Hydration of Potassiated Amino Acids in the Gas Phase

Henryk Wincel

Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland

The thermochemistry of stepwise hydration of several potassiated amino acids was studied by measuring the gas-phase equilibria, $AAK^+(H_2O)_{n-1} + H_2O = AAK^+(H_2O)_n$ (AA = Gly, AL, Val, Met, Pro, and Phe), using a high-pressure mass spectrometer. The AAK^+ ions were obtained by electrospray and the equilibrium constants $K_{n-1,n}$ were measured in a pulsed reaction chamber at 10 mbar bath gas, N_2, containing a known partial pressure of water vapor. Determination of the equilibrium constants at different temperatures was used to obtain the ΔH_n^o, ΔS_n^o, and ΔG_n^o values. The results indicate that the water binding energy in $AAK^+(H_2O)$ decreases as the K^+ affinity to AA increases. This trend in binding energies is explained in terms of changes in the side-chain substituent, which delocalize the positive charge from K^+ to AA in AAK^+ complexes, varying the AAK^+–H_2O electrostatic interaction.   (J Am Soc Mass Spectrom 2007, 18, 2083–2089) © 2007 American Society for Mass Spectrometry

K$^+$ and Na$^+$ ions are the most abundant metal cations in living systems. They play an important role in several biochemical functions such as enzyme regulation, transfer of metal ions from intracellular to extracellular environments, electrical excitability of nerves, stabilization of DNA structures and so on [1]. Therefore, the interaction between alkali metal cations and various amino acids (AAs) has attracted considerable attention, and many experimental and theoretical studies have been conducted [2–20]. These studies show that K$^+$ binds to AAs quite differently than Na$^+$. For example, in the case of aliphatic AAs such as glycine (Gly), alanine (Ala), and valine (Val), the Na$^+$ ion is coordinated to nitrogen and carbonyl oxygen (NO coordination) in the lowest energy conformers, while K$^+$ prefers to bind to the carbonyl and hydroxyl oxygen atoms of the charge-solvated form (OO coordination) [6, 8, 10, 16]. In proline (Pro), phenylalanine (Phe), and cysteine (Cys), the modes of K$^+$ binding are similar to those of the corresponding Na$^+$ complexes [3–5, 12, 20].

Molecular dynamics simulations of a bacterial potassium ion channel reveal a significant selectivity filter for K$^+$ compared with Na$^+$ ions [21, 22]. The different hydration state of Na$^+$ and K$^+$ in the channel inner pore is postulated to be a basic factor determining ionic selectivity [23, 24]. Investigations into the relative energetics of noncovalent interactions between single amino acids, metal ions and water molecules could provide important information to explain ion channel function at a molecular level. Despite the considerable amount of

experimental and theoretical studies that have been conducted on the binding of Na$^+$ and K$^+$ to amino acids, little data are available on the interactions of water molecules with metal ion/amino acid complexes. Because metal ions and biomolecules are normally surrounded by water in living systems, these interactions are of significant importance in understanding biological systems. Williams and coworkers [8, 25–31] studied the modes of metal ion and water binding in hydrated complexes of alkali metal cationized valine, glutamine, lysine, and α-methyl-proline using both blackbody infrared radiative dissociation (BIRD) experiments and theory. Armentrout et al. investigated the sequential bond energies of water to sodiated glycine [32] and proline [33] by threshold collision-induced dissociation (TCID) experiments, as well as by accurate theoretical calculations. Recently, Kamariotis et al. [34] conducted infrared (IR) spectroscopy on hydration of lithiated valine, correlating the results with their calculations. The effect of metal ion and water coordination on the structures of hydrated metal ion/glycine complexes have been studied theoretically [35, 36].

In the present paper, the hydration energies and entropies for a number of potassiated amino acids, AAK^+, were obtained from high-pressure mass spectrometry equilibria measurements in the gas phase. This work is a continuation of previous studies on the interaction of water molecules with protonated [37, 38] and sodiated [39] amino acids.

