Hydration Energies of Deprotonated Amino Acids from Gas Phase Equilibria Measurements

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Singly hydrated clusters of deprotonated amino acids were studied using an electrospray high-pressure mass spectrometer equipped with a pulsed ion-beam reaction chamber. Thermochemical data, ΔH^o, ΔS^o, and ΔG^o, for the hydration reaction $[AA - H]^- + H_2O = [AA - H]^- \cdot (H_2O)$ were obtained from gas-phase equilibria determinations for AA = Gly, Ala, Val, Pro, Phe, Lys, Met, Trp, Gln, Arg, and Asp. The hydration free-energy changes are found to depend significantly on the side-chain substituents. The water binding energy in $[AA - H]^- \cdot (H_2O)$ increases with the gas-phase acidity of AA. The anionic hydrogen bond strengths in $[AA - H]^- \cdot (H_2O)$ are compared with those of the cationic bonds in the corresponding $AAH^+ \cdot (H_2O)$ systems. (J Am Soc Mass Spectrom 2008, 19, 1091–1097) © 2008 American Society for Mass Spectrometry

Amino acid chemistry has been the subject of considerable attention during the past years because of its importance in understanding biological processes in living systems. In aqueous media at neutral pH, most of the naturally occurring amino acids exist in zwitterionic form, where the amino group at the N-terminus is usually protonated and the carboxylic group at the C-terminus is deprotonated. These groups are expected to interact with surrounding water, which is an integral part of a functioning biological system. Water molecules are directly involved in noncovalent interactions that play a central role in determining the structure and properties of macromolecules in living systems. Understanding these low-energy interactions is especially important because they provide a key to the secrets of cellular function in living organisms at the molecular level. Although most amino acids (AAs) in the gas phase exhibit a nonionic form, noncovalent interactions of their charged groups (H_3N^+- and $-CO_2^-$) with solvent molecules can be investigated separately by mass spectrometry after ion extraction from the solution into the gas-phase [1]. Studies of noncovalent interactions in hydrated gas-phase amino acid ions can provide detailed information about these interactions that is not available from solution studies, such as thermodynamic information for the binding energies of individual water molecules.

Most of the experimental and theoretical studies reported to date have focused on interactions of water molecules with protonated [2–15] and alkali-metal cationized amino acids [9, 16–29]. It is established that side
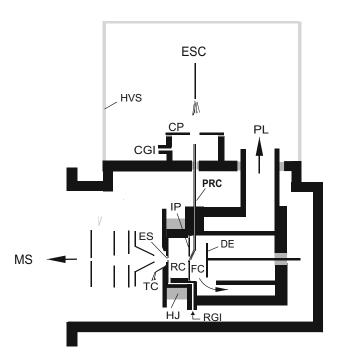
chains have a significant influence on the water binding energy to these cations [12, 13, 21, 28, 29].

While interactions of various organic molecules containing the carboxylate group ($-CO_2^-$) with water molecules have been the subject of numerous studies [30–34], very little research is available on hydration of deprotonated amino acids and peptides. Bowers and coworkers [8, 35] used an electrospray mass spectrometer equipped with a high-pressure drift cell to examine the interactions of deprotonated aspartic acid and deprotonated small peptides, such as dialanine and diglycine, with water. Degtyarenko et al. [36] employed ab initio molecular dynamic simulation to study the first hydration shell around charged groups (H_3N^+ and CO_2^-) of an L-alanine in a droplet of water.

This study presents the thermochemical properties for the hydration of a number of gas-phase deprotonated amino acids, $[AA - H]^-$, obtained from equilibrium experiments. The work is a continuation of previous studies on the hydration of protonated [12, 13] and cationized [28, 29] biomolecules in the gas phase.

