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ARTICLE *in* CHEMICAL PHYSICS · MAY 2012

Impact Factor: 1.65 · DOI: 10.1016/j.chemphys.2012.03.003

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Density functional theory study of interaction, bonding and affinity of group IIb transition metal cations with nucleic acid bases

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ARTICLE INFO

Article history:
Received 26 December 2011
In final form 7 March 2012
Available online 21 March 2012

Keywords:
Nucleobase
Tautomerization
Stability
Metal ion affinity
Monocoordination
Bicoordination

ABSTRACT

The structure, bonding, and energetics of the complexes obtained from the interaction between the most stable tautomeric forms of free DNA and RNA bases and Zn^{2+}, Cd^{2+} and Hg^{2+} cations have been studied using density functional B3LYP method. The 6-311+G (2df, 2p) basis set along with LANL2DZ pseudopotentials for the cations are used in the calculations. The tautomerization paths of the nucleobases are investigated and transition states between the tautomeric forms of the free bases are located. The relative stability of the complexes and the tautomers of the free nucleobases are discussed referring to MIA and relative energy values. For uracil, thymine and adenine, interaction of the metal cations with the most stable tautomers form the least stable molecular complexes. For cytosine and guanine, the stability of the metalated complexes differs significantly. The enthalpy (ΔH), entropy ($T\Delta S$) and free energy (ΔG) of the complexes at 298 K have also been calculated.

1. Introduction

Metalation of nucleobases significantly affects the properties and functions of DNA and RNA [1–4]. Metal cations can interact with both the phosphate and deoxyribose ring of the nucleic acids and also with the nucleic acid bases. When the ions interact with the phosphate group of DNA backbone, the interaction being solely electrostatic, they neutralize the negative charges of the phosphate group thereby screen the phosphate group and reduce the electrostatic repulsion within the group and stabilize the DNA. On the contrary, the metal ions interact with the nitrogenated bases in an inner shell coordinated manner or with water molecules and the interaction is not solely electrostatic. This type of interaction modifies the hydrogen bonding and the stacking interactions that stabilize the double helix and can modify the DNA/RNA in irreversible way. Metal ion coordination disrupts one or more hydrogen bonds in the base pair and modifies the transfer process of genetic information [5]. It may form unusual tautomers of the nucleobase by differential metal binding to specific base sites [6–9] and can create self assembled nanoscale arrays with distinct structure and properties [10–15]. Metal ion coordination along with metal binding sites, bond strengths and bonding mechanisms influence the structure and functions of nucleic acids.

Transition metal ions have wide range of importance in diversified fields which include catalysis, organometallic reactions and biochemistry [16]. Various types of cellular damage such as induction of oxidative DNA damage, epigenetic alterations [17,18], etc. have been identified that may contribute to their carcinogenic potentials. Also, their interaction with the bases can inhibit the DNA/RNA repair pathways. It is noteworthy that transition metal ions are more localized near the bases in their interaction with DNA/RNA which can strongly affect the electron distribution in the bases and consequently the tautomeric equilibria. Thus the effect of metal ions can favour the formation of rare tautomers, which are involved in many biochemical processes including point mutation.

Cadmium is a potent carcinogen in rodents [19,20] and has also been accepted as a category 1 human carcinogen [21]. Cadmium induced carcinogenicity involves both direct and indirect interaction of cadmium with DNA [22]. Cadmium binds preferably with the DNA bases rather than the DNA phosphate backbones perturbing the electron density in the heterocyclic ring; as a result of which the phosphodiester bonds may even be weakened and consequently the DNA may be damaged [23]. The interaction of nucleobases with heavy metals like mercury can provide a molecular basis for the environmental impacts of mercury compounds [24]. Increasing and extensive use of mercury in human applications has resulted in an environmental contamination and hence the understanding of the fundamentals of the interaction of mercury ions with DNA has a great significance [25,26]. Mercury can also influence the DNA repair mechanisms by displacing Zn^{2+} cofactor from the cysteine rich sites of DNA repair enzymes and hence inhibit their functions [27]. Hg^{2+} ions can directly interact with DNA molecules and can coordinate with the endocyclic as well as exocyclic nitrogen sites of nucleobases [28,29].

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http://dx.doi.org/10.1016/j.chemphys.2012.03.003

Zinc ions are capable of affecting the DNA in numerous ways. It is an important component of chromatin structure and can influence the DNA replication, transcription and repair [30]. Also, Zn^{2+} ions are used to stabilize DNA structure [31]. Zinc ions control the conformational changes that occur within the DNA structure and can initialize the distortion of the Watson–Crick guanine–cytosine base pair [31,32].

Many works have been reported in the literature where alkali [33–44], alkaline earth [5,45–49], and some transition mono- and divalent metal ions [8,47,50–63] interact with the DNA and RNA bases or base pairs. Toscano et al. [64] studied the interaction of bare zinc ion with different low lying tautomeric forms of nucleobases using density functional theory. Guillaumont et al. investigated the gas-phase interaction between heavy lead ions with two pyrimidic nucleobases experimentally as well as computationally [65]. Gaigeot and co-workers [66] quantum chemically studied the proton transfer in uracil induced by lead ions. Martinez and coworkers [6] studied theoretically the structure and bonding of aluminum-guanine complex, whereas Mazzuca et al. [67] studied the interaction of bare and hydrated aluminum ion with nucleic acid bases and monophosphate nucleotides.

The reactivity of metal ions, binding energies, complexation mechanisms, and enthalpies associated with reaction and interaction of metal ions with nucleobases can be studied without complicated solvent effects [68]. In fact, the gas phase study is often advantageous for the simpler validation of the problem involving lesser guesswork. The interaction of metal ions with a nucleic acid is dominated by the relative bond strength between the metal ion and the donor groups present in the free bases. The knowledge about the interaction with metal ions as well as the nature of metal ion binding with nucleobases, which are the major components of DNA and RNA, would greatly influence the understanding of how the metal ions interact with more complex nucleic acid structures. However, to the best of our knowledge, a detailed theoretical study of the interaction of group IIb metal ions with the nucleic acid bases has not been done so far.

The objective of the present study is to investigate in detail the complexation of uracil, thymine, cytosine, adenine and guanine nucleobases with Zn^{2+}, Cd^{2+} and Hg^{2+} ions, because these ions are biologically important due to their toxic and polluting effects and can compete among themselves for complexation with the nucleobases. The present work includes location of stable tautomers of the nucleobases, determination of their tautomerization paths, and their complexation with the metal cations by determining possible coordination sites, determination of nature of coordination, structure and stability of the complexes and an explanation of the influence of the tautomers on metal ion affinity values.

2. Computational details

All calculations have been carried out using Gaussian 09 [69] suite of quantum chemistry programs. Equilibrium geometries without symmetry considerations of the free nucleobases and their metalated complexes are determined by full optimization followed by harmonic frequency calculations to confirm the nature of minima, the transition states of all stationary points of free nucleobases and to estimate the zero-point vibrational energy (ZPVE) corrections. A Natural bond orbital analysis (NBO) has been performed on the global minimum of each complex and NBO charges are determined for the various atoms involved in complexation. The enthalpy (ΔH), entropy ($T\Delta S$) and free energy (ΔG) terms are also evaluated by thermochemical analysis at 298 K.

