Structures of Lithiated Lysine and Structural Analogues in the Gas Phase: Effects of Water and Proton Affinity on Zwitterionic Stability[†]

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The structures of lithiated lysine, ornithine, and related molecules, both with and without a water molecule, are investigated using both density functional theory and blackbody infrared radiative dissociation experiments. The lowest-energy structure of lithiated lysine without a water molecule is nonzwitterionic; the metal ion interacts with both nitrogen atoms and the carbonyl oxygen. Structures in which lysine is zwitterionic are higher in energy by more than 29 kJ/mol. In contrast, the singly hydrated clusters with the zwitterionic and nonzwitterionic forms of lysine are more similar in energy, with the nonzwitterionic form more stable by only ∼7 kJ/mol. Thus, a single water molecule can substantially stabilize the zwitterionic form of an amino acid. Analogous molecules that have methyl groups attached to either the N-terminus (NMeLys) or the side-chain amine (Lys(Me)) have proton affinities greater than that of lysine. In the lithiated clusters with a water molecule attached, the zwitterionic forms of NMeLys and Lys(Me) are calculated to be ∼4 and ∼11 kJ/mol more stable than the nonzwitterionic forms, respectively. Calculations of the potential-energy pathway for interconversion between the different forms of lysine in the lithiated complex indicate multiple stable intermediates with an overall barrier height of ∼83 kJ/mol between the lowest-energy nonzwitterionic form and the most accessible zwitterionic form. Experimentally determined binding energies of water are similar for all these complexes and range from 57 to 64 kJ/mol. These results suggest that loss of a water molecule from the lysine complexes is both energetically and entropically favored compared to interconversion between the nonzwitterionic and zwitterionic structures. Comparisons to calculated binding energies of water to the various structures show that the experimental results are most consistent with the nonzwitterionic forms.

Introduction

In solution, molecular structure is influenced by surrounding molecules and ions, as well as intramolecular interactions between the various functional groups in the molecule. Studying the effects of each of these types of interactions in solution can be quite challenging due to the many interactions that may be present. In the gas phase, interactions can be investigated individually. The structures of amino acids and how the structures are affected by other molecules and ions have been the subject of many recent studies.[1−41] The 20 naturally occurring amino acids all exist in their nonzwitterionic forms in isolation, but interactions with other molecules and ions can preferentially stabilize the zwitterionic forms of these molecules. The extent of this stabilization depends on a number of factors, including the proton affinity of the proton acceptor, the gas-phase acidity of the proton donor, the attachment of cations, and the effects of solvation of a charge by heteroatoms.

Attachment of a metal cation to an amino acid can stabilize the zwitterionic form relative to the nonzwitterionic form, with doubly charged cations typically having a greater effect than singly charged cations.[12−14,26,29] An addition of water molecules to a gas-phase amino acid can preferentially stabilize the zwitterionic form; nonzwitterionic glycine is more stable than its zwitterionic form by ∼90 kJ/mol in the gas phase[42] whereas the two forms are nearly isoenergetic with 3−5 water molecules attached.[43,44] The proton affinity of the proton acceptor also
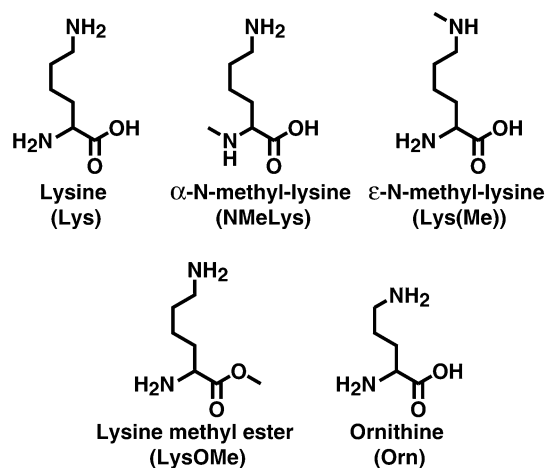
plays an important role in zwitterion formation.[2,6,45−48] Among aliphatic amino acids, the stabilities of the zwitterionic forms relative to their nonzwitterionic forms are directly related to their proton affinities.[2,6] However, the presence of heteroatoms in the side chains of some amino acids can play a significant role in the relative stabilities of the zwitterionic and nonzwitterionic forms. For example, the proton affinity of glycine is ∼165 kJ/mol lower than that of arginine, yet the nonzwitterionic forms of these amino acids are more stable than their zwitterionic forms by ∼90 kJ/mol for glycine and ∼15 kJ/mol for arginine.[42,49,50] Thus, a 165 kJ/mol difference in proton affinity results in a relative stabilization of the zwitterionic form of only 75 kJ/mol. The effects of heteroatoms can be even more significant with cationized amino acids where these atoms can result in reduced stabilization of the zwitterionic form. The nonzwitterionic form of glycine bound to a lithium ion is more stable than its zwitterionic form by ∼13 kJ/mol,[19,20,29] whereas for lithiated arginine this difference is ∼3 kJ/mol.[8] Despite having vastly different proton affinities, the relative zwitterionic stability of the respective clusters differ by only 10 kJ/mol.

The amino acid lysine plays an important role in protein structure and functionality. Lysine residues have been shown to be directly involved in phosphate transfer from ATP in many proteins.[51,52] Because lysine is a basic amino acid, the protonated side chain of lysine can interact with deprotonated acid residues resulting in salt bridges that can stabilize helical coils and other forms of secondary and tertiary protein structure. In the gas phase, lysine has the second highest proton affinity of the naturally occurring amino acids, reported to be between ∼940

SCHEME 1

Lysine
(Lys)

α-N-methyl-lysine
(NMeLys)

ε-N-methyl-lysine
(Lys(Me))

Lysine methyl ester
(LysOMe)

Ornithine
(Orn)

and 1015 kJ/mol based on calculations,[53-58] bracketing experiments,[59,60] and kinetic-method experiments.[54,56,57,61-64] The wide range of reported proton affinities can be attributed to a number of factors. The lowest-energy structure of isolated lysine used for many of the proton affinity calculations has an elongated side chain that does not interact with the rest of the molecule.[53-55] However, a structure in which the side chain undergoes hydrogen bonding with the proton of the carboxylic acid has been found by others to be ~9 kJ/mol lower in energy.[22,56] Protonated lysine has a strong hydrogen bond between the two amine groups, an interaction which may not be present in kinetic-method experiments in which lysine exists as a proton-bound dimer with a reference base. Extended kinetic-method experiments[54,56,64-66] for lysine provide proton affinity values similar to calculated values and are 20-30 kJ/mol higher than those determined by previous kinetic-method measurements.[53-58] The structures of cationized lysine complexes have been reported by several groups.[2,9,22] The structure of lysine bound to a silver cation is nonzwitterionic, with the metal ion interacting with the N-terminal amine group, carbonyl oxygen, and the amine of the side chain, or $N_{SC}N_TO$-coordination.[22] However, structures of Lys·M[+], M = Li, Na, K, have been reported to be both nonzwitterionic[9] and zwitterionic.[2]

Here, the structure of singly hydrated lithiated lysine and several structural analogues are investigated using both black-body infrared radiative dissociation (BIRD) and theory. Measured water threshold dissociation energies are compared to calculated binding energies, and the structures of these complexes are inferred from these comparisons. Calculations of the barrier height for isomerization between the zwitterionic and nonzwitterionic forms of lithiated lysine indicate that loss of a water molecule from these complexes is a lower-energy process and should occur prior to isomerization in these experiments.

