# Effect of Metal Ions (Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) and Water Coordination on the Structure and Properties of L-Arginine and Zwitterionic L-Arginine

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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-arginine is examined. The effects of metal ions (Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) and water on structures of Arg•M(H₂O)$_m$, $m = 0$, 1 complexes have been determined theoretically by employing the density functional theories (DFT) and using extended basis sets. Of the three stable complexes investigated, the relative stability of the gas-phase complexes computed with DFT methods (with the exception of K⁺ systems) suggests metallic complexes of the neutral L-arginine 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 arginine in the presence of the metal cations Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺ were also computed. Its gas-phase acidity considerably increases upon chelation. Of the Lewis acids investigated, the strongest affinity to arginine is exhibited by the Cu²⁺ cation. The computed Gibbs energies $\Delta G°$ are negative, span a rather broad energy interval (from −150 to −1500 kJ/mol), and are appreciably lowered upon hydration.

## 1. Introduction

L-α-Aminoacids 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-arginine (Arg) is an amino acid present in the proteins of all life forms. It is considered a semiessential amino acid, because although it is normally synthesized in sufficient amounts by the body, supplementation is sometimes required[1] (for example, because of inborn errors of urea synthesis, protein malnutrition, excess ammonia production, excessive lysine intake, burns, infection, peritoneal dialysis, rapid growth, or sepsis). L-Arginine is the main source for the generation of nitric oxide (NO) via NO synthase,[2] which causes blood vessel relaxation (vasodilation). Arginine has a guanidine group and is one of the strongest naturally occurring amino acids. Arginine-rich proteins always seem to exist in functional symbiosis with tightly bound but exchangeable counterions. The counterion-scavenging property of the guanidinium side chain of arginine is frequently used for recognition and formation of, for example, strong drug−receptor complexes.[3] Metal ions like Li⁺, Na⁺, K⁺, Mg²⁺, and Ca²⁺ are very important in living systems.[4] There have been numerous attempts[5,6] to prepare peptides from simpler compounds under conditions that resemble those of the primitive earth, and the presence of divalent cations (e.g., Mg²⁺, Cu²⁺, Ni²⁺, Zn²⁺, etc.) can enhance such a formation of peptides.[5–9]

Experimental spectroscopic studies on gas phase arginine demonstrate that it exists in a neutral form.[10] Other experiments suggest that protonated dimers of arginine are bound by a salt-bridge in the gas phase, and the most stable form of arginine itself is a zwitterion.[11] Calculations predict that in the absence of other stabilizing forces, the arginine zwitterion is not a stable species in the gas phase.[12–14] Melo et al.[15] have investigated guanidinium−carboxylate interaction at the HF and MP2 levels of the ab initio theory. In solvent-free environment, the neutral form of the complex has been found to be more stable than the zwitterionic (ionized) one. Recent DFT calculations indicate that arginine prefers the zwitterionic form when clustered together with at least one other arginine, even in the absence of solvent or net charge.[16] The zwitterionic form of arginine can also be stabilized by the presence of counterions and/or water molecules.[17,18] In order to investigate the nature of the interaction between metal cations and arginine in the gas phase, a number of theoretical studies have been conducted.[11–20] The effect of water molecules on the stability of the zwitterionic structure of glycine, valine, and tryptophan was also investigated.[21–26] In these works, the relative affinities of different modes of binding of a given metal cation were studied by using various levels of ab initio SCF and of DFT. In the most recent papers, Williams et al.[18,20,27] investigated the effect of water on the stability of the zwitterionic and nonzwitterionic arginine-Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺ and Ag⁺ complexes using infrared spectroscopy and computational chemistry. These calculations have shown that solvating lithiated arginine with a single water molecule preferentially stabilizes the zwitterionic form of this ion.[20]

Here, we use several methods of computational chemistry to investigate the structures of Arg•M (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) systems. Furthermore, we also study Arg•M(H₂O) (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) systems hydrated by one molecule of water. These metal cations have numerous and important biochemical functions in living systems. Their hydrated complexes with

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M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺ and Zn²⁺
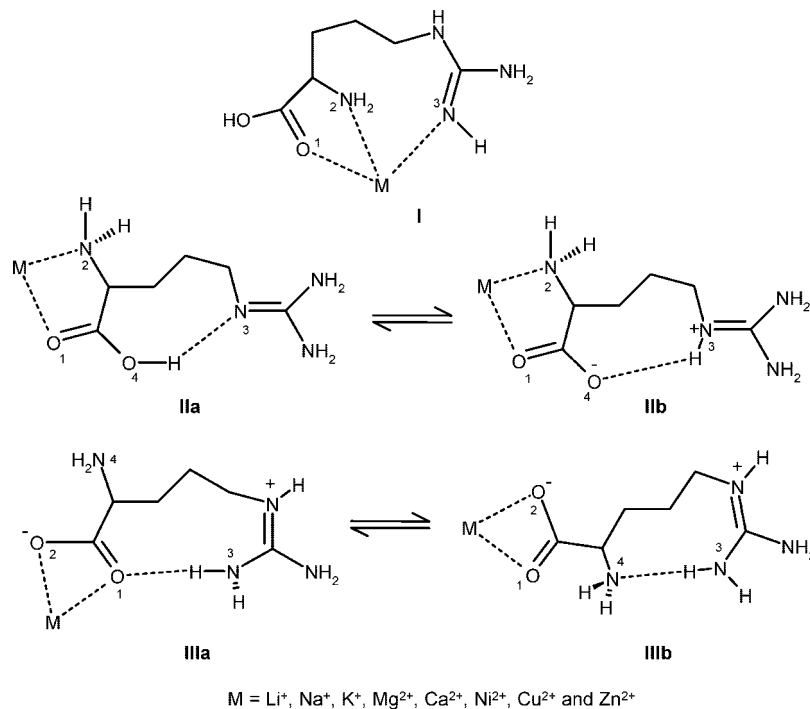
**Figure 1.** Structure and atom numbering of the arginine−metal ion complexes.

arginine should serve as simplest models for more complex protein−metal systems in an aqueous environment.

## 2. Computational Details

The geometries of the Arg•M and Arg•M(H₂O) (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) systems (Figure 1) have been completely optimized with the Gaussian 03 program,[28] by using the DFT methods[29–32] (B3LYP/6-31++G(d,p)[33–35] and BHandHLYP/6-31++G(d,p)[36]). For Ni, Cu, and Zn, we used the 6-31++G(d,p) Wachters−Hay[37,38] all electron basis set. The formation of metal−arginine complexes can be described by reaction A:

(A)
$$M(g) + Arg(g) \rightarrow Arg\bullet M(g)$$
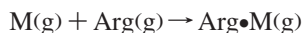
M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺. The gas-phase interaction enthalpy $\Delta H$ for reaction A is defined by eqs 1–3:

$$\Delta H = \Delta E + \Delta pV \tag{1}$$

$$\Delta H^{298} = \left[E_{M\cdots Arg}^{298} - \left(E_M^{298} + E_{Arg}^{298}\right)\right] + \Delta pV \tag{2}$$

$$\Delta H^{298} = E_{M\cdots Arg}^{298} - E_M^{298} - E_{Arg}^{298} - RT \tag{3}$$

where $E_{M\cdots Arg}^{298}$ is the energy of the complex, $E_M^{298}$ is the energy of the respective cation, and $E_{Arg}^{298}$ is the energy of the ligand at $T = 298.15$ K. In eq 3, the term $\Delta pV$ is substituted by $-RT$, because one mole of gas is lost with reaction A.

