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The interactions of square platinum(II) complexes with guanine and adenine: a quantum-chemical ab initio study of metalated tautomeric forms

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Abstract The influence of binding of square planar platinum complexes on tautomeric equilibria of the DNA bases guanine and adenine was investigated using the density functional B3LYP method. Neutral *trans*-dichloro(amine)-, +1 charged chloro(diamine)-, and +2 charged triamine-platinum(II) species were chosen for coordination to bases. Only the N_7 interaction site of the bases was considered. The calculations demonstrate that the neutral platinum adduct does not change the tautomeric equilibria of the bases. Furthermore, N_7 binding of the neutral Pt adduct moderately reduces the probability of protonation of the N_1 position of adenine. Larger effects can be observed for +1 and mainly +2 adducts, but these can be rationalized by electrostatic effects. Since the electrostatic effects are expected to be efficiently compensated for by a charged backbone of DNA and counterions in a polar solvent, no dramatic increase in mispair formation is predicted for Pt(II) adducts, which is in agreement with experiment. The interaction energies between Pt adducts and the nucleobases were also evaluated. These interaction energies range from ca. 210 kJ/mol for neutral adducts, interacting with both bases and their tautomers, up to 500 kJ/mol for the +2 charged adducts, interacting with the keto-guanine tautomer and the *anti*-imino-adenine tautomer. The surprisingly large interaction energy for the latter structure is due to the strong H-bond between the NH_3 ligand group of the metal adduct and the N_6 nitrogen atom of the base.

Key words DNA bases · Adenine · Guanine · Platinum complexes · Density functional theory calculations

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Introduction

In the 1960s, the square compound *cis*-dichlorodiammineplatinum (*cis*-DDP, cisplatin) was recognized as an active substance in antitumor treatment [1]. Since then, many studies have been devoted to the exploitation of platinum complexes, focusing on the influence of different ligands and conformers on cancer activity. A comparison of both *cis*- and *trans*-DDP and their derivatives is given in several papers [2–4]. Brabec et al. [5, 6] showed that different activities of Pt compounds are connected with different ways of bonding *cis*- and *trans*-DDP to DNA bases. Both *cis*- and *trans*-DDP interact predominantly with the N_7 of guanine, and only minor linkage to the N_7 position of adenine was observed. *Cis*-DDP bridges GG sequences in the same strand of DNA, while *trans*-DDP binds to GG bases of different DNA strands. The DDP interaction with the DNA strand usually supposes that the neighboring nucleobases are Pt-bridged (cf., NMR study [4] or X-ray crystal structures [3, 7]). Nevertheless there was also found such a structure which contains one extra nucleobase (thymine) in between two guanine bases of the same strand (using two-dimensional NOE NMR [8]). Such a platinated -GTG- sequence remarkably distorts the DNA helix. The important consequences of DNA interactions with DDP and its derivatives, as well as the structure-activity relationships, are discussed in an excellent review by Reedijk [9]. He analyzed several related structures of Pt-amino complexes, which are also active in anti-

cancer treatment. He assumed that the existence of a kink in the DNA chain, due to the intrastrand cross-link of Pt complexes on the same strand, causes unnatural geometric curvature in the DNA helix. This inflexible site should stop the "peptide decode/code machine" in the process of DNA transcription. A paper discussing a novel type of DDP analogue has appeared recently [10]. Here, the central platinum atom is Pt(IV) in the *trans*- or *cis*-[$Pt(OAc)_2I_2(en)$] complexes, and these compounds can be photolyzed by visible light, thereby creating cytotoxic species in vitro.

Despite of a large amount of experimental work devoted to Pt-DNA interactions, there is a lack of detailed information about its structure and energetics. Therefore, theoretical calculations complement the experimental studies. Until recently, computational studies were limited by the difficulty in theoretically describing transition metals and their complexes. In 1985, Kozelka et al. [11–13] applied molecular modeling to the interactions of Pt with DNA oligonucleotides. Empirical potentials used in their modeling have been based on quantum chemical calculations of *cis*-DDP at the Hartree-Fock (HF) level in the STO-3G minimal basis set. With this very simple model they have been able to reproduce some structural patterns of *cis*-DDP-DNA bases which were known from experiment. Recently, several papers appeared from the Carloni group on the structural aspects of the complexes between Pt and biomolecules. Their results are based on the application of the density functional theory (DFT), and a comparison of the optimized structures of cis-DDP and its derivatives with experimental data are summarized in an earlier paper [14]. The interaction of the *trans*-DDP-base pair of adenine-thymine has been studied [15] and compared with the experimental data of Krizanovic et al. [16]. In 1999, a detailed study of DDP [17] appeared in which several computational levels were compared and the charge densities and vibrational frequencies were evaluated.

Other computational efforts have usually concentrated more or less on very small species: Pt + CH_4 using effective core potentials (ECP) [18] and the DFT/HF hybrid method [19]. From the same theoretical group, the studies of the spin-orbit effect in Pt^+H (also in the frame of the DFT method) [20] and of the complex relativistic effects in Pt-CH_2^+ [21] were also published. A similar system (PtH) was calculated using the four-component Dirac-Fock method by Dyall [22]. His paper includes an extended comparison of two- and four-component methods with scalar wavefunctions and pseudopotentials. In this paper it can be clearly seen that the pseudopotential calculations are in very good accord with the results provided by the Dirac-Fock method. Some larger systems, such as benzene+Pt^+, were treated by Roszak and Balasubramanian [23] using average relativistic effective potentials [24] and the perturbation theory (MP2). Fantucci et al. [25, 26] calculated the dioxygen-platinum-$(PH_3)_2$ and Pt-phosphine species at a modest level of DFT approximation. In the paper of Navarro et al. [27], the binuclear Pt(II) complex is calculated byexploring the bonding nature of experimentally studied triazolopyrimidine-bridged biplatinum complexes. Also in this case, the DFT method was applied together with Hay-Wadt's ECP [28].