Experimental Methods

Chemicals. Lysine (Lys), lysine methyl ester (LysOMe), and ornithine (Orn) were obtained from Sigma Chemical Co. (Saint Louis, MO). α-*N*-methyl-lysine (NMeLys) and ε-*N*-methyl-lysine (Lys(Me)) were purchased from Bachem California Inc. (Torrance, CA). Lithium hydroxide was purchased from Aldrich Chemical Co. (Milwaukee, WI). The covalent structures of these molecules are shown in Scheme 1. All chemicals were used without further purification. Electrospray solutions were made to optimize the signal for AA·Li[+](H₂O) (*a*mino *a*cid or *a*mino *a*cid analogue), and were typically ~1 mM AA and 1-4 mM LiOH.

Mass Spectrometry. All dissociation experiments were performed on a home-built Fourier transform mass spectrometer with a 2.8 T superconducting electromagnet. The instrument and experimental methods are discussed in detail elsewhere.[6,67,68] Briefly, ions are generated using nanoelectrospray ionization and are accumulated in an ion cell for 8-12 s. Unwanted ions are ejected from the cell using a series of stored waveform inverse Fourier transform and chirp excitation waveforms. The hydrated ion cluster of interest then undergoes unimolecular dissociation for 0-600 s. Dissociation kinetics are obtained by measuring the abundance of the precursor and fragment ions as a function of reaction time. The temperature of the cell is controlled by cooling the copper jacket surrounding the cell with liquid nitrogen.[68] The copper jacket temperature is allowed to equilibrate for at least 8 h to ensure that the ions are exposed to a steady state radiative energy distribution from infrared photons emitted from the walls of the copper jacket and vacuum chamber.

Computational Details. Possible low-energy structures of AA, AA·H^{+}, AA·Li^{+}, and AA·Li[+](H₂O), AA = Lys, LysOMe, Orn, NMeLys, and Lys(Me), are determined by using a combination of conformational searching and chemical intuition. Initial structures were generated by performing Monte Carlo conformation searching with the MMFF94 force field using MacroModel 9.1 (Schrödinger, Inc. Portland, OR). For the AA and AA·H^{+} complexes, no constraints were placed on the molecules and 5000 conformations were generated with a Monte Carlo simulation. Upon generation of an additional 5000 structures, no new structures within 50 kJ/mol of the lowest-energy structure were found. All unique structures within 50 kJ/mol of the lowest-energy structure were used as starting structures for higher-level calculations. For the AA·Li^{+} and AA·Li[+](H₂O) complexes, 50 000 conformations were generated. These structures were grouped into "families" of structures with similar AA, lithium ion, and water molecule interactions. Representative structures from each family were used as starting structures for the higher-level calculations.

After identifying low-energy structures from the mechanics calculations, hybrid method density functional calculations (B3LYP) were performed using Jaguar v. 6.5 (Schrödinger, Inc., Portland, OR). Full geometry optimizations were performed at the 6-31G* and 6-31++G** levels. Zero-point energies and enthalpy corrections at 298 K were calculated from vibrational frequencies obtained using analytical derivatives of the 6-31++G** energy minimized Hessian. Structures were minimized to geometries yielding all positive frequency vibrational modes, indicating that all structures reported here are at local minima. Water binding energies, including zero-point energy and enthalpy corrections at 298 K, were calculated from these low-energy structures. Infrared transition dipole moments, used for the master equation modeling discussed in the following section, were calculated for select clusters using numerical derivatives of the 6-31++G** energy minimized Hessian.

Structures for the potential-energy pathways were performed using the 6-31G* basis set, and frequencies were calculated using analytical derivatives. Local minima structures were energy minimized to geometries yielding all positive frequency vibrational modes. Candidate transition states were obtained by changing the low-energy structures. Most transition-state structures were optimized by maximizing the energy along the reaction coordinate and minimizing the energy along all remaining degrees of freedom. This process yielded geometries with a single negative vibrational frequency. True transition-state structures in some relatively flat regions of the potential-

Lithiated Lysine and Structural Analogues

J. Phys. Chem. A, Vol. 110, No. 27, 2006 **8435**

energy surface were not identified. In these cases, a representative structure in that region is calculated. These structures are discussed individually where relevant.

Master Equation Modeling. The clusters studied here are not in the rapid energy exchange limit, meaning they do not have radiative absorption and emission rates that are significantly faster than their dissociation rates. To determine water threshold dissociation energies for these complexes, the experimentally measured kinetic data is numerically simulated using a master equation formalism. This modeling is discussed in detail elsewhere.[69] To summarize, the measured water dissociation rate constant depends on the rates of radiative absorption and emission, the transition-state entropy, and the binding energy of the water to the cluster. Radiative rates are obtained by combining Einstein coefficients determined from calculated absorption spectra for the clusters and a blackbody energy field at the temperature of the experiment. The transition-state entropy of the dissociation is not explicitly known. Loss of a water molecule from these clusters is expected to proceed through a relatively loose transition state, but a range of transition-state entropies corresponding to a "neutral" and "loose" transition state (Arrhenius preexponentials of 10^{13} and 10^{17} s^{-1}, respectively) is used to better assess the effect of this parameter. The water binding energy used to calculate the RRKM rate constants is also varied in the model. In addition, transition dipole moments are scaled by factors ranging between 0.6 and 1.2 to account for uncertainties in these calculated values.

Results and Discussion

Proton Affinities. Both theoretical and experimental values for the proton affinity of lysine[53-64,70] and ornithine[54] have been reported. However, values for the other analogue compounds in this study have not. Lowest-energy structures for both the protonated and neutral forms of these molecules were calculated, and these structures are shown in Figure 1. Proton affinities for all five molecules are obtained using eq 1

$$PA_{298} = -\Delta H_{298} = [E_{el}(AA \cdot H^+) - E_{el}(AA)] +$$
$$[ZPE(AA \cdot H^+) - ZPE(AA)] + [H_{298}(AA \cdot H^+) -$$
$$H_{298}(AA)] - (5/2)R*(298 \text{ K}) \quad (1)$$

where E_{el} is the electronic energy and ZPE is the zero-point energy. The resulting values are reported in Table 1.

