Proton Affinity and Gas-Phase Basicity of Urea

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Received: December 8, 1997; In Final Form: February 13, 1998

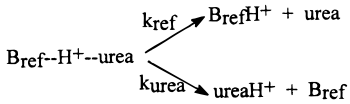
Urea undergoes O-protonation in the gas phase to yield a product that is thermodynamically more stable than the N-protonated isomer, as also is the case in aqueous solution. The proton affinity and gas-phase basicity of urea, determined by using the kinetic method, are 873.5 ± 5.0 and 841.6 ± 5.0 kJ/mol, respectively. These values are in excellent agreement with G2(MP2) calculations, which give PA = 872.4 kJ/mol. The entropy requirements for the competitive dissociation channels of the proton-bound heterodimers of urea and the chosen reference compounds are measured and lead to the conclusion that urea and these references have almost equal protonation entropies ($\Delta(\Delta S°) = 0.80$ J/kmol). In comparison with proton affinities of acetone and acetamide, the proton affinity of urea is understandably enhanced by resonance stabilization in both neutral and protonated urea, and an upper limit to the PA value is established by a resonance saturation effect. These considerations provide a basis for the explanation of some aspects of the reactivity of urea.

Introduction

Urea, the first synthetic organic compound, and its derivatives are of great industrial[1] and biomedical[2] significance. Urea is widely used to denature proteins in studies of protein folding−unfolding equilibria, although the mechanism of urea-driven denaturation is not yet clear.[3] Hydrophobic interactions with nonpolar protein groups and hydrophilic solvation of the peptide groups of proteins are proposed to describe the interaction between urea with the target proteins. In contrast to extensive condensed-phase studies, which bear on the acid/base properties of ureas, little attention has been paid to gas-phase measurements. Gas-phase photoelectron and microwave spectroscopy studies and, more recently, heats of formation determinations of urea and related compounds have been reported.[4,5] Remarkably, the proton affinity and gas-phase basicity of urea appear not to have been determined. Here, we report experimental values for these quantities using the kinetic method. The effects of protonation on the electronic structure of urea are also discussed in conjunction with its chemical reactivity.

Over the last several decades, mass spectrometry has been proved to be an increasingly valuable experimental technique to explore the intrinsic reactivity of charged species by providing reliable thermodynamic and kinetic data in the solvent-free environment. The gas-phase basicity (GB) and proton affinity (PA) of a molecule, defined, respectively, as the free energy change and enthalpy change associated with deprotonation, are fundamental properties that provide insights into the interrelationships between molecular structure, stability, and reactivity.[6] The equilibrium method,[7] threshold energy collision-induced dissociation,[8] ion exchange bracketing,[9] and the kinetic method[10] are all utilized to measure thermodynamic data. The kinetic method has the advantage of providing access to nonvolatile and thermally unstable compounds and applicability to various types of tandem mass spectrometers, although it is an approximate method, which should be used with care.[10i] Based on the rates of competitive dissociation of mass-selected cluster ions, the kinetic method has been successfully applied to a wide range of chemical systems for the determination of thermochemical properties, including proton affinity (and gas-phase basicity),[10a−c,j] metal−ligand dissociation energies,[10d−f] polyatomic cation affinity,[11] ionization energy,[12] and electron affinity.[13] The kinetic method has recently been used as a structural probe to investigate steric effects and inter- and intramolecular interactions in dimeric ions,[14−16] and as a check of ion structural identity.[10g,h]

For the purpose of the present study, a proton-bound heterodimer of a selected reference compound and urea, i.e., B_{ref}- - -H^+- - -urea, is generated by chemical ionization and dissociated by collision-induced dissociation as follows:



Here k_{ref} and k_{urea} are the rate constants for the competitive fragmentations of the activated cluster ion to yield $B_{ref}H^+$ and ureaH$^+$, respectively. According to transition state theory,[17] the ratio of the corresponding rate constants is given as

$$\ln\frac{k_{ref}}{k_{urea}} = \ln\frac{Q_{ref}^*}{Q_{urea}^*} + \frac{\epsilon^\circ_{urea} - \epsilon^\circ_{ref}}{RT_{eff}} \quad (1)$$

where Q_{ref}* and Q_{urea}* are the partition functions of the activated dimers for the two unimolecular dissociation channels, and ϵ°_{urea} and ϵ°_{ref} are the corresponding critical energies. It is assumed that the non-Boltzmann distribution of internal energies in the activated dimer ions can be represented by an effective temperature, T_{eff}, which is the actual temperature of a Boltzmann distribution of activated dimer ions which fragments to give the same fragment ion abundance ratio as observed for the dimer being dissociated.[18] If the reverse activation energies of the two channels are negligible or equal, $\epsilon^\circ_{urea} - \epsilon^\circ_{ref} = \Delta H^\circ_{H^+}$(ref)

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S1089-5639(98)00449-6 CCC: $15.00
Published on Web 04/02/1998

$-\Delta H°_{H^+}(\text{urea}) = \Delta\text{PA}$, and $\ln(Q_{\text{ref}}^*/Q_{\text{urea}}^*)$ is equal to the difference in entropy change for the two dissociation channels, viz. $-\Delta(\Delta S_{H^+})/R$, then eq 1 becomes

$$\ln\frac{k_{\text{ref}}}{k_{\text{urea}}} = \frac{-\Delta(\Delta S_{H^+})}{R} + \frac{\Delta\text{PA}}{RT_{\text{eff}}} \approx \frac{\Delta\text{GB}}{RT_{\text{eff}}} = \frac{\text{GB(ref)} - \text{BG(urea)}}{RT_{\text{eff}}} \quad (2)$$

