

DNA-Intrastrand Guanine, Guanine Cross-Linking by Cisplatin: Comparison of Three Model Compounds with Head-Head Orientation of the Nucleobases

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Abstract: A series of *cis*-[(NH₃)₂PtG₂]X₂ complexes (G = 9-ethylguanine, coordinated to Pt through N7) with X = NO₃⁻ (1), Cl⁻ (2), 1/2SO₄²⁻ (3), 1/2Pt(CN)₄²⁻ (4), and ClO₄⁻ (5) have been prepared, and the crystal structures of 3 and 4 have been determined. *cis*-[(NH₃)₂PtG₂]SO₄·4H₂O (3) crystallizes in the triclinic space group *P*1̄ with *a* = 10.727 (3) Å, *b* = 10.769 (3) Å, *c* = 12.976 (3) Å, α = 111.52 (2)°, β = 90.15 (3)°, γ = 109.88 (2)°, *V* = 1297.47 Å³, *Z* = 2. *cis*-[(NH₃)₂PtG₂]-[Pt(CN)₄]-3H₂O (4) crystallizes also in the triclinic space group *P*1̄ with *a* = 12.026 (2) Å, *b* = 12.026 (3) Å, *c* = 10.745 (2) Å, α = 110.05 (2)°, β = 95.59 (2)°, γ = 88.46 (2)°, *V* = 1484.96 Å³, *Z* = 2. The structures were refined to *R* = 0.069 (3) and 0.034 (4) and *R*_w = 0.072 (3) and 0.035 (4) on the basis of 3433 (3) and 3766 (4) independent reflections with *F*_o ≥ 2σ*F*_o. In both compounds, the two 9-ethylguanine ligands are oriented head-to-head, as is the case with the previously studied Cl salt 2. A comparison of the structures of 2, 3, and 4 shows differences in the dihedral angles between the G planes (68–78°) and between G and Pt coordination planes (51–131°), leading to considerable variations in interbase distances within the complex, e.g., between the O4 atoms (3.4–4.1 Å) or the C9' atoms (6.3–7.6 Å). The Raman solid-state spectra can be divided into three classes which, according to the crystal structures of 2, 3, and 4, differ in the degree of intramolecular base overlap. Like the Cl salt, 2, 3, and 4 are "real" models for an intrastrand cross-link of *cis*-Pt^{II} with two adjacent guanine bases in DNA, which is believed to be the major cross-link. From the geometries of the three closely related complexes, details concerning the expected local distortion of DNA may be deduced.

Structural details of bis(guanine) complexes of *cis*-diammineplatinum(II) residues have evoked considerable interest due to the fact that the antitumor agent *cis*-(NH₃)₂PtCl₂ has been shown to preferentially form cross-links of this type with adjacent guanine bases. Evidence for this cross-link as the major product in the reaction of cisplatin with nucleic acids comes from studies on the enzymatic digestion of platinated DNA or DNA models,² chemical degradation of platinated DNA,³ and an immunological study,⁴ as well as ¹H NMR work with small oligonucleotides containing GG sequences flanked by other bases.⁵ In particular, aspects such as the degree of steric distortion of DNA as a consequence of the GG cross-link,⁶ its effect on duplex stability and base pairing,^{5a,c} and its stability toward strong nucleophiles such as cyanide⁷ are of interest. Another point of interest relates to findings that *cis*-[(NH₃)₂Pt(Guo)₂]Cl₂ (Guo = guanosine), despite being a charged complex, shows antitumor activity⁸ and has antiviral properties.⁹

If one reviews the published structures on bis(guanine)-*cis*-diammineplatinum(II) complexes,¹⁰ one finds that, with the ex-

ception of two structures published in 1984 by us,¹¹ the two purine bases always are oriented head-to-tail, leading to a C₂ molecular symmetry. In all cases, Pt coordination is through N₇ of the guanine ligand. The head-tail arrangement of the two bases is also observed if the N7-platinated guanine ligand becomes deprotonated at N1, e.g., in *cis*-(NH₃)₂Pt(G⁻)₂ (G = 9-ethylguanine).¹² Since a head-tail arrangement of two adjacent guanine bases seems to be rather unlikely in native DNA, the relevance of most bis(guanine) structures as a model for a GG cross-link may be questioned. It has been suggested that the head-tail orientation of two bases may be the thermodynamically most favorable situation¹³ and explain why, unlike in solution,¹⁴ where rotation about the Pt-N7 bond is possible, in the solid state this arrangement appears to be the preferred one. This property is common also to all the other known *cis*-bis(ligand) complexes of (NH₃)₂Pt^{II} and Cl₂Pt^{II}, e.g., with cytosine bases,¹⁵ 1-methyluracil,¹⁶ α-pyridone,¹⁷ substituted imidazoles,¹⁸ 1,3,9-trimethylxanthine,¹⁹ 7,9-dimethylhypoxanthine,²⁰ 9-methylhypoxanthine,²¹

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inosine 5'-monophosphate,²² and dinucleotide models with bridging CH₂ groups.²³ On the other hand, as has been shown by us in the case of bis(1-methyluracil) complexes, it is possible to force the two nucleobases into a head-head arrangement through coordination of a second metal which links the two bases.²⁴

It was the obvious exception of *cis*-[(NH₃)₂PtG₂]Cl₂ and *cis*-[(NH₃)₂PtG₂]Cl_{1.5}(HCO₃)_{0.5} with the unexpected head-head orientation of the two guanine rings¹¹ which prompted the work described here. Specifically, we were interested in finding out the effect of the counterion(s) on the mutual orientation of the bases, the degree of flexibility of the system, and in particular the distortion of DNA that might be expected for a G,G intrastrand cross-link.

