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ORIGINAL ARTICLE

Effect of metal ions (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and water coordination on the structure and properties of L-histidine and zwitterionic L-histidine

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Abstract Interactions between metal ions and amino acids are common both in solution and in the gas phase. The effect of metal ions and water on the structure of L-histidine is examined. The effect of metal ions (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and water on structures of His·M(H_2O)m, $m = 0.1$ complexes have been determined theoretically employing density functional theories using extended basis sets. Of the five stable complexes investigated the relative stability of the gas-phase complexes computed with DFT methods (with one exception of K^+ systems) suggest metallic complexes of the neutral L-histidine to be the most stable species. The calculations of monohydrated systems show that even one water molecule has a profound effect on the relative stability of individual complexes. Proton dissociation enthalpies and Gibbs energies of L-histidine in the presence of the metal cations Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} were also computed. Its gas-phase acidity considerably increases upon chelation. Of the Lewis acids investigated, the strongest affinity to L-histidine is exhibited by the Cu^{2+} cation. The computed Gibbs energies ΔG are negative, span a rather broad energy interval (from −130 to −1,300 kJ/mol), and upon hydration are appreciably lowered.

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Introduction

L-α-Amino acids are the basic structural units of proteins. There are only 20 naturally occurring α-amino acids varying in size, shape and hydrogen bonding capacity of their side chains, enabling proteins to carry out a myriad of biological processes. Consequently, a fundamental understanding of their acid–base properties is of paramount importance.

L-Histidine (His) is an essential amino acid that is required for the production of histamine (Voet and Voet 1995; Zhang et al. 1997). It cannot be formed from other nutrients, and must be in the diet to be available to the body. Less well known is that L-histidine is required by the body to regulate and utilize essential trace minerals such as copper, zinc, iron, manganese, and molybdenum (Oakley et al. 2004; El Khoury and Hellwig, 2009). L-Histidine is also essential in forming many metal bearing enzymes and compounds (Voet and Voet 1995; Rebek 1990; Besant and Attwood 2005) (e.g. super oxide dismutase, ferritin, the iron uptake regulation protein-FUR, cerulplasmin, hemoglobin, metallothionein, and cysteine dioxygenase). Metals such as zinc, copper, and nickel are transported by binding with L-histidine, and such binding appears essential for rapid excretion of excess metal.

Histidine, an essential amino acid, has an imidazole functional group. The imidazole makes it a common participant in enzyme-catalyzed reactions. The unprotonated imidazole is nucleophilic and can serve as a general base, while the protonated form can serve as a general acid. The

residue can also serve in stabilizing the folded structures of proteins. Metal ions like Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+} are very important in living systems (Shriver et al. 1996). There have been numerous attempts (Rode 1999; Rode et al. 1993) to prepare peptides from simpler compounds under conditions that resemble those of the primitive earth, and the presence of divalent cations (e.g. Mg^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+} etc.) can enhance such a formation of peptides (Rode 1999; Rode et al. 1993; Plankensteiner et al. 2005; Remko and Rode 2000a, Remko and Rode 2001; Remko and Rode 2004). The catalytic effect of histidine on alanine and lysine salt-induced peptide formation was examined quite recently (Fitz et al. 2008), and catalytic effects of histidine enantiomers and glycine on the formation of dileucine and dimethionine have been studied by Li et al. 2009. It was shown that histidine might have played an important role in chemical peptide evolution (Fitz et al. 2008).

Theoretical studies on the gas-phase structure of neutral histidine demonstrate that it exists in one dominant form (Huang et al. 2006). Kovačević et al. (2005) have examined the gas-phase structure of histidine and its protonated form at the G3(MP2) level of the ab initio theory. In solvent free environment one preferred conformation of histidine stabilized by means of two hydrogen bonds was found (Kovačević et al. 2005). Complexes of L-histidine with monovalent and divalent cations were experimentally investigated in several publications (Lavanant et al. 1999; Gapaev and Dunbar 2003; Wang et al. 2008). Lavanant et al. (1999) used electrospray ionization MS/MS technique for study 1:1 complexes of L-histidine with Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}. They found that either solvated or unsolvated complexes could be formed depending upon source conditions. Gapaev and Dunbar (2003) examined Na^+ affinities of gas-phase amino acids (including histidine) in Fourier-transform Ion Cyclotron Resonance ion trap experiments and DFT/B3P86 calculations. In the most recent papers, Wang et al. (2008) investigated sodium ion affinities of asparagine, glutamine, histidine, and arginine by experimental (kinetic) and computational (MP2) approaches. This study has shown that the experimental and computed Na^+ affinities are in excellent agreement with each other (Wang et al. 2008). Fei et al. (2009) carried out a systematic search of the various structures of several metal histidine complexes. They found that the tridenated structures are the most stable for Li^+, Na^+, Mg^{2+} and Ca^{2+} His·M complexes. However, for the His·K^+ system the bidenate structure was the most stable one (Fei et al. 2009).

Here, we use several methods of computational chemistry to investigate the structures of His·M (M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems. Further, we also study His·M(H_2O) (M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems hydrated by one molecule of water. These metal cations have numerous and important biochemical functions in living systems. Their hydrated complexes with histidine should serve as simplest models for more complex protein–metal systems in an aqueous environment.

