# Generation of [La(peptide)]$^{3+}$ Complexes in the Gas Phase: Determination of the Number of Binding Sites Provided by Dipeptide, Tripeptide, and Tetrapeptide Ligands

**Tujin Shi, K. W. Michael Siu, and Alan C. Hopkinson***

*Department of Chemistry and Centre for Research in Mass Spectrometry, York University, 4700 Keele Street, Toronto, Ontario M3J 1P3, Canada*

*Received: July 4, 2007; In Final Form: September 13, 2007*

Gas-phase complexes [La(peptide)]$^{3+}$ containing 2−4 amino-acid residues have been investigated by electrospraying solutions containing $La^{3+}$ and the peptide; only complexes in which the peptide contained an arginine residue were observed. Using the coordination number of eight for $La^{3+}$ [Shi, T.; Hopkinson, A. C.; Siu, K. W. M. *Chem. Eur. J.* **2007**, *13*, 1142−1151] and the relative abundances of the hydrates [La(peptide)-$(H_2O)_n$]$^{3+}$, the number of binding sites provided by the peptides was deduced: Leu-Trp-Met-Arg, 7; Met-Arg-Phe-Ala, 6; Gly-Arg-Gly, 4; Gly-Gly-Arg 4; and Met-Arg, 4. Density Functional Theory calculations show that the zwitterionic form of Gly-Gly-Arg preferentially binds $La^{3+}$ through four coordination sites—the two amide oxygens and the two carboxy oxygens.

## Introduction

Metal ions play a vital role in many biological processes. Metal-ion-cationized peptides have been the subject of tandem mass spectrometric studies because their spectra are potentially useful for determining the amino-acid sequence in peptides and for elucidating the intrinsic interactions between the metal ion and the peptide.[1−26] However, gas-phase metal-ion complexes containing neutral (non-deprotonated) peptides have been reported only for monocations (alkali metal ions,[4,18,20,22−24,26] copper,[27,28] and silver[17,19,29−32]) and dications (calcium,[33] nickel,[15] copper,[15] and zinc[12,15]). Complexes of triply charged metal ions ligated by a neutral peptide are prone to undergoing charge reduction reactions by proton abstraction from the peptide[34−37] giving [M(peptide − H)]$^{2+}$. The only [La(peptide)]$^{3+}$ complexes that have been observed contained polypeptides[38] with a minimum of nine amino-acid residues, e.g., bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg); furthermore, all of the polypeptides examined had either basic arginine or cysteine residues, both of which have side chains that might be expected to interact with a triply charged metal ion. Whether coordination with the carbonyl oxygens of the peptide bonds is sufficient to stabilize a given [M(peptide)]$^{3+}$ complex is, therefore, an open question.

In our first attempts at producing [M(peptide)]$^{3+}$ complexes, we chose M = La because lanthanum has the lowest third ionization energy, 19.2 eV, of all trivalent metals.[39] In addition, by using the fact that the preferred coordination number of gas-phase $La^{3+}$ is eight, it is possible to determine the number of coordination sites provided by the peptide in any [La(peptide)]$^{3+}$ complex that is observed (vide infra).[40] Lanthanum has been used extensively to probe alkaline earth metal-binding sites (especially those for $Mg^{2+}$, $Ca^{2+}$) in proteins.[41] $La^{3+}$ and $Ca^{2+}$ have the same electronic structures as inert gases (xenon and argon, respectively) and have no valence-shell electrons available for back-donation; consequently, they behave as hard-acid cations, preferring to bind to "hard" bases (containing oxygen and fluorine) rather than to "soft" bases (containing nitrogen, phosphorus, and sulfur).[42] Hence, the interactions between peptides and the lanthanum trication or alkaline-earth metal dications, as opposed to transition metals ions, are essentially electrostatic.[43]

In a preliminary investigation, we were unable to produce [La$(Gly)_n$]$^{3+}$ complexes ($n = 2-5$) by electrospraying $La^{3+}$ and $(Gly)_n$. However, the presence of a relatively strong binding solvent did enable observation of complexes [La(Gly-Gly)$(CH_3CN)_n$]$^{3+}$, [La(Gly-Gly-Gly)$(CH_3CN)_n$]$^{3+}$, and [La(Gly-Ala)$(CH_3CN)_n$]$^{3+}$, albeit always in low abundance. Importantly, collision-induced dissociation (CID) of these complexes did not result in the loss of acetonitriles to ultimately produce [La$(Gly)_n$]$^{3+}$. Instead, charged-reduced complexes, [La(peptide − H)$(CH_3CN)_m$]$^{2+}$, resulting from dissociative, interligand proton transfer from the peptide to a departing acetonitrile, were produced. Under high collision energies, even the doubly deprotonated complex [La(peptide − 2H)]$^{+}$ could be produced.

One strategy to produce multiply protonated peptides of high charge, is to 'immobilize' the proton on an arginine residue.[44,45] Conceptually, in a [La(peptide)]$^{3+}$ complex, where the peptide contains an arginine residue, the peptide can be in the zwitterionic form with the $COO^-$ group binding the $La^{3+}$ ion and the carboxyl proton migrated to the basic side chain of the arginine. This arrangement essentially delocalizes a positive charge from the La to the arginine side chain. Bradykinin has two arginine residues and, as noted previously, the smallest [La(peptide)]$^{3+}$ reported to date had bradykinin as the peptide. Our strategy in the study of [La(peptide)]$^{3+}$ complexes was, therefore, to use arginine-containing peptides, starting with the larger (tetrapeptides) and, if successful, continuing with peptides of smaller sizes.

## Experimental Section

Experiments were performed on an MDS SCIEX (Concord, ON) API 3000 prototype triple-quadrupole mass spectrometer. Each sample was typically 1 mM peptide and 0.1 mM lanthanum (III) nitrate in a 50/50 water/methanol mixture. The sample was introduced into the pneumatically assisted electrospray ionization (ESI) source at a flow rate of 3 $\mu$L/min, and the lens voltages were optimized to produce abundant

10.1021/jp0752163 CCC: $37.00 
Published on Web 10/20/2007

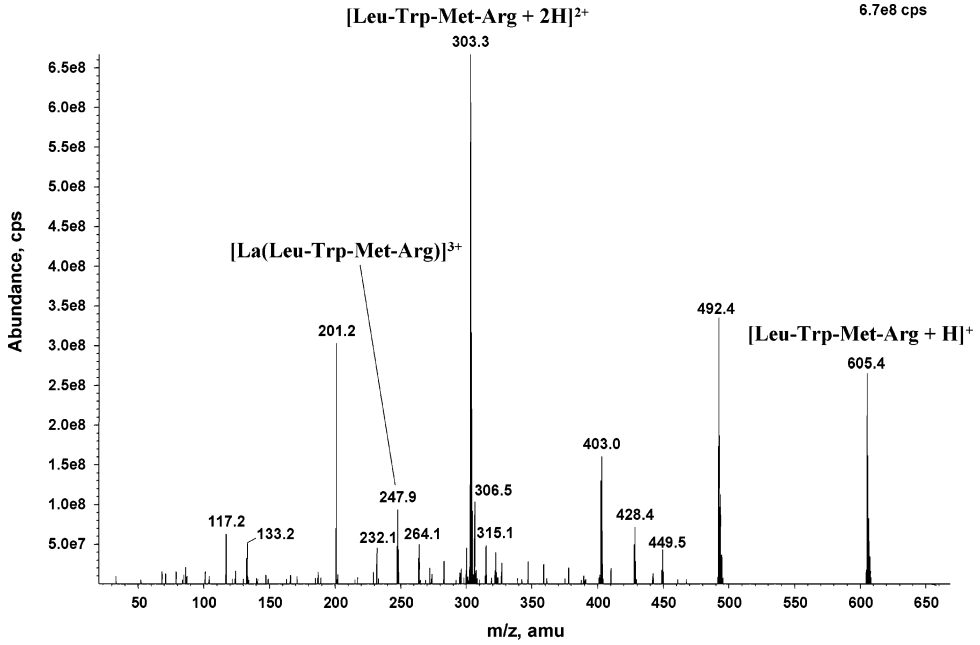



**Figure 1.** MS spectrum of electrospraying $La(NO_3)_3$ and Leu-Trp-Met-Arg solution at a declustering potential (DP) of 20 V.

