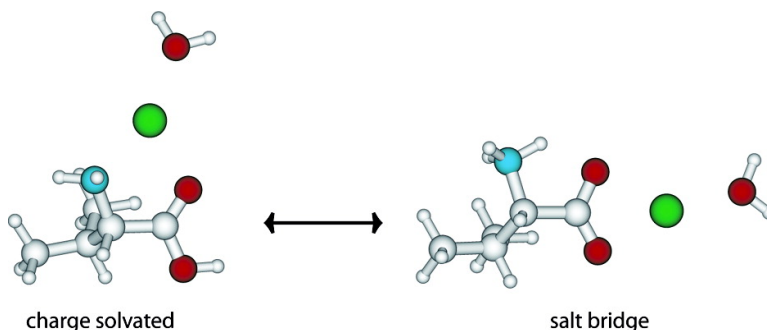## Article

Binding Energies of Water to Sodiated Valine and Structural Isomers in the Gas Phase: The Effect of Proton Affinity on Zwitterion Stability

Andrew S. Lemoff, Matthew F. Bush, and Evan R. Williams

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Binding Energies of Water to Sodiated Valine and Structural Isomers in the Gas Phase: The Effect of Proton Affinity on Zwitterion Stability

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Abstract: The structures of valine (Val) and methylaminoisobutyric acid (Maiba) bound to a sodium ion, both with and without a water molecule, are investigated using both theory and experiment. Calculations indicate that, without water, sodiated Val forms a charge-solvated structure in which the sodium ion coordinates to the nitrogen and the carbonyl oxygen (NO-coordination), whereas Maiba forms a salt-bridge structure in which the sodium ion coordinates to both carboxylate oxygens (OO-coordination). The addition of a single water molecule does not significantly affect the relative energies or structures of the charge-solvated and salt-bridge forms of either cluster, although in Maiba the mode of sodium ion binding is changed slightly by the water molecule. The preference of Maiba to adopt a zwitterionic form in these complexes is consistent with its higher proton affinity. Experimentally, the rates of water evaporation from clusters of Val·Na$^+$(H$_2$O) and Maiba·Na$^+$(H$_2$O) are measured using blackbody infrared radiative dissociation (BIRD). The dissociation rates from the Val and Maiba complexes are compared to water evaporation rates from model complexes of known structure over a wide range of temperatures. Master equation modeling of the BIRD kinetic data yields a threshold dissociation energy for the loss of water from sodiated valine of 15.9 ± 0.2 kcal/mol and an energy of 15.1 ± 0.3 kcal/mol for the loss of water from sodiated Maiba. The threshold dissociation energy of water for Val·Na$^+$(H$_2$O) is the same as that for the charge-solvated model isomers, while the salt-bridge model complex has the same water threshold dissociation energy as Maiba·Na$^+$(H$_2$O). These results indicate that the threshold dissociation energy for loss of a water molecule from these salt-bridge complexes is ∼1 kcal/mol less than that for loss of water from the charge-solvated complexes.

Introduction

The structure of a molecule in water is determined by a delicate balance between the intramolecular interactions and the intermolecular interactions between the molecule and the surrounding solvent. Solvent can have a significant effect on molecular structure. For example, amino acids exist as zwitterions in aqueous solution over a large pH range, but in the gas phase, the nonzwitterion form of amino acids is energetically favored. The structural difference between amino acids in solution and the gas phase is due to water preferentially stabilizing the zwitterionic form. Gas-phase studies can provide information about the intrinsic structure of a molecule in the absence of bulk solvent. In principle, it should be possible to obtain a detailed understanding of how water interacts with and influences the structure of molecules, such as amino acids, by studying hydrated gas-phase ions.

The intrinsic structure of glycine, the smallest and most simple amino acid, has been the subject of many theoretical investigations. At the thermodynamically calibrated BAC/MP4/6-31G**/6-31G* level of theory, the nonzwitterion form of glycine is 22 ± 2 kcal/mol lower in energy than the zwitterion form in the gas phase.[1] Theoretical calculations indicate that two water molecules can make the zwitterionic form of glycine a local

minimum on the potential energy surface, but the zwitterion is still ∼12 kcal/mol higher in energy than the nonzwitterion.[2] Theory suggests that three water molecules can make the two forms of glycine nearly degenerate in energy.[1] Other calculations indicate that the nonzwitterion form of aspartic acid with three water molecules is most stable.[3] The calculated vibrational spectrum of zwitterionic alanine with four water molecules is similar to the measured vibrational spectrum of alanine in solution, but different than isolated alanine.[4]

There are only a few experimental studies on the role of water on the formation of amino acid zwitterions. Blackbody infrared radiative dissociation[5] (BIRD) experiments indicate that lithiated valine with one and two water molecules adopts a unique gas-phase structure in which valine is nonzwitterionic, but the addition of a third water molecule changes valine into a zwitterion.[6-8] The structures of complexes consisting of valine,

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a single water molecule, and either Na$^+$ or K$^+$ have also been investigated.[6] It was found that valine remains nonzwitterionic and that a single water molecule does not significantly affect the structure or energetics of these complexes. Pioneering spectroscopic experiments by Peteanu and Levy on tryptophan–water clusters generated in a free jet expansion showed that the favored binding site for water is to the amine group of the tryptophan side chain.[9] Results from ultraviolet hole burn and infrared ion dip spectroscopy experiments of tryptophan with from one to three water molecules suggest that tryptophan with three water molecules could be zwitterionic, consistent with calculations which indicate that the zwitterion and nonzwitterion forms of tryptophan with three water molecules are comparable in energy.[10] A recent resonant two-photon ionization study of phenylalanine and its monohydrate indicates that a single water molecule hydrogen bonds to the hydroxyl group and does not induce significant structural change.[11]

