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CORRELATION BETWEEN THE STABILITIES OF Cu^{+}-CYTOSINE, Zn^{2+}- CYTOSINE COMPLEXES AND ENERGIES OF FRONTIER ORBITALS: DFT STUDY IN THE GAS PHASE

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ABSTRACT

Density functional theory (DFT) study is done to investigate the most stable Cu^{+} and Zn^{2+}- cytosine complexes. Metal ion affinities (MIA's) are determined at all possible basic sites of cytosine. Mullikan population analysis (MPA) method is adopted to see the possible charge transfer in these complexes. There exists interesting correlations between energies of frontier orbitals (HOMO and LUMO) of M^{n+}- cytosine complexes and their corresponding MIA values. Correlation between the net retained charges of metal ions in the complexes and corresponding MIA values is also investigated thoroughly.

Key words: DFT, Cytosine, Metal ion affinity, MPA, Bond lengths, HOMO-LUMO energies.

INTRODUCTION

Electrostatic interaction with metal ions is very important for the structural stability of oligonucleotides. The binding of metal ions as well as other ions by various organic compounds, components of DNA and RNA has been investigated for several years[1-3]. Recently, Rodger carried out studies on the interaction of alkali metal ions with pyridine and its analogues[4]. Zhu and his co workers carried out DFT studies on the interaction of NH_4^{+} ion with aromatic heterocyclics[2]. Conformational behaviour and function of DNA are influenced by the presence of metal ions. Sometimes, metal ion-nucleobase interaction may cause the stabilization of DNA triple or quadrupole helices, or can stabilize the base tautomers and may thus hinder the DNA replication process. Russo and his co workers carried out several studies on the interaction of a series of transition metal ions as well as alkali and alkaline earth metal ions with various purine and pyrimidine bases[5-7]. Such studies, when carried out in theoretical levels, help experimental researchers to rationalize their problems and eliminate guess works to large extents. Quantum mechanical evaluations at a higher level are providing excellent complements to experimental works. In this work the interaction of Zn (II) and Cu (I) with cytosine is explored using density functional theory (DFT) method[8] to obtain information on the binding of these metal ions with cytosine. Geometries and thermodynamic parameters of the metal ion-cytosine complexes are determined along with the construction of intrinsic models of these complexes. In the entire work our focus remains mainly on the possible

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correlation between the metal ion affinities and the retained charges of metals as well the energies of frontier orbitals of all the possible metal ion-cytosine complexes.

Copper and zinc are two trace elements essential to the human health. These are required for various metabolic processes. They can affect the structural integrity of DNA base pairs in the free or protein bound forms[9]. Copper combines with certain proteins to produce enzymes that act as catalysts in many body functions. It is most frequently used for the catalysis of the oxidation- reduction processes involving molecular oxygen. Zinc is found in many enzymes and takes part in the transcription of DNA, translation of RNA, as well as in cell division. It is held mainly in metallothionein reserves[10], interacts with large number of organic molecules and takes active role in the metabolism of RNA and DNA. As an efficient Lewis acid it is very useful as catalytic agent in hydroxylation and other enzymatic reactions. Carbonic anhydrase and carboxypeptidase are two important enzymes involving zinc. These are involved in the processes of carbon dioxide regulation and the cleavage of peptide linkages during digestion of proteins respectively[11,12]. Zinc fingers are extremely useful in the recognition of DNA sequences during replication and transcription[13]. However excessive concentration of these metal ions may interfere with the structural integrity of the nucleic acid polymer. Metallothioneins absorb both zinc and copper ions. So, excessive intake of any one of them may hamper the absorption of the other metal ion[10].

Researchers are constantly using DFT as an efficient tool for the study of molecular properties, especially of bigger systems, where it is found to be superior to the Hartee Fock (HF) and the Mollere Plesett (MP) methods[14]. DFT with B3LYP functional[15] has shown its reliability in predicting geometry, metal ion affinities (MIA's), enthalpy and free energy changes etc.

