Metal interactions with nucleobases, base pairs, and oligomer sequences; computational approach

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Abstract

This review summarizes computational studies devoted to interactions of metal cations with nucleobases, nucleotides, and short oligonucleotides considered as DNA/RNA models. Since this topic is very complex, basically only the results obtained using ab initio and DFT methods are discussed. The first part focuses mainly on the interactions of the isolated bases with metal cations in bare, hydrated and ligated forms. In the second part also adducts of metal cations with base pairs, stacked bases and larger systems are discussed.

Introduction

This article provides the brief overview of recent model calculations and simulations of metal interactions with nucleic acid (NA) bases, base pairs and short oligomers. For the historical reasons alkali metals and metals of alkaline earth are discussed first. All possible forms (or models) of the metal cations are considered, starting with bare cations, which had been studied mostly in older papers. In addition, complexes with hydrated or ligated cations investigated by more recent works are also reviewed. Despite the simplicity and the fact that bare cations overestimate the bonding energies due to exaggerated contribution of Coulomb interaction, these models enable a clear insight to the basic bonding characteristics and other electronic properties. Many studies have focused on transition metal complexes, motivated by know anti-cancer activity of cisplatin and related metallodrugs. While in the binding of alkali metals the electrostatic contribution dominates, the coordination covalent character is also an important term in the complexes of transition metals.

In general, the structure and function of DNA are dependent on metal ions. These ions can interact with many sites in DNA:[1] including the phosphate groups, the sugar moiety, and the DNA bases. Despite the metal cations usually interact with the phosphate group and, to a lesser extent, with the bases, cation-base interactions are expected to be involved in many important biophysical processes, such as different stabilization of DNA triple helices,[2] stabilization of quadruple helices,[3]and stabilization of the ribose-base stacking in Z-DNA.[4] It is assumed that the interaction of a divalent cation with the base can cause significant polarization of the bases associated with stabilization of certain H-bonded DNA base pairs and other interactions.[3-5] However, that most ions do not interact with nucleic acids in a direct manner but rather contribute to unspecific loose ion atmosphere around the nucleic acids.[6] Note that while theoretical studies usually deal with binding of cations to DNA, the RNA cation binding is much more biochemically important and diverse. Many folded RNAs contain indispensable specific structural ions which may also be directly involved in RNA catalysis.[7]

In the DNA double helix, the known sites for the cation coordination are mainly the N7 atoms of purines, while a simultaneous interaction with the guanine O6 atom is also acknowledged. Some other sites, such as N3 of cytosine and N1 of adenine, are blocked by the hydrogen bonding. It should be noted that the metal

cation interactions are not restricted only to the DNA bases. The cation can simultaneously interact with the phosphate group and is usually surrounded by water molecules or by various ligands. The coordinated metal cations can interact with the DNA base directly (inner-sphere coordination) or a water molecule can link the DNA base with the metal cation (outer-sphere coordination).[1b,8] Experimental studies on 5'-monophosphates revealed the following order of macrochelate coordination involving the N7 position of purines: GMP > IMP (I - inosine) > AMP.[1b] This order was explained as a result of different basicity of the N7 sites of guanosine, inosine, and adenine. It also correlates with the dipole moments of DNA bases.

I Properties of metal adducts with nucleobases

a) Interaction of bare cations with bases

The first models investigated in connection with metal – nucleobases interactions employed bare cations. One of the pioneering studies on this topics was published in 1970 by Rozsnyai and Ladik[9] who considered the influence of water and divalent ions on the base pairing. This paper was followed by del Bene's ab initio calculations.[10] She explored interactions of isolated Li^+ cation with all DNA bases. In this early work, all the basic features of modern quantum chemical calculations are already present – the structures were optimized at the HF/STO-3G level with single point calculations (SP) using double-zeta basis set (6-31G). As the most stable adduct, the $[Li\text{-}(Gua\text{-}O6,N7)]^+$ chelate was established (with association energy of 78.4 kcal/mol) followed by cytosine complex $[Li\text{-}(Cyt\text{-}O2,N3)]^+$ (77.1 kcal/mol). The interaction energy of the most stable adenine conformer $[Li\text{-}(Ade\text{-}N3)]^+$ was estimated to be substantially lower - about 48.4 kcal/mol. These energies clearly demonstrate the dominant role of monopol (the cation) - dipole moment (the nucleobases) electrostatic interaction. In the study, both O2 and O4 thymine complexes were predicted to be more stable than the adenine adducts by about 10 kcal/mol. Closely after this keystone study another work dealing with interactions of the A-T and G-C base pairs with Li^+ cation appeared.[11] In the most stable Li-A-T conformer, the Li cation was coordinated to O2 site of thymine. In the G-C pair, the N3 position of guanine was preferred by 4 kcal/mol over O6,N7 chelate structure. We would like to address here one important point. The numbers above, as well as

most other numbers in this study refer to gas phase interactions of metal cations with nucleic acids components. Such interactions are dominated by the ionic electrostatic effects which are drastically (almost completely) become extinct in nucleic acids as well as in typical bioinorganic experiments. This needs to be kept in mind while interpreting the results. For more discussion of various aspects of the interplay between the gas phase interactions and full systems see references.[12]

Metal coordination sites in ‚natural' nucleotides are a) oxygen atoms of phosphate groups where cations neutralize the negative charge (these sites can be considered quite unspecific for any cation), b) hydroxyl groups of sugar moiety usually chosen by alkali metals or metals of alkaline earth, c) nitrogen atoms of heterocyclic bases – especially N1, N3, and N7 atoms of purine and N3 of pyrimidine bases, which exhibit large affinity to cations or generally electrophilles (In DNA/RNA oligomeric sequences only sites in minor or major groove are accessible for interactions. It means that solely the N3 and N7 sites of purine bases are available for the interactions.), and d) oxygens of keto-groups (cytosine O2, guanine O6, and O2,O4 of thymine and uracil) as positions for binding of "hard"-cations, e.g. alkali metals (and less frequently for transition metal).

Comparing cation coordination and protonation of these active sites, large similarities can be noticed in the case of guanine. On the contrary, more remarkable differences are observed for adenine, uracil or thymine.

-- Table 1 --

Coordination of the Mg^{2+} cation to purine DNA bases was recently explored in many experimental as well as computational studies (e.g. ref.[13]) where bonding properties of selected mono- and divalent metal cations with N7 position of guanine and adenine were examined.

The interaction of bare monovalent (alkali metals and coinage metals) and divalent (alkaline earth and zinc group metals) cations with N7 site of purine NA bases was examined in gas phase using MP2/6-31G(d,p)//HF/6-31G(d,p) level of theory.[14] A graphical illustration of the dependence of the coordination distance on the atomic number of the cations is displayed in Fig. 1. The intermolecular M-N7 distance monotonically increases with the variation of atomic numbers for the alkali metals and metals of alkaline earths (cf. Fig. 1). This increase of the distances is more pronounced for the alkali metals where it exceeds 1Å. The calculated M-N7 distances for both types of metals correlate well with the known ionic radii, e.g.

ref.[15] The influence of the relativity for the 5s and 5p electrons (Cs^+, Ba^{2+}) is not as pronounced as for the 5d electrons (Au^+, Hg^{2+}).[16.]

-- Figure 1 --

The stabilization energies of base...M complexes were determined according to formula:

$$\Delta E^{Stab} = -[E^{Complex} - (E^{base}_{BSSE} - E^{metal}_{BSSE})] + \Delta E^{base}_{deform} \qquad \text{Eq (1)}$$

Here the E^{base}_{BSSE} represents total energy of the base (adenine or guanine) within the basis set superposition error (BSSE) scheme of Boys Bernardi.[17] The results are displayed in Fig. 2 and it is evident that the values for guanine complexes are systematically larger than those of adenine. This is due to the larger dipole moment of guanine and the more favorable orientation of the ions and guanine dipole moment as it can be seen in Figs. 3a) and c). The stabilization energies of the complexes with divalent ions are larger than those with monovalent ions and, as could be expected, the stabilization energies decrease with increasing atomic number of the metal ions. The only exception is revealed for the Au^+ and Hg^{2+} complexes where, due to the more pronounced relativistic effects, the respective stabilization energies are larger than the energies of the preceding cations (Ag^+ and Cd^{2+}).

-- Figure 2 --

In the coinage and zinc-group metal complexes, the bonding interaction is markedly stronger in comparison with coordination of the Ia and IIa metals. This is due to the presence of lower-energy vacant s-orbitals (compared with the same orbitals of the alkali metals), enabling to some extent the dative bonding into these orbitals from the occupied orbitals of the bases. This leads to the increase of covalent character of the interaction that explains the basic difference between coordination of K^+ and Cu^+ cations.

-- Figure 3 --

Complexes with Li^+ bare cation were computationally explored in gas phase by Ruso et al.[18] at the DFT(B3LYP) level within several basis sets. They found that the most stable complex of adenine and lithium is imino-tautomer with N6,N7 coordination. In this way a five-membered chelate is formed where Li^+-N6 bond is 1.971 Å, and Li^+-N7 distance is 2.022 Å. The remaining explored (amino) structures: $[Li\text{-}(Ade\text{-}N3,N9)]^+$, $[Li\text{-}(Ade\text{-}N6,N7)]^+$, and $[Li\text{-}(Ade\text{-}N3)]^+$, lie by about 2, 10, and 15 kcal/mol higher on the potential energy surface. In the guanine

adducts, the most stable structure is [Li-(Guan-O6,N7)]$^+$ followed by chelate [Li-(Gua-N3,N9)]$^+$, its enol form, and the enol form of the (O6,N7)-chelate, which are by 11, 12, and 15 kcal/mol less stable. The interaction of lithium cation with uracil yields complexes with an energy difference lower than that revealed between corresponding isolated isomers but the stability order remains unchanged. The most stable complex with uracil is [Li-(Ura-O4)]$^+$ adduct (cf. Fig. 4). The chelate structures [Li-(Ura-O2,N3)]$^+$ and [Li-(Ura-O4,N3)]$^+$ lie about 3 and 7 kcal/mol above the global minimum and the [Li-(Ura-O2)]$^+$ adduct is about 5 kcal/mol above the O4-conformer. This fact clearly shows the electrostatic origin of the interaction when one considers the direction of the uracil dipole moment. In the case of thymine similar picture is revealed, only the differences are slightly smaller. The relative energy of two higher lying tautomers with respect to [Li-(Thy-O4)]$^+$ adduct are 2 kcal/mol for (O2,N3)-chelate and 5 kcal/mol for (N3,O4)-chelate. In the cytosine complexes, the [Li-(Cyt-O2,N3)]$^+$ structure is the most stable minimum followed by enol tautomer of [Li-(Cyt-N1,O2)]$^+$, and the enol form of [Li-(Cyt-O2,N3)]$^+$ (where N1 proton is transferred to O2 site). These two complexes lie about 12 and 17 kcal/mol higher on the potential energy surface.

