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Hydrogen Bonding and Covalent Effects in Binding of Cisplatin to Purine Bases: Ab Initio and Atoms in Molecules Studies

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Ab initio and density functional calculations are employed to investigate the role of hydrogen bonding in the binding of cisplatin to the purine bases guanine and adenine. Through the use of the theory of atoms in molecules (AIM), it is shown that hydrogen bonds are ubiquitous in such systems, with N–H···N and N–H···Cl interactions present in addition to the expected N–H···O. This in turn means that the known stability of cisplatin–guanine complexes cannot be ascribed solely to hydrogen bonding and allows decomposition of total binding energy into contributions from covalent and hydrogen bonds. To do so, a new method for predicting hydrogen bond energies from bond critical point properties is proposed, employing partial least-squares analysis to remove the family dependence of simple models. Still more hydrogen bond motifs are found in bifunctional complexes of the general type purine–$[Pt(NH_3)_2]^{2+}$–purine, including purine···purine contacts, though again the energetics of these are insufficient to explain the observed trends in stability. Finally, the effect of platination on the pairing of guanine with cytosine is studied in a similar manner, revealing large redistributions of hydrogen bonding but surprisingly small overall changes in pairing energy.

Introduction

cis-Diamminodichloroplatinum(II) (*cis*-$[Pt(Cl)_2(NH_3)_2]$, cisplatin, or *cis*-DDP) is a widely used antitumor drug,[1,2] its biological activity having been discovered almost 40 years ago.[3] The first clinical trials started[4] in the early 1970s, and a few years later cisplatin was approved for treating ovarian and testicular cancer. The mechanism of platinum drugs has been studied for decades,[5,6] with DNA identified as the main target. When cisplatin attacks DNA, monofunctional adducts of $[Pt(Cl)(NH_3)_2]^+$ are initially formed, which subsequently form bifunctional inter- and intrastrand cross-link complexes.[7] This triggers structural rearrangements, preventing DNA transcription activity and/or inducing recognition by damage repair proteins,[8] ultimately resulting in cell death through apoptosis, necrosis, or both.[9] Despite its high activity and wide use, cisplatin has some critical drawbacks as an anticancer drug, including severe toxic side effects, inherent and acquired resistance, and limited solubility in aqueous solution, such that cisplatin must be administered intravenously.[5] In order to overcome these drawbacks, the search for new platinum drugs is intense. However, only three more platinum drugs have been registered for clinical use, namely oxaliplatin,[10] carboplatin,[11,12] and nedaplatin.[13]

In recent years, theoretical approaches have increasingly supported the search for new platinum drugs: cisplatin itself has been intensively studied at many different levels of theory, and its electronic structure deeply investigated.[14−16] The hydrolysis of cisplatin, a key step in activation to its active form, has been analyzed in order to clarify both thermodynamics and kinetics of the cisplatin activation

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path.[17−19] Finally, the interaction between cisplatin and DNA has been widely studied with several methods in order to glean crucial information regarding the known specificity of cisplatin for certain sites, and the effect of platination on nucleic acids.[20−23] It is this aspect of cisplatin's activity that concerns us here, though we note that such problems have previously been tackled using a variety of theoretical methods.

Leszczynski[23] et al. have performed extensive DFT and ab initio calculations on complexes of platinum with one and two DNA bases, in order to examine the fundamental properties of platinum−DNA interaction. As expected, they found the G−Pt−G structure to be the most stable, along with the mixed complex A−Pt−G. In order to clarify the preference of cisplatin for guanine over adenine, Lippard and co-workers[22] carried out DFT studies of adenine and guanine complexes with $[Pt(Cl)(NH_3)_2]^+$: both thermodynamics and kinetics of the complexes were taken into account, confirming that guanine is up to 20 times more reactive than adenine toward cisplatin. Furthermore, the ability of Pt to bind to purines was studied to elucidate the features of the Pt−purine interaction, suggesting a lack of π-back-donation between metal and base.[24]

Carloni's group[19] used Car−Parrinello MD methods to study the properties of the Pt−DNA bond, along with some thermodynamic aspects of hydrolysis of cisplatin: good agreement with reported experimental data confirmed the success of this method in treating cisplatin biochemistry. Furthermore, several studies[25−27] indicate that platination of guanine enhances its pairing energy with cytosine, presumably due to polarization of guanine's electron density. Lippert and co-workers evaluated the association constant for the platinated Watson−Crick base pairs, finding a substantial increase in the stability of the complex. Theoretical approaches[27] support the outcome that a significant enhancement of the pairing energy results from platination.

In the present work, we have made extensive use of ab initio and DFT methods, along with the theory of atoms in molecules (AIM), in order to explore the roles of covalent and hydrogen bonding on the platination of DNA bases. Our main goals are to probe the extent to which hydrogen bonds determine specificity of binding and to clarify the platination effect on the guanine−cytosine pair and the chemical reasons that lead to the geometrical distortion of the Watson−Crick pair.

