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DFT STUDY OF Cu^+-THYMINE AND Zn^{2+} -THYMINE COMPLEXES IN THE GAS PHASE : HOMO-LUMO APPROACH

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ABSTRACT

DFT study of the interaction of DNA base thymine with Zn^{2+} and Cu^+ ion is carried out. Most favourable sites of attachment of these ions in thymine are determined with the help of metal ion affinity (MIA) values. There are two susceptible sites of attachments of metal ions in thymine. Mulliken population analysis (MPA) method is used to determine the Mulliken charges of basic sites as well as the metal ions in all complexes. Possible correlation between the MIA and the retained charges of metal ions is thoroughly explored. Energies of frontier orbitals also correlate with the MIA values. Higher the energy gap between the HOMO and LUMO, higher is the stability of metal ion-thymine complexes.

Key words: DFT, Thymine, HOMO, LUMO, Zn^{2+}, Cu^+ ions.

INTRODUCTION

Metal ions play essential role in biological systems[1]. They are very effective in controlling an enzyme catalysed reaction. Both the conformational behaviour and functions of DNA are influenced by the presence of metal ions. Without appropriate metal ions, biochemical reactions catalysed by certain metalloenzymes would proceed either very slowly or not at all[2-3]. X-ray diffraction studies of proteins provide information regarding the binding of metal ions in the active sites of enzymes and thus helps in predicting the possible mechanism of the action of enzyme. Copper and zinc are two essential trace elements for human health. Zinc is present in all body fluids and tissues. It is an essential component of a large number of enzymes, which participate in various processes like synthesis and degradation of carbohydrates, proteins, nucleic acids and in the metabolism of other micronutrients[4]. It helps in the maintenance of cellular integrity by stabilizing the molecular structure of cellular components and membranes. Its role is very crucial in polynucleotide transcription and thus helps in the process of genetic expression. Carbonic anhydrase and carboxypeptidase are two important enzymes involving Zinc[1]. These are involved in the processes of carbon dioxide regulation and the cleavage of peptide linkages during digestion of proteins, respectively. 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[1-2]. Sometimes, metal ions responsible for the propagation of genetic information may produce errors in the information transfer, which may be either due to their attachments in wrong positions or their presence in excess. Metal ions are held mainly in metallothionein reserves and so the excessive intake of any one of them may affect the absorption of the other. Metal ions may bind either to the donor atoms of nucleobases or to the phosphate groups. Phosphate-binding of metal ions stabilizes the double helix

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but excessive stabilization may lead to the mispairing of bases, which in turn may lead to errors in the genetic code propagation. Phosphate binding of metal ions may also affect phosphodiester linkages and may cut RNA strands into pieces. It is for these reasons that studies of the effects of metal binding on nucleic acids are becoming so important[3-4].

Recently many studies are being carried out on the interaction of metal ions with nucleic acids both in the experimental and theoretical levels[5-6]. Such studies, when carried out in theoretical levels, help experimental researchers to rationalize their problems and eliminate guess works to large extents. Russo and his co-workers[8-10] carried out several studies on the interaction of a series of metal ions with various purine and pyrimidine bases. Many other researchers employed theoretical tools for exploring the interaction of several metal ions with amino acids as well. In this present work, DFT methods[11] are employed for the study of Zn^{2+} and Cu^+ -thymine complexes in terms of energies of their frontier orbitals. DFT has been efficiently used[12-17] by many researchers for the study of molecular properties of bigger systems and has been found to be superior to the Hartee Fock (HF) and the Mollere Plesett (MP) methods[18]. The principal aim of our present work is the determination of the structural, conformational and energetic properties of complexes that the two ions form with thymine. We have tried to find the possible correlation between the energies of HOMO's, LUMO's of these complexes and the metal ion affinities (MIA). Importance of the HOMO-LUMO energy gap in predicting the most favorable attachments of metal ions with thymine is thoroughly studied. DFT method adopted here is the B3LYP[19] i.e. Becke's three parameter hybrid functional[20] using Lee-Yang-Par[21] correlation function. DFT with B3LYP functional has been found to be highly reliable in similar studies in literatures[22,23].

