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Binding Study of the Drug *cis*-Dichlorodiammineplatinum(II) to $G_p^{5'}$ and $dG_p^{5'}$ by High Resolution Proton and Carbon-13 NMR Spectroscopy

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Abstract

The molecular mode of action leading to the anticancer activity of the drug *cis*-diamminedichloroplatinum(II), *cis*-DDP or *cis*-platinum is still the subject of speculation. In the present high field (400 MHz) ^1H NMR study the results on coupling constants for *cis*- and *trans*-diammine bis(guanosine-5′-monophosphate) and (d-guanosine-5′-monophosphate)platinum(II) complexes are presented and discussed. The ^1H and ^{13}C NMR chemical shifts obtained are consistent with the drug binding to N7 of each guanine. It has been found that the drug induces different conformational changes in the nucleotide from the *trans*-DDP isomer.

Introduction

Previous studies [1] on *cis*-platinum(*cis*-DDP) an anticancer drug with nucleic acids in aqueous solutions have attempted to unravel the mode of its action which is still the subject of much speculation. It is clear from the evidence available so far that *cis*-platinum interacts with DNA [2, 3] but the nature of this interaction is not known yet. There is evidence that the drug attacks DNA to form covalent bonds with the N7 atoms of single or adjacent guanine bases and that it does not intercalate between base-pairs [4–15].

Several studies with nucleosides and nucleotides have shown that *cis*-platinum binds to the N7 atom of the guanine molecule and it was found that this site seems to be the primary target when the drug reacts with DNA [3, 16, 17]. Indeed X-ray structural analysis results and models show that the N7 sites of DNA are well exposed to a nucleophilic attack [18]. Furthermore it has been suggested [19] that metal binding to N7 may also play an important role in the unwinding of the double helix since it is known that the N7 sites of guanine bases are specific targets for many denaturants including methylating agents. Because *cis*-platinum binds preferentially to DNA chains that have high contents of guanine and cytosine pairs [20], metal complexes of nucleotides containing these bases may then serve as models to study the interaction of the drug with DNA and metal ions in general with DNA. The main objective of our investigation was to define, at the chemical bond level, the conformational changes brought about by the binding of platinum agents and more specifically by the *cis*- and *trans*-DDP.

Although a 100 MHz ^1H NMR study of *cis*- and *trans*-DDP with $G_p^{5'}$ and $dG_p^{5'}$ has been recently published [11], most coupling constant values have not been reported. In the present work, a study at higher field (400 MHz) has yielded the coupling constants for *cis*- and *trans*-diammine bis(guanosine-5′-monophosphate or (d-guanosine-5′-monophosphate)-platinum(II) complexes, *cis*-$[Pt(NH_3)_2(G_p^{5'})_2]^{++}$ and *trans*-$[Pt(NH_3)_2(dG_p^{5'})_2]^{++}$, respectively.

The conformational changes deduced from these parameters are then compared to those induced by protonation or methylation and by metalation with K_2PtCl_4 which was reported in a previous work [21].

Experimental

Materials and NMR Measurements

The nucleotides, guanosine-5′-monophosphate ($G_p^{5'}$) and deoxy-guanosine-5′-monophosphate ($dG_p^{5'}$) disodium salts were purchased from Sigma Chemical Company. The *cis*-$Pt(NH_3)_2Cl_2$ was obtained from Engelhard and was used without further purification.

The solutions (20 mmol) were prepared by dissolving the *cis*- and *trans*-$[Pt(NH_3)_2(\text{nucleotide})_2]^{++}$ complexes as the chloride and perchlorate salts in D_2O (99.996 Kor Isotopes). The clear solutions were immediately used for the NMR studies. The NMR spectra were obtained with a Bruker WH-400

