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Perspective

Basis for Design and Development of Platinum(IV) Anticancer Complexes

Matthew D. Hall,*,†,‡ Howard R. Mellor,§ Richard Callaghan,§ and Trevor W. Hambley*,†

Centre for Heavy Metals Research, School of Chemistry, The University of Sydney, New South Wales 2006, Australia, Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, 37 Convent Drive, Bethesda, Maryland 20893-4256, and Oxford Drug Resistance Group, Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, U.K.

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Introduction

Platinum(II) complexes are widely employed in cancer chemotherapy, but their efficacy against the majority of malignancies is limited. The reasons for this failure are a combination of uni- and multicellular resistance, toxicity, and poor whole-body or cellular pharmacokinetic profiles.[1] The discovery,[2] chemistry,[3] and biology[4] of platinum drugs have been extensively reviewed in the literature. Briefly, it is generally accepted that platinum drugs effect their cytotoxic action by entering the cell and binding to DNA. This DNA lesion is recognized by nuclear housekeeping proteins that initiate the apoptotic cascade that leads to cell death,[4] though it is noted that a number of alternative cellular targets have also been proposed.[5] Cellular resistance to cisplatin is largely attributed to up-regulation of DNA repair and damage tolerance pathways, lowered intracellular accumulation, and inactivation by thiol containing reductants such as glutathione and metallothionein.[6,7] Before arriving at their ultimate target, a large proportion of platinum(II) drugs are lost because of protein binding in the bloodstream and side reactions leading to undesirable side effects.[8]

Platinum(IV) complexes offer the opportunity to overcome some of these problems; the octahedral geometry introduces two extra ligand sites, and the high kinetic inertness of the complexes lowers reactivity and the prospect of side reactions.[9] The axial ligands of platinum(IV) complexes offer a unique ability in drug design to modify the pharmacokinetic parameters of a prodrug, including the rate of reduction (E_p), the lipophilicity, molecular targeting, and microenvironmental targeting, in order to reduce side effects, increase activity, and target tumor sites, or the axial ligands themselves can confer additional cytotoxicity upon release. Despite this potential for drug design, no platinum(IV) complex is an approved drug (though three have entered clinical trials and one remains under trial).

The overwhelming weight of evidence in the literature favors the hypothesis that platinum(IV) complexes must be reduced to platinum(II) to be activated, and as such, the platinum(IV) complexes should be considered as prodrugs (Figure 1).[9] The most recent addition to the evidence for this comes from Farrell and co-workers who have used a bioinformatic analysis approach to assess 107 platinum(II) and platinum(IV) complexes in the National Cancer Institute's anticancer drug screen library.[10] The compounds were clustered into 12 groups, based on the similarities in their activity profile against the NCI-60 cell line panel; these groupings were dependent on the nature of the nonleaving ligands (dach,[a] silane, pyridine, etc.), and neither the leaving groups nor oxidation state of the complexes affected the spectrum of activity of a given complex against the NCI-60 panel.[10] This supports the hypothesis that the spectrum of activity of a given platinum(II) congener is not affected by oxidation. In keeping with this, inactive platinum(II) complexes such as $[PtCl(dien)]^+$ do not give rise to active platinum(IV) complexes.[11] For this reason, there are no "structure−activity" rules for platinum(IV) complexes per se except

* To whom correspondence should be addressed. For M.D.H.: phone, +1 301 496 1104; fax, +1 301 402 4273; e-mail, hallma@mail.nih.gov. For T.W.H.: phone, +61 2 9351 2830; fax, +61 2 9351 3329, e-mail, t.hambley@chem.usyd.edu.au.

† The University of Sydney.

‡ National Cancer Institute.

§ University of Oxford.

[a] Abbreviations: dach, 1,2-diaminocyclohexane; en, ethane-1,2-diamine; ER, estrogen receptor; GST, glutathione-*S*-transferase; MCR, multicellular resistance; NCI, National Cancer Institute; OAc, acetate; SPARC, satraplatin and prednisone against refractory cancer; SRIXE, synchrotron resonance induced X-ray emission.

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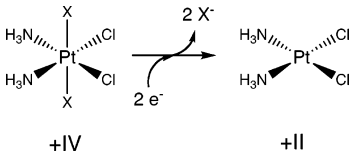


Figure 1. Exemplar platinum(IV) complex possessing the square-planar moiety $\{PtCl_2(NH_3)_2\}$ (cisplatin) and two axial ligands, X. The two-electron reduction to square-planar platinum(II), with loss of the axial ligands, is shown.

that the platinum(II) congener with which one constructs a platinum(IV) complex should be active.[12]

