The Proton Affinity and Entropy of Protonation of Lysinamide. The Effects of Intramolecular Proton Solvation†

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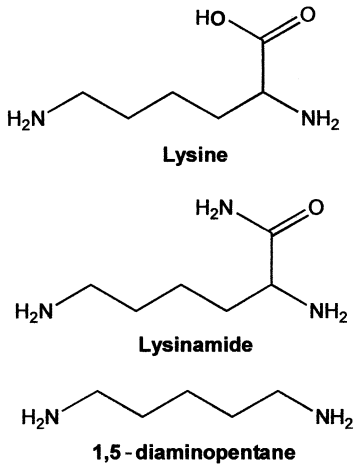
The equilibrium constants for the gas-phase proton transfer from protonated tri-*n*-propylamine to lysinamide at several temperatures have been measured using Fourier transform ion cyclotron resonance mass spectrometric techniques. The thermodynamic values obtained from a van't Hoff plot are $\Delta H = -4.36 \pm 0.85$ kcal mol^{-1} and $\Delta S = -12.25 \pm 2.34$ cal mol^{-1} K^{-1}. These values lead to derived values of the proton affinity (PA) and entropy of protonation (ΔS_p) of lysinamide of 241.4 ± 0.9 kcal mol^{-1} and 10.9 ± 2.2 cal mol^{-1} K^{-1}, respectively. A sophisticated calculation in the literature suggests that the former is identical with the PA of lysine as would be expected. The PA of lysinamide exceeds that of 1,5-diaminopentane by 2.5 kcal mol^{-1}, which is consistent with an expected favorable interaction between the carbonyl oxygen of the $CONH_2$ group and the strong hydrogen bond in protonated lysinamide. The ΔS_p value is in good agreement with a kinetic-method determination of the entropy of protonation of lysine. It is suggested that the currently accepted PA of lysine, which was determined by the kinetic method, is 3−4 kcal mol^{-1} too low. This discrepancy is suggested to be the result of the fact that the kinetic method measures activation entropies and enthalpies, rather than overall entropies and enthalpies, and thereby fails to measure the intramolecular proton-solvating interaction of the carbonyl group in lysine.

Introduction

The preferred conformation of gaseous protonated lysine might reasonably be assumed to involve solvation of the proton between the side-chain amino group and the N-terminal amino group. The thermodynamic consequences of such a strong hydrogen bond should be a proton affinity (PA) larger than that of a simple amine and a substantial negative entropy of protonation (ΔS_p). In addition to the amino groups it is possible that the lysine carbonyl group might contribute to an intramolecular solvating interaction with the proton. The role of the carbonyl should also be reflected in the thermodynamics of the protonation of lysine. We report here measurements of the PA and the ΔS_p of lysinamide. Lysinamide should have the same conformational preferences as lysine, although it is somewhat more volatile than lysine, thus facilitating the gas-phase equilibrium constant measurements necessary to determine these quantities. Note in addition that, unless the lysine is at the C terminus, lysinamide also models lysine in a peptide chain more closely than does lysine.

The PA of lysinamide has not been previously measured, but the several measurements of the PA of lysine[1−7] have been critically evaluated by Hunter and Lias[8] (HL). An ab initio calculation of the PA of lysine is also available in the literature.[9] Only one measurement of the ΔS_p of lysine has been reported, a kinetic-method[10−12] measurement by Wu and Fenselau.[6] The kinetic method derives PA and ΔS_p values from relative rate constants for decompositions of proton-bound dimers. The method requires known PAs for a number of reference bases. HL have compiled a new evaluation of the whole scale of known proton affinities.[8] To obtain lysine PA and ΔS_p values, they reanalyzed the results of the Wu and Fenselau study using the revised proton affinities of the bases used in that study. The HL study takes the reinterpreted results to be definitive for lysine, perhaps because no other measurement includes an entropy determination. The present measurement of ΔS_p and PA for lysinamide is relevant to that important judgment.