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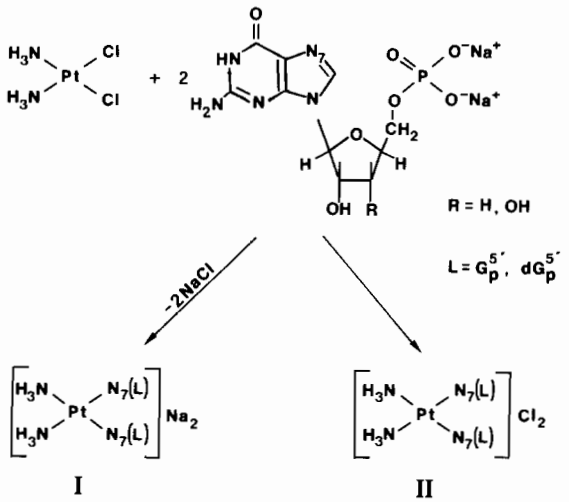
spectrometer located at "Le Laboratoire régional de RMN à haut champ" in Montreal. The chemical shifts are referenced relative to an internal standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (δ = 0.0 ppm) for ^{1}H NMR and dioxane (δ = 67.4 ppm) for ^{13}C NMR.

The pD of the solutions was measured with a Fisher Accumet 630 pH meter and corrected [22]. Homonuclear selective proton–proton decoupling and ^{31}P irradiation were carried out using standard Bruker accessories. The NMR parameters were derived from determined spectral simulation using a conventional program (PANIC) from the Bruker software package and/or by first order analysis for the well dispersed proton signals.

Preparation of the Complexes

Preparation of the Complexes, Cis-diammine-bis-(guanosine-5'-monophosphate) and Bis(d-guanosine-5'-monophosphate)platinum(II) Chlorides

The method of preparation was previously described [5]. The *cis*-$Pt(NH_3)_2Cl_2$ (0.4 mmol) was mixed with 0.82 mmol (a) $G_p^{5'}$ (or (b) $dG_p^{5'}$) in 90 ml of distilled water. The suspension was heated at 50 °C for about 3 to 5 h with continuous stirring. The clear solution was left overnight at room temperature; it was then concentrated under vacuum at 50 °C. Afterwards, the product was precipitated first with acetone and then with ether. The white precipitate was filtered, washed further, first with acetone, then with ether and dried in air. Yield 75% (0.3 mmol). The complexes have the formulae [32, 33]: *cis*-$[Pt(NH_3)_2(G_p^{5'})_2]Cl_2$ and *cis*-$[Pt(NH_3)_2(dG_p^{5'})_2]Cl_2$



Scheme 1. The $2Na^+$ are on $G_p^{5'}$ and do not come out. Analytical results support formula II [32, 33].

Preparation of the Complexes, Trans-diammine-bis(guanosine-5'-monophosphate) and bis(d-guanosine-5'-monophosphate)platinum(II) Perchlorates

These complexes have been prepared through modification of a recently published method [12]. A water solution containing 10^{-2} M *trans*-$Pt(NH_3)_2Cl_2$ and 2×10^{-2} M $AgClO_4$ was heated at 50 °C during one h. The AgCl precipitate formed was filtered and 2×10^{-2} M $G_p^{5'}$ or $dG_p^{5'}$ was added to the filtrate. The mixture was heated at 50 °C for one day. The clear solution was evaporated to dryness under vacuum and the residue was taken twice with D_2O (99.7%) followed by evaporation to dryness. Finally, the residue was dissolved in D_2O (99.996%) for the NMR measurements. The complexes formed were the corresponding perchlorate salts: *trans*-$[Pt(NH_3)_2(G_p^{5'})_2](ClO_4)_2$ and *trans*-$[Pt(NH_3)_2(dG_p^{5'})_2](ClO_4)_2$.

The above method to obtain the *trans*-perchlorates was necessary because with the chloride salts the reaction with both $G_p^{5'}$ or $dG_p^{5'}$ was never complete.

Results and Discussion

Chemical Shifts

The ^{1}H chemical shifts are given in Table I and the NMR spectra are shown in Figs. 1 and 2. The chemical shifts are similar to those reported in the literature [11]. Coupling with ^{195}Pt [5] has not been observed, probably at least in part because of the large contribution of the chemical shift anisotropy relaxation, especially at high fields; the satellites resulting from coupling with ^{195}Pt should be broad, and so are not detected [24].

