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# Molecular mechanisms of cytotoxic side effects of platinum anti-cancer drugs – a molecular orbital study

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## Abstract

The side effects of Pt drugs have been examined by evaluating the literature on Pt chemistry, pharmacology, cellular transport, and clinical efficacy and correlating these studies with molecular orbital computations. It is concluded that Pt chemotherapeutical regimes are dominated by side reactions, particularly hydrolysis in blood serum and delivery efficiency. For example, it is shown that transplatin is therapeutically inactive because it hydrolyses faster in blood serum than ciplatin, so little transplatin reaches its target DNA. The reactivity of charged hydrolysis products determines the severity of side effect. The reactivity indicators of the approved Pt drugs and their various hydrolysed species are calculated. The cellular uptake of Pt is fastest for neutral species, with high lipophilicity, since their desolvation penalties for crossing the cell membrane are lowest.

## Objective

*Cytotoxic side effects of antineoplastic chemotherapeutic Pt drugs*: to examine biophysical molecular properties that could be used to predict the propensity of Pt drugs to cause unwanted side effects

## Introduction

Chemotherapy, surgery and radiation are the main treatments for cancer. Platinum chemotherapeutics are the most widely prescribed drugs in modern oncology (administered to about 50 % of all cancer patients), either alone or in combination with other anti-cancer drugs and/or radiation therapy. Platinum drugs are used for the treatment of a broad spectrum of specific cancers, including testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, breast, cervical, stomach and prostate cancers, as well as Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, sarcomas, multiple myeloma, melanoma, and mesothelioma. One of the greatest successes in chemotherapeutics was the advent of cisplatin treatment of metastatic testicular cancer where the survival rate in 1970 was about 5% of young men, whereas now greater than 80% of such cases are cured. [Abu-Surrah 2006]

Patients receiving Pt chemotherapy experience severe side effects that limit the dose which can be administered. Management of this induced toxicity is crucial for the success of chemotherapy. Side effects of platinum therapy include general cell-damaging effects, such as nausea and vomiting, decreased blood cell and platelet

production in bone marrow (myelosuppression) and decreased response to infection (immunosuppression). More specific side effects include damage to the kidney (nephrotoxicity), damage to neurons (neurotoxicity) and hearing loss. [Boyiadzis 2007, Kelland 2000, 2007, Ko 2008]

The clinical efficacy of the common prescribed Pt drugs is limited by their particular effectiveness against particular cancers, their unwanted toxic side effects against normal tissue, intrinsic and acquired resistance, and delivery effectiveness. Reduced accumulation of Pt drugs in tumour tissue caused by reduced cellular uptake and/or increased efflux is one of the most critical factors determining intrinsic and acquired resistance. [Wernyj 2004] Cellular platinum accumulation is a major determinant of the sensitivity of a wide range of cancer cells to cisplatin [Hall 2008, Gately 1993, Koga 2000], carboplatin [Shen 2000], oxaliplatin [Grothey 2003, Hector 2001]. *Ovarian cancer patients who responded to platinum chemotherapy had higher tumor platinum concentrations at autopsy than those patients who showed no response to Pt drugs*. [Stewart 1988] However, Pt drugs also accumulate in some normal tissues, and induces toxicity in these tissues: in renal tubules during cisplatin-induced nephrotoxicity, cochlea organelles during cisplatin-induced ototoxicity, and dorsal root ganglion of patients and animal models of cisplatin or oxaliplatin induced peripheral neuropathy. [Krarup-Hansen 1999, Screnci 2008, Rybak 2009, More 2010] Overexpression of the transporter CTR1 stimulates cellular platinum drug uptake and cytotoxicity simultaneously. [Holzer 2004, Kabolizadeh 2007, Song 2004, Liang 2009]

Cisplatin, carboplatin and oxaliplatin are some of the most widely approved and prescribed anti-cancer drugs in the world. Nedaplatin has been approved for use in Japan (head and neck, testicular, lung, ovarian, cervical cancers), lobaplatin has been approved in China (chronic myelogenous leukaemia) and heptaplatin approved in South Korea (gastric cancer). Cisplatin was approved in 1978, for treating patients with metastatic testicular or ovarian cancer in combination with other drugs but also for treating bladder cancer. Carboplatin was approved in 1989 for initial treatment of advanced ovarian cancer in combination with other approved chemotherapeutic drugs. Oxaliplatin was approved in 1994 for use against metastatic colorectal cancer in combination with fluorouracil and folinic acid. Picoplatin and satraplatin, which is orally administered, have undergone extensive clinical trials, but are not yet approved. Well over 3000 Pt antineoplastic drugs have been examined in vitro, but to date, only cisplatin, carboplatin and oxaliplatin have received world wide approval. [Boulikis 2007] The failure modes of potential new drugs in human clinical trials have been undesirable side effects and more stringent requirements to demonstrate not just improved quality of life for the patient, but also significantly improved survival rates. This has led to a focus on drug delivery rather than seeking new drugs. [Wheate 2010]

The clinically related features of the Pt drugs relevant to this study have been extensively reviewed. [Wheate 2010, Abu-Surrah 2006, Alcindor 2011, Alderden 2006, Berners-Price 2000. Casini 2012, Di Pasqua 2012, Reedijk 2008, Pil 2002, Sooriyaarachchi 2011, Johnstone 2014, Galanski 2012] The following discussion highlights some important background aspects relevant to this study that have been previously discussed and documented in these review papers.

Cisplatin is intravenously administrated into blood stream plasma which has a fairly high chloride concentration (ca 100mM) which limits aquation of cisplatin (substituting a water ligand for a Cl ligand). The hydrolysis products of cisplatin interact with several proteins found in blood plasma, (human serum albumin) especially those that possess the cysteine and thiol groups, and other species such as glutathione and methionine, all of which have reducing properties. It is also likely that the small amount of the charged aquo complexes $\{(H_3N)_2Pt(H_2O)Cl\}^+$ and $\{(H_3N)_2Pt(H_2O)_2\}^{++}$ formed by hydrolysis of cisplatin in blood plasma can cause toxic side effects, such as nephrosis. The $\{(H_3N)_2Pt(H_2O)Cl\}^+$ species is considered the most important therapeutically and forms the majority of adducts with DNA *inside* the cell which induces apoptosis. One day after cisplatin administration, about 65-98% of the platinum is protein bound, resulting in deactivation of the drug and possibly causing some of the severe side effects. About 15-25% of the intact cisplatin is renally excreted within 2-4 hours, and 20-80% excreted in 24 hours, with the remainder bound to tissues or plasma protein. Cisplatin and other metal-based compounds are known to bind to several classes of peptides and proteins with different roles, including transporters, antioxidants, electron transfer proteins, RNA, and DNA-repair proteins. It is estimated that only about 1 % of the administered cisplatin reacts with nuclear DNA to form Pt-DNA adducts inside the cell which induce tumour cell death. The major dose-limiting effect is nephrotoxicity, which is dose dependent, cumulative and sometimes irreversible. [Casini 2012, Ivanov 1998, Kratz 1993, Barnham 1996, Lempers 1991]

**Carboplatin** is less clinically potent than cisplatin, and depending on the strain of cancer, carboplatin may only be 1/8 to 1/45 as effective. The clinical standard of dosage of carboplatin is usually a 4:1 ratio compared to cisplatin, ie for a regimen that usually requires a particular dose of cisplatin, about four times as much carboplatin is needed to achieve the same therapeutic effectiveness. Carboplatin has myelosuppression as its dose-limiting factor. Carboplatin and cisplatin work in similar ways, forming an identical type of adduct with DNA. They attack tumours similarly but carboplatin is less toxic to the nervous system and the kidneys, and its lower reactivity is thought to account for the fact that about 90% of carboplatin can excreted intact in the urine, unlike cisplatin. Carboplatin also stays in the body longer. It has a retention half-life of 30 hours versus cisplatin's 3 hours. About 50-70% is excreted within 24 hours, with 32% as intact carboplatin. About 87% is irreversibly bound to plasma proteins within 24 hours as Pt containing products, and slowly eliminated with a half life of about 5 days. Although it has a lower therapeutic activity than cisplatin, its decreased toxicity allows outpatient administration without need for forced diuresis and very high dosages (up to 2000 mg/dose) can be achieved with more antitumour efficacy. It is widely distributed in the body, mainly in the liver, kidney and skin. The pharmacokinetics is dose proportional, with no apparent accumulation after repeated daily dosing. Carboplatin exhibits lower reactivity and slower DNA binding kinetics, although it forms the same reaction products *in vitro* at equivalent doses with cisplatin. The ligand exchange reactions of carboxylate ligands on Pt (as in carboplatin) are kinetically much slower than for the chloride ligand (as in cisplatin). Carboplatin is activated when one arm of the carboxylate ligand is free, a process accelerated by nucleophiles, like sulphur containing species, chloride, carbonates in blood serum or in the cytoplasm. [Barnham 1996]

