Multiple Proton-Transfer Reactions in DNA Base Pairs by Coordination of Pt Complex

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The possibility of multiple proton-transfer reactions in DNA base pairs because of coordination of cisplatin is theoretically elucidated by density functional theory (DFT) and by quantum mechanics/molecular mechanics (QM/MM) methods with an ONIOM method. From the energetics of two base pairs with the cisplatin, it is theoretically confirmed that the Pt complex is likely to bind in the order *cis*-(CG)-Pt-(GC), *cis*-(CG)-Pt-(AT), *cis*-(TA)-Pt-(AT), where G, C, A, and T are guanine, cytosine, adenine, and thymine, respectively, and the Pt atom bonds to the N_7 site of G and A. This result supports the experimental evidence, where the structure *cis*-A-Pt-A is seldom observed at room temperature. The single proton-transfer reaction occurs in one of the two GC pairs. No simultaneous single proton-transfer reaction can occur in both base pairs. Two different single proton-transferred structures (*cis*-$(CG^*)_d$-Pt-$(GC)_p$ and *cis*-$(CG)_d$-Pt-$(G^*C)_p$, where the asterisk means a proton donor of G) are as stable as the original structures $(CG)_d$-Pt-$(GC)_p$. The same tendency was observed with *cis*-(CG*)-Pt-(AT). In contrast to cisplatin, multiple single proton-transfer reactions occur in the system consisting of two base pairs with transplatin. The optimized structure agrees with the experimental data for Pt-G coordination except for the hydrogen-bonding length.

Introduction

Since cisplatin ($Pt(NH_3)_2Cl_2$) was discovered by Rosenberg et al.[1] in 1969, Pt complexes have received much attention for their effect as antitumor drugs. Cisplatin distorts the structure of DNA by making a bridged structure with N_7 of guanine (G) or adenine (A). It causes a cell disorder that leads to apoptosis of the living cell.[2,3] Although other anticancer drugs now replace cisplatin, it is used as a benchmark comparator for new drugs. Because cisplatin contains only 11 atoms, it has been a good target for quantum chemistry and has been investigated from both the experimental and theoretical viewpoints. Experimentally, it is known that the bridged structure consists of 65% 1,2-d (GpG) (denoted as *cis*-G-Pt-G), 25% 1,2-d (ApG) (*cis*-G-Pt-A), and the rest other bridged structures.[4,5] Nevertheless, the existence of 1,2-d (ApA) (*cis*-A-Pt-A) is hard to confirm. The distorted DNAs are observed in X-ray analysis[6,7] at 1.65−2.50 Å resolutions and in NMR[8−10] experiments. These structures can be freely taken from the protein data bank (PDB). From theoretical aspects, cisplatin has many interesting topics such as a ligand substitution,[11−13] a hydration reaction,[14−17] differences with transplatin,[18−21] and DNA binding. Ligands of cisplatin become NH_3 and/or H_2O by hydration reactions, depending on the pH of the solution.[22,23] Note that the ligands of cisplatin in the human body are recognized as NH_3.

In view of the DNA binding, there have been many studies of the reaction between cisplatin and DNA bases.[24−27] In particular, Burda's group[28,29] assumed [*cis*-$Pt(NH_3)_2(N_7$-G(or A)),(N_7-G(or A))]$^{2+}$ as the bridging structures and estimated binding energies of Pt-G and Pt-A at the MP2/6-31+G level. They found that the ease of binding to the Pt atom was in the order *cis*-G-Pt-G, *cis*-G-Pt-A, and *cis*-A-Pt-A, and the angle of N_7-Pt-N_7 was about 90° for all cases. They confirmed that these bridges were stabilized by a hydrogen bond between G (or A) and a ligand of the Pt atom, such as H_2O or NH_3. Reactions between cisplatin and two DNA purine bases (such as 1,2-d (GpG), 1,2-d (GpA)) were studied by Raber et al.[30] and Costa et al.[31] Their results for reaction barriers and the reaction constants of substitution reactions reproduce the experimental data well.

There are two possible influences of Pt-DNA formation: (1) global structural changes, such as the distortion of the DNA structure, or (2) local structural changes, such as a DNA mutation because of proton-transfer reactions. The former case is very hard to tackle with full quantum chemistry computation, because such a large system is too huge to treat. For the latter case, the DNA mutation can be estimated by using small molecular systems such as several DNA base pairs. In 1963, Löwdin[32] proposed the possibility of a proton tunneling model in DNA base pairs. He also suggested a simultaneous double proton-transfer (DPT) model between AT and GC pairs. There have been many theoretical approaches to the proton-transfer reaction in the AT pair[33−35] and the GC pair.[35−37] The hydrogen bonding in the DNA base pair has been extensively studied theoretically, and there are many studies investigating the energy of hydrogen bonds.[38−43] In 2004, Hobza and his co-workers[40,41] computed very accurate hydrogen-bonding energies with the RI-MP2 method with complete basis set (CBS) corrections. Burda et al. evaluated the hydrogen-bonding energy of a Pt-bound GC pair at the MP2/6-31G (d)//HF/6-31G (d) level.[44] They also indicated the deprotonation of the N_1 site of G.

In our previous study,[45] we revealed that the platinum complex causes a single proton-transfer (SPT) reaction between N_1 (G) and N_3 (C) in the GC pair. Note here that the SPT reaction does not occur in the GC pair itself, but double proton transfer (DPT) does. Its reaction barrier decreases from 20−22 kcal/mol for the DPT reaction without the Pt complex to 1.5−3 kcal/mol for the SPT reaction with the Pt complex. The structure

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that undergoes the SPT reaction is as stable as the original structure. For further research, it is natural to ask what happens with two or more base pairs. In this paper, we will discuss the following two points: (1) binding energies between base pairs and cisplatin and (2) the possibilities of simultaneous single proton transfers in two or more base pairs.

