DOI: 10.1002/ejoc.200500516

Substituent Effects on the Gas-Phase Basicity of Formamidine Ureas

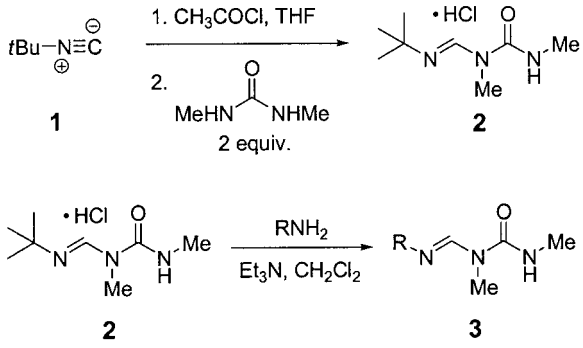
David D. Díaz,[a] M. G. Finn,*[a] and Masaaki Mishima*[b]

Keywords: Basicity / Formamidine / Urea / Protonation

The gas-phase basicities (GBs) for a representative set of six formamidine ureas with variations in the imino substituent [RN=CH–N(Me)C(O)NMe$_2$] were determined in proton-transfer equilibria by ion cyclotron resonance (ICR) mass spectrometry and further explored with calculations at the B3LYP/6-31+G* level. The GB values, ranging from 218.6 to 230.9 kcal mol^{-1}, were also compared with those previously reported for N^1,N^1-dimethyl-N^2-substituted formamidines. For all compounds investigated, protonation occurs preferentially at the imino nitrogen. In the cases of R = n-C_7H_{15}, Ph(CH$_2$)$_3$ and Ph, no stable *O*-protonated structures exist which can transfer proton to the N atom without a significant barrier. Relative GBs were linearly correlated to the inductive effect of the imine nitrogen substituents. The calculated structures are also given, and the calculated basicities are in good agreement with the observed values.

Introduction

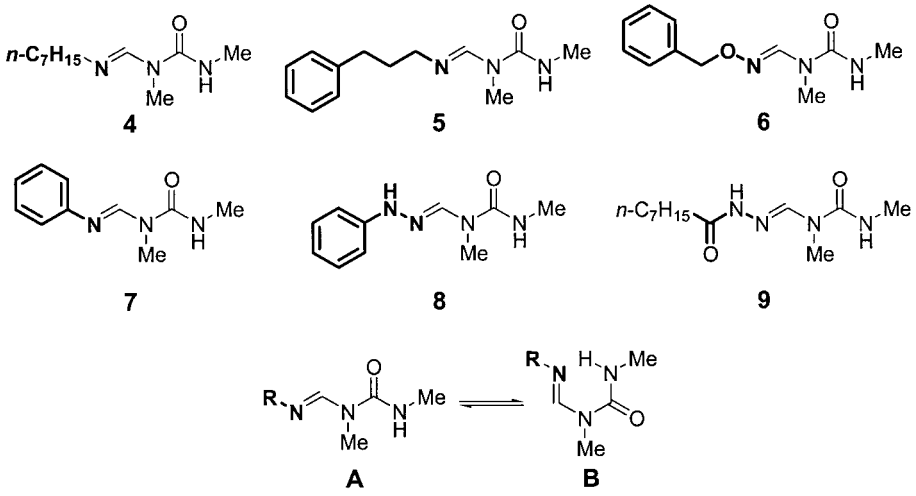
Formamidines are of interest as components of biologically active molecules[1] and as synthetic reagents and components of functional materials.[2] For the former application, formamidines (and the larger family of amidines) have advantageous qualities of structure, hydrogen-bonding ability, and a range of basicities that is thought to mimic that of amines.[3] We have recently reported a novel condensation between isonitriles and ureas in the presence of acid chlorides to give formamidine urea salts as precipitates in pure form (Scheme 1).[4] 1-(*tert*-Butylimino-methyl)-1,3-dimethylurea hydrochloride (**2**) derived from *tert*-butylisocyanide (**1**) was found to be an effective starting material for the fast preparation of formamidine ureas (**3**) of tunable reactivity by exchange of its amine/imine fragment with external primary nitrogen nucleophiles in non-protic solvents.[5] A varied manifold of reactivity has been uncovered for the formamidine urea moiety, including electrophilicity at the carbonyl carbon for sulfur nucleophiles to give thiolcarbamates,[6] electrophilicity at the formamidine carbon for nitrogen nucleophiles giving different products depending of the nature of the solvent,[5,7] widely variable hydrolytic stability controlled by the electronic nature of the imine substituent,[5] and alkylation/acylation at urea nitrogen through its conjugate base.[6] Since formamidines and ureas are each components of many biologically active molecules, their combination provides structures of potential pharmaceutical interest.