Computational method

All optimization and frequency calculations are done using B3LYP with 6-31G** basis sets as incorporated in the Gaussian 09' programme code (G09W)[24] in the gas phase. The basis set 6-31G (d, p) is large enough to reduce the basis set superposition error (BSSE)[25] to ~2-3 Kcal/mol[26]. Hence, in the present work, correction due to BSSE was not taken into account. There are four basic sites in thymine, in which metal ions as Lewis acids can attach. The lowest energy site of attachment of metal ions with thymine, is determined with the help of metal ion affinities (MIA) values, which are assumed to the negative of the enthalpy change during the following complexation process,

$$M^{n+}\text{ ion } (Zn^{2+} \text{ or } Cu^{+} \text{ ion}) \ + \ \text{Thymine} \rightarrow M^{n+}\text{-Thymine complex}$$

$$\text{Alternatively, MIA or } -\Delta H = [E^0 (M^{n+}) + E^0 (\text{Thymine})] - E^0 (M^{n+}\text{- Thymine complex})]$$

Where, E^0 represents absolute energies of molecules/ions. Mulliken Population analysis (MPA) method is applied to determine the retained charges of the metal ion as well as the attachment site of thymine to see the possible correlation of the same with MIA values. HOMO-LUMO energies of all the metal ion-thymine complexes are determined using the Gaussian programme and the same basis sets as above. Free energy changes (ΔG^0) during complexations at various positions are calculated at 298.15 K and 1 atmosphere pressure in the gas phase using the same basis sets. ΔG^0 is assumed to be the difference between the total free energies of the products and reactants. In all the calculations due consideration is given to the thermal corrections to the Gibbs free energy.

RESULTS AND DISCUSSION

At first all the stable tautomers of thymine are determined using G09W software (Figure 1). T1 has been found to be the most stable tautomer with absolute energy of -454.1488 hartee, while T2 and T3 are less stable than T1 with energies -454.1156 hartee and -454.1178 hartee respectively. Obviously T1 is energetically most prevalent and hence all studies are done with T1. Zn^{2+} and Cu^+ ions are placed at different sites around it and metal complexes so obtained are fully optimized with the DFT method using Gaussian software. All the optimized geometries of the metal ion-thymine complexes are shown in Fig. 2-9. All the complexes are mono co-ordinated and metal ions are seen to interact with the oxygen atoms only. Metalation of thymine results two types of complexes, viz. O1 and O9 complexes. Metalation at N6 and N8 of thymine produces unstable complexes and ultimately metal ions migrate to either of the two oxygen atoms for producing geometries those are energetically more favourable (Fig. 4, 5, 8, 9).

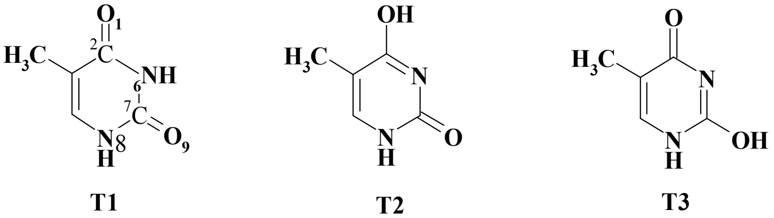

Fig. 1: Stable tautomers of thymine as obtained by G09W software

[In T1 positions of few selected sites are shown]

