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Interaction of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ with Ribose and Deoxyribose Diguanosine Phosphates†

Jean-Pierre Girault, Geneviève Chottard, Jean-Yves Lallemand, and Jean-Claude Chottard*

ABSTRACT: The three diguanosine phosphates GpG (4×10^{-4} M), d(GpG) (10^{-5} M), and d(pGpG) (10^{-5} M) have been reacted with *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ (1 Pt/dinucleotide) in water at pH 5.5 and 37 °C. In each case a single product is formed. The three complexes have been characterized by proton nuclear magnetic resonance (^{1}H NMR) and circular dichroism (CD) analyses. They are N(7)–N(7) chelates of the metal with an anti–anti configuration of the bases. They present a conformational change upon deprotonation of guanine N(1)H whose pK_a is ca. 8.7 (D_2O). Their CD spectra, compared to those of the free dinucleotides, exhibit an increase of ellipticity in the 275-nm region, which can be qualitatively related to the characteristic increase reported for platinated DNA and poly(dG)·poly(dC). These results are in favor of the hypothesis of intrastrand cross-linking of adjacent guanines, by the *cis*-$Pt^{II}(NH_3)_2$ moiety, after a local denaturation of DNA.

The mechanism of action of the antitumor *cis*-dichlorodiammineplatinum(II) complex is still the subject of investigations (Rosenberg, 1978). In the cell the active forms of the complex imply the aquation of one or both chloride ligands (Johnson et al., 1980). There is much evidence that suggests that DNA is the primary target of the platinum(II) drug (Roberts & Thomson, 1979). So that the antineoplastic activity of the *cis*-dichlorodiammineplatinum complex, compared to the inactivity of the trans isomer, can be explained, several hypotheses have been put forward that imply a bifunctional coordination of the *cis*-$Pt^{II}(NH_3)_2$ moiety (Roberts & Thomson, 1979). One of them proposes an intrastrand cross-linking of two adjacent guanines [Goodgame et al., 1975; Kelman & Peresie (1979) and previous work cited therein]. Platinum chelation by a d(GpG) sequence has been invoked to account for the gel electrophoretic pattern obtained after *Bam*H1 digestion of platinated DNA (Kelman & Buchbinder, 1978). Such a chelation is supported by the selective inhibition of the restriction endonuclease cleavage of platinated pSM1 DNA, at the cutting site which is adjacent to a $(dG)_4(dC)_4$ sequence (Cohen et al., 1980; Lippard, 1980).

We previously reported that ribose diinosine monophosphate (IpI)[1] (Chottard et al., 1978) and ribose diguanosine monophosphate (GpG)[1] (Chottard et al., 1980) give a single N(7)–N(7)-chelated complex upon reaction with *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$. In this paper we present the results of a comparative study of the binding of the *cis*-$Pt^{II}(NH_3)_2$ moiety to the three ribose and deoxyribose diguanosine phosphates: GpG, d(GpG), and d(pGpG).[1] These results show the generality of facile N(7)–N(7) platinum chelation by diguanosine phosphates and establish the configuration of the bases in the complexes formed. The CD[1] characteristics of these models for intrastrand cross-linking of adjacent guanines are compared with those of platinated DNA [Srivastava et al. (1978) and previous work cited therein; Macquet & Butour, 1978].

Materials and Methods

GpG, d(GpG), and d(pGpG) were used as ammonium salts. The experimental conditions for the reaction between the dinucleotides and *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ have been described previously (Chottard et al., 1980). The stoichiometric reactions (1 Pt/dinucleotide) were run at 4×10^{-4} M concentration for GpG and 10^{-5} M for d(GpG) and d(pGpG) at pH 5.5 and 37 °C. The analytical procedures have also been

† From the Laboratoire de Chimie, Ecole Normale Supérieure, 75231 Paris Cedex 05, France (J.-P.G., J.-Y.L., and J.-C.C.), and the Département de Recherches Physiques, Université Pierre et Marie Curie, 75230 Paris Cedex 05, France (G.C.). *Received June 17, 1981; revised manuscript received October 2, 1981.*

