Theoretical Study on the Interaction of Platinum Compounds with DNA Base Pairs

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Abstract The binding of a series of square planar Pt(II) adducts on the Watson-Crick base pair AT and GC was investigated using advanced quantum chemical method. The result showed that the AT base pair was mainly influenced by electrostatic effect, the GC base pair was influenced by both electrostatic and polarization effect. The platinated purine and pyrimidine base pair was moderately strengthened, whereas interaction between the purine and pyrimidine base pair was slightly influenced compared with that of the isolated one. Further calculations on the Pd(II) and Ni(II) analogs showed a similar trend. The natural bonding orbital (NBO) analysis of the second-order perturbative energy ΔE_2 well predicated strength of the H-bond in the base pair.

Keywords: Pt (II) adduct, Pd (II) adduct, Ni (II) adduct, Base pair, Hydrogen bond, HF method, DFT

Rosenberg's discovery of the ability of *cis*-Pt[(NH₃)₂Cl₂] (*cis*-DDP) to block DNA replication and cell division^[1] has influenced the development of inorganic metal coordination chemistry over the last 30 years^[2-5]. Today, cisplatin is considered as one of the most successful antitumor agent with annual sales of 500 million U.S. dollars^[6].

But a problem now being faced is the drug's toxic side effect, such as nephrotoxicity, nausea and intrinsic or acquired resistance^[7-8]. In efforts to improve the efficiency of the drug, researchers began to search for parallel synthesis of this compound by modifying or altering groups bound to the metal^[9-12]. Understanding the interaction of cisplatin or its analogs with potential biological targets can rationalize the development of new antitumor drugs with less toxic side effect or to help overcome the resistance problem.

Cisplatin can exert their role through specific coordination to the nucleic acids, such as direct binding to the nucleotides. The N₇ atom of guanine is the main metal binding site. Moreover, the N₇ of adenine is also an important binding site and should not be neglected^[13-14]. In the present paper, we systemically studied the influence of a series of Pt(II) adducts binding to the N₇ position of guanine and adenine on the GC and AT Watson-Crick base pairs. The Pd(II) and Ni(II) analogs were also investi-

gated for comparison.

Furthermore, the interaction of Pt(II) adducts with nucleotides has been the subject of intensive experimental^[15-16] and theoretical researches^[17-18] because of their significant effects on the genetic events such as DNA replication and transcription, as well as several metabolic processes. One of the most important properties is the relationship between the molecular structures and energies. The molecular structure can be efficiently studied by the experiment methods, while it is more difficult to combine the structural data with the energies. Recent advance of computational chemistry provides a promising way to unravel this fundamental link.

1 Computational details

All geometry optimization was carried out using the B3LYP method^[17] without any geometric restraint, the 6-31+G* basis set was used for the first- and second-row elements. And for the metal cations the LANL2DZ basis was used. Vibrational frequency was then computed at the same level of theory to verify that each complex was at the minimum on potential energy surface and no imaginary frequency was found.

The whole complex was considered as the following trimer, and the interaction energy of the trimer could be expressed in the

following way^[17]:

$$(I) \Delta E_{ABC} = E_{ABC} - (E_A + E_B + E_C) = \Delta E_{A-B} + \Delta E_{A-C} + \Delta E_{B-C}$$

(II) Additional interaction energy was obtained by reordering the three-body terms:

$$\Delta E_{A-BC} = E_{ABC} - (E_A + E_{BC})$$

$$\Delta E_{A-B} = E_{AB} - (E_A + E_B) = \Delta E_{ABC} - \Delta E_{AB-C}$$

ΔE_{A-B} was the interaction energy of AB complex, and ΔE_{A-BC} was the interaction energy between A and BC part. It should be noted that all of the interaction energy has been corrected for the basis set superposition error (BSSE)^[19,20]. Natural bonding orbital (NBO) analysis was performed finally.

All calculations have been carried out using the Gaussian 03 computer code^[21].

