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FACTORS GOVERNING THE STABILITIES OF Cu^+-GUANINE AND Zn^{2+}-GUANINE COMPLEXES : A DFT STUDY IN THE GAS PHASE

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ABSTRACT

Density functional theory (DFT) study is carried out to investigate the interaction of Cu^+ and Zn^{2+} ions in all possible basic sites of guanine. The most favorable site for the metalation of guanine was predicted on the basis of metal ion affinity values (MIA) and then attempted to investigate if there exists some correlation between the retained charges of metal ions and MIA or between the HOMO-LUMO energy gap and the MIA. In both types of complexes significant charge transfer is seen. MIA is seen to vary proportionately with the energy gap between the frontier orbitals.

Key words: DFT, Guanine, Metal ion affinity (MIA), Mulliken net charges, HOMO, LUMO.

INTRODUCTION

Recently many researchers have carried out their studies on the interaction of various metal ions as well as other ions with many organic molecules[1-5]. These studies not only provide vital information regarding those interactions but help experimental researchers to rationalize their problems and eliminate guess works to many extents. In fact, quantum mechanical evaluations at a higher level have provided an excellent complement to experimental works[6]. Russo and his co-workers recently carried out studies on the interaction of several metal ions (alkali, alkaline earth and many transitional metal ions) with DNA bases and results were seen to be in agreement with experimental results and were well within permissible error limits[7-10]. In the present work, interaction of Zn^{2+} and Cu^+ ions with guanine base was studied with a different approach to explore if there exists some correlation between the metal ion affinity and retained charges of metal ions or with the energies of frontier orbitals (energies of HOMO and LUMO) of the metal ion-guanine complexes. Role of the electron densities of frontier orbitals in analyzing reactivity have been reported in many studies[11].

Many cations are known to be involved in the synthesis, replication as well as the cleavage of DNA and RNA[12]. They can also affect their structural integrity in the free or protein bound forms. Excessive concentration of metal ions may sometimes disrupt the Watson-Crick hydrogen bonding and thus may compromise the structural integrity of the nucleic acid polymer. Both Zn^{2+} and Cu^+ ions are most frequently found in metalloenzymes. Their presence in the active center increases their biological importance and are responsible for many physiological processes taking place in living systems. Zinc is necessary for the

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expression of the activity of carbonic anhydrase, carboxypeptidase, alkaline phosphates and a variety of other enzymes. Copper is known for its participation in the metabolism of iron and zinc. It is most frequently used for the catalysis of the oxidation- reduction processes involving molecular oxygen[13,14]. In actual practice, study of the interaction of metal ions with nucleic acid bases is very tedious and time consuming. However, theoretical studies of the same with an intrinsic binding model certainly boost the understanding of the roles of metal ions in living systems[15-20].

Density functional theory (DFT)[21] has been widely used as an efficient quantum mechanical tool for studying molecular properties. DFT with B3LYP functional[22] has shown its reliability in predicting geometry, thermodynamics, metal ion affinities (MIA's) and also in the studies of M^{n+}-π or M^{n+}- heteroatom complexes. However, Metal ion-π interaction is ignored in the present studies as the M^{n+}-heteroatom interaction will be more favorable with guanine.[7] Results so far have shown that the basis set 6-31G (d, p) is large enough to reduce the basis set superposition error (BSSE) to ~2-3 Kcal/mol[3]. Hence, B3LYP/6-31G** method was used in this study and the BSSE correction was not taken into account.

EXPERIMENTAL

Computational method

All computations are done in the Gaussian 09W (G09W) software package[23]. Quantum mechanical methods are used to calculate the affinity of metal ions (Zn^{2+} or Cu^+ ion) with guanine base (MIA). The value of MIA may be regarded as the negative of the enthalpy change (ΔH) for the process

$$\text{Guanine} + M^{n+} \rightarrow \text{Guanine - } M^{n+}$$

It can also be calculated as the energy difference between the interacted and the un-interacted molecule/ion.

$$\text{Mathematically, MIA or } -\Delta H = |\, E^0\,(M^{n+}\text{-guanine complex}) - E^0\,(M^{n+}) - E^0\,(\text{Guanine})|$$