[1] Abbreviations: in dinucleoside monophosphates and dinucleotides, G and I represent guanosine and inosine; p to the left of a nucleoside symbol indicates a 5′-phosphate, and to the right it indicates a 3′-phosphate; H(8)-5′, H(8) proton of the 5′ guanine (at the 5′ end) of GpG; the dinucleoside monophosphates GpG, d(GpG), and IpI will be occasionally referred to as dinucleotides; Guo, guanosine; Ino, inosine; 5′-GMP, guanosine 5′-monophosphate; 5′-IMP, inosine 5′-monophosphate; HPLC, high-pressure liquid chromatography; NMR, nuclear magnetic resonance; DSS, sodium 4,4-dimethyl-4-silapentane-1-sulfonate; s, singlet; d, doublet; CD, circular dichroism; en, ethylenediamine; tn, trimethylenediamine; dien, diethylenetriamine; $NaDodSO_4$, sodium dodecyl sulfate.

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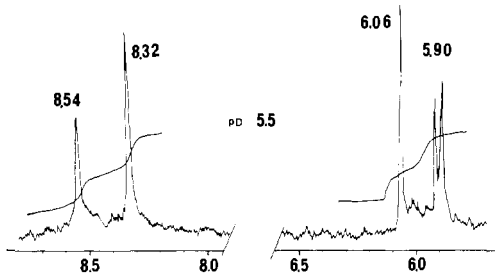

FIGURE 1: ^{1}H NMR spectrum (250 MHz, D_2O, DSS, 17 °C) of GpG[Pt] (10^{-3} M) at pD 5.5.

previously reported (Chottard et al., 1980) except for the following points:

HPLC analyses were performed on an Altex 420 liquid chromatograph, with 254-nm detection, on a Waters C18 μ-Bondapak (reverse-phase) column, using an aqueous $CH_3CO_2NH_4$ solution (10^{-2} M) as eluant A and $CH_3CO_2NH_4$ (10^{-2} M) in H_2O/CH_3OH (1:1) as eluant B, both solutions being brought to pH 4.0 by addition of CH_3CO_2H. The preparative separations were performed with the same column and eluant conditions.

High-pressure gel-permeation chromatography analyses were performed on a Waters μ-Porasil GPC 60-Å column, using an aqueous $CH_3CO_2NH_4$ solution (0.5 M) with 1% $NaDodSO_4$ at pH 4.0 (CH_3CO_2H added) as eluant.

The ^{1}H NMR spectra have been recorded on a Cameca TSN 250 spectrometer (250 MHz, Nicolet 1180 computer) and the CD spectra on a Jobin Yvon Mark III dichrograph ($[\theta]$ in deg·cm^2·dmol^{-1} per nucleotide residue) in previously reported conditions (Chottard et al., 1980). The T_1 relaxation time of protons was obtained by the inversion recovery method (180°-τ-90° sequences) at ca. 17 °C. The $T_{1/2}$ pulse width is 3 μs. The delay between the sequences was 15 s. The samples used for T_1 measurements were dissolved in 99.95% D_2O after two lyophilizations in this solvent. These solutions were introduced into NMR tubes, degassed on a vacuum line, and sealed.

Results

The reaction of 1 molar equiv of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ with any of the three diguanosine phosphates gives the same evolution of UV characteristics of the solution [dinucleotide, dinucleotide λ_{max}, complex λ_{max}, and ratios of complex/dinucleotide optical densities at pH 5.5 are GpG, 253, 261, and 0.87; d(GpG), 253, 261, and 0.92; d(pGpG), 253, 260, and 0.95]. HPLC monitoring of the reaction shows that d(pGpG) reacts faster than the two other dinucleotides: 1.7 × 10^{-4} M d(pGpG) is 90% converted after 30 min, while 5 × 10^{-4} M d(GpG) is 28% converted after 1 h.