In the present paper we analyze the influence of the *trans*-Pt adduct bound at the usual N_7 position of the purine (adenine, guanine) bases on their tautomeric equilibria. The reason for our study is that a change of tautomeric equilibria of the bases can induce the formation of mismatch base pairs and increase the probability of point mutations. Such processes could be the result of changes in the electron distributions of the bases upon metalation. The certain influence of metalation of bases on their tautomeric equilibria and mispair formation seems really likely when considering the crystallographic data of metalated bases (as reviewed by Lippert [29]). At first sight, the major contribution inducing proton shifts in metalated bases should be the ionic electrostatic contribution when the metal entity bears a nonzero charge. For example, in the gas phase, metalation of the N_7 position of guanine by a divalent cation having a charge of +2 could shift the proton from the guanine N_1 position to the cytosine N_3 position in the Watson-Crick base pair. However, this gas phase trend is not observed in experiments carried out in polar solvents. Polar solvents provide very efficient screening of the ionic groups and can even stabilize close contacts of two groups bearing the same charge [30–33]. Still, there is a marked increase in the acidity of the proton at the N_1 position as a consequence of N_7 purine-metal binding, which is on the order of 1.5–2 log units [34]. However, only a moderate effect of the charge of the metal entity is seen [34, 35], contrary to the gas phase trends. Also, crystals are strictly neutral and the ionic-electrostatic effects are suppressed. Thus a comparison of gas phase calculations and experiments is not easy and it is the reason why we pay large attention to platinum adducts with different charges.

There are further experiments showing proton shifts induced by the N_7 metalation of purines. Unusual base pairs involving N_7-metalated, N_1-deprotonated guanine (hemi-deprotonation) have been observed in crystal structures of platinated bases [36–39]. Adenine carrying metal entities at N_7 is capable of accepting a proton at N_1 irrespective of the charge of the metal entity, e.g. $PtCl_3^-$ [40, 41] and $ZnCl_3^-$ [42] on the one hand or *cis*-$(NH_3)_2Pt^{2+}$, $(dien)Pt^{2+}$ [43], and $(OH)_2(NH_3)_3Pt^{2+}$ [44] on the other. This clearly shows that the protonation is not due to electrostatic forces.

The present study mainly deals with the effect of N_7 platination on the keto-enol equilibrium of guanine and the amino-imino equilibrium of adenine. These proton shifts are not well documented by condensed

phase and solid state experiments. However, these tautomeric equilibria are involved in proton transfer processes, which might lead to point mutations [45 , 46]. Therefore, the effects of metals on the relative stability of the minor tautomers are of interest, even if the metalation does not make the rare tautomers to be prevalent species easily detectable in the experiments.

In this work we study the influence of platinum complex compounds on the tautomeric equilibria of both guanine and adenine isomers. To some extent our work may be compared with the paper of Zilberberg et al. [47] in which Pt with guanine was also calculated. However, only guanine was treated with positively charged Pt complexes: $Pt(NH_3)_3^{2+}$ and $Pt(NH_3)_2Cl^+$. In addition, the level of calculations was slightly lower.

Materials and methods

Computational details

Square planar platinum complexes with several of the most stable tautomers of guanine and adenine were studied. Besides the most stable form of adenine (major tautomer), we have also considered its imino tautomeric form $N_6H\text{-}H_1$ in two orientations: the *anti* and *syn* conformations (cf. Fig. 1). The notation is taken from the paper by Ha et al. [48]. In the case of guanine, two tautomers (with the keto and enol forms of O_6) were studied. Three platinum(II) complexes were chosen for coordination to DNA bases: neutral *trans*-dichlorodiamineplatinum, +1 charged *trans*-triaminechloroplatinum and, +2 charged tetraammineplatinum. The *trans* complexes were chosen owing to symmetrical reasons. From other papers [2, 5, 49] it is known that cisplatin and transplatin have practically the same coordination affinity to the N_7 site of the base. The corresponding complexes were obtained by replacing one amine ligand with a DNA base coordinated in the N_7 position. All the compounds were optimized using the density functional method with Becke's three-parameter hybrid exchange-correlation functionals [50, 51]:

$$E = AE_X^{\text{Slater}} + (1-A)E_X^{\text{HF}} + BE_X^{\text{Becke}} + (1-C)E_C^{\text{VWN}} + CE_C^{\text{LYP}} \quad (1)$$