Computational Methods

All ab initio and DFT calculations were performed using Gaussian03.[28] The work of several groups[29,30] shows that very high level calculations, including extrapolation to the complete basis set limit and treatment of correlation using, e.g., coupled cluster methods, are required for quantitatively accurate results on DNA base pairing. Such calculations are unfeasible for the large systems studied here, and in any case, our goal is to explore qualitative trends rather than achieve quantitative accuracy. Therefore, we have taken an alternative route and attempted to test this against experimental or high level theoretical results wherever possible. All geometry optimizations were carried out without symmetry constraints at the HF level using the 6-31G(d,p) basis set[31] on C, H, O, and N atoms and the SDD basis set and ECP[32] on Pt. Following harmonic frequency calculation confirmation as minima or transition state, subsequent single point energy and electron density calculations were performed using the standard B3LYP density functional[33,34] with a DGDZVP basis set[35] on C, H, O, and N and SDD on Pt. An essentially equivalent method has recently been shown to accurately reproduce the pairing energy of guanine with cytosine.[30]

Extensive use was made of Bader et al.'s[36] theory of atoms in molecules (AIM), which partitions molecules into constituent atoms on the basis of the electron density. In this work, we have concentrated solely on topological analysis of the density,[37] i.e., finding minima, maxima, and saddle points in the density. Properties at such critical points (CPs), especially at (3, −1) or bond CPs, have found extensive use in characterizing bonding interactions.[38] In particular, the build up of electron density at a bond CP is established as an excellent measure of bond strength and order, at least within families of related bond.[39] Bond CP properties have

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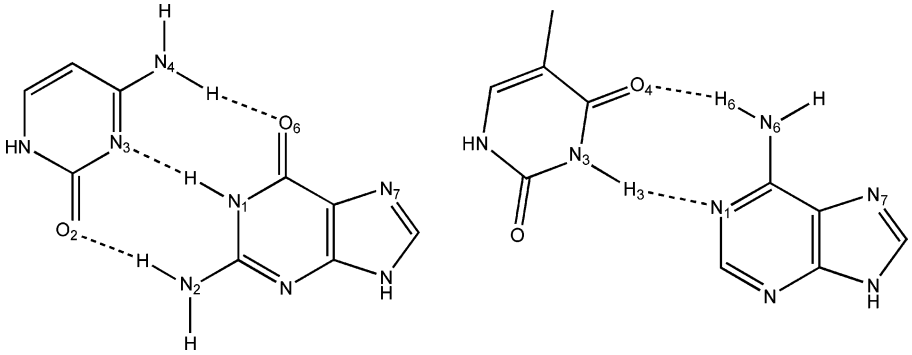

Figure 1. Numbering scheme for guanine−cytosine and adenine−thymine pair.

long been used to estimate the strength of hydrogen bonding interactions.[40] Many studies have demonstrated approximately linear relations between H-bond stabilization energy and both the increase in density at H···B bond CP and the decrease at A−H for a wide range of A−H···B systems. For instance, a recent study[41] showed a high-quality, family-independent relation between E_{HB} and $(\rho - \rho_0)/\rho_0$, where ρ is the density at the A−H bond CP in the H-bonded complex and ρ_0 is the equivalent value in the uncomplexed A−H donor.

In order to check how best to model the H-bonding interactions of cisplatin−DNA models, and to retrain such models at the theoretical level used, we extended the training set used in ref 41 to encompass a much wider range of hydrogen bonded species, including complexes of cisplatin with water, HF, etc. taken from our recent study.[18] Models of counterpoise corrected[42] hydrogen bond stabilization energy, E_{HB}, were then retrained, with all properties evaluated at the B3LYP/DGDZVP level (full details are reported as Supporting Information). Overall, $\rho_{H\cdots B}$ gave the best single parameter linear fit to E_{HB} ($r^2 = 0.96$, rms error = 1.74 kcal/mol), notably better than $[(\rho - \rho_0)/\rho_0]_{A-H}$ ($r^2 = 0.92$, rms error = 2.36 kcal/mol). However, both models showed some family dependence, with slightly different fits for H-bonds involving organics or inorganics. We therefore carried out a partial least squares (PLS) analysis to incorporate both density properties into a single model: using just one latent variable, PLS yielded a much less family-dependent fit, shown below (E_{HB} in kcal/mol, density properties in au)

$$E_{HB} = 0.384 + 187.07\rho_{H\cdots B} + 65.98[(\rho - \rho_0)/\rho_0]_{A-H} \quad (1)$$

$$n = 28;\ R^2 = 0.974;\ Q^2 = 0.972;\ \text{rms error} = 1.36$$

Q^2 is the cross-validated correlation coefficient, generated from omitting ca. 15% of data from each regression, a value close to the conventional R^2 indicating acceptable predictive as well as fitting accuracy. Further validation of the model comes from randomization of the *y*-data, which gives $R^2 = -0.113$ and $Q^2 = -0.215$ in the limit of fully randomized data, confirming that eq 1 does not suffer from overfitting. Thus, by combining density properties from A−H and H···B bonds, we are able to reduce the overall error of fitting by around 0.4 kcal/mol, and to produce a model equally applicable to organics or inorganics. To the best of our knowledge, combining closely related density properties with PLS to improve on simple linear fits to E_{HB} is a new approach, and one that appears worthy of further study.