In each case, G25 and G10 Sephadex and gel-permeation chromatographies show that the reaction product is monomeric (1 dinucleotide/Pt atom). A μ-Porasil column analysis at pH 4.0 shows that the complexes derived from GpG and d(GpG) on one hand and from d(pGpG) on the other hand have retention times, respectively, similar to those of *cis*-$[Pt(NH_3)_2(Guo)_2]^{2+}$ (Kong & Theophanides, 1974) and of *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]$ (Chu et al., 1978). HPLC analysis of the reaction products from the three diguanosine phosphates shows that in each case there is no unreacted dinucleotide and that one peak represents more than 95% of the product. The same result has been obtained from the slower reaction between d(GpG) and *cis*-$[Pt(NH_3)_2Cl_2]$. The complexes formed will now be noted GpG[Pt], d(GpG)[Pt], and d(pGpG)[Pt].

^{1}H NMR Analyses. The ^{1}H NMR spectra of GpG[Pt] at pD 5.5 and of d(GpG)[Pt] and d(pGpG)[Pt] at three typical

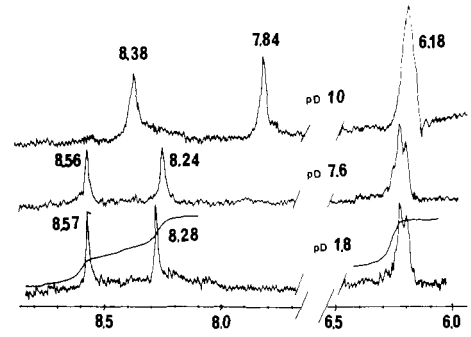

FIGURE 2: ^{1}H NMR spectra (250 MHz, D_2O, DSS, 17 °C) of d(GpG)[Pt] (10^{-3} M) at various pD values.

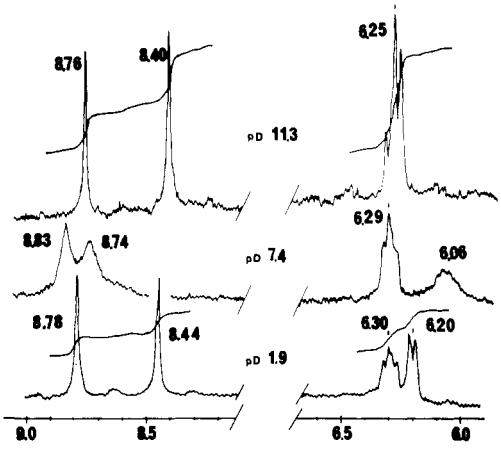

FIGURE 3: ^{1}H NMR spectra (250 MHz, D_2O, DSS, 17 °C) of d(pGpG)[Pt] (0.6 × 10^{-3} M) at various pD values.

Table I: Influence of N(7) Protonation on H(8) and H(1') Chemical Shifts of GpG, d(GpG), and d(pGpG) in D_2O

dinucleotide	pD	H(8)	Δδ-[H(8)]	H(1') ($J_{1'2'}$ in Hz)
GpG	1.95	8.9	0.9	6.0 d (5), 5.95 d (3)
	5.6	7.97,[a] 7.90[a]		5.85 d (5), 5.76 d (3)
d(GpG)	1.7	8.87	0.85	6.4 t, 6.26 t
	6.1	8.02,[a] 7.76[a]		6.16 t, 6.01 t
d(pGpG)	1.85	8.95	0.93	6.39 t, 6.28 t
	7.7	8.02[b]		6.17 t, 6.02[b]

[a] Signal broadening. [b] Broad signal. At pD values close to neutrality the H(8) signals of the three dinucleotides (ca. 10^{-3} M) are broad, a phenomenon that is probably due to intermolecular interactions (Ts'O et al., 1969; Borzo et al., 1980, and references cited therein). At acidic pD values a single sharp signal is observed for the two H(8) protons. (For the free deoxydinucleotides the spectrum is recorded immediately after acidification to avoid any hydrolysis of the phosphate linkage.)