Computational method

DFT method adopted here is the B3LYP i.e. Becke's three parameter hybrid functional[16] using Lee-Yang-Par[17] correlation function. All the structures are optimized using the 6-31G** basis set. Results obtained so far have shown that the basis set 6-31G (d, p) is large enough to reduce the basis set superposition error (BSSE)[18] to ~2-3 Kcal/mol[19]. Hence, B3LYP/6-31G** method was used, without taking the BSSE correction into account. To find out the most favorable site of attachment of metal ions with cytosine, metal ion affinities (MIA) values are determined, which are assumed to the negative of the enthalpy change of the following complexation process,

$(Zn^{2+}$ or $Cu^{+})$ ion + Cytosine $\rightarrow$ $(Zn^{2+}$or $Cu^{+})$-Cytosine complex

Alternatively, MIA = $[E^0(Zn^{2+}$ or $Cu^{+}) + E^0$(Cytosine)] – $[E^0(Zn^{2+}$or $Cu^{+})$-Cytosine complex]

Where, E^0 represents absolute energies of molecules/ions. All computations are done using B3LYP with 6-31G** basis sets as incorporated in Gaussian 09' code[20] in the gas phase. Retained charges of the basic sites as well as the metal atom are determined using the Mulliken Population analysis method (MPA). Bond lengths of some selected bonds in the optimized geometries, free energy changes during complexations at various positions are determined with the help of the Gaussian programme. Free energy changes are calculated at 298.15 K, using the same basis sets as earlier with the help of the following relation:

$$\Delta G^0 = \sum G^0_P - \sum G^0_R$$

All the free energy terms represent the total corrected standard free energy of the reactant (R) or the product (P). Correction of free energy term is needed to provide due consideration of the internal energy at the given temperature.

RESULTS AND DISCUSSION

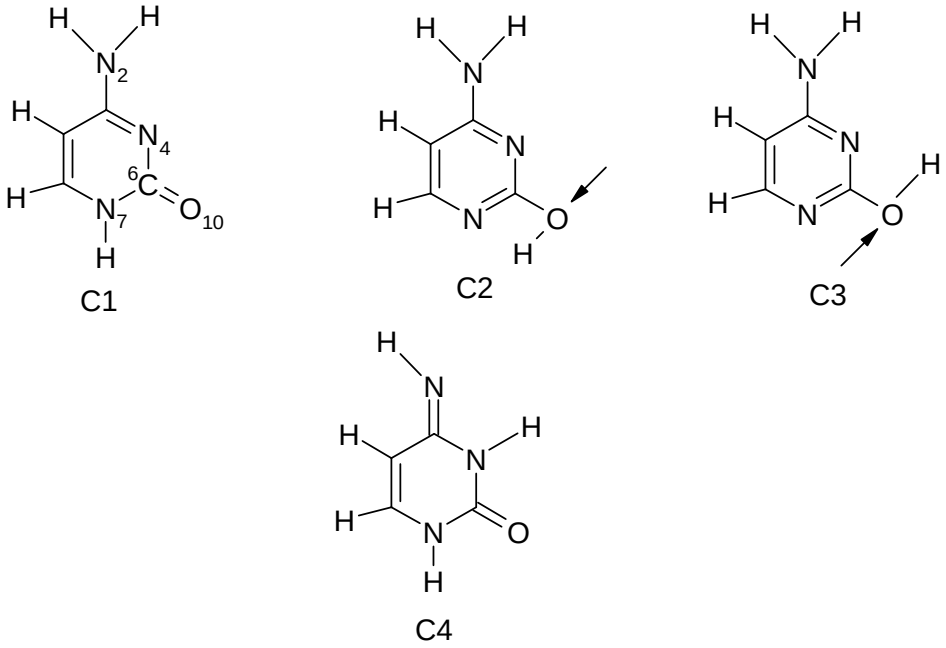

Fig. 1: Tautomers of Cytosine as obtained by G09W

[In C2 and C3, metal ions are attached in the directions specified by arrow marks. In C1, numbering of basic sites is done as per their positions in the optimized metal ion- cytosine complexes.]

