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DFT Studies of the Zinc Complexes of DNA Bases

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The metal cation interactions with DNA nucleobases have been studied by a variety of experimental and theoretical method.¹⁻⁷ It is known that the coordinated metal ions play a significant role in the biological action of nucleic acids. Especially, metal cations interact with the DNA bases, destroying the hydrogen bonding between the base pairs. Therefore, the structure of DNA is changed.⁸⁻¹⁰ So, the metal cations affect syntheses, replication and cleavage of DNA. Cerda and Wesdemiotis¹¹ have reported the alkali metal ions (Li⁺, Na⁺ and K⁺) affinities of the DNA bases, but they do not show the information on the binding site of the metal. Burda *et al.*¹² have studied on the interaction of guanine and adenine with Zn²⁺ at the Hartree-Fock (HF) and Moller-Plesset second-order perturbation theory (MP2). However the results are not sufficient to predict the preferred location of the binding sites. They also do not present investigation on the interaction of the zinc cation with thymine and cytosine. Actually, we can locate the structures for various zinc cation complexes including the some bridged formations.

In the present study, as a continuation of our study on the binding of metal cations with DNA bases¹³ we report a DFT investigation on the interaction of Zn²⁺ with DNA bases. We focus in this study our attention on the geometrical structures, association sites and association energies for the Zn²⁺ complexes of DNA bases to describe the structural and energetic features of these complexes. DFT calculations in this study are carried out at B3LYP level^{14,15} of theory using the Gaussian03 series of program.¹⁶ The geometry optimizations are performed with the 6-31G(d,p) basis set using energy gradient method¹⁷ and all structures are fully optimized without any constraint. Vibration frequencies are also calculated to confirm that all the stationary points correspond to true minima on the potential energy surface. The stationary conformers are obtained by verifying that all the harmonic frequencies are real. All energies are calculated with single point at the B3LYP level of theory with the 6-31++G(d,p) basis set using the optimized geometry calculated with 6-31G(d,p) to obtain reasonable energies. In order to obtain accurate association energies, basis set superposition errors (BSSE) are also subtracted from the calculated association energies in the full counterpoise (CP)

approximation.^{18,19} The zinc cation association energies (ΔE) are obtained by subtracting the sum of the energies of the base [E(B)] and zinc cation monomer [E(Zn²⁺)] from the energy of the full optimized base-Zn²⁺ complex [E(B-Zn²⁺)].

$$\Delta E = E(B - Zn^{2+}) - [E(B) + E(Zn^{2+})]$$

Results and Discussion

The optimized geometrical structures for Zn²⁺ complexes of DNA bases are shown in Figure 1.

The selected geometrical parameters for the optimized DNA bases and Zn²⁺ complexes of these bases are summarized in Table 1. And the computed zinc cation association energies are shown in Table 2.

As shown in Figure 1, the three distinct complexes of Zn²⁺ with adenine have been found. The most stable adenine complex is the bridging complex in which Zn²⁺ forms a five-membered ring, interacting with both N₆ and N₇. The zinc cation association energy of this complex is -213.79 kcal/mol as shown in Table 2. The bicoordination of zinc cation yields the more stable adenine-Zn²⁺ complex.

As shown in Table 1, association of adenine with Zn²⁺ is accompanied by structural changes within the pyrimidine ring. When Zn²⁺ binds at both N₁ and N₆, the notable change in bond lengths is an increase of 0.102 Å in the C₆-N₆ distance. The two dihedral angles (N₁C₆N₆H) of -10.0 and -170.1° by amino hydrogens in adenine change to 120.4 and -120.4° in N₁-N₆ complex, respectively. This is due to the repulsion between the Zn²⁺ and amino hydrogen on the N₁ side of the C₆-N₆ bond. The amino hydrogens rotate to reduce this repulsion. The N₁-Zn²⁺ and N₆-Zn²⁺ distances are calculated to be 1.939 and 2.051 Å, respectively. When Zn²⁺ binds at N₃ (AZ2 in Figure 1), the N₃-Zn²⁺ distance is 1.919 Å. For the bridging complex in which Zn²⁺ forms a five-membered ring (AZ3 in Figure 1), the N₇-Zn²⁺ distance is 1.907 Å and the N₆-Zn²⁺ is 2.013 Å. On the other hand, the C₅C₆N₆ angle changes notably, increasing by 6.8° in N₁-N₆ complex and decreasing by 6.8° in N₆-N₇ complex. This large change relates to bridging nature of the complex caused by interaction of Zn²⁺ with both N₁ and N₆, and with both N₆ and N₇, respectively.