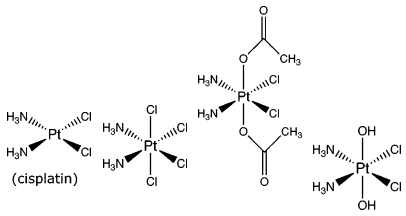
Design of Active Platinum(IV) Complexes

Aquation, the displacement of leaving ligands on platinum drugs by water, is one of the main considerations in the activation and deactivation of platinum(II) complexes[13] and has also been examined for platinum(IV) complexes using [^{1}H,^{15}N] HSQC 2D NMR.[14] ^{15}N-labeled platinum(IV) complexes with *trans*-diacetato and -dihydroxo ligands did not show significant aquation even after several weeks in solution. *cis*-$[PtCl_4(NH_3)_2]$ does aquate slowly, at a rate that is highly dependent on the amount of trace platinum(II) present (95% of starting material is intact after 42 h), and platinum(II) impurities have been shown to result in variable aquation of clinical preparations of tetraplatin.[15] In effect, aquation occurs at a rate much slower than that of reduction in biological media,[16] and platinum(IV) complexes can be designed with little concern for aquation interfering with pharmacokinetic parameters. This may allow the stabilization, by oxidation, of platinum(II) complexes that demonstrate a promising spectrum of activity but are hampered by poor pharmacokinetics.

While aquation does not appear to be a compromising feature, the reduction potential is of primary importance. Our investigations with a series of three model platinum(IV) complexes with axial chloro, acetato, and hydroxo ligands reveal that they have reduction potentials such that the ease of reduction occurs in the order Cl > OAc > OH.[17] In most of our studies, the platinum(IV) complexes have been based on the platinum(II) drug cisplatin (Table 1), *cis*-$[PtCl_4(NH_3)_2]$, *cis*,*trans*,*cis*-$[PtCl_2(NH_3)_2(OAc)_2]$, and *cis*,*trans*,*cis*-$[PtCl_2(NH_3)_2(OH)_2]$, for a number of reasons: the platinum(II) complex yielded is used in the clinic and its mechanism of action is relatively well understood; the starting material (cisplatin) is readily available for syntheses; the family of complexes have good solubility for biological studies; because all three complexes yield a common active drug on reduction, comparison of physical and biological properties of the series is less complicated. In some cases, we have employed the analogous series of platinum complexes based on $[PtCl_2(en)]$ (en = ethane-1,2-diamine) in part because the ethane bridge of the en ligand can be ^{14}C radiolabeled.[18]

The importance of the reduction potential has prompted us to probe the properties of platinum(IV) complexes required for activity (summarized in Table 1). Though the platinum(IV) complexes are taken into cells at a lower rate than their platinum(II) congeners,[19] X-ray absorption near edge spectroscopy (XANES) has been used to show that platinum(IV) complexes can indeed enter cells intact, and the proportion of three platinum(IV) complexes reduced intracellularly after 2 h was found to correlate with the reduction potentials of the complexes (Table 1).[20] This correlation was also observed when XANES was used to monitor the extent of reduction in growth medium[21] and by measuring total Pt-binding to protein incubated in media.[22] After 24 h of incubation with cells, all complexes are completely reduced,[20] and the distribution of platinum within

Table 1. Summary of the Features Determined for Cisplatin and Three Model Platinum(IV) Complexes with Cl, OAc, and OH Axial Ligands[a]



axial ligand			Cl	OAc	OH
E_p (mV)[b]			−260	−635	−880
% of Pt(IV)[c]	2 h		5	33	54
	24 h		0	1	0
IC_{50} (μM)[d]	A2780	2.5	3.3	17.9	21.9
	A2780 cisR	8.7	9.9	52.2	39.3
resistance factor[e]		3.4	3.0	2.9	1.8
log P_{oct} [f]		−2.28	−2.06	−2.20	−2.81
uptake (ng Pt/10^6 cells)[g]		4.93	5.14	2.82	2.10

[a] Values are statistically significant, but error values are removed to aid the reader in comparison. [b] Versus Ag/AgCl, from ref 81. [c] Percentage Pt(IV) remaining after incubation of complex with A2780 cells for 2 and 24 h; from ref 20. [d] Against the parental A2780 ovarian cancer cell line and the cisplatin-selected resistant cell line A2780 cisR, from ref 81. [e] Resistance factor is IC_{50}(cisR)/IC_{50}(A2780). [f] From ref 81. [g] Adapted from ref 19, after 3 h of exposure and 24 h of incubation with Jurkat cells. A similar pattern of Pt accumulation has been observed with these complexes in the A2780 cell line.[81]

cells was shown using synchrotron resonance induced X-ray emission (SRIXE) imaging to be similar to that in cells treated with their platinum(II) analogue, cisplatin.[23]

Bromine of the bromoacetate $[OC(O)CH_2Br]$ axial ligands in the complex *cis*,*trans*,*cis*-$[PtCl_2(OC(O)CH_2Br)_2(NH_3)_2]$ (which has a similar reduction potential and IC_{50} to its *trans*-acetato analogue) was employed as an elemental tag of axial ligands.[24] SRIXE imaging of cells treated with the complex showed a diffuse Br distribution throughout the cell, while Pt demonstrated localization similar to that for cisplatin, indicating substantial intracellular reduction of the complex and confirming loss of the axial ligands on reduction.[24] Collectively, these studies demonstrate that platinum(IV) complexes with low or intermediate reduction potentials can indeed be designed with the expectation that they will be able to arrive at and enter cells intact and that axial ligands (potentially with bioactive constituents tethered to them) are released along with the active platinum(II) complex on reduction.

