Interaction of Li+, Na+, and K+ with the Proline Amino Acid. Complexation Modes, Potential Energy Profiles, and Metal Ion Affinities

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The stationary points characterizing the potential energy profiles of the complexation process of the proline unusual α-amino acid with the alkali metal ions M+ (Li+, Na+ and K+) were investigated by density functional theory using the B3LYP hybrid potential and the 6-311++G** basis set. Different types of M+ coordinations on several proline conformers were considered. Results show that Li+, Na+, and K+ cations bind very similarly to the proline. In the M+-proline lowest-energy conformer, the cation appears always coordinated to both the oxygen atoms of the zwitterionic form of the amino acid which presents the up ring pucker. The complexes obtained by the interaction of the alkali ions with both the carbonyl oxygen and nitrogen of the α-amino acid were found, in all cases, at energy values not too far from those of the global minima. Absolute metal ion affinities were computed using various exchange-correlation functionals.

Introduction

Alkali metal ions are very important in living systems[1−4] as demonstrated by the fact that, in the last years, the most extensively studied species in the gas-phase biomolecular chemistry field are the alkali metal ions-peptide complexes.[5−15] Several experimental and theoretical data[16,17] are available for lithium affinity for small and medium sized organic and inorganic molecules, whereas much less work exists for the most biologically relevant sodium and potassium ions.

However, very recently, the gas-phase energetic and the nature of the binding of sodium ions with biological molecules have attracted the attention of both experimentalists and theoreticians[18−20] because of the importance of sodium compounds in the biological field and the possible use of sodium-cationized adducts in mass spectrometric studies.[20,21]

Our group has devoted detailed studies to the interaction of metal ions with biomolecules such as glycine and alanine amino acids[22,23] and DNA isolated bases[24−26] for understanding the role played by cations in the various biophysical processes.[1−5] In fact, the knowledge of accurate binding interactions through the metal ion affinities evaluation is important to predict in a polyfunctional macromolecule where the cations attachment occurs preferentially and how strong the binding at a particular site is giving information on the chemical groups directly involved in the biophysical processes.[1−5,27]

Concerning proline (Pro), we have evaluated the proton affinity[28] and the gas-phase basicity[29] using the same level of theory employed in the present work.

Li+, Na+, and K+ ions can be considered as Lewis acids such as H+, but they present a different behavior that reveals itself especially in the large ionic character of the bond formed with the ligands in which the alkali metal cations support the positive charge in the complexes.[30]

As indicated by previous works on a similar subject (i.e., Ag+−proline interaction),[31] we should expect, for all of the three studied systems, stable structures in which the cation gives rise to stabilizing ion pairs (salt bridges) with the carboxylate anion of the amino acid zwitterionic form.

In fact, notwithstanding, many studies have shown that most of amino acids do not assume the zwitterionic form in the gas phase,[32−39] and recent results[40] indicate that this form can be stabilized by the presence of an additional charge, thereby forming a salt bridge. It is now known that salt bridges are important in the chemistry of gas-phase biomolecule ions.[9,41−52] The existence of the complexes with the zwitterion form have also been suggested[42,43] to play a role in the fragmentations promoted by alkali metal ion binding of peptides.[9,46,47]

Using the kinetic method,[53,54] Bojesen et al.[55] have obtained absolute lithium and sodium ion affinities for glycine, alanine, and valine. For Pro−metal alkali complexes no experimental data exist, and the literature provides theoretical values only for the sodium−proline complex.[18]

The aim of the present work is the characterization of the low-energy conformers of the Pro−alkali metal complexes. Despite the fact that complexation geometry in the biological environment can be quite different from that of our complexes, this study can be useful to suggest modes of binding preferred in other chemical environments.

The first step of the work will concern the computation of equilibrium geometries of M+−proline (M+ = Li, Na, and K) for the stationary points characterizing the three potential energy profiles and their relative energies.

Then, the transition states for the interconversion between the various complexed conformers will be located.

Finally, the absolute metal ion affinities for each Pro site and the comparison of the results obtained by different exchange-correlation functionals will be reported.

Computational Methods

Eight coordination geometries were considered for the metal alkali ions on the six low-lying conformers of the Pro and on its two zwitterionic forms arising from the different puckering of the ring.