Scheme 1. General synthesis of formamidine ureas.

Raczynska and co-workers have pioneered the exploration of gas-phase basicity of amidines and N^1,N^1-dimethyl-N^2-alkyl/aryl formamidines as a function of substituent.[8] In the present work, we determined by ion cyclotron resonance (ICR) the gas-phase basicities of six formamidine ureas that differ in the imine substituent over a range of electron donating power (Scheme 2). The structures and experimental and theoretical basicities of these species will help to guide our use of the formamidine urea motif in applications to drug discovery and molecular recognition. It must be emphasized that, since the reactivity of formamidine ureas can be substantially altered by hydrogen-bonding contacts with protic solvents,[7] the gas-phase basicities discussed here represent only a starting point in understanding their chemistry.

[a] Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute,
10550 N. Torrey Pines Rd., La Jolla, CA 92037, USA
Fax: +1-858-784-8850
E-mail: mgfinn@scripps.edu
[b] Institute for Material Chemistry and Engineering, Kyushu University,
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812–8581, Japan
Fax: +81-92-642-2715
E-mail: mishima@ms.ifoc.kyushu-u.ac.jp



Scheme 2. Formamidine ureas investigated, and dominant conformations **A** and **B**.

Results and Discussion

A simple formamidine urea such as **4** exhibits two major ground-state conformations, one of which allows for intramolecular hydrogen bonding, and contains four heteroatoms which are potential sites of protonation (Scheme 2). All of the possible conjugate acids and conformations were therefore considered in order to properly evaluate the effects of the substituents on gas-phase basicity. DFT calculations at the B3LYP/6-31+G* level of theory were performed by standard methods, revealing the imine nitrogen to be the most basic site in each molecule (Table 1). The predicted structure of each N_{imine}-protonated conjugate acid is shown in Figure 1, along with two alternatives for C=O protonation (the next most favorable site). In each case, the formamidine urea core [N=C–*N*–C(O)–N] is planar and allows a hydrogen bond to bridge the imine nitrogen and the carbonyl oxygen atoms, indicated by dotted lines in Figure 1; the magnitude of the entropic penalty required for this type of conformational restriction was not investigated, but is expected to be small. For **8** and **9**, the predicted conformations of the *N*- and *O*-protonated structures are quite different with respect to the dihedral angle about the N–N bond at the imine center. In the *N*-protonated cations, the adjacent N center is rotated to take the two adjacent N–H bonds out of coplanarity, consistent with the observed dependence on inductive, rather than resonance, factors discussed below. In the higher-energy *O*-protonated forms, however, the formamidine unit and its adjacent nitrogen center are coplanar.

Table 1. Calculated proton affinities (PA) and gas phase basicities of R–N=CHN(Me)CONHMe at B3LYP/6-31+G* (298.15 K).

	Protonation Site[a]	PA[b] (kcal mol^{-1})	GB[c] (kcal mol^{-1})	$GB_{obsd.}$ (kcal mol^{-1})
4	N	235.7	228.0	230.0
5	N	236.0	227.7	230.9
6	N	225.4	216.7	218.6
6	O	219.9	210.9	
7	N	231.3	223.7	226.3
8	N	230.0	222.5	221.8
8	O	221.7	214.8	
9	N	227.7	219.8	221.0
9	O	219.2	211.0	

[a] N, protonation at the imino nitrogen; O, protonation at the amide oxygen. [b] The standard deviation from experimental values at this level of theory is estimated to be 3.2 kcal mol^{-1}. [c] Gibbs free energy associated with the loss of proton from the conjugate acid in the gas phase. The thermodynamic quantities of the proton from the Gaussian calculation are 1.481 kcal mol^{-1}, –6.275 kcal mol^{-1} and 26.014 cal·mol^{-1} K^{-1} for *H*, *G* and *S*, respectively.

