be too chemically inert to be of much use as anti-cancer drugs, but mono complexes...
would be more promising. The results of the substitution reactions with mono and bis complexes are discussed in section 5.5.

5.4.1.1. Mono oxadiazoline platinum(II) complexes with hydroxy-substituents.

Three mono oxadiazoline platinum(II) complexes with hydroxy-substituents were prepared, the procedure for which is described in the experimental section (8.5). It was not possible to produce a mono complex where X = para-hydroxy according to the scheme. This was for reasons of poor solubility. To successfully produce a mono complex with only a minimum of the bis complex, it is important to either have the platinum nitrile totally dissolved and always in excess to the nitrone in solution, or both starting materials completely dissolved and in 1:1 stoichiometry. Unfortunately trans-[PtCl₂(p-OH-C₆H₄CN)₂] is only sparingly soluble in chlorinated solvents, and only partially soluble in acetone or alcohols. On the other hand the nitrone is soluble in most common organic solvents. This means that the nitrone is always in excess, and monitoring the reaction by proton NMR spectroscopy revealed signals corresponding to the bis cycloaddition product soon after appearance of the mono signals. For these reasons only a bis cycloaddition product was produced.
5.4.1.1.1. Mono oxadiazoline platinum(II) complex made from trans-[PtCl$_2$(m-OH-C$_6$H$_4$CN)$_2$] and N-methyl-C-phenyl nitrone (38).

The platinum meta-hydroxybenzonitrile complex is much more soluble in acetone than its para-hydroxy isomer, and it was possible to get the correct 1:1 stoichiometric mix in solution. Mild conditions of 25 °C meant a mono complex was formed first. Applying heat, as little as 40 °C resulted in a mixture of mono and bis products. By monitoring the reaction with proton NMR spectroscopy, the reaction can be stopped, and the mono product isolated by column chromatography at the first appearance of bis signals. The kinetics of similar reactions has been reported$^{143}$, and this will be touched on in section 5.4.4.1.

5.4.1.1.2. Mono oxadiazoline platinum(II) complexes made from hydroxy-substituted nitrones.

Products were successfully made using meta- and para-OH-C$_6$H$_4$-CH=NMeO. Again, these nitrones are only sparingly soluble in chloroform, so the mixture is stirred and the nitrone gradually dissolves and reacts with the platinum benzonitrile complex. If moderate conditions of 30 °C are applied a mono complex is the result. As the platinum nitrile is in a large excess at the start and for most of the reaction, it therefore mimics first order kinetics. As the reaction nears completion the mechanism becomes less pseudo first order in character and more second order. The ortho-hydroxy nitrone was also attempted but although it was completely soluble in chloroform there was no significant reaction. Even with the application of heat, 60 °C for several days, there was only about 28% conversion and the products were mixed. As solubility is not a problem, this must be due to the electronic effect of the ortho-hydroxy group. This has an electron donating effect on the carbon of the HC$^\text{+}$-N functionality of the intermediate. This stabilises the intermediate (fig. 22) by rendering the C$^\text{+}$ less polar and consequently less reactive. Quantum chemical calculations$^{84}$ predict the first bond to form in the two step cycloaddition is between the O$^\text{+}$ of the nitrone and the nitrile carbon, so the electronic effect of the ortho-hydroxy group may not be a significant factor in the first step. There is also the possibility of steric effects of the ortho-substituent. The para-hydroxy group has a similar electronic effect and the reaction at

91
room temperature is likewise extremely slow. The progress of these reactions is depicted in the figure below.

Figure 41. The rate of formation of mono oxadiazoline platinum complexes made from hydroxy-substituted nitrones.

The form of the curves mirrors the findings of Desai et al.\textsuperscript{143}, for the reaction of unsubstituted nitrones with \textit{trans}-dichlorobis(benzonitrile) platinum(II). The present reactions are slower in reaching maximum conversion, as the temperature was lower at 30 °C rather than 40 °C. The lower temperature was chosen in the present study to avoid formation of the bis product. As previously mentioned, solubility is also an issue with the present reactions.

The maximal yields of the products were slightly improved by about 10% by reducing the temperature to 25 °C and lengthening the reaction time to three days. At this lower temperature the competing bis cycloaddition does not occur. This is aided by some of the mono cycloaddition product being precipitated with the passage of time.
5.4.1.2. Mono oxadiazoline platinum(II) complexes with glycol ether substituents.

Two complexes were made according to scheme 18; when $X = p$-$\text{CH}_2\text{O(}\text{CH}_2\text{)}_2\text{O}$-, $Y = \text{H}$, (41), when $Y = p$-$\text{CH}_2\text{O(}\text{CH}_2\text{)}_2\text{O}$-, $X = \text{H}$, (42). The motivation behind the synthesis of these complexes was the difficulty encountered due to the poor solubility of nitrones and platinum nitrile complexes with hydroxy-substituents. This problem was overcome by this modification as previously described.

5.4.1.2.1. The reaction of $\text{trans-[PtCl}_2(4-(2$-$\text{MeOC}_2\text{H}_4\text{O})-\text{C}_6\text{H}_4\text{CN})_2]$ with $\text{PhCH=NMeO}$ (41).

It was not possible to make a mono oxadiazoline platinum complex using a para-hydroxy substituted platinum nitrile complex, but with a para-glycol ether substituent this was successful. The cycloaddition is slower than with hydroxy- or non-substituted platinum benzonitrile and has to be heated for seven days at 30 °C. Close monitoring of the reaction using proton NMR spectroscopy is imperative and the reaction stopped at the first appearance of bis oxadiazoline platinum signals at 8.80 ppm. The characteristic signal corresponding to the ortho protons of the PtC=NC_6H_4 part of the complex are at 9.00 ppm. The corresponding reaction using a meta-substituted platinum nitrile was attempted, and although initially promising signals appeared in the proton NMR spectrum, as time progressed these signals got smaller coinciding with the appearance of many products, the main one being an aldehyde which could be from decomposition of the nitrone or of the oxadiazoline ring. After cycloaddition the resulting Pt-N=C_6H_4 bond is no longer linear, and the aryl ring is shifted towards the platinum. If the first cycloaddition is slow, the second cycloaddition may occur before the first one reaches completion. The bis cycloadduct may be unstable due to the two glycol ether groups coming into close proximity, depending on the conformation of the molecule. Decomposition of the bis cycloadduct would account for the appearance of signals corresponding to multiple products in the proton NMR spectrum, and the slow disappearance of the mono cycloadduct signals. Attempts to halt the reaction at the mono stage and work-up were thwarted by the reaction mixture being unstable and turning green on silica during chromatography. It was not possible to isolate a pure product.
5.4.1.2.2. The reaction of \( \text{trans-}[\text{PtCl}_2(\text{PhCN})_2] \) with \( 4-(\text{2-MeOC}_2\text{H}_4\text{O})-\text{C}_6\text{H}_4-\text{CH=NMEO} \) (42).

In contrast to the previous reaction, this cycloaddition occurred rapidly at 25 °C, yielding 40% of the mono cycloadduct in two hours, and 70% in seven hours. It then slowed down and after four days all the nitrone was consumed with no evidence of the bis cycloadduct in the proton NMR spectrum. This is in contrast to the corresponding hydroxy nitrone reaction where bis product formed before all the nitrone was consumed. As the glycol ether and hydroxy-substituents are electronically similar, this is difficult to explain. A purely speculative explanation may be the ability of the hydroxy group of the mono complex being able to hydrogen bond with the nitrone thus bringing it into the vicinity of the nitrile ligand and facilitating bis cycloaddition.

The analogous meta-substituted glycol ether nitrone reaction was carried out and although the proton NMR spectrum was very promising the product turned green with some black deposit on the silica during chromatography and only a poor yield of the product was recovered which quickly decomposed in solution (CDCl₃) in the NMR tube.

5.4.1.3. Mono cycloadditions where both the platinum nitrile complex and the nitrone have polar substituents.

Various reactions were attempted where the substituents were both either hydroxy- or glycol ether, or where the substituents were mixed. Although the proton NMR spectrum suggested successful cycloaddition in all cases, unfortunately the products did not crystallise out and it proved impossible to achieve any separation by chromatography or solvent extraction. It was regrettably decided not to pursue further this area of research at the present time. The proton NMR spectrum of one of these experiments is shown in figure 42.
5.4.1.4. Mono cycloaddition using cis-[PtCl₂(PhCN)₂] and 4-(2-MeOC₂H₄O)-C₆H₄-CH=NMeO.

cis-[PtCl₂(PhCN)₂] is far less soluble in chloroform than its trans isomer. It was difficult to achieve a 1/1 stoichiometry in solution. As a result, although signals indicative of a mono cycloadduct were initially seen in the proton NMR spectrum, with time, the signals disappeared, and the result was a mass or a mess of aromatic signals. It is known that cis bis oxadiazoline platinum complexes are unstable and rapidly decompose, and it is thought that the mono product was more soluble in chloroform than the starting nitrile and it underwent bis cycloaddition with the excess nitrone and then decomposed.

5.4.1.5. The characterisation of mono oxadiazoline platinum(II) complexes.

Various 1D and 2D NMR spectroscopic techniques as well FT-IR spectroscopy and mass spectrometry were used to characterise the complexes. This is illustrated by the full characterisation of the mono oxadiazoline platinum complex product 42 trans-[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(p-MeO-C₂H₄O-C₆H₄)}], in the experimental section (section 8.6.2)
As can be seen from figure 43 above, there are three aromatic ring systems present. The glycol ether substituted ring will result in a pair of doublets in the proton NMR spectrum, each equivalent to two protons, and a singlet equivalent to three protons. The two remaining phenyl rings will each produce a doublet equivalent to two protons, a triplet equivalent to two protons, and a triplet equivalent to one proton. Proton (fig. 44) and COSY NMR spectra (fig. 45) were used to assign the aromatic rings. The NMe will produce a singlet at \textit{circa} 3.00 ppm, and the CHN of the oxadiazoline ring will produce a singlet at 5.90 ppm.
Figure 45. The COSY 2D NMR spectrum of product 42, trans-\([\text{PtCl}_2(\text{PhCN})\{\text{N=C(Ph)-O-N(Me)-CH(p-MeO-C}_2\text{H}_4\text{O-C}_6\text{H}_4}\}]\).

Figure 46. The HMQC 2D NMR spectrum of product 42, trans-\([\text{PtCl}_2(\text{PhCN})\{\text{N=C(Ph)-O-N(Me)-CH(p-MeO-C}_2\text{H}_4\text{O-C}_6\text{H}_4}\}]\).
HMQC NMR (fig. 46) was used in conjunction with the $^{13}$C NMR spectrum to assign the carbon signals. Mass spectrometry (fig. 47) was used to assign the molecular peak and fragmentation pattern.

Figure 47. The MS-FAB spectrum of product 42 trans-$[\text{PtCl}_2(\text{PhCN})\{\text{N}=$\text{C(Ph)}$-$\text{O}$-$\text{N(Me)}$-$\text{CH}(p-\text{MeO}-\text{C}_3\text{H}_40-\text{C}_6\text{H}_4)\}]$.

5.4.2. Bis oxadiazoline platinum(II) complexes.

Bis cycloaddition introduces a second chiral centre to the platinum complexes, which can exist in either of two diastereoisomeric forms; $RS$ and $SR$ which are $meso$ compounds, and $RR$ and $SS$ which are enantiomers. In the present study a mixture of diastereoisomers has normally been produced, varying from 50 / 50 to 75 / 25, and the diastereoisomers have slightly different proton NMR spectra. In some instances one of the diastereoisomers crystallised out from the mix and an X-ray structure obtained (figure 50). This shows it to be the $RS$ isomer which being a $meso$ compound has a high degree of symmetry, specifically a centre of inversion.

The second cycloaddition is considerably slower than the mono cycloaddition by a factor of four$^{143}$. The forward reaction is favoured by an excess of nitrone and this will be expanded on in section 5.4.4.1. Bis oxadiazoline platinum complexes were made as shown in figure 48 below.
When $X = H$, $Y = \text{para-}OH$ (45),

$\text{meta-OH}$ (46),

$\text{para-}(2\text{-MeOC}_2\text{H}_4\text{O})$ (49).

When $Y = H$, $X = \text{para-}OH$ (47),

$\text{meta-OH}$ (48),

$\text{para-}(2\text{-MeOC}_2\text{H}_4\text{O})$ (50).

Figure 48. Bis oxadiazoline platinum complexes produced. (Exact reaction conditions are given in the experimental section 8).

5.4.2.1. Bis oxadiazoline platinum(II) complexes with hydroxy groups.

Four complexes were made successfully with hydroxy-substituents without much to report other than the solubility of the para-hydroxy substituted complex was poor in all organic solvents. In the case of complex 45 the product had to be dissolved in a mixture of deuterated acetone, deuterium oxide and sodium carbonate in order to acquire a $^{13}$C and $^{195}$Pt NMR spectrum. The solubility of the meta-hydroxy complexes was better in acetone and mixtures of DCM / ethyl acetate, and chromatography was possible for purification. Compound 48 is worthy of special note as one diastereoisomer crystallised out during manufacture, and it was difficult to dissolve, but the other one was so soluble in most mixtures of organic solvent, that it was impossible to re-crystallise.
5.4.2.2. Bis oxadiazoline platinum complexes with glycol ether groups.

Two complexes of this type were made according to figure 46. From the viewpoint of solubility the complexes were a success, being soluble in most common organic solvents. This property also enabled the purification of these complexes by chromatography. The solubility of the complexes in aqueous systems is discussed in section 5.7. The second cycloaddition reaction took considerably longer than for the corresponding hydroxy complexes. This may be due to the glycol ether groups of the mono complexes inhibiting the approach of the second molecule of nitrone in some way. In general the bis cycloaddition is slower than the analogous mono reaction, but these were particularly slow.

5.4.3. Cycloaddition reactions varying the halide.

Both mono and bis cycloaddition products were made where the halide was bromide or iodide, from the corresponding platinum bis benzonitrile complexes and N-methyl-C-phenyl nitrone. A bis complex (53) was attempted using PtBr₂(p-OH-C₆H₄CN)₂, but it is thought this was contaminated by a polymeric, possibly dimeric impurity, similar to the case already described for the analogous platinum chloro complex. In both cases the nitriles were made by the Kharasch method. To date a pure sample of this complex has not been isolated. There is little to report concerning the mono cycloadditions, the NMR and IR spectroscopy characterisation differed little from the chloro complex.

The bis cycloadditions proved to be much more interesting. In the case of the bromo complex, very broad proton NMR signals were observed. This could be explained by the bromide ions being larger in volume than the chloride ions and free rotation of the oxadiazoline ligands being inhibited. In the bis chloro complex, broad signals are observed for the CHN and NMe protons of the oxadiazoline ring. These are due to ring flipping about the tetrahedral NMe of the ring. The spectrum of the bis oxadiazoline bromo complex has much broader signals including the aromatic region, which are sharp in the analogous chloro complex. The bromo complex proton NMR
spectrum is shown in figure 49 below, and can be contrasted with figure 56, which is a chloro bis oxadiazoline complex.

Figure 49. The proton NMR spectrum of PtBr$_2$(oxa)$_2$ (52) at 298 K.

X-ray diffraction analysis was performed on the crystals produced in the reaction, and these were found to be the R,S isomer. The structure (figure 50) shows the phenyl ring of PhC=N of each ligand to be on opposing sides of the PtBr$_2$N$_2$ plane. This gives a high degree of symmetry to the complex and the crystals once formed are extremely difficult to re-dissolve in chloroform, presumably due to high lattice energy. Proton NMR spectroscopy was carried out overnight using one single crystal. This showed the crystal to be one isomer. It is also clear from the structure, simulated in figure 51, that free rotation of the phenyl rings would be difficult and this explains the broad aromatic signals. The oxadiazoline ring CH-N signal is also very broad and this is due to very restricted rotation of the Pt-N bond which means the oxadiazoline ligands are able to rock from side to side rather than completely rotate. The N-Me on the oxadiazoline although having free rotation itself is also affected by the lack of free rotation of the oxadiazoline ring. Another important feature is the tetrahedral geometry of the nitrogen (NMe) taking into consideration lone pair. This is able to invert faster than the time interval between the pulse and acquisition, an intrinsic part of the NMR experiment, so what is seen is an averaged signal which is consequently broad.
Figure 50 compares a simulation modelled from the X-ray crystal structure of the complex in figure 51 below, with the analogous chloro complex. This shows that the phenyl groups of the bromo complex are much closer together than its chloro analogue, suggesting there is hindrance to free rotation in the bromo complex.

Bromo-compound: the phenyl groups appear to be very close together.

Chloro-compound: there is a larger gap between the phenyl groups allowing more freedom of rotation.

Figure 50. Comparison of the simulated models (Molekel) of PtBr₂(oxa)₂ with PtCl₂(oxa)₂.
The corresponding iodide complex was expected to have even broader NMR signals due to the much larger iodide ions restricting free rotation of the oxadiazoline rings. The observed spectrum could not have been more surprising. Not only were the signals sharp but there were at least four observable for the NMe and CHN protons of the oxadiazoline ring. The proton NMR spectrum also suggests there are two diastereoisomers, and each of these has two conformations. This was concluded by observation of the signals between 8.60 and 8.80 ppm which are shown in figure 52 below. The signal at 6.05 ppm and doublet at 8.95 ppm belong to the mono cyclo adduct. It is hypothesized that this is due to total restriction of rotation of the rings and what is being observed are distinct conformations. On standing in solution for 24 hours most of these signals disappear leaving just two sets of signals (figure 53). Either there is a conformational change possibly by ligand exchange or some of the isomers are unstable and decompose. There was some precipitate observed suggesting either decomposition, or precipitation of the less soluble isomers but there were no extra signals in the proton NMR spectrum which would be expected from decomposition, i.e. signals corresponding to nitrone or mono oxadiazoline complex. To date it has not been possible to obtain an X-ray diffraction structure of the bis iodo complex.
Figure 52. Proton NMR spectrum of PtI₂(oxa)₂ (55) before purification showing four isomers, and inset the 8.6-8.8 ppm region which is the Pt-N=CPh ortho protons.

Figure 53. Proton NMR spectrum of PtI₂(oxa)₂ (55) after 24 hours and column chromatography (which only removed the unreacted nitrone).
5.4.4.1 NMR experiments with bis oxadiazoline platinum complexes to illuminate the mechanism of the cycloaddition reaction.

Experiments were carried out using both iodo and bromo bis oxadiazoline platinum complexes in order to see if a conformational change could be achieved through heating as shown below.

![Scheme 19](image)

Scheme 19. An attempted conformational change in bis oxadiazoline platinum complexes with bromo or iodo ligands achieved through heating.

A single crystal (one diastereoisomer) of each was dissolved in chloroform in NMR tubes and placed in a sand bath for 48 hours at 60 °C. No conformational change was observed but surprisingly signals corresponding to the mono oxadiazoline platinum complex appeared in both cases. It would be expected that if the reverse reaction happened then so should the forward reaction, but on further heating this did not occur. Conversion back to the bis complex was only observed when an excess of nitrone was added, and the mono complex signals disappeared with time. This would strongly suggest that for the mono reaction equimolar quantities of reagents can be used and the forward reaction is favoured following a second order type mechanism. For the second cycloaddition i.e. bis cycloaddition, the reverse reaction is favoured and an excess of nitrone has to be used to force the forward reaction. This would help explain why the bis reactions using hydroxy-substituted nitrones, which were poorly soluble in chloroform, were so slow. Also, for bis reactions it is important to choose a solvent in which the nitrone is soluble. Is it plausible that the second cycloaddition is reversible whereas the first is not? Observation of the crystal structure and model of PtBr₂(oxa)₂ (figs 50 and 51) show significant steric hindrance to free rotation of the phenyl rings. This may make the complex thermally unstable in solution when heated for lengthy periods as in this experiment. Formation of the mono cycloadduct
immediately alleviates this hindrance. In the mono complex the benzonitrile aromatic ring points away from the platinum centre due to the linear nature of the Pt-N=C-C bonds. Also considering the hybridisation states of the nitrogens bonded to the platinum, the nitrile has sp, and the oxadiazoline has sp\(^2\) hybridisation. The latter has greater p character than the nitrile and the stronger bond that results will labilise the Pt-N bond of the nitrile. This means the platinum will have less of a polarising effect on the C=N than on the equivalent bond in bis benzonitrile complexes, and is consequently less susceptible to cycloaddition. The mono cycloadduct is further stabilised as a result. Another factor to consider is the electronegativities of bromine (2.96) and iodine (2.66) which are lower than that of chlorine (3.16) on the Pauling scale. This means in complexes of the former two halides platinum is a weaker Lewis acid and the benzonitrile of the mono cycloadduct will not be so activated toward the second cycloaddition as in the chloro complex. This means for bromo and iodo complexes, the forward reaction has to be forced with an excess of nitrone, and if the bis cycloadduct is heated in solution the reverse reaction happens reverting to the more stable mono complex.

5.4.4.2. An NMR experiment at elevated temperatures to effect a conformational change using PtBr\(_2\)(oxa)\(_2\).

A proton NMR experiment was carried out using a single crystal dissolved in deuterated toluene as solvent to try and effect a conformational change. The spectrum obtained for the single crystal showed it was only one isomer. The temperature in the spectrometer was raised by increments of 10 °C up to 100 °C. Although the broad signals sharpened, no conformational change was observed, and the broad signals returned on cooling. The spectra are included in appendix 1.
5.4.4.3. A comparison of the $^{195}$Pt NMR spectral data for platinum complexes varying both the halide and the lone pair donating nitrogen ligand.

In section 5.3 a linear relationship was shown for the $^{195}$Pt NMR spectral data of mixed halide platinum(II) and platinum(IV) complex ions, which signified that the bonding of the halide is mainly one of $\sigma$ bonding. This result is further developed below in figure 54, not only varying the halide but also the other two ligands.

![Figure 54. The comparison of $^{195}$Pt NMR spectral data, varying ligands.](image)

Varying the non-halide ligand from bis-benzonitrile to benzonitrile / oxadiazoline, to bis-oxadiazoline shows a linear relationship for all three halides. This shows that $\sigma$ bonding predominates in these complexes, with negligible $\pi$ overlap or back bonding. In this respect the bonding is similar to that of the halide ligands, and is consistent with accepted theory on platinum square planar complexes with nitrogen donor ligands. This states that the main bonding is one of $\sigma$ end on overlap between the electrons of the platinum $dsp^2$ hybrid orbitals and in this case nitrogen lone pairs. $\pi$ overlap between $d^{19}$, $d^{18}$ and $d^{17}$ is limited in the case of the benzonitrile ligands due to the linear nature of the Pt-N≡C bonds. The triple bond $\pi$ system is in the square plane of the complex and not orientated towards it, as shown in figure 55 below.
Bonding to π systems by platinum is favoured when the π system is perpendicular to the square plane such as is the case with the acetylene ligand\textsuperscript{52} or as in Zeise's salt see figure 20, although it should be noted that acetylene can also bond end on after deprotonation. In the case of the oxadiazoline ligand, the Pt-N=C bond angle is 130.8°\textsuperscript{85}, so it is difficult to envisage any significant overlap of the double bond π system and the platinum π orbitals, though probably more than in the case of the nitrile.

5.4.5. The characterisation of bis oxadiazoline platinum complexes

Various 1D and 2D NMR spectroscopic techniques as well as IR absorption spectroscopy and mass spectrometry were used to characterise the complexes. This is demonstrated below by the full characterisation of [PtCl\textsubscript{2}{N=C(Ph)-O-N(Me)-CH(p-HO-C\textsubscript{6}H\textsubscript{4})}]\textsubscript{2}\textsuperscript{47}, the structure of which is shown below in figure 55 (enlarged for clarity).

![Figure 55](image)

Figure 55. The different orientations of π systems in platinum nitrile and acetylene complexes.

![Figure 56 (a)](image)

Figure 56 (a). The structure of [PtCl\textsubscript{2}{N=C(Ph)-O-N(Me)-CH(p-HO- C\textsubscript{6}H\textsubscript{4})}]\textsubscript{2}\textsuperscript{47}.
Figure 56 (b). The proton NMR spectrum of $[\text{PtCl}_2\{\text{N} = \text{C(Ph)} - \text{O} - \text{N(Me)} - \text{CH}(p-\text{HO-C}_6\text{H}_4)\}]_2(47)$ in $d_6$-DMSO.

Figure 57. The 2D COSY NMR spectrum of $[\text{PtCl}_2\{\text{N} = \text{C(Ph)} - \text{O} - \text{N(Me)} - \text{CH}(p-\text{HO-C}_6\text{H}_4)\}]_2(47)$. 

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As can be seen from figure 56, there are two aromatic ring systems; a pair of doublets each with an integration of two protons is expected from the $p$-OH-C$_6$H$_4$, and the phenyl rings will have a doublet with an integration of two for the ortho protons, a triplet with integration of two for the meta protons and a triplet with integration of one for the para proton. These can be clearly seen in the 1D proton and 2D COSY spectra (figs 56 and 57). The $^{13}$C signals can then easily be read off from the 2D carbon / proton correlation, HMQC (fig 58), and the $^{13}$C spectra.
The following fragmentation pattern is observed in figure 59 which is the MS-FAB spectrum of complex 47, MS-FAB\(^+\), m/z: 775.1 [M]\(^+\), 701.9 [M - 2HCl], 737.1 [M - HCl], 797.2 [M + Na]. The spectroscopic information together with elemental analysis (in section 8) leads one to the conclusion that a pure sample of product 47 has been prepared. Although an X-ray structure was not obtained of this particular complex, one was obtained of a similar complex\(^8\), and the proton NMR spectra of the two are similar enough to conclude the correct complex has been made. The full characterization of product 47 is in section 8.7.3.

5.4.6. Attempted unsuccessful cycloaddition reactions between \textit{trans}-dichlorobis(benzonitrile) platinum(II) and nitrones bearing electron withdrawing substituents.

Having electron deficient species in \textit{para} and \textit{ortho} positions of the phenyl ring of the nitrone, should render the nitrone more polar and consequently more reactive. Surprisingly the results of the reactions were not cycloaddition.
The following nitrones were chosen where $R = m$-CO$_2$H (8), $o$-SO$_3$Na$^+$ (10), $p$-(CH$_3$)$_2$N (included for its structural relationship), $p$-(Me)$_3$N$^+$ (12) and $p$-(Me)$_2$HN$^+$ (protonated derivative of 11). The latter being prepared by reaction of $p$-(CH$_3$)$_2$N-C$_6$H$_4$-C(H)=NOMe (product 11) with one molar equivalent of glacial acetic acid, and used without purification. When $R = m$-CO$_2$H, the reaction followed the normal cycloaddition route but with reduced yield of 10%.

5.4.6.1. Reaction with meta-carboxy substituted nitrone (8).

This nitrone was chosen as the substituent, being in the meta position, would have no electronic effect on the dipole, but it would hopefully make the product of cycloaddition more soluble in polar solvents. This nitrone was expected to be similar in reactivity to an unsubstituted nitrone. Surprisingly only a small amount of cycloaddition product, less than 10%, was evident in the proton NMR spectrum after reaction at 60 °C for 10 days. It is believed the reason for this is the choice of solvent used for the reaction. The nitrone is insoluble in chloroform so acetone was used. This is more polar and not only stabilises the dipolar nitrone, but also the proposed intermediate shown in figure 61 below.
Also visible in the proton spectrum was a signal equivalent to an aldehyde proton suggesting either hydrolysis of the nitrone or the intermediate. The starting nitrile complex and nitrone were also seen. Various mixtures of chloroform and acetone, and chloroform and methanol were also attempted, with no significant improvement in yield. It was concluded the reaction did not go to completion due to solvent stabilisation of the starting nitrone and intermediate and also because of a competing hydrolysis reaction.

5.4.6.2. The reaction of the remaining nitrones with trans-dichlorobis(benzonitrile) platinum(II).

The reactions of the other four nitrones are dealt with together as they gave a similar result. For reasons of solubility acetone was once again chosen as solvent. The reactions were carried out using 2/1 nitrone/platinum nitrile stoichiometry at room temperature for up to 140 hours, or 48 hours at 60 °C for two days. Both sets of conditions gave similar results. All four reactions result in a mixture of at least two products, one of which is suspected to be an aldehyde due to the appearance of a characteristic sharp singlet at around 10.00 ppm in the proton NMR spectra. There are two possibilities for an aldehyde being produced, firstly hydrolysis of the nitrone, which is unlikely as it would not explain the other product, and second hydrolysis at the C(H)-N bond of the intermediate. This might lead speculatively to structures (a) and (c) shown below in figure 62.

(a)  
(b)
Figure 62 a-d. Possible structures of the reaction of dichlorobis(benzonitrile) platinum(II) with nitrones 10, 11, 12 and the protonated derivative of 11.

The compounds (b) and (d) are highly unlikely to be made this way but correspond to signals in the mass spectrum. It should be stressed these latter two structures are highly speculative. The structures (c) and (d) are ring structures isomeric of (a) and (b) respectively. Platinum is known to form ring structures with nitrogens coordinated in *cis* positions,

The proton NMR spectra of the four reactions are very similar, only differing because of the different substituents on the aldehydes produced. There is also a doublet at about 8.90 ppm (*ortho* protons of Pt-N=C-Ph) and a singlet at 2.80 ppm (NMe), with the correct integration which is normally characteristic of a cycloaddition, however there is no broad singlet apparent at 5.90 ppm corresponding to the C(Ph)HN of the heterocycle, so an oxadiazoline can be ruled out. It is because of this similarity, especially the doublet at 8.80 ppm, that it is believed the reactions proceed to the intermediate stage of cycloaddition but not to the second stage of ring closure. The *ortho* protons of Pt-N=C-Ph would be in a similar environment in both cases. This is shown in figure 63 below and can be compared with figure 56, which is the proton spectrum of a bis oxadiazoline platinum complex.
Figure 63. The proton NMR spectrum of the products of reaction of trans-PtCl$_2$(PhCN)$_2$ with the protonated derivative of nitrone 11.

The $^{195}$Pt NMR signals of the reactions using nitrones 10 and 12 are identical at -2261 ppm using chloroform as solvent. So there is definitely a platinum species present that is different to the starting nitrile which has a signal at -2348 ppm. The former is the main platinum species present apart from a small residual signal at -2348 ppm. In the case of the protonated quaternary ammonium nitrone (derivative of 11) the signal is at -2248 ppm but the solvent used was D$_2$O, and the difference is small enough to be explained by solvent effects. In $^{195}$Pt NMR spectroscopy, half height line widths are used as a form of characterisation. Sometimes it is possible to tell something about the coordination environment from the line width, for example, whether the platinum is coordinated to two chlorines and two nitrogens, or to four nitrogens. In this particular case there is overlap, with known line widths ranging from 700 – 1700 Hz. The $^{195}$Pt NMR spectra and a table of known line widths are included in appendix 2.

In the mass spectrum, a case could be made for structures (a) and (c) with a peak at 566.9 which fits PtCl$_3$N$_4$O$_2$C$_{10}$H$_{20}$, [M-2HCl] at 494.0 with a very large relative abundance, and [M+Na] at 589.9. The isotopic patterns of these peaks are similar to the peaks at 775.1 and 701.9 which are the molecular ion peak and the [M-2HCl] of
the bis oxadiazoline platinum complex product 47 in figure 59. Both compounds contain the fragment PtCl₂N₄O₂ which is the major contribution to the isotopic splitting pattern. Both figures are reproduced in appendix 2 side by side for clarity. There is also a peak at 619.9 which could be [PtCl₂N₄O₄C₁₆H₅O⁺Na] representative of structures (b) and (d). This is shown in figure 64 below. It would be extremely difficult to explain mechanistically how (b) and (d) could be produced from the starting compounds, however production of (a) and (c) is very plausible by hydrolysis of the intermediate. Reactions can also take place during mass spectrometry which could explain spurious peaks.

Figure 64. Mass spectrum of the reaction between trans-[PtCl₂(PhCN)₂] and the protonated derivative of 11.

As the proposed product could not be isolated in pure form or recrystallised, and there is no evidence of purity the proposed structures are described as both tentative and speculative. However, the available evidence favours structures (a) and (c) over (b) and (d).
5.4.7 Variable temperature Proton NMR spectroscopy experiments using platinum oxadiazoline complexes and uncoordinated oxadiazoline.

Examination of the proton spectra of platinum oxadiazoline complexes, show some of the signals, particularly the singlet equivalent to CHN of the oxadiazoline ring at 5.90 ppm, to be broad. This suggests a conformational change of the said ring. This can only occur at the N-methyl of the ring, which has a lone pair of electrons and tetrahedral geometry. Inversion of the lone pair occurs as shown in figure 65 below.