Computed metal ion affinities (MIA's) for metalation at different sites along with the corresponding ΔG^0 values are given in the Table 1. In either case, metalation at O1 possesses the highest MIA as well as the lowest ΔG^0. Hence, metalation at O1 produces the most favourable metal ion (Zn^{2+} or Cu^+)-thymine complexes. Although Cu^+-T1 (N6) complex results by the initial metalation at N6 position, but after geometry optimization the metal ion migrates to the O1 position as seen in the Fig. 8. Thus, Cu^+-T1 (N6) is also an O1-complex and is the most favourable Cu^+-thymine complex. It differs from the Cu-T1 (O1) complex of Fig. 6 in the dihedral angle. Mulliken net charges of metal ions as well as the basic sites of the optimized geometries are given in Table 2. To see the possible correlation between the retained charges of metal ions and MIA values, the two parameters are plotted (Fig. 10 and 11). In the case of Zn^{2+}-thymine complexes, MIA values vary proportionately with the retained charge of the metal ion. On the other hand, In the case of Cu^+-thymine complexes, MIA values vary inversely with the retained charge of the metal ion. Table 2 shows that at an average of 0.75 and 0.33 units of negative charges are transferred from the thymine base to the Zn and Cu-atoms respectively. B3LYP/6-31G** studies of the two metal ions show that the LUMO energies of Zn^{2+} and Cu^+ ions are -0.7838 a.u. and -0.3499 a.u. respectively. Clearly, Zn^{2+} has the lower LUMO energy, which accounts for the higher charge transfer in Zn^{2+}-thymine complexes than that in Cu^+-thymine complexes. The higher charge transfer in turn accounts for the higher MIA values of Zn^{2+}-thymine complexes than that of Cu^+-thymine complexes. Computed Energies of frontier orbitals in the optimized geometries as obtained by Gaussian calculations are shown in the Table 4. It is seen that complexes with higher HOMO-LUMO energy gaps have higher MIA values too. The correlation is confirmed by plotting HOMO-LUMO energy differences and MIA values of all the complexes (Fig. 12 and 13). Bond lengths of a few selected bonds are shown in the Table 6. The elongation of the 2C = 1O bond length (usual C = O bond length is 1.20 Å) after metalation in either cases, indicates the possible charge transfer from oxygen (i.e.1O) to the metal atom.

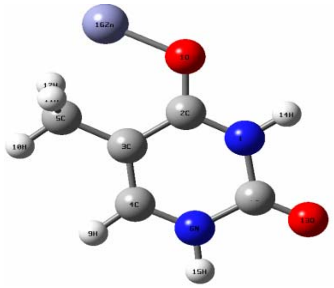

Fig. 2: Zn^{2+}-T1 (O1) Complex

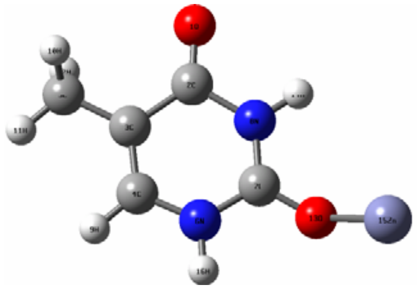

Fig. 3: Zn^{2+}-T1 (O9) Complex

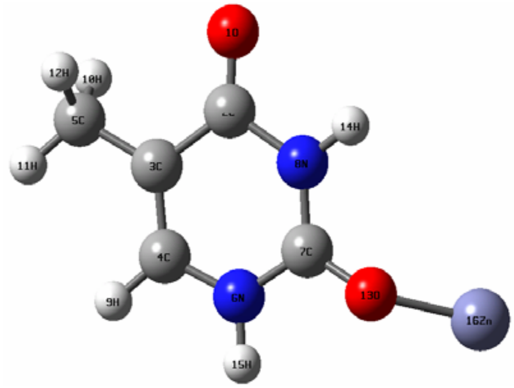

Fig. 4: Zn^{2+}-T1 (N6) Complex
(Metal ion migrates to O9)