Meanwhile, to extract the proton affinity of urea, eq 2 is rewritten as

$$\ln\frac{k_{\text{ref}}}{k_{\text{urea}}} = \frac{\text{PA}_{\text{ref}}}{RT_{\text{eff}}} - \left[\frac{\text{PA}_{\text{urea}}}{RT_{\text{eff}}} - \frac{\Delta S_{H^+}(\text{urea}) - \Delta S_{H^+}(\text{ref})}{R}\right] \quad (3)$$

and the term in the brackets in eq 3 represents an apparent gas-phase basicity of urea, viz., $\text{GB}^{\text{app}}(\text{urea})$, as defined by eq 4.

$$\text{GB}^{\text{app}}(\text{urea}) = \text{PA(urea)} - T_{\text{eff}}\Delta(\Delta S_{H^+}) \quad (4)$$

This treatment is derived from the work of Fenselau and co-workers[14] and Wesdemiotis and Cerda:[15] note that the quantity on the right-hand side of eq 4 could also be considered as an apparent PA since the $\Delta(\Delta S)$ term represents a small correction to the actual PA. Note also that the ratio of the rate constants is taken as equal to the ratio of the abundances of $B_{\text{ref}}H^+$ and $\text{urea}H^+$ in the product ion spectra of the proton-bound dimer. Hence it is evident that the natural logarithm of the ratio of the monomeric products is directly proportional to the difference in gas-phase basicities $\Delta(\Delta G°)$, or proton affinities $\Delta(\Delta H°)$, on the condition that $\Delta(\Delta S_{H^+})$ is zero. The former condition can be satisfied by using chemically similar compounds as references. On the other hand, provided that $\Delta(\Delta S_{H^+})$ is constant, one can measure both $\Delta(\Delta S_{H^+})$ and $\Delta(\Delta H°)$ by recording collision-induced dissociation of the heterodimers at multiple collision energies. This allows T_{eff}, i.e., the internal energy distribution of the cluster ion population, to be varied. A plot of $\ln(k_{\text{ref}}/k_{\text{urea}})$ at each collision energy versus the proton affinities of the reference bases yields a regression line whose slope and intercept provide T_{eff} and $\text{GB}^{\text{app}}(\text{urea})$, respectively (eqs 3 and 4). Then, a plot of $\text{GB}^{\text{app}}(\text{urea})/RT_{\text{eff}}$ versus $1/RT_{\text{eff}}$ provides $\Delta(\Delta S_{H^+})$ (from the intercept) and the unknown proton affinity of urea (from the slope).

Experimental Section

All experiments were performed using a Finnigan TSQ 700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA) with desorption chemical ionization (DCI). The temperatures of the ion source and the manifold were kept at 150 and 70 °C, respectively. All compounds are commercially available (Aldrich Chemical Co., Milwaukee, WI) and were used without further purification. Samples were prepared and introduced by depositing a 1 μL aliquot of a mixture of urea and a reference compound in a methanol solution onto the rhenium wire filament of a direct evaporation probe. The temperature of the direct evaporation probe was raised from ambient to 300 °C in 1.2 min, where it was kept constant for 0.5 min before being raised to 1200 °C in 0.2 min to pyrolyze any remaining material.

The proton-bound heterodimers of interest, generated in the source, were mass selected by using Q1 and dissociated in Q2 at three different collision energies, 2, 6, and 10 eV with argon at a nominal pressure of 0.4 mTorr, which corresponds to single-collision conditions.[19] The abundances of the fragment ions were measured from the product ion MS/MS spectrum by scanning Q3. Mass discrimination effects are minimized by using multiple reference compounds. The mass-to-charge ratios are reported here using the Thomson unit (1 Th = 1 Da/unit charge).[20]

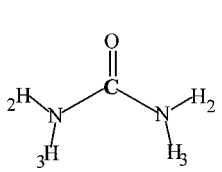
Ab Initio Calculations

Standard ab initio molecular orbital calculations were carried out with the G2(MP2) procedure without any symmetry constraint in the Gaussian 94 set of programs.[21] As the best known of the precise theoretical models, Gaussian-2 (G2) theory[22] is based on MP2 = FU/6-31G* geometries using all electrons, and the final total energies are calculated at the MP4SDTQ/6-311G** level with corrections from higher level calculations. In comparison with G2, the G2(MP2) program, in which the basis-set-extension corrections are obtained at the MP2 level, is less time-demanding and can still provide thermochemical data which have been reported to show an average absolute deviation of 6.6 kJ/mol from experimental values.[23]

Results and Discussion

Intrinsically, urea possesses two basic sites that might accept protons to form either an ammonium ion (proton addition to the nitrogen atom) or an oxonium ion (proton addition to the oxygen atom). On the basis of the G2(MP2) calculations, protonation at the oxygen atom is energetically more favorable than protonation at the nitrogen atom of the amide group. The proton affinities at the oxygen and nitrogen atoms are calculated as 872.4 and 810.9 kJ/mol, respectively. The optimized geometries for urea and both oxygen- and nitrogen-protonated urea are given in Figure 1. Upon protonation at the oxygen atom, the bond length of C═O increases from 1.225 Å (neutral urea) to 1.316 Å (protonated urea), whereas the C−N bond length decreases from 1.390 Å (neutral urea) to 1.326 Å, and ∠NCN increases from 113.0° to 122.9° due to the effect of protonation induced charge redistribution. The ab initio results are consistent with the crystal structures of urea,[24] urea nitrate,[25] and cocrystalline urea−carboxylic acid[26] and also with the spectroscopic observation that on protonation at the oxygen atom the CO stretching vibration is shifted to lower frequency and the NCN symmetric stretching vibration is shifted to higher frequency.[27] Although the structure of urea changes from C_{2v} to C_s symmetry upon protonation in the solid state, recent theoretical studies[28] suggest that the isolated urea molecule in the gas phase has two interconverting conformations with C_2 and C_s symmetries, respectively, and C_2 symmetry urea is slightly more stable than the C_s symmetry form. The structural difference in the gas phase and the solid-state phase environments has been attributed to the presence of extensive hydrogen bonding in the solid state.[28]

