Electronic Structure of Platinum(II) Antitumor Complexes and their Interactions with Nucleic Acid Bases. I

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Abstract

Using the semi-empirical all-valence method (GRINDOL) (recently modified and extended to transition series elements), electronic structure and intermolecular interactions of the model antitumor Pt(II) compounds with guanine and thioguanine have been calculated. Several possible models of antitumor action of platinum compounds are discussed. It is concluded that *cis*-Pt(II) complexes with guanine form stable intrastrand N7–N7 cross-links (but chelation to the O6 atom is also possible). The *trans*-isomers of platinum(II) exclusively form interstrand cross-links, but the *cis*-Pt(II) complexes with thioguanine form almost entirely the N7–S five-membered chelates.

Introduction

The interaction of metals and especially of Pt(II) with nucleic acid constituents has been the subject of extensive investigations in recent years after the discovery of Rosenberg *et al.* [1, 2] of the antitumor properties of *cis*-diamminedichloroplatinum(II) (*cis*-DDP). The investigations have shown that *cis*-DDP attacks DNA and inhibits new DNA synthesis [3].

All active Pt(II) compounds appear to have a square-planar geometry with a composition *cis*-PtA_2X_2, where A represents two monodentate (or one bidentate) amine ligands and X represents two monodentate (or one bidentate) anionic ligands. The *trans*-complexes are inactive as antitumor agents. For the *cis*-PtA_2X_2 complexes to be active, the X ligands should be easy-leaving groups (such as chloride ions), whereas the Pt–A bonds should be very stable, as for example Pt(II)–ammine.

In aqueous solution DDP undergoes slow hydrolysis and binds to the heterocyclic bases of the nucleic acids, preferentially to the N7 atoms of guanine.

Several models of *cis*-DDP binding to DNA have been proposed to account for the antitumor activity of *cis*-DDP but not its *trans*-isomer. The first model is that *cis*-DDP can bind to guanine (G) bases via chelation to the O6 and N7 atoms (N7–O6). Another proposes that the antitumor activity of *cis*-Pt(II) drugs derives from a specific affinity for two adjacent guanine bases of DNA at N7 sites (N7–N7). The above fundamental characteristics of the antitumor Pt(II) complexes were taken from several reviews which have appeared [2–8] during the last few years, describing a wide variety of aspects of platinum antitumor compounds as well as binding metals to nucleic acids.

In recent years a few theoretical studies devoted to the explanation and/or interpretation of the biological activity of some platinum(II) complexes have appeared. Modified Extended Hückel Method calculations with and without relativistic effects have been published [9, 10]. Abdul-Ahad and Webb [11] and Bersuker *et al.* [12] presented various correlations between some molecular properties (charges, bond orders, electrostatic potentials, etc.) and the biological activity of platinum complexes. Recently the *ab initio* SCF pseudo-potential calculations [13, 14] have been published. In some papers [15, 16] molecular mechanics calculations for large DNA fragments coordinated with *cis*-$Pt(NH_3)_2^{2+}$ were reported. Brostow *et al.* [17, 18] considered as a possible mechanism the shrinkage of DNA after platination.

In this paper we consider four models of coordination of Pt(II) complexes with the guanine base: the N7 monodentate binding; the N7–O6 five-membered chelate; the so-called N1 pK_a shift model; and (the most probable) the N7–N7 intrastrand cross-linking coordination. Some of these models are considered for 6-thioguanine, as well.

Method of Calculation

All the calculations have been performed using the modified [19, 20] INDO [21] scheme. The interaction energy ΔE_{CP} has been evaluated with the help of the counterpoise method of Boys and Bernardi [22], adapted to NDO-like methods [23]. In the case of hydrogen-bonded systems, the total interaction energy was calculated as a sum of the ΔE_{CP} and the dispersion energy, $\Delta E = \Delta E_{CP} + \Delta E_{DISP}$. In order

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to calculate the contribution of the dispersion energy, we used a semi-empirical London-type formula [24]. Experimental geometries for base pairs were assumed [25] in the calculations.

Results of Calculations

In the gas phase Pt(II) forms strong square-planar complexes [26]. However, solvation (hydration) processes play an important role in the formation of these complexes (mainly ions) and generally markedly decrease the respective interaction energies between the central platinum ion and the ligands.

To check the credibility of the results presented here, we compared interaction energies, geometrical parameters and energy differences between *cis*- and *trans*-isomers with experimental data or results of calculations obtained by more sophisticated methods for some Pt(II) complexes (Tables I, II, III) where good agreement has been obtained.

