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DFT Study of the Interaction of Thymine with Cu$^+$ and Zn^{2+}

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Abstract. *Interaction of the DNA thymine base with* Cu$^+$ *and* Zn^{2+} *was studied to explore: a) The metal binding energy (MIA) of thymine with* Cu$^+$ *and* Zn^{2+} *and b) The possible correlation between charge transfer and MIAs. The gas-phase* Cu$^+$ *and* Zn^{2+} *affinities of thymine, as well as the Mulliken charges, on the complexed metal cations were both determined at the same computational level, including the density functional level and employing the hybrid B3LYP exchange correlation potential in connection with the 6-311++G* (d,p) *basis set. All the molecular complexes were obtained by interaction between the most stable tautomer of thymine and two transition mono and divalent* (Cu$^+$, Zn^{2+}) *metal ions. To probe all possible binding sites, these two cations were placed around the thymine nucleobase and optimized. For both* Cu$^+$ *and* Zn^{2+}, *the complexes of thymine with O4 are the most stable structure. For complexes of thymine with mono cations* (Li$^+$, Na$^+$, K$^+$ *and* Cu$^+$) *and dications* (Mg^{2+}, Ca^{2+} *and* Zn^{2+}), *the results indicate a linear correlation between the transferred charge and metal binding energy. The results also indicate that the amount of charge transfer and bonding strength are the highest for the transion metal ions* Cu$^+$ *and* Zn^{2+}, *respectively.*

Keywords: *Divalent cations; Metal ion affinity; Thymine; Metal complexation; Charge transfer.*

INTRODUCTION

The reaction between metal ions and organic molecules in the gas phase is an ideal environment from which complexation mechanisms, binding energies, enthalpies and the reactivity of the metal ions can be obtained in the absence of any complicating solvent effects [1]. Indeed, the advantage of a study in the gas phase is that the rationalization of the problem is simpler and needs less guesswork. The vacuum approximation (isolated molecule) used in this work seems to be reasonable, because the active centers of most enzymes are rather hydrophobic and characterized by low dielectric constants [2]. An earlier suggestion was made that when nucleosides enter the active site of enzymes, water is displaced [3]. On the other hand, it is clear that more realistic theoretical calculations, in the presence of a solvent, can be also obtained. In this situation, it is possible to directly compare the data coming from the experimental investigations with theoretical calculations. In fact, the metal ions play a significant role in several biological processes [4]. Synthesis, replication and the cleavage of DNA and RNA, as well as their structural integrity, are affected by the presence of these ionized metals in the cell nucleus [5]. To understand the role of cations in the biophysics of DNA, it is necessary first to carry out a detailed interaction study of ions with an isolated base and nucleosides [6]. Whether and where a specific metal ion will interact with a nucleic acid is controlled, at least in part, by the relative bond strength between the metal ion and the possible donor group present in the nucleic acid chain [7]. Knowledge about the fundamental modes of metal ion binding to simple DNA and RNA components (nucleobases, nucleosides, etc) would greatly improve our understanding of how metal ions interact with more complex nucleic acid structures [8].

The Density Functional Theory [9] (DFT) has recently been widely recognized as an efficient quantum chemistry method for studying molecular properties [10]. DFT with the B3LYP functional [11] has shown its reliability in predicting the geometries, binding energies and frequencies of metal cation-π or metal cation-heteroatom complexes with fewer computer resources in comparison with other quantum chemistry methods, such as MP2 [12,13]. Furthermore,

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the published calculation results demonstrated that the basis set, 6-311++G (d,p), is large enough to generally reduce the Basis Set Superposition Error (BSSE) to ~ 1 kcal/mol [14]. Russo and his co-workers performed B3LYP/6-311+G $(2df, 2p)$ calculations on the interactions of alkali cations (Li^+, Na^+ and K^+) with adenine, cytosine, guanine, thymine and uracil [15,16]. They calculated the binding affinity between M^+ and all possible tautomers of these nucleic bases. Interestingly, their results are in good agreement with most of the experimental results. Weiliang Zhu and their co-workers performed B3LYP/6-311++G (d,p) calculations on the interactions of alkaline and alkaline earth cations with adenine, cytosine, guanine, thymine and uracil.