CHART 1



In contrast to expectation from theory, the Hunter and Lias (HL) lysine PA is slightly less than the HL PA of 1,5-diaminopentane.[8] Lysine can be thought of as 1,5-diaminopentane with a COOH carboxylic acid substituent on carbon 1 (see Chart 1). A stabilizing, solvating interaction of the carbonyl oxygen of the COOH group with the strong hydrogen bond in the protonated lysine should increase the PA of lysine by 2−3 kcal mol^{-1} relative to that of 1,5-diaminopentane.[9] Lysinamide might be expected to behave in the same way, so the present measurement provides a means to test the theoretical expectation.

The ΔS_p of lysine from the results of Wu and Fenselau as analyzed by HL (−10.0 cal mol^{-1} K^{-1}) is significantly less

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negative than the HL value for the ΔS_p of 1,5-diaminopentane (-16.7 cal mol^{-1} K^{-1}).[8] The negative entropy change in both cases results from the loss of free internal rotations that accompanies the formation of a strong hydrogen bond between the terminal amine groups in the protonated species. The COOH substituent in lysine presumably hinders internal rotations in the unprotonated lysine, thus lowering its entropy. Protonation therefore produces less loss of entropy in lysine than in 1,5-diaminopentane. A very similar effect should occur in lysinamide, which the present measurement can verify.

Experimental Section

Equilibrium constants were measured using methods previously described which we summarize here.[13,14] Lysinamide was introduced on a heated probe to the source cell of an FTMS 2000 Fourier transform ion cyclotron resonance mass spectrometer (ThermoFinnigan, Bremen, Germany).[15,16] A reference base, tri-*n*-propylamine, was introduced through the batch inlet to an indicated pressure of ca. 10^{-7} Torr. Ionization was produced by a short 20-eV electron beam pulse. Ion−molecule reactions converted most of the ionization to the two protonated parents within a few-second trapping time. Fourier transform ion cyclotron resonance (FT-ICR) mass spectra of the ions in the cell were obtained at various trapping times. Typically, the ratio of the two protonated parents was constant for trapping times between 10 and 60 s. Ejection experiments[17] verified the occurrence of reversible proton transfer. The long time ratio of the FT-ICR signals was taken as the ratio of the equilibrium ion concentrations. The ratio of the neutral concentrations was estimated from the FT-ICR mass spectrum of the mixture obtained at 70-eV electron energy and zero trapping time. The ionization cross sections of the two neutral species were taken to be proportional to their polarizabilities[18] as estimated by the method of Miller and Savich.[19]

The temperature was taken to be that provided by the instrument's temperature-control system. The main body of the vacuum system is encased in heaters, and thermocouples are located on the stainless steel wall of the vacuum system. The reported temperature readings are those of the thermocouple located outside the vacuum container near where the cell support makes contact with the inside of the vacuum container. After thermal equilibrium was established (sometimes after a number of hours), thermocouples near the end flanges of the container, more than 40 cm from the cell, gave the same or slightly lower readings (typically within less than 5 °C). Variation of the batch inlet temperature had no effect on the equilibrium constants measured. The electron gun is located some 40 cm from the cell, so it does not produce anomalous heating effects.

As in previous studies,[13] the validity of the temperature readings was tested by comparing the entropy of proton transfer to 1,6-hexanediol measured by the present apparatus with the high-pressure mass spectrometry result.[20] Excellent agreement was found. The procedures used for the hexanediol FT-ICR measurements were the same as those for the lysinamide measurements except that the diol was admitted to the vacuum system through the batch inlet.