Experimental

The experiments were performed with a high-pressure (HP) mass spectrometer using a pulsed ion-beam ESI ion source (Figure 1), which has been described in detail elsewhere [12]. Briefly, the reactant ions were obtained by electrospray from a silica capillary (ESC, 15 μm i.d., 150 μm o.d.) to which a negative voltage of 4 kV was applied. A solution containing ~2.0 mM the sample 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 (PRC) through

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Figure 1. Scheme of the high-pressure ion source with pulsed ion beam: (ESC) electrospray capillary; (HVS) high voltage shield; (CP) curtain plate; (CGI) curtain gas inlet; (PL) pumping lead; (PRC) pressure reducing capillary; (FC) fore-chamber; (DE) deflection electrode; (IP) interface plate; (RC) reaction chamber; (RGI) reaction gas inlet; (TC) thermocouple; (ES) ion exit slit; (HJ) electrically heated jacket.

which they were introduced into the fore-chamber (FC), and then deflected toward a 3 mm orifice in the interface plate (IP) leading to the reaction chamber (RC). Ions drifting across the RC toward the exit slit (ES) 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 (−46 V, 60 μs) to the deflection electrode (DE). 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 (0.1–0.25 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 RC temperature was monitored by an iron-constantan thermocouple (TC), 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). CH_3OH was purchased

from Chempur (Piekary Slaskie, Poland). The water was deionized with a Millipore purifier, type Elix 5 (Vienna, Austria).

Results and Discussion

General Description of Results

Electrospray ionization of amino acids and dipeptides in the negative ion mode produces both deprotonated monomers, $[AA − H]^-$, and dimers, $[AA − H]^- \cdot AA$. In the RC, where no neutral AA is present, the equilibria for the hydration of $[AA − H]^-$ have been dealt with in the following processes:

$$[AA − H]^- + H_2O \Leftrightarrow [AA − H]^- \cdot (H_2O) \tag{1}$$

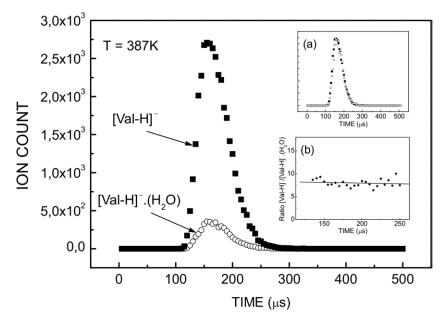$$[AA − H]^- \cdot AA \rightarrow [AA − H]^- + AA \tag{2}$$

At water partial pressures of 0.1–0.2 mbar, at which the present experiments were performed, the forward rates of reaction (1) are expected to proceed at the Langevin collision rate ($k_f \approx 10^{-9}$ molecule^{-1} cm^3 s^{-1}) and the reaction frequency is $k_f[H_2O] \approx 5 \times 10^6$ s$^{\times 1}$. This rate is several orders of magnitude greater than the dissociation rates of $[(Gly)_2 − H]^- \cdot (Gly)_2$ and $[(Ala)_2\text{-}H]^- \cdot (Ala)_2$ reaction (2), obtained using Arrhenius activation parameters of $E_a = 32.2$ kcal/mol and $A = 10^{17}$ s^{-1} measured by Bowers et al. [35] for $[(Gly)_2 − H]^- \cdot (Gly)_2$. These factors indicate that the product ions from reaction (2) should be sufficiently repopulated to establish equilibrium in reaction (1). Equilibrium attainment was checked by comparing the ATDs of the reactant and product ions (eq 1). The ions drifting through the RC to the exit slit undergo many switching reactions and their apparent mobilities should be equal. When equilibrium between two ions is established, their ATDs overlap (except for the scaling factor of the peak amplitude). This is illustrated in Figure 2 for the pair $[Val − H]^-$ and $[Val − H]^- \cdot (H_2O)$, and inset (a) of the figure shows that the normalized ATDs are the same. Also, inset (b) demonstrates that within the error limits and the limits of statistical noise, the ratio of $[Val − H]^-/[Val − H]^- \cdot (H_2O)$ remains essentially constant. These data imply that the system is at equilibrium under the present experimental conditions.