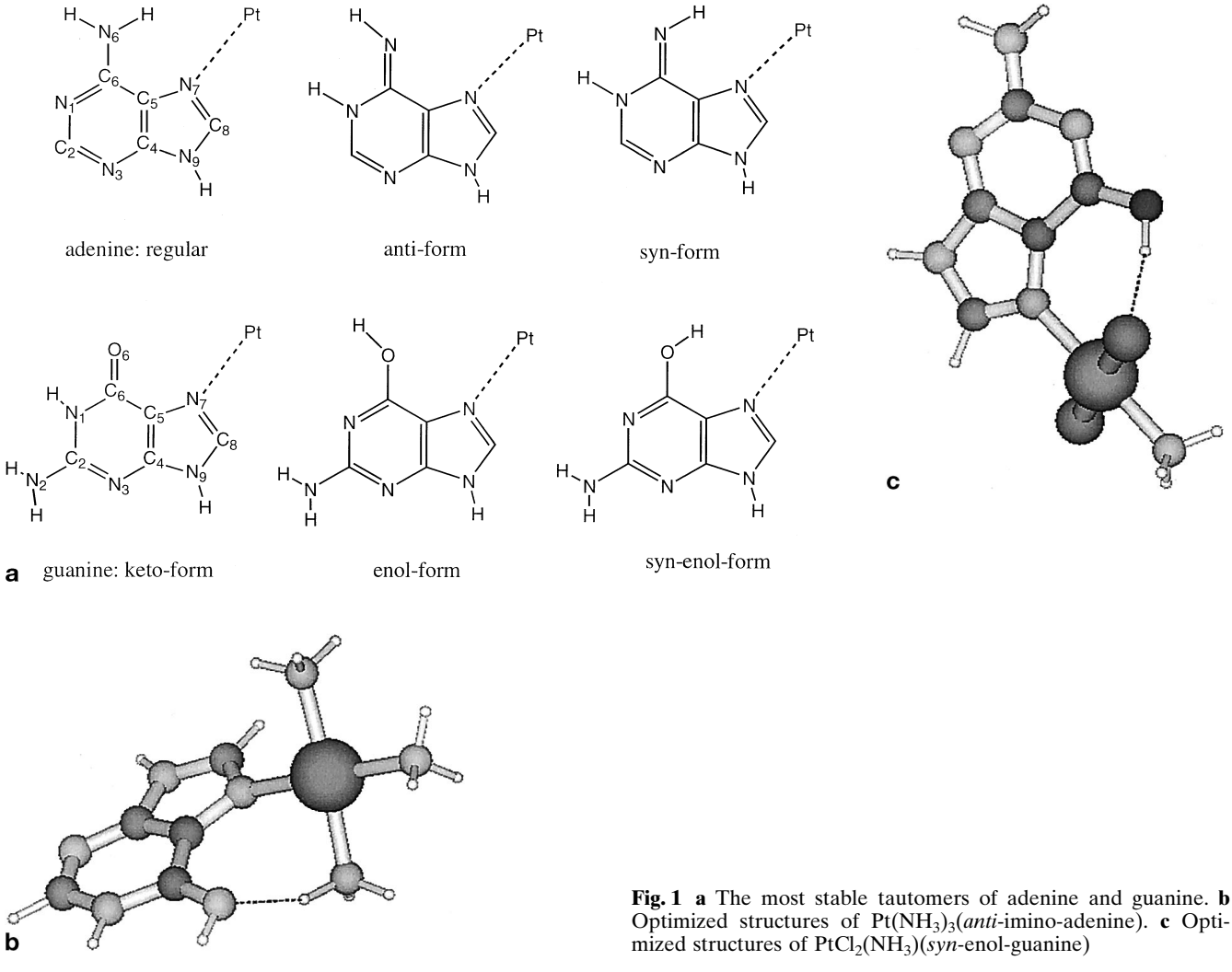

Fig. 1 **a** The most stable tautomers of adenine and guanine. **b** Optimized structures of $Pt(NH_3)_3$(*anti*-imino-adenine). **c** Optimized structures of $PtCl_2(NH_3)$(*syn*-enol-guanine)

Here E_C^{VWN} represents the local correlation term and E_C^{LYP} is a combination of both local and non-local correlation functionals. Standard 6-31G* basis sets were used for the H, C, N, and O atoms [52]. Chlorine and platinum were described with the energy-averaged MWB pseudopotentials and the suggested spd basis sets [53, 54]. Another set of f polarization functions was added on the platinum atom in the single point calculations for the final structures. The large influence of higher polarization functions is known from many papers. It was found that the extension of the basis set used in this paper from 1f to 2f+1g base functions can lead to a 30% increase in the interaction energy for "small systems" (in absolute value about 30 kJ/mol) [55]. However, here it was found that the influence of higher polarization functions on the ligated Pt(II)+adenine complex is only very small, with minor energy changes less than 10 kJ/mol. It seems that these higher polarization functions are not so crucial in the case of our complexes.

In several cases the optimized structures deviated significantly from the C_s symmetry since some specific additional interactions between the Pt adduct and the nucleobase were formed. Thus, for such structures studied we carried out two sets of calculations. Besides the unconstrained optimization, another optimization was performed enforcing the arrangement of the C_s point group. For the symmetric complexes the other interactions (Pt-ligand···X_6 site of base) are suppressed, and the Pt-N_7 interaction practically forms the only attractive term. It means that deviation from the symmetrical arrangement is caused by an interaction of an NH_3 ligand with the O_6 position of guanine or the N_6 position of adenine or the chloro ligand with hydrogen bound on the O_6/N_6 atoms. These additional interactions further stabilize the whole complex. In the case of adenine, pronounced pyramidalization of the NH_2 group was observed. Total energies from the final single point calculations were used for a comparison of the relative stability of the minor tautomers (ΔE^T). Since two forms of imino-adenine were distinguished, an additional superscript (ΔE^{T1} and ΔE^{T2}) was used for the *syn* and *anti* forms, respectively. Besides the differences in absolute energies, the binding energies of the ligated Pt-base were also calculated in individual complexes (ΔE^S). Corrections on the basis set superposition error based on the counterpoise method [56] were included in the calculation of these interaction energies:

$$\Delta E^S = E(\text{Pt species} - \text{base}) - E[(\textit{species} - \textit{gbase})] + E(\text{gPt species} - \text{base}) \quad (2)$$

Finally, the energies of the suggested exchange-ligand reaction were evaluated:

$$\text{Pt}(\text{NH}_3)_a\text{Cl}_b + \text{base} \rightarrow \text{Pt}(\text{NH}_3)_{(a-1)}\text{Cl}_b(\text{base}) + \text{NH}_3 \quad (3)$$

Such a reaction was considered because computation of the platinum species with only three ligands (and ghost functions in base position) seems to be inconsistent from the point of proper space electron delocalization on the platinum atom; cf., for example [57]. Thus in the exchange reaction, platinum always occurs in four-coordinated complexes.

Charges obtained from natural bond orbitals (NBO) [58] and fitted multipole electrostatic potential (MEP) by the Merz-Kolman procedure [59] were determined to verify the trends of the Mulliken population analysis. MO analyses were performed to better understand the coordination properties.

Results and discussion

The major obstacle of ab initio calculations is their gas phase nature. It sharply influences the outcome in calculations of systems with a nonzero charge because the electrostatic effects often dominate such systems. However, it can lead to erroneous conclusions if ab initio calculations are used to study model systems mimicking interactions in a polar solvent or crystal. The reason is that the polar solvent and counterions very efficiently compensate for the electrostatic effects associated with ions. For example, when a positively charged metal adduct binds to the N_7 position of guanine, it has (in the gas phase) a pronounced effect on the basicity of the N_1 position of guanine. This is a trivial consequence of the total charge of the system and is related to the electrostatic effects. However, in a polar solvent, the net charge residing on the metal group will be significantly reduced by the solvent effects. Therefore, in the present study, platinum adducts with different charges (0, +1, and +2) were considered. Even though the cisplatin adduct mostly carries a charge of +2, a comparison of the adducts with various charges would allow us to estimate the electrostatic effects on tautomerism. Let us once again reiterate that these electrostatic effects will be sharply reduced in a solvent. In other words, we assume that our gas phase results with a neutral adduct should be close to the effects exerted by all Pt(II) adducts in liquid and solid state phases, while calculations carried out for the +2 adduct will probably exaggerate the actual situation.