The equilibrium geometry and tautomeric equilibria of Arg•M and Arg•M(H₂O) (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) and corresponding zwitterionic forms were determined at the B3LYP/6-31++G(d,p) (for Cu²⁺ complexes, also BHandHLYP/6-31++G(d,p)) level of theory. Open-shell calculations (Cu²⁺ complexes) have been carried out by using a spin-unrestricted formalism. Five divalent metal cations, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺, are considered in this work. Mg²⁺ and Ca²⁺ are alkaline-earth cations with closed-shell electronic systems, and the others belong to the transition-metal cations.

Zn²⁺ is a d¹⁰ ion; therefore, its complex is a closed-shell system with a singlet ground state. Cu²⁺ is an open-shell system with a d⁹ (²D) ground state. A more complicated case is Ni²⁺, which may exist in its complexes both in high-spin and low-spin states (triplet and singlet, respectively). Thus, for Ni²⁺ complexes, the singlet and triplet states are considered.

## 3. Results and Discussion

**3.1. Molecular Structures.** Structures of Arg•M (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) 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 arginine, we also studied the structures of Arg•M(H₂O) (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) systems solvated by one molecule of water. The Cartesian coordinates (in Angstroms) of the fully optimized most stable species of the Arg•M and Arg•M(H₂O) (M = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ni²⁺, Cu²⁺, and Zn²⁺) systems are given in Table A of the Supporting Information. The numbering scheme is presented in Figure 1. An analysis of the harmonic vibrational frequencies of the optimized species proved that all of them are minima (zero number of imaginary frequencies). The conformational structure of isolated arginine has been investigated in several publications.[10–14] Simons et al.[14] carried out the so far most sophisticated calculations of the free energies of eight low-lying structures of arginine in the gas phase. Their high-level ab initio CCSD(T) method was able to determine the relative energies of these eight arginine structures within 2 kJ/mol. By exploring the Becke3LYP DFT optimizations, Ling et al. presented a large number of new structures of arginine that are more stable than any of those previously published.[39] On the basis of these results and the previous calculations of the arginine−alkali ion complexes,[17–19,40,41] we generated suitable starting geometries for three arginine complexes with monovalent and divalent cations (Figure 1). From experimental investigations,[42–44] it is known that α-amino acids and their derivatives prefer to form chelate

rings with metal cations. Structures **I**, **II**, and **III**, Figure 1, illustrate the metal ion chelate complexes of arginine and zwitterionic arginine. In structure **I**, metal cations are stabilized through interactions with the N-terminus and the oxygen atom of the C-terminal carboxylate of arginine. In structure **II**, arginine is present in the stable imine tautomer. Both experimental and theoretical investigations[45,46] have shown that in monosubstituted guanidines, the guanidine fragment in different physical states coexists in two tautomeric forms (amine and imine tautomers). Complex **II** combines the imine tautomer of neutral arginine with the metal cations studied. In this complex, the cation binds to both the N2 and the O1 sites of arginine. The intramolecular hydrogen bond of the O—H···N= type may stabilize the complex of the neutral imine form of arginine with the metal cations studied (system **IIa**, Figure 1). Intramolecular proton transfer enables the formation of the metal cation—zwitterionic arginine complexes **IIb** stabilized via O⁻···⁺HN interaction. The DFT optimization calculations led to the salt-bridge complexes **IIb** of zwitterionic arginine. In the salt-bridge structures **IIIa** and **IIIb**, the most stable structure for a metal cation and arginine is the one where the cation binds to both oxygen ends of the zwitterionic arginine. Structure **IIIa** corresponds to the fully optimized complexes of the alkali metal ions $Li^+$, $Na^+$, and $K^+$. These species are further stabilized via an intramolecular hydrogen bond O⁻···⁺HN= of the guanidinium $NH_2$ group and the negatively charged carboxyl moiety (Figure 1). For arginine complexes of bivalent cations ($Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$), the complexes **IIIb** result from geometry optimizations as the most stable species. Those species are further stabilized via an intramolecular hydrogen bond formed between the guanidinium $NH_2$ group and the $C_\alpha$-$NH_2$ moiety (Figure 1). The C—N and C=N bonds of the guanidine fragment in the complexes **IIb**, **IIIa**, and **IIIb** are almost the same long (about 1.34 Å). Apparently, a mesomeric effect is responsible for such an equalization of single and double bonds in the guanidinium moiety.

In order to evaluate the effect of water on the reactivity of the complexes studied, we also examined monohydrated complexes of arginine and its zwitterionic form. For an illustration of the geometric structure of these complexes, the optimized coordinated and hydrated systems (represented by the lithium species) are shown in Figure 2. Recently Bush et al. investigated singly hydrated clusters of Arg•$Li^+$ and Arg•$Na^+$ by using infrared spectroscopy and computational chemistry.[20] They showed that the interaction of these systems with a single water molecule preferentially stabilizes the zwitterionic forms. The monohydration of the Arg•M (M = $Li^+$, $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$) complexes (systems **I**–**III**, Figure 1) was modeled by the insertion of the water molecules at the proper coordination sites of monovalent and bivalent cations (Figure 2).

Selected structural parameters of the fully optimized metal complexes and their monohydrated analogues of system **I** are given in Table 1. In this complex, metal ions approach both the carboxyl and the guanidine group of neutral arginine. If M = $Li^+$, Williams and co-workers[19] showed that the lowest-energy complexes Arg•M contain canonical arginine (charge solvation) and zwitterionic arginine (salt bridge) if M = $Rb^+$, $K^+$, or $Cs^+$. The cations studied in system **I** optimized complexes always exhibit a tridentate coordination (Table 1). The arginine in those complexes always surrounds the metal cations and solvates the charge through multiple interactions with the carbonyl oxygen, the nitrogen of the $C_\alpha$—$NH_2$ moiety, and a terminal nitrogen atom of the guanidine part. The largest
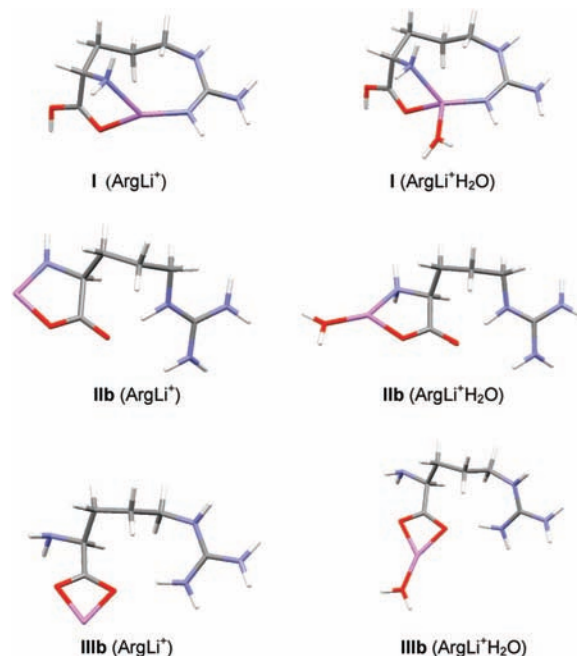


