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Poly(cis-dihaiodiamine Platinum(II)) Compounds: Synthesis and Biological Activity

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Poly(cis-dihalodiamine Platinum(II)) Compounds: Synthesis and Biological Activity

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ABSTRACT

Poly(cis-dihalodiamine platinum(II)) compounds are synthesized through solution condensation of solutions of tetrahaloplatinum(II) salts with diamines. Preliminary testing of five of these polymers shows that several affect virus and bacterial replication, and that all are toxic to HeLa (human) and L929 (mouse) tumor cells at concentrations above 300 μg/mL but are apparently nontoxic to mice at doses of up to 20 μg/g Swiss-Webster mouse.

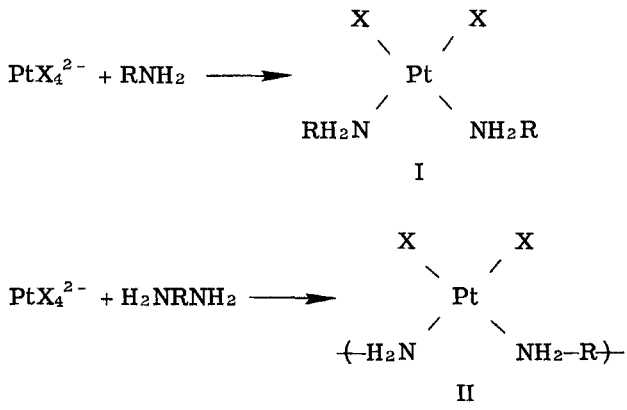
INTRODUCTION

We have been actively including metals into polymers for a number of reasons including use of such compounds as delivery agents in biological systems [1-4].

Malignant neoplasms are the second leading cause of death in the United States. Recently there has been considerable success in the utilization of cis-dichlorodiammine platinum(II) (c-DDP) coupled with other antineoplastic agents in the treatment of a wide variety of tumors in man [5-8]. Along with the positive attributes of c-DDP are a number of negative side effects which may in select situations be lethal [9-12]. Major complications include gastrointestinal, hematopoietic, immunosuppressive, auditory, and renal dysfunction, many associated with filtration of the c-DDP into the kidney areas. A number of approaches have been taken to minimize the toxicity of c-DDP including administering c-DDP along with other antineoplastic agents at reduced dose levels, hydration techniques, and more recently attempts at inclusion of platinum compounds into polymers, thereby limiting filtration of the polymer by the kidneys, and the synthesis of new compounds showing equal or enhanced activity but lowered toxicity [13-21]. The work reported here is concerned with the latter two modes of decreasing toxicity.

Structural requirements (thus far described) for the platinum compounds have been described elsewhere [22-29]. Briefly, active compounds are 1) typically neutral, 2) contain two inert and two labile ligands and 3) must have the corresponding ligands cis to each other.

It is well known that amines add cis to PtX_4^{2-} halides [25-27]. Here we report the initial synthesis of poly(cis-dihalodiamine platinum(II)) compounds of form II as possible antineoplastic drugs and preliminary biological assays of several of these compounds.



SYNTHETIC AND PHYSICAL CHARACTERIZATION

Following are typical synthetic procedures illustrating the synthetic approach. Potassium tetrachloroplatinate (6.22×10^{-4} mol in 10 mL H_2O) and potassium iodide (4.97×10^{-3} mol in 10 mL H_2O)

were separately dissolved, treated for 10 min on a boiling water bath, mixed, heated 20 min longer, and filtered to remove KCl. The resulting potassium tetraiodiplatinate solution was then mixed with an aqueous solution of 1,6-hexanediamine (7.83×10^{-4} *mol in* 10 *mL* of water) to immediately give a curdy, yellow solid, poly(cis-diiodo-1,6-hexamethylenediamine platinum(II)), DIHP, in 74% yield based on initial potassium tetrachloroplatinate. Elemental analysis (performed by Galbraith Labs., Knoxville, Tennessee) was in agreement with a structure of form II; %C, found = 12.0, theory = 12.8; %N, found = 4.9, theory 4.9; %H, found = 2.9, theory = 2.9; %Pt, found = 31.3, theory = 34.5; %Cl, found = 0.1, theory = 0.0; %I, found = 49.9, theory = 44.9. The following bands, with assignments, were present in IR spectra of the product (obtained utilizing Perkin-Elmer 457 and 735B spectrophotometers; all values given in cm^{-1}) N–H stretch, 2920, 2820; NH_2 bend, 1560; CH_2 bend, 1455; CH_2 rock, 720. The UV spectra of the compounds are consistent with a cis-dihalodiamino-platinum(II) compound with bands (obtained using a Carey 14 UV-visible spectrophotometer; wavelengths given in nm for chloro product) at 250, 310, 340, and 390 with identification based on Refs. 28 and 29. NMR spectra (obtained on a Varian EM360A spectrometer) in d_6-DMSO (using tetramethylsilane as a reference) showed three peaks; a broad band at 1.3 ppm (from the eight inner protons of the hexamethylene chain),