Computational Details

We first define two types of model systems: the "two base pair" (2bps) model and the "four base pair" (4bps) model. The former consists of two base pairs and cisplatin without the backbone molecules, such as sugar and phosphate groups, while the latter consists of four base pairs and the backbone molecules so that it includes the effects of the backbone molecules and base stacking.

The 2bps model is small enough to compute with the full quantum chemistry calculation. Density functional theory (DFT) was adapted and the modified Parr−Wang functional (mPW1PW91)[46] was chosen as an exchange−correlation functional, because the functional is modified to describe the hydrogen bonding. In this paper, the Stuttgart/Dresden effective core potentials (ECPs)[47] were used for the Pt atom and the 6-31G(d,p) basis for the other atoms. The validity of using this method will be discussed in the following section.

To investigate the effects of DNA stacking, the backbone and countercations, we then proceed to the 4bps model. It involves about 280 atoms, so we used the QM/MM method to reduce computational costs. We adopt an ONIOM method,[48] where we utilize the method used in the 2bps model for the QM part and the universal force fields (UFF)[49] for the MM part. In this paper, we treat two of the four base pairs as the QM part and the rest as the MM part for simplicity. We take the initial structure 1,2-d (CpX_1pX_2pT) from PDB (PDBID: 1a84), where X_1 and X_2 are purine moieties bound to the Pt complex so that there are three patterns of X_1 and X_2. The ligands of the cisplatin were assumed as NH_3, as in the human body. We also assumed that the Pt atom binds to N_7 of G and A. To keep the whole system neutral, we added sodium atom at every PO_4^- molecule as the countercation. The GAUSSIAN03 program package[50] was used throughout this work.

Results and Discussion

Assessment of the DFT Method. In our previous work, we computed the hydrogen-bonding energy at the MP2 level. Instead of MP2, we used the DFT method in this paper so that we first performed an assessment of DFT in the calculation of the system of interest. In general, the DFT method is poor at describing hydrogen bonds and van der Waals forces in DNA base pairs. We here confirm the validity of DFT methods from the viewpoints of hydrogen-bonding energy and of the reaction barrier of single proton-transfer (SPT) reactions.

From experiment, the bridged structure of [*cis*-Pt $(NH_3)_3$-GC]$^{2+}$ (denoted as GC-Pt in Table 1) is used as a model molecule. We adopt the DFT and MP2 methods, where we chose the most typical Becke 3 hybrid functional (B3LYP)[51] and mPW1PW91 as the exchange−correlation functional. The basis sets are all LanL2DZ[52] as in our previous work. The Stuttgart/Dresden effective core potential (ECP) was used for the Pt atom and Pople-type double-ζ basis sets with polarization functions were used for the other atoms.

Table 1 lists the results of the hydrogen-bonding energies of the GC pair. These are given by the energy difference between [*cis*-$Pt(NH_3)_3GC]^{2+}$ and [*cis*-$Pt(NH_3)_3G]^{2+}$ + C. Because of the coordination of cisplatin, the hydrogen-bonding energy increases by 7−11 kcal/mol at both the B3LYP and mPW1PW91 levels, but by 3 kcal/mol at the MP2 level. Although the DFT method tends to overestimate the hydrogen-bonding energy, it can be used at least for qualitative discussion, because its order does not change. We compared the reaction barrier of the SPT reaction using the same notation as in our previous study.[45] Table 2 lists results for the reaction barrier at the DFT and MP2 levels, where the energy differences ΔE_1 and ΔE_2 in Table 2 are schematically defined in Figure 1. These results indicate that there are no great differences between the DFT and MP2 methods. The difference for the energy barrier is 3 kcal/mol between all LanL2DZ and 6-311+G(d,p) in the DFT method. The 6-31+G(d) basis function gives a higher energy barrier than an accurate basis function such as 6-311+G(d,p), because 6-31G(d) and 6-31+G(d) do not include any polarized functions for hydrogen atoms. Thus, it is necessary to include the polarized functions at least for the hydrogen atom that relates to the SPT reaction. The energy obtained by using 6-31G(d,p) is almost the same as that by 6-31++G(d,p). Thus, the mPW1PW91 DFT with the 6-31G(d,p) basis is sufficient for a qualitative discussion for our interests.

TABLE 1: The Difference in Hydrogen Bond Energies between G and C (in kcal/mol)

	LanL2DZ	6-31G*	6-31G**	6-31+G*	6-311+G**
			B3LYP		
GC	35.3	30.9	31.0	26.7	26.2
GC-Pt	47.9	37.3	37.5	32.9	37.0
			mPW1PW91		
GC	36.1	31.0	31.3	27.6	27.2
GC-Pt	48.9	38.8	39.4	35.3	38.4
			MP2		
GC	38.7	31.3	30.9	29.3	
GC-Pt	47.8	34.1	34.0	32.5	

TABLE 2: The Energy Difference of Single Proton Transfer (in kcal/mol)[a]

	B3LYP		mPW1PW91		MP2	
	ΔE_1	ΔE_2	ΔE_1	ΔE_2	ΔE_1	ΔE_2
LanL2DZ	2.3	0.15	1.6	0.0	3.0	−0.72
6-31G*	5.8	1.0	5.1	0.93		0.10
6-31G**	4.6	0.90	3.9	0.79		−0.11
6-31+G*	6.4	1.5	5.6	1.4		0.19
6-31++G**	5.2	1.4	4.4	1.2		
6-311+G**	5.6	1.4	4.6	1.2		

[a] ΔE_1 and ΔE_2 are defined in Figure 1. The LanL2DZ basis function is used for all atoms. The Stuttgart/Dresden ECP was used for the Pt atom.