**Figure 2.** Overall structures of the B3LYP/6-31++G(d,p) optimized complexes of lithiated arginine and their hydrates.

equilibrium distances M···O and M···N were found for the coordination of the potassium cation (about 2.6−3.0 Å). On the other hand, transition metal cations coordinate to arginine at appreciably shorter M···O and M···N distances of about 1.9 Å. The chelate rings of system **I** arginine complexes are nonplanar. Larger fluctuations in the geometry upon metal cation coordination were observed for the coordinated guanidine group of the side chain and in the dihedral angle $\Phi$[C···O(1)···M···N(3)].

The interaction of inorganic cations with the anionic carboxylate group of zwitterionic arginine represents another category of complexes. In system **II**, Figure 1, metal cations are coordinated via both M···O and M···N bonds. The M···O(1) bonds are always shorter by about 0.1−0.2 Å than the analogous M···N(2) (M = $Li^+$, $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$) distances, indicating that in system **II**, metal cations form stronger bonds to the carbonyl oxygen atom of arginine (Table 2). The complexes are stabilized by means of almost linear intramolecular O(4)···H···N(3) hydrogen bonds. The five-membered chelate ring is practically planar in all eight complexes with a dihedral angle $\Phi$[C−O(1)···M···N(2)] of about 0−10°. In contrast to the alkaline metal complexes of type **II**, chelation of bivalent cations $Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$ produces a larger conformational rearrangement of the guanidinium moiety (Table 2).

Metal-coordinated arginine species **III**, in which metal cations are 2-fold coordinated to the negatively charged carboxylate group of zwitterionic arginine, represent alternative energetically stable structures computationally predicted[19,40] for Arg•M if M = $K^+$ or $Cs^+$. The fully optimized complexes **IIIa** of zwitterionic arginine with the alkali metal cations $Li^+$, $Na^+$, and $K^+$ are stabilized by means of the intramolecular hydrogen bond O(1)···H−N(3), formed by one of the oxygen atoms and the $NH_2$ group of the guanidine moiety with a bond length of about 1.65−1.75 Å (Table 3). Coordination of the bivalent cations $Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$ is connected with a conformational rearrangement of the arginine moiety. The most stable structure, with the exception of the Arg•$Cu^{2+}$ complex, corresponds to the **IIIb** species and is stabilized via hydrogen-bond interaction between the $C_\alpha$-$NH_2$ proton acceptor group

**TABLE 1: B3LYP/6-31++G(d,p) Optimized Relevant Bond Lengths (Angstroms), Bond Angles (Degrees), and Dihedral Angles (Degrees) for the Metal-Coordinated and Hydrated Arginine Species I**

| $(H_2O)_n$ | Arg•M$(H_2O)_n$−I | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Li$^+$ | Na$^+$ | K$^+$ | Mg$^{2+}$ | Ca$^{2+}$ | Ni$^{2+a}$ | Cu$^{2+}$ | Zn$^{2+}$ |
| $d[O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 1.965 | 2.300 | 2.672 | 2.008 | 2.342 | 1.977 | 1.975 | 2.030 |
| $n = 1$ | 2.032 | 2.336 | 2.707 | 2.033 | 2.363 | 2.038 | 2.013 | 2.075 |
| $d[N(2)\cdots M]$ | | | | | | | | |
| $n = 0$ | 2.115 | 2.472 | 2.968 | 2.151 | 2.569 | 2.047 | 2.014 | 2.059 |
| $n = 1$ | 2.162 | 2.507 | 3.003 | 2.679 | 2.597 | 2.067 | 2.045 | 2.093 |
| $d[N(3)\cdots M]$ | | | | | | | | |
| $n = 0$ | 1.936 | 2.296 | 2.729 | 1.985 | 2.367 | 1.877 | 1.845 | 1.885 |
| $n = 1$ | 1.986 | 2.331 | 2.762 | 2.188 | 2.391 | 1.914 | 1.938 | 1.923 |
| $d[M\cdots OH_2]$ | | | | | | | | |
| $n = 1$ | 1.970 | 2.301 | 2.743 | 2.047 | 2.411 | 2.058 | 2.015 | 2.082 |
| $\Theta[C-O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 110.4 | 115.1 | 123.2 | 112.5 | 120.0 | 112.2 | 111.0 | 110.2 |
| $n = 1$ | 112.5 | 116.5 | 123.1 | 115.5 | 121.0 | 112.1 | 112.8 | 112.3 |
| $\Theta[O(1)\cdots M\cdots N(2)]$ | | | | | | | | |
| $n = 0$ | 82.2 | 70.4 | 58.5 | 80.2 | 67.7 | 81.4 | 81.8 | 81.3 |
| $n = 1$ | 79.7 | 68.9 | 57.6 | 78.7 | 66.9 | 79.3 | 79.9 | 80.0 |
| $\Theta[O(1)\cdots M\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 131.1 | 127.1 | 111.8 | 138.7 | 132.2 | 139.1 | 138.5 | 134.3 |
| $n = 1$ | 120.6 | 120.5 | 110.2 | 125.9 | 125.2 | 145.1 | 167.0 | 125.7 |
| $\Theta[N(2)\cdots M\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 135.0 | 124.6 | 106.6 | 134.2 | 120.0 | 133.4 | 136.2 | 140.3 |
| $n = 1$ | 128.9 | 120.3 | 104.9 | 127.2 | 117.6 | 128.7 | 101.3 | 133.2 |
| $\Phi[C-O(1)\cdots M\cdots N(2)]$ | | | | | | | | |
| $n = 0$ | 25.5 | 25.4 | 25.6 | 23.9 | 20.8 | 23.6 | 25.9 | 24.9 |
| $n = 1$ | 22.3 | 24.3 | 27.4 | 18.4 | 19.6 | 25.0 | 23.5 | 18.8 |
| $\Phi[C-O(1)\cdots M\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | −120.4 | −93.6 | −71.0 | −127.1 | −90.1 | −128.9 | −133.6 | −134.5 |
| $n = 1$ | −107.1 | −89.4 | −67.8 | −109.7 | −88.8 | −122.4 | −73.1 | −118.0 |

[a] Values computed for triplet ground state of Ni$^{2+}$.

