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Original article

Cytotoxic activity and chemical reactivity of *cis*-platinum(II) and *trans*-palladium(II) complexes with diethyl (pyridinylmethyl)phosphates

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The authors wish to dedicate this work to the memory of Dr. Ewa Ciesielska from the Department of Molecular Pharmacology, Lodz Medical University, Poland.

Abstract

A series of square-planar platinum(II) and palladium(II) complexes of the formula *cis*-[$PtCl_2L_2$] and *trans*-[$PdCl_2L_2$] [L stands for diethyl (pyridin-2-ylmethyl)phosphate (2-pmOpe) or diethyl (pyridin-3-ylmethyl)phosphate (3-pmOpe) or diethyl (pyridin-4-ylmethyl)phosphate (4-pmOpe)] have been synthesized and tested in vitro for their cytotoxicity against mouse leukemia L1210 cells. The results indicated that the *cis*-platinum complexes showed superior activity than *trans*-palladium complexes, but lower in comparison to cisplatin. The chemical reactivity of the tested complexes has been determined in an in vitro NBP test. The platinum complexes exhibited very high chemical reactivity in NBP test, higher than cisplatin. The results showed no correlation between cytotoxicity and chemical reactivity for platinum complexes. Two platinum(II) complexes {*cis*-[$PtCl_2$(2-pmOpe)$_2$], *cis*-[$PtCl_2$(3-pmOpe)$_2$]} have been synthesized and characterized by IR, ^{1}H NMR, ^{31}P NMR, and elemental analysis.

Keywords: Cytotoxicity; L1210; Chemical reactivity; Platinum(II) complexes; Palladium(II) complexes; Pyridine derivatives

1. Introduction

Recently, a variety of studies have been devoted to searching new anticancer agents in a group of transition metal complexes. Platinum complexes are the subject of special interest because cisplatin, *cis*-diamminedichloridoplatinum(II) (*cis*-DDP), is a drug widely used in chemotherapy [1,2]. The application of this drug is limited by a lot of severe side effects, e.g. nephro-, neuro-, myelotoxicities [3–5]. In order to develop better chemotherapeutics than cisplatin, thousands of new cisplatin analogues with various types of ligands have been designed and tested [6,7]. In the last two decades, a lot of *trans*-configurated platinum complexes with high antitumor activity in both cisplatin-sensitive and cisplatin-resistant cell lines have been discovered [8].

Based on the structural analogy between platinum(II) and palladium(II) complexes, a number of palladium(II) complexes with neutral ligands such as pyridine derivatives [9,10], phosphonate derivatives of quinoline [11,12] or pyrazole derivatives [13] have been investigated and their significant cytotoxic activity has been proved.

In our previous study, we demonstrated the excellent in vitro activity of two cisplatin analogues: *cis*-[$PtCl_2$(4-pmOpe)$_2$] and *trans*-[$PtCl_2$(4-pmOpe)$_2$], with sterically hindered ligands – diethyl (pyridin-4-ylmethyl)phosphates [14]. The complexes showed cytotoxic effect similar to that of cisplatin and a stronger cytotoxic effect on cancer cells (A 549 and HT 29) than on normal human peripheral blood lymphocytes. This feature seems to be crucial in view of decreasing the side effects of the potential drugs.

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These promising preliminary findings encouraged us to study the cytotoxicity of the series of *cis*-platinum isomers with diethyl (pyridinylmethyl)phosphates (2-pmOpe, 3-pmOpe and 4-pmOpe) against another cancer cell line, L1210 mouse leukemia. We have also extended our investigations to a series of their corresponding *trans*-palladium(II) complexes to compare the influence of the type of central metal and the geometry of complexes on cytotoxic effect. Additionally, we present a study on chemical reactivity of platinum and palladium complexes in an in vitro Preussmann test to check the relationship between cytotoxicity and chemical reactivity of the tested compounds.

2. Results and discussion

2.1. Chemistry

The palladium(II) complexes: *trans*-[$PdCl_2$(2-pmOpe)$_2$], *trans*-[$PdCl_2$(3-pmOpe)$_2$] and *trans*-[$PdCl_2$(4-pmOpe)$_2$] were prepared from potassium tetrachloropalladate(II) ($K_2[PdCl_4]$) according to previously published method [15]. The platinum(II) complex *cis*-[$PtCl_2$(4-pmOpe)$_2$] was synthesized and characterized earlier [14].