Results and Discussion

(i) Monofunctional Platinum Adducts. Initial optimization of complexes of *cis*- and *trans*-$[Pt(Cl)(Pur)(NH_3)_2]^+$ (Pur = adenine or guanine) identified two stable binding sites for platinum complexes on guanine (O6 and N7) and two on adenine (N1 and N7): all other starting points (e.g., N3) for optimization either reverted to one of these, or was unstable. Table 1 shows that, as expected, the N7 guanine site is favored over the N7 of adenine by ca. 15 kcal/mol and O6 of guanine by ca. 12 kcal/mol. Complexation at N1 of adenine is relatively favorable, but as this site is blocked by hydrogen bonding in duplex DNA, this binding mode is not typically seen experimentally, and is therefore not considered further in this work. Further, cisplatin forms consistently more stable complexes than its trans analogue. While the affinity of cisplatin for guanine N7 is well established by many previous studies,[43−45] several features of Table 1 are worthy of further comment. First, the calculated binding energies are in excellent agreement with literature values, where available, supporting our choice of theoretical method.[22]

Table 1. Monofunctional Platinum Adducts

complex	binding energy (kcal/mol)[a]	r(Pt−X) (Å)	ρ_c(Pt−X) (au)
cisPt−G_{N7}	80.45 (80.69)[b]	2.092	0.1025
transPt−G_{N7}	68.54 (67.29)[c]	2.118	0.0964
cisPt−G_{O6}	68.69 (67.41)[c]	2.059	0.0933
transPt−G_{O6}	57.95 (59.22)[c]	2.129	0.0799
cisPt−A_{N7}	65.51 (65.47)[b]	2.077	0.1058
transPt−A_{N7}	56.04 (53.69)[c]	2.103	0.0996
cisPt−A_{N1}	71.56	2.062	0.1127

[a] Values in parentheses as described in footnotes *b* and *c*. [b] From ref 22. [c] Calculated value at the same level as ref 22.

Second, the difference in binding energy of cis- and transplatin is remarkably constant across three different binding sites, ranging from 12.0 kcal/mol for G_{N7} to 9.6 for A_{N7}, such that the preferred binding site of transplatin is also G_{N7}. The lesser stability of the trans- complexes is well-known and widely rationalized as a manifestation of the "trans effect".[46] However, that this difference is approximately constant is significant, because transplatin is much less able to form hydrogen bonds to guanine or adenine than is cisplatin (see below). Such hydrogen bonds have been

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Table 2. Geometrical and Electron Density Properties of Hydrogen Bond Interactions

	D−H···A	ρ(H···A) (au)	$\nabla^2\rho$(H···A) (au)	ρ_{A-H} (au)	r(H···A) (Å)	E_{HB}[a] (kcal/mol)
cisPt−G_{N7}	N−H···O	0.0293	0.1164	0.323	1.892	7.46
transPt−G_{N7}	N−H···O	0.0183	0.0748	0.328	2.104	4.21
cisPt−G_{O6}	N−H···Cl	0.0213	0.0694	0.330	2.278	5.74
transPt−G_{O6}	N−H···N	0.0204	0.0708	0.327	2.130	4.80
cisPt−A_{N7}	N−H···N	0.0175	0.0574	0.327	2.232	4.48
transPt−A_{N7}	N−H···N	0.0087	0.0313	0.330	2.568	0.52

[a] Calculated from eq 1.

proposed as the means by which cisplatin shows a preference for G_{N7}, but the results in Table 1 suggest that hydrogen bonding can play only a partial role in determining this preference. It is also evident that binding to G_{O6} is considerably weaker than to G_{N7}, reflecting the lesser importance of such carbonyl binding modes.

Table 1 also contains distance and bond CP data for all Pt−X bonds. Neither shows any clear relation with the total binding energy: the shortest Pt−N bond is found in cisPt−A_{N7}, while the most strongly bound complex, cisPt−G_{N7}, contains a Pt−N bond of intermediate length, albeit with rather high electron density. Moreover, the Pt−O bond in cisPt−G_{O6} is very short but, as measured by ρ_c, is weaker than any Pt−N bond. This suggests that overall binding energy must be considered as a sum of covalent and hydrogen bonding effects, and hence that properties of Pt−X bonds should not be expected to correlate with overall binding energy, but only with the covalent contribution to this.

As shown in Table 2, six of the seven complexes considered contain intramolecular base−ligand H-bonds, as evidenced by the presence of a (3, −1) CP and accompanying bond path. CisPt−G_{N7} contains the shortest intramolecular hydrogen bond of all monofunctional adducts studied (N−H···O = 1.892 Å), an interaction which also has the highest electron density and Laplacian at the H-bond CP. Only cisPt−A_{N1} contains no such H-bonds, instead adopting a conformation in which the planes of Pt-coordination and base are almost orthogonal (dihedral = 74.9°). Again, the trend of binding energies in Table 1 cannot be explained solely by these data: for instance, the N−H···N interaction in transPt−G_{O6} is shorter than the N−H···O of transPt−G_{N7}, but the latter complex is considerably more stable. It is notable that the complex with the highest overall binding energy, cisPt−G_{N7}, contains both a relatively strong Pt−N bond and the strongest N−H···O interaction, as measured by ρ_c.

Values of ρ_{A-H} and $\rho_{H\cdots B}$ may be used, via eq 1, to estimate hydrogen bond strengths, E_{HB}, also reported in Table 2. This analysis shows that the N−H···O contact in cisPt−G_{N7} is significantly stronger than any other present, but that all complexes except transPt−A_{N7} undergo substantial stabilization (4−6 kcal/mol) due to H-bonding. Thus, the extra stability conferred upon cisPt−G_{N7} by H-bonding is insufficient to explain the overall stability of this complex, echoing the conclusions of Lippard et al.[24] The complex transPt−A_{N7} contains the same N−H···N_6 contact as its cis analogue, but the steric requirements of trans coordination mean that in this case the H-bond is far from linear (143.7°), leading to much lower stabilization due to H-bonding here.