pD values are reported in Figures 1–3. The spectra of the three complexes exhibit several similarities and are comparable to the previously reported one of the diinosine monophosphate complex IpI[Pt] (Chottard et al., 1980). For the sake of comparison, the H(8) and H(1') chemical shifts of the free dinucleotides, at different pD values, are reported in Table I. For the three complexes, the two low-field signals, each one integrating for one proton, are assigned to the two guanine H(8) in the α position to coordinated N(7) for the following reasons: (i) their deshielding is in agreement with N(7) coordination of platinum (Kong & Theophanides, 1974, 1975; Chu et al., 1978; Chottard et al., 1980); (ii) none of them is downfield shifted upon acidification while a ca. +0.9-ppm shift is observed for the two H(8) signals of the three free dinucleotides when the pD is lowered from 7 to 1.8 (Table I);

Table II: Comparison of H(8) Deuterium Exchange Rates in D_2O, at pD 10 and 37 °C, for Diguanosine Phosphates and Bis(Guo)- and Bis(5′-GMP)-Platinum Complexes[a]

platinum complexes	H(8)[b]	k (h^{-1})	$t_{1/2}$ (h)
GpG[Pt]	3′ (●)	6×10^{-2}	11.6
	5′ (o)	4×10^{-2}	15
d(GpG)[Pt]	3′ (●)	22×10^{-2}	3.2
	5′ (o)	3×10^{-2}	23
d(pGpG)[Pt]	3′ (●)	3×10^{-2}	23
	5′ (o)	0.7×10^{-2}	97
$[Pt(NH_3)_2(5'\text{-GMP})_2]^{2-}$		1×10^{-2}	69.3
$[Pt(NH_3)_2(Guo)_2]^{2+}$		4.4×10^{-2}	15.8

[a] In these conditions, H(8) exchange for the free dinucleotides is undetectable or less than 5% (dpGpG) and 10% (dGpG) after 42 h. In each case the stability of the complex has been checked by recording its ^1H NMR spectrum after reprotonation and reacidification of the sample. [b] For the 3′ and 5′ assignments see text. See also Figures 4–6.

(iii) they can be removed by deuterium exchange with D_2O at basic pD (vide infra) (Chu et al., 1978; Chottard et al., 1980). Therefore, both N(7) of the diguanosine phosphates are coordinated to platinum. Each stoichiometric reaction gives a single mononuclear complex; the latter is an N(7)–N(7) chelate of the metal. The two other signals (which overlap for d(GpG)[Pt]) are assigned to the H(1′) protons. It is noteworthy that for GpG[Pt] one of them appears as a doublet and the other as a singlet (Figure 1). For free GpG and for the complexes *cis*-$[Pt(NH_3)_2(Guo)_2]^{2+}$ (Cramer & Dahlstrom, 1979) and *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]^{2-}$ (Chu et al., 1978), both H(1′) signals exhibit a $J_{1'2'}$ coupling. For d(pGpG)[Pt] (pD 1.9) (Figure 3) the lack of one $J_{1'2'}$ coupling is also observed for the 6.2-ppm signal.

For each of the three complexes studied, the two H(8) protons exhibit different chemical shifts, which show that they experience different environments. To get further information, we compared their rates of exchange with D_2O at pD 10 (Table II). For each dinucleotide complex one of the two H(8) protons is exchanged more slowly than the other. For d(pGpG)[Pt], one H(8) is more slowly exchanged than those of the other dinucleotide complexes and those of *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]^{2-}$. In the latter complex, with the two guanines in a head-to-tail arrangement (Marzilli et al., 1980; Kistenmacher et al., 1979), each H(8) proton is in the vicinity of a free 5′-phosphate. In basic conditions, the shielding of the H(8) by the anionic phosphate group slows down its deuterium exchange as shown by comparison with *cis*-$[Pt(NH_3)_2(Guo)_2]^{2+}$. The H(8) deuterium exchange data for the d(pGpG)[Pt] and *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]^{2-}$ complexes (Table II) allow us to assign the slowly exchanged proton of the former to the H(8)-5′ in the vicinity of the free 5′-phosphate. Moreover, the more labile H(8) of the d(pGpG)[Pt] complex is also more slowly exchanged than its analogues of the two other dinucleotide complexes.

