Three-Bond Platinum–Hydrogen Coupling in 9-Ethylguanine-N^7-Complexes of $(NH_3)_xPt(II)$: Influence of *trans*- and *cis*-Ligands

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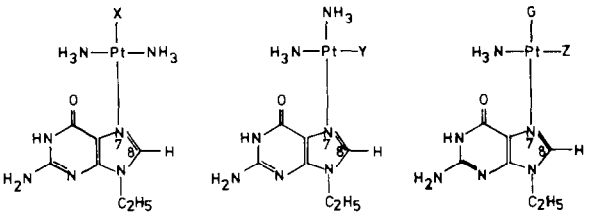
Factors influencing the magnitude of three-bond coupling $J_{^{195}Pt-N-C-^1H}$ have been studied for platinum complexes of amino acids [1] and cyclic diamines [2]. It has been found that the coupling constant is affected by several variables: the Pt oxidation state, the strength of the Pt–N bond and, interrelated with it, the nature of the ligand *trans* to the N–C–H group under consideration, and the conformation of the Pt–N–C–H fragment. Typically, values for $J_{^{195}Pt-N-C-^1H}$ in these compounds vary between 10 and 60 Hz [1]. Data on three-bond Pt–N–C–H coupling of Pt complexes containing N–bound heterocycles have been sparse until recently [3]. The present interest in the interaction of antitumor platinum coordination compounds with nucleobases has changed this picture [4–8]. A survey of three-bond coupling constants $J_{^{195}Pt-N-C-^1H}$ in complexes of Pt(II) containing planar heterocyclic ligands reported so far shows a smaller range of values, from approximately 20 Hz in complexes of 9-ethylguanine [6] and 7,9-dimethylhypoxanthine [7] to 40 Hz in complexes of N1-bound uracil and thymine [8]. This is probably a consequence of the *cis* orientation of the two coupling nuclei, ^{195}Pt and $^1H(8)$ in the planar Pt–N–C–H fragments which prevents any Karplus type dependence of ^3J from the dihedral angle between PtNC and NCH planes as observed in the saturated systems mentioned above. Therefore, the size of ^3J in such complexes should be a good indicator of the Pt–N(heterocycle) bond strength and the nature of the ligand *trans* to Pt–N, respectively.

The results presented here on the $^{195}Pt-^1H(S)$ coupling in complexes of 9-ethylguanine, G, of composition *trans*-$(NH_3)_2PtGX$, *I*, confirm this expectation and agree with earlier findings on the importance of the *trans*-influence of X on the coupling constant [9].

A comparison with the coupling constants observed for complexes of composition *cis*-$(NH_3)_2PtGY$, *II*, and *trans*-$G_2Pt(NH_3)Z$, *III*, reveals that ligands *cis* to the 9-ethylguanine also affect ^3J to a considerable extent, as does a change of solvent.



I *II* *III*

Scheme 1.

Experimental

trans- and *cis*-$(NH_3)_2PtCl_2$ were prepared according to Kauffman and Cowan from K_2PtCl_4 [10]. Nucleobases were obtained from Sigma and Acris Feinchemikalien, respectively.

trans-$[(NH_3)_2Pt(9\text{-}EtG)_2]Cl_2$ and *trans*-$[(NH_3)_2Pt(9\text{-}EtG)Cl]Cl$ were prepared on reaction of *trans*-$(NH_3)_2PtCl_2$ with 1 equivalent of 9-ethylguanine, 9-EtG (0.04 *M* Pt, H_2O, 40 °C, 48 h). After filtration of unreacted *trans*-$(NH_3)_2PtCl_2$ the solution (pH = 3.1) was evaporated to dryness, re-dissolved in a minimum of water and the two compounds separated by means of column chromatography over Sephadex G 10. Slow evaporation gave thin, colorless needles for both compounds. *Anal.* Calcd. for $[(NH_3)_2Pt(C_7H_9N_5O)_2]Cl_2 \cdot 1.5H_2O$: C, 24.53; H, 3.98; N, 24.52; Cl, 10.34; Pt, 28.46%. Found: C, 24.72; H, 4.10; N, 24.90; Cl, 10.40; Pt, 28.8%. Calcd. for $[(NH_3)_2Pt(C_7H_9N_5O)Cl]Cl \cdot 1.5H_2O$: C, 16.61; H, 3.59; N, 19.37; Pt, 38.53%. Found: C, 16.71; H, 3.62; N, 19.38; Pt, 38.4%. Yields: 32% each, based on Pt.