Experimental

The experiments were performed with a high-pressure mass spectrometer (HPMS) using a pulsed ion-beam

Address reprint requests to Professor Henryk Wincel, Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: wincel@ichf.edu.pl

ESI ion source, which has been previously described in detail [37]. Briefly, potassiated amino acids were obtained by electrospray from a silica capillary (15 μm i.d., 150 μm o.d.). The solution containing 2.0 mM AA and 2.0 mM KI in methanol was supplied to the capillary by a syringe pump at a rate of 0.8 μL/min. The clustered ions were desolvated by a dry nitrogen gas counter current and in a heated pressure reducing capillary through which they were introduced into the forechamber, and then deflected toward a 3-mm orifice in the interface plate leading to the reaction chamber (RC). Ions drifting across the RC toward the exit slit under the influence of a weak electric field (2V/cm at 10 mbar) were hydrated and reached equilibrium before being sampled to the mass analysis section of the mass spectrometer.

Mass spectra were registered with continuous ion sampling, while for equilibrium determination the ion beam was injected into the RC in a pulsing mode by applying short pulses (+34V, 60 μs) to the deflection electrode with repetition of 1 ms. The latter mode of operation allows for measurements of the arrival time distribution (ATD) of the ions across the RC.

The reagent gas mixture consisting of pure N_2 as the carrier gas at about 10 mbar and a known partial pressure of water vapor (0.02 to 0.25 mbar) was supplied to the RC via the heated reactant gas inlet (RGI) at a flow rate of ~100 mL/min. The pressure was measured with an MKS capacitance manometer attached near the inlet of the RGI. The amount of water introduced into the N_2 gas flow was kept constant throughout the temperature-dependent measurements of the equilibrium constants. Water concentrations were controlled continuously with a calibrated temperature and humidity transmitter (Delta OHM, Type DO 9861T, Caselle di Selvazzano, Italy) inserted into the carrier gas flow line. The RC temperature was monitored by an iron-constantan thermocouple, which was embedded close to the ion exit slit; the temperature can be varied from ambient to 300 °C by electrical heaters.

Chemicals

The amino acids were obtained from Aldrich Chemical Co. (Steinheim, Germany) KI and CH_3OH was purchased from Chempur (Poland). The water was deionized with a Millipore purifier, type Elix 5 (Vienna, Austria).

Results and Discussion

Determination of the Thermodynamic Data

The thermochemical properties of the hydration of AAK^+ were obtained by measuring the equilibrium constants, $K_{n-1,n}$, as a function of temperature for each $(n-1,n)$ reaction, eq1
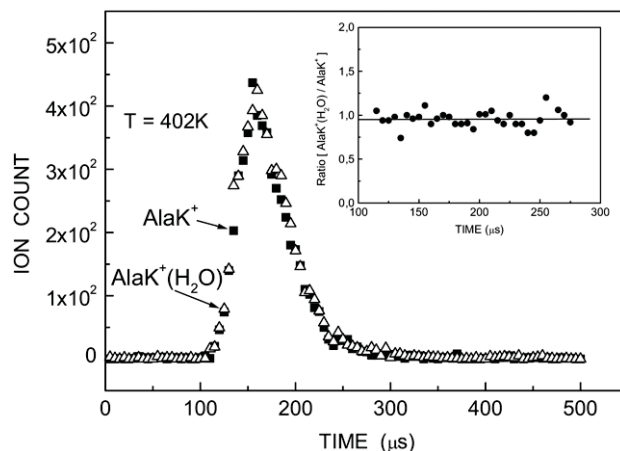
$$AAK^+(H_2O)_{n-1} + H_2O \Leftrightarrow AAK^+(H_2O)_n \tag{1}$$

Figure 1. Arrival time distributions of the reactant, $AlaK^+$, and product, $AlaK^+(H_2O)$, ions. The inset shows the ion intensity ratio of $[AlaK^+(H_2O)/AlaK^+]$ as a function of ion residence time.

