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Thermal degradation of platinum(IV) precursors to antitumor drugs

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Abstract Organoplatinum antitumor agents are very effective, broad-spectrum drugs used for the treatment of a variety of cancerous conditions. The two most prominent of these, Cisplatin [*cis*-diamminodichloroplatinum(II)] and Carboplatin [diammino(1,1-cyclobutanedicarboxylato) platinum(II)], are large scale commercial successes. The third, Oxaliplatin [((*trans*-1,2-diamminocyclohexane)oxalato)platinum(II)], is now commercially available. The administration of all these drugs is accompanied by severe side effects. For Cisplatin, the most debilitating of these is kidney damage and extreme nausea. Several approaches to generate drug-release formulations that might mitigate toxic side effects have been explored. Now, platinum(IV) compounds which are more inert than platinum(II) compounds, and consequently less toxic, but which may be reduced to platinum(II) species within the cell are being evaluated for effectiveness in the treatment of cancer. The thermal stability of several precursors to compounds of this kind has been examined by thermogravimetry. In general, these materials lose ligands sequentially to generate a residue of platinum. This behavior may be generally useful for the characterization of such materials.

Keywords Platinum(IV) prodrugs · Platinum(II) oxidation · Functionalized platinum drugs · Ligand lability · Thermal stability

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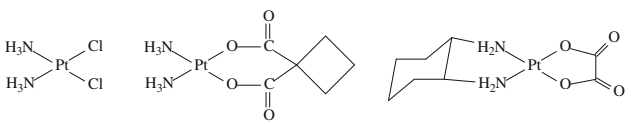
Introduction

Several developments have impacted the formulation of effective, non-toxic, sustained action organoplatinum antitumor drugs. The first was the serendipitous discovery of the remarkable biological activity of *cis*-dichlorodiammineplatinum(II) (Cisplatin) [1–8]. Cisplatin is a broad-spectrum cancer drug effective against a wide range of tumors. For many years, Cisplatin was the most widely used anticancer drug. It is often used in combination with organic antitumor compounds or with Carboplatin [diammino(1,1-cyclobutanedicarboxylato)platinum(II)], the second platinum anticancer drug to gain widespread commercial use. Carboplatin displays a somewhat different toxicity profile than does Cisplatin, making it an attractive compliment to Cisplatin [9–11]. All the compounds shown below reflect the structure required for antitumor activity (two inert *cis* ligands and two labile ligands; chlorine displays a near optimum hydrolysis rate under physiological conditions: half-life of about 1 h at 37 °C).



Cisplatin Carboplatin Oxaliplatin

The potential of these drugs has been limited because of severe side effects which accompany their administration. Among the most debilitating side effects induced by organoplatinum drugs are severe kidney damage [12] and extreme nausea (as a class, the platinum compounds are among the most effective nausea producing agents known, to the point that some patients refuse to complete the treatment regimen) [13, 14]. In an attempt to identify active

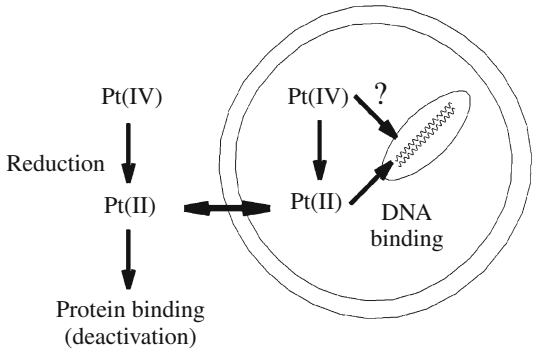
but less toxic drugs literally hundreds of platinum compounds in which the structure of the amine ligand has been varied have been synthesized and evaluated for antitumor activity. In the main, this has been a fruitless undertaking. While some ligands impart better solubility, activity, or toxicity than similar properties associated with compounds derived from simple ammonia ligands, no compounds with clearly superior performance have been found. Of the hundreds of compounds synthesized, fewer than thirty have entered clinical trials as antitumor agents [15, 16].

A second development has been the huge progress in the utilization of polymeric carriers for a variety of drugs [17–25]. The use of a polymer-drug conjugate may provide a number of advantages over the drug alone. These may include increased water solubility, sustained delivery of drug, reduced toxicity, enhanced biodistribution, and preferential penetration of abnormal tissue.