Carboplatin has fewer side effects than cisplatin which is thought to be due to its lower reactivity. A comparative study showed that cisplatin was 95% protein bound in the blood after one day, whereas carboplatin was 40% protein bound to the same three plasma proteins. [Sooriyaarachchi 2011] Carboplatin has a more favourable adverse effect profile than cisplatin, which has led to the replacement of cisplatin with carboplatin in many chemotherapeutic regimens. Hearing loss and peripheral neuropathy are rare with carboplatin, and nephrotoxicity is substantially less. Visual changes or loss of vision has been reported with high doses of carboplatin and hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, and hypocalcemia occurs in about 30% of patients during therapy with carboplatin but these are not as common or severe as with cisplatin. Carboplatin and cisplatin seem to be equally effective in ovarian, non-small cell and small cell lung cancers. However carboplatin has the same spectrum of activity as cisplatin, and is not effective against cisplatin resistant tumours.

**Oxaliplatin** is therapeutically indicated for metastatic colorectal cancer typically along with folinic acid and 5-fluorouracil (Folfox). Oxaliplatin itself has a modest effect on colorectal cancer, whereas cisplatin and carboplatin have no effect. Oxaliplatin has a half-life of about 14 minutes *in vivo* and the short half-life is explained, at least in part, by the reaction of oxaliplatin with chloride, glutathione, methionine, and cysteine at physiological concentrations. At the end of a 2 hour infusion, 15% Pt is present in blood, with the remainder distributed in tissue or eliminated in urine. Oxaliplatin undergoes rapid and extensive biotransformation to monochloro, dichloro and diaquo $DACHPt^{++}$ species, and there is little intact drug left after 2 hours. These biotransformations may be responsible for the dose limiting neurotoxic side effects, but it exhibits less ototoxicity and nephrotoxicity than cisplatin and carboplatin. It has been shown that oxaliplatin forms complexes with excess haemoglobin after one hour at room temperature, consuming about 60% of the oxaliplatin. Cisplatin and carboplatin formed one major and two minor complexes only after 24 and 96 h of incubation, respectively. After 24 h, there was a complete binding of oxaliplatin and cisplatin to the protein in red blood cells, but in contrast, carboplatin was only partially bound, with both the free and the protein-bound carboplatin species detected. [Mandal 2004] OxaliPt is mainly excreted in the urine, with 54% of the total Pt excreted within 5 days. The mechanism by which oxaliplatin exerts its therapeutic effects (which is different to cisplatin and carboplatin) appears to be via attachment to proteins which are vital for DNA transcription as well as forming Pt-DNA adducts. OxaliPt also has a role in initiating or intensifying tumorigenesis pathways. [Allan 2012] Oxaliplatin is more active against cell lines that are resistant to cisplatin and carboplatin, but cells eventually develop resistance to oxaliplatin as well. It is thought that $(DACH)PtCl_2$ is the actual species that enters the cell, [Alcindor 2011, Kweekel 2006] but there is contradictory evidence that oxaliplatin is the major effective species in human colon carcinoma cells, with the hydrolysis products $DACHPtCl_2$, $DACHPt^{+}Cl(H_2O)$ and $DACHPt^{++}(H_2O)_2$ making only minor contributions. The cytotoxicity levels were proportional to their cellular uptakes. [Luo 1998] An investigation of the concentrations of oxaliplatin and $Pt(DACH)Cl_2$ in plasma of colorectal cancer patients during (2 hours of infusion, 130 $mg/m^2$) and after infusion (up to 2 hours), showed that during infusion oxaliplatin accounted for 58 % (1 hour) and 63 % (2 hours) of the total platinum in plasma. At the end of infusion intact oxaliplatin in the administered sample decreased rapidly ($t_{1/2}$ = 0.25 h).

$Pt(DACH)Cl_2$ was not detected in the plasma, suggesting such previous reports were artefacts of sample preparation. [Ip 2008]

Despite the accepted "effective or clinical" half lives of 3, 30, and 0.25 hours for the unbound cisplatin, carboplatin and oxaliplatin (which are somewhat dependent on rates of infusion), there is evidence of long term retention of cisplatin and oxaliplatin over periods up to 20 years. Up to 10% of the circulating Pt remains active, and has implications for long term side effects, such as neurotoxicity and ototoxicity. [Sprauten, Brouwers] The volume of distribution of the Pt drugs is highly dependent on what species are present in blood plasma, since charged aquated species not only form complexes with human serum albumin, but can interact with various tissues particularly those containing zwitterionic phosphatidyl head groups, or ionic species such as carbonates in plasma. Clinically it is important to distinguish between short term side effects over a chemotherapy regime, and those longer term effects which can easily be overlooked.

*The efficacy of anti-tumour drugs, including comparative studies of Pt drugs, is complicated in vivo by tumour specific factors*. For example most solid tumours possess unique pathophysiological characteristics that are not observed in normal tissues or organs, such as extensive angiogenesis and hence hypervasculature, defective vascular architecture, impaired lymphatic drainage/recovery system, and greatly increased production of a number of permeability mediators. Human solid tumours are invariably less well-oxygenated than the normal tissues from which they arose. This *tumor hypoxia* leads to resistance to radiotherapy and anticancer chemotherapy as well as predisposing for increased tumour metastases. Prolonged hypoxia of the tumour tissue leads to necrosis, and necrotic regions are also characteristic of solid tumors. Hypoxia and necrosis represent clear differences between tumours and normal tissues and are potentially exploitable in cancer treatment. Hypoxia is implicated in resistance to chemotherapy and radiation therapy, via the free radical oxygen effect. It has been suggested that drugs that are effective under hypoxic conditions might be very effective. [Brown 2007, Gilkes 2014, Hockel 2001]

The phenomenon now known as the enhanced permeability and retention (EPR) has been observed to be universal in solid tumours. [Maeda] It has been shown that disorganised and leaky vascular endothelial cells that usually feed many solid tumours can allow passage of large entities up to ~1.7μm in size (bacterial or liposomal nanoparticle drug size) from the plasma into the tumours. Hypovascular metastatic cancers, such as liver, prostate, pancreatic tumours take up less anti-cancer drug than highly vasculated tumours (eg ovarian) so drug concentrations in the tumour are much lower than in plasma, rendering lower anti-cancer effectiveness. In addition, it has been shown that penetration of anti-cancer drugs is dependent on cellular packing density and interstitial fluid pressure. [Grantab] *This means that in vitro studies of drug efficacy may be misleading.* It also means that predicting drug side effects is very difficult, since protein bound Pt (such as in Pt bound human serum albumin HSA) may have anti-tumour properties, [Ivanov 1998] and may be able to accumulate in tumour cells by endocytosis if sufficient quantities of the Pt-HSA is available in the solid tumour. It is also known that cancer patients often have decreased HSA concentrations in their blood. The infusion of preformed Pt-HSA has increased survival times. The infusion of HAS prior to Pt chemotherapy may also be beneficial

by lowering the formation of hydrolysis products from intact Pt drugs and hence decreasing side effects. [Morris]

The characteristics of solid tumours make predictions of anti-cancer drug efficacy in humans from in vitro and animal in vivo studies somewhat suspect. In particular, $IC_{50}$ values of cell lines, drug cellular influx and efflux measurements, drug cytotoxicity, and other pharmacological measures widely used in the literature may be misleading. Actual human clinical Pt anti-cancer data efficacy is sparse, although side effects of Pt chemotherapeutrics is widely available, since the drugs have been in clinical use for many years. [Boyiadzis 2007, Kelland 2000, 2007, Ko 2008] *Clinical treatments of many cancers are now combination therapies, so predictions of the efficacy of Pt drugs needs to be able to accommodate the adjuvant therapies used with the Pt drugs*.