Computational details

The geometries of the His·M and His·M(H_2O) (M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems (Fig. 1) have been completely optimized with the Gaussian 03 program (Frisch et al. 2003), using the density functional theory methods (Hehre et al. 1986; Kohn and Sham 1965; Baerends 2000; Bickelhaupt and Baerends 2000) (B3LYP/6-31++G(d,p) (Becke 1993a; Lee et al. 1988) and BHandHLYP/6-31++G(d,p) (Note that these are the half-and-half functionals implemented in Gaussian 03 which are not the same as the ones proposed by Becke 1993b). The formation of metal–histidine complexes can be described by reaction (A):

$$\mathrm{M(g)} + \mathrm{His(g)} \rightarrow \mathrm{His \cdot M(g)} \quad \text{(A)}$$

M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}. The gas-phase interaction enthalpy ΔH (cation binding affinity) for reaction (A) is defined by the Eqs. 1–3:

$$\Delta H = \Delta E + \Delta pV \quad (1)$$

$$\Delta H^{298} = \left[E^{298}_{\mathrm{M\cdots His}} - \left(E^{298}_{\mathrm{M}} + E^{298}_{\mathrm{His}}\right)\right] + \Delta pV \quad (2)$$

$$\Delta H^{298} = E^{298}_{\mathrm{M\cdots His}} - E^{298}_{\mathrm{M}} - E^{298}_{\mathrm{His}} - \mathrm{RT} \quad (3)$$

where $E^{298}_{\mathrm{M\cdots His}}$ the energy of the complex, E^{298}_{M} the energy of the respective cation and E^{298}_{His} energy of the ligand at $T = 298.15$ K. In equation (3) the term ΔpV is substituted by $-$RT, as one mole of gas is lost with the reaction (A). The cation basicity is defined as the increment of Gibbs energy for the reaction A at $T = 298.15$ K.

The equilibrium geometries and tautomeric equilibria of His·M, and His·M(H_2O)

(M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and corresponding zwitterionic forms were determined at the B3LYP/6-31++G(d,p) [for Cu^{2+} complexes also BHandHLYP/6-31++G(d,p)] level of theory. Open shell calculations (Cu^{2+} complexes) have been carried out using a spin-unrestricted formalism. Five divalent metal cations, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}, are considered in this work. Mg^{2+} and Ca^{2+} are alkaline-earth cations with closed-shell electronic systems and the others belong to the transition-metal cations. Zn^{2+} is a d10 ion, so its complex is a closed-shell system with a singlet ground state. Cu^{2+} is an open shell system with a d9 (2D) ground state. A more complicated case is Ni^{2+}, which may exist in

