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Ion Thermochemistry of Low-Volatility Compounds in the Gas Phase. 1. Intrinsic Basicities of α-Amino Acids

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Abstract: Samples of biomolecules with low vapor pressures, specifically α-amino acids, were introduced by a direct insertion probe into the ion source of a pulsed ionization high-pressure mass spectrometer. The number density of an amino acid in the source was determined by a new technique based on the measurement of the rate of its protonation by t-$C_4H_9^+$, the chemical ionization reactant ion. The proton affinities (PA) of the amino acids were obtained from measurements of the thermodynamics of proton transfer equilibria between the amino acids and appropriate reference bases. The following PAs (referred to $PA(NH_3) = 202.3$ kcal mol^{-1}) were obtained: glycine (208.2), alanine (212.2), valine (213.9), leucine (214.5), phenylalanine (215.1), proline (218.4). Comparison with the proton affinities of alkylamines shows that substitution by a carboxyl group decreases the proton affinity of the amine function by 1.8–3.1 kcal mol^{-1}. Comparison with solution basicities shows that the effect of solvent (H_2O) on this substituent effect is minor, if any. On the basis of the measured PA values, the following gas-phase heats of formation $(\Delta H°_f)_g$ are determined: $GlyH^+$ (53), $AlaH^+$ (43), $LeuH^+$ (15), and $PheH^+$ (57). Comparison of $(\Delta H°_f)_g$ of the ion–molecule association products $CH_3NH_3^+\cdot CO_2$ and $C_2H_5NH_3^+\cdot CO_2$ with $(\Delta H°_f)_g$ of their isomers $GlyH^+$ and $AlaH^+$ shows that the hydrogen-bonded cluster ions are more stable by 11 and 8 kcal mol^{-1}, respectively, then their covalently bonded isomers. We also observed the formation of the hydrogen-bonded dimers $(Gly)_2H^+$ and $(Pro)_2H^+$. For the association reactions leading to these dimers we measured $\Delta H° = -31$ and -29 ± 2 kcal mol^{-1} and $\Delta S° = -33$ and -32 ± 5 cal mol^{-1} K^{-1}, respectively.

Measurements of proton transfer equilibria in the gas phase have yielded an extensive ladder of the relative intrinsic basicities and proton affinities (PA) of organic compounds.[1-3] These data make it possible to separate and identify the intrinsic structural effects and the solvent effects on the acid–base properties of molecules.[4,5] To date, such measurements have been performed generally on compounds which are gases or at least moderately volatile liquids under standard conditions. In the present work we extend such measurements to the gas-phase proton affinities of involatile biomolecules, specifically α-amino acids. The present measurements are made possible by the application of ion–molecule kinetics to determine the number density of the amino acid vapor in the ion source of our pulsed high-pressure mass spectrometer.

Experimental Section

The present work was performed using the Rockefeller University Chemical Physics Mass Spectrometer in the pulsed ionization mode which was described previously.[6]

To measure proton affinities of amino acids (A) we observe proton transfer equilibria (reaction 1) between A and reference bases B:

$$BH^+ + A \rightleftharpoons AH^+ + B \quad (1)$$

In order to determine the equilibrium constants K_1, the number density of A (N_A) in the ion source must be known. This presents a difficulty since N_A is lower by a factor of 10^3–10^4 than the number density of the carrier gas i-C_4H_{10} in the source and even then N_A is this high only at relatively elevated temperatures. Thus N_A cannot be measured by conventional methods. The experimental procedure that we use is to introduce the solid sample A into the source via a direct inlet probe which places the sample 6–10 mm from the zone in the source where ion–molecule reactions occur. The sample A volatilizes from the probe, and in the reaction zone it is protonated by the reaction

$$t\text{-}C_4H_9^+ + A \rightarrow AH^+ + C_4H_8 \quad (2)$$

The rate of disappearance of t-$C_4H_9^+$ and of the appearance of AH^+ is measured by pulsed high-pressure techniques, and the pseudo-