![Figure 65. The two conformations of the oxadiazoline ring.](image)

Considering the CNO part of the ring and the geometry surrounding the nitrogen, if this is thought of as the flap of an envelope then the left hand structure has the flap folding into the plane of the paper and the nitrogen obscures its lone pair of electrons. In the right hand structure the flap is pointing out of the plane of the paper and the lone pair (shown to the right for clarity) would be in front of the nitrogen, coming out of the plane of the paper. The broad signals are caused by rapid flipping from one conformation to the other so what is seen in the proton NMR spectrum is an average of the signals. It was decided to investigate whether by increasing the temperature or by lowering it, the conformation could be fixed in one position or the other. The following platinum complexes and oxadiazoline were used;

1. PtCl$_4$(PhCN)(oxa).
2. PtCl$_2$(PhCN)(oxa).
3. PtCl$_2$(oxa)$_2$.
4. 2-methyl-3-tolyl-5-phenyl-$\Delta^4$-1,2,4-oxadiazoline (shown in figure 66 below),
The uncoordinated oxadiazoline was made by the Hermkens method by a final year undergraduate within the group (Timothy Garland). The bis oxadiazoline platinum(II) complex contained the ligand shown in figure 66.

5.4.7.1. NMR experiment using PtCl₄(PhCN)(oxa).

The proton NMR spectrum of this platinum(IV) mono oxadiazoline complex at room temperature contains only sharp signals, in contrast to its platinum(II) counterpart. Raising or lowering the temperature in the range 213-333 K had no effect on the spectrum. It is considered this is due to the ligand being locked into a particular configuration by the presence of the axial chloro ligands. When the NMe attempts to flip it would push the phenyl group of CHPh in towards the chlorine, and this is resisted and the ring is prevented from flipping. In this way the conformation of the molecule as a whole is locked in place.

5.4.7.2. Variable temperature NMR experiments using free oxadiazoline and PtCl₂(PhCN)(oxa).

These two experiments are dealt with together because both behave similarly, and the spectra of the mono oxadiazoline platinum complex are displayed to show the result. The stacked plots shown in figure 67(a) clearly demonstrate the drift of the signals as the temperature increases. This drift is dependent on how far apart the two signals of the exchanging conformations are from each other. The coalescence point can be estimated at 283 K or thereabouts. At this temperature the flipping is at the same rate.
as the difference between the two signals in Hertz, and the NMR signal is at its broadest. At low temperature the speed of the flip slows down. Two distinct products should be visible, the main one at approximately 3.14 ppm and a minor product which is not obvious from the figure upfield of the main signal. The coalescence point shows the average of these signals. The flip is instantaneous so the molecule is in one conformation or the other. The broad signal is an artefact of the NMR experiment. The molecule is in a definite conformation but the operating speed of the spectrometer is not sensitive enough to pick it out. A good analogy is of a blurred photograph of a racing car. At any instant the car is solely in one position, but the camera shutter speed is too slow to pick it out.

![Figure 67(a). The proton NMR spectra stacked plot of the NMe protons of mono oxadiazoline platinum(II) from 213 K-313 K.](image)
Figure 67(b) The proton NMR spectra stacked plot of the CHN proton of mono oxadiazoline platinum(II) from 213 K-313 K.

Figure 67(c) The proton NMR spectra stacked plot of the C(Ph)=N ortho phenyl protons of mono oxadiazoline platinum(II).
Inspection of figure 67(b) confirms the proposed coalescence point at approximately 283 K. This figure shows the stacked plot for the CHN proton which occurs at ~ 6.00 ppm. In this case the minor product is downfield of the main conformation. Also noticeable is that the range of the drift is not as large as for the NMe protons. This may be due to the flip having less of a spatial effect on the CHN proton compared to that of the NMe group. This is best envisaged by observation of figure 65 and imagining the CNO part of the ring flipping up and down. Figure 63(c) does not illustrate any broadening of the doublet at approximately 9.00 ppm, therefore these protons are not involved in the exchange at this temperature. The C(Ph)=N ortho protons are on the opposite side of the ring to where the flip occurs, so the drift observed is thought to be due to local anisotropic effects rather than the flipping action. It is more likely a result of the spatial position of the protons in relation to the 5d lone pair electrons on the platinum centre.

5.4.7.3. Variable temperature NMR experiments using bis oxadiazoline platinum(II) complexes.

Bis oxadiazoline platinum complexes differ from their mono counterparts in the following ways, they not only exist as two diastereoisomers but can adopt different conformations as well. The oxadiazoline substituent phenyl rings can be on the same side of the PtX₂N₂ plane or on opposing sides. This is evident in the crystal structure shown in figure 48. These rings lie above and below the platinum centre and come fairly close together. This may inhibit complete free rotation of the phenyl rings, and also of the heterocycles about the Pt-N bonds. Examination of the stacked plot (figure 68) of this experiment showed that all the proton signals sharpen or broaden depending on the temperature, but there is very little drift observed. This may be due to a ring flip on one ligand of the complex resulting in the simultaneous opposite flip on the other ligand. This cancels out the overall effect of the flip. This is shown in figure 68 below.
Figure 68. The proton NMR spectra stacked plot with varying temperature for a bis oxadiazoline platinum(II) complex.

The coalescence point can be estimated at approximately 273 K. Curiously, considering the ortho phenyl protons of N=CPh at 8.80-9.00 ppm, which are four bonds away from the flipping nitrogen and represent the two diastereoisomers; as the temperature falls the diastereoisomer with the broad signal at coalescence becomes sharp. Also obvious is the appearance of a smaller signal between the two signals of the diastereoisomers. There is an exchange occurring but this is possibly a conformation change rather than a ring flip. The smaller signal could be the minor conformation product of the diastereoisomer closer to 9.00 ppm. There is virtually no drift of the other diastereoisomer. This feature is also seen in the 5.70 - 6.00 ppm range. If rotation about the Pt-N is frozen by steric effects, the conformational difference could be due to orientation of the oxadiazoline ligands, such as:

\[
\begin{align*}
N\text{Pt}^{-}N & \quad \text{or} \quad N\text{N}\text{Pt}^{-}N
\end{align*}
\]

At present it is not possible to state with any certainty what is occurring with the bis oxadiazoline platinum complex.
5.5. Substitution reactions of platinum complexes.

Prior to biological testing, it was considered useful to learn something about the reactivity of mono and bis oxadiazoline platinum complexes with regard to substitution. Potential platinum anticancer agents commonly fail in vivo due to substitution of the ligands by compounds containing sulphur moieties, such as metallothioneins, found in the bloodstream or the cytoplasm of cells\(^{29,30}\). This means the active drug never reaches its site of action. The functionalities involved in this substitution are thiols and thioesters. DMSO was chosen for the present reactions, not that it mimics the in vivo substitutions, but rather because it is the choice of solvent for biological testing and for making stock solutions in pharmaceutical chemistry. This means that any potential anti-tumour drugs would have to be stable in DMSO. This is expanded on in section 5.7, Biological testing. Platinum nitrile complexes and both bis and mono oxadiazoline platinum complexes were used for these substitutions. In order to test the possibility of the complexes binding to DNA, pyridines, amines, and imidazole were chosen. The nitrogen of pyridine in particular is similar to the N7 of guanine (figure 69) which is known to bind to cisplatin\(^{32}\).

![Figure 69. The structure of guanine (protons not shown).](image)

5.5.1. Substitution using DMSO.

5.5.1.1. Substitution using platinum nitrile complexes.

\([\text{PtCl}_2(p-\text{OH-C}_6\text{H}_4\text{CN})_2]\) and \([\text{PtCl}_2(p-\text{MeO-C}_6\text{H}_4\text{O-C}_6\text{H}_4\text{CN})_2]\) were chosen for investigation as it was considered the two substituents on the ring were similar electronically so the major difference would be a steric influence from the glycol ether
group. Reactions were carried out in the NMR tube using deuterated DMSO in large excess as solvent according to the scheme:

\[
\begin{array}{c}
\text{R} & \equiv & \text{N} & \text{Pt} & \equiv & \text{R} \\
\text{Cl} & \equiv & \text{N} & \text{Pt} & \equiv & \text{Cl} \\
\end{array}
\xrightarrow{\text{DMSO}}
\begin{array}{c}
\text{Cl} & \equiv & \text{Pt} & \equiv & \text{DMSO} & + & 2 \text{R} & \equiv & \text{N} \\
\end{array}
\]

Scheme 20. Substitution reactions of bis nitrile platinum complexes with DMSO.

The proton spectra were run initially (approximately after ten minutes), at two hours, and at 23 hours. The spectra were acquired at 298 K and the tubes stored at room temperature and 50% relative humidity. The results for the two experiments were similar, after ten minutes there had been approximately 20% substitution and 100% at two hours. This shows that the glycol ether substituent in the para position does not axially hinder substitution at the platinum centre. The intermediate product PtCl₂(nitrile)(DMSO) is not seen in the proton NMR spectra, only the starting platinum nitrile complex and the uncoordinated nitrile. This suggests that the second substitution occurs rapidly after the first one and the concentration of the intermediate complex never builds up to high enough concentration to be visible in the spectra. This is consistent with DMSO having a strong trans effect resulting in the nitrile ligand being labilised. The PtCl₂(DMSO)₂ complex is generally poorly soluble and precipitates as a white solid, so no further substitutions take place. Whilst the experiment in no way mimics the relative concentrations of drug and sulphur containing substances in vivo, the rapid exchange demonstrates that platinum nitrile complexes would not be suitable candidates for medical testing.

5.5.1.2. Substitution with DMSO using bis oxadiazoline platinum(II) complexes.

Due to the poor solubility of hydroxy-substituted bis oxadiazoline platinum complexes in chloroform and acetone, deuterated DMSO was used to perform NMR experiments as a matter of course. Bis oxadiazoline platinum complexes were found to be stable in DMSO for many weeks without any significant exchange. Reaction
only occurs when heat is applied (60 °C) for several days. It was considered that bis oxadiazoline platinum complexes might be too inert with regard to substitution to be of much use for biological testing.

5.5.1.3. Substitution using a mixture of mono and bis oxadiazoline platinum complexes.

PtCl$_2$(PhCN)(oxa) + DMSO $\rightarrow$ PtCl$_2$(oxa)(DMSO) + PhCN $\rightarrow$ PtCl$_2$(DMSO)$_2$ + oxa
PtCl$_2$(oxa)$_2$ + DMSO $\rightarrow$ PtCl$_2$(oxa)(DMSO) + oxa $\rightarrow$ PtCl$_2$(DMSO)$_2$ + oxa

Scheme 21. The sequence of substitutions in mono and bis oxadiazoline platinum(II) complexes by DMSO.

A mixture of mono and bis complexes in a 2 / 1 ratio was used in order to compare in situ the substitution of ligands by DMSO.

The unsubstituted platinum complexes shown in figure 70 below were used and the following three experiments carried out;

1. A large excess of DMSO (150 / 1 molar excess).
2. A smaller excess of DMSO (10 / 1 molar excess)
3. A stoichiometric amount of DMSO.

![Figure 70. (a) Mono oxadiazoline platinum complex. (b) Bis oxadiazoline platinum complex (these were made according to the Desai and Wagner method$^{140}$).](image)

Experiment 1.

30 mg of the mixture of mono and bis complexes was placed in an NMR tube with 0.5 ml of deuterated DMSO and proton NMR spectroscopy monitored over the following
24 hours. The signals corresponding to the mono complex gradually disappear, 70% in the first three hours. The product was a mixture of cis and trans PtCl₂(DMSO)(oxa) complexes. Unfortunately the bis oxadiazoline platinum complex does not dissolve so it was not possible to tell if it exchanged or not. Proton NMR signals equivalent to free oxadiazoline⁷⁸ were visible but this could be produced by substitution of the oxadiazoline ligand of the mono complex.

It is considered from observation of the proton NMR spectra, that over the first 24 hours the benzonitrile ligand of the mono complex is substituted by DMSO and the oxadiazoline ligand over the following five days. The presence of the large oxadiazoline ligand significantly slows down the rate of substitution of the benzonitrile ligand compared to platinum bis benzonitrile complexes. It was considered that the increased reactivity of mono oxadiazoline platinum complexes, with regard to substitution, compared to their bis counterparts would make them potential anti-tumour agents and good candidates for biological testing.

![Substitution reaction of a mono oxadiazoline platinum complex using a large excess of DMSO](image)

Figure 71. Substitution of the benzonitrile ligand in PtCl₂(PhCN)(oxa) using a large excess of DMSO at 25 °C, over the first 24 hours of reaction.

Figure 71 above shows the trend in the rate of exchange of DMSO for benzonitrile in PtCl₂(PhCN)(oxa). The percentage substitution is calculated from the signal integrals in the proton NMR spectra. The line is one of best fit. There are five points up to
approximately 3 hours and then one at twenty-two hours. This accounts for the rather sharp tailing off observed in the figure. The reaction should follow pseudo-first order kinetics as the DMSO remains in large excess throughout. To test this a plot of $\log\{[\text{PtCl}_2(\text{DMSO})(\text{oxa})]_{\text{infinity}} - [\text{PtCl}_2(\text{DMSO})(\text{oxa})]_{\text{time}}\}$ against time should be drawn (The first term is called $\log A$ in figure 72). The percentage of substitution used in figure 71 is directly proportional to concentration so this quantity was used, and the concentration (percentage) at infinity assumed to be 100%. The result is shown in figure 72 below. Whilst these graphs were generated from one experiment without repeats to reduce error, the line is a good fit and straight. This would suggest that over the initial stages of the substitution, pseudo first order kinetics is followed. This is in general agreement in cases where the solvent coordinates to square planar platinum complexes, displacing a ligand\(^2\).

![Expt. Mono oxadiazoline platinum complex, substitution using DMSO as solvent](image)

Figure 72. Expt. 1, plot of $\log A$ against time for the exponential part of figure 71.

Experiment 2.

In an attempt to prepare and isolate the platinum (DMSO)(oxa) complex, a second reaction was carried out using a much smaller excess of DMSO (10 molar). This was placed with 30 mg (0.05 mmol) of pure mono oxadiazoline platinum(II) complex in an NMR tube with one drop of deuterated chloroform to solvate it, and left for four days at room temperature. After this time proton NMR spectroscopy and TLC showed a mixture of products. Column chromatography was carried out using initially DCM to remove the benzonitrile and unreacted mono oxadiazoline platinum complex. Then DCM / ethyl acetate in a 3 / 1 ratio was used to elute the products. These were found to be a mixture of cis and trans $\text{PtCl}_2(\text{DMSO})(\text{oxa})$ complexes, as found in

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experiment one. This was the first time a trans complex of this type was seen. The cis complex has been reported\(^8\) starting with a mixed platinum (DMSO)(PhCN) complex but the synthesis is not without problems and a improvement would be beneficial.

Experiment 3.
The experiment was repeated using a stoichiometric amount of DMSO and deuterated chloroform as solvent in the NMR tube. At ambient conditions there was no exchange within 24 hours. The temperature was raised to 60 °C and the progress of the reaction monitored over the following six days (fig. 53). The exchange was slow, only 50% conversion after three days. Solely cis-PtCl\(_2\)(DMSO)(oxa) was formed, and some PtCl\(_2\)(DMSO)\(_2\) complex. This is consistent with existing theory that with DMSO platinum complexes, the trans isomer forms first, but is readily isomerised to the more stable cis isomer, or that both isomers are formed and the trans isomer goes on to form the bis DMSO platinum complex as a result of its strong trans effect. Under the conditions of this experiment not only is the cis isomer produced preferentially but the bis substitution is also forced.

![Substitution reaction of mono oxadiazoline platinum complex with DMSO using equimolar amounts at 60 °C](image)

Figure 73. Substitution of benzonitrile ligand in PtCl\(_2\)(PhCN)(oxa) by DMSO using equimolar quantities at 60 °C.
The progress of the reaction shows the same trend as expt 1, when DMSO is used as solvent (figure 71) but much slower. As equimolar quantities were employed, it might be suspected that the reaction follows a second order type mechanism. To test for second order kinetics a plot of the reciprocal of the concentration of starting platinum complex against time was generated. To satisfy the requirement for second order, the plot should be a straight line. However this was found not to be the case. The data were also treated in the same way as experiment 1, and a plot of logA against time produced what appeared to be a straight line for the bulk of the reaction, except for a kink in the first few hours. This can be seen in figure 74 (a).

![Figure 74 (a). DMSO exchange experiment 3, plot of logA against time.](image)

It is possible that the reaction is complicated by the bis reaction taking place as well as the mono substitution, and therefore the data are no longer wholly valid. The plots, figures 74 (b) and (c), are contained in appendix 4 for interest.

A trend in the rate of substitution of platinum nitrile and oxadiazoline complexes with DMSO has been established; PtCl$_2$(PhCN)$_2$ > PtCl$_2$(oxa)(PhCN) > PtCl$_2$(oxa)$_2$. As the rate of substitution decreases as the substituents become increasingly bulky, an associative mechanism for the substitution would be expected. If there was a dissociative mechanism at work, increasing steric hindrance of the ligands would not affect the rate of substitution. This is in agreement with published work $^{52,148}$. However this is not in agreement with previous reports that in the substitution of square planar platinum complexes, configuration is retained$^{52}$. Experiment 1 resulted in both cis and trans isomers.
5.5.2. Substitution reactions using pyridines.

\[
\text{PtCl}_2(\text{PhCN})(\text{oxa}) + \text{pyr} \rightarrow \text{PtCl}_2(\text{pyr})(\text{oxa}) + \text{PhCN} \rightarrow \text{PtCl}_2(\text{pyr})_2 + \text{oxa}
\]
\[
\text{PtCl}_2(\text{oxa})_2 + \text{pyr} \rightarrow \text{PtCl}_2(\text{oxa})(\text{pyr}) + \text{oxa} \rightarrow \text{PtCl}_2(\text{pyr})_2 + \text{oxa}
\]

Scheme 22. The sequence of substitutions in mono and bis oxadiazoline platinum(II) complexes by pyridine.

5.5.2.1. The reaction of pyridine with a mixture of PtCl$_2$(oxa)$_2$ and PtCl$_2$(PhCN)(oxa).

A similar approach to the DMSO substitution was initially adopted to investigate the susceptibility of bis and mono oxadiazoline platinum complexes toward substitution. A 50 / 50 mix of mono and bis oxadiazoline platinum(II) complexes was used and a thirty molar excess of pyridine without solvent. This was left at room temperature for four days. On addition of chloroform there was a white precipitate. This had a proton NMR spectrum consistent with a platinum bis pyridine complex. There was no evidence of mono oxadiazoline platinum complex, but the bis oxadiazoline platinum complex was clearly visible in the NMR spectrum and isolated by chromatography. The experiment was repeated using deuterated chloroform as solvent in the NMR tube and the proton NMR spectra acquired periodically. A mixture of products was obtained, again there was a white precipitate of platinum bis pyridine but the other two main products were not so easily identified. Close examination of the integration of the spectrum led speculatively to the following conclusion; the products were a mixture of the hydrolysis product of the mono oxadiazoline platinum complex and the hydrochloride salt of pyridine. These are shown in figure 75 (a) and (b) below.
Figure 75(a) The structure of the hydrolysis product of PtCl$_2$(PhCN)(oxa), PtCl$_2$(NH=C(OH)-Ph)(oxa).

Figure 75 (b). The hydrochloride salt of pyridine.

This is feasible as water, which always finds a way into deuterated chloroform, can produce hydrochloric acid, which would both facilitate the hydrolysis of the nitrile ligand, and produce the hydrochloride of pyridine. It should be stressed however, that these structures are not the only possibilities and remain speculative. The proton NMR spectrum is included in appendix 4. The experiment was repeated with the following modifications, pure mono oxadiazoline platinum complex was employed, the chloroform used was from an ampoule (0.05 ml) and only a stoichiometric amount of pyridine was used. It was considered the benzonitrile of the mono oxadiazoline platinum complex would be selectively substituted under these conditions. The NMR tube was left for four days at room temperature. After this time the reaction was checked by proton NMR spectroscopy which looked to be consistent with the desired product. Over the following two days the product crystallised out in the tube and X-ray diffraction analysis carried out. This confirmed the product as a mixed ligand Pt(oxa)(pyr) complex. While this structure is not a Pt(oxa)(PhCN) complex, nevertheless, this is the first X-ray structure obtained for a mono oxadiazoline platinum complex.
As can be seen from figure 76, it is a *trans* complex which is in contrast to DMSO substitution which prefers the *cis* configuration when coordinated to platinum. The coordination of pyridine tends to agree with previous reports that in substitution reactions of square planar platinum(II) complexes, configuration is retained. This is generally explained by an associative mechanism with a five coordinate bipyramidal intermediate. The two *trans*-chloride ligands assume the axial positions and the new ligand coordinates in the triagonal plane. On exit of the leaving group, the *trans* configuration is retained. This is shown in figure 77 below. What is obvious from the present work is that generalisations about the substitution reactions of platinum cannot be made, and the configuration of the products is dependent on the relationship between the ligands and platinum.

![Figure 76: Representation of the X-ray structure (Platon) of *trans*-platinum dichloride (oxa)(pyr) complex.](image)

![Figure 77: An associative, bipyramidal mechanism for platinum substitution reactions.](image)
5.5.2.2. Reaction of PtCl$_2$(oxa)(PhCN) with 2,6-diacetylpyridine.

Equimolar quantities of platinum complex and the di-substituted pyridine were placed in an NMR tube with 0.5ml of deuterated chloroform and left at room temperature. The proton NMR spectrum was monitored periodically but no reaction was evident after several days. This is not wholly unexpected as the acetyl groups are strongly electron withdrawing and delocalise the nitrogen lone pair in towards the ring. This effectively deactivates the nitrogen. There is also the possibility of steric hindrance by the ortho-substituents. The reaction was heated for 24 hours at 60 °C, with no reaction observed.

5.5.2.3. Reaction of PtCl$_2$(oxa)(PhCN) with DMAP.

The same procedure as for 2,6-diacetylpyridine was adopted. The dimethylamino-substituent introduces competition for coordination to platinum via the ring nitrogen. However, being strongly electron donating it activates the ring nitrogen in para position making it more strongly σ donating. Also the tertiary amino nitrogen is considerably more basic than the pyridine nitrogen with pKa values of 11 and 6 respectively. This is due to the different hybridisation states of the nitrogens. The amino nitrogen is $sp^3$ hybridised whereas the pyridine nitrogen is $sp^2$. This means that the pyridine nitrogen lone pair electrons are more closely bound to the nucleus than the amino nitrogen lone pair as the $sp^2$ hybrids have 33% s character and $sp^3$ have only 25% s character. It was expected that a mixture of products would be the outcome and this was the case. The $^{195}$Pt NMR spectrum showed the main product at -2173 ppm and at least four other minor products with signals ranging from -2006 to -2217 ppm. Chromatography only separated one pure product, which was not the main one, and this was more polar than the other products. On the TLC plate the isolated product stuck to the baseline and the eluent had to be made more polar to get it off the column. At this stage it was considered to be coordinated via the pyridine ring nitrogen, its $^{195}$Pt NMR signal was at -2035.6 ppm, slightly upfield of that for the PtCl$_2$(pyr)(oxa) complex at -2023 ppm, which was coordinated via the pyridine ring nitrogen. This is in contrast to Rochon’s findings for cis-diamine platinum complexes$^{140}$, ~ -2230 ppm for primary amines and ~ - 2180 ppm for secondary
amines. Considering the signal found for the platinum dimethylaminobenzonitrile complex (tertiary amine) at -2124.7 ppm, which is believed to be coordinated via the amino nitrogen, this is consistent with Rochon’s findings. The assignment is supported by the proton NMR spectrum where the dimethylamino protons display only one signal, indicating their possible equivalence. Coordination to the amino nitrogen should result in two signals as the chiral CHN(Ph) carbon renders the methyl groups non-equivalent.

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Pyridine complex</th>
<th>Free pyridine</th>
<th>Δδ</th>
</tr>
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<tr>
<td>$^1$H</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>o-</td>
<td>8.70 ppm</td>
<td>8.59 ppm</td>
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</tr>
<tr>
<td>m-</td>
<td>7.71 ppm</td>
<td>7.62 ppm</td>
<td>+0.09 ppm</td>
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<tr>
<td>p-</td>
<td>7.22 ppm</td>
<td>7.23 ppm</td>
<td>-0.01 ppm</td>
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<tr>
<td>$^{13}$C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o-</td>
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<td>149.9 ppm</td>
<td>+3.90 ppm</td>
</tr>
<tr>
<td>m-</td>
<td>138.1 ppm</td>
<td>135.9 ppm</td>
<td>+2.2 ppm</td>
</tr>
<tr>
<td>p-</td>
<td>125.3 ppm</td>
<td>123.7 ppm</td>
<td>+1.6 ppm</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Pyridine complex</th>
<th>Free DMAP</th>
<th>Δδ</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>8.21 ppm</td>
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<td>m-</td>
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<td>6.46 ppm</td>
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<tr>
<td>NMe₂</td>
<td>39.1 ppm</td>
<td>38.8 ppm</td>
<td>+0.3 ppm</td>
</tr>
</tbody>
</table>

Table 13. Contrast of the proton and $^{13}$C NMR signals of free and coordinated pyridine and DMAP.

Closer scrutiny of the proton and $^{13}$C NMR spectra of this experiment and the previous pyridine experiment show a difference (see table 13). Coordination to platinum via the pyridine nitrogen should increase the electron deficiency of the aromatic ring compared to the free ligand, resulting in a downfield shift of the NMR signals for both proton and carbon. This is the case in the unsubstituted pyridine experiment, but in the DMAP experiment the opposite is true for the proton NMR spectrum.
It is possible that the pyridine ring is experiencing some magnetic effect such as ring current effects, by being in close proximity to one of the aromatic rings of the oxadiazoline ligand. This suggests the possibility of a cis complex, however a molecular model shows that there would be excessive steric hindrance. This is the case for cis coordination via the amino nitrogen as well and this is shown in figure 78. In the event of trans coordination to the ring nitrogen, the pyridine and phenyl rings do not come into close contact at all, as can be seen in figure 76. Also free rotation about the C-N bond would make the methyl groups equivalent, consistent with the proton NMR.

![Figure 78. Possible cis-PtCl₂(DMAP)(oxa) complexes showing hindrance to free rotation.](image)

It is inconclusive whether the isolated complex is the cis or trans isomer but excessive steric hindrance would make the cis complex unlikely. In the spectrum of the analogous cis-DMSO complex, the methyl groups have distinctly different signals and the configuration of this complex has been previously confirmed as cis by X-ray crystallography. It is therefore unlikely that coordination is via the amino nitrogen. However, direct comparisons between a sulphur donor and a nitrogen donor ligand should be treated with caution. Another feasible explanation for the difference in the proton NMR signals is that if the platinum is electron withdrawing regarding the ring, then the amine nitrogen is electron donating by resonance and this accounts for a slight upfield shift of the NMR signals of the ortho and meta protons. Taking into account the $^{195}$Pt NMR signal and the other evidence, the complex is most likely trans-coordinated via the pyridine nitrogen.
5.5.2.4. Reaction of PtCl$_2$(oxa)(PhCN) with amines.

PtCl$_2$(PhCN)(oxa) + L → PtCl$_2$(oxa)(L) + PhCN → PtCl$_2$(L)$_2$ + oxa

Scheme 23. The sequence of substitutions in mono oxadiazoline platinum(II) complexes by amines.

5.5.2.4.1. Reaction with 3-aminophenol.

This ligand was chosen as it was considered the amine would easily displace the nitrile ligand, and the hydroxy group would both introduce a polar group and a hydrogen bonding motif. This would make the resulting complex more soluble in polar solvents and introduce a possible new binding site to DNA. Also, DNA and proteins in the cells and bloodstream contain amine groups, and these can substitute onto a potential drug and deactivate it. A successful exchange indicates if the starting complex will be easily deactivated in the bloodstream, or if it will bind to DNA. So if the exchange is rapid, within two hours, there is very little chance of the complex reaching the target DNA.

Observation of the proton NMR spectra acquired at regular intervals showed no substitution reaction had taken place, even when heat was applied (60 °C for 30 minutes). Rather the amine decomposed.

5.5.2.4.2. Reaction with 1-amino-2-propanol.

The reaction of PtCl$_2$(PhCN)(oxa) with this amine was rapid, with some reaction observed after only ten minutes at room temperature. This amine is of a similar basicity to concentrated ammonia solution (e.g. 0.880), but is considerably nucleophilic. Both benzonitrile and oxadiazoline ligands were replaced, the signals of the free oxadiazoline clearly visible in the proton spectrum. There was evidence of many products. As this amine is also extremely hygroscopic and is sold commercially containing 5% water this is suspected to be due to base hydrolysis of the ligands. However the most likely position for hydrolysis is the C(H)-N bond of the
heterocycle. This would result in an aldehyde and this is not apparent in the proton NMR spectrum.

5.5.2.5. Reaction of PtCl₂(oxa)(PhCN) with 2-amino-1-methylimidazole.

The use of the 2-amino-1-methylimidazole ligand introduces two nitrogen sites for coordination to platinum, an amino nitrogen and an heterocyclic nitrogen, the lone pair of the N1 ring nitrogen being part of the aromatic system. The reaction was carried out at room temperature and over the first 24 hours there was approximately 30% exchange. Four products were observed in the proton NMR spectrum. As no free oxadiazoline was evident in the spectra (see experimental section, substitution reactions), the products are presumed to be cis and trans isomers of a mixed Pt(imid)(oxa) complex, with the imidazoline coordinated by the N3 ring nitrogen, and cis and trans isomers coordinated via the amino nitrogen. Increasing the temperature to 50 °C made no difference to the progression of the reaction, which appeared to have reached completion at 30% conversion. Due to the low conversion and large number of products, no attempt was made to isolate the products. A copy of the proton spectrum for this reaction is included in the experimental section (substitutions).

5.5.2.6. Reaction of PtCl₂(oxa)(PhCN) with triphenylphosphine.

\[
\text{PtCl}_2(\text{oxa})(\text{PhCN}) + \text{P(Ph)}_3 \rightarrow \text{PhCN} + \text{PtCl}_2(\text{oxa})(\text{P(Ph)}_3)
\]

Scheme 24. The attempted substitution of benzonitrile by triphenylphosphine in a mono oxadiazoline platinum(II) complex.

The reaction of triphenylphosphine with this complex is rapid and proton NMR analysis was carried out immediately after the addition of a stoichiometric amount of the phosphine. Substitution occurs within fifteen minutes but exchanges carry on for several days. There is no one end product though undoubtedly the main end product is
a platinum triphenylphosphine complex with no oxadiazoline or benzonitrile ligand. It was expected, based on the evidence of the previous substitutions, that triphenylphosphine would exchange with the benzonitrile ligand. Whilst it was believed the expected product was apparent in the proton NMR spectrum, it was not possible to identify this complex (shown below in figure 79) in the mass spectrum. A tentative hypothesis is that triphenylphosphine replaces a chloride ligand resulting in a charged species (the proposed complex in figure 79). Stereoisomers of these are possible and there would be steric hindrance between the triphenylphosphine and the oxadiazoline ligands possibly leading to instability.

![Figure 79. The proposed and expected initial products of the reaction of triphenylphosphine with PtCl₂(oxa)(PhCN).](image)

The molecular weight of the proposed complex is 834.22 and a strong signal with the correct isotopic pattern was observed at 833.9 m/z (figure 80).

![Figure 80. MS-FAB signal at 833.9 of proposed complex, [PtCl(oxa)(PhCN)(tpp)]⁺](image)

This is further supported by the absence of signals corresponding to free benzonitrile in the ¹³C NMR spectra obtained at various times after the initial reaction. The CN and
quaternary C(1) signals at 118.8 and 112.4 ppm are distinctive and not overlapped by other signals, which unfortunately is the case for the C(2,6), C(3,5) and C(4) signals. More curiously the mono oxadiazoline platinum complex appears to be regenerated in part as the reaction proceeds. There is also evidence in the proton spectrum for some bis oxadiazoline platinum complex. It is difficult to explain why the benzonitrile or oxadiazoline ligands should undergo re-coordination after being freed. Sometimes in the NMR spectra it appears that a compound is increasing in concentration if another one is slowly precipitating. However this was not obvious.

$^{195}\text{Pt}$ and $^{31}\text{P}$ NMR spectroscopy was performed on the initial product in an attempt to characterise it before further exchanges took place (With the time required to carry out these processes further exchanges cannot be ruled out). The two sets of results were consistent. A doublet was apparent in the $^{195}\text{Pt}$ spectrum centred at -3598 ppm with a $^1J^{195}\text{Pt} - ^{31}\text{P}$ coupling constant of 3450 Hz. In the $^{31}\text{P}$ spectrum a singlet was seen at 3.83 ppm corresponding to uncoupled phosphorus, and a doublet (~ -4.5 / 12.3) centred at 3.83 ppm which also had a $^1J^{31}\text{P} - ^{195}\text{Pt}$ coupling constant of 3450 Hz representing phosphorous coupled to $^{195}\text{Pt}$. This is shown in figure 81 below.