The zwitterion form of gas-phase amino acids can be stabilized by the presence of a nearby charge. Calculations show that attachment of an electron to glycine in the gas phase decreases the energy of the zwitterionic structure from 20 to 9 kcal/mol above the nonzwitterionic conformer.[12] Similarly, the relative energy of the zwitterion form of arginine solvated by an excess electron is lowered by ∼6 kcal/mol, making it comparable in energy to the electron solvated nonzwitterion form.[13] Positive charges can also stabilize the zwitterionic form of amino acids. Amino acids readily interact with metal ions forming either charge-solvated structures in which the amino acids is nonzwitterionic or salt-bridge structures in which the amino acid is zwitterionic. The metal ion in the charge-solvated structures of glycine, for example, can interact with the nitrogen of the amine and the carbonyl oxygen (NO-coordination), or with both oxygens of the carboxylic acid group (OO-coordination). Calculations show that an attached alkali metal cation can lower the relative energy of the salt-bridge structure of glycine to only 1–4 kcal/mol higher than the charge-solvated structure.[14–18] This is presumably due to the larger dipole moment typically associated with the zwitterion form of the amino acid. Ion mobility experiments of sodiated and cesiated glycine indicate a charge-solvated structure.[14] Arginine is not a zwitterion by itself in the gas phase,[19–23] but protonated dimers of

arginine form salt-bridge structures in which one of the arginines is protonated and the other is a zwitterion.[22] The stability of gas-phase ionic complexes of arginine molecules has been attributed to cyclic arrays of the zwitterion form.[24] The lowest-energy forms of both the neutral gas-phase dimer and the trimer of arginine are structures in which all of the arginines are zwitterionic.[25] Thus, a net charge is not necessary to stabilize the higher order clusters of arginine. Zwitterion structures[26,27] have also been proposed for the unusually stable serine octameric clusters that have been observed in the gas phase.[26–28]

The magnitude of the charge also plays a large role in zwitterion stability. Glycine and alanine complexed with Cu$^+$ are nonzwitterionic, whereas they are zwitterionic when copper is divalent.[29,30] Similarly, the zwitterionic form of glycine when bound to the divalent alkaline earth metal ions Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} is 5–12 kcal/mol lower in energy than the nonzwitterionic conformer.[31] The size of the attached metal also influences the relative stability of the zwitterion and non-zwitterion forms. For the smaller alkali metal cations (Li$^+$, Na$^+$),[14–18] Ag$^+$,[32] and for the smallest alkaline earth cation Be^{2+},[31] nonzwitterionic glycine forms a NO-coordinated charge-solvated structure, while the larger alkali metal ions form OO-coordinated charge-solvated structures.[15] For arginine bound to alkali metal ions, both experiment and theory indicate that the structure of arginine changes from nonzwitterionic to zwitterionic with increasing metal ion size.[33] A similar conclusion has been recently reported for arginine and lysine based on relative metal ion binding affinities of the amino acid and its corresponding methyl ester.[34,35] The unusual dissociation behavior of potassiated arginine and cesiated arginine and lysine was attributed to these clusters containing the zwitterion form of the amino acid.[35] Ion mobility experiments of cationized arginine were inconclusive due to indistinguishable collisional cross sections for the charge-solvated and salt-bridge forms of this ion.[14] Calculations on a related molecule, sodiated *N*-amidino-glycine, indicate that the salt-bridge form is more stable, but the ion mobility results were more consistent with the charge-solvated form.[14]

The acidity of the proton-donating group and the basicity of the proton-accepting group of an amino acid also play a role in stabilizing the amino acid zwitterion. The guanidino side chain of arginine is significantly more basic than the amino group of glycine. The zwitterionic structure of neutral arginine is only 2.8 kcal/mol higher in energy than the nonzwitterion (vs ∼20 kcal/mol for glycine).[23,25] Cavity ring down experiments show

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no evidence for the presence of the arginine zwitterion,[20] although uncharged dimers of arginine are thought to exist as zwitterion pairs.[25]

Strittmatter et al. investigated the role of gas-phase basicity on salt-bridge formation of protonated trimers consisting of two identical basic molecules and trifluoroacetic acid.[36] The bases have gas-phase basicities ranging from 246 to 254 kcal/mol. On the basis of the dissociation pathways and energetics, the authors concluded that the protonated trimers consisting of the most basic bases have salt-bridge structures in which both bases are protonated and the trifluoroacetic acid is deprotonated. In contrast, the protonated trimers consisting of the least basic bases form charge-solvated structures. A subsequent computational study of uncharged dimers of trifluoroacetic acid and each of these basic molecules indicated that the structure of the dimer changes from a neutral pair to an ion pair as the proton affinity of the base increases,[37] in agreement with the experimental results on the protonated trimers.[36]

Bowers and co-workers investigated the relationship between the proton affinity and the structure of a group of amino acids and amino acid analogues.[16] They suggested that there is a "fairly linear relationship" between the proton affinity and the relative stability of the zwitterionic structure. This model predicts that sodiated amino acids with proton affinities greater than 217 kcal/mol exist as zwitterions in their most stable form, although other factors that influence the energy of charge-solvation structures also play a role. For example, the proton affinities of Gly_6 and Gly_{10} are ~25 and ~30 kcal/mol, respectively, higher than that of glycine itself.[38] Yet both experiment (for Gly_n, $n = 1-6$)[39] and theory ($n = 4, 5, 7, 10$)[38] indicate that these ions do not form zwitterions in the gas phase. The charge-solvated structures are significantly stabilized by the interactions with many polarizable groups in the larger peptides. For proline, which has a proton affinity of 220 kcal/mol, Möller−Plesset calculations at the MP2/6-311+G(2d,2p) level of theory have shown that the salt-bridge structure of the proline−alkali metal ion complex is 4−7 kcal/mol more stable than the charge-solvated structure for all alkali metal ions.[35] Proline is unusual among the amino acids in that the proton-accepting group at the N-terminal end is a secondary amine, which is more basic than a primary amine. In addition, the ring structure of proline reduces the ability of the amino acid to solvate the ion in the charge-solvated form.[40] While the calculations of Bowers and co-workers suggest that the salt-bridge form of sodiated valine should be marginally more stable than the charge-solvated form based on the proton affinity of valine (217.6 kcal/mol),[16] dissociation experiments with sodiated clusters of valine and valine methyl ester indicate a charge-solvated form.[35]

Previously, the effect of hydration and metal ion size on the structure of $Val \cdot M^+(H_2O)_n$, where M = Li, Na, K and $n = 1-6$, was studied by measuring the dissociation kinetics for the loss of a water molecule.[6,7] On the basis of the kinetic data, we concluded that the addition of three water molecules changes

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the structure of valine into a zwitterion for M = Li. For M = Na, the kinetic data indicate that the structure of the valine complex changes upon the addition of two water molecules, but we were unable to determine if Val became zwitterionic. The structures of $Val \cdot K^+(H_2O)$ were too similar to differentiate with our experiment. Here, we measure the threshold dissociation energy of water bound to sodiated valine and four structural isomers. In contrast to earlier predictions based on proton affinities,[16] we show that sodiated valine with one water molecule attached forms a charge-solvated structure. We also show that sodiated methylaminoisobutyric acid (Maiba) with one water molecule attached forms a salt-bridge structure. The difference in the relative zwitterionic stabilities between Val and Maiba is comparable to the 7.4 kcal/mol difference in proton affinities.

