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*Research Article*

# Bonding, Structure, and Stability of $[(Na)_n(Phe)_m]^{n+}$ Clusters: Some Surprising Results from an Experimental and Theoretical Investigation in Gas Phase

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Structure and stability of $[(Na)_n(Phe)_m]^{n+}$ clusters in the ground state were analyzed at the theoretical and experimental levels. Our experimental and theoretical findings showed that the $[(Na)_n(Phe)_m]^{n+}$ clusters in gas phase tend to form mainly planar rings of four members. The symmetry and the small dipole moment in these specific configurations suggested that their stability could be associated with an alignment of the water molecules, maximizing attractive electrostatic interactions caused by changes in the charge distribution of the clusters.

## 1. Introduction

Three-dimensional structures of proteins are strongly influenced by noncovalent interactions. Van der Waals bonding, hydrophobic interactions, hydrogen bonds, and ionic bonds are responsible for these structural effects and biological activity. Several individually weak bonds, acting cooperatively, often allow molecular recognition by precisely positioning partner atoms and groups [1].

Since metal ions are essential cofactors in many important proteins, several studies have been performed toward understanding the factors governing metal binding in metalloproteins [2].

Among metal ions, alkali metals chemistry has received an increasing interest during the past decades [3, 4], because their cations play an important role, especially in biochemical processes. They interact with proteins and peptides to control structural and regulating properties [5, 6]. For instance, the role of alkali cations in peptide conformation deserves special attention and the study of their interaction with amino acids is expected to give insights to support structural assumptions necessary to interpret some molecular biology phenomena.

In this line, phenylalanine (Phe) is often chosen as a representative unit of the hydrophobic backbone in a protein. In order to simulate what may occur in biology, where the alkali metal-hydrophobic core is an important component, we carried out a study of various $Na^+$ clusters with phenylalanine amino acids.

Alkali metal ion clusters present unusual structural, magnetic, and catalytic properties, which ultimately depend on their electronic structure, different from those of the ion alone [2].

The Electrospray Ionization Mass Spectrometry (ESI-MS) has been used as a tool to investigate the metal-bound tetrameric complexes [7, 8] and in general is useful for the study of noncovalently bound intermolecular clusters of biomolecules.

In general, the ESI-MS data are shown to display high correlations with expectations based on solution-phase studies [9–12]. However, it is not to be expected that the correlation will be perfect, since ion-molecule reactions may intervene and, in any event, the three-dimensional structure of the gas-phase complex cannot be the same as the solvated species [9]. Nevertheless, the operating hypothesis when using ESI for the study of cluster ions [13–15] is that it is possible to sample species present in solution, allowing gas-phase data to be acquired and compared with the solution data.

On the theoretical side, electronic structure calculations on alkali metal clusters pose a considerable challenge: the existence of multiple isomers, and the electronic nature of alkali metal ions, which leads to several interactions between the metal ions and ligands [16, 17].

Furthermore the nonbonded interactions can play an important role in the stability and structural chemistry of alkali metal clusters. In fact, nonbonded interactions modulate the conformations of virtually every molecule. The influence of electrostatic and dispersive forces on the conformation of biological macromolecules offers another well-known example of this phenomenon [2]. An approach to investigate this problem is the use of theoretical calculations. Calculations involving coordination compounds are, however, complicated by a variety of possible geometries and by different metal oxidation states [15]. For instance, it is well known that the use of post-Hratree–Fock techniques to describe complexes between metals and amino acids is limited by the complexity of the system to be studied. On the other hand, DFT methods have been increasingly applied to the study of the interaction of metals with biomolecules. This approach is interesting because it includes the effect of electronic correlations and allows for the calculation of larger systems [17].

Thus, the main goal of this paper was to study the interaction between phenylalanine and $Na^+$ ions in gas phase using theoretical and experimental approaches.

## 2. Methodology

*2.1. Studies by ESI-MS.* The analysis of the solution composition after the reaction was conducted by introducing aliquots of the solution into the ESI source (Agilent Technologies, Santa Clara, CA, USA) with a syringe pump at a flow rate of 5 mL $min^{-1}$. The spectra were obtained as an average of 50 scans of 0.2 s each. Typical ESI conditions were as follows: capillary temperature of 1508°C, carrier gas ($N_2$) at a flow rate of ca. 4 L $min^{-1}$, spray voltage of 4 kV, capillary voltage of 25 V, and tube lens offset voltage of 25 V.