**TABLE 2: B3LYP/6-31++G(d,p) Optimized Relevant Bond Lengths (Angstroms), Bond Angles (Degrees), and Dihedral Angles (Degrees) for the Metal-Coordinated and Hydrated Arginine Species II**

| $(H_2O)_n$ | Arg•M$(H_2O)_n$−II | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Li$^+$ | Na$^+$ | K$^+$ | Mg$^{2+}$ | Ca$^{2+}$ | Ni$^{2+a}$ | Cu$^{2+}$ | Zn$^{2+}$ |
| $d[O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 1.775 | 2.134 | 2.492 | 1.858 | 2.171 | 1.788 | 1.829 | 1.847 |
| $n = 1$ | 1.809 | 2.162 | 2.524 | 1.875 | 2.194 | 1.793 | 1.858 | 1.861 |
| $d[N(2)\cdots M]$ | | | | | | | | |
| $n = 0$ | 2.032 | 2.418 | 2.923 | 2.094 | 2.529 | 1.987 | 1.982 | 2.015 |
| $n = 1$ | 2.061 | 2.450 | 2.962 | 2.133 | 2.557 | 2.052 | 1.971 | 2.045 |
| $d[M\cdots OH_2]$ | | | | | | | | |
| $n = 1$ | 1.903 | 2.273 | 2.730 | 1.999 | 2.396 | 1.951 | 1.942 | 1.944 |
| $d[N(3)-H]$ | | | | | | | | |
| $n = 0$ | 1.067 | 1.079 | 1.090 | 1.025 | 1.033 | 1.019 | 1.019 | 1.021 |
| $n = 1$ | 1.075 | 1.085 | 1.098 | 1.030 | 1.037 | 1.024 | 1.024 | 1.027 |
| $d[O(2)\cdots H]$ | | | | | | | | |
| $n = 0$ | 1.538 | 1.499 | 1.468 | 1.811 | 1.735 | 1.917 | 1.918 | 1.864 |
| $n = 1$ | 1.511 | 1.480 | 1.447 | 1.763 | 1.706 | 1.843 | 1.841 | 1.789 |
| $\Theta[C-O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 115.4 | 121.9 | 131.4 | 115.0 | 126.7 | 115.0 | 115.8 | 109.6 |
| $n = 1$ | 116.6 | 122.6 | 131.6 | 117.3 | 127.2 | 118.8 | 116.6 | 113.9 |
| $\Theta[O(1)\cdots M\cdots N(2)]$ | | | | | | | | |
| $n = 0$ | 90.1 | 74.2 | 60.3 | 89.3 | 71.3 | 90.9 | 88.8 | 94.5 |
| $n = 1$ | 87.7 | 72.8 | 59.3 | 86.6 | 70.4 | 86.9 | 87.1 | 89.9 |
| $\Theta[O(2)\cdots H\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 174.8 | 177.1 | 177.9 | 163.8 | 168.1 | 160.1 | 159.1 | 161.0 |
| $n = 1$ | 175.7 | 175.9 | 178.4 | 166.4 | 169.4 | 163.2 | 163.0 | 164.7 |
| $\Phi[C-O(1)\cdots M\cdots N(2)]$ | | | | | | | | |
| $n = 0$ | 7.3 | 12.4 | 16.6 | 1.1 | 5.1 | 0.1 | 1.0 | 0.5 |
| $n = 1$ | 8.3 | 13.9 | 18.3 | 1.5 | 5.0 | 1.1 | 2.6 | 1.3 |
| $\Phi[C\cdots O(2)\cdots H\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 76.4 | 63.4 | 61.4 | 33.8 | 41.0 | 27.0 | 23.6 | 30.7 |
| $n = 1$ | 80.8 | 92.7 | 58.5 | 36.6 | 44.0 | 31.0 | 27.9 | 35.0 |

[a] Values computed for triplet ground state of Ni$^{2+}$.

**TABLE 3: B3LYP/6-31++G(d,p) Optimized Relevant Bond Lengths (Angstroms), Bond Angles (Degrees), and Dihedral Angles (Degrees) for the Metal-Coordinated and Hydrated Arginine Species III**

| | Arg•M(H_2O)_n−III | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $(H_2O)_n$ | Li$^+$ | Na$^+$ | K$^+$ | Mg$^{2+}$ | Ca$^{2+}$ | Ni$^{2+a}$ | Cu$^{2+}$ | Zn$^{2+}$ |
| $d[O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 1.929 | 2.299 | 2.746 | 1.971 | 2.302 | 1.912 | 1.994 | 2.009 |
| $n = 1$ | 1.885 | 2.336 | 2.788 | 1.976 | 2.306 | 1.954 | 1.992 | 1.958 |
| $d[O(2)\cdots M]$ | | | | | | | | |
| $n = 0$ | 1.854 | 2.190 | 2.546 | 1.959 | 2.284 | 1.905 | 2.028 | 1.987 |
| $n = 1$ | 1.972 | 2.214 | 2.578 | 1.985 | 2.324 | 1.901 | 1.912 | 1.978 |
| $d[M\cdots OH_2]$ | | | | | | | | |
| $n = 1$ | 1.898 | 2.275 | 2.716 | 1.995 | 2.398 | 1.955 | 1.924 | 1.951 |
| $d[N(3)\text{-}H]$ | | | | | | | | |
| $n = 0$ | 1.040 | 1.049 | 1.060 | 1.025 | 1.031 | 1.019 | 1.021 | 1.018 |
| $n = 1$ | 1.046 | 1.055 | 1.066 | 1.029 | 1.034 | 1.024 | 1.021 | 1.002 |
| $d[O(1)\cdots HN(3)]$ | | | | | | | | |
| $n = 0$ | 1.745 | 1.689 | 1.635 | | | | | |
| $n = 1$ | 1.701 | 1.654 | 1.605 | | | | | |
| $d[N(4)\cdots HN(3)]$ | | | | | | | | |
| $n = 0$ | | | | 2.120 | 2.022 | 2.246 | 4.554 | 2.288 |
| $n = 1$ | | | | 2.052 | 1.984 | 2.130 | 2.187 | 2.301 |
| $d[M\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 4.341 | 4.592 | 4.925 | 7.742 | 8.001 | 7.809 | 9.334 | 7.945 |
| $n = 1$ | 4.334 | 4.600 | 4.928 | 7.691 | 7.982 | 7.708 | 7.757 | 7.729 |
| $\Theta[C\text{-}O(1)\cdots M]$ | | | | | | | | |
| $n = 0$ | 82.2 | 86.2 | 88.3 | 86.6 | 90.4 | 88.4 | 88.9 | 86.7 |
| $n = 1$ | 87.2 | 86.3 | 88.3 | 88.2 | 91.2 | 89.8 | 88.0 | 89.0 |
| $\Theta[O(1)\cdots M\cdots O(2)]$ | | | | | | | | |
| $n = 0$ | 71.6 | 59.5 | 49.9 | 68.3 | 58.0 | 68.9 | 65.4 | 66.9 |
| $n = 1$ | 70.1 | 58.7 | 49.1 | 66.7 | 57.5 | 68.2 | 66.8 | 66.0 |
| $\Theta[O(1)\cdots H\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 165.2 | 164.4 | 164.3 | | | | | |
| $n = 1$ | 165.4 | 164.5 | 164.4 | | | | | |
| $\Phi[C\text{-}O(1)\cdots M\cdots O(2)]$ | | | | | | | | |
| $n = 0$ | −1.4 | −2.1 | −2.6 | 0.3 | 0.6 | −0.2 | 0.3 | 0.0 |
| $n = 1$ | −1.5 | −2.0 | −2.7 | −0.3 | −0.6 | 0.4 | 0.5 | −0.4 |
| $\Phi[C\cdots O(1)\cdots H\cdots N(3)]$ | | | | | | | | |
| $n = 0$ | 179.9 | −178.9 | −177.4 | | | | | |
| $n = 1$ | 178.7 | −177.1 | −177.3 | | | | | |