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Table I. Thermodynamic Values for Proton Transfer Reactions from Reference Bases to α-Amino Acids

amino acid (A)	ref base	$\Delta G°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, cal mol^{-1} K^{-1}	proton affinity of A,[d,e] kcal mol^{-1} values	av value	PA(A) − PA(NH_3)
$CH_2(NH_2)COOH$	$C_6H_5NH_2$	0.0[a]	0.0	0.0	208.8		
(glycine)	2-cyanopyridine	−1.9[b]			207.5	208.2	5.9
$CH_3CH(NH_2)COOH$	CH_3NH_2	−0.1[c]			211.4		
(alanine)	$C_6H_5NH_2$	−6.2	−4.2	2.2	213.0	212.2	9.9
$(CH_3)_2CHCH(NH_2)COOH$	$C_2H_5NH_2$	0.4[c]			213.6		
(valine)	n-$C_4H_9NH_2$	2.0[c]			214.0		
	$C_6H_5NH_2$	−5.4[c]			214.2	213.9	11.6
$(CH_3)_2CHCH_2CH(NH_2)COOH$	$C_2H_5NH_2$	0.1[c]			213.9		
(leucine)	$C_6H_5NH_2$	−6.0[b]			214.8		
	n-$C_4H_9NH_2$	1.1[b]			214.9	214.5	12.2
$PhCH_2CH(NH_2)COOH$	$C_6H_5NH_2$	−6.2[b]			215.0		
(phenylalanine)	n-$C_4H_9NH_2$	0.9[b]			215.1	215.1	12.8
	$(CH_3)_3CNH_2$	0.1[b]	0.5	0.7	218.3		
(proline)	n-$C_4H_9NH_2$	−2.5[b]			218.5	218.4	16.1

[a] For the results of temperature studies, the values of $\Delta G°$ at 500 K are given in the table. [b] $\Delta G°$ values measured at 570 ± 5 K. [c] $\Delta G°$ values measured at 520 ± 5 K. [d] Estimated accuracy ±1.5 kcal/mol. [e] Proton affinities of reference bases from ref 3. The absolute PA values are thus referred to PA(NH_3) = 202.3 kcal mol^{-1}. It is noted, however, that new measurements of $\Delta H°_f$ of the primary standard t-$C_4H_9^+$ yield PA(NH_3) ≈ 207 kcal mol^{-1},[21] in which case the absolute values quoted in Table I should be raised by ca. 5 kcal mol^{-1}.

first-order rate constant r_2 for reaction 2 is obtained. N_A is related to r_2 by

$$r_2 = k_2 N_A \tag{3}$$

where k_2 is the second-order rate constant for reaction 2. k_2 for the reactions of t-$C_4H_9^+$ with amino acids has not been measured, but it may be assumed that the reactions proceed with approximately unit collision efficiency. This assumption is justified on the basis that proton transfer reactions between thermal or near-thermal t-$C_4H_9^+$ ions and alkylamines have been found[7,8] to have rate constants in the range 1.4–1.9 × 10^{-9} cm^3 s^{-1}, which corresponds to a collision efficiency range of 0.8–1.0. We thus used 1.5 × 10^{-9} cm^3 s^{-1} for the value of k_2. Based on the available rate constant data, this value is almost certainly accurate to better than ±50%.

After N_A is thus determined, a volatile reference base B is admitted to the source and the equilibrium constant, K_1, for reaction 1 is measured. The measurement of pressure of B is straightforward using our standard laboratory procedures. After the equilibrium measurement B is removed, and N_A is measured again to verify that N_A was constant during the equilibrium measurement.

The temperature of the insertion probe can be varied independently of that of the source. The pressure of A in the source was controlled by the probe temperature, and this was set at values which produced pressures of A such that r_2 was in the range 5–50 × 10^3 s^{-1}. This is the observable range for r_2 with our method, and it in turn defines the measurable range of pressure of A. In general the probe temperatures used to produce measurable pressures of A were different from the source temperatures. However, one can calculate that at the source pressures involved in our experiments a molecule evaporating from the probe will undergo 150–300 collisions with isobutane molecules in the course of traveling to the ion formation and reaction zone. Furthermore, the AH^+ and BH^+ ions formed in the reaction zone will undergo 2–3 × 10^3 collisions with isobutane molecules during the 150–200-μs time during which equilibrium is observed. The temperature of the isobutane is that of the source, and thus all the reactants in equilibrium (reaction 1) are thermalized at the source temperature.

