Synthesis and *in vitro* Cytostatic Activity of Platinum(II) Nitrate Complexes with Propan-1-amine

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Abstract

The platinum(II) nitrate complexes *cis*- and *trans*-$[PtPra_2(NO_3)_2]$, $[PtPra_3X]NO_3$ and $[PtPra_4](NO_3)_2 \cdot nH_2O$ (Pra = propan-1-amine; X = Cl, Br or NO_3; $n = 0$ or 2) have been prepared and characterized by infrared and ^1H NMR spectroscopy and by thermal analysis (TG, DTG and DTA). The complexes have been tested for *in vitro* cytostatic activity against KB tumor cells. Their activity follows the order *cis*-$[PtPra_2(NO_3)_2]$ > $[PtPra_3Cl]NO_3$ > $[PtPra_3(NO_3)]NO_3$ > *trans*-$[PtPra_2(NO_3)_2]$ > $[PtPra_4](NO_3)_2$. The last species is inactive, whereas the activity of the *cis* adduct compares well with that of *cis*-$[Pt(NH_3)_2Cl_2]$ in analogous conditions.

Introduction

The platinum(II) complexes *cis*- and *trans*-$[PtL_2(NO_3)_2]$, where L is ammonia or amine, are widely used as intermediates in the synthesis of functionalized compounds to test as antitumor agents. Nitrates are generally obtained in aqueous solution, by reaction of the parent species PtL_2X_2 (X = halide) with silver nitrate, and then treated with the appropriate ligand, designed for a possible target specificity [1, 2]. Depending on the pH value, the aqueous solutions of diamino dinitrates can contain, along with the $[PtL_2(H_2O)_2]^{2+}$ cation, hydrolysis products which could affect the drug nature and its binding behaviour towards DNA [3–5]. Moreover platinum complexes containing polydentate ligands are able to coordinate silver nitrate. As an example, *trans*-$[Pt(NH_3)_2(meu)_2]$ (Hmeu = 1-methyluracil) has been found to bind two silver nitrate molecules forming a trinuclear complex in which the silver atoms are linked to the ligand exocyclic oxygens [6]. Recently we reported the synthesis and characterization of platinum(II) complexes of general formulae *cis*- and *trans*-$[PtL_2X_2]$, $[PtL_3X]X$ and $[PtL_4]X_2$, in which X was a halide and L was an unbranched aliphatic amine [7–10]. In particular the chloro derivatives of the ligands propan-1-amine (Pra), butan-1-amine (Bua), pentan-1-amine (Pea), hexan-1-amine (Hea) and heptan-1-amine (Hpa) were tested as cytostatic agents on tumoral KB cell line cultures [11]. As expected, the *trans* species were scarcely active, except for *trans*-$[PtBua_2Cl_2]$ ($ID_{50} \simeq 2 \times 10^{-6}$ mol l^{-1}), whereas the activity of the *cis* complexes followed the order Pra > Bua > Pea ≃ Hea ≃ Hpa. Among 1:3 and 1:4 adducts, the maximum activity was observed for the Pea derivatives. With the aim of extending the study to functionalized ligands, we thought it of interest to characterize nitrato complexes of platinum(II)–amine adducts of various stoichiometries.

In the present work we report the synthesis and characterization of the compounds *cis*- and *trans*-$[PtPra_2(NO_3)_2]$, $[PtPra_3X]NO_3$ (X = Cl, Br, or NO_3) and $[PtPra_4](NO_3)_2 \cdot 2H_2O$, along with a preliminary evaluation of their *in vitro* cytostatic activity against KB tumor cells.

Experimental

The reagents were PtX_2 (X = Cl or Br, Johnson Matthey), $K_2[PtCl_4]$ (Fluka), propan-1-amine (Pra, C. Erba) and $AgNO_3$ (Ventron). The complexes *cis*- and *trans*-$[PtPra_2X_2]$, $[PtPra_3X]X$ and $[PtPra_4]Cl_2 \cdot 2H_2O$ (X = Cl or Br) were prepared as reported in ref. 8. The synthesis of *cis*- and *trans*-$[PtPra_2(NO_3)_2]$ and $[PtPra_3(NO_3)]NO_3$ was carried out in dry-box filled with dinitrogen, using anhydrous solvents.