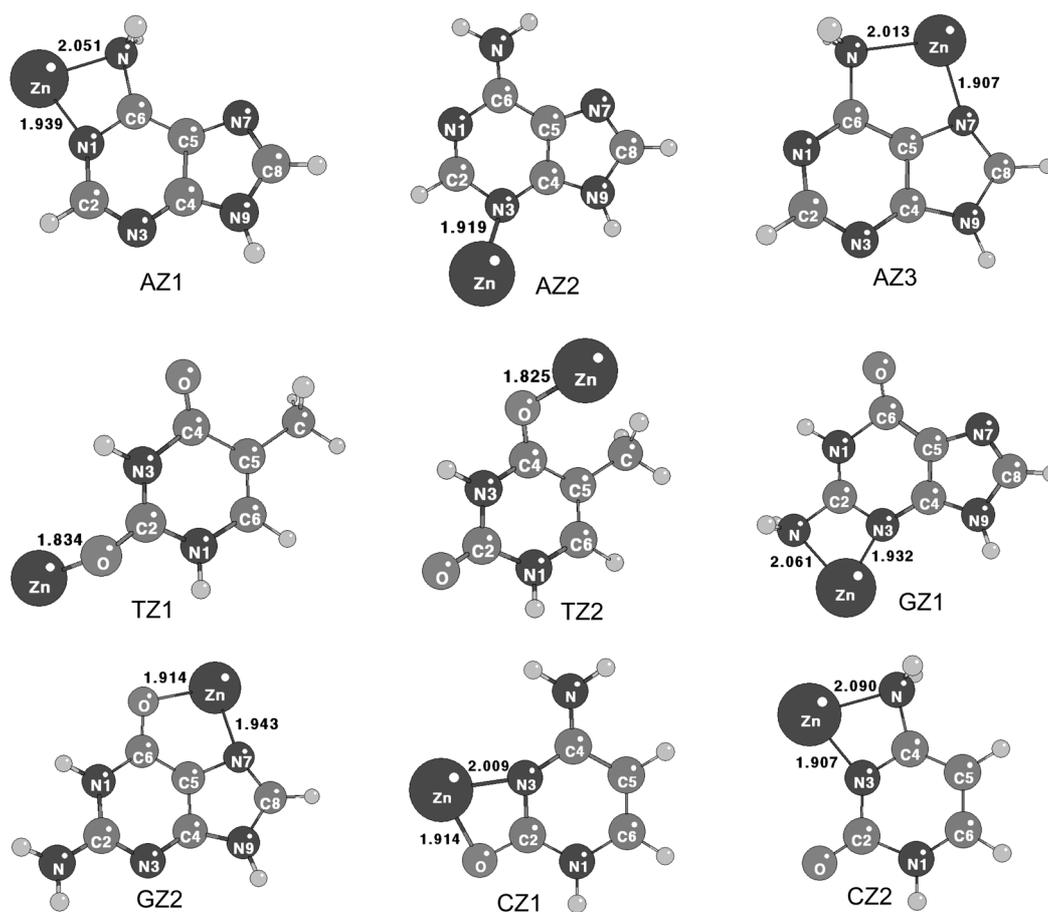


Figure 1. Optimized structures at B3LYP/6-31G(d,p) level of theory for zinc cation complexes of AZ) adenine, TZ) thymine, GZ) guanine, and CZ) cytosine. Selected distances are in Å.