2 Results and discussion

2.1 Geometry

Fig.1 Selected fully optimized structure of the complexes

Selected fully optimized structure of the complexes using the B3LYP method are presented in Fig.1 and the geometrical parameters are summarized in Table 1. It is very interesting for the $M^{2+}\text{-N}_7$ bond with the bond length partly depends on ligands trans to the N_7 position, which has been detected in a previous study^[18]. It can easily be explained as a well-known trans effect resulting from changes of the electronic density in the $M^{2+}\text{-N}_7$ region. The longest distance is found for the GC base pair metalated by $cis\text{-Pt}[(\text{NH}_3)\text{Cl}_2]$, the bond length is lengthened by about 0.003 nm with respect to the +2 charged GC base pair. On the other hand, the platinated AT base pair shows a similar trend with the longest bond length of about 0.206 nm found for the neutral charged complex. Pronounced intramolecular hydrogen bond has been detected in both base pairs ($\text{N}_9(\text{H})\cdots\text{O}_6$ in the GC, and $\text{N}_9(\text{H})\cdots\text{N}_6$ in the AT base pair). The $\text{N}_9(\text{H})\cdots\text{O}_6$ distance in the GC base pair metalated by $cis\text{-Pt}[(\text{NH}_3)_3]^{2+}$ is comparable to

Table 1 Calculated bond distances(nm) and angles(°) of Watson-Crick base pair GC and AT using the B3LYP method

GC	Pt-N ₇	Pt-N ₉	N ₉ -O ₆	Pt-N ₇ -C ₅	N-Pt-N ₇ -C ₅	N ₆ (H)···O ₆	N ₁ (H)···N ₃	N ₂ (H)···O ₂
3N	0.2047	0.2078	0.2778	128.0	55.5	0.3066	0.2929	0.2742
<i>cis</i> 2N	0.2054	0.2106	0.2784	131.8	46.7	0.2972	0.2948	0.2816
<i>cis</i> 1N	0.2080	0.2091	0.2859	132.5	42.6	0.2885	0.2960	0.2887
isolated	—	—	—	—	—	0.2824	0.2967	0.2945
AT	Pt-N ₇	Pt-N ₉	N ₉ -N ₆	Pt-N ₇ -C ₅	N-Pt-N ₇ -C ₅	N ₆ (H)···O ₄	N ₃ (H)···N ₁	N ₁ -C ₅ -N ₆ -H _x
3N	0.2050	0.2092	0.2975	127.8	53.1	0.2766	0.3076	138.6
<i>cis</i> 2N	0.2045	0.2130	0.3016	130.0	51.0	0.2858	0.3006	143.8
<i>cis</i> 1N	0.2062	0.2117	0.3200	129.1	56.7	0.2932	0.2950	155.5
isolated	—	—	—	—	—	0.2946	0.2914	180.0

H_x denotes N₆(H) adjacent to metal ions.

strong hydrogen bond found, for example, in the water dimer of about 0.276 nm^[22].

We will now discuss the geometries of the base pairs. In general, the pyrimidine base has only a negligible influence on the metal-purine system, which has been predicted in previous studies^[23-24]. The metal moiety, however, significantly influences the geometry of the base pairs. In the case of the GC base pair, the cytosine is slightly counter-rotated in the electric field of the metal moiety (rearrangement of the ion-molecular dipole moment), which leads to altered N₆(H₆)···O₄ bond length. The more positive charge that the metal moiety carries, the larger elongation of the distance is 0.024 and 0.015 nm with the +2 and +1 charged complexes, respectively. The distances of the neutral charged complex are slightly influenced, which suggest that polarization effect may play an important role. The central hydrogen bond N₃(H)···N₁ is moderately reduced, while changes of the third H-bond is just contrary to the one closest to the metal moiety.

In the AT case, the decreasing charge of the system leads to two converse trends for the two H-bonds. Decreased bond length of N₆(H)···O₄ has been found, the hydrogen bond is significantly strengthened for the +2 charged complex with obviously reduced distance by about 0.018 nm, whereas the N₃(H)···N₁ hydrogen bonds show a converse trend with the bond distance lengthened by about 0.016 nm. The +1 charged metal moiety,

however, has a moderate influence.

The amino group of isolated base is suggested to be flexible due to partial *sp*³ hybridization of its nitrogen atom, which has been noticed recently in B-DNA crystal as well as small-compound crystals and other similar DNA-drugs^[23,25]. Flexibility of the amino group influences fine aspects of DNA structure, molecular recognition and allows for formation of efficient out-of-plane H-bonds and weak donor-acceptor interaction. Partly pyramidal amino group of adenine is found for the AT base pair. One amino group H (adjacent to the metal cation) deviates significantly from the adenine plane with a dihedral angle of about 22°~41°, while the other is slightly influenced with dihedral angle of about 10°. So the H-bond N₆(H)···O₄ formed between adenine and thymine is not significantly influenced. The amino group H of cytosine in the GC base pair, however, is nearly coplanar.