For a standard state pressure of 1000 mbar the equilibrium constant is given by

$$K_{n-1,n} = (I_n \times 1000/I_{n-1} \times P) \tag{2}$$

where I_n and I_{n-} are the recorded ATD peak areas of the corresponding ions and P is the known partial pressure of water (in mbar). Equilibrium attainment was checked by comparing the ATDs of the reactant and product ions, and their ATDs were to be the same (except for the scaling factor of the peak amplitude). A typical example is shown in Figure 1 for $AlaK^+$ and $AlaK^+(H_2O)$. The inset of the figure shows that within the error limits and the limits of statistical noise, the ratio $[AlaK^+(H_2O)/AlaK^+]$ remains essentially constant, suggesting the attainment of equilibrium for the system under the present experimental conditions. Once the equilibrium constants at several temperatures are determined, the values for the enthalpy, ΔH_n^o, and entropy, ΔS_n^o, changes for the reaction (eq 1) can be evaluated from plots of the logarithm of ln $K_{n-1,n}$ against reciprocal temperature as defined by the van't Hoff equation,

$$\ln K_{n-1,n} = (\Delta S_n^0/R) - (\Delta H_n^0/RT) \tag{3}$$

As an example, the van't Hoff plots of the equilibrium constants for the systems studied are shown in Figure 2. No bending in the van't Hoff plots was observed through the present experiments. The weighted least-squares fitting procedure was used to obtain the slopes and intercepts of each line. The slopes determine the enthalpy change (ΔH_n^o) and the intercepts give the corresponding ΔS_n^o values. The reported ΔH_n^o and ΔS_n^o values are the averages of at least three measurements. The error limits show the statistical fluctuations; the absolute error could be considerably larger. The free-energy (ΔG_n^o) was obtained from $\Delta G_n^o = \Delta H_n^o - T\Delta S_n^o$. The thermochemical properties thus obtained are summarized in Table 1, together with the
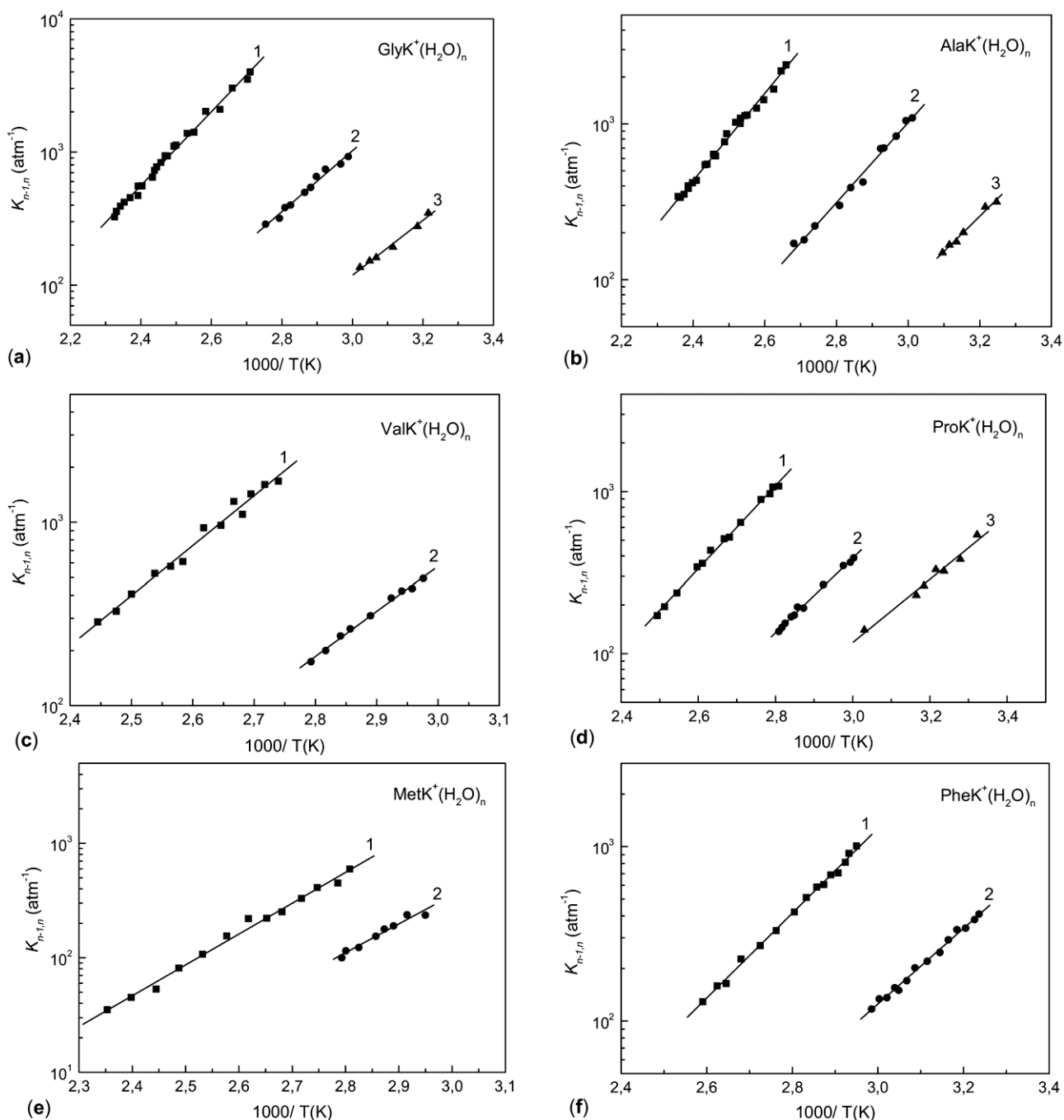
Figure 2. van't Hoff plots of equilibrium constants for the gas-phase reactions $AAK^+(H_2O)_{n-1} + H_2O = AAK^+(H_2O)_n$, where AA equals (**a**) Gly; (**b**) Ala; (**c**) Val; (**d**) Pro; (**e**) Met; (**f**) Phe. The numbers shown in the figures correspond to the value of n.