Here, E^0 stands for absolute energies of molecules/ions. All stable tautomers of Guanine are determined using G09W (Fig. 1). All calculations related to optimizations, Mulliken net charge determinations etc. are done using B3LYP with 6-31G** basis sets as incorporated in Gaussian 09' code in the gas phase. Free energy changes for the complexation processes are calculated to have an idea about the most favorable complex. It is done with due consideration of the free energy correction term arising due to the internal energy at 298.15 K. All calculations are done with the help of G09W software using the following relation and the same basis sets as above:

$$\Delta G_{\text{corr}}{}^{0} = \sum G^{0}{}_{\text{product, corr}} - \sum G^{0}{}_{\text{reactant, corr}}$$

Here, $\sum G^{0}{}_{\text{corr}}$ stands for the total corrected standard free energy of the species (reactant or product).

RESULTS AND DISCUSSION

Out of the five stable tautomers of Guanine, G1 has been found to be the most stable one (E^0 = -542.5652 Hartee), while G3 has been found to be the most unstable one, having an energy difference of nearly 13 Kcal/mol with that of G1. Others have energies intermediate between those of G1 and G3. At first all probable binding sites of guanine in the most stable tautomer of guanine (i.e. G1, in Fig. 1) are identified and then the two metal ions are allowed to interact in those selected sites one by one.

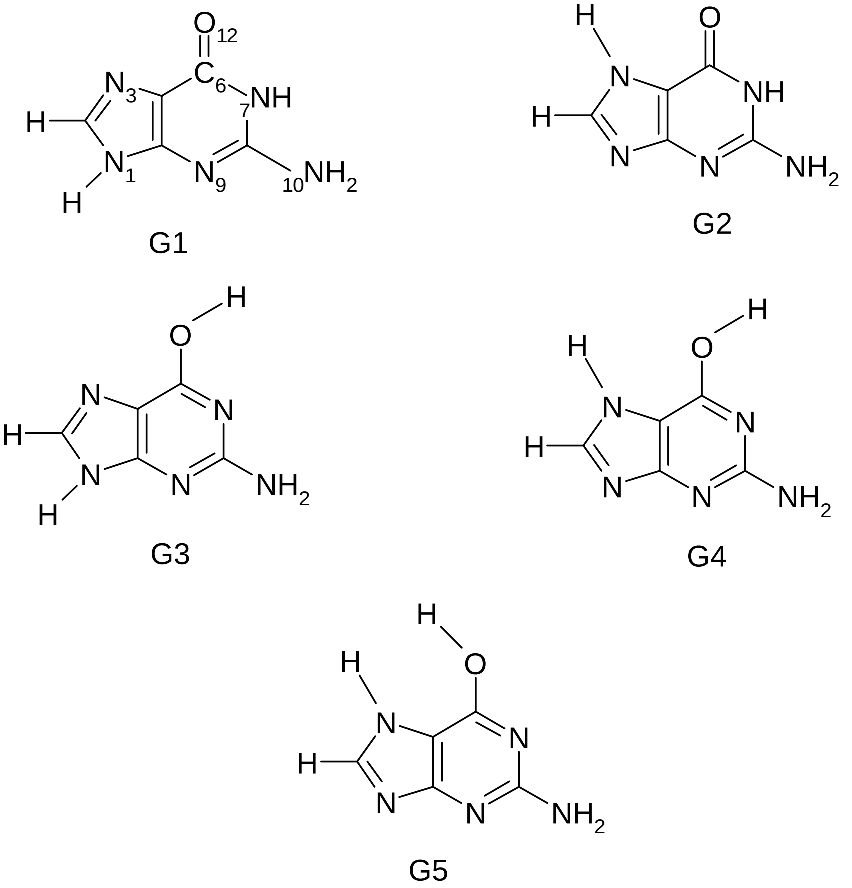
G1 G2 G3 G4 G5

Fig. 1: Five stable tautomers of Guanine as obtained with G09W software

[In the first figure atoms are numbered as per their positions in metal ion- guanine complexes]

Metal ion-guanine complexes so obtained are optimized and then the corresponding metal ion affinities are computed (Table 1) using B3LYP/6-31G** methods. Two metal ions exhibit different values of MIA's but the trend of their variation is similar in different binding sites. Structures of these complexes, as seen after Gaussian optimizations are shown in Fig. 2-13.