Charge states of cluster ions were determined by mass/charge ratio measurements and confirmed by higher resolution experiments and tandem mass spectrometry. Isolation of the ions of interest was achieved using a notched waveform to affect broadband excitation and ejection of the undesirable ions.

The d-phenylalanine and the salt (sodium chloride) were obtained from Aldrich. Methanol was purchased from Fisher Scientific and used to prepare the mobile phase, methanol–water (1 : 1 v/v), and also used to prepare 0.01 M solutions of amino acids and salts.

*2.2. Quantum Chemical Methods.* The calculations were carried out with the Gaussian 03 package [18]. Each conformer was fully optimized by PM3 [19] and Density Functional Theory (DFT) methods. The energy profile at selected DFT geometries along the reaction pathway was computed at HCTH level of theory using the LANL2DZ basis set. This computational procedure has been employed previously on similar systems with success [20, 21]. Furthermore, after each optimization, the nature of each stationary point was established by calculating and diagonalizing the Hessian matrix (force constant matrix). The unique imaginary frequency associated with the transition vector (TV) [22], that is, the eigenvector associated with the unique negative eigenvalue of the force constant matrix, was characterized. All discussions concerning the energy differences and the energy barriers refer to the $\Delta G$ term ((1), Figure 1), corrected for the zero point energy (ZPE) at 298.15 K in the Gaussian 03 program [20–23].

The basis on which the thermodynamic cycle approach rests is the fact that the (Gibbs) free energy is a thermodynamic state function. This means that as long as a system is changed in a reversible way the change in free energy $\Delta G$ will be independent of the path. Therefore, along a closed path or cycle one has $\Delta G = 0$. It can be used to study the relative free energy of solvation of species [24]. One has

$$\Delta G_{aq} = \Delta G_{SOLV}\left[(Na)_n\,(Phe)_m\right]^{n+} - \left[\Delta G_{SOLV}(Na)^+ + \Delta G_{SOLV}\,(Phe)\right] + \Delta G_g. \quad (1)$$

For all the species studied, we have checked $\langle S^2 \rangle$ values to evaluate whether spin contamination can influence the quality of the results. In all cases we have found that the calculated values differ from $S(S + 1)$ by less than 10%.

## 3. Results and Discussion

*3.1. Identification of the Cluster Formed via Online ESI-MS Monitoring.* In order to identify the behavior of alkali metal clusters in gas phase, we simulated the chemical reaction between d-phenylalanine amino acid and $Na^+$ ion. The identification of reaction intermediates was performed online by the ESI-MS equipment. It is worth noting that the signal corresponding to $m/z = 683$ was the most intense in the mass spectrum.

Figure 2 shows the whole mass spectrum obtained from the solution of phenylalanine with $Na^+$ ion. The main signal ($m/z = 683.0$) corresponds to four molecules of phenylalanine and one sodium ion. According to our calculations, the $m/z = 683.0$ fragment is due to tetramer formation between four molecules of phenylalanine amino acid with one $Na^+$ ion. It is interesting to mention that the $m/z = 683.0$ fragment might also refer to all tetramer multiples because eight molecules of phenylalanine bonded to two $Na^+$ ions can lead to the same fragment.

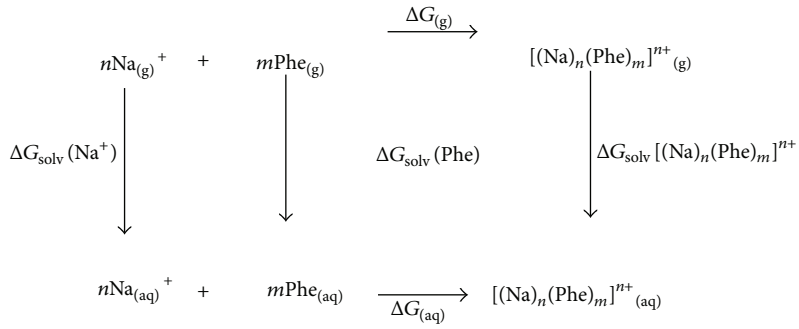



Figure 1: Thermodynamics cycle.