[La(peptide)]$^{3+}$ ions. For ternary complexes that contained La(III), peptide, and acetonitrile, methanol was substituted with acetonitrile. All peptides were purchased from Bachem Bio-Sciences (King of Prussia, PA) and were used as received. Lanthanum (III) nitrate and solvents were available from Sigma/Aldrich (St. Louis, MO).

MS/MS experiments were performed by mass-selecting the precursor ions using the first quadrupole, colliding them with a mixture of water and nitrogen in the second quadrupole, and mass-analyzing with the third quadrupole. The water/nitrogen mixture was boiled off from liquid nitrogen, which contained water as a minor component.[40,46,47] The collision gas pressure was varied to probe and control the extent of hydration in the products. For the sake of simplicity and consistency,[40] only results at a pressure of 8 mTorr are presented.

## Computational Section

Geometry optimizations and energy calculations were performed with Gaussian 03[48] using the B3LYP exchange-correlation functional.[49−51] The *sdd* relativistic effective core potential (ECP) was used for La,[52] and a doubly split-valence basis set 6-31G** for other atoms.[53−56] All stationary points were characterized by harmonic vibrational frequency calculations. Relative enthalpies at 0 K ($\Delta H°_0$) and relative free energies at 298 K ($\Delta G°_{298}$) are reported.

## Results and Discussion

**Tetrapeptides: Leu-Trp-Met-Arg (604 Da) and Met-Arg-Phe-Ala (523 Da).** Electrospraying a solution of lanthanum (III) nitrate and a tetrapeptide generated high abundances of [tetrapeptide + $n$H]$^{n+}$, where $n = 1-2$, and of the doubly charged complex, [La($NO_3$)(tetrapeptide)]$^{2+}$. Under "mild" conditions (declustering potential, DP = 20 eV), some [La(tetrapeptide)]$^{3+}$ was produced, but the abundance was relatively low (see Figure 1). Figure 2 shows the CID spectra of (a) [La(Leu-Trp-Met-Arg)]$^{3+}$ and (b) [La(Met-Arg-Phe-Ala)]$^{3+}$ at a laboratory collision energy ($E_{lab}$) of 15 eV and 8 mTorr with water/nitrogen as the collision gas. At such a relatively low collision energy, the predominant reaction was the addition of water to the complexes giving [La(Leu-Trp-Met-Arg)($H_2O)_n$]$^{3+}$ and [La(Met-Arg-Phe-Ala)($H_2O)_n$]$^{3+}$. The most abundant complexes were [La(Leu-Trp-Met-Arg)($H_2O$)]$^{3+}$ (Figure 2a) and [La(Met-Arg-Phe-Ala)($H_2O)_2$]$^{3+}$ (Figure 2b). In an earlier study,[40] we determined that the coordination number of $La^{3+}$ in the gas phase is eight, using a similar approach in which water was used as the auxiliary ligand. This coordination number was confirmed by density functional theory (DFT) calculations. In this current study, we are interpreting the relative abundances of the hydrates to mean that Leu-Trp-Met-Arg provides seven binding sites for $La^{3+}$, and Met-Arg-Phe-Ala provides six. Parenthetically, it is of note that there was a minor channel involving cleavage of the $C_\alpha-C_\beta$ bond of the tryptophan side chain, giving a product ion at *m*/*z* 130 and the complementary doubly charged ion [La(Leu-Trp-Met-Arg − 130)]$^{2+}$ at *m*/*z* 307. The *m*/*z* 130 ion has also been observed in the fragmentations of [Cu(dien)(Gly-Gly-Trp)]$^{\bullet 2+}$ (ref 57) and [Trp + H]$^+$.[58]

DFT calculations have shown that metal ions bind preferentially to the carbonyl oxygens and the terminal amino groups of peptides. For example, in [Ag(Gly-Gly-Gly)]$^+$, the $Ag^+$ is four-coordinate, attaching to the three carbonyl oxygens and the terminal nitrogen;[59] similarly, in [Na(Gly-Gly)]$^+$, the $Na^+$ is three-coordinate, attaching to the two carbonyl oxygens and the amino group.[60] In the [La(tetrapeptide)]$^{3+}$ complexes examined here, the peptides are probably zwitterionic with the carboxy group being bidentate. We envision that each of the peptide bonds will coordinate through its carbonyl oxygen and through the sulfur atom from the side chain of the methionine residue. In total, these interactions require six coordination sites; by analogy with [La(Gly-Gly-Arg)]$^{3+}$ (vide infra) the terminal amino group does not coordinate the $La^{3+}$, but instead functions as a proton acceptor from an amidic NH (see Scheme 1). In this regard, the coordination in the [La(peptide)]$^{3+}$ complexes differs from that in the singly charged [M(peptide)]$^+$ complexes. The seventh binding site provided by Leu-Trp-Met-Arg is probably the $\pi$-system of the indole, a more powerful electron-donor than the phenyl ring in Met-Arg-Phe-Ala. The extra stabilization provided by tryptophan is illustrated by DFT calculations, which gave the silver ion affinity of tryptophan to