A recent study [Sooriyaarachchi 2011] has found that cisplatin is 95% bound to human plasma protein after 24 hours, compared to 40% for carboplatin. Both drugs appeared to bind to the same three proteins, and in a phosphate buffered saline, the same hydrolysis product, probably $\{(H_3N)_2Pt(OH_2)_2\}^{++}$ was involved in protein binding. Similar Pt hydrolysis products were also found in phosphate buffered saline independent of the presence of blood plasma. This data suggests that it is the indiscriminate delivery of the administered drug and particularly its charged hydrolysis products to both malignant and healthy cells that is the cause of the various toxic side effects.

Comparison of the accumulation of cisplatin, carboplatin and oxaliplatin in MCF-7 breast cancer cells after 24 hours showed oxaliplatin had the highest uptake (ca 5.2 times as fast as carboplatin), closely followed by cisplatin (ca 4.2 times carboplatin) then carboplatin. The intracellular concentrations were proportional to the concentrations in the culture medium, consistent with a dominant passive diffusion uptake. [Ghezzi 2004] These data reflect the clinical half lives of the drugs.

The carboplatin uptake rates in small lung cancer cells are ten fold slower than for cisplatin for sensitive and resistant cells, and independent of ATP cell status. However cisplatin uptake is 2 fold slower in resistant cells compared to sensitive cells, but in ATP depleted cells, the rates are about the same. The uptake rate for the di-aquated species $\{(H_3N)_2Pt(H_2O)_2\}^{++}$ was found to be 40 times faster than the parent compound for both cell lines, but decreased dramatically for ATP depleted cells, indicating an active transport process for the charged species. These results appear to show that passive diffusion predominates for the neutral cisplatin species, but active transport is necessary to transport charged hydrolysed Pt species. The very slow hydrolysis of carboplatin means that little of the charged hydrolysis species exists in blood plasma, so the trans-cellular transport is predominantly passive diffusion. [Pereira-Maia 2003] The data for the di-aquated species seems anomalous since it is expected that a very large desolvation energy would be required before active uptake via a protein transporter. It is possible that the neutral hydrolysed species $\{(H_3N)_2Pt(OH)Cl\}$, or less likely $\{(H_3N)_2Pt(OH)_2\}$, were the actual species being transported since it is known that $\{(H_3N)_2Pt(OH)Cl\}$ is the dominant species formed at pH 7 (see following discussion also).

The extracellular pH of solid tumours falls in the range 6.0 to 7.0, whereas the extra- and intracellular pH for normal tissue is ~ 7.4. [Kozin 2001, Stubbs 2000] The

hydrolysis of cisplatin has been shown to be dominated by three equilibria following initial aquation to form mainly $\{(H_3N)_2Pt(H_2O)Cl\}^+$ and to a lesser extent, $\{(H_3N)_2Pt(H_2O_2\}^{++}$. The equilibria are: (1) $\{(H_3N)_2Pt(H_2O)Cl\}^+$ $\leftrightarrows \{(H_3N)_2Pt(HO)Cl\}$ with $pK_a$ 6.4, (2) $\{(H_3N)_2Pt(H_2O)_2\}^{++}$ $\leftrightarrows$ $\{(H_3N)_2Pt(OH)(H_2O)\}^+$ with $pK_a$ 5.4, (3) $\{(H_3N)_2Pt(OH)(H_2O)\}^+ \leftrightarrows$ $\{(H_3N)_2Pt(OH)_2)\}$ with $pK_a$ 7.2. *These data indicate that a dominant hydrolysis species in blood plasma is the neutral {$(H_3N)_2Pt(HO)Cl$} species*. [Berners-Price 1992] In the human T-cell lymphoma cell line, Jurkat, it was thought that the species $\{(H_3N)_2Pt(H_2O)Cl\}^+$ and/or $\{(H_3N)_2Pt(OH)Cl\}$ were preferentially removed from the in vitro cell media. [Tacka 2004]. It is known that smaller neutral species like cisplatin or $\{(H_3N)_2Pt(HO)Cl\}$ will preferentially cross cell membrane by diffusion in preference to charged Pt species, unless a specific cation transporter is available for the charged species. [Fong 2014, 2015] The equilibrium constant for (1) above indicate that the dominant species transported across the cell membrane for cisplatin is $\{(H_3N)_2Pt(OH)Cl\}$. The lower concentrations of charged Pt species in plasma and the need for higher energy to be supplied to substantially desolvate the charged species $\{(H_3N)_2Pt(H_2O)Cl\}^+$ before active transport by a OCT protein mitigate against such a process being significant, particularly if there are competing pathways which can preferentially transport neutral species.

It has also been shown [Di Pasqua 2012] that carbonates in the blood plasma react with carboplatin. Aged carboplatin in carbonate buffer was more toxic to human neuroblastoma, proximal renal tubule and Burkitt's lymphoma cells than fresh solutions. Cell toxicity increased with ageing time. The carbonate ion initially substitutes for one "arm" of the CBDCA cyclobutanedicarboxylate ligand, followed by various reactions to form eventually reactive species similar to those formed from the hydrolysis of cisplatin. Hence the cell lines showed cisplatin-like resistance to the aged buffered carboplatin solutions.

There are substantial differences in the stability and reactivity of cisplatin and carboplatin in blood plasma. Carboplatin in a ready-to-use aqueous solution has a long shelf life, attributed to the existence of a dimer-monomer equilibrium ($K\ M^{-1} \sim$ 391), which favour the dimeric species (81%). Also the rate constant for the initial hydrolysis of carboplatin, where one arm of the CBCA ligand is replaced by a water molecule, is several orders of magnitude slower than for cisplatin. [Burda 2005, Di Pasqua 2011, 2012] The monoaquation of carboplatin is about 10 times faster than the diaquation at pH 7. [Hay 1998] However the extent of the further rapid hydrolysis of the monaquated carboplatin to $\{(H_3N)_2Pt(H_2O)Cl\}^+$ by displacement of the CBCA ligand by $Cl^-$, to form $\{(H_3N)_2Pt(OH)Cl\}$, or the formation of $\{(H_3N)_2Pt(OH)_2\}$ by displacement of the CBCA ligand by water, then deprotonation, is unclear. [Pavelka 2007, Di Pasqua 2012]. The neutral $\{(H_3N)_2Pt(OH)Cl\}$ is the major species formed in blood serum, and along with the parent carboplatin are the species most likely to be transported across the cell membrane.

The carboplatin dimer is reported to exhibit greater in vitro anticancer activity and lower toxicity in mice than its parent compound, carboplatin. [Xie 2010] These observations, as well as the longer half life, are consistent with the lower known side effects of carboplatin in the body compared to cisplatin and oxaliplatin. Oxaliplatin is also known to exist as a dimer in intravenous aqueous solutions, and like carboplatin, possibly in the blood as well after administration. [Di Pasqua 2011] However the

greater reactivity of oxaliplatin compared to carboplatin, and the much shorter half life for oxaliplatin, suggests that only carboplatin has a significant monomer-dimer association in blood plasma which needs to be accounted for in drug transport processes into tumour cells.