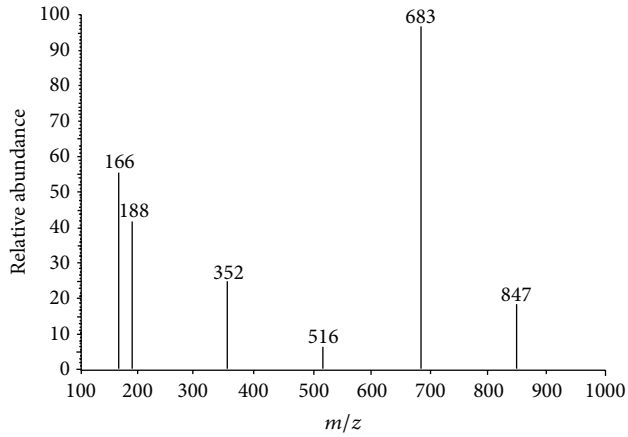



Figure 2: ESI mass spectra in the positive ion mode for monitoring the chemical reaction.

The $m/z$ = 188.0 fragment exists in the same proportion of molecules of phenylalanine and number of $Na^+$ ions. The $m/z$ = 188.0 fragment displays a less intense signal when compared to the fragment at $m/z$ = 683 (tetramer derivative fragments). Other less intense signals were observed in Figure 2; the fragment at $m/z$ = 353.0 is related to two phenylalanine molecules and one $Na^+$ ion, while the fragment at $m/z$ = 166 corresponds to protonated phenylalanine.

In line with our findings, we can therefore observe that it is likely that there is an extra stabilization with respect to the fragments from the tetramers.

*3.2. Theoretical Calculations.* In order to investigate the factors that govern the stabilization of the tetramer fragments, we have used theoretical calculations. Thus, we performed Gibbs free energy calculations for the fragments related to phenylalanine and $Na^+$ clusters found in the mass spectrum. For the fragment $m/z$ = 188, we carried out the theoretical calculations with two phenylalanine molecules and two $Na^+$ ions; for the fragment at $m/z$ = 353, two molecules of phenylalanine and one $Na^+$ ion were used; and for $m/z$ = 683, we have performed calculations using the tetramer. Each situation was investigated using different geometries and a coordination environment with the phenylalanine residues bonded to the cation through the $NH_2$, C=O, or OH groups. The calculated energies and geometries of the studied systems are reported in Table 1 at the DFT level. The semiempirical calculations were performed just for a step of preoptimization of the system.

Different potential binding sites (electron-rich sites) for the $Na^+$ ion on the free phenylalanine molecule were considered: the N and O ions and the aromatic ring, considering both the mono- and bidentate coordinations.

According to Table 1, for the fragment at $m/z$ = 353 (structures from **I** to **III**), the lowest free energy was obtained for the cluster model where the $Na^+$ cation is bonded only between the carboxyl groups of two molecules of phenylalanine (structure **II**). There is a difference of +240 and +64.27 kcal/mol for **I** and **III**, respectively. We got similar results for $m/z$ = 188 (structures **IV**–**VI**), because the energy values indicated that the most stable cluster was that with the $Na^+$ ion coordinated with the carboxyl groups without the participation of the amino group. For $m/z$ = 188, the energy difference between the structures **IV** and **V** is 303.53 kcal·mol$^{-1}$. For the fragment $m/z$ = 683 (structures **VII**–**X**), the $Na^+$ ion bonded alternately to the C=O and OH groups was the more stable cluster, revealing the following stability order: **X** > **VII** > **IX** > **VIII.**

From a topological point of view, very similar complexes were found for the other aromatic amino acids, in agreement with previous studies involving other metals [25, 26], which suggested that the hydroxyl substituent does not significantly influence the binding.