Preparation of Compounds

Solid samples of *cis*- and *trans*-$[PtPra_2(NO_3)_2]$ were prepared by reacting the corresponding *cis*-

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and *trans*-$[PtPra_2X_2]$ (X = Cl or Br) with $AgNO_3$ (molar ratio 1:2.2) in acetone with vigorous stirring (24 h; *ca.* 20 °C; in the dark). The resulting colourless solution was filtered over dried alumina. The filtrate was evaporated to a small volume and then pipetted in n-hexane. The first oily precipitate was discarded. The residual solution separated on standing white crystals of the compound, which were filtered, washed with n-hexane and dried *in vacuo*. The crude product was recrystallized twice from acetone/n-hexane. Yield 30–40%.

The species $[PtPra_3X]NO_3$ (X = Cl or Br) were prepared by addition of silver nitrate to a $[PtPra_3X]X$ (X = Cl or Br) solution in the minimum amount of methanol (molar ratio 1:1) with stirring (3 h). Silver halide was removed by filtration over alumina. White crystals of the complex were obtained by addition of abundant diethylether to the colourless filtrate. Yield 60–70%.

The complex $[PtPra_3(NO_3)]NO_3$ was prepared analogously by reaction of $[PtPra_3X]X$ and $AgNO_3$ in methanol (molar ratio 1:2.2, 6 h). The colourless filtrate was evaporated to a small volume and treated with diethylether. The first oily product was discarded. Addition of n-hexane until turbidity yielded white needles which were recrystallized from acetone/n-hexane. Yield 40%.

White crystals of $[PtPra_4](NO_3)_2 \cdot 2H_2O$ were separated by adding diethylether to the filtrate of the reaction of $[PtPra_4]Cl_2 \cdot 2H_2O$ with $AgNO_3$ in methanol (molar ratio 1:2; 3 h stirring). Yield 70%. Prolonged heating (*ca.* 130 °C) *in vacuo* yielded the anhydrous species $[PtPra_4](NO_3)_2$.

Measurements

Infrared spectra were registered on a Perkin-Elmer 580 B spectrophotometer as Nujol and Voltalef 10S (Ugine Kuhlmann) mulls between KBr and polyethylene discs. The KBr disc should be carefully dried to prevent bromide exchange. ^1H NMR spectra were obtained with a Jeol FX 90 Q spectrometer. The TG, DTG and DTA curves were obtained by the Netzsch STA 429 thermoanalytical equipment (dinitrogen atmosphere; flux rate, 250 cm^3 min^{-1}; heating rate, 5 °C min^{-1}; reference material, neutral Al_2O_3).

in vitro Cytostatic Activity Evaluation

The previously described method [12] was followed. Minimal Eagle's Medium (MEM) [13], supplemented with 1% non essential amino acids and 10% newborn calf serum, was used. The medium was buffered with *N,N*-bis[2-hydroxyethyl]-2-aminoethane sulfonic acid (BES) 3 mM, *N*-2-hydroxyethylpiperazine-*N'*-2-ethane sulfonic acid (HEPES) 3 mM, *N*-tris[hydroxymethyl]-methyl-2-aminoethane sulfonic acid (TES) 3 mM and Tricine 3 mM [14]. 10^5 KB cells, a human established tumour line, were incubated at 37 °C in Leighton tubes. After 24 h, the cells were attached to the glass and the medium was changed with MEM containing the compounds to be tested at 5 dose levels, previously dissolved immediately before use in sterile saline. Incubation was carried out at 37 °C for 72 h, the time interval in which exponential growth occurs. As a positive control cisplatin was always included. Cell growth was estimated by counting the viable cells which were detached from the glass surface with trypsin [15]. The cytostatic activity was evaluated as percentage of growth inhibition in the treated tubes with respect to the controls, on the basis of the formula $100 - [(T - B)/(C - B) \times 100]$, where B was the baseline (initial number of viable seeded cells) and T and C were the number of viable cells respectively in the treated and control tubes after 72 h incubation. The inhibition values were plotted against $\log D$, D being the drug concentration (mol l^{-1}) in MEM. From these curves the ID_{50} values (drug concentration at which the cells show a 50% growth inhibition) were obtained. The significance of the differences between control and treated groups was established by use of classical Student's t-test ($p < 0.01$).