Geometries

Basic geometrical parameters of all complexes are compiled in Table 1, which contains data for adenine,

Table 1 Main geometry characteristics of adenine complexes studied; distances in Å, angles in °; X_i designates atom (N/Cl) which forms an H-bond or is the closest to the N_6/O_6 base position (see the fourth column). Suffix cs means complexes with C_s restriction

No. Cl[b]	Pt-N_7	Pt-X_i	Pt-Cl	NH-N_6	Pt-N_7-C_5	N-Pt-N_7-C_5
0	2.057	2.092	–	2.024	128.0	51.5
0cs	2.046	2.102	–	4.022	128.7	90.1
1	2.083	2.084	2.320	2.309	126.4	58.5
1cs	2.078	2.087	2.322	3.761	126.8	90.4
2	2.050	2.076	2.322	3.286[a]	132.3	57.2
2cs	2.041	2.077	2.362	4.244[a]	128.8	90.6
anti Form						
0	2.067	2.076	–	1.808	129.1	58.9
0cs	2.054	2.098	–	3.327	124.3	88.7
1	2.101	2.065	2.320	1.903	130.8	55.2
1cs	2.088	2.084	2.324	3.431	127.9	88.6
2	2.038	2.069	2.371	4.231[a]	128.9	91.5
2cs	2.037	2.070	2.371	4.235[a]	128.9	91.6
syn Form						
0	2.054	2.103	–	3.287	125.8	62.1
0cs	2.050	2.101	–	3.858	126.1	89.8
1	2.084	2.087	2.087	3.632	126.4	72.9
1cs	2.084	2.088	2.321	3.688	126.6	89.8
2	2.041	2.074	2.365	4.123[a]	129.3	67.9
2cs	2.039	2.074	2.364	4.324[a]	128.0	91.1

[a] Cl-N_6 distance
[b] Number of chlorine atoms

Table 2 Main geometry characteristics of guanine complexes studied; distances in Å, angles in °; X_i designates atom (N/Cl) which forms an H-bond or is the closest to N_6/O_6 base position (see the fourth column). Suffix cs means complexes with C_s restriction; suffix hb means complex with *syn*-enol guanine rotamer

No. Cl[b]	Pt-N_7	Pt-X_i	Pt-Cl	NH-O_6	Pt-N_7-C_5	N-Pt-N_7-C_5
Keto form						
0	2.060	2.082	–	1.799	126.9	57.45
0cs	2.048	2.097	–	3.532	122.2	89.1
1	2.095	2.070	2.322	1.879	128.9	51.5
1cs	2.085	2.084	2.324	3.498	126.6	88.7
2	–	–	–	–	–	–
2cs	2.035	2.071	2.369	4.28[a]	127.3	91.5
Enol form						
0	2.050	2.092	–	2.041	127.3	60.2
0cs	2.044	2.098	–	3.677	126.1	89.4
1	2.085	2.078	2.322	2.138	128.0	57.9
1cs	2.083	2.086	2.323	3.508	127.7	89.6
2	2.038	2.072	2.368	3.558[a]	129.4	63.4
2cs	2.037	2.070	2.368	4.236[a]	128.5	91.1
2hb	2.048	2.077	2.356	3.093[a]	131.0	53.4

[a] Cl-O_6 distance
[b] Number of chlorine atoms

and Table 2, which contains data for guanine. It can be seen that the Pt-N_7 distance varies very little with different ligands. Slightly larger distances were found for monochloro complexes. In contrast to some of our previous work, where the metal-adenine and metal-guanine distances differed for various metal cations in both isolated (naked) or hydrated forms [60, 61, 62], essentially no differences in the metal-N_7 distances were found comparing the Pt-adenine and Pt-guanine complexes. The explanation rests on the fact that here only the N_7 position is involved in the interaction and the influence of the second site (O_6/N_6) is substantially reduced. Also, the character of the Pt-N bond is much more covalent (or dative) in comparison with more or less electrostatic interactions of the cations from the 1, 2, 11, and 12 groups of the periodic system. The Pt-N_7 distances are in acceptable agreement with the recently published results of Zilberberg et al. [47]. Their estimation for $Pt(NH_3)_3$-guanine and $Pt(NH_3)_2Cl$-guanine are 2.17 Å and 2.13 Å, respectively.

The dihedral angles (N-Pt···N_7-C_5) from Tables 1 and 2 point to the distortion of the Pt-ligands plane (perpendicular to the plane of the DNA base) owing to the ligand-O_6/N_6 interactions. It is interesting that the shortest [ligand(NH_3)···X_6] distance around 1.8 Å occurs in H_2N-H···O_6 (keto)guanine and H_2N-H···N_6 (*anti* form) adenine. Such a short distance is comparable with systems containing strong H-bonds which are known, for example, from dimers of water molecules [63, 64]. This unambiguously shows the strength of this additional H-bonded interaction. Similarly, relatively strong H-bonding also exists in the adenine-dichloroplatinum complex, where the Cl···N_6 distance is about 3.3 Å. This is much shorter than the distance in the HCl dimer [d(Cl-Cl) = 3.9 Å] [65] or d(Cl-N) = 3.8 Å in the H-Cl···HNH_2 system[1]. H-bonds in these Pt complexes are efficiently enhanced with the polarization effects introduced by the metal.

In the case of neutral dichloro-Pt(II) species with guanine, the *syn*-enol configuration was also examined. Here, the creation of an H-bond (O_6-H···Cl) leads to a relatively stable structure in comparison with other guanine tautomers. In Table 2 it may be noted that the distance Cl···H-O_6 = 3.1 Å is even shorter than previously discussed distance (Cl···H-N_6) from the regular adenine complex.

For the same neutral $PtCl_2(NH_3)$ species, we have also studied an alternative binding mode where Pt was attached to the O_6 position of guanine. The optimized geometry shows that the distance Pt-O_6 = 2.07 Å is slightly larger than the corresponding distances of Pt-N_7 in all the other structures. The total energy of this complex is about 53 kJ/mol higher than the one for symmetric $PtCl_2(NH_3)$-N_7(keto-guanine). It clearly reflects the known fact that the transition metals usually prefer nitrogen as an interaction site. Since the bonding energy to oxygen is substantially smaller, the chelate complex $Pt(NH_3)_2$-guanine coordinated simultaneously to the O_6 and N_7 positions was not studied. In addition, this chelate complex is not expected to occur in any available experiment.