literature results. The data for small n are given in this table, since determination of the hydration enthalpies for higher hydration steps requires temperatures below room temperature, which are not accessible with the present reaction chamber.

An additional set of experiments was conducted to provide a basis for comparison with the data obtained in the other laboratory. Table 1 shows that the present thermochemical values obtained for the reaction

$$K^+(H_2O)_{n-1} + H_2O \Leftrightarrow K^+(H_2O)_n \qquad (4)$$
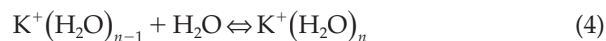
with $n = 2$ and 3 agreeing reasonably well with those reported in reference [40].

Comparison with Other Complexes

As expected, the water binding energies (BEs) to AAK^+ are smaller than those for $AANa^+$ of the analogous

Table 1. Experimental enthalpies, entropies, and free energies for the sequential hydration of K^+ and potassiated amino acids[a]. Values from the literature (in italics) are included for comparison

Ion	n	$-\Delta H_n^o$ (kcal/mol)	$-\Delta S_n^o$ (cal/mol K)	$-\Delta G_n^o$ (kcal/mol)[b]	Ref.
K^+	2	15.5 (0.6)	22.8 (1.6)	8.7 (1.1)	
		16.1[c]	*24.2[c]*	*8.9[c]*	[40]
	3	12.6 (0.6)	21.6 (1.6)	6.2 (1.1)	
		13.2[c]	*23[c]*	*6.3[c]*	[40]
$GlyK^+$	1	13.3 (0.5)	19.3 (1.1)	7.6 (0.8)	
	2	11.2 (0.6)	19.8 (1.9)	5.3 (1.1)	
	3	9.5 (0.8)	18.9 (1.8)	3.9 (1.3)	
$AlaK^+$	1	13.0 (0.6)	18.8 (1.4)	7.4 (1.0)	
	2	11.0 (0.4)	19.4 (1.1)	5.2 (0.7)	
	3	9.8 (0.6)	20.4 (2.0)	3.8 (1.2)	
$ValK^+$	1	12.6 (0.6)	19.4 (1.2)	6.9 (0.9)	
		(*13.6*; *16.1*)[d]			[7]
	2	11.2 (0.6)	21.2 (2.0)	4.9 (1.2)	
		7.5[e]			[25]
$MetK^+$	1	12.3 (0.6)	22.5 (1.9)	5.6 (1.1)	
	2	10.8 (1.0)	20.8 (2.6)	4.6 (1.8)	
$ProK^+$	1	11.9 (0.2)	19.4 (0.4)	6.2 (0.3)	
	2	10.9 (0.7)	21.3 (1.5)	4.6 (1.1)	
	3	9.0 (0.6)	17.4 (2.0)	3.8 (1.2)	
$PheK^+$	1	11.7 (0.5)	20.7 (1.5)	5.6 (0.9)	
	2	10.0 (0.5)	20.2 (1.5)	4.0 (0.9)	