--Figure 4--

The coordination of divalent metal cations with the phosphate group of various nucleotides (GMP, AMP, UMP, and CMP) was studied by Varnali.[19] In her study semiempirical PM3 method was used. From the results it follows that the most stable metal adducts are formed with the phosphate group of AMP closely followed by CMP for all explored metals.

The calculations of the NMR spin-spin coupling constants and the NMR shifts of the direct and water-mediated binding of a divalent metal cations to guanine were performed by Sychrovský.[13b] The intermolecular coupling constants (1)J(X, O6) and (1)J(X, N7) (X = Mg^{2+}, Zn^{2+}) were unambiguously assigned to the specific binding motif of the hydrated cation with O6 and N7 sites of guanine. The calculated coupling constants (1)J(Mg, O6) and (1)J(Zn, O6) were 6.2 and -17.5 Hz for the inner-shell complex where the cation is directly interacting with the guanine O6 position. For the inner-shell coordination of the cation at nitrogen N7, the calculated coupling constants (1)J(Mg,N7) and (1)J(Zn,N7) were 5.6 and -36.5 Hz, respectively. When the cation binding is water-mediated, the corresponding

coupling constants are zero. The calculated NMR shifts δ(N7) = -15.3 and -12.2 ppm upon the coordination of Mg^{2+} and Zn^{2+} ion are similar to the NMR shift of 19.6 ppm toward the high field measured by Tanaka[20] for the coordination of Cd^{2+} to the N7-guanine site.

The B3LYP/6-311+G(2df,2p) level was used to explore geometry of all possible adducts originating from the interaction of Cu^{2+} cation with the most stable tautomers of DNA and RNA free bases. [21] Several attachment sites for both purine and pyrimidine bases have been taken into account for possible formation of both mono-adducts and chelates. The copper ion (II) has the highest affinity for the most stable tautomer of guanine base.

Also, a comparison of various divalent metal cation complexes (Zn, Cu, Ni) with hypoxanthine and uracil was performed by Matsubara.[22] The B3LYP level stabilization energies of both M(II)-hypoxanthine and M(II)-uracil complexes reflect the strength of the M-N(base) interaction giving the same sequence Zn > Cu > Ni for both bases.

b) Metal interactions in implicit solvent model

The calculated interaction energies of the bare cations with nucleobases reveal drastic overestimation of the electrostatic interaction in comparison with experimental samples. This overestimation is clearly due to the uncompensated charge of the bare cation since cations in water solution are surrounded by solvent molecules. In this way the charge of the cation is screened and the electrostatic part of the metal-base interaction is substantially reduced. The role of electrostatic contribution in the case of the Pt-base coordination will be enlightened later. Since the approach of PCM models is very popular there is a large number of such studies. Here only a few recent works will be mentioned.

In 2008 Ai published a study[23] on tautomer equilibrium of adenine in presence of Zn^{2+} cation at the DFT level (B3LYP/6-311+G**). It was found that the $[Zn\text{-}(Ade\text{-}N6,N7)]^{2+}$ imino complex is the most stable structure in accord with the gas phase calculations of Kabeláč.[24] The latter calculations explored tautomers of all DNA bases in presence of Na^{+}, Mg^{2+}, and Zn^{2+} bare cations evaluated at the RI-MP2/TZVPP level of theory.

Metal cation binding to deoxyguanosine monophosphate was examined by Bouř.[25] Infrared spectra of complexes with Na^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+} cations were recorded and interpreted on the basis of density functional theory. The solvation effects were simulated by PCM and cluster models (combined explicit solvent and PCM). The coordination to the guanine N7 position was considered and obtained results predict a characteristic frequency blue-shift at 1578 cm^{-1}, in accord with experimental data. Binding to the phosphate group causes significant spectral changes in the sugar-phosphate vibration region but also notable frequency shifts of the carbonyl vibrations. The Cu^{2+} and Zn^{2+} cations induced the largest changes in measured vibrational absorption, which corresponds to the computationally determined strong interaction energies in the N7-complexes. The Cu^{2+} binding to guanine was revealed to be a two-step process, which was also confirmed by the microcalorimetry titration curve.

Another study on interaction of bare cations with metabolite of purine bases - uric acid should be mentioned.[26] The geometries of the complexes of Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, and Ca^{2+}metal cations with various nucleophilic sites of uric acid were optimized at the B3LYP/6-311++G(d,p) level. Single point energy calculations were performed at the MP2/6-311++G(d,p) level. It was found that cations mainly form chelate structures with a bidentate coordination. In the gas phase, the most preferred position for the interaction of Li^+, Na^+, and K^+ monovalent cations is between the N3 and O2 sites, while all divalent cations prefer coordination between the N7 and O6 sites of the urate. The influence of aqueous solvent on the relative stability of various complexes was examined by PCM model. The BSSE corrected interaction energies were also determined. It was found that aqueous solution has significant impact on the relative stability of complexes. The global minimum of urate with $Mg^{2+}$and Ca^{2+}cations is represented by the O2,N3-chelates in analogy with monovalent cations. Moreover, the relative energy differences are very small. Especially for the Ca^{2+} structures, practically energies of all conformers are in the range of 2 kcal/mol. The most stable structures are depicted in Fig.5.

--Figure 5--

The binding of first-row transition metal monocations (Sc+ - Cu+) to N7 of guanine and N7 or N3 of adenine nucleobases was studied using DFT approach with B3LYP functional. The electrostatic character of these interactions is mainly represented by

metal-ligand repulsion. The M^+-guanine binding energies are about 18-27 kcal/mol larger than those of M^+-adenine, the differences decreasing along the row.[27]

c) Interactions of explicitly hydrated cations

Another approach to more realistic description of metal cation interactions with nucleobases is represented by a model of the explicitly hydrated cations – usually up to hexacoordinated cations.

1. Hydrated alkaline earth and zinc-group metal cations

One of the first studies on this topic was published by Šponer et al.[28] In the study, pentaaqua divalent cation adducts (of Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+}) to the N7 position of guanine were explored at the MP2/6-31G*//HF/6-31G* level. Quasi-relativistic-energy-averaged Stuttgart pseudopotentials were used for the description of the cations. The interaction between hydrated cation and guanine is significantly reduced compared to the guanine-unsolvated cation model, cf. Table 2. The cations of IIb group together with Mg^{2+} are tightly bound to the N7 atom of guanine whereas the O6 site is involved in H-bonding with the aqua ligands from the metal hydration shell. The cations with greater radius (Ca^{2+}, Sr^{2+}, and Ba^{2+}) prefer simultaneous coordination to the N7 and O6 atoms of the base. Also, the cation-guanine distance increases with the atomic number. The energy difference between the N7 and N7-O6 types of coordination is rather small. Relativistic effects are apparent in the case of Hg^{2+}, similarly to the complexes with bare cation reported above.[14] The Zn^{2+} and Mg^{2+} cations show different balance between the cation-base and cation-water interactions. While the Zn^{2+}cation is bound more tightly to the base (93 kcal/mol) and its water shell is more flexible (203 kcal/mol) the different situation (with stronger metal-water binding) was found in the Mg^{2+} complex. The binding energy of (5w)Mg-N7(GC) is approximately 89 and $5H_2O$-Mg(GC) about 220 kcal/mol. The different binding picture for Zn and Mg cations can be partly explained as a shift from the interaction between nucleobase and hydrated cation (Mg) toward the hydration of a metalated base (Zn).

--Table 2 --

From Table 2 follows that despite the substantial reduction of the M-N7 interaction energy, the ratio of the energy values for guanine and adenine remains approximately two, similarly to the results obtained in the study of the bare

cations.[14] This confirms the dominant role of electrostatic term in these complexes. In platinum complexes substantially higher covalent contribution is demonstrated in the limit of total charge going to zero (Fig. 8, below).

The question, which coordination mode of hydrated Mg cation with DNA is dominant (direct metal-N7 coordination or indirect interaction by water molecule through the polarized H-bonding), was addressed by Bandyopadhyay.[29] Based on HF and DFT calculations the authors show that both binding modes are of similar importance.

The tautomeric equilibrium and hydrogen bonding in nucleotide 2'-deoxyguanosine monophosphate in interaction with hydrated $[Mg(H_2O)_4]^{2+}$ cation were studied at the MP2/cc-pVDZ//B3LYP/cc-pVDZ and B3LYP/aug-cc-pVTZ//B3LYP/cc-pVDZ levels of theory by Gorb.[30] The Mg^{2+} ion forms two inner-shell contacts with the nucleotide, similar to small phosphorylated molecules under physiological conditions. The hydrated magnesium cation in presence of the phosphate group can change the guanine tautomeric equilibrium in comparison to free guanine. The canonical O6-oxo form of guanine is more stable (by 6-8 kcal/mol) than the 06-hydroxo form in anti conformation. The interaction with Mg^{2+} ion is capable to suppress a spontaneous transient formation of the rare tautomer.

Very interesting case had been revealed when thioguanine base was explored.[31] In accord with the Pearson HSAB principle,[32] a stronger interaction with S6 site of thioguanine is observed for the heavier transition metal cations, as can be seen comparing columns $\Delta E_{\text{Mw-G}}$and $\Delta E_{\text{Mw-tG}}$ in Table 2. While in the case of alkaline earth cations (Mg, Ca) even mild weakening of the bonding energy is visible, the very robust adduct is formed with the Hg^{2+} cation. This very firm coordination is also partially the consequence of a smaller number of water molecules in the first hydration shell. Due to the strong Hg-S coordination two water molecules are push out from the hydration shell. Optimized N7,S6-chelate structure resembles the situation of bare cations, cf. Fig. 6b. However, a shorter Hg-S distance (2.50Å) was obtained comparing the Hg-N bond (2.57Å). Similar chelate structure was also found in the Cd^{2+} complex, despite the coordination with four water molecules, cf. Fig. 6c. A slightly longer Cd-S distance (2.67Å) than Cd-N (2.40Å) was obtained in this structure. In the remaining complexes no direct metal-sulphur interaction was found at the HF/6-31G* optimization level. Nevertheless, at the DFT

level, slightly different coordination pattern is revealed for Mg and Zn cations. The preferred structure contains six coordinated cation sphere, but only with four water molecules similar to the chelate arrangement of the Cd^{2+} complex[31] in Fig 6c.