Table 3. Covalent Contribution to Binding Energy, and Properties of Pt−X (X = O6 or N7) Bonds

	E_{cov} (kcal/mol)	ρ(Pt−X) (au)	$\nabla^2\rho$(Pt−X) (au)
cisPt−G_{N7}	72.99	0.1025	0.374
transPt−G_{N7}	64.33	0.0964	0.365
cisPt−G_{O6}	62.95	0.0933	0.471
transPt−G_{O6}	53.15	0.0799	0.397
cisPt−A_{N7}	61.03	0.1058	0.390
transPt−A_{N7}	55.52	0.0996	0.379

Table 4. Properties of Bifunctional Platinum Adducts

complex	binding energy (kcal/mol)	r(Pt−X) (Å)	ρ(Pt−X) (au)
G_{N7}−cisPt−G_{N7}	226.26 (223.94[a])	2.099	0.101
G_{N7}−transPt−G_{N7}	230.62	2.093	0.103
G_{O6}−cisPt−G_{O6}	211.95	2.082	0.088
G_{O6}−transPt−G_{O6}	212.83	2.076	0.089
		2.058	0.095
A_{N7}−cisPt−A_{N7}	190.64	2.060	0.112
A_{N7}−transPt−A_{N7}	196.14	2.060	0.111
		2.063	0.111
A_{N7}−cisPt−G_{N7}	208.86	2.077 (Pt−A)	0.107
		2.084 (Pt−G)	0.105
cisPt−G "chelate"	165.56 (164.16[a])	2.140 (N)	0.091
		2.117 (O)	0.087

[a] Calculated value at the same level as ref 22.

Our estimate of the N−H···N interaction in cisPt−A_{N7} (4.48 kcal/mol) agrees well with Friesner's result of ca. 5 kcal/mol.[22] Several studies, including those of Sponer[47] and Burda,[27] have shown significant pyramidalization of adenine NH2 groups on complexation to metals, a result supported by our calculations on this complex (sum of angles around N7 = 336.5°). The complex cisPt−G_{O6} is stabilized by a Pt−Cl···H interaction, the presence of which is perhaps unsurprising given our recent findings on the acceptor strength of Pt−Cl groups.[18] Thus, even in these relatively simple cases, the abundance of donor and acceptor groups means that almost all complexes are significantly stabilized by hydrogen bonding. Only in transPt−A_{N7} does this not hold: here also a (3, −1) CP corresponding to a hydrogen bond is found, but with such low properties that its energy is estimated at just 0.52 kcal/mol, i.e., effectively zero given the RMS error on eq 1.

Having estimated the H-bond energy in each complex, we can estimate the stabilization due to covalent binding of platinum to O6 or N7, E_{cov}, as the difference between overall stabilization, and E_{HB}, i.e., binding energy = E_{HB} + E_{cov}. These values are reported in Table 3, along with density properties of the Pt−X (X = O6 or N7) in each complex. Since eq 1 is approximate, and since such an approach ignores any cooperativity between E_{HB} and E_{Cov}, such values are necessarily only estimates. However, it is clear that cisPt−G_{N7} contains the strongest Pt−X bond in this series, approximately 9 kcal/mol greater than that in transPt−G_{N7}, while Pt−O bonds to guanine and Pt−N bonds to adenine are weaker again. Encouragingly, there is a linear relationship ($r^2 = 0.963$) between E_{Cov} and ρ(Pt−X) for the four guanine complexes, though this does not hold for adenine complexes. This finding is tested for more complexes below, but further

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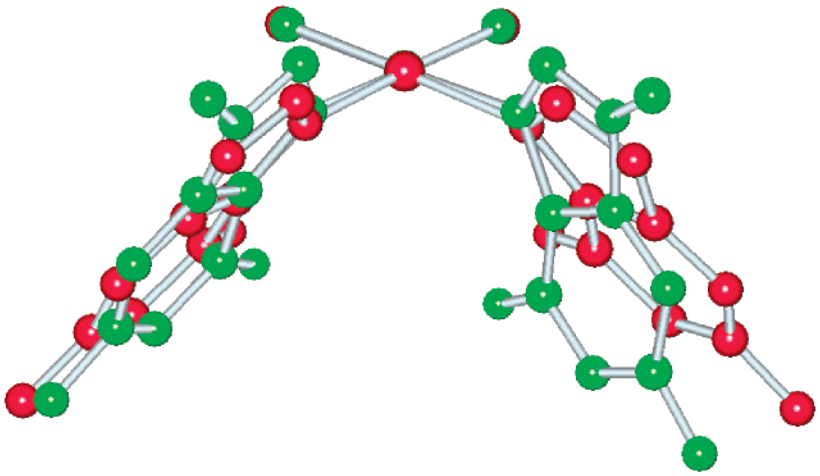

Figure 2. Comparison of X-ray (green) and optimized (red) structures of G_{N7}−cisPt−G_{N7}.

Table 5. Hydrogen Bonding in Bifunctional Adducts

complex	D−H···A	$\rho_{H\cdots A}$ (au)	$\nabla^2\rho_{H\cdots A}$ (au)	r(H···A) (Å)	E_{HB} (kcal/mol)	E_{cov} (kcal/mol)
G_{N7}−cisPt−G_{N7}	N−H···O (×2)	0.0207	0.0606	2.038	4.26	217.74
G_{N7}−transPt−G_{N7}	N−H···O (×2)	0.0232	0.0946	1.992	4.72	221.18
G_{O6}−cisPt−G_{O6}	N−H···N (×2)	0.0239	0.0816	2.054	4.93	202.09
G_{O6}−transPt−G_{O6}	N−H···N	0.0253	0.0860	2.021	5.12	202.59
A_{N7}−cisPt−A_{N7}	N−H···N	0.0224	0.0702	2.110	8.29	177.71
	N−H···N	0.0140	0.0442	2.317	4.64	
A_{N7}−transPt−A_{N7}	N−H···N	0.0289	0.0890	1.989	9.84	182.37
	N−H···N	0.0122	0.0389	2.393	3.93	
A_{N7}−cisPt−G_{N7}	N−H···O	0.0163	0.0698	2.088	5.19	200.22
	N−H···N	0.0164	0.0532	2.271	3.45	

work is required to establish whether such a relation is general, since the complexes studied here cover only a narrow range of binding energies. This approach therefore suggests that the extra stability of cisPt−G_{N7} over cisPt−A_{N7} is due to both covalent and hydrogen bonding effects, with the former dominating.