The chemical shifts of the two H(8) protons of the N(7)–N(7)-coordinated dinucleotides are affected differently by a pD variation. In the three cases (Figures 4–6) two titration curves are obtained with different amplitudes of the chemical shift variation. This clearly appears for the d(GpG)[Pt] complex whose titration curves do not cross each other. In the case of d(pGpG)[Pt] one proton (O in Figure 6) actually experiences two successive titrations. The first one ($pK_a \sim 7.1$ in D_2O) corresponds to that of the free 5′-phosphate group, as shown by the similar titration observed for the H(8) protons of the *cis*-bis(5′-GMP) complex. It also appears that the second proton (●) is sensitive to the 5′-phosphate titration, but the corresponding chemical shift variation is small

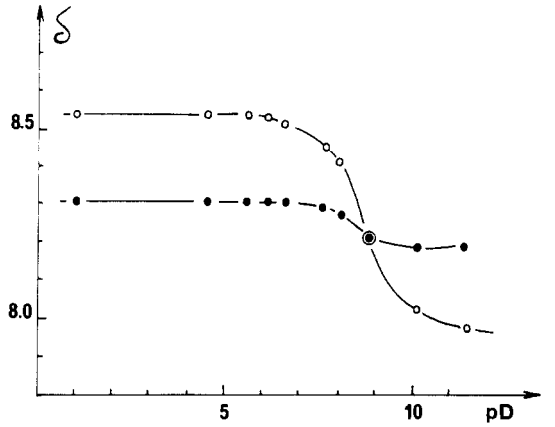

FIGURE 4: Variation of the chemical shifts of the H(8) protons vs. pD for GpG[Pt] (ca. 10^{-3} M). (●) H(8)-3′; (O) H(8)-5′.

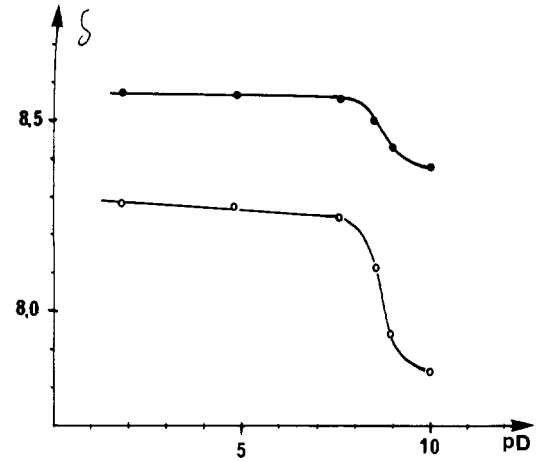

FIGURE 5: Variation of the chemical shifts of the H(8) protons vs. pD for d(GpG)[Pt] (2×10^{-3} M). (●) H(8)-3′; (O) H(8)-5′.

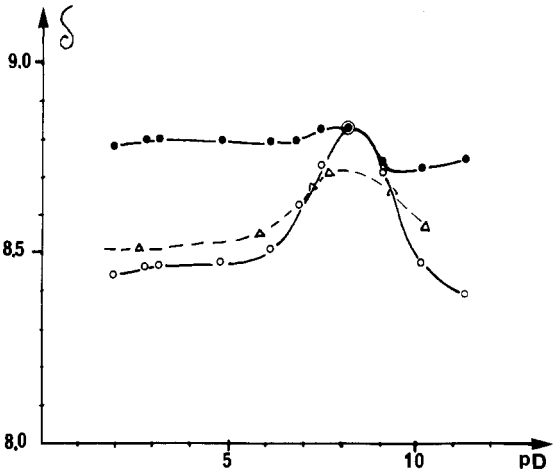

FIGURE 6: Variation of the chemical shifts of the H(8) protons vs. pD for d(pGpG)[Pt] (ca. 10^{-3} M) [(●) H(8)-3′; (O) H(8)-5′] and *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]$ (ca. 10^{-3} M) (△).