The aim of the present study is to explore the complexation of thymine with Cu^+ and Zn^{2+}, since these two cations are biologically important and may compete with other cations for complexation with thymine nucleobase. We have studied the coordination modes for Cu^+ and Zn^{2+} and compared them with those of Li^+, Na^+, K^+, Mg^{2+} and Ca^{2+}. Furthermore, employing B3LYP/6-311++G (d,p), the possible linear correlation between metal binding energy and charge transfer was explored for mono cations (Li^+, Na^+, K^+ and Cu^+) and dications (Mg^{2+}, Ca^{2+} and Zn^{2+}).

COMPUTATIONAL METHOD

First, using Spartan 06 software [17], we determined the most stable tautomer in thymine (T_1) (Figure 1) and placed the metal ions (Cu^+, Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+} and Zn^{2+}) at different sites around it. Then, the conformational search was performed with the MMFF method using Spartan 06 software, and the structures were arranged in the range of 0-10 kcal/mol according to their total energies. Finally, we applied the B3LYP method and the 6-311++G (d,p) basis set to optimize these structures. Optimization and frequency calculations of thymine complexes were performed using B3LYP/6-311++G (d,p) in the gas phase [18]. The values of Mulliken Charges on the atoms in the complexes were calculated with the same basis set. Metal Ion Affinity (MIA) was assumed to be the negative of the enthalpy variation (ΔH), namely the dissociation energy of the $B - M^{n+}$ bond for the process $B + M^{n+} \rightarrow B - M^{n+}$ where B represents thymine and M^{n+} is the particular metal ion [19].

RESULTS AND DISCUSSIONS

Thymine Complexes

At the first step of the work, we determined the thymine tautomers using Spartan 06 software. The three most stable thymine tautomers are shown in Figure 1. It has been shown that the evaluation of energetic barriers for the tautomerization of thymine is large, and the free thymine tautomers, T_2 and T_3, are separated by 12.6 kcal/mol and 18.3 kcal/mol from T_1 taken from [20].

Consequently, T_1 is substantially prevalent, irrespective of conditions [21]. The most stable complexes of thymine tautomer (T_1) with M^{n+} (Li^+, Na^+, K^+; Mg^{2+}, Ca^{2+}; Zn^{2+}, Cu^+) were determined by Spartan 06 software. The full geometry optimization of the complexes formed by alkaline and alkaline earth cations, as well as two transition mono and divalent metal ions (Zn^{2+} and Cu^+) with T_1, indicate that there are two types of coordination mode for these cations. In these coordination modes, cations interact with oxygen atom O2 (T_1 (II) $-M^{n+}$) and oxygen atom O4 (T_1 (I) $-M^{n+}$). The most stable complexes are formed in the location of the O4 atom (T_1(I) $- M^{n+}$). The values of absolute energy for the most stable complexes and the amounts of thymine metal ion affinity are given in Table 1.

Alkaline Metal Ions and Cu^+

Figure 2 shows the most stable complexes for these cations. Our calculated atomic charges by B3LYP 6-311++G (d,p) show that the two oxygen atoms in thymine are almost charged equally (see Table 2), while the hydrogen atom in the methyl group is less positively charged than the hydrogen atoms attached to nitrogen atoms. The values of charge for H1, H3 and H5 (in the methyl group) are 0.343e, 0.368e and 0.179e. Thus, the repulsion between M^{n+} and the hydrogen atom