It has been shown that many factors such as ring current effects, polarization of bonds by molecular charge distribution, anisotropy effects of different parts of the molecule, conformational changes, *etc.* may affect the shielding of the protons in nucleotide derivatives. The significant downfield shift of H8 in platinum complexes has previously been interpreted as a direct consequence of platinum binding to N7 [5]. For both type of complexes here this downfield shift is more important in the *trans*-complexes than in the *cis*-complexes (0.7 ppm as against 0.48 ppm). It would appear that the difference might be a consequence of the proximity of the two N7 atoms in *cis*-position which gives rise to mutual shielding in the *cis*-complexes. Only in the *cis*-derivatives can the purine bases be located sufficiently close to each other to experience mutual shielding created by the ring current [25] that leads to additional upfield shifts. In fact, compared to the *trans*-complexes, the protons H1' and H2' of the sugar of the *cis*-complexes are also shifted upfield by

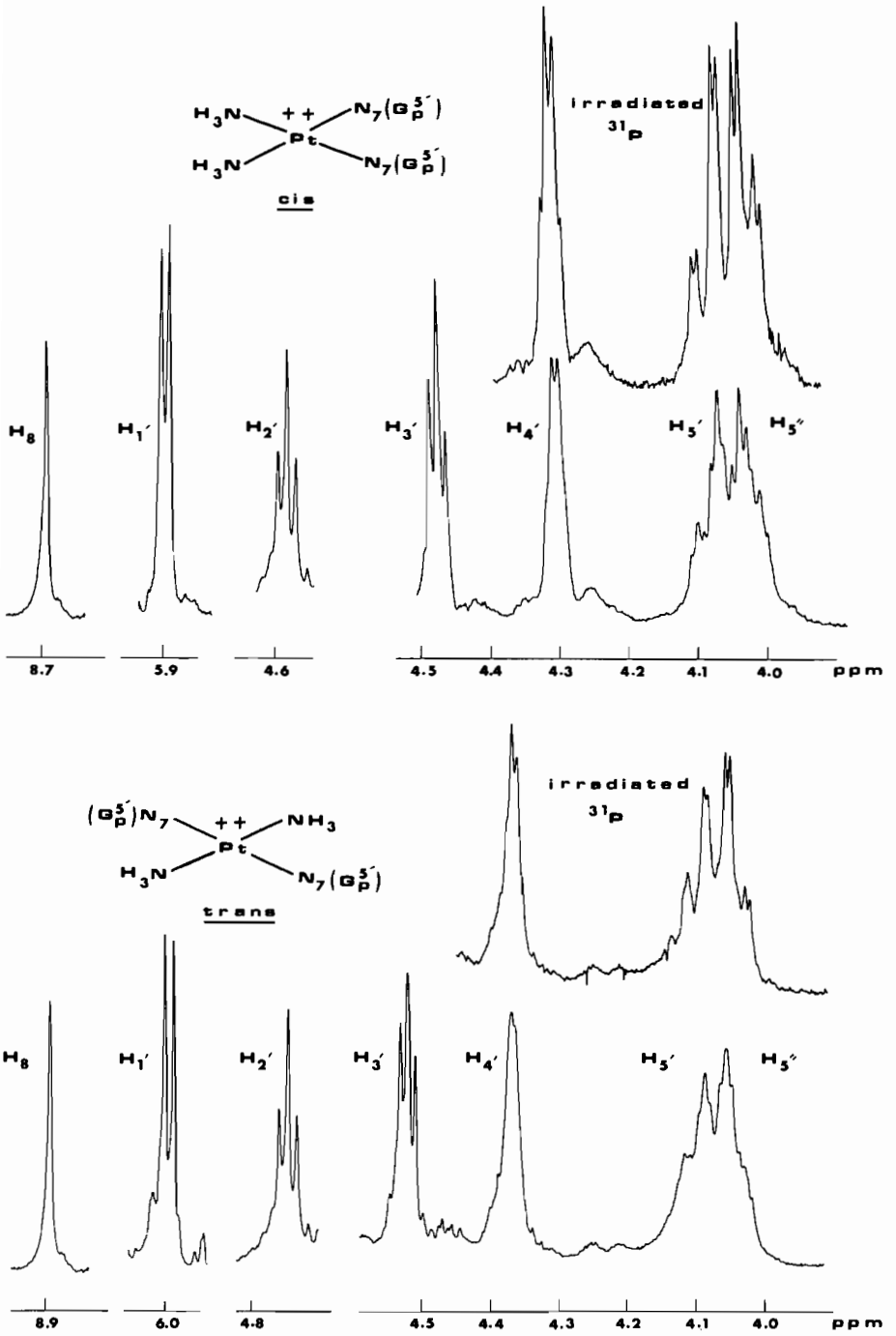


Fig. 1. 400 MHz ^1H NMR spectra of 20 mM $G_p^{5'}$ disodium salt in D_2O (pD = 8.3) at 43 °C and 20 mM $G_p^{5'}$ free acid (pD = 2.3) at 20 °C. Chemical shifts are given in ppm from internal reference DSS.

about 0.10 and 0.15 ppm, respectively. Although attempts of using ^1H chemical shifts (especially H1′ and H2′) as conformational probes have been made [26], the observed small changes in ^1H chemical shifts of the ribose moiety are not discussed further.

The ^{13}C chemical shifts are given in Table II. For both chloride and perchloride complexes, platination at N7 causes a downfield shift of the C8 resonance (~3 ppm), while protonation at N7 induces an upfield shift for this carbon (~−1.7 ppm). An