The results of the experimental determination of gas-phase basicity (GB) of **4**–**9** are listed in Table 1 and are represented graphically against relevant amines in Figure 2. Except for **8**, the observed GB values are consistently 2–3 kcal mol^{-1} greater than the calculated values, representing good agreement at this level of theory for protonation at the imino nitrogen.[9] For **6**, **8**, and **9**, stable *O*-protonated structures were obtained while **4**, **5**, and **7** had no corresponding structures. The calculated GB values for *O*-protonation are nearly constant at 213 ± 2 kcal mol^{-1}, indicating that the R group has no effect on the GB (as would be expected given the separation between the R group and the protonation site) and suggesting that *O*-protonation of **4**, **5**, and **7** is in the same range. The difference in GB value between *O*- and *N*-protonation may therefore be estimated at 11–13 kcal mol^{-1} for **4**, **5**, and **7**, and 6–9 kcal mol^{-1} for **6**, **8**, and **9**. Accordingly, it seems that when the difference in energy between *O*- and *N*-protonation is greater than 11 kcal mol^{-1}, there is no barrier to intramolecular proton transfer from the carbonyl oxygen atom to the imino nitrogen atom.

Although Hammett-type substituent constants are not available for most of the present compounds, we may estimate them from the values in literature for substituents of

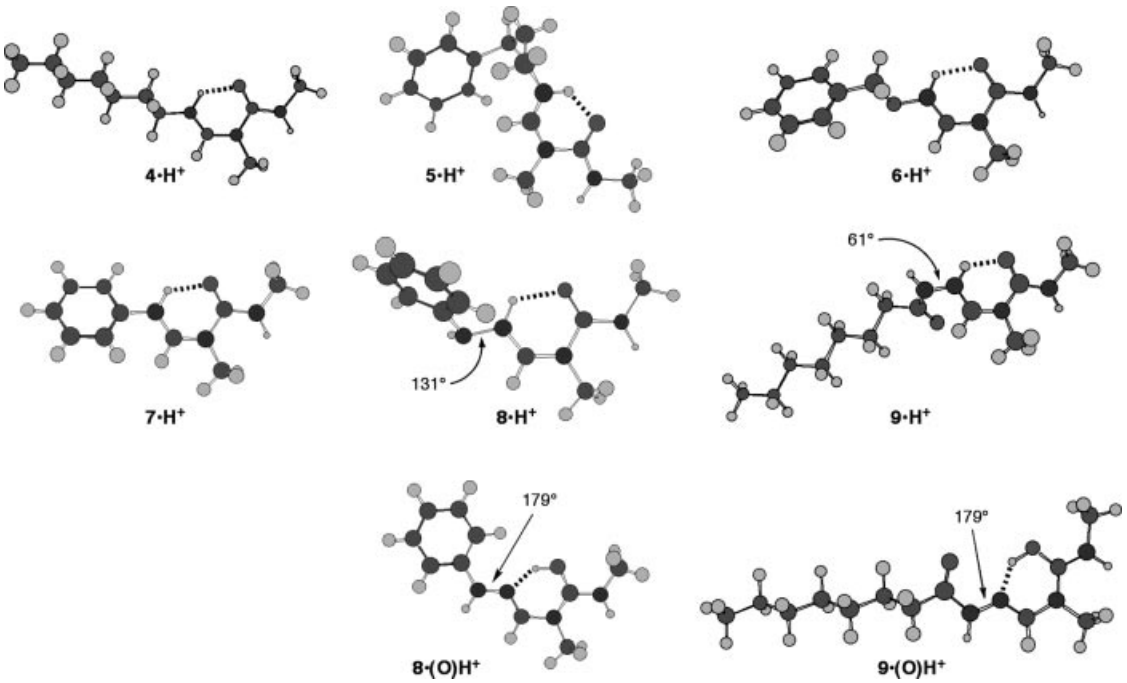


Figure 1. Calculated lowest-energy conformations of conjugate acids of **4**–**9**. The C–N–N–C dihedral angle is labeled for each protonated form of **8** and **9**.

similar structure.[10] In Figure 3 gas-phase basicities are plotted against estimated σ_I values, giving a good linear correlation with $\rho_I = -33$. A ρ_I value of similar magnitude was obtained for the gas-phase basicities of RCH_2NH_2.[11] The similarity in ρ_I value for these two systems suggests that substantial positive charge is found β to the R group (in other words, at the central formamidine carbon) in the conjugate acid of formamidine ureas. Such a charge distribution is achieved when the imino nitrogen, rather than the urea moiety, is the site of protonation.