The Pt(II) metalated AT base pair is further calculated using the HF method, the result is listed in Table 2. The hydrogen bond calculated by the HF method is longer than that calculated by the B3LYP method with the H-bond distance shows about 0.012 nm longer compared with data presented in Table 1. This indicates that inclusion of electron correlation will give relatively shorter bond length, whereas the bond angles change little.

2.2 Energetics

The main energy characteristics of Pt(II) metalated AT and GC complexes are presented in Table 3. The third column $\Delta E_{\text{Pt-Py}}$

Table 2 Calculated bond distances(nm) and angles(°) of Watson-Crick base pair AT using HF method

AT	Pt-N ₇	Pt-N ₉	N ₉ -N ₆	Pt-N ₇ -C ₅	N-Pt-N ₇ -C ₅	N ₆ (H)···O ₄	N ₃ (H)···N ₁
3N	0.2068	0.2099	0.3089	127.9	54.9	0.2894	0.3192
<i>cis</i> 2N	0.2070	0.2128	0.3070	131.3	48.7	0.2983	0.3122
<i>cis</i> 1N	0.2091	0.2117	0.3227	131.2	53.6	0.3050	0.3080
isolated	—	—	—	—	—	0.3073	0.3038

shows the total interaction energy of the trimer. It increases significantly with increased charges of the metal adducts, and the largest is found for the +2 charged complexes, with the interaction energy higher by about 160 and 120 $\text{kJ} \cdot \text{mol}^{-1}$ (in absolute value) than the +1 charged GC and AT base pairs, respectively, and about 330 and 250 $\text{kJ} \cdot \text{mol}^{-1}$ higher than the neutral ones. Thus the trimer is mainly influenced by electrostatic effect. Changes of the metalated GC base pairs, in addition, are slightly larger relative to that of AT, which show that polarization effect may be an important contribution for the GC base pair.

The fourth column $\Delta E_{\text{Pt-Pu}}$ denotes the bond strength of Pt-N₇, which is the dominant term of the trimer. Change of this term is in accord with the former. On the other hand, the N₇ position of guanine is more preferred over adenine, with the corresponding interaction energy $\Delta E_{\text{Pt-Pu}}$ of about 111 $\text{kJ} \cdot \text{mol}^{-1}$, 71 $\text{kJ} \cdot \text{mol}^{-1}$ and 26 $\text{kJ} \cdot \text{mol}^{-1}$ higher for the +2, +1 and neutral charged base pair in absolute value, respectively. This finding is in accord with previously studies that the guanine residue is more favored over adenine^[26-28]. The $\Delta E_{\text{Pt-Pu}}$ of the +2 charged base pair is in acceptable agreement with recent study^[29], which indicates that the energy decomposition used in the present study is reasonable.

The two-body interaction energy between the base pair is shown as $\Delta E_{\text{Pu-Py}}$. This term changes little, and its value is comparable with that of the isolated one (−117.2 $\text{kJ} \cdot \text{mol}^{-1}$ for the GC, and −43.9 $\text{kJ} \cdot \text{mol}^{-1}$ for the AT base pair), which indicates that this may not necessarily be the case for the clinical activity of cisplatin. Base pairing energies with the perturbation of Pt(II) adducts $\Delta E_{\text{Pt-Pu-Py}}$, however, increase moderately for both base pairs, significant changes have been detected for the +2 charged complexes, which indicates that the positive charged metal moiety may strengthen the base pairing as predicted in previous

investigations^[17,23,24]. With respect to the interaction energy $\Delta E_{\text{Pt-PuPy}}$ between the Pt(II) adduct and the base pair, we can see that this term is mainly influenced by $\Delta E_{\text{Pt-Pu}}$. In addition, perturbation by the pyrimidine base should be presented.

The interaction energy of the platinated AT base pairs calculated using the HF method is given in Table 3 for a comparison. From the data listed in the table, it's not difficult to deduce a similar trend, irrespective of the fact that the interaction energy has been dramatically decreased (in absolute value). The decreased interaction energy (with the largest decrease found for the $\Delta E_{\text{Pt-Pu-Py}}$ term up to 56.2 $\text{kJ} \cdot \text{mol}^{-1}$) largely results from the difference of the two methods^[17], which indicates that inclusion of the electron correlation is more important.