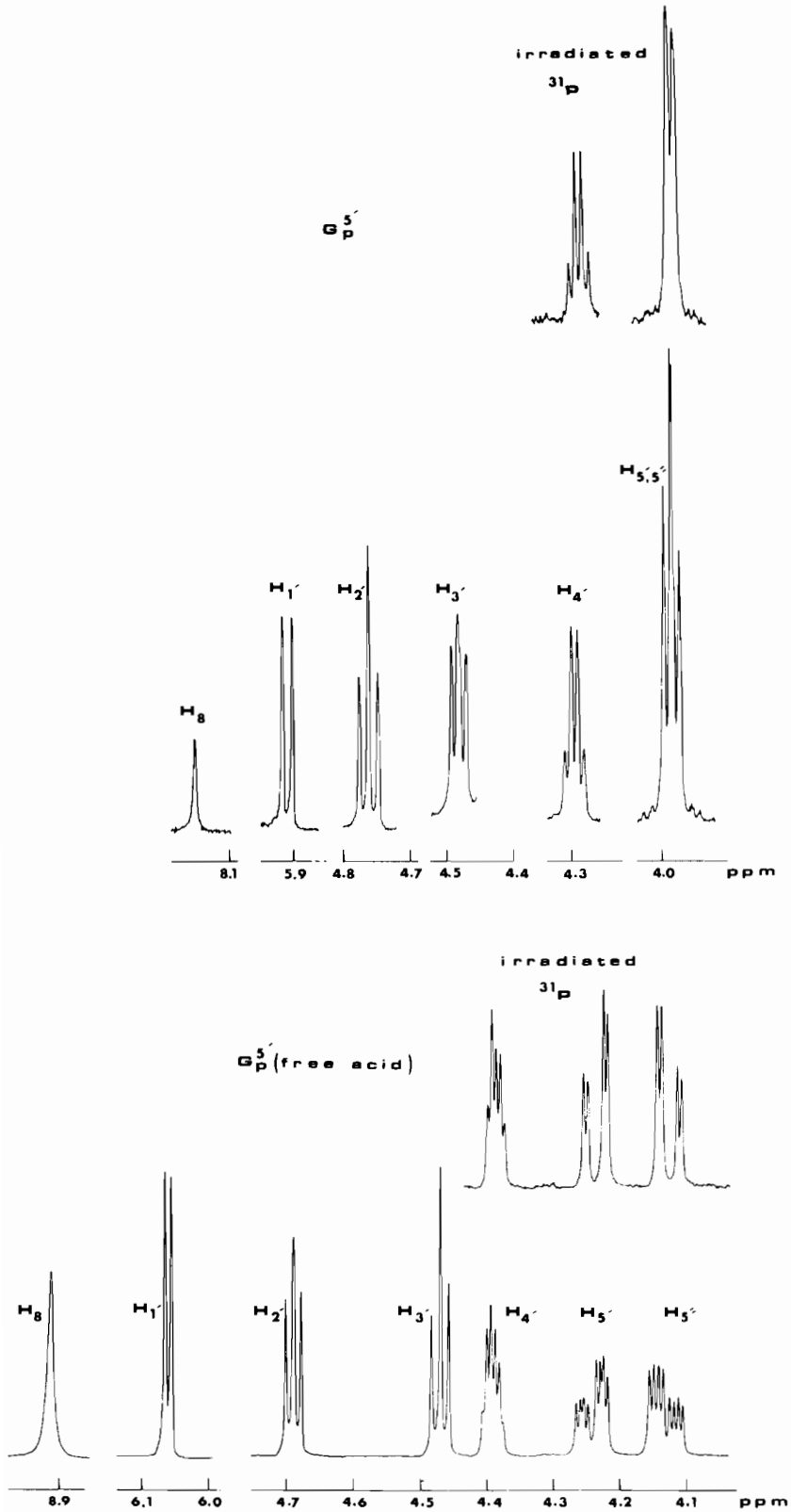


Fig. 2. 400 MHz ^{1}H NMR spectra of 20 mM $G_p^{5'}$ disodium salt complexes in D_2O with *cis*- (pD = 7.4) and *trans*-DDP (pD = 6.9) at 43 °C and 35 °C respectively. Chemical shifts are given in ppm from internal reference DSS.

TABLE I. ^1H NMR Chemicals Shifts for $G_p^{5'}$ and $dG_p^{5'}$ upon Platination and Protonation.[a]

Compounds	pD	T (°C)	H_8	H_1'	H_2'	H_2''	H_3'	H_4'	H_5'	H_5''
$G_p^{5'}$ (disodium salt)	8.3	43	8.148	5.907	4.759	–	4.480	4.294	3.983	3.983
cis-$[Pt(NH_3)_2(G_p^{5'})_2]Cl_2$	7.4	43	8.625	5.892	4.585	–	4.455	4.300	4.080	4.030
		$\Delta\delta$ *cis*	+0.477	−0.015	−0.174	–	−0.025	+0.006	+0.097	+0.047
trans-$[Pt(NH_3)_2(G_p^{5'})_2](ClO_4)_2$	6.9	35	8.900	5.998	4.752	–	4.517	4.360	4.090	4.050