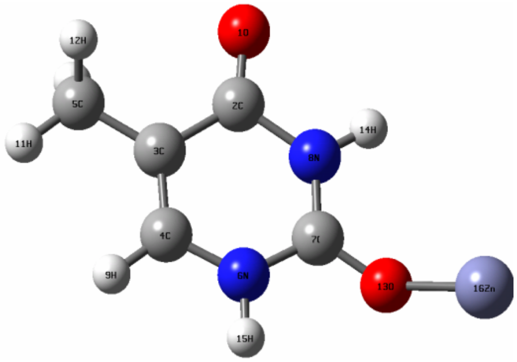

Fig. 5: Zn^{2+}-T1 (N8) Complex
(Metal ion migrates to O9)

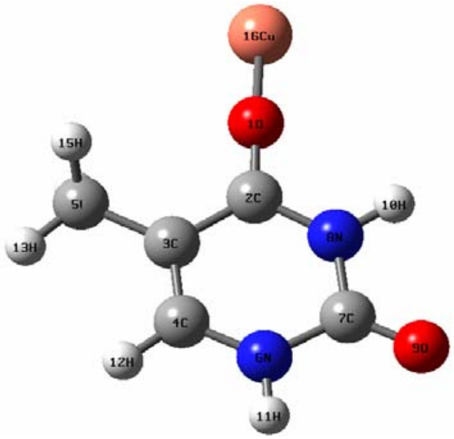

Fig. 6: Cu$^+$-T1 (O1) Complex
[Cu-O1-C2-N6 dihedral angle ≈ 87^0]

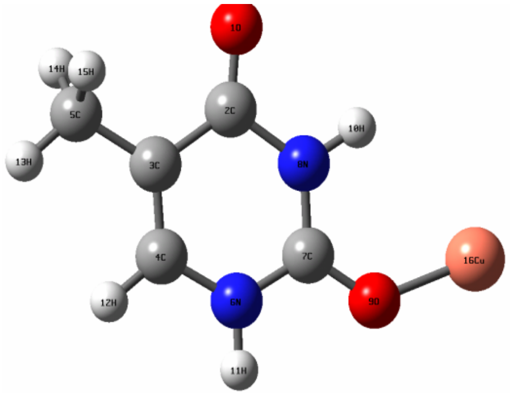

Fig. 7: Cu$^+$-T1 (O9) Complex
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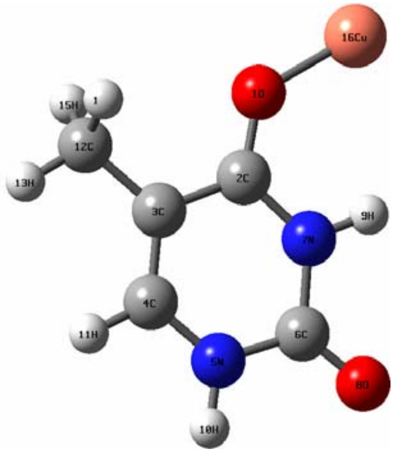

Fig. 8: Cu$^+$-T1 (N6) Complex
[Cu-O1-C2-N6 dihedral angle ≈ 0^0]
(Metal ion migrates to O1)

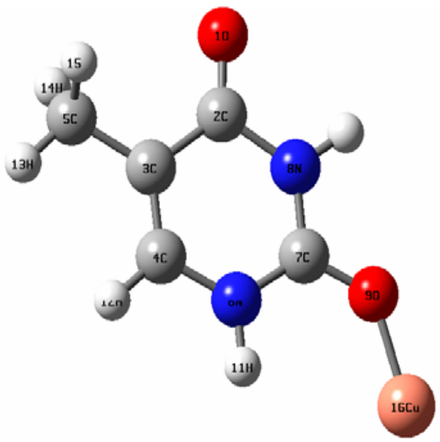

Fig. 9: Cu$^+$-T1 (N8) Complex
(Metal ion migrates to O9)

Table 1: Computed metal ion affinities (MIA's) (B3LYP/6-31G) of M^{n+}-thymine (T1) complexes and standard free energy (ΔG^0) changes during their formation**