Results and Discussion

The nitrato complexes (Table 1) were prepared by reaction of the appropriate chloro or bromo precursor with silver nitrate. Metathesis of the ionic halide in $[PtPra_3X]X$ and $[PtPra_4]X_2 \cdot 2H_2O$ (X = Cl or Br) was fast and the reaction to form $[PtPra_3X]NO_3$ and $[PtPra_4](NO_3)_2 \cdot 2H_2O$ was completed within 2 h. Conversely the substitution of covalently bonded halides was slower and required a slight excess of silver nitrate with respect to the stoichiometric amount. The preparation of the 1:2 adducts and of $[PtPra_3(NO_3)]NO_3$ has been carried out in anhydrous acetone at *ca.* 20 °C. In fact the presence of water increases the yield in oily untractable products. Moreover higher temperatures favour decomposition of the product and, in the case of *cis*-$[PtPra_2(NO_3)_2]$, partial *cis–trans* isomerization (checked by IR and NMR spectra of the resulting solid samples).

The stoichiometry and geometry of the complex can be easily inferred by the infrared bands in the $\nu(NH)$ (3300–3100 cm^{-1}) and $\delta(NH_2)$ (1650–1550 cm^{-1}) spectral regions (Table 2), very close in shape and intensity to those of the parent halide adducts [8, 9]. Accordingly *trans*-$[PtPra_2(NO_3)_2]$ shows beyond 3000 cm^{-1} sharp strong absorptions (at 3280 and 3235 cm^{-1}) whereas the *cis* isomer and the 1:3 adducts are characterized by a broad absorption at 3250 and 3230 cm^{-1} respectively. In the hydrated 1:4 species a strong H_2O absorption

TABLE 1. Analyses[a] and Cytostatic Activity on KB Tumour Cells (ID_{50})[b]

Compound	C (%)	H (%)	N (%)	ID_{50}
trans-[$PtPra_2(NO_3)_2$][c]	16.45(16.48)	4.12(4.15)	12.86(12.81)	7.94×10^{-6}
cis-[$PtPra_2(NO_3)_2$][c]	16.41(16.48)	4.18(4.15)	12.67(12.81)	0.27×10^{-6}
[$PtPra_3Cl$]NO_3[d]	22.98(23.01)	5.84(5.79)	11.82(11.92)	1.96×10^{-6}
[$PtPra_3Br$]NO_3[d]	21.22(21.02)	5.32(5.29)	10.78(10.89)	
[$PtPra_3(NO_3)$]NO_3[e]	21.29(21.78)	5.35(5.48)	13.91(14.11)	5.90×10^{-6}
[$PtPra_4$]$(NO_3)_2$[f]	26.02(25.95)	6.71(6.53)	15.06(15.13)	10.00×10^{-6}
]$PtPra_4$]$(NO_3)_2 \cdot 2H_2O$[g]	24.36(24.37)	6.79(6.82)	14.10(14.21)	10.00×10^{-6}

[a]Calculated values in parentheses. [b]Dose (molar concentration) at which the cells show a 50% growth inhibition. The upper limit criterium for significant cytostatic activity was 10.00×10^{-6} mol l^{-1}. [c]$C_6H_{18}N_4O_6Pt$. [d]$C_9H_{27}XN_4O_3Pt$ (X = Cl or Br). [e]$C_9H_{27}N_5O_6Pt$. [f]$C_{12}H_{36}N_6O_6Pt$. [g]$C_{12}H_{40}N_6O_8Pt$.