Unfortunately, the detailed interpretation of experimental data obtained for platinum complexes with guanine (see below) is complicated by the influence of solvent interactions, which are absent in the results of calculations presented in this paper. The solvent effect on the interaction energies between Pt(II) complexes and biologically important ligands will be published elsewhere [28]. In this paper we consider the interaction of Pt(II) with the guanine molecule only, because it is generally accepted that this base of DNA is the main initial target for the *cis*-platinum drugs.

TABLE I. Comparison of Binding Parameters of $Pt(NH_3)_3^{2+}$ to Bases

Base	*Ab initio* SCF [13]		This work	
	R_e (Å)	D_e (kcal/mol)	R_e (Å)	D_e (kcal/mol)
NH_3	2.07	72	2.06	68
H_2O	2.06	56	2.06	59
OH^-	1.91	297	1.95	305
G(N7)	2.00	114	2.00	135

TABLE II. Binding Energies and Equilibrium Bond Lengths for some PtX_4 Complexes

Complex	This work		$D_{e,exp}$ (kcal/mol)
	R_e (Å)	D_e (kcal/mol)	
$PtCl_4^{2-}$	2.29	181	173[a]
$Pt(OH)_4^{2-}$	2.00	151	
$Pt(H_2O)_4^{2+}$	2.01	65	66[b,c]
$Pt(NH_3)_4^{2+}$	2.08	75	70[b,d]

[a] See ref. 26. [b] See ref. 27. [c] From Table 2.10 and eqns. (2.17)–(2.19) of ref. 27. [d] From Table 2.11 of ref. 27, data for Ni(II).

TABLE III. Formation Energy (kcal/mol) for some Pt(II) Complexes

Complex[a]	This work		$\Delta E_{cis-trans}$ (kcal/mol)	
	cis	*trans*		
$(NH_3)_2PtCl_2$	−682.2	−700.4	18.2	18[b]
$(NH_3)_2Pt(OH)(H_2O)$	−515.0	−518.6	3.6	4[b]
$(NH_3)_2Pt(OH)_2$	−635.4	−665.6	30.2	26[b]
$(NH_3)_2Pt(H_2O)_2$	−288.7	−289.1	0.4	0[b]
$(NH_3)_2Pt(OH)Cl$	−659.6	−683.6	24.0	
$(NH_3)_2Pt(H_2O)Cl$	−530.6	−535.0	4.4	
$(NH_3)_2Pt$	−157.7	−174.1	16.4	22[b]
NH_3PtCl_2	−637.9	−647.2	9.3	
$(NH_3)_2PtCl$	−480.2	−488.5	8.3	
$(NH_3)_2PtH_2O$	−227.4	−229.8	2.4	
$(H_2O)_2PtCl_2$	−670.4	−680.8	10.4	

[a] Charges are omitted. [b] Results of SCF pseudo-potential calculations, see ref. 13.

(a) N7 Monodentate Binding

The N7 nitrogen atom of guanine has a strong kinetic preference for many ions and especially for Pt(II), and the so-formed Pt–N7(G) bond is very stable [3, 4, 8] (Table IV). (Note that platinum(II) complexes in a *cis*-conformation bind more strongly to the guanine than the corresponding *trans*-isomers.) Obviously, the N7 model is unable to explain the differences in antitumor activity between the *cis*- and *trans*-isomers.

The N7(G) atom is the main initial site of coordination of Pt(II) complexes and, after binding to one G(N7), a second reaction is to be expected [3–5, 8]. Reedijk [8] and Lippert [30] discussed several possibilities, for example: chelation to an O6 atom of the same guanine (N7–O6 model); chelation to the base in the opposite strand of double helical DNA; or chelation to a neighbouring G(N7) in the same DNA strand (the so-called N7–N7 model or intrastrand cross-linking). The N7 monodentate binding may be also considered as a initial step before deprotonation of N1–H1 (N1 pK_a shift model [29, 30]), because the Pt(II) complexes (or other electrophiles) coordinated at this site increase the acidity of the H1–N1 proton of guanine.

(b) The N7–O6 Model

Of all the proposed models to explain the anticancer activity of *cis*-DDP and the inactivity of the *trans*-isomers, the bidentate N7–O6 chelation model has caused the biggest controversy. Although structural crystallographic studies on model compounds have conclusively shown that such chelates can form

TABLE IV. Interaction Energies (kcal/mol) for some Pt(II) Complexes with Guanine

Pt(II) complex[a]	Model	R (Pt–N7) (Å) (optimized)	*cis*	*trans*
$Pt(NH_3)_2H_2O$	N7	2.02	−145.4	−140.8
$Pt(NH_3)_2$	N7	2.01	−159.5	−137.3
$Pt(NH_3)_2$	N7–O6	2.01[b]	−243.0	−134.0
$Pt(NH_3)_2H_2O$	N7–O6	2.01[b,c]	−125.0	−119.3
$Pt(NH_3)_2$	N7–N7	[d]	−282.0	[e]

[a]Charges are omitted. [b]R(Pt–O6) = 2.00, angle N7PtO6 = 103°. [c]Assumed, N–Pt–N, perpendicular to the G plane. [d]Geometry from ref. 53. [e]Due to the stereochemistry of *trans*-Pt(II), this compound cannot chelate neighbouring purines in a DNA structure.