Assessing the Efficacy of Platinum(IV) Complexes

During early drug development, ascertaining the biological properties is largely dependent on the use of simple cell monolayer systems. However, a major limitation of in vitro screening of potential anticancer drugs is that cell monolayers are unrepresentative of solid tumor tissue and the associated microenvironment. The cells comprising tumors are organized into a three-dimensional architecture that is often poorly vascularized, leading to regional microenvironmental heterogeneity characterized by factors such as decreased O_2 (hypoxia), high interstitial pressure, gradients of nutrients and metabolites, and decreased extracellular pH.[25] The microenvironmental effects described result in an altered and nonuniform tumor response to many chemotherapeutic agents. In most cases, this manifests as drug resistance, an effect that can be reproduced with many agents in vitro using cells grown in 3D cultures called spheroids, the overall phenomenon being commonly referred to as multicellular resistance (MCR).[26−28]

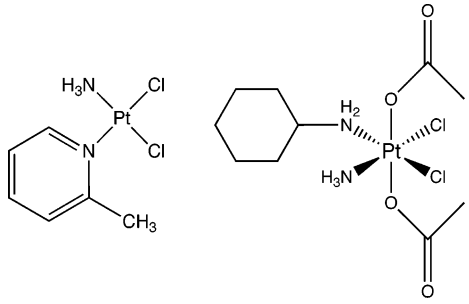
Encouragingly, it has been demonstrated that the platinum(IV) complexes outlined above maintain potency in spheroids equivalent to that in monolayer cultures, and therefore, these drugs do not appear to be subject to multicellular resistance.[29] It has been postulated that the hypoxic tumor microenvironment may favor reduction of platinum(IV) drugs because the lower pO_2 of poorly vascularized tumors results in a relatively reducing environment, thus improving efficacy.[30] In a direct comparison of normoxia and hypoxia maintained non-small-cell lung cancer spheroids, no improvement in their activity was observed, in contrast to what is observed for copper and cobalt complexes and drugs such as tirapazamine.[31] However, it is encouraging that unlike many anticancer drugs, platinum(IV) complexes do not lose activity against cells under hypoxic conditions, making them potential candidates for treating avascular tumors.[30]

A recent study has provided some insight into the pharmacokinetics of platinum(IV) drugs in solid tumor tissue. The multicell-layer (MCL) model is an in vitro tissue model that can be used to determine drug penetration and transport across tissues. The platinum(IV) compound *cis,trans,cis*-$[PtCl_2(OH)_2(en)]$ was shown to traverse a multicellular layer at the same rate as the ^{14}C-labeled cisplatin analogue $[PtCl_2(en)]$.[18] Mathematical modeling predicted that there should be a concentration gradient within the MCL decreasing from the free surface of the tissue downward, and SRIXE imaging shows a distribution gradient of Pt through the layer.[18] This was the first experimental verification of platinum drug distribution within an MCL solid tumor model and compared to the one predicted by mathematical modeling. Overall, studies in multicellular systems with platinum(IV) complexes have demonstrated the potential for this class of compound to exert activity in environments often associated with resistance to chemotherapeutic agents and that the drugs can indeed possess the intratumor pharmacokinetic parameters required to be efficacious in vivo.

When surveying the field, we posed the following question. Why have complexes that demonstrated promising preclinical activity failed in clinical trials? This challenge is not unique to platinum drugs of course, but there are some features unique to inorganic complexes and other drugs relying on reduction for activation.[32] During assessment of drugs for potential development using monolayer cytotoxicity such as the MTT assay, it is the most readily reducible, and therefore activatable, platinum(IV) complexes that demonstrate activity in cell culture.[33,34] As such, those complexes that would be the most rapidly reduced in vivo are those that are usually identified as being the most "active", whereas what is often being sought is more inert complexes. For this reason, monolayer cytotoxicity assays are not necessarily a sound basis for selection of candidates for further study. Certainly it seems that along with basic requirements for active platinum(IV) complexes, biological parameters such as rate of reduction by glutathione, cytotoxicity and spectrum of activity of the platinum(II) congener upon which the complex is based, and uptake studies in cells after short-term exposure to drug may be more reliable indicators of the potency and stability of platinum(IV) complexes. In vivo testing of platinum(IV) complexes in mouse tumor xenograft models are then expected to be the most informative predictor of clinical efficacy.