The same substituents that make the formamidine urea less basic by virtue of inductive electron-withdrawing power also make the formamidine urea skeleton more stable in aqueous solvents.[5–7] This suggests that imine protonation is crucial to hydrolysis and/or that resonance effects (principally the resonance donating abilities of heteroatom substituents on **6**, **8**, and **9**) are more important for hydrolysis than for protonation. We believe the latter is usually the case because studies at variable pH have shown that hydrolysis of formamidine ureas is often faster in more basic solution.[12] In any event, oxime ether, hydrazine, and hydrazide derivatives (such as **6**, **8**, and **9**, respectively) are among the most stable members of the formamidine urea class toward decomposition in water, while being the least basic.

The gas-phase basicities of formamidine ureas **4**–**9** vary over 12 kcal mol^{-1}, spanning the same range covered by alkyl-substituted pyridines to trialkylamines (Figure 2). *N*,*N*-Dimethylformamidines, studied by Raczynska and coworkers, show the same general trend of basicity vs. substituent; a set analogous to **4**–**9** is shown in Figure 2. Thus, oxime ether **15** is the least basic of the series, presumably as a consequence of the σ-electron withdrawing capacity of the methoxy group. *N*-Alkyl-substituted compounds **10**–**12** are the most basic, with Me_2N- and Ph-substituted structures in between. Interestingly, a comparison between similar formamidine urea and formamidine structures (**4** and **5** vs. **11** and **12**; **7** vs. **14**; **6** vs. **15**) shows them to have very similar basicities. Since the conjugate acids of formamidine ureas are stabilized by internal hydrogen bonding with the urea carbonyl group (Figure 1), such stabilization must be compensated by the electron-withdrawing power of the CONHMe group compared to the amidine methyl moiety. We suspect that the urea motif also engages in important intermolecular hydrogen bonding interactions in other situations.[14] The relatively large difference between **8** and **13**, both derived from hydrazines, may be due to the fact that **8** bears an *N*-phenyl substituent whereas **13** is an *N*,*N*-dialkylated structure; the relative electron-deficiency of phenyl is apparent in comparisons of **7** to **4** and **5**, or **14** to **11** and **12**.

Conclusions

Formamidine ureas have been found to be amidine-like in terms of their overall base strength and response to σ-electronic (inductive) effects at the imine nitrogen. Calculations lead us to expect that the most favored conformation of the protonated formamidine urea unit may be stabilized by an internal hydrogen bond. The interplay between inductive electronic effects, resonance electronic effects, sterics, and H-bonding on the behavior of formamidine ureas as molecular recognition motifs, nucleophiles, and electrophiles makes for a rich chemistry of molecules containing this interesting functional group.