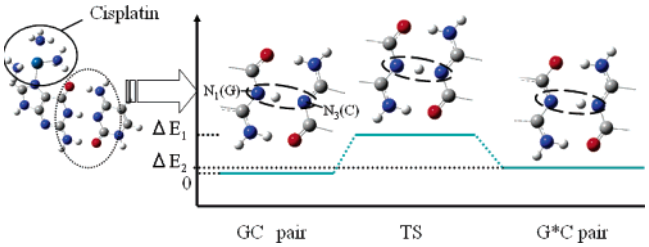

Figure 1. The reaction diagram of a single proton transfer between N_1 (G) and N_3 (C) of a Pt-bound GC pair. ΔE_1 and ΔE_2 are defined as the energy difference from the GC pair (kcal/mol).

2bps Model. Figure 2 shows all optimized geometries of the three types of model molecules: *cis*-(CG)-Pt-(GC), *cis*-(CG)-Pt-(AT), and *cis*-(TA)-Pt-(AT). The structure of *cis*-(CG)-Pt-(GC) was distorted in comparison with those in the DNA because of repulsion between the two O_6 atoms. Although one of the GC pairs keeps a planar structure, the other GC pair was

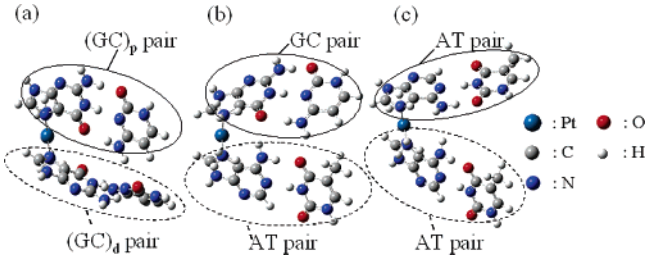

Figure 2. The optimized structure of the 2bps models: (a) *cis*-$(CG)_p$-Pt-$(GC)_d$, (b) *cis*-(CG)-Pt-(AT), and (c) *cis*-(TA)-Pt-(AT).

TABLE 3: Energy Difference of the Substitution Reaction (in kcal/mol)[a]

	$B_1 = G$, $B_2 = G$	$B_1 = G$, $B_2 = A$	$B_1 = A$, $B_2 = G$	$B_1 = A$, $B_2 = A$
ΔE_1	46.1 (47.9)	46.1 (47.9)	14.7 (16.4)	14.7 (16.4)
ΔE_2	24.5 (25.9)	6.9 (8.2)	38.2 (41.7)	2.4 (4.9)
total	70.5 (73.8)	52.9 (56.1)	52.9 (56.1)	17.1 (21.3)

[a] The "model" molecule was used. The optimized NH_3 and $[Pt(NH_3)_4]^{2+}$ is used for energy calculation. The numbers in parentheses represent the energy including zero-point energy.

greatly distorted. We distinguish them by referring to the former as the "$(GC)_p$ pair" and the latter as the "$(GC)_d$ pair", where p and d denote planar and distorted, respectively. Hereafter, we will describe the structure of the 2bps model in the form *cis*-$(GC)_p$-Pt-$(GC)_d$. Unlike the structures of *cis*-$(GC)_p$-Pt-$(GC)_d$, all base pairs in the *cis*-CG-Pt-AT and *cis*-TA-Pt-AT almost keep their planarity.

We evaluated the binding energy of cisplatin and the base pair. To estimate the hydrogen-bonding energy, we assumed a two-step reaction: (1) $[Pt(NH_3)_4]^{2+} + B_p\text{-}B'_p \rightarrow [Pt(NH_3)_3B_pB'_p]^{2+} + NH_3$ (reaction energy: ΔE_1) and (2) $[Pt(NH_3)_3B_pB'_p]^{2+} + B_dB'_d \rightarrow [cis\text{-}Pt(NH_3)_2B_pB'_pB_dB'_d]^{2+} + NH_3$ (reaction energy: ΔE_2), where B_x is A or G, B'_x represents the complementary base of B_x (x = p, d). Results are shown in Table 3. Comparing the ΔE_1 values, the binding energy of Pt-(GC) is much higher than that of Pt-(AT), by 30 kcal/mol. ΔE_1 is larger than ΔE_2 because of the Coulomb repulsion between the original $[Pt(NH_3)_3B_pB'_p]^{2+}$ and the additional base pair. Moreover the bases are likely to bind to the Pt complex in the order *cis*-(CG)-Pt-(GC), *cis*-(CG)-Pt-(AT), and *cis*-(TA)-Pt-(AT). In particular, the binding energy of the *cis*-(TA)-Pt-(AT) is remarkably low compared with those of *cis*-(CG)-Pt-(GC) and *cis*-(CG)-Pt-(AT). These results support both experimental evidence and the tendencies of the models studied by Burda and Leszyczynski,[28] as mentioned in the introduction. Therefore, we will focus on the models of *cis*-(CG)-Pt-(GC) and *cis*-(CG)-Pt-(AT) in further discussion.

Next, we discuss the possibility of multiple proton-transfer reactions in these systems. Here we depict a restricted two-dimensional potential energy surface (PES) of two different hydrogen atoms between N_1 ($G_{p/d}$) and N_3 ($C_{p/d}$) in Figure 3, where the geometry except for the two hydrogen atoms is fixed. Indeed, the rigid PES used here is a very rough approximation, because it does not consider the effect of structure relaxation. Nevertheless, it is at least useful to intuitively understand the proton-transfer reactions between bases. In this paper, we depicted this PES to confirm whether proton-transferred structures exist or not. The origin of the PESs is at the center of both hydrogen bonds, and the PESs were plotted every 0.05 Å. From this figure, there are three possible minima, at the points marked X in the figures. No two simultaneous SPT reactions are found, as denoted by ▲. We here confirmed that one SPT