Standard pressure is 1000 mbar.
[a]Errors are listed in parenthesis.
[b]ΔG^O at 298 K.
[c]Using high-pressure mass spectrometry [40].
[d]Binding energies calculated at the B3LYP/LACVP++** level of theory for zwitterionic (13.6 kcal/mol) and nonzwitterionic (16.1 kcal/mol) structure of $ValK^+(H_2O)$ [7].
[e]Using blackbody infrared radiative dissociation [25].

systems. For comparison, the available experimental gas-phase bond enthalpies and free energies for monohydrated AAM^+, M = Na and K are given in Table 2. These results can be easily understood when one considers that H_2O in the $AAM^+(H_2O)$ system interacts directly with the alkali metal cation, and the bonding is largely electrostatic. The stronger binding to $AANa^+$ than AAK^+ is consistent with the larger radius, the longer bond distances, and the weaker electrostatic interactions for K^+ compared with Na^+.

The data in Table 1 show a monotonic decrease in the water BEs ($-\Delta H_n^o$) with sequential addition of water molecules to AAK^+. Similar trends were observed upon sequential hydration of the analogous sodiated amino acids [29, 30, 32, 33, 39]. As an example, Figure 3 shows

Table 2. Enthalpy and free energy changes for the gas-phase hydration of the potassiated (AAK^+) and sodiated ($AANa^+$) amino acids

AA	$-\Delta H_1^o$ (kcal/mol)		$-\Delta G_1^o$ (kcal/mol)	
	AAK^+	$AANa^+$	AAK^+	$AANa^+$
Gly	13.3	17.9[a]	7.6	11.2[a]
Val	12.6	15.9[b]	6.9	9.7[b]
Pro	11.9	14.5[b], 15.8[c]	6.2	8.9[b], 9.0[c]
Met	12.3	13.7[b]	5.6	8.0[b]
Phe	11.7	13.6[b]	5.6	7.9[b]

[a]Using threshold collision-induced dissociation [32].
[b]Using pulsed ion-beam high-pressure mass spectrometry [39].
[c]Using threshold collision-induced dissociation [33].

the behavior of the hydration free energies ($-\Delta G_n^o$) as a function of n for $ProK^+(H_2O)_n$ and $ProNa^+(H_2O)_n$. For comparison, the inset shows an analogous plot for the $K^+(H_2O)_n$ and $Na^+(H_2O)_n$ systems. The observed decrease in binding energies of water can be rationalized by a partial delocalization of the charge on the water binding site(s) and increasing repulsive interactions
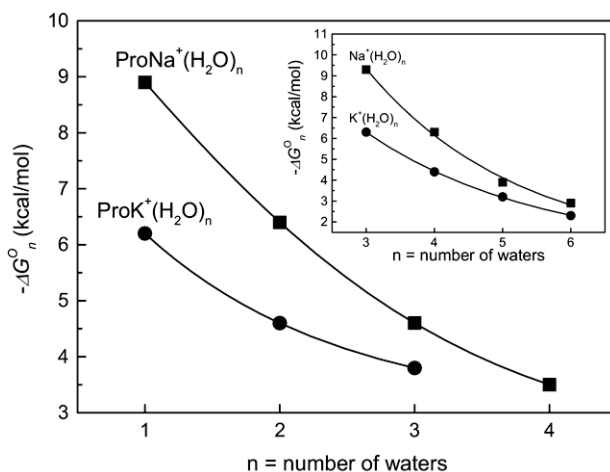
Figure 3. Comparison of the n dependence of the hydration free energies ($-\Delta G_n^O$) at 298 K for the $ProK^+(H_2O)_n$ and $ProNa^+(H_2O)_n$ complexes. The inset shows plots of the $-\Delta G_n^O$ values vs. n. The $-\Delta G_n^O$ values for $ProNa^+(H_2O)_n$, reference [39]; $K^+(H_2O)_n$ and $Na^+(H_2O)_n$, reference [40].

between ligated water molecules with successive addition to AAK.