Determination of Thermodynamic Properties

The enthalpy (ΔH^o) and entropy (ΔS^o) changes were determined from temperature-dependent studies of the equilibrium constants K_{eq} using the van't Hoff equation

$$\ln K_{eq} = (\Delta S^0/R) − (\Delta H^0/RT) \tag{3}$$

The equilibrium constants for the standard state pressure of 1000 mbar were obtained from the expression
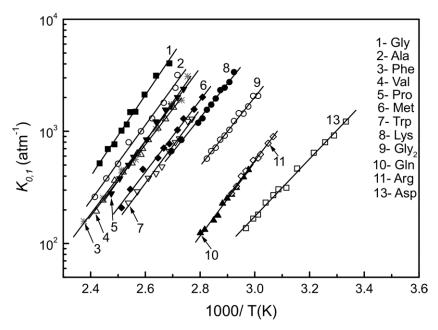
Figure 2. Arrival time distributions of the reactant $[Val - H]^-$, and product $[Val - H]^- \cdot (H_2O)$, ions. The insets show: (**a**) normalized at maximum; (**b**) ion intensities ratio of $[Val - H]^-/[Val - H]^- (H_2O)$ as a function of ion arrival time.

$$K_{eq} = (I_n \cdot 1000/I_{n-1} \cdot P) \tag{4}$$

where I_n and I_{n-1} are recorded ATD peak areas of $[AA - H]^- \cdot (H_2O)$ and $[AA - H]^-$, respectively, and P is the known partial pressure of the water (in mbar).

The results of measured equilibrium constants as functions of temperature for the systems studied are presented in the form of van't Hoff plots in Figure 3. All data in the van't Hoff plots are linear and no bending can be distinguished within the experimental scatter. The weighted

least-squares fitting procedure was used to obtain both the slopes and intercepts of each line. In this way the ΔH^o and ΔS^o values for hydration reactions (1) were determined, respectively. The values listed in Table 1 are the averages of at least three measurements and the error limits show the statistical fluctuations. Systematic error may be present and the absolute error could be considerably larger. The free-energy changes (ΔG^o) were obtained from $\Delta G^o = \Delta H^o - T \cdot \Delta S^o$. We determined the thermodynamic data for hydration of $CH_3CO_2^-$ for comparison with mea-

Figure 3. van't Hoff plots of equilibrium constants for the gas-phase reactions $[AA - H]^- + H_2O = [AA - H]^- \cdot (H_2O)$. Compounds AA are given in the figure.

Table 1. Experimental enthalpies, entropies, and free energies for the hydration of deprotonated acetic acid, amino acids and dipeptides[a]

Ion	$-\Delta H^o_n$(kcal/mol)	ΔS^o_n(cal/mol K)	$-\Delta G^o_n$(kcal/mol)[b]	Ref.
$CH_3COO_2^-$	16.4 (0.8)	25.4 (2)	9.0 (1.4)	
	16.0 (1.0)	22.5	9.3 (1.6)[c]	[31]
	16.4 (1.5)	~24	9.4 (0.3)[c]	[33]
[Gly-H]$^-$	16.0 (0.3)	26.6 (0.4)	8.2 (0.4)	
[Ala-H]$^-$	15.3 (0.4)	25.6 (1.2)	7.8 (0.8)	
[Pro-H]$^-$	15.4 (0.5)	26.5 (1.5)	7.6 (0.9)	
[Val-H]$^-$	14.3 (0.4)	24.2 (1.0)	7.2 (0.7)	
[Lys-H]$^-$	14.5 (0.6)	25.0 (1.3)	7.2 (1.0)	
[Phe-H]$^-$	14.5 (0.4)	25.0 (1.6)	7.2 (0.9)	
[Met-H]$^-$	14.5 (0.5)	25.3 (1.0)	7.1 (0.8)	
[Trp-H]$^-$	14.8 (0.5)	26.9 (1.4)	6.9 (0.9)	
[Gln-H]$^-$	14.4 (0.4)	30.8 (1.2)	5.4 (0.8)	
[Arg-H]$^-$	15.1 (0.5)	33.0 (1.4)	5.4 (0.9)	
[Asp-H]$^-$	12.3 (0.5)	27.0 (1.9)	4.4 (1.1)	
	9.2 (0.3)[c]			[8]
[(Gly)$_2$-H]$^-$	14.5 (0.7)	27.5 (1.5)	6.5 (1.1)	
	11.0 (0.3)[c]	14.5 (0.7)[c]	6.8 (0.5)	[35]
	15.8[d]			
[(Ala)$_2$-H]$^-$	11.7 (0.2)[c]	17.1 (0.4)[c]	6.7 (0.3)	[35]
	15.6[d]			