TABLE V. Equilibrium C6=O6 Distances and Frequency[a] of CO Stretching Mode in Platinated G Complexes

Complex	Model	ν_{CO} (cm^{-1})	$\Delta\nu$ (cm^{-1})	R_{CO} (Å)	ΔR_{CO} (Å)
Free G		1748	0	1.250	0.000
cis-$Pt(NH_3)_2H_2O^{2+}$	N7	1749	1	1.254	0.004
cis-$Pt(NH_3)_2^{2+}$	N7	1750	2	1.251	0.001
cis-$Pt(NH_3)_2^{2+}$	N7–O6	1656	−92	1.286	0.036
trans-$Pt(NH_3)_2^{2+}$	N7–O6	1615	−133	1.295	0.045

[a]The calculation of force constants were performed via the equation $k(CO) = k_1(CO)^{exp}k(CO)^{calc}/k_1(CO)^{calc}$, where k_1 is the force constant for a free CO molecule.

with 6-thiopurines [31, 32], evidence for chelation in 6-oxo ligands is less convincing, even when guanine is anionic, when one would expect O6 to be a better donor. Despite this, some authors [33–38] advocate the N7–O6 hypothesis, but others [4, 5, 8, 30, 39–41] strongly argue against it. The main evidence for the N7–O6 chelation is a shift of the stretching frequency of the C6=O6 bond to a lower energy, which could be related to the platination of G at N7 and to the perturbation of the carbonyl oxygen at C6, either by direct or indirect interaction with the Pt(II) bound to G. Some authors have been able to observe stretching frequency shifts of (in cm^{-1}): 75 [35], 95 [36], 32 [42], 90 [43]. It should be noted, however, that this shift to a lower energy does not always prove perturbation of the C=O bond, because deprotonated at the N1 site of guanine shows almost the same shift [30].

Very recently, Cozak *et al.* [44] provided the first crystallographic evidence for the formation of an N7–O6 chelate with a 6-oxopurine and Ti(III).

Our calculation results show (Table IV) that *cis*-$Pt(NH_3)_2$ moieties bind more strongly via bidentate N7–O6 chelation than via monodentate N7, whereas for *trans*-Pt(II) complexes the opposite trend is observed. Thus, we cannot deny the possibility of N7–O6 binding in the case of *cis*-Pt(II) compounds, at least. The calculated frequency of the C=O stretching mode (Table V) clearly shows that only N7–O6 chelation (but not N7 binding) of G may cause a large $\Delta\nu$(CO) shift (for both *cis*- and *trans*-complexes). The coordination to O6 reduces the double-bond character of C6=O6, as shown by the CO bond length being greater than in molecules with free O6. These changes (0.036 Å and 0.045 Å for *cis*- and *trans*-$Pt(NH_3)_2$, respectively) correlate well with the results of Cozak *et al.* [44] for Ti(III) complexes (ΔR_{CO} = 0.057 Å). These authors also observed a $\Delta\nu$(CO) shift after complexation of the order of 20–30 cm^{-1}.

TABLE VI. Deprotonation Energies (kcal/mol) for some Complexes of G and TG

Ligand	Site of coordination	G	TG
Free base		337	323
CH_3^+	N7	266	256
H^+	N7	247	
Mg^{2+}	N7[a]	181	168
Mg^{2+}	O6[b]	149	
cis-$Pt(NH_3)_2^{2+}$	N7	197	187
cis-$Pt(NH_3)_2H_2O^{2+}$	N7	196	
cis-$Pt(NH_3)G_2^{2+}$	N7–N7	192	
trans-$Pt(NH_3)_2H_2O^{2+}$	N7	197	
cis-$Pt(NH_3)_2^{2+}$	N7–O6	168	159
trans-$Pt(NH_3)_2^{2+}$	N7–O6	173	
Mg^{2+}	N7–O6[c]	129	

[a]Optimized R(Mg–N7) = 1.81 Å. [b]Optimized R(Mg–O6) = 1.90 Å. [c]Optimized R(Mg–N7) = 1.84 Å, R(Mg–O6) = 1.87 Å.