![Figure 81. The $^{31}\text{P}$ NMR spectrum of the reaction of triphenylphosphine with PtCl$_2$(oxa)(PhCN) after two hours.](image-url)
The coupling constant is consistent with published data for a phosphine ligand *trans* to a chlorine ligand, i.e. a *cis* complex\(^ {52,149} \). The relative integration was 1 / 4 / 1, and this is close to the ratio of magnetic platinum to non-magnetic platinum. There is also evidence in figure 81 of a *trans*-PtCl\(_2\)(PPh\(_3\))\(_2\) complex. Considering the doublet just visible above the baseline at 13.70 / 26.70 ppm which is centred at 20 ppm, and has a \(^{1}J_{^3P-^{195}Pt}\) coupling constant of 2632 Hz, this is consistent with published data for complexes of the type *trans*-PtCl\(_2\)(PR\(_3\))\(_2\)\(^ {149} \). A doublet corresponding to this complex was not so easy to spot in the \(^{195}Pt\) NMR spectra. There is also a doublet (~ 5.0 / 23.2) centred at 14.3 ppm which would also appear to be a *cis* complex, judging by the coupling constant but could not be seen in the \(^{195}Pt\) NMR spectra. The ratio of the two coupling constants 3450 / 2632 is 1.31 which is close to the published ratio of 1.41\(^ {52,149} \) for *cis* and *trans* isomers of the same formula. In the present study the structure of the complexes is not known with certainty. The \(^{31}P\) NMR signal of the suspected *trans* complex is downfield of those of the suspected *cis* complexes and this is also consistent with the literature\(^ {52,149} \), and explained by the more efficient back bonding from platinum to phosphorus in the *cis* complexes.

Spectra were acquired after 24 hours and at least five species were apparent, mostly downfield of the first to appear. These can only be presumed to be subsequent substitutions by a triphenylphosphine ligand. These signals\(^ {150} \) are consistent with published data. Clark and Martin\(^ {150} \) used a substituent summative approach to predict the \(^{195}Pt\) NMR signal of platinum bis phosphine complexes of the type PtCl\(_2\)(PR\(_3\))\(_2\). Adapting their approach to a mixed PtCl\(_2\)(oxa)(P(Ph)\(_3\)) complex gives a close correlation to the experimental results. Taking -2120 ppm for PtCl\(_2\)(oxa)\(_2\) and -4450 ppm for the PtCl\(_2\)(PPh\(_3\))\(_2\) gives an average of -3285 ppm for PtCl\(_2\)(oxa)(P(Ph)\(_3\)). Signals were found at -2919 ppm and -3390 ppm. The deviation of the former signal from the average is consistent with the findings of Clark and Martin for bulky phosphines. They explain the large deviation in terms of deshielding of the platinum centre due to steric effects of the bulky ligands. Crystallography shows the Pt-P bond to be longer in complexes containing bulky phosphine ligands\(^ {52,150} \). The latter signal could correspond to [PtCl(oxa)(PhCN)(P(Ph)\(_3\))]\(^+\) although it is impossible to say categorically, which complexes the signals correspond to. Whilst plenty of time could have been spent investigating these exchanges, further results were not considered in strict keeping with the aims of the project so the work was discontinued. It can be
concluded that in the case of substitution by triphenylphosphine, an initial rapid and selective reaction takes place, but then further substitutions take place and it is unclear what the initial product is.

Summing up, the various exchanges carried out with different ligands that bear similarity to components of the bloodstream and DNA, have given an indication how the complexes of the present study may behave *in vivo*. Bis oxadiazoline platinum complexes are resistant to substitution by sulphur containing compounds but they also do not exchange readily with pyridine. This may mean they are not suitable as candidates for anti-tumour agents. On the other hand their mono counterparts are more susceptible to substitution by pyridine, imidazoline, aliphatic amine and DMSO. It remains to be seen how they perform during *in vitro* testing.
5.6. Oxidative addition reactions of Platinum(II) oxadiazoline complexes. (All the following halogenations were carried out in an NMR tube and monitored by proton NMR spectroscopy).

\[
\text{trans-} \text{PtX}_2\text{L}_1\text{L}_2 + \text{Y}_2 \rightarrow \text{trans,trans,trans-} \text{PtX}_2\text{Y}_2\text{L}_1\text{L}_2
\]

where \(X = \text{Cl or Br}\) and \(Y = \text{Cl or Br}\), \(L_1 = \text{PhCN or oxo}\), \(L_2 = \text{oxo}\)

Scheme 25. The oxidation with halogens of mono and bis oxadiazoline platinum(II) complexes.

Oxidative addition reactions were attempted using the mono oxadiazoline platinum(II) complex \(\text{trans-[PtCl}_2(\text{PhCN})\{\text{N} = \text{C(Ph)-O-N(Me)-CH(Ph)}\}]\) and the elemental halogens, chlorine, bromine and iodine. Bis oxadiazoline platinum(IV) complexes have been previously reported\(^{81,82}\), but were made from platinum(IV) benzonitrile complexes. It was decided to attempt the production of these via the chlorination of platinum(II) complexes to see if the method was an improvement. The drawback with the previous method is that platinum(IV) benzonitrile complexes rapidly hydrolyse and can only be stored in a moisture free environment.

Additions were also attempted using hydrogen peroxide, benzoyl peroxide and tert-butyl-peroxide, intending to introduce polar hydroxy- and benzoyl-groups to the complexes and hopefully impart better solubility in polar solvents to the complexes. The mechanism of the addition of chlorine is one of induced dipole and electrophilic addition. This is shown in figure 82 below.

![Figure 82](image-url)
5.6.1. Chlorination of bis oxadiazoline platinum(II) complexes.

The complexes;
1. \([\text{PtCl}_2\{\text{N} = \text{C}(p\text{-MeO-C}_6\text{H}_4\text{-C}_6\text{H}_4)\text{-O-N(Me)-CH(Ph)}\}_2]\) (49)
2. \([\text{PtCl}_2\{\text{N} = \text{C(Ph)-O-N(Me)-CH(p-HO-C}_6\text{H}_4)\}_2]\) (47)
3. \([\text{PtCl}_2\{\text{N} = \text{C(m-HO-C}_6\text{H}_4)\text{-O-N(Me)-CH(Ph)}\}_2]\) (46)

were used for the oxidation reactions. Chlorine was bubbled through a solution of each complex in the NMR tube. This meant the progress of the reaction could be monitored by proton NMR spectroscopy. There was also a colour change from pale cold yellow to an intense warm yellow. The reactions were slow and chlorine had to be bubbled through them for two minutes to achieve a maximum conversion of 50%. Presumably the lack of reactivity is due to the bulky oxadiazoline ligands which hinder the chlorine and platinum centre coming into contact. The products were unstable and it was not possible to acquire full characterisations. There is also the possibility of chlorine reacting with the C=N double bond of the heterocycles and chlorination of electron rich aromatic rings.

The indicative signs of a successful oxidation in the proton NMR spectrum are a shift from \(~ 5.9\) ppm to \(6.7\) ppm corresponding to the C(Ph)H of the heterocycle, and from \(~ 8.8\) ppm to \(8.2\) ppm equivalent to the ortho protons of \(\text{C}_6\text{H}_4\text{C}=\text{N}\) of the heterocycle. Of the three complexes used the most successful was product 49 which has para-glycol ether substituents on the \(\text{N} = \text{C}-\text{C}_6\text{H}_4\text{-}\). This is a conjugated system and any electron donating effect of these groups can be delocalised into the heterocycle and to the platinum. So the phenyl rings may remain stable and resistant to chlorination. The delocalisation is shown in figure 83 below. This complex achieved 50% conversion and was stable long enough to attain \(^{195}\text{Pt}\) and \(^{13}\text{C}\) NMR spectra. A characteristic downfield shift from \(-2124.0\) to \(-98.2\) ppm consistent with oxidation from Pt (II) to Pt (IV) was seen in the \(^{195}\text{Pt}\) NMR spectrum.
The proton NMR spectrum of the reaction of product 47 was a mass of aromatic and aliphatic signals with little evidence of the desired product. There was an appreciable amount of starting material left but it was not possible to identify the products. This complex has para-hydroxy groups on the other aromatic ring system, i.e. C(H)C₆H₄ ring. The electron donating effect of these groups is not delocalised to the heterocycle, and activates the ring in ortho and para positions with reference to the position of the hydroxy group (see figure 84). It is possible these positions could be activated toward chlorination.

In the case of product 46 there was approximately 30% reaction but it was not the only product. The products were unstable and decomposed on standing. The meta-hydroxy group has no electronic effect on the ring but can be oxidised itself to a quinone.
5.6.2. Oxidation of mono oxadiazoline platinum complexes.

Due to the lack of success with bis oxadiazoline platinum(II) complexes it was decided to use mono oxadiazoline platinum(II) complexes. The platinum centre is much less hindered as can be seen in the x-ray structure of the platinum pyridine / oxadiazoline complex, figure 76, and should be consequently more susceptible to oxidation by chlorine.

5.6.2.1. Reaction of chlorine with mono oxadiazoline platinum complexes.

The complexes;

1. \[\text{[PtCl}_2\text{(PhCN)\{N=C(PhCN)-O-N(Me)-CH(Ph)\}}]\]
2. \[\text{[PtCl}_2\text{(p-MeOC}_2\text{H}_4\text{O-C}_6\text{H}_4\text{CN)\{N=C(p-MeOC}_2\text{H}_4\text{O-C}_6\text{H}_4)\-O-N(Me)-CH(Ph)\}}]\]

were used for this purpose. In contrast to the analogous reaction for bis complexes, and as expected, the reaction was rapid, the colour change evident in seconds. Proton NMR spectroscopy confirmed nearly 100% reaction. The products were precipitated with petroleum ether and isolated by filtration. Full characterisation was obtained for both. The reactions going to completion is expected as access to the platinum is easier, facilitated by the linear nature of the Pt-NCR bond of the nitrile ligand which makes the ligand stick straight out from the platinum, and in the square plane. This is not the case in the bis oxadiazoline complexes where the phenyl groups tend to wrap around the platinum centre above or below, hindering electrophilic attack by the halogen.

5.6.2.2. The reaction of bromine with \(\text{PtCl}_2\text{(PhCN)(oxa)}\).

In the hope of obtaining a mixed chloro / bromo platinum complex, \(\text{PtCl}_2\text{(PhCN)(oxa)}\) was reacted with a stoichiometric amount of bromine according to the equation

\[\text{[PtCl}_2\text{(PhCN)\{N=C(PhCN)-O-N(Me)-CH(Ph)\}}] + \text{Br}_2 \rightarrow \text{[PtBr}_2\text{Cl}_2\text{(PhCN)\{N=C(PhCN)-O-N(Me)-CH(Ph)\}}]\].

145
The reaction was monitored by proton NMR spectroscopy and was significantly slower than the analogous chlorination, taking minutes rather than seconds. One major product was visible in the proton NMR spectrum, however with the passage of time more products appeared. In the initial spectrum there was a negligible amount of [PtCl\(_2\) (oxa)\(_2\)] complex. The integration of the ortho phenyl protons at 8.60-8.80 ppm was considerably less than that of the -CH\(_2\)- group of diethyl ether (3.45 ppm), which was an impurity that was used as an internal reference. After two hours there was considerably more [PtCl\(_2\) (oxa)\(_2\)] than diethyl ether. This can be seen by comparing the aforementioned integrals in figures 85 (a) and (b) below. This can only be explained by an oxadiazoline ligand being displaced, presumably by a halogen, resulting in uncoordinated oxadiazoline. This would then replace a benzonitrile ligand in the residual [PtCl\(_2\) (oxa) (PhCN)] complex.

Figure 85(a). The proton NMR spectrum of the initial product of bromination of PtCl\(_2\) (PhCN) (oxa) after 10 minutes.
Figure 85(b). The proton NMR spectrum of the products of bromination of PtCl$_2$(PhCN)(oxa) after 140 minutes.

Figure 85 (b) also shows several signals between 6.60 and 7.00 ppm corresponding to the Ph-CH-N proton of the complex. It is believed these are due to ligand exchanges between chloride and bromide resulting in various combinations of ligands (this can be seen much clearer in figure 86 below, which represents the chlorination of PtBr$_2$(PhCN)(oxa)). There is possibly a small amount of Pt(IV)(oxa)$_2$ which would also explain the signals at 8.20 ppm, corresponding to the ortho phenyl protons. In a mono oxadiazoline platinum(II) complex these protons appear at 9.00 ppm, and in a bis complex they appear upfield between 8.60 and 8.80 ppm, and normally appear as a doublet and a broad singlet. These represent two diastereoisomers. It is therefore reasonable that the signals upfield (8.15 and 8.20 ppm) of the signal corresponding to the mono oxadiazoline platinum(IV) complex (8.38 ppm) are the bis oxadiazoline platinum(IV) complex. Another possibility is that they are the uncoordinated oxadiazoline, however they are not in strict agreement with Hermken's reported values at 8.04 ppm, deuterated chloroform being used in both cases.
Figure 86. The 8.0-9.0 ppm range of the proton NMR spectrum of the products of bromination of PtCl₂(PhCN)(oxa) after 140 minutes.

The apparent triplet at 8.15 ppm may possibly be a pair of overlapped doublets. If the ligands are locked in place by the presence of the axial halides, the two ortho phenyl protons of Pt-N=C-Ph may lose their equivalence but be similar enough to be overlapped.

As the reaction progressed there was an orange / red precipitate. This was filtered and dried and was found to have an elemental composition consistent with [PtBr₄(PhCN)(oxa)]. In the MS-FAB spectrum there is a signal at [M-2HBr] at 694.8. Assuming [PtBr₄(PhCN)(oxa)] to be insoluble, when it precipitates it effectively removes bromine from the system of exchanges. This means there should be a greater abundance of the chloride rich complexes in the final proton spectrum. This is borne out in the enlargement of the 6.5-7.0 ppm region of the stated spectrum, shown in figure 87 overleaf.
Figure 87. The 6.5-7.0 ppm range of the proton NMR spectrum of the bromination of PtCl$_2$(PhCN)(oxa) after 140 minutes.

5.6.2.3. The reaction of iodine with PtCl$_2$(PhCN)(oxa).

It was expected that this reaction would be slow, but there was no observed oxidation reaction at all, even after the application of heat for several days. This is very likely due to the large size of iodine compared to chlorine making coordination of iodine much more difficult, and the fact that iodine is considerably less reactive compared to chlorine.

5.6.2.4. The reaction of iodine chloride with PtCl$_2$(PhCN)(oxa).

Not being deterred by the failure with iodine it was decided to attempt the reaction using iodine chloride. This is a covalent compound but has considerable ionic character and the electron poor iodine should be more susceptible to nucleophilic attack than molecular iodine. Also the steric hindrance would be reduced by only incorporating one iodine ligand. Again, there was no apparent oxidation. After 24 hours there was evidence of degradation in the proton NMR spectrum and some residue in the tube.
5.6.3. The oxidation of PtBr$_2$(PhCN)(oxa) with halogens.

5.6.3.1. The reaction of PtBr$_2$(PhCN)(oxa) with chlorine.

It would be expected that the products of this reaction would be the same as for the reaction between bromine and PtCl$_2$(PhCN)(oxa). However in the twenty minutes that elapsed between addition of chlorine and the running of the initial proton NMR spectrum, five compounds had formed. It is thought that the initial product was not stable and various ligand exchanges took place. Considering the Pt(IV)-N-CH(Ph) proton, after twenty minutes, there were five signals visible centring at 6.70 ppm and these correspond to the different combinations of bromide and chloride in the platinum complexes, i.e. PtBr$_4$L$^2$ (not seen), PtBr$_3$Cl$^1$L$^2$, PtBr$_2$Cl$_2$L$^1$L$^2$, PtBrCl$_3$L$^1$L$^2$ and PtCl$_4$L$^1$L$^2$. The signals are shown in figure 88 below. Chloride rich species predominate and it is thought this is due to, firstly, the insolubility of bromo platinum(IV) complexes, and secondly the difficulty delivering a stoichiometric amount of chlorine gas. Despite flushing the solution with nitrogen, it was considered more important to acquire an initial proton NMR spectrum than to thoroughly de-gas the solution.

![Figure 88](image_url)

Figure 88. The 6.0-7.0 ppm range of the initial (after approximately 20 minutes) proton NMR spectrum of the reaction of chlorine with [PtBr$_2$(PhCN)(oxa)].
After one hour there was some orange / red precipitate and the solution was yellow. Proton NMR spectroscopy showed [PtCl$_4$(PhCN)(oxa)] to be the predominant product in solution. In contrast to the bromination of [PtCl$_3$(PhCN)(oxa)], there was no bis oxadiazoline platinum(II) complex visible in the proton NMR spectrum acquired at the end of the reaction (70 minutes), and this had been evident in the initial starting material and the initial proton NMR spectrum. Again, this is considered to be due to oxidation by excess chlorine. It is believed the signals surrounding 6.60 ppm in figure 88 are [PtX$_4$(oxa)$_2$] species. Platinum NMR spectroscopy was also carried out but was not successful for the following reasons; firstly, plenty of time and concentrated solutions are required to acquire $^{195}$Pt NMR spectra, so the process does not lend itself to the analysis of rapid ligand exchanges. Secondly, as the reaction proceeded a red precipitate collected on the sides of the NMR tube which causes inhomogeneity of the sample in the spectrometer. Lastly, with many species present at any one time, there was not sufficient concentration of any one complex present to be visible in the spectra.

5.6.3.2. The reaction of PtBr$_2$(PhCN)(oxa) with bromine.

Following the addition of a stoichiometric amount of bromine solution there was an almost immediate reaction with a red precipitate. However proton NMR spectroscopy revealed that the reaction was only 50% complete, even after allowing a few minutes for further reaction to take place. A further stoichiometric amount was added resulting in more precipitate, but the NMR spectrum showed that the oxidation was 80% complete. Similar to the bromination of PtCl$_3$(PhCN)(oxa) in section 5.6.2.2, there was also a doublet apparent at 8.20 ppm. This grew as the reaction progressed, and as the red solid precipitated, the proton NMR spectrum simplified. After three hours, there were two major products left in solution in a ratio of 2:1. The minor product is bis oxadiazoline platinum(II) complex, and this is characterised by its broad signals. The major is thought to be a decomposition product of the oxadiazoline and is given the tentative structure shown in figure 89 below.
Figure 89. Proposed structure for the oxadiazoline decomposition product following bromination of [PtBr$_2$(PhCN)(oxa)].

Figure 90. The proton NMR spectrum of the reaction of bromine with [PtBr$_2$(PhCN)(oxa)] after 3 hours, tentatively thought to be the structure in figure 89.

Examination of figure 90 shows that the integration is roughly correct for the stated ratio of the proposed mixture. The broad signals are a good match for those found experimentally for the cycloaddition product PtBr$_2$(oxa)$_2$ (see figure 49). As there was negligible dibromo bis oxadiazoline platinum(II) complex present at the start, this must be produced in the same way as in the bromination of PtCl$_2$(PhCN)(oxa) experiment. The red residue is most likely a mixture of the desired product [PtBr$_4$(PhCN)(oxa)] and a [PtBr$_5$]$^2^-$ species. Elemental analysis is inconclusive but consistent with a mixture of the two in a 4:1 ratio. It was possible to completely assign
the proton NMR spectrum of the mixed halide signals between 6.5 and 7.00 ppm, including the signal corresponding to the Ph-CH-N of \([\text{PtBr}_4(\text{PhCN})(\text{oxa})]\) at 7.00 ppm. In the earlier mixed halogen experiments this was an assumption.

5.6.3.3. Summary of \(^{195}\text{Pt}\) NMR spectral data of mixed halogen mono oxadiazoline Platinum(IV) complexes.

\(^{195}\text{Pt}\) NMR spectroscopy was also carried out on all the mixed halogen complexes and the data summarised in table 14 and figure 91 below;

<table>
<thead>
<tr>
<th>No. in graph</th>
<th>Complex</th>
<th>(^{195}\text{Pt} \delta) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{PtBr}_4(\text{PhCN})(\text{oxa})])</td>
<td>-1649.1</td>
</tr>
<tr>
<td>2</td>
<td>([\text{PtBr}_3\text{Cl}(\text{PhCN})(\text{oxa})])</td>
<td>-1325.2</td>
</tr>
<tr>
<td>3</td>
<td>([\text{PtBr}_2\text{Cl}_2(\text{PhCN})(\text{oxa})])</td>
<td>-976.5</td>
</tr>
<tr>
<td>4</td>
<td>([\text{PtBrCl}_3(\text{PhCN})(\text{oxa})])</td>
<td>-647.8</td>
</tr>
<tr>
<td>5</td>
<td>([\text{PtCl}_4(\text{PhCN})(\text{oxa})])</td>
<td>-340.7</td>
</tr>
</tbody>
</table>

Table 14. \(^{195}\text{Pt}\) NMR signals for mixed halide mono oxadiazoline platinum(IV) complexes.

Figure 91. \(^{195}\text{Pt}\) NMR signals for mixed halide mono oxadiazoline platinum(IV) complexes.
Examination of the table and graph show a summative trend as bromine is replaced by chlorine going from PtBr₄⁻ to PtCl₄⁻. The straight line demonstrates that the main bonding type is that of σ rather than π, and reinforces the evidence found for platinum complexes with mixed halides in section 5.3.6. The graph also shows increased shielding of the platinum nucleus moving from PtCl₄⁻ to PtBr₄⁻, and this is presumably due to the larger size of the bromine with its associated electron cloud.

5.6.4 The reaction of PtI₂(PhCN)(oxa) with chlorine.

Due to the lack of success with the reaction of iodine with PtCl₂(PhCN)(oxa), it was considered the analogous reaction using the diiodo platinum mono oxadiazoline complex and the much more reactive halogen, chlorine, would be more successful. Proton NMR spectroscopy showed an almost immediate reaction, which suggested a platinum(IV) species, but the product decomposed. The chlorine then attacked the ligands and many aromatic and aliphatic signals were apparent in the NMR spectrum within minutes. There was a black precipitate increasing with time which could be platinum iodide or elemental platinum. There was not a sufficient concentration of any one platinum species to obtain a decent ¹⁹⁵Pt NMR spectrum.

5.6.5. The reaction of PtCl₂(PhCN)(oxa) with peroxides.

\[
\text{trans-PtCl}_2(\text{PhCN})(\text{oxa}) + \text{ROOR} \rightarrow \text{trans,trans,trans-PtCl}_2(\text{OR})_2(\text{PhCN})(\text{oxa})
\]

where \( R = \text{H, benzoyl, tert-butyl} \).

Scheme 26. Attempted oxidation of mono oxadiazoline dichloro platinum(II) complex with peroxides.

The previously reported method of Tilset and co-workers¹⁵¹ was employed where a stoichiometric amount of peroxide is used with acetone as solvent. The reactions were stirred at ambient temperature and the products should precipitate out. Using all three peroxides previously mentioned there was no reaction at room temperature. The reactions were refluxed for 24 hours but there was also no reaction. Tilset and co-workers use platinum(II) complexes with methyl ligands and neutral ligands such as
bipyridine, the halides are counter ions. With our compounds the chlorides are in the coordination sphere and are fundamentally different to Tilset’s compounds. It is difficult to offer an explanation why Tilset’s reactions work and ours do not. His reactions were rapid, ten minutes at room temperature or two hours at -10 °C. Possibly with our complexes, the reaction is slow and the peroxides react with the solvent, acetone, first.
5.7. The aqueous solubility and biological activity of platinum oxadiazoline complexes.

The following complexes (figures 92 and 93, and table 15) were chosen to be tested biologically for anti-tumour effect. The criteria used to select them were; the ease of manufacture, the yield and purity, and the reproducibility of the synthesis. The mono oxadiazoline platinum complexes are generally easier to make and purify than their bis counterparts. Both mono and bis complexes with similar substituents were chosen to compare the difference in activity of the two types of complex. If time and money had allowed, we would have gone on to test substituents in different positions such as an hydroxy group in para or meta position.

![Figure 92. Bis oxadiazoline platinum complexes tested for biological anti-tumour activity.](image)

<table>
<thead>
<tr>
<th>Test name</th>
<th>Complex no.</th>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>JS5</td>
<td>45</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>JS7</td>
<td>49</td>
<td>H</td>
<td>MeO-C₂H₄O⁻</td>
</tr>
<tr>
<td>JS4</td>
<td>47</td>
<td>OH</td>
<td>H</td>
</tr>
</tbody>
</table>

Table 15. Bis oxadiazoline platinum complexes tested biologically for anti-tumour effect.
5.7.1 The Solubility of mono and bis oxadiazoline platinum complexes.

The major obstacle encountered with previous platinum oxadiazoline complexes was that they were not only insoluble in water, but also in DMSO/aqueous mixtures. This meant that in vitro testing was not possible as the choice of solvent of biologists is DMSO. This is because it is non-volatile and consistent amounts of the compounds being tested can be delivered to the cells. Unless potential drugs can be dissolved in DMSO they will never be tested as the methodology used by biologists are entrenched. In the present project, a milestone was passed when the complexes with polar substituents proved to be soluble in DMSO and DMSO/aqueous mixtures. To be of any use as an intravenous drug, the complexes have to be soluble in water. Platinum complexes are notoriously insoluble in aqueous systems. Cisplatin is only soluble 1-2 mg/ml in water at room temperature, and this rises to 8-10 mg/ml at 60 °C\textsuperscript{152}. This is considered to be the minimum requirement for cisplatin to be of use as a drug.

In the first instance UV absorption spectroscopy was used in an attempt to determine the solubility of bis oxadiazoline platinum complexes. However this proved to be impossible as the bis complexes made are varying mixtures of diastereoisomers, and

Figure 93. Mono oxadiazoline platinum complex tested biologically for anti-tumour activity, JS6, complex 41.
the solubility of each isomer is different. They are both poorly soluble but one is more insoluble than the other. Making a standard solution of the mixture was therefore not possible. It was decided to determine the solubilities by weight difference. Biologists prefer to use solubilities measured in phosphate buffered saline that has the serum concentration of 9 mg / ml. However the concentration proved to be so low, that the amount of the phosphate buffer and sodium chloride greatly exceeded the amount of complex in solution. The inaccuracy meant that the results were not realistic. Lastly, solubilities were carried out in distilled water at 25 °C. Saturated solutions were made utilising a sonic bath at 40 °C and then transferring to a sand bath at 25 °C with stirring for two days. The sample vials were allowed to settle at 25 °C and four 1ml aliquots withdrawn by syringe and allowed to evaporate slowly over four days, in open topped pre-weighed vessels, in the sand bath at 25 °C. The results are shown in table 16 below. The mono oxadiazoline platinum complexes were treated in the same way. Proton NMR spectroscopy carried out on the residues of JS4 and JS7 after this revealed a small amount of decomposition of JS4, less than 10%, and no decomposition of JS7. This is important as many medicinal preparations are in aqueous solution and if there is significant decomposition in water, then the doses can only be prepared a few hours before use and cannot be stored in aqueous solution. As a rule of thumb half lives in aqueous solution should be greater than 24 hours.

Proton NMR spectroscopy was not carried out on the complexes dissolved in water so it is impossible to say if they dissolved or if ligands exchanged with water.

<table>
<thead>
<tr>
<th>Test name</th>
<th>Substituent</th>
<th>Aqueous solubility at 25°C mg / ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>JS3</td>
<td>p-hydroxy (nitrone) mono</td>
<td>4.2 – 4.3</td>
</tr>
<tr>
<td>JS4</td>
<td>p-hydroxy (nitrone) bis</td>
<td>0.2 – 0.8</td>
</tr>
<tr>
<td>JS5</td>
<td>p-hydroxy (nitrile) bis</td>
<td>0.6 – 1.1</td>
</tr>
<tr>
<td>JS6</td>
<td>p-glycol ether (nitrile) mono</td>
<td>0.2 – 0.6</td>
</tr>
<tr>
<td>JS7</td>
<td>p-glycol ether (nitrile) bis</td>
<td>0.2 – 0.6</td>
</tr>
</tbody>
</table>

Table 16. The solubility range of the platinum complexes undergoing biological testing, in water at 25 °C
The two obvious trends that emerge from table 16 are that mono complexes are more soluble than their bis counterparts, and hydroxy-substituted complexes are more soluble than glycol ether substituted ones. When the solubility values are very low, caution should be taken as even small inaccuracies when weighing can lead to significant error in the apparent solubility. Also, in the case of JS4, there was some decomposition of the complex observed in the proton NMR spectrum acquired after the solubility test. If the decomposition products are water soluble then this will necessarily give a false result. Whilst the solubilities of the bis complexes are lower than the desirable level, there are formulation tricks such as encapsulation that can improve the delivery of the drug. More important is the dose related to solubility. The dose should be soluble in 20 ml of water. Estimation of the dose, which requires animal testing, is not within the scope of the present project. In short poor solubility is not an insurmountable barrier to drug development.

### 5.7.2 Stock solutions used in biological testing.

It is common practice for biologists to make stock solutions in DMSO. This is because it is non-volatile and does not evaporate every time the lid is removed. This facilitates very accurate dilutions with water, and exactly the right amount of complex is applied to the cells. As cisplatin takes approximately two days to solvate in DMSO using a sonicator, this does raise the question whether cisplatin is dissolving or exchanging. Proton NMR spectroscopy was carried out using cisplatin and DMSO, and a peak was apparent at 3.5 ppm within five minutes, and it continued to grow for many days. This is shown in figure 94 below.

![Figure 94 (a) The initial proton NMR spectrum of cisplatin in D_2O with a twenty molar excess of DMSO.](image-url)
This cannot be the ammine groups in this position, and can only be DMSO exchanging. The question is what ligand is being exchanged? A quick literature search revealed the answer. Sundquist et al. carried out a similar experiment monitoring the exchange between DMSO and both cisplatin and transplatin, using $^{195}$Pt NMR spectroscopy. Exchange was apparent within the hour. They isolated a product in the transplatin experiment, and X-ray diffraction analysis showed a chloride ligand replaced by a DMSO ligand. The result was the cationic complex, trans-$[\text{PtCl(DMSO)(NH}_3)_2]^+$. Using proton NMR spectroscopy this exchange is apparent in minutes, and the technique is much faster to perform as the tuning and matching associated with $^{195}$Pt NMR is unnecessary with proton NMR.

This raises further important questions concerning cisplatin, more specifically, is the biological testing carried out from 1964-76 wholly valid, and does the introduction of a DMSO ligand affect the activity. To answer the first question, as cisplatin has been approved for thirty years and has been used as an effective drug in the treatment of particularly testicular cancer, the biological testing that went before is largely irrelevant. Cisplatin was approved despite being extremely cytotoxic. To answer the second question, work has been carried out on the rates of exchange of DMSO substituted platinum complexes and DNA nucleotides. It has been found that solvation of transplatin in DMSO for as little as five minutes not only increases the rate of substitution with DNA, threefold over short reaction times (< 1 hour) and twofold over longer times (6 hours), but also affects the type of adducts produced. The major product, 92% after 42 hours when DMSO is excluded, was found to be the guanine-guanine bis adduct. In sharp contrast, when $[\text{PtCl(DMSO)(NH}_3)_2]^\text{-Cl}$ was

Figure 94 (b) The proton NMR spectrum of cisplatin in D$_2$O with a twenty molar excess of DMSO after twelve days.
used, many adducts were produced, only 17% after 47 hours being the guanine-
guanine bis adduct. As this adduct is considered to be important in the anti-tumour
effect of platinum complexes, solvation of these complexes in DMSO can give a
falsely negative picture of biological testing and has to be called into question\textsuperscript{133}.

The aforementioned complexes of the present study were all solvated in DMSO, and
were compatible with aqueous mixtures. This was a significant improvement on
previously reported platinum oxadiazoline complexes\textsuperscript{81-83,85}. The bis complexes used
are resistant to substitution by DMSO, as has already been stated; however the mono
complexes can be substituted in a matter of days at room temperature, when DMSO is
used as a solvent. As the stock solutions used for biological testing are kept in the
fridge, and the DMSO will be in the solid state, it is unknown whether exchange takes
place under these conditions. When diluted with water the rate of substitution would
also be reduced, and at 4 °C in the fridge, may not occur at all.