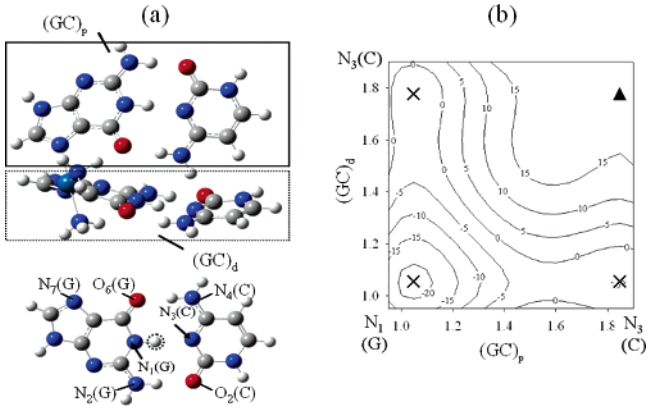

Figure 3. (a) Definitions of variables in a 2bps model of *cis*-$(CG)_p$-Pt-$(GC)_d$. Only the hydrogen atom surrounded by the dotted line can move. (b) The potential energy surface of hydrogen atoms. The numbers on each axis represent the distance between N_1 (G) and the hydrogen atom (in A). The origin is set at the point where both hydrogen atoms are at the middle of the hydrogen bonding.

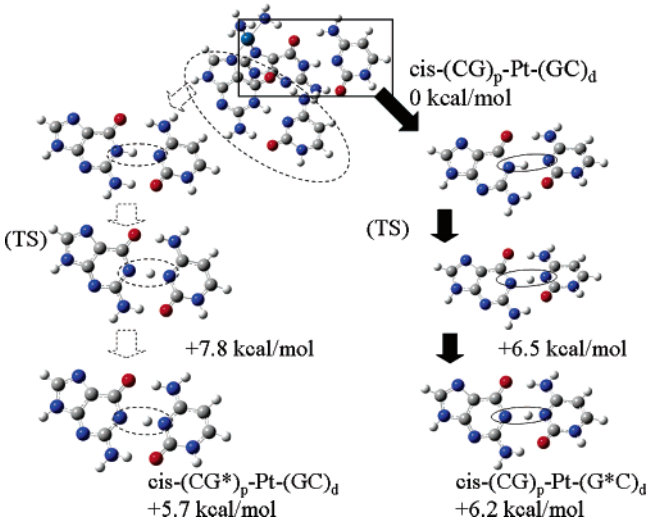

Figure 4. The reaction diagram for single proton transfer between N_1 (G) and N_3 (C) of the 2bps model of *cis*-(CG)-Pt-(GC). The numbers in the figure denote relative energies measured from *cis*-$(CG)_p$-Pt-$(GC)_d$.

reaction can occur even in two GC pairs. Figure 4 shows the results of geometry optimization of *cis*-$(CG)_p$-Pt-$(GC)_d$, *cis*-$(CG^*)_p$-Pt-$(GC)_d$, and *cis*-$(CG)_p$-Pt-$(G^*C)_d$, where G* again means the proton donor of G. This result is similar to the SPT reaction in one GC pair, where the reaction barrier is about 5−6 kcal/mol. The difference of the energy barrier between *cis*-$(CG^*)_p$-Pt-$(GC)_d$ and *cis*-$(CG)_p$-Pt-$(G^*C)_d$ is because of the difference in their planarity. The energy barrier of the SPT reaction in two GC pairs increases compared with one GC pair, as shown in Table 1. A structure of simultaneous SPT, *cis*-$(CG^*)_p$-Pt-$(G^*C)_d$, cannot be found, as expected from the potential surface depicted in Figure 3.

To analyze why the simultaneous SPT reaction does not occur in *cis*-(CG)-Pt-(GC), we consider models of *trans*-(CG)-Pt-(GC), *trans*-(CG)-Pt-(G*C), *trans*-(CG*)-Pt-(GC), and *trans*-(CG*)-Pt-(G*C). Their structures were optimized as shown in Figure 5. From the figure, two GC pairs keep their planarity, so we call this system *trans*-$(CG)_1$-Pt-$(GC)_2$. Unlike cisplatin, the double SPT structure *trans*-$(CG^*)_1$-Pt-$(G^*C)_2$ does exist if the two GC pairs are coordinated by the platinum complex in the trans position. The energy difference between *trans*-$(CG)_1$-Pt-$(GC)_2$ and *trans*-$(CG^*)_1$-Pt-$(G^*C)_2$ is about 8.7 kcal/mol, comparable to the sum of the energy differences (8.6 kcal/mol)

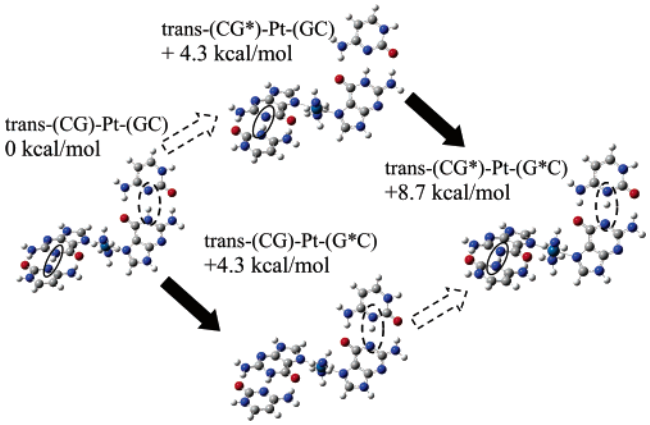

Figure 5. The reaction diagram of single proton transfer between N_1 (G) and N_3 (C) of the 2bps model of *trans*-(CG)-Pt-(GC)). The numbers in the figure denote relative energies measured from *trans*-(CG)-Pt-(GC). The dashed line arrows correspond to the SPT reaction indicated by the dashed circles. The solid arrows correspond to the SPT reaction indicated by the solid circles.