Protonation of the side chain of lysine is more favorable than protonation of the N-terminus by 17 kJ/mol. The resulting lowest-energy form of protonated lysine is one in which the protonated side chain cyclizes and donates hydrogen bonds to the N-terminus and the carbonyl oxygen. This structure has been reported previously.[53-56] For neutral lysine, the side chain cyclizes and accepts a hydrogen bond from the carboxylic acid. Both this structure[22,56] and a structure in which the side chain is extended and does not interact with the carboxylic acid group[53-55] have been previously reported to be lowest-energy structures. We find the extended side-chain structure to be 7 kJ/mol higher in energy at the B3LYP/6-31++G** level of theory with zero-point energy and ΔH(298 K) corrections.

The protonated structure of Orn is similar to that of protonated lysine, but for neutral Orn, a structure in which the carboxylic acid acts as a hydrogen donor to the N-terminus, which in turn donates a hydrogen bond to the side-chain amine, is slightly favored. These structures are different than those reported previously for these two forms of Orn, which indicated an extended structure for neutral Orn and a protonated side chain
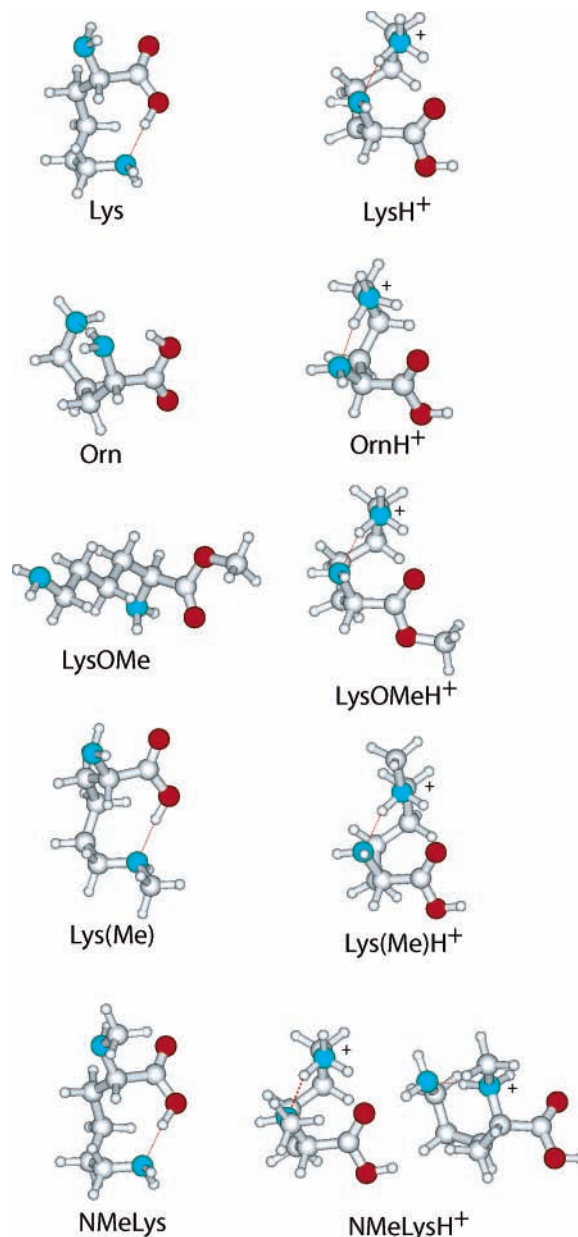

Figure 1. Lowest-energy structures of AA and AA·H$^+$ at the B3LYP/6-31++G** level of theory.

that cyclizes and interacts solely with the N-terminus for protonated Orn.[54] Those structures were also identified in this search but were found to be 12 and 7 kJ/mol higher in energy, respectively.

The PAs of Lys and Orn are calculated to be nearly identical (within 1 kJ/mol), consistent with experimental results of Amster and co-workers who used the bracketing method to measure gas-phase basicities.[60] PA values for these two amino acids measured by Poutsma and co-workers using the extended kinetic method differ by 10 kJ/mol.[54] However, our calculated values for these two complexes are in good agreement with those previously calculated for Lys (995–1004 kJ/mol)[54,55] and Orn (993–994 kJ/mol)[54] and are well within the range of many experimentally determined values.[53,54,56,59,60,70]

A methyl group on the N-terminus (NMeLys) of Lys increases the basicity of this site, resulting in two nearly isoenergetic lowest-energy forms of the protonated species: one in which the side chain is protonated and acts as a double donor similar to the lowest-energy protonated form of lysine and the

TABLE 1: Proton Affinities (PA) and Relative Energies, in kJ/mol, of Low-energy Structures of AA·Li$^+$ and AA·Li$^+$(H$_2$O) at the B3LYP/6-31++G Level of Theory, Including Zero-point Energy and ΔH(298 K) Corrections[a]**

AA	PA	nonzwitterionic (NZ)			zwitterionic (ZW)				NZ-ZW
		A0	B0	C0	D0	E0	F0	G0	
Lys	996.5	0	20.2	[b]	33.9	34.7	29.1	36.2	−29.1
NMeLys	998.7	0	16.8	[b]	31.3	21.3	31.5	14.2	−14.2
Lys(Me)	1012.6	0	21.6	[b]	18.0	29.3	11.8	34.8	−11.8
Orn	997.6	0	34.0	30.2	25.1	23.5	31.1	54.9	−23.5
LysOMe	1012.0	0							
	PA	A1	B1	C1	D1	E1	F1	G1	NZ-ZW
Lys	996.5	0	3.4	[c]	6.6	7.1	7.3	14.4	−6.6
NMeLys	998.7	6.9	3.7	[c]	11.2	0	17.0	0.8	3.7
Lys(Me)	1012.6	11.4	13.1	[c]	0.6	11.2	0	21.8	11.4
Orn	997.6	0	18.3	12.0	6.2	2.9	[d]	47.4	−2.9
LysOMe	1012.0	0							

[a] Structural designations refer to geometries analogous to those presented in Figures 2 and 3. [b] Minimizes to structure F0. [c] Minimizes to structure F1. [d] Minimizes to structure C1.

other in which the side chain interacts solely with the protonated N-terminus. The lowest-energy structure of the neutral form is similar to that of lysine. The PA of NMeLys is only about 2 kJ/mol higher than that of Lys, whereas methylation of the side-chain nitrogen, Lys(Me), results in a much higher PA for this molecule (1013 kJ/mol) than that for Lys (997 kJ/mol). The lowest-energy structures for this molecule in both the neutral and protonated forms are nearly identical to those of Lys. The methyl ester of Lys, LysOMe, is also much more basic than Lys (PA LysOMe = 1012 kJ/mol), consistent with results for other esters compared to their corresponding acidic forms.[9]

Structures. Lysine can adopt either a nonzwitterionic or zwitterionic form in the lithiated complexes. There are two general families of nonzwitterionic lithiated structures common to lysine and the analogue molecules. In the N$_{SC}$N$_T$O-coordinated structure (A0, Figure 2), Li$^+$ interacts directly with both nitrogen atoms and the carbonyl oxygen. In the N$_{SC}$O-coordinated structure (B0, Figure 2), Li$^+$ interacts with the nitrogen atom of the side chain and the carbonyl oxygen, with the carboxylic acid donating a hydrogen bond to the N-terminus. The latter structure is substantially less stable (>15 kJ/mol higher in energy) for Lys and the three analogue compounds that have an acidic hydrogen. In contrast, when one water molecule is attached to lithiated lysine (B1, Figure 3), the N$_{SC}$O structure is preferentially stabilized relative to the A1 structure by more than 15 kJ/mol. The B structures of ornithine are particularly unstable relative to A; apparently, the shorter side chain prevents optimal solvation of Li$^+$ in the former structure.