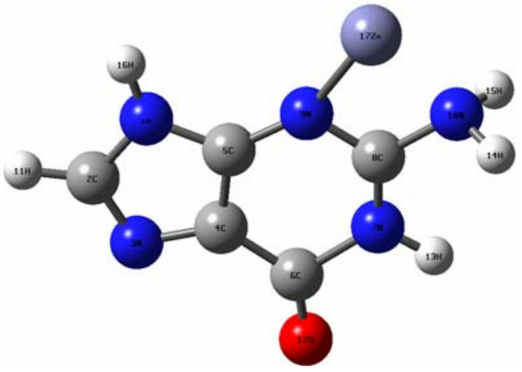

Fig. 2: Zn^{2+}-G1 (N1) complex

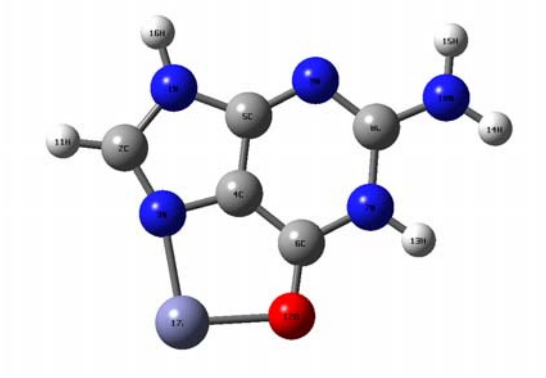

Fig. 3: Zn^{2+}-G1 (N3) complex

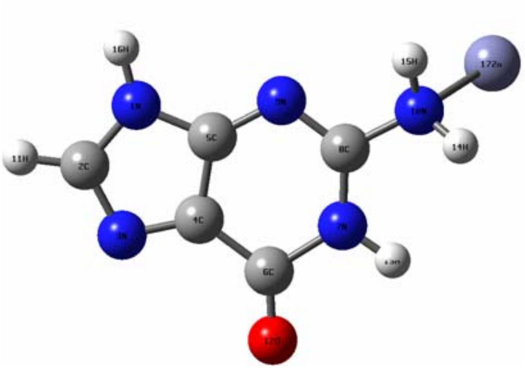

Fig. 4: Zn^{2+}-G1 (N7) complex

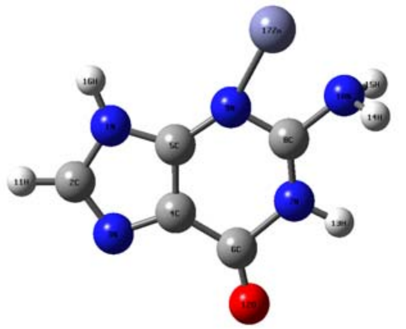

Fig. 5: Zn^{2+}-G1 (N9) complex

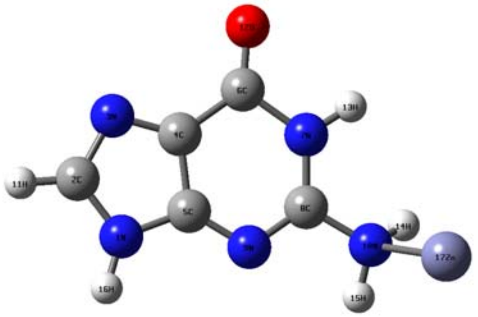

Fig. 6: Zn^{2+}-G1 (N10) complex

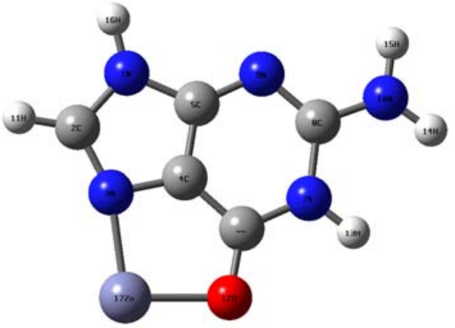

Fig. 7: Zn^{2+}-G1 (O12) complex

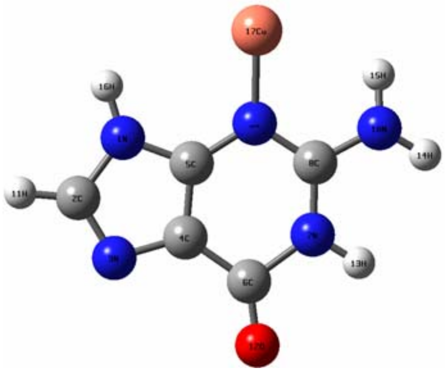

Fig. 8: Cu^{+}-G1 (N1) complex

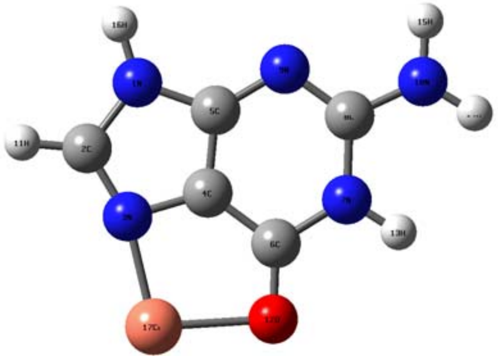

Fig. 9: Cu^{+}-G1 (N3) complex

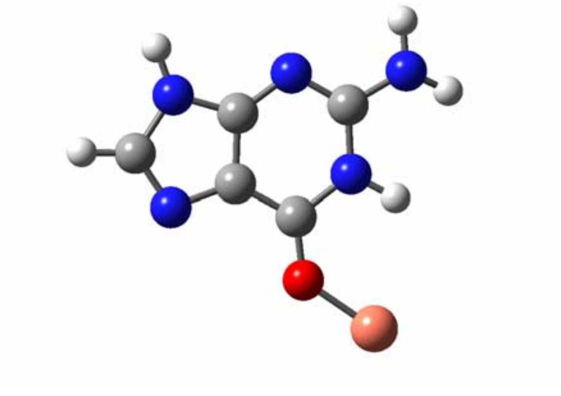

Fig. 10: Cu^{+}-G1 (N7) complex

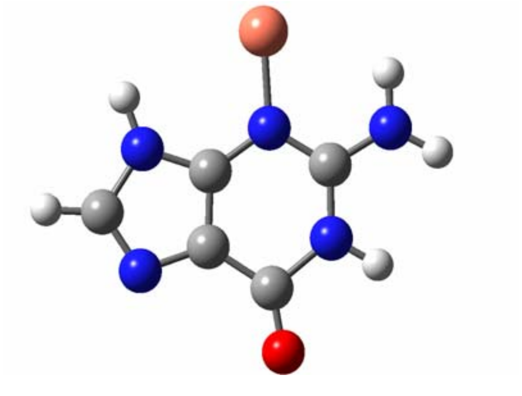

Fig. 11: Cu^{+}-G1 (N9) complex

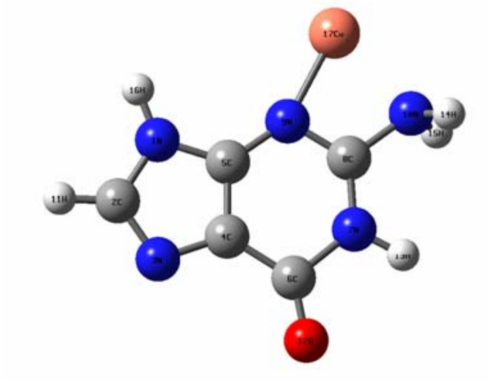

Fig. 12: Cu^{+}-G1 (N10) complex

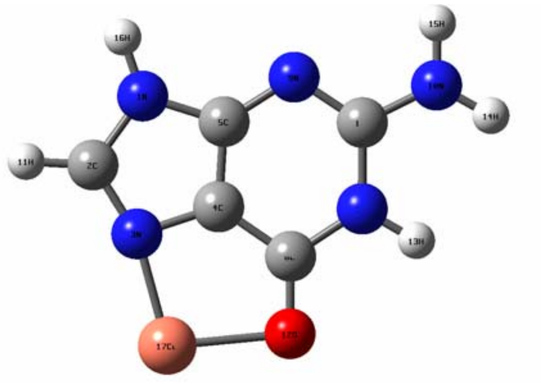

Fig. 13: Cu^{+}-G1 (O12) complex

In both the cases, MIA value is found to be the highest for the metalation in the O12 position of Guanine. MIA for metalation in the N3 position is similar to that in the O12 position (difference < 0.001 kcal/mol) in both the cases. Structures of Zn^{2+}- guanine complexes show that both N3 and O12 atoms compete for the metal ion and in the resultant geometry the latter occupies a position in between them (Fig. 3 and 7), leading to the formation of strain free five member rings in them, which accounts for their high MIA values. The trend of MIA's and hence the stability of complexes can be correlated to the retained net charges on metal atoms. Computed Mulliken net charges of the interaction sites obtained by the Mulliken population analysis (MPA) are given in Tables 2 and 3. It is seen that M^{n+}-G1 (N3) and M^{n+}-G1 (O12) complexes have similar retained charges on metal atoms and basic sites (i.e. N and O atoms). At the same time they have similar MIA values. In the cases of Zn^{2+}-G1 complexes, it can be generalized that higher the retained