Results

The time variation of the concentrations of the reactant and product ions of reaction 1

$$(n\text{-}C_3H_7)_3NH^+ + \text{lysinamide} \rightarrow (\text{lysinamide})H^+ + (n\text{-}C_3H_7)_3N \quad (1)$$

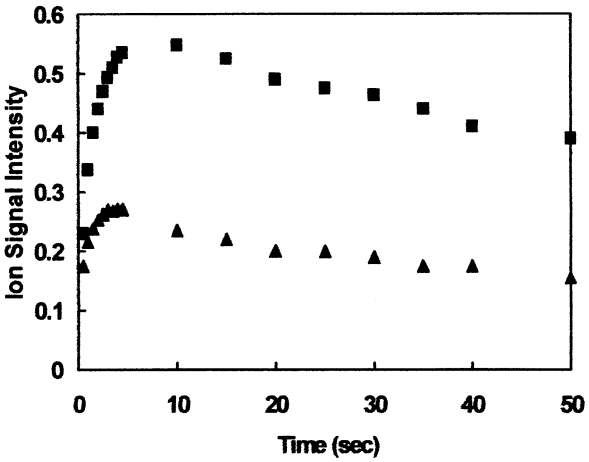

Figure 1. Variation of ion abundance with time in lysinamide and $(n\text{-}C_3H_7)_3N$ vapor at a nominal total pressure of 10^{-7} Torr and a temperature of 90 °C. The ratio of the pressure of the amine to that of lysinamide is 2.3. The ions are trapped in the cell of an FT-ICR mass spectrometer after ionization is initiated by electron ionization. The squares represent the abundance of $(n\text{-}C_3H_7)_3NH^+$, and the triangles represent the abundance of (lysinamide)H^+.

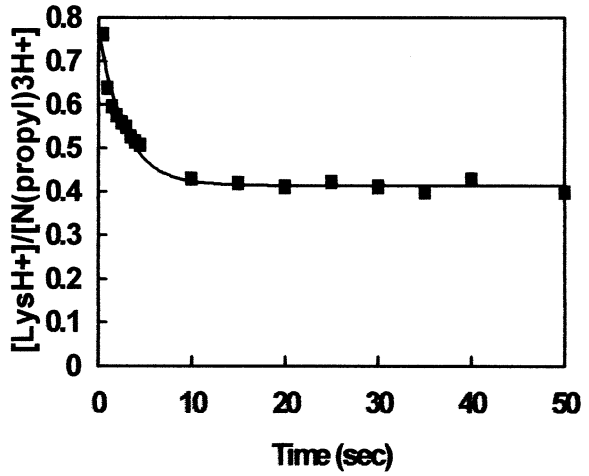

Figure 2. Ratio of the (lysinamide)H^+ and $(n\text{-}C_3H_7)_3NH^+$ abundances varying with time and approaching equilibrium as a result of reaction 1. The squares are data from abundances in Figure 1. The line represents a nonlinear least-squares fit to the data of a simple kinetic model for the approach to equilibrium.

for a typical case is shown in Figure 1. The typical approach to equilibrium is illustrated in Figure 2. The results of equilibrium constant measurements at temperatures of 75, 90, and 110 °C are summarized in a van't Hoff plot in Figure 3. The thermodynamic values obtained from the plot are ΔH(reaction 1) $= -4.36 \pm 0.85$ kcal mol^{-1} and ΔS(reaction 1) $= -12.25 \pm 2.34$ eu. The uncertainties reflect the deviations from linearity of the van't Hoff plot (2.13 times the standard deviation or 90% confidence limits for four degrees of freedom).

The proton affinity (PA) and gas-phase basicity (GB) of M are defined as ΔH and ΔG_{298} of reaction 2, which leads to eqs 3 and 4

$$MH^+ \rightarrow M + H^+ \quad (2)$$

$$PA[(n\text{-}C_3H_7)_3N] - PA(\text{lysinamide}) = \Delta H(\text{reaction}) \quad (3)$$

$$GB[(n\text{-}C_3H_7)_3N] - GB(\text{lysinamide}) = \Delta G_{298}(\text{reaction}) \quad (4)$$