S. No.	Complexes	Zn^{2+}-Thymine complex		Cu^{+}-Thymine complex	
		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	**M^{n+}-T1 (O1)**	-188.7292	197.3260	-85.6269	94.0966
2	**M^{n+}-T1 (N6)**	-176.4009	183.6523	-88.0994*	96.5469*
3	**M^{n+}-T1(N8)**	-176.4047	183.6523	-83.5568	91.7041
4	**M^{n+}-T1(O9)**	-176.4021	183.6523	-84.9549	93.0908

[*Cu^{+}-T1(N6) is also an O1-complex and it differs from Cu^{+}-T1 (O1) complex in the dihedral angle and co-planarity, figures 6 and 8].

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

Complex	Positions	Mulliken Charge (Q/e)	Complex	Positions	Mulliken Charge (Q/e)
Zn^{2+}-T1 (O1)	O1	-0.6298	**Zn^{2+}-T1 (N6)**	O1	-0.3444
	N6	-0.1719		N6	-0.5158
	N8	-0.2296		N8	-0.5868
	O9	-0.3320		O9	-0.6357
	Zn	1.2448		Zn	1.1792
Zn^{2+}-T1(O9)	O1	-0.3444	**Zn^{2+}-T1(N8)**	O1	-0.3443
	N6	-0.5158		N6	-0.5159
	N8	-0.5869		N8	-0.5869
	O9	-0.6359		O9	-0.6360
	Zn	1.1794		Zn	1.1795
Cu^{+}-T1(O1)	O1	-0.6185	**Cu^{+}-T1(N6)**	O1	-0.5899
	N6	-0.5595		N6	-0.5601
	N8	-0.6012		N8	-0.6054
	O9	-0.4304		O9	-0.4282
	Cu	0.6911		Cu	0.6608
Cu^{+}-T1(O9)	O1	-0.4295	**Cu^{+}-T1(N8)**	O1	-0.4233
	N6	-0.5589		N6	-0.5601
	N8	-0.5999		N8	-0.5937
	O9	-0.5916		O9	-0.5902
	Cu	0.6711		Cu	0.6645

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

Complex	HOMO-LUMO energies (a.u.) (B3LYP/6-31G**)		Difference (in Kcal/mol)	MIA (Kcal/mol)
Zn^{2+}-T1 (O1)	HOMO	-0.5731	38.6427	197.3260
	LUMO	-0.5115		
Zn^{2+}-T1 (N6)	HOMO	-0.5547	22.2142	183.6523
	LUMO	-0.5193		
Zn^{2+}-T1 (N8)	HOMO	-0.5547	22.1954	183.6523
	LUMO	-0.5193		
Zn^{2+}-T1 (O9)	HOMO	-0.5547	22.2079	183.6523
	LUMO	-0.5193		
Cu^{+}- T1 (O1)	HOMO	-0.3832	80.2015	94.0966
	LUMO	-0.2586		
Cu^{+}- T1 (N6)	HOMO	-0.3909	80.8559	96.5469
	LUMO	-0.2620		
Cu^{+}- T1 (N8)	HOMO	-0.3924	78.1074	91.7041
	LUMO	-0.2679		
Cu^{+}- T1 (O9)	HOMO	-0.3907	78.8165	93.0908
	LUMO	-0.2651		

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

Zn^{2+}- thymine (O1)		Thymine	Cu^{+}-thymine (O1)		Thymine
Bond	**Bond Length (Å)**	**Bond Length (Å)**	**Bond**	**Bond Length (Å)**	**Bond Length (Å)**
Zn-1O	1.8255	-	Cu-1O	1.7318	-
1O=2C	1.3078	1.2217	1O=2C	1.2650	1.2217
2C-6N	1.3415	1.4076	2C-6N	1.3675	1.4076
6N-7C	1.4227	1.3857	6N-7C	1.4062	1.3857
7C=9O	1.1913	1.2175	7C=9O	1.2050	1.2175
7C-8N	1.4170	1.3901	7C-8N	1.3933	1.3901