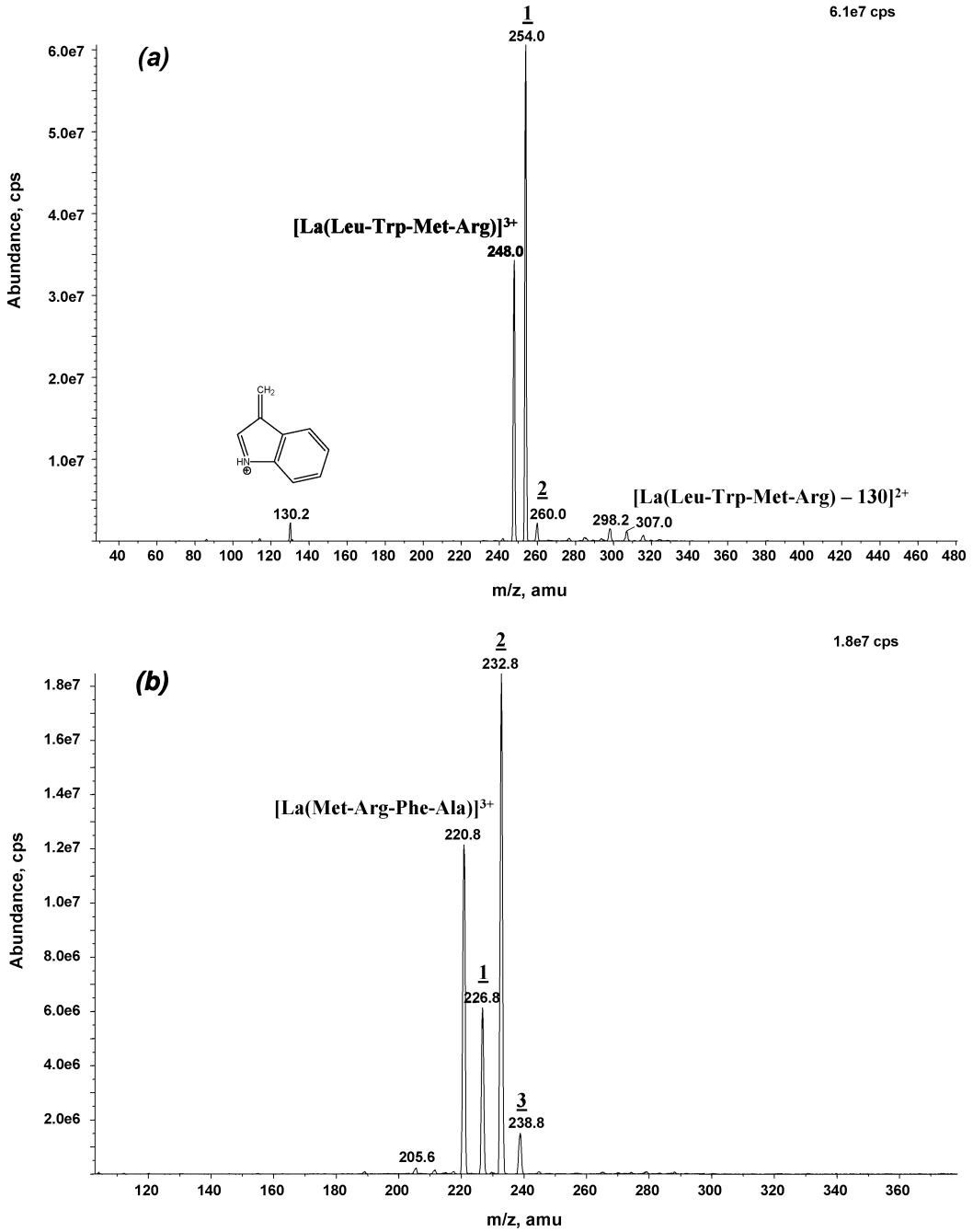



**Figure 2.** CID spectra of (a) [La(Leu-Trp-Met-Arg)]$^{3+}$ and (b) [La(Met-Arg-Phe-Ala)]$^{3+}$ at an $E_{lab}$ = 15 eV and 8 mTorr of water/nitrogen; *n* gives the hydration number in [La(tetrapeptide)$(H_2O)_n$]$^{3+}$.

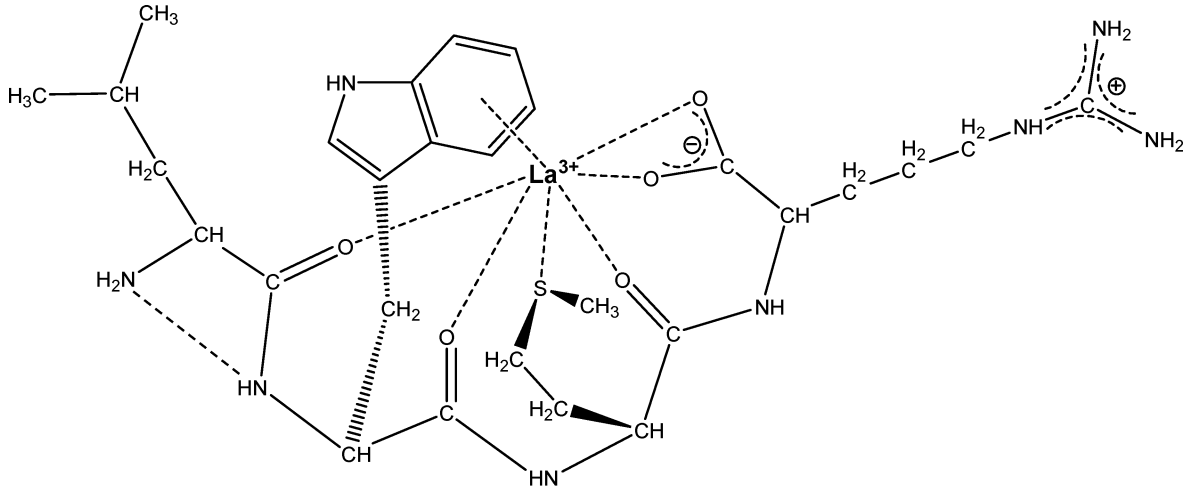
be 62.2 kcal/mol, 5.7 kcal/mol higher than that of phenylalanine.[61] The difference in metal-ion affinities of these two amino acids is likely to be higher for $La^{3+}$ because of the triple charge.

**Tripeptides: Gly-Gly-Arg and Gly-Arg-Gly.** As mentioned in the Introduction, electrospraying a solution of $La^{3+}$ and Gly-Gly-Gly failed to produce the complex [La(Gly-Gly-Gly)]$^{3+}$, but instead resulted in the charge-reduced species [La(Gly-Gly-Gly − H)]$^{2+}$. However, replacing one glycine residue in the tripeptide with an arginine residue *did* result in low abundance of [La(Gly-Gly-Arg)]$^{3+}$ and [La(Gly-Arg-Gly)]$^{3+}$. Again, the arginine residue apparently plays a key role in stabilizing the triply charged lanthanum complexes. The CID spectra of [La(Gly-Gly-Arg)]$^{3+}$ and [La(Gly-Arg-Gly)]$^{3+}$ at an $E_{lab}$ of 15 eV and 8 mTorr of water/nitrogen are shown in Figure 3, parts a and b, respectively.

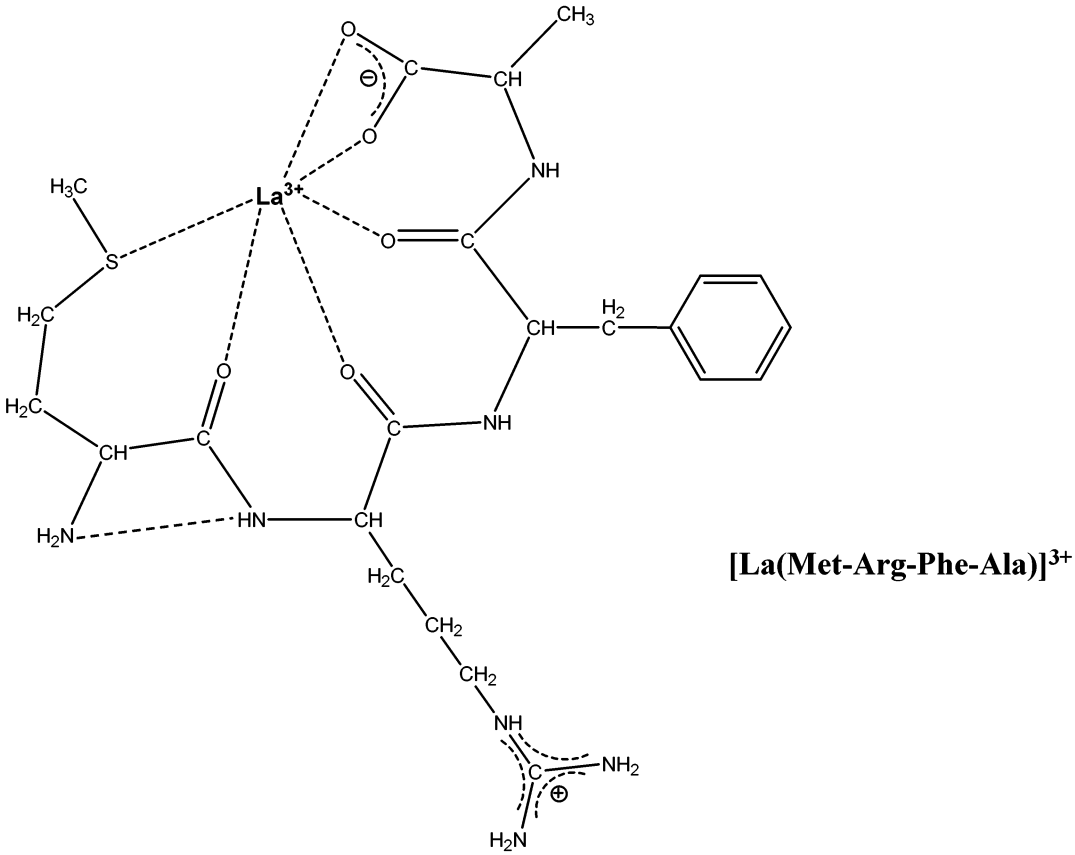
Two reaction channels are apparent: charge reduction and water attachment. In charge reduction, [La(Gly-Gly-Arg)]$^{3+}$ and [La(Gly-Arg-Gly)]$^{3+}$ eliminated protonated methanimine, $H_2N{=}CH_2^+$, to give the doubly charged complexes [La(tripeptide) − $(H_2N{=}CH_2)$]$^{2+}$. These doubly charged product ions then associated with water giving [La(Gly-Gly-Arg) − $(H_2N{=}CH_2)$ + $nH_2O$]$^{2+}$ and [La(Gly-Arg-Gly) − $(H_2N{=}CH_2)$ + $nH_2O$]$^{2+}$. Protonated methanimine has a *m*/*z* value of 29 and is unobservable, as this lies below the low mass cutoff of the API 3000 mass spectrometer.