To generate stable proton-bound heterodimeric ions, acetophenone, acrylamide, *m*-bromoaniline, 4-fluorobenzamide, dimethylformamide, and benzamide were chosen as reference compounds for determination of the proton affinity of urea. When subjected to low-energy collision-induced dissociation, the heterodimers of the cluster ion, ref- -H^+- -urea, fragmented readily to yield only the two corresponding protonated monomeric components. This result shows (i) that loosely proton-bridged symmetric cluster ions are indeed generated and (ii) that the required rapid conversion between two protonated ion−dipole complexes is satisfied: these are two key prerequisites to the application of the kinetic method.[10] A typical product ion mass spectrum, that for the acrylamide- -H^+- -urea cluster ion, is shown in Figure 2. The proton affinities, gas-phase



bond length (Å)

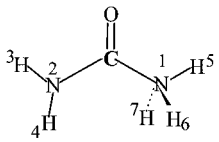
OC	1.225
CN	1.390
NH	1.013

bond angle

OCN	123.5
CNH_2	111.9
CNH_3	116.2
NCN	113.0

G2(MP2) Energy

-224.928126 hartree



bond length (Å)

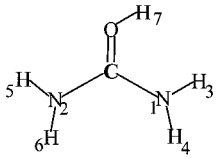
OC	1.198
CN_1	1.580
CN_2	1.333
N_1H_5	1.031
N_2H_3	1.016

bond angle

N_2CN_1	110.6
CN_2H_3	117.2
CN_1H_5	105.4
CN_2H_4	125.2
CN_1H_7	113.0
CN_1H_6	113.0

G2(MP2) Energy

-225.234631 hartree



bond length (Å)

OC	1.316
CN_1	1.326
CN_2	1.319
OH_7	0.977
N_1H_3	1.013
N_1H_4	1.014

bond angle

CN_1H_3	122.1
CN_2H_5	118.8
N_1CN_2	122.9
COH_7	114.3
CN_1H_4	121.5
CN_2H_6	122.9

G2(MP2) Energy

-225.258041 hartree

Figure 1. Optimized geometries of neutral, N-protonated, and O-protonated urea.

TABLE 1: Proton Affinities, Gas-Phase Basicities, and Natural Logarithm of Protonated Monomer Abundance Ratios from Dissociation of Heterodimers[a]

			$\ln(k_{ref}/k_{urea})$		
reference	PA, kJ/mol	GB, kJ/mol	2 eV	6 eV	10 eV
acetophenone	861.6	829.7	-3.90 ± 0.13	-3.61 ± 0.15	-2.86 ± 0.12
acrylamide	870.4	839.4	-0.98 ± 0.06	-1.09 ± 0.15	-0.74 ± 0.03
m-bromoaniline	873.2	841.4	0.42 ± 0.05	0.48 ± 0.04	0.81 ± 0.05
p-fluorobenzamide	877.4	846.0	2.37 ± 0.07	2.02 ± 0.04	1.61 ± 0.04
dimethylformamide	886.2	855.2	3.29 ± 0.08	2.64 ± 0.05	1.94 ± 0.06
benzamide	891.5	860.0	5.38 ± 0.11	4.44 ± 0.08	4.23 ± 0.18

[a] Proton affinities and gas-phase basicities are adopted from ref 29. [b] Absolute errors are estimated over multiple replicates.

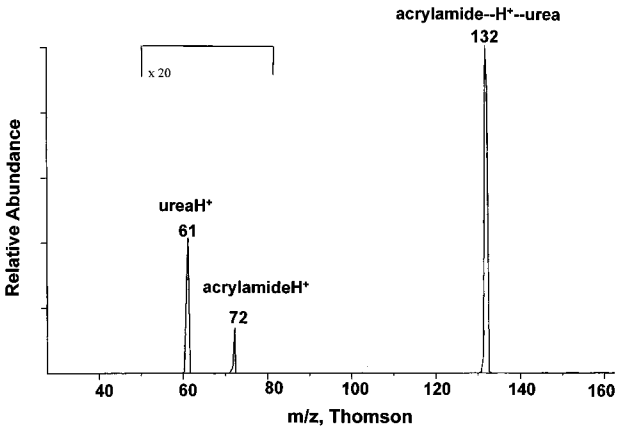


Figure 2. Product ion spectrum of proton-bound dimer acrylamide--H^+- -urea dissociated at 6 eV collision energy.

basicities, and natural logarithms of the intensity ratios of the protonated monomers formed from the corresponding heterodimers at 2, 6, and 10 eV (laboratory frame of reference) are listed in Table 1.

According to eq 2, plotting the $\ln(k_{ref}/k_{urea})$ values from the MS/MS experiments versus gas-phase basicities of the reference compounds should provide a linear regression line whose slope and intercept yield the effective temperature and gas-phase basicity of urea (Figure 3). From the three regression lines, generated at three different collision energies, the gas-phase basicities of urea are measured as 841.5 kJ/mol at 2 eV, 842.1 kJ/mol at 6 eV, and 841.3 kJ/mol at 10 eV. The fact that the gas-phase basicity of urea shows little dependence on the collision energy indicates that $\Delta(\Delta S_{H^+})$ is very small or negligible. Therefore, the average value gives the gas-phase basicity of urea as 841.6 ± 5.0 kJ/mol. As a relative method, the kinetic method can be used to distinguish small differences in thermochemical quantities (about ± 1.0 kJ/mol), although the error limits of the absolute values are larger than this, due chiefly to the uncertainty in the proton affinity, gas-phase basicity, or other thermodynamic values of the reference compounds.[10,15] Since the proton affinity and gas-phase basicity values of reference compounds used in the present study were reported with a typical error of 5 kJ/mol, the proton affinity and gas-phase basicity of urea cannot be measured to much better than 5 kJ/mol neglecting the error reduction effect of multiple reference compounds.