A third development has been the discovery of dendritic polymers [26, 27]. Dendrimers offer multiple modes of drug incorporation. In particular, the poly(amidoamine) [PAMAM] dendrimers are attractive as drug carriers. They are water-soluble, multivalent, and in general, non-toxic [28–30]. Dendrimers are highly branched macromolecules with precisely controlled size, shape, and end-group functionality. They represent unique core–shell structures consisting of three basic architectural components: a core, an interior of cells (generations) that have repeating branch-cell units, and terminal functional groups (outer shell or periphery). Each generation is built sequentially from a predecessor to form a symmetrical, nearly monodisperse structure of precise molecular mass and nanoscale dimensions [31]. For PAMAM dendrimers half-generation structures are carboxyl-terminated; full generations are amine-terminated. Both types of functionality are useful for drug conjugation [32].

A fourth development has been the discovery that functionalized, water-soluble carbon nanotubes are able to traverse the cell membrane by endocytosis to deliver a chemotherapeutic agent [33–38]. This has been exploited for the delivery of organoplatinum prodrugs [37, 38]. Approximately 65 platinum(IV) units per nanotube may be loaded [38]. This is comparable to the number of (diamminocyclohexane)platinum(II) units that may be attached to the surface of a generation 4.5 poly(amidoamine) [PAMAM] dendrimer [32]. Further, the multivalent prodrug may be functionalized with a folate component to specifically target folate receptor-enriched tumor cells [37].

Finally, a fifth development has been the recognition that platinum(IV) compounds could act as prodrugs for delivery of effective antitumor agents [37, 39–41]. With respect to their platinum(II) counterparts, platinum(IV) compounds possess a greater kinetic inertness. Thus, more of the platinum species may reach the targeted region prior to decomposition. When platinum(II) compounds are oxidized to



Scheme 1 Possible fate of organoplatinum(IV) compounds in cancer chemotherapy

platinum(IV) species two additional coordination sites become available for the introduction of functionality to enhance uptake via drug targeting, to inhibit resistance, to improve biodistribution, to modify lipophilicity, or to provide monomers for the generation of polymeric prodrugs. It is thought that platinum(IV) compounds are reduced to platinum(II) species in the cell which act as the effective antitumor agent for interaction with DNA (Scheme 1).

Experimental

General

In general, reactions were carried out in a dry (all glassware was dried in an oven overnight at 120 °C and allowed to cool under a stream of dry nitrogen prior to use) three-necked, round-bottomed flask fitted with Liebig condenser bearing a gas-inlet tube, a magnetic stirring bar (or Trubore stirrer), and a pressure-equalizing dropping funnel (or syringe port). Thermal decomposition temperatures were obtained using a TA Instruments 2950 Hi-Res TGA instrument interfaced with the Thermal Analyst 2100 control unit. Most generally, a heating rate of 10 °C min^{-1} was used. TA Universal Thermal Analysis software was used for data analysis. Samples (5–10 mg) were contained in a platinum pan. Extrapolated degradation onset temperatures were determined from the derivative plot of mass loss versus temperatures. The sample compartment was purged with dry nitrogen at 50 cm^3 min^{-1} during analysis. Nuclear magnetic resonance (NMR) spectra were obtained using a 10–25% solution in dimethyl sulfoxide-d_6 and a Varian Mercury 300 MHz spectrometer. Proton and carbon chemical shifts were reported in parts-per-million (δ) with respect to tetramethylsilane (TMS) as internal reference ($\delta = 0.00$). Infrared (IR) spectra were obtained using solid solutions (1%) in anhydrous potassium bromide (as discs) using a Nicolet MAGNA-IR 560 spectrometer. Absorptions were recorded in wave numbers (cm^{-1}).

Materials

Common solvents and reagents were obtained from ThermoFisher Scientific or the Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride in a nitrogen atmosphere prior to use; methylene chloride from calcium hydride. Potassium tetrachloroplatinate(II) and *cis*-dichloro(diammine) platinum(II) were obtained from Alfa Aesar and used as received. Nitrogen dioxide (≥99.5%) was from Aldrich.