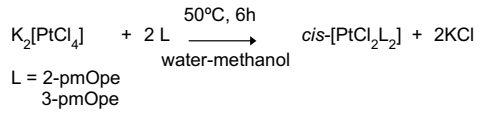
Two platinum(II) complexes: *cis*-[$PtCl_2$(2-pmOpe)$_2$] and *cis*-[$PtCl_2$(3-pmOpe)$_2$] were prepared by the reaction of appropriate diethyl (pyridinylmethyl)phosphate with potassium tetrachloroplatinate(II) ($K_2[PtCl_4]$) in water–methanol medium (Scheme 1).

The complexes are stable yellow solid soluble in ethanol, acetone, chloroform, dimethylformamide and dimethylsulfoxide. The structures of the complexes were determined by a combination of elemental analysis, IR and NMR (^{1}H, ^{31}P) spectroscopy. In both cases, ligands are bound to platinum(II) ions in a monodentate fashion through the nitrogen atoms of pyridines and two chlorine atoms giving square-planar complexes (Fig. 1). The complexes adopt a *cis* geometry, which is consistent with the preparation method [16] based on the kinetic *trans* effect [17].

2.2. Spectroscopic measurements

2.2.1. ^{1}H NMR study

Full characterization by ^{1}H NMR spectra of the two platinum(II) complexes: *cis*-[$PtCl_2$(2-pmOpe)$_2$] and *cis*-[$PtCl_2$(3-pmOpe)$_2$] was done. The chemical shifts (ppm) and coupling constants (Hz) for the complexes and the free ligands [15] are listed in Table 1. The spectra of the complexes compared to those of the free ligands show considerable differences. Significant shifts are observed for the protons in the vicinity of the coordination site i.e. the selected protons of



Scheme 1

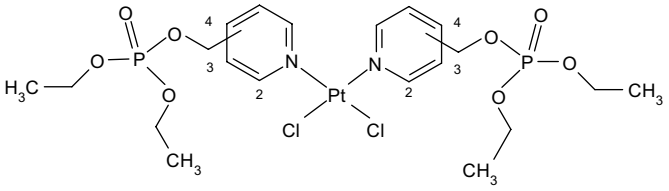


Fig. 1. Structure of *cis*-[$PtCl_2$(pmOpe)$_2$] isomeric complexes.

pyridine ring or the methylene protons of the py–CH_2O– group. The chemical shifts of the protons of diethyl ester groups are similar to those in the spectra of the ligand.

In the spectrum of the complex *cis*-[$PtCl_2$(2-pmOpe)$_2$] the greatest shift is found for methylene protons of the py–CH_2O– group when compared to the free ligand 2-pmOpe. They are downfield shifted by 1.08 ppm. A smaller but still remarkable downfield shift of 0.55 ppm is found for the proton H(6) of pyridine ring. These shifts are caused by the decrease in electronic density of the heteroaromatic ring coordinated to the platinum ion [11,18]. Both methylene protons of the py–CH_2O– group and the sixth proton of pyridine ring [H(6)] are closely adjacent to the coordination place, nitrogen atom of pyridine. The other protons of pyridine ring i.e. H(3), H(4), H(5) are too distant from the coordination place to change their chemical shifts after complexation.

In the spectrum of the complex *cis*-[$PtCl_2$(3-pmOpe)$_2$] the most pronounced downfield shift of 0.40 ppm is observed for H(2)H(6) protons of pyridine ring. Similar to the previous complex these protons are also closely adjacent to the nitrogen atom–electron pair donor and their downfield shift indicates the decrease in electron density on the 3-substituted pyridine ligands with coordination to the platinum. The methylene protons of the py–CH_2O– group are not shifted as they are far distant from the coordination site.