Recent Progress in the Field

The reactivity of platinum(IV) complexes with biomolecules and the clinical development of platinum(IV) complexes have been reviewed previously,[9,35] and that material will not be reproduced here. Reports of platinum(IV) complexes of platinum(II) analogues or biomolecules continue,[36,37] but these rarely yield complexes with new cytotoxicity profiles, and oxidation does not necessarily guarantee improved stability. For example, Battle et al. recently demonstrated that generation of the platinum(IV) version of the clinical drug AMD473 (**1**) did not confer stability because of steric bulk around the platinum(IV) center destabilizing the higher oxidation state.[38]



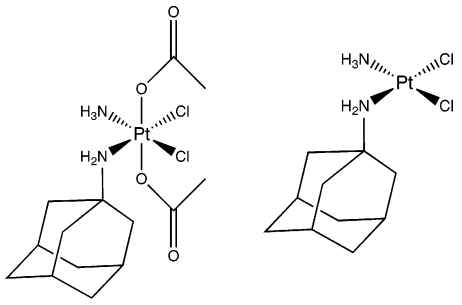
1 **2**

There have been exciting recent developments in platinum(IV) design, including novel compounds that employ moieties that aim to overcome clinical resistance and toxicities, and further understanding of the bioinorganic chemistry of satraplatin (JM216, **2**). These developments are outlined below and are discussed in the context of an understanding of the mechanism of action of platinum(IV) complexes previously described above.

Satraplatin (**2**) was designed as a lipophilic drug able to be administered orally because of its inertness and with rapid cellular uptake that could overcome accumulation defects in resistant cells.[39,40] It is the only platinum(IV) drug currently undergoing clinical trials, and mechanistic examinations are ongoing.[41] McKeage and co-workers have investigated the fate of **2** in fresh whole human blood and found that it has a half-life of 6.3 min that appears to be dependent on the presence of red blood cells because **2** has a half-life on the hour time scale in human plasma and cell culture medium.[42] Furthermore, it was shown that its reduction can be mediated by heme proteins such as hemoglobin or cytochrome *c* in the presence of NADH because of reduction by the heme metal.[43] The reduction of Pt(IV) complexes by Fe(II) is well-known,[44] but this is the first report of Pt(IV) drug reduction by Fe(II) observed in a biological sample and represents a new class of reductants to be considered in preclinical assessments.

Kozubik and collaborators have reported the synthesis of a lipophilic platinum(IV) complex tethered to 1-adamantylamine[45] (LA-12, **3**) that is highly lipophilic and is not cross-resistant with cisplatin in vitro.[46] The complex is only four carbon atoms different from **2** (the cyclohexylamine is replaced with an adamantylamine ligand) and demonstrated no cross-resistance with cisplatin and similar activity to satraplatin.[47] The authors of this series of studies also show that **3** is more effective than its platinum(II) congener LA-9 (**4**) in sensitive and resistant cells. It is particularly interesting that increasingly lipophilic platinum(IV) complexes are observed to overcome resistance, as it appears to uphold the hypothesis stated above that lipophilic platinum(IV) drugs should overcome cisplatin resistance because they do not rely on the energy-dependent uptake "lost" in platinum(II) drug-resistant cell lines. The efficacy of this drug was recently confirmed in preclinical mouse studies that were consistent with in vitro observations.[48]

This promising activity has led to an investigation of the mechanism of action of **3** by Brabec and co-workers.[49] Increased accumulation compared to cisplatin in A2780 and A2780 cisR



3 **4**

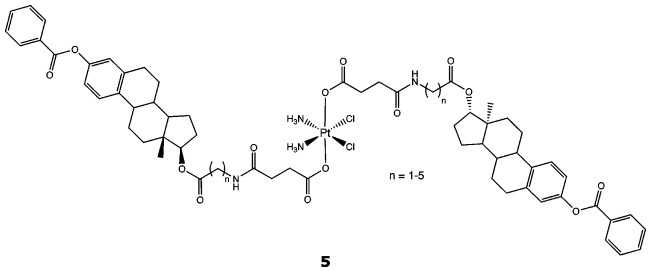
(cisplatin-resistant) ovarian cancer cell lines was observed, but accumulation in the resistant line was approximately 25% that of the parental line, and nuclear lesions were effectively analogous to those of cisplatin. Also, the adducts formed by **3** with DNA were less efficiently repaired and resulted in different protein−DNA cross-links.

An interesting discord in the literature is the perceived role of glutathione (GSH) in the activity of platinum(IV). The reduction of **3** by ascorbate was found by Brabec and co-workers to proceed at a rate similar to that of **2**, reduction being required for activation of the drug.[49] When the reaction of GSH with **3** and cisplatin was assessed, it was found that both reactions occur at a similar rate. This observation, along with the greater potency of **3** over cisplatin against the A2780 cisR cisplatin-resistant ovarian cancer cell line (which expresses high levels of reduced GSH[50]), led the authors to conclude that "deactivation" of **3** by thiol-containing molecules was not relevant to potential cellular resistance. However, reaction of **3** with GSH is most likely not "deactivation" but reduction to platinum(II), resulting (initially at least) in activation.[9] Therefore, it is entirely possible that the high efficacy of **3** against the resistant A2780 cisR cell line is due to an increased rate of intracellular reduction. Pendyala et al. have previously found a positive correlation between intracellular GSH levels and the activity of iproplatin and tetraplatin (but not platinum(II) complexes) that supports this hypothesis.[51] Indeed, it may be desirable for the platinum(IV) drug to arrive intact in resistant cells to be reduced and activated by GSH, and this may represent a mechanism of circumvention of cisplatin resistance.