Optimization and vibrational analysis of all systems have been performed using the Becke three-parameter hybrid (B3LYP) exchange-correlation functional [70,71] in the framework of density functional theory (DFT) in conjunction with the BS basis set. It is worth mentioning that DFT has widely been recognized as an effective quantum chemistry method for studying molecular properties with its reliability in predicting the geometries and energetics of metal cation-π and metal cation-heteroatom complexes as compared to other quantum chemistry methods [70–72]. The composition of the basis set BS is as follows:

BS = 6-311+G (2df, 2p) for H, C, N and O [73] and LANL2DZ relativistic pseudopotentials [74–76] for Zn, Cd and Hg.

To choose the basis set, we take help from the works on determination of metal affinity for biological systems [33,77–79] and also from the fact that the relativistic pseudopotential is essential for elements such as mercury for which the non-relativistic all-electron approach cannot be successfully applied [47]. In search of the global minimum, a number of initial guess geometries have been considered, but the global minimum for different free nucleobase tautomers and their metal ion complexes have been successfully located by analyzing the initial guess geometries and the geometries reported in other works.

The transition states (TS) of interconversion between different tautomeric states of the free nucleobases are located using the same B3LYP/BS method. The character of the stationary points, either minimum with energy points for which all vibrational frequencies are real or saddle points characterized by one imaginary frequency, are confirmed by vibrational analysis performed at the B3LYP/BS level. To locate the possible interconnecting TS between the located minima, synchronous transit-guided quasi-Newton (STQN) method with QST2 and QST3 options [80] implemented in Gaussian 09 have been used. The IRC algorithm has been used to connect the located TSs to corresponding minima [81].

Metal ion affinity (MIA) is computed as the negative of the enthalpy variation for the metalation process which can be represented by the following nucleobase-M^{2+} reaction:

$$N_b + M^{2+} \rightarrow N_bM^{2+} \quad (1)$$

MIA is explicitly calculated as

$$MIA = -\left[E_{el}(N_bM^{2+}) - E_{el}(N_b) - E_{el}(M^{2+}) + (E_{vib}(N_bM^{2+}) - E_{vib}(N_b))\right] \quad (2)$$

where N_b is a particular nucleobase and M^{2+} represents a particular metal ion. E_{el} is the electronic energy obtained from SCF calculation and E_{vib} is the zero point energy at 0 K and includes zero-point energy as well as the temperature corrections from 0 to 298 K when enthalpy is calculated at 298 K. The basis set superposition errors (BSSE) are taken into account for the most stable nucleobase-metal ion complexes using the complete counterpoise (CP) method of Boys and Bernardi [82] and are then used to correct the MIA values.

3. Results and discussions

Nucleobases have an inherent tendency to tautomerize. In accordance with the experimental findings and previous theoretical works, it is established that the DNA and RNA free bases exist in both canonical and non-canonical tautomeric forms. Figures F1 and F2 in the supporting information depict the fully optimized structure of the most stable free tautomers of uracil, thymine, cytosine, guanine and adenine. Figs. 1 and 2 shows the equilibrium geometries and the structural parameters for the most stable systems obtained from metalation of various tautomers of the nucleobases. The O4 atom of uracil and thymine, the N3 and O2 atoms of cytosine and the N7, N9 and O6 atoms of guanine and adenine are the known attacking sites for metal ion coordination. The coordination of transition metal cations is associated with a covalent-type d-orbital-lone pair bonding interaction, and this contribution along with the usual electrostatic interaction may be responsible

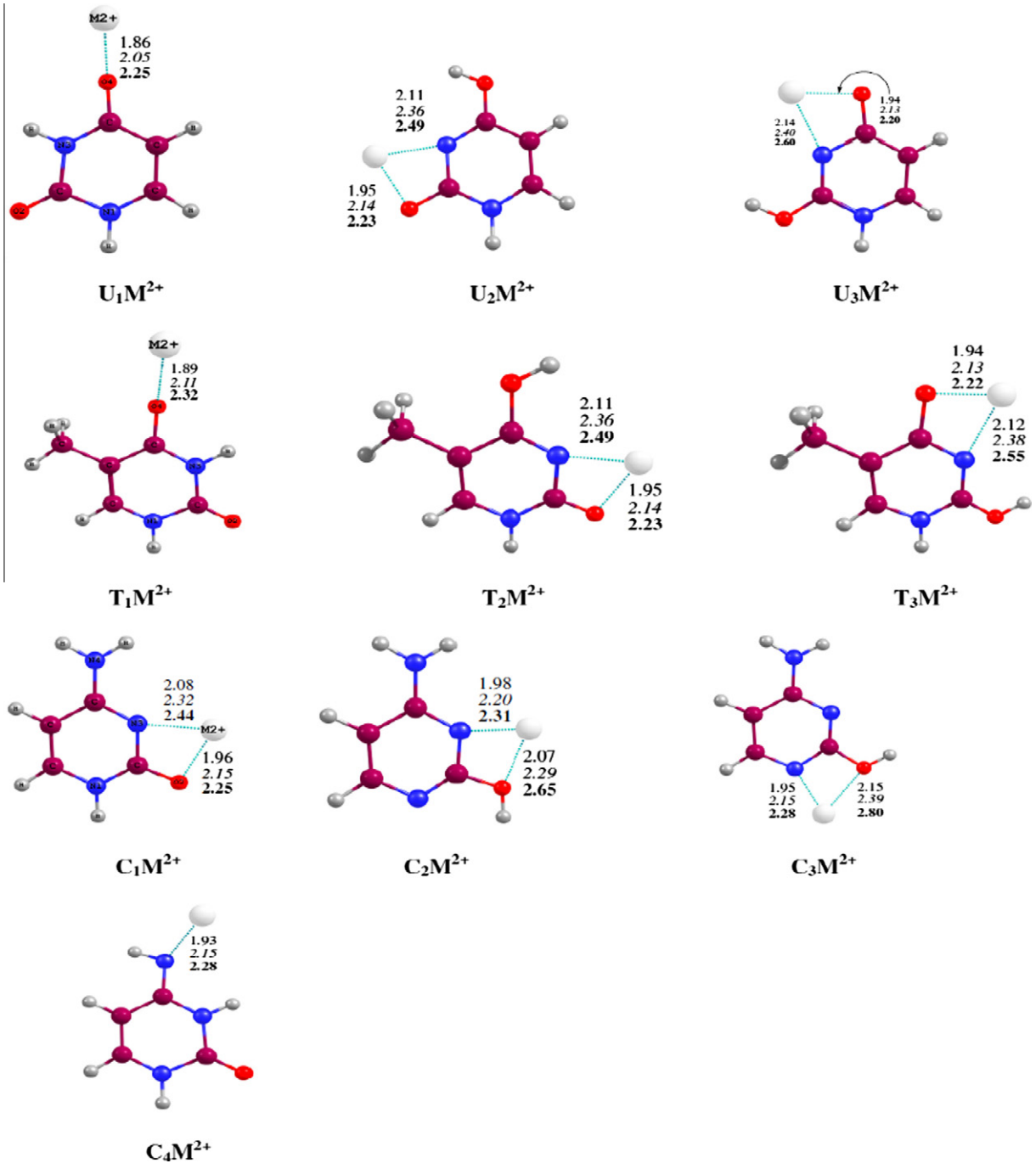

Fig. 1. B3LYP/BS optimized structures of the uracil, thymine and cytosine complexes with M^{2+} (M^{2+} = Zn^{2+}, Cd^{2+} and Hg^{2+}) cations. Bond lengths are in angstroms (Values for Cd^{2+} cations are in italics, whereas values for Hg^{2+} are in bold faces).

