Published in final edited form as:

Eur J Inorg Chem. 2009 April 1; 2009(10): 1293–1302. doi:10.1002/ejic.200801118.

Towards Antitumor Active *trans*-Platinum Compounds

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Abstract

Substitution of NH_3 by a range of amines in *trans*- $[\text{PtCl}_2(\text{NH}_3)_2]$ produces compounds with cytotoxicity significantly improved over the parent transplatin and in many cases equivalent to that of cisplatin. This microreview summarizes the chemistry and biology of *trans*-platinum compounds containing principally planar amines and succinctly reviews the current status of anticancer relevance of the *trans*-platinum geometry. The nature of bifunctional DNA adducts (intrastrand, interstrand) is remarkably dependent on the nature of the amine. Further, the stability of monofunctional adducts allows for competitive production of DNA-protein crosslinks and overall the results suggest that the *trans*-platinum chemotype may offer significant potential for design of selective DNA-protein crosslinking agents. A subset of proteins known to bind to DNA modified by *trans*-platinum is that comprised of zinc fingers – model studies show the potential for formation of heteronuclear thiolate-bridged species as precedent for zinc displacement from the biomolecule.

1 Introduction

Cisplatin and its analogs oxaliplatin and carboplatin are effective anticancer agents in the treatment of a variety of tumors. Platinum-based combinatorial chemotherapy has also been used with agents such as bleomycin, paclitaxel and 5-fluorouracil, with improved outcomes for patients. 1 The profound success of cisplatin cannot overshadow its clinical shortcomings such as toxic side effects and the development of resistance. The effectiveness of cisplatin lies in its ability to induce DNA damage. The subsequent recognition of the platinum-DNA adducts by cellular proteins may shield the lesion from repair resulting in a definitive cytotoxic insult to the cell. Carboplatin and oxaliplatin are direct structural analogues of cisplatin and similar DNA binding is expected. Studies have shown that cellular sensitivity to cisplatin, as well as clinical resistance to cisplatin is multifactorial, with a major mechanism being the ability of cells to repair DNA damage by nucleotide excision repair and mismatch repair. 1· 2 Resistance mechanisms also include decreased drug accumulation and/or cellular detoxification by thiol containing compounds such as plasma proteins (extracellular) and glutathione (intracellular).

The motivation for study of new compounds comes from the desire to expand the number of tumors susceptible to platinum drug treatment and to overcome clinical resistance to the currently used drugs. The lack of chemotherapeutic activity of the *trans* isomer *trans*- $[\text{PtCl}_2(\text{NH}_3)_2]$ has long been noted and this distinct difference remains the enduring structure-activity relationship for development of platinum antitumor compounds. Other, early, empirical rules such as the need for charge neutrality or a bifunctional compound (two leaving groups) have been defied. 3· 4 It is now clear that substitution of NH_3 by a range of amines actually produces compounds with cytotoxicity significantly improved over the parent transplatin and in many cases equivalent to that of cisplatin. This microreview summarizes the chemistry and biology of *trans*-platinum compounds containing principally

planar amines and succinctly reviews the current status of anticancer relevance of the *trans*-platinum geometry.

2 Cytotoxicity of *trans*-platinum Compounds

Substitution of the carrier ligand NH_3 by planar amines such as pyridine was first reported to activate the *trans* geometry producing cytotoxicity equivalent to that of cisplatin.⁵⁻⁷ In general, the *trans* platinum aromatic heterocycles (TPA) complexes have cytotoxicities similar to that of their *cis* isomers and cisplatin while being markedly more effective than transplatin, Table 1. In a panel of human ovarian carcinoma (HOC) cell lines it is also clear that *trans*- $[\text{PtCl}_2(\text{py})_2]$ displays collateral sensitivity (is non-cross-resistant), retaining activity in tumor cell lines resistant to cisplatin.⁶ The pattern of cytotoxicity, even in this limited panel, is also different with cell lines such as HX/62 exhibiting higher sensitivity to *trans*- $[\text{PtCl}_2(\text{py})_2]$ than to cisplatin. The activation using planar amines is general and is also seen for the series *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{L})]$ (L = pyridine, isoquinoline, quinoline, thiazole etc.), Figure 1.⁸

An important criterion for any potential new platinum drug is to display a different profile of antitumor activity in comparison to the clinically used agents. Analysis of cytotoxicity data of 107 platinum compounds from the NCI human tumor panel using clustered image maps, the COMPARE algorithm and other numerical methods identified 12 groups, 11 of which showed distinctive activity profiles. One such group (Pyridine Group) consisted of only *trans*-platinum complexes with planar amines, including *trans*- $[\text{PtCl}_2(\text{py})_2]$. The group was identified as having a novel cytotoxicity profile and activity in cisplatin and oxaliplatin-resistant lines. Further, the activity profile of the Pyridine Group is poorly correlated with that of a representative set of alkylating agents, by Pearson correlations. The COMPARE activity profile is also poorly correlated with cisplatin and carboplatin.¹¹ The overall analysis of the compounds in the NCI database clearly support the view that structurally different sets of platinum compounds, including the TPA series, display pre-clinical properties distinct from agents such as cisplatin and oxaliplatin, with implications also for potential differences in clinical activity.