Bioactive Axial Ligands

One of the challenges of platinum(IV) design and synthesis is the inertness of the complexes that generally renders ligand substitution reactions an impractical synthetic route. This means that one must ensure that the platinum(II) moiety desired can be oxidized to platinum(IV) without compromising structure, which has historically limited axial ligands to those easily incorporated during oxidation. Initially the hydroxo axial ligands were generated from oxidation with hydrogen peroxide, or the chloro axial ligands were generated by oxidation with Cl_2 gas or by displacement of hydroxo ligands in concentrated hydrochloric acid. A scheme of available synthetic routes for varying platinum(IV) axial ligands is shown in Figure 2.

The carboxylation of hydroxo ligands with anhydrides or acyl chlorides reported by Giandomenico opened up the possibility of ligand-based chemistry for drug design, which circumvented the need for ligand substitution reactions, as the hydroxo ligand is not displaced (Figure 2).[52−54] While variations on this theme have been explored, such as mixed carboxylate species,[55,56] Navarro-Ranninger and colleagues used this feature to ring-open cyclic anhydrides on hydroxo ligands, leaving pendent acetate groups for further reactivity (Figure 2).[57] Lippard and co-workers used this synthetic methodology to attach a bioactive moiety, estrogen, as a series of estradiol 3-benzoate ligands (**5**) to target platinum to estrogen receptor positive [ER(+)] breast cancer cells, an innovative first example of platinum(IV) drug design that targets a molecular feature of a tumor type of particular interest. The estradiol 3-benzoate ligands were generated upon intracellular reduction and resulted in the up-regulation of HMGB1, a protein known to shield platinated DNA from nucleotide excision repair (and hence allow apoptosis to be induced).[58]



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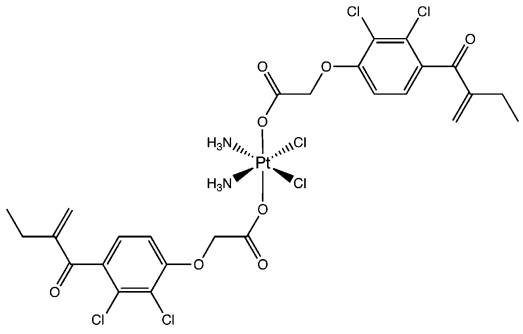
Dyson and co-workers considered the postulated role of glutathione-*S*-transferase (GST) in resistance to platinum-based therapy and conjugated the clinically tested GST inhibitor ethacrynic acid (2-[2,3-dichloro-4-(2-methylidenebutanoyl)phenoxy]acetic acid) axially as the deprotonated ethacrynate to create a Pt(IV) complex coined ethacraplatin (**6**).[59] This complex yields cisplatin and 2 equivalents of the inhibitor on reduction and demonstrated in vitro cytotoxicity earlier and at lower concentrations than cisplatin alone. Not only did the lipophilic complexes demonstrate rapid uptake that exceeded that of cisplatin, the complex was found to be a potent GST inhibitor in its own right that was shown by mass spectrometry to bind to GST.[59]



6

The functionalization of platinum(IV) that Lippard and Dyson have employed lends itself to a combinatorial library approach to drug synthesis similar to that already reported by Lippard and co-workers for platinum(II) complexes[60] to explore conjugated small molecules and peptides for targeting individual tumor types or as a cytotoxic chaperone for the delivery of drugs that present solubility or reactivity issues themselves (Figure 2).[61]

In this spirit, Keppler and co-workers optimized the carboxylation of *trans*-dihydroxo complexes by succinic anhydride and demonstrated that the uncoordinated terminal carboxylic acids can be reacted with amines and alcohols yielding amides and esters, respectively.[62] These generic reaction schemes allow for a vast array of organic compounds to be conjugated to platinum(IV) complexes in a fashion that should not disrupt the activity of either the ligand or the Pt center on reduction.