though reproducible. For this complex it is noteworthy that each H(8) proton has similar chemical shifts at both ends of the titration curve. The titration curves obtained for the three diguanosine phosphate complexes give a pK_a value of 8.6–8.8 (D_2O) for the apparent acid involved, which can be identified as the guanine N(1)H group (the 3′,5′-phosphate, with $pK_a \simeq 1$, cannot interfere). The differentiation of the two H(8) protons, based on their different deuterium exchange rates (Table II), allows us to assign the titration curve with the large chemical shift variation to the more slowly exchanged proton (O in Table II and Figures 4–6). The stability of each complex

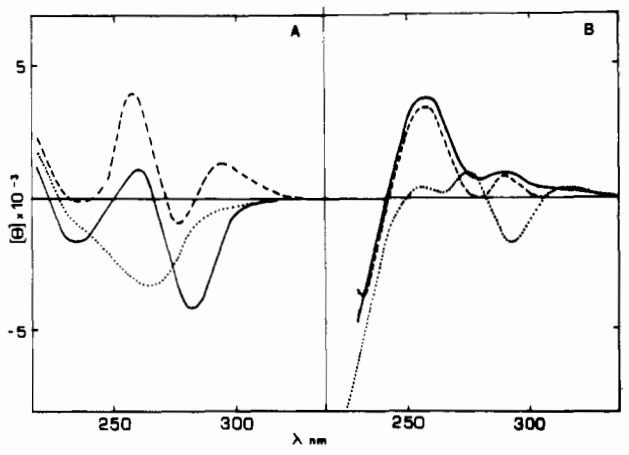

FIGURE 7: CD spectra of (A) d(GpG), 1.3×10^{-4} M, 0.05 M NaCl, 25 °C, at pH (—) 6.3, (--) 1.5, and (···) 11.4 and (B) d(GpG)[Pt], 1.7×10^{-4} M, 0.05 M NaCl, 25 °C, at pH (—) 7, (--) 1.7, and (···) 10.1.

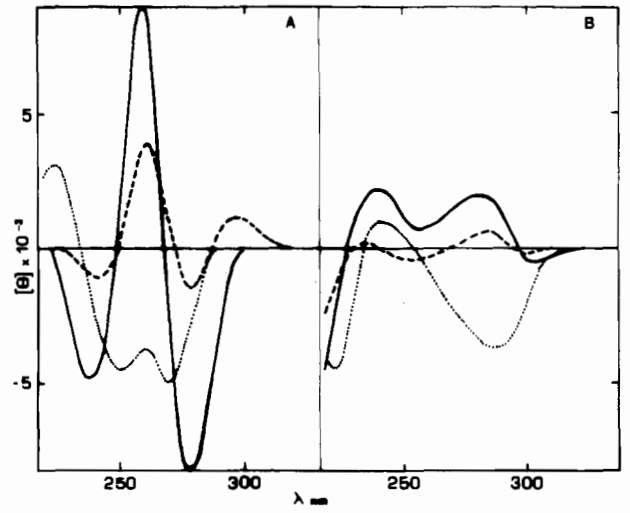

FIGURE 8: CD spectra of (A) d(pGpG), 1.5×10^{-4} M, 0.05 M NaCl, 25 °C, at pH (—) 6.5, (--) 1.2, and (···) 11.4 and (B) d(pGpG)[Pt], 1.8×10^{-4} M, 0.05 M NaCl, 25 °C, at pH (—) 6.3, (--) 1.8, and (···) 11.

to acidic and basic conditions has been checked, and it is noteworthy that the deoxy complexes are much more stable than the corresponding dinucleotides at acidic pH.

Preliminary investigations with the GpG[Pt] complexes have shown that the two H(1′) protons have the same T_1 relaxation time of 0.9 ± 0.1 s [that of the two H(8) protons being 0.5 ± 0.05 s]. After a complete H(8) deuterium exchange (sealed tube, 1.5 h at 80 °C), the two H(1′) protons have a relaxation time of 1.1 ± 0.1 s. In these experiments the water signal precluded the study of the H(2′) protons.