Calculations show that there are four stable tautomers of cytosine (Fig. 1). Out of these tautomers, C2 and C3 are energetically similar, only relative attachments of metal ions in them are different. Others have different energies. C1 is the most stable with the lowest energy (-394.9413255 hartee), while C4 is the least stable with energy (-394.9393422 hartee). C2 has energy intermediate between those of C1 and C4. In our present study, metal ion complexes with the most stable tautomer of cytosine (C1) are discussed. Optimized geometries of complexes as obtained by Gaussian calculations are given in Fig. 2-9. It is seen that complexes resulting from the metalation at N4, N7 and O10 positions of cytosine are similar and their MIA values are also identical (Table 1). Thermodynamic calculations show that N4 complexation is the most favourable one since it involves the lowest ΔG^0 value (Table 1). Complexation at N2 and N7 are not favourable, since both these positions are sterically hindered to some extent by the adjacent H atoms. Positions N4 and O10 compete for the metal ion and in the resultant geometry of Zn^{2+}-cytosine complexes, metal ions occupy a position intermediate between these two basic sites. Bond distances involving the metal ion are given in Fig. 3 and 5. In both the cases, additional four member, coplanar rings are formed after metalation, which accounts for their high stability and high MIA values. Additional ring formation is not seen in the cases of Cu^{+}-cytosine complexes (Fig. 6 to 9). To explore the possible correlation between the retained charges of metal ions after complexation and MIA, Mulliken charges obtained by MPA method are given in the Table 2. It is seen from the table that in the case of Zn^{2+}-cytosine complexes, MIA values decrease with increasing retained charge of Zn, while in the case of Cu^{+}-cytosine complexes, MIA values increase with lowering in the retained charge of Cu. These correlations are graphically represented in Fig. 10 and 11. It is expected that stabilities of complexes should be more with higher charge transfer in them. In Cu complexes, low retained charge of Cu means, high charge transfer, which accounts for the trend in the variation of MIA values and hence their stabilities. However, in the case of Zn^{2+}-cytosine complexes, trend of charge transfer being opposite, their stabilities can be best explained in terms of the formation of additional planar rings in N4 and O10 complexes. In our previous studies of similar complexes[21-26], the

HOMO-LUMO approach was found to be very helpful for justifying the order of stabilities of complexes. Energies of frontier orbitals and the corresponding gap between them in the metalated complexes are calculated using the same basis sets and are shown in the Table 3. HOMO-LUMO energy gap being the highest in N4 complexes, they are the most stable. Both Zn^{2+} and Cu^{+}-cytosine complexes show similar variations in the HOMO-LUMO energies. Possible correlations between the MIA and the difference between HOMO-LUMO energies are graphically represented and are shown in Fig. 16 and 17. In the case of Zn^{2+}-cytosine complex, HOMO-LUMO energy gaps vary almost linearly with increasing MIA values (Slope 0.1575, Fig. 16). B3LYP/6-31G** calculations show that LUMO energy of Zn^{2+} ion is lower by nearly 272 kcal/mol than that of Cu^{+} ion. The lower value of the LUMO energy of Zn^{2+} ion suggests that charge transfer in Zn^{2+}-cytosine complex is easier than that in Cu^{+}-cytosine complex. It explains the higher MIA values of Zn^{2+}-cytosine complexes as compared to the Cu^{+}-cytosine complex in Table 1. At an average 0.72 unit of negative charge is transferred from cytosine to the Zn^{2+} ion, while 0.37 unit of charge is transferred to the Cu^{+} ion. Selected bond lengths of the most stable N4 metalated complexes are given in Table 4. The elongation of the carbonyl bond length in the cytosine-metal ion complexes is an indication of the charge transfer in the complexes.