for the binding of IIb metal cations to the different binding sites of the nucleobases. It is evident that the metal cations are either monocoordinated or bicoordinated to the nucleobases. The preference of the complexes for bicoordination than monocoordination can be attributed to the fact that in the bicoordinated complexes the bond lengths of the nitrogen-metal cation bond and that of the oxygen-metal cation bond are nearly equal, leading to more symmetric orientation of the metal cation with respect to nitrogen and oxygen atoms that allows strong interactions. The bonds between the metal cations and the nucleobases are mainly due to charge transfer between ligand and metal during complexation.

The relative energies of the low lying free tautomers of the nucleobases and their affinities for zinc, cadmium and mercury ions are computed at B3LYP/BS level and are summarized in Table 1. The tautomerization paths of all the nucleobases are shown in Figs. 3–7 for uracil, thymine, cytosine, guanine and adenine, respectively. From Table 1 and Fig. 3, it is apparent that U_1 is the most stable canonical diketonic tautomer of uracil. Both the non-canonical forms, U_2 and U_3, are obtained by a proton shift from N3 atom to O4 atom for U_2 and to O2 atom for U_3 via transition states, TS_{12} and TS_{31}. For thymine also, as seen from Fig. 4, the situation remains the same. From Fig. 5 and Table 1, it is clear that the

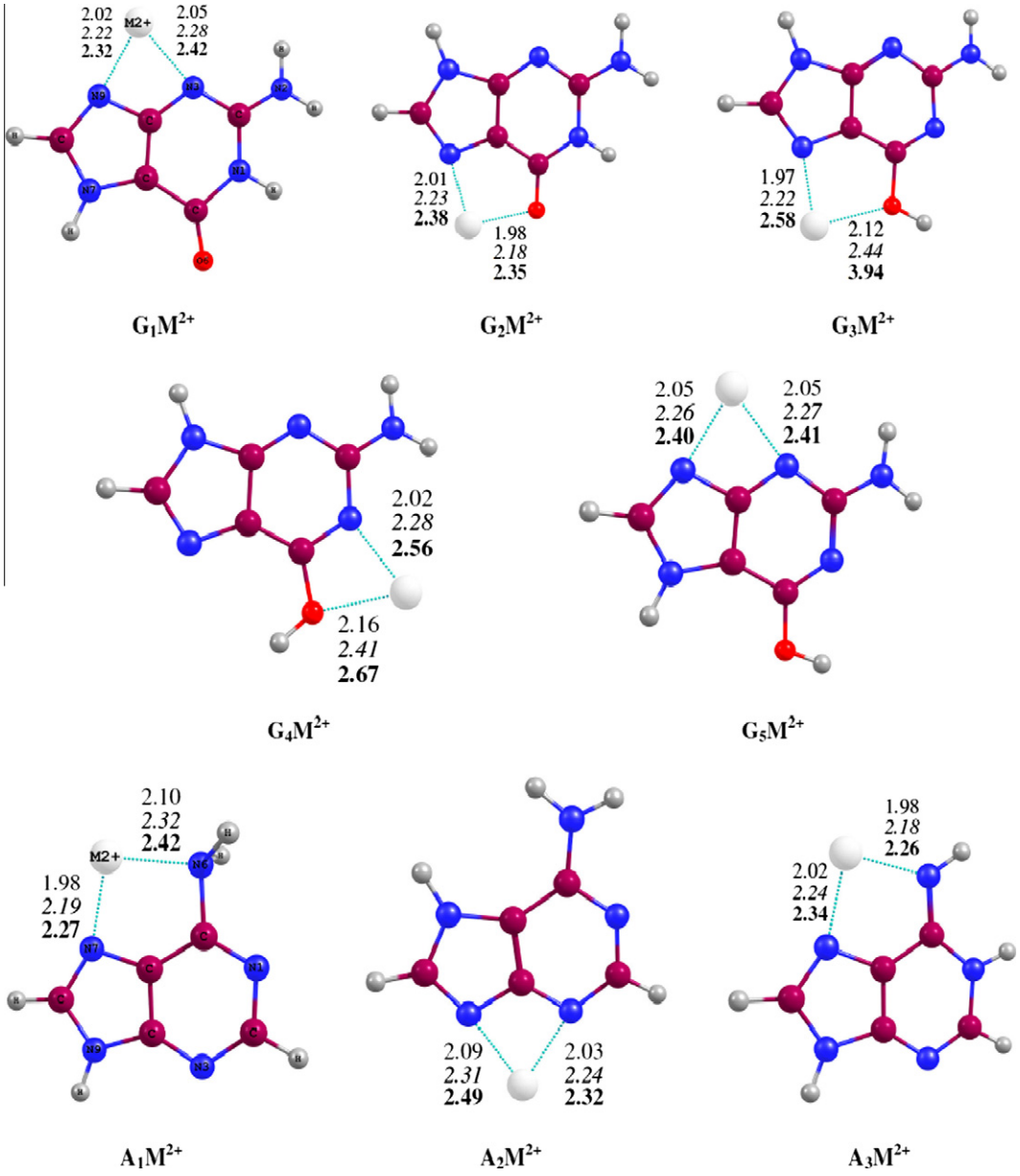

Fig. 2. B3LYP/BS optimized structures of the guanine and adenine complexes with M^{2+} (M^{2+} = Zn^{2+}, Cd^{2+} and Hg^{2+}) cations. Bond lengths are in angstroms (Values for Cd^{2+} cations are in italics, whereas values for Hg^{2+} are in bold faces).

canonical C_1, the hydroxyl (O2—H) C_2, the hydroxyl (O2—H) rotamer C_3 and the imino C_4 tautomers of cytosine fall in a narrow range of energy values but their interconversion processes involve high energy barriers which support the experimental findings [83–87] of simultaneous occurrence of more than one tautomeric form of cytosine. This is also supported by the density functional study of Mazzuca et. al. [88] on the tautomerization processes of dehydrated and monohydrated cytosine. Like cytosine, the five low lying tautomers, G_1, G_2, G_3, G_4 and G_5, having very little energy difference between them, have been located for guanine. The G_1 and G_2 tautomers are interconversible by a proton shift between the N7 and N9 atoms through transition states, $TS_{12\ (1)}$ and $TS_{12\ (2)}$. The G_3 is obtained from G_2 after a proton shift from N1 to O6 through the transition state, TS_{23}. The G_4, a rotamer of G_3, is obtained after the molecule passes through the corresponding transition state, TS_{34}. The interconversion between G_5 and G_1 tautomers is possible by a proton shift between N1 and O6 atoms through the transition state, TS_{51}. For adenine, three tautomeric forms are selected. These are the canonical A_1, the N7—H bonded A_2 and the imino A_3 forms. For adenine, uracil and thymine, the energy differences between the canonical tautomers and the other oxo tautomeric forms are very high, and their spontaneous interconversion and interconversion at very high temperature during experiments are quite unlikely.