Results and Discussion

The results of our studies are given in Table I. For the first three systems studied (alanine–aniline, glycine–aniline, and proline–*tert*-butylamine) the temperature variations in the equilibrium constants were measured, which, of course, constitutes the experimental determination of the entropy changes in the reactions. The van't Hoff plots for these experiments are given in Figure 1. The largest $\Delta S°$ value obtained is only 2.2 cal mol^{-1} K^{-1}; proton transfer reactions are generally found[3] to have entropy changes dominated by rotational symmetry number changes; and the compounds studied here are sufficiently asymmetric that rotational symmetry number changes are negligible. Thus as an approximation we can assume that for proton transfer reactions between amine bases and amino acids the entropy change is zero, and $\Delta G° = \Delta H°$. Proton affinities can then be obtained from the much less time-consuming procedure of measuring equilibrium constants at only one temperature. Eleven values of proton affinities obtained in this way are given in Table I.

In the last column of Table I we quote the proton affinities as related to that of ammonia. These values are obtained from our measurements and using the relative proton affinities of the reference compounds taken from ref 3. In all the discussions and conclusions in this paper only the relative proton affinities of the amino acids and of other amines are of interest. The validity of the following discussion is qualitatively and quantitatively independent of the absolute PA values which may be subject to revisions with changes in the accepted PA value of the primary standard i-C_4H_8 (see footnote 21).

In the cases where temperature studies are performed the uncertainty in the values of k_2 and consequently of N_A introduces an error of ±2 cal mol^{-1} K^{-1} in the value of $\Delta S°$. For measurements at 500 K this introduces an error of ±1 kcal mol^{-1} into the measurements of $\Delta G°$. Taking into account these uncertainties and those resulting from assuming that $\Delta S° = 0$ for measurements at a single temperature we estimate an uncertainty of 1.5 kcal mol^{-1} in the proton affinity values given in Table I. Equilibria were established between each amino acid and two or three reference bases. The agreement between the proton affinities for a given amino acid as obtained from measurements with the different reference bases is in all cases within about 1 kcal mol^{-1}.

α-Amino acids (A) may be considered as carboxyl derivatives of parent amines (designated here simply as RNH_2). The effect of the –COOH group on the proton affinity of the amine group is given by $\Delta PA = PA(RNH_2) - PA(A)$. ΔPA values for four of the amino acids studied here are listed in Table II. From Table II one sees that substitution by the electron-withdrawing –COOH group causes a decrease in the proton affinity of the amine group, but by a relatively small amount, namely, 1.8–3.1 kcal mol^{-1}. The fact that the proton affinities of the amino acids are always close to those of the parent amines suggests that the amino acids are protonated on the amine function. This result agrees with a previous interpretation of the fragmentation of thermal or near-thermal AH^+

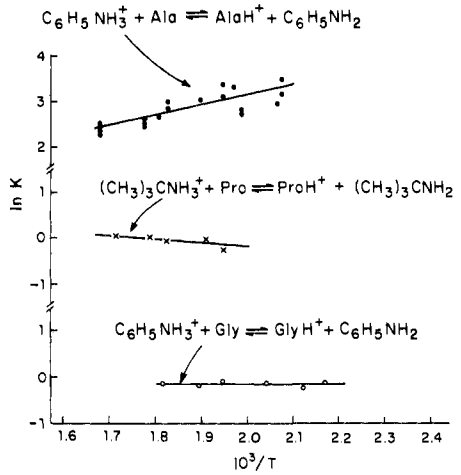


Figure 1. van't Hoff plots for proton transfer equilibria between amino acids and reference bases, as indicated.