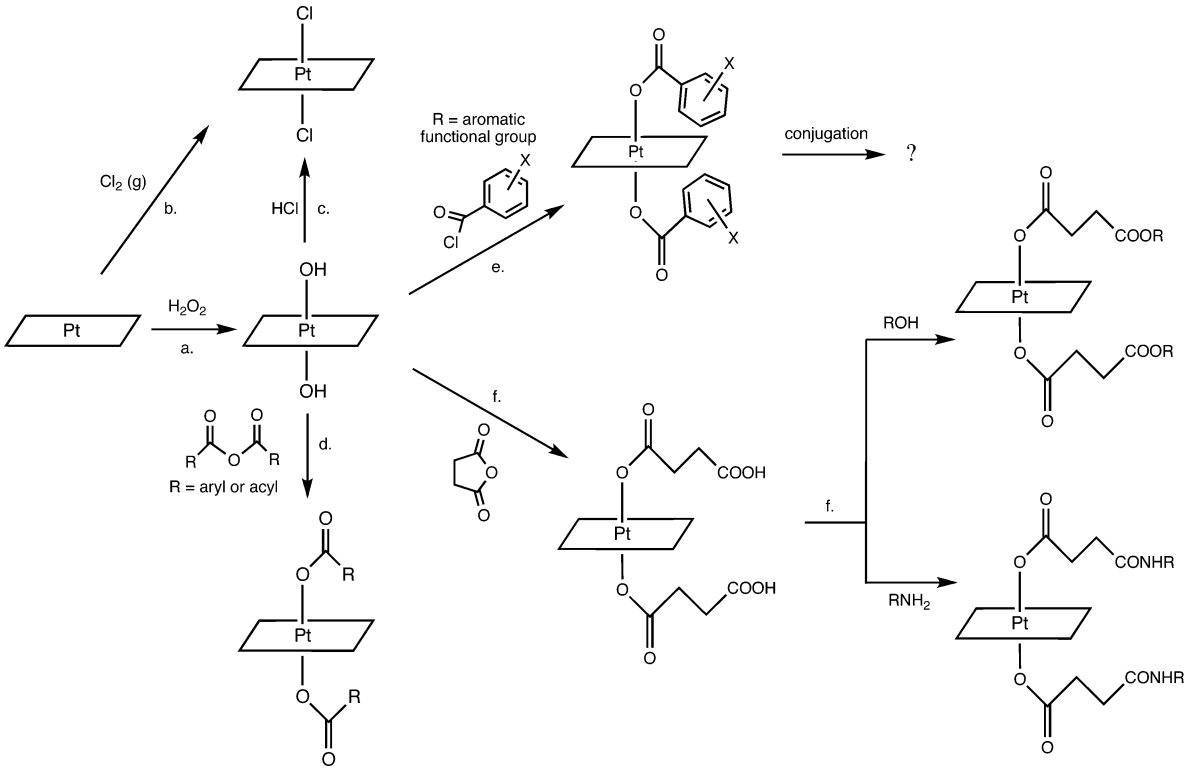
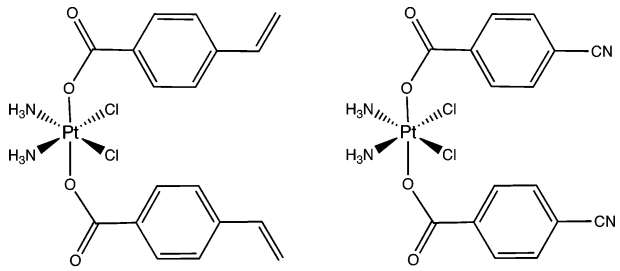


Figure 2. Schematic showing the syntheses of platinum complexes with a range of axial ligands reported in the literature. It is generally accepted that the platinum(II) congener must itself be capable of effecting cytotoxicity for the platinum(IV) complex to be active. Sample references for each step of the synthetic scheme are as follows. (a) Oxidation of platinum(II) complexes with hydrogen peroxide to yield *trans*-dihydroxo ligands: Vollano, J. F.; et al. *J. Med. Chem.* **1987**, *30*, 716−719. (b) Oxidation with chlorine gas to produce *trans*-dichloro ligands: Kauffman, G. B.; Cowan, D. O. *Inorg. Synth.* **1967**, *7*, 236−239. (c) Hydrolysis of hydroxo ligands with hydrochloric acid yielding *trans*-dichloro axial ligands: Ellis, L. T.; Hambley, T. W. *Aust. J. Chem.* **1995**, *48*, 793−806. (d) Carboxylation of hydroxo ligands with anhydrides: Giandomenico, C. M.; et al. *Inorg. Chem.* **1995**, *34*, 1015−1021. (e) Carboxylation of hydroxo ligands with acyl chlorides (functionalized aromatic carboxylate ligands): Ang, W. H.; et al. *J. Med. Chem.* **2005**, *48*, 8060−8069. (f) Carboxylation of hydroxo ligands with succinic anhydride and further conjugation with amines and alcohols: Reithofer, M.; et al. *Eur. J. Inorg. Chem.* **2006**, 2612−2617.

Dyson and co-workers took a slightly different approach in the synthesis and characterization of a range of platinum(IV) complexes with functionalized aromatic carboxylates (for example, **7**) in the axial sites that allow for other means of developing drugs for molecular targeting and altering pharmacokinetic properties.[63] These "precursor" complexes themselves all showed, relative to cisplatin, dramatically increased log *P* values with concordant uptake and, for most complexes, 10-fold improved cytotoxicity. While the reduction potentials were not reported for these complexes, there are good relationships between the increased accumulation and activity, though **8** represents the potential pitfall of striving for increasingly "organic" platinum(IV) drugs, as it was suggested to be a substrate for the multidrug-resistant protein P-glycoprotein,[63] a thoroughly undesirable property. A P-glycoprotein inhibitor tethered axially may be an interesting solution because ultimately P-glycoprotein inhibition could prove to be synergistic in the context of combinatorial chemotherapeutic regimes regularly employed in the clinic.