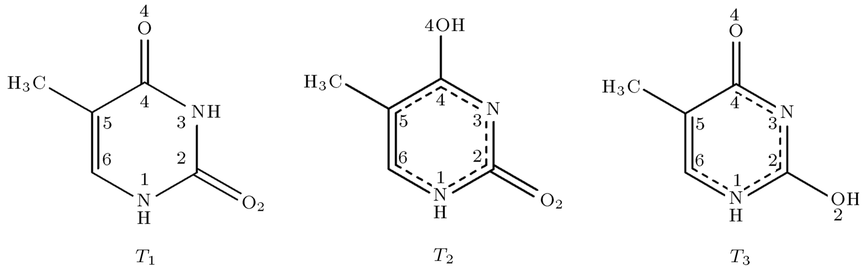
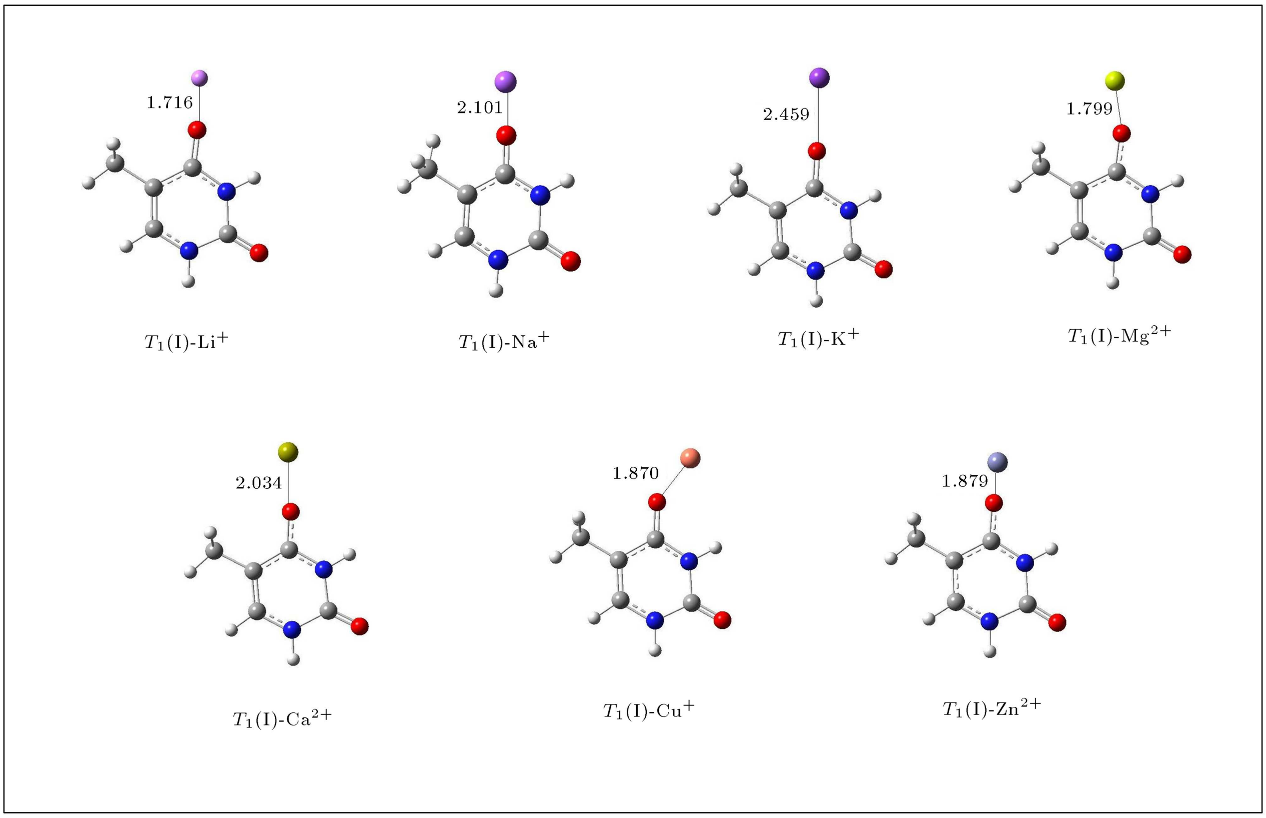


Figure 1. Low-lying tautomeric forms for thymine nucleobase.

Table 1. Absolute energies (E in au), energies for the most stable complexes at 298.5 K and metal ion affinity (MIA in kcal/mol) for thymine at 298.5 K by B3LYP/6-311++G (d, p).