Taking ΔH(reaction 1) and ΔS(reaction 1) as temperature-

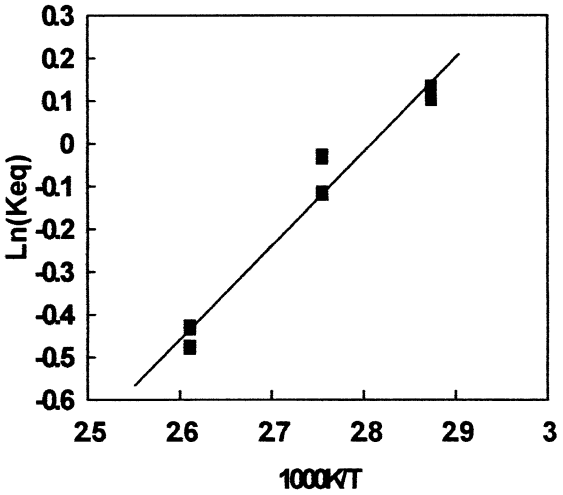

Figure 3. van't Hoff plot of equilibrium constants for reaction 1 against reciprocal temperature.

TABLE 1: Thermochemistry of Protonation of Lysine and Lysinamide

species	PA[a] (kcal mol^{-1})	ΔS_p[b] (cal mol^{-1} K^{-1})	GB[c] (kcal mol^{-1})	method
(n-C_3H_7)$_3$N	236.9	1.34	229.5	ICR[d,e]
1,5-diaminopentane	238.9	−16.7	226.1f	HPMS, ICR[d,e]
1,5-diaminopentane	238.8			theory[f]
lysine	238.0	−10.1		kinetic[d,e]
lysine	241.4			theory[f]
lysinamide	241.3 ±0.9	−10.9 ± 2.3	230.2 ± 1.1	FT-ICR[d,g]

[a] PA = proton affinity or ΔH for reaction 2. [b] ΔS_p = entropy of protonation or ΔS for half-reactions. [c] GB = gas-phase basicity or ΔG_{298} for reaction 2. [d] ICR, ion cyclotron resonance mass spectrometry; HPMS, high-pressure mass spectrometry; FT-ICR, Fourier transform ion cyclotron mass spectrometry. [e] Reference 8. Uncertainty in ref 8 proton affinity scale is ±2 kcal mol^{-1}. [f] Reference 12. [g] Present results. Uncertainties from linear regression of data in van't Hoff plot (Figure 3) represent 90% confidence limits.

independent gives -0.71 ± 1.10 kcal mol^{-1} for ΔG_{298}(reaction 1). Using eqs 3 and 4 and combining the PA[8] (236.9 kcal mol^{-1}) and GB[8] (229.5 kcal mol^{-1}) of tri-*n*-propylamine with ΔH(reaction 1) and ΔG_{298}(reaction 1) gives 241.3 ± 0.9 and 230.2 ± 1.1 kcal mol^{-1}, respectively, as the PA and GB of lysinamide. In HL, the uncertainties in the PA and GB values of tri-*n*-propylamine were neglected in determining the uncertainties in the PA and GB values of lysinamide. Specifying the uncertainties in the HL values is a complex issue that is discussed below. HL defined ΔS_p of M as ΔS of the half-reaction 5,[8] leading to eq 6. Although eq 5 is not balanced, HL found the corresponding entropy to be useful because it reflects the entropic effect of protonation unique to M. Although it eliminates the entropy of the proton, the entropy of the proton is not needed to find the entropy change of a proton-transfer reaction. Combining two half-reactions such as eq 5 gives a proton transfer and an equation such as eq 6.

$$M \rightarrow MH^+ \quad (5)$$

$$\Delta S(\text{reaction 1}) = \Delta S_p(\text{lysinamide}) - \Delta S_p[(n\text{-}C_3H_7)_3N] \quad (6)$$

Using ΔS(reaction 1) with the HL value of ΔS_p[(n-C_3H_7)$_3$N] (1.34 cal mol^{-1} K^{-1})[8] in eq 6 leads to a value of -10.9 ± 2.3 cal mol^{-1} K^{-1} for ΔS_p(lysinamide). The thermochemical values derived from the present results are compared with various literature values in Table 1.