The toxicity of Pt drugs are directly related to the ease that the leaving group is aquated. Platinum complexes with highly labile ligands, such as water or nitrate, are very toxic whereas ligands such as bis-carboxylates, which aquates very slowly, are significantly less toxic. For example, the 1,1-cyclobutanedicarboxylate group of carboplatin, which aquates with a rate constant of $10^{-8}$ $s^{-1}$, compared with $10^{-5}$ $s^{-1}$ for the Cl of cisplatin, renders carboplatin less reactive than cisplatin. The oxalate ligand of oxalipaltin also reduces the severity of side effects compared to cisplatin. [Wheate 2010] Charged aquo hydrolysis products of cisplatin and oxaliplatin which exist in small quantities in blood plasma may be a cause of clinical side effects, are responsible for the essentially irreversible Pt-HAS formation, as well as interaction with other tissues. These *charged Pt species are potent electrophiles* that can react with a variety of nucleophiles, such as nucleic acids and sulfhydryl group of proteins. The long term retention of cisplatin and oxaliplatin and their biotransformation products over many years has implications for long term side effects, particularly if Pt species can be released from "stored" tissue and re-enter the blood stream. The hydrolysis of oxaliplatin results in the single charged aquo monodentate oxalate complex $pK_a$ 7.6, followed by formation of the doubly charged diaquo complex, $pK_a$ 6.1. [Gill 1982, Zhang 2006 ] Hence hydrolysis occurs rapidly at the physiological pH 7.4 level, to give ca. 83% diaquo and 17% monaquo/hydroxo species, which is consistent with the short half life and high reactivity for this drug in the body. These species would be expected to be highly reactive in blood serum. However, another $pK_a$ determination of the first hydrolysis step found a $pK_a$ of 7.2, and the reverse reaction of the first hydrolysis to be faster than the forward reaction, indicating that oxaliplatin is quite stable at pH 7.4. [Jerremalm 2003] It is known that the singly charged monoaquo species of cisplatin and carboplatin are preferentially initially formed by hydrolysis at physiological pH levels. [Berners-Price 2000, Hay 1998, Di Pasqua 2012, Pavelka 2007] The hydrolysis of oxaliplatin is less clear, and in blood serum, it is likely that reactions with blood proteins, as well as further reactions to form chloro, hydroxyl species could occur. The initial formation of charged hydrolysis products is consistent with the known greater reactivity in blood serum, and shorter clinical half life.

There is evidence that cisplatin resistant cells may have altered or defective endocytic recycling compartments (ERC) which reduces the uptake of the drug. [Liang 2006]. The ERC is a network of tubular membranes which is located in the perinuclear region of the cell, and most membrane components pass through it along their endocytic recycling pathways from the plasma membrane to the lysosome. This pathway also involves endosomes which are membrane bounded compartments. Molecules internalized from the plasma membrane can follow this pathway all the way to lysosomes for degradation, or they can be recycled back to the plasma membrane. These processes provide potential pathways for Pt containing species to be recycled back to the plasma membrane and into the blood plasma for wider circulation by exosomes.

It has been pointed out that slow kinetic lability (the rate that ligands eg water can exchange) of Pt anti-tumour drugs is on about the same timescale as cellular division, implying that when these drugs do reach their targets intact, Pt-ligand dissociation is not a dominant process. [Reedijk 2008] Kinetic lability is also associated with increased side effects, which is one of the reasons that possibly explains why transplatin is therapeutically inert, whereas cisplatin is active. Transplatin is generally more reactive than cisplatin because of the known "trans effect" $Cl > NH_3$, [Mikola 1994, 1996] and the faster side reactions such as hydration or reaction with the nucleobases of serum proteins, mean that clinical concentrations arriving at the target DNA are greatly reduced compared to cisplatin.

Cisplatin is considered to accumulate in the cell after passing through the cell membrane by passive diffusion and by active transport processes involving the organic cation transporters (hOCT) and Cu-transporters (Ctr1, Ctr2). Other proteins participating in cisplatin regulation in the cell include ATP7A and ATP7B (two kinds of copper-efflux-transporting P-type adenosine triphosphate). Ctr1 plays a role in uptake and ATP7B regulates efflux processes. ATP7A is involved in copper transport from the cytoplasm to secretory vesicles via the Golgi complex, and then out of the cell. In cells treated with cisplatin, ATP7A mediates its inclusion in vesicles and, in some cell lines, it brings about cell detoxification. [Gately 1993, Howell 2010, Ivy 2013, Liu 2012] The overexpression of the organic cation transporters (OCT1 and OCT2) help facilitate entry of oxaliplatin into cells, and the propensity of colorectal cancer cells to overexpress these transporters may explain the efficacy of this drug in the treatment of colorectal cancer. [Zhang 2006]

An extensive review of in vitro, in vivo and human studies has shown that membrane transporters are major determinants of the pharmacology of platinum anti-cancer drugs. Members of the ATP-binding cassette (ABC), solute carrier (SLC) and ATPase membrane protein superfamilies (ABCC2, CTR1, CTR2, OCT1, OCT2, OCT3, OCTN1, OCTN2, MATE1, MATE2-K, ATP7A, ATP7B, ABCG2, ABCC1, ABCC4 and ABCB1) have been found to contribute to the net accumulation (influx and efflux) of platinum drugs (cisplatin, oxaliplatin, oxaliplatin) in malignant and normal tissues. Some key findings were: ABCC2 is an efflux transport of cisplatin, CTR1 is an uptake transporter of cisplatin and other platinum drugs, and it may play a role in platinum toxicities, ATP7A and ATP7B appear to be efflux transporters of cisplatin, oxaliplatin and carboplatin, but not all studies were positive, but both appear to have contributed to resistance to platinum drugs, OCT1 is an uptake transporter of oxaliplatin, cisplatin, carboplatin, picoplatin and pyriplatin, OCT2 is an uptake transporter of cisplatin, oxaliplatin and picoplatin. [Liu 2012]

There was no saturation of cisplatin, (and tetraplatin and JM221) after 2 hours in ovarian carcinoma cells, but resistant cells showed the lowest accumulation, attributed to reduced uptake not increased efflux. [Mistry 1992] The early uptake of a series of oxaliplatin analogues by cisplatin-sensitive and -resistant ovarian carcinoma and in an oxaliplatin-sensitive and -resistant ileocecal colorectal adenocarcinoma cell line was mainly by passive diffusion (as indicated by a relationship between lipophilicity and uptake), but later the uptake was independent of lipophilicity, indicating a change of uptake mechanism. The reactivity of the oxaliplatin analogues with the nucleotides 2′-deoxyguanosine 5′-monophosphate and 2′-deoxyadenosine 5′-monophosphate, and the cytotoxicity (as measured by the MTT assay) showed that increased reactivity and

reduced lipophilicity were associated with high cytotoxic activity. Resistance was influenced by lipophilicity but not by reactivity. [Buss 2011, 2012] However as will be shown later in this paper, lipophilicity alone is not a good measure of cell membrane permeability.

In human ovarian carcinoma cells, cisplatin triggered redistribution of ATP7A and ATP7B from the perinuclear region to more peripherally located sites in the cytosol, and quick return of the proteins back to the *trans*-Golgi network indicated that cisplatin-controlled trafficking of the transporters may indicate an efflux pathway of the drug. Cisplatin exposure had no effect on protein localisation in the resistant cell line and the cisplatin-resistant cells were found to have significantly less lysosomes than the sensitive cells. [Kalayda 2008]

The intracellular chloride ion concentration is relatively low (4-20mM), and about 4mM in the cell nucleus) enabling the labile chloride ions to be replaced by water molecules. These positively charged species $\{(H_3N)_2Pt(H_2O)Cl\}^+$ and $\{(H_3N)_2Pt(H_2O)_2\}^{++}$ form adducts with DNA. The mono cationic species forms the large majority of the DNA adducts. [Pil 2002] These cations would not be easily actively effluxed from the cell, since a large desolvation energy has to be supplied before a transport protein (eg multiple drug resistant protein etc) can transport the charged species. The intracellular environment is rich in thiol-containing species, such as glutathione and metallothionein, that are known to react with Pt species forming neutral species, which can more easily be effluxed out of the cell.