Experimental Methods

Chemicals. Valine (Val) and methylaminoisobutyric acid (Maiba) were obtained from Sigma Chemical Co. (Saint Louis, MO). The monohydrate of betaine (Bet) and the hydrochloride salts of alanine ethyl ester (AlaOEt) and sarcosine ethyl ester (SarOEt) were obtained from Aldrich Chemical Co. (Milwaukee, WI). Sodium hydroxide was purchased from Fisher Scientific (Fair Lawn, NJ). All chemicals were used without further purification. Electrospray solutions were made to 1.0 mM AA (amino acid or amino acid analogue) and 2.0 mM sodium hydroxide using deionized water.

Mass Spectrometry. All dissociation experiments were performed on a home-built Fourier transform mass spectrometer with a 2.7 T superconducting electromagnet. Ions are formed by nanoelectrospray ionization using 0.78 mm inner diameter borosilicate capillaries that are pulled to a tip diameter of between 3 and 5 μm using a Flaming− Brown micropipet puller (Sutter Instruments model P-87, Novato, CA). A platinum wire inserted down the center of the other end of the capillary is used as an electrode and is held at a potential of ~1 kV. The tip of the nanospray capillary is placed approximately 1 mm from the electrospray interface. Electrospray generated ions are accumulated in the ion cell for a period of 3−5 s, after which time a mechanical shutter is closed to stop additional ions from entering the cell. Nitrogen gas is pulsed into the ion cell at a pressure of ~2 × 10^{-6} Torr during the ion accumulation period to assist in ion trapping and thermalization. After a 2 s delay, the base pressure in the vacuum chamber returns to <1 × 10^{-8} Torr. Unwanted ions are ejected from the cell using a series of stored waveform inverse Fourier transform (SWIFT) and chirp excitation waveforms. The hydrated ion cluster of interest is then allowed to undergo unimolecular dissociation for times ranging from 0 to 300 s. Following the variable reaction delay, the product ions are excited for detection using a frequency sweep with a rate of 2200 Hz/ μs. A detection bandwidth of 4000 kHz is used. Data are acquired using an Odyssey data system (Finnigan MAT, Bremen, Germany). Dissociation kinetics are obtained by measuring the abundance of the parent and daughter ions as a function of reaction time.

For experiments involving a heated cell, the temperature of the entire vacuum chamber is raised by using electrically resistive heating blankets located on the outside of the chamber. For experiments below ambient temperature, the copper jacket surrounding the cell is cooled to a uniform temperature. This is done by regulating the opening and shutting of a solenoid that controls the flow of liquid nitrogen around the outside of the copper jacket. Prior to all experiments, the temperature is allowed to equilibrate overnight (>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.

Although the copper jacket is at a known temperature, there are holes in the jacket that make possible the introduction of sample and electrical

connections into the ion cell. These openings allow radiation from other parts of the vacuum chamber to enter the ion cell and interact with the ions. The electrical connections conduct heat to the ion cell inside the copper jacket. For these reasons, the internal energy distribution of the ions is not well characterized when the copper jacket is at a significantly lower temperature than the vacuum chamber. For the temperature range used in this experiment, the temperature that the ions experience inside the cell has been accurately calibrated to the temperature of the copper jacket. The procedure by which this is done and the accuracy of BIRD data at reduced temperatures are reported elsewhere.[41]
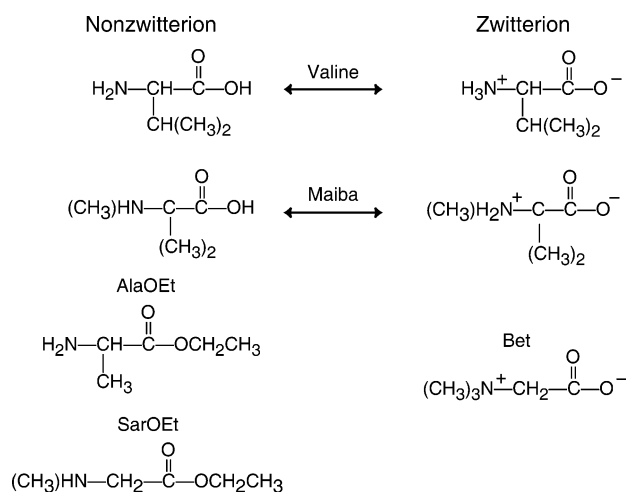
Computational Details. Lowest-energy structures of AA·Na$^+$ and AA·Na$^+$(H$_2$O), AA = Val, AlaOEt, Bet, have been previously reported.[6] Possible low-energy structures of Maiba and SarOEt are determined by using a combination of conformational searching and chemical intuition. Structures of AA·Na$^+$ and AA·Na$^+$(H$_2$O) clusters were generated using Monte Carlo conformation searching with the MMFF94 force field using Macromodel 7.1 (Schrodinger, Inc., Portland, OR). For the initial search, no constraints were placed on the molecules, and 5000 conformations were generated with a Monte Carlo simulation. All of the lowest-energy structures within 5 kcal/mol of the lowest-energy conformer were identified in the first 1000 iterations; no additional lowest-energy structures were found subsequently, indicating that the majority of lowest-energy structures obtainable from these molecular mechanics calculations were identified. For Maiba, the lowest-energy structure was found 276 times. Starting structures for higher-level calculations were chosen from this group of structures. In several instances, additional structures which were more than 5 kcal/mol less stable than the lowest-energy structure were also chosen. In no instance were these additional higher energy structures found to be the most stable structure at higher levels of theory.

After lowest-energy structures were identified from the mechanics calculations, hybrid method density functional calculations (B3LYP) were performed using Jaguar v. 4.0 and 4.1 (Schrodinger, Inc., Portland, OR) with increasingly large basis sets. The basis sets used were 6-31G* full optimization, 6-31+G* full optimization, 6-311++G** single-point energy calculation at the 6-31+G*-optimized geometry, and 6-31++G** full optimization.

In the BIRD experiments, the measured dissociation rate depends on the rates of radiative absorption and emission, the transition state entropy of the dissociation, and the binding energy of the water to the ion. We can numerically simulate the experiment by modeling these processes using a master equation formalism. This is discussed in detail elsewhere.[42] Briefly, 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. Dissociation processes are included in the model by using microcanonical dissociation rate constants calculated with RRKM theory. Typically, the transition state entropy of the dissociation is not known, so we model a range of transition state entropies which results in a range of dissociation rate constants. The binding energy used to calculate the RRKM rate constants is also varied in the model. Modeling was done for each of the isomers assuming both a "neutral" and a "loose" transition state (Arrhenius preexponentials of 10^{13} and 10^{17} s^{-1}, respectively). Dissociation of water from these clusters should go through a relatively loose transition state, but a wider range was used to better assess the effect of this parameter. In addition, the transition dipole moment multiplication factor was varied between 1.0 and 1.6 to better determine the range of threshold dissociation energies and to better model the experimental results.