In order to confirm the above mentioned speculation, the Pd(II) and Ni(II) analogs calculation has been also involved in the present study, and the energies are summarized in Table 4. Changes of the trimer interaction energy and the two body term $\Delta E_{\text{M-PuPy}}$ can be regarded as different affinity of the metal cations to the N₇ atom of the purine base, which can be deduced from the interaction energy $\Delta E_{\text{M-Pu}}$. The change, however, is quite smaller compared with the difference results from electrostatic effect. The results can be summarized as the following: First, electrostatic effect is the key role in determining the trimer interaction, while for the GC base pair, polarization effect plays an important role. Second, interaction energy of $\Delta E_{\text{M-Pu-Py}}$ increased with increased charges of the system, which is mainly affected by electrostatic effect. Base pairing energy $\Delta E_{\text{Pu-Py}}$, however, is slightly influenced with respected to the isolated one. Finally, no

Table 3 Calculated interaction energies of Pt(II) complexes ($\text{kJ} \cdot \text{mol}^{-1}$)

B3LYP	Complex	$\Delta E_{\text{Pt-Pu-Py}}$	$\Delta E_{\text{Pt-Pu}}$	$\Delta E_{\text{Pu-Py}}$	$\Delta E_{\text{Pt-Pu-Py}}$	$\Delta E_{\text{Pt-PuPy}}$
GC	3N	−654.4	−491.1	−116.7	−163.3	−537.7
	<i>cis</i> 2N	−487.9	−353.4	−117.6	−134.5	−370.3
	<i>cis</i> 1N	−320.5	−197.8	−117.7	−122.7	−202.8
AT	3N	−472.7	−379.6	−40.4	−93.1	−432.3
	<i>cis</i> 2N	−349.6	−281.5	−45.1	−68.1	−304.5
	<i>cis</i> 1N	−223.7	−171.8	−50.0	−51.9	−173.7
AT*	3N	−416.5	−340.6	−29.0	−75.9	−387.5
	<i>cis</i> 2N	−315.6	−260.3	−32.5	−55.3	−283.1
	<i>cis</i> 1N	−203.3	−163.1	−36.1	−40.2	−167.2

*Obtained using HF method

Table 4 Interaction energies of the Pd(II) and Ni(II) analogs using the B3LYP method($\text{kJ} \cdot \text{mol}^{-1}$)

	GC	$\Delta E_{\text{M-Pu-Py}}$	$\Delta E_{\text{M-Pu}}$	$\Delta E_{\text{Pu-Py}}$	$\Delta E_{\text{M-Pu-Py}}$	$\Delta E_{\text{M-PuPy}}$
Pd ²⁺	3N	−607.6	−445.0	−117.0	−162.6	−490.6
	<i>cis</i> 2N	−437.8	−303.6	−117.8	−134.2	−320.0
	<i>cis</i> 1N	−284.0	−162.2	−117.9	−121.8	−166.1
Ni ²⁺	3N	−619.0	−453.8	−116.4	−165.2	−502.6
	<i>cis</i> 2N	−441.9	−290.3	−118.3	−151.6	−323.6
	<i>cis</i> 1N	−284.4	−159.6	−118.2	−124.8	−166.2
	AT	$\Delta E_{\text{M-Pu-Py}}$	$\Delta E_{\text{M-Pu}}$	$\Delta E_{\text{Pu-Py}}$	$\Delta E_{\text{M-Pu-Py}}$	$\Delta E_{\text{M-PuPy}}$
Pd ²⁺	3N	−425.0	−331.6	−39.7	−93.4	−385.3
	<i>cis</i> 2N	−298.6	−230.4	−44.7	−68.2	−253.9
	<i>cis</i> 1N	−183.3	−130.7	−49.6	−52.6	−133.7
Ni ²⁺	3N	−428.0	−338.0	−38.7	−90.0	−389.3
	<i>cis</i> 2N	−299.0	−230.7	−43.9	−68.3	−255.1
	<i>cis</i> 1N	−180.5	−128.6	−49.5	−51.9	−131.0

Table 5 Some significant donor-acceptor bond orbital interactions and the second-order perturbation stabilization energies ΔE_2 for the Pt(II) complexes using the B3LYP method ($\text{kJ} \cdot \text{mol}^{-1}$)