In addition to the two structures identified for lysine and the other analogues, ornithine can adopt a third nonzwitterionic structure in which the metal ion interacts with the carbonyl oxygen and the N-terminus (N$_T$O-coordination), similar to interactions previously observed for many nonzwitterionic cationized amino acids with aliphatic side chains. Nonzwitterionic structures with this coordination scheme are not stable for the remaining clusters studied here; in all other cases, this structure minimized to the zwitterionic F0 or F1 for the zero and one water molecule containing clusters, respectively. For ornithine, C0 and C1 are more stable than the analogous zwitterionic structures (F0 and F1, respectively); apparently, the shorter side chain of ornithine destabilizes the zwitterionic N$_T$O-coordinated structure.

There are four different modes of metal ion binding found in low-energy structures of the zwitterionic form. In structures D0 and E0 (Figure 2), Li$^+$ interacts predominantly with one or
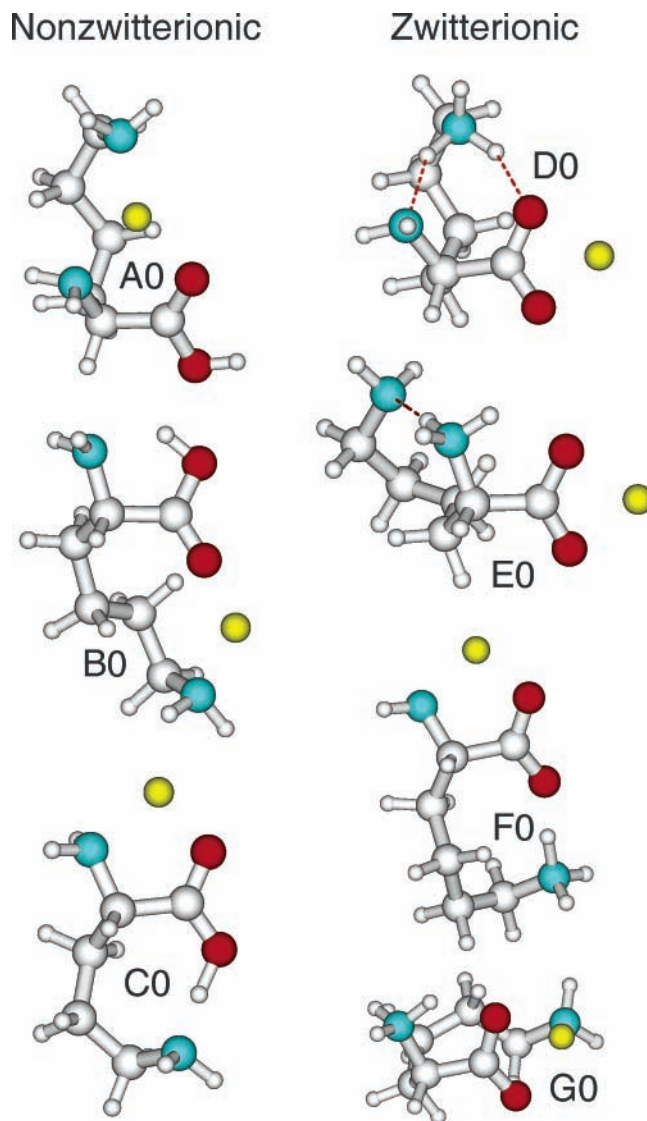

Figure 2. Low-energy structures of Lys·Li$^+$ at the B3LYP/6-31++G** level of theory. Note that the cluster labeled C0 is Orn·Li$^+$; this structure minimizes to F0 for the other molecules studied.

both oxygen atoms of the carboxylate group (O- and OO-coordination, respectively). This metal ion coordination mode is similar to that observed for the zwitterionic forms of other cationized amino acids.[5−7,71,72] Li$^+$ can also undergo N$_T$O-coordination similar to the C structures but with the acidic proton of the carboxylic acid transferred to the side-chain amine (F0 and F1). This structure is stable for all the complexes with acidic protons studied here, except for Orn·Li$^+$(H$_2$O). The lithium ion can also interact with the carboxylate group and the side-chain nitrogen (G0). Of the four compounds, this structure is most favored for NMeLys due to the higher proton affinity of the N-terminus, which is a secondary amine. This structure is least favored for Orn, which does not provide optimal coordination of the metal ion due to the shorter side chain.

Proton Affinity and Zwitterionic Stability. Without a water molecule, the nonzwitterionic structure, A0, is the most stable form of all these lithiated clusters (Table 1). All other structures are substantially higher in energy. For Lys, F0 is the lowest-energy zwitterionic form and this structure is 29 kJ/mol higher in energy than the lowest-energy nonzwitterionic form (A0). The PA of NMeLys is only about 2 kJ/mol higher than that for Lys, yet the most stable zwitterionic structure, G0, is much closer in energy (+14 kJ/mol) to A0. For select amino acids
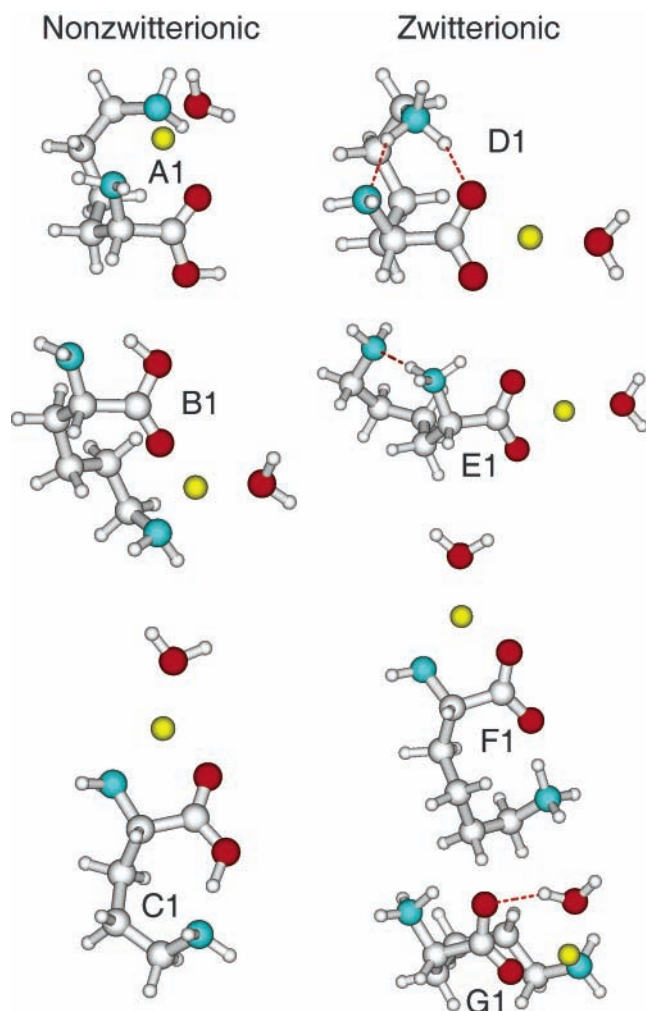
Lithiated Lysine and Structural Analogues