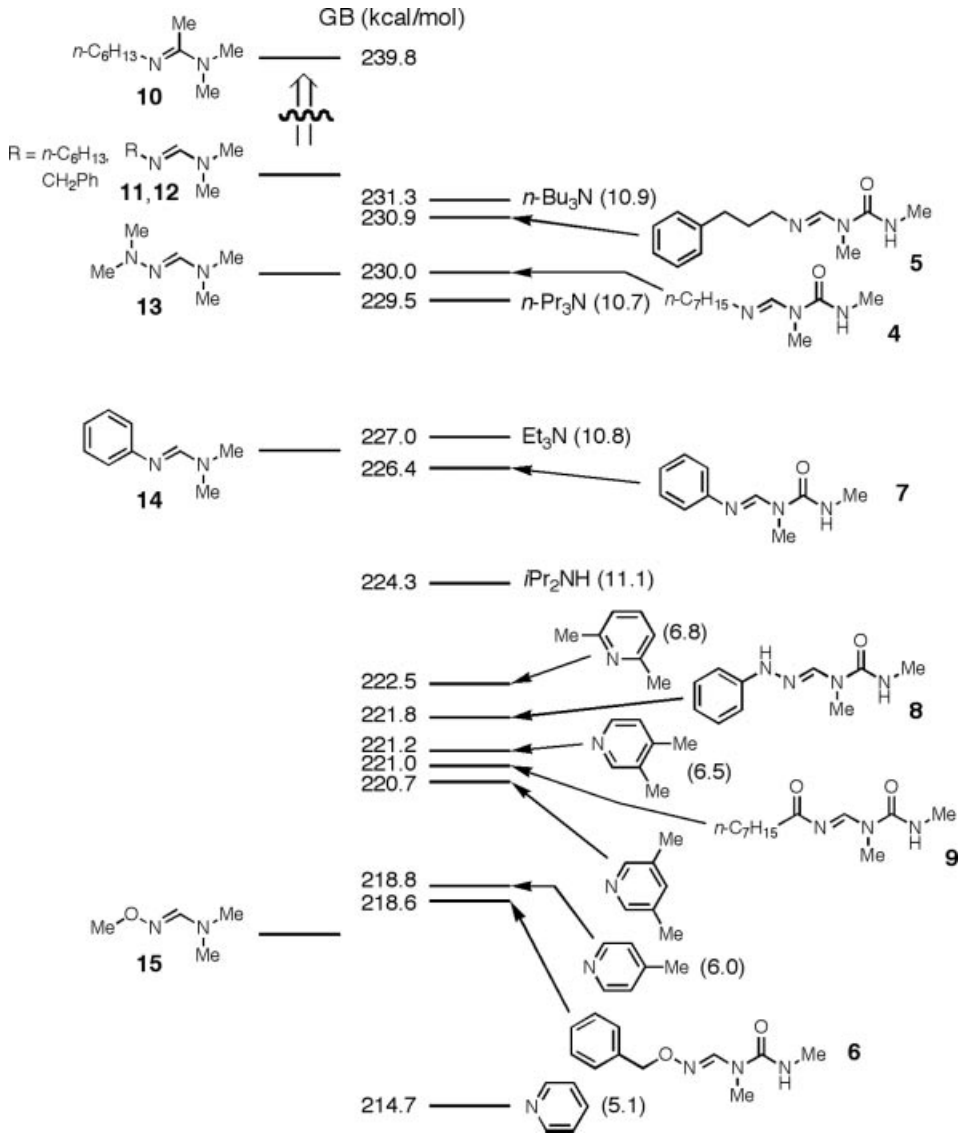


Figure 2. Observed GB values for **4**–**9** and published values for relevant standards. Values in parentheses are pK_a's of the conjugate acids in water.[13] Values of GB for *N*,*N*-dimethylamidines **10**–**15** are averages of those reported in the following papers: **10**,[8e] **11**,[8b,8e] **12**,[8c,8e] **13**,[8a,8d,8e] **14**,[8a,8e] **15**.[8a,8d]

Experimental Section

Synthesis: Reagents for synthesis were commercial compounds (Aldrich, Acros or Fluka). All formamidine ureas used in this study were freshly synthetized and purified as reported in our previous studies from 1-(*tert*-butyliminomethyl)-1,3-dimethylurea hydrochloride (**2**) according to Scheme 1.[4,7] A typical procedure is described below. Compounds **6**, **7**, and **9** have been described previously.[5]

Compound 5: Et_3N (74 μL, 0.52 mmol) was added to a solution of 1-*tert*-butyliminomethyl-1,3-dimethylurea hydrochloride[4a] (100 mg, 0.48 mmol) in dry CH_2Cl_2 (5 mL) at room temperature under nitrogen. The reaction mixture was stirred for 10 min, after which time 3-phenyl-1-propylamine (72 mg, 0.53 mmol) was added in one portion. The initial suspension turned in a clear solution within 1 min and after 30 min the appearance of a precipitate was visible. The mixture was stirred at room temperature overnight and the precipitated formed was removed by filtration through Whatman® filter paper and the liquid concentrated under vacuum. The residue was purified by flash chromatography over silica gel (eluent, EtOAc; R_f 0.45) to afford **5** (84 mg, 75% yield) as colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.81–1.91 (m, 2 H), 2.65 (t, J = 7.6 Hz, 2 H), 2.87 (s, 3 H), 3.15 (s, 3 H), 3.33 (t, J = 6.2 Hz, 2 H), 7.18 (d, J = 7.0 Hz, 3 H), 7.28 (d, J = 7.0 Hz, 2 H), 7.68 (s, 1 H), 9.37 (br. s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 27.0, 33.4, 33.8, 34.5, 56.2, 126.3, 128.7, 128.8, 142.2, 152.5, 157.1. IR (thin film): $\tilde{\nu}$ = 3332, 2942, 1668, 1582, 1316, 1074, 994, 740 cm^{-1}. MS: *m*/*z* (%) = 256 (2) [M + Na]$^+$, 235 (15) [M + 2]$^+$, 234 (100) [M + 1]$^+$. HRMS calcd. for $C_{13}H_{20}N_3O$ 234.1601, found 234.1600.