The relative tautomer stabilities and interaction energies between Pt adducts and bases

The main results are summarized in Table 3. Let us first discuss the relative tautomeric energies designated as ΔE^T. In the case of non-metalated guanine, the enol form is destabilized by ca. 11 kJ/mol with respect to the keto form. Gould found 5.9 kJ/mol [75] for geometries obtained with optimization using the Hartree-Fock method and DFT single-point calculations and 7.8 kJ/mol with the MP2 method. For Pt complexes, two sets of calculations were made. One set of structures (designated cs) was optimized with the restriction of the planar DNA base and with the plane of the Pt complex perpendicular to it. The other set of calculations has been performed without any constraints (see Computational details). Both constrained and unconstrained calculations provide similar trends (see Table 3); so, let us comment on the data for unconstrained structures. The gap between

[1] The most stable structure of the (HCl)···(NH_3) system is the Cl-H···NH_3 arrangement [d(Cl-N) = 3.11 Å and ΔE^{BSSE} (MP2/6-31G*) = 42.0 kJ/mol]; however, the HCl···H-NH_2 coordination preserves the donation from the Cl atom to amine. Here d(Cl-N) = 3.86 Å and ΔE^{BSSE}(MP2/6-31G*) = 2.4 kJ/mol. The change from H-Cl to Pt-Cl means substantial charge redistribution (from about 0.25e to 0.50e in dependence of the population), so that the estimated strength of the H-bond in Pt-Cl···H-NH_2 is remarkably higher

Table 3 Interaction energies between the metal adduct and bases (ΔE^S) and relative stabilities of the minor tautomers with respect to the major forms (ΔE^T). All energies in kJ/mol

	Adenine					Guanine		
	Regular	*syn*	anti	syn	*anti*	Keto	Enol	
No. Cl	ΔE^S	ΔE^{S1}	ΔE^{S2}	ΔE^{T1}	ΔE^{T2}	ΔE^S	ΔE^S	ΔE^T
–	–	–	–	50.9[a]	79.0[a]	–	–	10.7[b]
0	−408.3	−407.3	−491.1	50.9	−16.7	−503.4	−457.2	53.5
0cs	−381.5	−404.5	−467.8	20.3	−14.2	−483.5	−450.7	43.0
1	−250.0	−252.6	−301.4	42.6	23.2	−305.2	−278.0	35.7
1cs	−244.9	−251.9	−281.9	39.1	38.7	−288.6	−273.5	24.6
2	−230.8	−213.6	−207.9	52.7	93.5	–	−212.8	10.0[c,d,e]
2cs	−217.6	−211.9	−207.9	53.0	85.5	−211.2	−211.6	8.9

[a] Non-metalated base; cf. MP2/6-31G** calculations [31] of 51.3 and 79.7 kJ/mol

[b] Non-metalated base; cf. MP4(SDQ)/6-31G**//HF/6-31G** calculations of Gould [75] which show a difference of 7.8 kJ/mol

[c] Taken from the symmetric form of the keto guanine complex

[d] ΔE^S(hb) = −241.3 kJ/mol; hb means guanine *syn*-enol form with H_6 in *syn* arrangement (cf. Fig. 1), which enables formation of an O-H···Cl bond; ΔE^T(hb) = −9.2 kJ/mol, subtracted from the symmetric keto form of the guanine complex

[e] $\Delta E^S(O_6)$ = −150.1 kJ/mol; O_6 means interaction site on keto guanine; $\Delta E^T(O_6)$ = 53.0 kJ/mol; relative stability related to the symmetric keto form of guanine complex

the keto and enol tautomers sharply increases to 54 kJ/mol for the +2 adduct. This can be easily understood since the positive charge of Pt, located near N_7, must destabilize a proton shift from N_1 to O_6. However, when reducing the charge on the metal group by two chlorines there is no effect on the tautomeric equilibrium by metalation until the *syn*-enol rotamer is considered. For this complex, a more advantageous arrangement with the strong H-bonded structure takes place: $\Delta E^T \approx -9$ kJ/mol in comparison with the keto structure of guanine. All these results indicate that the effect seen for the +2 adduct with three amines is primarily of electrostatic origin. Not surprisingly, the Pt adduct with one chlorine having a charge of +1 shows about half of the effect of the +2 charged Pt adduct.

In case of the adenine tautomers, two imino forms must be considered. Firstly, the remaining hydrogen on N_6 is oriented towards the Pt adduct (*syn* tautomer); and secondly, this hydrogen is oriented in the opposite direction so that the N_6 nitrogen can serve as an H-acceptor for the amine groups of the Pt adduct (cf. Fig. 1). The results can be summarized as follows. In accord with other authors [48, 66], the relative energies ΔE^T of the non-metalated tautomers are about 51 kJ/mol for the *syn*- and 79 kJ/mol for the *anti*-imino forms of adenine. For a neutral Pt adduct, the metalation has only a minor effect on the tautomerism, as observed before for guanine. Charged Pt adducts exhibit pronounced stabilization for the *anti*-imino tautomers since a strong H-bond is formed between an amine ligand-group (H_i) and the N_6 atom of adenine (cf. increased partial charge for N_6 and H_i in Table 5). For a +2 Pt adduct, this tautomer even becomes a minimum, although for a non-metalated base this tautomer is considerably less stable than the other two tautomers. The effect of metalation on the relative stability of the *syn* tautomer with respect to the major form is rather small; a larger reduction in the energy difference is seen only for a +2 charged Pt adduct when applying the symmetry constraint specified above.

In general, the behavior of platinated adenine and guanine is opposite. Positively charged Pt adducts tend to stabilize minor tautomers of adenine and destabilize the enol tautomer of guanine. An exception is the dichloroplatinum complex with the guanine *syn*-enol form, which is more stable than the dichloroplatinum-(keto guanine) structure. For both the adenine *anti* form with positively charged Pt adducts and the neutral $PtCl_2$-guanine *syn*-enol complex, the increased stabilization can be considered as a consequence of an additional, relatively strong, H-bond interaction.