5.7.3.1 The biological testing of platinum oxadiazoline complexes.

The biological testing was carried out by Dr. Helen Coley of the Postgraduate
Medical School, The University of Surrey. The cell lines reported are PEO1 which is
a human ovarian cancer cell line and PEO1CarboR which is a carboplatin resistant
cell line cultured by Dr. Coley which is cross resistant to cisplatin. Its resistance is
approximately five-fold. The assay used is a colorimetric assay called MTT [3-(4,5-
dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]. This is reduced by living
cells to a pink formazan compound. A spectrophotometer then measures the intensity
of the colour and the dose required for a 50% kill can be calculated. This type of assay
has been used for about twenty years, and was a significant improvement on the
previously used Clonogenic assay which involved cell counting\textsuperscript{154}.
5.7.3.2 The results of biological testing, the MTT assay.

Cytotoxicity testing was determined by the MTT assay. Cells were seeded into 96 well plates (figure 95), left overnight and then treated with a range of increasing drug concentrations. The assay was terminated after 72 h (or 96 h according to the doubling time of the cell line in question) of drug treatment by addition of 20 μl of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (obtained from Sigma, 5 mg / ml PBS (phosphate buffered saline)). After 4 h the media was aspirated and formazan crystals formed were re-suspended in 200 μl of DMSO. Absorbance was read at 540 nM using a Multiskan RC spectrophotometer (Labsystems, UK) and Genesis Software (Life Sciences UK). IC₅₀ values were determined as the drug concentration of drug necessary to cause a 50% reduction in cell viability compared to untreated controls. The results to date are summarised in table 17 overleaf.
<table>
<thead>
<tr>
<th>CELL LINE</th>
<th>cisplatin</th>
<th>carboplatin</th>
<th>JS4</th>
<th>JS5</th>
<th>JS6</th>
<th>JS7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEO1</td>
<td>1.34 (0.82)</td>
<td>32.6 (11.6)</td>
<td>16.6 (3.4)</td>
<td>8.7 (3.0)</td>
<td>16.3 (3.3)</td>
<td>39.6 (19.3)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEO1CisR (cisplatin resistant)</td>
<td>5.1 (1.4)</td>
<td>138</td>
<td>15.6 (1.9)</td>
<td>6.9 (0.92)</td>
<td>11.2 (5.3)</td>
<td>nd</td>
</tr>
<tr>
<td>PEO1carboR (carboplatin resistant)</td>
<td>6.3 (2.6)</td>
<td>130.7 (43.5)</td>
<td>25.5 (13.4)</td>
<td>8.9 (4.9)</td>
<td>5.2 (1.8)</td>
<td>43.6 (15.4)</td>
</tr>
<tr>
<td>SK-OV3</td>
<td>13.1 (2.1)</td>
<td>92.8 (6.1)</td>
<td>32.3 (3.7)</td>
<td>10.4 (3.2)</td>
<td>35.8 (5.0)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW948</td>
<td>44.8 (13.3)</td>
<td>nd</td>
<td>29.4 (4.30)</td>
<td>9.6 (1.9)</td>
<td>22.3 (8.9)</td>
<td>nd</td>
</tr>
<tr>
<td>Colon cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-TERA</td>
<td>0.78 (0.27)</td>
<td>nd</td>
<td>7.3 (0.7)</td>
<td>1.95 (0.9)</td>
<td>6.1 (0.6)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

nd = not done. The values shown are IC₅₀ values in μMol. The values are the means for >3 repeat assays, with the standard deviation shown in brackets.

Table 17. Summary of the IC₅₀ values of platinum oxadiazoline complexes (structures shown above) with those for cisplatin and carboplatin for comparison.
The most important point to note is that all the tested compounds, except JS7, have IC<sub>50</sub> values lower than that of carboplatin in the cell lines where all were tested. The best performance was by JS5 which was at least three times more effective than carboplatin in PEO1, and more than ten times more effective in the carboplatin resistant cell line. Another important feature is the ratio IC<sub>50</sub> PEO1CaboR / IC<sub>50</sub> PEO1. For JS5 this is ~ 1 compared to 4.33 for carboplatin. This means JS5 is as active in the carboplatin resistant cell line as it is in PEO1. Also noteworthy is that the activity of JS5 is comparable to that of cisplatin in all the cell lines. Particularly promising is that JS5 is active in a variety of cell lines including colon cancer where its activity surpasses that of cisplatin. As cisplatin is extremely toxic it is not generally used as the benchmark by which other potential drugs are measured. Today carboplatin fills that role, and in the cell lines tested, JS4, JS5 and JS6 surpassed the activity of carboplatin. Of particular interest is the low IC<sub>50</sub> value for JS6 used in the carboplatin resistant cell line (PEO1CaboR) compared to that for the carboplatin sensitive cell line (PEO1), 5.2 and 16.3. The fact that JS6 is more cytotoxic in the resistant cell line than the sensitive cell line suggests a DNA interaction other than the accepted one for carboplatin. This may be an important feature in overcoming platinum resistance in cancer cell lines which is a common reason for the failure of novel drug candidates.

The poor performance of JS7 apparent by the large standard deviations and IC<sub>50</sub> values was disappointing after initially promising results. One possible explanation why the good results could not be repeated with the passage of time (6 months) is that the complex was not stable in DMSO / water solution. However the mono complex with the similar substituent (JS6) appears to be stable judging by the test results. Another more plausible reason may be that the complex gradually precipitated out of solution, being in the cold environment of the fridge.

Within the constraints of the doctorate, no data was acquired relating to the toxicity of the tested complexes, but this would have to be done in the next stage of testing if the complexes are to progress.

Without the benefit of DNA / complex interaction studies, attempts to rationalise the results are little more than speculation. Regarding the accepted binding mode of Pt-N7 of guanine, it is easy to see how cisplatin fits into the position whereas the more bulky
complexes of the JS series would have difficulty. This would explain why cisplatin is more active in most cell lines but does not explain why the JS series are more active in SW948 colon cancer. If the oxadiazoline is substituted during binding, then the free ligand may interact with DNA on its own. The bulky ligands open up the possibility of other binding sites apart from Pt. The hydroxy groups could hydrogen bond or the phenyl rings might experience van der Waal's attraction. There is also the possibility of hydrolysis of the oxadiazoline ring producing further binding sites. Another aspect to consider is the DNA repair mechanism and apoptosis, the cells self destruct mechanism. With cisplatin it may be easier for the repair mechanism to cut out the DNA adducts, than for the JS series where the platinum is sterically hindered by the bulky ligands. Consequently apoptosis may occur more readily in cells which have DNA bound to a JS complex, whereas in the corresponding cells bound to cisplatin, the repair may take place.

Summing up, the complexes selected for testing, with the exception of JS7, proved to be more efficacious than carboplatin in all the cell lines tested. JS5 was particularly promising being comparable in activity to cisplatin. Whilst the solubilities of the JS series are below the desirable levels, the problem can be overcome. The complexes are also acceptably stable in aqueous solution. Within the scope of the doctorate, biological testing has proceeded as far as possible and further development will require external collaboration. The type of work required is toxicity studies on animals and DNA / complex interaction studies.

In keeping with the current project, it was decided to attempt to make ruthenium nitrile complexes, and use the same method of cycloaddition of nitrile to nitrone to make ruthenium oxadiazoline complexes. Having searched Beilstein, only a handful of papers on the subject of ruthenium coordinated nitrile complexes were found, and all but one turned out to be electrochemistry experiments using cyclic voltammetry. The other paper, by Duff and Heath\textsuperscript{155}, although it contained non-electrochemical synthesis, had very little characterization of the complexes, however on checking some of their references it was decided to mimic their method.


Two coordinated nitrile complexes were attempted, using a modification of a synthesis by Dehand and Rose\textsuperscript{156}. The first was $[\text{RuCl}_3(\text{PhCN})_3]$\textsuperscript{155-157} of which there are two possible structures shown in figure 96. The X-ray structure of the \textit{mer} isomer has been described\textsuperscript{157}.

![Figure 96. The facial and meridional structures of $[\text{RuCl}_3(\text{PhCN})_3]$.](image)

This was difficult to isolate without contamination by the product of reduction $[\text{RuCl}_2(\text{PhCN})_4]$, so it was decided to make the latter complex instead. The \textit{trans} structure is shown in figure 97 below, which is suggested by only one CN band in the IR spectrum at 2244 cm\textsuperscript{-1}, but no X-ray structure has been published.
The two structures of [NBu$_4$]$^+$[RuCl$_4$(PhCN)$_2$]$^-$ shown below in figure 98 are also possible but only the trans isomer has been previously reported$^{155}$. 

![Possible structures of [NBu$_4$]$^+$[RuCl$_4$(PhCN)$_2$]$^-$](image)

This complex was not attempted as the synthesis involved extra steps and there was no spectroscopic evidence for cycloaddition whatsoever with the other ruthenium nitrile complexes.

### 6.2. Ruthenium acetonitrile complexes

The same aqueous method as for platinum acetonitrile was used as already described. The two starting materials used were ruthenium trichloride hydrate, and potassium hexachlororuthenate. Both turned black and it is likely both were reduced to metallic ruthenium or ruthenium oxides. There was no evidence in the infra-red spectra of either to suggest a successful ligand exchange, and the ruthenium acetonitrile complexes are known to be yellow orange in colour.

### 6.3 Attempted cycloadditions using [Ru(II)(Cl)$_2$(PhCN)$_4$]

Cycloaddition using an analogous method to platinum was attempted using chloroform as solvent and $N$-methyl-$C$-phenyl nitron. A black precipitate was
produced and proton NMR spectroscopy of the reaction mixture showed no appropriate signals present. The most likely explanation is that the ruthenium(II) is reduced to metallic ruthenium(0), either by the chloroform used as solvent in the reaction, and/or the reaction conditions. The reaction was repeated using benzonitrile as solvent. After three days the product was precipitated using ether but again, there was no cycloaddition product evident in the proton NMR spectrum.

Cycloaddition was also attempted using microwave irradiation (fifteen minutes at 60 °C followed by fifteen minutes at 100 °C) and the aforementioned starting materials, employing DCM as solvent. Proton NMR spectroscopy of the crude product indicated no cycloaddition had taken place. The reaction mixture was reduced under vacuum and a brown solid precipitated using diethyl ether. Proton NMR spectroscopy of the solid revealed no signals in the aromatic region. The remaining solute was concentrated and placed in the freezer for two days. Clear crystals were formed, the proton NMR spectrum and elemental analysis of which were consistent with benzamide.

For completeness, cycloadditions were attempted in the NMR tube using other nitrones, namely N-methyl-C-\(p\)-(dimethylamino)phenyl nitrone, and N-methyl-C-\(p\)-(2-methoxyethoxy)phenyl nitrone, and chloroform as solvent. Although the former nitrone did not give the desired cycloaddition product from reaction with the bis benzonitrile platinum(II) complex, there was an unexpected reaction, this was chosen to see if it would behave with ruthenium in the same way. Analyses of the products in both cases showed little reaction of any type had taken place, and proton NMR spectroscopy suggested they were mainly raw material and a small amount of aldehyde.

6.4 One pot synthesis starting with ruthenium trichloride hydrate.

A one pot synthesis using ruthenium trichloride hydrate, benzonitrile and N-methyl-C-\(p\)-phenyl nitrone was also attempted. The reaction mixture was heated at 120 °C for four days, and turned green. A solid was precipitated using diethyl ether, but proton NMR spectroscopy showed no aromatic signals at all. It was concluded that the green colour
was simply ruthenium in a different oxidation state. Considering ruthenium's standard reduction potentials\textsuperscript{158}:

\[
\begin{align*}
\text{Ru}^{3+} + 3e & \rightarrow \text{Ru}^{0} \quad E^0 (V) = 0.758, \\
\text{Ru}^{2+} + 2e & \rightarrow \text{Ru}^{0} \quad E^0 (V) = 0.600, \\
\text{Ru}^{3+} + e & \rightarrow \text{Ru}^{2+} \quad E^0 (V) = 0.249,
\end{align*}
\]

which are all positive, meaning the Gibb's free energy will be negative, reduction is favoured.

### 6.5 Direct addition of an uncoordinated oxadiazoline to ruthenium

Due to the failure of these attempts at cycloaddition it was decided to perform a direct addition of an uncoordinated oxadiazoline to ruthenium trichloride hydrate.

The oxadiazoline was attempted according to Hermkens et al.\textsuperscript{73} using benzonitrile, N-methyl-C-phenyl nitron and toluene as solvent. It was refluxed for ten days and the solvent regularly topped up to prevent the mixture becoming increasingly polar. Despite at least ten attempts at this reaction, it was not possible to produce the desired product, and the main products were breakdown products of the nitron, namely benzaldehyde. Every attempt was made to exclude water from the reaction including dried solvents and nitrogen. The reaction was also attempted by microwave irradiation, and in a sealed pressure vessel, also without success. The reaction was attempted using N-methyl-C-p-(dimethylamino)phenyl nitron, and this was similarly unsuccessful. It was therefore not possible to test if an oxadiazoline could be directly added to ruthenium trichloride.

### Conclusion

At this stage, rather than waste more time it was decided to suspend the investigation of ruthenium, and concentrate on platinum, and perhaps try other transition metals later on. It was concluded that ruthenium does not activate nitriles toward cycloaddition in the same way as platinum does. The reasons for this are not known for certain but speculatively it might be suggested the coordination sphere of ruthenium(III) is more crowded than platinum(II), octahedral versus square planar,
and this prevents the nitrone attaining a favorable position for reaction. Secondly, the ruthenium benzonitrile complex necessarily has benzonitrile ligands in cis position, cycloaddition of cis-platinum(II) nitrile complexes is much slower than their trans counterparts and the products less stable. Possibly for ruthenium nitriles the rate is so slow that no reaction takes place. Both have similar Pauling electronegativity values (2.2) so it would not be expected that platinum should activate the nitrile more so than ruthenium. The chemistry of ruthenium is different to platinum, ruthenium(III) is able to accommodate many neutral ligands and hold a positive charge in a way that is not so common for platinum(II), and cycloaddition, or lack of it, is another example of this difference in chemistry.
7.1 Future Work

Inevitably when time and money are governing factors there will be areas of a project where it would have been both profitable and interesting to investigate a certain area in greater depth. This project is no exception, however a line has to be drawn between investigation and obsession and with the main aims of the project in mind the following areas emerge.

1. A further look at ruthenium where the results obtained were no reflection of the effort put in. Possibly different heterocycles could be synthesized and attached to ruthenium.

2. Another look at the reaction of nitrones containing electron deficient substituents and platinum nitrile complexes, where it was not possible to conclusively assign the products. If any of the proposed structures could be isolated they could well possess anti-tumour activity and biological testing might be beneficial.

3. The ligand exchange using mono oxadiazoline platinum(II) and triphenylphosphine was perplexing. As they were rapid, they might be elucidated by low temperature NMR spectroscopy.

4. With oral bioavailability in mind, further solubility tests of the platinum oxadiazoline complexes made and not tested, and likewise further biological testing including DNA binding studies.

5. Producing complexes with greater solubility in water possibly starting from $\text{PtCl}_2(m,p$-di-OH-C$_6$H$_4$CN)$_2$, or by substitution of the benzonitrile ligand of mono oxadiazoline platinum complexes by more hydrophilic ligands.

6. Extending the multinuclear platinum work starting with the dinitrone made from terephthaldehyde could lead to all sorts of possibilities of exchanges with the mono cycloadduct, or bis cycloaddition using different more polar nitrones.

The latter three are all intended to extend the present work, and develop complexes with improved solubility in polar solvents, improved bioavailability and elucidate the mechanism of action of the complexes anti-tumour effect.
7.2. Conclusions.

1. The [2+3] cycloaddition of novel platinum nitrile complexes to novel nitrones has been carried out successfully, to produce a bank of mono and bis oxadiazoline platinum complexes.
2. For the first time, platinum oxadiazoline complexes have been made that are soluble in polar non chlorinated solvents, and the said complexes are compatible with DMSO / water mixtures.
3. For the first time the structure of a mono oxadiazoline platinum(II) complex has been determined by X-ray diffraction analysis.
4. Both mono and bis oxadiazoline platinum complexes have been tested biologically for anti-tumour effect in vitro, and have been found to be as good as, or better than carboplatin, in ovarian, colonic and testicular cancer cell lines.

Figure 99. Bis oxadiazoline platinum complexes tested for biological anti-tumour activity, substituents shown in table 18.

<table>
<thead>
<tr>
<th>Complex no.</th>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>49</td>
<td>H</td>
<td>MeO-C_2H_4O-</td>
</tr>
<tr>
<td>47</td>
<td>OH</td>
<td>H</td>
</tr>
</tbody>
</table>

Table 18. Bis oxadiazoline platinum complexes tested biologically for anti-tumour effect.
5. One particular complex JS6, proved to be more cytotoxic in carboplatin resistant ovarian cancer than the platinum sensitive cell line, and this suggests a different mechanism of action than the accepted guanine,N7 binding mode.

6. A significant improvement of the Williamson ether synthesis using microwave irradiation has been developed. This is a rapid method for the production of phenyl ethers in high yield with good purity.

Scheme 27. The microwave synthesis of phenyl ethers, X= Br or Cl.
8. Experimental procedure

Materials and Instrumentation. Solvents were obtained from commercial sources and used as received. C, H and N elemental analyses were carried out on a Leeman CE 440 automatic analyser. Infrared spectra (4000-400 cm\(^{-1}\)) were recorded on Perkin Elmer 2000 FTIR in KBr pellets. EI, CI and positive MS-FAB spectra of the samples in 3-nitrobenzyl alcohol (NBA) matrices, were obtained on a Thermoquest MAT 95XL instrument. \(^{1}\)H and \(^{13}\)C 1D experiments were acquired on a Bruker 300 spectrometer unless otherwise stated, and 2D \(^{1}\)H, \(^{13}\)C and 1D \(^{31}\)P and \(^{195}\)Pt NMR experiments were acquired on a Bruker DRX 500 spectrometer at ambient temperature, if not indicated otherwise. \(^{195}\)Pt NMR chemical shifts are given relative to aqueous K\(_2\)[PtCl\(_4\)] = -1630 ppm, with half height line widths in parenthesis. Molecular models were drawn using the Molekel package and are based on information gained from the X-ray structures which are generated using the Platon programme. Details of bond lengths and angles will be published in the aforementioned forthcoming publications.

8.1 Preparation of nitrones.

Below is a typical procedure for the production of nitrones, specific conditions vary from aldehyde to aldehyde and these are summarized in the table below.

8.1.1 N-Methyl-C-phenyl nitrone

A mixture of N-methyl-hydroxylamine hydrochloride (24 mmol, 2.0 g), Na\(_2\)CO\(_3\) (24 mmol, 2.544 g) and benzaldehyde (24 mmol, 2.546 g), dichloromethane (40 ml) and methanol (10 ml) was refluxed with stirring for ca. 4 hours. The solvent was then evaporated (rotavapor) and the residue extracted three times with dichloromethane, 20 ml each time. The solution was then evaporated close to dryness, hexane was added and finally, the product was crystallised in the freezer. The final crystals, (white), which were obtained were weighted and found out to be 2.2 g in total. The yield is 66%.
Scheme 28. Production of nitrones.

<table>
<thead>
<tr>
<th>No.</th>
<th>Aldehyde</th>
<th>Reaction conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzaldehyde</td>
<td>4 / 1 DCM / MeOH, reflux for 4 hrs, Na₂CO₃, evaporate, extract with DCM, precipitate with hexane.</td>
</tr>
<tr>
<td>2</td>
<td>Salicylaldehyde</td>
<td>4 / 1 MeCN / EtOH, reflux for 12 hrs, Na₂CO₃, evaporate, extract with DCM, precipitate with hexane.</td>
</tr>
<tr>
<td>3</td>
<td>3-hydroxybenzaldehyde</td>
<td>4 / 1 DCM / MeOH, reflux for 4 hrs, Na₂CO₃, evaporate, the resulting oil was recrystallised from methanol in the freezer for 4 days.</td>
</tr>
<tr>
<td>4</td>
<td>4-hydroxybenzaldehyde</td>
<td>4 / 1 EtOH / MeCN, reflux for 20 hrs, Na₂CO₃, evaporate, the resulting oil was recrystallised from methanol in the freezer for 4 days.</td>
</tr>
<tr>
<td>5</td>
<td>2-(2-methoxyethoxy)-benzaldehyde</td>
<td>4 / 1 MeCN / EtOH, reflux for 12 hrs, Na₂CO₃, evaporate, extract with DCM.</td>
</tr>
<tr>
<td>6</td>
<td>3-(2-methoxyethoxy)-benzaldehyde</td>
<td>4 / 1 MeCN / EtOH, reflux for 12 hrs, Na₂CO₃, evaporate, extract with DCM.</td>
</tr>
<tr>
<td>7</td>
<td>4-(2-methoxyethoxy)-benzaldehyde</td>
<td>4 / 1 DCM / MeOH, reflux for 36 hrs, Na₂CO₃, 1.5 molar excess of N-methyl hydroxylamine added in 2 lots at the start and at 18 hours, evaporate, extract with DCM.</td>
</tr>
<tr>
<td>8</td>
<td>3-carboxybenzaldehyde</td>
<td>4 / 1 DCM / MeOH, reflux for 4 hrs, Na₂CO₃, evaporate, recrystallise from hot methanol, disregard the initial ppt of fine white powder which is inorganic.</td>
</tr>
<tr>
<td>9</td>
<td>4-carboxybenzaldehyde</td>
<td>4 / 1 DCM / MeOH, reflux for 20 hrs, Na₂CO₃, evaporate. The product was insoluble in organic solvents and could not be isolated, a proton nmr spectrum was acquired of the crude.</td>
</tr>
</tbody>
</table>
Table 19. Summary of nitrone produced with reaction and work-up conditions.

8.1.1 N-Methyl-C-phenyl nitrone (1).

White crystalline solid, yield 66%.

Analytical data:

Formula: C₈H₈NO, MW 135.17. \(^1\)H NMR spectrum in CDCl₃, \(\delta\) (ppm): 3.81 (s, 3H, NMe), 7.35 (s, 1H, CH=N), 7.39 (m, 3H, Ph) and 8.20 (2H, 7.9 Hz, Ph(2,6)).

\(^1^3\)C NMR spectrum in CDCl₃, \(\delta\) (ppm): 54.3 (NMe), 128.3, 128.4, 130.3, 135.1 (CH=N and CH of Ph), 130.4 (C₁ of Ph). IR (KBr), selected bands, cm\(^{-1}\): 3058, 2994, 2932 w ν(C-H), 1595 ν(C=N).

8.1.2 N-Methyl-C-o-hydroxyphenyl nitrone (2).

A cream crystalline solid, yield is 85%.

Analytical data:

Formula C₈H₈NO₂, MW 151.16, Anal. calc.% C: 63.56; H: 6.00; N: 9.27; found, C: 63.27; H: 6.00, N: 9.26.

\(^1\)H NMR spectrum in CDCl₃, \(\delta\) (ppm): 3.80 (s, 3H, NMe), 6.82 (t, 7.8 Hz, H, ArCH), 6.91 (d, 7.8 Hz, H, ArCH), 7.01 (d, 7.8 Hz, H, ArCH), 7.34 (t, 7.8 Hz, H, ArCH), 7.49 (s, H, CH=N) and 12.40 (s, H, OH).
$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 52.0 (NMe), 116.7 (1C, ArC(3)H), 119.1 and 120.1 (2C ArC(4 and 6)H), 132.2(1C, CH=N), 134.1 (1C, ArC(5)H), 142.2 (1C, ArC(1)), 159.5 (C=O, ArC(2)OH).

IR (KBr), selected bands, cm$^{-1}$: 1587, $\nu$(C=N).

Accurate MS-CI, 151.0631, theoretical, 151.0628.

8.1.3 $N$-Methyl-$C$-$m$-hydroxyphenyl nitrone (3).

Cream crystalline solid, yield. 30%

Analytical data:
Formula: C$_8$H$_9$NO$_2$, MW 151.16, Anal. calc.%, C: 63.56; H: 6.00; N: 9.27; found, C: 62.97; H: 5.92, N: 9.08.

$^1$H NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 3.72 (s, 3H, NMe), 6.79 (d, 7.8 Hz, 1H, ArC(4)H), 7.21 (t, 7.8 Hz, 1H, ArC(5)H) and 7.41 (d, 1H, ArC(6)H 7.8 Hz ), 7.96 (s, 1H, ArC(2)H), 7.74 (s, H, CH=N), 11.35 (s, OH).

$^{13}$C NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 53.9 (NMe), 113.8 (1C, ArC(2)H ), 116.9 (1C, ArC(4)H ), 119.2 (1C, ArC(6)H ), 119.8 (1C$_q$, ArC(1) ), 129.1 (1C, ArC(5)H ), 134.5 (CH=N) and 157.0 (1C, ArC(3)O).

IR (KBr), selected band, cm$^{-1}$: 1608 $\nu$(C=N).

MS-EI, m/z: 150, 151 [M, isotopic pattern], 152 [M$^+$], and 137 [M$^+$ - Me].

Accurate MS-CI, 151.0628, theoretical, 151.0628.

8.1.4 $N$-Methyl-$C$-$p$-hydroxyphenyl nitrone (4).

Cream crystalline solid, yield 35%.

Analytical data:
Formula: C$_8$H$_9$NO$_2$, MW 151.16, Anal. calc.%, C: 63.56; H: 6.00; N: 9.27; found, C: 63.16; H: 5.97, N: 9.28.

$^1$H NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 3.82 (s, 3H, NMe), 7.98 (d, 8.8 Hz, 2H, ArC(2,6)), 7.51 (d, 8.8 Hz, 2H, ArC(3,5)), 8.31 (s, 1H, CH=N), 10.04 (s, OH).

$^{13}$C NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 53.2 (NMe), 115.2 (2C, ArC(3,5)), 129.7 (2C, ArC(2,6)), 133.6 (1C, CH=N), 160.1 (1C, ArC(4)O), 121.6 (1C, ArC(1)).

IR (KBr), selected band, cm$^{-1}$: 1603 $\nu$(C=N), 3300 w, 2919 w, $\nu$(CH).
MS-CI, m/z: 151 and 150 [M isotopic pattern], 134 [M – OH].
Accurate MS-CI, 151.0628, theoretical, 151.0628

8.1.5 N-Methyl-C-o-(2-methoxyethoxy)phenyl nitrone (5).

A pale brown oil, yield is 90%.
Analytical data:
Formula C$_{11}$H$_{15}$NO$_3$, MW 209, Anal. calc.%, C: 63.14; H: 7.23; N: 6.69; found, C: 61.92; H: 7.23, N: 6.78.
$^1$H NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 3.83 (s, 3H, NMe), 3.42 (s, 3H, MeO), 3.72 (t, 4.6 Hz, 2H, CH$_2$O), 4.18 (t, 4.6 Hz, 2H, OCH$_2$), 7.00 (t, 8.3 Hz, 1H, ArC(5)H), 7.10 (d, 8.3 Hz, 1H, ArC(3)H), 7.36, (t, 8.3 Hz, 1H, ArC(4)H), 9.17 (d, 8.3 Hz, H, ArC(6)H), 7.87 (s, CH=N)
$^{13}$C NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 54.7 (NMe), 58.2 (MeO), 67.8 (CH$_2$O), 70.23 (O-CH$_2$), 119.9 (C$_q$, ArC (1)), 127.8 (CH=N), 112.0 (ArC(3)H), 120.3 (ArC(4)H), 127.2 (ArC(6)H), 131.1 (ArC(5)H), 155.5 (ArC(2)-O). IR (KBr), selected bands, cm$^{-1}$: 1656, v(C=N).
MS-EI, m/z: 209 [M], 210 [M$^+$], 151 [M - HC=N(CH$_3$)O], 134 [M – CH$_3$OC$_4$H$_4$O].
Accurate MS-CI, 209.1046, theoretical, 209.1046.

8.1.6 N-Methyl-C- m-(2-methoxyethoxy)phenyl nitrone (6).

A pale brown oil, the yield was 86%.
Analytical data:
$^1$H NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 3.79 (s, 3H, MeN), 3.32 (s, 3H, MeO), 3.67 (t, 4.5 Hz, 2H, CH$_2$O), 4.10 (t, 4.5 Hz, 2H, OCH$_2$), 7.01 (d, 7.9 Hz, 1H, ArC(4)H) , 7.34 (t, 7.9 Hz, 1H, ArC(5)H), 7.65 (d, 7.9 Hz, 1H, ArC(6)H), 7.82 (s, CH=N), 8.07 (s, 1H, ArC(2)H).
$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 54.3 (NMe), 59.1 (OMe), 70.9 (O-CH$_2$), 67.4 (CH$_2$O), 113.0 (C$_q$, ArC (1)), 114.3 (ArC(2)H), 117.7 (ArC(4)H), 121.6 (ArC(6)H), 131.7 (ArC(5)H), 135.2 (CH=N) and 158.6 (ArC(3)-O).
IR (KBr), selected bands, cm\(^{-1}\): 1659, v(C=N).

MS-FB, \(m/z\): 209 [M], 210 [M\(^+\)], 151 [M - HC=N(CH\(_3\))O], 134 [M - CH\(_3\)OC\(_4\)H\(_4\)O].
Accurate MS-CI, 209.1049, theoretical, 209.1046.

8.1.7 \(N\)-Methyl-\(C\)-\(p\)-(2-methoxyethoxy)phenyl nitrone (7).

A pale yellow oil, the yield was 80%

Analytical data:
Formula C\(_{11}\)H\(_{15}\)NO\(_3\), MW 209, Anal. calc.\%, C: 63.14; H: 7.23; N: 6.69; found, C: 61.80; H: 7.27; N: 6.73.

\(^1\)H NMR spectrum in CDCl\(_3\), \(\delta\) (ppm): 3.44 (s, 3H, NMe), 3.76 (s, 3H, MeO), 3.76 (m 2H, CH\(_2\)O), 4.15 (m 2H, OCH\(_2\)O), 6.96 (d, 7.5 Hz, 2H, ArC(3,5)H), 8.19 (d, 7.5 Hz, 2H, ArC(2,6)H), 7.39 (s, CH=N)

\(^{13}\)C NMR spectrum in CDCl\(_3\), \(\delta\) (ppm): 55.0 (NMe), 59.3 (OMe)), 67.7(CH\(_2\)O), 70.7 (OCH\(_2\)O), and 115.0 (ArC (2,6) H), 123.2 (ArC (1)-CH=N), 130.9 (ArC(3,5)H), 136.3 (CH=N), 160.7 (ArC(4)-O),

IR (KBr), selected bands, cm\(^{-1}\): 1610, v(C=N).

MS-EI, \(m/z\): 209 [M], 210 [M\(^+\)], 151 [M - HC=N(CH\(_3\))O], 134 [M - CH\(_3\)OC\(_4\)H\(_4\)O].
Accurate MS-CI, 209.1018, theoretical, 209.1046.

8.1.8 \(N\)-Methyl-\(C\)-\(m\)-carboxyphenyl nitrone (8).

A white solid 1.5 g. Yield. 84%, mpt, 161-163 °C.

Analytical data:
Formula: C\(_9\)H\(_9\)NO\(_3\), MW 179.17, Anal. calc\%, C: 60.33; H: 5.06; N: 7.82; found, C: 59.48; H: 4.99; N: 7.65.

\(^1\)H NMR spectrum in d\(_6\)-DMSO, \(\delta\) (ppm): 3.77 (s, 3H, NMe), 7.37 (t, 8.3 Hz, 1H, ArC(5)H), 7.88 (s, 1H, CH=N), 7.91 (d, 8.3 Hz, ArC(6)H), 8.43 (d, 8.3 Hz, 1H, ArC(4)H), and 8.52 (s, 1H, ArC(1)H).

\(^{13}\)C NMR spectrum in d\(_6\)-DMSO, \(\delta\) (ppm): 169.3 (COOH), possibly 128.3 (ArC(3), C-COOH), possibly 97.0(ArC(1)), 53.8 (NMe), 134.1 (CH=N) 127.3, 128.4, 129.3, 130.4 (ArC (2,4,5,6)H).

IR (KBr), selected band, cm\(^{-1}\): 1607 v(C=N).
8.1.9 *N*-Methyl-**C**-**p**-carboxyphenyl nitrone (9).

The solid product was filtered off but proved to be too polar and insoluble in organic solvents, to be separated from the inorganic starting materials. Proton NMR and infrared spectra were obtained from the crude.

**Formula:** C₉H₉NO₃, M.W. 179.16.

**H NMR spectrum** in d₆-DMSO, δ (ppm): 3.77 (s, 3H, NMe) 7.88 (d, 8.2 Hz, 2H, ArC(3,5)H), 7.92 (s, CH=N), 8.16 (d, 8.3 Hz, 2H, ArC(2,6)H).