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Calculations were performed using the Gaussian 98 package.[56] The three-parameter functional usually abbreviated as B3LYP which includes Becke's gradient exchange correction[57] and the Lee, Yang, and Parr[58] correlation together with 6-311++G** basis set was used for the geometry optimization and for the localization of transition states. The influence of different exchange correlation functionals (B1LYP,[59,58] BHandHLYP,[60,58] B88LYP,[61,58] PW91PW91,[62−66] and MPW1PW91[67]) on the metal ion affinity values reproduction, was investigated performing optimizations starting from the B3LYP equilibrium geometry of the absolute minima. Zero-point vibrational energies were computed to confirm the nature of local minima or transition states of the stationary points on the potential energy profiles, at all levels of theory.

On the basis of the experience acquired by our group in the study of interaction of the alkali metal ions with other ligands, the basis set used here is adequate to reduce the basis set superposition error (BSSE) effects; nevertheless, the BSSE was explicitly computed, for the most stable complexes Pro−M$^+$, following the counterpoise method[68,69] implemented in the Gaussian 98 code.

Metal ion affinity (MIA) was considered as the negative of the enthalpy variation (ΔH) for the following ion association process:

$$Pro + M^+ \rightarrow Pro\text{-}M^+$$
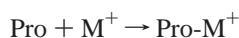
where Pro denotes the α-amino acid and M$^+$ the particular charged ion. Enthalpy contributions (ΔH) were obtained by a thermochemical analysis at 298 K using the vibrational frequencies at each level of theory.

Results and Discussion

Proline is the only naturally occurring amino acid with a secondary α-amino group which explains its more basic character with respect to many other α-amino acids. The reduced conformational flexibility arising from the restrictions imposed by the ring makes the Pro an important residue for the specific function in the β and γ turns of polypeptides chains.[70]

The conformational behavior of Pro was the subject of several theoretical studies.[71−74] A recent B3LYP quantum-mechanical investigation[75] performed using a basis set different from that employed in our study suggested that Pro exists into 15 low-energy conformers falling in a range of about 7 kcal/mol. In this same work,[75] the prediction of IR spectral parameters of Pro is also reported.

In the present investigation, we have considered as starting geometries for each series of Pro−M$^+$ calculations six free Pro conformers in a range of energy of 4.4 kcal/mol (see Figure 1). These geometries are the same as those investigated in our recent study on the proton affinity of the Pro[28] and more precisely are derived by the combination of different factors that take into account the possibility for the carboxyl group, H−O−C=O, to assume the cis or trans arrangement, the two dispositions (pucker-up or pucker-down) of the pyrrolidine ring, and the orientation of the carboxyl group with respect to the ring. Between the lowest energy conformers found in the previous B3LYP study,[74] we have taken into account only six minima. The other structures suggested by the same previous B3LYP investigation[75] were not considered by us because they do not have a suitable disposition of the attachment sites for the metal ions. In the work of Hoyau and Ohanessian,[18] only few structures of Pro have been considered hypothesizing the other isomers at significantly higher energy.
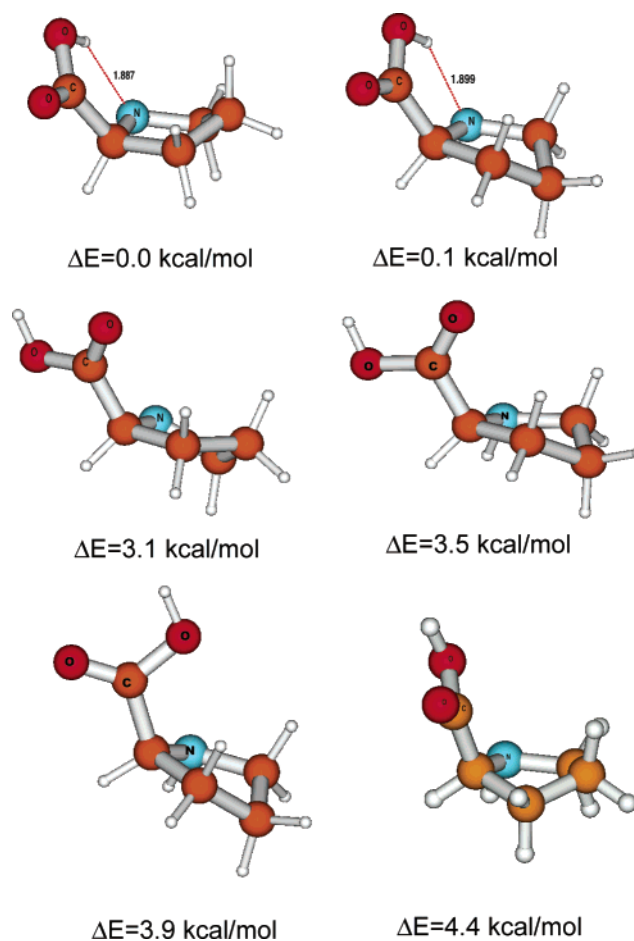