trans-$[(NH_3)_2Pt(9\text{-}EtG)(1\text{-}MeC)](ClO_4)_2$ was prepared from *trans*-$[(NH_3)_2Pt(1\text{-}MeC)Cl]Cl$ (with 1-MeC being 1-methylcytosine) and 9-EtG. The crystal structure of this compound has been reported [11], details will be published elsewhere.

cis-$[(NH_3)_2Pt(9\text{-}EtG)_2]Cl_2$ and *cis*-$[(NH_3)_2Pt(9\text{-}EtG)Cl]Cl$ were obtained on reaction of *cis*-$(NH_3)_2PtCl_2$ with 1 equivalent of 9-EtG (0.04 *M* Pt, H_2O, 40 °C, 48 h). Fractional crystallization of the resulting clear solution (pH = 2.5–3) gave the sparingly soluble 1:1-product as a white powder, unreacted *cis*-platin, and the well soluble 2:1-product as colorless crystals. *Anal.* Calcd. for $[(NH_3)_2Pt(C_7H_9N_5O)Cl]Cl \cdot 0.5H_2O$ (after 30 min drying at 100 °C): C, 17.21; H, 3.31; N, 20.08; O, 4.92; Pt, 39.95%. Found: C, 17.00; H, 3.20; N, 19.88; O, 4.63; Pt, 40.2%. Calcd. for $[(NH_3)_2Pt(C_7H_9N_5O)_2]Cl_2 \cdot 3H_2O$: C, 23.60; H, 4.25; N, 23.59%. Found: C, 23.46; H, 4.01; N, 23.97%. Yields: 35% (1:1-complex), 12% (1:2-complex). The formulation of the 1:1-product as *cis*-$[(NH_3)_2Pt(9\text{-}EtG)Cl]Cl$ is supported by IR

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(ν(Pt–Cl) at 336 cm^{-1}) and by the fact that it reacts with 1-MeC and 2 equivalents of $AgClO_4$ to *cis*-$[(NH_3)_2Pt(9\text{-EtG})(1\text{-MeC})](ClO_4)_2$, which previously had been isolated in a different way and structurally characterized [12].

cis-$[(NH_3)_2Pt(9\text{-EtG})Cl]NO_3$ was obtained by ion exchange of the respective Cl complex, crystallization and recrystallization from hot water. Colorless crystals. *Anal.* Calcd. for $[(NH_3)_2Pt(C_7H_9N_5O)Cl]NO_3 \cdot H_2O$: C, 16.05; H, 3.27; N, 21.40; Cl, 6.67; Pt, 37.25%. Found: C, 16.14; H, 3.08; N, 21.74; Cl, 6.62; Pt, 37.8%. IR: ν(Pt–Cl) at 349 cm^{-1}.

$[(NH_3)_3Pt(9\text{-EtG})]Cl_2$ was prepared on reaction of *cis*-$[(NH_3)_2Pt(9\text{-EtG})Cl]Cl$ with an excess of NH_3 (0.01 *M* Pt, reflux 15 min) and evaporation to dryness. The crude product was redissolved in water, brought to pH 6.5 by means of HCl and crystallized. NH_4Cl was removed by stirring the product in excess EtOH. Recrystallization from water. Colorless needles. Yield 85%. *Anal.* Calcd. for $[(NH_3)_3Pt(C_7H_9N_5O)]Cl_2 \cdot H_2O$: C, 16.35; H, 3.90; N, 21.79; Pt, 37.9%. Found: C, 16.61; H, 3.81; N, 21.58; Pt, 37.9%.