At a relatively low collision energy of 15 eV, both [La(Gly-Gly-Arg)]$^{3+}$ and [La(Gly-Arg-Gly)]$^{3+}$ associated with water molecules to form complexes [La(tripeptide)$(H_2O)_n$]$^{3+}$, where $n$ = 1−5. Among these complexes, the tetrahydrates, [La(tripeptide)$(H_2O)_4$]$^{3+}$, have the highest abundances (see Figure 3,

**SCHEME 1**




**[La(Leu-Trp-Met-Arg)]$^{3+}$**




**[La(Met-Arg-Phe-Ala)]$^{3+}$**

parts a and b) under a wide range of CID conditions. This strongly suggests that Gly-Gly-Arg and Gly-Arg-Gly plus four water molecules make up the primary solvation shell of $La^{3+}$. We envision that two binding sites are from the anionic carboxy group, a product of proton migration from the carboxylic group to the basic side chain of the arginine residue, and the other two binding sites are the two carbonyl oxygens of the peptide bonds (Scheme 2).

To verify the aforementioned conclusions regarding $La^{3+}$ coordination, low-energy CID of $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)_n]^{3+}$ and $[La(Gly\text{-}Arg\text{-}Gly)(CH_3CN)_n]^{3+}$ were examined. These complexes were produced in high abundances when electrospraying $La^{3+}$ and the tripeptide in the presence of acetonitrile. Figure 3c shows a CID spectrum of $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)_2]^{3+}$ at an $E_{lab}$ of 15 eV. Two reaction channels, auxiliary ligand loss and water attachment, operating individually or in tandem were apparent, and resulting in $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)_2(H_2O)_n]^{3+}$ ($n = 1-3$) and $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)(H_2O)_n]^{3+}$ ($n = 1-4$). Among the hydrates, $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)_2\ (H_2O)_2]^{3+}$ and $[La(Gly\text{-}Gly\text{-}Arg)(CH_3CN)(H_2O)_3]^{3+}$ had the highest abundances. These results strongly corroborate the earlier conclusion that Gly-Gly-Arg provides four $La^{3+}$ binding sites.

The six lowest-energy structures of $[La(Gly\text{-}Gly\text{-}Arg)]^{3+}$ as determined by DFT are shown in Figure 4. Complexes containing Gly-Gly-Arg in its canonical form have higher energies (by

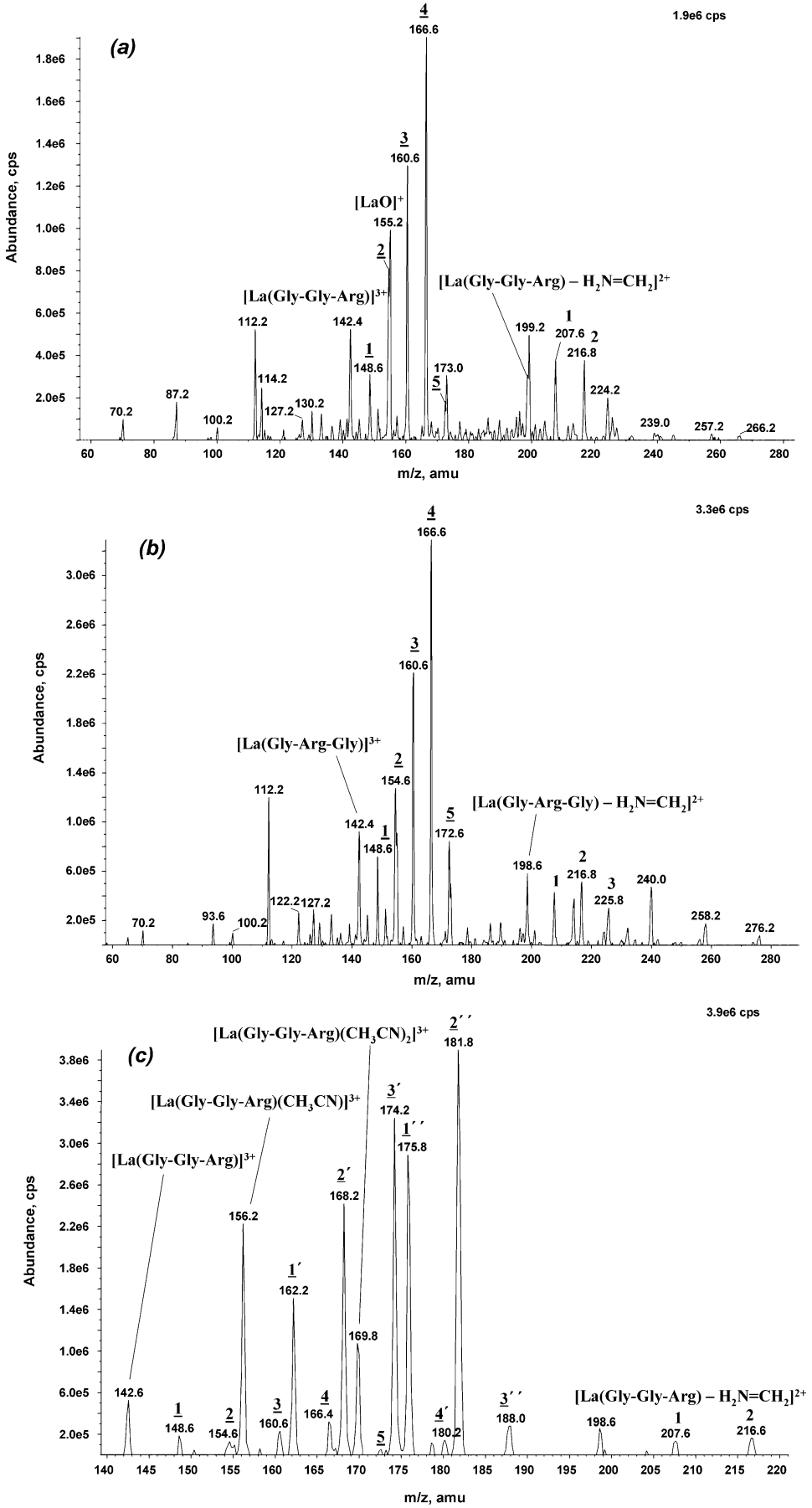



**Figure 3.** CID spectra of (a) $[La(Gly-Gly-Arg)]^{3+}$, (b) $[La(Gly-Arg-Gly)]^{3+}$, and (c) $[La(Gly-Gly-Arg)(CH_3CN)_2]^{3+}$ at an $E_{lab} = 15$ eV and 8 mTorr of water/nitrogen; $n$ gives the hydration number in $[La(tripeptide)(H_2O)_n]^{3+}$, $n'$ in $[La(tripeptide)(CH_3CN)(H_2O)_n]^{3+}$, $n''$ in $[La(tripeptide)(CH_3CN)_2(H_2O)_n]^{3+}$, and $n$ in $[La(tripeptide) - (H_2N{=}CH_2) + nH_2O]^{2+}$.