Figure 1. B3LYP/6-311++G** optimized structures of Pro most stable conformers. Hydrogen bonds are given in Å.

The complexes formed by the Pro with the alkali cations include also those deriving from the α-amino acid zwitterion form (see Figure 2 where the structures **1** and **2** are the corresponding metalated forms). Carbonyl oxygen and nitrogen atoms were chosen as the most probable metal-coordinating sites in the formation reaction of the complexes. This choice agrees with the analysis of the Pro−Ag$^+$ experimental structures.[31] Furthermore, the greater rigidity of Pro with respect to the simplest glycine amino acid should oblige the metal cations to interact just with the selected sites. It is evident that, in all cases studied, the geometry of the adducts obtained is determined by the electrostatic and polarization interactions between the cation and the ligand molecule.

Proline−Li$^+$. The Li$^+$ metalation process of proline gives eight stable structures (see Figure 2) that fall in an energy range of about 12 kcal/mol (see Table 1). The obtained stability order for complexes is the following: **1** > **2** > **5** > **6** > **4** > **3** > **7** ≈ **8**. The **2**, **3**, **6**, **7** and **1**, **4**, **5**, **8** conformer sets present the ring puckering down and up, respectively. In almost all of the studied metalated forms, the Li$^+$ cation appears to be bicoordinated to the Pro.

Complex **4** is the only structure in which the lithium ion appears monocoordinated to the carbonyl oxygen. In the corresponding structure **3**, that differs by **4** only for the puckering of the pyrrolidine ring, the cation keeps the bicoordination. In particular, in complex **4**, the distance between the Li$^+$ and the hydroxyl oxygen assumes a value of 3.512 Å versus 2.095 Å in the form **3**. This fact could induce one to think that the ring can play a decisive role in determining the cation coordination, but this hypothesis is immediately confuted by
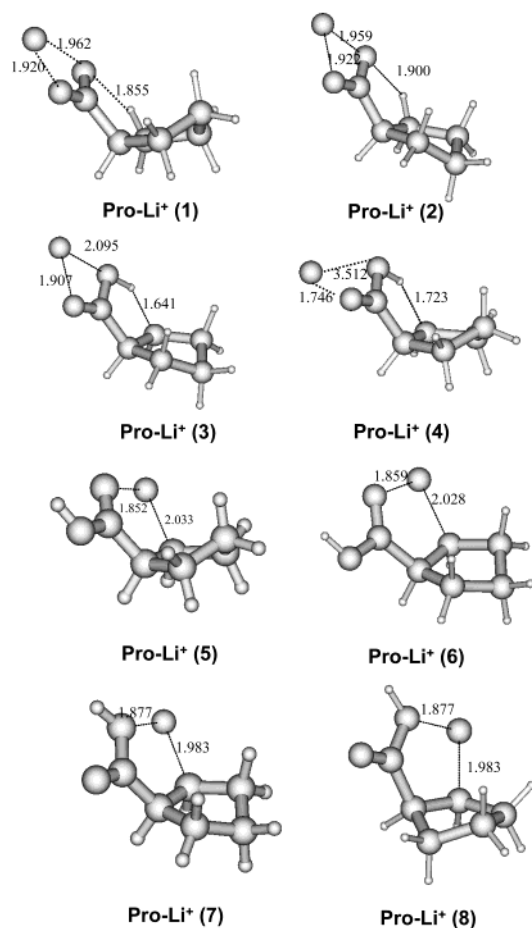
Figure 2. B3LYP/6-311++G** optimized structures of Li+−Pro complexes. Distances are in Å.