charge on Zn, or higher the retained negative charge on N3 or O12 atom, higher is the MIA value. It is expected that lower the value of the retained charge on the metal atom, higher is the charge transfer and hence higher will be the MIA as well of stability of complexes, but O12 and N3 complexes of Zn have exceptionally high MIA values, which may be attributed to the extra stability provided by the strain free additional five member ring formations in both the cases. However, results are exactly according to our expectations in the cases of Cu^{+}-G1 complexes. Copper complexes at N3 and O12 positions of guanine have the lowest values of retained charges on the Cu atom [0.6219, Table 3] and hence they possess the highest MIA values too. Net retained charges on metal atoms can be graphically correlated and such correlation plots for the complexations of the two metal ions are given in Fig. 14 and 15 respectively. In both the figures equations of the straight lines are given to have an idea about the nature of slopes of the plots. In Fig. 15, the negative value of slope helps us to confirm the nature of the plot for the variation of MIA with the retained charges on Cu. The two correlations are quite opposite of each other. In the case of Zn^{2+}-G1 complexes MIA increases with increasing retained charges of Zn (slope = 0.005, Fig. 14). On the other hand, in the case of Cu^{+}-G1complexes, negative value of slope (-0.0002, Fig. 15) shows that MIA increases with the lowering of the retained charge of Cu. Another type of correlation is seen between the MIA and the difference between the HOMO and LUMO energies in the complexes. It is expected that higher the difference between the HOMO and LUMO energies, higher should the stability and hence higher should be the MIA value of the metal ion-guanine complex. Corresponding plots for either type of complexes are given in Fig. 16 and 17. In Table 4, it is seen that both Zn^{2+}-G1 (N3) and