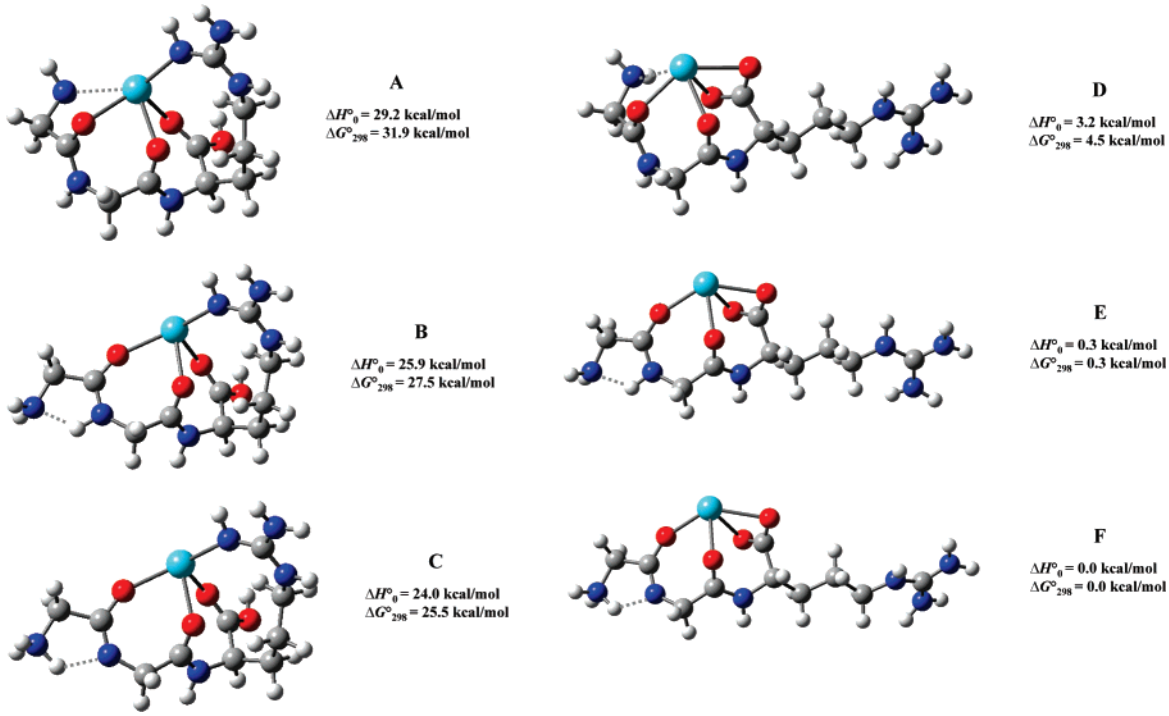
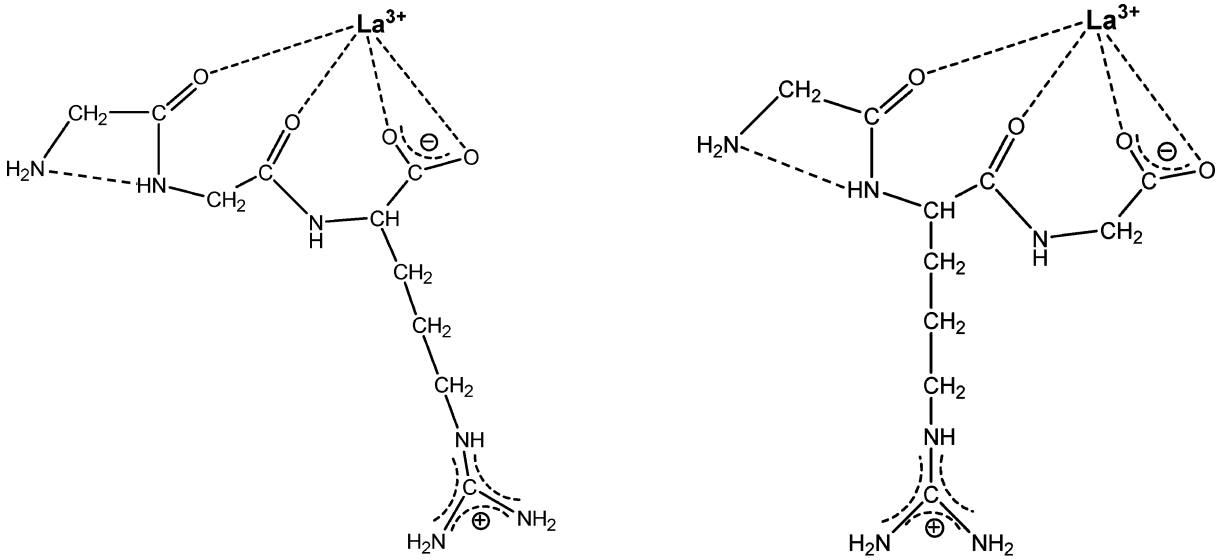



**Figure 4.** Low-energy structures of [La(Gly-Gly-Arg)]$^{3+}$ complexes at the B3LYP/*sdd*/6-31G** level of theory. Upper values are relative enthalpies at 0 K ($\Delta H°_0$); lower, italicized values are relative free energies at 298 K ($\Delta G°_{298}$).

**SCHEME 2**




more than 20 kcal/mol) than those containing the peptide as a zwitterion. Among the canonical structures, the pentacoordinate structure **A** is slightly higher in enthalpy **(**by 3.3 kcal/mol) than the tetracoordinate structure **B**, indicating that the hydrogen bond between the N-terminal amide hydrogen and the amino nitrogen is slightly *stronger* than the interaction between $La^{3+}$ and the N-terminal nitrogen. Structure **B** can isomerize into **C** by transferring the amidic proton to the N-terminal nitrogen; structure **C** is 1.9 kcal/mol lower in enthalpy than **B**.

Proton transfer from the carboxylic group to the basic side chain generates the zwitterionic form, and effectively delocalizes the positive charge. In structure **D**, $La^{3+}$ is *pentacoordinated* to the zwitterionic peptide, and the binding sites are the N-terminal nitrogen, the two amide oxygens, and the two carboxylic oxygens. By contrast, in structures **E** and **F**, both lower in enthalpy than **D** by approximately 3 kcal/mol, $La^{3+}$ is only *tetracoordinated* to four oxygens, but there is *an additional hydrogen bond* between the N-terminal amide hydrogen and the amino nitrogen. Structure **E** can isomerize into **F** by transferring the amidic proton to the amine nitrogen, and once again, it is noteworthy that the lower coordination of $La^{3+}$ is more than compensated for by the strong hydrogen bond. Similarly, among the structures of deprotonated [La(Gly-Gly-Gly − H)]$^{2+}$ the lowest-energy structure also has $La^{3+}$ bound