TABLE 4: The Differences in Energy in the "2bps Model" Molecules (in kcal/mol)

	cis-$(CG)_p$-Pt-$(GC)_d$	
$(CG)_p/(GC)_d$	none	SPT between N_1 and N_3
none	0	6.2
SPT between N_1 and N_3	5.7	N/A[a]
	trans-$(CG)_1$-Pt-$(GC)_2$	
$(CG)_1/(GC)_2$	none	SPT between N_1 and N_3
none	0	4.3
SPT between N_1 and N_3	4.3	8.7
	cis-(CG)-Pt-(AT)	
GC/AT	none	DPT (N_1 and N_3), (N_6 and O_4)
none	0	17.5
SPT between N_1 and N_3	−1.0	15.2

[a] The optimized structure cannot be available.

TABLE 5: Sum of the Charges by Natural Bond Orbital (NBO) Analysis

	cis-$(CG)_p$-Pt-$(GC)_d$	*cis*-$(CG^*)_p$-Pt-$(GC)_d$	*cis*-$(CG)_p$-Pt-$(G^*C)_d$
G_p or G^*_p	0.26	−0.43[a]	0.25
G_d or G^*_d	0.24	0.25	−0.44[a]
C_p	0.10	0.58[b]	0.33
C_d	0.10	0.32	0.58[b]
Pt	0.73	0.69	0.70
ligands	0.59	0.58	0.58

	trans-$(CG)_1$-Pt-$(GC)_2$	*trans*-$(CG^*)_1$-Pt-$(GC)_2$	*trans*-$(CG)_1$-Pt-$(G^*C)_2$	*trans*-$(CG^*)_1$-Pt-$(G^*C)_2$
G_1	0.23	−0.46[a]	0.22	−0.47[a]
C_1	0.12	0.85[b]	0.11	0.84[b]
G_2	0.21	0.21	−0.47[a]	−0.48[a]
C_2	0.11	0.11	0.84[b]	0.82[b]
Pt	0.72	0.69	0.70	0.69
ligands	0.61	0.60	0.61	0.60

[a] The sum does not contain the H atom transferred to the N_3 of C. [b] The sum contains the H atom transferred from G.

between *trans*-$(CG)_1$-Pt-$(GC)_2$ and *trans*-$(CG^*)_1$-Pt-$(GC)_2$ (4.3 kcal/mol) and between *trans*-$(CG)_1$-Pt-$(GC)_2$ and *trans*-$(CG)_1$-Pt-$(G^*C)_2$ (4.3 kcal/mol). Therefore, this indicates that the two different SPT reactions occur almost independently.

Next, the sum of charges obtained by the natural bonding orbital (NBO) is analyzed. Table 5 lists the results of the sum of the NBO charges. Every part of *cis*-$(CG)_p$-Pt-$(GC)_d$ has a positive charge, but both C_p and C_d are almost neutral. When the SPT reaction occurs, the whole charge of a proton donor G* becomes negative. On the other hand, both C_p and C_d become positive after the SPT reaction. The proton donor G* is negative whereas a proton acceptor C is positive. It is expected that these Coulomb repulsions of C_p and C_d and of G_p and G_d prevent more SPT reactions from *cis*-$(CG)_p$-Pt-$(G^*C)_d$ and $(CG^*)_p$-Pt-$(GC)_d$. In particular, this change of charge distribution can be seen in the case of *trans*-$(CG)_1$-Pt-$(GC)_2$, in which the two guanines become negative while the two cytosines become positive. When two GC pairs are distant, the effects of the Coulomb repulsion between them are smaller than that in cisplatin, permitting the structure *trans*-$(CG^*)_1$-Pt-$(G^*C)_2$. This result indicates that *cis*-$(CG^*)_p$-Pt-$(G^*C)_d$ cannot react because of the repulsion between the two G*C pairs.

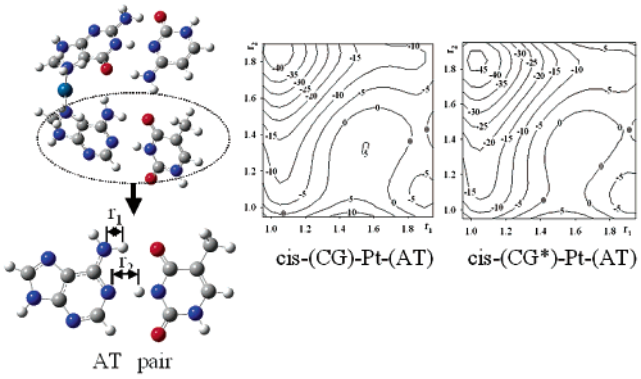

Figure 6. Definitions of variables in the 2bps model of the *cis*-(CG)-Pt-(AT). The numbers in the contour plots represent the energy (in kcal/mol).

The SPT reaction between N_1 and N_3 of the GC pair also occurs with *cis*-(CG)-Pt-(AT). The result is similar to the one GC pair shown in the beginning of this section. The structure is not distorted in spite of the SPT reaction between the GC pair. Then, we must know the possibilities of more proton transfers in the AT pair. These pairs have two hydrogen bonds N_6 (A)-O_4 (T) and N_1 (A)-N_3 (T). We show a restricted two-dimensional potential energy surface in Figure 6, where variables r_1 and r_2 denote the distances N_6-H and N_1-H, and the other geometries are fixed. Figure 6 shows two local minima, both *cis*-(CG)-Pt-(AT) and *cis*-(CG*)-Pt-(AT). This implies that a multiple SPT reaction occurs in *cis*-(CG)-Pt-(AT). Nevertheless, the energy difference between local minima is so large that the proton-transfer reaction may not occur at room temperature. The tendency does not change after the SPT reaction in the GC pair occurs. Table 4 summarizes the possibilities for multiple proton-transfer reactions in all the systems. Note that the SPT reaction occurs in the platinum-bound GC pair, and the DPT reaction occurs in the AT pair. The DPT reaction can also be found even after the SPT reaction between N_1 (G) and N_3 (C) has occurred. The SPT reaction in the AT pair cannot occur, because the Pt complex binding increases the distance between N_1 (A) and N_3 (T). In every case of the DPT reactions, the product of the DPT reaction becomes more unstable than the original structure. This result is similar to the DPT reaction in the base pairs without the Pt complex as investigated by Guallar's group.[36]

4bps Models. We found that SPT structures of the *cis*-(CG)-Pt-(GC) type can exist even in 4bps models. Two different optimized structures are shown in Figure 7, which shows one planar GC and one distorted GC pair as well as the 2bps model of *cis*-(CG)-Pt-(GC). We also found that the backbone and stacking bases do not move from their original geometry much during the SPT reaction.