Zn^{2+}-G1 (O12) complexes have nearly the same and highest values of the HOMO-LUMO energy gap and they have the highest MIA values too. Similarly, in the cases of Cu^{+}-G1complexes, the difference between the HOMO and LUMO energies suggests that N3 and O12 complexes should have the highest MIA values [Table 5]. Two plots show similar variations in MIA values with the changing differences between the HOMO-LUMO energies. To confirm whether N3 or O12 is the favorable complex in either case, we have computed free energy changes during the formation of all complexes and it shows that in either case, formation of the O12 complexes are more favorable since in their cases, values of ΔG^0's are more negative. Calculated values of the standard free energy changes are given in the Table 1. Values of bond lengths of few selected bonds in the most stable metal ion-guanine complexes are given in table 6 and are compared with the corresponding values in the free guanine base. Lengthening of 6 C = 12O bond in either complexes is due to the charge transfers taking place in these complexes. In all the complexes majority of the positive charge is located on the metal atom. MPA values of Tables 2 and Table 3 shows that 0.73 and 0.38 units of negative charges are transferred from guanine to the metal ions in Zn^{2+} and Cu^+-guanine complexes respectively. Higher charge transfer in the case of Zn^{2+}-guanine complex may be due to the higher charge of the free metal ion (2 units) than that in the case of Cu^+-guanine complex (one unit positive charge). B3LYP/6-31G** calculation of Zn^{2+} and Cu^+ ions show that LUMO energies of the two ions are nearly -0.7838 and -0.3499 hartee respectively. The lower LUMO energy of Zn^{2+} ion suggests that charge transfer in Zn^{2+}- guanine complex is easier than that in Cu^+-guanine complex. It accounts for the higher MIA values of Zn^{2+}- guanine complexes as compared to the Cu^+-guanine complex in Table 1.