The proton affinity of Maiba was determined at the B3LYP/6-31+G*//B3LYP/6-311++G* level of theory by subtracting the enthalpies at 25 °C of Maiba and H$^+$ from MaibaH$^+$. Enthalpies of Maiba and MaibaH$^+$ were determined by summing the total molecular

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Scheme 1

energies, zero-point energies, and the enthalpy contribution from rotation, translation, and vibration at 25 °C. The proton enthalpy is the sum of translational energy of the proton at 25 °C and RT.

Results and Discussion

The structures of complexes of sodiated methylaminoisobutyric acid (Maiba) and valine (Val) with one water molecule were investigated using both BIRD experiments and theory. In these experiments, structural information, that is, zwitterion versus nonzwitterion, is deduced by comparing kinetic data for loss of the water molecule from the ion of interest measured over a wide temperature range to that for model compounds of known structure. Maiba, Val, and the compounds that are models for the zwitterionic and nonzwitterionic forms of these complexes are all isomers. Betaine (Bet) is used as a model of the zwitterionic forms of both Val and Maiba, while alanine ethyl ester (AlaOEt) and sarcosine ethyl ester (SarOEt) are models of the nonzwitterionic forms of Val and Maiba, respectively. SarOEt models the amino methyl group in nonzwitterionic Maiba, and AlaOEt models the primary amine in the non-zwitterion form of Val. The structures of these molecules are shown in Scheme 1.

For SarOEt, AlaOEt, and Bet to be good model compounds for nonzwitterionic and zwitterionic Val and Maiba, the mode of metal ion and water binding in the model complex should be the same as that of the amino acid complex. We have done a substantial amount of modeling which indicates that this is indeed the case, as will be discussed later. In these experiments, complexes are activated by absorption of infrared photons that are emitted by the walls of the temperature controlled jacket surrounding the ion cell and by the ion cell plates. The dissociation rates of these complexes depend strongly on the infrared absorption rates as well as the binding energy of water to the complex. If these isomeric complexes have identical water binding energies, then the photon absorption rate is directly related to the measured water dissociation rate; a 10% decrease in the photon absorption rate results in a 10% decrease in the water dissociation rate.[7] The calculated absorption spectra of Bet·Li$^+$(H$_2$O), AlaOEt·Li$^+$(H$_2$O), and both zwitterionic and charge-solvated Val·Li$^+$(H$_2$O) are qualitatively similar,[6] which suggests that the sodiated AA clusters investigated here ought to have similar photon absorption rates as well. Complexes with similar modes of water and metal ion binding should have
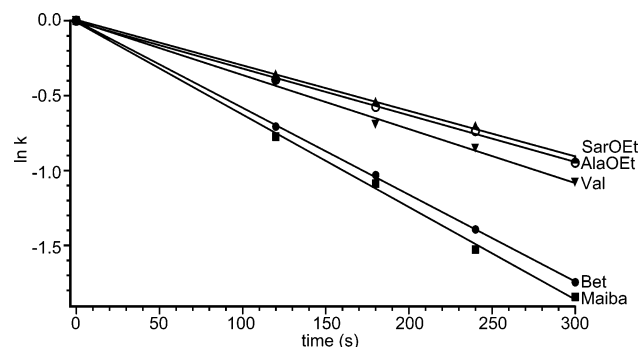
Figure 1. BIRD kinetics for the loss of a water molecule from AA·Na$^+$(H$_2$O) clusters at $T = -5$ °C. The identity of the AA is labeled in the figure.

Table 1. Values of the Zero-Pressure Limit Dissociation Rate Constants for the Loss of a Single Water Molecule from AA·Na$^+$(H$_2$O) Measured by BIRD at $T = -5$ and 36 °C

AA	rate (s^{-1}), –5 °C	rate (s^{-1}), 36 °C
valine	0.0036 ± 0.0001	0.049 ± 0.001
sarcosine ethyl ester	0.0030 ± 0.0001	0.044 ± 0.001
alanine ethyl ester	0.0031 ± 0.0001	0.045 ± 0.002
Maiba	0.00618 ± 0.00004	0.068 ± 0.002
betaine	0.00580 ± 0.00004	0.059 ± 0.002

similar transition state entropies ($\Delta S^\ddagger$). We do not explicitly model dissociation transition states for these complexes, but rather model a very wide range of transition state entropies for the water dissociation process with the Arrhenius A-factors of 10^{13} (neutral transition state) and 10^{17} s^{-1} (loose transition state). This range is significantly larger than that expected for the complexes. Our model isomers should have similar methods of water binding as do Val and Maiba, and thus the transition states should be similar between all of the complexes studied here. Therefore, any differences between the transition state entropies ($\Delta S^\ddagger$) and between photon absorption rates for the complexes should be minimal and should not significantly affect the rates of water dissociation. Instead, differences between the dissociation rates of water for the complexes are primarily due to differences in the water binding energy.

Water Dissociation Kinetics. Zero-pressure limit BIRD rate constants for the evaporation of a single water molecule from AA·Na$^+$(H$_2$O), AA = Maiba, Bet, and SarOEt, were measured at cell temperatures between −5 and 78 °C and between −5 and 61 °C for AA = Val and AlaOEt. Previous experiments have shown that the zero-pressure limit for ions of this type is reached at pressures in the low to mid 1×10^{-8} Torr range.[43,44] The dissociation occurs at pressures below 1×10^{-8} Torr, consistent with energy transfer to the ions determined only by rates of blackbody photon absorption and emission. Rate constants were determined from the slope of ln{[AA·Na$^+$(H$_2$O)]/([AA·Na$^+$(H$_2$O)] + [AA·Na$^+$])} versus time. An example of the kinetic data, measured at −5 °C, is shown in Figure 1. All of the data can be fit well by straight lines with correlation coefficients ≥0.998, indicating first-order kinetics.