**IR (KBr), selected band, cm⁻¹:** 1595 ν(C=N).

8.1.10 *N*-Methyl-**C**-2-(sodium sulphonate)-phenyl nitrone (10).

White crystalline solid, yield 91.7%, m.p. 270 °C.

**Analytical data:**

**Formula:** C₈H₈N₂O₄SNa, MW 237.21, **H NMR spectrum** in d₆-DMSO, δ (ppm): 3.78 (s, 3H, NMe), 7.34 (m, 2H, ArC(4,5)), 7.84 (d, 8.9 Hz, H, ArC(5)H) and 8.57 (s, CH=N), and 9.26 (d, 8.9 Hz, H, ArC(2)H).

**C NMR spectrum** in d₆-DMSO, δ (ppm): 55.1 (NMe), 97.2 (ArC(1)-C=N), 126.8, 126.5 (ArC(6,5)H), 128.6, 128.4 (2C, ArC(3,4)H), 131.9 (CH=N), 169.3 (ArC(2)-S).

**IR (KBr), selected bands, cm⁻¹:** 1656, ν(C=N).

MS-EI, *m/z:* 236 [M], 208 [M –NMe].

Accuracy MS-EI, 236.9910, theoretical, 237.0066.

8.1.11 Benzenamine, *N*,*N*-dimethyl-4-[(methylimino)methyl]-, *N*-oxide; nitrone (11).

Orange crystalline solid, the yield is approximately 90%.

**Analytical data:**

**Formula:** C₁₀H₁₄N₂O, MW 178.23. Anal. calc. for C₁₀H₁₄N₂OCl HCl, %: C: 55.94; H: 7.04; N: 13.04; found, C: 52.86; H: 7.15, N: 13.37.
$^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 3.12 (s, 6H, N(CH$_3$)$_2$), 4.05 (s, 3H, NMe), 6.75 (d, 9.3 Hz, 2H, ArC(3,5)H), 8.09 (d, 9.3 Hz, 2H, ArC(2,6)H), 8.45 (s, 1H, CH=N).

$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): not observed (CH=N), not observed (ArC(1)-CH=N), 39.7 (NMe$_2$), 48.5 (NMe), 111.6 (ArC(3,5)H), 136.4 (ArC(2,6)H), 152.0 (ArC(4)--N). IR (KBr), selected bands, cm$^{-1}$: 3004, 2923, 2832, $\nu$(C-H), 1698, $\nu$(C=N).

MS-EI, $m/z$: 177, 178 [M, isotopic pattern], 179 [M$^+$], 163 [M - Me], 148 [M - 2Me], 134 [M - (Me)$_2$N].

Accurate MS-CI, 178.1101, theoretical, 178.1101.

8.1.12 Benzenammonium methyl sulphate, N,N,N-trimethyl-4-[(methylimino)methyl]-, N4-oxide; nitrotrone. (12).

Yellow crystalline solid, the yield is approximately 82%, mpt, 120-122 °C.

Analytical data:
Formula: C$_{12}$H$_{20}$N$_2$O$_5$S, MW 304.1. Anal. calc.%: C: 47.35; H: 6.62; N: 9.20; found, C: 44.06; H: 6.67, N: 9.20.

$^1$H NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 3.38 (s, 3H, MeSO$_2$), 3.63 (s, 9H, N(CH$_3$)$_3$), 3.83 (s, NMe), 8.05 (d, 8.3 Hz, and s, 3H, ArC(3,5)H and CH=N), 8.21 (d, 8.3 Hz, 2H, ArC(2,6)H).

$^{13}$C NMR spectrum in d$_6$-DMSO, $\delta$ (ppm): 52.75 (MeSO$_2$), 54.26 (NMe), 56.15 (NMe$_2$), 120.7 (ArC(3,5)H), 128.7 (ArC(2,6)H), 132.3 (CH=N), possibly 121.7 or 131.9 (ArC(1)), 161.3 (ArC(4)--N).

IR (KBr), selected bands, cm$^{-1}$: 1690, $\nu$(C=N).

MS-EI, $m/z$: 303, 304 [M, isotopic pattern], 289 [M - CH$_3$], 274 [M - 2CH$_3$], 259 [M - 3CH$_3$].

Accurate MS-CI, 303.9900, theoretical, 304.1087.
8.1.13 \( N,N'\)-dimethyl-\( p \)-phenylenedinitrune, \( N,N'\)-(1,4-phenylenedimethylidyne)bis-
\( N,N'\)-dioxide
1,4-di-(CH=N(Me)O)-C\(_6\)H\(_4\) (13).

White crystalline solid, the yield is 77%.

Analytical data:
Formula C\(_{10}\)H\(_{12}\)N\(_2\)O\(_2\), MW 304.1, \(^1\)H NMR spectrum in d\(^4\)-CD\(_3\)OD, \( \delta \) (ppm): 3.88 (s, 6H, NMe), 7.86(2H, CH=N), 8.31 (s, 4H, C\(_6\)H\(_4\)).
\(^{13}\)C NMR spectrum in d\(^4\)-CD\(_3\)OD, \( \delta \) (ppm): 138.7 (CH=N), 133.8 (2C, ArC (1,4)-
C=N), 130.3 (4C, ArC (2,3,5,6) H), 54.5 (ONMe).
Accurate MS-CI, 192.0892, theoretical, 192.0893.

8.2 Glycol ether substituted precursors.

Typical procedure: A pyrex cylindrical reaction tube adapted to the SmithCreator\textsuperscript{TM}
(Personal Chemistry/Biotage) was charged with formylphenol or hydroxybenzonitrile
(5 mmol), anhydrous K\(_2\)CO\(_3\) (5 mmol, 680 mg), 2-haloethylmethylether (6 mmol, 0.56
ml of the bromo-compound or 15 mmol, 1.37 ml of the chloro-compound), 1.5 ml
methanol and a magnetic stirrer bar. The tube was septum-sealed and irradiated with
microwaves at the set temperature and reaction time given in Table 7 (reproduced
below, table 20). The temperature was measured by IR detection and maintained
constant by modulated irradiation of 300 W down to 8 W. The reaction mixture was
cooled to room temperature, the solvent was evaporated under reduced pressure and
the solid residue extracted with hexane (3 x 50 ml). After evaporation of the solvent,
TLC and NMR-spectroscopy, pure products were obtained the analytical data of
which are below.
<table>
<thead>
<tr>
<th>Comp.</th>
<th>R =</th>
<th>pKa&lt;sup&gt;aa&lt;/sup&gt;</th>
<th>X = Br</th>
<th>X = Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>4-CHO</td>
<td>7.61</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>3-CHO</td>
<td>8.98</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>16</td>
<td>2-CHO</td>
<td>8.37</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>17</td>
<td>4-C=N</td>
<td>7.97</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>3-C=N</td>
<td>8.61</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>19</td>
<td>2-C=N</td>
<td>6.86</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>20</td>
<td>3,4-OHC&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;CN</td>
<td>-</td>
<td>160</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 20. Reaction conditions and yields.

Analytical data:

8.2.1. 4-(2-methoxyethoxy)benzaldehyde (14).

Clear oil. Formula: C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>, MW 180.20, <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub>, δ (ppm):
3.43 (s, 3H, MeO), 3.75 (m, 2H, CH<sub>2</sub>-O), 4.17 (m, 2H, O-CH<sub>2</sub>), 7.00 (d, 8.8 Hz, 2H, ArC(3,5)H), 7.95 (d, 8.8 Hz, 2H, ArC(2,6)H), and 9.85 (s, CHO).

<sup>13</sup>C NMR spectrum in CDCl<sub>3</sub>, δ (ppm): 190.8 (CHO), 163.8 (ArC(4)-O), 132.0 (ArC(2,6)H), 130.1 (ArC (1)-CHO), 114.9 (ArC(3,5)H), 70.7 (CH<sub>2</sub>-O), 67.7(O-CH<sub>2</sub>), 59.3 (OMe).

IR (KBr), selected bands, cm<sup>-1</sup>: 1687, ν(C=O).

8.2.2. 3-(2-methoxyethoxy)benzaldehyde (15).

Clear oil. Formula: C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>, MW 180.20, <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub>, δ (ppm):
3.23 (s, 3H, MeO), 3.55 (t, 4.7 Hz, 2H, CH<sub>2</sub>O), 3.95 (t, 4.7 Hz, 2H, OCH<sub>2</sub>), 7.00 (m, 1H, ArC(4)H), 7.22 (m, 3H, ArCH) and 9.74 (s, CHO).
$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 191.9 (CHO), 159.2 (ArC(3)–O), 130.0 (ArC(5)H), 137.7 (ArC(1)–CHO), 123.3 (ArC(6)H), 121.7 (ArC(4)H), 113.0 (ArC(2)H), 70.7 (CH$_2$–O), 67.7(O–CH$_2$), 59.3 (OMe).

IR (KBr), selected bands, cm$^{-1}$: 1687, $\nu$(C=O).

8.2.3. 2-(2-methoxyethoxy)benzaldehyde (16).


$^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 3.20 (s, 3H, MeO), 3.55 (t, 4.5 Hz, 2H, CH$_2$O), 3.97 (t, 4.5 Hz, 2H, OCH$_2$), 6.76 (overlapped d and t, 8.5 Hz, 2H, ArC(3,5)H), 7.26 (t, 8.5 Hz, 1H, ArC(4)H), 7.60 (d, 8.5 Hz, 1H, ArC(6)H) and 10.30 (s, CHO).

$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 180.3 (CHO), 161.1 (ArC(2)–O), 135.8 (ArC(4)H), 127.8 (ArC(6)H), 120.7 (ArC(5)H), 124.9 (ArC(1)–CHO), 112.8 (ArC(3)H), 70.6 (CH$_2$–O), 68.0 (O–CH$_2$), 58.9 (OMe).

IR (KBr), selected bands, cm$^{-1}$: 1687, $\nu$(C=O).

Accurate MS-CI, 181.0864, theoretical, 181.0859.

8.2.4. 4-(2-methoxyethoxy)benzonitrile (17).

Clear oil. Formula: C$_{10}$H$_{11}$NO$_2$, MW 177.20, $^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 3.44 (s, 3H, MeO), 3.76 (t, 4.7 Hz, 2H, OCH$_2$), 4.15 (t, 4.7 Hz, 2H, CH$_2$O), 6.97 (d, 8.7 Hz, 2H, ArC(3,5)H), 7.57 (d, 8.7 Hz, 2H, ArC(2,6)H).

$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 162.1 (ArC(4)–O), 134.0 (ArC(2,6)H), 118.8 (C≡N), 104.1 (ArC(1)–C≡N), 115.4 (ArC(3,5)H), 70.7 (CH$_2$–O), 67.7(O–CH$_2$), 59.3 (OMe).

IR (KBr), selected bands, cm$^{-1}$: 2216 $\nu$(C≡N), 1197, 1176 $\nu$(C=O).

Accurate MS-EI, 177.0788, theoretical, 177.0784.
8.2.5. 3-(2-methoxyethoxy)benzonitrile (18).

Clear oil. Formula: C_{10}H_{11}NO_2, MW 177.20, ¹H NMR spectrum in CDCl₃, δ (ppm):
3.31 (s, 3H, MeO), 3.63 (t, 4.7 Hz, 2H, OCH₂), 4.00 (t, 4.7 Hz, 2H, CH₂O), 7.03 (m, 3H, ArC(2,4,6)H), 7.23 (m, 1H, ArC(5)H).
¹³C NMR spectrum in CDCl₃, δ (ppm): 158.8 (ArC(3)–O), 130.3 (ArC(5)H), 112.9 (ArC(1)–C=N), 124.4 (ArC(6)H), 119.7 (ArC(4)H), 118.6 (C=N), 117.5 (ArC(2)H), 70.6 (CH₂-O), 67.7 (O-CH₂), 58.9 (OMe).
IR (KBr), selected bands, cm⁻¹: 2231, ν(C≡N), 1059, 1034, ν(C-O).
Accurate MS-EI, 177.0784, theoretical, 177.0784

8.2.6. 2-(2-methoxyethoxy)benzonitrile (19).

White solid. Formula: C_{10}H_{11}NO_2, MW 177.20, Anal. calc. %, C: 67.78; H: 6.26; N: 7.90; found, C: 67.29; H: 6.12, N: 7.87.
¹H NMR spectrum in CDCl₃, δ (ppm): 3.33 (s, 3H, MeO), 3.68 (t, 4.7 Hz, 2H, OCH₂), 4.12 (t, 4.7 Hz, 2H, CH₂O), 6.91 (m, 2H, ArC(3,5)H), 7.39 (m, 2H, ArC(4,6)H).
¹³C NMR spectrum in CDCl₃, δ (ppm): 160.5 (ArC(2)–O), 134.5 (ArC(4)H), 133.6 (ArC(6)H), 112.6 (Ar(3)CH), 121.0 (ArC(5)H), 116.5 (C=N), 102.0 (ArC(1)–C=N), 70.6 (CH₂-O), 68.8 (O-CH₂), 59.3 (OMe).
IR (KBr), selected bands, cm⁻¹: 2227, ν(C≡N), 1291, 1262, ν(C-O), 1129, 1113, ν(C-O).
Accurate MS-EI, 177.0782, theoretical, 177.0784

8.2.7. 3,4-di(2-methoxyethoxy)benzonitrile (20).

Colourless oil. Formula: C_{13}H_{18}NO₄, MW 252.29, Anal. calc. %, C: 61.89; H: 7.19; N: 5.55; found, C: 61.43; H: 6.44, N: 5.95.
Rf 0.33, 3/1 DCM/ethyl acetate, single spot.
¹H NMR spectrum in CDCl₃, δ (ppm): 3.44 (s, 6H, 2MeO), 3.77 (m, 4H, (CH₂)₂), 4.16 (m, 4H, (CH₂)₂), 7.14 (d, 9.0 Hz, H, ArC(5)H), 7.39 (d, 9.0 Hz, H, ArC(6)H), 7.25 (s, 1H, ArC(2)H).
13C NMR spectrum in CDCl₃, δ (ppm): 154.5 (ArC(4)-O), 150.4 (ArC(3)-O), 128.1 (ArC(6)H), 119.9 (ArC(2)H), 118.1 (C=N), 114.9 (ArC(5)H), 105.0 (ArC(1)-C=N), 70.0 (CH₂-O), 72.1 (O-CH₂), 59.6 (OMe).

IR (KBr), selected bands, cm⁻¹: 2225, ν(C=N), 1050, 1034, ν(C-O).

Accurate MS-CI, 252.1225, theoretical mass, 252.123

8.3. Miscellaneous methylations.

Method of alkylation reproduced from section 5.2.

\[
\begin{align*}
\text{R}^+ + (\text{Me}_2\text{SO}_4) & \xrightarrow{\text{N}_2, 70 \degree C, 1 \text{ hour}} \text{R-N}^+ \text{-SO}_4\text{CH}_3 \\
\text{R} = \text{CN (22) or CHO (21)}
\end{align*}
\]

Scheme 29. Quaternisation of tertiary amines.

The method employs a fourfold excess of the alkylating agent as solvent, mild conditions of 1 hour warming at 70 °C under a nitrogen atmosphere. Excess of dimethyl sulphate is removed with diethyl ether and the product easily purified by washing with successive portions of diethyl ether and DCM.

8.3.1. (4-Formylphenyl)trimethylammonium methylsulphate (21)

Analytical data:

Yellow solid, yield 75%, mpt, 163-165 °C.

Formula: C₁₁H₁₇N₂O₅S, MW 275.1, Anal. calc.%: C: 47.98; H: 6.22; N: 5.08; found, C: 47.77; H: 6.40, N: 5.02.

1H NMR spectrum in d₆-DMSO, δ (ppm): 3.38 (s, 3H, MeSO₄), 3.67 (s, 9H, N(CH₃)₃), 8.15 (d, 9.0 Hz, 2H, ArCH), 8.23 (d, 9.0 Hz, 2H, ArCH) and 10.15 (s, CHO).
13C NMR spectrum, d6-DMSO, δ (ppm): 192.05 (CHO), 152.0 (ArC(4)-N), 137.0 (ArC (1)-CHO), 130.76 (ArC(2,6)H), 121.63 (ArC(3,5)H), 56.24 (NMes), and 52.74 (MeSO4)

IR (KBr), selected bands, cm⁻¹: 3019, 1700, ν(C=O).

MS-EI, m/z: 275 [M], 164 [M - CH₂SO₄⁻].

Accurate MS-EI, 274.9899, theoretical, 275.0822.

8.3.2. (4-Cyanophenyl)trimethylammonium methylsulphate (22).

White solid 1.46 g, yield 54%, mpt, 184-186 °C.

Formula: C₁₁H₁₆N₂SO₄, MW 272.3, Anal. calc.%, C: 48.51; H: 5.92; N: 10.29; found, C: 48.23; H: 6.00; N: 10.11.

1H NMR spectrum in d6-DMSO,

δ (ppm): 3.38 (s, 3H, MeSO₄⁴⁻), 3.64 (s, 9H, (CH₃)₂N), 8.20 (m, 4H, ArC(2,3,5,6)H).

13C NMR spectrum, d6-DMSO, δ (ppm): 150.3 (ArC(4)-N), 134.3 (ArC(2,6)H), 117.3 (CN), 113.1 (ArC (1)-C≡N), 122.3 (ArC(3,5)H), 56.3 (NMes), and 52.6 (MeSO₄⁻)

IR, (KBr), selected band, cm⁻¹: 2230 ν(C=N).

MS-FAB, m/z: 273 [M⁺], 162 [M - counter ion], 253 [M - 2Me].

8.3.3. Imine made from aniline and p-dimethylaminobenzaldehyde135 (23).

N,N-dimethyl-4-[(methylimino)phenyl]- benzene.

Method. Equimolar quantities (5 mmol) of the starting material were dissolved in DCM (10 ml), a few molecular sieves were added and the mixture stirred under reflux for 6 hours. The sieves were filtered out and the reaction mixture reduced under vacuum. The remaining starting material was removed with diethyl ether and the product recrystallised from methanol and diethyl ether. No mineral acid was included contrary to the reference.

Analytical data:

Yellow crystalline solid, yield is 83%.
Formula: C₁₅H₁₆N₂, MW: 224.2 ¹H NMR spectrum in CDCl₃, δ (ppm): 3.11 (s, 6H, N(CH₃)₂), 8.33 (s, 1H, HC=N), 7.77 (d, 8.5 Hz, 2H, C-Ph) 7.18 (overlapped m, 3H, C=N-Ph) 7.37 (d, 7.7 Hz, 2H, =N-Ph) and 6.74 (d, 8.5 Hz, 2H, C-Ph).

¹³C NMR spectrum in CDCl₃, δ (ppm): 40.7 (2C of (CH₃)₂N), 163.3 (C=N), 132.1, 112.9 (4C OF C₆H₄), 130.5, 126.7, 122.3 (5C of C₆H₅), 124.9 (Cq of C₆H₅), 153.9 or 154.9 (N-Cq of C₆H₄), 153.9 or 154.9 (C-Cq of C₆H₄).

8.4. Platinum(II) bis nitrile complexes.

The three routes used were; (specific conditions are included in table 21 below)

1. A variation on the Hoffmann and Bugge method¹³⁶, used by Walton¹³⁹ and Eysel et al.,⁹¹ which is an aqueous route starting with potassium tetrachloroplatinate. Dichlorobis(acetonitrile) platinum(II) was used as a starting point for many of the complexes made in this section.

\[ [\text{PtCl}_2(\text{MeCN})_2] \]

K₂[PtCl₄] (300 mg) is dissolved in distilled water (10 ml). The solution was pipetted off from the insoluble impurities and acetonitrile (0.5 ml) added and shaken. The resulting orange solution was sealed in a flask and left at room temperature for 7 days to exchange. The product appears as yellow crystals as the solution pales to yellow and is recovered by filtration. A second crop of paler yellow crystals is precipitated after removal of the first crop. These are varying mixtures of cis and trans isomers.

\[ \text{PtCl}_2(p\text{-OH-C}_6\text{H}_5\text{CN})_2 \]

At least a 10 molar excess of 4-hydroxybenzonitrile (420 mg) was dissolved in toluene / chloroform (2 ml, 4/1). [PtCl₂(MeCN)₂] (100 mg) was added and the mixture stirred at 85 °C for 85 hours. The reaction mixture is reduced under vacuum and the
excess free ligand removed using diethyl ether (3 x 20 ml). The product is 90% trans complex with a small amount of cis complex.

2. To produce a predominantly trans product a variation on the Kharasch method of direct ligand attachment to platinum was employed, using platinum dihalide and the desired ligand.

\[ \text{trans-}[\text{PtBr}_2(\text{PhCN})_2] \].

Platinum(II) bromide (300 mg) was dissolved in hot (100 °C) benzonitrile (3 ml) and the mixture stirred at this temperature for 30 minutes. By this time the solution had turned yellow. The hot solution was filtered and allowed to cool and a yellow precipitate filtered off. A second crop was obtained by the addition of diethyl ether to the solution. The product was washed with diethyl ethyl and dried. The product is predominantly trans, if pure trans is required chromatography using DCM as eluent is carried out the trans isomer running first.

3. The Ramberg and Bugge aqueous route was used to make cis complexes. These were made for characterization purposes as cis complexes are of limited value for cycloaddition reactions.

\[ \text{cis-PtCl}_2(p-\text{OH-C}_6\text{H}_5\text{CN})_2 \].

\[ \text{K}_2[\text{PtCl}_4] \] (300 mg) is dissolved in distilled water (10 ml). The solution was pipetted off from the insoluble impurities and saturated with p-hydroxybenzonitrile. The excess free ligand is removed by filtration and the solution stoppered in a flask. It is left at room temperature for 14 days and the product appears as yellow / green crystals. These are isolated by filtration and any free ligand removed with diethyl ether.

Specific reaction conditions for all the platinum nitrile complexes made are contained in tables 21 a-c below.
<table>
<thead>
<tr>
<th>Product</th>
<th>No</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCl₂(PhCN)₂</td>
<td>24</td>
<td>2 days, 60 °C, CHCl₃. Reduce under vacuum, precipitate with diethyl ether. Chromatography on silica using DCM as eluent.</td>
<td>Mixture of cis and trans isomers</td>
</tr>
<tr>
<td>PtCl₂(p-OH-C₆H₄-CN)₂</td>
<td>25</td>
<td>4 days, 60 °C, CHCl₃. Reduce under vacuum and remove free ligand with diethyl ether.</td>
<td>Unstable products mixture of cis and trans isomers.</td>
</tr>
<tr>
<td>PtCl₂(m-OH-C₆H₄-CN)₂</td>
<td>26</td>
<td>4 days, 60 °C, CHCl₃. Same work-up as 25.</td>
<td>Mainly trans product</td>
</tr>
<tr>
<td>PtCl₂(p-OH-C₆H₄-CN)₂</td>
<td>27</td>
<td>2 days, 60 °C, CHCl₃. Same work-up as 25.</td>
<td>High yield mainly cis</td>
</tr>
<tr>
<td>PtCl₂(p-Me₃N-C₆H₄-CN)₂</td>
<td>n/a</td>
<td>10 days, 60 °C, CHCl₃/MeCN 4/1</td>
<td>No product isolated</td>
</tr>
<tr>
<td>PtCl₂(p-CO₂H-C₆H₄-CN)₂</td>
<td>n/a</td>
<td>4 days, 60 °C, THF</td>
<td>No product isolated</td>
</tr>
<tr>
<td>PtCl₂(n-MeOC₂H₄O-H-C₆H₄-CN)₂</td>
<td>28</td>
<td>10 days, 90 °C, no solvent.</td>
<td>Product unstable in solution</td>
</tr>
<tr>
<td>PtCl₂(p-MeOC₂H₄O-H-C₆H₄-CN)₂</td>
<td>29</td>
<td>10 days, 90 °C, no solvent. Chromatography on silica using DCM/EA, 5/1</td>
<td>Trans product</td>
</tr>
<tr>
<td>PtCl₂(o-MeOC₂H₄O-H-C₆H₄-CN)₂</td>
<td>n/a</td>
<td>10 days, 90 °C, no solvent.</td>
<td>No product isolated</td>
</tr>
<tr>
<td>PtCl₂(3,4-di-(MeOC₂H₄O)-H-C₆H₄-CN)₂</td>
<td>30</td>
<td>14 days 90 °C, no solvent. Same work-up as 29</td>
<td>Trans product</td>
</tr>
<tr>
<td>PtCl₂(p-Me₂N-C₆H₄-CN)₂</td>
<td>35</td>
<td>7 days, 60 °C, CHCl₃ Same work-up as 25.</td>
<td>Low yield, coordination via Me₂N</td>
</tr>
<tr>
<td>PtCl₂(m,p-di-OH-C₆H₄-CN)₂</td>
<td>36</td>
<td>10 days, 90 °C, same work-up as 25.</td>
<td>Poor yield</td>
</tr>
<tr>
<td>PtCl₂(p-NO₂-C₆H₄-CN)₂</td>
<td>37</td>
<td>7 days, 60 °C, CHCl₃, same work-up as 25.</td>
<td>Low yield, used for characterisation only</td>
</tr>
</tbody>
</table>

* optimum conditions, 45 hours in 4/1 toluene/chloroform at 85 °C

Table 21 (a). Method 1.
<table>
<thead>
<tr>
<th>Product</th>
<th>No</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCl₂(PhCN)₂</td>
<td>24</td>
<td>1 hr, 110 °C, precipitated with pet. ether and filter. Chromatography on silica, eluent DCM.</td>
<td>mainly trans product</td>
</tr>
<tr>
<td>PtCl₂(m-OH-C₆H₄-CN)₂</td>
<td>26</td>
<td>0.5 hr, 85 °C, remove free ligand with diethyl ether.</td>
<td>mainly trans product</td>
</tr>
<tr>
<td>PtCl₂(p-OH-C₆H₄-CN)₂</td>
<td>27</td>
<td>0.5 hr, 120 °C, remove free ligand with diethyl ether.</td>
<td>high yield mainly trans but contaminated with a suspected polymeric impurity. Impossible to purify.</td>
</tr>
<tr>
<td>PtCl₂(p-MeO-C₂H₄-O-H-C₆H₄-CN)₂</td>
<td>29</td>
<td>2 hrs 100 °C, chromatography on silica, DCM/EA, 5/1 as eluent.</td>
<td>trans product isolated</td>
</tr>
<tr>
<td>PtBr₂(PhCN)₂</td>
<td>31</td>
<td>1 hr, 110 °C, same work-up as 24</td>
<td>high yield trans product</td>
</tr>
<tr>
<td>PtBr₂(m-OH-C₆H₄-CN)₂</td>
<td>32</td>
<td>0.5 hr, 85 °C, remove free ligand with diethyl ether.</td>
<td>high yield trans product</td>
</tr>
<tr>
<td>PtBr₂(p-OH-C₆H₄-CN)₂</td>
<td>33</td>
<td>0.5 hr, 120 °C, remove free ligand with diethyl ether.</td>
<td>high yield trans product, contaminated with a polymeric impurity.</td>
</tr>
<tr>
<td>PtI₂(PhCN)₂</td>
<td>34</td>
<td>1 hr, 110 °C, same work-up as 24</td>
<td>low yield unstable trans product</td>
</tr>
<tr>
<td>PtCl₂(p-NO₂-C₆H₄-CN)₂</td>
<td>37</td>
<td>7 days toluene 90 °C, remove free ligand with diethyl ether</td>
<td>low yield, used for characterisation only</td>
</tr>
</tbody>
</table>

Table 21(b) Method 2.
<table>
<thead>
<tr>
<th>Product</th>
<th>No</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCl₂(o-OH-C₆H₄-CN)₂</td>
<td>25</td>
<td>10 days, RT, water filter out crystals and remove free ligand with diethyl ether.</td>
<td>poor yield cis isomer</td>
</tr>
<tr>
<td>PtCl₂(m-OH-C₆H₄-CN)₂</td>
<td>26</td>
<td>14 days, RT, water, same work-up as 25</td>
<td>mixture of cis and trans isomers.</td>
</tr>
<tr>
<td>PtCl₂(p-OH-C₆H₄-CN)₂</td>
<td>27</td>
<td>10 days, RT, water, same work-up as 25</td>
<td>low yield cis product</td>
</tr>
<tr>
<td>PtCl₂(p-CO₂H-C₆H₄-CN)₂</td>
<td>n/a</td>
<td>10 days RT, water</td>
<td>no product isolated, for characterisation only</td>
</tr>
<tr>
<td>PtBr₂(PhCN)₂</td>
<td>31*</td>
<td>10 days, RT, water, solvent extraction with DCM.</td>
<td>low yield trans product</td>
</tr>
<tr>
<td>PtBr₂(m-OH-C₆H₄-CN)₂</td>
<td>32*</td>
<td>14 days, RT, water.</td>
<td>no product isolated</td>
</tr>
<tr>
<td>PtBr₂(p-OH-C₆H₄-CN)₂</td>
<td>33*</td>
<td>10 days, RT, water.</td>
<td>low yield trans product</td>
</tr>
<tr>
<td>PtI₂(PhCN)₂</td>
<td>34*</td>
<td>10 days, RT, water.</td>
<td>no product isolated.</td>
</tr>
<tr>
<td>PtCl₂(m-p-di-OH-C₆H₄-CN)₂</td>
<td>36</td>
<td>10 days, RT, water.</td>
<td>no product isolated</td>
</tr>
<tr>
<td>PtCl₂(p-NO₂-C₆H₄-CN)₂</td>
<td>37</td>
<td>10 days, RT, water, no work-up.</td>
<td>low yield, used for characterisation only.</td>
</tr>
</tbody>
</table>

* a seven fold molar excess of KI or KBr was also added as appropriate.

Table 21(c). Method 3.

8.4.1. [PtCl₂(PhCN)₂] (24).

Formula: C₁₄H₁₀N₂Cl₂Pt, MW 472.23

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.57 (t, 7.9 Hz, 4H), 7.74 (t, 7.7 Hz, 2H) and 7.79 (d, 7.4 Hz, 4H)(Ph).

¹³C NMR¹³⁸ in CDCl₃ δ (ppm): trans; 109.0 (ArC(1), C₂), 133.7 (ArC(2,6)H), 129.5 (ArC(3,5)H), 135.4 (ArC(4)H), 116.8 (C=N).

cis; 109.1 (ArC(1), C₂), 133.7 (ArC(2,6)H), 129.6 (ArC(3,5)H), 135.2 (ArC(4)H), 115.3 (C=N).

IR spectrum (selected bands), cm⁻¹: 2285 (cis), 2289 (trans) ν(C=N).

¹⁹⁵Pt NMR¹⁴⁰ spectrum in δ₆-acetone δ (ppm): -2350.0 (trans), 2284.0 (cis).
8.4.2. Formula: \([\text{PtCl}_2(\sigma\text{-HO-C}_6\text{H}_4\text{-CN})_2]\) (25).

Formula: \(\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{Cl}_2\text{Pt}\), MW 504.23, yellow crystals, yield 42\% (Unstable)

\(^1\)H NMR spectrum in \(d_6\)-acetone \(\delta\) (ppm): 7.10 (m, 2H, ArCH), 7.17 (m, 2H, ArCH), 7.63 (m, 2H, ArCH), 7.72 (m, 2H, ArCH).

\(^1^3\)C NMR spectrum in \(d_6\)-acetone \(\delta\) (ppm): 162.3 (ArC=O), 137.4, 126.1, 117.2 116.3 (ArCH), 115.4 (C=N), not seen, possibly 96.5 (ArC(1)-C=N).

IR, (KBr), selected band, cm\(^{-1}\): 2280 (cis), 2288 (trans), \(\nu\)(C=CN).

\(^{195}\)Pt NMR spectrum in \(d_6\)-acetone \(\delta\) (ppm): -2332.8 (trans) (1610 Hz).

8.4.3. \([\text{PtCl}_2(m\text{-HO-C}_6\text{H}_4\text{-CN})_2]\) (26).

Formula: \(\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{Cl}_2\text{Pt}\), MW 504.23, yellow crystals, yield 81\%.

Anal. calc.%: C: 33.36; H: 1.98; N: 5.56; found: C: 35.25; H: 1.90, N: 5.55.

\(^1\)H NMR spectrum in \(d_6\)-acetone (trans) \(\delta\) (ppm): 7.35 (t, 8.0 Hz, 2H, ArC(5)H), 7.42 (s, 2H, ArC(2)H), 7.52 (overlapped m, 4H, ArC(4,6)H), 9.46 (s, 2H, OH).

(cis) \(\delta\): 7.35 (t, 8.0 Hz, 2H, ArC(5)H), 7.40 (s, 2H, ArC(2)H), 7.55 (overlapped m, 4H, ArC(4,6)H), 9.51 (s, 2H, OH).