Let us now discuss the interaction (binding) energies between the Pt adducts and the base designated as (ΔE^S). They basically describe the strength of the Pt-N_7 interaction. In the case of non-planar complexes, the ligand-O_6/N_6 site interaction is also included. In general, the more chlorine atoms that are bound to Pt, the weaker is the interaction energy. This can be explained as a reduction of the adduct charge-base dipole moment interaction. The binding energy of the neutral Pt adduct is the same, around 210–240 kJ/mol for all species studied. For charged +1 and +2 adducts, an increase in binding energy is observed, as is expected. Furthermore, there are differences between the bases and their tautomers. Binding to the guanine keto form is more efficient than to the enol form owing to the larger dipole moment of the keto form (μ = 6.5 and 3.3 D for the keto and enol forms, respectively). This is the reason why the enol tautomer is more stable in such a positively charged Pt complex in comparison with the keto form. The situation for adenine is more complicated. The interaction between the +1 and +2 adducts and the adenine major form is weaker compared to guanine. This reflects the lower dipole moment of adenine, as described in our previous studies, e.g. [60]. The *syn* tautomer has rather

similar binding energies as the major adenine tautomer. However, the *anti* form exhibits pronounced interaction with positively charged Pt adducts owing to the strong H-bonding between the amine ligand and N_6. Also, its dipole moment is the largest of the adenine tautomers ($\mu = 4.5$ D). Comparing the energies ΔE^S with and without symmetry restriction, the additional stabilization due to the H-bond can be illuminated. Thus, it can be seen from Table 3 that the strongest H-bond is created in the non-symmetrical adenine major form of the complex with $Pt(NH_3)_3$ (about 27 kJ/mol above the symmetrical structure).

Interaction of Pt complexes with purine bases can be compared with the previously studied hydrated cations of zinc group metals. Here we can focus on the systems with a hydrated mercury cation, which is close to Pt in the Periodic Table of elements. In spite of some small covalent bonding, the electrostatic character prevails in the case of mercury. Two immediately visible reasons are: (1) the relation of the interaction energies cation-adenine/cation-guanine (231.3/384.5 kJ/mol [60, 67]) are proportional to the ratio of base dipole moments (2.47/6.55 D); the deviation shows the influence of the covalent character; and (2) partial charges are relatively high (e.g., $\delta = 1.64$e), with the NBO analysis of electron density at the MP2 level of $Hg^{2+}(H_2O)_5$-guanine. This ionic character is much more suppressed for platinum complexes.

There is one another interesting point to be mentioned. Complexes containing platinum species with two and three NH_3 ligands have very similar interaction energies for the most stable tautomers, the adenine *anti* form and the guanine keto form; ΔE^S for adenine (*anti* form) is about 10–20 kJ/mol smaller. On the other hand, the corresponding complexes with the major adenine form have interaction energies about 100 kJ/mol (for +2 charged adducts) and 50 kJ/mol (for +1) smaller. This can be explained by the efficient H-bonding contribution observed for adenine *anti*-imino tautomers enhanced by the electrostatic term.

The platination energy of the guanine N_7 position can also be compared with Zilberberg et al.'s results [47]. Their estimation of the binding energy ($\Delta E^S = 840$ kJ/mol at the HF/LANL1DZ level without BSSE corrections) of the $Pt(NH_3)_3$-keto-guanine complex is comparable with our results.

Ligand-exchange energetics

Regarding the ligand-exchange reaction, another point of view can be obtained. The reaction energies are summarized in Table 4. It follows from the table that if it were not for the additional factors (the entropy and vibration energies), the reaction would not occur or would be endothermic for dichlorinated species. It means that dichlorodiamineplatinum is not willing to exchange the NH_3 groups by means of a base. Nevertheless, the absolute value of the reaction energy ($\Delta E^R \approx 20$ kJ/mol) is not high enough for unambiguous conclusions. For these dichlorinated complexes, only marginal differences in reaction energies can be seen. The reaction is slightly more feasible in the case of the adenine *anti* form and the guanine *syn*-enol form, which are stabilized by the H-bond. For complexes with one chloro ligand, substantial differences can be noticed among adenine tautomeric forms. The reaction energy of the *anti* form exhibits the most pronounced exothermic behavior and is nearly twice as high as the other forms ($\Delta E^R = -78$ kJ/mol). The same relations are valid for the tautomers with three NH_3 ligands. This trend is in qualitative accord with the behavior of the interaction energies. The reaction energy of the adenine *anti* form can be again compared with the corresponding energy of the guanine-containing complex in the keto form. For these structures the exchange reaction belongs to exothermic reactions with a ΔE^R of about -160 kJ/mol.

Protonation energy of the adenine N_1 position

Since the protonation of DNA bases is a very important phenomenon, occurring in many biochemical processes, the protonation energy of metalated adenine was also examined. Protonation of adenine is known to stabilize mismatch base pairs such as AH^+···C and AH^+···G (cf. [68, 69]). For the reason explained in the Introduction, only the neutral Pt adduct was considered for this calculation since it would not make any sense to calculate the gas-phase protonation energy of a non-neutral molecule. The calculations

Table 4 Ligand-exchange reaction: $Pt(NH_3)_aCl_b + base \rightarrow Pt(NH_3)_{(a-1)}Cl_b + NH_3$, in kJ/mol

Adenine	ΔE^R	Guanine	ΔE^R
Major		Keto	
Cl0	−66.9	Cl0	−171.9
Cl0cs	−52.7	Cl0cs	−156.4
Cl1	−25.9	Cl1	−81.5
Cl1cs	−22.5	Cl1cs	−66.5
Cl2	11.4	Cl2	–
Cl2cs	19.5	Cl2cs	24.5
anti-Imino		Enol	
Cl0	−162.5	Cl0	−129.1
Cl0cs	−145.8	Cl0cs	−124.2
Cl1	−78.3	Cl1	−56.5
Cl1cs	−62.8	Cl1cs	−52.7
Cl2	25.9	Cl2	22.7
Cl2cs	26.1	Cl2cs	23.9
syn-Imino		Cl2hb[a]	4.6
Cl0	−83.5	–	–
Cl0cs	−83.2	–	–
Cl1	−34.1	–	–
Cl1cs	−34.3	–	–
Cl2	21.3	–	–
Cl2cs	21.7	–	–

[a] hb means guanine *syn*-enol form

should reveal whether the metal binding changes the electronic structure of the aromatic ring to such an extent that it enhances the probability of protonization of the N_1 position. The answer to this question is negative. The protonation energy of non-metalated adenine is 237.2 kcal/mol (992 kJ/mol) (similar results have been obtained by Del Bene [70] or more recently by Lippert and co-workers [71]), while the protonation energy of neutral metalated adenine is 230.5 kcal/mol (964 kJ/mol) at the same level of theory. Thus the metalation in fact reduces the probability of protonation of the N_1 ring position of adenine. The optimized geometry parameters of the protonated complex are very close to the non-protonated complex. The interaction energy between the neutral Pt adduct and the base in the protonated complex is about 25 kJ/mol weaker than ΔE^S of the non-protonated adenine-Pt complex. This result points to the slightly lower stability of the platinated bases in an acidic environment, but the platinum influence on the N_1 basicity and protonation energy is not remarkable. Thus we can conclude that platination of the N_7 position of adenine will not promote formation of mispairs such as $AH^{+}\cdots C$ and $AH^{+}\cdots G$ known in DNA.