Standard pressure is 1000 mbar.
[a]Errors are listed in parentheses.
[b]ΔG^o at 293 K.
[c]Using high-pressure mass spectrometry.
[d]Binding energy calculated with density functional theory [35].

surements from other laboratories [31, 33]. As shown in Table 1, these values are in reasonable agreement with those obtained in other experiments.

The present ΔH^o value for [Asp − H]$^-$ · (H$_2$O) is significantly higher than that measured by Bowers and coworkers [8]. For [(Gly)$_2$ − H]$^-$ · (H$_2$O), both ΔH^o and ΔS^o values obtained in the present work are also substantially higher than those experimentally determined by Bowers et al. [35], but the ΔG^o values are in good agreement. The water binding energy calculated by these authors for [(Gly)$_2$ − H]$^-$ · (H$_2$O) agrees reasonably well with the hydration enthalpy (ΔH^o) of the present work, Table 1.

Hydration and Structural Information

As can be seen from Table 1, for all the deprotonated AAs under investigation, the hydration enthalpies are approximately the same and close to that of CH$_3$CO$_2$−, with the exception of [Asp − H]$^-$. These AAs are expected to be ionized via deprotonation of the carboxyl group, and similar solvation of the carboxyl group for each of these anions is consistent with their similar hydration enthalpies.

The ΔS^o values for the hydrates of [Gly − H]$^-$, [Ala − H]$^-$, [Pro − H]$^-$, [Val − H]$^-$, [Phe − H]$^-$, [Lys − H]$^-$, [Met − H]$^-$, and [Trp − H]$^-$ are similar within the experimental error limits (Table 1). This finding is also consistent with the same modes of water coordination in these hydrates. The favorable geometry for these systems, based on calculations for HCO$_2^-$ · (H$_2$O) [30], and [(Ala)$_2$ − H]$^-$ · (H$_2$O) [35], is expected to be a doubly hydrogen-bonded structure such as **1**. The doubly hydrogen-bonded structure is more stable, by ~3 kcal/mol, than the singly bonded one, **2** [35].

For the [Gln − H]$^-$ · (H$_2$O) and [Arg − H]$^-$ · (H$_2$O) complexes, we obtain greater $-\Delta S^o$ values than those for the systems discussed above (see Table 1), implying a loss in the freedom of H$_2$O motion in these complexes. This observation can be rationalized by the fact that in both cases, beside the amino group, the side chains have active sites (O and NH, respectively), which interact with H$_2$O with the formation of an intermolecular hydrogen bonding structure such as those shown schematically below, **3** and **4**.

In the case of [Asp − H]$^-$, the relatively low value of $-\Delta H^0$ can be attributed to the formation of cyclic

R = side chain

1

2

3

4

5 **5a**

Figure 4. Plot of the hydration free energies, $-\Delta G^o$, at 293 K for the hydration of deprotonated amino acids, $[A - H]^-$ versus corresponding gas-phase acidity of AA, ΔH_{ac}^o. The ΔH_{ac}^o values are taken from reference [38].

conformation via the O–H . . . O$^-$ intramolecular hydrogen bond. Theoretical calculations [38, 39] clearly show that aspartic acid forms an anion with the lowest energy and a strong hydrogen-bonded ring structure between the main chain CO_2^- and the CO_2H side-chain groups, as illustrated above, **5**. Such bonds exhibit bond energies in the range of 14–28 kcal/mol [40].