Sponer et al. investigated possible binding of hydrated cations to nucleobases in a cation – pi manner but concluded that such interactions are very unlikely in nucleic acids as they are out-competed by conventional cation binding patterns. The suggestion of existence of cation-pi interactions in DNA was shown to be a case of misinterpretation of structural data. [33]

--Figure 6--

2. Complexes of hydrated copper cations with guanine

Interaction of hydrated Cu(I)/Cu(II) cations with guanine represents another interesting explored system. In this case also redox properties under hydration and complexation can be compared to copper complexes with water ammonium.[34] One of the examined features of the copper complexes involves the number of coordinated ligands. While the Cu(I) complexes prefer two-coordinated structures, the geometry of Cu(II) complexes has usually the coordination number four or five, in accord with the small inorganic copper complexes studied previously.[35] Also, the affinity of various active sites of the metalated guanine for water molecules in comparison with non-metalated (isolated) base was explored. The resulting preference for individual conformers determined at the B3LYP/6-311++G(2df,2pd) level can be seen in Table 3 and the most stable structures are displayed in Fig. 7. The affinity of isolated base was explored by Poltev et al.[36] who used empirical potentials. They found that in the case of hydration of guanine with a single water molecule, the global minimum structure has one water molecule between O6 and N1 sites, followed by the N1-N2 water adduct. Unfortunately the N9 position was not considered. In another study[37] various tautomeric forms of guanine and cytosine and their influence on Watson-Crick H-bonding were explored. From these results, it is clear that there is no substantial change due to the polarization effects of Cu(I) cation revealed by semiempirical methods, in comparison with the MP2 approach. Another comparison concerns metal-N7 bonding energies where one of our earlier

works on metal coordination to purine DNA bases can be used.[14,38] Despite the fact that in the earlier investigations only bare cations were considered at the MP2/6-31G(d) //HF/6-31G(d) level, the interaction energy is relatively similar to the analogous energies of these hydrated structures.

--Table 3--

--Figure 7--

The adducts of the hydrated copper(II) cation with guanine were explored in study of Pavelka.[35b] Various numbers of water molecules were considered in combination with the different coordination pattern of the Cu^{2+} cation. The most stable structures are summarized in Table 4 and displayed in Fig. 8. The full set of investigated structures can be viewed in the original paper.[35b]

--Table 4--

-- Figure 8--

From this study it follows that the penta-coordination of Cu(II) is in these complexes visibly less convenient than in case of the small inorganic complexes (for both purely aqua ligands[39] or mixed aqua-ammine ligands[35a]). The Cu(I) complexes do not create chelate structures since linear monoaqua-form with the remaining water molecules in the solvation shell is substantially more stable. In the monoaqua Cu(I) and Cu(II) complexes, the strength of Cu-N7 bond (-81/-230 kcal/mol for Cu(I)/Cu(II)) and Cu-O(aq) bond (-35/46 kcal/mol) roughly follow formal electrostatic relationship. Higher preference for N7 coordination in Cu(II) complex is related to the possibility of the higher electron transfer of more polarizable nitrogen atom.

d) Interaction with platinum metal complexes.

One of the most frequently studied metals in connection with nucleobases is platinum. Since late 60-ties when B. Rosenberg published his study on anticancer activity of cisplatin[40] a lot of efforts is devoted to this compound and its derivatives, as well as some other transition metal complexes where similar activities can be expected. One of the early calculations were performed by Basch et al.[41] and somewhat later by Lipinski.[42] Since then a vast number of studies can be found in literature on this topic. A lot of DFT and ab initio calculations were performed, especially on platinum interactions with nucleobases, nucleotides, and other DNA

models. One of important questions, which had to be solved, concerned tautomeric equilibria due to the possible point mutations. This topic was addressed in several studies considering various nucleobases. Since metalodrugs are generally expected to coordinate predominately in the major groove of genomic DNA the discussion starts with the interaction in N7 position of purine bases.

1. The tautomeric equilibrium of the metalated nucleobases

Several platinum complexes with varying total charge were explored at B3LYP/6-31G(d) level:[43] neutral trans-dichloro-diamine-platinum, +1 charged trans-triamine-chloro-platinum and, +2 charged tetraamine-platinum. Two tautomers of guanine were considered - keto and enol forms as well as N6-amino and, syn- and anti-imino forms of adenine. In this way the role of electrostatic contribution could be elucidated. Despite the gas phase calculations, the bonding energy and tautomeric relations in solvent can be easily estimated (i.e., extrapolated). In Fig. 9, the relative tautomeric stabilization energies are displayed.

--Figure 9--

From this figure it follows that the trans-imino-tautomer of adenine is better stabilized under platination, which could lead to mispairing. In case of guanine, the regular keto form is more stable in the case of charged complexes. Moreover, the enol preference in electroneutral complex is caused by additional H-bonding stabilization between platinum ligand (aqua or chloro) with hydrogen from the enol group (cf. Fig. 10a), which may not be present in solvent due to competitive H-bonding interactions. This study in general suggests that the largest part of the tautomeric effects of the N7 platination is due to gas phase effects which are assumed to be annihilated in real condensed phase conditions.

--Figure 10--

Šponer[44] explored metalation of the exocyclic amino group of cytosine and adenine nucleobases by Pt(II) and Hg(II) complexes. Metalation induces protonation of the N3 site of cytosine and N1 atom of adenine. Hence, it causes a proton shift from an exocyclic to an endocyclic N atom (similar to situation in Fig 10b). In this way the metal-assisted process can lead to the generation of rare nucleobase tautomers. The calculations demonstrate that metalation of the exocyclic amino group of nucleobases significantly increases the protonation energy of the aromatic rings of nucleobases by about 30-34 kcal/mol for the Pt(II) adduct and by about 10-

14 kcal/mol for the Hg(II) adduct. This study demonstrates a tautomeric shift that is caused by changes of the electronic structure of nucleobases and is unrelated to electrostatic effects. Thus the authors suggest to separate purely electrostatic effects from non-electrostatic (molecular orbital) contributions. The former ones are expected to be rather unimportant in aqueous solution or x-ray crystallography experiments, where the systems are overall strictly neutral. The non-electrostatic contributions are assumed to remain insensitive to the environment and fully expressed under usual experimental conditions.

Rare tautomers of 1-methyluracil (MeUH) and 1-methylthymine (MeTH) in coordination with Pt(II) complexes were explored by van der Wijst et al.[45] Comparing the calculations in gas phase and water, the influence of the solvation effects can be estimated. They also showed that relative stabilization energies of the Pt(II) complexes with various tautomers of MeUH and 1-MeTH differ from the isolated tautomers. This leads to the conclusion that some rare tautomers may become favored under metalation.

2. Interaction of nucleobases with half-sandwich Ru(II) complexes

Recently computations on ruthenium complexes with nucleobases were published by Futera.[46] In his comprehensive study interactions of piano-stool ruthenium metallodrug with nucleobases were investigated. In the same study the reaction profile of the chloro-ligand replacement by water molecule and the role of the arene-ring size were also explored. From the point of this review an important part of Futera's study deals with interactions of Ru(II) with various sites of all the nucleobases in vacuum and under implicit solvent model. For the optimized structures, the bonding and stabilization energies were determined. Characteristics of the most stable conformers are summarized in Table 5. In order to make a comparison between various conformers easier, the total energies are also included. From the Table 5 follows that in the case of purine bases, the most stable adenine structure (Ru-(Ade-N1) conformer) differs from the most stable guanine complex (Ru-(Gua-N7) conformer) as revealed in the gas-phase calculations. Nevertheless, in the PCM model, the N7-conformer represents the most stable form of the both purine nucleobases. This change of adenine global minimum follows from the general reduction of the electrostatic forces, which are substantially screened in PCM approaches. In gas phase, the Ru-(Ade-N1) coordination is enhanced by

favorable orientation of the adenine dipole moment of about 2.70 D (determined at the MP2/6-31++G(d,p), gas-phase level) aiming in N1–C8 direction while the guanine dipole of 6.36 D points in N7–N3 direction, as can be seen in Fig. 3. Even larger dipole moment was predicted for N1-guanine tautomer with proton transferred to N7 atom (μ = 9.55 D). This dipole value correlates with the fact that the Ru-(Gua-N1) adduct exhibits the highest ΔE^{BE}(Ru-(base-N)) bonding energy among all the explored complexes (interestingly, in both gas phase and PCM approach). The analogous effect of decreased electrostatic enhancement is also responsible for the change in energy preference in the case of cytosine adducts. The Ru-(Cyt-O2) structure becomes the least stable in water (by more than 7 kcal/mol) and the most stable adduct is Ru-(Cyt-N1) closely followed by the Ru-(Cyt-N3) complex with practically the same stabilization and total electronic energies. The thymine and uracil bases favor the N3 coordination regardless the environment. This preference is in accord with different orientation of the dipole moment of uracil and thymine in comparison with cytosine (cf. Fig. 3). Another computational study dealing with interaction of different forms of ruthenium complexes with DNA bases was published recently.[47] Here similar bonding energies (in comparison to Futera's work) were obtained for relevant structures in both gas phase and PCM.

--Table 5--

Molecular mechanism for the replacement of chloro-ligand by water and subsequently of aqua-ligand by nucleobase was also explored by Futera[46]. Similarly to platination process, the hydration reaction is mildly endoergic (ΔG=2kcal/mol). Formation of the guanine adduct is exoergic by ca 7 kcal/mol. Nevertheless, all these reactions are faster in the case of the ruthenium complex (in equimolar concentrations) since the activation barriers are lower, e.g. the values for replacement of both adenine and guanine are about 18 kcal/mol while in the cisplatin case analogous barriers are ca 20 kcal/mol (cf. Table 9). Moreover, while 'simple' mechanism was found in adenine reaction (as displayed in Fig.11a), a two-step reaction mechanism was suggested for the guanine replacement (Fig. 11b).

--Figure 11--

In these mechanisms, a lower activation barrier for adenine replacement corresponds to higher rate constant (1.7 $M.s^{-1}$ vs. 0.5 $M.s^{=1}$). Nevertheless, since the minimum associated with the reaction coordination ("direct reactant") is about 4

kcal/mol higher than the global minimum it means the concentration of the form corresponding to this local minimum will be by three orders of magnitude lower (according to the Boltzmann equilibrium law). Different situation occurs for analogous local minimum of guanine. Here the instant concentration (equilibrium occurrence) of local reaction minimum is comparable to the global minimum and therefore, the real reaction rate will be actually substantially higher for the process of guanine replacement.

Osmium complexes were also considered as possible metallodrugs. The hydrogenation energies of various nitrogen heterocycles in presence of osmium tetraoxide were investigated and published by Deubel.[48] While hydrogenation of pyrimidine bases is exothermic, the C4-C5 bond does not have a tendency to hydrogenate.

An interesting study on the difference between protonation and metalation of the N7 position of deoxyguanosine was published by Baik et al.[49] While under protonation the glycoside N9-C1' bond breaks, the Pt(II) adduct does not change the strength of the glycosidic bond substantially, as can be noticed from the Fig. 12

--Figure 12--

II The metal coordination to multiple nucleobase systems

a) Interaction with base pairs

1. Metal cations from Ia, Ib, IIa, and IIb groups

The influence of metal coordination from major groove on the enhancement of base pairing was explored by Burda et al.[38] The energy decomposition for these systems requires besides total stabilization and pair energies also the non-additive three-body contribution.