Despite earlier findings that transplatin displayed no anti-tumour effects, the later discovery that many trans platinum complexes were clinically effective caused a re-evaluation of the mechanism of cytotoxic behaviour and a search for more effective platinum drugs. Transplatin has a greater reactivity compared to cisplatin and aquates approximately 4 times faster than cisplatin, and, following a 4-hour incubation with red blood cells, transplatin reacts with 70% of the glutathione, whereas cisplatin reacts with only 35%. This greater reactivity can be rationalized in terms of the known trans effect in Pt(II) complex chemistry. The high reactivity of transplatin with proteins and peptides reduces its effective anti-tumour concentrations and may be the cause of side effects. Cytotoxic trans platinum complexes form different types of DNA adducts than the cisplatin analogues. [Abu-Surrah 2006, Alderden 2006]

Reactive oxygen species, formed by cellular interactions with charged Pt species, are also thought to be the cause of severe side effects of cisplatin, such as including nephrotoxicity, ototoxicity and hepatotoxicity, which can be reduced by the addition of antioxidants. Evidence of oxidative stress caused by cisplatin include: increases in superoxide anion, hydrogen peroxide, hydroxyl radical, depletion of antioxidants GSH-peroxidase and GSH-reductase, mitochondrial dysfunction, as well as apoptosis in normal as well as cancerous cells. [Deavall 2012]. Reactive oxygen species are particularly important in hypoxic environment of solid cancerous tumours.

## Results and Discussion

It is clear from the introduction above on the origin of side effects that there are several dominant features:

(a) The reactivity of the Pt species in blood serum, which includes the formation of charged species from hydrolysis in the blood serum and within the cytosol, and the formation of highly reactive free radical species such as ROS within the cells of hypoxic solid tumours
(b) The "effective or clinical" half lives and longer term retention of Pt species in the body
(c) The ease which various Pt species can cross cell membranes and change the homeostasis with the cell

The reactivity of various Pt drugs, and their hydrolysis products, and their free energies of solvation are shown in Table 1. As alluded to above, the redox potentials of the various Pt species are measures of their reactivity, [Jungwith 2011, Kovacic 2000] particularly under the hypoxic reducing conditions which characterise tumour tissue. As these values are not known, or easily measurable under the different bodily environments, the IE and EA values in neutral water have been calculated. The electrophilicity of Pt drug species is directly related to the charge on Pt, so this property is another measure of reactivity when nucleophilic species are present.

A general model for the permeability of drugs crossing cellular membranes has been developed. It has shown that passive diffusion rates are negatively dependent on water desolvation and lipophilicity with smaller dependencies on dipole moment and molecular volume. [Fong 2015] Originally applied to drug permeability across the blood brain barrier, this model has been shown to be applicable to other cell membranes, and sometimes to active transport processes as well. The major finding applicable to this study is that charged drugs at the physiological pH have very large desolvation energies, as well as large dipole moments, both of which mitigate against charged species penetrating the hydrophobic leaflets of the cell membrane. Neutral species have greater permeability than charged species.

The extensive review of active membrane transporters [Liu 2012] has shown that cisplatin, carboplatin, oxaliplatin, (as well as JM118, picoplatin, pyriplatin) are transported in vitro and more importantly in human clinical studies (ATP7A, ATP7B, ABCC2, ABCG2, ABCB1/MDR1, OCT2 and CTR1). What is unknown from these studies is the actual species that are transported, since hydrolysis products are produced in aqueous environments, and these products can react with blood serum proteins. Also the specific environment in the solid tumour is unknown. The degree of desolvation of the transported species in the protein environment of the various transporters is unknown, but some degree of desolvation must occur within the lipid bilayer environment of the transporter. The X-ray structure of the P-glycoprotein (Pgp, ABCB1) is known [Li 2013] but there is no data on Pt-transporter structures or binding interaction. Using synthetic proteins corresponding to hCTR1 mets motifs, an attempt to examine the binding interaction between Pt drugs and the human hCTR1 extracellular N-terminus methionine rich motifs that might be the Pt binding sites. The studies suggest that cisplatin and carboplatin react with the mets rich motifs of the synthetic peptide with a loss of the diammine ligands, but oxaliplatin retains it diammine ligand on co-ordination of Pt to the peptide. [Crider 2009] The X-ray structure of hCTR1 [de Feo 2009] shows that the trimeric structure consists of a pore stretching across the membrane bilayer, and sealing both ends of the pore, are extracellular and intracellular domains which provide additional metal binding sites.

Consistent with the existence of distinct metal binding sites, it was that hCTR1 stably binds 2 Cu(I)-ions through 3-coordinate Cu–S bonds, and that mutations in one of these putative binding sites results in a change of coordination chemistry. Assuming a similar binding for Pt species, it appears that a Pt-S binding also occurs with hCTR1.

Whatever the actual mechanism of Pt interaction with the various transporter proteins, it is speculated that actual Pt species transported by these transporters are likely to be the neutral species formed by hydrolysis rather than the charged species since the desolvation energies required for the charged species are so much greater than the neutral species shown in Table 1. [Fong 2015]

The reactivity of the hydrolysis products in blood serum can be class differentiated for the Pt drugs into (a) the neutral administered species, (b) neutral hydrolysis products, and (c) their charged hydrolysis products. Class (a) and (b) all have low solvation energies, higher lipophilicities, lower charges on Pt, and lower reduction potentials (ie lower electron affinities).

It is noted that the neutral hydrolysis product of cisplatin, $(NH_3)_2PtCl(OH)$, which is the dominant species in blood plasma, has very similar properties to cisplatin, especially its solvation energy, all of which suggest that this species is probably the major species, along with cisplatin, transported across the cell membrane, and these species can then undergo easy hydrolysis in the low $Cl^-$ environment of the cytoplasm, eventually forming apoptotic adducts with DNA. Similarly the major neutral hydrolysis species of carboplatin, $(NH_3)_2Pt\ Cl(OH)$, and oxaliplatin, DACHPtCl(OH) or $DACHPt^{++}(OH)_2$, along with the neutral mother drugs, are probably the major transported and intracellular apoptotic species as well. This would be consistent with their known behaviours in blood plasma. [Di Pasqua 2011, 2012, Tacka 2004, Pavelka 2007, Hay 1998, Berners-Price 2000, Kweekel 2005] The neutral hydrolysis products of nedaplatin, lobaplatin, heptaplatin and picoplatin have similar solvation and lipophilicity characteristics to their parent drugs, (and vastly different from the charged hydrolysis species) suggesting that these neutral species can cross the cell membrane as easily as the parent drugs.

The rate constant for the first hydrolysis dechlorination step of cisplatin at is $1.3x10^{-4}\ s^{-1}$ [Burda 2005] whereas the value for carboplatin is $5.2x10^{-9}\ s^{-1}$ and for transplatin is $1.1x10^{-3}\ s^{-1}$. [Pavelka 2007, Burda 2005] The data for cisplatin and carboplatin are consistent with the known reactivity with plasma proteins and the general lower clinical reactivity of carboplatin. The free energy of hydration of cisplatin is 7.0 kcal/mol compared with a value of 6.8 kcal/mol for transplatin in aqueous solutions. The trans-$[Pt(NH_3)_2Cl(H_2O)]^+$ species and the trans-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ species undergo deprotonation to form the hydroxyl species faster than the corresponding cisplatin species. [Burda 2005] Transplatin is also predicted to react with plasma proteins in the blood about 8.5 times as fast as cisplatin, consistent with the notion that the cytotoxic inertness of transplatin is due to the side reactions that consume the drug before it can reach its target. It is also known that the reactivity towards nucleobases of the trans-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ species is 7-8 times as fast as the trans-$[Pt(NH_3)_2Cl(H_2O)]^+$ species, which amplifies the rate of side reactions with serum proteins. [Mikola 1996] The rate that the hydrolysis products of these drugs will react with electronegative sites on plasma proteins can be gauged from the large charges on Pt for these ionic species, which is a direct measure of their electrophilicity. It is clear

that the aqueous hydration rate for cisplatin and transplatin are different from the reactivity rates with nucleobases of serum proteins. [Burda 2005, Mikola 1996]

Little is known about the active species of picoplatin, nedaplatin, lobaplatin, and heptaplatin in blood plasma, but similar arguments would apply to those for cisplatin, carboplatin and oxaliplatin based on the data in Table 1. The data for nedaplatin shows that it has a very similar cellular uptake and reactivity ability to cisplatin, which is not expected given its quite different chemical structure. It is considered to give fewer side effects (nausea, vomiting and nephrotoxicity) than other Pt drugs. [Koshiyama] Picoplatin also has very similar properties to cisplatin, which probably reflects its similar structure.