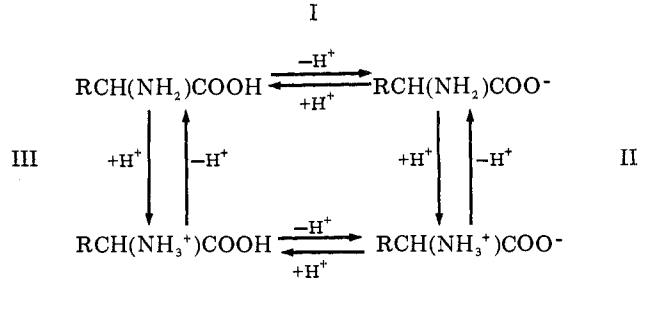
ions generated by H^+ transfer from t-$C_4H_9^+$.[9] In considering the site of protonation it must be noted, however, that proton exchange between the $-NH_3^+$ group and other parts of the ion is possible when an excited AH^+ is generated from a high-energy species such as CH_5^+ or H_3^+.[10]

The fact that the proton affinity of the amino acid is lower than that of the parent amine suggests that internal solvation by hydrogen bonding between the $-NH_3^+$ and -COOH groups is not significant, since this would tend to stabilize the protonated $-NH_3^+$ group and increase the proton affinity. The absence of internal solvation is also suggested by the small $\Delta S°$ values for reaction 1, since internal hydrogen bonding in the AH^+ ions would yield a cyclic structure having structural rigidity. This would make $\Delta S°$ for the reaction significantly negative.[3]

The gas-phase substituent effect of the -COOH group on the basicity of the amine function may be compared with the analogous substituent effect in solution. In this comparison we assume that the amino acid vapor is in the neutral, i.e., nonzwitterion, form.[11] Therefore the reaction of interest is

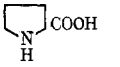
$$RCH(NH_3^+)COOH \rightleftarrows RCH(NH_2)COOH + H^+ \quad (4)$$

Since the amino acids of interest are zwitterions in solution, reaction 4 is not directly observed in solution. Nevertheless, $\Delta H°_{298}$ for reaction 4 in solution may be obtained from the following thermodynamic cycle:



Reactions II and IV are the acid and base dissociation of the zwitterion, and ΔH_{298} for these processes in solution is obtained from measurements of the temperature dependence of the corresponding pK values.[12] The enthalpies for the acid dissociation of the neutral amino acids (process I) are approximated by the enthalpies of dissociation of the corresponding carboxylic acids.[12] ΔH_{298} for process III (i.e., reaction 4) is then obtained from $\Delta H_{III} = \Delta H_I + \Delta H_{II} - \Delta H_{IV}$. The necessary data to calculate $\Delta H_{III}(aq)$ for glycine and alanine are given by Cohn and Edsall.[12] The enthalpies of base dissociation of the corresponding parent amines are also given in the same source.

Table II. Proton Affinity Differences $\Delta PA = PA(RNH_2) - PA(A)$

amino acid	parent amine	PA(parent amine)[a] − PA(amino acid), kcal mol^{-1}
$CH_2(NH_2)COOH$	CH_3NH_2	3.1
$CH_3CH(NH_2)COOH$	$CH_3CH_2NH_2$	1.8
$(CH_3)_2CHCH(NH_2)$-COOH	$(CH_3)_2CHCH_2$-NH_2	2.6
		3.1

[a] PA of the first three parent amines from ref 3. PA(pyrrolidine) from PA(pyrrolidone) − $PA(CH_3NH_2)$ = 10.2 kcal mol^{-1} (ref 4) and $PA(CH_3NH_2)$ = 211.3 kcal mol^{-1} (ref 3). See also footnote 21.

The substituent effect of interest in solution is given by $\Delta\Delta H° = \Delta H°_{(aq)}(RNH_2) - \Delta H°_{(aq)}(A)$. Comparing the enthalpy of dissociation of methylamine and glycine, we find that $\Delta\Delta H°$ = 1.2 kcal mol^{-1}. The corresponding substituent effect in the gas phase, ΔPA, is 3.1 kcal mol^{-1}. Comparing the proton affinities of ethylamine and alanine, we find that in aqueous solution $\Delta\Delta H°$ = 1.7 kcal mol^{-1}; in the gas phase ΔPA = 1.6 kcal mol^{-1}. Thus, the decrease in the basicity of the amino group upon α substitution by -COOH is of a similar magnitude in the gas phase and in solution for both compounds. This result shows that the contribution of solvation to this substituent effect is small, and the solution values reflect intrinsic molecular properties.