The studied complexes were partitioned into three subsytems: the two bases (B_1, B_2) and a metal cation (M). The total stabilization energy (ΔE^{Stab}) is, within the BSSE counterpoise error, defined as:

$$\Delta E^{Stab} = -\{E(B_1, B_2, M) - [E(B_1, gB_2, gM) + E(gB_1, B_2, gM) + E(gB_1, gB_2, M)] \quad \text{Eq (2)}$$

where E(B_1, B_2,M) represents total energy of the whole complex, and e.g., E(B_1, gB_2, gM) is a total energy of the base B_1in presence of the basis functions on ghost systems B_2 and M. Alternatively, the total stabilization energy ΔE can be expressed in terms of pair stabilization energies and the three-body contribution:

$$\Delta E^{Stab} = E(B_1 - B_2) + E(B_1 - M) + E(B_2 - M) + E(3)] \qquad \text{Eq (3)}$$

where each pair stabilization energy is calculated within the BSSE scheme. For example the E(B_1-B_2) energy can be determined from formula:

$$E(B_1 - B_2) = -\{E(B_1, B_2, gM) - [E(B_1, gB_2, gM) + E(gB_1, B_2, gM)] \quad \text{Eq(4).}$$

Besides these pairwise energies, interactions of one subsystem of the complex (metal or pyrimidine) with the remaining part were also evaluated. The interaction of thymine with (metal + adenine) subsystem can be determined as:

$$E(MA - T) = -\{E(A, T, M) - [E(A, gT, M) + E(gA, T, gM)] \qquad \text{Eq (5)}$$

The whole systems can be regarded as a composition of a strongly bonded metal cation - purine base part plus two weak interactions: metal cation – remote pyrimidine base and Watson-Crick H-bonded base pair. The latter two terms represent only a small perturbation of the first one, and their mutual influence is basically very small. Therefore, it is not surprising that similar geometry and energy parameters for metal coordination were obtained, comparing with the same characteristics found in ref.[14] Also, the obtained geometries match well the results reported by Anwander et al.[5] for complexes with Ca^{2+}, Mg^{2+}, and Zn^{2+}. Some small differences origin from a smaller basis set, which they have used: too short distances between the purine base and the metal cation, especially for the Zn^{2+} complexes (our calculations predicts 1.95 Å for the Zn^{2+}GC complex, while Anwander reported 1.72 Å).

The metal cation significantly influences the geometry of the base pair. The (C)O2...H-N2(G) H-bond lengths in the GC complexes are systematically reduced, in comparison with the isolated pair. This reduction is largest for bivalent ions (0.3 Å). The central H-bond N3-H...N1 remains practically unchanged, and the third N4-H...O6 H-bond, which is closest to the metal cation, is significantly lengthened in comparison with the isolated GC pair. The elongation is again the largest for bivalent ions (0.65 Å in Zn^{2+}GC and Mg^{2+}GC). In the AT pair, the metal cations affect the H-bonds in a different way. The (T)O4...H-N6 H-bond, which is closer to the metal-ion coordination site, shows substantial shortening (0.35 Å in complexes

with Zn^{2+} and Mg^{2+}), while the other H-bond (N3-H...N1) is lengthened (by 0.18 Å in Zn^{2+}AT complex). The geometric rearrangements of the pair structures can be regarded as rotation around the center of the pyrimidine ring towards the metal vcation in the case of the AT pair, and away from it in the case of the GC pair.

Basically, the same dependencies of the stabilization energies on increasing atomic numbers of metal cations are observed in metal-purine-pyrimidine complexes like in previously published metal-purine species.[14] Stabilization energies of complexes with divalent ions are larger than those of monovalent ions, and M-GC stabilization energies are larger than those for M-AT complexes. Both conclusions reflect the dominant role of the ion-dipole electrostatic contribution to the stabilization energy of these complexes.

Compared with the study of Anwander[5] very close agreement was obtained for complexes of Ca^{2+} with base pairs (within 5 kcal/mol). However, larger differences were found in Mg^{2+}- containing systems (≈ 20 kcal Mg^{2+}-AT and ≈ 40 kcal Mg^{2+}-GC; the values in the Burda's work describe larger stabilization - for both base pairs). However, the use of a minimal basis set (MBS) for zinc (all-electron calculations) nearly doubles the stability (ΔE^{HF}(MBS:Zn^{2+}-GC)=448 kcal/mol versus Burda's ΔE^{HF}(AREP:Zn^{2+}-GC)=254 kcal/mol and ΔE^{HF}(MBS:Zn^{2+}-AT)= 328 kcal/mol versus ΔE^{HF}(AREP:Zn^{2+}-AT)= 158 kcal/mol).

The H-bond WC interactions in the AT pair within the geometries of MAT complexes are systematically weakened in comparison with the isolated optimized AT pair (ΔE^{MP2} = 12.3 kcal/mol). This weakening, which is larger for divalent ions amounts to about 4 kcal/mol, leading to AT pairing energy of ca 8 kcal/mol. A similar weakening of H-bonds was expected to occur in the MGC complexes. However, it was found that ΔE^{MP2} of H-bonds in the GC pair within the MGC complexes are a little stronger (with Ca^{2+} - Ba^{2+} exceptions) than those of the H-bonds in the isolated GC pair (ΔE^{MP2} = -26.3 kcal/mol). It can be shown that these changes correspond to the geometry deformation under the metal coordination. Nevertheless, from the energy decomposition it can be concluded that H-bond strength of GC or AT pair, calculated as a pairwise interaction energy within the optimized MGC or MAT complexes, is influenced only slightly by cations.

However, metal cations bound to the WC base pairs dramatically (directly or indirectly) change many characteristics of the base pairing. Actually, one should

consider not pairwise energies of the G-C and A-T pairs but the MG-C and MA-T H-bonding energies and these values are systematically higher – up to 24 kcal/mol for A- T and 48 kcal/mol for G-C H-bonding in the presence of Zn^{2+} cation. It amounts to nearly two times enhancement of the original base pairing energy.

--Table 6--

Similar conclusions are also reported in other studies on the metal - nucleobases interactions. Trimer base arrangement was explored using a similar computational model. The enhancement of G.GC(rH), G.GC(H), A.AT(rH), T.AT(H) and some other base interactions including reverse Hoogsteen pairs GG(rH) and AA(rH) was proved in presence of Li^+ and Ca^{2+} cations.[50] A study on the strength of H-bonding of WC base pairing under metalation at various active sites of bases concluded that the N3(Adenine) site available in the minor groove has higher chances for platination, in comparison with the N7-site of the base.[51]

An interesting idea is related to a replacement of proton in H-bonding by metal. In this way the non-canonical A-C base pair was examined with the coinage metal cations (Cu^+, Ag^+, and Au^+) used as a bridge between both bases,[52] cf. Fig. 13. The possibility of additional water coordination to metal was also considered. In the original paper it is concluded that these metal bridged complexes are substantially more stable than original (protonated) base pair. The water coordination does not influence the strength of metal bridge substantially nevertheless, its presence has some impact on the geometry of the complexes. Comparing bonding properties of all three metal cations, it was found that Ag cation coordinates relatively weakly which is in good accord with the previous results.[14,38] Slightly shorter bond length d(M-N7-Adenine) than d(M-N3-Cytosine) contradicts the estimated bonding energies since ΔE^{M-A} is smaller than ΔE^{M-C}. This can be explain by two facts a) the electrostatic contribution to the metal coordination is much smaller in adenine case (see the size and orientation of the dipole moments of both bases in Fig. 3) and b) the metal-cytosine interaction cannot be considered purely of the M-N3 character and simultaneously, the M-O2 contribution plays non-negligible role.

--Figure 13--

The results of investigation on Cu^+/Cu^{2+} interaction with AT and GC pairs were published by Sodupe's group.[53] The influence of metal cations coordinated to N-7 of guanine on the intermolecular proton-transfer reaction in guanine-cytosine base pair

was studied with the B3LYP density functional. Gas phase metal cation interaction stabilizes the ion pair structure derived from the N1-N3 single-proton-transfer reaction, the effects being more pronounced for the divalent cation than for the monovalent one. For Cu2+-GC the reaction is largely favored due to both electrostatic and oxidative effects. Hydration of the metal cation reverts this trend due to the screening of electrostatic effects.

In the section on interaction of hydrated metal complexes the Sponer study[28] was mentioned where in addition to purine nucleobases also the GC, AT, and AA base pairs were considered. Since the metal-purine base interaction is not substantially influenced by remote pyrimidine base we will focus on base pair enhancement and some changes observed in comparison with study on bare metal cations complexes.[38] The strength of the guanine-cytosine Watson-Crick base pair is enhanced by ca. 20-30% due to the coordination of the hydrated cation, while in the case of bare cations this enhancement was about 60-90%. From Table 7 follows that the bare cations deform the base pair geometry more noticeably than the hydrated cations. Only in the Ba^{2+} case the hydration sphere is H-bonded to O6 guanine site more strongly than other cations decreasing the GC base pairing energy.

--Table 7--

In addition, an interesting comparison of Zn and Mg hydrated cations in Pu-Pu-Py triplexes was carried out[54] where a hydrated metal is coordinated to the N7 position of purine base attached to the Watson-Crick base pair. Using this model metal assisted triplex stabilization was studied. It was shown that in both A.A and G.G the Hoogsteen pairing is strengthen under metalation. A substantially stronger enhancement of (MG).G pairing was revealed (19.8 and 20.4 kcal/mol for Mg and Zn cations, respectively), in comparison with similar adenine structures where practically no additional stabilization was detected (only about 2.7 kcal/mol for both metal cations). In another study[54] a more extended set of divalent metal cations (Mg, Ca, Sr, Ba, Zn, Cd, and Hg) hydrated by five water molecules was explored with rAA and AT base pairs interacting with N7 site of adenine confirming the previously obtained results.

Schreiber et al.[55] explored the Ag(I) adducts with DNA base and the influence of Ag(I) coordination for adenine-cytosine mispairing. Their calculations showed that in gas phase the canonical form of cytosine is stabilized upon metalation, whereas

the lowest energy structure of Ag-adenine corresponds to the imino tautomer. The most stable metalated adenine-cytosine mispair was formed from the canonical cytosine and adenine tautomers. Other types of A-C pairs (e.g. reverse Wobble) were found much less stable. The same authors also performed an interesting study dealing with the role of Ag(I) cation on electronic spectra of the A-C pairs using very accurate MS-CASPT2 approach.[56]

Interestingly, possibilities of so-called M-DNA crosslink stabilization of GC base pairs by divalent zinc has been investigated by Fuentes-Cabrera et al.[57]

2. Enhancement of base pairing by Pt complexes

Several well-executed studies related to platinum metal interactions with base pairs and the influence of metal complexes on the strength of pairing should be mentioned.

Molecular structures of several Pt complexes with the Watson-Crick AT and GC base pairs were optimized using the B3LYP method. The interaction energies were analyzed using B3LYP, and MP2 approaches.[58] Platination causes some distortion in the H-bond arrangement of the base pairs. The pyrimidine bases rotate around their centre of mass under the influence of the charged Pt entities. This effect is quite general and was already discussed above.[28,38,54] The metal-binding affects the strength of individual H-bonds involved in the base pairing.