Synthesis

cis-Dichloro-trans-dihydroxy-cis-diammineplatinum(IV) [42, 43]

cis-Dichloro-diammineplatinum(II) (3.01 g, 0.01 mol) was suspended in 75 cm^3 of water and 114 cm^3 of 30% aqueous hydrogen peroxide (0.10 mol; tenfold excess). The mixture was stirred at 50 °C in a nitrogen atmosphere and the absence of light for an hour at solvent reflux. The mixture was allowed to cool and to stand at 5 °C overnight for crystallization of the product. The bright yellow solid which formed was collected by filtration at reduced pressure and washed, successively, with cold water, ethanol, and diethyl ether. The solid was dried over Drierite at reduced pressure (15 Torr) to afford 2.57 g (77.3% yield) of the dihydroxy compound.

cis-Dichloro-trans-disuccinato-cis-diammineplatinum(IV)

A solution of 0.27 g (2.67 mmol) of succinic anhydride and 0.21 g (0.67 mmol) of *cis*-dichloro-*trans*-dihydroxy-*cis*-diammineplatinum(IV) in 5.0 cm^3 of dimethylsulfoxide was stirred in nitrogen in the absence of light at 70 °C for 24 h. The solution was allowed to cool and the solvent was removed by lyophilization. The residual solid was suspended in dichloromethane to remove succinic anhydride. The insoluble material was collected by filtration at reduced pressure and washed with several portions of dichloromethane. Recrystallization from acetone (−23 °C) afforded the disuccinato compound as yellow needles which were collected by filtration at reduced pressure, washed with cold acetone, and dried over Drierite at reduced pressure to provide 0.202 g (63.1% yield) of the expected product [37, 41].

cis-Dichloro-trans-hydroxo/ethoxo-cis-diammineplatinum(IV)

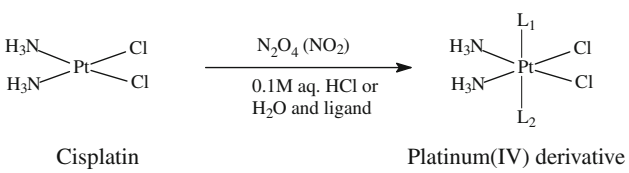
To a stirred suspension of 0.50 g (1.67 mmol) of *cis*-dichlorodiammine platinum(II) in 625 cm^3 of ethanol maintained at 70 °C was added 2.1 cm^3 of aqueous hydrogen peroxide solution. The resulting mixture was stirred for 5 h at 70 °C. The mixture was allowed to cool and most of the solvent was removed by rotary evaporation at reduced pressure. The residue was treated with 75 cm^3 of diethyl ether to provide a suspension of a bright yellow solid. The solid was collected by filtration at reduced pressure, washed, successively, with cold ethanol and diethyl ether, and dried over Drierite at reduced pressure to afford 0.397 g (66.2% yield) of the hydroxo/ethoxo compound.

Results and discussion

The observation that platinum(IV) compounds might act as robust prodrugs for the delivery of effective platinum(II) chemotherapeutic agents has opened a wide range of possibilities for the formulation of antitumor drugs. In general, a platinum(II) compound is oxidized to a platinum(IV) species which may add ligands to generate compounds which display potential as antitumor agents or which provide reactive sites suitable for the attachment of a range of functionality [37, 43]. In one approach, *cis*-dichloro(diammine) platinum(II) is oxidized with dinitrogen tetroxide in the presence of a suitable ligand (L) to produce a suitable platinum(IV) compound directly [43]. This is illustrated in Scheme 2.

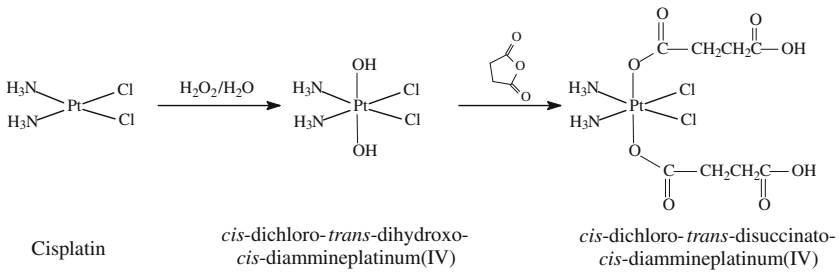
This procedure seems to be unreliable and to lack generality for the convenient generation of useful platinum(IV) compounds. In a second, more useful, approach the platinum(II) compound is oxidized to generate the corresponding dihydroxy platinum(IV) compound. The hydroxyl groups are sufficiently nucleophilic to react with good electrophiles, most commonly succinic anhydride, to generate compounds with functionality that may be used for the attachment of a variety of groups [37] (Scheme 3).

The approach has been utilized for the attachment of both a carbon nanotube carrier and a folate targeting moiety [37]. All the compounds have been characterized using infrared spectroscopy and thermogravimetry. Infrared spectra are displayed in Fig. 1. The depicted transformations are readily apparent from these spectra. Conversion of Cisplatin to the corresponding dihydroxo compound introduces a hydroxyl absorption at 3459 cm^{-1} into the spectrum. Transformation of the dihydroxo to the disuccinato compound generates a spectrum lacking the hydroxyl absorption but containing an ester carbonyl absorption.