Dissociation rate constants for the loss of water from all five complexes are given in Table 1 for $T = -5$ and 36 °C. At both temperatures, the dissociation rate constants for Val, SarOEt,
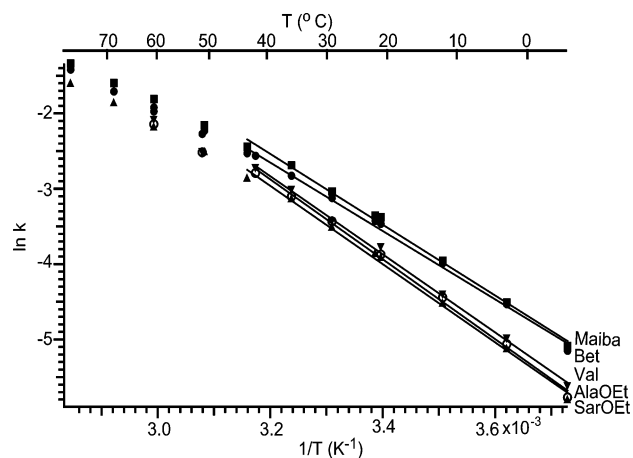

Figure 2. Arrhenius plot for the loss of a water molecule from AA·Na$^+$(H$_2$O). The data are fit between −5 and 42 °C for AA = AlaOEt and Val, and between −5 and 43 °C for AA = Maiba, SarOEt, and Bet.

and AlaOEt are similar, differing by ∼16% at −5 °C and by ∼10% at 36 °C, respectively. Rate constants for Maiba and Bet are also similar at both temperatures, differing by 6.3% and 12.9% at −5 and 36 °C, respectively. In contrast, the rate constants measured for Val, SarOEt, and AlaOEt differ significantly from those measured for Maiba and Bet at both temperatures. The average value measured for Val, AlaOEt, and SarOEt differs from the average value measured for Maiba and Val by 84% and 39% at −5 and 36 °C, respectively. These results suggest a different water interaction in Val, AlaOEt, and SarOEt versus Maiba and Bet.

Arrhenius Plots. From the zero-pressure limit rate constants measured as a function of temperature, Arrhenius plots for the dissociation of water from the five sodiated AAs can be obtained (Figure 2). The data are fit between −5 and 42 °C for the AlaOEt and Val complexes, and between −5 and 43 °C for the Bet, Maiba, and SarOEt complexes. Correlation coefficients for these Arrhenius plots over the range of temperatures selected are >0.9995. The Arrhenius plots for Val·Na$^+$(H$_2$O), AlaOEt·Na$^+$(H$_2$O), and SarOEt·Na$^+$(H$_2$O) are very similar, and those for Bet·Na$^+$(H$_2$O) and Maiba·Na$^+$(H$_2$O) are also quite similar. The data are not fit over the entire temperature range due to curvature in the Arrhenius data at high temperatures. This curvature can be due either to rapid dissociation of water from the ion clusters which results in a shift in the internal energy of the ions to lower values with increasing temperature[45,46] or to the presence of two or more structures.[47]

To determine the extent of curvature expected in the zero-pressure Arrhenius plot for a single structure, master equation modeling was performed to calculate rate constants for Maiba and Val over the entire experimental temperature range using water threshold dissociation energies of 15.2 and 15.9 kcal/mol, respectively. These values are obtained from master equation modeling of just the kinetic data at lower temperatures (−5 to 42 °C) where the Arrhenius data are linear. The results of this modeling are shown in Figure 3. The modeling clearly indicates that there is significant curvature at the higher temperatures even though only a single structure is used in the

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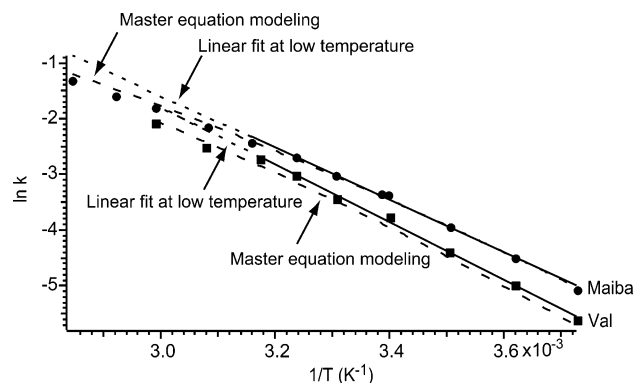
Figure 3. Master equation modeling of dissociation rate constants of water from Val·Na$^+$(H$_2$O) and Maiba·Na$^+$(H$_2$O). The solid lines represent the fit to the low-temperature kinetic data (−5 to 42 °C). The short dashed lines represent an extrapolation of the best fit line to higher temperature. The long dashed lines represent the results from master equation modeling using $E_0 = 15.9$ and 15.2 kcal/mol for AA = Val and Maiba, respectively.

Table 2. Values for the Zero-Pressure Limit Activation Energies (E_a) and the Log of the Arrhenius Prefactor (log A) for the Loss of a Single Water Molecule from AA·Na$^+$(H$_2$O) Measured by BIRD over the Linear Region of the Arrhenius Plots (−5 to 43 °C)

AA	E_a (kcal/mol)	log A
valine	10.4 ± 0.2	6.0 ± 0.1
sarcosine ethyl ester	10.4 ± 0.2	5.9 ± 0.2
alanine ethyl ester	10.6 ± 0.2	6.1 ± 0.2
Maiba	9.5 ± 0.2	5.4 ± 0.2
betaine	9.0 ± 0.2	5.2 ± 0.2

modeling. This high-temperature deviation is due to the internal energy of the ion population shifting even further from a true Boltzmann distribution which is a result of the rapid dissociation of the higher energy population. This phenomenon is described in detail elsewhere.[46] The experimental data have slightly more curvature than the modeling indicates. The modeling takes into account about 70% of the curvature. The remaining discrepancy could be due to the presence of a small fraction of another structure appearing at higher temperature or to some errors in the modeling.

The measured zero-pressure Arrhenius activation energies, E_a, and preexponential factors, A, obtained from the linear regions of the Arrhenius plots (Figure 2) are given in Table 2. The E_a values for Val·Na$^+$(H$_2$O), AlaOEt·Na$^+$(H$_2$O), and SarOEt·Na$^+$(H$_2$O) are ∼10 kcal/mol. Both the E_a and the log A values are indistinguishable within experimental error. The

E_a values for Maiba·Na$^+$(H$_2$O) and Bet·Na$^+$(H$_2$O) are ∼9 kcal/mol, and the log A values are similar.

The Arrhenius data clearly suggest a similar water binding interaction in Val·Na$^+$(H$_2$O), AlaOEt·Na$^+$(H$_2$O), and SarOEt·Na$^+$(H$_2$O), which is different from the water binding interaction in Maiba·Na$^+$(H$_2$O) and Bet·Na$^+$(H$_2$O).