(ii) Bifunctional Platinum Adducts. It is known that when cisplatin binds to DNA, the major products are 1,2 intrastrand GG and AG adducts,[7] where platinum binds to both bases at the N7 position. We have therefore investigated a number of bifunctional adducts using the same methods as above, simply by replacing the chloride ion in the monofunctional complexes with an appropriate base. Table 4 contains binding energies and selected geometrical parameters of these bifunctional adducts, and the optimized geometry of a representative compound, G_{N7}−cisPt−G_{N7}, is shown in Figure 2.

Further support for the choice of method comes from the overall good agreement of optimized geometry of cisPt−G_{N7} with a structure of *cis*-[Pt(NH_3)$_2$] complexed to GpG obtained by Sherman et al. via X-ray diffraction,[48] as shown in Figure 2 (phosphate and sugar groups have been omitted from the X-ray structure for clarity). Coordination about the Pt center and internal geometry of each guanine are almost exactly reproduced, as are the geometry and orientation of one guanine. The orientation of the second ring is shifted by ca. 12° from the X-ray geometry, as measured by the dihedral angle between the planes of each ring. However, differences in orientation of similar magnitude are also found between the four independent molecules within the crystalline unit cell, so such a difference can probably be ascribed to crystal packing forces. Such forces would also explain why the optimized geometry is very close to C_s symmetry, unlike the X-ray structures which are all substantially asymmetrical.

As expected, complexes at the N7 site of guanine are most stable, though interestingly the complex of transplatin is more stable than that of cisplatin, perhaps due to decreased steric repulsion between bases, a hypothesis explored further below. Indeed, all trans complexes considered are more stable than their cis isomers. Such complexes are unlikely to form in a single strand of DNA due to the constraints of the backbone but could conceivably form across strands. This is in accord with the hypothesis that cisplatin's activity is related more to its ability to form 1,2 intrastrand linkages than simply to the strength of binding. Complexes through the O6 site of guanine are less stable and show less difference between cis and trans complexes, while adducts of adenine are less stable still, while the mixed complex A_{N7}−cisPt−G_{N7} has intermediate stability. Our calculations also corroborate previous findings[20,21] that a "chelate" complex with [Pt(NH_3)$_2$]$^{2+}$ bound to O6 and N7 of a single guanine is stable, albeit with rather lower binding energy and hence less experimental importance than the more conventional bifunctional complexes.

Table 5 contains details of hydrogen bonds within bifunctional complexes. For the bis-guanine complexes,

(48) Sherman, S. E.; Gibson, D.; Wang, A. H.-J.; Lippard, S. J. *Science* **1985**, *230*, 417.

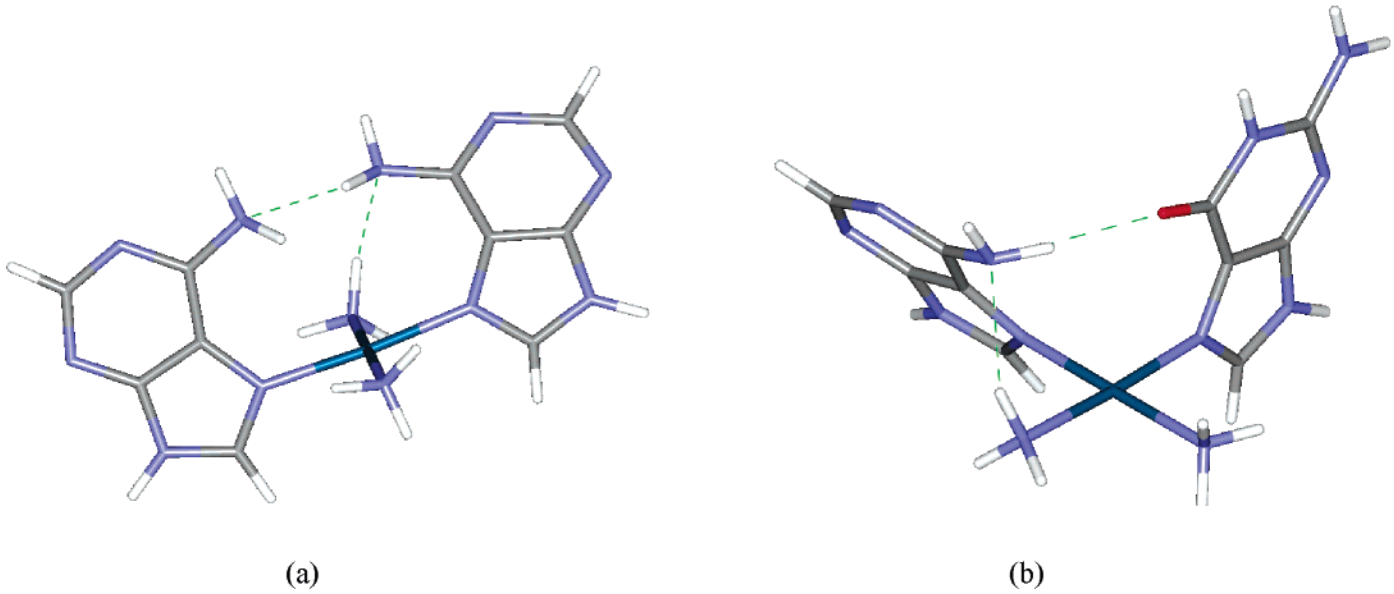

Figure 3. Optimized geometry of (a) A_{N7}−transPt−A_{N7} and (b) A_{N7}−cisPt−G_{N7}.