The most stable complex formed by the interaction of metal cation and a particular nucleobase can be explained with the help of metal ion affinity (MIA) values. Generally, density functional methods give different stability orders of the tautomers and their related complexes when compared to *ab initio* or other methods, particularly for the class of tautomers where the relative energy differences are very small. The anomaly in stability does not influence the MIA values significantly, rather the stability of the complexes originating from different tautomers play the decisive role in determining the MIA values. Also, following the order of metal

Table 1
Relative (ΔE in kcal mol^{-1}) Energies and Zinc, Cadmium and Mercury Metal Affinities (MIA in kcal mol^{-1}), at 0 K and corrected by BSSE, for the DNA and RNA Bases computed at B3LYP/BS Level.

	Base	Base-Zn^{2+}			Base-Cd^{2+}		Base-Hg^{2+}	
	ΔE	ΔE	MIA	MIA [a]	ΔE	MIA	ΔE	MIA
U1	0.0	21.6	158.7	175.6	23.2	128.0	13.1	141.1
U2	11.7	0.5	191.5	207.9	4.9	162.9	2.1	163.7
U3	18.9	0.0	199.3	214.4	0.0	165.2	0.0	173.2
T1	0.0	17.8	168.9	185.9	16.6	135.3	7.2	150.4
T2	12.7	1.3	198.1	219.5	0.9	163.6	2.3	170.2
T3	18.3	0.0	205.1	221.1	0.0	170.2	0.0	178.2
C1	0.0	0.0	209.3	226.1	0.0	174.1	0.0	180.4
C2	1.2	35.2	176.7	193.8	31.7	144.8	27	154.6
C3	1.9	20.4	190.9	207.0	18.9	157.1	14.1	168.2
C4	2.6	31.9	178.5	195.8	30.4	145.0	21.4	161.7
G1	0.0	20.7	207.7		18.8	171.4	13.1	184.7
G2	0.5	0.0	228.9	246.8	0.0	190.8	0.0	196.2
G3	1.5	31.6	198.2	213.8	28.1	163.7	13.9	183.2
G4	1.9	41.1	189.3	204.3	36.2	155.9	17.9	177.8
G5	4.1	18.5	214.0	230.4	16.3	178.1	12.6	187.2
A1	0.0	26.2	195.1	212.9	24.2	156.1	23.2	162.5
A2	7.9	15.1	214.0	229.9	9.3	178.9	5.8	187.8
A3	18.4	0.0	239.7	259.1	0.0	198.7	0.0	204.1

[a] From Ref. [64] (values calculated at 298 K).

ion affinity, the Zn^{2+}, Cd^{2+} and Hg^{2+} ions prefer to attack the nucleobases in the order G > C > A > T > U.

3.1. Uracil

Among the three stable tautomers located for the free uracil nucleobase, U_2 and U_3 are separated by 11.7 and 18.9 kcal mol^{-1} from U_1, which is the lowest energy tautomer and is taken as reference. The interaction with the Zn^{2+}, Cd^{2+} and Hg^{2+} metal cations produces the corresponding complexes, U_1—M^{2+}, U_2—$M^{2+}$and U_3—M^{2+}, that follow exactly the reverse order of stability.

In U_1—M^{2+} complexes, the ions lie out of the molecular plane by more than 100° and are monocoordinated to the O4 atom with a distance of 1.86 Å for Zn^{2+}, 2.05 Å for Cd^{2+} and 2.25 Å for Hg^{2+}. The U_1—Zn^{2+}, U_1—Cd^{2+} and U_1—Hg^{2+} complexes lie 21.6, 23.2 and 13.1 kcal mol^{-1} above the global minima, U_3—Zn^{2+}, U_3—Cd^{2+} and U_3—Hg^{2+}, respectively.

The U_2—Zn^{2+}, U_2—Cd^{2+} and U_2—Hg^{2+} complexes lie 0.5, 4.9 and 2.1 kcal mol^{-1}, respectively, above the corresponding global minima, U_3—M^{2+} and are almost isoenergetic to the global minima. The zinc cation is bicoordinated, as its distance from the N3 and O2 atoms are 2.11 Å and 1.95 Å, respectively. The cadmium ion is quite far from the N3 atom (2.36 Å), but its distance from the O2 atom is 2.14 Å, and hence it can also be considered as bicoordinated. For mercury, the corresponding bond lengths are 2.49 Å and 2.23 Å, indicating slight inclination towards monocoordination. The preference for monocoordination is more pronounced in the U_3—Hg^{2+} complex in which the N3—Hg^{2+} distance is 2.60 Å, whereas the O4—Hg^{2+} distance is 2.20 Å. For U_3—Zn^{2+} and U_1—Cd^{2+} complexes, the N3—Zn^{2+} and O4—Zn^{2+} bond lengths are 2.14 Å and 1.94 Å, respectively, whereas in case of U_3—Cd^{2+} complex the corresponding bond lengths are 2.40 Å and 2.13 Å, respectively. In all bicoordinated complexes, the M^{2+}—O bonds are shorter than the M^{2+}—N bonds.

The BSSE corrected MIA values computed at 0 K are collected in Table 1. For the most stable complexes, U_3—Zn^{2+}, U_3—Cd^{2+} and U_3—Hg^{2+}, the MIA values are 199.3, 165.2 and 173.2 kcal mol^{-1}, respectively. In general, MIA value is an indicator of the most stable complex formed by the cation and the nucleobase. But it is observed here that the most stable complex is formed by the least stable low lying tautomeric form of uracil. This behaviour was also observed for other transition metals in various studies made so far [50–52]. However, the high energy difference between free low lying tautomers restricts the formation of complexes originating from the tautomers, U_2 and U_3 having relatively higher energy. This indicates that though U_3—Zn^{2+}, U_3—Cd^{2+} and U_3—Hg^{2+} are the most stable complexes of uracil followed by U_2—Zn^{2+}, U_2—Cd^{2+} and U_2—Hg^{2+} complexes, the tautomeric forms, U_2 and U_3, are probably absent under physical as well as experimental conditions.