TABLE VII. Effect of Electrophilic Substituent on the Hydrogen Bond Energy in the G···C Pair

Ligand	Site	ΔE[a]	Other results
CH_3^+	N7(G)	−7.4	−7.5[b], −6.3[d], −1.7[e]
H^+	N7(G)	−8.0	−10.0[c]
Mg^{2+}	N7(G)–O6(G)	−16.4	−13.0[c], −5.2[f]
cis-$Pt(NH_3)_2^{2+}$	N7(G)–O6(G)	1.5	

[a] Defined as $\Delta E = \Delta E$(ligand G···C) − ΔE(G···C). [b] Ref. 63 (STO-3G results). [c] Ref. 64 (STO-3G results, data for H^+ and Li^+ cations). [d] Ref. 65 (CNDO/2 results). [e] Ref. 66 (STO-3G results, data for NH_4^+ cation). [f] Ref. 67, data for Li^+ (minimal basis set).

TABLE VIII. Interactions Energies (ΔE) between Hydrogen Bonded Base Pairs (kcal/mol)

Pair	Geometry	ΔE
G···C	B-DNA [25]	−24.37
A···T	B-DNA [25]	−11.26
G^-···T	as B-DNA [25]	−0.35
cis-$Pt(NH_3)_2$(N7–O6)G^-···T	as B-DNA [25]	−11.65
G^-···G	[46]	−33.26
cis-$Pt(NH_3)_2G^-$···G	[46]	−24.80

It should be noted that deprotonation (H1) energies of coordinated (in the N7, O6 region) guanine are greatly diminished as compared to free guanine (Table VI). This denotes that coordinated guanine is a stronger acid and can be easily deprotonated even at neutral pH [29, 30, 45]. Additionally, interaction of a *cis*-Pt(II) complex with G via N7–O6 chelation leds to weakness of the hydrogen bond with cytosine (Table VII).

(c) The N1 pK_a Shift Model

This model, proposed by Lippert [29, 30], is based on the known observation that deprotonation of the G base at N1 is facilitated through Pt(II) (or any other electrophile) coordinated in the N7, O6 region ($\Delta pK_a = 1.6$ [29, 30]). When G is deprotonated, the hydrogen bonding energy with cytosine is reduced. Thus, selectivity for cytosine is greatly prevented, and other bases such as guanine or thymine can form hydrogen bonds with deprotonated G, *i.e.* G^-···G or G^-···T [29, 30, 37, 46, 47]. The platinated guanine anion forms hydrogen bonds with thymine with energy comparable to the A···T pair (Table VIII). Because in the G^-···T pair the distance between the two sugar C1′ atoms remains almost the same as in the A···T pair [30], there is no geometrical restriction to such a mispair. Such a mispair can lead to base-substitution mutation GC———AT [29, 30, 37], which is actually observed [48], and eventually to cell death [37]. The second possibility is coordination of G^- with G [29, 30, 46, 47]. In spite of large interaction energies in this system (Table VIII), the G^-···G pair cannot fit into the DNA double helix because the deoxyribose positions are on the opposite side of the base pair and the C1′–C1′ distance is *ca.* 13 Å [30], instead of 10.85 Å in B-DNA [25]. (However, Lippert discussed some another possible ways in which a G^-···G pair could occur in the DNA helix [30].) From a theoretical point of view, the N1 pK_a shift model has, however, some disadvantages, because deprotonation energies are almost the same for both isomers, depending only on the coordination site (Table VI). In other words, the pK_a values for guanine coordinated with the *cis*- or *trans*-isomers of Pt(II) should be similar, too. Thus, in our opinion, the N1 pK_a model alone is unable to explain fundamental differences in biological activity between *cis*- and *trans*-platinum(II) isomers. It seems, however, that this model together with the N7–O6 one can be useful.

(d) The N7–N7 Intrastrand Cross-linking Model

It is now generally accepted that the most frequent lesion induced by the platinum drugs is a DNA cross-link between two neighbouring guanine residues on the same strand [41, 49–51]. The attraction of such an interaction is that it can only occur for the *cis*-form of DDP and not for the *trans*-isomer. Recently, Sherman *et al.* [52] have solved the X-ray crystal structure of the *cis*-$Pt(NH_3)_2^{2+}$(d(GpG)) adduct. Unfortunately, we are unable to perform optimization of geometry for this large system by quantum-chemical calculations, and calculations for this complex are conducted for a one geometry given by Lippert *et al.* [53] for a similar *cis*-$Pt(NH_3)_2^{2+}$-$(9EtG)_2$ complex. The results of calculations suggest that this adduct is very stable (Table IV), obviously due to the two strong Pt–N7 bonds. This bidentate bonding is approximately two times stronger than the monodentate N7 bonding of *cis*-$Pt(NH_3)_2H_2O^{2+}$, and about 40 kcal/mol stronger than another bidentate N7–O6 chelation (Table IV). The *cis*-$Pt(NH_3)_2(G_2)^{2+}$ complex will be additionally stabilized in a real structure of DNA by electrostatic attraction between Pt(II) and phosphate ions and via hydrogen bonds between ammine hydrogens and phosphate oxygen [52].