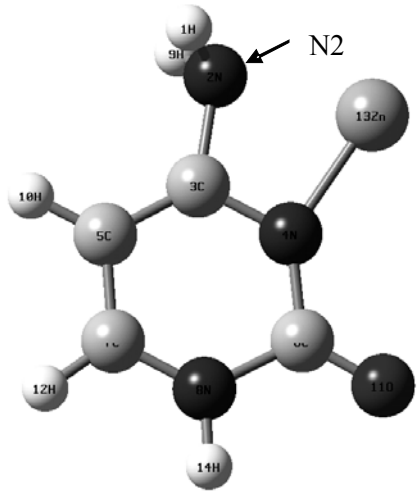

Fig. 2: Zn^{2+}-C1 (N2) Complex

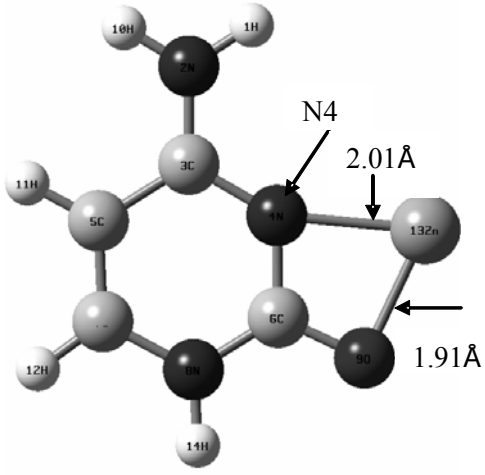

Fig. 3: Zn^{2+}-C1 (N4) Complex

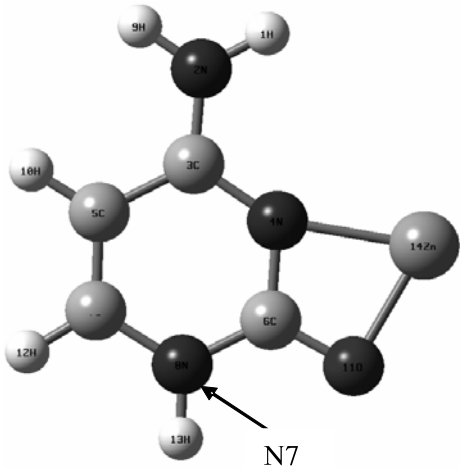

Fig. 4: Zn^{2+}-C1 (N7) Complex

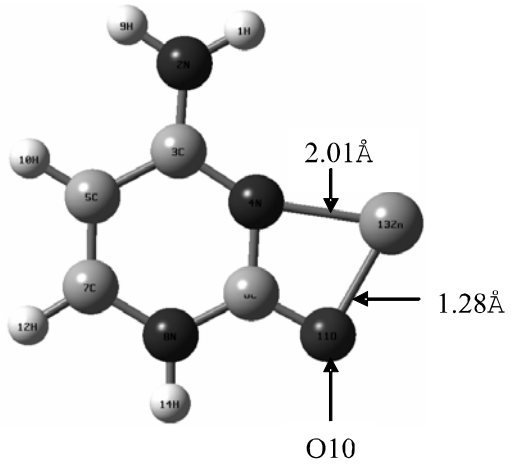

Fig. 5: Zn^{2+}-C1 (O10) Complex

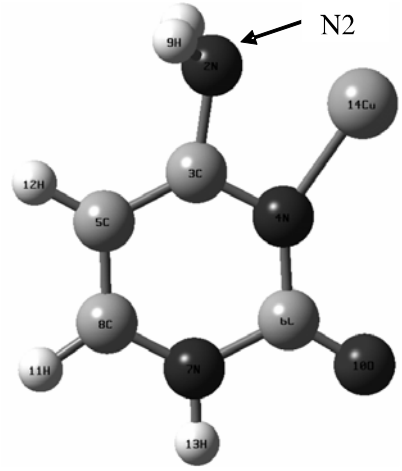

Fig. 6: Cu^{+}-C1 (N2) Complex

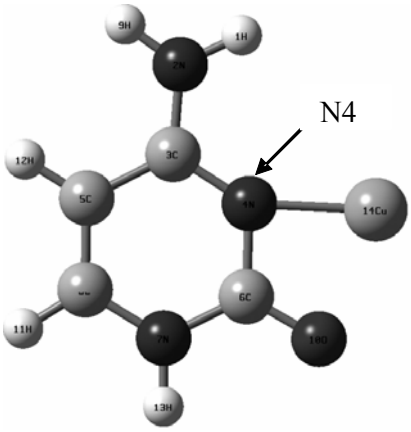

Fig. 7: Cu^{+}-C1 (N4) Complex

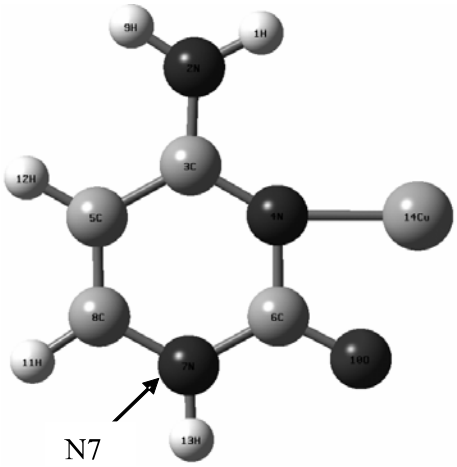

Fig. 8: Cu^{+}-C1 (N7) Complex

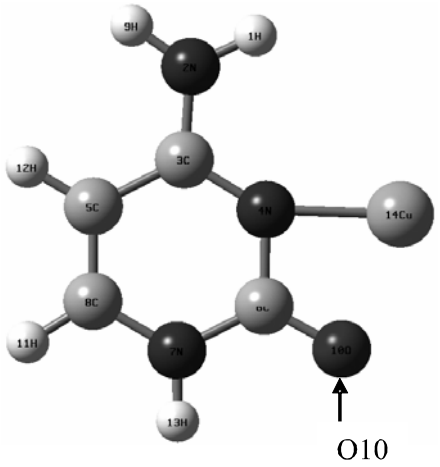

Fig. 9: Cu^{+}-C1 (O10) Complex

Table 1: Computed metal ion affinities (MIA's) (B3LYP/6-31G) of Metal ion-Cytosine (C1) complexes and standard free energy (ΔG^0) changes during their formation.**

		Zn^{2+}-Cytosine complex		Cu^{+}-Cytosine complex	
S. No.	**Position**	**Standard Free energy change with the correction due to internal energy (ΔG^0)**	**MIA (Kcal/mol)**	**Standard Free energy change with the correction due to internal energy (ΔG^0)**	**MIA (Kcal/mol)**
1	N2	-209.6431	219.9788	-100.6542	109.5012
2	N4	-231.6434	242.4218	-116.3623	126.1330
3	N7	-231.6433	242.4225	-116.3617	126.1332
4	O10	-231.6415	242.4225	-116.3610	126.1325