Population analysis

Partial charges from the Mulliken population analysis, MEP, and NBO were performed and the NBO results are summarized in Table 5. Here it can be seen that the different platinum species remarkably influence only the closest sites on the base (N_7 position). Otherwise, some indistinct changes may be noticed. Nevertheless, some polarization effects can be observed. Decreased charges on the N_1 and N_2 atoms and increased changes on N_7 and partially on O_6/N_6 demonstrate some charge redistribution. The MEP method, in contrast to the other two methods, does not give results with such polarization trends. Especially, electron distributions on the Pt and N_7 atoms are strikingly different. A probable explanation can be seen in the fact that the Merz-Kollman type of analysis needs van der Waals radii which are used in the fitting procedure, and the chosen value r_{Pt}=1.75 Å according to [72] is not proper for this purpose. Similar obstacles could be overcome using another type of population, Bader's "atoms in molecule" [73] population, but the AIM method is not directly available for pseudopotentials. An interesting finding is the estimation of a partial charge on Pt. It is predicted to be substantially smaller than 2+; the Mulliken value is about 0.6*e*, and the NBO guess is slightly more than 0.3*e*. Thus, platinated complexes can be hardly considered as ionic compounds.

Supposing a reaction belongs to the class of orbital controlled reactions, then information about the shape and order of the frontier orbitals plays the essential role in deciding the chemical reactivity and behavior of the compound (e.g. see [74]). The discussion of various MOs begins with complexes where the C_s point group of symmetry was held. One common feature to all of the examined complexes, both adenine and guanine, is the shape of the LUMO. It is basically a

Table 5 Partial charges based on NBO population analysis (in *e*); adenine: r regular, *a anti*, *s syn* forms; guanine: k keto and e enol forms; N/Cl_i and H_i denote population on the atom which interacts with O_6/N_6 site of base; $H_{6.7}$ means hydrogen from amine or imino group oriented towards Pt adduct; $H_{1/6.1}$ is hydrogen from amine group oriented out of Pt or, in imino case, located on N_1 base atom

	N/Cl_i	H_i	Pt	N_7	N_6	N_1	$H_{6.7}$	$H_1/_{6.1}$
Aden. r	–	–	–	−0.498	−0.804	−0.563	0.425	0.422
Aden. *a*	–	–	–	−0.454	−0.694	−0.626	0.338	0.426
Aden. *s*	–	–	–	−0.478	−0.732	−0.602	0.374	0.442
r Cl0	−1.044	0.461	0.683	−0.542	−0.887	−0.486	0.420	0.454
a Cl0	−1.042	0.461	0.695	−0.522	−0.783	−0.596	0.463	0.401
s Cl0	−1.041	0.457	0.683	−0.533	−0.719	−0.580	0.351	0.476
r Cl1	−1.028	0.445	0.597	−0.549	−0.847	−0.516	0.421	0.442
a Cl1	−1.025	0.452	0.614	−0.524	−0.756	−0.605	0.385	0.451
s Cl1	−1.028	0.443	0.599	−0.540	−0.708	−0.589	0.367	0.463
r Cl2	−0.562	–	0.569	−0.488	−0.801	−0.549	0.431	0.421
a Cl2	−0.577	–	0.589	−0.455	−0.681	−0.619	0.354	0.434
s Cl2	−0.561	–	0.556	−0.468	−0.702	−0.596	0.385	0.449
	N/Cl_i	H_i	Pt	N_7	O_6	N_1	N_2	$H_{1/6}$
Guan. k	–	–	–	−0.453	−0.596	−0.658	−0.844	0.433
Guan. e	–	–	–	−0.466	−0.666	−0.625	−0.826	0.497
k Cl0	−1.040	0.464	0.693	−0.520	−0.645	−0.626	−0.782	0.464
e Cl0	−1.038	0.460	0.693	−0.531	−0.720	−0.557	−0.766	0.538
k Cl1	−1.024	0.453	0.614	−0.521	−0.629	−0.636	−0.804	0.453
e Cl1	−1.024	0.445	0.614	−0.535	−0.699	−0.581	−0.789	0.526
k Cl2cs	−0.575	–	0.582	−0.452	−0.580	−0.653	−0.827	0.437
e Cl2	−0.570	–	0.578	−0.466	−0.653	−0.607	−0.818	0.507
e Cl2hb	−0.542	−0.552	0.567	−0.488	−0.677	−0.565	−0.818	0.507