It was concluded that ligands attached to the Pt(II) cation form rather strong intramolecular H-bonds with the X6 exocyclic site of purine bases. The adenine amino group adopts a pyramidal-rotated geometry and its nitrogen serves as H-bond acceptor for the ammine ligands of cisplatin.

The Pt-binding has comparable effect on the base pairing stability as binding of hydrated metals of IIa and IIb groups. In the electroneutral form, the Pt-adduct practically does not influence the base pair stability. Charged Pt adducts substantially strengthen the stability of G.C base pair via polarization effects. The influence of the +2 charged Pt-adduct is even larger compared with hydrated metals of IIa and IIb groups. No such polarization effects have been revealed for the A.T base pair. However, gas phase stability of this pair is effectively enhanced by long-range electrostatic interaction between the charged metal group and thymine.

The dependence of the stabilization and Pt-N7 bonding energies on the total charge of the complex is displayed in Fig 14a. Here, the role of electrostatic

contributions is clearly demonstrated for the both kinds of energies. Interestingly, in electroneutral complexes, the Pt-N7 bonding energies are similar in guanine and adenine structures (≈ 50 kcal/mol). In the Fig 14b the base pairing energies are drawn showing that the geometry deformations do not basically influence these values. Nevertheless, the interaction of metalated purine base with pyrimidine base is substantially strengthened, especially in charged complexes (e.g. in complexes of hydrated cisplatin).

It is important to point out that the effect of base pair stabilization enhancement due to cation binding has been confirmed experimentally by Sigel and Lippert.[59]

--Figure 14--

Zilberberg et al. reported the influence of chelated cisplatin complex with guanine(O6,N7) on Watson-Crick base pairing.[60] In such chelate structures, more distinct perturbation of base pairing was revealed. However, such chelate binding pattern is unlikely to be relevant to experimental conditions.

b) Interactions of hydrated cations with nucleotides

Sponer et al.[61] studied the coordination of hydrated zinc and magnesium group divalent cations to the N7 position of purine nucleotides. They showed that the sugar-phosphate backbone provides significant screening of the charge of the metal, while the backbone geometry is affected by the cation, Polarized water molecules of the cation hydration shell form very strong hydrogen bond bridges between the cation and the anionic oxygen atoms of the phosphate group. Weaker hydrogen bonds are formed between the cation hydration shell and the exocyclic purine X6 atoms. The cation binding to N7 of adenosine monophosphate forces the adenine amino group to adopt nonplanar conformation. Its nitrogen atom serves as an H-acceptor for a water molecule from the cation hydration shell. Cation binding to N7 does not lead to any major changes in the geometry of the base pairing. However, the stability of the base pairing can be increased by polarization of the purine base by the cation and by long-range electrostatic attraction between the hydrated cation and the other nucleobase. The stability of guanine-cytosine Watson-Crick base pairing is enhanced by the polarization mechanism while the stability of the adenine-

thymine Watson-Crick base pair is amplified by the electrostatic effects as shown in the case of base pairs model discussed previously.[38] Also, the guanine-guanine reverse-Hoogsteen base pairing is stabilized by both contributions while the adenine-adenine reverse-Hodgsteen system is not influenced by the cation. Binding of a cation to the N7 of guanine promotes transfer of its H1 proton to the N3 acceptor site of cytosine. However, the negatively charged backbone exerts a significant screening effect on this potentially mutagenic process, and the probability of such a proton transfer in DNA should be only moderately enhanced by a cation binding.

A comprehensive study dealing with a coordination of hydrated cations Zn(II) and Mg(II) to guanosine 5' monophosphate was performed by Gresh[62] in order to obtained parameters for polarizable molecular mechanics for metal - DNA and RNA simulations.

Inner-shell binding of selected hydrated metal ions (Mg^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+}) to the guanine N7 position was investigated in relation to outer- and inner-shell binding to an anionic phosphate group.[63] The study was focused on the mutual interplay between the metal-phosphate and metal-nucleobase binding and the role of nonelectrostatic effects in the metal binding. The analysis of the equilibrium structures and the energy decompositions reveal that these effects substantially contribute to the differences in the coordination behavior of the studied metal ions. The Zn^{2+} and Cd^{2+} cations show a clear preference (compared to Mg^{2+}) to bind to N7 of guanine. The selectivity amounts to approximately 3-4 kcal/mol. This energy difference is sufficient to provide enough binding selectivity in the condensed phase where the dominant pair electrostatic terms (ion-ion, molecule-ion) are attenuated. Cu^{2+} shows even stronger relative preference for N7 binding and it has also different coordination requirements. The nucleobase's N7 metal binding causes approximately 20-30 kcal/mol destabilization of the metal-phosphate outer-shell binding, due to nonelectrostatic effects.

c) Metal Interactions with Stacked Bases

Cisplatin bridges between two consequent bases (1,2-GpG) are believed to be the key structure for triggering the apoptotic process. Recently several studies on these cross-linked structures have been published. The properties of Pt-bridges were explored[64] showing that relatively strong Pt-N7 coordination is formed. The process of aqua ligand replacement by nucleobase is mildly exoergic in both steps: forming a) a monofunctional adduct and consequently b) the cross-linked structure. Stabilization energies of the Pt-GG, Pt-GA, and Pt-AA bridges are collected in Table 8. The relative amount of these values correlates well with the relative abundance of individual structures in real samples, assuming the gas phase calculations require some additional rescaling in correspondence to the reduced electrostatic interactions in solvent.

--Table 8 --

The influence of the sugar phosphate backbone on the strength of Pt-bridger was also examined.[64b] Some additional stabilization of the Pt cross-linked structures appeared as a result of the interaction between negatively charged phosphate group and Pt cation.

One of the first papers studying transition states of the replacement aqua ligand by nucleobase was published by Chval.[65] His model was based on the gas phase calculations and the estimated activation barrier is too low in comparison with experimental value. This situation was improved in studies of Raber[66] and Baik.[67] They have taken into account the hydration effects employing implicit solvent model. Especially, the Raber's results are in fairly good accord with experimental data. Activation barriers of monoaqua and diaqua Pt(II) complexes are summarized in Table 9 for both guanine and adenine replacement of the first and second leaving (aqua) ligand.

--Table 9--

c) Metal adducts in oligomeric sequences

The infrared (IR) and vibrational circular dichroism (VCD) spectra of guanosine-5'-hydrazide have been measured and analyzed on the basis of ab initio modeling.[68] The B3LYP/6-31G(d,p) calculations predict that guanine, forming a clear solution in deuterated DMSO, is present in monomeric form in this solvent, whereas strong gelation in a phosphate buffer is due to the formation of a guanine-quartet structure.

Here, the four bases are linked by hydrogen-bonded guanine moieties and stabilized by an alkali metal cation. The DFT prediction of the IR and VCD spectra are based on the nearly planar quartet structure, which is slightly distorted from the C_{4h} symmetry. The guanine bases interact via four Hoogsteen-type hydrogen bonds and a sodium cation is positioned in the middle of the guanine quartet. The obtained results are in very good agreement with the experimental spectra, indicating that calculated structure is the highly probable in the gel state.

The guanine quartets were examined also by Gu.[69] The normal four-stranded Hoogsteen-bonded G-quartet structures were optimized in the gas-phase with a monovalent cations obtaining the stability order $Li^+ > Na^+ > K^+$. However, after the correction on solvent effects, the stability sequence of the monovalent cation−guanine-tetrad complexes follows the opposite trend $K^+ > Na^+ > Li^+$. The preferential binding of potassium over sodium and lithium in water solutions reproduces the experimental ion selectivity of the guanine quadruplex. Moreover, weak stabilization energy of the K^+−G-quartet in the coplanar form corresponds with the fact that the potassium cation tends to locate between two successive quartets. These results are in accord with the study of Hud et al.[70] on the ion selectivity of the guanine quartets in water solutions, which are govern by the relative free energies of hydration. The experimental data on the cation−oxygen distances in the sodium ion complex are 2.34 ± 0.02 Å. This value matches the HF value of 2.33 Å. The slightly shorter Na^+−O6 distance were predicted by the DFT approach together with a significant shortening of the hydrogen bonds suggesting an overestimation of the H-bonding in the guanine quartets at the DFT level. Very comprehensive study on metal-quartet interactions has been published also by Meyer et al.[71] It is to be noted, however, that in principle accurate studies of quadruplex-ion interactions would require inclusion of the whole solvated quadruplex fragment, due to the unique balance of molecular interactions in this important noncanonical DNA.[72]

Similar topic was examined also by Ida.[73] In this study, molecular dynamics was employed exploring G-quadruplex stabilized by Na and Rb cations, which were found to be tightly bound to quadruplex structure. Moreover, in d(G(4)T(4)G(4) sequences the Na^+ ions are found to be located in the diagonal T-4 loop region of the G-quadruplex, which is formed by two strands of d(G4T4G4) sequence. Authors proposed that the loop Na^+ ion is located above the terminal G-quartet, coordinating to four guanine 06 atoms from the terminal G-quartet and one 02 atom from a loop

thymine base and one water molecule. The Na^+ coordination was also supported by quantum chemical calculations on ^{23}Na chemical shifts.

Larger systems like metal adducts to oligomer sequences or metal interactions with higher number (n>5) of nucleobases are difficult to treat using standard quantum chemical tools. Therefore, most of these studies are performed with combined QM/MM or classical MM and MD simulations.

Montrel et al.[74] compared experimentally observed coordinations of metal ion to DNA oligonucleotides using electrostatic potential (EP) along the helix. Their calculations have been performed for three different models of the oligonucleotide duplex [d(CGCGAATTCGCG)2] using several variants of EP calculations, including a solution of non-linear Poisson-Boltzmann equation (NPBE). The N7 atom of guanine adjacent to adenine base was recognized as the most negative site in the major groove.

The influence of sodium cations and chain length on the structure and dynamics of single strand DNA of polythymidylate was studied using molecular dynamics simulations.[75] The base stacking interaction increases with the length of oligomeric chain of the strand. Sodium ions interact with the phosphate groups as well as with keto oxygens of the thymine bases. Formation of simultaneous phosphate and keto complexes were observed for one of the sodium ions with lifetimes around 1 ns.

Poison-Boltzmann solvent model was used for examination of polynucleotides[76] in presence of K^+ Na^+ and Mg^{2+}. Stability of rare tautomers for N4 metalated cytosine in environments with various dielectric constant from gas phase (ε=0) to implicit water model (ε =78) is revealed in ref.[77]

Conclusion

In this review the results of recent investigations on metal interactions with nucleobases, base pairs, and some larger models (including base stacking or oligomer sequences) are summarized.