2.1 *Trans*-platinum compounds with N-donor ligands other than aromatic heterocycles

Use of other carrier ligands besides planar amines subsequently showed that enhancement of cytotoxicity by replacement of NH_3 was a general phenomenon. Notably iminoethers, aliphatic amines and heterocyclic aliphatic amines have all been used to generate a broad array of potentially useful compounds, Figure 2. The cytotoxicity data for the various series has been very well summarized recently.¹²⁻¹⁵ In general it is reasonable to say that most compounds display cytotoxicity in the micromolar (1-20 μM) range and the compounds consistently display cytotoxicity in cisplatin-resistant cells.

2.2. Cytotoxic *trans*-platinum compounds with N_2O_2 Donor Sets

In conjunction with the carrier ligand modification, optimization of the *trans* geometry can be attained by modification of leaving group. Use of organic amines reduces aqueous solubility and the compounds of Figure 2 still retain the Cl-Pt-Cl axis, expected to be more reactive than a N-Pt-Cl axis due to the *trans* influence. To address the poor aqueous solubility of the $[\text{PtN}_2\text{Cl}_2]$ chemotype, the use of carboxylates as leaving groups was introduced. Complexes *trans*- $[\text{Pt}(\text{O}_2\text{CR})_2(\text{L})(\text{L}')]]$ are very water-soluble and surprisingly stable toward hydrolysis, resembling carboplatin in their chemical reactivity (See below). Carboxylate derivatives have shown similar cytotoxicities to their parent chlorides, Table 1.^{9, 16} The use of carboxylate ligands also affords these *trans*-platinum compounds increased cellular accumulation even in cisplatin and oxaliplatin-resistant cell lines.^{9, 16}

The carboxylate strategy is a general one – as evidenced by the solution properties of *trans*-[Pt(O₂CCH₃)₂(isopropylamine)(*N*-methylimidazole)]¹⁷. The cytotoxicity may be further modulated by changing the nature of the carboxylate leaving group.^{18, 19} In this respect most notable is the formate derivative, *trans*-[Pt(O₂CH)₂(NH₃)(iquin)], which has an IC₅₀ of 7.2 μM in HCT116 WT colon carcinoma cells compared to 5.4 μM for cisplatin; while in A2780 human ovarian cells, *trans*-[Pt(O₂CH)₂(NH₃)(4-pic)] has a IC₅₀ of 6.2 μM compared to that of cisplatin at 3.0 μM. These compounds have further been shown to activate p53 and PARP cleavage with higher levels of apoptosis than cisplatin at early time-points, pathways once thought to be restricted to cisplatin and its congeners.²⁰

2.3 Platinum IV compounds

Although the anticancer activity of Pt(IV) complexes has been noted since 1967, their development has not been explored to a similar level as that of Pt(II) compounds. In theory, Pt(IV) compounds can serve as prodrugs, being reduced to the Pt(II) analogues under physiological conditions.²¹ JM335, (*trans,trans,trans*-[PtCl₂(OH)₂(NH₃)(cyclohexylamine)]), is one of the most potent Pt(IV) compounds developed as part of a collaborative effort by Johnson Matthey and the Institute of Cancer Research along with over 300 other compounds including picoplatin and satraplatin.²² Other Pt(IV) compounds studied include *trans,trans,trans*-[PtCl₂(OH)₂(dimethylamine)(isopropylamine)].²³

3 Chemistry

3.1. Aqueated *Trans*-platinum species. Hydrolysis of *trans*-platinum

Similar to cisplatin, the neutral *trans*-platinum compound needs to be activated to the monoaqua or diaqua species to react with DNA (Scheme 1). Abstraction of the first chloride from *trans*-[PtCl₂(NH₃)₂] by silver salts is relatively easy due to the mutual *trans* effect of Cl⁻. Removal of the second chloride is not so easy as it is now *trans* to the weaker H₂O ligand.²⁴ An interesting study by McGowan *et al.* measured the first hydrolysis step of *trans*-[PtCl₂(NH₃)(pic)] to be 2.6×10^{-5} ; 12.7×10^{-5} and 5.2×10^{-5} s⁻¹ for the 2-picoline, 3-picoline and 4-picoline compounds respectively, Table 2.25 Under the conditions of the experiment, little hydrolysis of the second chloride was observed.

The equilibrium constants for the formation of the monoaqua species are also approximately an order of magnitude lower than those reported for cisplatin, but similar to those for transplatin.²⁵ The pK_a values for major types of *trans*-platinum compounds are also shown in Table 2. The values are similar for most *trans*-platinum compounds and note that the first pK_a of the diaqua species is uniformly lower than for the *cis*-isomer by an order of magnitude. The nature of the amine does have some effect on the pK_{a1} – coordinated water is more acidic in the presence of a planar amine than NH₃, agreeing with earlier results on the [Pt(bipy)(H₂O)₂]²⁺ ion.²⁶ Under physiological conditions (pH 7.4), the monoaqua TPA species is therefore likely to exist as the hydroxo species. Interestingly, *trans*-[PtCl(OH)(NH₃)₂].H₂O may be isolated as a stable solid.²⁷ In diaqua species, the pK_{a2} values indicate that an equilibrium should exist between aqua and hydroxo species, making it possible for reaction between N-donor ligands such as that of the N7 of guanine.