\(^{13}\)C NMR spectrum (mixture of isomers, mainly trans in \(d_6\)-acetone \(\delta\) (ppm):

158.0 (ArC=O), 132.1, 126.0, 124.1, 120.3 (ArCH), 118.5 (C=N), 110.2 (ArC(1)-C=N).

MS-FAB, \(m/z\): 504 [M\(^+\)], 527 [M + Na], 468.4 [M - Cl], 433 [M - 2Cl], 485 [M - 1 ligand], 470.4 [M - 2OH], 353.5 [M - Cl and 1 ligand].

IR, (KBr), selected band, cm\(^{-1}\): 2292 (cis), 2316 (trans) \(\nu\)(C=CN).

\(^{195}\)Pt NMR spectrum in \(d_6\)-acetone \(\delta\) (ppm): -2369.0(1075 Hz)(trans), 2275.1(1200 Hz)(cis)

8.4.4. \([\text{PtCl}_2(p\text{-HO-C}_6\text{H}_4\text{-CN})_2]\) (27).

Formula: \(\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{Cl}_2\text{Pt}\), MW 504.23, yellow crystals, yield 88\%.

Anal. calc.%: C: 33.36; H: 1.98; N: 5.56; found: C: 33.75; H: 1.97, N: 5.32.
\( ^1 \)H NMR spectrum in \( d_6 \)-acetone (\textit{trans}), \( \delta \) (ppm): 7.13 (d, 8.7 Hz, 4H, ArC(3,5)H), 7.87 (d, 8.7 Hz, 4H, ArC(2,6)H), 9.99 (s, 2H, OH).

(\textit{cis}) \( \delta \): 7.00 (d, 8.7 Hz, 4H, ArC(3,5)H), 7.62 (d, 8.7 Hz, 4H, ArC(2,6)H), 9.99 (s, 2H, OH).

\( ^{13} \)C NMR spectrum in \( d_6 \)-acetone (\textit{trans}), \( \delta \) (ppm): 162.2 (ArC–O), 120.0 (C=N), 135.0, 117.3 (ArC(2,6 or 3,5)H), 101.6 (ArC (1)-C=N).

\( ^{13} \)CNMR spectrum in \( d_6 \)-acetone (\textit{cis}), \( \delta \) (ppm): 164.4 (ArC–O), 117.0 (C=N), 137.1, 117.7 (ArC(2,6 or 3,5)H), 99.5 (ArC (1)-C=N).

MS-FAB, m/z: 504 [M\(^+\)], 527 [M + Na], 468.5 [M – Cl], 433 [M - 2Cl], 485 [M - 1 ligand], 470.4 [M - 2OH], 353.5 [M - Cl and 1 ligand].

IR, (KBr), selected band, cm\(^{-1}\): 2287 v(C=N).

\( ^{195} \)Pt NMR spectrum in \( d_6 \)-acetone \( \delta \) (ppm): \textit{cis} -2244.3, \textit{trans} -2339.4 (1075 Hz).

8.4.5. \textit{trans}-[PtCl\(_2\)(\textit{m}-MeOC\(_2\)H\(_4\)O-C\(_6\)H\(_4\)-CN)\(_2\)] (28)

Formula: C\(_{20}\)Cl\(_2\)H\(_{22}\)N\(_2\)O\(_4\)Pt, MW 620.4, yellow solid, 48 mg, yield 55%.

\( ^1 \)H NMR spectrum in CDCl\(_3\) \( \delta \) (ppm): 7.31 (overlapped m, 8H, C\(_6\)H\(_4\)), 4.15 (m, 4H, OCH\(_2\)), 3.78 (m, 4H, CH\(_2\)O), 3.45 (s, 6H, MeO).

\( ^{13} \)C NMR spectrum in CDCl\(_3\) \( \delta \) (ppm): 159.0 (ArC(3)–O), 119.9(C=N), 130.9 (ArCH), 126.4 (ArCH), 123.1 (ArCH), 118.3 (ArCH), not seen (ArC (1)-C=N), 70.6 (CH\(_2\)-O), 68.1(O-CH\(_2\)), 59.3 (OMe).

MS-FAB, m/z: 621[M\(^+\)], 583 [M-HCl],

IR, (KBr), selected band, cm\(^{-1}\): 2292 v(C=N).

\( ^{195} \)Pt NMR spectrum in CDCl\(_3\) \( \delta \) (ppm): -2345.8 (535).

8.4.6. \textit{trans}-[PtCl\(_2\)(\textit{p}-MeOC\(_2\)H\(_4\)O-C\(_6\)H\(_4\)-CN)\(_2\)] (29).

Formula: C\(_{20}\)Cl\(_2\)H\(_{22}\)N\(_2\)O\(_4\)Pt, MW 620.4, yellow solid, 55 mg, yield 62%.

Anal. calc for C\(_{20}\)H\(_{22}\)Cl\(_2\)N\(_2\)O\(_4\)Pt\(\%\), C, 38.72; H, 3.57; N, 4.52. Found: C, 38.27; H, 3.54; N, 4.26.
**8.4.7. trans-[PtCl₂(m,p-di(MeOCH₂H₄O)-C₆H₄-CN)₂] (30).**

Formula C₂₆Cl₂H₃₄N₂O₈Pt, MW 768.4, yellow solid, yield 48%
Rf 0.18, single spot in TLC, 4/1 DCM/ethyl acetate as eluent.

**H NMR spectrum in CDCl₃ δ (ppm):** 7.4 (m, 2H, C₆H₂), 7.19 (m, 2H, C₆H₂), 6.88 (m, 2H, C₆H₂), 4.15 (m, 4H, ArC₆(OCH₂)), 4.23 (m, 4H, ArC₆(3)OCH₂), 3.78 (m, 8H, CH₂ of MeOCH₂), 3.44 (s, 12H, MeO).

**13C NMR spectrum in CDCl₃ δ (ppm):** 155.1, 149.1 (ArCO), 129.2 (ArCH), 117.3 (C=N), 117.2 (ArCH), 113.2 (ArCH), 100.1 (ArC (1)-C=N), 70.0 (CH₂-O), 72.1 (O-CH₂), 59.3, 59.4 (OMe).

**MS-FAB, m/z: 767.0 [M⁺], 791.1 [M+Na], 763.0 [M-Me], 731 [M-HCl].**

**IR (KBr), selected band, cm⁻¹:** 2284 ν(C=N).

**195Pt NMR spectrum in CDCl₃ δ (ppm):** -2315.5 (1075 Hz).

**8.4.8. trans-[PtBr₂(PhCN)₂] (31).**

**Analytical data:** Orange / yellow solid, formula: C₁₄H₁₀N₂Br₂Pt, yield is 86%. MW 561.13.

**Anal, calcd for C₁₄H₁₀Br₂N₂Pt:%, C, 29.97; H, 1.80; N, 4.99. Found: C, 29.83; H, 1.68; N, 4.81.**

**H NMR (500 MHz, CDCl₃) δ(ppm):** 7.57 (t, 7.9 Hz, 4H), 7.74 (t, 7.7 Hz, 2H) and 7.79 (d, 7.4 Hz, 4H)(Ph). **13C NMR (125.7 MHz, CDCl₃) δ(ppm):** 119.1 (C=N), 109.4 (C₆), 129.7, 133.9 and 135.5 (10C, Ph).

Accurate MS-FAB⁺, m/z: 558.56 for C₁₄H₁₀⁷⁹Br₂N₂Pt, theoretical 558.8853.

IR spectrum (selected bands), cm⁻¹: 2288 ν(C=N).

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ(ppm) -2860 (750 Hz).

8.4.9. trans-[PtBr₂(m-HO-C₆H₄-CN)]₂ (32).

MW 593.128, yellow crystals, yield 73%, formula: C₁₄H₁₀O₂Br₂N₂Pt,
Anal. calcd for C₁₄H₁₀O₂Br₂N₂Pt: %, C, 28.34; H, 1.68; N, 4.72. Found: C, 28.33; H, 1.65; N, 4.58.

¹H NMR spectrum in d₆-acetone δ (ppm): 7.37 (m, 2H, ArCH), 7.39 (m, 2H, ArCH), 7.46 (m, 2H, ArCH), 7.56 (s, 2H, ArCH), 9.48 (s, 2H, OH).

¹³C NMR (75 MHz, d₆-acetone) δ/ppm 119.2 (C=N), 110.2 (Cq), 120.3, 124.2, 125.9 and 132.1 (CH)(ArCH), 158.8 (ArC=O).

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ(ppm) -2860 (750 Hz). ¹⁹⁵Pt NMR spectrum in d₆-acetone δ: -2872.7, (535 Hz).

IR, (KBr), selected band, cm⁻¹: 2292 (cis) 2316 (trans) ν(C=N).

8.4.10. trans-[PtBr₂(p-HO-C₆H₄-CN)]₂ (33).

MW 593.128, yellow crystals, yield 80%, formula: C₁₄H₁₀O₂Br₂N₂Pt,

¹H NMR spectrum in d₆-acetone δ (ppm): 7.13 (d, 8.5Hz, 4H, ArC(3,5)H), 7.84 (d, 8.5 Hz, 4H, ArC(2.6)H), not seen (s, 2H, OH).

¹³C NMR (125.7 MHz, d₆-acetone) δ/ppm 99.3 (Cq), 117.2 (C=N), 117.8 and 137.0 (CH)(ArCH), 164.6 (C ArC=O).

IR, (KBr), selected band, cm⁻¹: 2287 ν(C=N).

¹⁹⁵Pt NMR spectrum in d₆-acetone δ: -2832.9, (1075 Hz).
8.4.11. trans-[Pt₂(PhCN)₂] (34).

Formula: C₁₄H₁₀I₂N₂Pt, MW 655.13, orange yellow solid. (unstable), yield is 56%.

Anal. calc'd for C₁₄H₁₀I₂N₂Pt: %, C, 25.67; H, 1.54; N, 4.28. Found: C, 25.17; H, 1.36; N, 4.08.

¹H NMR (300 MHz, CDCl₃) δ(ppm) 7.57 (t, 7.95 Hz, 4H), 7.73 (t, 7.8 Hz, 2H) and 7.78 (d, 7.2 Hz, 4H)(Ph). ¹³C NMR (75 MHz, CDCl₃) δ(ppm) 109.4 (Cq), 122.8 (C=N), 129.5, 133.5 and 135.2 (CH)(Ph).

MS-FAB⁺, m/z: 655.6 [M]+, 526.8 [M-2HI]+, 551.9 [M-PhCN]+.

IR spectrum (selected bands), cm⁻¹: 2287 ν(C≡N).

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ(ppm) -3934.7 (750 Hz).

8.4.12. [PtCl₂(4-Me₂N)-C₆H₄-CN)₂] (35)

Formula: PtCl₂N₄C₁₆H₂₀, MW 559.4, pale yellow powder, 87% (impure, product not isolated).

¹H NMR (300 MHz, d₆-acetone) δ(ppm); 2.95 (s, 6H, Me), 7.96 (m, 2,6 or 3,5, 4H), 7.61 (m, 2,6 or 3,5, 4H)(ArCH).

MS-FAB⁺, m/z: 558.9 [M]+, 485.0[M-2HCl]⁺.

IR spectrum (selected bands), cm⁻¹: 2244 ν(C≡N).

¹⁹⁵Pt NMR (107.3 MHz, d₆-acetone) δ(ppm) -2124.7 (400 Hz) (diamine), -2135.3 (possibly Pt(II) monoamine/MeCN).

8.4.13. [PtCl₂(4-CO₂H-C₆H₄-CN)₂] (possibly hydrolysed to the amide, product not isolated).

¹H NMR (300 MHz, d₆-acetone) δ(ppm) 7.91 (m, 4H ArCH), 7.82 (m, 4H ArCH).

IR spectrum (selected bands), cm⁻¹: 2236 (C≡N of free ligand), 1595 ν(NH₂C=O).

¹⁹⁵Pt NMR (107.3 MHz, d₆-acetone) δ(ppm) -2034.2 (535 Hz)
8.4.14. Formula: \([\text{PtCl}_2(m,p\text{-di-HO-C}_6\text{H}_4\text{-CN})_2]\) (36).

Formula: \(\text{PtCl}_2\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4\), MW 536.2, yellow crystals, yield <20%.

\(^1\text{H}\) NMR spectrum in \(d_6\)-acetone (trans), \(\delta (\text{ppm})\): 7.10 (s, 2H, ArC(2)H), 7.03 (d, 10.0 Hz, 2H, ArC(2 or 3)H), 7.38 (d, 10.0 Hz, 2H, ArC(2 or 3)H).

\(^{13}\text{C}\) NMR spectrum in \(d_6\)-acetone (trans), \(\delta (\text{ppm})\): 147.1, 155.1 (2 ArC–O), 128.6, 120.1, 117.3 (3ArCH), 98.6 (ArC(1)-C=N), 119.0 (C=N).

MS-FAB, \(m/z\): 536.8 [M\(^+\)], 559.9 [M + Na], 499.8 [M – HCl], 463.8 [M – 2HCl].

IR, (KBr), selected band, cm\(^{-1}\): 2341 Br. v(C=N).

\(^{195}\text{Pt}\) NMR spectrum in \(d_6\)-acetone \(\delta (\text{ppm})\): trans -2303.3 (750 Hz), much smaller signal at -2270 (cis), also at -2214 ppm.

8.4.15. \([\text{PtCl}_2(4\text{-NO}_2\text{-C}_6\text{H}_4\text{-CN})_2]\) (37). Product not isolated.

\(^1\text{H}\) NMR (300 MHz, \(d_6\)-acetone) \(\delta (\text{ppm})\) (thermal method) 8.55 (d, 10.0 Hz, 4H), 8.27 (d, 10.0 Hz, 4H)(ArCH). (Aqueous method) 8.41 (d, 9.0 Hz, 4H), 8.02 (d, 9.0 Hz, 4H)(ArCH).

Possible hydrolysis product; 7.70 (m, 2H), 7.02 (d, 9.0 Hz, 2H)(ArCH), 9.79 (br. s, NH\(_2\)).

IR spectrum (selected bands), cm\(^{-1}\): 2284 (thermal), 2288 (aqueous) v(C=N).

\(^{195}\text{Pt}\) NMR (107.3 MHz, \(d_6\)-acetone) \(\delta (\text{ppm})\) (aqueous), -2300.7 (1075 Hz), (thermal) -2269.6 (270 Hz), -2240 ppm, possibly a hydrolysis product (amide).

8.5 trans-platinum(II) mono oxadiazoline complexes with hydroxy-substituents.

Below is a typical procedure for the manufacture of a mono oxadiazoline platinum complex. Specific conditions are included in table 22 below.

Reaction of \([\text{PtCl}_2(\text{C}_6\text{H}_5\text{CN})_2]\) with \(p\text{-HO-C}_6\text{H}_4\text{CH}=\text{NOMe}\)

\(\text{trans-}[\text{PtCl}_2(\text{PhCN})(\text{N}=\text{C(Ph)}-\text{O}-\text{N(Me)}-\text{CH}(p\text{-HO-C}_6\text{H}_4))](40)\).

Platinum bis-benzonitrile (47.2 mg, 0.1 mmol) and nitrone (16.1 mg, 0.1 mmol) were
placed in a flask with 1 ml of chloroform. This was placed in a sand bath at 25 °C under nitrogen and stirred vigorously. The progress of the reaction is monitored by proton NMR and stopped at the first appearance of bis oxadiazoline signals at 8.80 ppm (approximately 3 days). The product is purified by chromatography using firstly DCM to remove the nitrile complex, then DCM/ethyl acetate 10/1 as eluent to recover the platinum oxadiazoline complex. Great care should be taken if working at room temperature over 35 °C that the bis compound is not formed.

<table>
<thead>
<tr>
<th>Prod. No.</th>
<th>Reaction Conditions</th>
<th>Work-Up Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Equimolar ratio, acetone, 48hrs, 30°C</td>
<td>Chromatography / DCM/EA, 10/1 as eluent</td>
</tr>
<tr>
<td>39</td>
<td>Equimolar ratio, chloroform, 72hrs, 30°C</td>
<td>Chromatography/DCM/EA, 10/1, as eluent</td>
</tr>
<tr>
<td>40</td>
<td>Equimolar ratio, chloroform, 72hrs, 25°C</td>
<td>Chromatography / DCM/EA, 10/1, as eluent</td>
</tr>
<tr>
<td>41</td>
<td>Equimolar ratio, chloroform, 7 days, 25°C</td>
<td>Chromatography / DCM/EA, 4/1 as eluent</td>
</tr>
<tr>
<td>42</td>
<td>Equimolar ratio, chloroform, 48hrs, 30°C</td>
<td>Chromatography / DCM/EA, 4/1 as eluent</td>
</tr>
<tr>
<td>43</td>
<td>Equimolar ratio, chloroform, 10days, 30°C</td>
<td>Chromatography / DCM/EA, 4/1 as eluent</td>
</tr>
<tr>
<td>51</td>
<td>Equimolar ratio, chloroform, 25°C 48 hrs</td>
<td>Chromatography / DCM, as eluent</td>
</tr>
<tr>
<td>54</td>
<td>Equimolar ratio, chloroform, 25°C 48 hrs</td>
<td>Chromatography / DCM as eluent</td>
</tr>
</tbody>
</table>

Table 22. The reaction conditions and work-up procedures for the syntheses of mono oxadiazoline platinum complexes, (chromatography on silica).

8.5.1. Reaction of trans-[PtCl₂(m-HO-C₆H₄-CN)]₂ with PhCH=NOMe
trans-[PtCl₂(m-HO-C₆H₄)\{N=C(m-HO-C₆H₄)-O-N(Me)-CH(Ph)}](38)

Analytical data:
Yellow solid, yield is 60%.
Formula: C₂₂H₁₉Cl₂N₃O₅Pt, MW 639.39. Anal. calc.%, C, 41.33; H, 3.00; N, 6.57.
Found: C, 41.54; H, 2.88; N, 6.32.

¹H NMR spectrum in d₆-acetone, δ (ppm): 3.09 (sharp s, 3H, NMe), 6.08 (s, 1H of NCH), 7.68 (m, 2H of Ph.), 7.47 (m, 3H of Ph.), 7.25 (overlapped m, ArC(4)H of C₆H₄-CN), 7.27 (overlapped m, ArC(2,6)H of C₆H₄-CN), 7.51 (overlapped m, ArC(3,5)H of C₆H₄-CN), 7.38 (d, 7.7 Hz, ArC(4)H, C₆H₄-CN), 7.44 (overlapped m, ArC(5)H, C₆H₄-CN), 7.51 (overlapped m, ArC(5)H, C₆H₄-CN), 8.36 (d, 7.7 Hz, ArC(6)H, C₆H₄-CN), 8.47 (s, ArC(2)H, C₆H₄-CN), 9.19, 9.37 ( s, 2H, OH).

¹³C NMR spectrum in d₆-acetone, δ (ppm): 46.0 (NMe), 94.9 (NCHN), 117.3 (C=N), 117.4 (ArC(2) of C₆H₄-CN), 123.0 (ArC(6) of C₆H₄-CN), 130.0 (meta ArC(5) of
C₆H₄C=N, 125.2 (ArC(4) of C₆H₄C=N), 128.7, 128.8 (ArC(2,6 and 3,5) of Ph.), 130.1 (ArC(4) of Ph), 109.5 (ArC(1)C≡N), 130.5 (ArC(5) of C₆H₄C≡N), 125.2 (either 6 or 4 ArC of C₆H₄C≡N), 119.5 (ArC(1) of C₆H₄C≡N), 122.5 (either 6 or 4 ArC of C₆H₄C≡N) 156.0, 156.1 (2 ArC(3)–O), 122.5 (Cq, N=C-C₆H₄), 164.5 (C=N), 135.2 (Cq, Ph).

³¹Pt NMR spectrum in d₆-acetone, δ (ppm): -2237.1 (750 Hz).
IR, (KBr), selected band, cm⁻¹: 2283 ν(C≡N), 1596 ν(C≡N).
MS-FAB, m/z: 639.0 [M]+, 662.3 [M+Na]+, 603.0 [M-HCl], 566.0 [M-2HCl], 537.0 [M-PhCN].

8.5.2. Reaction of *trans*-[PtCl₂(C₆H₅CN)₂] with m-HO-C₆H₄CH=NOMe

*trans*-[PtCl₂(PhCN)(N=C(Ph)-O-N(Me)-CH(m-HO-C₆H₄))] (39).

Yellow crystalline solid, yield is 74%.

Formula: C₂₂H₁₉Cl₂N₃O₂Pt, MW 623.389. Anal. calc.%, C, 42.39; H, 3.07 ; N, 6.44 .

Found: C, 42.45; H, 2.85; N, 6.71.

¹H NMR spectrum in CDCl₃, δ (ppm): 3.09 (sharp s, 3H, NMe), 5.93 (s, 1H of NCHN), 6.09 (s, H, OH), 8.98 (d, 7.5 Hz, ArC(2,6)H of PhC≡N), 7.59 (overlapped m, ArC(3,5)H of PhC≡N), 7.68 (overlapped m, ArC(4)H of PhC≡N), 7.26 (overlapped m, 3H ArC(2,4,5)H of C₆H₄), 6.90 (d, 7.6 Hz, ArC(6)H of C₆H₄), 7.47 (t, 7.5 Hz, ArC(3,5)H of PhCN), 7.63 (m, ArC(4)H of PhCN), 7.67 (m, ArC(2,6)H of PhCN).

¹³C NMR spectrum in CDCl₃, δ (ppm): 46.3 (NMe), 94.7 (N-C(C₆H₄-O)HN), 117.1 (C≡N), 130.8 (ArC(2,6) of PhC≡N), 129.2 (ArC(3,5) of PhC≡N), 128.8 (ArC(4) of PhC≡N), 116.0 (2 or 4), 117.3 (4 or 2), 120.9 (6), 130.0 (5) (4 ArC of m-OH-C₆H₄), 134.8 (ArC(2,6) of PhCN), 134.2 (ArC(3,5) of PhCN), 133.9 (ArC(4) of PhCN), 109.5 (ArC(1)C≡N), 156.5 (ArC(3)–O), 164.9 C≡N(of oxa), 122.1 (Cq ArC(1) of N=C-Ph), 136.8 (Cq ArC(1), C₆H₄ of oxa).

³¹Pt NMR spectrum in d₆-acetone, δ (ppm): -2225.6 (775 Hz).
IR, (KBr), selected band, cm⁻¹: 2289 ν(C≡N), 1597 ν(C≡N).
MS-FAB, m/z: 623.8 [M]+, 646 [M+Na]+, 586.8 [M-HCl], 550.9 [M-2HCl], 520.9 [M-PhCN].
8.5.3. Reaction of trans-[PtCl₂(C₆H₅CN)₂] with p-HO-C₆H₄CH=NMe

trans-[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(p-HO-C₆H₄)}](40).

Yellow crystalline solid, yield is 71%.

Formula: C_{22}H_{19}Cl₂N₂O₂Pt, MW 623.389. Anal. calc.%, C, 42.39; H, 3.07; N, 6.44.

Found: C, 42.10; H, 2.95; N, 6.42.

^{1}H NMR spectrum in d₆-acetone, δ (ppm): 3.02 (sharp s, 3H, NMe), 5.89 (s, 1H of NCH), 8.57 (s, H, OH), 8.98 (d, 7.2 Hz, ArC(2,6)H of PhC=N), 7.69 (overlapped m, ArC(3,5)H of PhC=N), 7.85 (t, 7.0 Hz, ArC(4)H of PhC=N), 7.53 (d, 8.5 Hz, ArC(2,6)H of p-OH-C₆H₄), 6.90 (d, 8.5 Hz, ArC(3,5)H of p-OH-C₆H₄), 7.69 (overlapped multiplet, ArC(3,5)H of PhCN), 7.81 (m, ArC(4)H of PhCN), 7.92 (d, 7.2 Hz, ArC(2,6)H of PhCN).

^{13}C NMR spectrum in d₆-acetone, δ (ppm): 46.0 (NMe), 94.8 (NCHN), 116.0 (C=N), 130.6, 130.7 (4 ArC 2,6 and 3,5 C of PhC=N), 128.6 (ArC(4) of PhC=N), 115.7 (3,5), 129.3 (2,6), (4 ArC of p-OH-C₆H₄), 134.7, 134.1, 133.6, (5 C of PhCN), 109.7 (ArC(1)C=N), 157.5 (ArC(4)-O), 163.1 (C=N of oxa), 122.3 (C_q ArC(1) of N=C-Ph), 132.2 (C_q ArC(1) of C₆H₄ of oxa).

^{195}Pt NMR spectrum in d₆-acetone, δ (ppm): -2220.1 (1075 Hz).

IR, (KBr), selected band, cm⁻¹: 2288 ν(C=N), 1596 ν(C=N).

MS-FAB, m/z: 623.9 [M]⁺, 645.9 [M+Na]⁺, 587.0 [M-HCl], 551 [M-2 HCl], 520.9 [M-PhCN], 418 [M-2 PhCN].

8.6 Platinum(II) mono oxadiazoline complexes with glycol ether substituents.

Specific reaction conditions and work-up procedures are contained in table 23.

8.6.1. Reaction of trans-[PtCl₂(p-MeOCH₂CH₃CN)₂] with PhCH=NMe

trans-[PtCl₂(p-MeOCH₂CH₃CN){N=C(p-MeOCH₂CH₃CN)-O-N(Me)-CH(Ph)}](41).

Analytical data:

Formula: C_{28}H_{31}Cl₂N₃O₂Pt, pale yellow solid. MW 755.546, yield is 67%.
Rf 0.24, single spot, 3/1 DCM/ethyl acetate. Anal calc.%, C, 44.50; H, 4.10 ; N, 5.56 .
Found: C,42.96; H, 3.87; N, 5.44.

$^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 3.05 (s, 3H, NMe), 3.77 (m, 4H, CH$_2$ of O-CH$_2$-OCH$_3$), 4.2 (m, 4H, CH$_2$ of C$_6$H$_5$-O-CH$_2$), 3.46 (m, 6H, MeO), 5.94 (s, 1H of NCH), 6.98 (d, 8.5 Hz, ArC(3,5)H, C$_6$H$_4$-O of nitrile ligand), 7.63 (d, 5.8 Hz, ArC(2,6)H, C$_6$H$_4$-O of nitrile ligand), 7.45 (m, 3 ArCH, Ph of oxadiazoline ligand)
7.70 (d, 8.5 Hz, 2ArC(2,6)H of N=C-C$_6$H$_4$-O. of oxadiazoline ligand), 9.04 (d, 8.5 Hz, 2ArC(2,6)H of N=C-C$_6$H$_4$-O, of oxadiazoline ligand).

$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 163.7, 163.9 (2C, ArC(4)-O), 133.1 (ArC(2,6) C$_6$H$_4$-O of oxadiazoline ligand ), 128.7, 128.6, 129.9, (5C, ArCH, Ph of oxadiazoline ligand), 114.6 (ArC(3,5), ArC of C$_6$H$_4$-O of oxadiazoline ligand), 115.5(3,5), 135.5(2,6) (4ArC of nitrile ligand), 70.8 (CH$_2$-O), 67.9 (O-CH$_2$), 59.5 (OMe), 46.8 (NMe), 94.7 (NCHN of heterocycle), 163.2 (C=N of heterocycle), 134.2 (C$_q$, Ph), possibly 128.9 (C$_q$, ArC(1), O-C$_6$H$_4$-C=N),101.3 (C$_q$, C-C=N), 117.3 (C=N).

$^{195}$Pt NMR spectrum in CDCl$_3$, $\delta$ (ppm): -2216 (790 Hz).
IR, (KBr), selected band, cm$^{-1}$: 2281 v(C=N), 1603 v(C=N).
MS-FAB, m/z: 756.2 [M$^+$], 778.5 [M+Na], 718.9 [M-HCl], 682.9 [M-2HCl], 652.9 [M-PhCN], 549.0 [M-2PhCN].

8.6.2. Reaction of trans-[PtCl$_2$(C$_6$H$_4$CN)$_2$] with p-MeO-C$_6$H$_4$O-C$_6$H$_4$CH=NOMe
trans-[PtCl$_2$(PhCN){N=C(Ph)-O-N(Me)-C(Ph)=C(Ph)}(p-MeO-C$_6$H$_4$O-C$_6$H$_4$)](42).

Analytical data:
Formula: C$_{25}$H$_{33}$Cl$_2$N$_3$O$_2$Pt, MW 681.488. Yellow crystalline solid, yield 71%. Anal.
calc.%, C, 44.05; H, 3.70 ; N, 6.16 . Found: C, 43.91; H, 3.55; N, 6.10.

$^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 3.04 (s, 3H, NMe), 3.76 (m, 2H, (CH$_2$)$_2$), 4.13 (m, 2H, (CH$_2$)$_2$), 3.46 (m, 3H, MeO), 5.93 (s, 1H of NCH), 7.00 (d, 7.5 Hz, ArC(3,5)H of C$_6$H$_4$-O-), 7.72 (overlapped multiplet, ArC(2,6)H of C$_6$H$_4$-O-), 7.49 (t, 7.2 Hz, ArC(3,5)H of PhCN), 7.67 (overlapped m, 3C, ArC(2,4,6)H of PhCN), 7.56 and 7.59(overlapped m, 3C, ArC(3,4,5)H of PhC=N), 8.99 (d, 8.0 Hz, ArC(2,6)H, PhC=N). $^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 46.0 (NMe), 59.4 (OMe), 67.2 (O-
Reaction of cis-[PtCl₂(C₂H₅CN)₂] with p-MeO-C₆H₄O-C₆H₄CH=NOMe
cis-[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(p-MeO-C₆H₄O-C₆H₄)}](43). 
(Complex is unstable, so only a partial characterisation was obtained)
8.6.3 Reaction of \( \text{trans-}[\text{PtCl}_2(3,4-\text{di(MeOC}_2\text{H}_4\text{O})\text{C}_6\text{H}_4\text{CN})_2] \) with PhCH=NOMe
\( \text{trans-}[\text{PtCl}_2(3,4-\text{di(MeOC}_2\text{H}_4\text{O})\text{C}_6\text{H}_4\text{CN})\{\text{N}=\text{C}(3,4-\text{di(MeOC}_2\text{H}_4\text{O})\text{C}_6\text{H}_4)\text{-O-N(Me)}-\text{CH(Ph)}\}] \) (44).

Analytical data:
Formula: \( \text{C}_{34}\text{H}_{43}\text{Cl}_2\text{N}_3\text{O}_9\text{Pt} \), pale yellow solid. MW 903.70, yield is 59%. Anal calc.\%, C, 45.19; H, 4.80; N, 4.65. It was not possible to obtain an elemental analysis as the product was waxy and impossible to scrape off the sides of the flask. Even when precipitated from solution with hexane and dried on a Schlenk line the powder sheared when the spatula attempted to scoop it up. \( R_f \), eluent 3/1 DCM/ethyl acetate, 0.05.

\( ^1\text{H} \) NMR spectrum in CDCl\(_3\), \( \delta \) (ppm): 3.04 (s, 3H, NMe), 3.78 (overlapped m, 8H, CH\(_2\) of CH\(_2\)-O), 4.21 (overlapped m, 8H, CH\(_2\) of O-CH\(_2\)), 3.47 (overlapped m, 12H, MeO), 5.93 (s, 1H of NCH), 6.92 (d, 8.5 Hz, ArC(6)H, \( \text{C}_6\text{H}_3\)CN), 7.31 (d, 8.5 Hz, ArC(5)H, \( \text{C}_6\text{H}_3\)CN), 7.13 (s, ArC(2)H, \( \text{C}_6\text{H}_3\)CN), 7.70 (d, 6.7 Hz, 2ArCH, Ph of oxadiazoline ligand), 7.45 (m, 3ArCH, Ph of oxadiazoline ligand), 7.05 (d, 8.5 Hz, ArC(5)H, of N=C-C\(_6\text{H}_3\) of oxadiazoline ligand), 8.58 (d, \( \text{meta} \) 2.0 Hz, ArC(6)H of N=C-C\(_6\text{H}_3\) of oxadiazoline ligand, 8.5 Hz), 8.79 (s, \( \text{meta} \) 2.0 Hz, 1 ArC(2)H of N=C-C\(_6\text{H}_3\) of oxadiazoline ligand).