3.2. Thymine

The most stable tautomeric form of thymine is T_1 followed by T_2 at 12.7 kcal mol^{-1} and T_3 at 18.3 kcal mol^{-1}. On interaction with

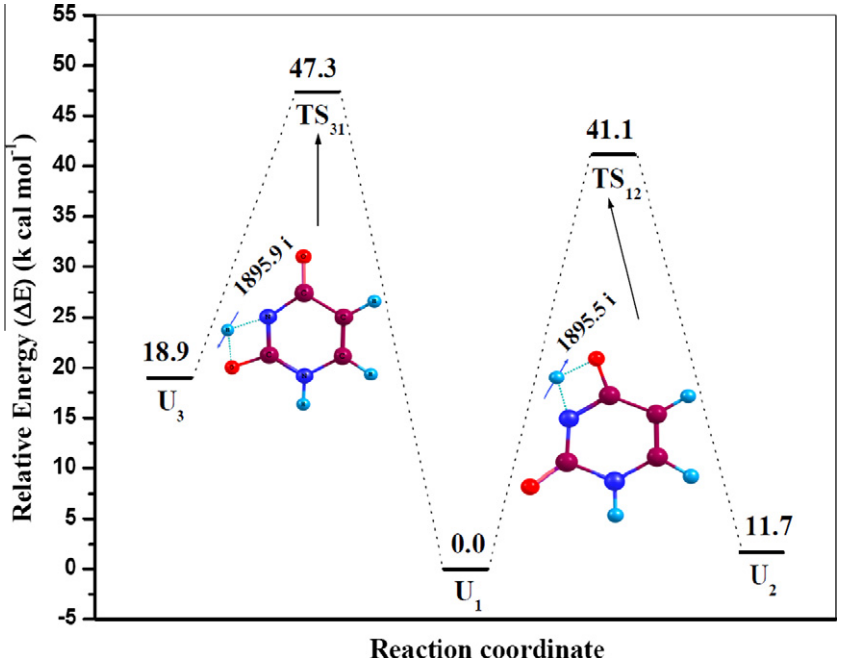

Fig. 3. B3LYP/BS minimum energetic tautomerization path for uracil tautomers.

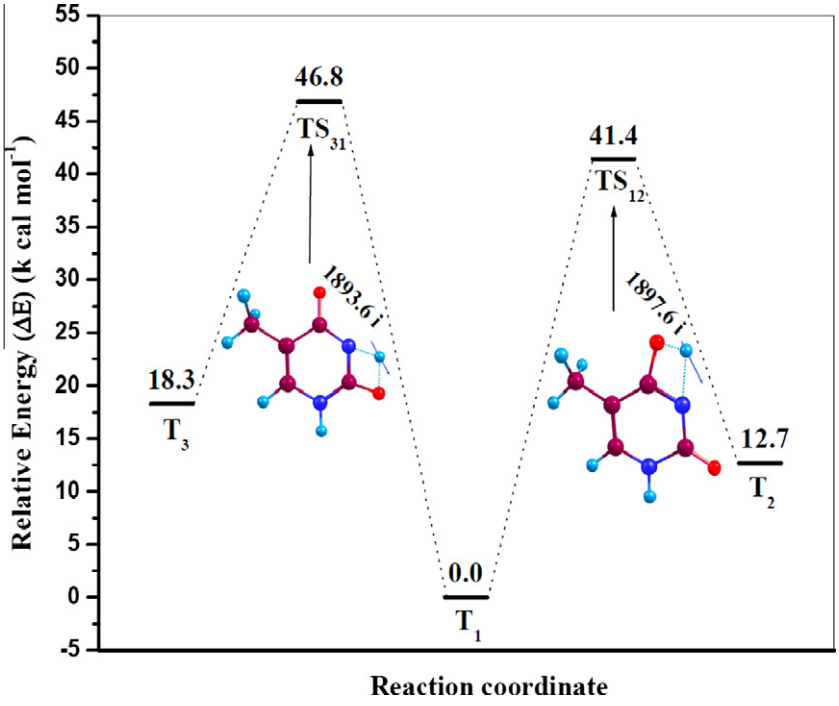

Fig. 4. B3LYP/BS minimum energetic tautomerization path for thymine tautomers.

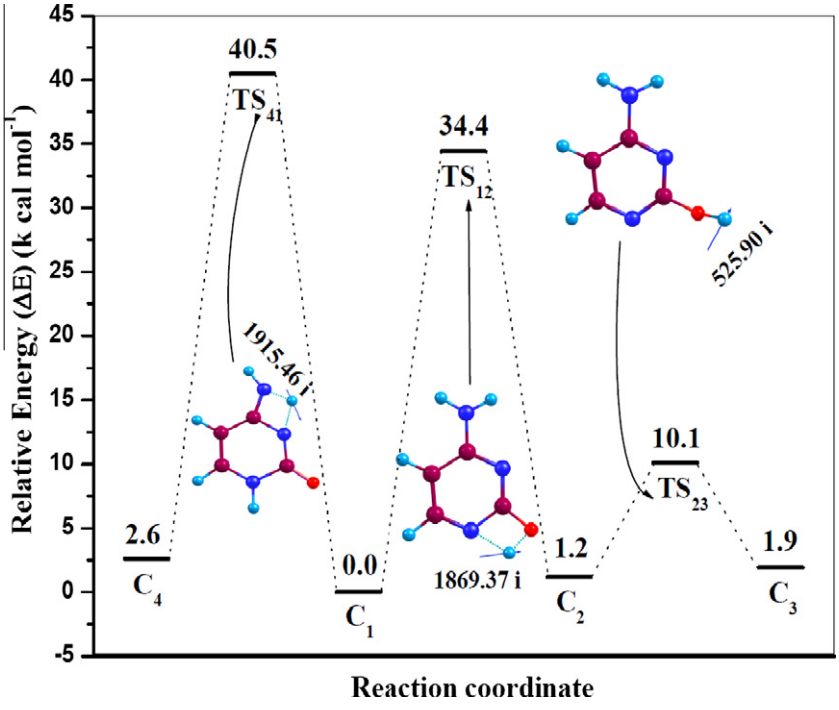

Fig. 5. B3LYP/BS minimum energetic tautomerization path for cytosine tautomers.

the Zn^{2+}, Cd^{2+} and Hg^{2+} metal cations, corresponding complexes, T_1—M^{2+}, T_2— $M^{2+}$and T_3—M^{2+} are formed, which once again follow the reverse order of stability.

The lowest energy tautomer of the free nucleobase T_1 has only one suitable coordination site, the O4 atom and give rise to the monocoordinated adducts, T_1—Zn^{2+}, T_1—$Cd2^{+}$ and T_1—Hg^{2+}, which lie 17.8, 16.6 and 7.2 kcal mol^{-1} above the respective global minima, T_3—Zn^{2+}, T_3—Cd^{2+} and T_3—Hg^{2+}. The corresponding bond lengths are 1.89 Å, 2.11 Å and 2.32 Å, respectively.