The hydrogen-bonded cyclization stabilizes the ionic reactant and weakens the intermolecular hydrogen bonding interaction between the H_2O molecule and the CO_2^- group, **5a**, due to the charge delocalization on the solvating group. This effect is evident when the hydration free-energy $(-\Delta G^o)$ of 4.5 kcal/mol for $[Asp - H]^-$ is compared to that for $[Ala - H]^-$ (7.8 kcal/mol) or $[Va - H]^-$ (7.2 kcal/mol), Table 1.
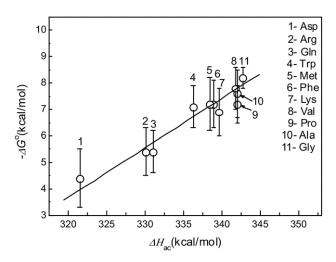
A similar situation is also observed for both the deprotonated dicarboxylic acids, $HCO_2\text{-}(CH_2)_n\text{-}CO_2^-$ [33], and the protonated alkane diamines, $H_2N\text{-}(CH_2)_nNH_3^+$ [2], where cyclization with the formation of internal strong hydrogen bonding has been shown to occur. For example, the $-\Delta G^o = 5.4$ kcal/mol [33] for the hydration of succinic acid, $HCO_2\text{-}(CH_2)_2\text{-}CO_2^-$, is much lower than that of 9.3 kcal/mol [33] for propionic acid, $C_2H_5CO_2^-$ of comparable size. Similarly, the $-\Delta G^o$ value of 6.2 kcal/mol [2] obtained for $NH_2(CH_2)_3NH_3^+$ is smaller than that of 8.8 kcal/mol [41] for $n - C_3H_7NH_3^+$.

Correlation Between Hydration Free Energies and Acidities

As shown in Table 1, the side chains have a significant effect on water binding energies to $[AA - H]^-$. A plot of the hydration free energies versus the corresponding gas-phase acidities (ΔH_{ac}^o) of AAs obtained experimentally by Poutsma et al. [38] is shown in Figure 4.

A linear correlation exists between the $-\Delta G^o$ values and the corresponding ΔH_{ac}^o. An analogous correlation was previously obtained by Kebarle and coworkers [33] for a series of singly hydrated anions of the carboxylic acids and some oxo acids. This effect is attributed to the charge delocalization from the anionic sites by electron withdrawing groups, resulting in lower hydrogen-bonding interactions with H_2O, dominated by electrostatics. The correlation between ΔG^o and ΔH_{ac}^o arises from the fact that the gas-phase acidity is thermochemically related to the electron affinity, (EA), by eq 5.

$$\Delta H_{ac}^o = D(AA - H) + IP(H) - EA([AA - H]) \quad (5)$$

Since the ionization potential of hydrogen, $IP(H) = 313.6$ kcal/mol, is constant, and the bond strength in the carboxylic CO_2H group is approximately constant, $D(O–H) \approx 106$ kcal/mol [42], the electron affinity of the $[AA - H]$ radical is expected to be a key factor in determining the residual charge density on the CO_2^- group in $[AA - H]^-$ anions.

In the $[AA - H]^- \cdot (H_2O)$ systems studied here, the electron withdrawing effect of the side-chain substituents is reflected in smaller $-\Delta G^o$ values for these complexes, Table 1, in comparison to that of the simplest amino acid, $[Gly - H]^- \cdot (H_2O)$. As can be seen from the table, the $-\Delta G^o$ values for these complexes follow the order $[Gly - H]^- > [Ala - H]^- > [Pro - H]^- > [Val - H]^- \approx [Lys - H]^- \approx [Phe - H]^- > [Met - H]^- > [Trp - H]^- > [Gln - H]^- \approx [Arg - H]^- > [Asp - H]^-$. This trend is consistent with the relative ordering of ΔH_{ac}^o recommended by Poutsma and coworkers [38]. Generally, the differences between the values of neighboring positions in the ordering of both $-\Delta G^o$ and ΔH_{ac}^o are within the experimental error.