values are broadly similar to those in Table 2 for monofunctional adducts; i.e., replacement of Cl^- with guanine does not strongly affect the pattern of H-bonding. However, each N−H···O H-bond in G_{N7}−cisPt−G_{N7} is ca. 3 kcal/mol weaker than that in cisPt−G_{N7}, perhaps due to strain resulting from the proximity of two large bases. The two bis-adenine complexes reported in Table 5 form substantially asymmetric complexes. In both complexes, hydrogen bonds form a Pt−N−H···N_6−H···N_6−C ring structure (see Figure 3), in which Pt−N−H···N_6 is considerably shorter and stronger than N_6−H···N_6. Indeed, the former interaction in A_{N7}−transPt−A_{N7} is the strongest found in any complex considered in this study. Attempts to reoptimize this complex to the more expected symmetrical structure reverted to this structure in all cases. A similar pattern is seen in A_{N7}−cisPt−G_{N7}, where N−H···N and N−H···O H-bonds form an analogous ring structure, though the energy of these contacts is considerably lower than in the bis-adenine complexes. While the formation of such a motif would be hindered by a DNA backbone, the variety of H-bonds found in such apparently straightforward complexes is nonetheless remarkable. In contrast, however, no intramolecular H-bonds are present in the chelate structure, since both NH_3 groups are too remote from the guanine to form such interactions.

Again, we can estimate the contribution from covalent Pt−X bonds to overall binding energies by subtracting the sum of E_{HB} for all H-bonds in each complex; trends in E_{Cov} for monofunctional adducts are conserved here. These results confirm that the stability of G_{N7}−cisPt−G_{N7} and G_{N7}−transPt−G_{N7} is largely due to covalent effects, since in both cases the H-bonding characteristics are unremarkable. The extra stability of trans complexes also appears to be due largely to covalent bonding, rather than to reduced steric repulsion. While the trends noted for monofunctional complexes are conserved in Tables 4 and 5, i.e., binding energy of G_{N7} > G_{O6} > A_{N7}, values for bifunctional complexes are considerably more than twice the values for monofunctional adducts throughout. This effect is largest for G_{O6}−transPt−G_{O6} (97 kcal/mol), falling to 47 kcal/mol for G_{N7}−cisPt−G_{N7}. This appears to result from increased covalent binding of bases to the doubly charged $[Pt(NH_3)_2]^{2+}$ center, since the presence of extra H-bonds contributes at most around 10 kcal/mol.

Table 6. Hydrogen Bond Energies in Free and Platinated G≡C Pairs (kcal/mol)

	C−N_4H_4···O_6−G	G−N_1H_1···N_3−C	G−N_2H_2···O_2−C	E_{HB}	ΔE
G≡C	8.37	7.54	6.56	22.47	0.00
cisPt−G_{N7}≡C	4.89	8.76	8.95	22.60	+0.13
transPt−G_{N7}≡C	4.90	9.09	9.13	23.12	+0.65
cisPt−G_{O6}≡C	1.52	6.84	9.45	17.81	−4.66
G_{N7}−cisPt−G_{N7}≡C	3.78	9.66	10.63	24.07	+1.60
G_{N7}−transPt−G_{N7}≡C	3.80	9.38	10.52	23.70	+1.23
A_{N7}−cisPt−G_{N7}≡C	3.57	9.80	10.98	24.35	+1.88

(iii) Effect of Platination on Base Pairing. The pairing of guanine with cytosine has a long history of experimental and theoretical study,[30,47,49−52] so we comment only briefly on our findings on this. The BSSE corrected binding energy for G≡C is 25.14 kcal/mol, somewhat above the experimental value of 21.00 kcal/mol.[53] Interestingly, eq 1 performs rather better in predicting this pairing energy, giving individual H-bond energies of 8.37, 7.54, and 6.56 kcal/ mol for C−N_4H_4···O_6−G, G−N_1H_1···N_3−C, and G−N_2H_2···O_2−C (Table 6, see Figure 1 for numbering), which sum to 22.47 kcal/mol. Thus, our chosen method appears to be capable of providing accurate, BSSE-free H-bond energies even in cases where multiple H-bonds are present.

Table 6 details how platination at various sites affects the pattern of G≡C pairing. It is clear that in all cases significant changes result from the covalent binding of platinum, and that the pattern of changes is broadly conserved. Throughout,

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(50) Popelier, P. L. A.; Joubert, L. *J. Am. Chem. Soc.* **2002**, *124*, 8725.
(51) Guerra, C. F.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. *Chem. Eur. J.* **1999**, *5*, 3581.
(52) Popelier, P. L. A.; Joubert, L. *Phys. Chem. Chem. Phys.* **2002**, *4*, 4353.
(53) Yanson, I. K.; Teplitsky, A. B.; Sukhodub, L. F. *Biopolymers* **1979**, *18*, 1149.