\( ^{13}\text{C} \) NMR spectrum in CDCl\(_3\), \( \delta \) (ppm): 46.2 (NMe), 70.5, 70.6, 70.7, 70.8 (4C of O-CH\(_2\)), 68.6, 68.7, 68.9, 69.0 (4C of CH\(_2\)-O), 59.38, 59.33, 59.27, 59.20 (4C of OMe), 154.9, 154.1 (2C, ArC(4)-O), 149.2, 148.4 (2C, ArC(3)-O), 116.0 (ArC(2)H, \( \text{C}_6\text{H}_3\) of oxadiazoline ligand), 112.9 (ArC(5)H, \( \text{C}_6\text{H}_3\) of oxadiazoline ligand), 125.7 (ArC(6)H, \( \text{C}_6\text{H}_3\) of oxadiazoline ligand), 128.7, 128.6 (overlapped signals) (5C, ArCH, Ph of oxadiazoline ligand), 117.1 (ArC(6)H of nitrile ligand), 113.1 (ArC(2)H of nitrile ligand), 129.8 (ArC(3)H of nitrile ligand), 94.8 (NCHN of heterocycle), 117.3 (CN), possibly 114.2 (ArC(1) of nitrile ligand), not seen (C=N), possibly 123.4 (ArC(1), \( \text{C}_6\text{H}_3\) of oxadiazoline ligand), possibly 130.0 (C\(_\beta\), ArC(1) of Ph).

\( ^{195}\text{Pt} \) NMR spectrum in CDCl\(_3\), \( \delta \) (ppm): -2217.4 (1320 Hz).

IR, (KBr), selected band, cm\(^{-1}\): 2284 (C=N), 1594 (C=N).

MS-FAB, \( m/z \): 903.9 [M]+, 925.9 [M+Na]+, 830.1 [M-2HCl]+.
8.7 *Trans* platinum(II) bis oxadiazoline complexes with hydroxy groups.

Below is a typical procedure for the manufacture of a platinum(II) bis oxadiazoline complex. Specific conditions are included in table 23 below.

**Preparation of trans-[PtBr₂[N=N(Ph)-O-N(Me)-CH(Ph)]₂].**

*trans*-PtBr₂(PhCN)₂ (28 mg, 0.05 mmol) and C-phenyl-N-methyl-nitron (15.6 mg, 0.12 mmol) were dissolved in deuterated chloroform (1 ml) and placed in a vial with magnetic stirrer bar and fitted with an airtight lid. This was placed in a sand bath at 60 °C for 48 hours. The reaction was monitored periodically by proton NMR, observing the disappearance of a doublet at 9.00 ppm which represents the *ortho* phenyl protons of the mono oxadiazoline platinum, and the appearance of signals between 8.60 and 8.80 ppm which correspond to the *ortho* phenyl protons of the desired bis oxadiazoline platinum. The product is purified by column chromatography using DCM as eluent.

<table>
<thead>
<tr>
<th>Prod. No.</th>
<th>Reaction Conditions</th>
<th>Work-Up Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>2.2/1 molar ratio, acetone, 7 days, 50°C</td>
<td>Reduce under vacuum, wash with ether.</td>
</tr>
<tr>
<td>46</td>
<td>2.2/1 molar ratio, acetone, 7 days, 50°C</td>
<td>Chromatography/DCM/EA, 10/1, as eluent</td>
</tr>
<tr>
<td>47</td>
<td>2.2/1 molar ratio, acetone/CHCl₃ 1/1, 7 days, 50°C</td>
<td>Insoluble diastereoisomer recovered by filtration and washed with ether. Remaining solution underwent chromatography / DCM/EA, 10/1, as eluent</td>
</tr>
<tr>
<td>48</td>
<td>2.2/1 molar ratio, acetone/CHCl₃ 1/1, 7 days, 50°C</td>
<td>Insoluble diastereoisomer recovered by filtration and washed with ether. Remaining solution underwent chromatography / DCM/EA, 10/1, as eluent</td>
</tr>
<tr>
<td>49</td>
<td>2.2/1 molar ratio, CHCl₃, 7-10 days, 50°C</td>
<td>Chromatography / DCM/EA, 10/1 as eluent</td>
</tr>
<tr>
<td>50</td>
<td>2.2/1 molar ratio, CHCl₃, 7-10 days, 50°C</td>
<td>Chromatography / DCM/EA, 10/1 as eluent</td>
</tr>
<tr>
<td>52</td>
<td>2.2/1 molar ratio, chloroform, 60°C, 72 hrs</td>
<td>Chromatography / DCM, as eluent</td>
</tr>
<tr>
<td>53</td>
<td>2.2/1 molar ratio, acetone, 60°C, 5 days</td>
<td>Reduce under vacuum, Chromatography/ether as eluent</td>
</tr>
<tr>
<td>55</td>
<td>2.2/1 molar ratio, chloroform, 60°C, 72 hrs</td>
<td>Chromatography / DCM as eluent</td>
</tr>
</tbody>
</table>

Table 23. Reaction conditions and work-up procedures of bis oxadiazoline platinum complexes.
8.7.1. Reaction of \( \text{trans-}[\text{PtCl}_2(p-\text{HO-C}_6\text{H}_4\text{CN})_2] \) with PhCH=NO

\( \text{trans-}[\text{PtCl}_2\{N=C(p-\text{HO-C}_6\text{H}_4)-\text{O-N}(\text{Me})-\text{CH(Ph)}\}_2] \)(45).

Analytical data:

Yellow cream solid, yield is 55%. 2 diastereoisomers in 55/45 proportion.

Formula: \( \text{C}_{30}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_4\text{Pt} \), MW 774.4. Anal. calc. %, C, 46.51; H, 3.64 ; N, 7.20 .

Found: C, 46.02; H, 3.62; N, 7.46.

\( ^1\text{H} \) NMR spectrum in \( d_6\)-acetone, 500 MHz,

1\text{st} diastereoisomer; \( \delta \) (ppm): 2.94 (broad s, 6H, NMe), 5.92 (br. s, 2H of NCH), 6.88 (d, 8.5 Hz, 4H, ArC(3,5)H(C_6H_4)), 8.82 (br. d, 4H, unresolved, ArC(2,6)H(C_6H_4)), 7.45 (br. m, 6H, Ph), 7.60 (br. m, 4H, Ph), 9.50 (s, 2H, OH).

\( ^{195}\text{Pt} \) NMR spectrum in \( d_6\)-acetone / \( D_2\text{O} / \text{Na}_2\text{CO}_3 \), \( \delta \) (ppm): -2027.3 (1075 Hz), \( d_6\)-acetone, 2120.6.

2\text{nd} diastereoisomer (mixture with 1\text{st}); \( \delta \): 2.95 (broad s, 6H, NMe), 5.95 (br. s, 2H of NCH), 7.00 (br. d unresolved, 4H, ArC(3,5)H(C_6H_4)), 8.78 (br. d unresolved, ArC(2,6)H(C_6H_4)), 7.43 (br. m, 6H, Ph), 7.66 (br. m, 4H, Ph). \( ^{195}\text{Pt} \) NMR spectrum in \( d_6\)-acetone / \( D_2\text{O} / \text{Na}_2\text{CO}_3 \), -2048.8 (1075 Hz), in \( d_6\)-acetone 2141.2.

\( ^{13}\text{C} \) NMR spectrum in \( d_6\)-acetone, 10% \( D_2\text{O}, \text{Na}_2\text{CO}_3 \), \( \delta \) (ppm): 45.6 (NMe), 94.2 (NCHN), 104.3 (ArC(1), C_6H_4, C_4), 119.6 (3,5), 133.3 and 133.4 (2,6), 2 diastereoisomers) (8 ArCH of C_6H_4), 128.5 (2,6 or 3,5), 128.6 (3,5 or 2,6), 129.0 (4) (10 ArCH, Ph), 163.3 (C=N of oxadiazoline ring), 164.3 (ArC(4)=O), 137.3 C_4 of Ph.

IR, (KBr), selected band, cm\(^{-1}\): 1607 v(C=N).

MS-FAB, \( m/z \): 774.7 [M]\(^+\), at 703.8 [M - 2HCl]\(^+\), 798 [M + Na]\(^+\), 814 [M + K]\(^+\).

8.7.2. Reaction of \( \text{trans-}[\text{PtCl}_2m-\text{HO-C}_6\text{H}_4\text{CN})_2] \) with PhCH=NO

\( \text{trans-}[\text{PtCl}_2\{N=C(m-\text{HO-C}_6\text{H}_4)-\text{O-N}(\text{Me})-\text{CH(Ph)}\}_2] \)(46).

(unsable in soln. \( d_6\)-acetone)

Analytical data:

Yellow cream solid, yield is 43%. 2 diastereoisomers in roughly 50/50 proportion.

Formula: \( \text{C}_{30}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_4\text{Pt} \), M 774.4. Anal. calc. %, C, 46.51; H, 3.64 ; N, 7.20 .

Found: C, 44.16; H, 3.75; N, 6.40.
**H NMR spectrum in d<sub>6</sub>-acetone, δ (ppm): 2.97 (sharp s, 6H, NMe), 5.91, 5.99 (2 diastereoisomers), (s, 2H of NCH), 7.21, 7.18 (2 diastereoisomers, multiplets, 2 ArC(4)H of C<sub>6</sub>H<sub>4</sub>-C=N), 7.43, 7.38 (2 diastereoisomers, overlapped multiplets, 2 ArC(5)H, C<sub>6</sub>H<sub>4</sub>-C=N), 7.43, 7.38 (2 diastereoisomers, overlapped multiplets, 6 ArC(4 and 2,6)H of Ph), 7.59, 7.65 (2 diastereoisomers, overlapped multiplets, 4 ArC(3,5)H of Ph), 7.89, 7.94 (2 diastereoisomers, broad pair of singlets, 2ArC(2)H, C<sub>6</sub>H<sub>4</sub>-C=N), 8.62, 8.72 (2 diastereoisomers, pair of doublets, 7.5 Hz, 2ArC(2)H, C<sub>6</sub>H<sub>4</sub>-C=N), 8.95 (s, 2H, OH).

**C NMR spectrum in d<sub>6</sub>-acetone, δ (ppm): 46.5 (NMe), 95.5 (NCHN), 117.4, 117.5 (2 diastereoisomers) (ArC(2)H of C<sub>6</sub>H<sub>4</sub>-C=N), 122.9, 123.1 (2 diastereoisomers) (ArC(6)H of C<sub>6</sub>H<sub>4</sub>-C=N), 121.6 (ArC(4)H of C<sub>6</sub>H<sub>4</sub>-C=N), 129.43, 129.39 (2 diastereoisomers, ArC(5)H of C<sub>6</sub>H<sub>4</sub>-C=N), 122.9 (ArC(1), C<sub>q</sub> of C<sub>6</sub>H<sub>4</sub>-C=N), 129.0 (ArC(3,5)H of Ph), 129.9 (ArC(2,6)H of Ph), 130.59, 130.64 (2 diastereoisomers, ArC(4)H of Ph), 158.0 (ArC(3)-O), 164.3 (C=N of oxadiazoline ring), 135.2 (C<sub>q</sub> of Ph).

**Pt NMR spectrum in d<sub>6</sub>-acetone, δ (ppm): -2133.6 (1075 Hz).

IR, (KBr), selected band, cm<sup>-1</sup>: 1605 v(C=N).

MS-FAB, m/z: 774.0 [M]+, at 701.1 [M - 2HCl], 798.0 [M + Na], 672.1 [M-PhCN], 568.0 [M-2PhCN].

8.7.3. Reaction of trans-[PtCl<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>CN)<sub>2</sub>] with p-HO-C<sub>6</sub>H<sub>4</sub>CH=NOMe

trans-[PtCl<sub>2</sub>{N=C(Ph)-O-N(Me)-CH(p-HO-C<sub>6</sub>H<sub>4</sub>)<sub>2</sub>}]<sup>[47]</sup>.

Pale yellow solid, the yield is 48%. 2 diastereoisomers in roughly 5/2 proportion

Formula: C<sub>30</sub>H<sub>28</sub>Cl<sub>2</sub>Na<sub>4</sub>O<sub>4</sub>Pt, MW 774.4. Anal. calc.% C: 46.51; H: 3.64; N: 7.23; found, C: 45.97; H: 3.61, N: 7.46.

**H NMR spectrum in d<sub>6</sub>-DMSO, δ (ppm): 2.88 (s, 6H, NMe), 5.86 (s, 2H of NCH), 6.84 (d, 8.6 Hz, 4H(3,5), C<sub>6</sub>H<sub>4</sub>), 7.41 (d, 8.6 Hz, 4H(2,6), C<sub>6</sub>H<sub>4</sub>), 7.57 (t, 8.0 Hz, 4H, ArC(3,5)H, PhC=N), 7.81 (t, 8.0 Hz, 2H, ArC(4)H, PhC=N), 8.74 (d 8.0 Hz, 4H, ArC(2,6)H, PhC=N), 9.69 (s, H, OH).

**C NMR spectrum in d<sub>6</sub>-DMSO, δ (ppm): 45.5 (NMe), 93.6 (NCHN), 114.9 (3,5), 129.8 (2,6) (8 ArCH, C<sub>6</sub>H<sub>4</sub>), 133.8 (2C, ArC(4)H of Ph), 128.4 (4C, ArC(3,5)H of Ph), 129.9 (4C, ArC(2,6)H of Ph), 123.5 (C<sub>q</sub>, ArC(1) of N=CPh), not seen (C<sub>q</sub>, ArC(1) of C<sub>6</sub>H<sub>4</sub>), 158.3 (ArC(4)O), 162.5 (C=N).
$^{195}$Pt NMR spectrum in $d_6$-acetone, $\delta$ (ppm): -2118.8, possibly -2115.0 (1075Hz).

IR, (KBr), selected band, cm$^{-1}$: 1604 $\nu$(C=N).

MS-FAB$^+$, $m/z$: 775.1 [M]$^+$, 701.9 [M - 2HCl], 737.1 [M - HCl], 797.2 [M + Na].

8.7.4. Reaction of trans-[PtCl$_2$(C$_6$H$_5$CN)$_2$] with m-HO-C$_6$H$_4$CH=NOMe

trans-[PtCl$_2$(N=C(Ph)-O-N(Me)-CH(m-HO-C$_6$H$_4$))]$_2$(48).

Pale yellow solid, the yield is 51%. 2 diastereoisomers one of which precipitates.

Precipitated diastereoisomer.

Formula: C$_{30}$H$_{28}$Cl$_2$N$_4$O$_4$Pt, MW 774.4. Anal. calc.(for mixture of diastereoisomers)
C, 46.51; H, 3.64; N, 7.20 . Found: C, 45.02; H, 3.78; N, 6.46.

$^1$H NMR spectrum in $d_6$-acetone, $\delta$ (ppm): 2.97 (s, 6H, NMe), 8.74 (s, 2H of OH), 5.94 (s, 2H of NCH), 6.95 (d, 9.1 Hz, 2H, ArC(2 or 4)H of C$_6$H$_4$-CH=N), 7.08 (s, 2H, ArC(2 or 4)H of C$_6$H$_4$-CH=N), 7.15 (d, 9.1 Hz, 2H, ArC(6)H of C$_6$H$_4$-CH=N), 7.30 (t, 9.1 Hz, 2H, ArC(5)H of C$_6$H$_4$-CH=N), 7.49 (t, 8.5 Hz, 4H, ArC(3,5)H of PhC=N), 7.71 (m, 2H, ArC(4)H of PhC=N), 8.62 (d, 8.5 Hz, 4H, ArC(2,6)H, Ph of PhC=N).

$^{13}$C NMR spectrum in $d_6$-acetone, $\delta$ (ppm): 46.1 (NMe), 94.9 (NCHN), 115.6 (ArC(2 or 4)H of C$_6$H$_4$-CH=N), 116.5 (ArC(4 or 2)H of C$_6$H$_4$-CH=N), 120.2 (ArC(6)H of C$_6$H$_4$-CH=N), 129.3 (ArC(5)H of C$_6$H$_4$-CH=N), 128.9 (2C, ArC(3,5)H of PhC=N), 130.5 (2C, ArC(2,6)H of PhC=N), and 133.8 (1C, ArC(4)H of PhC=N), not seen (C$_q$, N=CPh), not seen (C$_q$, C$_6$H$_4$), not seen (C$_q$, N=CPh), possibly 122.8 (C$_q$, N=CPh),

Soluble diastereoisomer.

Formula: C$_{30}$H$_{28}$Cl$_2$N$_4$O$_4$Pt, MW 774.4. $^1$H NMR spectrum in $d_6$-acetone, $\delta$ (ppm): 2.99 (s, 6H, NMe), 8.50 (s, 2H of OH), 5.95 (s, 2H of NCH), 6.96 (d, 9.5 Hz, 2H, ArC(4)H of C$_6$H$_4$-CH=N), 7.09 (s, 2H, ArC(2)H of C$_6$H$_4$-CH=N), 7.16 (d, 9.5 Hz, 2H, ArC(6)H of C$_6$H$_4$-CH=N), 7.31 (t, 9.5 Hz, 2H, ArC(5)H of C$_6$H$_4$-CH=N), 7.48 (m, 4H, ArC(3,5)H of PhC=N), 7.72 (m, 2H, ArC(4)H of PhC=N), 8.87 (d, 8.1 Hz, 4H, ArC(2,6)H, Ph of PhC=N).

$^{13}$C NMR spectrum in $d_6$-acetone, $\delta$ (ppm): 45.8 (NMe), 94.9 (NCHN), 115.4 (ArC(2 or 4)H of C$_6$H$_4$-CH=N), 116.3 (ArC(2 or 4)H of C$_6$H$_4$-CH=N), 120.0 (ArC(6)H of C$_6$H$_4$-CH=N), 130.5 (ArC(5)H of C$_6$H$_4$-CH=N), 128.5 (ArC(3,5)H of PhC=N), 130.5 (ArC(2,6)H of PhC=N), and 133.7 (ArC(4)H of PhC=N), possibly 122.8 (C$_q$, N=CPh),
127.5 (C=, C=H), 157.6 (ArC(3)O), possibly 160.9 (C=N).

$^{195}$Pt NMR spectrum in $d_6$-acetone, $\delta$ (ppm): -2148.9 (1075 Hz), one isomer seen.

IR, (KBr), selected band, $cm^{-1}$: 1601 $\nu$(C=N).

MS-FAB, $m/z$: 775.1 [M$^+$], 701.9 [M - 2HCl], 737.1 [M - HCl], 797 [M + Na].

oxadiazoline free ligand at 255.


Specific reaction conditions and work-up procedures are contained in table 23.

8.8.1. Reaction of trans-[$PtCl_2(p$-MeOC$_2$H$_4$O-C$_6$H$_6$CN)$_2$] with PhCH=NO Me

trans-[$PtCl_2(N=C(p$-MeO-C$_2$H$_4$O-C$_6$H$_4$)-O-N(Me)-CH(Ph))$_2$](49).

NMR showed a mixture of diastereoisomers, roughly 50/50 proportions.

Yellow solid 40 mg, yield approximately 45%.

Analytical data:
Formula: C$_{36}$H$_{44}$Cl$_2$N$_4$O$_6$Pt, MW 890.7. Anal. calc.% C: 48.54; H: 4.52; N: 6.29; found, C: 47.28; H: 4.53, N: 6.29.

$^1$H NMR spectrum in CDCl$_3$, 2 diastereoisomers 50/50, $\delta$ (ppm): 2.91, 2.94 (s, 6H, NMe), 3.79 (m, 4H, CH$_2$O), 4.19 (m, 4H, OCH$_2$), 3.47 (m, 6H, OMe), 5.88 (s, 2H of NCH), 6.82 (m, 6H, ArC(3,5)H of C$_6$H$_4$O), 7.48 (m, 6H, of Ph), 7.60 (m, 4H, of Ph), 8.66 (d, 8.5 Hz, 2H, ArC(2,6)H, C$_6$H$_4$O), 8.82 (br. m, 2H, ArC(2,6)H, C$_6$H$_4$O). (The last 2 signals equivalent to 4 protons and indicative of 2 diastereoisomers).

$^{13}$C NMR spectrum in CDCl$_3$, $\delta$ (ppm): 162.9 (ArC(4)-O), 133.0, 132.7 (2 diastereoisomers), 114.3 (4C ArCH (2,6 and 3,5 of C$_6$H$_4$O)), 129.6 (ArC (1)-C=N), 136.4 (ArC (1)-C-N of Ph.), 128.5, 128.6 and 129.5 (5C, ArCH of Ph), 70.8 (CH$_2$O), 67.6 (O-CH2), 59.3 (OMe), 46.3 (NMe), 94.7 (NCHN), 163.0 (C=N of oxadiazoline ring).

$^{195}$Pt NMR spectrum in CDCl$_3$, $\delta$ (ppm): -2106.8 (775 Hz) and -2124.2 (775 Hz), 2 diastereoisomers in roughly equal proportion.

IR, (KBr), selected band, $cm^{-1}$: 1605 $\nu$(C=N).

MS-FAB, $m/z$: 891.2 [M$^+$], 913.1 [M+Na], 854.2 [M-HCl], 817.3 [M-2HCl], 788.2 [M-PhCN].
8.8.2. Reaction of trans-[PtCl₂(C₆H₅CN)]₂ with p-MeO-C₂H₄O-C₆H₄CH=NOMe

trans-[PtCl₂{N=C(Ph)-O-N(Me)-CH(p-MeO-C₂H₄O-C₆H₄)}₂](50).

NMR showed a mixture of diastereoisomers in roughly 60/40 proportion.
Yellow/brown solid 40 mg, yield approximately 41%.
Analytical data:

¹H NMR spectrum in CDCl₃, 2 diastereoisomers 60/40, δ (ppm): 2.91, 2.94 (s, 6H, NMe), 3.78 (m, 4H, CH₂O), 4.18 (m, 4H, OCH₂), 3.46 (m, 6H, MeO), 5.85 (s, 2H of NCH), 7.39 (m, 4H, ArC(3,5)H, of PhC=N), 7.65 (overlapped multiplet, possibly 2H, ArC(4)H of PhC=N), 7.49 (overlapped m, 4H, of C₆H₄O), 7.01 (d, 4H, ArC(3,5)H of C₆H₄O, 8.0 Hz), 8.66 (d, 8.0 Hz, ArC(2,6)H, PhC=N), 8.77 (broad multiplet, ArC(2,6)H, PhC=N). (The last 2 signals equivalent to 4 protons and indicative of 2 diastereoisomers).

¹³C NMR spectrum in CDCl₃, δ (ppm): 159.9 (ArC(4)-O), 130.6, 130.5, 130.2 (5C ArCH (PhC=N)), 114.6 (3,5), 128.3 (2,6) (4C of C₆H₄O), 71.0 (CH₂-O), 67.3 (OCH₂), 59.3 (OMe), 46.1 (NMe), 94.5 (NCHN), 163.9 (C=N of oxadiazoline ring), 132.3 (Cq, CHPh), 125.8, (Cq of C₆H₄O).

¹⁹⁵Pt NMR spectrum in CDCl₃, δ (ppm): -2103.4 (775 Hz) and -2120.3 (1075 Hz), 2 diastereoisomers in roughly 60/40 proportion.

IR, (KBr), selected band, cm⁻¹: 1605v (C=N).
MS-FAB, m/z: 891.0 [M]+, 854.2 [M-HCl], 817.0 [M-2HCl], 788.9 [M-PhCN].

8.9 Platinum(II) dibromo oxadiazoline complexes.

Specific reaction conditions and work-up procedures are contained in table 22 (mono cycloadduct), and table 23 (bis cycloadduct).

8.9.1. Preparation of trans-[PtBr₂(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}](51).
Analytical data:
Formula: C₂₂H₁₉Br₂N₅Opt, yellow orange solid, the yield is 73%.
Anal. caled for C_{22}H_{16}Br_{2}N_{3}OPt: MW 696.29, % C, 37.95; H, 2.75; N, 6.03. Found: C, 38.22; H, 2.71; N, 5.86.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 3.08 (s, 3H, NMe), 6.00 (s, 1H, N-CH-N), 7.45 (m, 3H) and 7.73 (d, 7.4 Hz, 2H)(CH-Ph), 7.59 (t, 7.7 Hz, 2H), 7.66 (m, 1H) and 9.00 (d, 8.1 Hz, 2H)(N=C-Ph), 7.50 (t, 7.7 Hz, 2H), 7.66 (m, 1H) and 7.69 (m, 2H)(N=CPh).

\(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) (ppm): 46.4 (NMe), 95.6 (N-CH-N), 110.2 (C\(_q\), N=CPh), 118.5 (C=O), 122.5 (C\(_q\), N=CPh), 128.7, 128.8, 130.1 (5C, ArCH of CHPh), 129.4, 133.7, 134.2 (5C, ArCH of PhCN), 129.3, 131.1, 134.9 (5C, ArCH of N=CPh), 135.6 (C\(_q\), CHPh), 164.4 (C=O).

\(^{195}\)Pt NMR (107.3 MHz, CDCl\(_3\)) \(\delta\) (ppm): -2693 (750 Hz).

IR spectrum (selected bands), cm\(^{-1}\): 2291 w v(O\(\equiv\)N), 1622 w v(C=N).

MS-FAB*, m/z: 696.8 [M]\(^+\), 615.9 [M - HBr]\(^+\), 535 [M - 2 HBr]\(^+\), [M - PhCN]\(^+\), 432.2 [M - 2 HBr - PhCN]\(^+\).

Accurate MS-FAB*, m/z: 694.5350 for C_{22}H_{16}Br_{8}\text{BrN}_{3}O^{194}\text{Pt}, theoretical 694.96.

8.9.2. Preparation of trans-[PtBr\(_2\){N=C(Ph)-O-N(Me)-CH(Ph)}\(_2\)](52).

Analytical data:

Formula: C\(_{30}\)H\(_{28}\)Br\(_2\)N\(_4\)O\(_2\)Pt, yellow orange solid, the yield is 71%.

Anal. caled for C\(_{30}\)H\(_{28}\)Br\(_2\)N\(_4\)O\(_2\)Pt: MW 831.46, % C, 43.34; H, 3.39; N, 6.74. Found: C, 42.91; H, 3.26; N, 6.68.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): First diastereoisomer, 2.99 (s, 6H, NMe), 5.98 (broad s, 2H, N-CH-N), 7.62 (m, 2H, ArC(4)H, C=NPh), 7.40 (m, 4H, ArC(3,5)H, C=NPh) and 8.68 (d, 7.8 Hz, 4H, ArC(2,6)H, N=C-Ph), 7.57 (m, 4H, ArC(2,6 or 3,5)H, CHPh), 7.43, 7.47 (m, 6H, ArC(4 and 2,6 or 3,5)H of CHPh)).

Second diastereoisomer (mixture with first diastereoisomer). 2.99 (s, 6H, NMe), 5.81 (broad) (s, 2H, N-CH-N), 7.51 (overlapped m, 6H, ArC(4 and 3,5)H of N=CPh and 4H, ArC(3,5 or 2,6)H of CHPh), and 7.59 (broad m, 6H, ArC(4 and 3,5 or 2,6)H of CHPh), and 8.83 (broad m, 4H, ArC(2,6)H, N=C-Ph).

\(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) (ppm): mixture of diastereoisomers, 46.5 (NMe), 95.8 (N-CH-N), 123.0 (C\(_q\), N=CPh), 136.2 (C\(_q\) of CHPh), 131.0 (2C, ArC(2,6)H of
C=NPh), 130.9 (2C, ArC(3,5)H of C=NPh), 133.4 (C, ArC(4)H of C=NPh), 129.3, 128.5, 130.0 and 129.9 (5C, ArCH of CHPh), 163.5, 164.8 (C=N), 163.5, 164.8 (C=N).

195Pt NMR (107.3 MHz, CDCl3) δ (ppm): -2523 (1500 Hz).

IR spectrum (selected bands), cm⁻¹: 1628 s ν(C=N).

MS-FAB⁺, m/z: 831.8[M⁺], 750.9 [M – HBr]⁺, 670.0 [M – 2 HBr]⁺, 464.0 [M – 2 HBr – 2PhCN]⁺.

Accurate MS-FAB⁺, m/z: 831.426 for C₃₀H₂₈Br₂N₄O₂Pt, theoretical 831.0201.

8.9.3. Preparation of trans-[PtBr₂(N=C(p-OH-C₆H₄−)O-N(Me)-CH(Ph))]⁺(53).

(Impure, contains possibly a dimeric platinum oxadiazoline complex)

Impurity data (obtained by comparison with the spectra of similar products):

1H NMR spectrum in d₆-acetone, δ (ppm): 2.75, (broad s, 6H, NMe), 6.10 (broad s, 2H, NCH), 8.87 (broad m, 4H, ArC(2,6)H of p-OH-C₆H₄-C=N), 6.95 (broad m, 4H, ArC(3,5)H of p-OH-C₆H₄-C=N), 7.45 (broad overlapped multiplet, 10ArCH of PhCN), 9.60 (s, OH).

13C NMR spectrum in d₆-acetone, δ (ppm): 40.6 (NMe), 95.2 (NCHN) from HMOC, N=C-C₆H₄ and CHPh carbons between 125.0 and 135.0.

195Pt NMR spectrum in d₆-acetone, δ (ppm): -2538.5 broad; (1500 Hz).

Proposed structure;

Analytical data: (desired product).

Yellow orange solid, yield is 49%, 2 diastereoisomers.

Formula: C₃₀H₂₈Br₂N₄O₂Pt, MW: 863.45. Anal. calcd for C₃₀H₂₈Br₂N₄O₂Pt: %, C, 41.73; H, 2.84; N, 6.49. Found: C, 42.33; H, 3.17; N, 6.50. 1H NMR spectrum in d₆-acetone, δ (ppm): 3.00 (broad s, 6H, NMe), 6.05, 5.91 (broad s, 2H of NCH), 7.40, 7.46, 7.70, (broad multiplets, 10H of PhCN), 8.65, 8.80, (broad m, 4H, ArC(2,6)H of p-OH-C₆H₄-C=N), 7.07 (m, 4H, ArC(3,5)H of p-OH-C₆H₄-C=N, 8.6 Hz), 9.65 (broad s, OH).

13C NMR spectrum in d₆-acetone, δ (ppm): 45.6 (NMe), 94.2 (NCHN), 104.3 (C₆, ArC(1), C=NC₆H₄-O), 134.0 (2,6), 116.0 (3,5)(4C, ArCH of p-OH-C₆H₄-C=N), 130.1, 128.9, 129.9 (5C of Ph), 131.0 (C₆, ArC(1), CHPh), 163.2 (C=N of
oxadiazoline ring), 163.0 (ArC(4)–O).

$^{195}$Pt NMR spectrum in d$_6$-acetone, $\delta$ (ppm): -2518.0 broad; -2518.5 sharp (535 Hz).

IR (KBr), selected band, cm$^{-1}$: 1608 v(C=N).

MS-FAB, $m/z$: 863.7 [M$^+$], at 782.8 [M - HBr], 701.9 [M - 2HBr], 886.8 [M + Na].


Specific reaction conditions and work-up procedures are contained in table 22 (mono cycloadduct), and table 23 (bis cycloadduct).

8.10.1. Preparation of trans-[PtI$_2$(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}](54).

Analytical data:
Pale brown solid, the yield is 76%.

Anal. calcd for C$_{22}$H$_{10}$I$_2$N$_3$OPt: MW 790.29, C, 33.44; H, 2.42; N, 5.32. Found: C, 33.30; H, 2.38; N, 5.08.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 3.11 (s, 3H, NMe), 6.07 (s, 1H, N-CH-N), 7.51 (3,5), 7.68, 7.70 (2,6 and 4), (PhCN), 8.93 (d, 8.0 Hz, ArC(2,6)H)(N=C-Ph), 7.57 (overlapped m, 3H)(N=CPh), 7.46 (2,6 or 3,5), 7.76 (3,5 or 2,6), 7.77 (ArC(4)H)(overlapped multiplets, CHPh).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 46.1 (NMe), 96.4 (N-CH-N), 110.2 (C$_q$, N=CPh), 121.9 (N=C), 122.6 (C$_q$, N=CPh), 134.7, 131.0, 128.6 (5C, ArCH of N=CPh), 133.9, 133.3, 129.3 (5C, ArCH of PhCN), 128.4, 129.6, 130.1 (5C, ArCH of CHPh), 133.5 (C$_q$, CHPh), 164.4 (C=N).

$^{195}$Pt NMR (107.3 MHz, CDCl$_3$) $\delta$ (ppm): -3695.4 (750 Hz)

IR spectrum (selected bands), cm$^{-1}$: 2290 v(C=N), 1622 v(C=N).

MS-FAB$^+$, $m/z$: 790.9 [M$^+$], 661.9 [M – HBr$^+$], 533.9 [M – 2HBr$^+$], 431.0[M – 2 HBr – PhCN$^+$].

8.10.2. Preparation of trans-[PtI$_2$(N=C(Ph)-O-N(Me)-CH(Ph))$_2$](55).

Analytical data:
Pale brown solid, the yield is 68%.
Anal. calcd for C_{30}H_{28}I_{2}N_{4}O_{2}Pt: MW 925.46, C, 38.93; H, 3.05; N, 6.05. Found: C, 38.42; H, 3.02; N, 5.75.