Lowest-Energy Structures. A computational investigation of all of the complexes was performed to determine if our model isomers have modes of water and metal ion binding similar to those of Maiba and Val, and to obtain parameters for the master equation modeling used to obtain threshold dissociation energies. Figure 4 shows some of the stable structures and their relative energies for Val·Na$^+$ and Maiba·Na$^+$. Only one reasonable family of structures for zwitterionic Val·Na$^+$ and Maiba·Na$^+$ was found. A family is defined as a group of structures that have the same metal ion−AA interactions and differ only by rotations around C−C bonds.

The lowest-energy structures for the charge-solvated and salt-bridge forms of Maiba·Na$^+$, Val·Na$^+$, and the structural isomers are shown in Figure 5. For the zwitterionic AAs, the sodium ion interacts with both of the oxygens of the carboxylate group (OO-coordination), consistent with previous results on metal ion binding to other zwitterionic amino acids.[14−18,48] For all of the lowest-energy structures of the nonzwitterionic AAs, the
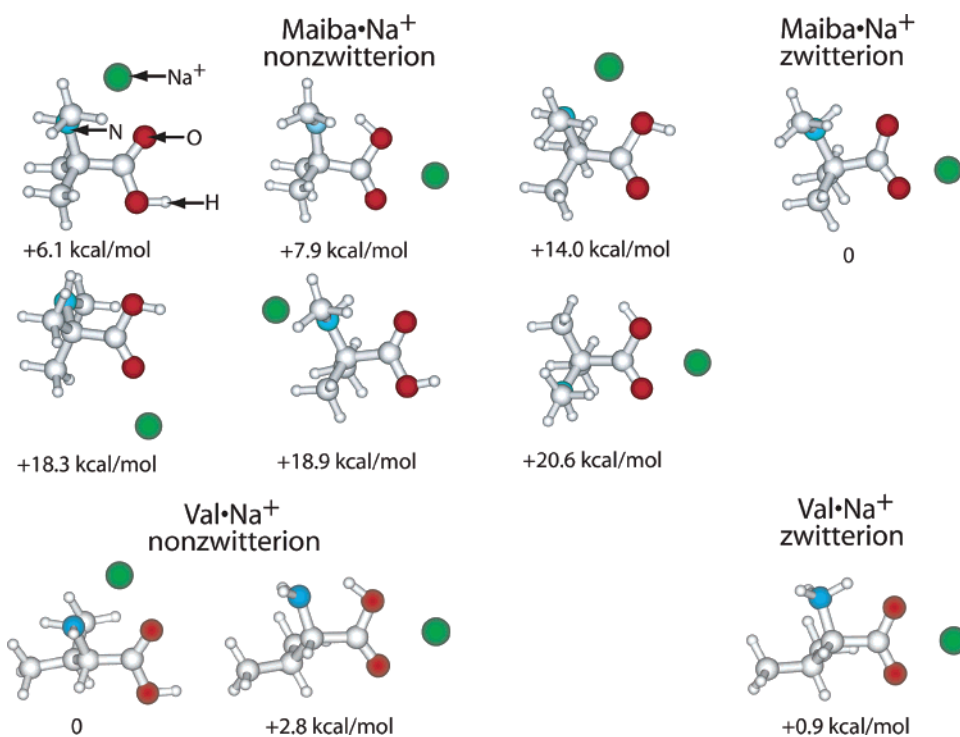

Figure 4. B3LYP/6-31+G* optimized structures and relative energies (in kcal/mol) for Maiba·Na$^+$ and Val·Na$^+$ clusters.
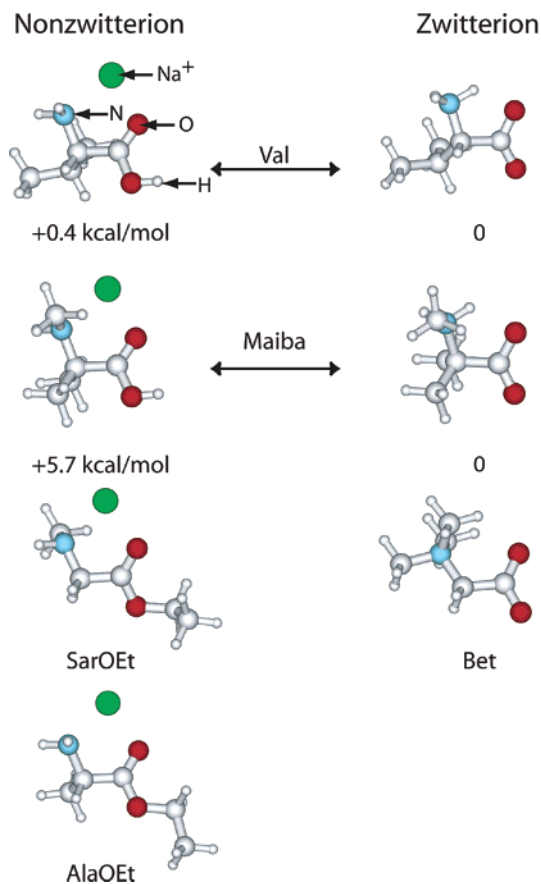
Figure 5. Lowest-energy structures of AA·Na⁺ complexes at the B3LYP/6-31++G** level of theory. Relative energies (in kcal/mol) for the AA = Val and Maiba complexes include zero-point energy corrections and Gibbs free energy corrections at 298 K.

Table 3. Relative Energies (in kcal/mol) of AA·M⁺ and AA·M⁺(H₂O) at Various Levels of Theory[a]

method/basis set	Val·Na⁺ (CS)	Val·Na⁺ (SB)	Val·Na⁺ (H₂O)(CS)	Val·Na⁺ (H₂O)(SB)
B3LYP/6-31G*	0.7	**0**	**0**	0.5
B3LYP/6-31+G*	0.8	**0**	1.4	**0**
B3LYP/6-31+G*// B3LYP/6-311++G**	**0**	0.9	**0**	2.0
B3LYP/6-31++G**	0.2	**0**	**0**	0.4
ΔZPE	−0.1	0	0	0.3
ΔG(25 °C)	0.3	0	0	0.8
total B3LYP/6-31++G** (25 °C)	0.4	**0**	**0**	1.5

method/basis set	Maiba·Na⁺ (CS)	Maiba·Na⁺ (SB)	Maiba·Na⁺ (H₂O)(CS)	Maiba·Na⁺ (H₂O)(SB)
B3LYP/6-31G*	7.0	**0**	5.7	**0**
B3LYP/6-31+G*	7.8	**0**	7.0	**0**
B3LYP/6-31+G*// B3LYP/6-31++G**	6.1	**0**	5.0	**0**
B3LYP/6-31++G**	6.1	**0**	5.1	**0**
ΔZPE	−0.7	0	−1.0	0
ΔG(25 °C)	0.3	0	−0.6	0
total B3LYP/6-31++G** (25 °C)	5.7	**0**	3.5	**0**