Solvation Effect and Water Binding Energies

The water binding ratio $(GlyK^+ - H_2O)/(GlyNa^+ - H_2O)$ is identical to that obtained [16] for $(Gly - K^+)/(Gly - Na^+)$, 0.74. The BEs of the first (13.3 $\pm$ 0.5 kcal/mol) and second (11.2 $\pm$ 0.5 kcal/mol) water molecules in $GlyK^+(H_2O)_n$ are very close to those of the third (13.2 kcal/mol) and fourth (11.8 kcal/mol) water to K^+ in the $K^+(H_2O)_n$ system [40]. Similar results have also been obtained by Armentrout and coworkers [32] for $GlyNa^+(H_2O)_n$. They found using the TCID method that the BEs of the first (17.9 $\pm$ 1.2 kcal/mol) and second (13.1 $\pm$ 1.7 kcal/mol) water molecules in $GlyNa^+(H_2O)_n$ are close to those of the third (16.7 $\pm$ 1.4 kcal/mol) and fourth (13.1 $\pm$ 1.4 kcal/mol) water to Na^+ in the $Na^+(H_2O)_n$ cluster. These observations indicate that the solvation effect provided by glycine on both Na^+ and K^+ is nearly equivalent to that of the first and second attached water molecules in the $Na^+(H_2O)_n$ and $K^+(H_2O)_n$ systems. As can be seen in Table 1, the BEs of a water molecule in the $AAK^+(H_2O)$ complexes follow the order $GlyK^+ > AlaK^+ > ValK^+ > MetK^+ > ProK^+ > PheK^+$. Although the differences in the measured $-\Delta H_n^o$ values are small and generally are within the range of experimental uncertainty, the general trend is evident. A plot of the binding energies in $AAK^+(H_2O)_{n\ =\ 1,2}$ vs. the corresponding K^+ ion affinities of AAs is shown in Figure 4. The K^+ affinity values calculated by Tsang and coworkers [13] were used for this figure. Because in this work no value exists for the binding affinity of $K^+(Met)$, we take the experimental value of 33.9 $\pm$ 2.6 kcal/mol from reference [41] determined by Armentrout and coworkers. The K^+

scale was anchored by $K^+(Gly)$, taking the value reported by Armentrout et al. [16], 29.4 kcal/mol, and 28.3 kcal/mol [13] as the reference value. This adjustment to the K^+ scale of reference [13] leads to the value of 32.8 kcal/mol for $K^+(Met)$, which was used for Figure 4. As can be seen in this figure, a linear relationship between the measured $-\Delta H_n^o = 1,2$ values and the potassium ion affinities is found. The correlation coefficients for the binding of the first and second water molecules are 0.99 and 0.83, respectively. The $-\Delta H_2^O$ values show a significantly larger deviations from the straight line plot than these of $-\Delta H_1^O$. Now, it is not clear whether the observed deviations for $-\Delta H_2^O$ are due to larger experimental errors or due a special intrinsic difference in the binding of the second water molecule in the $AAK^+(H_2O)_2$ complexes. A very good linear correlation between the measured $-\Delta H_1^O$ values and the K^+ affinities of AAs, Figure 4, can be explained as being a consequence of direct interaction of the first water molecule with the K^+ ion of $AAK^+(H_2O)$ and the electrostatic nature of the $AAK^+ - H_2O$ binding. The net positive charge retained on the metal ion in AAK^+ is expected to depend on the electron withdrawing effect of AA, determining the magnitude of the K^+ affinity values to AAs. The charge density on the metal ion in $AAK^+(H_2O)$ should decrease as the metal ion affinity of AA increases. The effect of the side chain illustrated here by a decrease in the water binding energies in $AAK^+(H_2O)_{n\ =\ 1,2}$ and previously [39] for $AANa^+(H_2O)_{n\ =\ 1,2}$ with increasing K^+ and Na^+ affinities to AA, respectively, is in line with observations [4, 14, 18] that the binding of K^+ and Na^+ to amino acids is dominated by the interaction with the amino acid backbone and enhanced by interaction with the side-chain substituent. The binding enhancement effect of the phenyl substituent is manifested by the difference in the K^+ binding energies to Ala (29.6 kcal/mol [13] and Phe (34.8 kcal/mol [13], while the electron withdrawing effect is demonstrated by the observed difference between the hydration energies for $AlaK^+$ and $PheK^+$, Table 1. Although this method of estimating influence is not fully satisfactory because the aliphatic portion is expected to contribute to the $Ala - K^+$ binding as well, the comparison shows the magnitude of the aromatic side-chain substituent effects on the enhancement in the $AA - K^+$ binding ($\sim$17%) and weakening ($\sim$11%) of the AAK^+–H_2O interaction.