Comparison with Protonated Amino Acids

A comparison between the anionic and cationic binding strengths is provided in Table 2. With the exception of Lys, the ΔG^o values for $[AA - H]^- \cdot (H_2O)$ are similar within 2 kcal/mol or less to those for the corresponding complexes, $AAH^+ \cdot (H_2O)$. This confirms the electrostatic nature of water interaction with the anionic and cationic sites of AAs. Although the variation of the ΔG^o values with the nature of the AA displays a similar trend, small differences between the values for the corresponding complexes can be found, e.g., $[(Gly)_2 - H]^- \cdot (H_2O)$ versus $(Gly)_2H^+ \cdot (H_2O)$ and $[(Ala)_2 - H]^- \cdot (H_2O)$ versus $(Ala)_2H^+ \cdot (H_2O)$. These differences may indicate stronger H-bonding interactions in both cat-

Table 2. Free energies[a] of monohydration of deprotonated and protonated amino acids and dipeptides[a]

AA	$[AA-H]^-$	AAH^+
Gly	8.2 (0.4)	9.4 $(1.2)^b$ 9.7 $(0.3)^c$
Ala	7.8 (0.8)	8.8 $(0.5)^b$
Val	7.2 (0.7)	7.8 $(0.8)^d$
Pro	7.6 (0.9)	7.7 $(0.7)^b$
Phe	7.2 (0.9)	7.6 $(0.8)^b$
Met	7.1 (0.8)	7.2 $(0.9)^d$
Lys	7.2 (1.0)	5.2 $(0.3)^c$
Arg	5.4 (0.9)	4.5^e
$(Gly)_2$	6.5 (1.1); 6.8 $(0.5)^f$	8.8 $(0.3)^c$
$(Ala)_2$	6.7 $(0.3)^f$	7.4 $(0.1)^g$

[a]Free energy change in kcal/mol, standard state 1000 mbar at 293 K.
[b]Ref. [13].
[c]Ref. [2].
[d]Ref. [12].
[e]Ref. [37].
[f]Ref. [35].
[g]Ref. [5].

ionic complexes, resulting from higher positive charge density concentrated on $-NH_3^+$ compared with a more diffusive negative charge on the $-CO_2^-$ group [8]. However, this explanation is inconsistent with findings for other anionic and cationic pairs for which the ΔG^o values are essentially the same (Table 2). Possibly in hydrated dipeptides the water molecule could also be involved in intramolecular H-bonding interactions with the chains, and the observed differences in the ΔG^o values for these complexes may reflect the consequences of this effect.

The greater $-\Delta G^o$ value found for $[Lys-H]^- \cdot (H_2O)$ than for $LysH^+ \cdot (H_2O)$ is attributable to the fact that $LysH^+$ forms a cyclic structure with an intramolecular hydrogen bond between the N-terminal amino group and the amine of the side chain [43]. As discussed above, the ions that form such internally H-bonded cyclic structures generally show weaker interactions with solvent molecules than those which form extended conformations.

Conclusions

Noncovalent interactions between the water molecule and deprotonated amino acids were investigated. The water binding energies in $[AA-H]^- \cdot (H_2O)$ complexes were obtained for 11 amino acids. The observations indicate a substantial effect of the side-chain substituents on the binding strengths in these complexes. A similar trend has been previously observed for protonated systems, $AAH^+ \cdot (H_2O)$. The data obtained from model systems provide a better understanding of the interaction between anionic and cationic sites of amino acids with water molecules.

Acknowledgments

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