The corresponding effective temperatures of the activated cluster ions are also calculated from Figure 3 and found to be 410, 476, and 569 K, respectively. As mentioned in the Introduction, T_{eff} is a measure of the internal energy of the activated cluster ions; it is more precisely defined as the excess internal energy per degree of freedom.[30] The results reflect the expected trend of increased energy deposition with increased collision energy from 2 to 10 eV under single-collision conditions.[18−19]

To deconvolute the entropy contribution to the gas-phase basicity of urea from the enthalpic term, a set of plots of $\ln(k_{ref}/k_{urea})$ was made against the proton affinities of the reference

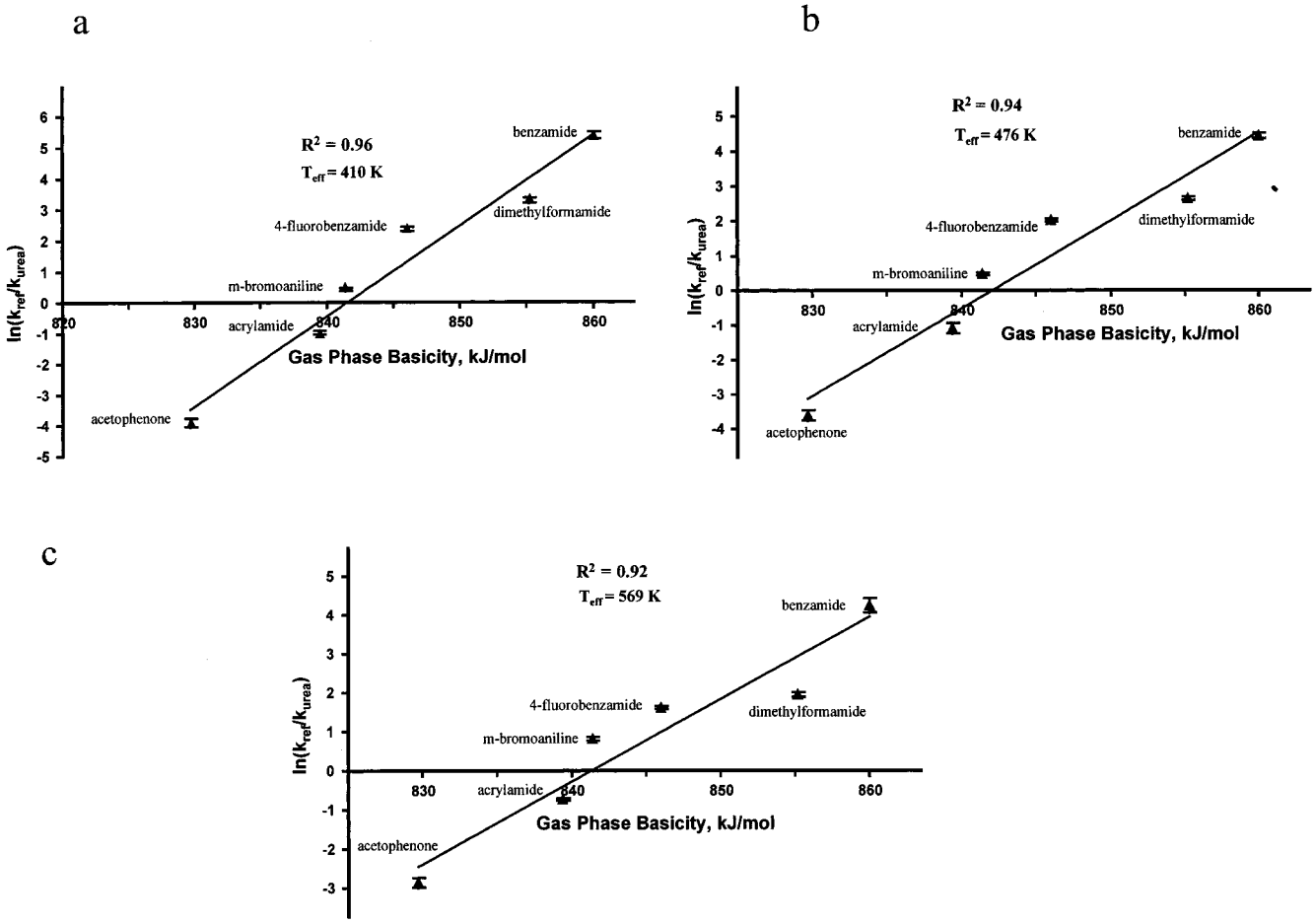


Figure 3. Natural logarithm of the ratios of the protonated monomers $\ln(k_{ref}/k_{urea})$ versus gas-phase basicities of reference bases: (a) 2 eV (T_{eff} = 410 K), (b) 6 eV (T_{eff} = 476 K), and (c) 10 eV (T_{eff} = 569 K).