[* Positions of atoms in metal ion-thymine complexes are shown in Fig. 1, T1]

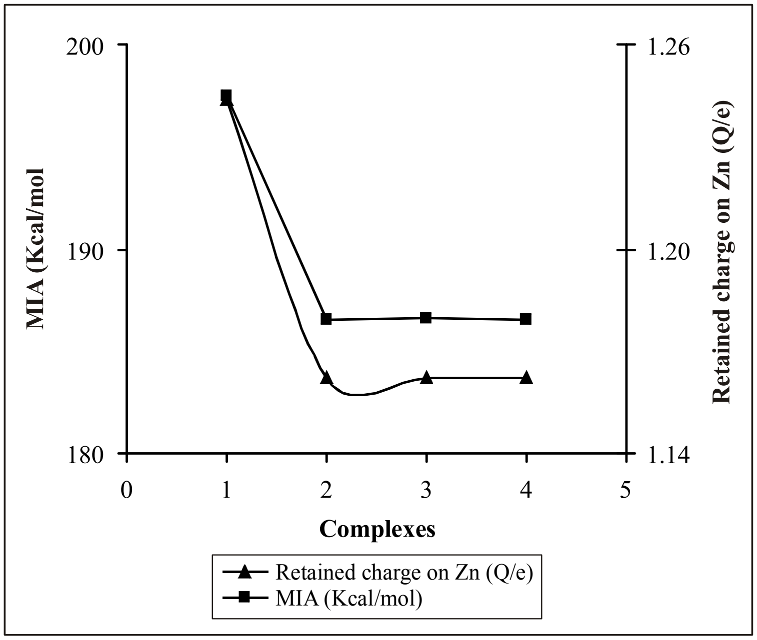

Fig. 10: Correlation between the MIA (in Kcal/mol) and retained charge (Q/e) of Zn

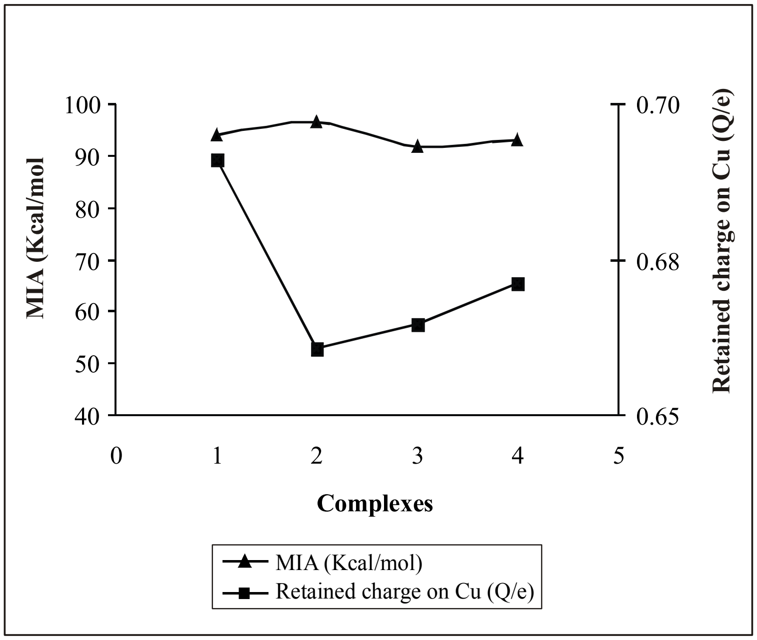

Fig. 11: Correlation between the MIA (in Kcal/mol) and retained charge (Q/e) of Cu