cis-$[(NH_3)_2Pt(9\text{-EtG})(1\text{-MeU})]ClO_4$ (with 1-MeU being the 1-methyluracil anion) was prepared analogous to the corresponding 1-methylthymine compound [6b]. Details will be given elsewhere.

cis- and *trans*-$[(NH_3)_2Pt(9\text{-EtG})D_2O](NO_3)_2$ were prepared *in situ* from $[(NH_3)_2Pt(9\text{-EtG})Cl]Cl$ and 2 equivalents of $AgNO_3$ in D_2O (0.1 *M* Pt, 3–5 °C, 6 h). *trans*-$[(NH_3)_2Pt(9\text{-EtG})I]^+$ was prepared *in situ* by addition of 1 equivalent of KI to a solution of the aquo species. $[(NH_3)_2Pt(9\text{-EtG})(Me_2SO)]^{2+}$ species were prepared on addition of a small amount of $Me_2SO\text{-}d_6$ to a solution of the aquo complex. The compounds were not isolated.

^1H NMR spectra were recorded on a Jeol JNM-FX 60 Fourier-transform spectrometer in D_2O and $Me_2SO\text{-}d_6$, respectively. $[N(CH_3)_4]BF_4$ was used as an internal standard in aqueous solutions (3.1869 ppm downfield from sodium 3-(trimethylsilyl)propanesulfonate), while tetramethylsilane was used as internal reference in Me_2SO solutions. Concentrations usually were 0.1 *M* Pt. pD values were determined by means of a glass electrode and addition of 0.4 units to the meter reading.

Results

The ^1H NMR spectra of a series of 9-ethylguanine complexes of $(NH_3)_xPt(II)$ with x = 1, 2 (*cis*- and *trans*-isomers), and 3 have been recorded. Coordination of Pt(II) at the guanine ligand in all cases is through N7, as evident from side bands of the H8 resonance due to coupling with the ^{195}Pt isotope (natural abundance 33.8%, I = 1/2).

In Table I chemical shifts of H8 and $^{195}Pt\text{–}N\text{–}C\text{–}^1H(8)$ coupling constants of *trans*-$(NH_3)_2Pt(9\text{-EtG})X$ compounds are listed. Despite the relatively narrow range of 12 Hz for ^3J values, a trend can be seen which follows the usual *trans*-influence order of the ligand X [9], decreasing ^3J with increasing *trans*-influence: $Me_2SO > NH_3 > N(\text{nucleobases}) \simeq I^- > Cl^- > H_2O$.*

TABLE I. Chemical Shift of H8 Resonance and $^3J_{^{195}Pt\text{–}N\text{–}C\text{–}^1H(8)}$ of 9-Ethylguanine Complexes *trans*-$(NH_3)_2Pt(9\text{-EtG})X$, *I*.

X[a]	δ [ppm]	^3J [Hz]	Solvent, pD
D_2O	8.327	32.2	D_2O, pD = 2.5
Cl^b	8.368	28.8	D_2O, pD = 4.6
	8.527	26.9	$Me_2SO\text{-}d_6$
I	8.347	25.8	D_2O, pD = 5.0
9-EtG(N7)[b]	8.495	25.9	D_2O, pD = 2.9
1-MeC(N3)[c]	8.339	25.1	D_2O, pD = 5.0
	8.388	24.7	$Me_2SO\text{-}d_6$
$NH_3{}^b$	8.343	24.4	D_2O, pD = 6.0
	8.793	23.9	$Me_2SO\text{-}d_6$
Me_2SO^d	8.409	20.3	D_2O, pD = 2.9
	8.442	20.0	$Me_2SO\text{-}d_6$

[a]Donor atom underlined. [b]Chloride salt. [c]Perchlorate salt. [d]S-coordination confirmed by use of undeuterated Me_2SO (1 ppm downfield shift of CH_3 resonances, $^3J_{Pt\text{–}S\text{–}C\text{–}H}$ = 27 Hz).