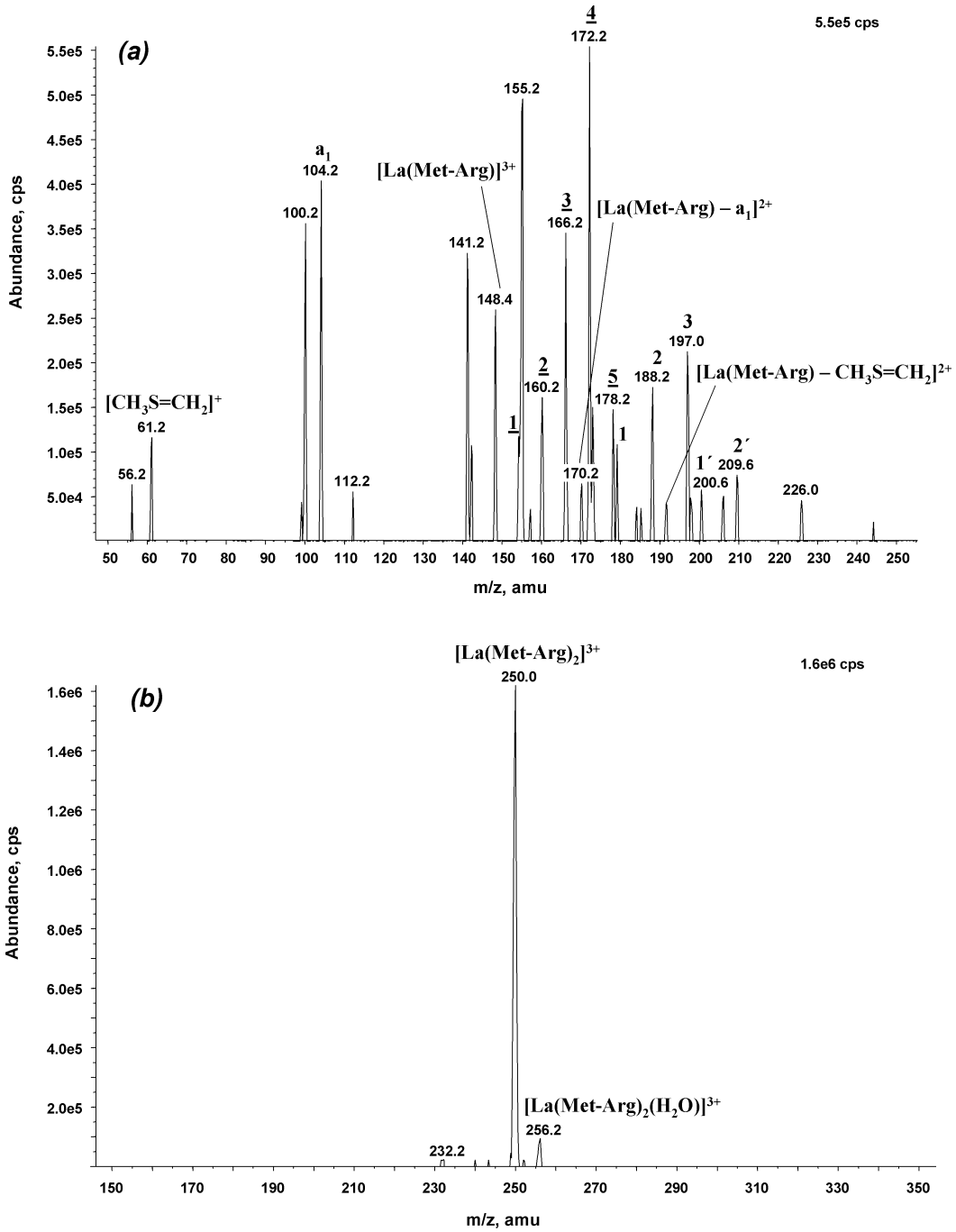



**Figure 5.** CID spectra of (a) $[La(Met\text{-}Arg)]^{3+}$ (at an $E_{lab} = 15$ eV), and (b) $[La(Met\text{-}Arg)_2]^{3+}$ (at an $E_{lab} = 30$ eV) with 8 mTorr of water/nitrogen; $n$ gives the hydration number in $[La(Met\text{-}Arg)(H_2O)_n]^{3+}$, $n$ in $[La(Met\text{-}Arg) - a_1 + nH_2O]^{2+}$, and $n'$ in $[La(Met\text{-}Arg) - (CH_3S{=}CH_2) + nH_2O]^{2+}$.

to four oxygens from the amide and the carboxylic groups, and the N-terminal nitrogen is hydrogen-bonded to an amidic hydrogen.

**Dipeptide: Met-Arg.** For the dipeptides, the presence of an arginine residue was not sufficient to stabilize the [La-(dipeptide)]$^{3+}$ complexes and attempts at producing complex $[La(Gly\text{-}Arg)]^{3+}$ were unsuccessful; only the charge-reduced complex $[La(Gly\text{-}Arg - H)]^{2+}$ was observed. However, electrospraying a solution containing $La^{3+}$ and the dipeptide Met-Arg produced $[La(Met\text{-}Arg)]^{3+}$, albeit in low abundance. We attribute the existence of this complex ion to the introduction of an additional binding site, the sulfur atom in the side chain of the methionine residue.

The CID spectrum of $[La(Met\text{-}Arg)]^{3+}$ at an $E_{lab}$ of 15 eV and 8 mTorr of water/nitrogen (Figure 5a) reveals two charge-separation channels. The first involves formation of the $a_1$ ion plus $[La(Met\text{-}Arg) - a_1]^{2+}$, and the second fragmentation of the side chain of the methionine residue yielding methylated thioformaldehyde, $H_2C{=}S^+{-}CH_3$, and $[La(Met\text{-}Arg) - H_2C{=}S{-}CH_3]^{2+}$. The most abundant channel, however, is the addition of water to form complexes $[La(Met\text{-}Arg)(H_2O)_n]^{3+}$, where $n = 1{-}6$, of which the most abundant is $[La(Met\text{-}Arg)(H_2O)_4]^{3+}$. This indicates that Met-Arg contributes four sites to $La^{3+}$ binding.

In the Q1 scan, the relative abundance of $[La(Met\text{-}Arg)_2]^{3+}$ was higher than that of $[La(Met\text{-}Arg)]^{3+}$. Furthermore, very little fragmentation of $[La(Met\text{-}Arg)_2]^{3+}$ occurred under CID conditions, even at an $E_{lab}$ as high as 30 eV (Figure 5b), and the adduction of *only* one water molecule to $[La(Met\text{-}Arg)_2]^{3+}$ was observed and in very low abundance throughout a wide range