Thus, in order to shed some light on this fact from a thermodynamic point of view, we carried out potential energy curve (PEC) calculations varying the Na–O=C, Na–OH, and Na–$NH_2$ bond lengths (Figure 3). The Gibbs free energy data indicated that the carboxyl group seems to have a more stable chemical bond with the $Na^+$ ion than both the amino and hydroxyl groups of the amino acid residue. In this line, we have also observed that hydroxyl groups increased the strength of the intracluster hydrogen bonds between the amino acids molecules.

Turning now to the potential energy curve, it is clear that the most stable chemical bond involved the cation with the carbonyl group. The same free energy values were observed

Table 1: Relative Gibbs free energy values obtained with proposed cation at the DFT level.

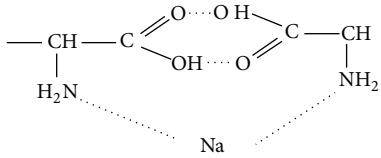
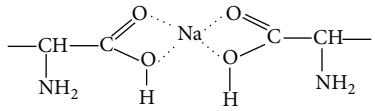
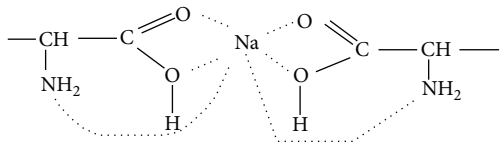
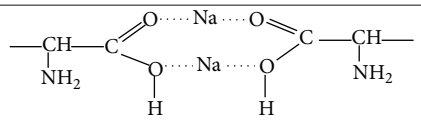
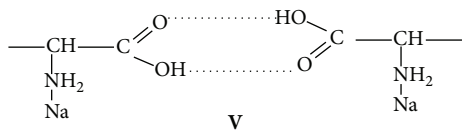
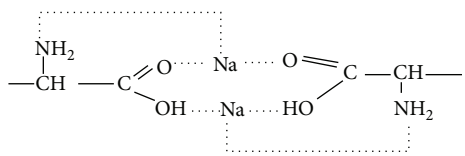
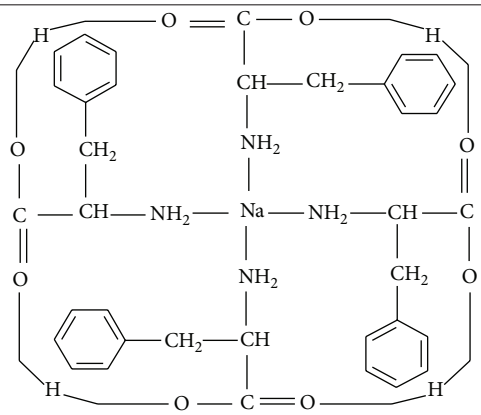
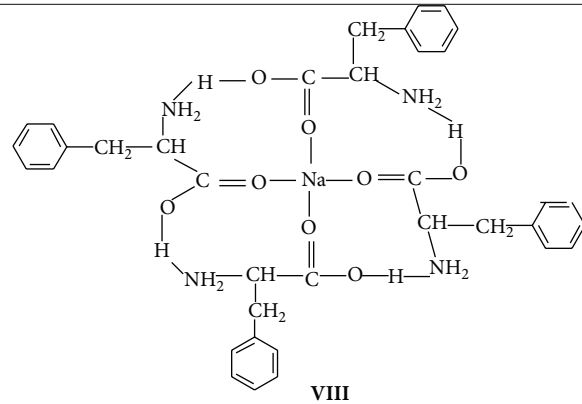
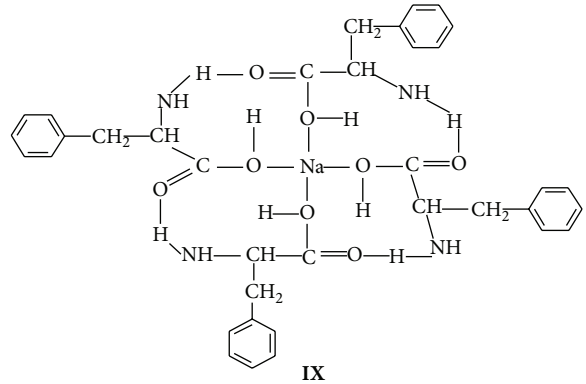
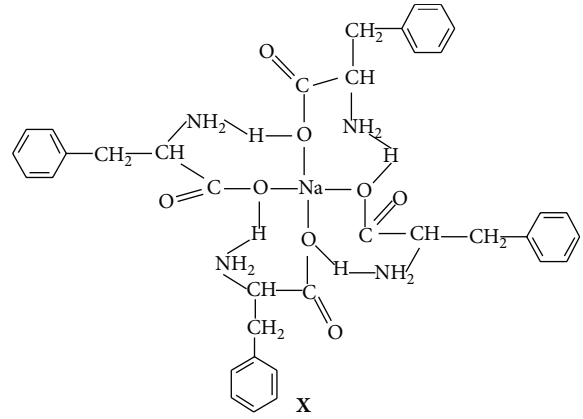
| Fragment ($m/z$) | Coordination environment | $\Delta\Delta G$ (kcal/mol) |
|---|---|---|
| 353<br>$[(Na)\,1\,(Phe)\,2]^{+1}$ |  <br>**I** | 240.46 |
| |  <br>**II** | 0.00 |
| |  <br>**III** | 64.27 |
| 188<br>$[(Na)\,2\,(Phe)\,2]^{+2}$ |  <br>**IV** | 0.00 |
| |  <br>**V** | 303.54 |
| |  <br>**VI** | 5.65 |
| |  <br>**VII** | 16.40 |