		$\Delta\delta$ *trans*	+0.752	+0.091	−0.007	–	+0.037	+0.066	+0.107	+0.067
$G_p^{5'}$ (free acid)	2.3	20	8.909	6.057	4.686	–	4.468	4.388	4.240	4.128
		$\Delta\delta$ acid	0.761	+0.150	−0.073	–	−0.012	+0.184	+0.257	+0.145
$dG_p^{5'}$ (disodium salt)	8.0	20	8.150	6.305	2.800	2.486	4.702	4.204	3.931	3.931
cis-$[Pt(NH_3)_2(dG_p^{5'})_2]Cl_2$	7.3	20	8.629	6.270	2.677	2.576	4.704	4.223	4.020	4.020
		$\Delta\delta$ *cis*	+0.479	−0.035	−0.123	+0.090	+0.002	+0.019	+0.089	+0.089
trans-$[Pt(NH_3)_2(dG_p^{5'})_2](ClO_4)_2$	6.8	35	8.848	6.372	2.780	2.580	4.737	4.270	4.024	4.024
		$\Delta\delta$ *trans*	+0.698	+0.067	+0.20	+0.094	+0.035	+0.066	+0.093	+0.093
$dG_p^{5'}$ (free acid)	1.25	20	8.931	6.403	2.752	2.660	4.684	4.308	4.134	4.088
		$\Delta\delta$ acid	+0.0781	+0.098	−0.048	±0.174	−0.018	+0.104	+0.203	+0.157