The two association sites for Zn^{2+} complex with thymine have been found, one at each carbonyl group, as shown in Figure 1. The O-Zn^{2+} distances are 1.834 and 1.825 Å in the O_2 and O_4 complex, respectively. When Zn^{2+} associates at the O_4 , the $\text{C}_4\text{C}_5\text{C}(\text{CH}_3)$ angle increases by 2.2° reducing the repulsion between the Zn^{2+} and two methyl hydrogens. The association energy of this complex is -184.27 kcal/mol and is slightly preferred to O_2 complex, which is -177.77 kcal/mol.

As shown in Figure 1, there are two distinct complexes of Zn^{2+} with guanine. One is the four-membered bridging complex in which Zn^{2+} interacts with both N_2 and N_3 , the other is the complex in which Zn^{2+} forms a five-membered ring with both O_6 and N_7 .

The association energies of these complexes are -187.21 and -246.71 kcal/mol. Therefore, the five-membered ring formation is about 59.50 kcal/mol more stable than the four-membered ring formation. This result means that the five-membered ring formation is favored with respect to formation of four-membered ring because of the minor annular strain. As shown in Table 2, the $\text{O}_6\text{-N}_7$ five-membered ring complex is the strongest of the Zn^{2+} complexes with the DNA bases. This tendency is similar to that obtained for the alkali metal ion complexes,^{13,20,21} and it is shown that the

imino nitrogen is preferred over the amino one.

In five-membered ring complex (GZ2 in Figure 1), The $\text{C}_5\text{C}_6\text{O}_6$ angle decreases notably by 10.4° . This large change is also associated with the bridging nature of complex. The $\text{O}_6\text{-Zn}^{2+}$ and $\text{N}_7\text{-Zn}^{2+}$ distances are found to be 1.914 and 1.943 Å, respectively. On the other hand, the two N-Zn^{2+} distances in four-membered ring complex (GZ1 in Figure 1) are found to be 2.061 and 1.932 Å.

The two bridged complexes have been found in the cytosine molecular in which Zn^{2+} forms four-membered ring with $\text{O}_2\text{-N}_3$ and $\text{N}_3\text{-N}_4$ as shown in Figure 1. The $\text{O}_2\text{-N}_3$ bridging complex is slightly preferred to $\text{N}_3\text{-N}_4$ complex. In the $\text{O}_2\text{-N}_3$ complex, the $\text{N}_1\text{-C}_2$ distance decreases by 0.090 Å and $\text{N}_1\text{C}_2\text{O}_2$ angle increases by 5.1° with complexation. These results lead to enhancement of the simultaneous interaction of Zn^{2+} with O_2 and N_3 . The $\text{O}_2\text{-Zn}^{2+}$ and $\text{N}_3\text{-Zn}^{2+}$ distances are 1.914 and 2.009 Å, respectively. In this complex, the O-Zn^{2+} distance is longer than the corresponding ones in the thymine complexes, whereas the N-Zn^{2+} distance is longer than the corresponding ones in the adenine complexes. The zinc cation association energy of this complex is -226.84 kcal/mol. In the $\text{N}_3\text{-N}_4$ complex, the N-Zn^{2+} distances are calculated to be 1.907 and 2.090 Å.

In conclusion, there are three distinguishable Zn^{2+}

Table 1. Selected geometrical parameters for the optimized bases and base-Zn²⁺ complexes (bond lengths in Å and bond angle in degree)