TABLE 1: Relative Stabilities of Minima and Transition States on the Pro−M+ (M+ = Li+, Na+, and K+) Potential Energy Profiles[a]

species	Li+	Na+	K+
1	0.0	0.0	0.0
TS1	2.5	2.7	2.7
2	0.4	0.5	0.2
3	9.9	6.3	3.5
TS3	12.4	8.7	5.8
4	8.5	6.5	3.4
TS4	29.3	26.0	22.0
6	2.1	5.1	5.8
TS5	3.4	5.9	6.5
5	1.3	4.2	4.9
TS6	40.5	42.0	42.0
7	10.7	13.2	13.7
TS7	11.5	14.4	-
8	11.1	13.6	-

[a] Data are in kcal/mol.

the complexes **7** and **8** in which the distances M+−N and M+−O are practically the same. In this case, the puckering seems to be irrelevant on both the distance values and metal ion coordination. Although the structures **3** and **4** derive from the two free proline lowest minima, they are not the most stable complexes. Instead, the **1** and **2** structures that arise from the zwitterionic forms of the free amino acid become the most energetically favored, confirming that the interaction with a charged system can reverse the gas-phase findings. Similar behavior was observed in our previous work on the M+−alanine system[23] and in other investigations regarding different metal−amino acid interactions.[31,76] The **5** and **6** systems follow in
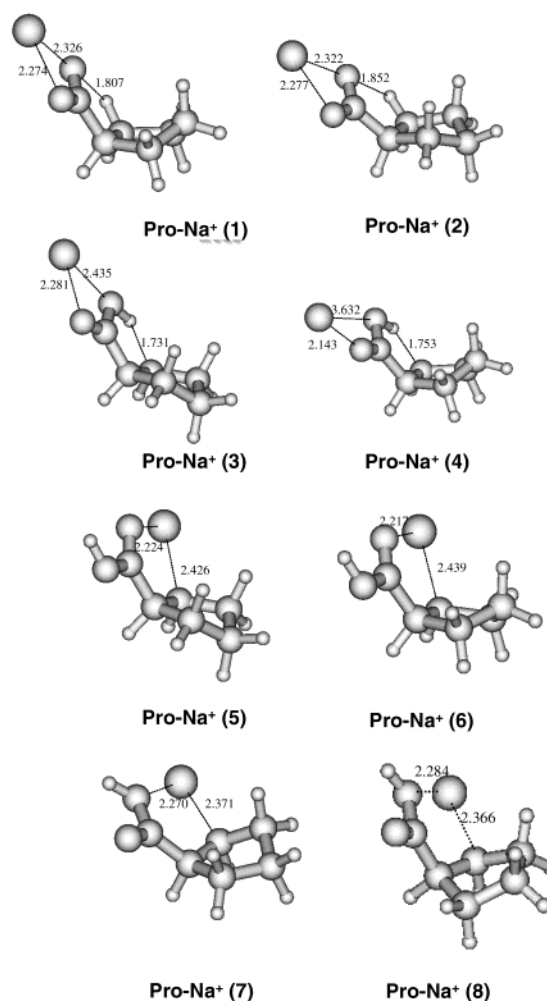

Figure 3. B3LYP/6-311++G** optimized structures of Na+−Pro complexes. Distances are in Å.

energy the **1** and **2** minima. They are characterized by the conventional orientation (cis topology) of carboxylic group typical of the common amino acids.

The stability of the various lithium complexes is consistent with the presence of a bicoordination of the cation with the oxygen atoms of the zwitterion, with the presence of stabilizing hydrogen bonds and with the puckering up or down of the ring in order of importance. Structures **1** and **2** are characterized by all of these factors. Natural charge analysis shows that the ligand transfers to the cation, in all the complexes, only a small amount of electrons (about 0.044 |e|) underlying a strong ionic character of the bond.