Use of mutually *trans* carboxylates reduces the rate of hydrolysis by approximately two orders of magnitude in comparison to chlorides, Table 2. Indeed, observed rate constants for carboxylate *trans*-platinum compounds are similar to that of carboplatin. The compounds are significantly more inert than one might expect from two mutually *trans* ligands with weak *trans* effect and *trans* influence. Thus, it is notable that the cytotoxicity of TPA compounds with carboxylate ligands is very close to the chlorides, despite their “carboplatin-like” properties, that very little hydrolyzed species is apparent at biological pH– production of aquated species of carboplatin and oxaliplatin is pH dependent²⁹⁻³¹.

The measured IC₅₀ values could represent a balance between lesser deactivation and increased intracellular platinum accumulation.^{9, 16}

3.2 Reactions with sulfur residues of proteins and peptide models

Deactivation of transplatin by thiol containing compounds such as human serum albumin (HSA, plasma) and glutathione (GSH, intracellular) may contribute to the observed differences in antitumor activity of *cis* and *trans*-DDP. Incubation of *trans*-[PtCl₂(OH)₂(dimethylamine)(isopropylamine)] and its Pt(II) analogue, cisplatin and transplatin with HSA over a 24 day time period showed both *trans*-[PtCl₂(OH)₂(dimethylamine)(isopropylamine)] and cisplatin have similar profiles with substantially less binding compared to transplatin and the Pt(II) analogue.²³ The effects of sterically bulky ligands in the *trans* geometry on GSH and methionine reactivity have not been systematically studied or compared with transplatin.³²⁻³⁴ However, monofunctional adducts of both *trans*-[PtCl₂(isopropylamine)(3-hydroxymethyl-pyridine)] and *trans*-[PtCl₂(isopropylamine)(4-hydroxymethyl-pyridine)] were shown to react with GSH by HPLC analysis, albeit to a lesser extent than transplatin.²³

4 DNA binding and adduct formation

4.1 DNA binding

DNA is the established primary target of platinum compounds in cells, making DNA adduct formation one of the key determinants of platinum-mediated cytotoxicity. The extent and nature of these DNA adducts has been used to explain the differences in biological activity of *cis* and transplatin. Indeed, the hypothesis that altered modes of DNA binding, and the subsequent differences in protein recognition and downstream processing, may eventually translate into a different profile of antitumor activity has been a driving force for development and design of potential platinum-based clinical agents. Bifunctional compounds may produce interstrand (IXL) and intrastrand crosslinks and monofunctional adducts. Cisplatin forms a variety of adducts of which the 1,2-GG intrastrand predominates, with other lesions including 1,2-AG intrastrand, 1,3-GNG intrastrand and to a lesser extent the 1,2-GG interstrand crosslink. In contrast, geometric constraints prevent the formation of 1,2 cross-links by transplatin – instead 1,3-intrastrand cross-links are formed.³⁵ Interstrand crosslinks of transplatin are formed between G and C residues of the same base pair, Figure 3. Monofunctional (and also bifunctional intrastrand) adducts may convert to interstrand crosslinks. The slow rate of conversion of monofunctional to bifunctional interstrand may account for the fact that transplatin forms very few IXL in cells.³⁵ Replacement of NH₃ by an amine as carrier ligand affects both the structural nature of adducts as well as the kinetics of formation.³⁶⁻³⁷ A summary of the effect of amine ligand on DNA adduct formation is shown in Table 3.

4.2 Effect of carrier ligand on DNA adduct formation

The presence of a planar ligand results in formation of significantly more interstrand crosslinks in comparison to parent *trans*-[PtCl₂(NH₃)₂]. In the specific case of thiazole, interstrand, intrastrand and monofunctional adducts are almost equally distributed as adducts.³⁶ Further, the interstrand crosslinks are formed between the adjacent guanines of GC base pairs, similar to that of cisplatin, Figure 4.⁴⁸ Thus, the planar amine forces the crosslink to be more “cisplatin-like” and is an example of using steric effects to turn a presumably non-toxic into a toxic lesion. The cation [Pt(9-EtGua)(5'-GMP)(NH₃)(quin)]²⁺ gives conformers for both guanine residues and quinoline at room temperature due to restricted rotation.⁴⁹

In contrast, bulky piperidine and piperazine ligands produce more intrastrand crosslinks whereas, in the presence of two iminoether ligands very few bifunctional crosslinks are formed at all. This latter fact may be attributed to steric reasons as the *trans*-[PtCl₂(NH₃)(E-iminoether)], compound shows significantly more interstrand cross-linking in plasmid DNA than either its *cis* isomer or cisplatin.⁵⁰ However steric effects with two bulky carrier groups are not universal – *trans*-[PtCl₂(py)₂] is as efficient as *trans*-[PtCl₂(NH₃)(planar ligand)] in forming interstrand crosslinks in plasmid DNA.⁵¹ When L = 2-Me-butylamine or *sec*-butylamine mainly interstrand cross-links are formed in ~40-50% proportion.⁴¹