Parameter	Adenine				Thymine			Guanine			Cytosine		
	Base	AZ1	AZ2	AZ3	Base	TZ1	TZ2	Base	GZ1	GZ2	Base	CZ1	CZ2
N ₁ -C ₂	1.344	1.365	1.289	1.365	1.390	1.354	1.417	1.371	1.317	1.414	1.430	1.340	1.430
C ₂ -N ₃	1.337	1.320	1.410	1.342	1.340	1.334	1.423	1.312	1.342	1.340	1.373	1.371	1.412
N ₃ -C ₄	1.339	1.328	1.357	1.322	1.407	1.455	1.342	1.358	1.382	1.323	1.320	1.372	1.348
C ₃ -C ₆	1.411	1.373	1.433	1.383	1.352	1.377	1.388	1.441	1.447	1.387	1.359	1.356	1.405
N ₁ -C ₆	1.345	1.368	1.371	1.304	1.380	1.377	1.337	1.440	1.529	1.363	1.355	1.382	1.330
C ₆ -N ₆	1.356	1.458	1.311	1.490									
C ₂ -O ₂					1.218	1.294	1.191				1.220	1.284	1.194
C ₄ -O ₄					1.222	1.200	1.308						
C ₆ -O ₆								1.218	1.188	1.300			
R		1.939 ^b	1.919 ^c	1.907 ^f		1.834 ^g	1.825 ^g		1.932 ^e	1.943 ^f		1.914 ^g	1.907 ^e
N ₁ C ₂ N ₃	128.9	123.0	126.5	126.8	112.5	117.3	111.7	123.6	124.1	123.2	116.1	120.9	111.3
C ₂ N ₃ C ₄	111.1	115.9	113.8	113.8	128.2	125.6	125.3	112.5	115.8	114.5	120.3	120.9	123.2
C ₃ C ₆ N ₆	122.3	129.1	123.5	115.5									
C ₅ C ₆ O ₆								131.4	134.1	121.0			
C ₄ C ₅ C(CH ₃)					117.7	117.9	119.9						
N ₃ C ₄ C ₅					114.5	113.9	119.8						
N ₁ C ₂ O ₂					123.2	118.7	124.5				118.2	123.3	123.9
N ₃ C ₄ N ₄											116.9	120.2	108.3
∠		92.4 ^b	107.2 ^c	96.4 ^f		139.4 ^h	114.8 ⁱ		93.3 ^e	95.0 ^f		90.3 ^h	96.6 ⁱ
N ₁ C ₆ N ₆ H ^a	-10.0	120.4	0.4 ^d	57.6									
	-170.1	-120.4	-179.5 ^e	-57.6									
N ₁ C ₂ N ₂ H ^a								169.9	60.6	180.0			
								34.3	-60.6	0.0			
N ₃ C ₄ N ₄ H ^a											9.8	0.0	120.3
											164.5	180.0	-120.3

^aThe hydrogen atoms are in amino group. ^bThe N₁-Zn²⁺ distance and C₆N₁Zn²⁺ angle. ^cThe N₃-Zn²⁺ distance and C₂N₃Zn²⁺ angle. ^dThe amino hydrogen cis to N₁-C₆. ^eThe amino hydrogen trans to N₁-C₆. ^fThe N₇-Zn²⁺ distance and C₅N₇Zn²⁺ angle. ^gThe O-Zn²⁺ distance. ^hThe C₂O₂Zn²⁺ angle. ⁱThe C₄O₄Zn²⁺ angle. ^jThe C₄N₃Zn²⁺ angle.

Table 2. B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) energies (E in au) and zinc cation association energies (ΔE_c in kcal/mol) of DNA bases

Base	Association site	E	ΔE _c ^a
Adenine	N ₁ -N ₆	-2245.847158	-209.20
	N ₃	-2245.826220	-197.21
	N ₆ -N ₇	-2245.854866	-213.79
Thymine	O ₂	-2232.612095	-177.77
	O ₄	-2232.623199	-184.27
Guanine	N ₂ -N ₃	-2321.050344	-187.21
	O ₆ -N ₇	-2321.144683	-246.71
Cytosine	O ₂ -N ₃	-2173.484565	-226.84
	N ₃ -N ₄	-2173.449015	-203.91

^aΔE_c = ΔE + BSSE

complexes with adenine and are two Zn²⁺ complexes with thymine. For the guanine-Zn²⁺ complex, there are two bridging complexes, one at N₂ and N₃, and the other at O₆ and N₇. In the cytosine-Zn²⁺ complex, we can locate the two structures with bridged formation.

For the association energy of the Zn²⁺ complexes with DNA bases, the most stable complexes are the bridging complexes with guanine and cytosine at both O and N.

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