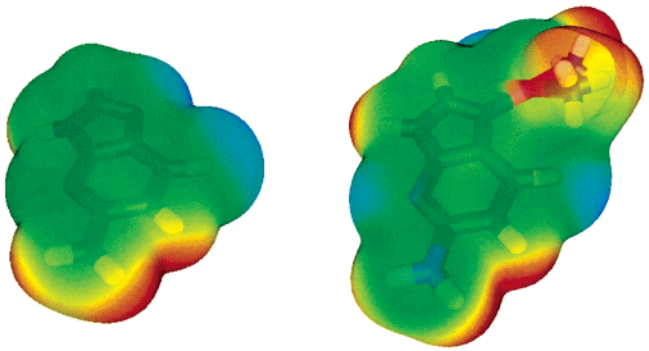

Figure 4. Isosurface (0.001 au) MEP of guanine and cisPt−G_{N7} (blue is negative, red positive).

the strongest H-bond in free G≡C is weakened by between 40% and 80% of its original value. This might be expected where the H-bond acceptor atom for this interaction, G_{O6}, is involved directly in platination, and indeed, the largest changes are seen where this is the case. However, substantial disruption of G_{O6}'s acceptor ability also stems from coordination at G_{N7}. It is not clear whether this is due to the inductive effect of the positive metal center, or to the direct effect of the Pt−N−H···O H-bond already present. Some evidence for the former scenario may come from the fact that the C−N_4H_4···O_6−G H-bond is weaker in the dicationic bifunctional adducts than the monofunctional ones.

In contrast, H-bonds in which guanine acts as an H-bond donor are generally stronger in platinated complexes than in free G≡C. This is more pronounced for G−N_2H_2···O_2−C, wherein increases of 35−65% are observed, whereas smaller increases are seen in G−N_1H_1···N_3−C in most cases, and even a small decrease is found for cisPt−G_{O6}≡C. This decrease is clearly seen in electron density properties but is not apparent from consideration of geometrical properties alone: neither H···N nor N···N distances (not reported) change from their free G≡C values in this case. Also, that a larger increase in donor strength is found at N_2−H_2, i.e., furthest from the site of platination, goes against electrostatic arguments which would suggest that N_1−H_1 should be affected more.

Clearly, platination substantially changes the bonding and electron distribution within the guanine, yielding more subtle changes in the pattern of H-bonding than might initially be expected. Figure 4 shows the molecular electrostatic potential (MEP) on the 0.001 au isodensity surface for guanine and cisPt−G_{N7}. Drastic changes are evident throughout the molecule, most notably at O6 but also at most other donor and acceptor sites. The acceptor ability of O6 is almost completely lost, with only a very small region of negative potential associated with this atom, while N3's negative MEP is significantly enhanced, such that this site becomes the global minimum. Donor strengths of N_1−H_1 and N_2−H_2 are less apparently less affected by platination at N7, nor is any major difference between these two sites apparent in Figure 4.

Despite these changes, the overall strength of G≡C pairing is remarkably insensitive to platinum binding at G_{N7}, the largest change being +1.9 kcal/mol in the case of A_{N7}−cisPt−G_{N7}≡C, and just +0.13 kcal/mol for cisPt−G_{N7}≡C.

Table 7. Effect of Platination on Geometry of GC Pairing

	angle between C═O vectors in G and C (deg)	dihedral between mean planes of G and C (deg)
GC	172.42	0.00
cisPt−G_{N7}≡C	170.85	7.42
transPt−G_{N7}≡C	172.96	2.18
cisPt−G_{O6}≡C	158.66	29.07
G_{N7}−cisPt−G_{N7}≡C	175.35	1.33
G_{N7}−transPt−G_{N7}≡C	173.96	1.38
A_{N7}−cisPt−G_{N7}≡C	175.25	2.57

Such changes are essentially insignificant, given the statistical error associated with eq 1. Binding to G_{O6}, on the other hand, reduces the overall stabilization by 4.7 kcal/mol, due to a massive reduction in the strength of C−N_4H_4···O_6−G, offset slightly by an increase in the strength of G−N_2H_2···O_2−C. These results contradict previous suggestions[27] that platination enhances the hydrogen bonding between guanine and cytosine, suggesting a more subtle redistribution of stabilization. An alternative explanation for the observed[26] increase in formation constant of cisPt−G_{N7}≡C over G≡C is discussed below.

The effect on G≡C of the chelating bifunctional adduct has been addressed before,[20,21] albeit not using AIM methods, so only a brief discussion is given. Here, all classical Watson−Crick H-bonds are destroyed, and the mutual planarity of bases is lost, with a dihedral angle of 63°. However, there remains substantial overall stabilization: only one intermolecular H-bond CP was found in this case, a very short, strong C═O···H−N contact (H···O = 1.642Å), predicted to have an energy of 26.43 kcal/mol. Thus, if present, such a chelate would have a drastic effect on base pairing and DNA structure, though the results in Table 4 suggest this is energetically unlikely.

This redistribution of H-bond energy leads to geometrical changes in the G≡C pair, characterized in Table 7 as (a) the angle between C═O vectors in G and C and (b) the dihedral angle between the mean planes of each base. The free G≡C pair is exactly planar, and the C═O vectors are almost exactly antiparallel. This arrangement is broadly conserved in all complexes other than cisPt−G_{O6}≡C, with less than 2° change in C═O vectors and up to 7.4° in the dihedral between mean planes, the largest changes being found for cisPt−G_{N7}≡C. The geometry of this complex appears to show that the N−H···O H-bond from cisplatin induces this change in dihedral by "attacking" the bottom face of guanine's C═O, leading the N−H···O from cytosine to shift round to the top face, such that the two H-bonds to O6 are approximately collinear (161.2°). In contrast, platination at O6 leads to large changes in geometry, with ca. 15° change in C═O···C═O angle and almost 30° between the mean planes of G and C, both of which can be ascribed to the almost complete loss of the C−N_4H_4···O_6−G interaction (see Figure 5).