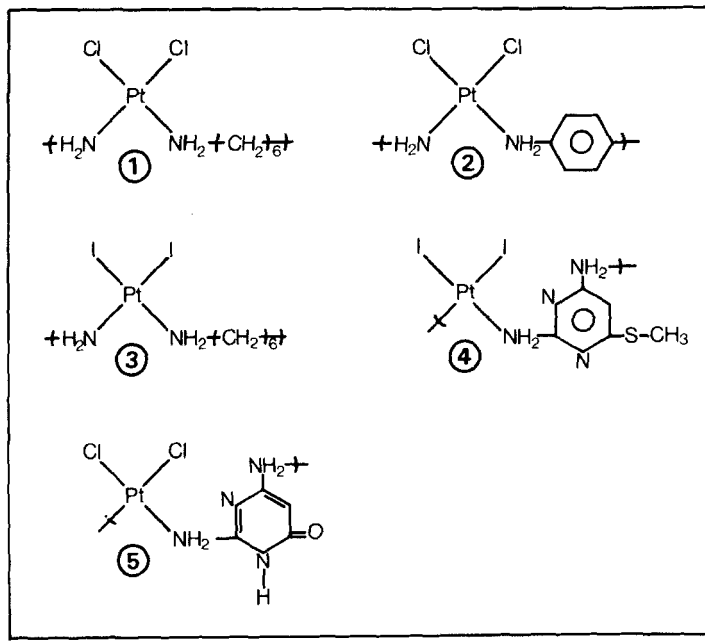


FIG. 1. Platinum polyamine structures and identification numbers.

TABLE 1. Percent Inhibition of Platinum Compounds on Escherichia coli Growth

Pt compound	Approximate concentration (μg/mL) 200	100	50	20	Control (DMSO)
1	0	0	0	0	0
2	100	75	Not done	0	0
3	100	75	10	0	0
4	0	0	0	0	0
5	100	75	10	0	0

TABLE 2. Effects of Platinum Compounds on Viral Replication in HeLa Cells

Concentration μg/mL	Compound 1 Pfu[a]/mL	1 % Control	2 Pfu/mL	2 % Control	3 Pfu/mL	3 % Control
10	3.4×10^6	10	6.5×10^7	200	3.2×10^7	100
20	1.1×10^7	34	3.2×10^7	100	3.2×10^7	100
Control	3.2×10^7	-	3.2×10^7	-	3.2×10^7	-

[a]Plaque forming units.

a broad multiplet at 2.6 ppm (from the methylene protons), and a multiplet at 3.7 ppm. A weight-average molecular weight (obtained using a Brice-Phoenix 2000 light-scattering photometer) of 4200 was found.

The above was repeated except a more nearly equal molar amount of the $PtCl_4^{2-}$ and diamine (2.84 mmol of each reactant) was utilized and led to the synthesis (73% yield) of a high molecular weight product with a weight-average molecular weight of 1.5×10^6 via light-scattering photometry. Thus product chain length can be easily and effectively controlled through control of the ratio of reactants. The polymers synthesized and tested are shown in Fig. 1.

TABLE 3. Percent CPE[a] of Platinum Compounds on Cells in a Monolayer Culture

Pt compound	Concentration (μg/mL)									
	5		10		20		30		50	
	HeLa	L929	HeLa	L929	HeLa	L929	HeLa	L929	HeLa	L929
1	0	0	0	0	0	0	25	25	100	100
2	0	0	0	0	0	0	25	25	100	100
3	0	0	0	0	0	0	25	25	100	100
4	0	0	0	0	0	0	25	25	100	100
5	0	0	0	0	0	0	25	25	100	100

[a]Cytopathic effect after 24 h of treatment with the indicated concentration of Pt compound.

BIOLOGICAL CHARACTERIZATION

The effect of the platinum polyamines on bacterial growth was studied in MacConkey agar plates seeded with a heavy suspension of Escherichia coli. The cultures were incubated for 18 h. Good inhibition was found for Compounds 2, 3, and 5 (Table 1). Inhibition was confined to the areas of the "drop," indicating the compounds do not diffuse through the agar.

The effect of the platinum polyamines on viral replication in HeLa cells was studied. The HeLa cell monolayer cultures were treated at polymer concentrations of 10 and 20 μg/mL for 16 h. The cultures were then washed and infected with Poliovirus type 1. The virus was harvested 24 h later. Table 2 contains results of such experiments, showing that the polyamines show a wide response of activity so the compounds can either enhance, suppress, or have no effect on the replication of an RNA virus. In related studies it was found that concentrations of up to 20 μg/mL of the five polymers are not overtly toxic to either HeLa cells (human tumor) or L929 cells (mouse tumor) in monolayer culture (Table 3). It is evident that at least Compounds 1 and 2 (Table 2) are biologically active at these concentrations in that they alter the amount of virus produced in HeLa cells. Concentrations of any of the five polymers in excess of 30 μg/mL were toxic to both HeLa and L929 cells within 24 h (Table 3). Thus biological activity can be effectively controlled through control of dosage level.

Preliminary experiments with mice show that they can tolerate a dosage of 400 μg of Compound 4 (highest concentration tested) with no apparent ill effects. This dose is in excess of tenfold greater than that necessary to destroy either HeLa of L929 tumor cells.

In summary, polyplatinum(II) amines can be easily synthesized which show biological activity toward virus and bacterial replication, to both HeLa human and L929 mouse tumor cells at low concentrations, and no overt toxicity to mice at greater than tenfold dosage concentrations.

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