[a] $\Delta\delta$ is the difference between the disodium salt and the N7 metalated or protonated species.

upfield shift of about −3 ppm has also been observed for carbons C5 and C6 upon platination and −7 ppm upon protonation. For the remaining carbons of the base, the effects caused by N7 platination are smaller (see Table II). The carbon shifts induced in the *cis*-complexes are slightly more important than those in the *trans*-complexes. Similar changes in ^{13}C chemical shifts have been reported on metal binding to aromatic heterocycles [27, 28].

Coupling Constants

The coupling constants were obtained straightforwardly from the 400 MHz ^1H NMR spectra. For example, the spectra in Fig. 1 reveals the spectral changes of $G_p^{5'}$ on protonation and Fig. 2 upon complexation with *cis*-$Pt(NH_3)_2Cl_2$ and *trans*-$Pt(NH_3)_2Cl_2$. Homonuclear and ^{31}P decoupling experiments were also used to simplify the analysis.

A broadening of the lines is observed on some ^1H NMR spectra at 20 °C. To narrow lines and avoid interference from the residual HOD signal, spectra are recorded at 20, 35 and 43 °C. All concerned coupling constants were determined from the spectral analysis and are summarized in Table III.

The rotation about the Pt–N7 bond has a significant energy barrier [26]. The simplicity of the spectra reveals that the *cis*- and *trans*-$[Pt(NH_3)_2L_2]^{++}$ complexes (L = $G_p^{5'}$ and $dG_p^{5'}$) have an effective two fold (C_2) symmetry axis bisecting the N7–Pt–N7 bonds at temperatures higher than 20 °C.

The conformational changes are reflected in the values of proton–proton coupling constants. It has been shown [29] that these parameters can be used to calculate conformational populations determined from J_{H-H} values which show interesting trends. These populations of conformers are summarized for *cis*- and *trans*-$[Pt(NH_3)_2L_2]^{++}$ in Table IV and are compared to those of the disodium salt, the free acid forms of $G_p^{5'}$ and $dG_p^{5'}$ and $K[PtCl_3(G_p^{5'})]$. Although absolute conformational populations slightly vary with temperature the trend of the conformational differences remains the same.

The C2′ *endo* (^2E) ⇄ C3′ *endo* (^3E) equilibrium determined from $J_{1'-2'}$ and $J_{3'-4'}$ remains unchanged upon complexation with the *trans*-$[Pt(NH_3)_2L_2]^{++}$, while the ^3E population in the *cis*-$[Pt(NH_3)_2L_2]^{++}$ complexes slightly increases. It is interesting to note that this increase of the ^3E population is comparable to the change induced by complexation of $G_p^{5'}$ with K_2PtCl_4 [21] (see Table IV). This sugar conformational change, however, does not seem to be a very significant effect in the platinum interaction with the nucleotide. The conformational change about the C4′–C5′ bond, however is more significant. In fact, it has been found that the gg population of $G_p^{5'}$ and $dG_p^{5'}$ increased upon N7 coordination to the platinum atom carrying two positive charges both with *cis*- and *trans*-$[Pt(NH_3)_2L_2]^{++}$. It increased more with *trans*- than with *cis*-DDP. This behaviour is similar to protonation or methylation of the N7 site, but to a lesser extent. The increase in gg population is contrasted with the decrease of the gg conformer population when N7 is coordinated to platinum carrying a negative charge ($PtCl_3^-$), studied earlier [21]. Repulsion of the negatively charged $PtCl_3^-$ with the phosphate group was proposed to explain the decrease of the gg population. Thus, in the case of *cis*- and *trans*-$[Pt(NH_3)_2L_2]^{++}$ the negatively charged phosphate group is brought close to the positively charged platinum by electrostatic attraction which can explain the significant increase of the gg population. In the case of *trans*-$[Pt(NH_3)_2L_2]^{++}$, where the two L's are diametrically opposite to each other, the approach of the phos-

TABLE II. ^{13}C Chemical Shifts of $G_p^{5'}$ and $dG_p^{5'}$ upon Platination and Protonation.