Comparison to Lysine. The PA value obtained for lysinamide (241.3 ± 0.9 kcal mol^{-1}) is somewhat larger than the HL values for lysine (238.0 kcal mol^{-1}) and for 1,5-diaminopentane (238.9 kcal mol^{-1}). The three molecules each contain five carbon chains with terminal amine groups capable of di-solvating a proton. The differences in the PAs could reflect conformational preferences important in determining peptide conformations. Consideration of the origin of these differences is therefore important. Before considering conformational explanations of the differences, it is necessary to examine the possibilities of various kinds of measurement error.

The uncertainty in the difference between the present lysinamide result and the reported PA of lysine is difficult to assess. In addition to the measurement error in the present measurement of the difference between the proton affinities of (n-C_3H_7)$_3$N and lysinamide, the uncertainty in the difference between the proton affinities of (n-C_3H_7)$_3$N and lysine on the HL scale must be considered.

HL took the uncertainty in the absolute values in their scale to be ±2 kcal mol^{-1}.[8] The error in relative values in the scale might be lower, but there is no simple, objective way to assess how much less. The relative proton affinities of the amines were derived from equilibrium constant measurements using ion cyclotron resonance[21a] (ICR) and high-pressure mass spectrometry[21b] (HPMS) methods. The relative proton affinities were then anchored to experimental and theoretical absolute proton affinities. The reported temperatures of the original equilibrium constant measurements were adjusted to provide consistency between the ICR results, the HPMS results, and the various absolute proton affinities. The equilibrium measurements provided free energies, whereas the experimental and theoretical methods used to find absolute proton affinities usually provided energies or enthalpies. To connect the relative and absolute values, it was therefore necessary to assign entropies. This was done in the HL analysis on the basis of theory, statistical mechanics, temperature-dependent equilibrium constant measurements, requirements of consistency among various determinations, and finally requirements of "reasonableness". The adjusted measurements from different laboratories using different methods are quite consistent, especially over short ranges and especially for values derived from equilibrium constant measurements. This consistency suggests an estimated error in such adjusted relative measurements of no more than ±1.0 kcal mol^{-1}, significantly less than the 3.3 kcal mol^{-1} difference between the present measurement of PA(lysinamide) and the HL value of PA(lysine).

The uncertainty in the HL value for PA(lysine) might differ from that of other amines. The lysine PA value was derived from kinetic measurements using the HL proton affinities of a series of bases.[8] The uncertainty in the lysine PA depends in a complicated way on the uncertainties in the proton affinities of the bases, as well as uncertainties in the kinetic measurements. Furthermore, Armentrout has recently pointed out that the method of analysis originally used in kinetic-method determinations masks the actual measurement error, and he suggests methods for finding statistically valid estimates of error.[22] Armentrout also points out that applying his method of error analysis to kinetic-method results in the literature frequently gives very large uncertainties.[22] Unfortunately, the data in the literature[6] are insufficient to reanalyze the kinetic-method results on PA(lysine) using the techniques suggested by Armentrout. We are therefore unable to determine in an entirely objective way whether the difference between the present determination of the lysinamide PA and the HL lysine PA is simply the result of imprecision in the measurements or an indication that lysine and lysinamide actually have different PAs. Nevertheless, one

of the two must be the case. Either the kinetic method gives a value of PA(lysine) different from that of lysinamide, or there is a substantial error in one or both measurements. We address this issue further below in connection with a consideration of theoretical calculations of the lysine PA and the conformational preferences indicated by the calculations.