2.2.2. IR study

The assignments of the most noticeable IR spectra bands of the complexes are given in Section 4. The absorption bands in the range 1616–1392 cm^{-1} are assigned to different vibration modes of the pyridine ring. These vibrations are appreciably shifted by about 20–30 cm^{-1} to higher frequencies after complexation with respect to the free ligands. It proved that the nitrogen atom of pyridine ring is engaged as the electron donor atom in the complexes [19]. Very strong bands at 1260 cm^{-1} and 1278 cm^{-1} are assigned to the P=O group vibrations of *cis*-[$PtCl_2$(2-pmOpe)$_2$] and *cis*-[$PtCl_2$(3-pmOpe)$_2$] complexes, respectively. These characteristic bands attributed to the phosphate ester groups remain not shifted when compared to the free ligands as the complexes contain only N-bonded monodentate pyridine ligands. In the far-IR region of the complexes' spectra are observed the Pt–N and Pt–Cl vibrations characteristic for diamminedichloridoplatinum complexes [20,21]. The bands assigned to (Pt–Cl) vibrations of *cis*-[$PtCl_2$(2-pmOpe)$_2$] and *cis*-[$PtCl_2$(3-pmOpe)$_2$] complexes are centered at 342 cm^{-1} and 320 cm^{-1}, respectively, as expected for *cis* geometry [22,23]. *cis*-Dichlorido complexes often show

Table 1
^{1}H NMR spectral data

Complex	OCH_2CH_3	OCH_2CH_3	(py)CH_2O	(py)H(5)	(py)H(3)	(py)H(4)	(py)H(6)
$[PtCl_2(2\text{-pmOpe})_2]$	1.39 (t) $^3J_{HH}=6.9$	4.21 (d q) $^3J_{HH}=6.9$	*6.25* (d) $^3J_{HP}=6.3$	7.17–7.20 (m)	7.58 (d)	7.70–7.73 (m)	*9.12* (d)
2-pmOpe [15]	1.34 (t) $^3J_{HH}=6.9$	4.15 (d q) $^3J_{HH}=6.9$	*5.17* (d) $^3J_{HP}=7.8$	7.23–7.27 (m)	7.51 (d)	7.72–7.77 (m)	*8.57* (d)
	OCH_2CH_3	OCH_2CH_3	(py)CH_2O	(py)H(5)	(py)H(4)	(py)H(2)H(6)	
$[PtCl_2(3\text{-pmOpe})_2]$	1.34 (t) $^3J_{HH}=7.2$	4.12 (d q) $^3J_{HH}=7.2$	5.07 (d) $^3J_{HP}=8.1$	7.31–7.35 (m)	7.87 (d)	*8.96–9.06* (m)	
3-pmOpe [15]	1.34 (t) $^3J_{HH}=7.1$	4.12 (d q) $^3J_{HH}=7.1$	5.08 (d) $^3J_{HP}=8.1$	7.31–7.35 (m)	7.76 (d)	*8.57–8.64* (m)	

two bands of medium intensity as the vibrations are additive [21,24], but in some cases the (Pt–Cl) vibrations are observed as a single broad band because the bands overlap [18]. The characteristic bands involving (Pt–N) vibrations of nitrogen atom of pyridine are in the region of 520–450 cm^{-1} [25,26].

2.3. Cytotoxic activity

The cytotoxic activity of the tested compounds expressed as IC_{50} values is shown in Table 2. The platinum(II) compounds were approximately 8–10-fold more active than their palladium(II) analogues. The position of diethyl methyl phosphate residue in the pyridine ring does not seem to play a significant part in the cytotoxicity for both series of complexes [19,25]. The most important factor influencing the biological activity of these classes of compounds seems to be the central atom of the complexes. The complexes with platinum atom are clearly more active (Table 2). Much lower biological activity of the palladium(II) complexes when compared with platinum(II) compounds may be the result of low chemical reactivity or/and different configuration of the complexes as all the tested palladium complexes possess a *trans* configuration whereas platinum complexes adopt a *cis* configuration.

2.4. Reactivity with nucleophilic nitrogen of NBP

The chemical reactivity of *cis*-Pt(II) and *trans*-Pd(II) complexes with diethyl (pyridinylmethyl)phosphates has been evaluated based on an in vitro test with 4-(4′-nitrobenzyl)pyridine (NBP) (Preussmann test) [27–30]. Alkylating compounds as well as coordination complexes of transient metals react with the nucleophilic nitrogen atom of the pyridine ring of NBP. The reaction product transforms in alkaline media into a coloured solution, which can be quantitated colorimetrically. The results of the NBP test are presented in Table 2. It was found that the platinum based isomers with diethyl (pyridinylmethyl)phosphates were 2–3 times more active than cisplatin, whereas their palladium analogues were significantly less reactive and yielded very little amount of coloured products. These results indicated that the replacement of Pt(II) atom with Pd(II) in the coordination complex possessing diethyl (pyridinylmethyl)phosphate non-leaving ligands reduces reactivity of this class of compounds toward nucleophilic centers.