(e) Interaction of cis-Pt(NH$_3$)$_2^{2+}$ with 6-Thioguanine (TG)

Contrary to the N7–O6 chelate model of binding of *cis*-Pt complexes, the so-called N7–S five-membered chelates are well known in the 6-thiopurines (and in other similar compounds) [31, 32, 54–58].

The calculated energies of interactions of the *cis*-Pt(NH$_3$)$_2^{2+}$ (or *cis*-Pt(NH$_3$)$_2$H$_2$O^{2+}) with TG are −155.7, −338.6 and −302.3 kcal/mol for the N7, N7–S and N7–N7 models, respectively. For the N7 and the N7–N7 models, we assumed geometries as for G. In the case of the N7–S interaction, optimized geometry was used (R(Pt–S) = 2.21 Å, R(Pt–N7) = 2.01 Å and S–Pt–N7 angle = 94°) which compare well with experimental data (for Pd(II) complexes) of Heitner and Lippard [31]: 2.29 Å, 2.01 Å and 91°, respectively. The main difference between the platinum complexes with TG and G is that in the former case the N7–S model is energetically more stable than the N7–N7 one (compare data for G, Table IV). The energy of the H1 deprotonation in TG (free as well as coordinated) is smaller (about 10 kcal/mol) than in the corresponding guanine complexes (Table VI). But TG alone is already a stronger acid than G [55], thus it seems that the N1 pK_a shift model proposed by Lippert [29, 30] originally for G complexes should be more attractive for the N7–S chelated TG. The calculated value of the hydrogen bond energy in *cis*-Pt(NH$_3$)$_2^{2+}$(N7–S)TG$^-$···T (−11.0 kcal/mol) is also comparable to the value of −11.26 kcal/mol obtained for the A···T pair (Table VIII).

TABLE IX. Calculated Formation Energies ΔE (in kcal/mol) for some Pt(II) Complexes with G and TG

Complex[a]	Model	ΔE
cis-Pt(NH$_3$)$_2$G	N7–O6	−400.7
cis-Pt(NH$_3$)$_2$(H$_2$O)G	N7	−372.8
cis-Pt(NH$_3$)$_2$G	N7	−317.2
cis-Pt(NH$_3$)$_2$G$_2$	N7–N7	−439.5
trans-Pt(NH$_3$)$_2$(H$_2$O)G	N7	−370.6
trans-Pt(NH$_3$)$_2$G	N7	−311.6
trans-Pt(NH$_3$)$_2$G	N7–O6	−308.1
trans-Pt(NH$_3$)$_2$G$_2$	N7–N7[b]	−448.7
cis-Pt(NH$_3$)$_2$(H$_2$O)TG	N7	−383.1
cis-Pt(NH$_3$)$_2$TG	N7–S	−496.3
cis-Pt(NH$_3$)$_2$(TG)$_2$	N7–N7[c]	−460.0

[a]Charges are omitted. [b]Assumed, both R(Pt–N7) = 2.01 Å, two G bases are coplanar. [c]Geometry assumed, as in *cis*-Pt(NH$_3$)$_2$G$_2$, ref. 53.

Discussion

This discussion is based on the results of calculations of interactions as well as of binding energies (Tables III and IX) obtained for Pt(II) complexes in the 'gas phase', but some comments on the solvent effect will be given. More detailed discussion of the solvent effect and the phosphate group will be given elsewhere [28].

First, we consider two aquation reactions of DDP, *i.e.*

$$PtA_2Cl_2 + 2W = PtA_2W_2^{2+} + 2Cl^- \quad E_1$$

and

$$PtA_2Cl_2 + 2W = PtW_2Cl_2 + 2A \quad E_2$$

where A and W denote ammonia and water molecules, respectively. The calculated values (see data in Table III) of E_1 and E_2 for a *cis*- (*trans*)-isomer are equal to 394 (411) and 12 (20) kcal/mol, respectively. These results show, that in the 'gas phase' dissociation of chloride ions (where E_1 is much greater than E_2) is practically impossible. But in the solvent (water), due to a large stabilization of Cl$^-$ and $PtA_2W_2^{2+}$ ions, this reaction is more favourable (E_1 is in the order of a few kcal/mol) and, in addition, E_1 is slightly smaller than E_2. Secondly, we assume (as in refs. 3, 5 and 8) that aquation products of *cis*- or *trans*-DDP will be attacked by the guanine (or thioguanine) base. In Fig. 1 we show a schematic energy diagram for the cases studied in this paper.