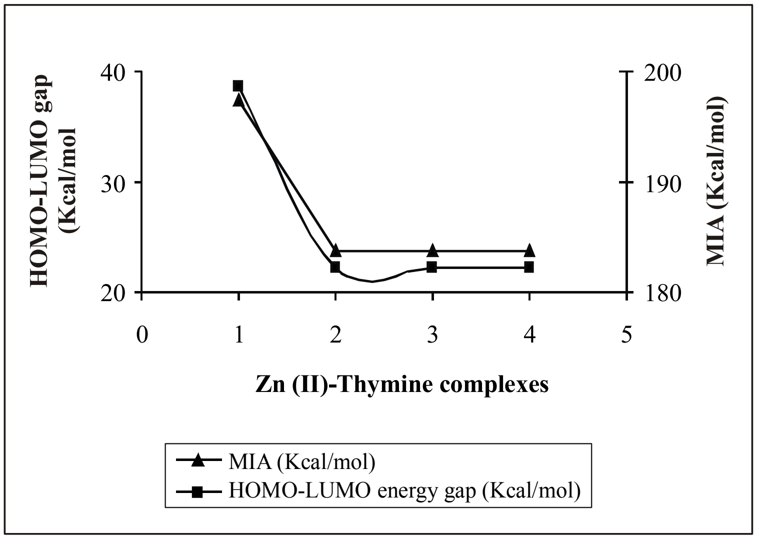

Fig. 12: Correlation between the MIA and the difference between the HOMO-LUMO energies of Zn^{2+}-thymine complexes

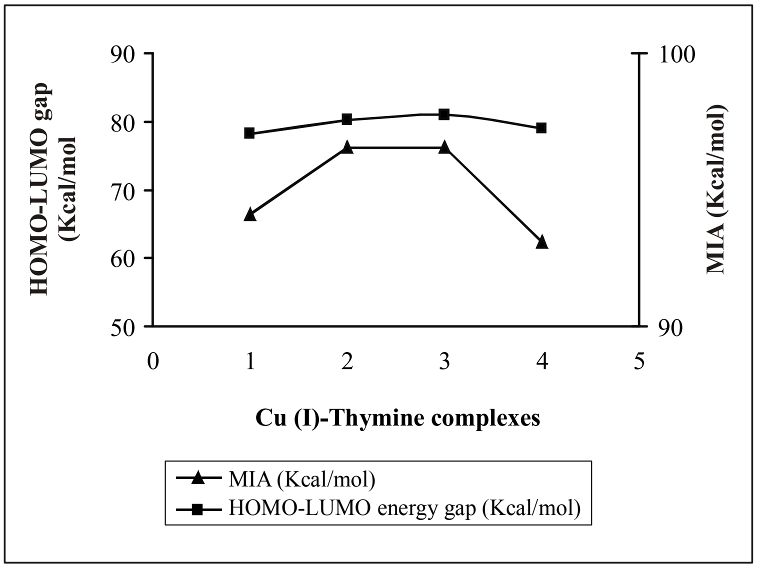

Fig. 13: Correlation between the MIA and the difference between the HOMO-LUMO energies of Cu$^+$-thymine complexes

CONCLUSIONS

(i) Zn^{2+} or Cu$^+$ ion may undergo complexation either at O1 or at O9 position of thymine but the most stable complex results by the interaction at the O1 position.

(ii) Zn^{2+}-thymine complexes have higher metal ion affinities than Cu$^+$-thymine complexes. Both the complexes show similar trends in the variation of MIA values. The change of MIA can be correlated to the retained charges of metal atoms. There exists contrasting correlations in the two cases. Cu$^+$-thymine 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+}-thymine^2 complexes, MIA values decrease with decrease in the retained charge on the metal atom.

(iii) Charge transfer is more in the case of Zn^{2+}-thymine complexes than that in the case of Cu^{+}-thymine complexes, which accounts for the higher MIA values of Zn^{2+}-complexes.

(iv) 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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