Compound 4: Colorless oil (hygroscopic). R_f = 0.4 (80% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.4 Hz, 3 H), 1.21–1.31 (m, 10 H), 1.51–1.57 (m, 2 H), 2.77 (s, 3 H), 3.15 (s, 3 H), 3.30 (t, J = 7.0 Hz, 2 H), 4.48 (br. s, 1 H), 8.66 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 15.6, 24.4, 28.4, 28.8, 29.0, 30.8, 32.1, 33.5, 58.5, 153.5, 158.7. IR (thin film): $\tilde{\nu}$ = 3333, 2926, 1650, 1545, 1312, 1070, 672 cm^{-1}. MS: *m*/*z* (%) = 236 (4) [M + Na]$^+$, 215 (12) [M + 2]$^+$, 214 (100) [M + 1]$^+$ (100). HRMS calcd. for $C_{11}H_{24}N_3O$ 214.1914, found 214.1914.

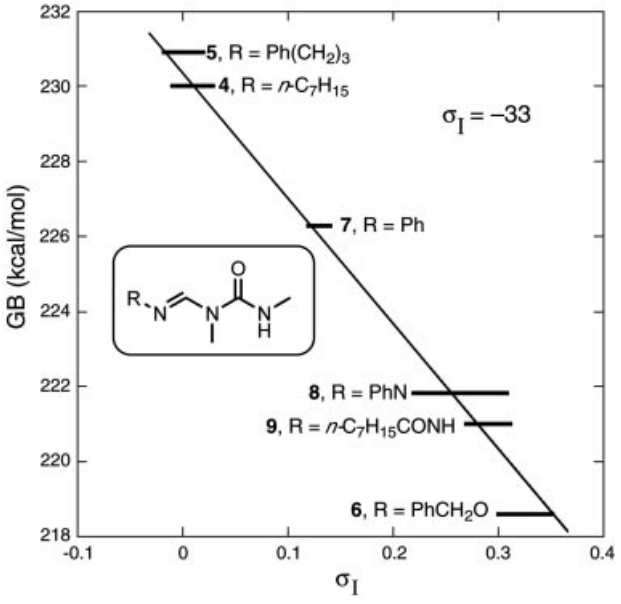


Figure 3. Plot of GB vs. substituent parameter σ_I.

Compound 8: Yellow solid (hygroscopic). R_f = 0.6 (EtOAc); m.p. 165 ± 1 °C. ^{1}H NMR (CD_3OD): δ = 2.71 (s, 3 H), 3.10 (s, 3 H), 6.57 (t, J = 7.3 Hz, 1 H), 6.78–6.80 (m, 2 H), 7.03 (t, J = 7.7 Hz, 2 H), 8.33 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 27.6, 30.3, 113.1, 119.2, 129.8, 138.7, 148.7, 158.6. IR (thin film): $\tilde{\nu}$ = 3278, 2958, 2888, 1652, 1592, 1519, 1274, 1060, 742 cm^{-1}. MS: *m*/*z* (%) = 229 (6) [M + Na]$^+$, 208 (7) [M + 2]$^+$, 207 (100) [M + 1]$^+$. $C_{10}H_{14}N_4O{\cdot}0.5H_2O$: calcd. C 55.80, H 7.02, N 26.03; found C 56.18, H 7.34, N, 25.74.

Gas-Phase Basicity Determination: Equilibrium-constant measurements were performed with an Extrel FTMS 2001 spectrometer at a constant magnetic field strength of 3.0 T equipped with an IonSpec Data Station. Details of the experimental techniques used for measuring the equilibrium constants (K) were similar to those used for the previously described proton-transfer measurements.[15] Only significant changes and/or additional procedures are given here.