J. Phys. Chem. A, Vol. 110, No. 27, 2006 **8437**

Figure 3. Low-energy structures of Lys·Li$^+$(H$_2$O) at the B3LYP/6-31++G** level of theory. Note that cluster labeled C1 is Orn·Li$^+$-(H$_2$O); this structure minimizes to F1 for the other molecules studied.

with aliphatic side chains, methylation of the N-terminus increases the proton affinity of the molecule by ∼30−35 kJ/mol; for the cationized form of these amino acids, this methylation preferentially stabilizes the zwitterionic form by ∼20−25 kJ/mol.[2,6]

For Lys(Me), the highest PA amino acid studied here, F0 is the most stable zwitterionic form and this structure is about 12 kJ/mol higher in energy than nonzwitterionic A0. The difference in PA for Lys(Me) and Lys (16 kJ/mol) results in a relative stabilization of the zwitterionic form by 17 kJ/mol. As has been reported in other studies, increasing the PA of the protonation site translates into an increased relative stabilization of the zwitterionic form in the absence of other competing factors.[2,6,46−48]

The difference in energy between the zwitterionic form, F0, and the nonzwitterionic form, A0, for Orn is similar to that for Lys. However, E0 is the lowest-energy zwitterionic structure for Orn. The side chain cyclizes to solvate the protonated N-terminus in this structure, and apparently, the seven-membered ring that occurs for Orn is favored over an eight-membered ring for Lys.

Water and Zwitterionic Stability. The effect of adding a single water molecule to the relative energies of these structures is surprisingly substantial. Both the zwitterionic and nonzwitterionic structures are very comparable in energy for all these hydrated complexes. These calculations indicate that the nonzwitterionic form, A1, is still most stable for Lys and Orn, but

the zwitterionic forms are most stable for NMeLys and Lys-(Me). The lowest-energy form of NMeLys is E1, whereas D1 and F1 are essentially isoenergetic for Lys(Me). In contrast to the comparable complexes without a water molecule, the nonzwitterionic form B1 is comparable in energy to A1 for Lys, NMeLys, and Lys(Me). In structure B1, Li$^+$ coordinates to two heteroatoms in the amino acid and to the water molecule. In the gas phase, up to four water molecules can directly interact with Li$^+$ and the interaction energy with each water molecule decreases with sequential hydration.[73,74] In A1, the metal ion is coordinated to four heteroatoms. However, the similar energy of A1 compared to B1 indicates that the interactions with these four heteroatoms are not optimal. The relative stabilization gained by making additional interactions with the metal ion is decreased whereas the stability of the intramolecular hydrogen bonding interaction between the acidic hydrogen and the N-terminus should be relatively independent of metal ion coordination.

The proton affinities of the analogues that have secondary amines, NMeLys and Lys(Me), are higher than that of lysine by 2.2 and 16.1 kJ/mol, respectively. Yet, the differences in energy between the zwitterionic and nonzwitterionic forms for Lys, NMeLys, and Lys(Me) in AA·Li$^+$ are 29.1, 14.2, and 11.8 kJ/mol, respectively. These results suggest that increased proton affinity contributes to a preferential stabilization of the zwitterionic forms of these amino acids but that this relationship is less direct than that observed previously for amino acids with aliphatic side chains.[2,6]

For Orn, the zwitterionic form E1 is very competitive with the nonzwitterionic form A1 (+3 kJ/mol). As was the case without water, the zwitterionic form of Orn with a water molecule is closer in energy to the nonzwitterionic form compared to Lys.

Structural Isomerization. A key question in experimental studies of complexes, such as those investigated here, is whether various structures can interconvert under the experimental conditions used. Our calculations indicate that many structures can exist that are nearly isoenergetic and that many are likely to have very small interconversion barriers. We have grouped such similar structures into broader "families" of structures, shown in Figures 2 and 3. Of particularly interest is the barrier for interconverting the zwitterionic and nonzwitterionic forms of the molecule in these complexes. This barrier for Lys·Li$^+$ has not been determined either experimentally or computationally. However, information about the potential for conversion between the lowest-energy nonzwitterionic (NO-coordinated) and zwitterionic (OO-coordinated) forms of sodiated glycine has been calculated by Hoyau and Ohanessian.[20] The overall barrier height was reported to be 78.2 kJ/mol at the MP2/6-31G* level of theory, although the authors noted the possibility that there may be a lower-energy pathway.[20] Attachment of a water molecule to this complex will likely lower the barrier for interconversion between the nonzwitterionic and zwitterionic forms, but we have not attempted to quantify this effect.[20,35]

We have reproduced the potential-energy pathway calculation for Gly·Na$^+$ at the B3LYP/6-31G* level of theory to determine how the results of the density functional theory calculations compare to earlier MP2 results. The resulting potential-energy pathway for interconversion is largely similar to that previously found with MP2 calculations. However, the previously reported pathway had one additional transition state and local minimum involving torsion of the amine and the shift of the metal ion that did not appear necessary in our surface. The pathway for this interconversion was also calculated for Gly·Li$^+$ and is
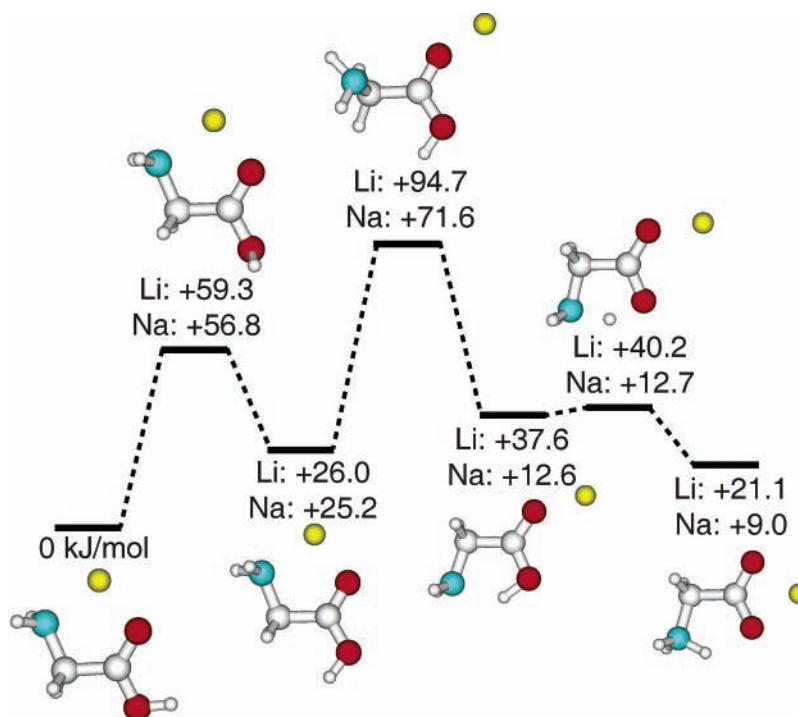
Figure 4. Potential-energy pathway for conversion of Gly·Li$^+$ from its lowest-energy nonzwitterionic form to its lowest-energy zwitterionic form at the B3LYP/6-31G* level of theory. Relative energies (kJ/mol) include zero-point energy and ΔH(298 K) corrections. Values are also included for the relative energies of the comparable Gly·Na$^+$ structures.