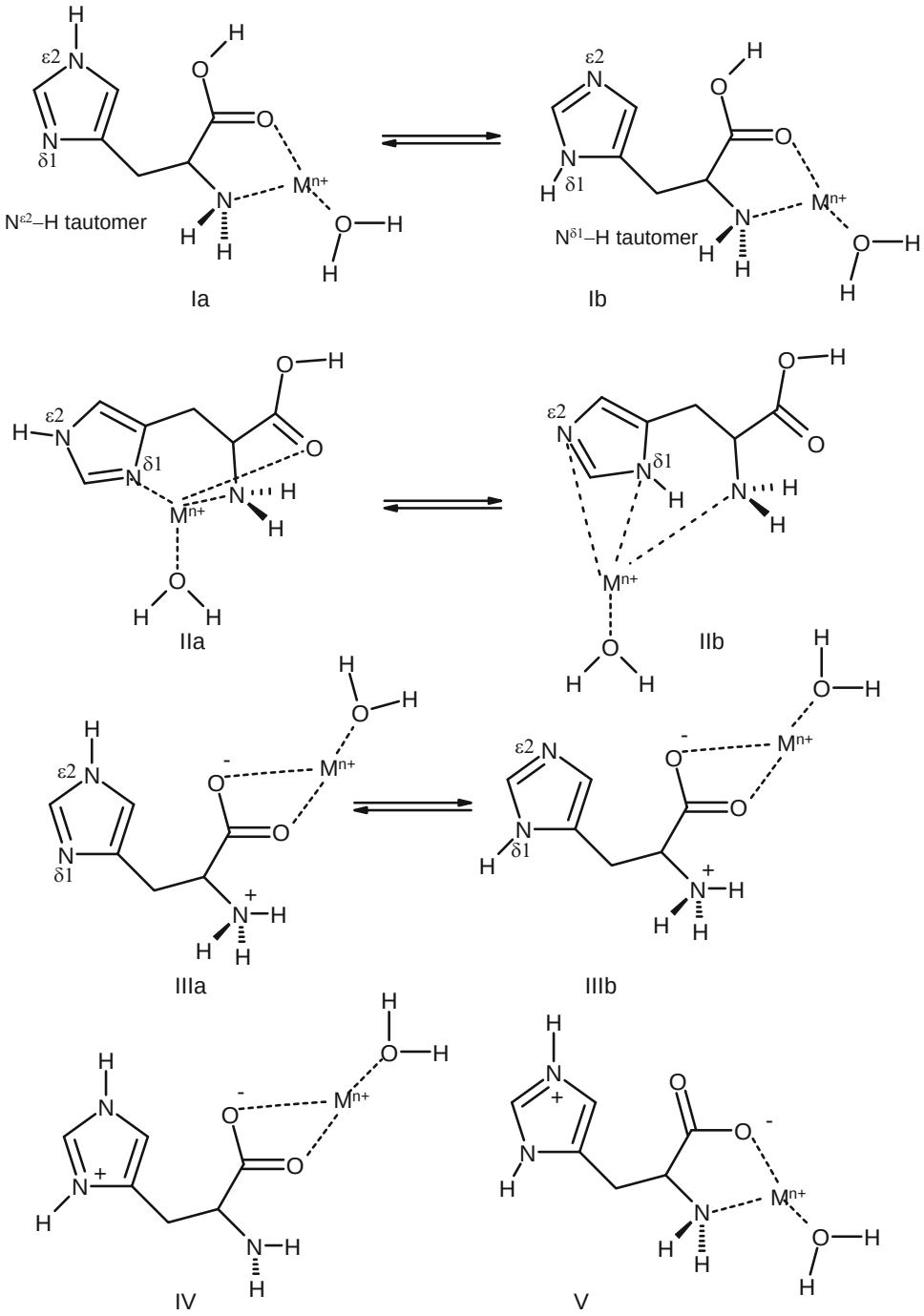

Fig. 1 The structure and atom numbering of the histidine–metal ion complexes His·M(H_2O)m, $m = 0.1$; Mn^+ = (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}). Letters **a** and **b** stand for Nε2–H and Nδ1–H tautomers, respectively

its complexes both in high-spin and low-spin states (triplet and singlet, respectively). Thus, for Ni^{2+} complexes, like in our previous paper (Remko et al. 2008), the more stable triplet state is considered.

It has been shown (Johnson et al. 1993; Oliphant and Bartlett 1994; Kapp et al. 1996) that the density functional theory method yields results, which compare favorably with the corresponding results, obtained using the high-level ab initio coupled-cluster method.

The Becke3LYP method in conjunction with a triple zeta basis set reproduces thermodynamic quantities (Alcamí et al. 1999) of the cation-Lewis base complexes within the targeted accuracy of about 10 kJ/mol. Hence, DFT can sometimes be an economic alternative to ab initio methods for studying larger metal ion–Lewis base complexes. The values of metal affinities computed using DFT are comparable to ab initio results and mostly in good agreement with the corresponding experimental data

(Alcamí et al. 1999; Remko 1997; Remko and Rode 2000b, Marino et al. 2000; Sousa et al. 2007a).

Results and discussion

Molecular structures

Structures of His·M ($M = Li^+$, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) ionic complexes were investigated. In order to determine the effect of metal cations and water on the relative stability and geometric structure of the neutral and zwitterionic species of histidine, we also studied the structures of His·M(H_2O) ($M = Li^+$, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems solvated by one molecule of water. An analysis of the harmonic vibrational frequencies of the optimized species proved that all of them are minima (zero number of imaginary frequencies).

In the absence of experimental gas-phase data of histidine structure the initial conformations of histidine in the metal–histidine complexes were deduced from theoretical investigations (Huang et al. 2006; Kovačević et al. 2005) and available crystal structures of the histidine metal complexes (Sakurai et al. 1978; Madden et al. 1972). Based on these results and the previous calculations of the histidine–alkali ion complexes (Gapaev and Dunbar 2003; Wang et al. 2008) we generated suitable starting geometries for five histidine complexes with monovalent and divalent cations (Fig. 1). From experimental investigations (Wang et al. 2008; Siegel and Martin 1982) it is known, that α-amino acids and their derivatives prefer to form chelate rings with metal cations. Structures **I**–**V** in Fig. 1 illustrate the chelated metal ion complexes of histidine and zwitterionic histidine. The imidazole moiety of histidine may act as a proton donor, a proton acceptor, and a nucleophilic reagent. Moreover, its imidazole ring is able to produce tautomerism (Nε2–H and Nδ1–H tautomers, Fig. 1).

Of the five stable complexes investigated, the relative stability of the gas-phase complexes computed with DFT methods suggest, with one exception of K^+ system, metallic complexes **IIa**, Fig. 2 of the neutral L-histidine to be the most stable species. In the most stable complex **IIa**, the lithium cation is bicoordinated to histidine with complexation to the two nitrogens. This way of complexation is also preserved in the monohydrated His·Li^+ complex. The histidine of the His·Na^+ complex has tridentate complexation using two nitrogen and carbonyl oxygen atoms, respectively. Gapaev and Dunbar (2003) also found, from their DFT/B3P86 calculations, conformer **IIa** of the His·Na^+ complex to be the most stable structure. Of the monovalent cations studied (Li^+, Na^+, and K^+) the K^+ complex prefers in gas phase the zwitterionic structure **IIIa** of the Nε2–H tautomer. Histidine coordinates K^+ in this complex by means of two oxygen atoms of the ionized carboxyl group (Fig. 2). However, the energy gap between the two most stable complexes (systems **IIa** and **IIIa**) of monovalent cations studied is low (within 8–12 kJ/mol) and is further lowered in hydrated complexes (Table 2). Aqueous solution stabilize salt bridge conformers of the His·M(H_2O) ($M = Li^+$, Na^+, K^+) complexes. In water solution zwitterionic histidine–monovalent cation complexes will exist. The global minimum salt bridge structure of the His·K^+ complex was also found recently using the B3LYP/6-311+G(2df,p)//B3LYP/6-311G* model chemistry (Fei et al. 2009). The reason for the preference the salt bridge structure for potasiated systems with basic amino acids like histidine and arginine may be, at least partly explained by their preferred binding sites (Remko et al. 2008; Fei et al. 2009). Ryzhov et al. (2000) found that Na^+ and K^+ ions are coordinated by π electrons of the aromatic substituent and carbonyl oxygen. Moreover, Na^+ has the tendency to associate with amino nitrogen, whereas K^+ interacts weakly with oxygen of the carboxylic group (Fei et al. 2009).