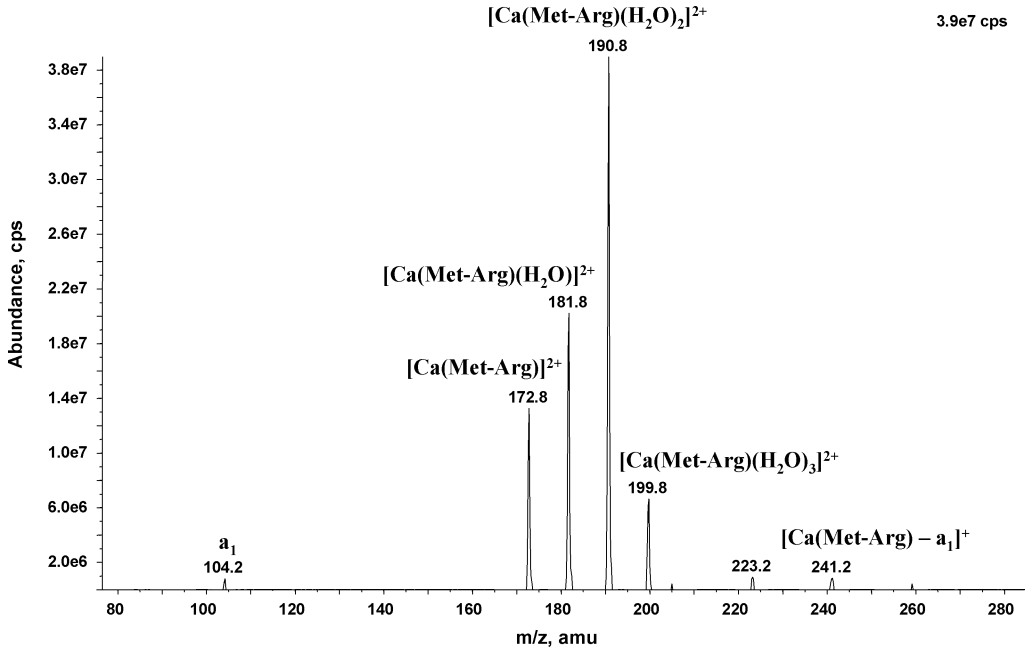
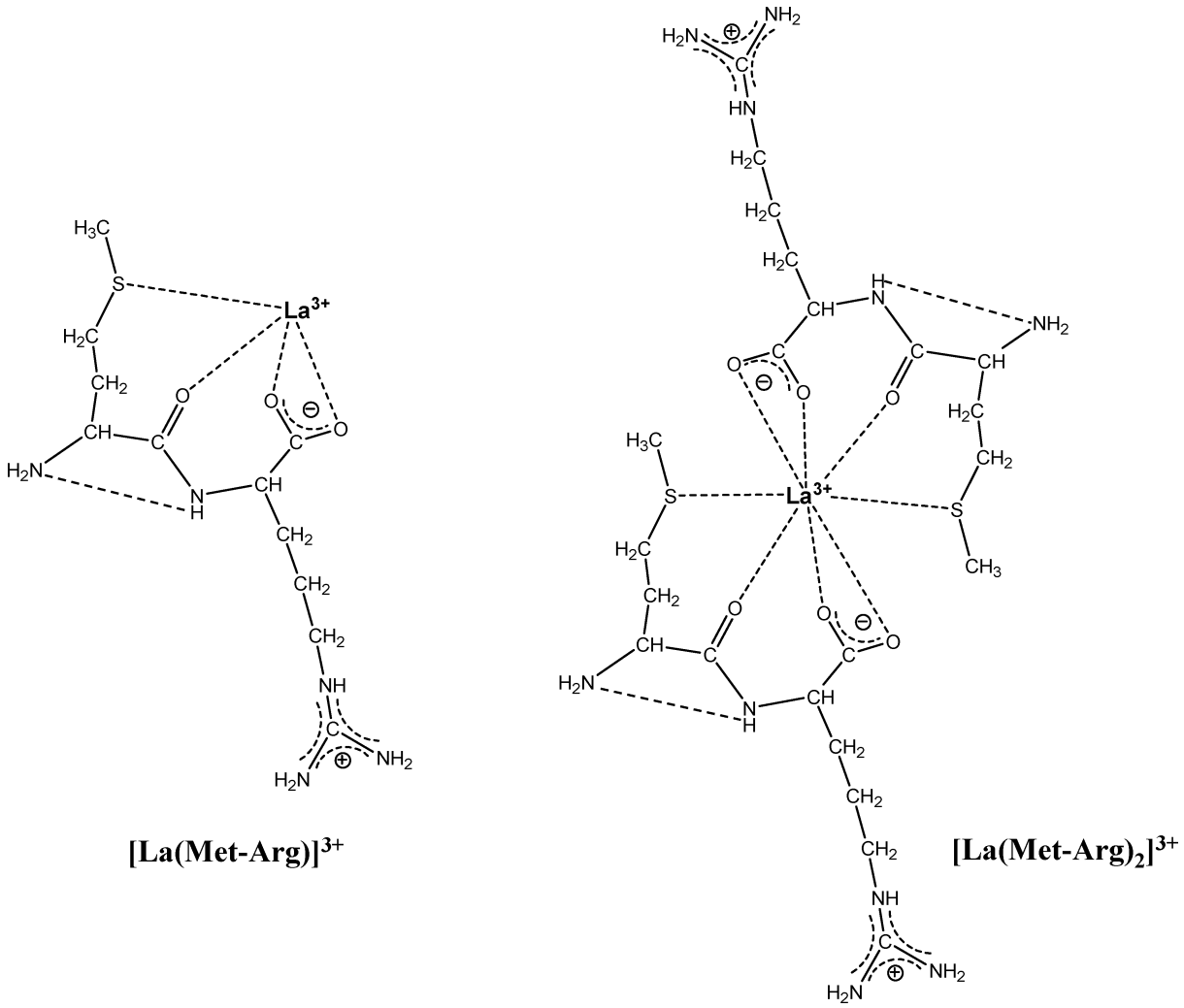



**Figure 6.** CID spectrum of [Ca(Met-Arg)]$^{2+}$ at an $E_{lab}$ = 15 eV and 8 mTorr water/nitrogen.

**SCHEME 3**




of experimental conditions. These experimental observations strongly support the hypothesis that in [La(Met-Arg)$_2$]$^{3+}$ the $La^{3+}$ is octacoordinate and has its eight coordination sites saturated by two Met-Arg peptides (Scheme 3).

Calcium(II) is well-known to be six-coordinate in the gas phase.[40] To corroborate the above findings on Met-Arg, we examined $[Ca(Met\text{-}Arg)]^{2+}$. In the low-energy CID spectrum ($E_{lab}$ of 10 eV) of $[Ca(Met\text{-}Arg)]^{2+}$ (Figure 6), there was some fragmentation of the peptide backdone, leading to the charge-separation products $a_1$ plus $[Ca(Met\text{-}Arg)] - a_1]^+$. However, the predominant channel was association with water, forming the adducts $[Ca(Met\text{-}Arg)(H_2O)_n]^{2+}$, where $n = 1-3$. The product in highest abundance has $n = 2$, verifying the conclusion that Met-Arg provides four binding sites.

## Conclusions

Complexes of tripositively charged metal ions bound to small peptides are rarely observed in the gas phase. We observed, however, that if one of the residues is arginine, it is possible to produce complexes of the type $[La(peptide)]^{3+}$, in which the peptide contains, four, three or even only two residues. The arginine residue delocalizes the positive charge with the peptide being in the zwitterionic form and the carboxylic proton having relocated to the guanidine group of the arginine side chain. In the case of the dipeptide, the only complex that we observed was $[La(Met\text{-}Arg)]^{3+}$; we attribute the extra stability of this complex to ligation of the $La^{3+}$ by the S atom from the side chain of the methionine residue.

Knowing that the preferred coordination number of $La^{3+}$ in the gas phase is eight, and observing the number of additional monodendate ligands required to make the most abundant complex enables us to deduce the number of binding sites provided by each peptide. For the tetrapeptides, Met-Arg-Phe-Ala has six binding sites and Leu-Trp-Met-Arg seven, leading us to conclude that in addition to coordination through five oxygen atoms and the sulfur, Leu-Trp-Met-Arg also coordinates through the indole group of the tryptophan residue. For the tripeptides, complexes of the type $[La(tripetide)(monodentate\ ligand)_4]^{3+}$ are the most abundant, indicating that the tripeptide provides four binding sites. DFT calculations show that the lowest energy structure of $[La(Gly\text{-}Gly\text{-}Arg)]^{3+}$ contains a zwitterionic peptide bound to the $La^{3+}$ through the four oxygen atoms. Finally, in $[La(Met\text{-}Arg)]^{3+}$, the dipeptide is zwitterionic and provides four binding sites—the three oxygens and the sulfur. The complex $[La(Met\text{-}Arg)_2]^{3+}$ has all eight coordination sites of $La^{3+}$ occupied and is very stable.

**Acknowledgment.** This study was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada. Hardware support by MDS SCIEX is gratefully acknowledged.