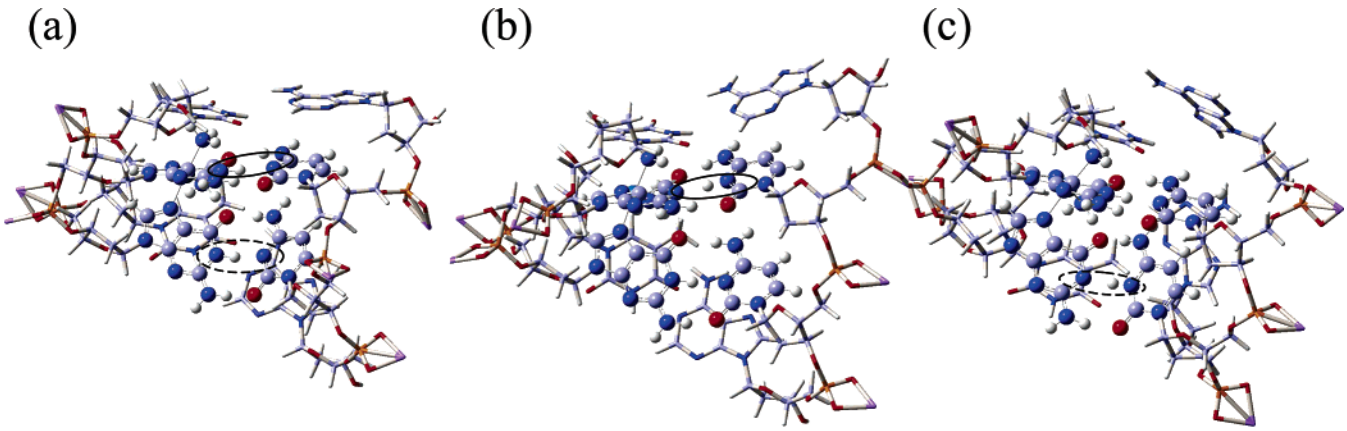

Figure 7. The optimized structures of the 4bps models of (a) *cis*-$(CG)_p$-Pt-$(GC)_d$, (b) *cis*-$(CG^*)_p$-Pt-$(GC)_d$, and (c) *cis*-$(CG)_p$-Pt-$(G^*C)_d$.

TABLE 6: The Differences of Energy in the "4bps Model" Molecules (in kcal/mol)[a]

cis-$(CG)_p$-Pt-$(GC)_d$	0
cis-$(CG^*)_p$-Pt-$(GC)_d$	+3.2
cis-$(CG)_p$-Pt-$(G^*C)_d$	+3.0

[a] We set the energy of *cis*-$(CG)_p$-$(GC)_d$ without sodium atoms as 0.

TABLE 7: Optimized Geometries and Experimental Data from the Protein Data Bank[c]

	cis-$(CG)_p$-Pt-$(GC)_d$	*cis*-$(CG^*)_p$-Pt-$(GC)_d$	*cis*-$(CG)_p$-Pt-$(G^*C)_d$	1A84	1AU5	1KSB
			Pt-G coordination			
Pt-G_p[a]	2.04	2.03	2.04	2.05	1.96	2.01
Pt-G_d[a]	2.04	2.04	2.03	2.05	1.98	2.01
G_p-Pt-G_d[b]	89.4	91.4	89.6	90.1	87.4	88.6
G_p-Pt-L_1-G_d	53.7	58.6	63.3	40.8	−1.4	56.9
G_p-Pt-L_2-G_d	69.2	69.5	64.6	72.9	−17.5	55.3
			hydrogen bond length			
$(O_6)_p$-$(N_4)_p$	2.84	2.62	2.85	2.97	2.73	2.76
$(N\text{-})_p$-$(N_3)_p$	2.85	2.77	2.87	3.01	2.96	2.86
$(O_2)_p$-$(N_2)_p$	2.73	2.92	2.79	2.91	2.87	2.91
$(O_6)_d$-$(N_4)_d$	2.82	2.92	2.65	3.28	2.80	2.83
$(N_1)_d$-$(N_3)_d$	2.81	2.84	2.76	2.99	2.71	2.89
$(O_2)_d$-$(N_2)_d$	2.75	2.74	2.96	2.59	2.96	2.85

[a] The distance Pt-G is defined as the distance between Pt and N_7 of guanine as shown in Figure 3. [b] The angle G_p-Pt-G_d is defined as N_7 (G_p)-Pt-N_7 (G_d). [c] The unit of distance is angstroms, the unit of angle is degrees.

We extracted the QM part, i.e., the 2bps and Pt complex, from the 4bps model to investigate the energy differences between *cis*-$(CG)_p$-Pt-$(GC)_d$ and $(CG^*)_p$-Pt-$(GC)_d$ or *cis*-$(CG)_p$-Pt-$(G^*C)_d$. The energies of these model molecules are assumed to be approximately those of their QM part. The energetics of $(CG)_p$-Pt-$(GC)_d$ and $(CG^*)_p$-Pt-$(GC)_d$ are shown in Table 6. From this table, the energy differences between the original structure and the proton-transferred structures are estimated as 3−3.5 kcal/mol. From these results, the energy barrier of the SPT reaction is estimated to be lower than the case of the 2bps model.