GC	$\text{N}_4(\text{H}) \cdots \text{O}_6$		$\text{N}_1(\text{H}) \cdots \text{N}_3$		$\text{N}_2(\text{H}) \cdots \text{O}_2$	
	d(LPO ₆)	a(BD* N_4 -H)	d(LPN ₃)	a(BD* N_1 -H)	d(LPO ₂)	a(BD* N_2 -H)
GC	69.7		87.1		43.4	
3N	23.0		113.9		95.8	
<i>cis</i> 2N	32.6		100.8		68.5	
<i>cis</i> 1N	39.2		92.3		52.0	
AT	$\text{N}_6(\text{H}) \cdots \text{O}_4$		$\text{N}_3(\text{H}) \cdots \text{N}_1$			
	d(LPO ₄)	a(BD* N_6 -H)	d(LPN ₁)	a(BD* N_3 -H)		
AT	110.3		38.1			
3N	54.4		100.7			
<i>cis</i> 2N	72.3		63.5			
<i>cis</i> 1N	92.3		42.7			

d and a represent donor NBO and acceptor NBO, respectively. LP and BD* denote lone pair and antibonds, respectively.

strong influence of different metal cations has been detected.

2.3 Natural bond orbital analysis

It has been proposed that the NBO analysis allows one to separate the H-bond interaction energies in second-order perturbative expression (ΔE_2) of easily interpreted form^[30]. If ΔE_2 for a donor bond orbital transferred to an acceptor antibond orbital is large, it indicates that there is strong interaction between the two bonds, and the larger the ΔE_2 is, the stronger the H-bond interaction will be^[31-32]. ΔE_2 concerning the major H-bond in the two base pairs is given in Table 5.

In the case of the GC base pairs, the value of ΔE_2 with the H-bond $\text{N}_4(\text{H}) \cdots \text{O}_6$ is decreased with the largest reduction of about $46.7 \text{ kJ} \cdot \text{mol}^{-1}$ found for complex metalated by the +2 charged *cis*-[Pt(NH₃)₃]²⁺, which indicates that the H-bond is dramatically weakened. On the other hand, the other two H-bonds all strengthened and the largest ΔE_2 of about $113.9 \text{ kJ} \cdot \text{mol}^{-1}$ and $95.8 \text{ kJ} \cdot \text{mol}^{-1}$ is found for the +2 charged complex with H-bond $\text{N}_1(\text{H}) \cdots \text{N}_3$ and $\text{N}_2(\text{H}) \cdots \text{O}_2$, respectively.

With respects to the H-bond formed in the AT base pairs, change of ΔE_2 with the hydrogen bond $\text{N}_6(\text{H}) \cdots \text{O}_4$ is just contrary to that of $\text{N}_3(\text{H}) \cdots \text{N}_1$, the former is weakened with the largest reduced ΔE_2 detected for the +2 charged complex about $55.9 \text{ kJ} \cdot \text{mol}^{-1}$, on the other hand, the later is strengthened with ΔE_2 increased by about $62.6 \text{ kJ} \cdot \text{mol}^{-1}$ for the same complex.

3 Concluding remarks

In the present paper, we have systematically studied the

influence of square planar Pt(II) on the Watson-Crick base pairs AT and GC. The results show that the trimer is strengthened. The platinated AT base pair is strengthened by electrostatic effect, the GC base pair, however, is strengthened by both electrostatic and polarization effect. On the other hand, the interaction between the metalated purine and pyrimidine base is moderately influenced, while the two-body interaction term of purine and pyrimidine base-pairing energy changes little compared with that of the isolated one. The Pd(II) and Ni(II) analogs investigations confirmed our assumption.

The platinated AT base pair is additionally investigated by the HF approach and compared with that of the B3LYP method, the results show that neglect of the electron correlation dramatically increased the interaction energy of the system studied.

The natural bond orbital (NBO) analysis of the major H-bond interaction energies in second-order perturbative expression (ΔE_2) has been analyzed finally, and the values of ΔE_2 well predicate changes of the H-bond.

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铂配合物与 DNA 碱基对间相互作用的理论研究^{*}

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摘要 用量子化学方法研究一系列 Pt(II)配合物作用于嘌呤碱基 N₇ 位点后对 Watson-Crick 碱基对 AT、GC 的影响. 计算结果显示铂配体与碱基对 AT、GC 的作用以静电作用为主, 同时极化作用也是影响 GC 碱基对的重要因素. 静电作用极大地增强了铂化嘌呤碱基与嘧啶碱基间的相互作用, 而嘌呤碱基与嘧啶碱基间作用与未铂化碱基对作用相近. Pd(II) 和 Ni(II) 的相关研究得到类似的结果. 碱基对间氢键作用“二阶微扰能”分析结果与氢键强弱变化一致.

关键词: Pt(II)配合物, Pd(II)配合物, Ni(II)配合物, 碱基对, 氢键, HF 方法, 密度泛函理论(DFT)
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