Experimental Section

Preparation. *cis*-[(NH₃)₂PtG₂](NO₃)₂·2H₂O (**1**): Freshly prepared *cis*-[(NH₃)₂Pt(H₂O)₂](NO₃)₂ (2 mmol) and G (4 mmol) were reacted in water (suspension, 0.02 M Pt; 2 h, 60 °C; 12 h, 20 °C) and then filtered, and the precipitate (280 mg) was washed with 2 × 5 mL water. On slow evaporation of the filtrate (pH 3.5), 300 mg of **1** was collected. The combined precipitates were recrystallized from water to give colorless, transparent microcubes. Anal. Calcd for C₁₄H₂₈N₁₄O₁₀Pt: C, 22.49; H, 3.78; N, 26.23; Pt, 26.09. Found: C, 22.68; H, 3.76; N, 26.84; Pt, 26.1.

cis-[(NH₃)₂PtG₂]Cl₂·3H₂O (**2**) was prepared as previously described¹¹ or alternatively in 90% yield by passing **1** over an anion-exchange column in the Cl⁻ form and subsequent slow evaporating the filtrate.

cis-[(NH₃)₂PtG₂]SO₄·4H₂O (**3**) was both obtained in a way analogous to **1** (using Ag₂SO₄ instead of AgNO₃ to prepare the diaqua species) in 95% yield and by treating **2** with the calculated amount of Ag₂SO₄ (40 h at 40 °C), filtering AgCl, and slow evaporating at 30 °C (yield 85%). Crystals suitable for X-ray work were obtained on recrystallization from water. Anal. Calcd for C₁₄H₃₂N₁₂O₁₆SPt: C, 22.25; H, 4.28; N, 22.25; S, 4.25; Pt, 25.81. Found: C, 22.85; H, 4.37; N, 22.63; S, 3.92; Pt, 25.3 (better fit for trihydrate).

cis-[(NH₃)₂PtG₂][Pt(CN)₄]·3H₂O (**4**) originally was isolated from an aqueous solution of **1** or **2** to which KCN (2 equiv per Pt) had been added.²⁵ Alternatively, **4** was obtained by treating an aqueous solution of **2** (0.008 M Pt) with 1 equiv of K₂Pt(CN)₄·3H₂O at 60 °C. From the filtered, clear solution, crystals of **4** formed on slow cooling. After filtration of the first crystalline batch, more material precipitated on slow evaporation of the solution in air: total yield 78%. Anal. Calcd for C₁₈H₃₀N₁₆O₃Pt₂: C, 22.98; H, 3.22; N, 23.83; Pt, 41.47. Found: C, 22.94; H, 3.18; N, 24.32; Pt, 41.4.

cis-[(NH₃)₂PtG₂](ClO₄)₂·H₂O (**5**) was prepared as previously described.²⁶

Spectra. Infrared spectra were recorded on a Perkin-Elmer 580 grating spectrometer from KBr pellets and Nujol mulls (CsJ windows). Raman spectra were taken on a Coderg PH 1 with Krypton laser excitation (647.1 nm, 100–700-mW power, depending on sample stability in the laser beam). Wavenumber calibration was achieved by means of indene. Spectral slit widths were as indicated; scan rates usually were 10 cm⁻¹ min⁻¹.

Crystallography. X-ray measurements were carried out at room temperature on a Philips-PW 1100 single-crystal diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71069 Å). The dimensions of the crystals used were 0.3, 0.3, 0.3 mm (**3**) and 0.2, 0.2, 0.2 mm (**4**). Both compounds crystallize in the triclinic space group P $\bar{1}$ with Z = 2. Crystal data for **3** are as follows: a = 10.727 (3) Å, b = 10.769 (3) Å, c = 12.976 (3) Å, α = 111.52 (2)°, β = 90.15 (3)°, γ = 109.88 (3)°, V = 1294.47 Å³, ρ_{calcd} = 1.931, ρ_{obsd} = 1.95 g cm⁻³. Crystal data for **4** are as follows: a = 12.026 (2) Å, b = 12.292 (3) Å, c = 10.745 (2) Å, α = 110.05 (2)°, β = 95.59 (2)°, γ = 88.46 (2)°, V = 1484.96 Å³, ρ_{calcd} = 2.104, ρ_{obsd} = 2.08 g cm⁻³. The cell parameters of **3** and of **4** were calculated from 35 reflections ((**3**) 24° < 2θ < 37°; (**4**) 28° <

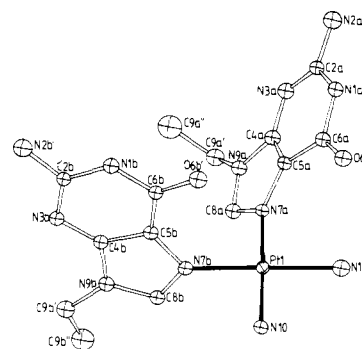


Table I. Positional Parameters and Temperature Factors (\AA^2) for **3** and **4**^a