Compound		C_2	C_4	C_5	C_6	C_8	C_1'	C_2'	C_3'	C_4'	C_5'
$G_p^{5'}$ (disodium salt)		155.08	152.19	117.10	159.86	138.22	88.20	71.52	75.08	85.03	64.73
cis-$[Pt(NH_3)_2(G_p^{5'})_2]Cl_2$		155.48	150.50	114.30	156.75	141.15	88.98	70.16	75.71	84.61	63.91
	$\Delta\delta$ *cis*	0.40	−1.69	−2.80	−3.11	2.93	0.78	−1.36	0.63	−0.42	−0.82
trans-$[Pt(NH_3)_2(G_p^{5'})_2](ClO_4)_2$		155.30	151.54	114.47	157.30	141.20	88.71	71.26	75.42	85.76	64.26
	$\Delta\delta$ *trans*	0.22	−0.64	−0.63	−2.56	2.98	0.51	−0.26	0.34	0.73	−0.47
$G_p^{5'}$ (free acid)		156.08	150.43	109.74	156.08	136.50	90.34	70.22	75.42	84.81	64.64
	$\Delta\delta$ acid	1.00	−1.76	−7.36	−3.78	−1.72	2.12	−1.3	0.34	−0.22	−0.09
$dG_p^{5'}$ (disodium salt)		154.54	151.87	116.76	159.44	138.20	84.12	39.70	72.27	87.03	64.81
cis-$[Pt(NH_3)_2(dG_p^{5'})_2]Cl_2$		155.21	150.37	114.26	156.75	141.01	84.12	40.11	70.71	86.91	64.25
	Δ *cis*	0.67	−1.50	−2.50	−2.69	−2.81	0.00	0.41	−1.56	−0.12	−0.56
trans-$[Pt(NH_3)_2(dG_p^{5'})_2](ClO_4)_2$		155.31	151.28	114.65	157.44	141.18	85.50	40.30	72.06	87.65	64.73
	$\Delta\delta$ *trans*	0.77	−0.59	−2.1	−2.00	2.97	1.38	0.60	−0.21	0.62	−0.08
$dG_p^{5'}$ (free acid)		156.01[a]	150.19	109.81	156.16[a]	136.54	86.84	40.48	71.34	87.40	65.18
	$\Delta\delta$ acid	1.47	−1.68	−6.95	−3.28	−1.67	2.72	0.78	−0.93	0.37	0.37

[a] Assignment may be interchanged.

TABLE III. Proton–Proton and Proton–Phosphorus Coupling Constants (Hz) of $G_p^{5'}$ and $dG_p^{5'}$ upon Platination and Protonation.

Compounds	T (°C)	1′2′	1′2″	2′2″	2′3′	2″3′	3′4′	4′5′	4′5″	5′5″	5′5″	5″p 4′p
$G_p^{5'}$ (disodium salt)	43	6.0	–	–	5.1	–	3.6	4.1	4.1	?	5.0	5.0 ⩽ 1.5
cis-$[Pt(NH_3)_2(G_p^{5'})_2]Cl_2$	43	4.4	–	–	4.6	–	4.7	3.4	3.6	−11.7	4.7	4.4 ⩽ 1.5
trans-$[Pt(NH_3)_2(G_p^{5'})_2](ClO_4)_2$	43	4.4	–	–	5.1	–	3.7	2.5	2.9	−11.8	3.9	4.4 ⩽ 1.5
$G_p^{5'}$ (free acid)	20	3.9	–	–	5.5	–	5.1	2.55	2.6	−11.9	4.4	5.4 ⩽ 2.5
$dG_p^{5'}$ (disodium salt)	20	7.6	6.3	−13.9	6.1	3.2	3.1	4.3	4.3	?	5.2	5.2 ⩽ 1.5
cis-$[Pt(NH_3)_2(dG_p^{5'})_2]Cl_2$	20	5.7	6.5	−14.0	6.2	4.7	3.8	4.1	4.1	?	4.0	4.0 ⩽ 1.5
trans-$[Pt(NH_3)_2(dG_p^{5'})_2](ClO_4)_2$	35	6.6	6.4	−14.0	6.1	3.3	~3.0	3.0	3.0	?	~2.00	~2.0 ⩽ 1.5
$dG_p^{5'}$ (free acid)	20	6.4	6.1	−14.1	4.4	5.9	3.7	3.1	3.3	−11.7	4.5	5.6 ⩽ 1.5