Table 2
Cytotoxic activity of the complexes against L1210 mouse leukemia

Complex	IC_{50}[a] (μM)	Relative chemical reactivity
$[PtCl_2(2\text{-pmOpe})_2]$	37.5 ± 5.7	218
$[PtCl_2(3\text{-pmOpe})_2]$	40.3 ± 3.5	301
$[PtCl_2(4\text{-pmOpe})_2]$	51.6 ± 8.2	140
$[PdCl_2(2\text{-pmOpe})_2]$	285 ± 41	27
$[PdCl_2(3\text{-pmOpe})_2]$	270 ± 29	38
$[PdCl_2(4\text{-pmOpe})_2]$	310 ± 45	37
Cisplatin	1.1 ± 0.2	100

[a] IC_{50} is the complex concentration inhibiting 50% of the cell growth after 72 h exposure of L1210 cells to the complex.

2.5. Cytotoxic activity vs. chemical reactivity

Cytotoxic activity and chemical reactivity of tested compounds are shown in Table 2. Compounds containing Pt(II) were more cytotoxic and also exhibited higher chemical reactivity in the NBP test than their palladium analogues. Thus there is no discrepancy between the biological activity of novel complexes and their ability to react with nucleophilic centers when complexes containing Pt(II) or Pd(II) are compared. However, no clear correlation exists between chemical reactivity of Pt(II) complexes exhibited in NBP test and their biological activity when cisplatin and Pt(II) complexes with diethyl (pyridinylmethyl)phosphates are compared. Cisplatin which was 1.4–3 times less reactive in NBP test than its diethyl (pyridinylmethyl)phosphate derivatives exhibited about 40 times higher cytotoxicity in terms of IC_{50}. This discrepancy between chemical reactivity and cytotoxicity [31] of cisplatin and Pt(II) complexes based on phosphate ligands may be due to the different conditions of reaction of platinum drugs with nitrogen atom in NBP test and with nucleophilic targets in cells. NBP is a small molecule with only one nucleophilic center which is easily accessible for an alkylator. Nucleophilic atoms in DNA seem to be less accessible for reactions with Pt(II) complexes especially for those containing bulky ligands which are present in the novel complexes. Thus NBP test which is valuable for chemical characterization of Pt and Pd coordination complexes to describe their reactivity with nucleophilic targets does not seem to be adequate for the prediction of biological activity of these classes of compounds.

3. Conclusions

We conclude that Pd(II) *trans*-complexes containing phosphate ligands do not seem to be promising potential anticancer agents as their cytotoxic activity was about 300 times lower than the reference compound cisplatin. The biological significance of the introduction of phosphate ligands into the coordination complex of Pt(II) is not clear. This structural modification leads to the increase of chemical reactivity with simultaneous decrease of cytotoxicity. However, the resulting compounds are still significantly active against several cancer derived cell lines [14] and the presence of bulky non-leaving phosphate ligands seems to influence the specificity of interaction with cellular targets which gives a chance for the development of novel drugs that are more specific toward cancer cells. It is also possible that the novel coordination complexes may retain activity toward cancer cells that are resistant to cisplatin.

4. Experimental section

4.1. Chemistry

Diethyl (pyridinylmethyl)phosphates: 2-pmOpe, 3-pmOpe and 4-pmOpe were synthesized according to the reported procedure [15]. Potassium tetrachloroplatinate(II) ($K_2[PtCl_4]$) was purchased from Aldrich. Solvents were purified by standard techniques. $CDCl_3$ for NMR spectroscopy was obtained from Dr. Glaser AG Basel.

4.1.1. General procedure for platinum(II) complexes

An aqueous solution (3 ml) of $K_2[PtCl_4]$ (0.250 mmol, 104 mg) was added to a solution of appropriate diethyl (pyridinylmethyl)phosphate (0.500 mmol, 123 mg) dissolved in 2 ml of methanol. The reaction mixture was magnetically stirred and heated in an oil bath at 50 °C for 6 h in the dark. After this period, brownish oil formed at the bottom of the reaction flask. The aqueous-methanol solution was decanted and the oily residue was treated with ethanol (2 ml). The insoluble part of the oil was rejected. The yellow filtrate was evaporated giving the final complex. The product was washed with cold water, methanol and diethyl ether, and air dried.