There are interesting differences between *cis* and *trans* isomers containing planar ligands. In general *cis*-[PtCl₂(py)₂] was 2-3 times more efficient at binding calf thymus (CT) and pUC19 DNA than *trans*-[PtCl₂(py)₂].⁵¹ This was also the case for poly (dG)-poly(dC) DNA, albeit to a lesser extent. In contrast, in poly(dG-dC)-poly(dG-dC) DNA the *trans* compound was the more effective at binding.⁵² While *cis*-[PtCl₂(py)₂] was able to bind DNA more efficiently than its *trans* isomer, *trans*-[PtCl₂(py)₂] had higher unwinding angles ($\phi=17^\circ$) than *cis*-[PtCl₂(py)₂] ($\phi=4^\circ$)⁵¹, actually reversing the trend seen for PtCl₂(NH₃)₂ isomers where the *cis* isomer exhibited higher unwinding angles than the *trans*. Table 4. However, it should be noted that *trans*-[PtCl₂(NH₃)(quin)] was more efficient at binding CT DNA than its *cis* isomer.^{39, 53} This variation in the trend could be due to steric effects of the larger quinoline group.

4.3 DNA binding of N₂O₂ donor sets

In comparison to the chloride species, the carboxylates show less DNA binding and consequently interstrand cross-linking over time. This can be attributed to the observed lower rate constants for hydrolysis. The general trend showed that the more reactive formate derivatives exhibited significantly more DNA damage than the acetate or hydroxyacetate compounds, and in cells produced similar levels of DNA damage as *trans*-[PtCl₂(NH₃)(tz)]¹⁹. The influence of the carrier ligand is exemplified by the higher rate of interstrand cross-links seen for the *trans*-[Pt(O₂CH)₂(NH₃)(iquin)] as compared to the *trans*-[Pt(O₂CH)₂(NH₃)(4-pic)]²⁰. Interestingly, similar steric effects were also observed in binding to ubiquitin.⁵⁵

4.4 Conversion of monofunctional to bifunctional adducts

A key determinant of the formation of cross-links, inter or intra, is the stability of the monofunctional adduct formed by these *trans*-platinum compounds. The monofunctional adducts formed by *trans*-[PtCl₂(NH₃)(tz)] lead to bending and unwinding angles similar to that of cisplatin (See below); however, monofunctional adducts are very slowly converted to a bifunctional mode.⁵⁴ *trans*-[PtCl₂(NH₃)(quin)] adducts persist for 48h in the monofunctional state; similarly the *trans*-[PtCl₂(NH₃)(tz)] compound shows only a 2-5% conversion rate to interstrand cross-links after 24h, increasing to 40% within 48h.⁵⁴ These results are markedly different from transplatin, which has a 70% conversion rate.

5 Structural consequences of DNA adduct formation. Protein recognition of *trans*-platinum-DNA adducts

A multitude of proteins recognize platinated DNA adducts.⁵⁶ In cells the tumor suppressor protein p53 is activated in response to damage induced by *trans*-platinum compounds.^{19, 57} This activation confirms that *trans*-platinum-treated cells process and respond to the damage, at least initially, in a similar manner to that of cisplatin. Interestingly, in a cell-free assay, DNA modified by *trans*-[PtCl₂(NH₃)(4-hydroxymethylpyridine)] reduces the affinity of p53 protein to bind to its consensus sequence. The diminution is comparable to that of cisplatin.⁵⁸

One well characterized system is that of recognition of Pt-DNA adducts by high mobility group (HMG) proteins. The crystal and molecular structure of HMG recognition to duplex DNA containing a cisplatin 1,2-GG intrastrand crosslink has allowed the molecular details of this interaction to be studied.⁵⁹⁻⁶⁰ The duplex bending caused by the adduct is a critical feature in protein recognition. Further, specific proteins like HMGB1 may protect the 1,2 GG cross-link from repair by excinuclease activity thus augmenting the cytotoxicity of the drug.⁶¹ Transplatin modified DNA and the monofunctional platinated adducts of compounds such as $[\text{PtCl}(\text{NH}_3)_3]\text{Cl}$ are not recognized by this group of proteins.