3					4				
atom	X	Y	Z	U	atom	X	Y	Z	U
Pt1	0.6776 (1)	-0.0343 (1)	0.4034 (1)	0.021 (1)	Pt1	0.0432 (1)	0.2111 (1)	0.0665 (1)	0.026 (1)
N10	0.7060 (12)	0.0479 (13)	0.5683 (10)	0.025 (3)	N11	-0.1266 (5)	0.1935 (6)	0.0504 (7)	0.033 (2)
N11	0.6836 (14)	0.1532 (15)	0.3940 (12)	0.037 (3)	N10	0.0452 (6)	0.2087 (6)	0.2561 (7)	0.039 (2)
N1a	0.3898 (13)	-0.1203 (13)	0.0529 (11)	0.029 (3)	N1a	0.1833 (5)	-0.0266 (6)	-0.3800 (7)	0.034 (2)
C2a	0.4215 (15)	-0.1987 (15)	-0.0455 (12)	0.027 (3)	C2a	0.1563 (6)	0.0155 (7)	-0.4814 (8)	0.032 (2)
N2a'	0.3441 (15)	-0.2307 (15)	-0.1412 (12)	0.042 (4)	N2a'	0.1942 (6)	-0.0514 (7)	-0.6017 (8)	0.050 (2)
N3a	0.5213 (14)	-0.2432 (14)	-0.0526 (11)	0.034 (3)	N3a	0.0949 (5)	0.1105 (6)	-0.4669 (7)	0.036 (2)
C4a	0.5871 (16)	-0.2062 (16)	0.0486 (13)	0.031 (4)	C4a	0.0645 (6)	0.1639 (7)	-0.3414 (8)	0.032 (2)
C5a	0.5628 (15)	-0.1367 (15)	0.1541 (12)	0.025 (3)	C5a	0.0878 (6)	0.1296 (7)	-0.2322 (8)	0.030 (2)
C6a	0.4601 (16)	-0.0771 (16)	0.1591 (13)	0.029 (3)	C6a	0.1505 (6)	0.0262 (7)	-0.2493 (8)	0.032 (2)
O6a'	0.4298 (11)	-0.0014 (11)	0.2444 (9)	0.035 (3)	O6a'	0.1773 (5)	-0.0185 (5)	-0.1650 (6)	0.040 (1)
N7a	0.6526 (12)	-0.1194 (12)	0.2391 (10)	0.022 (3)	N7a	0.0401 (5)	0.2106 (6)	-0.1222 (7)	0.031 (2)
C8a	0.7337 (16)	-0.1914 (16)	0.1788 (13)	0.031 (4)	C8a	-0.0070 (7)	0.2899 (7)	-0.1645 (9)	0.036 (2)
N9a	0.6973 (13)	-0.2439 (13)	0.0635 (11)	0.031 (3)	N9a	0.0045 (5)	0.2636 (6)	-0.2975 (7)	0.032 (2)
C9a'	0.7588 (18)	-0.3236 (19)	-0.0223 (15)	0.043 (4)	C9a'	-0.0383 (8)	0.3290 (8)	-0.3824 (10)	0.048 (2)
C9a''	0.6846 (25)	-0.4814 (28)	-0.0608 (22)	0.075 (7)	C9a''	-0.0908 (10)	0.4463 (11)	-0.3041 (12)	0.069 (3)
N1b	0.3645 (13)	-0.5303 (13)	0.3416 (10)	0.030 (3)	N1b	0.3834 (6)	0.0076 (6)	0.1617 (7)	0.039 (2)
C2b	0.4230 (15)	-0.6277 (15)	0.3366 (12)	0.024 (3)	C2b	0.4848 (7)	0.0615 (7)	0.1628 (8)	0.034 (2)
N2b'	0.3399 (15)	-0.7646 (16)	0.3093 (12)	0.042 (3)	N2b'	0.5779 (6)	0.0016 (7)	0.1766 (8)	0.045 (2)
N3b	0.5560 (12)	-0.5927 (13)	0.3562 (10)	0.026 (3)	N3b	0.4929 (6)	0.1626 (6)	0.1497 (7)	0.037 (2)
C4b	0.6222 (15)	-0.4547 (15)	0.3783 (12)	0.026 (3)	C4b	0.3928 (7)	0.2064 (7)	0.1252 (8)	0.034 (2)
C5b	0.5728 (15)	-0.3474 (16)	0.3833 (12)	0.026 (3)	C5b	0.2902 (6)	0.1573 (7)	0.1134 (8)	0.027 (2)
C6b	0.4316 (15)	-0.3887 (15)	0.3686 (12)	0.024 (3)	C6b	0.2806 (6)	0.0550 (7)	0.1439 (8)	0.029 (2)
O6b'	0.3669 (11)	-0.3072 (12)	0.3759 (9)	0.037 (3)	O6b'	0.1945 (4)	0.0066 (5)	0.1583 (6)	0.037 (1)
N7b	0.6807 (13)	-0.2170 (13)	0.4097 (10)	0.026 (3)	N7b	0.2095 (5)	0.2303 (6)	0.0859 (7)	0.031 (2)
C8b	0.7896 (15)	-0.2434 (16)	0.4214 (12)	0.027 (3)	C8b	0.2642 (7)	0.3209 (8)	0.0840 (9)	0.040 (2)
N9b	0.7611 (13)	-0.3852 (13)	0.4041 (11)	0.030 (3)	N9b	0.3770 (6)	0.3107 (6)	0.1080 (7)	0.039 (2)
C9b'	0.8571 (18)	-0.4509 (18)	0.4130 (14)	0.039 (4)	C9b'	0.4601 (9)	0.4010 (9)	0.1306 (11)	0.059 (3)
C9b''	0.9966 (23)	-0.3700 (24)	0.4039 (19)	0.064 (6)	C9b''	0.4471 (12)	0.4911 (13)	0.2675 (15)	0.093 (4)
S1	1.0049 (4)	0.2152 (5)	0.2454 (4)	0.038 (4)	Pt2	-0.2586 (1)	0.5635 (1)	0.2812 (1)	0.037 (1)
O10	1.0172 (28)	0.1081 (28)	0.1487 (23)	0.138 (9)	C1	-0.2626 (8)	0.6523 (9)	0.4733 (11)	0.052 (3)
O11	1.0955 (17)	0.3531 (17)	0.2543 (14)	0.075 (4)	N1	-0.2646 (9)	0.7003 (10)	0.5852 (12)	0.086 (3)
O12	0.8716 (20)	0.2083 (20)	0.2464 (16)	0.093 (5)	C2	-0.3258 (8)	0.6992 (8)	0.2425 (10)	0.046 (2)
O13	1.0512 (24)	0.1878 (24)	0.3392 (20)	0.117 (7)	N2	-0.3681 (8)	0.7752 (9)	0.2237 (10)	0.071 (3)
O20	0.8428 (17)	0.0623 (18)	-0.0445 (14)	0.078 (5)	C3	-0.2502 (7)	0.4693 (8)	0.0879 (10)	0.042 (2)
O21	0.0401 (22)	0.9313 (24)	0.3349 (19)	0.108 (7)	N3	-0.2486 (7)	0.4113 (7)	-0.0201 (9)	0.055 (2)
O22	0.9670 (25)	0.4418 (25)	0.110 (21)	0.125 (8)	C4	-0.2006 (8)	0.4287 (9)	0.3239 (10)	0.049 (2)
O23	0.0493 (37)	0.7305 (38)	0.1497 (31)	0.196 (14)	N4	-0.1714 (8)	0.3466 (9)	0.3483 (10)	0.072 (3)
					O10	0.3737 (7)	0.7897 (7)	0.2064 (8)	0.074 (2)
					O11	0.6814 (7)	0.2222 (8)	0.4742 (9)	0.088 (3)
					O12	0.4639 (13)	0.1352 (13)	0.4832 (16)	0.184 (6)