Table 1: Computed metal ion affinities (MIA's) (B3LYP/6-31G) of Metal ion-Guanine (G1) complexes and standard free energy (ΔG^{0}corr) changes during their formation**

S. No.	Position	Zn^{2+}-Guanine complex		Cu^+-Guanine complex	
		Standard free energy change with the correction due to internal energy (ΔG^0_{corr})	MIA (Kcal/mol)	Standard free energy change with the correction due to internal energy (ΔG^0_{corr})	MIA (Kcal/mol)
1	N1	-194.8588	203.5346	-91.0958	98.3645
2	N3	-254.0621	264.4194	-130.6158	139.6259
3	N7	-177.9358	185.8631	-95.9484	104.7558
4	N9	-194.8594	203.5346	-91.1956	98.3211
5	N10	-177.9352	185.8630	-93.0895	101.3996
6	O12	-254.0653	264.4195	-130.6195	139.6263

Table 2: Computed Mulliken Net charges (Q/e) on various atoms of Zn^{2+}-guanine complexes

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Zn^{2+}-G1 (N1)	N1	-0.5678	**Zn^{2+}-G1 (N9)**	N1	-0.5678
	N3	-0.4032		N3	-0.4032
	N7	-0.5769		N7	-0.5769
	N9	-0.7385		N9	-0.7386
	N10	-0.7657		N10	-0.7657
	O12	-0.3254		O12	-0.3253
	Zn	1.1647		Zn	1.1647

Cont…

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Zn^{2+}-G1 (N3)	N1	-0.5799	**Zn^{2+}-G1 (N10)**	N1	-0.5376
	N3	-0.7218		N3	-0.4002
	N7	-0.6321		N7	-0.5987
	N9	-0.5271		N9	-0.4796
	N10	-0.6053		N10	-0.7224
	O12	-0.6378		O12	-0.3237
	Zn	1.2682		Zn	0.7901
Zn^{2+}-G1 (N7)	N1	-0.5377	**Zn^{2+}-G1 (O12)**	N1	-0.5799
	N3	-0.4002		N3	-0.7219
	N7	-0.5988		N7	-0.6321
	N9	-0.4795		N9	-0.5271
	N10	-0.7224		N10	-0.6053
	O12	-0.3237		O12	-0.6377
	Zn	1.1790		Zn	1.2682

Table 3: Computed Mulliken Net charges (Q/e) on various atoms of Cu$^+$-guanine complexes

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Cu$^+$-G1 (N1)	N1	-0.5886	**Cu$^+$-G1 (N9)**	N1	-0.5909
	N3	-0.4460		N3	-0.7462
	N7	-0.6267		N7	-0.6317
	N9	-0.7687		N9	-0.7742
	N10	-0.6328		N10	-0.6357
	O12	-0.4202		O12	-0.7214
	Cu	0.6299		Cu	0.6330
Cu$^+$-G1(N3)	N1	-0.5932	**Cu$^+$-G1(N10)**	N1	-0.5729
	N3	-0.6067		N3	-0.4485
	N7	-0.6362		N7	-0.5831
	N9	-0.5599		N9	-0.6525
	N10	-0.6360		N10	-0.7290
	O12	-0.5892		O12	-0.4165
	Cu	0.6219		Cu	0.6296

Cont…

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Cu$^+$-G1(N7)	N1	-0.5797	**Cu$^+$-G1(O12)**	N1	-0.5932
	N3	-0.4659		N3	-0.6068
	N7	-0.6110		N7	-0.6362
	N9	-0.5439		N9	-0.5599
	N10	-0.6388		N10	-0.6359
	O12	-0.5997		O12	-0.5892
	Cu	0.6294		Cu	0.6219

Table 4: Computed HOMO-LUMO energies in Zn^{2+}-G1 complexes

Complex	HOMO-LUMO energies (a.u.) (B3LYP/6-31G**)		Difference (in Kcal/mol)	MIA (Kcal/mol)
Zn^{2+}-G1 (N1)	HOMO	-0.5322	23.5496	203.5346
	LUMO	-0.4946		
Zn^{2+}-G1 (N3)	HOMO	-0.5295	47.8771	264.4194
	LUMO	-0.4532		
Zn^{2+}-G1 (N7)	HOMO	-0.5294	25.7389	185.8631
	LUMO	-0.4884		
Zn^{2+}-G1 (N9))	HOMO	-0.5322	23.5371	203.5346
	LUMO	-0.4947		
Zn^{2+}-G1 (N10)	HOMO	-0.5294	25.7515	185.8630
	LUMO	-0.4884		
Zn^{2+}-G1 (O12)	HOMO	-0.5295	47.8394	264.4195
	LUMO	-0.4532		