Thus, after the aquation reactions, $PtA_2W_2^{2+}$ ions react with the N7 atom of G or TG, with loss of one water molecule. These reactions for all cases studied in this paper are energetically allowed (ΔE values are in the order of −80 kcal/mol), but in the solvent [28], due to large solvation of a smaller $PtA_2W_2^{2+}$ cation, they are generally diminished (*i.e.* they are less negative). In this state the PtA_2W G(N7)$^{2+}$ may dissociate the next labile water molecule and 'search' for a second site of coordination [8].

In the models studied in this paper, the second site of coordination may be the O6 atom in the same molecule (*i.e.* N7–O6 chelation) or the N7 atom in a neighbouring guanine base (N7–N7 model) for a *cis*-isomer, or any nitrogen atom of another base (for a *trans*-isomer). When only energy differences are considered (*i.e.* without solvent effect and the entropy term), the *cis*-isomer forms a stable intrastrand N7–N7 cross-link with guanine (but chelation to the O6 atom is also favourable); the *trans*-isomer exclusively binds to another guanine base; but the *cis*-isomer with TG forms almost entirely the N7–S chelate.

The interactions between *trans*-Pt(II) complexes with G may be considered as a rather crude model for a so-called interstrand cross-linking between nucleobases on the opposite strand of DNA. In the case of free guanine, N7–N7 binding is energetically

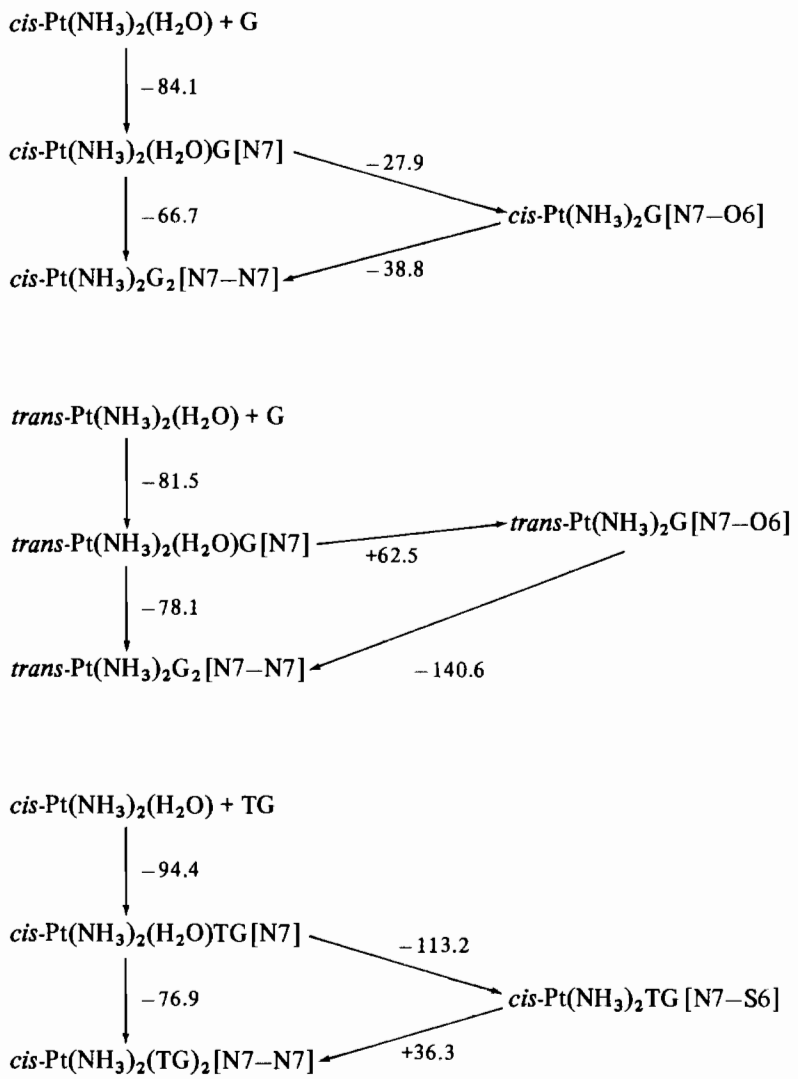

Fig. 1. Schematic energy diagram (kcal/mol) for some possible reactions of Pt(II) complexes with G and TG.

favourable over the monodentate N7 coordination, but in a real structure of DNA, similar cross-linking is expected to be more difficult, because a severe distortion of the DNA helix is needed.