TABLE IV. Conformational Populations for $G_p^{5'}$ and $dG_p^{5'}$ upon Platination and Protonation.

Compounds	T (°C)	^3E	C(4')–C(5')		C(5')–O(5')	
			gg	gt, tg	g'g'	g't', t'g'
$G_p^{5'}$ (disodium salt)	43	38	57	43	72	28
cis-$[Pt(NH_3)_2(G_p^{5'})_2]Cl_2$	43	50	69	31	76	24
trans-$[Pt(NH_3)_2(G_p^{5'})_2](ClO_4)_2$	35	39	86	14	80	20
$G_p^{5'}$ (free acid)	20	54	89	11	73	27
$K[PtCl_3(G_p^{5'})]$[a]	20	51	36	64	72	28
$dG_p^{5'}$, (disodium salt)	20	33	53	47	71	29
cis-$[Pt(NH_3)_2(dG_p^{5'})_2]Cl_2$	20	40	57	43	82	18
trans-$[Pt(NH_3)_2(dG_p^{5'})_2](ClO_4)_2$	35	32	~79	~21	~100	0
$dG_p^{5'}$ (free acid)	20	39	75	25	72	28

[a]The values for this complex were taken from reference 21.

phate group to platinum is favoured from space requirements which may explain the higher gg population of the *trans*- as against to the *cis*-DDP.

The data in Table IV also show the conformational change about the C5'–O5' bond. Because of the large error in determining these values only large deviations are significant. The population deviations are again larger with the *trans*-$[Pt(NH_3)_2L_2]^{++}$ compound than with the *cis*-$[Pt(NH_3)_2L_2]^{++}$ (see Table IV). This implies that the *trans*-DDP disrupts more effectively the structure of the nucleotide, since it affects to a greater degree the conformation populations of the nucleobase. This result suggests that the *trans*-DDP disrupts more effectively the DNA double helix than the *cis*-DDP, the antitumor drug which is milder in its conformational inducements, when it is fixed at the N7 of the guanine base. This result is in agreement with previous experiments [30, 31].

Conclusion

The ^1H and ^{13}C chemical shifts of the platinum complexes are consistent with a structure in which the platinum atom is covalently linked to the N7 atoms of two guanine bases. The nucleotides $G_p^{5'}$ and $dG_p^{5'}$ behave similarly upon complexation with the *cis*- or *trans*-DDP. The ^1H and ^{13}C chemical shifts induced to the nucleotide by the platinum moiety $Pt(NH_3)_2^{++}$ attached at the N7 site of the base are compared. The *cis*- and *trans*-DDP induce different conformational changes in the nucleotide upon linkage of the N7 site to the platinum. The conformational differentiation between *cis*- and *trans*-DDP in their reactivity towards the nucleotides ($G_p^{5'}$ and $dG_p^{5'}$) may be related to the anticancer activity of the *cis*-DDP and the inactivity of the *trans*-DDP which disrupts more effectively the nucleotide structure. The result with K_2PtCl_4 further substantiates this conclusion, since K_2PtCl_4 also alters the gg conformation of the nucleotide by increasing the gt conformation at the expenses of the gg conformers.

Acknowledgements

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