Most of the compounds investigated in this study are solids with low volatility. Accordingly, the solid sample direct-inlet systems and all vacuum-chamber systems were kept at 80–100 °C. The ionization gauge was directly set at the main vacuo chamber to read the precise pressure in the ICR cell, and was shielded from the strong magnetic field by use of magnetic shield foil (Fe-Ni alloy).[16] The background pressure was kept below 10^{-7} Pa. The proton-transfer equilibrium ($B + B_0H^+ = BH^+ + B_0$) was achieved within 1 to 10 s of initiation of the reaction depending on the pressure of neutrals, and the equilibrium constant K for the reaction was evaluated from the expression $K = [BH^+][B_oH^+]/[B_o][B]$. The relative abundances of ions BH^+ and B_oH^+ were determined by the relative intensities of ICR mass spectra signals when the equilibrium was attained. The pressures of the neutral reactants were measured by means of a Bayard-Alpert type ionization gauge with appropriate correction factors being applied to correct the gauge readings for the different ionization cross sections of various compounds.[17] The overall pressures of the reagents were maintained at 0.5 to 1×10^{-4} Pa by controlled rates through leak valves (Anelva) from a parallel inlet manifold into the reaction cell in the vacuum chamber. Each experiment was performed at several ratios of partial pressures and at different overall pressures. The average uncertainty was ±0.2 kcal mol^{-1} in most cases. More than two reference compounds were used to ensure the internal consistency of the data. The occurrence of the proton transfer reaction was examined by an ion-eject experiment.

The experimental ΔG^o values given in Table 1 have been extracted from the following direct equilibrium measurements (+ means the first compound is the stronger base): **4** vs. nPr$_3$N (+0.5 kcal mol^{-1}), **4** vs. nBu$_3$N (–1.4 kcal mol^{-1}), **5** vs. nPr$_3$N (+1.4 kcal mol^{-1}), **5** vs. Et$_3$N (+4.2 kcal mol–1), **5** vs. nBu$_3$N (–0.4 kcal mol^{-1}), **6** vs. pyridine (+3.8 kcal mol^{-1}), **6** vs. 4-methylpyridine (–0.2 kcal mol^{-1}), **7** vs. iPr$_2$NH (+2.0 kcal mol–1), **7** vs. Et$_3$N (–0.6 kcal mol^{-1}), **8** vs. 3,4-dimethylpyridine (+0.4 kcal mol^{-1}), and **8** vs. 2,6-dimethylpyridine (–0.6 kcal mol^{-1}), **9** vs. 3,5-dimethylpyridine (+0.4 kcal mol^{-1}), and **9** vs. 3,4-dimethylpyridine (–0.2 kcal mol^{-1}). The GB values of reference bases used in this study are as follows: nBu$_3$N, 231.3; nPr$_3$N, 229.5; Et$_3$N, 227.0; iPr$_2$NH, 224.3; 2,6-dimethylpyridine, 222.5; 3,4-dimethylpyridine, 221.2; dimethylpyridine, 220.7; 4-methylpyridine, 218.8; pyridine, 214.7.[18]

Calculations

Conformational searches were carried out using the Spartan '04 program (Wavefunction Inc.) and several conformers which have the lowest-energy were further optimized at RHF/3-21G* level of theory to search the lowest energy conformer (global minimum). Finally, the geometries were fully optimized at the B3LYP/6-31+G* level of theory with normal convergence using the Gaussian 98 program.[19] Vibrational normal mode analyses were performed at the same level to ensure that each optimized structure was a true minimum on the potential energy surface and to calculate the thermal correction needed to obtain the Gibbs free energies. The zero point energies used for the thermal correction were unscaled.

Acknowledgments

M. M. thanks the Ministry of Education, Culture, Sport, Science and Technology, Japan; D. D. and M. G. F. thank The Skaggs Institute for Chemical Biology and the Spanish MECD (Ministerio de Educación, Cultura y Deportes de España; Secretaría de Estado de Educación y Universidades) for a postdoctoral fellowship cofinanced by Fondo Social Europeo. We are grateful to Prof. Ewa Raczynska for helpful discussions.

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[9] Compound **8** also shows an anomalous equivalence in calculated energy between conformations **A** and **B** in Scheme 2. For the five other formamidine ureas studied, the free energy of conformation **B** was calculated to be more stable than **A** by 2.3–3.7 kcal mol^{-1}, presumably because of the intramolecular H-bond allowed in **B**.

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Received: July 11, 2005
Published Online: November 10, 2005