The studies dealing with metal cations (in naked, hydrated, and ligated forms) provide various details on their interactions with nucleobases, however such models are in many cases oversimplified. Despite the fact that some sites on the isolated nucleobase (especially in adenine) exhibits higher affinity to metal cations, in DNA

helix not all of them are available for interactions since they are involved in H-bonding (purine N1 site) or in the glycosidic bond (N9 site).

All forms of metal cations enhance the Watson-Crick base pairing interaction if their positive charge is not fully compensated. The different mechanism for the A.T and G.C adducts was revealed. While in A.T the direct electrostatic link between remote thymine (negatively charged O4) and metal cation exists, in the G.C pair the non-additive three-body term is important since the positively charged NH_2 exo-group is in the proximity of the metal cation.

Clearly, metalation at the N7 position leads into many new, exceptional properties of the studied systems that are dependent on characteristics of involved metals. Some of them are discussed in details in various parts of this text.

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Table 1 Preferred sites for metalation and protonation

Base	Coordination	Protonation
	N7>N1	N1>N7
Cytosine	N3	N3
Guanine	N7 >N1	N7 > N1
Thymine, Uracil	O2 >O4	O4 > O2

Table 2: Interaction energies in the complexes of solvated cation (Mw)-(N7)purine (G/tG/A).

	$\Delta E_{\text{Mw-G}}$	$\Delta E_{\text{Mw-tG}}$	ΔE_{MG} bare	$\Delta E_{\text{Mw-A}}$	ΔE_{MA} bare
Mg^{2+}	**-89.3**	**-84.8**	-198.7	**-46.0**	-107.9
Ca^{2+}	**-82.6**	**-80.1**	-133.9	**-33.5**	-61.6
Sr^{2+}	**-76.0**	**-**	-	**28.9**	-48.9
Ba^{2+}	**-71.2**	**-71.4**	-118.3	**-28.1**	-54.4
Zn^{2+}	**-93.8**	**-90.1**	-237.2	**-53.7**	-152.9
Cd^{2+}	**-87.9**	**-107.6**	-192.6	**-45.9**	-116.6
Hg^{2+}	**-94.3**	**-149.2**	-208.0	**-55.3**	-141.1

Table 3 The relative differences of ΔG and ΔE^{Stab} and Cu-N7 and Cu-O binding energies for the selected conformers in kcal/mol

Conformer	*ΔG*	ΔE^{Stab}	*E(Cu-N)*	*E(Cu-O)*
1	**0.0**	-168.4	83.4	60.4
2	1.1	-167.9	81.0	59.9
3	2.6	-165.3	80.4	60.7
4	3.5	-166.5	74.4	60.6
5	3.6	-167.7	76.5	60.1

Table 4: Relative differences of Gibbs energies ΔG and stabilization energies ΔE^{stab} (in kcal/mol) with respect to global minima structure. Abbreviation *c.n.* corresponds to the type of coordination and *struct.* is used for identification of the optimized structure in Fig. 8.

System	c.n.	*struct.*	ΔG^{total}	$\Delta\Delta E^{stab}$
$[CuG(H_2O)_4]^{2+}$	4	*4b*	2.2	4.6
	4^{chel}	*4j*	0.0	0.0
	4^{chel}	*4k*	2.0	1.0
	5^{chel}	*4g*	4.3	4.9
$CuG(H_2O)_5]^{2+}$	4	*5a*	2.8	0.0
	4^{chel}	*5w*	0.0	1.7
	4^{chel}	*5y*	1.1	1.0
	5^{chel}	*5h*	6.4	5.4

Table 5 Bonding and stabilization energies (in kcal/mol); for easier comparison of various adducts also total energies (in a.u.) are presented.

	Ru(bz)(Ade-N1)		Ru(bz)(Ade-N3)		Ru(bz)(Ade-N7)		Ru(cym)(Ade-N7)	
Adenine	in vacuo	COSMO	in vacuo	COSMO	in vacuo	COSMO	in vacuo	COSMO
$\Delta E^{BE}(ade)$	-72.7	-48.7	-69.1	-47.7	-69.7	-50.3	-65.4	-50.2
ΔE^{Stab}	431.1	389.2	426.9	387.9	426.2	390.0	441.4	396.5
$E^{Total}+900$	-81.612	-81.880	-81.605	-81.879	-81.606	-81.881		
Guanine	Ru(bz)(Gua-N1)		Ru(bz)(Gua-N3)		Ru(bz)(Gua-N7)		Ru(cym)(Gua-N7)	
$\Delta E^{BE}(gua)$	-103.9	-59.7	-56.4	-45.3	-90.7	-56.0	-86.1	-57.2
ΔE^{Stab}	442.7	390.9	412.6	384.7	449.7	395.3	465.6	383.3
$E^{Total}+1000$	-56.687	-56.944	-56.637	-56.939	-56.695	-56.955		
Cytosine	Ru(bz)(Cyt-N1)		Ru(bz)(Cyt-N3)		Ru(bz)(Cyt-O2)			
$\Delta E^{BE}(cyt)$	-89.5	-56.0	-79.0	-52.8	-84.0	-45.9		
ΔE^{Stab}	441.1	392.6	438.4	392.2	444.6	389.2		
$E^{Total}+900$	-9.447	-9.710	-9.444	-9.709	-9.449	-9.701		
Thymine	Ru(bz)(Thy-N1)		Ru(bz)(Thy-N3)		Ru(bz)(Thy-O2)		Ru(bz)(Thy-O4)	
$\Delta E^{BE}(thy)$	-65.0	-46.5	-82.8	-51.3	-53.9	-31.3	-60.0	-34.7
ΔE^{Stab}	407.4	372.3	424.9	380.3	412.5	374.0	420.2	376.2
$E^{Total}+900$	-68.436	-68.717	-68.467	-68.727	-68.440	-68.717	-68.454	-68.721
Uracil	Ru(bz)(Ura-N1)		Ru(bz)(Ura-N3)		Ru(bz)(Ura-O2)		Ru(cym)(Ura-O4)	
$\Delta E^{BE}(ura)$	-61.6	-45.9	-79.8	-51.1	-50.8	-31.7	-59.1	-34.3
ΔE^{Stab}	403.2	371.2	422.7	380.5	410.5	375.3	419.3	377.3
$E^{Total}+900$	-29.240	-29.527	-29.274	-29.539	-29.247	-29.531	-29.262	-29.534

Table 6 Enhancement of Watson-Crick base pairing energy under the metalation. (energies calculated at the MP2/6-31G** level)

Metal	E(M-A)	E(A-T)[a]	E(M-AT)	E(MA-T)	E(M-A-T)	E(M-G)	E(G-C)[a]	E(M-GC)	E(MG-C)	E(M-G-C)
Cu^{+}	-54.5	-12.0	-58.6	**-16.1**	-70.5	-79.9	-27.2	-86.1	**-33.3**	-113.3
Ag^{+}	-36.0	-12.0	-40.0	**-16.0**	-52.0	-64.2	-27.0	-69.0	**-31.8**	-96.1
Au^{+}	-55.0	-12.0	-59.1	**-16.1**	-71.1	-75.9	-27.0	-81.8	**-32.9**	-108.8
Zn^{2+}	-152.9	-10.8	-165.9	**-23.8**	-176.7	-237.2	-26.1	-259.4	**-48.2**	-285.4
Cd^{2+}	-116.6	-10.9	-129.3	**-23.6**	-140.2	-192.6	-25.9	-211.3	**-44.6**	-237.2
Hg^{2+}	-141.1	-10.9	-153.8	**-23.7**	-164.7	-207.9	-25.9	-228.0	**-45.9**	-253.9
Mg^{2+}	-107.9	-10.8	-120.7	**-23.5**	-131.5	-198.6	-25.9	-217.8	**-45.1**	-243.8
Ca^{2+}	-61.6	-11.1	-73.1	**-22.6**	-84.2	-133.8	-25.7	-146.9	**-38.8**	-172.6
Sr^{2+}	-48.9	-11.2	-59.8	**-22.1**	-71.0					
Ba^{2+}	-51.4	-11.2	-62.3	**-22.1**	-73.5	-118.8	-25.6	-130.4	**-37.2**	-156.0

Table 7 Difference in base-pair energies under the metalation. (in kcal/mol)

	ΔE_{GC} (hydr)	ΔE_{GC} (bare)
Mg^{2+}	-26.4	-26.0
Ca^{2+}	-26.3	-25.8
Sr^{2+}	-25.8	-
Ba^{2+}	-23.2	-25.6
Zn^{2+}	-26.4	-26.1
Cd^{2+}	-26.3	-26.0
Hg^{2+}	-26.2	-25.9

Table 8 Stabilization energies of the Pt-cross-linked structures (in kcal/mol)

	ΔE^{stab}(MP2)
Pt-a_2A_2	491.5
Pt-a_2AG	514.6
Pt-a_2G_2	528.3

Table 9 Substitution energies for the aqua ligand replacement by purine base (in kcal/mol)

1st step	chloro/aqua	diaqua
Guanine	21.4[a] 25.6[b] 14[c]	19.5[a] 21.8[b] 17.9[c] 18.3[d]
Adenine	24.0[a] 37.6[b] 14.5[c]	24.8[a] 34.5[b] 14.5[c]
2nd step		
GG hh		22.5[a] 23.4[e]
GA hh		28.6[a]

[a]ref.[66], [b]ref. [67], [c]ref. [65],experimental data: [d]ref.[78], and [e]ref.[79]

Caption to Figures

Figure 1 Metal-base distances for Ia, Ib monovalent and IIa and IIb divalent cations interaction with N7 (and O6) guanine and adenine sites.

Figure 2 Stabilization energies of metal-base complexes for Ia, Ib, IIa, and IIb metal cations interacting in N7(,O6) position of the base.

Figure 3 Orientation and size of the isolated NA bases: a) guanine b) N7 protonated guanine tautomer c) adenine d) cytosine, e) thymine, f) uracil. Standard atom numbering is used (e.g. textbook of Saenger[1a]).

Figure 4 Structure of the [Li-(Ura-O2,N3)]+ cation (enol form of O2,N3-chelate).

Figure 5 The optimized structures of the metal complexes with urate a) O2,N3-chelate, b) O6,N7-chelate.

Figure 6 Different cases of hydrated-metal coordination to thioguanine: a) Zn, b) Cd, and c) Hg.

Figure 7 The most stable conformers of [Cu(H2O)5(N7-guanine)]+ complex.

Figure 8 The most stable structures in complexes with 4 and 5 water molecules.

Figure9 Stabilization energies of the platinum-base complexes in dependence on total charge of the a) adenine and b) guanine complex.

Figure10 Structure of platinum(II) complexes with a) enol-tautomer of guanine and b) trans-imino-tautomer of adenine

Figure 11 a) Reaction coordinate for replacement of water by adenine and b) guanine

Figure12 Reaction energy profile of the free energies for dissociation of N9-C1' glycoside bond of dGuo, $dGuo(H)^+$, and $dGuo(Pt)^+$ in solvent.

