DFT Studies on Binding of $Pt(NH_3)_2Cl^+$ to Guanine

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The binding of Pt(II) complexes to DNA bases has been the subject of extensive experimental and theoretical studies in recent years after the discovery of Rosenberg *et al.*[1,2] of the antitumor activity of *cis*-diamminedichloroplatinum(II) (*cis*-DDP or *cis*platin). The many results of investigation have shown that *cis*platin attacks DNA base and inhibits DNA replication.[3]

On the other hand, monofunctional binding sites of the neutral base guanine have been investigated for the $Pt(NH_3)_2Cl^+$ (PDAC). The results have shown that the N7 site on guanine has been identified as a preferred site.[4] Basch *et al.*[5] have studied on binding of $Pt(NH_3)_3^{2+}$ to nucleic acid bases by *ab initio* calculation. They have reported that the binding energy of N7 site of the guanine is found to be greater than O6 site.

Until recently, more detailed theoretical studies for binding of PDAC to the guanine have not been attempted because this system has need of a large and expensive calculation.

In this study, the binding of guanine to the *cis*- and *trans* isomers of PDAC is chosen as a suitable model system. The N7 site is considered for binding of guanine to PDAC.

The minimum energy geometries of *cis*- and *trans*-PDAC, guanine, and PDAC complexes of guanine are optimized by density functional theory (DFT). DFT calculations are carried out at B3LYP level[6] of theory with the LANL1MB and LANL2DZ basis sets using the Gaussian 94 series of program[7] on the RS6K IBM workstation. The geometries for all structures are fully optimized with the LANL1MB basis sets, whereas energies have been obtained with the LANL2DZ basis sets using the optimized structures with LANL1MB. LANL2DZ is double-zeta basis set containing effective core potential (ECP) representations of electrons near the nuclei for post-third row atoms. Geometry optimizations of all structures are carried out using energy gradients methods.[8] All structures are converged to 10^{-7} au. Vibration frequencies are also calculated at B3LYP level to confirm that all the stationary points correspond to true minima on the potential energy surface. All frequency calculations are performed using numerical second derivatives and verified that all structures are true minima by frequency analysis and obtained all positive Hessian eigenvalue.

The optimized geometrical structure is shown in Figure 1 for *cis*-$Pt(NH_3)_2ClG^+$.

As seen in Figure 1, the optimum Pt-N7(G) distance in the *cis*-$Pt(NH_3)_2ClG^+$ complex is found to be 2.188 Å. The $Pt(NH_3)_2Cl^+$ fragment geometry is shown with tetrahedral conformation about each nitrogen atom. That is, one H atom of NH_3 is nearly in the plane and the other two lie symmetrically above and below it, where N-H bond lengths are about 1.05 Å. The guanine is oriented nearly perpendicular to the square-planar complex of PDAC with dihedral angle of 90.5° for C5-N7-Pt-Cl.

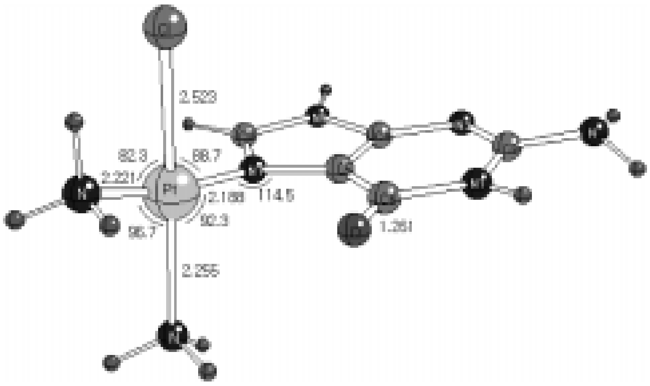

Figure 1. Optimized structure for *cis*-$Pt(NH_3)_2ClG^+$ complex of guanine.

The $PtCl_4^{2-}$ complex, on the other hand, has D_{4h} symmetry. But owing to the loss of this symmetry in *cis*-$Pt(NH_3)_2ClG^+$ complex, X-Pt-Y (X, Y = Cl, N or N, N) angles differ from the ideal value of 90°. The bond angles of N7(G)-Pt-N and N7(G)-Pt-Cl are 92.3° and 88.7°, respectively. And the angles of N-Pt-N and N-Pt-Cl in $Pt(NH_3)_2Cl^+$ moiety are 96.7° and 82.3°, respectively as seen in Figure 1. The angle of N-Pt-N is considerably greater than that of N-Pt-Cl in $Pt(NH_3)_2Cl^+$ moiety. Two characteristics may be responsible for this: the existence[9] of intraligand hydrogen bond interaction between the chlorine ligand and H atom on NH_3, and the repulsion owing to hydrogen atoms between two ammonia ligands. In the calculation, the bond length between the chlorine and the closest ammonia hydrogen is 2.560 Å, but is 3.465 Å for distance between two closest hydrogens in each NH_3 ligand. This result is in good agreement with the fact[10] that H-Cl distance is shorter in *cis*platin, consistent with the existence of the H bond, than in *trans*platin. The presence of the hydrogen bond is also confirmed by comparing the bond populations between the chlorine and the closest ammonia hydrogen, and between the two closest hydrogens in each ammonia ligand. These values are calculated to be 0.0021 and 0.0000, respectively.