Proline−Na+. The B3LYP/6-311++G** relative energies of the eight Pro−Na+ complexes are reported in Table 1 together with other theoretical data. The stability order seems to be determined by the same factors as in the lithium systems and thus remains very similar to that obtained in the case of the above-discussed cation, apart from few exceptions which concern the **3**, **7**, and **8** structures. A net energy gap exists between structure **3** (6.3 kcal/mol) and systems **8** and **7** (13.2 and 13.6 kcal/mol, respectively). Again, the most stable conformer involves the attachment of the sodium ion to the carboxylate group of the zwitterionic Pro (structure **1** of Figure 3). This result is in agreement with a previous theoretical study performed at HF/6-31G* and MP2/6-31G*//HF/6-31G* levels,[18] in which only four structures having the ring puckering in up were reported (see Table 1). Further comparison to define the agreement between the density functional conformers sequence
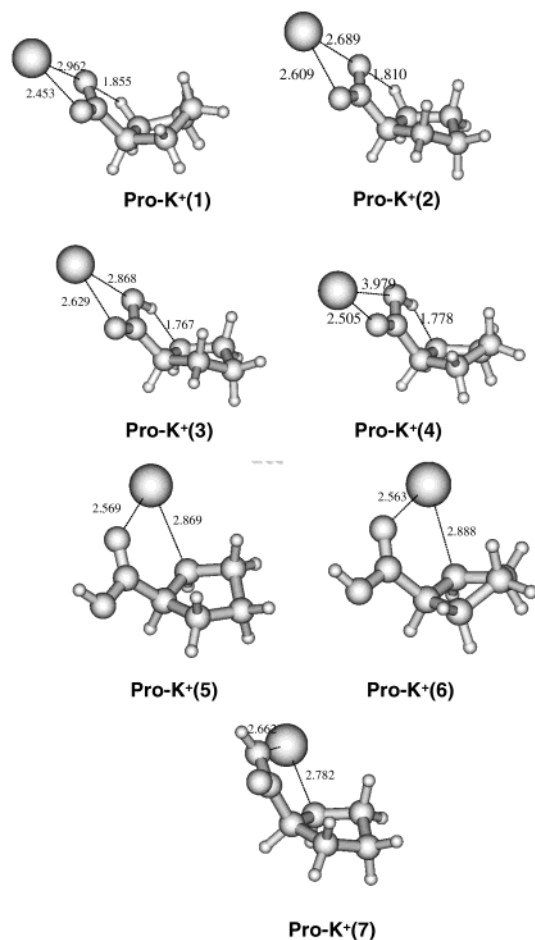
Figure 4. B3LYP/6-311++G** optimized structures of K$^+$−Pro complexes. Distances are in Å.

and the ab initio one cannot be made because of the reduced number of structures examined in the study of Hoyau et al.[18] However, the comparisons are possible for the geometrical parameters with regard to the common structures **1**, **4**, and **6**. Beyond the differences in the bond lengths due to the different theoretical approaches, structures **1** and **6** are practically the same in the two studies. Indeed, in our structure **4**, the distances between the metal ion and oxygen atoms are very far from the HF ones of the work of Hoyau et al.[18] (1.753 versus 2.238 Å (carbonyl oxygen) and 3.632 versus 2.512 Å (hydroxyl oxygen)). From these values, it emerges that complex **4** is monocoordinated at the density functional level and bicoordinated at the HF one.

A recent study on the determination of the nature of the binding in the gas-phase complexes of sodium ions[20] has revealed the importance of electrostatic and polarization interactions in determining the geometry of the adducts. Natural charge analysis attributes to the Na$^+$ cation a positive charge which is on average 0.970 |e|. Thus, the ligand transfers to the cation a smaller amount of charge than to Li$^+$ ion and the bond is slightly more ionic.