It is also known that the hydrolysis products of cisplatin, carboplatin and oxaliplatin can form dimers and oligmers in aqueous environments [Sooriyaarachchi 2011, Di Pasqua 2011, 2012, Esteban-Fernandez 2010, Berners-Price 2000]. A chloride bridged dimer of cisplatin has been found in cisplatin nanocapsules, along with the parent compound. [Chupin 2004] A dimer of carboplatin has been characterised, and reportedly exhibits greater in vitro anticancer activity and lower toxicity in mice. [Xie 2010] Table 1 shows the dimer has a high solvation energy and larger molecular size (as expected), which mitigate against passive diffusion. However, the Ctr1 or OCAT transporters could be active, particularly since the dimer is overall neutral and has a low charge on the Pt atoms. It is also possible that the report showing a higher toxicity for the dimer is confounded by the monomer-dimer equilibrium.

The charge on Pt is directly related to the electrophilicity of the Pt species in the blood plasma and would be expected to react with nucleophilic sites on various proteins such as sulphur or nitrogen sites. An examination of the charges on Pt for the hydrolysis products of cisplatin and transplatin, $(NH_3)_2Pt^{+}Cl(OH_2)$ and $(NH_3)_2Pt^{++}(OH_2)_2$, shows that the tranplatin species have higher charges. This observation is consistent with the charged transplatin hydrolysis products having a greater reactivity with blood serum albumin and related proteins, which may explain the cytotoxic inertness of transplatin compared to cisplatin, particularly when it is known that cisplatin is 95% bound to human plasma protein after 24 hours. [Sooriyaarachchi 2011] There have been many views on the origin of this puzzling difference [Lippert 1996] particularly when other trans Pt species do show cytotoxic behaviour. The lower desolvation energy for transplatin compared to cisplatin in Table 1 suggests that cellular uptake is not the cause of the difference. [Fong 2015] There are some differences in Pt-DNA adduct formation for the cis- and trans isomers, but are not thought to be sufficient to explain the inertness of transplatin. [Lippert 1996] Cisplatin is also known to bind irreversibly to erythrocytes where it fragments haemoglobin. [Mandal 2004] However there is contradictory data from kinetic and equilibrium data for cisplatin and transplatin which indicates that the first hydration–dechlorination step in water for cisplatin $\Delta G$ 3.1 kcal/mol can be compared with the value of $\Delta G$ 4.1 kcal/mol for transplatin. The corresponding equilibrium constants pK were 2.19 and 2.92 respectively. It would also be expected that this reaction would be faster for transplatin, based on the well known trans effect for Pt(II) complexes, where the $Cl^-$ has a stronger kinetic trans affect than the $NH_3$ ligand. But the reversible reaction of the hydration-dechlorination is faster than the forward reaction *in water* (which explains the anomalous equilibrium data) but *in blood*, where serum albumin and erythrocytes can react with the charged species formed by

hydration–dechlorination, then these entities can trap the charged Pt species by reacting with them. So it appears the dominant reason that transplatin is not cytotoxic is that little of the drug can reach its target DNA, being consumed by hydrolysis in the blood and consequent side reactions. Since only about 1% of cisplatin reaches its intracellular target, then faster extracellular hydrolysis of transplatin means that far less than 1% of transplatin would reach its intracellular target.

It can be concluded that side effects of Pt drugs in the body can be measured or ranked using the desolvation uptake and lipophilicity criteria for accumulation into cells, and the reactivity criteria of the charge on Pt, and electron affinity (as a measure or reduction potential) or the difference in ionization energy and electron affinity (which measures the inherent chemical stability).

Some of the Pt(IV) drugs (tetraplatin, cis-$(H_3N)_2PtCl_4$, Satraplatin, LA-12, Asplatin) which are being considered clinically, have also been examined to compare with the approved Pt(II) drugs. It is known that these compounds are prodrugs, which are thought to passively diffuse through cell membranes, then are reduced intracellularly into the active apoptotic Pt(II) species (by reducing agents such as glutathione etc). The higher stability of Pt(IV) compounds compared to Pt(II) compounds is thought to produce fewer side effects from hydrolysed products in the blood serum. [Graf 2012] Table 1 shows that the neutral Pt(IV) drugs examined do have moderately low desolvation energies, reasonable lipophilicity, low charges on Pt, and higher reduction potentials (than the Pt(II) drugs) consistent with the prodrug model.

An objective of the Pt(IV) prodrug approach has been that fewer side effects should occur when these drugs are intravenously administered since Pt(IV) complexes are generally more stable than Pt(II) complexes. Since a finding in this study is that the reactivity of Pt(II) drugs in blood plasma determine the extent of side effects and how much free drug is then available to permeate the cell barrier and hence reach it target DNA within the cell, a comparative study of the Pt(IV) prodrug, satraplatin, its active metabolite JM118 (cyclohexylamine)amminoPt(II)dichloride and cisplatin with human blood plasma can shed light on the likely drug disposition and delivery in tumour tissue, as well as potential side effects. It has been shown [Bell 2008] that stability-wise: satraplatin > cisplatin > JM118, degradation-wise: satraplatin > JM118 > cisplatin (in terms of number of Pt products formed) or satraplatin > cisplatin > JM118 (in terms of the extent of degradation, a kinetic factor). *After 2 hours*, 40% of satraplatin was intact, 30% was irreversibly bound to plasma protein, and ca. 30% was Pt degradation products. For JM118, 25% was intact, 65% was irreversibly protein bound and ca. 10% was Pt degradation products. For cisplatin, 25% was intact, 40% was irreversibly protein bound and ca. 10% was Pt degradation products. The hydrolysis products of satraplatin are formed by the stepwise replacement of the Cl ligands by OH ligands (after initial aquation), [Raynaud 1996] and these species are the likely reactants with plasma proteins. The charges on Pt increase as the number of OH ligands increase, indicating that binding to plasma proteins is greatest for the dihydroxy-satraplatin species. As the desolvation penalties and lipophilicity for transport across the cell membranes are similar for satraplatin, and the two hydroxy species, it is likely that all three neutral species can passively diffuse into the cells. The data shows that Pt(IV) satraplatin is 1.6 times more stable in plasma than the Pt(II) drugs, so cellular uptake for satraplatin would be expected to be higher than for cisplatin. Once inside the cell, the reduction potentials for the metabolite JM118

(formed from reduction of satraplatin by glutathione and other reducing entities) and its hydrolysis products (cyclohexylamine)(ammine)$Pt^{+}(H_2O)Cl$ and (cyclohexylamine)(ammine)$Pt^{++}(H_2O)_2$, are very similar to the Pt charge, desolvation energies and electron affinity properties of cisplatin, indicating very similar DNA adduct forming abilities. However clinical trails show disappointing progression free survival results for satraplatin, which were not sufficiently superior to cisplatin.

## Experimental methods

All calculations were carried out using the Gaussian 09 package on optimised structures. Electrostatic potential at nuclei were calculated using the CHELPG method in Gaussian 09. The atomic charges produced by CHELPG are not strongly dependant on basis set selection. Using the B3LYP level of theory, calculated atomic charges were almost invariant amongst the basis sets 6-31G(d), 6.311(d,p), 6-311+(2d,2p), 6-311G++(3df,3dp). Errors between calculated and experimental dipole moments were 3%. [Martin 2005, Kubelka] All calculations were at the B3LYP/6-$311^{+}$G**(6d, 7f) level of theory for all atoms except for Pt where the relativistic ECP SDD Stuttgart-Dresden basis set for transition metals was used. The atomic radii used for neutral Pt(II) and charged/ionic Pt(II) species (4 coordinated square planar configuration) in the CHELPG calculations were 1.75 and 0.74 A respectively, and for neutral 6 coordinated octahedral Pt(IV) complexes, a radius of 1.75 A was used. (http://www.webelements.com/platinum/atom_sizes.html).