The challenge in generating complexes that are molecularly targeted by virtue of the bioactive components tethered to carboxylate axial ligands is that the half-life of dicarboxylate complexes in biological environments is relatively short. It has been demonstrated (Table 1) that after 2 h 67% of *cis,trans,-cis*-$[PtCl_2(OAc)_2(NH_3)_2]$ is reduced in cells,[20] and the in vitro half-lives of **2** in human blood plasma ($t_{1/2}$ = 5.3 h) and human whole blood (6.3 min) suggest that new drugs with axial acetate ligands may not persist intact long enough for the novel axial group to modify the uptake and distribution of the complex. High protein binding (93%) is observed in human plasma



7 **8**

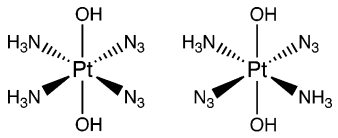
ultrafiltrates,[64] and intact **2** is not observed in patient plasma ultrafiltrates.[65] **2** has a much longer half-life of 22 h in supplemented cell culture medium, which means that selective properties of platinum(IV) complexes are more pronounced during in vitro screening than would be seen in vivo.[42]

While reduction potentials for the new complexes described above have not generally been reported, these are crucial to understanding the activity relationships, potential for reduction, and whether bulkier axial ligands will prevent outer-sphere reduction mechanisms from taking place that may protect these complexes from reduction. It is too early to say that axial groups tethered via carboxylate groups do not remain bound long enough to modify the in vivo properties of the complex, but as yet, there is no clear evidence that they do. Most platinum(IV) drug design has centered on the manipulation of carboxylate donors (Figure 2), and the incorporation of new organic functional groups into axial groups is necessary to extend the reduction potential range. Stronger ligands, such as the alkoxy

ligands we and others have utilized, can be expected to give rise to complexes that are more resistant to reduction.[66−68]

Potentiating Reactive Platinum(II) Complexes

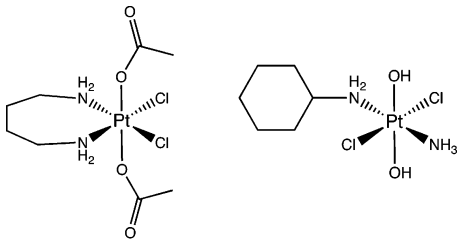
An excellent example of the potential of platinum(IV) complexes is the recent work by Sadler and co-workers, who have designed the *trans*-dihydroxo platinum(IV) complexes **9** and **10** that incorporate azide ligands in lieu of "traditional" chloro leaving groups in cisplatin and transplatin moieties,[69,70] that seem to demonstrate a number of "rule-breaking" properties.[12] The design allows for the drugs to be photoactivated by taking advantage of the photochemical features of azides, ligands that would be far too labile to be useful in platinum(II) complexes. The inert dihydroxoplatinum(IV) complexes are nontoxic in the dark (a property much desired in the clinic because it minimizes side effects), but upon irradiation with UVA light they demonstrate good cytotoxicity against 5637 human bladder cancer cell lines. Indeed, the *trans*-diammine complex **10** is as cytotoxic as cisplatin and is not cross-resistant with the cisplatin-resistant cell line 5637-CDDP.[70] Promisingly, the complexes appear to kill cells by a mechanism different from that for cisplatin perhaps because the species yielded is so highly reactive (yet to be identified but potentially a "diaqua" species that is probably not present in appreciable quantity during the aquation of cisplatin in vivo[13]). The complexes almost immediately coordinate to calf thymus DNA upon irradiation in vitro and can form lesions with DNA that transplatin itself does not, though it remains to be seen whether these would be subject to DNA-repair resistance pathways.[70] Further, the photoactivation does not rely on the presence of oxygen unlike current photodynamic therapy, thus avoiding the pitfalls of microenvironmental tumor hypoxia described above.[71]



9 **10**

Kim and co-workers synthesized a series of Pt(IV) complexes with 1,4-butanediamine ligands and hydroxide, acetate, and trifluoroacetate axial ligands. It is noted that complexes with axial trifluoroacetate ligands have reduction potentials very close to those with chloro axial ligands and are readily reduced.[72] In vitro and in vivo preclinical screening showed that *cis,trans*-$[PtCl_2(OAc)_2(1,4\text{-butanediamine})]$ (**11**, coined K101) and its *trans*-difluoroacetate analogue showed improved activity against colorectal and breast cancer cell lines.[73] Activity assays in mice showed that **11** had activity similar to that of cisplatin but with diminished toxicity, and it was selected for further study.[73] **11** elicited growth inhibitory action in twice as many colorectal cancer patient tissues (35 patients) as cisplatin in a three-dimensional culture system, and it was found that cell death was due to apoptosis, though apoptosis was associated with the p53 and ERK1/2 pathways (as for cisplatin), suggesting that ultimately cross-resistance may occur.[74]