We next compare the optimized structure with experimental data from the protein data bank (PDBID: 1A84,[8] 1AU5,[9] 1KSB[10]) as summarized in Table 7. The hydrogen-bonding lengths of 1A84 and the optimized structure show poor agreement with each other, where the distance between $(O_6)_d$ and $(N_4)_d$ is about 3.3 Å in the former, which is too great to form hydrogen bonds. Except for this result, the optimized 4bps model of *cis*-$(CG)_p$-Pt-$(GC)_d$ agrees well with the experimental data and the error is within 0.05 Å. On the other hand, the error of the hydrogen-bonding length is significant, e.g., the hydrogen-bonding length of $(O_2)_2$-$(N_2)_2$ is 2.75 Å for the 4bps model of *cis*-$(CG)_p$-Pt-$(GC)_d$ and 2.96 Å for 1AU5. This is because the energies of *cis*-$(CG^*)_p$-Pt-$(GC)_d$ and $(CG)_p$-Pt-$(G^*C)_d$ are as stable as those of *cis*-$(CG)_p$-Pt-$(GC)_p$ so that the mean of these structures may be observed in the experiment because of the low-energy barrier of the SPT reaction. Indeed, the error is improved when the structures of *cis*-$(CG^*)_p$-Pt-$(GC)_d$ and *cis*-$(CG)_p$-Pt-$(G^*C)_d$ are taken into account. In this case, it is possible that the dynamic fluctuations may dominate the structure of the system.

Although solvent effects are very important for the systems treated in this article, we did not include the water environment. For further research, it is also necessary to discuss the possibilities of proton transfer in larger systems. The fragment molecular orbital (FMO) method[53] is possibly a better way to investigate these effects explicitly. In particular, Ishikawa et al.[54] performed a single point calculation of cisplatin and large-scale DNA including the environmental water molecules with the FMO method. In general, there are many local minima in a large-scale molecule, such as the proton-transferred GC pair as indicated in this paper. In such systems, it is necessary to consider not only the optimized structure but also structural fluctuations.[55] The mean structure between the original and the SPT structures may be observed at room temperature. The dynamic effects will be investigated in our future work.

Conclusions

The ease of binding to cisplatin was in the order *cis*-(CG)-Pt-(GC), *cis*-(CG)-Pt-(AT), and *cis*-(TA)-Pt-(AT) when complementary base pairs were taken into account. From their energetics, the structure of *cis*-(TA)-Pt-(AT) is rarely found at room temperature. The SPT reaction can occur in systems that consist of two base pairs and cisplatin. The reaction barrier is as low as 6−7 kcal/mol, which is similar to the case of one GC pair with cisplatin, and the SPT structure is as stable as the original structure. From these results, it is possible that the coordination of cisplatin to DNA causes a mispairing of the GC pair that leads to a mutation of the DNA. The SPT reaction causes this in one of the GC pairs. On the other hand, two simultaneous SPT structures like *cis*-(CG*)-Pt-(G*C) are forbidden. This is explained by analysis of charge distributions. After one SPT reaction occurs, the proton donor of G becomes negative and the proton acceptor of C positive. The other C also becomes positive, so that the subsequent SPT reaction from the other G is forbidden by Coulomb repulsion. We observed multiple SPT reactions in a system that consists of two base pairs with transplatin. In this case, the distance between the two base pairs is greater so that the Coulomb interaction between

them is weak. The SPT reaction between G and C can occur with *cis*-(CG)-Pt-(AT). This result is similar to the case of one GC pair.

By using the QM/MM method, the SPT reaction is also shown to occur in the system consisting of cisplatin and four base pairs containing the backbone molecules (4bps model). Without the effects of the backbone and the stacking base pairs, the structure of *cis*-$(CG)_p$-Pt-$(GC)_d$ is so distorted that it cannot describe the actual structure in the DNA. The optimized structure of the 4bps *cis*-(CG)-Pt-(GC) model agrees with results from NMR experiments in view of the Pt-G coordination, but not of the hydrogen-bonding length. Because the structures of *cis*-$(CG^*)_p$-Pt-$(GC)_d$ and *cis*-$(CG)_p$-Pt-$(G^*C)_d$ are as stable as the original one, their mean structures may be observed in experiments.