$\mathbf{M^{n+}}$	**Structures**	$\boldsymbol{E}$	$\boldsymbol{E_0}$**+TC**	**MIA**
$\mathbf{Li^+}$	Li^+-T_1 (I)	-461.6450002	-461.518787	51.8
$\mathbf{Na^+}$	Na^+-T_1 (I)	-616.4222082	-616.2912016	33.6
$\mathbf{K^+}$	K^+-T_1 (I)	-1054.080335	-1053.954911	26.7
$\mathbf{Mg^{+2}}$	Mg^{2+}-T_1 (I)	-653.7388308	-653.613384	138.7
$\mathbf{Ca^{2+}}$	Ca^{2+}-T_1 (I)	-1131.35214	-1131.22655	105.7
$\mathbf{Zn^{2+}}$	Zn^{2+}-T_1 (I)	-2232.895385	-2232.771127	180.8
$\mathbf{Cu^+}$	Cu^+-T_1 (I)	-2094.544931	-2094.415595	54.8



T_1(I)-Li^+ T_1(I)-Na^+ T_1(I)-K^+ T_1(I)-Mg^{2+}

T_1(I)-Ca^{2+} T_1(I)-Cu^+ T_1(I)-Zn^{2+}

Figure 2. The most stable complexes of thymine with Li^+, Na^+, K^+; Mg^{2+}, Ca^{2+}; Zn^{2+} and Cu^+ cations by B3LYP/6-311++G (d, p) level. Distances are in angstrom.

in the methyl group should be weaker than that of the hydrogen atom attached to nitrogen. This might be the reason for the binding in T_1 (I) $- M^{n+}$ being stronger than that in T_1 (II) $-M^{n+}$. In the most stable complexes for these cations, the retained charge on the complexed metal cations are 0.731e, 0.950e, 0.977e and 0.659e for Li^+, Na^+, K^+ and Cu^+, respectively (see Table 2). In all these complexes, the measured bond strength is in this order: $Cu^+ > Li^+ > Na^+ > K^+$. This order is easily understood on the basis of charge transfer values. These values can be measured based upon the retained charge density on the complexed metal cations (Table 2). The lower the retained charge density is on the complexed metal ion, the more charge transfer is expected. Table 2 shows that the least retained charge density on the complexed metal cations belongs to the Cu^+ cation. Therefore, the thymine MIA value for Cu^+ is the highest value in comparison with alkaline cations. There are some variations in bond lengths in the most stable complexes. For example, due to charge transfer from O4 to M^+ (Li^+, Na^+, K^+ and Cu^+), C=O4 bond length increases, whereas the N3-C4 bond length decreases due to resonance N3 with C=O4 (Table 3).

Table 2. The calculated Mulliken charges (Q/e) for the complexed metal cations and hetroatoms, Dipole moments (Debye) for the most stable thymine complexes by B3LYP/6-311++G (d,p).

M$^+$-T_1	Q_{N1}	Q_{N3}	Q_{O2}	Q_{O4}	Q_{Metal}	μ
Li$^+$-T_1 (I)	-0.356	-0.435	-0.256	-0.364	0.731	10.41
Na$^+$-T_1 (I)	-0.363	-0.446	-0.270	-0.496	0.950	14.57
K$^+$-T_1 (I)	-0.364	-0.424	-0.277	-0.514	0.977	11.01
Mg^{2+}-T_1 (I)	-0.319	-0.444	-0.165	-0.108	1.390	18.87
Ca^{2+}-T_1 (I)	-0.332	-0.429	-0.190	-0.565	1.675	17.91
Zn^{2++}-T_1 (I)	-0.280	-0.414	-0.125	-0.171	1.045	5.26
Cu$^+$-T_1 (I)	-0.371	-0.466	-0.253	-0.132	0.659	3.77
T_1	-	-	-0.345	-0317	-	-

Table 3. Selected geometrical parameters for the optimized cation-O4 complexes (bond lengths in A° and bond angles in degree).