shown in Figure 4. This pathway has similar local-minimum and transition-states structures to those calculated for Gly·Na$^+$, and energies for these structures are reported for both metal ions. For Gly·Na$^+$, the calculated barrier height is 71.6 kJ/mol, which is in excellent agreement with previous calculations.[20] This barrier height is similar to the binding energy of a water molecule to sodiated glycine ($\sim$75 kJ/mol).[35] This result indicates that interconversion between the zwitterionic and nonzwitterionic forms of Gly in this complex is energetically comparable to that for the loss of a water molecule. However, the interconversion between these two forms of the molecule occurs over a moderately complex surface. This would be expected to result in effectively a "tight" transition state compared to that for the loss of a water molecule, that is, loss of a water molecule should be entropically favored.

Replacement of Na$^+$ with Li$^+$ in the Gly complex has a significant effect on the interconversion barrier. The potential-energy pathway for conversion between zwitterionic and non-zwitterionic forms of Gly·Li$^+$ is shown in Figure 4. The overall barrier height is 94.7 kJ/mol, compared to 71.6 kJ/mol for Gly·Na$^+$. Breaking the interaction between the metal ion and the amine, which is necessary to move the metal ion from NO-coordination to OO-coordination, requires more energy for lithium than it does for sodium, consistent with the much higher affinity of glycine for lithium.[20,75,76] Although the binding energy of water to lithiated glycine has not been reported, this value for lithiated valine is $\sim$90 kJ/mol[5] and should be comparable to that for lithiated glycine. The water binding energy for sodiated valine is $\sim$5 kJ/mol less than that for sodiated glycine.[6,35] Although the barrier height for structural interconversion may be reduced in complexes with a single water molecule attached, these results suggest that, for a lithiated complex with a single water molecule, loss of the water molecule is likely to be the most favorable process from both an energy and entropy standpoint, that is, loss of a water molecule should occur well before interconversion between the nonzwitterionic and zwitterionic forms.

To investigate how the side chain of Lys influences the barrier height for structural interconversion between the nonzwitterionic and zwitterionic forms, potential-energy pathways for these processes were calculated for lithiated Lys (Figures 5 and 6). It should be emphasized that the potential-energy surface for this complex is more complicated than that for glycine and that lower-energy pathways could exist. Thus, the overall barrier reported here should be taken as an upper bound to the amount of energy required for the structural conversion. Effects of small side-chain rearrangements on the overall barrier height were not fully characterized. These contributions are expected to be small relative the interactions involving heteroatoms, so calculations were run with favorable arrangements of the aliphatic portion of the side chain.

Three high barriers were identified in these surfaces. The transition from A0 to B0 (Figure 5, 83.3 kJ/mol) is considerably higher than the water binding energies measured here. This is the lowest barrier identified for converting A0 to one of the other families of structures identified in this study, indicating that A0 should not isomerize to another family of clusters in these experiments. The reverse activation barrier (B0 to A0) is only 55.4 kJ/mol and would be energetically accessible in these experiments, although this process is not expected to be entropically favored. Additionally, both G0 to E0 (Figure 5, 108.1 kJ/mol) and A0 to F0 (Figure 6, 134.4 kJ/mol) require large rearrangements of the side chain, effectively eliminating all interactions between the side chain and other heteroatoms at the transition state. In contrast, two pairs of families have transition-state structures that are only $\sim$20 kJ/mol higher in energy than the respective reactant and product local-minima structures and would readily rearrange in these experiments. B0 converts to form G0 with a relatively minor shift of the metal ion followed by proton transfer where as E0 converts to form D0 with the rotation of the backbone nitrogen and proton transfer.

To the extent that the barriers for Lys·Li$^+$(H$_2$O) are comparable to those for Lys·Li$^+$, these calculations suggest that there

Lithiated Lysine and Structural Analogues

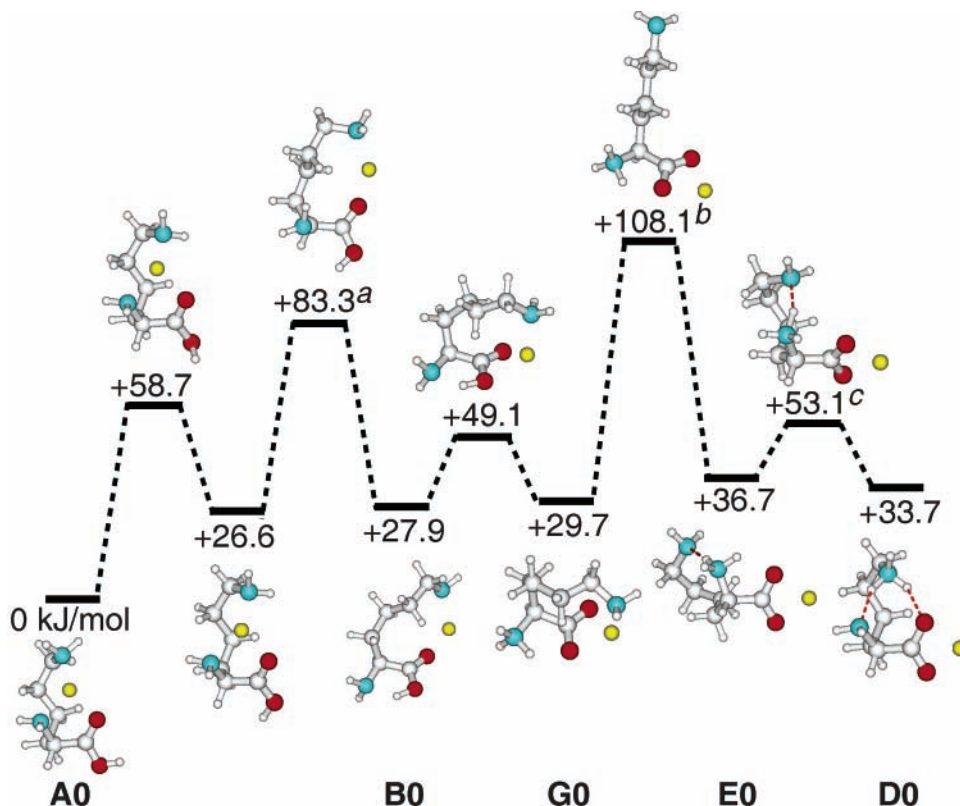*J. Phys. Chem. A, Vol. 110, No. 27, 2006* **8439**