Proline−K$^+$. In the K$^+$−proline interaction, only seven stable structures were obtained. In fact, complex **8** collapses into isomer **7** during the geometry optimization. The stability order of the low-energy complexes of K$^+$−Pro system is quite different from the two previous cases studied: **1** > **2** > **4** > **3** > **5** > **6** > **7**. The energies of the minima are collected in Table 1. The main differences are with regard to the systems **3**, **4**, **5**, and **6**. The structures in which the cation is bound to the nitrogen and oxygen atoms (**5** and **6** of Figure 4) become much less stable than those in which the proline is a zwitterion (**1** and **2** of Figure

4). This behavior, already evident for the sodium complexes, can be probably due to the increased metal ion size and is in agreement with the experimental observation[40,55] that underline a preference for the N,O coordination in the case of H$^+$ and Li$^+$ cations and for the O,O one in the presence of larger cations. In fact, the **5** and **6** complexes lie at only 1.3 and 2.1 kcal/mol, at 4.2 and 5.1 kcal/mol, and at 4.9 and 5.8 kcal/mol with respect to the global minimum **1**, for the Li$^+$−Pro, Na$^+$−Pro, and K$^+$−Pro systems, respectively. A closer look at Table 1 shows also that the energy gaps that separate the **3** and **4** K$^+$−Pro conformers from the absolute minimum are sensibly reduced and these two forms gain energy sufficient to overcome in stability the **5** and **6** complexes.

As in the other two cases, the K$^+$−Pro complexes are bicoordinated with the only exception of the conformer **4**.

The charge transfer is, in this case, even less pronounced than in the lithium and sodium complexes. Natural charge analysis suggests a K$^+$ ion which retains in its complexes about 0.982 |e|.

Potential Energy Profiles. The potential energy profiles for the M$^+$−Pro (M$^+$ = Li, Na, and K) interactions are shown in Figure 5. The relative energies of the transition states (TS) are collected in Table 1 together with those of minima and the equilibrium geometries in Figure 6. As in the case of the alkali metal ions−alanine interaction,[23] the shape of the paths is very similar for the three studied systems, but the height of the energetic barriers between the various minima decreases as the metal ion size increases, except for the barrier which connects the structures **5** and **7** (TS6) that is higher in the Na$^+$−Pro and K$^+$−Pro paths rather than in the Li$^+$−Pro one. In the interaction proline−K$^+$, the conformer **8** was not found, so the corresponding **7** → **8** connection is absent. The transition states TS1, TS3, TS5, and TS7, which represent the barriers for the transformations **1** → **2**, **3** → **4**, **6** → **5**, and **7** → **8**, respectively, describe a simple puckering change of the Pro ring and lie at energy values very low with respect to the other barriers (see Table 1). All of the attempts for finding the transition state (TS2) of the interconversion between the **2** and the **3** structures failed. In this case, the structural change, represented only by the migration of the bridging proton between the −OH group of the carboxylic moiety and the nitrogen atom, occurs without barrier. In fact, in a preview work concerning the case of rubidiated and sodiated glycine,[77] the same isomerization has shown a very small barrier. Probably, this barrier in the Pro−M$^+$ systems disappears because of the minor flexibility of the ligand and the not suitable mutual orientation of the involved groups in the hydrogen migration. The transition states (TS4) originate from the cleavage of the H bond between the nitrogen atom of the ring and the −OH group and the simultaneous rotation of the −OH group around the C−C$_\alpha$ bond, with the formation of a new bicoordinated complex (N,O bicoordination) (structure **6**). Transition states TS4 are characterized by the following relative energy values: 29.3, 26.0, and 22.0 kcal/mol for Li$^+$, Na$^+$, and K$^+$, respectively. The TS6 are four-centers transition states. They involve a hydrogen shift between the two oxygen atoms of the −COOH moiety and occur with evident difficulty as confirmed by the high values of the energetic barriers (40.5, 42.0, and 42.0 kcal/mol) for the three metal species.