Bivalent cations Mg^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} behave differently. Due to the large Gibbs energy gap between the most stable complex **IIa** and the other systems (**I**, **III**, **IV**, and **V**) the most stable complex **IIa** is dominant in gas phase. The histidine in these complexes provides also tridentated complexation using two nitrogen and carbonyl oxygen atoms, respectively. The net preference of histidine for this complex is also preserved in the His·M(H_2O) ($M = Mg^{2+}$, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems solvated by one molecule of water (Tables 1, 2). An interesting situation is observed for the His·Ca^{2+} complex. In the gas phase the calcium dication may coordinate with the different forms and tautomers of histidine with practically the same probability (Tables 1, 2). Thus, the energy difference among the Ca^{2+} complexes of neutral Nε2–H tautomer and two zwitterionic forms of histidine (complexes **IIa**, **IIIa**, and **IV**) are very close, with complex **IIa** being the most stable one (Tables 1, 2). One molecule of coordinated water shifts the absolute stability towards the **IV** complex of the His·Ca^{2+} system (Table 2). However, due to the low energy barrier of about 5 kJ/mol all three species (**II**, **III**, and **IV**, respectively) may coexist.

Proton dissociation enthalpies and Gibbs energies

Histidine contains a strongly basic functional group. This high basicity increases the stability of zwitterionic histidine in the gas phase relative to other amino acids, which do not contain this basic moiety. As our calculations have shown, most of the metal cations studied coordinate neutral histidine

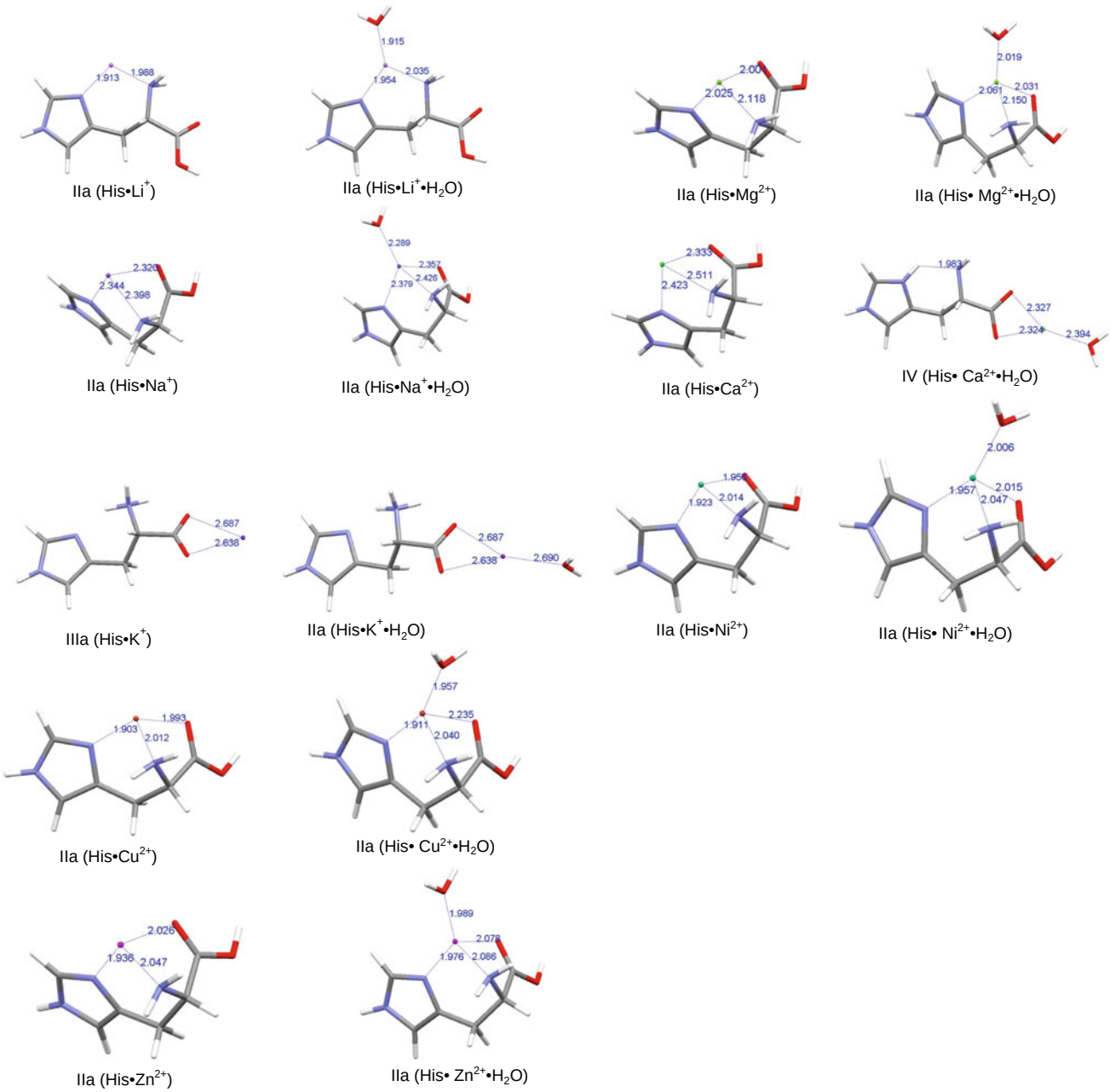

Fig. 2 Overall structures of the most stable histidine–metal ion complexes and their hydrates