[a] Values computed for triplet ground state of Ni$^{2+}$.

and a NH_2 group of the side chain (Figure 1). For the complex **IIIb** of the Arg•Cu$^{2+}$ system, an extended structure without intramolecular hydrogen bond of the C$_\alpha$−N$\cdots$H−N(3) type is characteristic (Figure 3). For the Arg•M (M = Mg$^{2+}$, Ca$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$) complexes **IIIb**, the M$\cdots$N(3) distances were found to be considerably longer (by about 4−4.5 Å) than the analogous M$\cdots$N(3) lengths in complexes of alkali metals Li$^+$, Na$^+$, and K$^+$ (Table 3). For such a conformational rearrangement, the strong repulsion between bivalent cations and the cationic head of arginine can apparently be held responsible.

Monohydration of the Arg•M (M = Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$) complexes results in slight changes of the optimum geometry of the parent metal complexes (Tables 1–3). The equilibrium distances M$\cdots$O and M$\cdots$N slightly increase upon hydration in most cases. With regard to valence angles, changes (by about 1−3°) were observed in the values of the valence angle C−O(1)$\cdots$M of the parent metal complexes in monohydrated systems. The O(1)$\cdots$M$\cdots$N(2) angle in the complexes of arginine extends over a relatively large interval (60−90°) and slightly decreases upon hydration. The chelate rings of the metallic complexes **II** and **III** are almost planar [with respect to dihedral angles C−O(1)$\cdots$M$\cdots$N(2) and C−O(1)$\cdots$M$\cdots$O(2)], and the planarity of this moiety is also preserved in the monohydrated complexes. Larger changes of conformations of chelate rings upon hydration were only observed in complex **I** [see dihedral angles C−O(1)$\cdots$M$\cdots$N(2) and C−O(1)$\cdots$M$\cdots$N(3) in Table 1].
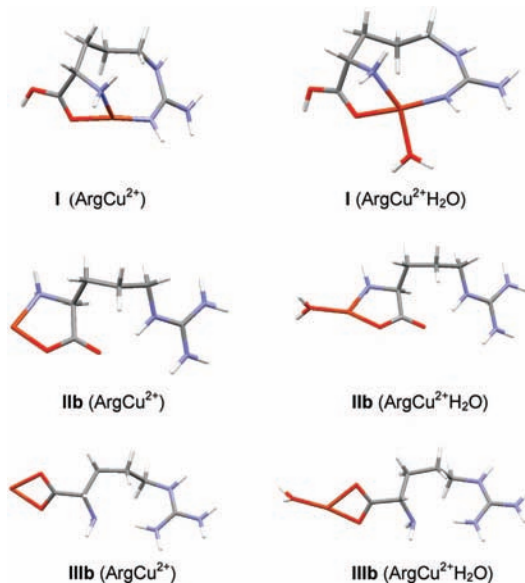


**Figure 3.** Overall structures of the BHandHLYP/6-31++G(d,p) optimized complexes of the arginine−Cu$^{2+}$ complexes and their hydrates.

**3.2. Relative Energies.** The relative Gibbs energies computed at the DFT levels of theory of three different types of arginine metal complexes and their monohydrated species are

**TABLE 4: Relative Stability (Gibbs energy, kJ/mol) of Neutral and Zwitterionic Metal Ion Complexes I−III of Arginine (Arg•M)**[a]

| method | Li$^+$ | Na$^+$ | K$^+$ | Mg$^{2+}$ | Ca$^{2+}$ | Ni$^{2+}$ | Cu$^{2+}$ | Zn$^{2+}$ |
|---|---|---|---|---|---|---|---|---|
| **I** | | | | | | | | |
| B3LYP/6-31++G(d,p) | 0 | 0 | 0 | 0 | 0 | 0; 0$^b$ | 0 | 0 |
| BHandHLYP/6−31++G(d,p) | | | | | | | 0 | |
| **II** | | | | | | | | |
| B3LYP/6-31++G(d,p) | 10.0 (IIb) | 0.8 (IIb) | −14.2 (IIb) | 88.7 (IIb) | 31.0 (IIb) | 69.5; 35.5$^b$ (IIb) | 70.3 (IIb) | 114.6 (IIb) |
| BHandHLYP/6-31++G(d,p) | | | | | | | 93.7 (IIb) | |
| **III** | | | | | | | | |
| B3LYP/6-31++G(d,p) | 37.7 (IIIa) | 14.2 (IIIa) | −5.1(IIIa) | 89.9 (IIIb) | 2.1 (IIIb) | 114.2; 86.3$^b$ (IIIb) | 76.2 (IIb) | 146.0 (IIIb) |
| BHandHLYP/6-31++G(d,p) | | | | | | | 126.4 (IIIb) | |

*a* Most stable systems are in parenthesis. *b* Values computed for triplet ground state of Ni$^{2+}$.

**TABLE 5: Relative Stability (Gibbs energy, kJ/mol) of Hydrated Neutral and Zwitterionic Metal Ion Complexes of Arginine (Arg•MxH$_2$O)**[a]

| method | Li$^+$ | Na$^+$ | K$^+$ | Mg$^{2+}$ | Ca$^{2+}$ | Ni$^{2+}$ | Cu$^{2+}$ | Zn$^{2+}$ |
|---|---|---|---|---|---|---|---|---|
| **I(H$_2$O)** | | | | | | | | |
| B3LYP/6-31++G(d,p) | 0 | 0 | 0 | 0 | 0 | 0; 0$^b$ | 0 | 0 |
| BHandHLYP/6-31++G(d,p) | | | | | | | 0 | |
| **II(H$_2$O)** | | | | | | | | |
| B3LYP/6-31++G(d,p) | −18.2 (IIb) | −11.4 (IIb) | −20.3 (IIb) | 33.5 (IIb) | 15.5 (IIb) | 14.9; 17.9$^2$ (IIb) | −20.9 (IIb) | 30.2 (IIb) |
| BHandHLYP/6-31++G(d,p) | | | | | | | 8.9 (IIb) | |
| **III(H$_2$O)** | | | | | | | | |
| B3LYP/6-31++G(d,p) | 5.3 (IIIa) | 1.3 (IIIa) | −8.0 (IIIa) | 31.0 (IIIb) | −10.8 (IIIb) | 49.2; 61.1$^2$ (IIIb) | −2.7 (IIIb) | 51.8 (IIIb) |
| BHandHLYP/6-31++G(d,p) | | | | | | | 30.0 (IIIb) | |