bases. It is displayed in Figure 4, and according to eq 3, the slope and intercept of this plot provide the effective temperature of the activated dimers and the apparent gas-phase basicity of urea (i.e., $\Delta G^{app}{}_{H+}°$(urea) defined in eq 4). The resulting values are collected in Table 2. Based on these data, a second plot of $\Delta G^{app}{}_{H^+}°(\text{urea})/RT_{eff}$ versus $1/RT_{eff}$ was constructed to extract the proton affinity of urea from the slope and the difference in the relative entropy change upon the cleavage of urea- -H^+ and reference- -H^+ bonds within the cluster ions, viz, $\Delta(\Delta S_{H^+})$, from the intercept. The excellent linear correlation of the latter plot (R^2 = 0.9999), shown in Figure 5, is expected, given the nature of the plot, provided that $\Delta(\Delta S_{H^+})$ is constant. This constancy confirms that the reference bases are chemically similar to each other, and the small value of $\Delta(\Delta S_{H^+})$, 0.80 J/(Kmol), demonstrates that the similarity extends also to urea. The proton affinity of urea is then measured to be 873.5 ± 5.0 kJ/mol. The small and nearly negligible $\Delta(\Delta S_{H^+})$ value (experimental error limit is ±2.0 J/(K mol) suggests that each of the reference compounds and urea are monocoordinated to the proton without intramolecular hydrogen bonding within the hydrogen-bridged dimer ions or the product protonated monomers. Although the kinetic method actually measures the relative activation entropy difference in two competing dissociation channels, viz., $\Delta(\Delta S^*_{H^+})$, if the dissociation of the loosely bonded cluster ion goes through a product-like transition state, $\Delta(\Delta S^*_{H^+})$ is then very similar to the corresponding relative dissociation entropy, viz., $\Delta(\Delta S_{H^+})$. For cluster ions formed by a monodentate ligand with a bidentate ligand, the value of $\Delta(\Delta S)$ was estimated to be larger than 10 J/(K mol) in the studies of Na^+ [15] and H^+ [31] complexation reactions. The entropy loss upon protonation of urea is expected to be slightly larger than that for protonation of the reference bases: the molecular symmetry of urea is changed from C_{2v} to the lower C_s symmetry upon O-protonation (based on solid-state results) and two C−N rotors are frozen. This is so even though the result lies within the experimental error of the measurement. (Note that in the dissociation of dimers formed by chemically similar ligands, rovibrational entropy is the major contributor to $\Delta(\Delta S_{H^+})$ and its magnitude is mainly dependent on the number of restricted internal rotors in a ligand due to protonation.)[15,32] In summary, at 298 K, the entropy change upon protonation of urea ($\Delta S_{H^+}°$(urea)) and the heat of formation of protonated urea are estimated to be 107.0 ± 2.0 J/(K mol) and 421.0 ± 5.0 kJ/mol ($\Delta H_f°$(urea) = −235.51 ± 1.21 kJ/mol, $\Delta H_f°(H^+)$ = 1530.0 kJ/mol). It is possible to cross-check the kinetic method results using GB = PA − $T\Delta S$ and literature values[29] of the protonation entropy, ΔS_{H^+}(ref). The measured PA(urea) = 873.5 ± 5 kJ/mol, $\Delta(\Delta S)$ = 0.80 J/(K mol), and the average ΔS_{ref} = 105.4 J/(K mol) at 298 K yield a calculated gas-phase basicity of urea of 841.9 ± 5 kJ/mol. This result is in excellent agreement with the experimental value of 841.6 ± 5 kJ/mol.

The large increase in proton affinity on going from acetone (PA = 812.0 kJ/mol)[29] to acetamide (PA = 864.0 kJ/mol)[29] is mainly due to resonance stabilization by the amine group attached to the carbonyl group in both neutral and protonated urea. Upon protonation at the amide oxygen atom, enhanced resonance effect increases the partial negative charge on the oxygen atom and partial positive charge on the nitrogen atom and strengthens the tendency of the amide group to participate in bridging with surrounding molecules.[33] When the methyl