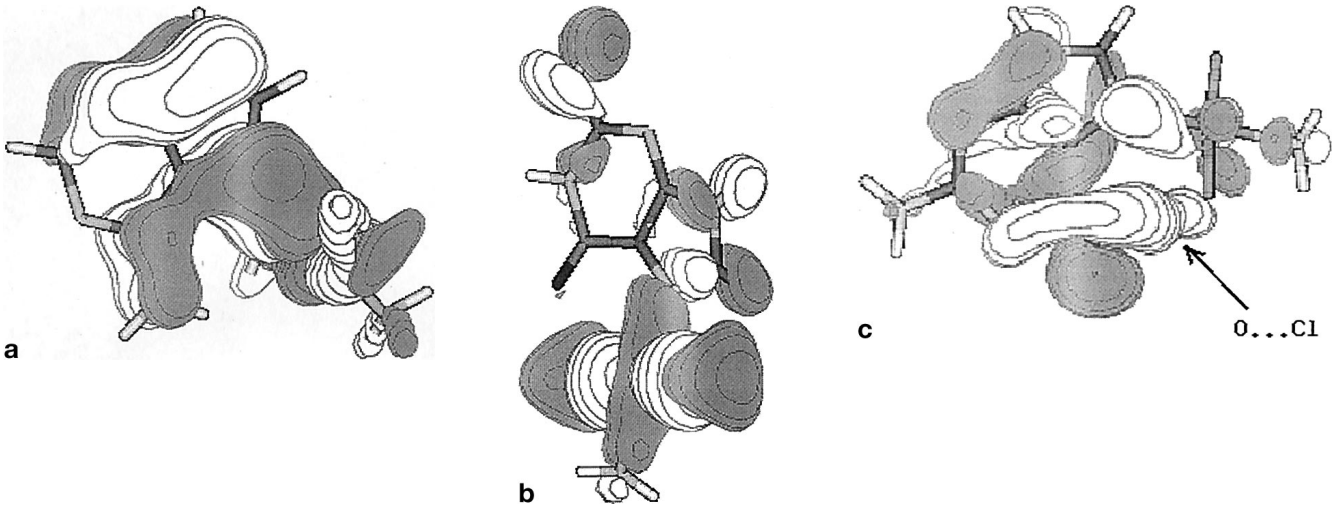

Fig. 2 **a** An example of the bonding combination of base σ orbital and d AO of Pt: 49th MO of Pt-$(NH_3)_3$-adenine (regular form). **b** An example of the bonding combination of p AO on the nitrogen [(NH_3) groups and base N_7] with d AO of Pt: 43th MO of Pt-$(NH_3)_3$-guanine (keto form). **c** Bonding combination of p (O_6)+s (H)+p (Cl) indicating the O-H···Cl interaction in $PtCl_2(NH_3)$guanine (*syn*-enol): 45th MO of Pt-$(NH_3)Cl_2$-guanine (*syn*-enol form)

vacant d-orbital of Pt with little antibonding contribution from all of the four ligands.

In the case of the Pt adducts with three NH_3 ligands, the HOMOs are the π-orbital of the base. A little deeper, after several (1–3) π-base orbitals, a set of 1+2 (degenerate) MOs with a high portion of Pt d-orbitals follows. The gap between these orbitals is about $\Delta e = 0.25$ a.u. The higher non-degenerated one usually contains some Pt 6s contribution. Only the non-bonding or antibonding combinations of Pt AOs with AOs of the interacting atoms from individual ligands appear before the lowest π-orbital of the base. The only exception from this scheme is the bonding combinations of the Pt AOs and the π-orbitals of the bases (with one nodal plane perpendicular to base plane, cf. Fig. 2a). After the lowest π-orbital of the base, three MOs follow where the Pt orbitals are involved in a bonding combination with the AOs of the nitrogen atoms of the NH_3 group and the N_7 position of the base (cf. Fig. 2b).

Complexes with one chloro ligand have similar ordering. The one exception is in the complex with the *anti* form structure, when the HOMO is not the π-orbital of adenine but an equivalent antibonding combination of the chlorine p-orbitals and the Pt d-orbitals. All bonding combinations of Pt-Cl can be found before the third-lowest π-orbital of the base. Also, the other previously mentioned MOs with the σ-bonding combination of Pt-N are promoted above the lowest π-orbital of the base. The largest influence of various tautomers is in the dichloro-complexes. For both guanine-containing systems, antibonding combinations of Pt-Cl form the HOMO and HOMO-1 orbitals followed by a d-electron pair of Pt and the first π-orbital of the base. The complex with the *anti* form of adenine has a similar ordering; only the HOMO-1 (a′) and HOMO-2 (a) orbitals are inverted. However, these orbitals are almost energetically degenerate. In the case of adenine, major and *syn* forms, the highest π-orbital of the base lies between the HOMO and HOMO-2 antibonding combinations of Pt-Cl.

In complexes with C_1 group symmetry, the cancellation of orthogonal subspaces causes some additional mixing of the MOs from the originally different irreps, making the MO analyses more complicated. In the case when an additional H-bond takes place, the mixture of the corresponding AOs appears in some MOs; for example in Fig. 2c, some bonding combination of $p(O_6)$+s(H)+p(Cl) is indicative of the O-H···Cl interaction in the complex $PtCl_2(NH_3)$(*syn*-enol-guanine).

Conclusions

The Pt-N_7 distances are similar in all investigated complexes, that is, considering the three platinum species and all tautomeric forms of both DNA bases. Small differences in several complexes are due to the additional H-bond interaction of the ligand group (NH_3 or Cl) with the O_6/N_6 site.

The most important conclusion is that while charged Pt adducts have a pronounced effect on guanine tautomerism and stabilization of the major form, binding of a neutral adduct does not bring any substantial change in guanine tautomerism. This indicates that the effect of a +2 Pt adduct observed in the gas phase might be mostly attributed to electrostatic effects. Since electrostatic effects are compensated for in polar solvents as well as in crystals, we predict that the actual effect on the tautomerism of the Pt binding to N_7 in these environments should be rather small.

In case of adenine, its *anti*-imino form is the global energy minimum when it interacts with the $Pt(NH_3)_3$

species. Investigating stabilization and exchange reaction energies, this tautomer exhibits in absolute values the highest energies for the charged [$Pt(NH_3)_3$ and $Pt(NH_3)_2Cl$] species. It means that the *anti* form is stabilized by these platinum species. However, when considering a neutral adduct, again no pronounced effect on adenine tautomerism is observed.

Binding of the Pt adduct to the N_7 position of adenine slightly reduces the probability for protonation of the N_1 position of adenine. It rules out the possibility of metal-assisted stabilization of mispairs analogous to protonated $AH+\cdots C$ and $AH^{+}\cdots G$ base pairs.

The adenine *anti* form and guanine keto form are very similar when these tautomers interact with charged $Pt(NH_3)_3$ and $Pt(NH_3)_2Cl$. The higher stability of these structures is due to a combined effect of the larger dipole moment and an efficient H-bonding to the base.

As to the treatment of neutral and charged Pt adducts, it can be noticed that the charged complexes exhibit some additional electrostatic terms of uncompensated charge. These extra terms are responsible for an increase in stabilization, interaction potential, and reaction energies. A basic explanation can be seen in the monopole ($Pt^{\delta+}$)-dipole (base) electrostatic energy. That is why energies for guanine-containing charged systems intensify more quickly in comparison with the charged systems of adenine, in spite of the same energy ratio in the case of neutral complexes where dative coordination Pt-N_7 dominates.

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