*a* Most stable systems are in parenthesis. *b* Values computed for triplet ground state of Ni$^{2+}$.

reported in Tables 4 and 5. DFT (with one exception) suggests metallic complexes (system **I**) of the neutral L-arginine to be the most stable species (Table 4). According to DFT B3LYP results for Li$^+$, Na$^+$, Mg$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$, the relative stability decreases as follows: **I** > **II** > **III**. A different order of stability of individual species is observed for K$^+$ (**II** > **III** > **I**) and Ca$^{2+}$ (**I** > **III** > **II**) complexes (Table 4). Because the singlet Ni$^{2+}$ ion and its arginine complexes are higher in energy than the corresponding triplet species, the relative Gibbs energies for triplet Arg•Ni$^{2+}$ complexes have also been computed. Although the relative energy differences for the high spin state Ni$^{2+}$ species are appreciably lower, the stability sequence is the same (Table 4).

Because it was recently demonstrated[47,48] that functionals such as BHLYP with larger percentages of exact exchange (50%) than the commonly used[49] B3LYP (20%) for open-shell complexes compare better to the highly correlated ab initio CCSD(T) method, the open-shell Arg•Cu$^{2+}$ complexes were also investigated by means of the half-and-half functional[36] BHandH-LYP implemented in the G03 computer code.[28] The relative energy profiles of the Arg•Cu$^{2+}$ systems computed by using BHandHLYP functional follow the order of stability determined by using the B3LYP DFT method. However, the differences in relative stabilities are somewhat larger. BHandHLYP relative Gibbs energies are about 20−50 kJ/mol larger than those obtained with B3LYP (Table 4).

Previous examinations of the Arg•M (M = Li$^+$, Na$^+$, and K$^+$) complexes have shown that with increasing alkali-metal ion size, arginine changes from its neutral to zwitterionic form.[18,19] Our B3LYP results are in agreement with calculations by Williams et al.[18,19] Complex **I** of the Arg•Li$^+$ system is by 10.0 kJ/mol more stable than the Arg•Li$^+$ complex (system **II**). For the Arg•Na$^+$ complex, our calculation slightly favors, in agreement with the experiment,[19] the charge-solvated form **I**, whereas for the Arg•K$^+$ species, the most stable structure is a salt bridge **II**. For Arg•Na$^+$, the energy difference between conformers **I** and **II** is, however, small (about 1 kJ/mol). For

the arginine complexes with the divalent cations Mg$^{2+}$, Ca$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$, the thermodynamically most stable species are the neutral ones (Table 4, system **I**).

Hydration of the metal-coordinated complexes of arginine species by one water molecule was investigated for systems **I−III**, in which water directly solvates the metal ion and no additional interactions are formed. The DFT calculations of monohydrated systems **I−III**, Table 5, indicate that even one water molecule has a profound effect on the relative stability of individual complexes. For the arginine complexes with the alkaline cations Li$^+$, Na$^+$, and K$^+$, the thermodynamically stable species are, in contrast to the complexes without water, zwitterionic ones (system **IIb**). In the case of the alkaline-earth cations Mg$^{2+}$ and Ca$^{2+}$, the situation is different. Although the relative stability of the Mg$^{2+}$ complexes does not change upon hydration, the hydration of the Arg•Ca$^{2+}$ species results in a net preference for the zwitterionic complex **III**, Table 5. The monohydration does not change the relative stability of the transition metal complexes Arg•M (M = Ni$^{2+}$ and Zn$^{2+}$). In the case of Cu$^{2+}$ complexes, half-and-half functional BHandH-LYP prefers the neutral species Arg•Cu$^{2+}$(H$_2$O) of the system **I**, whereas the B3LYP method predicts the zwitterionic complex **II** as the most stable one (Table 5). 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.[50] The calculated spin density at the copper center for the unhydrated system **I** is 0.73 with the BHandHLYP functional, whereas it decreases to only 0.51 with the B3LYP method.

**3.3. Proton Dissociation Enthalpies and Gibbs Energies.** Arginine contains a strongly basic functional group. This high basicity increases the stability of zwitterionic arginine in the gas phase relative to other amino acids. However, recent experiments have shown that isolated arginine is not a zwitter-ion. Cavity-ring down laser absorption spectra of jetcooled

**TABLE 6: Computed Gas-Phase Proton Dissociation Enthalpies and Gibbs Energies in the Presence of Li+, Na+, K+, Mg2+, Ca2+, Ni2+, Cu2+, and Zn2+ Calculated at the B3LYP/6-31++G(d,p) Level**

| species | $\Delta H^{298}$, kJ/mol | $\Delta S^{298}$, J/K mol | $\Delta G^{298}$, kJ/mol | $\Delta H^{298}_{exp}$, kJ/mol | $\Delta G^{298298}_{exp}$, kJ/mol |
|---|---|---|---|---|---|
| Arg | 1384.4 | 111.0 | 1350.9 | $1388 \pm 13^a$; $1381 \pm 9^b$ | $1359 \pm 13^a$ |
| ArgLi+ | 1054.6 | 107.8 | 1022.5 | | |
| ArgNa+ | 1077.0 | 107.1 | 1045.1 | | |
| ArgK+ | 1098.3 | 106.3 | 1066.3 | | |
| ArgMg2+ | 661.5 | 109.7 | 628.8 | | |
| ArgCa2+ | 716.3 | 112.4 | 682.8 | | |
| ArgNi2+ | 618.8 | 111.1 | 585.7 | | |
| ArgNi2+ | $585.7^c$ | $110.2^c$ | $552.9^c$ | | |
| ArgCu2+ (B3LYP) | 634.3 | 113.1 | 600.6 | | |
| ArgCu2+ (BHandHLYP) | 646.4 | 110.1 | 613.7 | | |
| ArgZn2+ | 647.7 | 109.7 | 615.0 | | |

$^a$ Reference 52. $^b$ Reference 53. $^c$ Values computed for triplet ground state of Ni2+.