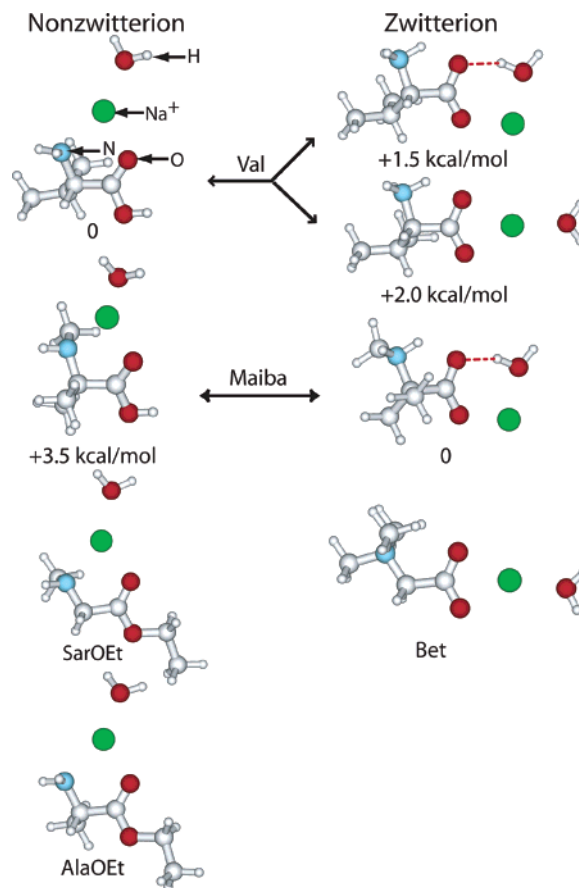[a] CS = charge-solvated form, ZW = salt-bridge form.

Figure 6. Lowest-energy structures of AA·Na⁺(H₂O) complexes at the B3LYP/6-31++G** level of theory. Relative energies (in kcal/mol) for the AA = Val and Maiba complexes include zero-point energy corrections and Gibbs free energy corrections at 298 K.

sodium ion interacts with both the amino nitrogen and the carbonyl oxygen (NO-coordination). This mode of sodium binding is consistent with earlier studies of sodium cationized glycine. The nonzwitterion 0 K structures where Na⁺ is OO-coordinated for both Maiba·Na⁺ and Val·Na⁺ are 2−3 kcal/mol higher in energy (without zero-point energy corrections) than the NO-coordinated structures (Figure 4).

The relative energies of the zwitterion and nonzwitterion structures of Maiba·Na⁺ and Val·Na⁺ structures and their isomers are listed in Table 3. At the B3LYP/6-31G*, B3LYP/6-31+G*, and B3LYP/6-31++G** levels of theory, zwitterionic Val·Na⁺ is more stable than the nonzwitterion by <1 kcal/mol, but at the B3LYP/6-31+G*//B3LYP/6-311++G** level, nonzwitterionic Val is more stable than the zwitterion by 0.9 kcal/mol. These calculations indicate that both structures are nearly the same in energy at the levels of theory used. The zwitterionic form of Maiba is calculated to be more stable than the nonzwitterionic form by 5−8 kcal/mol.

Lowest-energy structures for AA·Na⁺(H₂O) are shown in Figure 6. For the nonzwitterion form of Val and the non-zwitterionic isomers, addition of a water molecule does not change the structure of the AA. The metal ion is still NO-coordinated, and the water molecule interacts directly with the sodium ion. There is a slight change in the structure of the zwitterionic isomers of Maiba·Na⁺(H₂O) and Bet·Na⁺(H₂O).

In these structures, the sodium ion interacts more with one of the oxygens in the carboxylate group, while the water molecule interacts with the sodium ion and hydrogen bonds to the other carboxylate oxygen. These structures are nearly isoenergetic with the ones in which the sodium ion interacts equally with both

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Table 4. Threshold Dissociation Energies (in kcal/mol) for Loss of Water from AA·Na$^+$(H$_2$O) Determined from Master Equation Modeling of BIRD Experiments

AA	threshold dissociation energy
valine	15.9 ± 0.2
sarcosine ethyl ester	16.0 ± 0.3
alanine ethyl ester	16.0 ± 0.3
Maiba	15.1 ± 0.3
betaine	14.9 ± 0.3

oxygen atoms of the carboxylate group and water interacts with just the sodium ion (Figure 6, Val). Both structures are likely to be present and rapidly interconverting in these experiments.

The relative energies of the zwitterion and nonzwitterion structures of Maiba·Na$^+$(H$_2$O) and Val·Na$^+$(H$_2$O) are listed in Table 3. While different basis sets give slightly different results, nonzwitterionic Val is more stable than the zwitterion by 1.5 kcal/mol at the B3LYP/6-31++G** level of theory, including zero-point energy and Gibbs free energy corrections. Again, these structures are nearly isoenergetic at the levels of theory used. The zwitterionic form of Maiba is more stable than the nonzwitterionic form by 3.5 kcal/mol at the B3LYP/6-31++G** level of theory, including zero-point energy and Gibbs free energy corrections. This result is consistent with our experiments which indicate that water dissociates similarly from Maiba·Na$^+$(H$_2$O) and the zwitterionic model Bet·Na$^+$(H$_2$O).

Threshold Dissociation Energies for the Loss of Water. From master equation modeling of the BIRD kinetic data, threshold dissociation energies (E_o) for the loss of water from these complexes can be determined. To fit the experimental data, it is necessary to increase the calculated transition dipole moments.[36] Adequate fits could be obtained using transition dipole moment multiplication factors of 1.2 and 1.4, but not with 1.0 and 1.6. This is unexpected, because it was possible to model Val·Li$^+$(H$_2$O) without needing to vary the transition dipole multiplication factor.[8] This may be due in part to the small temperature correction used in the cooled cell experiments. We are investigating this further. Results from this modeling are given in Table 4.

Values of E_0 for Val·Na$^+$(H$_2$O), SarOEt·Na$^+$(H$_2$O), and AlaOEt·Na$^+$(H$_2$O) are ∼16 kcal/mol, whereas for Maiba·Na$^+$(H$_2$O) and Bet·Na$^+$(H$_2$O), the energies are ∼15 kcal/mol. The difference in threshold dissociation energy between the nonzwitterion and zwitterion model compounds is small (∼1 kcal/mol), but this difference is clearly distinguishable in this experiment. Although there could be small errors in the absolute values of E_0 that are not included in the model, the relative values should be quite accurate due to both the similarity of the modeling parameters for these isomers and the acquisition of the experimental data under identical conditions.