A detailed analysis of the structures of DNA adducts of *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{tz})]$ allows examination of factors affecting protein recognition. The conformational changes of the monofunctional adduct are most similar to that of cisplatin (Table 4) and therefore it is not surprising that the lesion is recognized with high affinity by HMG-family proteins. Furthermore, the interstrand cross-link bends DNA with an angle of distortion, 22° , toward the minor groove but may be a substrate for some HMG family proteins. The details, and the consequences for NER (Nucleotide Excision Repair), are summarized in Table 4. Unlike *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{tz})]$, *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{quin})]$ adducts were not recognized by HMGB1.⁶² Unlike cisplatin, *trans*- $[\text{PtCl}_2(\text{E-iminoether})_2]$ adducts are not recognized by either HMGB1a or HMGB1b.³⁷ Similarly, there was no recognition of DNA cross-linked by *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{pip})]$ by HMGB1, which is not surprising as DNA bends towards the minor groove.⁴⁰

Since the monofunctional adduct contains a further substitution-labile chloride ligand, one might assume that ternary DNA-protein crosslinks could be formed with HMG proteins. Control of conditions allows observation of crosslinking of HMG group proteins 1 and 2 to platinated DNA in micrococcal nuclease accessible regions of chromatin.⁶³ DNA modified by *cis*-DDP may also undergo photoinduced cross-linking to HMG1 proteins upon irradiation.⁶⁴ No ternary DNA-Pt-protein crosslinking is observed between monofunctional TPA adducts and HMG proteins.⁵⁴ An explanation may be found by examining the molecular model of the monofunctional adduct, Figure 5. In this case monofunctional platination in the major groove results in the Pt-Cl bond pointing into the major groove, rather than the minor groove where HMG associates. The stability of the monofunctional adduct with respect to bifunctional adduct conversion may also be explained by noting the stacking interactions of thiazole with the neighbouring bases.

6 Novel cellular protein targets for TPA compounds. Induction of topoisomerase-DNA compounds

The most striking feature of the biological activity of transplanar amine (TPA) compounds is the production of single-stranded protein-associated DNA strand breaks in cells. The pharmacology of these strand breaks was suggested to be remarkably similar to those produced by topoisomerase poisons.⁶⁵ This is a unique result in platinum chemistry. At 24 and 48h exposure of breast cancer MCF-7 cells to *trans*- $[\text{PtCl}_2(\text{NH}_3)(\text{thiazole})]$, the formation of DNA-topoisomerase I (Topo I) complexes is detected, coincident with a high degree of apoptosis. Trace levels of Topo I-DNA complexes were observed at $10\mu\text{M}$ dose but at $50\mu\text{M}$ there was substantial increase in the level of the protein-DNA complex. Similar effects were seen for *trans*- $[\text{PtCl}_2(\text{py})_2]$.⁶⁵ In contrast, no trapping of Topoisomerase II-DNA complexes was seen. The ability to produce Topo I-DNA adducts follows the same order as that of the production of strand breaks: *trans*- $[\text{PtCl}_2(\text{py})_2] > \text{trans}-[\text{PtCl}_2(\text{NH}_3)(\text{tz})] \gg \text{trans}-[\text{PtCl}_2(\text{NH}_3)(\text{quin})]$. The *cis* isomers produce very little protein-associated strand breaks and, as a corollary, do not form ternary protein-DNA adducts. Furthermore the effect appears restricted to those *trans* compounds containing planar rings. Treatment with cisplatin at the same concentrations also did not result in any detectable Topo I-DNA

complexes. Topoisomerases – enzymes that relieve torsional strain in DNA and which play important roles in replication and transcription – have been recognized in cancer therapy as an attractive target for inhibition since the 1970's.⁶⁶ The structural resolution of Topo-DNA complexes has added to the attraction of this area.⁶⁷ The fact that the induction of Topoisomerase I-DNA complexes is part of the biological response to TPA compounds, and is a property not shared by *cis*-DDP and congeners, suggests that cytotoxic *trans*-platinum complexes with planar amines have a different cellular injury response in comparison to that of cisplatin.

A further unusual target for TPA compounds has been mentioned as telomerase. Treatment of MCF-7 cells with varying concentrations of *trans*-[PtCl₂(py)₂] for 24h induced a small and rapid decrease of telomerase activity.⁶⁸ Telomerase activity was restored within 5 days after continuous exposure to drug. The time course of telomerase inhibition and telomere dynamics did not correlate with observed cell death but the observed initial reduction could be explained by rapid distribution of drug into cellular compartments. In a cell-free assay the *trans*-pyridine compound showed a dose dependent inhibition of semi-purified telomerase and a telomerase inhibitory effect.⁶⁸ It is of interest that stabilization of human telomeric quadruplex DNA and inhibition of telomerase has also been shown by platinum-phenanthroline and platinum-acridine complexes, suggesting that the structural role of planar ligands may have some effect.⁶⁹ 70 Many telomerase-inhibitory compounds are large delocalized planar aromatic systems.

7 Ternary DNA-protein crosslink formation

Topoisomerases relax supercoiled DNA by formation of transient phosphodiester linkages between the backbone phosphate and a tyrosine residue on the protein. Ternary adduct formation by platinum would prevent the reannealing step and release of the bound protein, resulting in the observed strand breaks. By analogy with known mechanisms of Topo inhibition, the limiting mechanisms for formation of ternary DNA-protein adducts involve interactions between a mono- (or bifunctional) Pt-DNA adduct and a protein site on topoisomerase, Figure 6.