^a Anisotropic temperature factors for Pt and S are given in the supplementary material.

sulfate, or N of the tetracyanoplatinate. In addition, the guanine protons at N1 and at the exocyclic amino group act as proton donors in hydrogen bonds with water oxygens and the cyano groups.

A point of interest in the crystal structures of all four crystallographically studied bis(9-ethylguanine) complexes is the orientations of the ethyl groups of the guanine ligands. In all cases, the ethyl group of one guanine ligand is roughly coplanar with the endocyclic atoms of the ring, while CH₃ of the ethyl group of the second guanine is substantially outside the plane of the rest of the ring and either bent toward the second ring (Cl⁻, Cl⁻/HCO₃⁻, and SO₄²⁻) or away from it (Pt(CN)₄²⁻). The differences in the relative orientation of the C9'' groups are responsible for different degrees of base overlap as previously discussed.¹¹ While there is intermolecular base stacking of 3.3–3.4 Å between rings having C9'' either coplanar with the ring or pointing away from each other, the intermolecular base–base distance is much too long for any stacking interaction if the C9'' groups are pointing toward each other.

Comparison of Structures. In Figure 2, conformational drawings of **2**, **3**, and **4** are given. The structure of the mixed Cl⁻/HCO₃⁻ compound is not included because it is rather similar to **2**. Table IV reports conformational parameters of all three compounds. The dihedral angles listed conform to the convention introduced by Kistenmacher et al.^{15a,36} As can be seen from the conformational

drawings, the cation geometries of **2** (Cl⁻) and **4** (Pt(CN)₄²⁻) resemble each other more than that of **3** (SO₄²⁻). In a simplified representation, the principal difference between the two types is shown in Figure 3. It visualizes the different degrees of intramolecular base overlap, which is larger in **2** and **4** than in **3**. The data listed in Table IV reflect the rather large flexibility of the overall geometry in the bis(base) complexes: even though the dihedral angles between the two rings differ relatively little (68–76°), the dihedral angles between the rings and the Pt coordination planes are extremely variable (51–131°), leading to variations in the intramolecular separations of the O6 sites (3.4–4.1 Å) and the C9' atoms (6.3–7.6 Å). Since, with nucleotides, the distances between the C9' sites represent the glycoside bond separation (ca. 6.5 Å 2(B-DNA), the values suggest that an arrangement as observed in **2** (6.25 Å) or **3** (6.45 Å) would probably fit better into DNA than that of **4** (7.59 Å). Moreover, the deviations of Pt from the guanine planes are variable: while in **4**, the Pt is almost coplanar with both rings, Pt is out of the plane of one of the two guanine rings in **3** by 0.36 Å, corresponding to a 10° deviation from coplanarity.

Vibrational Spectra. IR and Raman spectra of solid samples of compounds **1–5** have been recorded and compared. Apart from the expected differences due to different counterions, differences in the positions of a number of bands and in particular in relative intensities are observed. This is to be seen especially well in the Raman spectra. These can be qualitatively divided in three groups: **1** and **2**; **4**; **3** and **5**, with the first two groups having a greater similarity with each other than with the third one. In Figure 4, sections of the Raman solid-state spectra are shown which contain

(36) Kistenmacher, T. J.; Orbell, J. D.; Marzilli, L. G. In "Platinum, Gold, and Other Metal Chemotherapeutic Agents"; Lippard, S. J., Ed.; American Chemical Society: Washington, DC, 1983; ACS Symp. Ser. No. 209, p 191.