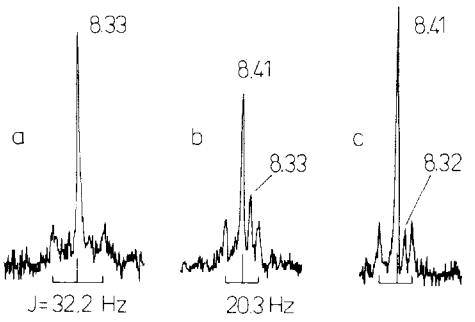

Fig. 1. H8 resonance of 9-ethylguanine of (a) *trans*-$[(NH_3)_2Pt(9\text{-EtG})D_2O]^{2+}$ (0.1 *M* Pt, D_2O, pD 2.5). (b) Immediately after addition of 25% (volume) of $Me_2SO\text{-}d_6$ (pD = 2.9). (c) 1 h after spectrum (b); temperature 30 °C. The new resonance at 8.41 ppm is assigned to *cis*-$[(NH_3)_2Pt(9\text{-EtG})(Me_2SO\text{-}d_6)]^{2+}$.

The two extremes observed in the present study, X = D_2O (^3J = 32.2 Hz) and X = Me_2SO (^3J = 20.3 Hz) are depicted in Fig. 1. *trans*-$[(NH_3)_2Pt(9\text{-EtG})D_2O]^{2+}$, like its corresponding *cis*-isomer, is unstable in aqueous solution, as evident from the appearance

*A recent X-ray structure determination by Orbell *et al.* [16] has been interpreted by a *trans*-influence order Cl > N-(guanine). It is felt that there may be an alternative interpretation as a result of a combination of *cis*- and *trans*-influences.

of a number of new resonances with time and a decrease in pD. There is some evidence that this is due to the formation of oligomers and/or metal migration, and this is the subject of ongoing studies. Coordination of Me_2SO prevents these processes to occur with the *trans* isomer. Other ligands with a high *trans*-influence such as PEt_3, $S_2O_3^{2-}$, SCN^-, and CN^- did not permit recording of spectra because of formation of a precipitate (PEt_3, SCN^-, CN^-) and immediate replacement of the guanine ligand trans to X, respectively ($S_2O_3^{2-}$, CN^-, PEt_3). On the other hand, with $X = F^-$ formation of a stable complex could not be achieved in aqueous solution due to the poor ligating properties of the fluoro ligand, though a substantial broadening of the ^{195}Pt satellites was evident.

In Tables II and III chemical shifts of H8 and $^{195}Pt-N-C-^1H(8)$ coupling constants of *cis*-$(NH_3)_2$-Pt(9-EtG)Y and *trans*-$(9\text{-EtG})_2Pt(NH_3)Z$ compounds are listed. Two important features are noticed: firstly, there is a definite influence of the ligand *cis* to the guanine on the ^3J values. Even though in *cis*-$(NH_3)_2$-Pt(9-EtG)Y the guanine ligand always has an identical ligand *trans* to itself, NH_3, coupling constants of H8 in aqueous solution vary between 22.0 Hz (D_2O,H3) and 25.9 Hz (1-MeU-N3), thus covering one third of the ^3J range observed in *trans*-$(NH_3)_2Pt(II)$ complexes (Table I). Secondly, the data in Tables II and III confirm the above mentioned finding that $^{195}Pt-N-C-^1H(8)$ coupling constants are generally smaller in Me_2SO-d_6 than in D_2O. Differences in respective ^3J values in most cases may not be considered significant, yet for *cis*-$[(NH_3)_2Pt(9\text{-EtG})_2]^{2+}$ and *trans*-$[(9\text{-EtG})_2Pt(NH_3)(1\text{-MeC})]^{2+}$ differences of 4 Hz are observed when going from one solvent to the other.