Figure 5. Potential-energy pathway for conversion of Lys·Li$^+$ from its lowest-energy nonzwitterionic form (A0) to the B0, D0, E0, and G0 forms at the B3LYP/6-31G* level of theory. Relative energies (kJ/mol) include zero-point energy and ΔH(298 K) corrections. (a) This structure was energy minimized with the dihedral angle of the backbone constrained. Various attempts to find the true local maxima failed to converge, but the relatively small energy changes calculated during those searches suggest that this structure is very similar to that of the true transition state. (b) This local minimum structure is a representative low-energy structure in which the side chain interacts with none of the heteroatoms of the amino acid backbone. (c) This structure was optimized with the orientation of the backbone amine and one degree of freedom in the side chain constrained. This structure is representative of the energy in a region where only one of the two hydrogen-bonded interactions is preserved. Various structures with this criteria yielded similar energies, suggesting that this is a good approximation for the energy of the transition state.

TABLE 2: Diabatic Binding Energies of Water for AA·Li$^+$(H$_2$O) (in kJ/mol) from Density Functional Calculations at the B3LYP/6-31++G Level of Theory, Including Zero-point Energy and ΔH(298 K) Corrections[a]**

AA	expt.	A1	B1	C1	D1	E1	F1	G1
Lys	58 ± 2	58	75 (55)		86 (52)	86 (51)	80 (51)	80 (44)
NMeLys	57 ± 1	58	78 (61)		85 (54)	86 (65)	80 (48)	78 (64)
Lys(Me)	63 ± 2	56	76 (54)		85 (67)	85 (56)	79 (67)	80 (45)
Orn	64 ± 2	66	82 (48)	84 (54)	85 (60)	87 (63)		73 (19)
LysOMe	60 ± 2	56						

[a] The adiabatic binding energy is included in parentheses when this value differs from the diabatic value. Experimentally measured water binding energies (in kJ/mol) are determined from the master equation modeled threshold dissociation energies. Structural designations refer to geometries analogous to those presented in Figure 3.

could be four classes of structures: A1, B1/G1, E1/D1, and F1. Within each of these four classes, numerous low-energy conformers are likely represented but only limited interconversion between these classes would be expected in these experiments.

Water Binding Energies. The binding energy of a water molecule in a complex can be a useful indicator of the structure of the complex, indicating, for example, differences between zwitterionic and nonzwitterionic forms of a molecule in the structure.[5-7] Binding energies are calculated from the low-energy AA·Li$^+$ and AA·Li$^+$(H$_2$O) structures and are given in Table 2. A comparison to adiabatic binding energies is only appropriate when the structure of the reactant resembles that of the lowest-energy products or when the barrier to isomerization

is less than the binding energy. Given the large enthalpic barriers to isomerization discussed in the previous section and that the direct loss of a water molecule should be entropically favored over rearrangement, it is likely that the structures of transition-state ions in these kinetically controlled experiments strongly resembles those of the reactants. In that case, a diabatic binding energy corresponding to the energy difference between the reactant ion and the lowest-energy product ion with the same metal ion coordination would be the best comparison to the experimental value.

The binding energy of a water molecule in each of the complexes was determined using blackbody infrared radiative dissociation (BIRD). Zero-pressure limit (ZPL) dissociation rate constants for the loss of a water molecule from AA·Li$^+$(H$_2$O), AA = Lys, Orn, LysOMe, NMeLys, Lys(Me), are measured in the cell of a FT-ICR mass spectrometer at temperatures between −40 and 22.5 °C. Representative kinetic plots are shown in Figure 7. All the data can be fit well by straight lines with correlation coefficients ≥0.99, indicating first-order kinetics. These experiments are done with the pressure inside the ion cell below 10^{-8} Torr so that the internal energy distribution of the ions is determined only by the exchange of photons with the blackbody radiation field and by the dissociation process.[67,77]

Arrhenius plots, obtained by measuring the ZPL dissociation rate constants over a ~60° temperature range, are shown in Figure 8. Correlation coefficients for the fit data are ≥0.998. The ZPL Arrhenius activation energies (E_a) and preexponential factors (A) obtained from the Arrhenius plots are given in Table 3.
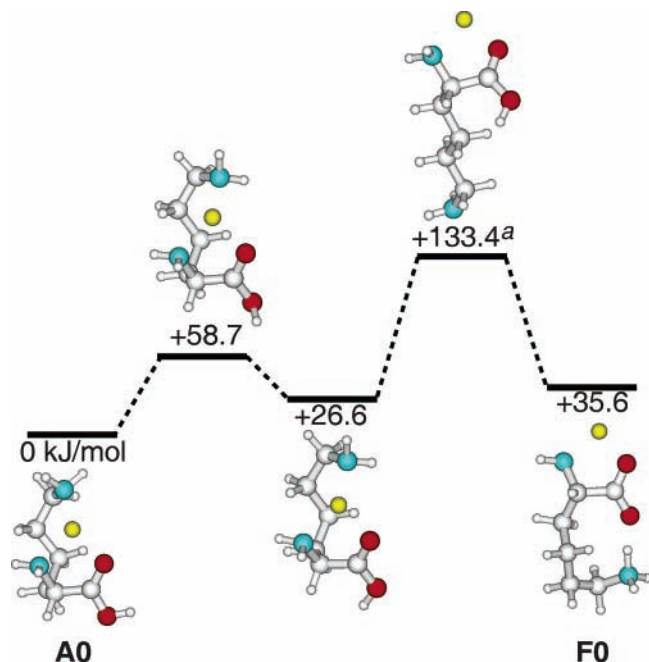
Figure 6. Potential-energy pathway for conversion of Lys·Li$^+$ from its lowest-energy nonzwitterionic (A0) form to its lowest-energy zwitterionic form (F0) at the B3LYP/6-31G* level of theory. Relative energies (kJ/mol) include zero-point energy and ΔH(298 K) corrections. (a) This local minimum structure is a representative low-energy structure in which the side chain interacts with none of the heteroatoms of the amino acid backbone.
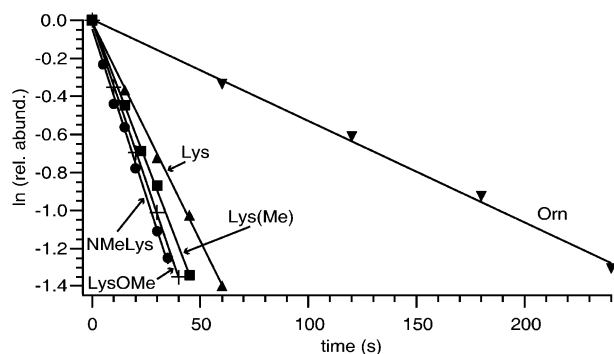