Table II. Interatomic Distances (Å) and Angles (deg) of *cis*-[(NH₃)₂PtG₂](SO₄)·4H₂O (**3**) and *cis*-[(NH₃)₂PtG₂][Pt(CN)₄]₂·3H₂O (**4**)

	3		4	
(I) Pt Coordination Sphere				
Pt1-N10	1.970 (12)		2.046 (7)	
Pt1-N11	2.047 (14)		2.044 (6)	
Pt1-N7a	1.962 (11)		2.022 (7)	
Pt1-N7b	2.010 (12)		2.002 (6)	
N10-Pt1-N11	93.2 (5)		87.8 (3)	
N10-Pt1-N7a	178.3 (4)		178.9 (3)	
N10-Pt1-N7b	87.8 (5)		91.8 (3)	
N11-Pt1-N7a	88.1 (5)		91.3 (3)	
N11-Pt1-N7b	177.1 (5)		179.0 (2)	
N7a-Pt1-N7b	90.9 (5)		89.2 (3)	
	3		4	
	ring a	ring b	ring a	ring b
(II) Guanine Ligands				
N1-C2	1.365 (20)	1.377 (19)	1.367 (10)	1.401 (10)
C2-N2'	1.356 (21)	1.348 (20)	1.386 (11)	1.377 (10)
C2-N3	1.305 (20)	1.343 (19)	1.335 (10)	1.304 (10)
N3-C4	1.342 (21)	1.328 (19)	1.364 (11)	1.345 (10)
C4-C5	1.374 (21)	1.408 (20)	1.379 (11)	1.365 (11)
C5-C6	1.442 (21)	1.416 (21)	1.426 (11)	1.414 (11)
C6-O6'	1.230 (18)	1.271 (18)	1.225 (9)	1.256 (9)
C6-N1	1.404 (20)	1.351 (19)	1.420 (10)	1.377 (10)
C5-N7	1.379 (19)	1.403 (19)	1.418 (10)	1.382 (10)
N7-C8	1.410 (19)	1.313 (19)	1.305 (10)	1.316 (10)
C8-N9	1.392 (20)	1.381 (19)	1.373 (11)	1.367 (11)
N9-C4	1.408 (20)	1.395 (20)	1.367 (10)	1.363 (11)
N9-C9'	1.449 (22)	1.459 (21)	1.460 (12)	1.455 (12)
C9'-C9''	1.493 (31)	1.484 (28)	1.552 (15)	1.528 (17)
C6-N1-C2	124.6 (13)	125.0 (13)	123.8 (7)	123.4 (7)
N2'-C2-N1	117.3 (13)	116.8 (13)	114.2 (7)	115.8 (7)
N2'-C2-N3	118.5 (14)	119.8 (13)	122.9 (8)	119.9 (7)
N1-C2-N3	124.2 (14)	123.4 (13)	122.8 (8)	124.2 (7)
C2-N3-C4	111.9 (13)	111.5 (12)	114.3 (7)	112.6 (7)
N9-C4-N3	122.9 (14)	125.2 (13)	126.9 (7)	124.8 (7)
N9-C4-C5	106.1 (13)	105.1 (13)	105.5 (7)	107.6 (7)
N3-C4-C5	130.9 (14)	129.6 (14)	127.6 (7)	127.6 (8)
N7-C5-C4	114.0 (13)	109.3 (13)	108.6 (7)	108.9 (7)
N7-C5-C6	129.8 (13)	134.4 (13)	133.7 (7)	131.0 (7)
C4-C5-C6	115.6 (13)	116.2 (13)	117.7 (7)	119.6 (7)
O6'-C6-C5	126.3 (14)	126.3 (14)	127.0 (8)	129.2 (7)
O6'-C6-N1	121.4 (14)	119.7 (13)	119.4 (7)	119.0 (7)
C5-C6-N1	112.2 (13)	113.9 (12)	113.6 (7)	111.8 (7)
Pt1-N7-C5	135.8 (10)	127.9 (10)	128.8 (5)	128.2 (5)
Pt1-N7-C8	122.3 (9)	125.0 (10)	124.6 (6)	126.0 (6)
C5-N7-C8	101.8 (11)	106.2 (12)	106.6 (7)	105.7 (7)
N7-C8-N9	112.4 (13)	112.1 (13)	110.2 (7)	112.0 (8)
C9'-N9-C8	126.7 (13)	126.8 (13)	127.2 (7)	126.1 (8)
C9'-N9-C4	127.7 (13)	125.9 (13)	123.7 (7)	127.3 (7)
C8-N9-C4	105.6 (12)	107.3 (12)	109.1 (7)	105.9 (7)
C9''-C9'-N9	111.3 (16)	114.6 (15)	113.1 (8)	107.4 (9)
	3		4	
(III) Anions				
S1-O10	1.402 (27)	Pt2-C1	1.982 (11)	
S1-O11	1.434 (17)	Pt2-C2	1.987 (10)	
S1-O12	1.407 (20)	Pt2-C3	2.012 (10)	
S1-O13	1.475 (24)	Pt2-C4	1.959 (10)	
		C1-N1	1.146 (13)	
		C2-N2	1.120 (12)	
		C3-N3	1.136 (11)	
		C4-N4	1.164 (12)	

three of the four most intense and at the same time highly characteristic guanine modes³⁷ around 1580, 1500, and 1380 cm⁻¹. The high intensity of the latter in the spectra of the SO₄²⁻ and ClO₄⁻ salts is in marked contrast to the other spectra. We attribute it to the very much reduced intramolecular base overlap between the two rings in the case of the SO₄²⁻ salt, **3**, as compared to **2**

(37) (a) Delabar, J. M.; Majoube, M. *Spectrochim. Acta* **1978**, *34A*, 129. (b) Lord, R. L.; Thomas, G. J. *Ibid.* **1967**, *23A*, 2551.