Figure 13 Cytosine-M^+-Adenine complexes, M=(Cu,Ag, Au)

Figure 14 a) the stabilization and metalation M-N7 energies b) enhancement of the Watson-Crick pairing energies for AT and GC base pairs.

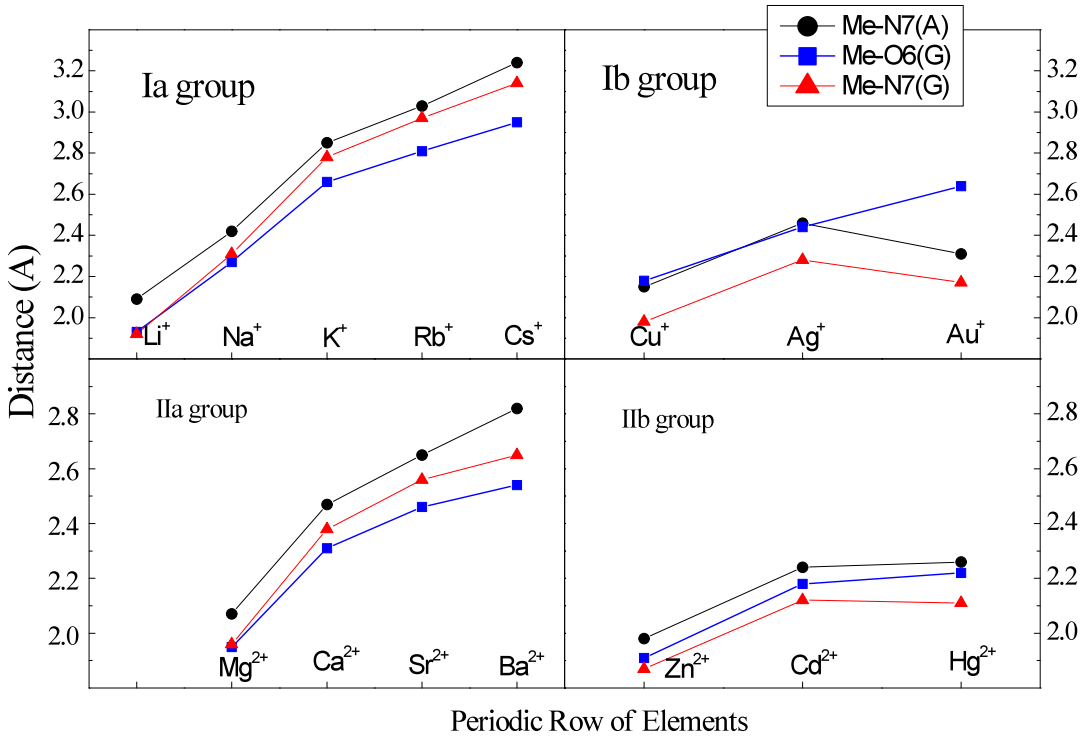


Figure 1

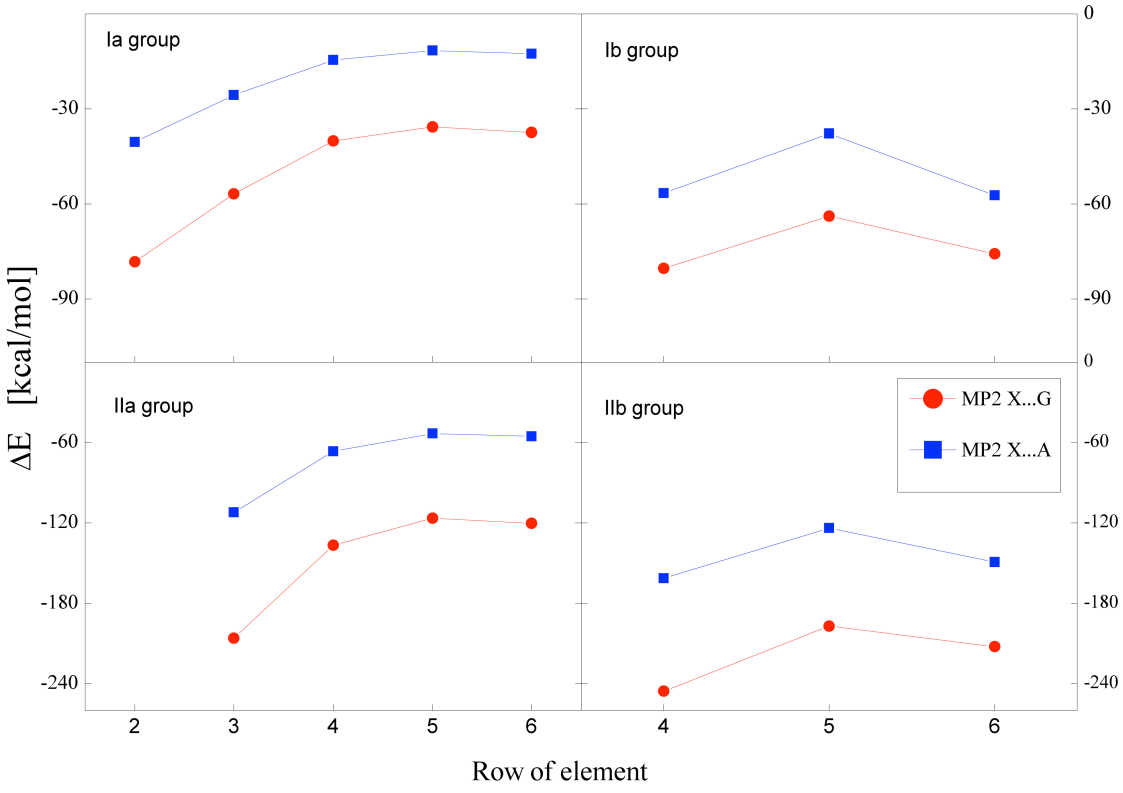


Figure 2

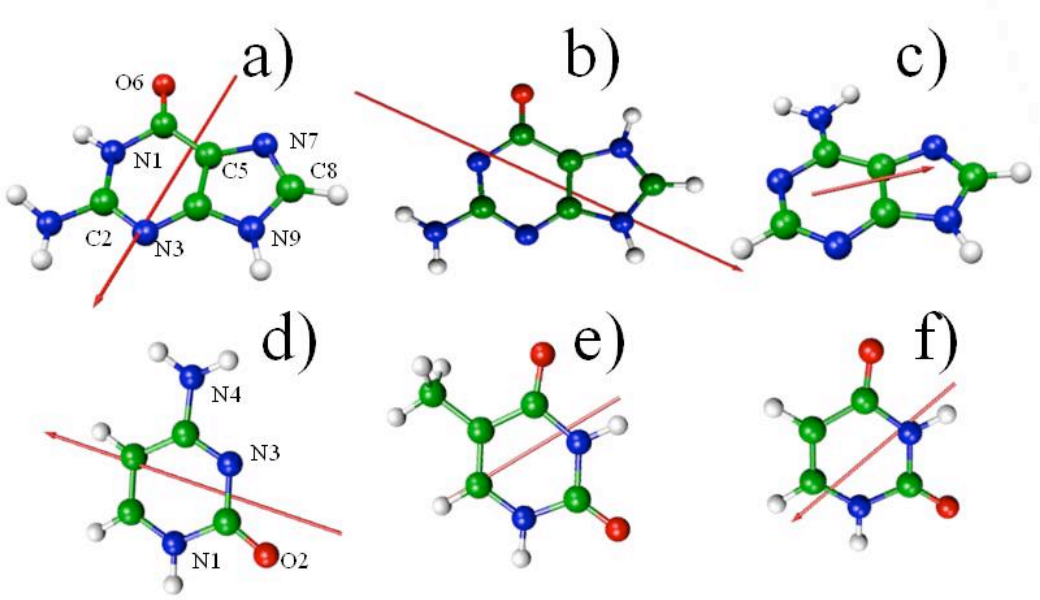


Figure 3

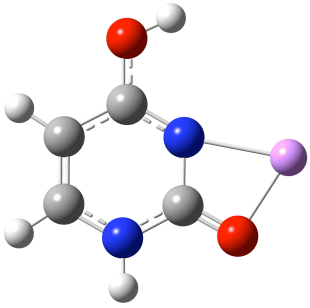
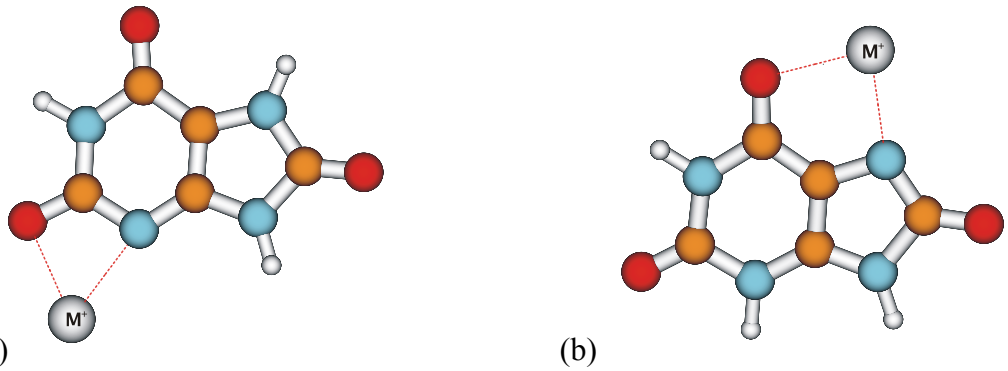


Figure 4



(a) (b)