in the complex **IIa**. The acidic carboxyl group of histidine in proteins may also be present in its deprotonated form. The deprotonation of protein amino acids has been investigated experimentally (Voet and Voet 1995), more recently even in the gas phase (O'Hair et al. 1992; Jones et al. 2007). Histidine is a polyprotic acid. It is often found in the active site of proteins as a dual function proton donor and acceptor. The pK_a of side-chain is about 6.0, which is close to physiological pH and therefore may exist with either a neutral side chain or protonated side-chain under physiological conditions, depending on the local environment.

However, gas-phase studies enable the exploration of the reactivities of molecules without the effect of solvent. An important parameter of the histidine gas-phase reactivity is its gas-phase acidity, ΔG_{acid}, the Gibbs energy change for the reaction His $\rightarrow$ H^+ + His^-. Thermodynamic parameters (proton dissociation enthalpies, entropies and Gibbs energies) for this reaction and deprotonation reactions of the His·M complexes of the system **IIa** combining neutral histidine with metal cations were computed in the same way as in our previous publication (Remko and Rode 2006). The accurate gas-phase acidity of histidine

Table 1 Relative stability (Gibbs energy ΔG^{298} in kJ/mol) of neutral and zwitterionic metal ion complexes **I–V** of histidine (His·M)

System	Method	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
I	B3LYP/6-31++G(d,p)	20.5 (**Ia**)	32.1 (**Ia**)	21.5 (**Ia**)	163.0 (**Ia**)	106.9 (**Ia**)	153.9 (**Ia**)	43.4 (**Ia**)	98.0 (**Ia**)
	BHandHLYP/6-31++G(d,p)							45.9 (**Ia**)	
II	B3LYP/6-31++G(d,p)	0 (**IIa**)	0 (**IIa**)	8.0 (**IIa**)	0 (**IIa**)	0 (**IIa**)	0 (**IIa**)	0 (**IIa**)	0 (**IIa**)
	BHandHLYP/6-31++G(d,p)							0 (**IIa**)	
III	B3LYP/6-31++G(d,p)	7.8 (**IIIa**)	11.5 (**IIIa**)	0 (**IIIa**)	71.0 (**IIIa**)	5.4 (**IIIa**)	163.6 (**IIIa**)	56.7 (**IIIa**)	102.5 (**IIIa**)
	BHandHLYP/6-31++G(d,p)							73.0 (**IIIa**)	
IV	B3LYP/6-31++G(d,p)	13.3	24.4	19.1	71.1	5.4	126.9	31.4	102.2
	BHandHLYP/6-31++G(d,p)							77.2	
V	B3LYP/6-31++G(d,p)	100.7	132.6	131.3	132.6	102.8	123.7	52.1	128.3
	BHandHLYP/6-31++G(d,p)							101.3	

Most stable systems are in parenthesis

Table 2 Relative stability (Gibbs energy, ΔG^{298} in kJ/mol) of hydrated neutral and zwitterionic metal ion complexes **I–V** of histidine (His·M·H_2O)

System	Method	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
I (H_2O)	B3LYP/6-31++G(d,p)	11.1 (**Ia**)	20.8 (**Ia**)	21.3 (**Ia**)	130.1 (**Ia**)	98.2 (**Ia**)	54.1 (**Ia**)	50.9 (**Ia**)	81.9 (**Ia**)
	BHandHLYP/6-31++G(d,p)							86.3 (**Ia**)	
II (H_2O)	B3LYP/6-31++G(d,p)	0 (**IIa**)	0 (**IIa**)	7.7 (**IIa**)	0 (**IIa**)	5.0 (**IIa**)	0 (**IIa**)	0 (**IIa**)	0 (**IIa**)
	BHandHLYP/6-31++G(d,p)							0 (**IIa**)	
III (H_2O)	B3LYP/6-31++G(d,p)	1.0 (**IIIa**)	3.8 (**IIIa**)	0 (**IIIa**)	42.5 (**IIIa**)	4.6 (**IIIa**)	230.1 (**IIIb**)	43.4 (**IIIa**)	58.6 (**IIIa**)
	BHandHLYP/6-31++G(d,p)							100.7 (**IIIa**)	
IV (H_2O)	B3LYP/6-31++G(d,p)	11.8	21.6	22.0	42.5	0	95.2	2.0	58.7
	BHandHLYP/6-31++G(d,p)							40.8	
V (H_2O)	B3LYP/6-31++G(d,p)	102.9	122.1	122.1	112.7	106.8	98.8	34.9	100.8
	BHandHLYP/6-31++G(d,p)							76.7	

Most stable systems are in parenthesis

was recently determined using an electrospray ionization-quadrupole ion trap instrument (Jones et al. 2007). However, the deprotonation reaction of this amino acid in the presence of metal cations has not been investigated so far, either experimentally or theoretically. Table 3 contains, besides the experimental gas-phase acidity (enthalpy) of parent histidine also the proton dissociation enthalpies, entropies, and Gibbs energies of histidine in the presence of the metal cations Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}, respectively. The gas-phase acidity of neutral histidine calculated by us is higher than those experimental values reported in the literature (Table 3). The discrepancy may partly arise from the accuracy of the theoretical method applied and also from the way of the calculation of deprotonation energy. With respect to the existence of several stable rotational species of neutral and zwitterionic L-histidine (Fig. 1), the enthalpy of deprotonation may be computed between two arbitrary species, but only the differences between the most stable species can have physical meaning and can be compared with experiments. Theoretical values of enthalpy and Gibbs energy of deprotonation shown in Table 3 were computed using the most stable species of histidine and its anion. This table also contains deprotonation energy for zwitterionic histidine, which was computed to be slightly greater. Thus in the gas-phase the deprotonation of neutral histidine is energetically more favorable reaction (Table 3).