The difference between the HL value for PA(1,5-diaminopentane) and the present PA(lysinamide) value depends in a simpler way on the accuracy of the HL scale. That is, it depends directly on the difference between the HL values of PA(1,5-diaminopentane) and PA[$(n\text{-}C_3H_7)_3N$]. As indicated above, the self-consistency of the values in the HL scale that depend on gas-phase equilibrium constant measurements suggests that the difference between the 1,5-diaminopentane and $(n\text{-}C_3H_7)3N$ proton affinities (2.0 kcal mol^{-1}) is in error by no more than $\pm$1.0 kcal mol^{-1}. Combining this error estimate with the estimated error in ΔH(reaction 1) gives 2.4 $\pm$ 1.1 kcal mol^{-1} for the PA difference between lysinamide and 1,5-diaminopentane. The present results thus indicate that PA(lysinamide) is significantly larger than PA(1,5-diaminopentane). The consideration of theoretical results presented below provides a conformational explanation of this difference.

The ΔS_p of lysinamide (-10.9 ± 1.1 cal mol^{-1} K^{-1}) is only slightly more negative than the HL value for lysine (-10.0 cal mol^{-1} K^{-1}). Because very similar structural changes should be involved in protonating the two molecules, this agreement in the entropy ΔS_p is expected and provides support for the reliability of the kinetic-method determination of the lysine ΔS_p value. The ΔS_p value of 1,5-diaminopentane (-16.7 cal mol^{-1} K^{-1}),[8] however, is significantly more negative than those of lysine and lysinamide. As mentioned in the Introduction, the probable explanation for this difference is that the internal rotations in neutral lysinamide are more sterically hindered than those in 1,5-diaminopentane, thus decreasing the entropy of the neutral lysinamide relative to that of 1,5-diaminopentane.

Comparison with Theoretical Calculations. A theoretical calculation[9] of the PA of lysine gives 241.4 kcal mol^{-1}, in nearly exact agreement with our result of 241.3 kcal mol^{-1} for the PA of lysinamide. The computational approach involved performing a high-level ab initio calculation (MP2/TZ2P//DZP) on a model compound and adjusting the results slightly (net adjustments of 1.5 kcal mol^{-1} or less) on the basis of semiempirical calculations. The model used was 1,4-diaminobutane in lieu of 1,5-diaminobutane because experiment and semiempirical calculations suggested that the PA of 1,4-diaminobutane is within 1 kcal mol^{-1} of the PA of 1,5-diaminopentane. The MP2/TZ2P//DZP methodology gives results comparable in quality to MP2/6-311+(2d,2p)//6-31G(d).[9] The semiempirical adjustments were based on MNDO/M, AM1, and PM3 calculations. All three methods gave adjustments that agreed to within $\pm$0.5 kcal mol^{-1}, and the average of the adjustments from the three methods was used. The ab initio result for PA(1,4-diaminobutane) was 239.9 kcal mol^{-1},[9] in excellent agreement with the HL value of 240.3 kcal mol^{-1}.[8] Applying the semiempirical adjustments[9] gave 241.4 kcal mol^{-1} for PA(lysine) and 238.8 kcal mol^{-1} for PA(1,5-diaminopentane), the latter in nearly exact agreement with the experimental HL value[8] (238.9 kcal mol^{-1}). The fact that both theory and experiment indicate that PA(1,4-diaminobutane) exceeds PA(1,5-diaminopentane) by about 1 kcal mol^{-1} is reminiscent of the generally observed small increase in ring strain with ring size for rings with seven or more members.[23] Protonation of the diamines, of course, involves formation of seven- and eight-membered rings.