The relatively large solvent dependence contrasts other findings on no such effects (or only small ones) [2a, 13], and is not readily explained. While the simultaneous differences in chemical shifts of H8 in the two solvents may be indicative of an influence of different intracomplex base overlap in the case of *cis*-$[(NH_3)_2Pt(9\text{-EtG})_2]^{2+}$, the virtually identical shifts of H8 of *trans*-$[(9\text{-EtG})_2Pt(NH_3)(1\text{-MeC})]^{2+}$ in D_2O and Me_2SO-d_6 seem to point against such a possibility. An alternative explanation—weak Me_2SO coordination through the axial positions of the tetracoordinated Pt—might, if reasonable at all, be expected to play a more important role in sterically less-demanding compounds as compared to bis- or tris-nucleobase complexes, where the solvent effect is largest. As to the *cis*-influence of Y in type *II* complexes on the coupling of the Pt–N–C–H fragment, despite the limited number of examples containing different donor atoms Y, it is evident that the *trans*-influence of ligands used in the compounds described here does not greatly outweigh their *cis*-influence.

TABLE II. Chemical Shift of H8 Resonance and $^3J_{^{195}Pt-N-C-^1H(8)}$ of 9-Ethylguanine Complexes *cis*-$(NH_3)_2Pt(9\text{-EtG})Y$, *II*.

Y[a]	δ [ppm]	^3J [Hz]	Solvent, pD	Ref.
D_2O	8.311	22.0	D_2O, pD = 2.5	
Me_2SO	8.349	22.4	D_2O, pD = 2.8	
Cl^b	8.245	23.9	D_2O, pD = 3.9	
	8.388	21.7	Me_2SO-d_6	
NH_3^c	8.343	24.4	D_2O, pD = 6.0	Table 1
	8.793	23.9	Me_2SO-d_6	
9-EtG(N7)[c]	8.127	24.2	D_2O, pD = 6.0	
	8.225	20.2	Me_2SO-d_6	
1-MeC(N3)	8.074	24.4	D_2O, pD = 5.0	6a
	8.168	23.5	Me_2SO-d_6	
1-MeT(N3)[d]	7.902	24.9	D_2O, pD = 5.8	6b
	8.135	24.6	Me_2SO-d_6	
1-MeU(N3)	7.918	25.9	D_2O, pD = 3.7	
	8.123	24.2	Me_2SO-d_6	

[a]Donor atom underlined. [b]Nitrate salt. [c]Chloride salt. [d]1-MeT = 1-methylthymine anion.

TABLE III. Chemical Shift of H8 Resonance and $^3J_{^{195}Pt-N-C-^1H(8)}$ of 9-Ethylguanine Complexes *trans*-$(9\text{-EtG})_2Pt(NH_3)Z$, *III*.

Z[a]	δ [ppm]	^3J [Hz]	Solvent, pD	Ref.
NH_3	8.495	25.9	D_2O, pD 2.9	Table I
1-MeC(N3)	8.196	25.4	D_2O, pD 5.4	6c
	8.201	21.0	Me_2SO-d_6	

[a]Donor atom underlined.

Molecular orbital calculations, IR spectroscopic data, and equilibrium constants measurements [14, 15] previously have provided evidence that *cis*- and *trans*-influence, unlike the kinetic *cis*- and *trans*-effects, can be of comparable magnitude. With *cis*-$(NH_3)_2Pt(9\text{-EtG})Y$ compounds, the ^3J values suggest the following *cis*-influence order: $H_2O \simeq Me_2SO > Cl^- \simeq NH_3 \simeq$ N(nucleobases). Thus the order for Y ligands does not follow the *trans*-influence order of X ligands in *trans*-$(NH_3)_2Pt(9\text{-EtG})X$.

It is the combination of *cis*- and *trans*-influences of the ligands on the Pt-N7(guanine) bond which leads to the situation that in 9-ethylguanine complexes of *cis*- and *trans*-$(NH_3)_2Pt(II)$, the *trans*-isomer usually exhibits a larger $^{195}Pt-N-C-^1H$ coupling constant than the respective *cis*- isomer, *e.g.* $(9\text{-EtG})_2$, 25.9 *vs.* 20.2 Hz; (9-EtG)(1-MeC), 25.1 *vs.* 23.5 Hz; (9-EtG)Cl, 28.8 *vs.* 23.9 Hz; (9-EtG)D_2O, 32.2 *vs.* 22.0 Hz. Only with (9-EtG)Me_2-SO this sequence is reversed, with $^3J = 22.4$ Hz for the *cis*-isomer and 20.3 Hz for the *trans*-isomer.

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