Trans complexes have received increased attention over the past 10 years, as it is realized that increased steric bulk around the platinum center can stabilize them and increase anticancer efficacy.[75] Oxidation to platinum(IV) may allow further stabilization and increases in activity, and this possibility has led to a number of recent studies. JM355 (**12**) is a platinum(IV) complex with a trans equatorial plane (the equatorial plane is the trans isomer contained by **2**) and showed activity against a



11 **12**

range of cisplatin-resistant cell lines.[76] Lemma showed that the *trans*-dichloro moiety in **12** allowed it to be readily reduced by glutathione (half-life of 23 s at physiological temperature and pH),[77] which accounts for the high reactivity of JM335 that hampers its in vivo efficacy.[76] Navarro-Ranninger and co-workers have reported all-trans platinum(IV) complexes that have slowed protein-binding kinetics and activity against tumor xenografts as a result of this improved stability.[78]

Clinical Status

At the time of this writing, clinical trials with satraplatin (**2**) are ongoing and the efficacy of orally administered satraplatin in the treatment of hormone-refractory prostate cancer is currently being investigated.[41,79] Reversible myelosuppression is the dose-limiting toxicity,[80] and the nephrotoxicity, neurotoxicity, and ototoxicity observed with other platinum drugs in the clinic have not been observed. The most recent data from the phase III SPARC trial (**2** plus prednisone versus prednisone alone) indicate that median progression-free survival is significantly greater for the satraplatin arm and numerically greater for overall survival, though final results of the SPARC trial are awaited.[79]

Conclusions

It is clear from the new classes of drug design outlined above that several Pt(IV) complexes are being developed that target unique features of tumor cells that may result in activity against intrinsically resistant cells or improve patient comfort through better targeting to the tumor site. Furthermore, the development in Pt(IV) ligand chemistry available to the synthetic chemist, presented in Figure 2, should yield new complexes for testing against molecular targets identified as being unique to cancer cells. While the potential for conjugation to axial ligands is exciting, there is a need for synthetic chemistry to be developed to allow for new donor groups to be coordinated in the axial positions to allow for a wider range of reduction potentials and reactivities.

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Biographies

Matthew D. Hall received his B.Sc. (Hons) in Science and his Ph.D. in Chemistry from the University of Sydney, Australia, under Professor T. W. Hambley, working on understanding the mechanism of action of platinum(IV) complexes and synchrotron radiation techniques for metals in medicine. Following a 1-year postdoctoral fellowship with Professor Val C. Culotta at the Johns Hopkins School of Public Health, he is now a postdoctoral fellow at the Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, under Dr. Michael Gottesman. His current areas of research interest are metal-based drugs, the mechanisms of cisplatin resistance and multidrug resistance, and drug design strategies to overcome them.

Howard R. Mellor completed his D.Phil. at the Glycobiology Institute, Department of Biochemistry, University of Oxford, under

the supervision of Dr. Terry Butters, where he worked on the design, synthesis, and biological evaluation of novel inhibitors of glycolipid and oligosaccharide biosynthesis for the treatment of inherited metabolic disorders and hepatitis viral infections. He subsequently worked as a postdoctoral fellow in Dr. Richard Callaghan's laboratory in the Nuffield Department of Clinical Laboratory Sciences in Oxford, examining the role of tumor microenvironmental factors, such as hypoxia, on anticancer drug resistance. He has recently taken up a position in Prof. Adrian Harris' laboratory at the Weatherall Institute of Molecular Medicine in Oxford, investigating the role of various HIF-1 (hypoxia inducible factor-1) regulated proteins in cancer.

Richard Callaghan received his B.Sc. (Hons) at the University of Melbourne, Australia, in Biochemistry and Pharmacology. His Ph.D. was awarded in Pharmacology at the University of Melbourne. He then undertook postdoctoral research studies at McMaster University (Canada), the University of Toronto (Canada), and the Institute of Molecular Medicine at Oxford University (U.K.). Since 1997, he has run the Oxford Drug Resistance Laboratory at Oxford University. His research interests involve the contributions of membrane transport processes in disease. In particular, research is aimed at molecular mechanisms of multidrug resistance in cancer.

Trevor W. Hambley received his B.Sc. (Hons) degree from the University of Western Australia in 1977. His Ph.D. was on the molecular modeling of metal complexes with Dr. Michael Snow at the University of Adelaide, Australia. Postdoctoral studies followed at the Australian National University in 1982 with Glen Robertson and Alan Sargeson and in 1983 at CSIRO Energy Chemistry, Lucas Heights. His move east across Australia was completed in 1984 when he moved to the University of Sydney where he is a Professor in the School of Chemistry and has recently completed a term as Head of School. His scientific interests are in the area of medicinal inorganic chemistry with emphases on platinum anticancer agents, hypoxia selective metal complexes, MMP binding agents, and metal-based anti-inflammatory drugs. He has won awards for research and for postgraduate teaching and has published more than 440 books, reviews, and papers.

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