Circular Dichroism Analyses. The CD spectra of GpG and of GpG[Pt] at different pH values have been respectively reported by Ogasawara et al. (1975) and Zimmer et al. (1976) and by Chottard et al. (1980). Figures 7 and 8 give the corresponding data for d(GpG), d(GpG)[Pt] and d(pGpG), d(pGpG)[Pt], respectively. For the three free dinucleotides, the influence of pH on the CD spectra is comparable. At neutral and acidic pH values a negative band is observed at 277–280 nm. The couplet of d(pGpG) is more intense than those of the two other dinucleotides. In this case we have checked that the amplitude of the bisignated curve between λ_+ (259 nm) and λ_- (277 nm) is not affected when the concentration varies from 7×10^{-4} to 2×10^{-5} M, therefore excluding the contribution of intermolecular interactions. For the three platinum complexes at pH 6.5–7 the CD spectra exhibit two positive bands at 260–290 nm for GpG[Pt] and d(GpG)[Pt] and 240–280 nm for d(pGpG)[Pt]. At acidic pH values the same type of CD curve is observed for each complex. At pH >8 the spectra become different with the appearance of a negative band.

Discussion

All the preceding results point to an overall similarity between the three monomeric and mononuclear N(7)–N(7)-chelated complexes GpG[Pt], d(GpG)[Pt], and d(pGpG)[Pt].

The H(8) deuterium exchange data, for the d(pGpG)[Pt] complex, allowed us to assign the slowly exchanged proton to the H(8)-5′. Moreover, both the H(8)-5′ and H(8)-3′ exchange rates are decreased by the presence of the terminal 5′-phosphate, which implies that in the chelated complex the two guanines have an anti–anti configuration corresponding to a relative head-to-head arrangement of the bases.

The 20% increase of the T_1 relaxation time of the two H(1′) protons of GpG[Pt], after the complete deuterium exchange of the two H(8) protons, appears too small to suggest the existence of a guanine in a syn configuration (Neumann et al., 1979). Moreover, the identity of the relaxation times of the two H(1′) protons rules out syn–anti and anti–syn configurations for GpG[Pt]. The overall similarity of the spectral characteristics of the three diguanosine phosphate complexes studied leads to the conclusion that they all possess the same structure. They are N(7)–N(7) chelates of the metal with an anti–anti configuration of the bases and a right-handed screw turn of the stack. For the three complexes, the H(8)-5′ is the more slowly exchanged of the two H(8) protons at pD 10. From the examination of the Corey–Pauling–Koltun (CPK) models it appears as relatively hindered in the various conformations of the N(7)–N(7)-chelated complexes.

As previously noted for IpI[Pt] and GpG[Pt] (Chottard et al., 1980) the diguanosine phosphate complexes present a rather large decrease of the guanine N(1)H pK_a, down to 8.6–8.8 (D_2O) as compared to 9.8 (D_2O) for 5′-GMP (Izatt et al., 1971). Smaller decreases of 0.3 and 0.6 log unit have been reported respectively for the *cis*- and *trans*-bis(5′-GMP) complexes (Chu et al., 1978). N(1)H dissociation induces different NMR upfield shifts for the two H(8) protons of the diguanosine phosphate complexes (Figures 4–6). This difference could result from a modification of the ring current diamagnetic anisotropy effects, due to a change in the relative orientation of the adjacent guanines upon deprotonation. The H(8)-5′ appears as the most sensitive to this conformational change. Actually these upfield shifts are small for the two H(8) protons of the d(pGpG)[Pt] complex, if one compares the data at pD 1.9 and 11.3 (Figure 3). This is the result of the deshielding effect of the anionic free 5′-phosphate (Figures 6 and 3) (at pD 7.4 both signals are broad probably because the pD is close to the 5′-phosphate pK_a). This deshielding effect on both H(8) protons is in agreement with an anti–anti configuration.