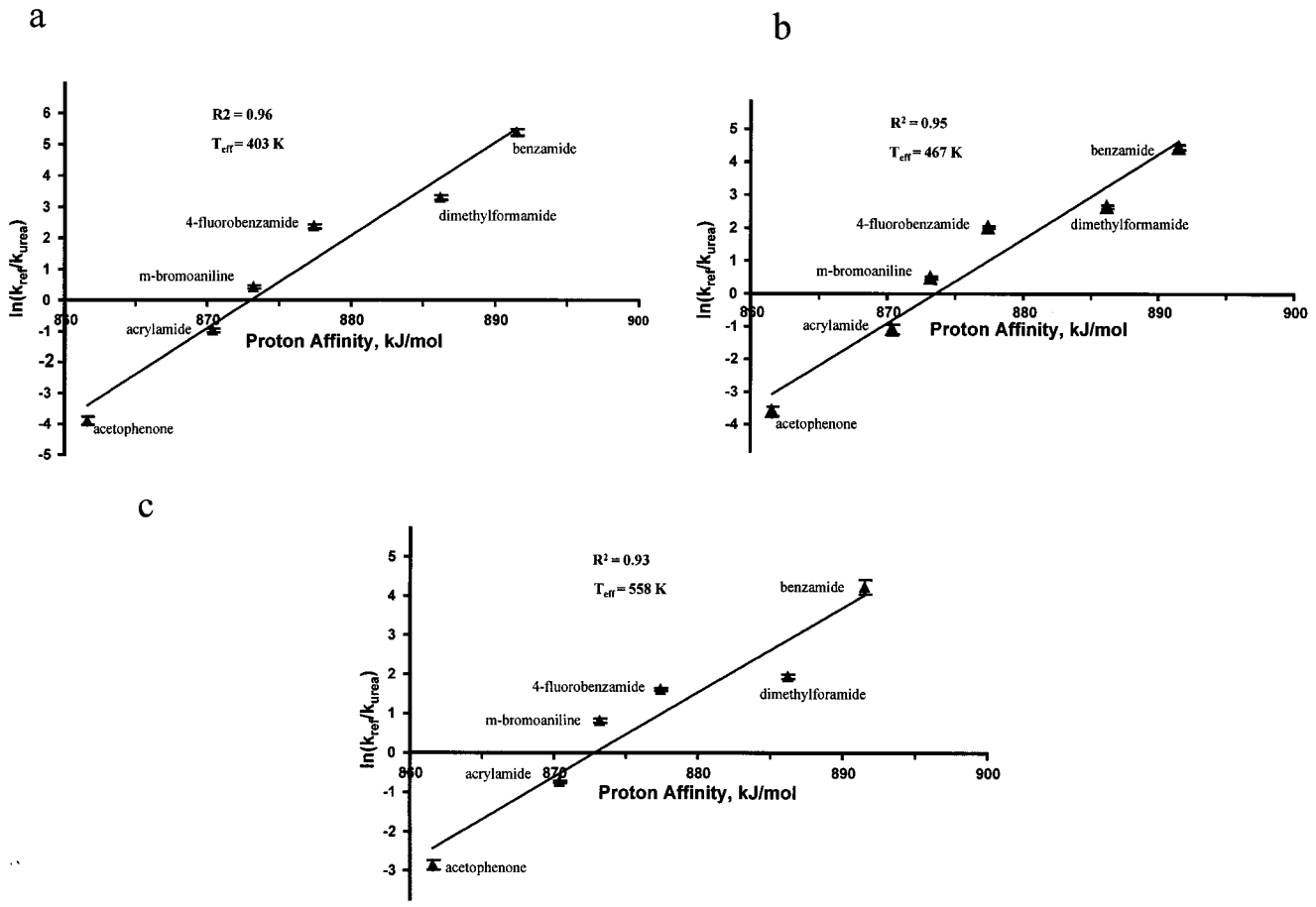


Figure 4. Natural logarithm of the ratios of the protonated monomers $\ln(k_{ref}/k_{urea})$ versus proton affinities of reference bases: (a) 2 eV (T_{eff} = 403 K), (b) 6 eV (T_{eff} = 467 K), and (c) 10 eV (T_{eff} = 558 K).

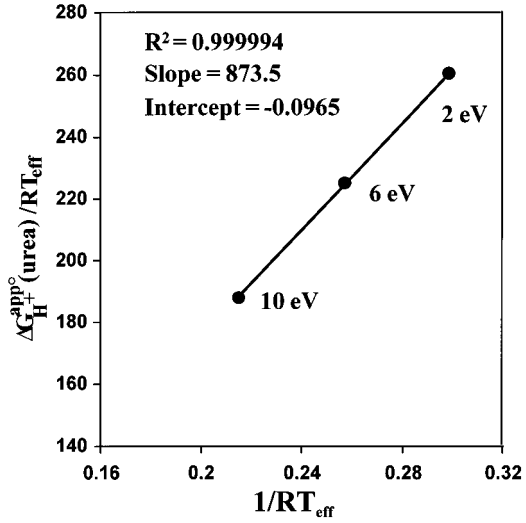


Figure 5. Plot of $\Delta G^{app}{}_{H^+}°(urea)/RT_{eff}$ versus $1/RT_{eff}$ for heterodimers ref- $-H^+$- -urea.

TABLE 2: Effective Temperatures T_{eff} and Apparent Gas-Phase Basicities of Urea Extracted from Figure 4

collision energy	T_{eff}, K	$\Delta H^{app}{}_{H^+}°$(urea), kJ/mol
2 eV	403	873.1
6 eV	467	873.2
10 eV	558	872.7

group of acetamide is replaced by a second amine group, a much smaller increase in proton affinity from 864.0 kJ/mol (acetamide)[29] to 873.5 kJ/mol (urea) results, showing the effect of resonance saturation.[34] This resonance saturation effect indicates that upon O-protonation, the positive charge is mainly localized in $C(O)-NH_2$ and not on the central carbon atom, which is consistent with the results of studying substituent effects on the proton affinity (PA) in the gas phase[34] and basicity (pK_{BH+}) in the solution phase of benzamides.[35] Therefore, the proton affinity of urea is governed by both resonance stabilization and resonance saturation effects, and the acidity of amine groups of urea is enhanced upon O-protonation.

Conclusions

The proton affinity and gas-phase basicity of urea with O-protonation are determined to be 873.5 ± 5.0 and 841.6 ± 5.0 kJ/mol, respectively, by using the kinetic method. The ΔG values measured by the kinetic method were checked by combining the measured ΔH values and $\Delta(\Delta S)$ values with literature values of the entropies of protonation of the reference compounds, and excellent agreement was found. In the gas phase, O-protonated urea is thermodynamically more favorable than the N-protonated isomer, which is consistent with condensed-phase studies, and the corresponding proton affinities of urea are calculated with G2(MP2) methodology to be 872.4 kJ/mol at oxygen and 810.9 kJ/mol at the nitrogen atom, respectively. Although neutral urea has three near-degenerate lowest molecular orbitals ($\sigma(4b_1) \approx \pi(1a_2) \approx \pi(2b_2)$), product ion stability considerations indictate that it is mainly the first, that containing the oxygen lone pair, that is utilized to bind the proton. The constant and nearly negligible entropy difference ($\Delta(\Delta S_{H^+}°) = 0.80$ J/(K mol) associated with the two competitive dissociation channels of the activated proton-bound cluster ions formed by the reference bases with urea provides additional experimental evidence for preferential protonation at the oxygen atom. The

proton affinity of urea is controlled by the combination of resonance stabilization and resonance saturation effects, and these account for not only the geometry change of urea upon protonation but also aspects of its chemical reactivity. Furthermore, these results are consistent with the view that the intrinsic properties of carbonyl and thiocarbonyl compounds are controlled by resonance stabilization and electrostatic interactions induced by the substituents and that the former is the dominant force in carbonyl compounds, especially amides, as pointed out by Frenking,[28a] Wiberg,[36a] and Abboud et al.[36b−d]

Amides, the basic unit of peptides and proteins, are structurally related to urea. Extensive kinetic and dynamical studies of interactions between amides and protons[34,37] or alkali metal ions[38] have recently been carried out in the gas phase in order to develop better strategies for peptide sequencing by mass spectrometry and a better understanding of ion−membrane channel interactions. These results confirm that the O-protonated amide is thermodynamically favored over the N-protonated isomer, as is also the case for urea, although N-protonation may be faster than O-protonation. These results are consistent with the behavior in solution; namely, protonation of amides in acidic solutions occurs at the oxygen atom of the amide group, but the N-protonated isomer is involved in hydrogen bonding and in proton exchange reaction of amides.[35] The binding in some protonated peptides shows contributions from auxiliary binding, in the form of salt bridging.[39] This is not the case in most of the proton-bound dimers studied so far,[40] although recent data for clusters involving the strongly basic amino acid, such as arginine, have provided evidence for salt bridging.[41] On the other hand, since amides show less Coulombic stabilization than urea upon protonation, it is expected that urea derivatives are probably better candidates for studying salt bridging phenomenon. Therefore, the methods utilized here provide a further means to recognize such bonding in model systems, and future experiments will examine guanidine and other model systems in this context.