Table 2: Computed Mulliken Net charges (Q/e) on various atoms of Metal ion-Cytosine complexes

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Zn^{2+}-C1 (N2)	N2	-0.7712	**Zn^{2+}-C1 (N4)**	N2	-0.5868
	N4	-0.7514		N4	-0.7652
	N7	-0.5227		N7	-0.5418
	O10	-0.3587		O10	-0.5749
	Zn	1.2699		Zn	1.2784
Zn^{2+}-C1(N7)	N2	-0.5868	**Zn^{2+}-C1(O10)**	N2	-0.5868
	N4	-0.7652		N4	-0.7652
	N7	-0.5418		N7	-0.5418
	O10	-0.5749		O10	-0.5749
	Zn	1.2785		Zn	1.2785
Cu^{+}-C1(N2)	N2	-0.7227	**Cu^{+}-C1(N4)**	N2	-0.6129
	N4	-0.6334		N4	-0.6938
	N7	-0.5329		N7	-0.5535
	O10	-0.4254		O10	-0.5428
	Cu	0.6531		Cu	0.6197
Cu^{+}-C1(N7)	N2	-0.6129	**Cu^{+}-C1(O10)**	N2	-0.6129
	N4	-0.6938		N4	-0.6938
	N7	-0.5535		N7	-0.5535
	O10	-0.5428		O10	-0.5428
	Cu	0.6196		Cu	0.6197

Table 3: Computed HOMO-LUMO energies in metal ion-cytosine complexes

Complex	HOMO-LUMO energies (a.u.) (B3LYP/6-31G**)		Difference (in Kcal/mol)	MIA (Kcal/mol)
Zn^{2+}-C1 (N2)	HOMO	-0.5834	55.6171	219.9788
	LUMO	-0.4947		
Zn^{2+}-C1 (N4)	HOMO	-0.5823	56.1191	242.4218
	LUMO	-0.4928		
Zn^{2+}-C1 (N7)	HOMO	-0.5823	56.1317	242.4225
	LUMO	-0.4928		
Zn^{2+}-C1 (O10)	HOMO	-0.5823	56.1379	242.4225
	LUMO	-0.4928		