The bicoordinated complexes formed by the interaction of T_2 tautomer with the metal cations are T_2—Zn^{2+}, T_2—Cd^{2+} and T_2—Hg^{2+}, which lie 1.3, 0.9 and 2.3 kcal mol^{-1}, respectively, above the corresponding global minima, T_3—M^{2+}. Although these energy differences are very small rendering the T_2—M^{2+} complexes almost isoenergetic to the T_3—M^{2+} complexes, energetically the formation of the T_3—M^{2+} complexes are favored over the T_2—M^{2+} complexes. The greater stability of the T_3—M^{2+} complexes can be attributed to the closeness of the O4 atom to the donor

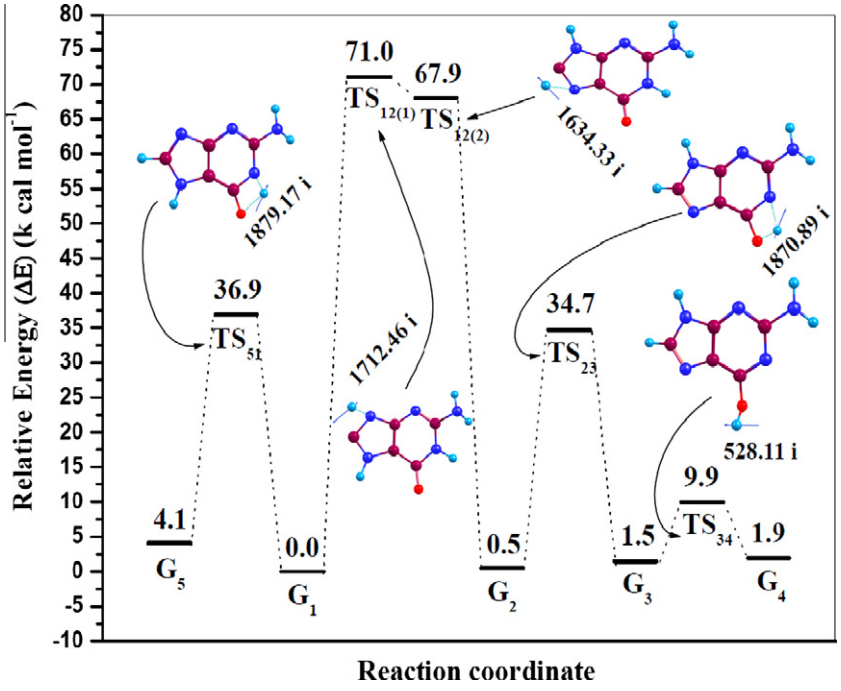

Fig. 6. B3LYP/BS minimum energetic tautomerization path for guanine tautomers.

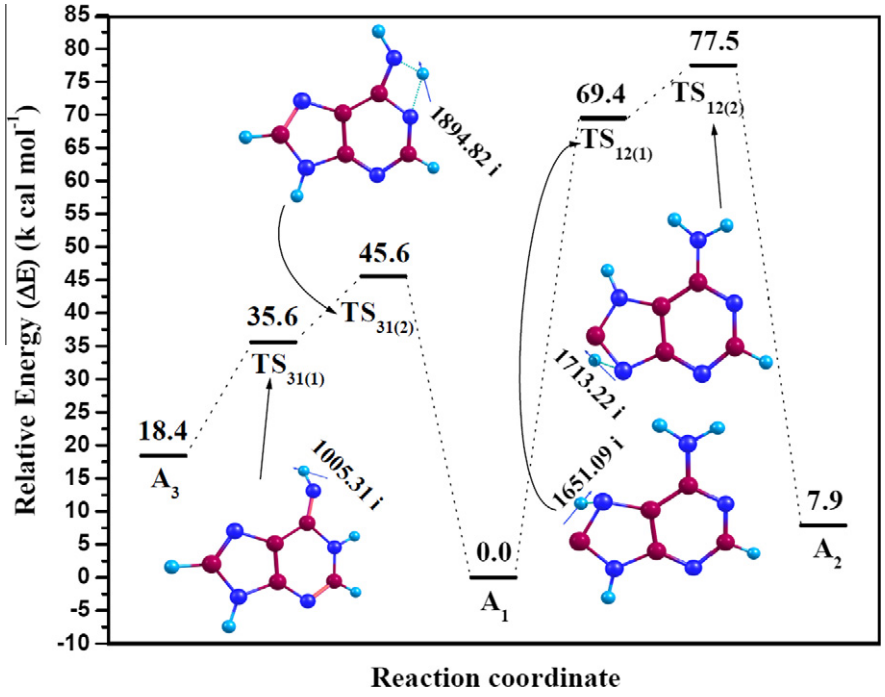

Fig. 7. B3LYP/BS minimum energetic tautomerization path for adenine tautomers.

group,–CH_3, which increases its negative charge thereby favoring the interaction with the cations. For T_2—M^{2+} complexes, the N3—M^{2+} distances are 2.11, 2.36 and 2.49 Å for zinc, cadmium and mercury, respectively, whereas the corresponding O2—M^{2+} distances are 1.95, 2.14 and 2.23 Å, respectively. For T_3—M^{2+} complexes, the O4—M^{2+} bond lengths are 1.94, 2.13 and 2.22 Å, for zinc, cadmium and mercury, respectively, but the N3—M^{2+} distances are larger. Particularly for mercury, this bond length is 2.55 Å, which is considerably longer indicating that the T_3—Hg^{2+} complex is weekly bicoordinated.

The BSSE corrected MIA values computed at 0 K for the T_1—M^{2+}, T_2—$M^{2+}$and T_3—M^{2+} complexes show the same trend, but these values are slightly higher than the corresponding values for uracil. Similarly, it can be concluded that for thymine also the T1 tautomer is the only one which can exist under physical condition.

3.3. Cytosine

From Table 1, the stability of cytosine complexes with zinc cation follows the order C_1—Zn^{2+}> C_3—Zn^{2+}> C_4—Zn^{2+}> C_2—Zn^{2+}, and

their corresponding relative energy differences are distinctly higher than those of the free tautomers which are almost isoenergetic. All complexes are bicoordinated, except C_4—Zn^{2+}. In C_1—Zn^{2+} complex, the N3—Zn^{2+} and O2—Zn^{2+} bond lengths are 2.08 and 1.96 Å, respectively. The corresponding bond lengths in the C_2—Zn^{2+} complex are 1.98 and 2.07 Å, respectively. For C_3—Zn^{2+} complex, the N1—Zn^{2+} and O2—Zn^{2+} bond distances are 1.95 and 2.15 Å, respectively. In the monocoordinated C_4—Zn^{2+} complex, the N4—Zn^{2+} distance is 1.93 Å.

The cadmium complexes also behave in a similar way with the same order of stability and higher relative energy differences between the complexes as compared to the low lying tautomeric forms of the free cytosine. The most stable C_1—Cd^{2+} complex is bicoordinated having the N3—Cd^{2+} and O2—Cd^{2+} bond lengths 2.32 and 2.15 Å, respectively. In the least stable C_2—Cd^{2+} complex, the N3—Cd^{2+} distance is 2.20 Å, whereas the O2—Cd^{2+} distance is 2.29 Å. The C_3—Cd^{2+} complex, which is third in the order of stability, is also bicoordinated with the N1—Cd^{2+} and O2—Cd^{2+} bond lengths of 2.15 and 2.39 Å, respectively. Finally, the C_4—Cd^{2+} complex is monocoordinated with the N4—Cd^{2+} bond distance, 2.15 Å.

When the cytosine tautomers form complexes with mercury, the same order of stability is observed. In the most stable C_1—Hg^{2+} complex, which is bicoordinated, the N3—Hg^{2+} bond length is 2.44 Å, whereas the O2—Hg^{2+} bond length is 2.25 Å. In C_2—Hg^{2+} complex, the corresponding bond lengths are 2.31 and 2.65 Å, respectively, and the complex is weakly bicoordinated. In C_3—Hg^{2+} complex, the N1—Hg^{2+} bond length is 2.27 Å, but the O2—Hg^{2+} bond length is 2.80 Å, which is too long for a bicoordinated complex. Thus the complex has an inclination towards monocoordination. This week bicoordination in the C_2—Hg^{2+} complex and near monocoordination in the C_3—Hg^{2+} complex are probably due to the weakening of the O2—Hg^{2+} bonds in both these complexes due to the presence of hydrogen atom linked to the O2 atom. The C_4—Hg^{2+} complex is purely monocoordinated having N4—Hg^{2+} bond distance, 2.28 Å.