Table 5: Computed HOMO-LUMO energies in Cu$^+$-G1 complexes

Complex	HOMO-LUMO energies (B3LYP/6-31G**) (a.u.)		Difference (Kcal/mol)	MIA (Kcal/mol)
Cu$^+$-G1 (N1)	HOMO	-0.3630	57.1363	98.3645
	LUMO	-0.2719		
Cu$^+$-G1 (N3)	HOMO	-0.3321	91.2876	139.6259
	LUMO	-0.1866		

Cont…

Complex	HOMO-LUMO energies (B3LYP/6-31G**) (a.u.)		Difference (Kcal/mol)	MIA (Kcal/mol)
Cu$^+$-G1 (N7)	HOMO	-0.3535	63.6039	104.7558
	LUMO	-0.2521		
Cu$^+$-G1 (N9)	HOMO	-0.3620	55.4865	98.3211
	LUMO	-0.2736		
Cu$^+$-G1 (N10)	HOMO	-0.3562	75.6172	101.3996
	LUMO	-0.2357		
Cu$^+$-G1 (O12)	HOMO	-0.3321	91.2688	139.6263
	LUMO	-0.1866		

Table 6: Selected bond lengths (in Å) in the most stable metal ion-guanine complexes obtained by B3LYP/6-31G calculation**

Zn^{2+}- Guanine (O12)		Guanine	Cu$^+$-Guanine (O12)		Guanine
Bond	Bond Length (Å)	Bond Length (Å)	Bond	Bond Length (Å)	Bond Length (Å)
12O-6C	1.2998	1.2178	**12O-6C**	1.2596	1.2179
6C-4C	1.3869	1.4407	**6C-4C**	1.4115	1.4407
4C-3N	1.3867	1.3817	**4C-3N**	1.3901	1.3818
3N-Zn	1.9423	-	**3N-Cu**	1.8815	-
Zn-12O	1.9143	-	**Cu-12O**	1.9907	-

* Positions of carbon atoms in metal ion-guanine complexes are shown in Fig. 1, G1

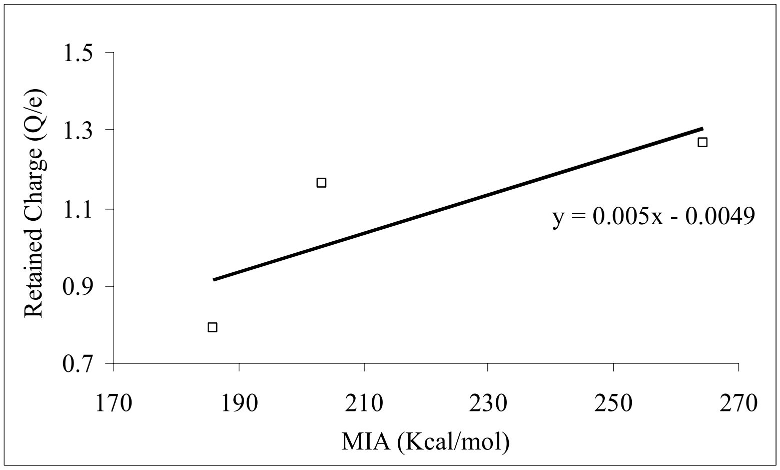

Fig. 14: Correlation between the MIA and the retained charges of Zn in Zn^{2+}-Guanine complexes

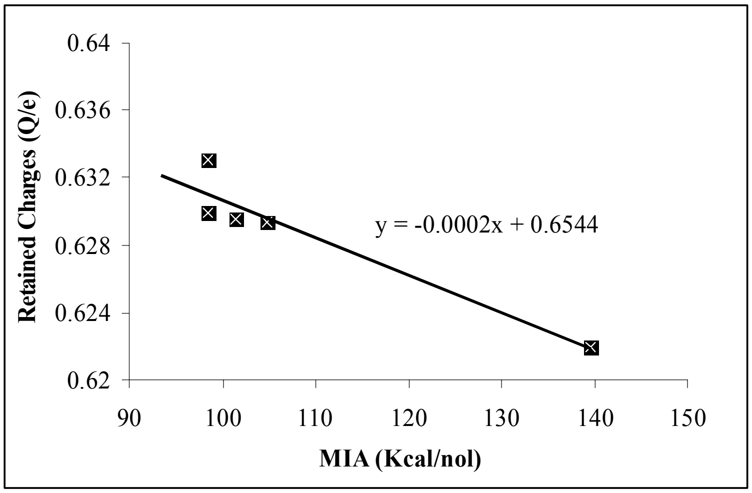

Fig. 15: Correlation between the MIA and the retained charges on Cu in Cu^+-Guanine complexes