The proton affinities obtained in the present work may be used to calculate the heats of formation of protonated amino acids in the gas phase. To do so we combine our data with heats of formation of amino acids in the gas phase, which in turn are calculated from their heats of combustion and their heats of sublimation as measured recently by Gaffney et al.[13] The following gas-phase heats of formation are obtained (kcal mol^{-1}): $GlyH^+$ (53), $AlaH^+$ (43), $LeuH^+$ (15), and $PheH^+$ (57). (Note that these values are obtained using the reference $PA(NH_3)$ = 202.3 kcal mol^{-1}. Using $PA(NH_3) \approx 207$ kcal mol^{-1} (see footnote 21), the above values would be changed to 48, 38, 10, and 52 kcal mol^{-1}, respectively.)

Comparing the heats of formation of ions of known structures with those of isomers of unknown structures can be used as a tool to provide information about the unknown structures. We shall use our present data in this manner, to investigate whether protonated amino acids can be formed by the association of ammonium ions with carbon dioxide. Recently, we observed[14] the following reactions:

$$CH_3NH_3^+ + CO_2 \rightleftarrows CH_3NH_3^+ \cdot CO_2 \quad (5)$$

$\Delta H° = -13.2$ kcal mol^{-1}, $\Delta S° = -21.4$ cal mol^{-1} K^{-1}

$$C_2H_5NH_3^+ + CO_2 \rightleftarrows C_2H_5NH_3^+ \cdot CO_2 \quad (6)$$

$\Delta H° = -11.2$ kcal mol^{-1}, $\Delta S° = -20.8$ cal mol^{-1} K^{-1}

On the basis of the entropy changes, which are characteristic of ion–molecule clustering, we proposed that the products are hydrogen-bonded cluster ions. However, the empirical formulas of the product ions in (5) and (6) are identical with those of protonated glycine and protonated alanine, respectively, and thus the formation of new covalent bonds between the reactants in reactions 5 and 6 could lead to $GlyH^+$ and $AlaH^+$, respectively. Indeed, it has been observed in several instances that ion–molecule condensation results in new covalently bonded ions. For example, carbonium ions associate with water to yield

protonated alcohols,[15,16] with ammonia to yield protonated amines,[14] with HCN to yield protonated isocyanides,[17] and with CO to yield acylium ions.[18] To examine whether reactions 5 and 6 behave similarly, we calculate $\Delta H°_f$ of the products of reactions 5 and 6 as 42 and 35 kcal mol^{-1}, respectively. (Based on PA(NH_3) = 202.3 kcal mol^{-1}. Using PA(NH_3) ≈ 207 kcal mol^{-1}, we would obtain $\Delta H_f°$ = 37 and 30 kcal mol^{-1}, respectively.) Comparing with the heats of formation of $GlyH^+$ and $AlaH^+$ as given above, we find that the products of the association reactions are not identical with $GlyH^+$ and $AlaH^+$. This is in agreement with the conclusion we made on the basis of $\Delta S°$ of the association reactions. Furthermore, we make the unexpected observation that the products of reactions 5 and 6, which are thus assumed to be hydrogen-bonded cluster ions, are more stable by 11 and 8 kcal mol^{-1}, respectively, than their covalently bonded isomers $GlyH^+$ and $AlaH^+$. This intuitively unexpected result is rationalized on the basis that the heats of formation of the neutral species ($CH_3NH_2 + CO_2$) and $CH_2(NH_2)COOH$ are similar (−5.5 − 94.4 = −99.9 and −104 kcal mol^{-1}), respectively. However, the electron-withdrawing effect of -COOH in the amino acid destabilizes the charge on $CH_3(NH_3^+)COOH$, as we found earlier; in contrast, the ion-neutral electrostatic and hydrogen-bonding forces stabilize the charge in $CH_3NH_3^+ \cdot CO_2$. The greater stability of the cluster ion thus results from the opposite effects of intramolecular charge destabilization by -COOH in the covalently bonded structure as opposed to the intermolecular charge stabilization by CO_2 in the cluster ion.