Solvent calculations used optimised gas state geometries. Generally good agreement was found with published X-ray structures for similar Pt complexes. [Adams 2008, Bruck 1984 1985, Beagley 1985, Neidle 1980, Dodoff 2012, Tyagi 2008, Galanski 2004, Lippert 1981, Senguptal 2009, Varbanov 2013, Xie 2010, Perez 2000] Some examples were studied using optimised structures in water, and although small difference were observed, these did not change the various trends (eg. solvation energies for neutral versus charged Pt species) which are central to the results from this study. It is noted that very high accuracy for each calculation is not the object of this computational study, rather the method relies on comparative differences between different species and various trends amongst different classes of species.

Ionization energies (IE) and electron affinities (EA) were calculated as vertical values in water, where the optimised configuration in water was used to calculate the excited states. Some adiabatic IE and EA values were calculated to see if any solvent effects were operating in the excited states, by re-optimising the excited state structures in water. There were small differences indicating some solvent effects in the excited state. To test the accuracy of the computational method, $Me_2Pt(PMe_3)_3$ and $Me_2Pt(NMe_2CH_2CH_2NMe_3)$ had calculated gas IE of 7.3 and 7.2eV which can be compared with the NIST literature experimental values 7.2eV and 7.0eV, indicating the computational model gives accurate results.

The accuracy of the chosen solvation energy model has been tested by comparing the differences in solvation energies in water between cis- and trans-$(H_2O)_2PtCl_2$ which is -1.0 kcal/mol compared to the experimental value of - 0.1 kcal/mol (Hush 2005), and within the mean unsigned error of 0.6 - 1.0 kcal/mol in the solvation free energies of tested neutrals, and 4 kcal/mol on average for ions for the SMD solvent method (Marenich 2009). It has been found that the B3LYP / 6.31G+* combination gives reasonably accurate PCM and SMD solvation energies for some highly polar polyfunctional molecules, which are

not further improved using higher level basis sets [Rayne 2010]. Adding diffuse functions to the 6-311$^{+}$G** basis set had no significant effect on the solvation energies with a difference of less than 1% observed, which is within the literature error range for the IEFPCM/SMD solvent model. Desolvation energies are essentially the reverse of the solvation energies.

## Conclusions

A review of the literature reveals that intravenous Pt based anti-cancer therapy is driven by side effects (drug hydrolysis in blood plasma, followed by binding of the charged hydrolysis products to serum proteins etc) and delivery efficiency in the first instance. The reactivity of the Pt drugs in blood serum decides how much of the administered drug actually reaches the cell membrane to begin uptake via passive diffusion or by the active transporters hCtr1 or OCT (particularly for oxaliplatin). The reactivity of the charged Pt species is related to the severity of side effects elsewhere in the body. The molecular reactivities of the various charged Pt species from the currently approved Pt drugs have been calculated and can be useful clinical guides to the likely severity of side effects. It is demonstrated that the reason that transplatin is therapeutically inert but cisplatin is active is because transplatin is hydrolysed faster in blood serum so virtually no transplatin reaches its target, whereas about 1% of cisplatin reaches its intracellular DNA target. [Pil 2002, Gananski 2012] Some hydrolysis products of the six approved Pt drugs are neutral species, which along with the neutral administered drug, are transported across the cell membrane more easily than any charged hydrolysis species, indicating these neutral species are the therapeutically active agents.

The therapeutic efficacy of the Pt drug in the cell is driven by (a) what proportion of the administered drug survives intact in the blood serum or is hydrolysed to a neutral species, and (b) how fast such species can penetrate the cell membrane and enter the cytosol. These two factors are dominant rate determining first order effects in apoptosis, since processes such as efflux from the cell, DNA repair and other signalling mechanisms are secondary effects which can only occur after the Pt drug enters the cytosol. It is shown that the transport of Pt drugs and hydrolysed neutral species across the cell membrane is determined by desolvation and lipophilicity of the drug, with smaller contributions from the dipole moment and molecular size. Desolvation is particularly important as charged Pt species have very large desolvation penalties.

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**Table 1. Solvation energies, molecular volumes, dipole moments, atomic charge on Pt, lipophilicity, ionization energies and electron affinities for various Pt drug species**