Cont…

Complex	HOMO-LUMO energies (a.u.) (B3LYP/6-31G**)		Difference (in Kcal/mol)	MIA (Kcal/mol)
Cu^+-C1 (N2)	HOMO	-0.3406	65.3750	109.5012
	LUMO	-0.2364		
Cu^+-C1 (N4)	HOMO	-0.3369	74.1289	126.1330
	LUMO	-0.2188		
Cu^+-C1 (N7)	HOMO	-0.3368	74.1227	126.1332
	LUMO	-0.2187		
Cu^+-C1 (O10)	HOMO	-0.3369	74.1164	126.1325
	LUMO	-0.2187		

Table 4: Selected bond lengths (in Å) in the most stable metal ion-cytosine complexes Obtained by B3LYP/6-31G calculation**

Zn^{2+}- Cytosine (N4)		Cytosine	Cu^+-Cytosine (N4)		Cytosine
Bond	**Bond Length (Å)**	**Bond Length (Å)**	**Bond**	**Bond Length (Å)**	**Bond Length (Å)**
4N-Zn	2.008	-	4N-Zn	1.8779	-
4N-6C	1.3706	1.3721	4N-6C	1.3787	1.3721
6C-10O	1.2844	1.2200	6C-10O	1.2458	1.2200
10O-Zn	1.9137	-	10O-Cu	2.0937	-

[* Positions of Carbon atoms in metal ion-adenine complexes are shown in Fig. 1, C1]

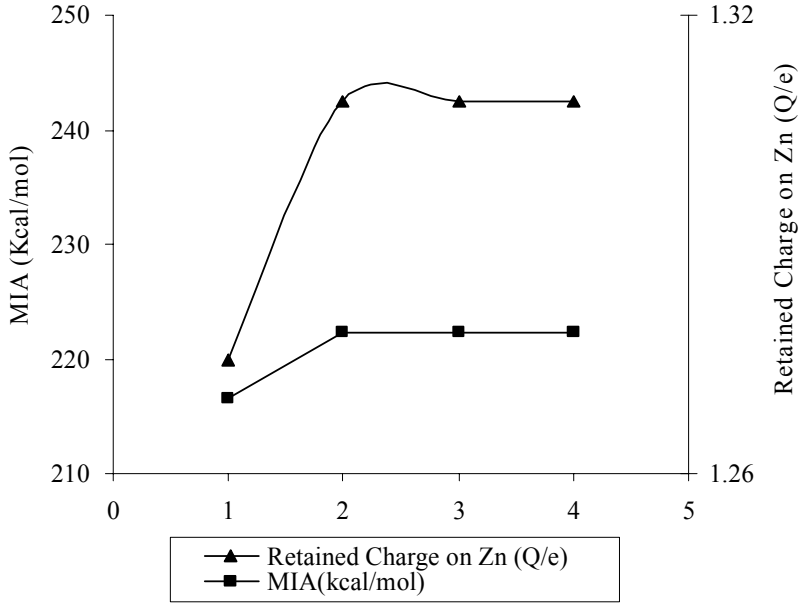

Fig. 10: Correlation between the MIA (in Kcal/mol) and retained charge (Q/e) of Zn

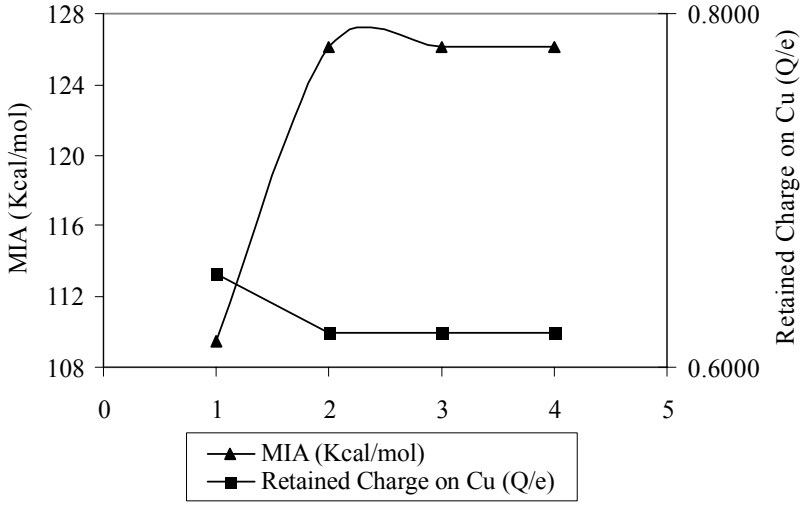

Fig. 11: **Correlation between the MIA (in Kcal/mol) and retained charge (Q/e) of Cu**