**TABLE 7: B3LYP/6-31++G(d,p) Calculated Gas-Phase Enthalpies, $\Delta H$, Entropies, $\Delta S$, and Gibbs Energies, $\Delta G$, of the Ion−Arginine Systems**

| system | complex | $\Delta H^{298}$, kJ/mol | $\Delta S^{298}$, J/mol K | $\Delta G^{298}$, kJ/mol |
|---|---|---|---|---|
| **I** | Arg···Li+ | −366.8 | −128.6 | −328.5 |
| **IIb** | Arg···Li+ (H2O) | −293.2 | −129.9 | −254.3 |
| **I** | Arg···Na+ | −259.0 | −113.5 | −225.1 |
| **IIb** | Arg···Na+ (H2O) | −217.9 | −113.4 | −184.2 |
| **IIb** | Arg···K+ | −180.6 | −96.2 | −151.9 |
| **IIb** | Arg···K+ (H2O) | −153.8 | −93.6 | −125.9 |
| **I** | Arg···Mg2+ | −1071.8 | −145.1 | −1027.7 |
| **I** | Arg···Mg2+ (H2O) | −884.1 | −178.3 | −830.8 |
| **I** | Arg···Ca2+ | −698.9 | −128.0 | −659.8 |
| **IIIb** | Arg···Ca2+ (H2O) | −618.2 | −118.7 | −582.6 |
| **I** | Arg···Ni2+ | −1595.3 | −169.6 | −1544.5 |
| **I** | | $−1297.6^a$ | $−156.8^a$ | $−1250.9^a$ |
| **I** | Arg···Ni2+ (H2O) | −1218.6 | −218.1 | −1153.8 |
| **I** | | $−1082.0^a$ | $−188.9^a$ | $−1025.7^a$ |
| **I** | Arg···Cu2+ | −1451.5 | −158.5 | −1403.8 |
| **IIb** | Arg···Cu2+ (H2O) | −1054.4 | −141.6 | −1011.8 |
| **I** | Arg···Cu2+ BHandHLYP | −1357.4 | −166.3 | −1308.4 |
| **I** | Arg···Cu2+ (H2O) BHandHLYP | −1051.2 | −197.4 | −992.2 |
| **I** | Arg···Zn2+ | −1325.9 | −151.6 | −1279.8 |
| **I** | Arg···Zn2+ (H2O) | −1012.5 | −185.9 | −957.1 |

$^a$ Values computed for triplet ground state of Ni2+.

arginine do not exhibit a peak corresponding to the calculated carboxylate asymmetric stretching of the zwitterion.[10] High-level computations have confirmed that neutral arginine is more stable than zwitterionic arginine in the absence of an additional charge.[12] However, theory predicts that the zwitterionic arginine is only less stable than arginine by 4−12 kJ/mol, depending on the level of theory.[12] The deprotonation of protein amino acids has been investigated experimentally,[51] more recently even in the gas phase.[52,53] It is well-known[51] that L-arginine is a strong acid with $pK_a$ = 1.80 (in water) and, therefore, may ionize at the physiological $pH$. However, gas-phase studies enable the exploration of the reactivities of molecules without the effect of solvent. An important parameter of the arginine gas-phase reactivity is its gas-phase acidity, $\Delta G_{acid}$, the Gibbs energy change for the reaction Arg → H+ + Arg−. Thermodynamic parameters (proton dissociation enthalpies, entropies, and Gibbs energies) for this reaction and deprotonation reactions of the Arg•M complexes of the system **I** combining neutral arginine with metal cations were computed in the same way as in our previous publication.[54] The accurate gas-phase acidity of arginine was recently determined by using an electrospray ionization-quadrupole ion trap instrument.[53] However, the deprotonation reaction of this amino acid in the presence of metal cations has not been investigated so far, neither experimentally nor theoretically. Table 6 contains acidities of arginine and its charge-solvated complexes (system **I**, Figure 1). With respect to the existence of several stable rotational conformers of arginine, the enthalpy of deprotonation may be computed between two arbitrary species, but only the differences between the most stable species have a physical meaning and can be compared with experiment. Of the three possible arginine anions studied by removing the lithium cation in the systems **I−III**, Figure 2, the most stable anion is stabilized by the intramolecular hydrogen bond C−O−···H−N with the guanidine moiety. Among the three different stable rotational conformers of neutral arginine studied, the conformer stabilized by the intramolecular hydrogen bond formed by the hydroxyl group and the imino nitrogen atom of the guanidine moiety was computed at the B3LYP level as the most stable structure. The computed enthalpy and Gibbs energy (1384.4 and 1350.9 kJ/mol) correspond very well (within the error limits of experiments) to the experimentally estimated quantities (Table 6). These results, as well as the comparisons of the B3LYP results with highly accurate CBS-Q level of theory, show that DFT performs quite

well[53,55−57] and should be used as a relatively inexpensive alternative for the investigation of acidity of larger organic systems. The proton dissociation enthalpies, entropies, and Gibbs energies were also computed in the presence of the metal cations Li+, Na+, K+, Mg2+, Ca2+, Ni2+, Cu2+, and Zn2+ (Table 6). In the presence of metallic cations, the acidity of arginine increases in the order K+ < Na+ < Li+ < Ca2+ < Mg2+ < Zn2+ < Cu2+ < Ni2+. Metal-coordinated arginine is by about 200−700 kJ/mol more acidic than the noncoordinated arginine. Divalent cations exhibit, as expected, a considerably larger effect on the acidity of arginine, and thus, it will be fully deprotonated if it coordinates to divalent metal cations.

**3.4. Gas-Phase Interaction Enthalpies, Entropies and Gibbs Energies of the Arg•M (M = Li+, Na+, K+, Mg2+, Ca2+, Ni2+, Cu2+, and Zn2+) Complexes.** The stability of the different forms of amino acids can be substantially modified by specific noncovalent interactions with nearby molecules and ions.[58] The calculated interaction enthalpies, entropies, and Gibbs energies of the arginine-metal ion complexes studied at the Becke3LYP level of the DFT are given in Table 7. 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 species (Tables 4 and 5). 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. It has been shown[59−61] that the DFT method yields results which compare favorably with the corresponding results obtained by using the high-level ab initio coupled-cluster method. The Becke3LYP method in conjunction with the triple-ζ basis set reproduces thermodynamic quantities[62] 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 by using DFT are comparable to ab initio results and mostly in good agreement with the corresponding experimental data.[26,62−66]

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 7 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 arginine, the entropy change due to complexation is about −100 to −200 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 $\Delta G^o$ are negative and span a rather broad energy interval (from −150 to −1500 kJ/mol).