Comparison with Other Results

The literature provides water binding energies only for $ValK^+(H_2O)_{n\ =\ 1,2}$ systems [7, 25]. Williams and coworkers [7] showed, based on the BIRD technique, that the K^+ ion in the $ValK^+(H_2O)$ complex is OO-coordinated. However, from these experiments they were unable to distinguish whether the valine in this system was nonzwitterionic 1, or zwitterionic 2, in form.

The binding energies of water calculated by these authors at the B3LYP/LACVP++** level of theory

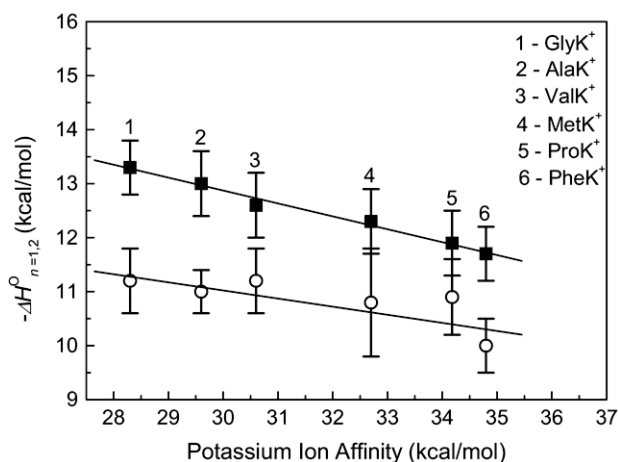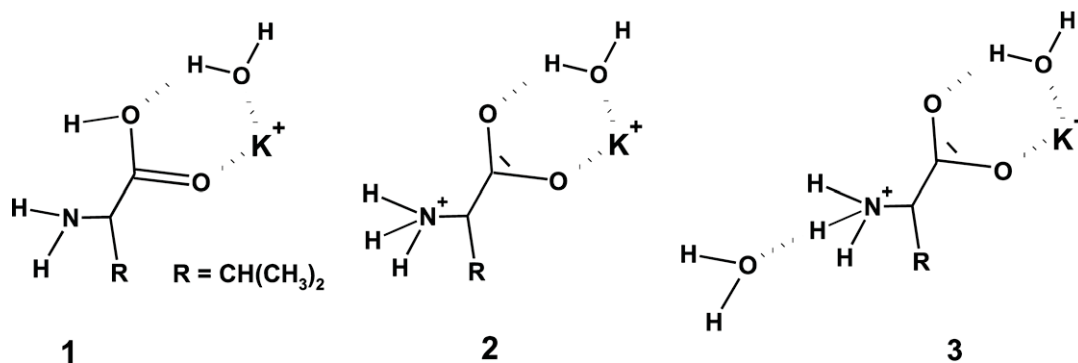**Figure 4.** Plot of the binding energies ($-\Delta H_n^O = 1,2$) for the first (■) and second (○) water molecule in the $AAK^+(H_2O)_{n\ =\ 1,2}$ complexes vs. corresponding potassium ion affinity of amino acids (AAs). For Gly, Ala, Val, Pro, and Phe, the potassium ion affinity values are taken from reference [13].; for Met, from reference [41], see text.