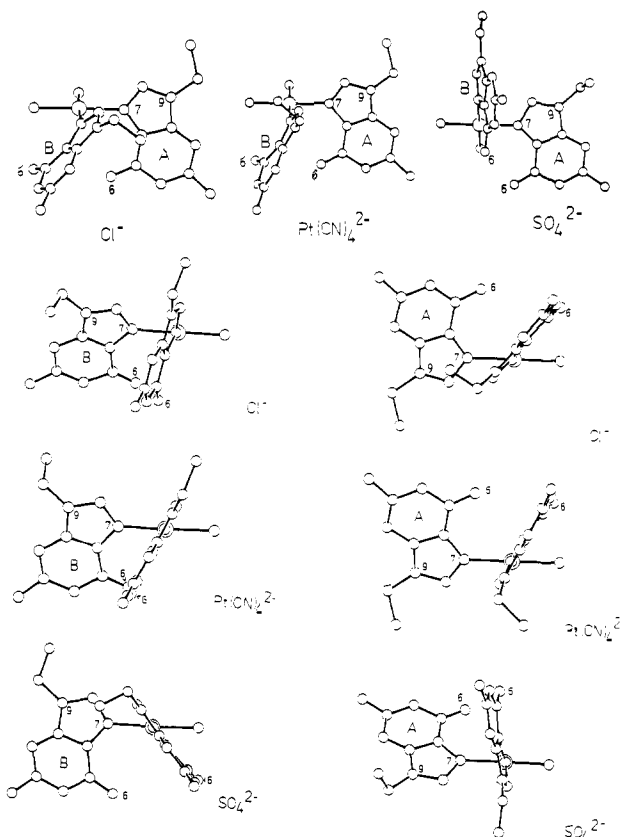


Figure 2. Conformational drawings of three *cis*-[(NH₃)₂PtG₂]²⁺ cations: (a, top) Ligand A is placed in the paper plane and the N(7A)-Pt vector is leftward. (b, bottom) Determination of dihedral angles between the Pt coordination plane and the G planes by placing one Pt-N7 vector perpendicular to the paper plane and the second one pointing to the left.

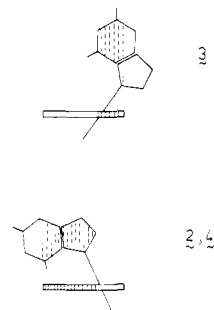


Figure 3. Simplified representation of the difference between the sulfate salt **3** and chloride and tetracyanoplatinate(II) salts **2** and **4**, indicating the differences in base overlap.

and **4**, rather than to differences in intermolecular base stacking in the three types of complexes. While intermolecular base stacking causes a Raman hypochromic effect,³⁸ leading to a decrease in signal intensity which, with guanine for example, also influences the above-mentioned bands,³⁹ intermolecular base stacking in the solid state does not exceed the dimer level. It is hard to imagine that stacking of two bases can cause a hypochromic effect large enough to reduce the intensity of the 1380-cm⁻¹ band in **1**, **2**, and **4** to 50% of that in **3** and **5**. This interpretation is supported by the similarity between solution spectra (H₂O; Me₂SO) (Figure 5) and the solid-state spectra of **2**: even though there is stacking between the B rings in solid **2** (3.37 (2) Å), yet no stacking in solution (vide infra), the intensity patterns are rather similar.

There are three arguments pointing against any significant intercomplex stacking of *cis*-[(NH₃)₂PtG₂]²⁺ cations in solution:

(38) Tomlinson, B. L.; Peticolas, W. L. *J. Chem. Phys.* **1970**, *52*, 2154. (39) Small, E. W.; Peticolas, W. L. *Biopolymers* **1971**, *10*, 1377.

Table III. Possible Hydrogen Bonding Interactions (Distances in Å, Angles in deg) in **3** and **4**^a

3				4			
O6a'-N11	2.91	Pt-N11-O6a'	90	(I) Intramolecular			
				O6b'-N10	2.97	Pt1-N10-O6b'	108
				(II) Intermolecular			
N10-O6b' ¹	2.99	Pt1-N10-O6b' ¹	103	N11-O6a' ⁸	2.92	Pt1-N11-O6a' ⁸	108
N11-O6b' ¹	2.99	Pt1-N11-O6b' ¹	101	N11-O6b' ⁸	2.78	Pt1-N11-O6b' ⁸	110
N10-O21 ²	2.90	Pt1-N10-O21 ²	113	N10-N1 ⁹	3.02	Pt1-N10-N1 ⁹	111
N11-O12	2.85	Pt1-N11-O12	106	N10-N4	3.12	Pt1-N10-N4	101
N1a-O20 ³	2.78	C2a-N1a-O20 ³	118	N1a-O11 ³	2.81	C2a-N1a-O11 ³	108
O11-N1b ⁴	2.77	S1-O11-N1b ⁴	125	N1b-O10 ¹⁰	2.89	C2b-N1b-O10 ¹⁰	122
O13-N2b ⁴	3.01	O13-N2b'-C2b ⁴	117	N2a'-O11 ³	3.15	C2a-N2a'-O11 ³	120
				O6a'-N2b' ³	2.98	C6a-O6a'-N2b' ³	95
				O6b'-N2a' ¹¹	2.90	C6b-O6b'-N2a' ¹¹	117
O10-O20	2.91	S1-O10-O20	110	N2-O10 ¹²	3.10	C2-N2-O10 ¹²	119
O11-O22	2.91	S1-O11-O22	107	N4-O11 ¹²	3.06	C4-N4-O11 ¹²	123
O21-O13 ⁵	2.70	O21-O13-S1 ⁵	127				
O22-O23 ⁶	3.18			O11-O12	2.88		
O21-O23	2.61						
O22-O23 ⁷	2.77						
O20-O23 ⁶	2.94						

^aSymmetry transformations: ¹1 - x, -y, 1 - z. ²1 - x, 1 - y, 1 - z. ³1 - x, -y, -z. ⁴x + 1, y + 1, z. ⁵x - 1, y + 1, z. ⁶1 - x, 1 - y, -z. ⁷x + 1, y, z. ⁸-x, -y, -z. ⁹-x, 1 - y, 1 - z. ¹⁰x, -1 + y, z. ¹¹x, y, 1 + z. ¹²-1 + x, y, z.