The MIA values for the cytosine-zinc complexes range from the maximum value of 209.3 kcal mol^{-1} for the C_1—Zn^{2+} complex to a minimum value of 176.7 kcal mol^{-1} for the C_2—Zn^{2+} complex. In case of cadmium, the trend remains unchanged, where the MIA values range from 174.1 kcal mol^{-1} for the C_1—Cd^{2+} to 144.8 kcal mol^{-1} for the C_2—Cd^{2+}. For the cytosine-mercury complexes, the MIA values also have the same nature of variation where it ranges from 180.4 kcal mol^{-1} for the C_1—Hg^{2+} to 154.6 kcal mol^{-1} for the C_2—Hg^{2+} complex. As observed from Table 1, all free tautomers of cytosine lie in a narrow range of energy (0.0–2.6 kcal mol^{-1}), and their simultaneous presence confirms the coexistence of all the adduct complexes. Therefore, the reliability or the choice of the most appropriate MIA value depends on the order of stability of the complexes, which incidentally follows slightly different order of stability than that of the free tautomers. This implies that energetically and thermodynamically the most favoured complexes are the C_1—M^{2+} complexes, and hence the most probable free tautomer is C_1. Again, if we look into the tautomerization path of cytosine (Fig. 5) for studying the interconversion between the tautomers, it is evident that the C_1—C_4 as well as the C_1—C_2 conversions involve a proton shift through the transition states, TS_{41} and TS_{12}, respectively, whereas C_3 is simply a rotamer where the C_2—C_3 conversion takes place simply through a rotation of a proton around the O2—H bond involving the transition state, TS_{23}. From Fig. 5, it can also be suggested that the interconversion between the C_1—C_4 free tautomers as well as between the C_1—M^{2+}—C_4—M^{2+} complexes and also between the C_1—C_2 free tautomers as well as between the C_1—M^{2+}—C_2—M^{2+} complexes might not be possible due to the large barrier heights for the conversions, but due to the comparatively smaller barrier height for the conversion between the C_2 and C_3 free tautomers, the interconversion may be possible. This together with high experimental temperatures further leads us to conclude that the corresponding interconversion between the C_2—M^{2+} and C_3—M^{2+} complexes is also possible. Experimentally measured IR spectra in low temperature inert gas matrixes prove the presence of both C_1 and C_2 tautomers in appreciable proportionate concentrations [83–87]. Hence the presence of the free tautomer C_1 and the corresponding C_1—M^{2+} complexes as well as the presence of C_2 tautomer and the corresponding C_2—M^{2+} complexes and the conversion of the C_2—M^{2+} complex to the C_3—M^{2+} complex are possible.

3.4. Guanine

Guanine molecule has five different free tautomers. The relative energy differences between two tautomers vary from 0 to 4.1 kcal mol^{-1}. The interaction of these tautomers with metal cations gives rise to different bicoordinated complexes whose stability order, irrespective of metal cation, is G_2—M^{2+}>G_5—M^{2+}>G_1—M^{2+}>G_3—M^{2+}>G_4—M^{2+}. Of these complexes, the G_2—M^{2+} and G_3—M^{2+} complexes are characterized by the presence of five member ring along with the metal cation. The formation of five member rings is favoured to the formation of four member rings. From Fig. 4, it is clear that the N7 and O6 atoms are the most favoured binding sites of the guanine tautomers for the metal cations provided the O6 atom is not involved in the O-H bond. The N3 and N9 atoms are the second set of preferred atoms for the metal cation binding. It may be concluded that if the most negative imino nitrogen and carbonyl oxygen (estimated by NBO charge) of the complexes are involved in binding with the metal cations rather than the hydroxyl group and/or amino nitrogen, the complexes become more stable. This explains the order of stability of the complexes.

In G_1—M^{2+} complexes, the metal cations are attached to the guanine molecule at the N3 atom with bond distances 2.05, 2.28 and 2.42 Å for zinc, cadmium and mercury, respectively, and at the N9 atom with bond lengths 2.02, 2.22 and 2.32 Å, respectively, for the same cations. For the G_2—M^{2+} complexes, zinc, cadmium and mercury cations are attached to the N7 atom with bond lengths 2.01, 2.23 and 2.38 Å, respectively, whereas the same metal cation-O6 bond distances are 1.98, 2.18 and 2.35 Å, respectively.

In the G_3—M^{2+} complexes, the H atom linked to the O6 atom of the guanine tautomer makes the M^{2+}—O6 bond slightly weaker with bond lengths 2.12, 2.44 and 3.94 Å for zinc, cadmium and mercury, respectively, compared to the M^{2+}—N7 bonds with bond distances 1.97, 2.22 and 2.58 Å, respectively, for the same metals. Similarly for G_4—M^{2+} complexes, the M^{2+}—O6 bonds are weaker than the M^{2+}—N1 bonds for the same reason. Here, the M^{2+}—O6 bond lengths (2.16, 2.41 and 2.67 Å for zinc, cadmium and mercury, respectively) are greater than the M^{2+}—N1 bond lengths (2.02, 2.28 and 2.56 Å for zinc, cadmium and mercury, respectively). For G_5—M^{2+} complexes, the metal cations are also attached to the N3 and N9 atoms. The bond distances of zinc, cadmium and mercury with the N3 are 2.05, 2.27 and 2.41 Å, respectively, and that with the N9 atom are 2.05, 2.26 and 2.40 Å, respectively.

The MIA values at 0 K for the guanine complexes show the same trends for all the metal cations. For the most stable G_2—M^{2+} complex, the maximum values are 228.9, 190.8 and 196.2 kcal mol^{-1} for zinc, cadmium and mercury, respectively. Like cytosine, the free guanine tautomers lie within a small energy range of 4.1 kcal mol^{-1} which implies possible presence of all the tautomers and corresponding complexes. The tautomerization path, as depicted in Fig. 6, indicates that the interconversion between the G1 and G2 tautomers is rather difficult due to presence of large energy barriers between them. Again, interconversion between the G_2—G_3 tautomers is fairly possible, because the energy barrier between them is comparatively less than that between the G_1—G_2 tautomers. Since the barrier between the G_3—G_4 tautomers is very small, the interconversion between these two is also possible. Thus

Table 2
Enthalpy (ΔH = MIA), free energy (ΔG) and entropy ($T\Delta S$) variations for the formation process of Base-Zn^{2+}, Base-Cd^{2+} and BaseHg^{2+} complexes at 298 K computed at B3LYP/BS level.