Table 1: Continued.

| Fragment ($m/z$) | Coordination environment | $\Delta\Delta G$ (kcal/mol) |
|---|---|---|
| |  **VIII** | 232.00 |
| 683<br>$[(Na)\,1\,(Phe)\,4]^{+1}$ |  **IX** | 106.30 |
| |  **X** | 0.00 |

for both Na–OH and Na–N chemical bonds. Indeed, a deeper analysis reveals that the C=O group is the most promising group to bind with the cation, stabilizing the cluster formed between the amino acid phenylalanine and the cation $Na^+$. It seems that a smaller cation leads to better H-bonding among the molecules bound to the cation. Thus, the tetramer formed should have the form shown in Figure 4.

The tetrameric cluster of Phe and the $Na^+$ ion is clearly a magic number cluster, as illustrated by the data shown in Figure 3. In fact, monovalent cations may stabilize the tetraplex cluster with guanine in the order $K^+ > Na^+ > Li^+$ [27–30].

Regarding this hypothesis, the higher stability of alkali metal ion clusters with amino acids containing "magic numbers" can be related to the predominance of electrostatic effects over van der Waals or other intermolecular effects. The lower stability for those clusters containing magic numbers +1 also reflects the difficulty of stabilization of the electrostatic interaction, because the tetrameric systems distribute the electronic charge in a uniform way, resulting in a smaller dipole moment.

Table 2 shows that the magic numbers concerning the $[(Na)1(Phe)2]^+$ and $[(Na)1(Phe)4]^+$ have a small dipole moment, so that the relative stability of the magic number ($m = 4, 8, \ldots$) observed both theoretically and experimentally can be rationalized at the molecular level due to an arrangement between the dipoles, which can be indicated as responsible for the stability of $[(Na)_n(Phe)_m]^{n+}$

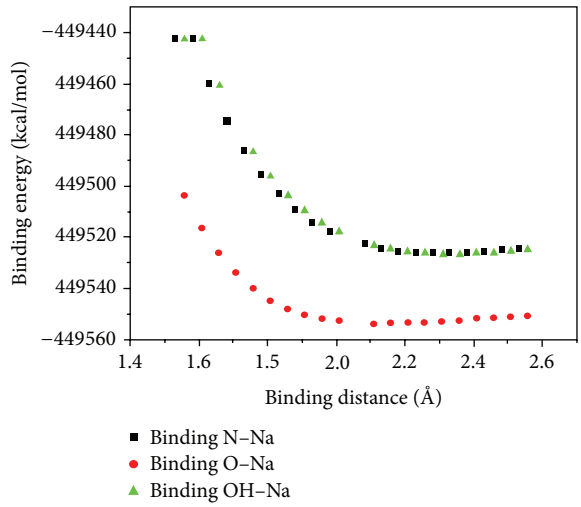



Figure 3: Potential energy curve for the chemical bond between the $Na^+$ ion with $NH_2$, C=O, and OH groups.