In the presence of metallic cations, the acidity of histidine increases in the order: $Li^+ \leq K^+ < Na^+ < Ca^{2+} < Mg^{2+} < Zn^{2+} < Cu^{2+} < Ni^{2+}$. Histidine coordinated by monovalent metal cations is by about 200 kJ/mol more acidic than the non-coordinated histidine. Divalent cations exhibit, as expected, a considerably larger effect on the acidity of histidine. Thus divalent metal ions cause histidine to deprotonate.

Gas-phase interaction enthalpies, entropies and Gibbs energies of the His·M ($M = Li^+$, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) complexes

The calculated interaction enthalpies, entropies and Gibbs energies of the histidine–metal ion complexes studied at the

Table 3 Computed gas-phase proton dissociation enthalpies and Gibbs energies in the presence of Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} calculated at the B3LYP/6-31++G(d,p) level

Species	ΔH^{298} (kJ/mol)	ΔS^{298} (J/K mol)	ΔG^{298} (kJ/mol)
His	1,427.5 (exp. 1,385 ± 13[a]; 1,375 ± 8[b])	126.0	1,389.9
His^+	1,436.8	119.8	1,401.2
His Li^+	1,100.2	101.2	1,069.8
His Na^+	1,071.8	107.3	1,040.0
His K^+	1,095.6	110.1	1,063.2
His Mg^{2+}	635.2	109.3	602.4
His Ca^{2+}	699.1	108.9	666.5
His Ni^{2+}	597.0	109.4	564.4
His Cu^{2+} (B3LYP)	585.9	111.1	552.8
His Cu^{2+} (BHandHLYP)	612.4	96.9	583.5
His Zn^{2+}	613.0	110.7	580.2

[a] O'Hair et al. 1992

[b] Jones et al. 2007

Table 4 B3LYP/6-31++G(d,p) calculated gas-phase enthalpies, ΔH, Entropies, ΔS, and Gibbs energies, ΔG, of the ion–histidine systems

System	Complex	ΔH^{298} (kJ/mol)	ΔS^{298} (J/mol K)	ΔG^{298} (kJ/mol)
IIa	His···Li+	−304.1	−106.5	−272.4
IIa	His···Li+ (H_2O)	−248.9	−134.4	−208.9
IIa	His···Na+	−241.6	−119.8	−205.9
IIa	His···Na+ (H_2O)	−201.5	−133.1	−161.8
IIIa	His···K+	−164.9	−106.9	−133.1
IIIa	His···K+ (H_2O)	−139.4	−113.6	−105.1
IIa	His···Mg^{2+}	−977.5	−148.3	−933.3
IIa	His···Mg^{2+} (H_2O)	−825.4	−176.4	−772.4
IIa	His···Ca^{2+}	−637.8	−137.9	−596.9
IV	His···Ca^{2+} (H_2O)	−558.2	−108.7	−525.6
IIa	His···Ni^{2+}	−1,256.4	−155.1	−1,209.8
IIa	His···Ni^{2+} (H_2O)	−1,196.0	−177.7	−1,143.1
IIa	His···Cu^{2+}	−1,304.9	−150.4	−1,260.1
IIa	His···Cu^{2+} (H_2O)	−976.3	−184.9	−921.1
IIa	His···Cu^{2+} BHandHLYP	−1,219.3	−157.8	−1,178.1
IIa	His···Cu^{2+} (H_2O) BHandHLYP	−976.8	−207.0	−915.4
IIa	His···Zn^{2+}	−1,200.2	−151.2	−1,154.9
IIa	His···Zn^{2+} (H_2O)	−949.6	−183.6	−894.9

Becke3LYP level of the density functional theory are given in Table 4. No corrections for basis set superposition errors (BSSE) were incorporated into the results since B3LYP calculations of the metal cation affinities of organic and biological molecules with the larger basis set 6-311++G(d,p) changed the interaction energy only slightly (Hoyau et al. 1999; Remko and von der Lieth 2006). This table also presents the available interaction enthalpies and Gibbs energies for selected copper complexes computed at the BHandHLYP level of theory. The interaction energies were computed as the difference between the most stable complex species (Tables 1, 2) and the isolated components. The enthalpies and Gibbs energies of all complexes vary in the same way, and the entropic effect does not change the relative stability of individual complexes. In real molecular complexes the tendency to associate is described by Gibbs energies. It is, therefore, important to know the role of entropy in the processes studied. Table 4 also lists the differences in S^o values of the complexes and the isolated species. The formation of a single cationic metal–ligand complex from a pair of species necessarily involves a loss of entropy. In the case of the metallic complexes of histidine, the entropy change due to complexation is some −100 to −180 J/mol K and calculated enthalpies and Gibbs energies follow the same trend in the acidity of the metal cations studied. Larger entropy changes are exhibited upon coordination of bivalent metal cations. The computed Gibbs energies ΔG^{298} are negative and span a rather broad energy interval (from −130 to −1,300 kJ/mol). Histidine involves harder (O) and softer (N) basic center. The nitrogen Nδ1 atom of the imidazole moiety of histidine (Fig. 1) is the most favorable site for protonation (Kovačević et al. 2005).