Acknowledgment. This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences.

Note Added in Proof: We have recently learned of a determination of GB(urea) = 841.0 ± 1.3 kJ/mol by Notario, R.; Castaño, O.; Herreros, M.; Abboud, J. L. M. *J. Mol. Struct.* (*THEOCHEM*) **1996**, *371*, 21.

References and Notes

(1) (a) *Chem. Eng. News* **1987**, *65*, 21. (b) Raab, W. P. *Cosmet. Toiletries* **1990**, *105*, 97. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992. (d) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press Inc.: New York, 1985.

(2) (a) Rawn, J. D. *Biochemistry*; Carolina Biological Supply Company: North Carolina, 1989. (b) Thomas, G. C.; George, S. *Chem. Rev.* **1997**, *97*, 829. (c) Franco, L.; Andrei, M.; Andrea, C. *Science* **1994**, *266*, 801. (d) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380.

(3) (a) Tanford, C. *Adv. Protein Chem.* **1969**, *24*, 1. (b) Privalov, P. L. *Crit. Rev. Biochem. Mol. Biol.* **1990**, *25*, 281. (c) Neri, D.; Billeter, M.; Wider, G.; Wüthrich, K. *Science* **1992**, *227*, 1559. (d) Liepinsh, E.; Otting, G. *J. Am. Chem. Soc.* **1994**, *116*, 9670. (e) Schellman, J. A.; Gassuer, N. C. *Biophys. Chem.* **1996**, *59*, 259. (f) Hakin, A. W.; Groft, L. L.; Marty, J. L.; Rushfeldt, M. L. *Can. J. Chem.* **1997**, *75*, 456.

(4) (a) Mines, G. W.; Thompson, H. W. *Spectrochimica* **1975**, *31A*, 137. (b) Debies, T. P.; Rabalais, J. W. *J. Electron Spectrosc. Relat. Phenom.* **1974**, *3*, 315. (c) Brown, R. D.; Godfrey, P. D.; Storey, J. *J. Mol. Spectrosc.* **1975**, *58*, 445.

(5) Kabo, G. Y.; Miroshnichenko, E. A.; Frenkel, M. L.; Kozyro, A. A.; Simirskii, V. V.; Krasulin, A. P.; Vorob'eva, V. P.; Lebedev, Y. A. *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1990**, 662.

(6) Uggerud, E. *Mass Spectrom. Rev.* **1992**, *11*, 389.

(7) (a) Bowers, M. T. *Gas-Phase Ion Chemistry*, Vols. 1−3; Academic: New York, 1979. (b) Futrell, J. H., Ed. *Gaseous Ion Chemistry and Mass Spectrometry*; Wiley: New York, 1986. (c) Kebarle, P. *Annu. Rev. Phys. Chem.* **1979**, *28*, 445. (d) J. E. Szulejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 7839.

(8) Armentrout, P. B. *Thermochemical Measurements by Guided Ion Beam Mass Spectrometry*. In *Advances in Gas-Phase Ion Chemistry*; Adams, N., Babcock, L. M., Eds.; JAI Press Inc.: Connecticut, 1992; Vol. 1, p 83.

(9) Munson, M. S. B.; Field, H. F. *J. Am. Chem. Soc.* **1966**, *87*, 3294.

(10) (a) McLuckey, S. A.; Cameron, D.; Cooks, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 1313. (b) Cooks, R. G.; Kruger, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 1279. (c) Cooks, R. G.; Patrick, J. S.; Kotiaho, T.; McLuckey, S. A. *Mass Spectrom. Rev.* **1994**, *13*, 287. (d) Eller, K.; Schwartz, H. *Organometallics* **1989**, *8*, 1820. (e) Operti, L.; Vaglio, G. A.; Gord, J. R.; Freiser, B. S. *Organometallics* **1991**, *10*, 104. (f) Chen, L. Z.; Miller, J. M. *J. Organomet. Chem.* **1993**, *448*, 225. (g) Wenthold, P. G.; Hu, J.; Squires, R. R. *J. Am. Chem. Soc.* **1996**, *118*, 11865. (h) Hu, J.; Hill, B. T.; Squires, R. R. *J. Am. Chem. Soc.*, in press. (i) Wong, P.; Cooks, R. G. *Acc. Chem. Res.*, in press. (j) Decouzon, M.; Gal, J.-F.; Herreros, M.; Maria, P.-C.; Murrel, J.; Todd, J. F. J. *Rapid Commun. Mass Spectrom.* **1996**, *10*, 242.

(11) Yang, S. S.; Chen, G.; Ma, S.; Cooks, R. G.; Gozzo, F.; Eberlin, M. N. *J. Mass Spectrom.* **1995**, *30*, 807.

(12) Wong, P.; Ma, S.; Cooks, R. G. *Anal. Chem.* **1996**, *68*, 4254.

(13) Chen, G.; Cooks, R. G. *J. Mass Spectrom.* **1995**, *30*, 1167.

(14) (a) Cheng, X.; Wu, Z.; Fenselau, C. *J. Am. Chem. Soc.* **1993**, *115*, 4844. (b) Wu, Z.; Fenselau, C. *Rapid Commun. Mass Spectrom.* **1994**, *8*, 777.

(15) (a) Cerda, B. A.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11884. (b) Cerda, B. A.; Hoyau, S.; Ohanessian, G.; Wesdemiotis, C., Personal communication.

(16) (a) Yang, S. S.; Wong, P.; Ma, S.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **1996**, *7*, 198. (b) Shen, W.; Wong, P.; Cooks, R. G. *Rapid Commun. Mass Spectrom.* **1997**, *11*, 71. (c) Vékey, K.; Czira, G. *Anal. Chem.* **1997**, *69*, 1700.