Tautomer	$\Delta H^{298\ K}$ kcal mol^{-1}			$\Delta G^{298\ K}$ kcal mol^{-1}			$T\Delta S^{298K}$ kcal mol^{-1}		
	Zn^{2+}	Cd^{2+}	Hg^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}
U1	157.3	128.2	141.1	149.7	120.5	133.9	7.6	7.7	7.2
U2	189.7	157.8	163.7	180.8	149.2	155.4	8.9	8.6	8.3
U3	197.7	165.5	173.2	188.7	156.9	164.8	8.9	8.6	8.4
T1	167.2	135.3	150.2	158.4	128.1	143.4	8.8	7.2	6.8
T2	196.3	163.8	170.1	187.4	155.2	162.1	8.9	8.6	8
T3	203.2	170.3	178.2	194.4	161.7	169.9	8.8	8.6	8.3
C1	207.4	174.2	180.4	198.6	165.6	172.1	8.8	8.6	8.3
C2	175.2	144.5	154.3	167.2	136.8	147.2	8	7.7	7.1
C3	188.6	156.9	168	180.6	149.3	160.4	8	7.6	7.6
C4	176.1	145.1	161.7	168.3	137.4	154	7.8	7.7	7.7
G1	205.3	171.3	184.1	197	163.2	176.6	8.3	8.1	7.5
G2	226.8	190.8	196.1	217.8	182	187.7	9	8.8	8.4
G3	195.7	163.5	182.9	187.4	155.6	176.1	8.3	7.9	6.8
G4	186.6	155.6	177.6	178.8	148.1	169.6	7.8	7.5	8
G5	211.8	178	187.3	203.3	169.7	178.9	8.5	8.3	8.4
A1	211.8	156.7	180.2	183	146.7	171	28.8	10	9.2
A2	211.9	178.9	187.7	203.3	170.6	179.8	8.6	8.3	7.9
A3	237.6	199	204.1	228.3	189.9	195.8	9.3	9.1	8.3

energetically and thermodynamically, the most probable and possible tautomer of the guanine nucleobase is G_2, and hence the G_2—M^{2+} complexes are the most stable. Also, the existence of the G_3 and G_4 tautomers is also possible.

3.5. Adenine

The interaction of the metal ions with the three tautomers located for adenine gives rise to three sets of stable complexes. The A_1, A_2 and A_3 are the three most stable tautomers with A_2 and A_3 have higher relative energy than A_1 by 7.9 and 18.4 kcal mol^{-1}, respectively. The corresponding complexes are A_1—M^{2+}, A_2—$M^{2+}$and A_3—M^{2+}, of which A_3—M^{2+} is the most stable complex followed by A_2—$M^{2+}$and A_1—M^{2+}. The metalation process that gives this reverse order of stability is attributed to the stabilization of the metal ions by the interaction of most negative imino nitrogen, which is highly reactive towards positively charged ions than amino groups. Also, the size of the formed ring is important; the formation of the complexes containing five-member ring is energetically favored.

The A_1—Zn^{2+}, A_1—Cd^{2+} and A_1—Hg^{2+} complexes lie 26.2, 24.2 and 23.2 kcal mol^{-1} above the global minima, A_3—Zn^{2+}, A_3—Cd^{2+} and A_3—Hg^{2+}. The metal cations are attached to the adenine in bicoordinated manner via the N6—M^{2+} and N7—M^{2+} bonds having bond lengths 2.10 and 1.98 Å for zinc, 2.32 and 2.19 Å for cadmium and 2.42 and 2.27 Å for mercury, respectively. The N7 atom is the most negative nitrogen atom that makes the N7—M^{2+} bond lengths smaller than the N6—M^{2+} bond distances.

In A_2—M^{2+} complexes, the metal cation is bicoordinated with the nucleobase with the N3—M^{2+} and N9—M^{2+} bonds. The N3 and N9 atoms are the two most negative nitrogen atoms in the A_2—M^{2+} complexes. The formation of four member ring on metalation develops certain strain within the cyclic ring which accounts for the lesser stability of the complexes than their corresponding global minima, A_3—M^{2+}. The A_3—M^{2+} complexes, which are also the most stable complexes, are bicoordinated with the metal cations being attached to the two most negative nitrogen atoms N6 and N7 of the nucleobase through the N6—M^{2+} and N7—M^{2+} bonds. The bond lengths are 1.98 and 2.02 Å for zinc, 2.18 and 2.24 Å for cadmium and 2.26 and 2.34 Å for mercury, respectively.

The BSSE corrected MIA values at 0 K given in Table 1 show similar trend as that of uracil and thymine. This leads to the hypothesis of absence of the complexes, A_2—M^{2+} and A_3—M^{2+}, in experiment due to large energy differences between the free tautomers, A_1, A_2 and A_3.

3.6. Entropic contributions

A variety of experimental difficulties and constrains involved in the methods make the measurement of MIA unfeasible [89]. This prevents the evaluation of the entropic effects (ΔS) and in turn the evaluation of free energy variations (ΔG) becomes extremely difficult. On the contrary, theoretical computation followed by thermochemical analysis at desired temperature is far easier to evaluate the entropic as well as the enthalpic contributions. The ΔH, ΔS and ΔG calculated at 298 K are reported in Table 2. The ΔS values for different complexes for same nucleobase vary from 0 to 20 cal mol^{-1}K^{-1} for zinc, 0 to 1 cal mol^{-1}K^{-1} for cadmium and 0.1 to 1.2 cal mol^{-1}K^{-1} for mercury. The effect of these variations is negligible on the relative differences between different species.

4. Conclusions

The interactions of the free bases of DNA and RNA with Zn^{2+}, Cd^{2+} and Hg^{2+} ions have been investigated using density functional B3LYP method in conjunction with 6-311+G(2df, 2p) basis set for the H, C, O and N atoms and relativistic pseudopotential LANL2DZ basis set for the metal cations. It is observed from our calculation that in all complexes the metal cations are either monocoordinated or bicoordinated with the free bases. When the cations are monocoordinated, they are attached to the nucleobase molecule through oxygen atom, whereas when they are biccordinated, they are preferably connected via nitrogen atoms. For uracil, thymine and adenine, the most stable complexes are formed with the least stable free tautomers. Owing to large energy differences between the free tautomers, it can be concluded that only the canonical forms exist under physical conditions. Also, in case of adenine, high reactivity of the imino nitrogen towards the metal cations is also responsible for the reverse order of stability of the complexes formed. For cytosine and guanine, the order of stability of the complexes is influenced by the coexistence of more than one free tautomer within a narrow energy range. In case of cytosine, the complexes have almost the same order of stability as that of the free bases and C_1 is the most stable tautomer followed by C_2. In guanine, the order of stability is influenced by the binding of the metal cations with the most nega-

tive imino nitrogen and carbonyl oxygen. Thus there is a clear indication of the influence of tautomers on the MIA values and also on the stability of the complexes. The order of preference to attack the nucleobases by the metal ions is G > C > A > T > U.

Acknowledgements

S. Bagchi gratefully acknowledges the authority of Netaji Subhash Engineering College, Garia, Kolkata, India for allowing him to carry out research work at IACS. D. Mandal is grateful to the Council of Scientific and Industrial Research (CSIR), Govt. of India for providing him Senior Research Fellowship (SRF). Thanks are due to the reviewer for making constructive comments and suggestions to improve the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemphys.2012.03.003.

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