There is precedence for DNA-protein formation mediated by *trans*-platinum. The long-lived nature of the monofunctional adduct of *trans*-DDP has been exploited previously for DNA/RNA-protein cross-linking. This approach, allowing contact points between RNA and protein, was demonstrated with the ribosome from *E. coli* and an aminoacyl-tRNA synthetase/tRNA complex.⁷¹ Likewise, *trans*-DDP has been used to cross-link the zinc-finger nucleocapsid protein to HIV-1 RNA.⁷² However, ternary DNA-Pt-protein crosslink formation is not a general feature of *trans*-platinum compounds with sterically hindered amines. As noted, no ternary DNA-HMG protein formation was noted for the monofunctional adduct of *trans*-[PtCl₂(NH₃)(tz)]⁵⁴. Monofunctional adducts of transplatin itself on 44-mer DNA templates are stable in the presence of a variety of DNA-binding proteins – KF⁺, histone H1 and NF-κB.⁷³ In contrast, oligodeoxyribonucleotide platinated by *trans*-[PtCl₂(*E*-iminoether)₂] cross-links histone H1 and the subsequent DNA-protein crosslinks inhibit DNA replication and repair.³⁷ Overall the results suggest that the *trans*-platinum chemotype may offer significant potential for design of selective DNA-protein crosslinking agents.

7.1 Models for ternary DNA-protein formation

Nucleobase cations of general formula [PtCl(L)(L')(Nucleobase)]⁺ represent convenient structures for studying competitive reactions of model DNA (e.g. N-donor 5'-guanosine monophosphate, 5'-GMP) or protein (e.g. S-donor *N*-acetylmethionine, *N*-AcMet) residues. The effects of complex geometry and the nature of L and L' on the kinetic differences

between S and N-donors gives a measure of the possible preferences for protein over DNA interaction.⁷⁴⁻⁷⁶ The 1:1 reactions with 5'-guanosine monophosphate (5'-GMP) or *N*-AcMet of (SP-4-2)-[PtCl(9-EtGua)(NH₃)(L)]⁺ [L = NH₃ or quinoline], showed that displacement of Cl⁻ showed clear kinetic preference for the sulfur in both cases, with the sterically more hindered quinoline compound reacting more slowly ($\sim t_{1/2}$'s = 1.5 and 3.5 h with *N*-AcMet against 7 and 17 h for 5'-GMP for L = NH₃ or quinoline respectively). The S/N ratio (estimated by $t_{1/2}$ (5'-GMP)/ $t_{1/2}$ (*N*-Ac-*L*-Met)) was even greater for *trans*-[PtCl(9-EtGua)(py)₂]⁺. This sulfur preference also extends to the *cis* isomer of the latter compound. A unique feature of the *trans*-platinum-mononucleobase compounds is that the Pt-Cl bond undergoes extremely slow hydrolysis. A major difference between the requirements for nucleotide and sulfur binding to Pt(II) is that the latter substitution proceeds *via* direct substitution of chloride whereas N7 binding may require prior hydrolysis of the chloride.⁷⁷

7.2 Interactions of trans-platinum mononucleobase compounds with Zinc Fingers and Zinc Finger models

The high sulfur affinity of *trans*-platinum-mononucleobase compounds has been exploited in reactions with proteins containing zinc-finger motifs with cysteine and methionine residues. This important family of DNA-regulating proteins is widespread and a large number of zinc-finger proteins is recognized as encoded by the human genome.^{78, 79} Zinc fingers have become important cellular targets for potential anti-cancer drugs as well as HIV inactivation. Interaction of the C-terminal finger of HIV NCp7 protein with *trans*-[PtCl(9-EtGua)(py)₂]⁺ results in Zn ejection from the peptide accompanied by loss of tertiary structure.⁸⁰ Targeting the NCp7-DNA interaction for drug design represents a conceptual advance over electrophiles designed for chemical attack on the zinc finger alone. The results demonstrate examples of a new platinum structural class targeting specific biological processes, distinct from the bifunctional DNA-DNA binding of cytotoxic agents like cisplatin. The results confirm the validity of a chemical biological approach for metallodrug design for selective ternary DNA(RNA)-protein interactions.

In order to provide precedents for the possible interactions of platinum DNA adducts with zinc finger proteins, complexes such as *trans*-[PtCl(9-EtGua)(py)₂], and [Pt(dien)Cl]Cl (dien = diethylenetriamine) and [Pt(terpy)Cl]Cl (terpy = 2,2': 6',2''-terpyridine) were exposed to the Zn dithiolate, N, N'-bis(2-mercaptoethyl)-1,4-diazacycloheptanezinc(II) dimer, [Zn(bme-dach)]₂.^{81, 82} The products defined by Electrospray Ionization Mass Spectrometry (ESI-MS), x-ray crystallography and ¹⁹⁵Pt-NMR spectroscopy yielded evidence for Zn-(μ-SR)-Pt bridges followed by zinc ejection from the N₂S₂ coordination sphere and subsequent formation of a trimetallic Zn-(μ-SR)₂-Pt-(μ-SR)₂-Zn bridged species.