Table IV. Conformational Parameters of *cis*-[(NH₃)₂Pt(9-EtG)₂]X₂ Complexes

	2 (Cl ⁻) ^b	3 (SO ₄ ²⁻)	4 (Pt(CN) ₄ ²⁻)
(I) Dihedral Angles (deg) between Planes ^a			
Pt coord plane/G plane a	104.6 ^c	51.0	116.6
Pt coord plane/G plane b	130.8 ^c	80.0	118.9
G plane a/G plane b	68.0	75.4	78.0
(II) Deviations (Å) of Pt from Guanine Planes			
from plane a	0.20	0.08	0.00
from plane b	0.12	0.36	0.02
(III) Selected Intracomplex Distances, Å			
N(7a)-N(7b)	2.81	2.83	2.83
O(6a')-O(6b')	3.76	4.10	3.37
C(9a')-C(9b')	6.25	6.45	7.59

^aEquations given in the supplementary material, together with deviations of atoms from best planes. ^bFrom ref 11. ^cAngles defined according to the convention introduced by Kistenmacher et al.^{15a,36}

Firstly, the Raman solution spectra in water do not show any changes in relative and absolute intensities of the individual signals between +20 and +80 °C. Secondly, the ¹H NMR spectra (D₂O, 30 °C) give no indication of any significant intercomplex base stacking. In the concentration range 0.2–0.01 M G, the H8 resonance has no concentration dependency, with a very small shift for CH₃ (0.02 ppm) and CH₂ (0.05 ppm) only, in agreement with similar results observed with N7-platinated 9-methyladenine.⁴⁰ Thirdly, the similarity between the intensity patterns in the two different solvents, with H₂O in principle favoring stacking and Me₂SO preventing stacking, also points against any large effects of intermolecular stacking on the intensities of the Raman modes.

G,G Cross-Link and DNA Distortion. All four structurally characterized bis(9-ethylguanine) complexes have in common the rather large dihedral angle between the two base planes of 72 ± 4° and the short N7–N7 distance of 2.82 Å (av). While these two alterations—displacement of the two bases from a normally coplanar arrangement to a tilted one and shortening of the N7–N7 distance from 3.9 Å in DNA⁴¹ by more than 1 Å—are dramatic at their own, when combined they actually counterbalance each other in part as far as the effect on DNA is concerned: It explains why the O6–O6 separation within the complex is only moderately altered (see Table IV) as compared to two parallel guanines in a DNA strand, where this distance is estimated to be around 3.5–3.6 Å. One might expect that apart from changes

(40) Beyerle-Pfnür, R.; Lippert, B., unpublished results.

(41) Arnott, S.; Hukins, D. W. L. *Biochem. Biophys. Res. Commun.* **1972**, *47*, 1504.

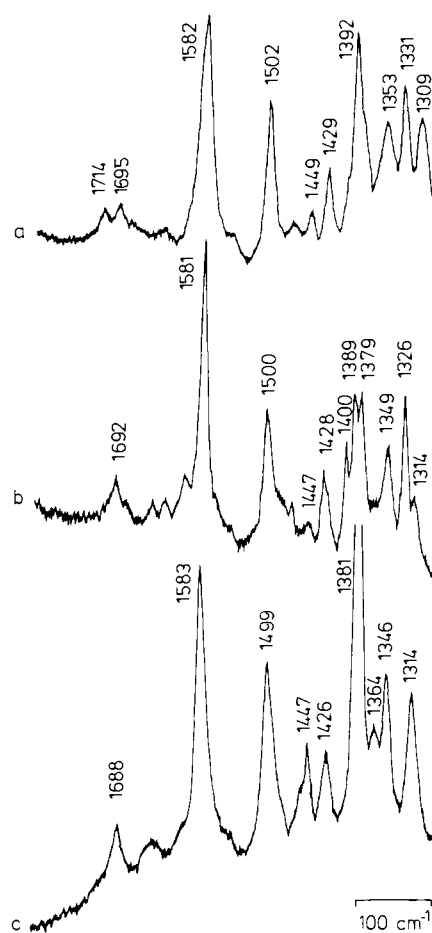


Figure 4. Raman solid state spectra between 1300 and 1800 cm⁻¹ of (a) the Cl⁻ salt **2**, (b) the [Pt(CN)₄]²⁻ salt **4**, and (c) the [SO₄]²⁻ salt **3**. The NO₃⁻ salt **1** has a Raman spectrum virtually identical with that of **2** in the range shown; the spectrum of the ClO₄⁻ salt **5** looks very similar to that of **3**.

due to electronic reasons,²⁶ which could weaken hydrogen bonds with cytosines at the opposite DNA strand, the steric conditions for such a hydrogen-bonding interaction are not as severely disturbed in the G,G complex as it looks at first glance. Indeed, NMR results obtained with a decamer DNA fragment having the two central guanines platinated indicate that at least at low