Parameter	**Base**	**Li$^+$-T_1 (I)**	**Na$^+$-T_1 (I)**	**K$^+$-T_1 (I)**	**Mg^{2+}-T_1 (I)**	**Ca^{2+}-T_1 (I)**	**Zn^{2+}-T_1 (I)**	**Cu$^+$-T_1 (I)**
N_1-C_2	1.390	1.390	1.391	1.382	1.421	1.423	1.424	1.384
C_2-N_3	1.386	1.456	1.426	1.394	1.415	1.413	1.412	1.412
N_3-C_4	1.407	1.3714	1.371	1.382	1.347	1.354	1.356	1.368
C_5-C_6	1.352	1.445	1.362	1.355	1.380	1.387	1.456	1.367
N_1-C_6	1.380	1.364	1.362	1.367	1.3458	1.348	1.329	1.368
C_2-O_2	1.218	1.220	1.274	1.255	1.194	1.194	1.180	1.212
C_4-O_4	1.222	1.257	1.255	1.244	1.387	1.354	1.296	1.264
C_4-C_5	1.463	1.437	1.444	1.448	1.409	1.412	1.422	1.435
N_1-C_2-N_3	112.5	111.7	111.9	112	111.1	111.1	111.5	111.7
C_2-N_3-C_4	128.2	127.2	127.5	127.7	125.9	126.2	125.8	126.9
C_4-C_5-C(CH_3)	117.7	120.1	119.8	119.6	121.8	121.8	122	120
N_3-C_4-C_5	114.5	117.2	116.4	116.1	119.9	119.4	119.6	117.6
N_1-C_2-O_2	123.2	124.7	124.6	124.4	125.4	125.5	123.5	125.2

Alkaline Earth Metal Ions and Zn^{2+}

The most stable coordination modes for alkaline earth cations (Mg^{2+} and Ca^{2+}) and Zn^{2+} are shown in Figure 2. The Zn^{2+} ion, the same alkaline earth cation, forms the most complex in location of oxygen atom (O4). The retained charges on the complexed metal cations are 1.390e, 1.675e and 1.045e for Mg^{2+}, Ca^{2+}, Zn^{2+}, respectively. In all these complexes, the measured bond strength is in this order: Zn^{2+} > Mg^{2+} > Ca^{2+}. This order is easily understood on the basis of charge transfer values. These values can be obtained by means of measuring the retained charge density on the complexed metal cations. The lower the retained charge density is, the more charge transfer is expected. Results show that the least retained charge density on the complexed metal cation belongs to the Zn^{2+} cation. Therefore, the thymine MIA value for Zn^{2+} is the highest value in comparison with alkaline earth cations. There are some variations in bond length in these complexes as the same complexes of alkaline and Cu$^+$ cations (Table 3). For example, due to the charge transfer from O4 to M^{2+} (Mg^{2+}, Ca^{2+} and Zn^{2+}), the bond length in the carbonyl group (C=O4) increases, whereas the N3-C4 bond length decreases due to resonance N3 with C=O4. On the other hand, N1-C6 and C4-C5 bond lengths decrease, and the C5-C6 bond length increases due to resonance N1 with the double bond (C6-C5). The changes of N1-C6, C4-C5 and C5-C6 bond lengths are also seen in complexes of alkaline and Cu$^+$ cations. In a comparison of Zn^{2+} and Cu$^+$ cations, the amount of thymine metal ion affinity for Zn^{2+} ion is higher than the thymine metal ion affinity for Cu$^+$ because of the greater charge of Zn^{2+}

rather than Cu^+. Then, the Zn^{2+} ion can compete with the Cu^+ ion in complexation with thymine.

Correlation Between Charge Transfer and Binding Strength

Each complex formed by a cation with a nucleobase was divided into two parts: cation and nucleobase. The Mulliken charges located on these two parts have been calculated by B3LYP 6-311++G (d, p) on the most stable complexes. The data suggest that a charge transfer takes place during the complexation reaction and also demonstrate that the higher charge transfer leads to stronger metal binding. On average, the transferred positive charge from the metal cation to the nucleobase (i.e. Q') is in the order of $Q'(Zn^{2+}) > Q'(Mg^{2+}) > Q'(Ca^{2+})$ for dications, and $Q'(Cu^+) > Q'(Li^+) > Q'(Na^+) > Q'(K^+)$ for mono cations.