Scheme 2 Generation of platinum(IV) compounds by oxidation with dinitrogen tetroxide

Scheme 3 Synthesis of *cis*-dichloro-*trans*-dihydroxo-*cis*-diammineplatinum(IV) and *cis*-dichloro-*trans*-disuccinato-*cis*-diammineplatinum(IV)



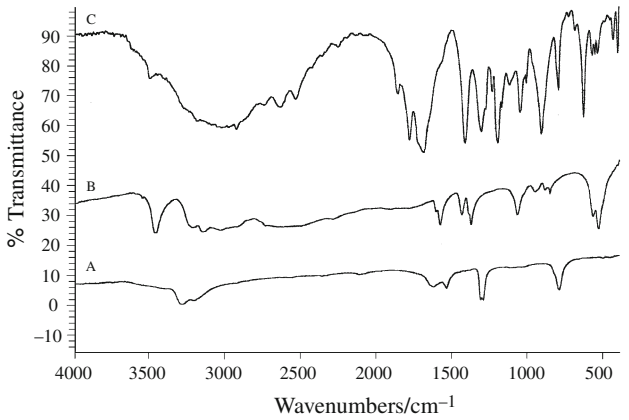


Fig. 1 Infrared spectra for **a** *cis*-dichloro(diammine)platinum(II), **b** *cis*-dichloro-*trans*-dihydroxo-*cis*-diammineplatinum(IV), and **c** *cis*-dichloro-*trans*-disuccinato-*cis*-diammineplatinum(IV)

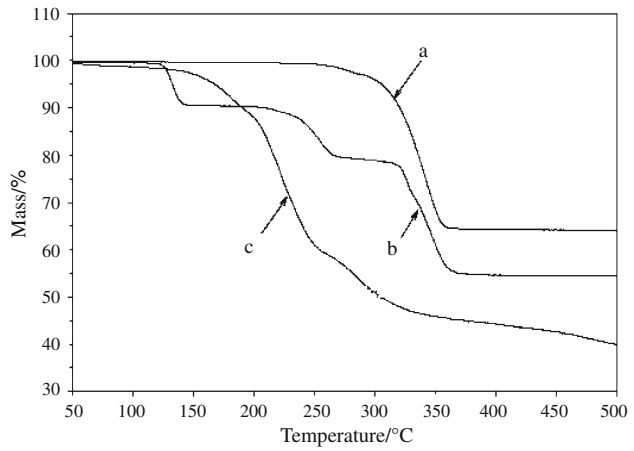


Fig. 2 Thermal decomposition of **a** *cis*-dichloro(diammine)platinum(II), **b** *cis*-dichloro-*trans*-dihydroxo-*cis*-diammineplatinum(IV), and **c** *cis*-dichloro-*trans*-disuccinato-*cis*-diammineplatinum(IV)

Thermograms for the decomposition of these compounds are contained in Fig. 2.

As can be seen all of the compounds undergo sequential ligand loss to afford a residue of platinum. For example, the dihydroxy intermediate displays an initial mass loss with an extrapolated onset temperature of 125 °C corresponding to the loss of the hydroxyl ligands, followed by the loss of the ammonia ligands (233 °C), and finally loss of the chloride ligands (321 °C) to leave a residue of platinum. This is summarized in Table 1.

Table 1 Thermal decomposition of *cis*-dichloro-*trans*-dihydroxo-*cis*-diammineplatinum(IV)

Mass loss	Onset temperature/ °C	Loss/% of initial mass		Fragments
		Observed	Calculated	
I	125	10.1	10.18	Hydroxyl ligands
II	233	11.9	10.18	Ammine ligands
III	321	23	21.26	Chloride ligands
Residue	400	55	58.38	

Conclusions

The thermal decomposition of several Pt(IV) precursors to antitumor drugs has been examined using thermogravimetry. In general, decomposition is well behaved and reflects sequential loss of ligands to generate a residue of platinum. Initial decomposition for *cis*-dichloro-*trans*-dihydroxy-*cis*-diamminoplatinum(IV) occurs at relatively low temperature (125 °C) and reflects the loss of hydroxyl ligands. Conversion of the hydroxyl groups to succinate esters lead to a thermally more stable compound with initial decomposition corresponding to loss of the succinato ligands at 233 °C. The thermal decomposition of these compounds is very well behaved and may form the basis for a general method of analysis [ligand present; elemental composition (% Pt)] for material of this kind.

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