predict that the ValK$^+$–H$_2$O interaction in the nonzwitterionic form (16.1 kcal/mol) is stronger than in the zwitterionic one (13.6 kcal/mol). The latter value is close to that of 12.6 ± 0.6 kcal/mol obtained in the present study, implying that the valine in ValK$^+$(H$_2$O) adopts a zwitterionic form, **2**. The barrier between Structure **1** and Structure **2** is expected to be small compared with that for water loss, and the energy gained upon the hydration of ValK$^+$ (12.6 kcal/mol) is most probably sufficient for the interconversion **1** → **2**, which simply involves the migration of a proton across the hydrogen bond from the hydroxyl oxygen to the amine group. Once Structure **2** is formed, it can be collisionally stabilized at the conditions maintained in the reaction chamber, and there is a low probability of back isomerization, **2** → **1**. Thus, the ValK$^+$(H$_2$O) complex can further react as a zwitterionic Structure **2**. This conclusion is consistent with that deduced from the BIRD experiments of Williams and coworkers [25] that the valine in ValK$^+$(H$_2$O)$_2$ is zwitterionic.

These authors also found that the second water molecule does not bind to the metal ion but rather interacts with the valine itself, and the most likely structure could be like **3**, in which the second water is hydrogen bonded to the −NH$_3^+$ charge center. It should be noted that conformer **3** lies 3.1 kcal/mol higher in energy than the ground-state nonzwitterionic conformation [25], in which the second water molecule is bonded directly to K$^+$ of Structure **1**.

Table 1 indicates that the binding energy of the second water in ValK$^+$(H$_2$O)$_2$ obtained in the present experiments, 11.3 ± 0.3 kcal/mol, is significantly higher than that derived from the BIRD experiments [25], 7.5 kcal/mol. As noted by these authors, the latter value is almost certainly somewhat lower than the true one because of experimental difficulties with the measured dissociation kinetics of relatively weak potassiated clusters. It is worth mentioning that the water binding energies previously determined for ValNa$^+$(H$_2$O)$_{n = 1,2}$ and GlnNa$^+$(H$_2$O)$_{n = 1,2}$ from our high-pressure equilibrium measurements [39] are in excellent or good agreement with the experimental values obtained from the BIRD kinetics studies [25, 26, 29, 30].

As mentioned above, the lowest energy structures of aliphatic amino acids, GlyK$^+$ and AlaK$^+$, are similar to that of ValK$^+$, indicating the small influence, if any, of the aliphatic portions of the side chain on the structural arrangements in these complexes. The measured binding energy values of the first water molecule in these three complexes are similar (12.6 to 13.3 kcal/mol) and close to that calculated [7] for the zwitterionic form of ValK$^+$(H$_2$O), which is lower than that for the nonzwitterionic structure, Table 1. Therefore, although speculative, it seems very likely that GlyK$^+$(H$_2$O)$_{n = 1,2}$ and AlaK$^+$(H$_2$O)$_{n = 1,2}$ formed in the present experiments have the structures analogous to those of ValK$^+$(H$_2$O)$_{n = 1,2}$.

Conclusion

The sequential binding energies of water to potassiated amino acids (glycine, alanine, valine, methionine, proline, and phenylalanine) were investigated by pulsed high-pressure mass spectrometry with electrospray ionization. Generally, the water binding energies to AAK$^+$ are weaker than to AANa$^+$ and, in both instances, decrease with the increasing number of water molecules. A good correlation was obtained between the binding energies of the water molecule in the AAK$^+$(H$_2$O) complexes and the corresponding potassium ion affinities to amino acids, showing the decrease in the AAK$^+$ − H$_2$O binding energies with the increasing AA–K$^+$ bond strength. This relationship is analogous to that reported previously for AANa$^+$(H$_2$O)$_{n = 1,2}$ complexes.

Acknowledgments

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