The selectivity of the base histidine towards cationic metal Lewis acids may be analyzed on the basis of hardness, charge, and ion size of cations studied. The preferred ligand atoms can also classify the coordination of individual metal cations. It is well known that certain metal ions (hard Lewis acids) exhibit higher affinity for oxygen (O)-donor ligands, whereas metal ions acting as soft Lewis acids prefer to co-ordinate to nitrogen donors (Remko 1997; Remko and Rode 2000b, Marino et al. 2000; Sousa et al. 2007a; Fraústo da Silva and Williams 1991). Thus, the harder the Lewis acid, the stronger is the preference for O compared with N. For histidine complexes of the alkali metals the following order of stability was found: $Li^+ > Na^+ > K^+$. The same stability order one would expect based on their ionic radii (Fraústo da Silva and Williams 1991; Harvey and Porter 1963) [K^+ (1.33 Å), Na^+ (0.95 Å), Li^+ (0.6 Å)]. It is interesting to note that two of the His·M (M = Li^+, Na^+ and K^+) complexes involve bidentate binding except the His·Na^+ complex, which is tridentate (Fig. 2). The alkali metal cations have s^0 electron configurations and thus spherically symmetric electron densities. The alkali metal cation–histidine bond lengths are mainly determined by the size of the cations, namely the larger the radius, the longer the bond distances and the weaker the interaction (Remko and Rode 2000b, 2006) (Fig. 2). According to Jockusch et al. (1999) and Cerda and Wesdemiotis (2000) the preference of the K^+ cation to form a salt bridge arises from its lower tendency for solvation, a result of its lower charge densities and higher polarizabilities due to its larger size. The substantially larger K^+ ion can interact sterically more effectively with the acidic part of histidine, thereby optimizing anion-cation attractive forces and, hence, salt bridges.

Bivalent cations, because of their higher positive charge of +2, are always bonded substantially more strongly to histidine than lithium, sodium, or potassium cations (Table 4). The stability of the alkaline-earth metal Mg^{2+} and Ca^{2+} complexes of histidine also obeys the selection by ion size [Ca^{2+} (1.0 Å), Mg^{2+} (0.65 Å)] (magnesium complex of histidine is by about 400 kJ/mol more stable than calcium complex). A third category of species is the histidine complexes with Ni^{2+}, Cu^{2+} and Zn^{2+} ions. The Gibbs interaction energies show a decreasing binding affinity in the order $Cu^{2+} > Ni^{2+} > Zn^{2+}$. According to the highest interaction energies (Table 4) the transition metal Cu^{2+} is most effectively recognized by the basic center of histidine. It is interesting that the M···O and M···N distances are varying from nickel to zinc within the relatively short interval of 1.90–2.0 Å (Fig. 2), and they do not correlate with the ionic radii (Fraústo da Silva and Williams 1991; Harvey and Porter 1963) for Ni^{2+} (0.72 Å), Cu^{2+} (0.69 Å), and Zn^{2+} (0.65 Å), respectively. In the complexation of transition metal cations Ni^{2+}, Cu^{2+}, and Zn^{2+}, the charge transfer is important (Marino et al. 2000). The largest metal dissociation Gibbs energy was computed for the system His·Cu^{2+} (B3LYP method, Table 4). The highest interaction energy of the Cu^{2+} histidine complexes may be partially explained by the different electronic character of the Cu^{2+} cation (open shell system). The different internal polarizability of the whole Cu^{2+} complexes is presumably one of the main reasons for this difference. It was shown (Poater et al. 2004; Norberg et al. 2005) that functionals such as BHLYP with larger percentages of exact exchange (50%) than the commonly used (Rimola et al. 2007) B3LYP (20%) for open-shell complexes compare better to the highly correlated ab initio CCSD(T) method, the open-shell His·Cu^{2+} complexes were also investigated by means of the half-and-half functional BHandHLYP implemented in the G03 computer code. BHandHLYP relative Gibbs energies for His·Cu^{2+} complex are about 80 kJ/mol larger than with B3LYP (Table 4).

The discrepancy in the results of the different DFT methods used for the prediction of the relative stability of open shell systems containing Cu^{2+} cations may be explained by the shortcomings of the B3LYP method to correctly describe the delocalized nature of the Cu^{2+} complexes (Sousa et al. 2007b).