In general, intramolecular H-bond types and strengths in the G≡C paired complexes do not differ greatly from those reported in Tables 2 and 5, and so are not reported. Estimation of all inter- and intramolecular H-bond energies gives the covalent contribution to the overall binding energy (Table 8). Combining these values with those in Tables 3

Table 8. Covalent and H-Bond Contributions to Binding Energy of Platinated G≡C Pairs

	binding energy (kcal/mol)	E_{HB} (kcal/mol)	E_{cov} (kcal/mol)	r(Pt−X)[a] ‘(Å)	$\sum\rho$(Pt−X) (au)
cisPt−G_{N7}≡C	111.89	30.56	81.33	2.080	0.106
transPt−G_{N7}≡C	102.06	27.48	74.58	2.105	0.100
cisPt−G_{O6}≡C	97.63	23.21	74.42	2.069	0.106
G_{N7}−cisPt−G_{N7}≡C	266.51	36.99	229.52	2.082 2.095	0.208
G_{N7}−transPt−G_{N7}≡C	270.18	34.22	235.96	2.076 2.095	0.209
A_{N7}−cisPt−G_{N7}≡C	245.74	36.23	209.51	2.077 2.088	0.212

[a] Where two values given, the first corresponds to the base involved in a G≡C pair.

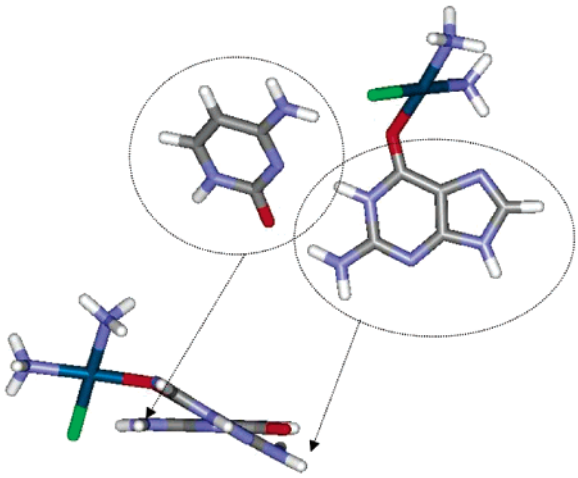

Figure 5. Schematic of cisPt−G_{O6}≡C, showing the dihedral between planes of G and C.

and 4 further confirms the excellent linear relation between E_{cov} and ρ(Pt−X) for guanine complexes ($r^2 = 0.99$). Moreover, this analysis indicates an increase in E_{cov} in the G≡C paired complexes compared with their unpaired analogues. For instance, the simple G_{N7} adduct of cisplatin shows an increase of 8.3 kcal/mol when paired with cytosine, with a corresponding decrease in bond length and increase in BCP density. This effect is even more pronounced in other adducts, such that the average increase in E_{cov} on addition of cytosine is 11 kcal/mol, reflected in bond lengths and electron densities throughout. Thus, although the formation energy of platinated G≡C pairs is greater than that of isolated guanine, our analysis suggests this is due to the formation of stronger Pt−X bonds rather than to enhanced hydrogen bonding between guanine and cytosine, as proposed previously.[27]

Conclusions

Through the use of ab initio, DFT, and AIM methodologies, we have shown the following: (i) Calculations at the B3LYP/DGDZVP(SDD)//HF/6-31G(d,p)(SDD) level are capable of reproducing literature (where available) or higher-level theoretical geometries and binding energies of complexes of cisplatin with purine bases. (ii) Electron density properties and partial least-squares analysis can be used to form an accurate, family-independent model of H-bond strength, which can then be used to decompose the total binding energy of cisplatin−purine complexes into covalent and H-bond contributions. (iii) Hydrogen bonds are ubiquitous in such complexes, with N−H···O, N−H···N, and N−H···Cl contacts all observed. Thus, the known preference of cisplatin for the N7 position of guanine cannot be explained on the basis of H-bonding alone, even though this complex contains one of the strongest H-bonds found. (iv) Complexes of cisplatin with two purine bases follow the same general trend of stability as do single base complexes, although trans complexes are generally more stable than their cis counterparts. An even greater variety of H-bond motifs is present in such bifunctional complexes, with purine··· purine contacts dominating structures containing adenine in particular. (v) Platination at the N7 position of guanine has a dramatic effect on the hydrogen bonds involved in pairing to cytosine, weakening (C)N_4−H_4···O_6(G) but strengthening (G)N_1−H_1···N_3(C) and (G)N_2−H_2···O_2(C), leading to large changes in the geometry of the G≡C pair, but only small differences in the total binding energy. Platination at O6 or chelation to N7 and O6, on the other hand, destroys the normal Watson−Crick pattern of H-bonding, though substantial pairing energy remains.

Acknowledgment. The authors are grateful to the Cardiff Visualisation facility and EPSRC’s National Service for Computational Chemistry for generous allocations of computing resources, and to Miss Efi Mantzourani for assistance in preparing figures.

Supporting Information Available: Optimized geometries of all species as Cartesian (*xyz*) coordinates and all data for the development of eq 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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