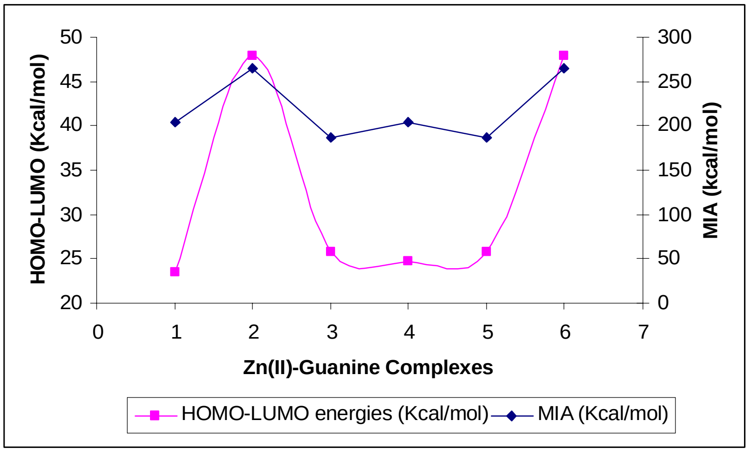

Fig. 16: Correlation between the MIA and the difference between the HOMO-LUMO energies in Zn^{2+}-Guanine complexes

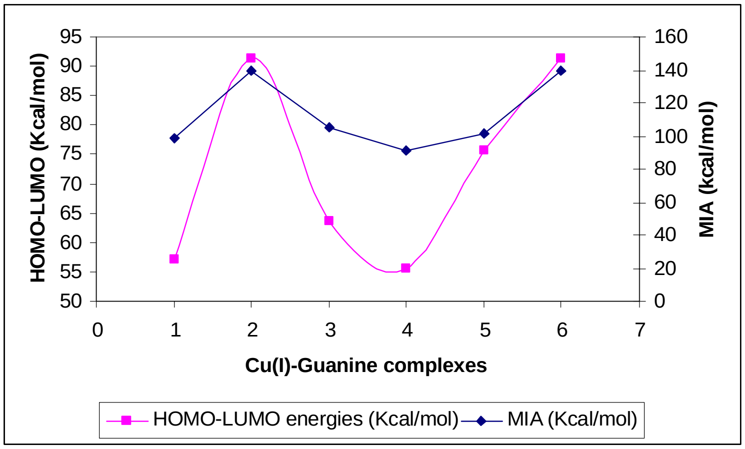

Fig. 17: Correlation between the MIA and the difference between the HOMO-LUMO energies in Cu^+-Guanine complexes

CONCLUSION

(i) Zn^{2+} ion produces stable complex with guanine at O12 position. In fact in the resultant structure it lies at a distance midway between N3 and O12, resulting in the formation of an additional five member ring, which explains the high MIA as well as the high thermodynamic stability (low ΔG) of Zn^{2+}-guanine complexes at N3 and O12 positions.

(ii) Cu^{+} ion also produces stable complex with guanine at O12 position. Although no additional ring formation is seen in this case, but the high charge transfer or the low retained charge on Cu accounts for the high MIA and low ΔG value during O12 complexation.

(iii) There exists opposing correlations between the retained charges on metal atom and MIA values in the two cases. In Cu^{+}-guanine complexes MIA values increase with decrease in the retained charge on Cu, while the opposite is true for Zn^{2+}-guanine complexes.

(iv) The lengthening of the C = O bond length after metalation in the either case takes place due to the charge transfer taking place in such complexes.

(v) There exists a fair correlation between the HOMO-LUMO energy gap and the MIA values of the complexes. MIA values increase with increasing gap between the HOMO and LUMO energy levels.

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