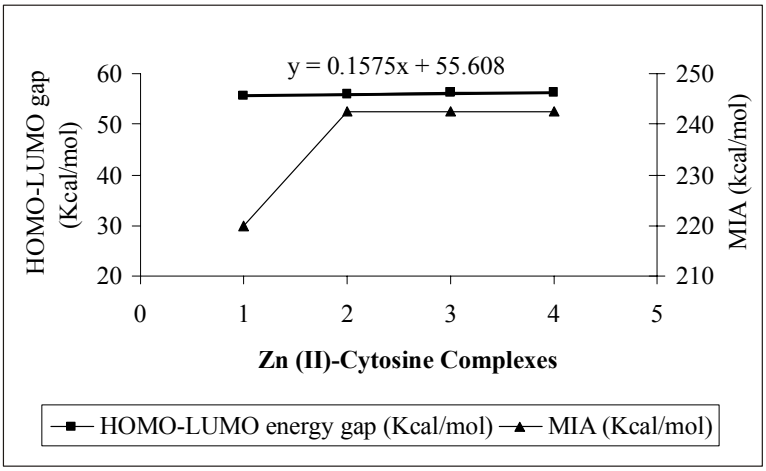

Fig. 12: Correlation between the MIA and the difference between the HOMO-LUMO energies in Zn^{2+}-Cytosine complexes

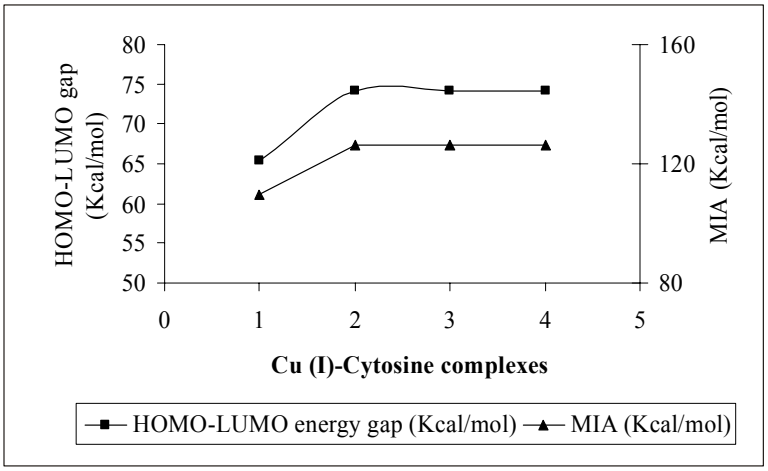

Fig. 13: Correlation between the MIA and the difference between the HOMO-LUMO energies in Cu^{+}-Cytosine complexes

CONCLUSION

Both Zn^{2+} and Cu^{+} ions produce stable complexes with cytosine at N4 position. Both the complexes show similar trends in the variation in the MIA values. In the case of Zn^{2+} complexes, there is additional ring formation during metalation. The change of MIA can be correlated to the retained charges of metal atoms. However, there exists opposing correlations in the two cases. Cu^{+}-cytosine complexes exhibit increase in MIA values with the decrease in the retained charge on Cu. On the other hand, in the case of Zn^{2+}-cytosine complexes, MIA values decrease with decrease in the retained charge on the metal atom. It is seen that higher the HOMO-LUMO energy gap, higher is the MIA and hence stability of complexes. Both Zn^{2+} and Cu^{+} complexes show similar variations in the MIA values with HOMO-LUMO energy gap. Variation of MIA can be explained on the basis of the HOMO-LUMO energy gap.

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