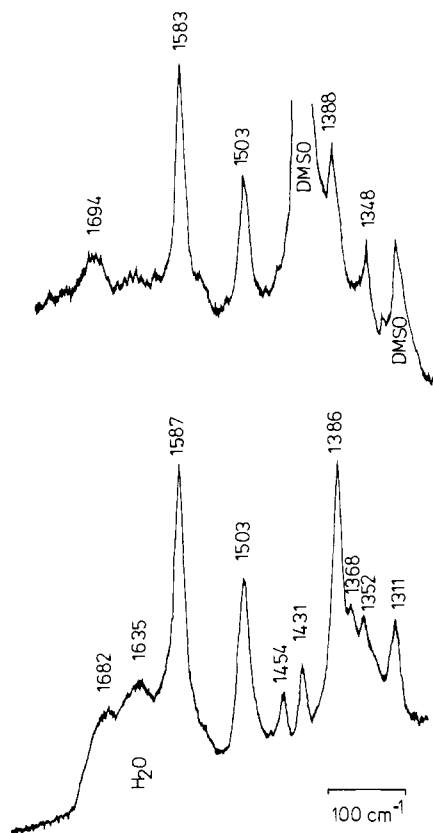


Figure 5. Raman solution spectra of the ClO_4^- salt **5** in Me_2SO (0.2 M Pt, resolution 2 cm^{-1}) (top) and of the sulfate **3** in H_2O (0.07 M Pt, resolution 4 cm^{-1}) (bottom). The choice of the anion has no effect on the spectrum in H_2O in the range depicted.

temperatures, base pairing is maintained.^{5c} Nevertheless, a severe distortion of base stacking in DNA as a consequence of G,G cross-linking is to be expected. In Figure 6, the arrangements are compared between two 9-ethylguanines placed parallel as two guanines in DNA (A) and the two 9-ethylguanines cross-linked by *cis*-(NH_3)₂Pt^{II} (B and C). The tilting of the bases, together with their head-head arrangement, results in the solid state in a pseudohelicity with respect to the mutual orientation of the C9' atoms of both bases as depicted in Figure 6 for the $\text{Pt}(\text{CN})_4^{2-}$ (B) and the SO_4^{2-} salts (C). The pseudohelical orientation of the two guanines is the more pronounced, the more the dihedral angle between the G planes and the Pt coordination plane deviates from 90° , a situation given in all G,G complexes studied in this work. Due to the relatively unhindered rotation of the bases about the Pt-N(7) bonds, an interconversion of both pseudoenantiomers is expected in solution. Furthermore, it should be noted that within the crystal, both pseudoenantiomers are present in equal amounts. With respect to the handedness of the DNA helix, Figure 6 demonstrates that the model cross-links studied might be accommodated both in right- and left-handed DNA. In either case, the helix continuity of this type of cross-link is expected to be

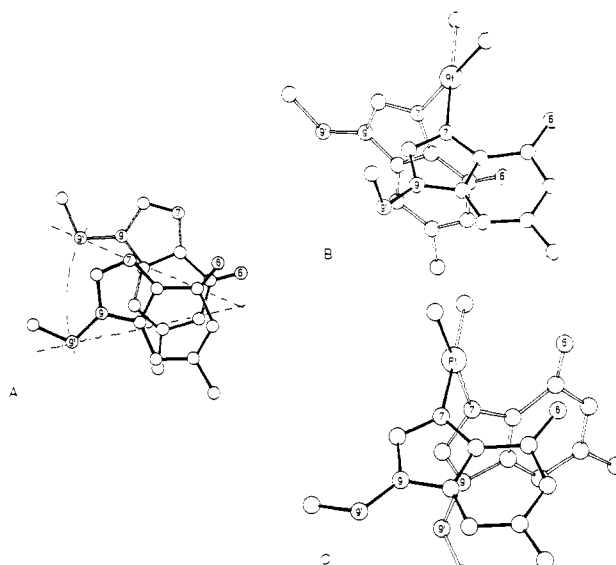


Figure 6. View along an imaginary helix axis of DNA with two parallel guanines rotated by 36° (A) and with the two guanines cross-linked by *cis*-(NH_3)₂Pt^{II} as in the $[\text{Pt}(\text{CN})_4]^{2-}$ compound **4** (B) and the SO_4^{2-} compound **3** (C).

affected by forcing two adjacent bases (and probably neighboring bases as well) in a strongly tilted orientation.

If one compares our models with a model proposed by den Hartog et al.,⁶ which is based on a NMR conformational analysis of a GpG complex of cisplatin in solution, one finds differences which refer in particular to the dihedral angles of the G planes (53° in GpG-Pt vs. 72° (av) in our compounds) and the deviations of Pt from coplanarity with guanine (estimated 0.56 and 0.65 \AA in GpG-Pt vs. a maximum of 0.36 \AA in one out of eight G planes in our compounds). Thus the model based on solution studies assumes a considerably more efficient intracomplex base stacking than the solid-state structures in our models. While this difference is not unrealistic in view of the expected differing effects of Pt on negatively charged guanine nucleotides and neutral 9-ethyl-guanine ligands, a definite answer on the validity of these models can be expected only from the successful determination of a crystal structure of a guanine dinucleotide complex of cisplatin. Certainly, our results have shown that in a complex of *cis*-Pt^{II}, two identical heterocyclic ligands need not invariably be in a head-tail orientation as has been anticipated.^{13,42}

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, DFG, and the Technische Universität München for financial support and Degussa for a generous loan of K_2PtCl_4 .

Supplementary Material Available: Listings of observed and calculated structure factors, atomic parameters, least-squares planes, and deviations of atoms (35 pages). Ordering information is given on any current masthead page.