(17) Robinson, P. J.; Holbrook, K. A. *Unimolecular Reactions*; Wiley-Interscience: London, 1972.

(18) (a) Vékey, K. *J. Mass Spectrom.* **1996**, *31*, 445. (b) Bojesen, G.; Breindahl, T. *J. Chem. Soc., Perkin Trans.* **1994**, *2*, 1029.

(19) Holmes, J. L. *Org. Mass Spectrom.* **1985**, *20*, 169.

(20) Cooks, R. G.; Rockwood, A. L. *Rapid Commun. Mass Spectrom.* **1991**, *5*, 93.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Reploge, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binky, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision D. 2*; Gaussian, Inc.: Pittsburgh, PA, 1995.

(22) Curtiss, L. A.; Raghavachari, K.; Trucks, G. A.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221.

(23) (a) Curtiss, L. A.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1993**, *98*, 1293. (b) Scott, A. P.; Radom, L. *Int. J. Mass Spectrom. Ion. Processes* **1997**, *160*, 73.

(24) (a) Wyckoff, R. W. G. *Z. Kristallogr.* **1932**, *81*, 102. (b) Wyckoff, R. W. G. *Z. Kristallogr.* **1934**, *89*, 462.

(25) Worsham, J. E., Jr.; Busing, W. R. *Acta Crystallogr.* **1969**, *B25*, 572.

(26) (a) Lynch, D. E.; Smith, G.; Byriel, K. A.; Kennard, C. H. L. *Aust. J. Chem.* **1991**, *44*, 809. (b) Smith, G.; Baldry, K. E.; Byriel, K. A.; Kennard, C. H. L. *Aust. J. Chem.* **1997,** *50*, 727.

(27) (a) Redpath, C. R.; Smith, J. A. S. *Trans. Faraday Soc.* **1962**, *58*, 462. (b) Stewart, J. E. *J. Chem. Phys.* **1957**, *26*, 248. (c) Wen, N.; Brooker, M. *J. Phys. Chem.* **1993**, *97*, 8608. (c) Kolodziejski, W.; Wawer, I.; Wozniak, K.; Klinowski, J. *J. Phys. Chem.* **1993**, *97*, 12147.

(28) (a) Gobbi, A.; Frenking, G. *J. Am. Chem. Soc.* **1993**, *115*, 2362. (b) Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1994**, *59*, 2552. (c) Dixon, D. A.; Matsuzawa, N. *J. Phys. Chem.* **1994**, *98*, 3967.

(29) Hunter, E. P.; Lias, S. G. *J. Phys. Chem. Ref. Data*, to be published.

(30) (a) Lee, H.; Beauchamp, J. L. *Presented at the 209th National Meeting of the American Chemical Society*, Anaheim, CA, April 2−7, 1995. (b) Craig, S. L.; Zhang, M.; Choo, B.; Brauman, J. I. *J. Phys. Chem. A* **1997**, *101*, 19.

(31) (a) Meot-Ner, M. *J. Am. Chem. Soc.* **1983**, *105*, 4906. (b) Sharma, R. B.; Blades, A. T.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, *106*, 510.

(32) (a) Searles, S. K.; Kebarle, P. *Can. J. Chem.* **1969**, *47*, 2619. (b) Woodin, R. L.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 501.

(33) Staveren, C. J.; Arts, V. M. L. J.; Grootenhuis, P. D. J.; Droppers, W. J. H.; Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc*. **1988**, *110*, 8134.

(34) (a) Grützmacher, H. F.; Caltapanides, A. *J. Am. Soc. Mass Spectrom*. **1994**, *5*, 826. (b) Witt, M.; Grützmacher, H. F. *Int. J. Mass Spectrom. Ion Processes* **1997**, *164*, 93.

(35) (a) Perrin, C. L. *Acc. Chem. Res*. **1989**, *22*, 268. (b) De Maria, P.; Barbieri, C. L.; Spinelli, D.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1991**, 373.

(36) (a) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc*. **1992**, *114*, 8644. (b) Abboud, J.-L. M.; Mó, O.; Paz, J. L. G. de; Yãñez, M.; Esseffar, M.; Bouab, W.; EI−Mouhtadi, M.; Mokhlisse, R.; Ballesteros, E.; Herreros, M.; Homan, H.; Lopez-Mardomingo, C.; Notario, R. *J. Am. Chem. Soc*. **1993**, *115*, 12468. (c) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Phys. Org. Chem*. **1994**, *7*, 511. (d) Homan, H.; Herreros, M.; Notario, R.; Abboud, J.-L. M.; Esseffar, M.; Mo, O.; **Y**ãñez, M.; Foces-Foces, C.; Ramos-Gallardo, A.; Martinez-Ripoll, M.; Vegas, A.; Molina, M. T.; Casanovas, J.; Jiménez, P.; Roux, M. V.; Turrión, C. *J. Org. Chem*. **1997**, *62*, 8503.

(37) (a) Lin, H.; Ridge, D. P.; Uggerud, E.; Vulpius, T. *J. Am. Chem. Soc*. **1994**, *116*, 2996. (b) Klassen, J. S.; Kebarle, P. *J. Am. Chem. Soc*. **1997**, *119*, 6552. (c) Scheiner, S.; Wang, L. *J. Am. Chem. Soc*. **1993**, *115*, 1958.

(38) Klassen, J. S.; Anderson, S. G.; Blades, A. T.; Kebarle, P. *J. Phys. Chem*. **1996**, *100*, 14218.

(39) (a) Campbell, S.; Rogers, M. T.; Marzluff, E. M.; Beauchamp, J. L. *J. Am. Chem. Soc*. **1995**, *117*, 12840. (b) Schnier, P. D.; Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc*. **1996**, *118*, 7178.

(40) Schnier, P. D.; Price, W. D.; Strittmatter, E. F.; Williams, E. R. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 771.

(41) Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc.* **1997**, *119*, 11988.