TABLE 2. Selected Infrared Absorptions

Compound	Frequency (cm^{-1})						
trans-[$PtPra_2(NO_3)_2$]		3280s, 3232s, 3137w	1590w	1502s		1259s	950s
cis-[$PtPra_2(NO_3)_2$]		3280sh, 3250sbr, 3230sh, 3155w	1585w	1515s		1268s	965s
[$PtPra_3Cl$]NO_3		3250sh, 3230sbr, 3148mbr	1581s		1345[a]		
[$PtPra_3Br$]NO_3		3260sh, 3230sbr, 3142mbr	1577s		1350[a]		
[$PtPra_3(NO_3)$]NO_3		(3248, 3215)mbr, 3148sbr	1602m	1512m	1365[a]	1273s	976m
[$PtPra_4$]$(NO_3)_2$		3200sbr, 3138sbr	1632sh, 1613m		1370[a]		
[$PtPra_4$]$(NO_3)_2 \cdot 2H_2O$	3420sbr	3220sbr, 3145mbr, 3110sh	1648mbr		1360[a]		

[a]Broad strong band with two shoulders in the 1340–1310 and 1315–1290 cm^{-1} ranges.

is observed around 3420 cm^{-1} and both water and amine bending modes should contribute to the medium absorption at 1648 cm^{-1}. The 1:3 complexes present the intense $\delta(NH_2)$ band in the 1580–1600 cm^{-1} range. The corresponding absorption in the 1:2 adducts is weak and at higher energy in the *trans* isomer (1590 cm^{-1}) with respect to the *cis* analogue (1583 cm^{-1}), as generally observed in the halide derivatives of similar geometries. The 1:2 complex spectra contain three strong bands consistent with the presence of monodentate nitrate [5, 16] and assigned to NO_2 asym stretching (*trans*, 1502 cm^{-1}; *cis*, 1515 cm^{-1}), NO_2 sym stretching (*trans*, 1259 cm^{-1}; *cis*, 1268 cm^{-1}) and ν(N–O) (oxygen coordinated to platinum; *trans*, 950 cm^{-1}; *cis*, 965 cm^{-1}). Those bands are absent in the complexes which contain ionic nitrate, such a moiety being characterized by a strong absorption at *ca.* 1360 cm^{-1}. Accordingly [$PtPra_3(NO_3)$]NO_3 shows the absorptions of both ionic (1365 cm^{-1}) and monodentate (1512, 1273 and 976 cm^{-1}) nitrato groups. The platinum–halide stretching frequencies in [$PtPra_3X$]NO_3 (Table 3), observed at 334 (X = Cl) and 240 (X = Br) cm^{-1}, are close to the value found for the analogous [$PtPra_3X$]X (X = Cl, 333 cm^{-1}; X = Br, 235 cm^{-1}). The ionic complexes show a broad band of medium intensity in the 270–310 cm^{-1} range probably related to Pt–N stretchings, on the basis of assignments for analogous compounds [17–19].

The thermal analysis data of all complexes are summarized in Table 3. Degradation of the 1:2 adducts starts at 85 °C and occurs in a single step with massive weight loss (*ca.* 50%) within 300 °C. At higher temperature a slow decomposition process is observed, which ends at *ca.* 600 °C. The DTA curves show exothermic peaks of variable intensity in repeated tests, due possibly to reaction of the nitrato decomposition products with traces of oxygen left in the furnace. The thermograms of the [$PtPra_3X$]NO_3 adducts show a trend very similar to that of the related [$PtPra_3X$]X species, with a first degradation step concerning the release of one Pra molecule and a second one related to pyrolysis of the intermediate [$PtPra_2X(NO_3)$]. The presence of covalent halide confers thermal stability to the mixed 1:3 adducts (decomposition temperature, 175 °C) in respect to [$PtPra_3(NO_3)$]NO_3, whose degradation starts at 95 °C. In this case Pra release and decomposition of covalent nitrate should occur simultaneously and the endothermic peaks at 113 and 140 °C correspond to a weight loss higher than that expected for evolution of one Pra molecule. The thermograms of [$PtPra_4$]$(NO_3)_2 \cdot 2H_2O$ are shown in Fig. 1. The first endothermic peak corresponds to partial dehydration of the complex,

TABLE 3. Infrared Absorptions (600–250 cm^{-1}) and Thermal Data (in dinitrogen)