The threshold dissociation energies for loss of water from Val·Na$^+$(H$_2$O), SarOEt·Na$^+$(H$_2$O), and AlaOEt·Na$^+$(H$_2$O) are the same within error, indicating that water is bound similarly in these three complexes. This is consistent with the structures identified by modeling which show that the sodium ion interacts with the amino nitrogen and the carbonyl oxygen and the water molecule interacts directly with the sodium ion for each of these complexes. Similarly, the threshold dissociation energies of water from Maiba·Na$^+$(H$_2$O) and Bet·Na$^+$(H$_2$O) are indistinguishable, suggesting that the water molecule is bound similarly

in the two complexes. Again, this is consistent with the lowest-energy structures identified with theory which show that the sodium ion interacts with the oxygens of the carboxylate group and the water molecule interacts with the sodium ion and one carboxylate oxygen.

Water binding energies determined from the relative energies of the AA·Na$^+$ and AA·Na$^+$(H$_2$O) lowest-energy structures are given in Table 5. To the extent that these dissociation reactions have a negligible reverse activation barrier, the threshold dissociation energies should equal the water binding energies. At the highest level of theory (B3LYP/6-31++G**), the binding energy of water to SarOEt, AlaOEt, and the nonzwitterionic form of Maiba is ∼18 kcal/mol, whereas the binding energy of water to Bet and the zwitterionic forms of Val and Maiba is ∼17 kcal/mol. The difference in the average binding energy of water to the nonzwitterionic and zwitterionic species studied here is consistent with the ∼1 kcal/mol difference in the threshold dissociation energies determined by BIRD for the nonzwitterion and zwitterion complexes. The ab initio binding energies calculated here are all ∼2 kcal/mol higher in energy than those determined by BIRD. It should be noted that the binding energies decrease with increasing level of theory, indicating that binding energies may decrease further at an even higher level of theory.

Effect of Proton Affinity. A number of factors affect the relative stabilities of the zwitterionic forms versus the charge-solvated forms of amino acids, including the solvating abilities of the amino acid side chains, the presence of cations, and cation−π cloud interactions.[16,33,49] The proton affinity of an amino acid also has a significant effect on the stability of the zwitterionic form relative to the nonzwitterion. On the basis of the measured proton affinity of valine, the zwitterion or salt-bridge form of sodiated valine is predicted to be marginally more stable than the nonzwitterion or charge-solvated form.[16] Our results clearly indicate that sodiated valine and sodiated valine with one water molecule are nonzwitterionic.

The proton affinity of Maiba has not been previously reported. To obtain an estimate of this value, the proton affinity was calculated at the B3LYP/6-311++G** level of theory to be 225.0 kcal/mol at 25 °C. The difference between the proton affinities of Maiba and valine is ∼7.4 kcal/mol. On the basis of this difference in proton affinities, the zwitterion form of Maiba should be stabilized by approximately 7−8 kcal/mol relative to that of Val. From the calculated energies of the lowest-energy structures of Val and Maiba, the relative zwitterionic energy difference is approximately 5−7 kcal/mol. This indicates a roughly linear relationship between proton affinity and the relative zwitterionic energy as suggested by Bowers.[16] However, the proton affinity of glycine is 211.9 kcal/mol, which is 5.7 kcal/mol lower than that of valine. Solely on the basis of this proton affinity difference, nonzwitterionic sodiated glycine should be 6.6 kcal/mol more stable than the zwitterion (Val·Na$^+$ is nonzwitterionic by 0.9 kcal/mol, Table 3). However, the nonzwitterionic form of sodiated glycine has been calculated to be more stable than the zwitterionic form by 3 kcal/mol.[28,29] Thus, other factors affect the zwitterionic stability to at least a small extent, such as charge distribution of the amino acid and

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Table 5. Binding Energies of Water (in kcal/mol) for AA·M⁺(H₂O) Determined from Density Functional Calculations at Various Levels of Theory[a]

AA	B3LYP/6-31G*	B3LYP/6-31+G*	B3LYP/6-31+G*// B3LYP/6-311++G**	B3LYP/6-31++G**
valine (CS)	22.9	18.5	18.5	18.1
Maiba (CS)	24.3	18.7	18.0	18.0
sarcosine ethyl ester	23.1	19.0	18.3	18.0
alanine ethyl ester	22.6	18.5	17.5	17.6
valine (SB)	22.1	18.9	15.5	17.3
Maiba (SB)	20.6	17.3	16.2	16.6
betaine	21.2	17.3	16.8	16.8

[a] All energies include a zero-point energy correction at the B3LYP/6-31++G** level of theory. CS = charge-solvated form, SB = salt-bridge form.

interactions of the metal ion with the side chain, even in amino acids with similar functional side chains.

Conclusions

Both the theoretical and the experimental results indicate that Val·Na⁺(H₂O) has a charge-solvated structure, while Maiba·Na⁺(H₂O) has a salt-bridge structure. Calculations show that the lowest-energy structures of Val·Na⁺ and Val·Na⁺(H₂O) have the sodium ion NO-coordinated to nonzwitterionic valine, with the water molecule in Val·Na⁺(H₂O) interacting solely with the sodium ion. The charge-solvated Val·Na⁺(H₂O) structure is 1.5 kcal/mol more stable than the salt-bridge structure at the B3LYP/6-31++G** level of theory, with zero-point energy and Gibbs free energy corrections. In the lowest-energy structure of Maiba·Na⁺, the sodium ion interacts with both of the carboxylate oxygens, while in Maiba·Na⁺(H₂O), the sodium ion interacts primarily with one oxygen, with the water molecule interacting with the other oxygen and with the sodium ion. The salt-bridge structure of Maiba·Na⁺(H₂O) is 3.5 kcal/mol more stable than the charge-solvated structure at the B3LYP/6-31++G** level of theory with zero-point energy and Gibbs free energy

corrections at 298 K. The experimental results indicate a charge-solvated structure for Val·Na⁺(H₂O) and a salt-bridge structure for Maiba·Na⁺(H₂O), in agreement with theory.

These results clearly show that proton affinity plays a significant role in the stabilization of zwitterions in the gas phase. The difference between the proton affinities of Maiba and valine (7.4 kcal/mol) is similar to the relative energy difference between zwitterionic forms of Maiba·Na⁺ and Val·Na⁺ (approximately 4−7 kcal/mol). Other factors affecting the relative energy difference between the zwitterion and non-zwitterion forms of these ions, such as the distribution of charge about the amino acid and interactions of the amino acid side chain with the metal ion, appear to be small for these ions.