| Species in water | Solvatn Energy | CDS | Molec Volume | Dipole μ | Pt Charge | Lipop-hilicity | (IE – EA) | EA |
|---|---|---|---|---|---|---|---|---|
| **$(NH_3)_2PtCl_2$ Cisplatin** | -33.1 | 4.4 | 76.2 | 16.8 | 0.15 | -14.3 | 4.9 | 1.4 |
| (Adiabatic) | -29.0 | 4.6 | 109.8 | 17.1 | 0.134 | -11.9 | 3.5 | 2.8 |
| $(NH_3)_2PtCl(OH)$ | -40 | 4.8 | 78.6 | 16.3 | 0.33 | -13.5 | 5.0 | 1.0 |
| $(NH_3)_2Pt^+Cl(OH_2)$ | -87.3 | 5.3 | 85.9 | 14.8 | 2.484 | -40.3 | 4.6 | 2.1 |
| (Adiabatic) | -91.2 | 5.5 | 83.6 | 15.0 | 2.363 | -33.0 | 3.3 | 3.3 |
| $(NH_3)_2Pt^{++}(OH_2)_2$ | -222.3 | 6.4 | 77.7 | 5.2 | 2.726 | -101.7 | 4.5 | 2.4 |
| **$(NH_3)_2Pt$ CBDC Carboplatin** | -33.1 | 8.6 | 130.5 | 18.5 | 0.073 | -13.4 | 4.9 | 1.4 |
| (Adiabatic) | -39.5 | 9.8 | 162.1 | 22.4 | 0.159 | -13.4 | 3.7 | 2.4 |
| $(NH_3)_2Pt$ CBDCH(OH) | -37.5 | 8.7 | 158.1 | 16.8 | 0.141 | -13.0 | 4.2 | 1.6 |
| $(NH_3)_2Pt\ ^+CBDC^-(OH_2)$ | -91.1 | 8.7 | 191.3 | 34.2 | 2.598 | -28.7 | 5.0 | 1.8 |
| $(NH_3)_2Pt\ ^+CBDCH(OH_2)$ | -90.6 | 8.9 | 150.3 | 14.5 | 2.514 | -36.9 | 4.0 | 2.6 |
| Carboplatin Dimer | -92.4 | 10.2 | 243.5 | 8.6 | 0.107 | -31.2 | 2.0 | 2.1 |
| **DACHPtOxalate Oxaliplatin** | -45.8 | 6.9 | 144.6 | 24.6 | 0.171 | -20.1 | 3.7 | 2.8 |
| DACHPtOxalateH(OH) | -47.1 | 7.2 | 178.9 | 17.8 | 0.426 | -17.2 | 2.4 | 3.4 |
| $DACHPt^+Oxalate^-(OH_2)$ | -82.3 | 7.8 | 158.3 | 29.5 | 2.424 | -28.0 | 4.2 | 2.2 |
| $DACHPt^{++}(OH_2)_2$ | -207 | 5.9 | 123.9 | 4.6 | 2.614 | -95.0 | 4.5 | 2.3 |
| $DACHPt(OH)_2$ | -46.4 | 4.5 | 147.9 | 15.3 | 0.298 | -16.4 | 2.4 | 2.3 |
| **$DACHPtCl_2$** | -39.8 | 4.2 | 147.3 | 20.8 | 0.142 | -20.4 | 2.4 | 2.5 |
| DACHPt(OH)Cl | -48.3 | 4.3 | 177.9 | 20.4 | 0.231 | -19.8 | 2.4 | 2.4 |
| $DACHPt^+(H_2O)Cl$ | -81.6 | 5.0 | 157.6 | 12.5 | 2.242 | -38.5 | 2.1 | 2.9 |
| $DACHPt^{++}(OH_2)_2$ | -212.4 | 5.8 | 115.4 | 2.8 | 2.682 | -97.3 | 4.5 | 2.3 |
| **DACHPtCBDC** | -52.6 | 7.3 | 186 | 21.9 | 0.287 | -22.3 | 1.3 | 2.5 |
| DACHPtCBDCH(OH) | -50.9 | 8.0 | 193.8 | 9.6 | 0.324 | -19.2 | 1.3 | 2.3 |
| $DACHPt^+CBDC^-(OH_2)$ | -83.1 | 8.5 | 245.1 | 30.5 | 2.696 | -31.5 | 1.3 | 2.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **$(NH_3)_2Pt$(HydroxyAcetato) Nedaplatin** | -46.3 | 6.5 | 79.2 | 17.2 | 0.205 | -15.3 | 1.3 | 2.8 |
| $(NH_3)Pt^{+}$(HydroxyAcetato$^{-}$)$(OH_2)$ | -98.7 | 8.1 | 91.4 | 36.1 | 2.195 | -25.8 | 1.9 | 1.8 |
| $(NH_3)$Pt(HydroxyAcetato$^{-}$)(OH) | -101.1 | 7.4 | 96.2 | 35.2 | 0.251 | -10.2 | 1.8 | 1.6 |
| $(NH_3)$Pt(HydroxyAcetatoH)(OH) | -55.3 | 7.8 | 105.8 | 21.4 | 0.293 | -17.0 | 1.9 | 2.1 |
| **$(NH_3)$(MePyrid)$PtCl_2$ Picoplatin** | -26.3 | 5.7 | 141.3 | 17.8 | 0.183 | -15.9 | 4.5 | 1.8 |
| $(NH_3)$(MePyrid)$Pt^{+}Cl(OH_2)$ | -65 | 6.6 | 131.8 | 9.8 | 2.101 | -33.5 | 4.5 | 2.1 |
| $(NH_3)$(MePyrid)PtCl(OH) | -30.0 | 6.0 | 124.1 | 15.9 | 0.305 | -14.2 | 4.1 | 1.8 |
| $(NH_3)$(MePyrid)$Pt^{++}(OH_2)_2$ | -196.5 | 7.5 | 135.1 | 6.9 | 2.31 | -92.5 | 4.4 | 2.4 |
| **BAMCBPtLactate Lobaplatin** | -48.1 | 6.2 | 181.2 | 16.3 | 0.157 | -19.3 | 2.8 | 1.6 |
| BAMCBPt$^{+}(OH_2)$Lactate$^{-}$ | -95.2 | 8.3 | 199.6 | 34.5 | 2.951 | -25.4 | 1.9 | 1.7 |
| BAMCBPt(OH)Lactate$^{-}$ | -125.1 | 7.6 | 204.6 | 37.8 | 0.252 | -37.7 | 2.0 | 1.5 |
| BAMCBPt(OH)LactateH | -56.5 | 7.9 | 178.8 | 17.3 | 0.277 | -20.9 | 2.9 | 1.5 |
| BAMCBPt$^{++}(OH_2)_2$ | -215.2 | 6 | 116.3 | 8.9 | 2.734 | -98.6 | 2.1 | 2.5 |
| **MDDMAPtMalonate Heptaplatin** | -47.2 | 8.8 | 204.1 | 17.3 | 0.236 | -19.6 | 3.0 | 2.6 |
| MDDMAPt$^{+}$Malonate$^{-}(OH_2)$ | -100 | 9.4 | 236.23 | 34.4 | 2.66 | -32.1 | 3.1 | 2.6 |
| MDDMAPtMalonate$^{-}$(OH) | -134.7 | 9.3 | 251.4 | 45.9 | 0.202 | -43.3 | 3.1 | 2.5 |
| MDDMAPtMalonateH(OH) | -60.0 | 9.6 | 205.5 | 16.1 | 0.186 | -20.5 | 3.0 | 2.7 |
| MDDMAPt$^{++}(OH_2)_2$ | -216.1 | 7.5 | 181.3 | 13 | 2.482 | -95.6 | 3.1 | 2.7 |
| **$(NH_3)_2PtCl_2$ Transplatin** | -16.8 | 4.5 | 95.9 | 0 | 0.112 | -9.0 | 4.6 | 1.5 |
| (Adiabatic) | -18.4 | 4.6 | 91.0 | 0 | 0.052 | -9.7 | 3.3 | 2.8 |
| $(NH_3)_2$PtCl(OH) Trans | -23.2 | 4.8 | 90.1 | 2.5 | 0.217 | -8.5 | 4.7 | 1.1 |
| $(NH_3)_2Pt^{+}Cl(OH_2)$ Trans | -77.4 | 5.4 | 62.4 | 10.2 | 2.973 | -35.4 | 4.6 | 2.2 |
| $(NH_3)_2Pt^{++}(OH_2)_2$ Trans | -222.3 | 6.5 | 79.9 | 4.1 | 2.856 | -96.7 | 3.9 | 3.1 |
| **DACH$PtCl_4$ Tetraplatin Pt(IV)** | -31.5 | 2.8 | 147 | 17.5 | 0.308 | -16.2 | 3.7 | 3.7 |
| **$(H_3N)_2PtCl_4$ Cis Pt(IV)** | -33.6 | 4.6 | 135.1 | 15.6 | 0.457 | -15.0 | 4.5 | 3.2 |
| **Satraplatin Pt(IV)** | -52 | 7.7 | 200.1 | 23.6 | 0.553 | -19.4 | 3.7 | 3.1 |
| **LA-12 Pt(IV)** | -46.4 | 7.9 | 236.6 | 23.1 | 0.475 | -19.7 | 2.7 | 3.2 |
| **Asplatin Pt(IV)** | -45.3 | 9.3 | 225.7 | 18.9 | 1.014 | -18.4 | 4.1 | 2.6 |
| **Glutathione** | -48.5 | 4 | 175.6 | 7.8 | | -14.5 | 4.9 | 1.7 |
| | | | | | | | | |

**Footnotes**:

All ionization properties are vertical (same optimised geometry in gas and water) unless shown as adiabatic (where the ionized geometry was optimised in the solvent, resulting in small changes to the geometry). Vertical (and adiabatic) ionization energies and electron affinities are in eV. Solvation energies are in kcal/mol. The CDS solvation values are the non-electrostatic components including cavity formation terms. Molecular volumes are in $cm^3$/mol. Dipole moments μ are in D. The atomic charges on Pt are in a.u. Lipophilicity is the solvation energy in n-octane, essentially a repulsive effect for polar and charged molecules.

Carboplatin =$(NH_3)_2$Pt CBDC where CBDC is cyclobutane-1,1-dicarboxylate, $(NH_3)_2Pt^{+}$ CBDC$^{-}$(OH) has one arm of the bidentate cyclobutane-1,1-dicarboxylate ligand free with the free carboxylate as an anion and a hydroxyl ligand in its place, and $(NH_3)_2Pt^{+}$ CBDCH(OH) has one arm of the bidentate cyclobutane-1,1-dicarboxylate ligand free with the free carboxylate as an acid and a hydroxyl ligand in its place.

Oxaliplatin is (*cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N**]oxalato(2-)-*O,O**] platinum; DACH is 1,2 cyclohexanediamine. DACHPtOxalateH(OH) has one arm of the bidentate oxalate ligand free with the free carboxalate as an acid and a hydroxyl ligand in its place. DACHPt$^{+}$Oxalate$^{-}(OH_2)$ ) has one arm of the bidentate oxalate ligand free with the free carboxalate as an anion and a water ligand in its place.

Nedaplatin is diammine[(hydroxy-κO)acetato(2-)-κO]platinum, $(NH_3)$Pt(HydroxyAcetato$^{-}$)(OH) has one arm of the bidentate hydroxyacetate ligand free with the free carboxalate as an anion and a hydroxyl ligand in its place.

Lobaplatin is 1,2-diammino-methy lcyclobutane-platinum (II) lactate or BAMCBPtLactate, and BAMCBPt(OH)LactateH has one arm of the bidentate BAMCB ligand free with the free carboxalate as an acid and a hydroxyl ligand in its place.

Heptaplatin is [SP-4-2-[4R-(2a,4a,5b)]]-[2-(1-Methylethyl)-1,3-dioxolane-4,5-dimethanamine-N,N'][propanedioato(2-)-O,O']-platinum or MDDMAPtMalonate, and MDDMAPt$^{+}$MalonateH(OH) has one arm of the MDDMAP ligand free with the free carboxalate as an acid and a hydroxyl ligand in its place

Picoplatin is (2-methylpyridine)ammineplatinumdichloride