**Supporting Information Available:** Cartesian coordinates and electronic energies for all structures are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) Russell, D. H.; McGlohon, E. S.; Mallis, L. M. *Anal. Chem.* **1988**, *60*, 1818.
(2) Adams, J. *Mass Spectrom. Rev.* **1990**, *9*, 141.
(3) Teesch, L. M.; Adams, J. *J. Am. Chem. Soc.* **1990**, *112*, 4110.
(4) Teesch, L. M.; Adams, J. *J. Am. Chem. Soc.* **1991**, *113*, 812.
(5) Hu, P. F.; Gross, M. L. *J. Am. Chem. Soc.* **1992**, *114*, 9161.
(6) Zhao, H.; Reiter, A.; Teesch, L. M.; Adams, J. *J. Am. Chem. Soc.* **1993**, *115*, 2854.
(7) Zhao, H.; Adams, J. *Int. J. Mass Spectrom. Ion Process.* **1993**, *125*, 195.
(8) Reiter, A.; Zhao, H.; Adams, J. *Org. Mass Spectrom.* **1993**, *28*, 1596.
(9) Reiter, A.; Teesch, L. M.; Zhao, H.; Adams, J. *Int. J. Mass Spectrom. Ion Processes* **1993**, *127*, 17.
(10) Hu, P. F.; Gross, M. L. *J. Am. Chem. Soc.* **1993**, *115*, 8821.
(11) Reiter, A.; Adams, J.; Zhao, H. *J. Am. Chem. Soc.* **1994**, *116*, 7827.
(12) Loo, J. A.; Hu, P. F.; Smith, R. D. *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 959.
(13) Hu, P. F.; Gross, M. L. *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 137.
(14) Hu, P. F.; Sorensen, C.; Gross, M. L. *J. Am. Soc. Mass Spectrom.* **1995**, *6*, 1079.
(15) Hu, P. F.; Loo, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 11314.
(16) Lin, T.; Glish, G. L. *Anal. Chem.* **1998**, *70*, 5162.
(17) Lee, V. W. M.; Li, H. B.; Lau, T. C.; Siu, K. W. M. *J. Am. Chem. Soc.* **1998**, *120*, 7302.
(18) Lee, S. W.; Kim, H. S.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1998**, *120*, 3188.
(19) Chu, I. K.; Guo, X.; Lau, T. C.; Siu, K. W. M. *Anal. Chem.* **1999**, *71*, 2364.
(20) Lin, T.; Payne, A. H.; Glish, G. L. *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 497.
(21) Kish, M. M.; Wesdemiotis, C. *Int. J. Mass Spectrom.* **2003**, *227*, 191.
(22) Feng, W. Y.; Gronert, C.; Fletcher, K. A.; Warres, A.; Lebrilla, C. B. *Int. J. Mass Spectrom.* **2003**, *222*, 117.
(23) Anbalagan, V.; Patel, J. N.; Niyakorn, G.; Van Stipdonk, M. J. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 291.
(24) Newton, K. A.; McLuckey, S. A. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 607.
(25) Bulleigh, K.; Howard, A.; Do, T.; Wu, Q.; Anbalagan, V.; Van Stipdonk, M. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 227.
(26) Cerda, B.; Cornett, L.; Wesdemiotis, C. *Int. J. Mass Spectrom.* **1999**, *193*, 205.
(27) Shields, S. J.; Bluhm, B. K.; Russell, D. H. *Int. J. Mass Spectrom.* **1999**, *183*, 185.
(28) Shields, S. J.; Bluhm, B. K.; Russell, D. H. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 626.
(29) Li, H. B.; Siu, K. W. M.; Guevremont, R.; LeBlanc, J. C. Y. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 781.
(30) Chu, I. K.; Shoeib, T.; Guo, X.; Rodriquez, C. F.; Lan, T. C.; Hopkinson, A. C.; Siu, K. W. M. *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 163.
(31) Anbalagan, V.; Perera, B. A.; Silva, A. T. M.; Gallardo, A. L.; Barber, M.; Barr, J. M.; Terkarli, S. M.; Talaty, E. R.; Van, Stipdonk, M. J. *J. Mass Spectrom.* **2002**, *37*, 910.
(32) Chu, I. K.; Cox, D. M.; Guo, X.; Kireeva, I.; Lau, T. C.; McDermott, J. C.; Siu, K. W. M. *Anal. Chem.* **2002**, *74*, 2072.
(33) Nemirovskiy, O. V.; Gross, M. L. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1020.
(34) Blades, A. T.; Jayaweera, P.; Ikonomou, M. G.; Kebarle, P. *Int. J. Mass Spectrom. Ion Processes* **1990**, *101*, 325.
(35) Cheng, Z. L.; Siu, K. W. M.; Guevremont, R.; Berman, S. S. *Org. Mass Spectrom.* **1992**, *27*, 1370.
(36) Walker, N. R.; Wright, R. R.; Stace, A. J.; Woodward, C. A. *Int. J. Mass Spectrom.* **1999**, *188*, 113.
(37) Vukomanovic, D.; Stone, J. A. *Int. J. Mass Spectrom.* **2000**, *202*, 251.
(38) Shvartsburg, A. A.; Jones, R. C. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 406.
(39) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 84th ed.; CRC Press: Roca Baton, FL, 2004.
(40) Shi, T.; Hopkinson, A. C.; Siu, K. W. M. *Chem. Eur. J.* **2007**, *13*, 1142.
(41) Dudev, T.; Chang, L. Y.; Lim, C. *J. Am. Chem. Soc.* **2005**, *127*, 4091.
(42) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; Wiley & Sons: New York, 1988.
(43) Evans, C. H. *Biochemistry of the Lanthanides*; Plenum: New York, 1990.
(44) Dongré, A. R.; Jones, J. L.; Somogyi, A.; Wysocki, V. H. *J. Am. Chem. Soc.* **1996**, *118*, 8365.
(45) Cox, K. A.; Gaskell, S. J.; Morris, M.; Whiting, A. *J. Am. Soc. Mass Spectrom.* **1996**, *7*, 522.
(46) Shi, T.; Orlova, G.; Guo, J.; Bohme, D. K.; Hopkinson, A. C.; Siu, K. W. M. *J. Am. Chem. Soc.* **2004**, *126*, 7975.
(47) Shi, T.; Zhao, J.; Hopkinson, A. C.; Siu, K. W. M. *J. Phys. Chem. B* **2005**, *109*, 10590.
(48) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V. Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J. Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.;

Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B 04; Gaussian, Inc.: Pittsburgh, PA, 2003.

(49) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098.

(50) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(51) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.

(52) Dolg, M.; Stoll, H.; Sovin, A.; Preuss, H. *Theor. Chim. Acta* **1989**, *75*, 173.

(53) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(54) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *16*, 217.

(55) Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5609.

(56) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

(57) Bagheri-Majdi, E.; Ke, Y. Y.; Orlova, G.; Chu, I. K.; Hopkinson, A. C.; Siu, K. W. M. *J. Phys. Chem. B* **2004**, *108*, 11170.

(58) El Aribi, H.; Orlova, G.; Hopkinson, A. C.; Siu, K. W. M. *J. Phys. Chem. A* **2004**, *108*, 3844.

(59) Shoeib, T.; Rodriquez, C. F.; Siu, K. W. M.; Hopkinson, A. C. *Phys. Chem. Chem. Phys.* **2001**, *3*, 853.

(60) Kish, M. M.; Wesdemiotis, C.; Ohanessian, G. *J. Phys. Chem. B* **2004**, *108*, 3086.

(61) Shoeib, T.; Siu, K. W. M.; Hopkinson, A. C. *J. Phys. Chem. A* **2002**, *106*, 6121.