Compound	Frequency (cm^{-1})	Decomposition interval (°C)	TG weight loss (%)		DTA peaks (°C)[a]
			Found	Calculated	
trans-[$PtPra_2(NO_3)_2$]	618w, 414vw, 394vw, 350s, 261vw	85–650	56.0	55.4(2Pra + $2NO_3$)	b
cis-[$PtPra_2(NO_3)_2$]	538w, 468w, 412vvw, 330sbr, 275w	85–550	55.2	55.4(2Pra + $2NO_3$)	b
[$PtPra_3Cl$]NO_3	612sh, 598w, 415w, *334*m, 270mbr	175–210	13.1	12.6(Pra)	204md
		210–550	45.2	45.9(2Pra + Cl + NO_3)	b
[$PtPra_3Br$]NO_3	600w, 410w, 392w, 340vw, 280mbr, *240w*	175–205	11.2	11.5(Pra)	197md
		205–550	51.1	50.6(2Pra + Br + NO_3)	b
[$PtPra_3(NO_3)$]NO_3	610vw, 525vvw, 470vw, 398vw, 318sh, 298mbr, 245vw	95–550	61.9	60.7(3Pra + $2NO_3$)	113md, 140d[b]
[$PtPra_4$]$(NO_3)_2$	595w, 408w, 300mbr, 240vw				
[$PtPra_4$]$(NO_3)_2 \cdot 2H_2O$	650wbr, 600w, 404w, 310mbr, 240w	80–140	5.3	5.3(1.75 H_2O)	125d
		140–175	0.8	0.8(0.25 H_2O)	171d
		180–190	19.8	20.0(2Pra)	185d
		190–500	39.2	40.9(2Pra + $2NO_3$)	b

[a]d = decomposition endotherm; m = melting endotherm. [b]Broad exotherms are generally observed in the 150–350 °C temperature interval, whose position and intensity depend on the presence of residual oxygen in the furnace.

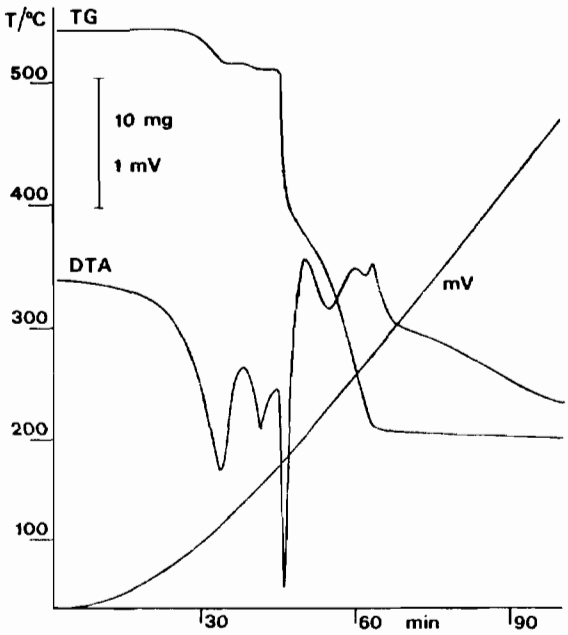

Fig. 1. Thermograms of [$PtPra_4$]$(NO_3)_2 \cdot 2H_2O$ (50.40 mg).

the residual H_2O (0.2–0.4 mol in four different samples) being evolved at 170 °C. The anhydrous species is stable up to 180 °C. The weight loss related to the sharp endotherm at 185 °C is consistent with evolution of two Pra molecules, followed by exothermic degradation of the *trans*-[$PtPra_2(NO_3)_2$] intermediate.

The ^1H NMR spectra of the adducts (Table 4) contain broad signals for the NH_2, α-CH_2 and β-CH_2 proton groups, whereas CH_3 protons give rise to sharp triplets. In all spectra the NH_2 resonances show the satellites due to coupling between protons and ^{195}Pt isotope (*J ca.* 65 Hz). Whereas the chain proton signals are almost unchanged, distinct NH_2 signals are observed for the *cis* (4.6 ppm) and *trans* (3.85 ppm) isomers. The spectra of the 1:3 adducts show two NH_2 signals, the downfield one (at *ca.* 5.5 ppm) having half the intensity of the stronger one (at *ca.* 4.4 ppm). The presence of two NH_2 resonances should depend on the different environment of the amine molecules in the square planar [$PtPra_3X$]$^+$ moiety, the low field signal belonging to the molecule *trans* to the covalently bound nitrate or halide. The solvent influences the position of the NH_2 signals, which in deuterated acetone appear downfield with respect to those observed in $CDCl_3$ (*cis*, 5.2 ppm; *trans*, 4.7 ppm; [$PtPra_3(NO_3)$]NO_3, 5.7w–5.0 ppm; [$PtPra_4$]$(NO_3)_2$, 5.75 ppm). In spite of the low solubility of the 1:2 adducts in deuterated chloroform, the proton NMR spectra in this solvent suggest the presence of isomer mixtures in *cis*-[$PtPra_2(NO_3)_2$] samples. In fact the isomer NH_2 resonances are *ca.* 0.8 ppm apart in