8 Cytotoxicity and *in vivo* efficacy of *trans*-platinum drugs

Space precludes a detailed analysis of cellular effects by *trans*-platinum compounds. As stated, there is an extensive literature on cytotoxicity and also DNA modifications by *trans*-platinum compounds.¹¹⁻¹⁵ There is somewhat less information on *in vivo* antitumor activity. Nevertheless some evidence of *in vivo* activity has been reported.^{8, 11-15, 44} The *trans*-[PtCl₂(NH₃)(tz)] shows moderate activity against P388 leukemia.⁸ In Lewis lung carcinoma xenografts, *trans*-[PtCl₂(E-iminoether)₂] decreased the level of lung metastases over that of the vehicle control but levels were still higher than that of cisplatin. Furthermore, there was no significant enhancement in survival in mice treated with *trans*-EE (33 days) over vehicle control (30 days).⁸³ The complex also showed significant in P388 leukemia, but less than cisplatin.⁸⁴ The therapeutic efficacy of the *trans*-[PtCl₂(NH₃)(pip-pip)] and *trans*-[PtCl₂(NBA)(pip-pip)] was evaluated in Balb/c mice with either A2780 or A2780cisR. Though exhibiting similar cytotoxicities, cisplatin was able to extend the life expectancy by 160% while *trans*-[PtCl₂(NH₃)(pip-pip)] and *trans*-[PtCl₂(NBA)(pip-pip)]

only 79% to 46% respectively. Furthermore, though both compounds have similar cytotoxicities, *trans*-[PtCl₂(NH₃)(pip-pip)] showed no improvement in outcome of Balb/c/A2780cisR mice whereas both cisplatin and *trans*-[PtCl₂(NBA)(pip-pip)] did.⁸⁵

JM335 was one of the most active Pt(IV) compounds that showed activity against ADJ/PC6 tumor, a cisplatin resistant murine plasmacytoma xenograft.⁸⁶ JM355 was also the most effective at delaying tumor growth, as much as 2 months in the case of PXN/100.⁸⁷ *trans*-[PtCl₂(dimethylamine)(isopropylamine)] at 30mg/kg showed no antitumor effects compared to untreated control in the human ovarian CH1 xenograft, was attributed to its' inactivation by plasma proteins. However, the Pt(IV) analog *trans,trans,trans*-[PtCl₂(OH)₂(dimethylamine)(isopropylamine)] was effective at delaying the growth progression of CH1 xenografts at 15mg/kg for 15 days, similar to that of cisplatin.²³

9 Summary

The use of sterically hindering amines in the *trans*-platinum geometry affords many complexes with cytotoxicity equivalent to that of cisplatin. Indeed, examining the diversity of amine used (Fig. 2) it appears that transplatin itself is the exception ! The chemistry and DNA binding modes of cytotoxic *trans*-platinum agents shows a rich carrier ligand-dependent diversity, both with respect to the structural consequences of the adducts produced and their stability and reactivity. Mechanistic studies also indicate that the *trans*-platinum scaffold may be especially useful for design of selective ternary DNA-protein crosslinking agents. Noteworthy in this respect is the ability to crosslink zinc finger proteins with subsequent zinc ejection from the protein. Finally, although some *in vivo* antitumor activity has been reported there is not such a wide variety of data available as there is for the *cis* chemotype. This may be due to the expense of *in vivo* studies but also to as yet unstudied issues of drug metabolism and biodistribution. While the greatest emphasis has been placed on comparing the target (DNA) interactions of cytotoxic *trans*-platinum compounds with those of cisplatin and congeners, the ultimate determinant of drug efficacy probably lies more in the pharmacokinetic and pharmacodynamic realm than with specific drug-DNA interactions. Nevertheless, modification of the "parent" *trans*-[PtCl₂(NH₃)₂] molecule by substitution of NH₃ with a host of amines has produced a rich chemistry and biology of the *trans* geometry, which may eventually be translated to the development of clinically useful drugs.

Acknowledgments

This work was supported by grants from The National Institutes of Health and The National Science Foundation. It is a pleasure to acknowledge the collaborations of Viktor Brabec and his group as well as the contributions of Uli Bierbach to the DNA-binding studies of TPA complexes.

11 Dedication This review is dedicated to the memory of Lloyd R. Kelland a friend and collaborator, and a great advocate for platinum. Ar dheis Dé go raibh a hanam.

Definitions

ipa	isopropylamine
pz	piperazine
pip	piperadine
mba	2-methylbutylamine
dma	dimethylamine

sba *sec*-butaneamine

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Figure 1.
Cytotoxic transplanar amine platinum compounds (TPAs)

Figure 2.
Structures of selected trans-platinum compounds with carrier ligand other than planar amines

Scheme 1.

Proposed scheme for hydrolytic activation of transplatin

Figure 3. Interstrand cross-link for cisplatin 45⁸⁷³, 46 (left) and transplatin47 (right) highlighting the markedly different DNA bending induced by platinum compounds.

Figure 4. Schematic representation of the modes of DNA interstrand cross-linking by transplatin (left), cisplatin (center), and *trans*-[PtCl₂(NH₃)(iquin)]. The latter is a representative example of the effect of a planar amine on DNA adduct structure. 48· 49

Figure 5.
Molecular model of the monofunctional DNA adduct of *trans*-[PtCl₂(NH₃)(tz)].