The minimum-energy conformation of protonated lysine found theoretically benefits from a stabilizing interaction between the proton-bound amino groups and the carbonyl oxygen of the COOH group.[9] This interaction accounts for the difference between PA(lysine) and PA(1,5-diaminopentane). Lysinamide should have a very similar interaction involving the carbonyl oxygen of the $CONH_2$ group, and hence, we expect that lysine and lysinamide should have essentially the same PA values. We conclude that the agreement between the theoretical PA of lysine and the present result for lysinamide indicates that the present result has at least the accuracy of the HL scale in both an absolute and relative sense. We also conclude that the lysinamide PA reflects a subtle stabilizing interaction involving the carbonyl oxygen as well as the strong hydrogen bond between the amino groups.

The theoretical results and the present measurement both indicate that PA(lysine) should be 2$-$3 kcal mol^{-1} greater than PA(1,5-diaminopentane). Instead, the HL scale has PA(lysine) about 1 kcal mol^{-1} *less* than PA(1,5-diaminopentane). This, in turn, indicates that the kinetic-method value used in the HL scale underestimates the lysine PA by 3$-$4 kcal mol^{-1}. This error is somewhat greater than the usual 2 kcal mol^{-1} absolute accuracy of the scale and more substantially greater than the usual 1 kcal mol^{-1} relative accuracy of the scale. If this error is not the result of experimental measurement error, it is probably the result of the failure of some underlying assumption in the kinetic method.

One factor that suggests that measurement imprecision is not the source of the lysine$-$lysinamide discrepancy comes from the results used to assign values for 1,4-diaminobutane in the HL scale. Kinetic-method values for the PA and ΔS_p of that species are in very good agreement (within 0.3 kcal mol^{-1} and 0.3 cal mol^{-1} K^{-1} respectively) with ICR and HPMS values,[8] and as noted above, the HL value for PA(1,4-diaminobutane) is in very good agreement with the ab initio result.

The possibility remains that the apparent error in the kinetic determination of PA(lysine) is the result of a failure of the underlying assumptions of the kinetic method. The kinetic method actually measures activation enthalpies and activation entropy changes rather than differences in the properties of separated reactants and products of proton transfer. The transition state for dissociation of a proton-bound dimer is very loose, but the products are not entirely separated. A transition state could, for example, have intermolecular interactions that interfere with such subtle intramolecular interactions as that between the carbonyl oxygen and the proton-bound amino groups in protonated lysine. Such an effect would account for the fact that the kinetic method appears to underestimate the PA of lysine although it gives the PA of 1,4-diaminobutane very accurately. Such an effect might also account for the fact that the kinetic-method ΔS_p value is not quite as negative as that from the equilibrium constant measurement.

Conclusions

The PA and ΔS_p values for lysinamide determined here are 241.4 $\pm$ 0.9 kcal mol^{-1} and -10.9 ± 2.3 cal mol^{-1} K^{-1}, respectively. The former is in excellent agreement with a sophisticated theoretical calculation of the PA of lysine, as would be expected. The PA of lysinamide exceeds that of 1,5-diaminopentane by 2.5 kcal mol^{-1}, consistent with the theoretical results on lysine and 1,5-diaminopentane as well as with an expected favorable interaction between the carbonyl group and the solvated proton in protonated lysinamide. The ΔS_p value is in good agreement with the kinetic-method ΔS_p of lysine in

the HL compilation.[8] It is significantly less than the ΔS_p of 1,5-diaminopentane probably because the hindered rotations in the neutral lysinamide reduce its entropy so that there is less loss of entropy upon protonation and formation of a strong internal hydrogen bond.

The kinetic-method PA of lysine as given by HL is probably somewhat too low. It is slightly less than the PA of 1,5-diaminopentane, whereas it is expected to be slightly more. It is also less than the PA of lysinamide, whereas lysine and lysinamide might be expected to have nearly the same PA. The discrepancy is suggested to be the result of the fact that the kinetic method measures activation enthalpies and entropies rather than overall enthalpies and entropies of reaction. The kinetic method thus measures the effect of di-solvation of the proton by the lysinamide amino groups, because that effect is present in the transition state, but it does not measure the weaker solvating interaction of the carbonyl with the proton, which is evidently not present in the transition state.

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