Figure 5

a) **b)** **c)**

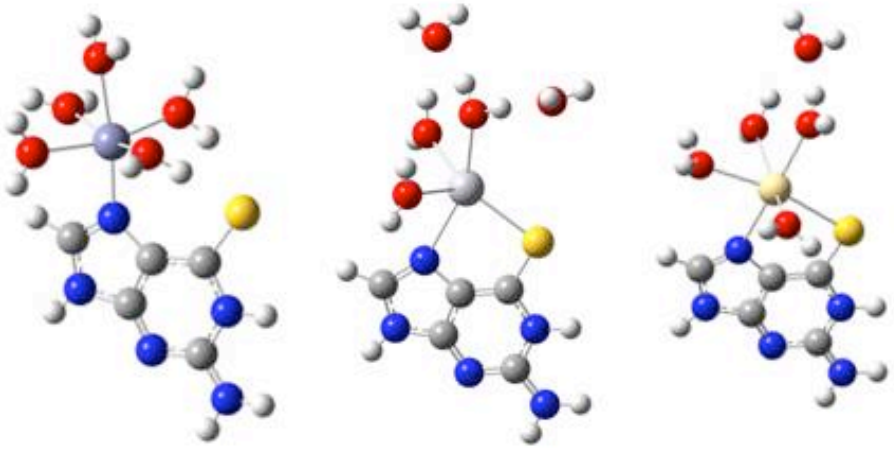


Figure 6

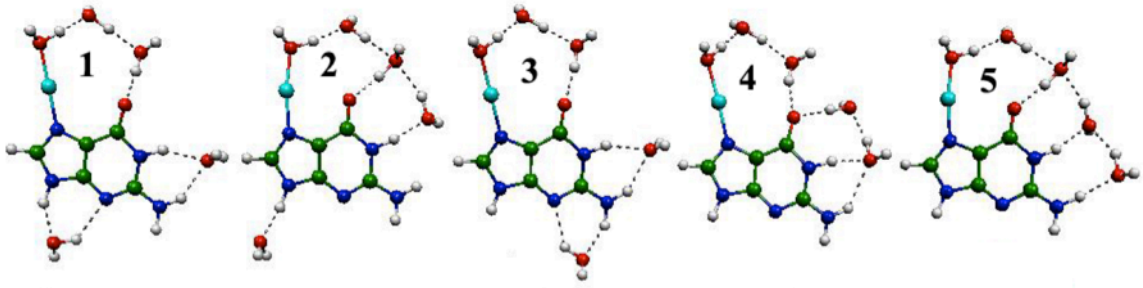


Figure 7

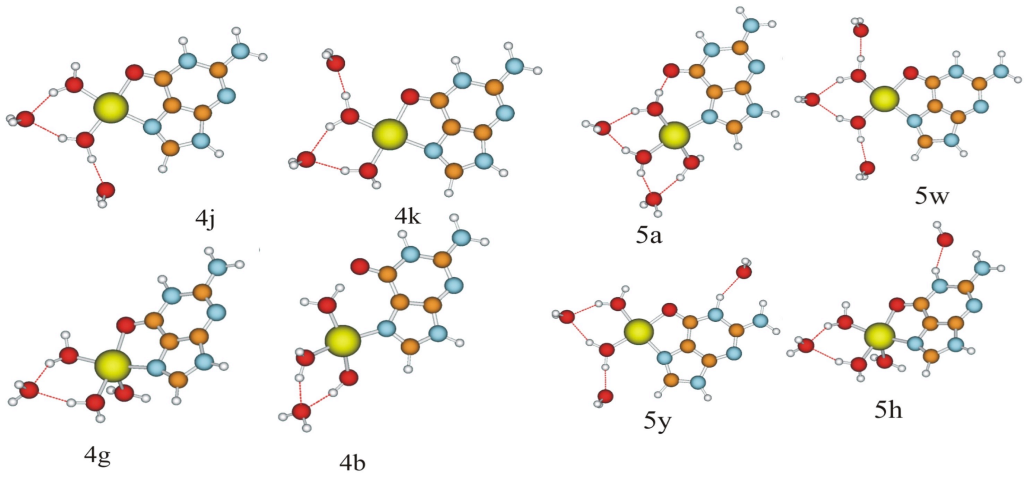
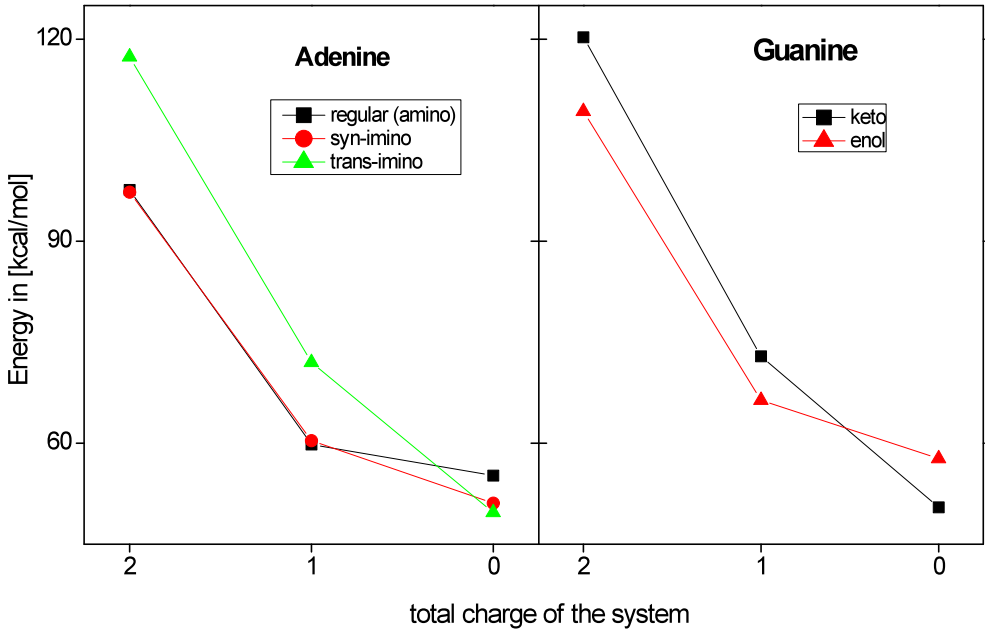


Figure 8

Figure9



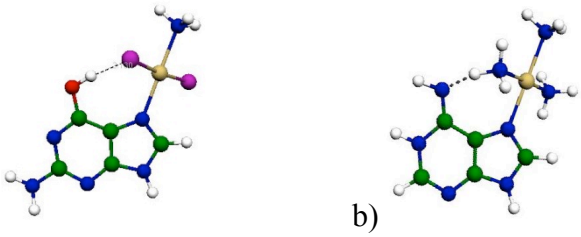


Figure10

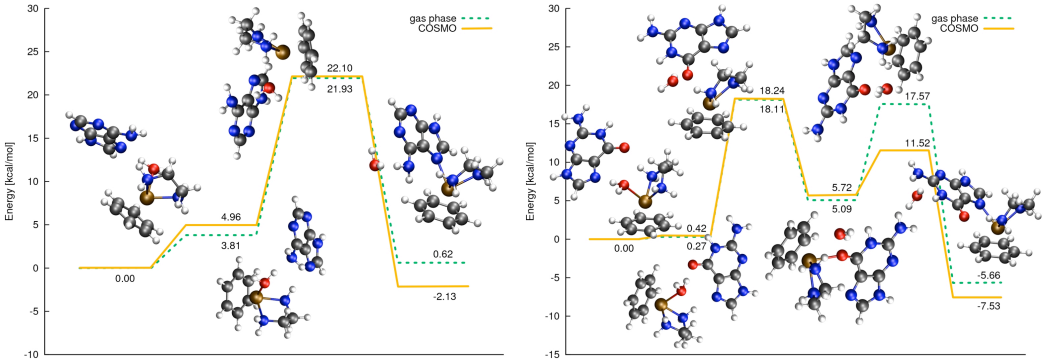


Figure 11

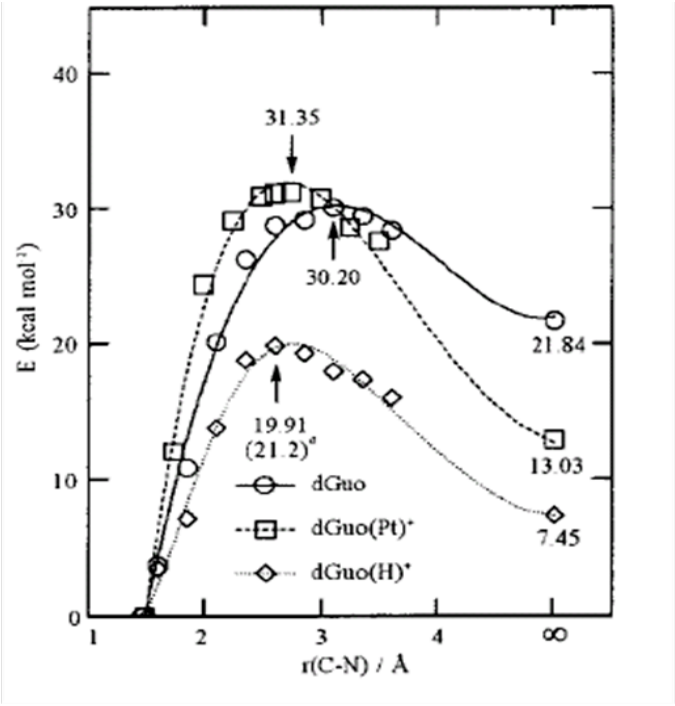


Figure12

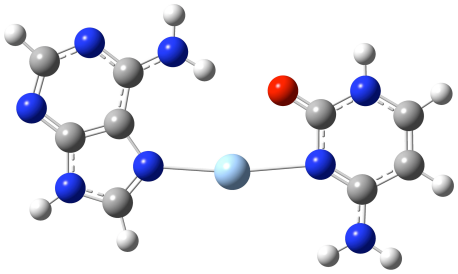


Figure 13

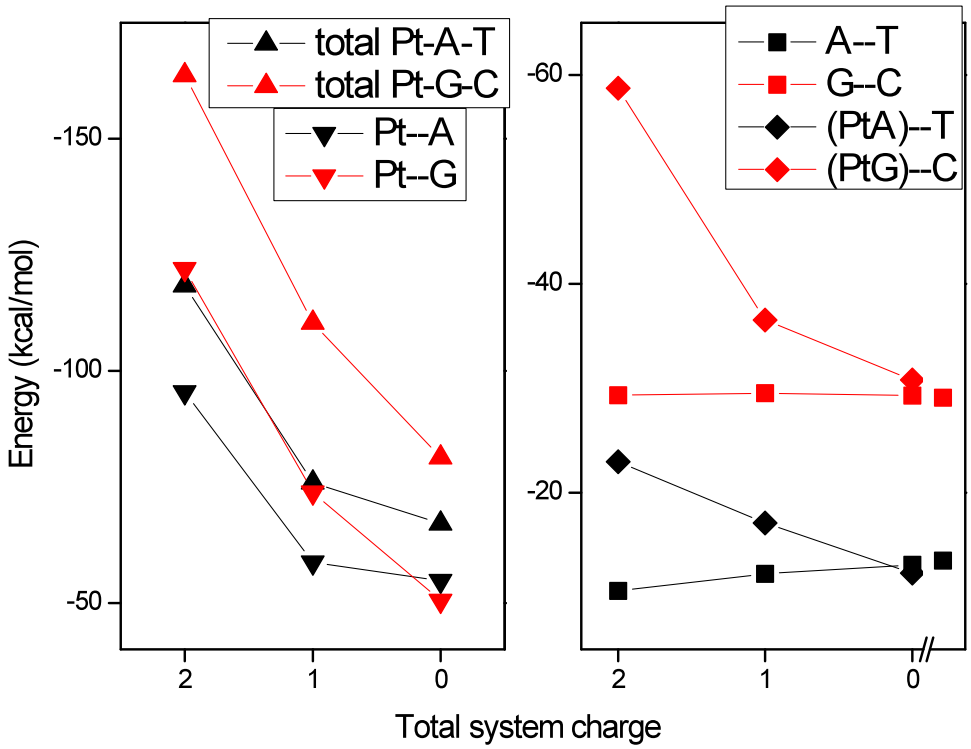


Figure 14