For one of the H(1′) protons of the GpG[Pt] and d(pGpG)[Pt] complexes, we have noticed the absence of a $J_{1'2'}$ coupling (Figures 1 and 3). The same observation had been made for the IpI[Pt] and ApA[Pt] complexes (Chottard et al., 1980). The ribose coupling constants are sensitive to base stacking and backbone conformations (Davies, 1978). The absence of the ribose or of one of the deoxyribose H(1′)–H(2′) couplings appears characteristic of the N(7)–N(7)-chelated structure of the purine dinucleotide complexes. It suggests that in this type of complex one furanose ring adopts a particular puckered form. In the absence of a more detailed study

of this puckering, it looks as though this furanose adopts N-type conformations (Davies, 1978). Examination of the CPK models of the complexes suggests that N-type conformations of the 5′ ribose could relieve some of the strain imposed to the ribose–phosphate backbone by the N(7)–N(7) chelation of the metal.

The three diguanosine phosphate complexes, with the anti–anti arrangement of the purines, can be considered as simple models of the local structures that could result from an intrastrand cross-linking of two adjacent guanosines in DNA. CD studies have shown that binding of the *cis*-$Pt^{II}(NH_3)_2$ moiety to DNA, at low Pt/dinucleotide ratios, gives a characteristic enhancement of ellipticity at ca. 275 nm [Srivastava et al. (1978) and previous work cited therein; Macquet & Butour, 1978]. The CD spectra of the diguanosine phosphate complexes studied have a common characteristic feature. At neutral and acidic pH values the three of them present a broad positive band in the 275–290-nm region instead of the negative band that is always present for the free and protonated dinucleotides (Figures 7 and 8). This change in the CD spectra appears as directly related to the N(7)–N(7) chelation of the metal, because the spectra reported for solutions of GpG plus Zn^{2+} and Cu^{2+} (Zimmer et al., 1976) are similar to those of protonated GpG (Ogasawara et al., 1975). Very recently there has been a report of enhanced CD spectra observed for $[Pt(tn)(5'\text{-GMP})_2]^{2-}$ and $[Pt(tn)(5'\text{-dGMP})_2]^{2-}$ compared to $[Pt(tn)(Guo)_2]^{2+}$ and [Pt(dien)(5′-GMP)]. This enhancement has been related to that observed for platinated DNA (Marzilli & Chalilpoyil, 1980). However, X-ray structures determined for several IMP and GMP *cis*-bis(nucleotide)Pt^{II} complexes have shown that they possess a 2-fold axis of symmetry (Marzilli et al., 1980). Such a head-to-tail arrangement of the purines is certainly maintained in solution as observed for $[Pt(NH_3)_2(Guo)_2]^{2+}$ (Cramer & Dahlstrom, 1979), and it is different from that of adjacent anti–anti purines in a right-handed helical structure. In our cases the ellipticity increase, $\Delta[\theta]$ per nucleotide, at 275 nm and neutral pH, between the free dinucleotide and its complex can be respectively evaluated to 5.1×10^3 for GpG[Pt], 3.8×10^3 for d(GpG)[Pt], and 9.6×10^3 for d(pGpG)[Pt]. It does not seem possible to do any relevant quantitative correlation between the $\Delta[\theta]$ of such simple dinucleotide model complexes and those of platinated DNA ($\Delta[\theta] \sim 4 \times 10^3$) or poly(dG)·poly(dC) ($\Delta[\theta] \sim 5 \times 10^3$) at 275 nm (Woody, 1977).

In conclusion, ribose and deoxyribose diguanosine phosphates easily give N(7)–N(7) chelates of platinum with an anti–anti configuration of the bases. The CD spectra of these complexes exhibit an increase of ellipticity in the 275-nm region, which can be qualitatively related to the characteristic increases reported for platinated DNA and poly(dG)·poly(dC). These results are in favor of the hypothesis of intrastrand cross-linking of adjacent guanines, by the *cis*-$Pt^{II}(NH_3)_2$ moiety, after a local denaturation of DNA [Kelman & Peresie (1979) and previous work cited therein; Lippard, 1980].

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