Binding Energies. In Table 2 are reported the absolute MIA values obtained at different levels of calculations with the aim to define the influence of the exchange-correlation potentials on the interaction of alkali metal cations with Pro. The MIA values were computed for the most stable isomer of the free
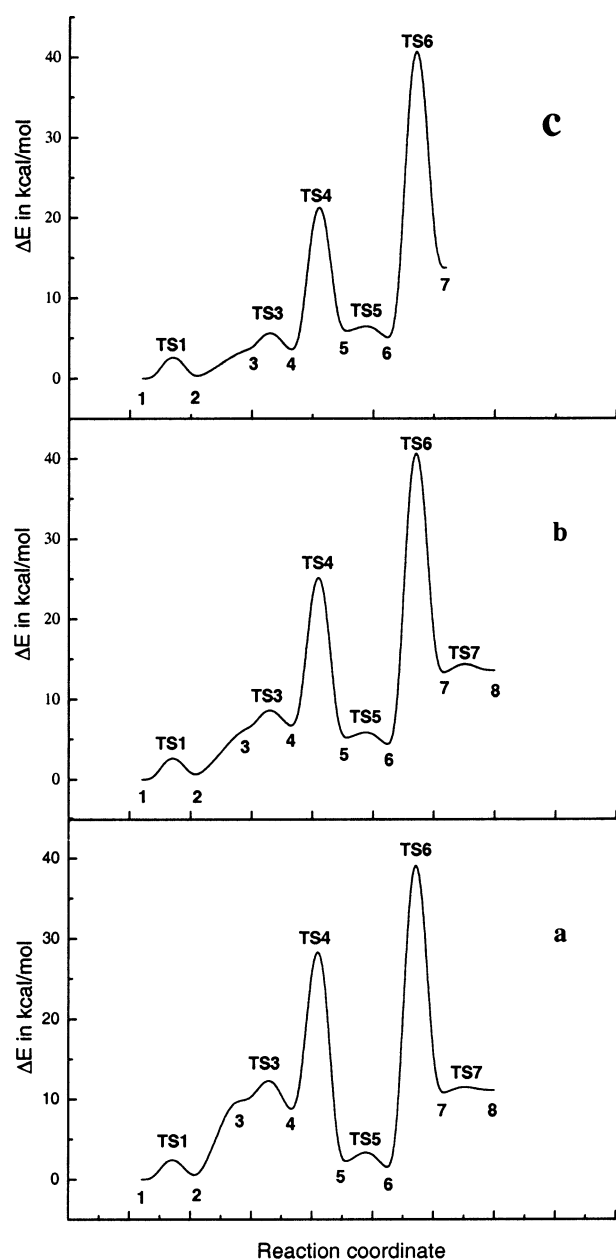
Figure 5. B3LYP/6-311++G** potential energy profiles for the metalation processes of the Pro by (a) Li$^+$, (b) Na$^+$, and (c) K$^+$ alkali metal ions. Relative energies (ΔE) are in kcal/mol.
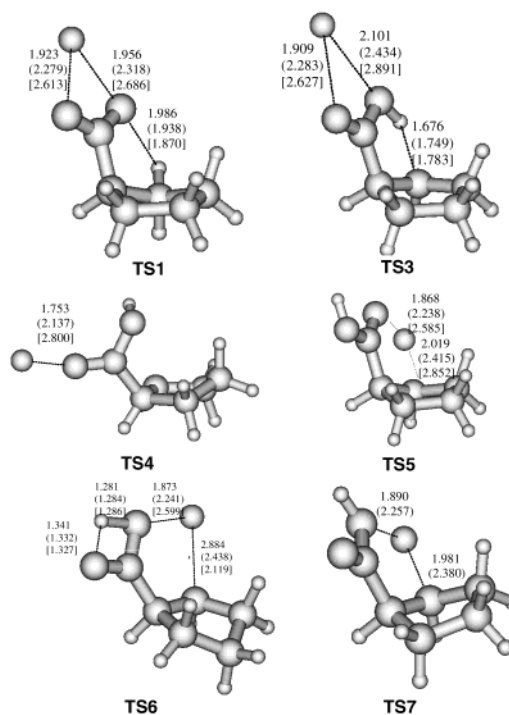

Figure 6. B3LYP/6-311++G** optimized structures of transition states on the potential energy profiles for the metalation processes of the Pro by Li$^+$, (Na$^+$), and [K$^+$] alkali metal ions. Distances are in Å.