Figure 7. Blackbody infrared radiative dissociation kinetics for the loss of a water molecule from AA·Li$^+$(H$_2$O) clusters at $T = 0$ °C.
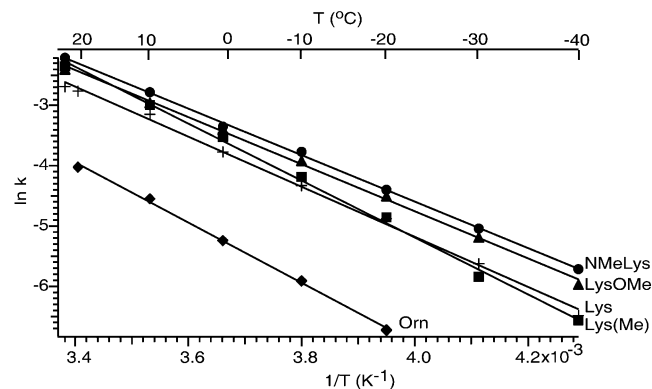

Figure 8. Zero-pressure limit Arrhenius plots for the loss of a water molecule from AA·Li$^+$(H$_2$O). The data are fit between −40 and 22.5 °C.

Because the internal energy of these ions is not given by a true Boltzmann distribution, these data must be modeled to obtain values for the threshold dissociation energies, E_0, for the

TABLE 3: Zero-pressure Limit Arrhenius Parameters E_a (in kJ/mol) and A (s^{-1}) for Loss of Water from AA·Li$^+$(H$_2$O)^a

AA	E_a	log A	E_0
Lys	35 ± 1	5.0 ± 0.2	57 ± 2
Orn	41 ± 1	5.7 ± 0.2	63 ± 2
LysOMe	33 ± 1	4.7 ± 0.1	57 ± 2
NMeLys	32 ± 1	4.7 ± 0.1	57 ± 1
Lys(Me)	40 ± 1	5.9 ± 0.1	63 ± 2

^{a} Threshold dissociation energies (E_0) (in kJ/mol) for loss of water from AA·Li$^+$(H$_2$O) are determined from master equation modeling of the BIRD kinetic data.

loss of a water molecule from AA·Li$^+$(H$_2$O). A master equation approach in which the rates for radiative absorption and emission, as well as dissociation, are calculated as a function of ion energy is used to simulate the experimental data with the only adjustable factor being the threshold dissociation energy. A relatively wide range of values for the transition dipole moments and transition-state entropies are used to account for uncertainties in these calculated values. The E_0 values determined from this modeling are given in Table 3. The values for Lys, LysOMe, and NMeLys are indistinguishable, as are those for Orn and Lys(Me).

To directly compare the calculated and experimentally derived values of the water binding energy, the BIRD threshold dissociation energies are converted into binding enthalpies. If there is no significant reverse activation barrier for loss of a water molecule from these clusters, binding enthalpies can be calculated using eq 2

$$\Delta H(T) = E_o + E_{vib}^T(AA \cdot M^+) + E_{vib}^T(H_2O) - E_{vib}^T(AA \cdot M^+(H_2O)) + 4RT \quad (2)$$

where $T = 298$ K and E_{vib}^T is the vibrational energy at temperature T. The binding enthalpies of water for AA·Li$^+$-(H$_2$O) are given in Table 2.

The experimentally derived water binding energy values are all similar, spanning a 7 kJ/mol range. The values for Lys, NMeLys, and LysOMe are more comparable to each other than to those for Lys(Me) and Orn, which are both somewhat higher. The experimentally derived values are all within 7 kJ/mol of the values calculated for structure A1. These values are also very close to that both calculated and measured for LysOMe which cannot form a zwitterionic structure. In contrast, the diabatic binding energy values for all the zwitterionic structures range from 9 to 29 kJ/mol higher.

Although the values of the adiabatic binding energies are similar to the experimentally measured values for most zwitterionic forms, it is unlikely that significant structural conversion between zwitterionic forms D1, E1, and G1 and nonzwitterionic forms would occur due to the very high barrier for this process (vide supra). It should be noted that experimentally obtained water binding energies to some similar complexes can be lower than those calculated using B3LYP by 8 kJ/mol or more,[5−7,78−80] although some recent work suggests that these values can be more similar.[71,72] The calculated adiabatic binding energies for the zwitterionic forms of lysine are 6−14 kJ/mol *lower* than the experimental value. Thus, the experimental data is most consistent with the nonzwitterionic form A1 for lysine in the complex.

The only previously reported water binding energies to cationized amino acids with heteroatom-containing side chains are for lithiated and sodiated glutamine.[71,72] The modes of metal ion and water binding in Gln are similar to those of structure

Lithiated Lysine and Structural Analogues

J. Phys. Chem. A, Vol. 110, No. 27, 2006 **8441**

A1. The experimentally measured binding energies of water to Gln and Lys are 64 ± 1[71] and 58 ± 2 kJ/mol, respectively. This indicates that Li$^+$ has a stronger interaction with the side chain of Lys than with that of Gln. This could be due to the additional methylene groups in the Lys side chain relative to Gln, which allow for increased conformational flexibility and an improved interaction with the metal ion. The binding energies of water to complexes of cationized glutamine and asparagine differ by $\sim 0-3$ kJ/mol. Asparagine has one less methylene group in its side chain than glutamine resulting in less solvation of the metal ion.[71] Ornithine, which has the same length side chain as Gln, has a water binding energy of 64 ± 2 kJ/mol, identical to that for Gln.

It is interesting to note that the threshold dissociation energy for Lys(Me) is slightly greater than that for the other molecules except Orn. This small difference in the interaction energy of a water molecule to Lys(Me) suggests that the lithiated Lys(Me) complex with a water molecule may have a different structure than the NMeLys and LysOMe complexes.

Conclusions

The structures of clusters of Lys·Li$^+$ and related compounds, both with and without a water molecule attached, were investigated using density functional theory calculations and BIRD experiments. For the clusters without a water molecule, the calculations indicate that the molecules are not zwitterionic and that the metal ion interacts with both nitrogen atoms and the carbonyl oxygen. With a water molecule, the zwitterionic and nonzwitterionic structures are much closer in energy and the zwitterionic form is calculated to be most stable for NMeLys and Lys(Me). Although there is a trend toward the increased stability of the zwitterionic form with increasing proton affinity, this relationship is not nearly as direct as that reported previously for aliphatic amino acids and analogues due to the competing effects of charge solvation by the heteroatom in the side chain in these clusters.

Calculations of energetics for interconversion between the most stable nonzwitterionic form and all zwitterionic forms of lithiated Lys indicate multiple intermediates and an overall barrier height that is higher than the measured binding energy of water to these complexes. Although these calculations were done on complexes without a water molecule, these results do suggest that the loss of a water molecule should be both energetically and entropically favored over isomerization under typical experimental conditions.

The water binding energies in these complexes are all very similar. By comparison to calculated diabatic water binding energies for the possible structures, the experimentally measured values indicate that the nonzwitterionic form is most stable for all complexes.

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