Figure 6.
Postulated competition between DNA-DNA and DNA-protein crosslink formation in trans-Pt adducts

In vitro cytotoxicity (IC₅₀, μM) of transplanaramine (TPA) platinum compounds in a human ovarian cell line panel. 6-9

Table 1

Compound	HX/62	SKOV-3	PXN94	4IM	4IMcisR	CHI	CHIsR
<i>trans</i> -[PtCl ₂ (py) ₂]	4.5	5.9	7.7	2.2	2.0 (0.91)	1.6	1.7 (1.1)
<i>trans</i> -[PtCl ₂ (tz) ₂]	4.1	6.2	9.6	2.2	1.6 (0.73)	1.3	1.4 (1.1)
Transplatin	245	255	222	57	69 (1.2)	30	68.5 (2.3)
Cisplatin	12.6	4.4	3.0	0.23	1.4 (6.1)	0.1	0.67 (6.7)
<i>trans</i> -[Pt(O ₂ CCH ₃) ₂ (py) ₂]		31.0		14.0	4.5 (0.32)	19.0	4.1 (0.22)
<i>trans</i> -[Pt(O ₂ CCH ₃) ₂ (NH ₃)(tz)]		96.0		21.5	7.2 (0.33)	24.0	8.2 (0.34)
<i>trans</i> -Pt(O ₂ CCH ₃) ₂ (NH ₃)(iquim)]		40.0		22.0	5.8 (0.26)	20.0	7.4 (0.37)

tz=thiazole; py=pyridine; iquin=isoquinoline; quin=quinoline; bztz=benzothiazole (see Figure 1)

Table 2

Effect of carrier ligand on pK_a values of the diaqua species and rate constant for the first hydrolysis step of various *trans*-(diam(m)ine)platinum(II) complexes and cisplatin.

Compound	pK_{a1}	pK_{a2}	k_1 (s^{-1})	Reference
<i>cis</i> -[PtCl ₂ (NH ₃)]	5.37	7.21	2.5×10^{-5}	25, 28
<i>trans</i> -[PtCl ₂ (NH ₃) ₂]	4.35	7.40	9.8×10^{-5}	25, 28
<i>trans</i> -[PtCl ₂ (NH ₃)(mba)]	4.16	7.17	--	25
<i>trans</i> -[PtCl ₂ (NH ₃)(ipa)((S)-mba)]	4.21	7.33	--	25
<i>trans</i> -[PtCl ₂ (NH ₃)(2-pic)]	4.03	7.01	2.6×10^{-5}	25
<i>trans</i> -[PtCl ₂ (NH ₃)(3-pic)]	3.97	6.78	12.7×10^{-5}	25
<i>trans</i> -[PtCl ₂ (NH ₃)(4-pic)]	3.94	6.88	5.2×10^{-5}	25
<i>trans</i> -[Pt(O ₂ CCH ₃) ₂ (py) ₂]	3.87	6.70	3.2×10^{-7}	9
<i>trans</i> -[Pt(O ₂ CCH ₃) ₂ (NH ₃)(quin)]	3.89	7.01	3.7×10^{-7}	9
<i>trans</i> -[Pt(O ₂ CCH ₃) ₂ (NH ₃)(iquin)]	3.78	6.92	7.4×10^{-7}	9

Table 3

Effect of carrier ligand on distribution of DNA adducts for transplatinum complexes

[PtCl ₂ (L)(L')]	interstrand CLs/adduct (%) ^a	monofunctional lesions/adduct (%) ^a	intrastrand CLs/adduct (%) ^a	Reference
cisplatin	6	~1-4	~90	38
transplatin	12	~60	~28	38
NH ₃ ,thiazole	30-40	33	27-37	36, 39
NH ₃ ,piperidine	26	15	59	40
NH ₃ ,piperazine	18	22	60	40
NH ₃ , 4-picoline	40	34	26	40
NH ₃ , 2-methylbutyl- amine	40	36	24	41
(E-iminoether) ₂	10	90	0	42, 43

^a Adapted from ref. 44

Table 4

Summary and comparison of structural characteristics of DNA cross-links of *trans*-[PtCl₂(NH₃)(tz)] (*t*-PtTz), transplatin and cisplatin.⁵⁴

	1,3-intra-strand XL of <i>t</i> -PtTz	Interstrand XL of <i>t</i> -PtTz	Monofunctional adduct of <i>t</i> -PtTz	Interstrand XL of transplatin	Interstrand XL of cisplatin	1,2-intra-strand XL of cisplatin
Frequency	20-40%	30-40%	30-40%	~12%	~6%	~90%
DNA bending	40° toward minor groove	22° toward minor groove	34° toward major groove	~20° toward minor groove	40-45° toward minor groove	32-34° toward major groove
DNA unwinding	15°	20°	12°	~12°	76-79°	13°
HMGB1a affinity	> 1.5 μ M	> 1.5 μ M	38.5 nM	ND	> 1.5 μ M	30.8 nM
HMGB1b affinity	> 30 μ M	13.40 μ M	2.05 μ M	ND	4.60 μ M	1.85 μ M
NER by eukaryotic excinuclease (relative excision)	1.0	no	1.4	no	no	1.5