4.1.1.1. cis-[PtCl$_2$(2-pmOpe)$_2$]. Yield: 42.0 mg (22%). M.p. 87–91 °C. IR (CsI) ν_{max} (cm^{-1}): (py-ring) 1612 (s), 1486 (m), 1442 (m), 1394 (w); (P=O) 1260 (s, br); (P–O–C) 1121 (w), 1041 (vs, br), 987 (m); (Pt–N) 517 (w), 450 (vw); (Pt–Cl) 342 (m, br); (vs: very strong; s: strong; m: medium; w: weak; vw: very weak; br: broad). ^{31}P NMR (300 MHz, $CDCl_3$): $\delta = -0.337$. ^{1}H NMR data are summarized in Table 1. Anal. $C_{20}H_{32}N_2O_8P_2Cl_2Pt$: Calcd: C, 31.76; H, 4.26; N, 3.70. Found: C, 31.30; H, 3.61; N, 4.26.

4.1.1.2. cis-[PtCl$_2$(3-pmOpe)$_2$]. Yield: 87.2 mg (46%). M.p. 146–149 °C. IR (CsI) ν_{max} (cm^{-1}): (py-ring) 1616 (m), 1489 (m), 1447 (m), 1392 (w); (P=O) 1278 (s, br); (P–O–C) 1118 (m), 1040 (vs), 985 (m); (Pt–N) 518 (m), 488 (vw); (Pt–Cl) 320 (m, br); (vs: very strong; s: strong; m: medium; w: weak; vw: very weak; br: broad). ^{31}P NMR (300 MHz, $CDCl_3$): $\delta = -0.239$. ^{1}H NMR data are summarized in Table 1. Anal. $C_{20}H_{32}N_2O_8P_2Cl_2Pt \cdot H_2O$: Calcd: C, 31.01; H, 4.39; N, 3.62. Found: C, 30.96; H, 4.51; N, 4.43.

4.1.2. Physical measurements

Melting points were determined with Böetius apparatus. Elemental analyses of C, H and N were performed with a Perkin Elmer 2400 microanalyzer. Infrared spectra were recorded in the range 4000–200 cm^{-1} on an ATI Mattson Infinity Series FTIR™ spectrometer using CsI pellets. ^{1}H NMR, ^{31}P NMR spectra were collected in a Mercury 300 MHz spectrometer in $CDCl_3$ solution. All the chemical shifts were reported using the standard (δ) notation in parts per million relative to tetramethylsilane (1%) as internal standard.

4.2. Cytotoxicity assay

L1210 leukemia cells purchased from the Institute of Immunology and Experimental Therapy, Polish Academy of Sciences (Wrocław) were grown in RPMI 1640 medium (Gibco) supplemented with 10% fetal calf serum (Gibco) at 37 °C in 5% CO_2 atmosphere. Cell viability was determined by the tetrazolium dye [32] with minor modifications. Cells were seeded in 24-well plates (2×10^4 cells/well) and treated for 72 h with drugs in triplicate in a final volume of 2 ml. Then 0.13 ml of sterile water solution of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (Sigma) (5 mg/ml) was added to each well for an additional 3 h. The blue formazan precipitate was dissolved in dimethylsulfoxide and the absorbance of solutions was measured at 540 nm.

4.3. Chemical reactivity test (NBP test)

The investigated compounds (5 μmol) were dissolved in 1 ml of 2-methoxyethanol and placed into test tube with 1 ml of 4-(4′-nitrobenzyl)pyridine (NBP) (5% solution in 2-methoxyethanol). The samples were heated at 100 ± 5 °C for 1 h and then quickly cooled to 20 °C. 2-Methoxyethanol (2.5 ml) and piperidine (0.5 ml) were added to the sample to give a total volume of 5 ml and a final concentration of the tested compounds of 10^{-5} mol/l. The absorbance of the solutions was quickly measured at 545 nm in the presence of 2-methoxyethanol as a chemical reference. Cisplatin was used as a positive control. Relative chemical reactivity is presented in Table 2.

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