Attachment of Cu^+ and Cu^{2+} to histidine in the gas phase has been recently investigated at the B3LYP and BHLYP levels of theory (Rimola et al. 2006). Both B3LYP and BHLYP, in agreement with our calculations, provided structure **IIa** (Fig. 2) of the His·Cu^{2+} to be the ground-state complex (Rimola et al. 2006). Their calculated binding enthalpies (−1,201.8 kJ/mol) and Gibbs energies (−1,159.1 kJ/mol) using the BHLYP method correspond well to the same system computed by us using the BHandHLYP method (Table 4). Attachment of sodium cation to histidine in the gas phase has been investigated experimentally (Gapaev and Dunbar 2003; Wang et al. 2008). Depending on the experimental method used the sodium ion affinities are found within a relatively large energy interval of −185 to −228 kJ/mol. A comparison of the B3LYP computed enthalpy (−241.6 kJ/mol) for the binding of sodium cation to histidine and available experimental values shows that DFT and experimental data agree well. Calculations by Wang et al. (2008) delivered histidine sodium affinity values of −235 and −232 kJ/mol [MP2/6-311+G(2d,2p)//MP2/6-31G(d) and MP2/6-311+G(2d,2p)//HF/6-31G(d) methods] and are in good agreement with our calculations using the B3LYP/6-31++G(d,p) method (Table 4). The observed discrepancies between theoretically computed and available experimental metal affinities of histidine could be partly due to some uncertainty in the interpretation of experimental data (Wang et al. 2008; Kish et al. 2003) which introduces larger errors in the absolute metal ion affinities.

Water molecules are directly involved in noncovalent interactions that play a central role in determining the structure and properties of biomacromolecules in living systems. Jockusch et al. (2001) conducted theoretical modeling of the stepwise hydration of valine-alkali metal ion complexes. The thermochemistry of stepwise hydration of several potasiated and sodiated amino acids was studied also experimentally (Wincel 2007a; b). It was shown that the first water molecule binds directly to the Na^+ or K^+ ions of sodiated and potassiated amino acids (Jockusch et al. 2001; Remko and Rode 2006). In order to evaluate the effect of metal hydration on the dissociation enthalpy and Gibbs energy of the metallic histidine complexes investigated in Table 4 the corresponding dissociation energies of the His·M(H_2O) systems are also presented. The interaction enthalpies and Gibbs energies were computed as the energy differences between the most stable species (Tables 1, 2). Monohydration causes a considerable lowering of the metal interaction Gibbs energies. However, the destabilization effect of water coordination is not regular for all metallic systems investigated. In the His·M(H_2O) (M = Li^+, Na^+, K^+) complexes the following order of stability was found: $Li^+ > Na^+ > K^+$, which well correlates with the Gibbs interaction energies of the non-solvated complexes (Table 4). The situation is different with the hydration of the divalent metallic complexes of histidine. The hydration of the His·Ca^{2+} complex results in protonation of the histidine, which can induce spontaneous proton-transfer reaction from the COOH group of the backbone to the imidazole sidechain, and an additional stabilization of the hydrated structure by means of an intramolecular hydrogen bond of the N–H···NH_2 type (Fig. 2). This structural rearrangement of the complex His·Ca^{2+} (H_2O) provides a lower destabilization of the His···Ca^{2+} bond (by 71 kJ/mol) in comparison to the His···Mg^{2+} bond (161 kJ/mol) of the His·Mg^{2+} (H_2O) system (Table 4).

A third category of species are the histidine complexes with Ni^{2+}, Cu^{2+} and Zn^{2+} ions. The Gibbs interaction energies (B3LYP method) of the monohydrated complexes show a decreasing binding affinity now in the order $Ni^{2+} > Cu^{2+} > Zn^{2+}$. The His···$Ni^{2+}$ bond of the high-spin nickel complexes is upon hydration considerably less destabilized (by about 67 kJ/mol) compared to similar His···Cu^{2+} and His···Zn^{2+} bonds, where the Gibbs energy is lowered by about 250–260 kJ/mol (Table 4). Corresponding values for Gibbs energies are by about 20–25% lower than values for the His·M (M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) complexes. Thus hydration of the metal ions, in which water directly solvates the metal ion and no additional interactions are formed appreciably weakens the interaction between histidine and metallic cations. This weakening of the metal-coordinated bonds M···O and M···N in the His· Ca^{2+} (H_2O) complex leads to the preferential stabilization of the salt bridge (zwitterionic) structure.

Summary and conclusions

This theoretical study was set out to determine stable configurations and the interaction enthalpies and Gibbs energies for eight complexes between histidine and monovalent, and bivalent cations. Using theoretical methods the following conclusions can be drawn:

Our model calculations of the molecular structure and relative stability of the charge-solvated and salt bridge His·M (M = Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) systems indicate that, with the single exception of the His·K^+ systems, metal complexes (system **IIa**) of neutral L-histidine are the most stable species.

The DFT calculations of monohydrated systems **I**–**V** indicate that even one water molecule has a profound effect on the relative stability of individual complexes. For the histidine complexes with K^+, the thermodynamically stable species are, in contrast to the complexes with other cations, zwitterionic ones. While the relative stability of the Mg^{2+} complexes does not change upon hydration, the hydration of the His·Ca^{2+} species results in a net preference for the zwitterionic complex **IV**. The monohydration does not change the relative stability of the transition metal complexes His·M (M = Ni^{2+}, Cu^{2+} and Zn^{2+}).

The acidity of histidine in the presence of metal cations considerably increases.

Among the Lewis acids investigated, the strongest affinity to histidine is exhibited by the Cu^{2+} cation. The computed Gibbs energies ΔG^{298} are negative, span a rather broad energy interval (from −130 to −1,300 kJ/mol), and are appreciably lowered upon hydration.

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Note added in proof Following initial submission several papers were published about structure and properties of histidine and its complexes with metal cations (Tavasoli and Fattahi 2009a, b; Rai et al. 2009; Dunbar et al. 2009). Our results for metal–histidine complexes are in agreement with conclusions of these publications.

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