The optimized geometric structure is shown in Figure 2 for the *trans*-$Pt(NH_3)_2ClG^+$.

Since no experimental values have been reported for the $Pt(NH_3)_2ClG^+$ complexes, it is impossible to compare with experimental geometry for the optimized structure. The opti-

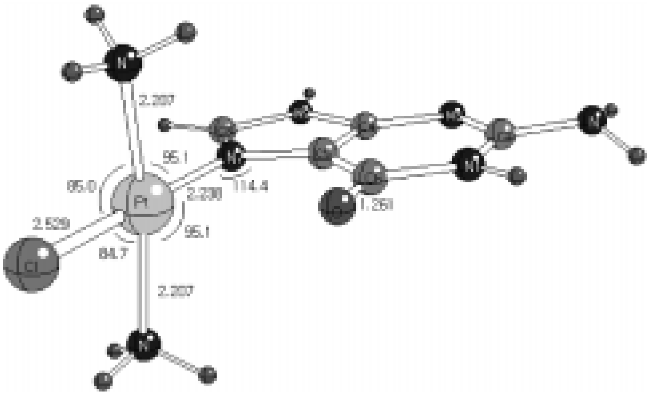

Figure 2. Optimized structure for *trans*-$Pt(NH_3)_2ClG^+$ complex of guanine.

mum Pt-N7(G) distance is calculated to be 2.238 Å as shown in Figure 2. The $Pt(NH_3)_2Cl^+$ fragment geometry is found with about 85° N-Pt-Cl bond angles, tetrahedral conformation about each nitrogen atom, and N-H bond lengths of about 1.05. The guanine is oriented nearly perpendicular to the square-planar complex of PDAC like in *cis*-$Pt(NH_3)_2ClG^+$ complex. The two dihedral angles are 87.9° and 93.3° for C5-N7-Pt-N. Both of the bond angles for N7(G)-Pt-N are calculated to be about 95°. Two N-Pt-Cl angles in $Pt(NH_3)_2Cl^+$ moiety are nearly same each other with about 85° and are smaller than those of N7(G)-Pt-N by about 10°. This feature is due to the hydrogen bonds between chlorine and the closest hydrogen in each ammonia ligand. The bond lengths between the chlorine and the two closest ammonia hydrogens are calculated to be 2.677 Å and 2.694 Å. Both distances are almost same. The existence of hydrogen bond is also confirmed by the bond population. The bond populations between chlorine and the closest hydrogen in each NH_3 ligand are 0.0005 and 0.0004.

The total energies for each compound and binding energies for $Pt(NH_3)_2ClG^+$ complexes of guanine are summarized in Table 1.

As shown in Table 1, the *trans*-conformation is calculated to be energetically more favorable by about 12.2 kcal/mol for the $Pt(NH_3)_2Cl^+$. This compares with the corresponding calculated energies of 18 kcal/mol and 22 kcal/mol[9] for $Pt(NH_3)_2Cl_2$ and $Pt(NH_3)_2^{2+}$, respectively. No direct comparison with experimental is possible, but the trend in calculated isomeric energy is in agreement with available experimental result that *trans*platin appears to be more stable, with an isomerization energy of 3 kcal/mol.[11] The isomeric energy may play a role in relative reactivity. A same result is found for the $Pt(NH_3)_2ClG^+$, where the energy of *trans*-conformation is also 1.4 kcal/mol greater than that of *cis*-conformation as can be seen in Table 1.

On the other hand, the binding energies of *cis*- and *trans*-$Pt(NH_3)_2ClG^+$ are calculated to be 79.1 kcal/mol and 68.4 kcal/mol at LANL2DZ level, respectively. In the calculation, the *cis*-$Pt(NH_3)_2ClG^+$ turns out to be energetically more favorable by about 10.7 kcal/mol. This value agrees very well with estimation of 7.5 kcal/mol by Zilberberg *et al.*[13] The result obtained in this study suggests that the *cis*platin bind more strongly to the guanine base than *trans*platin.

Table 1. Total energies of guanine and Pt(II) complexes, and binding energies for Pt(II) complexes with guanine at the LANL2DZ level

	Coordinaton site of Guanine	Total Energy (a.u.)	$\Delta E_{cis\text{-}trans}$ (kcal/mol)	E_{bind}[a] (kcal/mol)
Guanine		-542.433359		
cis-$Pt(NH_3)_2Cl^+$		-247.012245		
trans-$Pt(NH_3)_2Cl^+$		-247.031645	12.2(8.3)[b]	
cis-$Pt(NH_3)_2ClG^+$	N7	-789.571722		79.1
trans-$Pt(NH_3)_2ClG^+$	N7	-789.573922	1.4	68.4
$Pt(NH_3)_3G^{2+}$	N7			117.0[c]
	O6			95.0[c]
cis-$Pt(NH_3)_2G^{2+}$	N7-O6			158.3[d]

[a]E_{bind} is the binding energy for guanine in platinum complexes. [b]Reference 12. [c]Reference 5. [d]Reference 13.

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