The interaction of *cis*-Pt(II) with TG is interesting from yet another point of view. It is known that TG alone is also an antitumor drug [59, 60] and can be incorporated into the DNA helix instead of G [61]. The antitumor action of TG is enhanced in combination with not only *cis*-DDP [62] but also in combination with some Pd(II) complexes [60], which are inactive alone. Because Pd(II) and Pt(II) complexes have the same sites of coordination, it is interesting to know why inactive Pd(II) complexes enhance antitumor activity of TG. In spite of the unknown mechanism of the anticancer activity of TG, it seems that a high ability to bind any soft metal cations in the vicinity of the N7–S region facilitate the H1 deprotonation and consequently may cause a severe lesion in the DNA.

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References

1 B. Rosenberg, L. van Camp and T. Krigas, *Nature (London) 205*, 698 (1965).

2 B. Rosenberg, L. van Camp, E. B. Grimley and A. J. Thomson, *J. Mol. Biol., 242,* 1347 (1967).
3 A. T. M. Marcelis and J. Reedijk, *Recl. Trav. Chim. Pays-Bas, 102,* 121 (1983).
4 J. J. Roberts and A. J. Thomson, *Prog. Nucleic Acid Res. Mol. Biol., 22,* 71 (1979).
5 A. L. Pinto and S. J. Lippard, *Biochim. Biophys. Acta, 780,* 167 (1985).
6 M. J. Cleare, *Coord. Chem. Rev., 12,* 349 (1974).
7 S. J. Lippard (ed.), 'Platinum, Gold and other Metal Chemotherapeutic Agents: Chemistry and Biochemistry', ACS Symposium Series, No. 209, 1983.
8 J. Reedijk, *Pure Appl. Chem., 59,* 181 (1987).
9 T. P. Carsey and E. A. Boudreaux, *Chem.-Biol. Interact., 30,* 189 (1980); *Int. J. Quantum Chem., 18,* 469 (1980).
10 A. S. Dimoglo, Ju. M. Chumakov and J. B. Bersuker, *Teoret. Eksp. Khim., 16,* 666 (1980); *17,* 88 (1981); *Koord. Khim., 12,* 1879 (1980).
11 P. G. Abdul-Ahad and G. A. Webb, *Int. J. Quantum Chem., 21,* 1105 (1982).
12 A. S. Dimoglo, J. N. Czoban, Ju. M. Chumakov and J. B. Bersuker, *Khim.-Pharm. Zh.,* 60 (1982).
13 H. Basch, M. Krauss, W. J. Stevens and D. Cohen, *Inorg. Chem., 24,* 3313 (1985); *25,* 684 (1986).
14 K. J. Miller, E. R. Taylor, H. Basch, M. Krauss and W. J. Stevens, *J. Biomol. Struct. Dyn., 2,* 1157 (1985).
15 J. Kozelka, G. A. Petsko, S. J. Lippard and G. J. Quigley, *J. Am. Chem. Soc., 107,* 4079 (1985); *Inorg. Chem., 25,* 1075 (1986).
16 T. W. Hambley, *Inorg. Chim. Acta, 137,* 15 (1987).
17 N. Turkkan, K. Jankowski and W. Brostow, *Theochemistry, 30,* 299 (1986).
18 K. Jankowski, N. Turkkan and W. Brostow, *J. Mol. Struct., 110,* 255 (1984).
19 J. Lipiński, H. Chojnacki and A. Nowek, *Acta Phys. Pol., A53,* 229 (1978).
20 J. Lipiński and J. Leszczyński, *Int. J. Quantum. Chem., 22,* 253 (1982); *Theoret. Chim. Acta, 63,* 305 (1983); *Z. Naturforsch., Teil A, 42,* 160 (1987).
21 J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory', McGraw Hill, New York, 1970.
22 S. F. Boys and F. Bernardi, *Mol. Phys., 19,* 553 (1970).
23 J. Lipiński and H. Chojnacki, *Int. J. Quantum Chem., 19,* 891 (1981).
24 Y. K. Kang and M. S. Ihon, *Theoret. Chim. Acta, 61,* 41 (1981).
25 S. Arnott, S. D. Dover and A. J. Wonacott, *Acta Crystallogr., Sect. B, 25,* 2192 (1969).
26 R. M. de Jonge, *J. Inorg. Nucl. Chem., 38,* 1821 (1978).
27 F. Basolo and R. G. Pearson, 'Mechanisms of Inorganic Reactions', Wiley, New York, 1967.
28 J. Lipiński, paper in preparation.