TABLE 2: Metal Ion Affinities (kcal/mol) for Pro−M$^+$ (M$^+$ = Li$^+$, Na$^+$, and K$^+$) Systems Obtained by Different Exchange-Correlation Functionals

methods	Pro−Li$^+$	Pro−Na$^+$	Pro−K$^+$
B3LYP/6-311++G**	64.21	47.32	34.62
B1LYP/6-311++G**	64.52	47.44	34.48
BHandHLYP/6-311++G**	65.40	47.88	34.74
MPW1PW91/6-311++G**	62.97	46.04	34.38
MP2/6-311+G(2d,2p)//MP26-31G*		44.20[a]	
PW91PW91/6-311++G**	63.87	47.76	35.92
B88LYP/6-311++G**	63.68	47.21	34.47

[a] From ref 18.

Pro, which is not the zwitterionic form of the amino acid but corresponds to isomer **I** of Figure 1.

For the sodium ion, only one theoretical binding energy value[18] is available for the comparison with the present study. A combined experimental-theoretical work on alkali metal ion binding to amino acids appeared recently in the literature[78] and yielded MIA values for proline which are, however, relative to the corresponding Pro methyl esters and for this reason difficult to use as comparison data. Employing our previous determinations of the absolute lithium and sodium ions affinities of glycine[22] and α-alanine,[23] and the relative scale obtained experimentally for all amino acids,[55] we can evaluate the reliability of our theoretical approach in the reproduction of the relative Li$^+$ and Na$^+$ affinities including the new data for proline. K$^+$ affinities obtained in the present work represent, to our knowledge, the first literature indication on absolute MIA. In all of the computations, the MIA values decrease in going from Li$^+$ to K$^+$ cation. The B3LYP binding energies are slightly smaller than those obtained using B1LYP and BHandHLYP potentials contrarily to the results yet found in the case of the interaction of the α-alanine with copper ions.[79] In fact, the absolute values of MIA for α-alanine−Cu$^+$/Cu^{2+} systems[79] appeared strongly overestimated but, in the case of interaction with alkali metal ions the B3LYP shows generally a better performance[22,23] than in the cases involving transition metal ions. Indeed, the MPW1PW91 calculations gave MIA values for Pro−Li$^+$ and Pro−K$^+$ complexes slightly different from those obtained by the other hybrid potentials. In particular, the MPW1PW91 MIA value for Pro−K$^+$ of 34.38 kcal/mol is almost the same than the value obtained at the B1LYP level (34.48 kcal/mol). A different behavior can be observed at the PW91/PW91 level that yields, for the Pro−K$^+$ complex, a MIA value of 35.92 kcal/mol.

It is worth noting that the use of no-hybrid potentials such as B88LYP produces MIA values smaller than those obtained at the B3LYP level. This behavior was also observed in studies regarding other similar systems.[80]

In principle, the value of MIA of a given metal ion for a series of similar compounds should increase as the polarizability of the side chains increases. The results of the comparison of all our data with the experimental relative scale of lithium and sodium ion affinities of Bojesen et al. for the 20 common

α-amino acids[55] confirm the trend Pro > Ala > Gly. Because of the lack of experimental or theoretical confirmation concerning both absolute and relative values of MIA in the case of Pro, no indication about the specific performance of the particular exchange correlation functional in the reproduction of these quantities can be suggested; however, the obtained results are very similar.

Conclusions

DFT B3LYP/6-311++G** calculations indicate that the salt-bridge form of alkali ions complexes becomes progressively more stable with respect to the conventional form with increasing cation size.

Metal ions prefer to form Pro-M⁺ bicoordinated complexes whose stability order is **1 > 2 > 5 > 6 > 4 > 3 > 7 ≈ 8, 1 > 2 > 5 > 6 > 3 > 4 > 7 > 8**, and **1 > 2 > 4 > 3 > 5 > 6 > 7** for lithium, sodium, and potassium cations, respectively.

Potential energy profiles for the considered metalation processes show similar shapes with energy barriers that decreases as the metal ion size increases.

B3LYP, B1LYP, BHandHLYP, B88LYP, and MPW1PW91 exchange-correlation functionals give metal ion affinity values that differ between them by less than 1 kcal/mol and propose unambiguously the affinity trend Pro > Ala > Gly.

This work yields quantities which may be inaccessible or complementary to experiments and represents the first quantum chemical approach in which the gas-phase complexation between alkali metal ions and proline are considered and absolute metal ion affinities are evaluated.

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