Arginine involves harder (O) and softer (N) basic centers. The nitrogen atom of the >C=NH group of the guanidine moiety of arginine is the most favorable site for protonation. The reason why a guanidine group attached to the aliphatic chain in arginine protonates more easily than the $C_\alpha$−NH$_2$ group can be explained by an efficient accommodation of the positive charge in the larger guanidium group. The selectivity of the base arginine toward 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 coordinate to nitrogen donors.[64−67] Thus, the harder the Lewis acid, the stronger is the preference for O compared to N. For arginine complexes of the alkali metals, the following order of stability was found: Li$^+$ > Na$^+$ > K$^+$, the same stability order that one would expect on the basis of their ionic radii[67,68] [K$^+$ (1.33), Na$^+$ (0.95), Li$^+$ (0.6)]. It is interesting to note that two of the Arg•M (M = Li$^+$, Na$^+$, and K$^+$) complexes involve tridentate binding except the Arg•K$^+$ complex, which is bidentate (Table 4). The alkali metal cations have s$^0$ electron configurations and thus spherically symmetric electron densities. The alkali metal cation−arginine 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[26,64] (Tables 1−3). According to Cerda and Wesdemiotis,[40] 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 arginine, thereby optimizing stabilizing 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 arginine than lithium, sodium, or potassium cations (Table 7). The stability of the alkaline-earth metal Mg$^{2+}$ and Ca$^{2+}$ complexes of arginine also obeys the selection by ion size [Ca$^{2+}$ (1.0), Mg$^{2+}$ (0.65)] (magnesium complex of arginine is by about 400 kJ/mol more stable than calcium complex). A third category of species are the arginine complexes with Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$ ions. The Gibbs interaction energies show a decreasing binding affinity in the order Cu$^{2+}$ > Zn$^{2+}$ > Ni$^{2+}$. According to the highest interaction energies (Table 7), the transition metal Cu$^{2+}$ is most effectively recognized by the basic center of arginine. It is interesting that the M⋯O and M⋯N distances from nickel to the zinc cation are varying within the relatively short interval of 1.80−2.0 Å, and they do not correlate with the ionic radii[67,68] for Ni$^{2+}$ (0.72), Cu$^{2+}$ (0.69), and Zn$^{2+}$ (0.65). In the complex-

ation of transition metal cations Ni$^{2+}$, Cu$^{2+}$, and Zn$^{2+}$, the charge transfer is important.[65] The largest metal dissociation Gibbs energy was computed for the system Arg•Cu$^{2+}$ (Table 7). The highest interaction energy of the Cu$^{2+}$ arginine 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.

Attachment of two metal cations (Na$^+$, Cu$^+$) to arginine in the gas phase has been investigated experimentally.[41,69,70] Wesdemiotis et al.[70] used the electrospray ionization technique for determination of sodium binding enthalpies to arginine, found to amount to −225 kJ/mol, first, and more recently,[41] corrected to −242 kJ/mol. A comparison of the B3LYP computed enthalpy (−259.0 kJ/mol) for the binding of sodium cation to arginine and available experimental values shows that DFT and experimental data agree well. Calculations by Wang et al. delivered arginine sodium affinity values[41] of −245 and −251 kJ/mol for a charge-solvation structure [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 performed by using the B3LYP/6-31++G(d,p) method (Table 7). The observed discrepancies between our theoretically computed and available experimental metal affinities of arginine could be partly due to some uncertainty in the interpretation of experimental data[41,69] which introduces larger errors in the absolute metal ion affinities. From the computational point of view, there is also some uncertainty in computations of metal ion affinities. The large flexibility of the side chain of the arginine makes the identification of the stable structures a computational challenge.[21] Quite recently, Wang et al.[41] examined in detail the effect of rotational isomerism of arginine on the strength of the Arg•Na$^+$ complex by considering a total of 13 structures of Arg•Na$^+$. They found that the differences in interaction enthalpies of salt-bridge and charge-solvated structures are small (about 10 kJ/mol). The value associated with the charge solvation isomer is somewhat closer to the experimental result[41] of −242 kJ/mol. By assuming the salt bridges **IIb** and **IIIb**, our DFT calculation yields interaction enthalpies of −254 and −242 kJ/mol, respectively. Our results for the Arg•Na$^+$ are thus compatible with previous ab initio SCF calculations[41] and the experimental interaction enthalpy of −242 kJ/mol.

In order to evaluate the effect of metal hydration on the dissociation enthalpy and Gibbs energy of the metallic arginine complexes investigated in Table 7, the corresponding dissociation energies of the Arg•M(H$_2$O) systems are also presented. The interaction enthalpies and Gibbs energies were computed as the energy differences between the most stable species (Tables 5 and 7). Monohydration causes a considerable lowering of the interaction enthalpies and Gibbs energies. Corresponding values for Gibbs energies are by about 20−25% lower than values for the Arg•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 arginine and metallic cations. However, hydrogen-bond strengths in systems **II** and **III** are practically unaffected. This weakening of the metal coordinated bonds M⋯O and M⋯N in the Arg•M(H$_2$O) (M = Li$^+$, Na$^+$, K$^+$, and Ca$^{2+}$) complexes leads to the preferential stabilization of the salt bridge (zwitterionic) structures. For the open-shell system Arg•Cu$^{2+}$(H$_2$O), the B3LYP DFT method assumes salt bridge **IIa** as the most stable one, whereas both half-and-half functionals of the DFT theory

predict charge-solvated structure **I** as the most stable one (Table 7). Poater et al.[47] recently investigated $Cu^{2+}(H_2O)$ complexes by using different density functional and post-Hartree−Fock methods (CCSD(T)). Among the different functionals studied, BHLYP provided the best results for $Cu^{2+} \cdots H_2O$ interaction energy compared to CCSD(T). When considering a good performance of half-and-half functionals for this open-shell copper complex[47] and similar results for $Cu^{2+}$−ligand systems,[48] it is reasonable to assume that also the open-shell $Arg \cdot Cu^{2+}(H_2O)$ complex will exist in the charge-solvated system **I**, such as $Arg \cdot M(H_2O)$ ($M = Mg^{2+}$, $Ni^{2+}$, and $Zn^{2+}$) complexes. Our results are in full agreement with recent theoretical calculations by Bush et al.[20] of the $Arg \cdot M(H_2O)$ systems ($M = Li^+$, $Na^+$) performed by using several density functionals. The salt-bridge structures were found to be the most stable ones and were also observed experimentally.[20]

## 4. Summary and Conclusions

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

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

2. The DFT calculations of monohydrated systems **I**−**III** indicate that even one water molecule has a profound effect on the relative stability of individual complexes. For the arginine complexes with alkaline cations $Li^+$, $Na^+$, and $K^+$, the thermodynamically stable species are, in contrast to the complexes without water, zwitterionic ones. Although the relative stability of the $Mg^{2+}$ complexes does not change upon hydration, the hydration of the $Arg \cdot Ca^{2+}$ species results in a net preference for the zwitterionic complex **III**. The monohydration does not change the relative stability of the transition metal complexes $Arg \cdot M$ ($M = Ni^{2+}$ and $Zn^{2+}$). In the case of $Cu^{2+}$ complexes, the half-and-half functional BHandHLYP prefers the existence of the neutral species $Arg \cdot Cu^{2+}(H_2O)$ of system **I**.

3. The computed proton dissociation enthalpy and Gibbs energy of arginine (1384.4 and 1350.9 kJ/mol), respectively, correspond within the error limits of experiments to the experimentally estimated quantities, and in the presence of metal cations, the acidity of arginine considerably increases.

4. Among the Lewis acids investigated, the strongest affinity to arginine is exhibited by the $Cu^{2+}$ cation. The computed Gibbs energies $\Delta G^\circ$ are negative, span a rather broad energy interval (from −150 to −1500 kJ/mol), and are appreciably lowered upon hydration.

**Supporting Information Available:** This material is available free of charge via the Internet at http://pubs.acs.org.

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