TABLE 4. ^{1}H NMR Data (ppm; $CDCl_3$; *T ca.* 27 °C)

Compound	NH_2 [a]	α-CH_2	β-CH_2	CH_3
trans-[$PtPra_2(NO_3)_2$]	3.85	2.7	1.75	0.96
cis-[$PtPra_2(NO_3)_2$]	4.6	2.7	1.7	0.94
[$PtPra_3Br$]NO_3	5.5w, 4.2	2.7	1.65	1.01, 0.94
[$PtPra_3(NO_3)$]NO_3	5.6w, 4.6	2.7	1.7	1.00, 0.94
[$PtPra_4$]$(NO_3)_2$	5.3	2.65	1.7	0.97

[a]Broad signal. Coupling with ^{195}Pt (*J ca.* 65 Hz) is observed.

$CDCl_3$, whereas they superimpose in deuterated acetone owing to the large proton–^{195}Pt coupling value.

As shown in Table 1, *cis*-[$PtPra_2(NO_3)_2$] displays a noticeable cytostatic activity against KB cells. The ID_{50} value (0.27×10^{-6} M) is close to that observed for cisplatin (0.37×10^{-6} M) in parallel control tests and is lower than the corresponding value for *cis*-[$PtPra_2Cl_2$] (0.52×10^{-6} M) [11]. The morphological examination of the cells treated with *cis*-[$PtPra_2(NO_3)_2$] and incubated for 48 h showed significant cellular damage with pycnosis of the nucleus and vacuolated cytoplasm. The cells were large and swollen. The same effect was observed by us on cells treated with cisplatin, in accordance with literature reports [20].

As expected, the activity of *trans*-isomer (ID_{50} = 7.94×10^{-6} M) is appreciably lower (thirty times).

The 1:3 complexes show a certain effect but with ID_{50} values much higher than that of the 1:2 respective *cis*-compound. [$PtPra_3Cl$]NO_3 produced the same cytological pattern to that observed for *cis*-[$PtPra_2(NO_3)_2$]. It should be noted that the substitution in [$PtPra_3Cl$]NO_3 ($ID_{50} = 1.96 \times 10^{-6}$ M) of the covalent halide with the easily aquated nitrato group causes a significant activity decrease for [$PtPra_3(NO_3)$]NO_3, the ID_{50} value being 5.90×10^{-6} M. The 1:4 dinitrato adduct has been found inactive.

Comparing the data with those obtained by us in previous researches on analogous complexes in which the leaving groups were represented by chloro ions [11], the same order of activity for the various stoichiometries (1:2 1:3 1:4) is noted. Nevertheless, whereas the respective ID_{50} values of the 1:3 and 1:4 complexes appear comparable, the 1:2 *cis*-complexes exhibit a significantly different activity the nitro derivative having twice the effect compared to that of the parent chloro compound. Therefore the presence of the nitrato group seems to favour the cytostatic activity of diamine–platinum moieties. An analogous trend was observed by Macquet and Butour [21] who found, against *in vitro* L1210 cell growth, an ID_{50} value of 1.54×10^{-6} M for *cis*-[$Pt(NH_3)_2(H_2O)_2$]$(NO_3)_2$ and a value of 2.33×10^{-6} M for the parent dichloro derivative. The same authors report ID_{50} values of 3.85×10^{-6} M for platinum adducts with ethylenediamine and 6.13×10^{-6} M for nitro and chloro derivatives respectively [21]. Similar results were also obtained by Brunner *et al.* [22] for $PhCH_2CH(NH_2)$–CH_2NH_2 (ID_{50}: NO_3, 0.75×10^{-6} M; ID_{50}: Cl, 2.40×10^{-6} M).

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