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References and Notes

(1) Rosenberg, B.; van Camp, L.; Trosko, J. L.; Mansour, V. H. *Nature* **1969**, *222*, 385.
(2) Van Garderen, C. J.; Van Houte, L. P. A. *Eur. J. Biochem.* **1994**, *225*, 1169.
(3) Fuertes, M. A.; Alonso, C.; Pérez, J. M. *Chem. Rev.* **2003**, *103*, 645.
(4) Yang, X.-L.; Wang, A. H.-J. *J. Pharmacol. Ther.* **1999**, *83*, 181.
(5) Eastman, A. *Biochemistry* **1986**, *25*, 3912.
(6) Schepman-Fichtinger, A. M.; van Oosteron, A. T.; Lohman, P. H. M.; Berends, F. *Cancer Res.* **1987**, *47*, 3000.
(7) Ohndorf, U. M.; Rould, M. A.; He, Q.; Pacbo, C. O.; Lippard, S. J. *Nature* **1999**, *399*, 708.
(8) Coste, F.; Malinge, J. M.; Serre, L.; Shepard, W.; Roth, M.; Leng, M.; Zelwer, C. *Nucleic Acids Res.* **1999**, *27*, 1837.
(9) Gelasco, A.; Lippard, S. J. *Biochemistry* **1998**, *37*, 9230.
(10) Yang, D.; Van Boom, S. S.; Reedik, J.; van Boom, J. M.; Wang, A. H. *Biochemistry* **1995**, *34*, 12912.
(11) Basch, H.; Krauss, M.; Stevens, W. J.; Cohen, D. *Inorg. Chem.* **1985**, *24*, 3313.
(12) Dobrogoriskaia-Mereau, I. A. I.; Nemukhin, A. V. *J. Comput. Chem.* **2005**, *26*, 865.
(13) Hush, N. S.; Schamberger, J.; Bacskay, G. B. *Coord. Chem. Rev.* **2005**, *249*, 299.
(14) Roberazzi, A.; Platts, A. J. *J. Comput. Chem.* **2004**, *25*, 1060.
(15) Costa, L. A. S.; Rocha, W. R.; De Almeida, W. B.; Dos Santos, H. F. *Chem. Phys. Lett.* **2004**, *387*, 182.
(16) Burda, J. V.; Zeizinger, M.; Šponer, J.; Leszczynski, J. *J. Chem. Phys.* **2000**, *113*, 2224.
(17) Carloni, P.; Andreoni, W.; Hutter, J.; Curioni, A.; Giannozzi, P.; Parrinello, M. *Chem. Phys. Lett.* **1995**, *234*, 50.
(18) Burda, J. V.; Zeizinger, M.; Leszyczynski, J. *J. Comput. Chem.* **2005**, *26*, 907.
(19) Iwamoto, M; Mukundan, S., Jr.; Marzilli, L. G. *J. Am. Chem. Soc.* **1994**, *116*, 6238.
(20) Leng, M.; Brabec, V. *Int. Agency Res. Cancer* **1994**, *125*, 339.
(21) Brabec, V.; Šíp, M.; Leng, M. *Biochemistry* **1993**, *32*, 11676.
(22) Appleton, T. G.; Pescb, F. J.; Weinken, M.; Menzer, S.; Lippard, B. *Inorg. Chem.* **1992**, *31*, 4410.
(23) Mikola, M.; Arpalahti, J. *Inorg. Chem.* **1996**, *35*, 7556.
(24) He, Q.; Zhou, L.; Zhang, Z. *Chin. J. Chem.* **2005**, *23*, 1355.
(25) Baik, M. H.; Frisner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 14082.
(26) Zilberberg, I. L.; Avdeev, V. I.; Zhidomirov, V. I. *J. Mol. Struct.* (*Theochem*) **1997**, *418*, 73.
(27) Pelmenschinov, A.; Zilberberg, I. L.; Leszczynski, J.; Famulari, A.; Sinori, M.; Raimondi, M. *Chem. Phys. Lett.* **1999**, *314*, 496.
(28) Burda, J. V.; Leszczynski, J. *Inorg. Chem.* **2003**, *42*, 7162.
(29) Zeizinger, M.; Burda, J. V.; Leszczynski, J. *Phys. Chem. Chem. Phys.* **2004**, *6*, 3585.
(30) Rabor, J.; Zhu, C.; Eriksson, L. A. *J. Phys. Chem. B* **2005**, *109*, 11006.
(31) Costa, L. A. S.; Hambley, T. W.; Rocha, W. R.; De Almeida, W. B.; Dos Santos, H. F. *Int. J. Quantum Chem.* **2006**, *106*, 2129.
(32) Löwdin, P.-O. *Rev. Mod. Phys.* **1963**, *35*, 724.
(33) Florián, J.; Hrouda, V.; Hobza, P. *J. Am. Chem. Soc.* **1994**, *116*, 1457.
(34) Hrouda, V.; Florián, J.; Hobza, P. *J. Phys. Chem.* **1993**, *97*, 1542.
(35) Guallar, V.; Douhal, A.; Moreno, M.; Lluch, J. M. *J. Phys. Chem. A* **1999**, *103*, 625.
(36) Noguera, M.; Sodupe, M.; Bertrán, J. *Theor. Chem. Acc.* **2004**, *112*, 318.
(37) Kryachiko, E. S.; Sabin, J. R. *J. Quantum Chem.* **2003**, *91*, 695.
(38) Kurita, N.; Inoue, H.; Sekino, H. *Chem. Phys. Lett.* **2003**, *370*, 161.
(39) Ogawa, T.; Kurita, N.; Sekino, H.; Kitao, O.; Tanaka, S. *Chem. Phys. Lett.* **2003**, *374*, 271.
(40) Šponer, J.; Jurečka, P.; Hobza, P. *J. Am. Chem. Soc.* **2004**, *126*, 10142.
(41) Jurečka, P.; Hobza, P. *J. Am. Chem. Soc.* **2003**, *125*, 15608.
(42) Roberazzi, A.; Platts, J. A. *J. Biol. Inorg. Chem.* **2005**, *10*, 854.
(43) Roberazzi, A.; Platts, J. A. *J. Phys. Chem.* **2006**, *110*, 3992.
(44) Burda, J. V.; Šponer, J.; Hrabakova, J.; Zeizinger, M.; Leszczynski, J. *J. Phys. Chem. B* **2003**, *107*, 5349.
(45) Matsui, T.; Shigeta, Y.; Hirao, K. *Chem. Phys. Lett.* **2006**, *423*, 331.
(46) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.
(47) Stevens, W. J.; Basch, H.; Krauss, M. *J. Chem. Phys.* **1984**, *81*, 6026.
(48) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357.
(49) Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.
(50) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
(51) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(52) Fuentealba, P.; Preuss, H.; Stall, H.; Szentpaly, L. V. *Chem. Phys. Lett.* **1989**, *89*, 418.
(53) Kitaura, K.; Sawai, T.; Asada, T.; Nakano, T.; Uebayashi, M. *Chem. Phys. Lett.* **1999**, *312*, 319.
(54) Ishikawa, T.; Mochizuki, Y.; Nakano, T.; Amari, S.; Mori, H.; Honda, H.; Fujita, T.; Tokiwa, H.; Tanaka, S.; Komeiji, Y.; Fukuzawa, K.; Tanaka, K.; Miyoshi, E. *Chem. Phys. Lett.* **2006**, *427*, 159.
(55) Shigeta, Y.; Takatsuka, K. *J. Chem. Phys.* **2005**, *123*, 131101.