29 B. Lippert, *J. Am. Chem. Soc., 103,* 5691 (1981).
30 B. Lippert, in S. J. Lippard (ed.), 'Platinum Gold and other Metal Chemotherapeutic Agents: Chemistry and Biochemistry', ACS Symposium Series, No. 209, 1983.
31 H. I. Heitner and S. J. Lippard, *Inorg. Chem., 13,* 815 (1974).
32 E. Sletten and A. Apeland, *Acta Crystallogr., Sect. B, 31,* 2019 (1975).
33 M. M. Millard, J. P. Macquet and T. Theophanides, *Biochim. Biophys. Acta, 402,* 166 (1975).
34 J. P. Macquet and T. Theophanides, *Bioinorg. Chem., 5,* 59 (1975).
35 G. Pneumatikakis, N. Hadjiliadis and T. Theophanides, *Inorg. Chem., 17,* 915 (1978).
36 J. Dehand and J. Jordanov, *J. Chem. Soc., Chem. Commun.,* 598 (1976).
37 B. Rosenberg, *Biochimie, 60,* 859 (1978).
38 L. G. Marzilli, B. De Castro and C. Solorzano, *J. Am. Chem. Soc., 104,* 461 (1982).
39 F. J. Dijt, G. W. Canters, J. H. J. den Hartog, A. T. M. Marcelis and J. Reedijk, *J. Am. Chem. Soc., 106,* 3644 (1984).
40 G. Raudaschl-Sieber, L. G. Marzilli, B. Lippert and K. Shinozuka, *Inorg. Chem., 24,* 989 (1985).
41 A. D. Kelman and H. J. Peresie, *Cancer Treat. Rep., 63,* 1445 (1979).
42 A. J. P. Alix, L. Bernard, M. Manfait, P. K. Ganguli and T. Theophanides, *Inorg. Chim. Acta, 55,* 147 (1981).
43 H. A. Tajmir-Riahi and T. Theophanides, *Can. J. Chem., 62,* 1429 (1984).
44 D. Cozak, A. Mardhy, M. J. Olivier and A. L. Beauchamp, *Inorg. Chem., 25,* 2600 (1986).
45 A. Pasini and R. Mena, *Inorg. Chim. Acta, 56,* L17 (1981).
46 Y. Yamagata, S. Fukumoto, K. Hamada, T. Fujiwara and K. Tomita, *Nucl. Acid Res., 11,* 6475 (1983).
47 F. Faggiani, B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem., 21,* 3216 (1982).
48 D. J. Beck and R. R. Brubaker, *Mut. Res., 27,* 181 (1974).
49 G. L. Cohen, J. A. Ledner, W. R. Bauer, H. M. Ushay, C. Caravana and S. J. Lippard, *J. Am. Chem. Soc., 102,* 2487 (1980).
50 T. D. Tullius and S. J. Lippard, *J. Am. Chem. Soc., 103,* 4620 (1981).
51 A. Eastman, *Biochemistry, 22,* 3927 (1983).
52 S. E. Sherman, D. Gibson, A. H-J. Wang and S. J. Lippard, *Science, 230,* 412 (1985).
53 B. Lippert, G. Raudaschl, C. J. L. Lock and P. Pilon, *Inorg. Chim. Acta, 93,* 43 (1984).
54 M. A. Bruck, H.-J. Korte, R. Bau, N. Hadjiliadis and B.-K. Teo, in S. J. Lippard (ed.), 'Platinum, Gold and Metal Chemotherapeutic Agents: Chemistry and Biochemistry', ACS Symposium Series, No. 209, 1983, p. 245.
55 N. Hadjiliadis and T. Theophanides, *Inorg. Chim. Acta, 15,* 167 (1975).
56 B. T. Khan, S. V. Kumari, K. M. Mohan and G. N. Goud, *Polyhedron, 4,* 1617 (1985).
57 A. Grigoratos and N. Katsaros, *Inorg. Chim. Acta, 108,* 41 (1985).
58 Y. Wei-da, L. Mei-Qing and P. Shi-gi, *Inorg. Chim. Acta, 106,* 65 (1985).
59 R. W. Sidwell, S. M. Sellers, G. J. Dixon and F. M. Schabel Jr., *Cancer Res., 28,* 35 (1968).
60 S. Kirchner, Y. K. Wei, D. Francis and J. G. Bergman, *J. Med. Chem., 9,* 369 (1966).
61 G. A. Le Page and I. G. Junga, *Cancer Res., 23,* 739 (1963).
62 B. Rosenberg, *Met. Ions Biol. Syst., 11,* 127 (1981).
63 P. Otto, J. Ladik and S. C. Lin, *J. Mol. Struct., 123,* 129 (1985).
64 J. E. Del Bene, *J. Mol. Struct., 124,* 201 (1985).
65 G. Klopman and A. Ray, *Cancer Biochem. Biophys., 6,* 31 (1982).
66 A. Sarai and M. Saito, *Int. J. Quantum Chem., 28,* 399 (1985).
67 K. P. Sagarik and B. M. Rode, *Inorg. Chim. Acta, 78,* 81 (1983).