However, Cu^+ and Zn^{2+} cations have the highest charge transfer and metal ion affinity through the mono and dications. Based on our computed results, the calculated LUMO energy (employing B3LYP 6-311++G (d, p) for the Zn^{2+} (-0.801a.u) is lower than that of Cu^+(-0.398 a.u). Therefore, the electrons should be easier to transfer from thymine to Zn^{2+} with respect to Cu^+. More interestingly, our results indicate (as seen in Figures 3) that the linear correlation between the MIA values and the retained charge on cations is still observed when we add the data points of Cu^+ [i.e. Cu^+ affinity and $Q'(Cu^+)$, and Zn^{2+} affinity and $Q'(Zn^{2+})$] to the corresponding lines for mono cations and dications (see Figures 3a and 3b, respectively). This linear correlation strongly suggests that the higher charge transfer between the metal and the ligand (thymine) leads to the stronger metal binding energy.

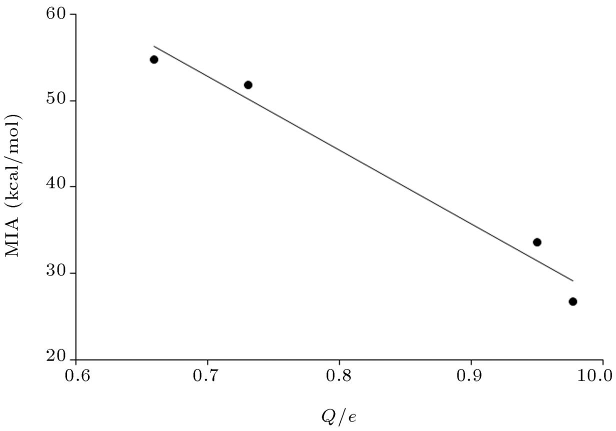


Figure 3a. The relation between metal ion affinity (MIA in kcal/mol) and the retained charge on the complexed metal cation (Q/e) for T_1 (I)-M^+ complexes. R-squared value is 0.9724.

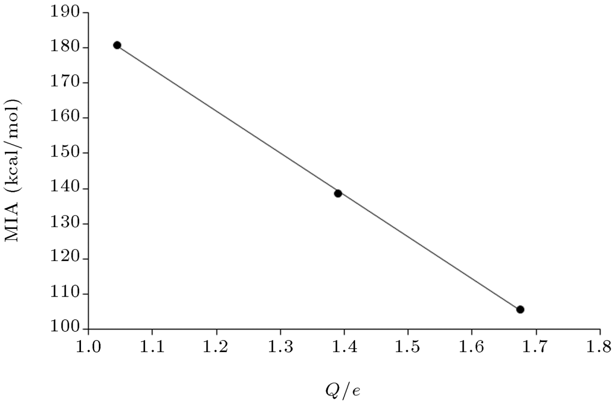


Figure 3b. The relation between metal ion affinity (MIA in kcal/mol) and the retained charge on the complexed metal cation (Q/e) for T_1 (I)-M^{2+} complexes. R-squared value is 0.9998.

CONCLUSION

Based on B3LYP/6-311++G (d, p) calculations, the coordination modes for the interaction of two transition mono and divalent (Cu^+, Zn^{2+}) metal ions with thymine are similar to the coordination modes for alkaline and alkaline earth metal cations. Results demonstrate that the amount of charge transfer between the metal cation and thymine is the dominant factor affecting the metal binding strength between the metal cation and thymine. The amounts of MIA for mono and divalent cations are in the order: $Zn^{2+} > Mg^{2+} > Ca^{2+}$ and $Cu^+ > Li^+ > Na^+ > K^+$. These results indicate that Zn^{2+} and Cu^+ can effectively compete with alkaline and alkaline earth cations for complexation with thymine. Furthermore, our results show the linear correlation between MIA values and the retained charge on mono cations (Cu^+, Li^+, Na^+ and K^+) and dications (Zn^{2+}, Mg^{2+} and Ca^{2+}).

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