Due to many of the signals of the two diastereoisomers being distinct and fully assignable, the results are presented in tabular form for clarity.

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>1\textsuperscript{st} diastereoisomer, yield 45%</th>
<th>2\textsuperscript{nd} diastereoisomer, yield 55%</th>
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<td>1\textsuperscript{H ppm}</td>
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<tr>
<td>C=NPh, \textit{ortho}</td>
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<td>m, 7.46</td>
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<td>122.7</td>
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<td>Na</td>
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<tr>
<td>CHPh, \textit{para}</td>
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</tr>
<tr>
<td>C\textsubscript{q}CHPh</td>
<td>135.7 or 136.0</td>
<td>Na</td>
</tr>
</tbody>
</table>

\textsuperscript{n.b.} Where carbon signals have been given to two decimal places it is to differentiate from another close signal.

Table 24. The proton and \textsuperscript{13}C NMR of trans-[PtI\textsubscript{2}(N=C(Ph)-O-N(Me)-CH(Ph))\textsubscript{2}]

\textsuperscript{195}Pt NMR (107.3 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm): 2 diastereoisomers, -3445, -3458 (Hz).

IR spectrum (selected bands), cm\textsuperscript{-1}: 1635s \(\nu\)(C=N).

MS- FAB\textsuperscript{+}, \textit{m/z}: 925.8[M\textsuperscript{+}], [M - HI]\textsuperscript{+}, [M - 2 HI]\textsuperscript{+}, [M - 2 HI - 2PhCN]\textsuperscript{+}.

8.11. Mono cycloadditions using the dinitrone of terephthaldehyde.

Reaction of trans-[PtCl\textsubscript{2}(PhCN)\textsubscript{2}] with 1,4- di(HC=N(Me)O)-C\textsubscript{6}H\textsubscript{4}

Preparation of trans,trans-[1,4-di(PtCl\textsubscript{2}(PhCN)(N=C(Ph)-O-N(Me)-CH))-(C\textsubscript{6}H\textsubscript{4})] (56).
Specific reaction conditions and work-up procedures are contained in table 20.

Formula Pt₂Cl₆N₂O₂C₃₈H₁₂, MW 1136.67, yellow crystalline solid, yield 71% Anal. calcd. %, C, 40.15; H, 2.84; N, 7.39. Found: C, 40.15; H, 2.97; N, 7.50.

2 diastereoisomers in roughly 60/40 proportion.

1H NMR (500 MHz, CDCl₃) δ (ppm): 3.05 (s, 6H, NMe), 6.07, 6.04 (s, 2H, N-CH-N), 7.80 (d, 4 ArC(2,6)H, 7.5 Hz)(PhCN), 7.57 (overlapped m ArC(3,5)H)(PhCN), 7.75 (m, ArC(4)H)(PhCN), 7.60 (overlapped m, ArC(3,5)H)(N=C-Ph), 7.68 (overlapped m, ArC(4)H)(N=C-Ph), 8.98 (overlapped m, ArC(2,6)H)(N=C-Ph), 7.88, 7.90 (s, 4 H)(N-C-C₆H₄-C-N).

13C NMR (75 MHz, CDCl₃) δ (ppm): 46.0 (NMe), 94.2 (N-CH-N), 121.6 (2C)(C₄, PhN=C), 130.8 (4C, ArCH(2,6))(PhC=N), 129.3 (4C, ArCH(3,5))(PhC=N), 134.7 (2C, ArCH(4))(PhC=N), 134.1 (4C(2,3,5,6)(C₆H₄), 129.1 (2C)(C₆H₄-CHN) 133.8 (4C, ArCH(2,6)(PhCN), 128.6 (4C, ArCH(3,5)(PhCN), 135.3 (2C, ArCH(4)(PhCN), 109.8 (2C, C₂)(PhCN), 116.6 (2C, CN)(PhCN), 165.0, 165.8 (2C)(C=N).

195Pt NMR, CDCl₃ δ (ppm): -2246.1 (1070 Hz).

IR, (KBr), selected band, cm⁻¹: 2286 ν(C=N), 1601 ν(C=N).

MS-FAB, m/z: 1136.9 [M]⁺, 1100.0 [M-HCl], 1063.0 [M-2HCl], 1032.8 [M-PhCN], 929.8 [M-2PhCN].

Reaction of cis-[PtCl₂(PhCN)₂] with 1,4- di(HC=N(Me)-O)-C₆H₄

Preparation of cis,cis-[1,4-di{PtCl₂(PhCN)(N=C(Ph)-O-N(Me)-CH)}-(C₆H₄)]

This complex was unstable turning green as the reaction progressed, so only a partial characterisation is provided. The product was not isolated.

1H NMR (500 MHz, CDCl₃) δ (ppm): 3.11 (s, 6H, NMe), 6.25 (s, 2H, N-CH-N), 7.82 (d, 4 ArC(2,6)H, 7.7 Hz)(PhCN), 7.59 (overlapped m ArC(3,5)H)(PhCN), 7.74 (m, ArC(4)H)(PhCN), 7.57 (overlapped m, ArC(3,5)H)(N=C-Ph), 7.67 (overlapped m, ArC(4)H)(N=C-Ph), 9.03(br), 9.09 (overlapped m, ArC(2,6)H)(N=C-Ph), 7.88, 7.90 (s, 4 H)(N-C-C₆H₄-C-N).
8.12. Platinum(IV) oxadiazoline complexes; oxidative additions reactions.

A typical procedure for the oxidation reactions is shown below.
Preparation of \( \text{trans-[PtCl}_2(\text{PhCN})(\text{oxx})] \).

\( \text{trans-[PtCl}_2(\text{PhCN})\{\text{N=}(\text{Ph})-\text{O}-\text{N}(\text{Me})-\text{CH}(\text{Ph})}\} \) (30 mg, 0.05 mmol) were dissolved in deuterated chloroform (0.5 ml) in an NMR tube and dry chlorine gas bubbled through the solution using an NMR tube pipette (in the case of bromination, an equimolar amount of bromine dissolved in deuterated chloroform was used). When a colour change is observed from cold yellow to warm yellow \( \text{n.b.} \) (approximately 30 seconds depending on the flow rate), proton NMR is performed to monitor the progress of the reaction. The disappearance of the broad singlet at 5.90 ppm and appearance of a sharp singlet at 6.72 ppm is indicative of a complete reaction. The product is precipitated with petroleum ether and washed with diethyl ether and dried \( \text{in vacuo} \). \( \text{n.b.} \) stated colour change is for the chlorination only, for the bromination proton NMR is used to monitor the reaction and more bromine added if required.

8.12.1. Bromination of \( \text{trans-[PtCl}_2(\text{PhCN})\{\text{N=}(\text{Ph})-\text{O}-\text{N}(\text{Me})-\text{CH}(\text{Ph})}\}] \) \( \text{(57).} \)

Formula: PtBr\(_2\)Cl\(_2\)N\(_3\)O\(_2\)C\(_2\)H\(_{19}\), MW 767.197,

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) (ppm): 3.26 (s, 3H, NMe), 6.84 (s, 1H, N-CH-N), 7.80 (d, 7.4 Hz, ArC(2,6)H), 7.57 (m, ArC(3,5)H), 7.42 (m, ArC(4)H)(PhCN or PhCHN), 7.43, 7.55 (m, ArC(2,6 or 3,5)H), 7.57 (m, ArC(4)H)(PhCN or PhCHN), 7.55 (m, ArC(3,5)H), 7.69 (t, 7.5Hz, ArC(4)H), 8.32 (d, 7.5 Hz, ArC(2,6)H)(N=C-Ph).

\(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \( \delta \) (ppm) 46.8 (NMe), 93.8 (N-CH-N), 107.6 (C\(_\Phi\), N=CPh), 118.1 (N=C), 123.2 (C\(_\Phi\), N=CPh), 126.2 (CH), 127.9 (CH), 128.5 (CH), 129.1 (CH), 129.6 (CH), 134.3(CH), 136.4 (CH), (CHPh, N=CPh and N=CPh), 132.0 (ArC(2,6)(N=CPh), 134.8(ArC(4)H), 137.7 (C\(_\Phi\), CHPh), 173.8 (C=N).

\(^{195}\)Pt NMR (107.3 MHz, CDCl\(_3\)) \( \delta \) (ppm): - 649.0, (1000 Hz).

IR spectrum (selected bands), cm\(^{-1}\): 2316 \( \nu \)(C=N), 1625, \( \nu \)(C=N).

MS-FAB\(^{+}\), \( m/z \): 604.9 [M-2HBr], 568.9 [M-2HBr-HCl].
8.12.2. Bromination of trans-[PtBr₂(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}](58).

Formula: PtBr₄N₃OC₂₂H₁₉, MW 856.100, Anal. calc. for C₂₂H₁₉Br₄N₃OPt; C, 30.86; H, 2.22; N, 4.91. Found: C, 30.58; H, 2.21; N, 4.95. (red residue from the bromination of the chloro complex is a good fit for C₂₂H₁₉Br₄N₃OPt).

(initial product)

¹H NMR (500 MHz, CDCl₃) δ (ppm): 3.29 (s, 3H, NMe), 7.01 (s, 1H, N-CH-N), 7.46 (m, 3H), 7.39 (m, 1H), 7.73 (m, 1H), 7.80 (d, 8.0 Hz, 2H), 7.55 (overlapped m, 4H, (2H, ArC(3,5)H of N=C-Ph), 7.67 (overlapped m, 2H, (1H, ArC(4)H of N=C-Ph), 8.35 (d, 7.5 Hz, 2H, ArC(2,6)H of N=C-Ph).

¹³C NMR (125.7 MHz, CDCl₃) δ (ppm): 47.1 (NMe), not seen, possibly 93.0 (N-CH-N), not seen, possibly 111.0 (C₉, N=CPh), not seen, possibly 113.0 (N=C), not seen (C₉, N=CPh), 128.5 (CH), 128.8 (CH), 129.3 (CH), 129.7 (CH), 131.0 (ArC(2,6)H), 133.6 (CH), 135.7 (CH), (N=CPh and N=CPh, CHPh), and not seen (C=N).

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ (ppm): -1649.1 (214 Hz).

(final product after precipitation of red residue, thought to be PhC(H)=NMe).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 4.16 (s, NMe), 7.55 (t, 7.4 Hz, (ArC(3,5)H), 7.67 (t, 7.4 Hz, (ArC(4)H), 8.24 (d, 7.4 Hz, ArC(2,6)H), 8.27 (s, HCN),

¹³C NMR (125.7 MHz, CDCl₃) δ (ppm): 52.03 (NMe), 150.6 (HCN), 133.6 (ArC(2,6)H), 135.7 (ArC(4)H), 129.7 (ArC(3,5)H).

Small signals also seen for bis bromo platinum oxadiazoline complex.

Red residue:

IR spectrum (selected bands), cm⁻¹: 2315 ν(C=N), 1627, ν(C=N).


8.12.3. Chlorination of trans-[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}](59).

Formula: PtCl₄N₃OC₂₂H₁₉, MW 678.29,

¹H NMR (500 MHz, CDCl₃) δ (ppm): 3.19 (s, 3H, NMe), 6.68 (s, 1H, N-CH-N), 7.36 (t, 7.2 Hz, ArC(4)H), 7.40 (t, 7.2 Hz, ArC(3,5 or 2,6)H), 7.54 (overlapped m, ArC(2,6 or 3,5)H(PhCH-N)); 7.87 (d, 8.0 Hz, ArC(2,6)H(PhCN), 7.56 (overlapped m, ArC(3,5)H(PhCN), 7.42 (t, 8.0 Hz, ArC(4)H(PhCN); 7.67 (t, 8.4 Hz,
ArC(4)H(N=C=Ph), 7.52 (overlapped m, ArC(3,5) H)(N=C=Ph), and 8.27 (d, 8.4 Hz, ArC(2,6)H)(N=C=Ph).

13C NMR (125.7 MHz, CDCl3) δ (ppm): 46.9 (NMe), 92.8 (N=CH-N), 107.8 (Cq, N=CPh), 117.2 (N=C), 123.2 (Cq, N=CPh), 126.4, 128.2, 128.7 (ArC)(PhCH-N); 129.8 (C(3,5)H), 134.6 (C(2,6)H), 136.7 (C(4)H)(PhCN); 135.0 (C(4)H), 127.9 (C(2,4)H), 132.3 (C(1,6)H), (CHPh, N=CPh)); 137.3, 138.1 (Cq, CHPh), 173.2 (C=N).

195Pt NMR (107.3 MHz, CDCl3) δ (ppm): -340.7 (750 Hz).

IR spectrum (selected bands), cm⁻¹: 2314 ν(C=N), 1629, ν(C=N).

MS-FAB, m/z: 676, [M]⁺, 639.5, [M-HCl], 572.0 [M-PhCN], 469 [M-2PhCN].


Characterisation is incomplete due to decomposition of the complex.

Formula: PtCl₄N₂O₅C₂₈H₃₂, M.W. 827.46,

1H NMR (500 MHz, CDCl₃) δ (ppm): 3.17 (s, 3H)(NMe), 3.46 (overlapped m, 6H)(MeO), 3.78 (overlapped m, 4H)(OCH₂), 4.17 (overlapped m, 4H)(OCH₂), 6.66 (s, 1H)(N=CH-N), 7.86 (d, 8.5 Hz, 2H)(PhCH-N), 7.35, 7.38, (overlapped m, 3H)(PhCH-N); 7.02 (overlapped m, 2H)(RO-C₆H₄-CN), 7.76, (d, 8.5 Hz, 2H)(RO-C₆H₄-CN); 7.11 (d, 8.4 Hz, 2 meta H)(N=C−C₆H₄OR) and 8.35 (d, 8.4 Hz, 2 ortho H)(N=C− C₆H₄OR).

13C NMR (125.7 MHz, CDCl₃) δ (ppm): 46.8 (NMe), 59.32 (MeO), 68.12, 70.42 (OCH₂), 92.7 (N=CH-N), 117.3 (N=C), 123.2 (Cq, N=CPh), 126.3, 136.8 (5C, ArCH)(PhCH-N), 138.5, 116.3 (4C, ArCH)(RO-C₆H₄-CN), 117.3 (ArC(3,5)H)(N=CC₆H₄-OR), 134.9 (ArC(2,6)H)(N=CC₆H₄-OR); 138.1 (Cq, CHPh), 166.8 (C=N).

195Pt NMR (107.3 MHz, CDCl₃) δ (ppm) -289.8 (750 Hz).
8.13. Substitution reactions of \([\text{PtCl}_2(\text{PhCN})\{\text{N} = \text{C(Ph)} - \text{O-N(Me)} - \text{CH(Ph)}\}]\) .

(These were carried out as described in the results and discussion)

A typical procedure for this reaction is:

\([\text{PtCl}_2(\text{PhCN})\{\text{N} = \text{C(Ph)} - \text{O-N(Me)} - \text{CH(Ph)}\}]\) (15 mg, 0.025 mmol) and dry pyridine (1.975 mg, 0.025 mmol) were placed in a NMR tube and solvated with dry deuterated chloroform (0.05 ml). This was left for four days at room temperature and then the proton NMR checked. This was consistent with the desired product. Over the next 48 hours the product crystallized out in the tube, and X-ray diffraction confirmed the product.

8.13.1. Reaction of pyridine with trans-\([\text{PtCl}_2(\text{PhCN})\{\text{N} = \text{C(Ph)} - \text{O-N(Me)} - \text{CH(Ph)}\}]\) .

trans-\([\text{PtCl}_2(\text{Pyr})\{\text{N} = \text{C(Ph)} - \text{O-N(Me)} - \text{CH(Ph)}\}]\) [61].

Analytical data:

Pale yellow crystalline solid, the yield is 77%.

Formula: \(\text{PtCl}_2\text{N}_3\text{OC}_2\text{H}_9\), MW 583.368.

\(^1\text{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta \) (ppm): 3.07 (s, 3H, NMe), 6.03 (s, 1H, N-CH-N), 7.67 (m, ArC(4)H)(PhC=N), 7.59 (t, ArC(3,5)H)(N=C-Ph), 9.05 (d, 8.5 Hz, ArC(2,6)H)(N= C-Ph), 8.74 (d, 6.6 Hz, ArC(2,6)H)(pyr), 7.22 (t, 6.6 Hz, ArC(3,5)H)(pyr), 7.71 (m, ArC(4)H)(pyr), 7.45 (m, 3H)(PhCH-N) and 7.76 (d, 7.1 Hz, ArC(2,6)H)(PhCH-N).

\(^{13}\text{C} \text{NMR (125.7 MHz, CDCl}_3\) \(\delta \) (ppm): 46.4 (NMe), 95.0 (N-CH-N), 153.8 (2C of pyr.), 125.3 (2C of pyr.), 138.1 (ArC(4) of pyr.), 133.8 (ArC(4) of PhC=N), 128.8 (ArC(3,5) of PhC=N), 130.9 (ArC(2,6) of PhC=N), 128.7 (ArC(2,6) of Ph), 129.8, 128.9 (3C of Ph), 122.8 (C, ArC(1), N=C-Ph), 136.3 (C, ArC(1), Ph), not seen (C=N).

\(^{195}\text{Pt} \text{NMR (107.3 MHz, CDCl}_3\) \(\delta \) (ppm): -2023.1 (1070 Hz).

IR spectrum (selected bands), cm\(^{-1}\): 1450, 1348, 1118, 692.5, 1625 \(\nu\) (C=N).

MS-FAB\(^+\), \(m/z\): 584.0 [M]\(^+\), 547.0 [M - HCl]\(^+\), 510.1 [M - 2 HCl]\(^+\), 481.1 [M - PhCN]\(^+\).

X-ray crystal structure figure 76.
8.13.2. Reaction of 4-dimethylaminopyridine (DMAP) with

\[ \text{trans-}[\text{PtCl}_2(\text{PhCN})\{\text{N}=\text{C}(\text{Ph})\odot \text{N}(\text{Me})\odot \text{CH}(\text{Ph})}\}] \]

\[ [\text{PtCl}_2(\text{DMAP})\{\text{N}=\text{C}(\text{Ph})\odot \text{N}(\text{Me})\odot \text{CH}(\text{Ph})}\}] \]

The procedure for this reaction is the same as for the pyridine substitution. The reaction mixture then undergoes column chromatography on silica using DCM as eluent which removes the main product as part of a mixture. The column is then eluted with DCM / methanol, 4/1 which renders the product below.

Analytical data:
Pale yellow crystalline solid, the yield is 27%.
Formula: PtCl$_2$N$_4$OC$_2$H$_4$, MW 626.44

$^1$H NMR (500 MHz, d$_6$-acetone) δ (ppm): 2.95 (s, 6H, N(Me)$_2$), 3.05 (s, 3H, NMe), 6.22 (s, 1H, -CH-N), 7.81 (t, 7.0 Hz, ArC(4)H(N=C-Ph)), 7.72 (t, 7.0 Hz, ArC(3,5)H(N=C-Ph)), 9.15 (s, 7.0 Hz, ArC(2,6)H(N=C-Ph)), 7.13 (d, 7.5 Hz, 2H)(DMAP), 6.06 (d, 7.5 Hz, 2H)(DMAP), 7.37 (m, 3H)( PhCH-N) and 7.64 (d, 6.5 Hz, ArC(2,6)H)(PhCH-N).

$^{13}$C NMR (125.7 MHz, CDCl$_3$) δ (ppm): 47.0 (NMe), 39.0 (NMe$_2$), 95.2 (N-CH-N), 108.1 (2C of DMAP), 151.4 (2C of DMAP), 134.7 (ArC(4) of PhC=N), 128.0 (ArC(3,5) of PhC=N), 129.8 (ArC(2,6) of PhC=N), 128.9 (ArC(2,6) of Ph), 130.16, 130.18 (ArC(3,4,5) of Ph), possibly 134.9 (C$_q$, ArC(1) CHPh), 157.5 or 158.9 possibly (C$_q$ of DMAP) 162.6 (C=N), not seen (C$_q$, ArC(1) N=CPh).

$^{195}$Pt NMR (107.3 MHz, CDCl$_3$) δ (ppm): -2035.6.

IR spectrum (selected bands), cm$^{-1}$: 1622 ν(C=N), 1542, 1448, 1390, 1338, 1223, 1205, 1162, 1121, 1065, 1028.
MS-FAB$^+$, m/z: 590.0 [M - HCl]$^+$, 553.0 [M - 2HCl]$^+$, 547.0 [M - C$_3$H$_7$N]$^+$, 523.0 [M-PhCN], 503.0 [M-DMAP].

8.13.3. Reaction of DMSO with trans-[PtCl$_2$(PhCN)\{N=C(Ph)-O-N(Me)-CH(Ph)\}].

[PtCl$_2$(PhCN)\{N=C(Ph)-O-N(Me)-CH(Ph)\}](30 mg, 0.05 mmol) and DMSO (3.8 mg, 0.05 mmol) were placed in an NMR tube with one drop of deuterated chloroform to solvate it, and left for four days at room temperature. After this time proton NMR and TLC showed a mixture of products. Column chromatography was carried out using
initially DCM to remove the benzonitrile and unreacted mono oxiazoline platinum complex. Then DCM / ethyl acetate in a 3/1 ratio was used to elute the products.

cis-[PtCl₆(DMSO){N=C(Ph)-O-N(Me)-CH(Ph)}](63).
Formula: C₁₇H₃₀N₂O₂PtCl₂, MW 582.4. White crystalline solid, yield 71%.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.55, 2.75 (s, 3H, NMe), 6.10 (s, 1H, N-CH-N), 7.50 (m, 3H)(PhCH-N), 7.61 (t, 7.8 Hz, ArC(4)H)(N=C-Ph), 7.70 (t, 7.2 Hz, ArC(3,5)H)(N=C-Ph), 7.86 (m, ArC(2,6)H)(PhCH-N) and 8.72 (d, 7.8 Hz, ArC(2,6)H)(N=C-Ph).

¹³C NMR (125.7 MHz, CDCl₃) δ (ppm): 46.5 (NMe), 94.3 (N-CH-N), 123.7 (C₄, ArC(1))(N=CPh), 129.9, 130.3 and 134.1 (ArCH)(N=CPh), 128.8, 128.9 and 129.0 (ArCH)(CHPh), 136.5 (ArC(1))(CHPh).

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ (ppm): -3058.3 (750 Hz).

IR spectrum (selected bands), cm⁻¹: 1633 ν(C=N), 1494, 1450, 1406, 1353, 1313, 1147, 1024, 777, 697.3, 440.5.

MS-FAB⁺, m/z: 582.9 [M+H]⁺, 604.9 [M+Na]⁺, 546.0 [M-HCl]⁺, 510.0 [M-2HCl]⁺.

trans-[PtCl₂(d₆-DMSO){N=C(Ph)-O-N(Me)-CH(Ph)}](64). This characterisation was obtained from experiment 1 in the results and discussion, where d₆-DMSO was used as solvent.

White crystalline solid, yield <10%. (not isolated)

¹H NMR (300 MHz, CDCl₃) δ (ppm): {[(CD₃ not seen, d₆-DMSO), 3.09 (s, 3H, NMe), 5.99 (s, 1H, N-CH-N), 7.45 (m, 3H)(PhCH-N), 7.58 (m, ArC(4)H)(N=C-Ph), 7.70 (m, ArC(3,5)H)(N=C-Ph), 7.98 (m, ArC(2,6)H)(PhCH-N) and 8.69 (m, 2 ortho H)(N=C-Ph),

¹⁹⁵Pt NMR (107.3 MHz, CDCl₃) δ (ppm): -3058.3 (350 Hz).

8.13.4. Reaction of triphenylphosphine with trans-[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}].

A typical procedure for this reaction is;

[PtCl₂(PhCN){N=C(Ph)-O-N(Me)-CH(Ph)}] (15 mg, 0.025 mmol) and triphenylphosphine (6.55 mg, 0.025 mmol) were placed in a NMR tube and solvated with deuterated chloroform (0.05 ml). This was left for 10 minutes at room
temperature and then the proton NMR checked. The desired product was not isolated due to further ligand exchange.

\[ \text{[PtCl}_2(\text{P(Ph)}_3)\{\text{N=C(Ph)-O-N(Me)-CH(Ph)}\}\} \]

The initial product reaches maximum concentration in approximately 30 minutes. Exchanges then take place resulting in numerous products.

**Analytical data:**

Product not isolated

**Formula:** PtCl\(_2\)N\(_2\)OPC\(_3\)\(_3\)H\(_{29}\), MW 766.56

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 3.06 (s, 3H, NMe), 6.17 (s, 1H, N-CH-N), 7.48 (m, 3H)(CH–Ph), 7.78 (m, H)(CH–Ph), 7.06 (d, 7.5 Hz, ArC(2,6)H)(CH-Ph), 7.39 (m, 6ArC(2,6 or 3,5)H of P(Ph)_3), 6.95 (m, 6ArC(2,5 or 3,6)H of P(Ph)_3), 7.59 (t, 7.0 Hz, 3ArC(4)H of P(Ph)_3), 7.72 (m, 1H)(PhC=–N), 7.55 (t, 7.3 Hz, ArC(3,5)H)(N=C–Ph) and 8.30 (d, 7.3 Hz, ArC(4,6)H)(PhC=N).

\(^13\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) (ppm): 46.36 (NMe), 94.97 (N-CH-N), 153.8 (2C of tpp.), 125.3 (2C of P(Ph)_3), 128.9 (1C of P(Ph)_3), 138.3 (ArC(4) of PhC=N), 128.8 (ArC(3,5) of PhC=N), 130.9 (ArC(2,6) of PhC=N), 128.7 (ArC(2,6) of PhCN), 129.8, 128.9 (3C of PhCN), 130.7, 128.5, 132.4 (C of PhCN).

\(^{195}\)Pt NMR (107.3 MHz, CDCl\(_3\)) \(\delta\)(ppm): doublet, -3598, \(^{1J}\)\(^{195}\)Pt-\(^{31}\)P, 3450 Hz, -2919 and -3390, possibly PtCl\(_2\)(oxa)(P(Ph)_3).

\(^{31}\)P NMR (202.46 MHz, CDCl\(_3\)) \(\delta\)(ppm): singlet, 3.83, doublet 3.83, \(^{1J}\)\(^{31}\)P-\(^{195}\)Pt, 3450 Hz, (cis complex, trans P(Ph)_3-Pt-Cl bond) 20.1, singlet, 20.1 doublet, \(^{1J}\)\(^{31}\)P-\(^{195}\)Pt, 2632 Hz, (trans-PtCl\(_2\)(P(Ph)_3))\(_2\), singlet, 14.31, doublet 14.31, \(^{1J}\)\(^{31}\)P-\(^{195}\)Pt, 3665 Hz, (cis).

IR spectrum (selected bands), cm\(^{-1}\): 2229 \(\nu\)(CN)(free PhCN is 2232), 1664, 1436, 1098, 910.1, 729.3, 692.1, 542.7, 515.7 and 499.6.

MS-FAB\(^+\), m/z: 833.9 [PtCl(PhCN)(oxa)(P(Ph)_3)]\(^+\).

8.13.5 Reaction of PtCl\(_2\)(oxa)(PhCN) with 2-amino-1-methylimidazole.

Reaction did not go to completion and no product was isolated. The same procedure as the previous triphenylphosphine reaction was adopted.
Figure 101. The proton NMR spectrum of the reaction of 2-amino-1-methylimidazole with PtCl$_2$(oxa)(PhCN).

8.14. Ruthenium benzonitrile complexes

Ruthenium trichloride hydrate (0.60 g, 2.3 mmol) was heated at 125 °C in a mixture of methanol (2.5 cm$^3$) and benzonitrile (10 cm$^3$) for 42 hours. The yellow crystalline product can be filtered out and a second crop precipitated on addition of diethyl ether (30 ml).

Formula [C$_{28}$H$_{20}$Cl$_2$N$_4$Ru], MW 584.46, Yellow crystals 1.41g, yield 98%.

$^1$H NMR spectrum in CDCl$_3$, $\delta$ (ppm): 7.97 (d, 7.2 Hz, 2H, PhCN), 7.57 (t, 7.2 Hz, H, PhCN), 7.47 (m, 7.2 Hz, 2H, PhCN).

IR, (KBr), selected band, cm$^{-1}$: 2242, v(CN).

References


34. J. Reedijk, PNAS, 2003, **100**, 3611.


69. L. Wohler and F. Martin, Ber., 1909, 42, 3958.


Appendix 1. Variable temperature $^1$H NMR spectra of PtBr$_2$(oxa)$_2$ showing sharpening of signals but no conformational change.

Pt Br$_2$(oxa)$_2$, 1H spectrum at 298K

PtBr$_2$(oxa)$_2$ at 328K
PtBr$_2$(oxa)$_2$ at 403K
Appendix 2. The Mass-FAB spectra of product 47 and the speculative product PtCl₄N₄O₂C₁₆H₂₀.

Figure 59. The MS-FAB spectrum of [PtCl₂{N=C(Ph)-O-N(Me)-CH(p-HO-C₆H₄)}₂](47).

Figure 64. Mass spectrum of the reaction between trans-[PtCl₂(PhCN)₂] and the protonated derivative of 11.
Figure 102. A comparison of the isotopic pattern of two significant peaks from figures 59 and 64 respectively, which contain the PtCl$_2$N$_4$O$_2$ isotopic contribution.

Table 25. Comparison of the $^{195}$Pt NMR shifts and half height line-widths of various PtX$_2$N$_2$ complexes. (Ref. K$_2$PtCl$_4$)

<table>
<thead>
<tr>
<th>Complex</th>
<th>Shift (ppm)</th>
<th>Line-width (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-PtCl$_2$(nitrile)$_2$*</td>
<td>-2320 to -2370</td>
<td>500 - 1500</td>
</tr>
<tr>
<td>trans-PtBr$_2$(PhCN)$_2$</td>
<td>-2860</td>
<td>750</td>
</tr>
<tr>
<td>trans-PtI$_2$(PhCN)$_2$</td>
<td>-3935</td>
<td>750</td>
</tr>
<tr>
<td>trans-PtCl$_2$(nitrile)(oxa)*</td>
<td>-2210 to -2240</td>
<td>770 - 1300</td>
</tr>
<tr>
<td>trans-PtBr$_2$(PhCN)(oxa)</td>
<td>-2693</td>
<td>750</td>
</tr>
<tr>
<td>trans-PtI$_2$(PhCN)(oxa)</td>
<td>-3695</td>
<td>750</td>
</tr>
<tr>
<td>trans-PtCl$_2$(oxa)$_2$*</td>
<td>-2027 to -2140</td>
<td>775 - 1100</td>
</tr>
<tr>
<td>trans-PtBr$_2$(oxa)$_2$</td>
<td>-2523</td>
<td>1500</td>
</tr>
<tr>
<td>[Pt(NH$_3$)$_4$]$^{2+}$ (hex)</td>
<td>-2575</td>
<td>1500</td>
</tr>
</tbody>
</table>

*Varying phenyl ring substituent.
As can be seen from the table, varying phenyl ring substituents can have a large effect of line-width whereas being coordinated to different halogens does not necessarily have an effect. Being coordinated to different nitrogen environments does not necessarily affect the line-width as can be seen for the ammonia complex compared to the others. Therefore there is no easy correlation between ligand and line-width.
Appendix 3. Plots testing for first and second order kinetics in DMSO substitution experiment 3.

An expansion of the kink in figure 74 (a) shows that over the first eight hours the reaction is not first order (figure 74 (b)), log A falling exponentially.

Figure 74 (b). DMSO exp. 3, plot of log A against time, first 8 hours.

To test for second order kinetics a plot of the reciprocal of the concentration of starting platinum complex against time was generated. To satisfy the requirement for second order, the plot should be a straight line. However this was found not to be the case as can be seen in figure 74 (c). Most likely what is going on is a mixture of mechanisms and the equimolar reaction does not solely follow first or second order kinetics. As the trans complex is only made when DMSO is in large excess, it can be concluded that the reaction producing this complex follows a first order type mechanism.

Figure 74(c). Expt. 3: Plot of 1/C against time to test the requirement for second order kinetics.
Appendix 4. The proposed hydrolysis product from the attempted substitution of PtCl$_2$(PhCN)(oxa) with pyridine.

$\text{PtCl}_2$(PhCN)(oxa) / Pyridine substitution, proton NMR spectrum.

![Proton NMR spectrum]

$\text{PtCl}_2$(pyr)(oxa) $\neq$ PtCl$_2$(oxa)($\text{C}_6\text{H}_5\text{C(OH)=NH}$)

The major product is possibly the structure on the right, but not excluding other solutions.