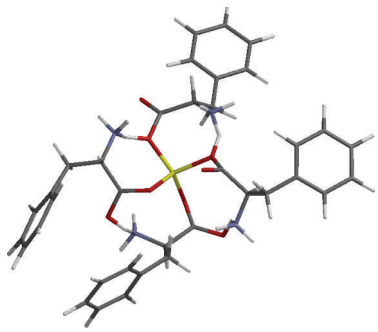


Figure 4: Geometry for the most stable conformation of the $Na^+$-phenylalanine tetramer.

clusters. In addition, the tetrameric clusters present stronger intramolecular hydrogen bond among the carboxyl groups of the phenylalanine molecule. $[(Na)_n(Phe)_m]^{n+}$ clusters also tend to form maximum number of planar rings of four members, because it is well known that this kind of molecular structure maximizes the hydrogen bond strength. Therefore the stable conformer of the $[(Na)_n(Phe)_m]^{n+}$ clusters tends to form a maximum number of planar rings of four members, as already noted by Lee for water rings [31]. Recently, the discovery of the serine tetramer and octamer may also reinforce our rationalization [15, 32, 33]. Despite the importance of the alkali metals chemistry in biochemical process, few theoretical and experimental works are devoted to the understanding of this subject at the molecular level.

The presence of the aromatic ring in the side chain of the amino acid might be another important molecular aspect necessary for stabilizing the tetrameric structure. In fact, it may help the coordination with the metal, because the charge on the metal may be better dispersed. The comparison of Phe with the nonaromatic amino acids has been taken as a useful indication of the extent of charge delocalization in the metal complexes [34].

Table 2: Conformation versus the calculated dipole moment (Debye).

| Conformation | Dipole moment (Debye) |
|---|---|
| **I** | 10.63 |
| **II** | 3.99 |
| **III** | 7.76 |
| **IV** | 3.35 |
| **V** | 4.82 |
| **VI** | 4.10 |
| **VII** | 4.16 |
| **VIII** | 7.77 |
| **IX** | 4.74 |
| **X** | 2.87 |

According to Meyer, most observations concerning the cation-$\pi$ interaction can be rationalized by the fact that the sp2 carbon is more electronegative than hydrogen [35]. This situation generates 6 local C–H bond dipoles around the benzene ring, which create an overall charge distribution that is a build-up of negative charge in the center of the ring and a belt of positive charge around the edge. Thus, cations are attracted to the negative electrostatic potential over the face to the benzene ring. In this line, the cation interacts with the face, not the edge, of the ring [36].

Recently, the electrostatic model developed by Dougherty and coworkers describes trends in binding energy based on differences in electrostatic attraction [37]. Interaction energies of cation-$\pi$ pairs correlate well with electrostatic potential above the $\pi$ face of arenes. Besides electrostatic attraction, other electronic effects can take place in cation-$\pi$ bonding. In this context, it should be kept in mind that transition metals have the ability to share electron density with $\pi$-systems through d-orbitals, creating bonds that are highly covalent in character and cannot be modeled as a classical cation-$\pi$ interaction [37]. For a deeper understanding of the nature of this interaction, it is need to employ QM methods with electronic correlation.

## 4. Conclusion

From our experimental and theoretical findings, we noticed that the structures of $[(Na)_n(Phe)_m]^{n+}$ clusters tend to form mainly planar rings of four members. Thus, our data indicated that the formation of $[(Na)_n(Phe)_m]^{n+}$ clusters in gas phase was built up based on maximizing the number of planar shaped four-membered rings as occurs with the water clusters [30, 38]. In this work, we used the ESI-MS method; this technique might enable us to be more specific about the nature of the species contained in gas phase, as well as about their fragmentation scheme. Furthermore, this method highlights intermediary species with a very short lifetime; activated complexes, such as species are reported in Table 1. Our data indicated that clusters are formed in the electrospray process both by direct transfer from solution and by gas-phase aggregation. This interpretation is influenced

by comparison with theoretical calculations which reveal formation of tetrameric clusters.

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