In addition to proton affinity measurements, the determination of N_A by the present method makes it possible to study quantitatively other ion-molecule processes, such as association. For example, in the course of the present work we also observed the equilibrium reactions involved in the formation of the proton-bound dimers $(Gly)_2H^+$ and $(Pro)_2H^+$. Quantitative measurements of the equilibria yielded the values $\Delta H°$ = −31 ± 2 and −29 ± 2 kcal mol^{-1}, respectively, and $\Delta S°$ = −33 ± 5 and −32 ± 5 cal mol^{-1} K^{-1}, respectively. The $\Delta H°$ value for $(Pro)_2H^+$ is more negative than a previous result of 20 kcal mol^{-1}, which was obtained by a continuous ionization technique and a different sample introduction procedure.[19] The time-resolved result obtained here is more reliable. The enthalpies and entropies of association for the amino acids are more negative than those observed in the formation of protonated amine dimers,[20] which are generally in the range $\Delta H°$ = −21 to −25 kcal mol^{-1} and $\Delta S°$ = −24 to −27 cal mol^{-1} K^{-1}. The enhanced bonding and constrained geometry which are reflected in the thermodynamic values for the amino acids may be indicative of multiple hydrogen bonding in the protonated dimers of these polyfunctional molecules.

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(21) Recent values of $\Delta H°_f(t\text{-}C_4H_9\cdot)$ = 12 kcal mol^{-1} (W. Tsang, *Int. J. Chem. Kinet.*, **10**, 821 (1978)), combined with IP($t\text{-}C_4H_9\cdot$) = 151.7 kcal mol^{-1} (J. Dyke et al., quoted by F. A. Houle and J. L. Beauchamp, *J. Am. Chem. Soc.*, **100**, 3290 (1978), footnote 44) and $\Delta H°_f(H^+)$ = 365.7 kcal mol^{-1} can be used to obtain PA($i\text{-}C_4H_8$) = 198.0 kcal mol^{-1}. This value, combined with PA(NH_3) − PA($i\text{-}C_4H_8$) = 8.6 kcal mol^{-1} (ref 2), yields PA(NH_3) = 206.6 kcal mol^{-1}. This is higher than the value of PA(NH_3) = 202.3 kcal mol^{-1} which was used in ref 3 and throughout the present paper. Using the more recent reference value, all proton affinities will be higher, and all ion heats of formation will be lower by 4.3 kcal mol^{-1} than the values quoted in the paper. Note, however, that all the discussion in this work is based on relative proton affinities of amines and amino acids, and the conclusions are qualitatively and quantitatively unaffected by the absolute PA values.

Tetracyclines. 9. Total Synthesis of *dl*-Terramycin

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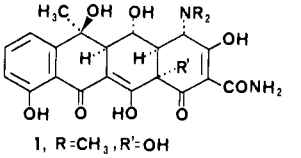
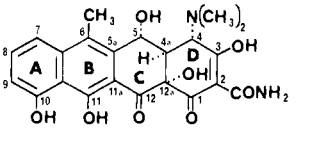
Abstract: The total synthesis of *dl*-terramycin is described in detail.

During recent decades, terramycin has proved to be a most useful antibiotic. As a member of the tetracycline family of antibiotics it possesses broad-spectrum, antibacterial effects and is active against rickettsias, certain large viruses, protozoa, and parasites.[2] Its structure was initially proposed in 1952 by a research group at Chas. Pfizer in conjunction with Woodward[3] several years after Finlay and colleagues announced preparation of the antibiotic by cultivation of *Streptomyces rimosus*.[4] The configuration proposed in 1953[3] was later revised after consideration of X-ray data[5] of terramycin and NMR spectra of a terramycin transformation product.[6] The structure of terramycin is thus depicted as **1**.



1, R=CH_3, R'=OH
2, R=H, R'=H



Anhydroterramycin

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