

Theoretical Studies of Solvent Effect on the Basicity of Substituted Pyridines

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Molecular orbital calculations have been carried out of the basicities of substituted pyridines in the gas phase at the HF/6-31G*, MP2/6-31G*, and B3LYP/6-31G* levels and in solution based on the isodensity surface-polarized continuum model (IPCM). The correlated gas-phase MO basicities, especially at the MP2 level, agree well with the experimental gas-phase results. The IPCM model with MP2/6-31G* and B3LYP/6-31G* geometries also reproduces well the solvation free energy difference, ΔG_s° , between the pyridinium ion and neutral pyridine in water, although it leads to a somewhat greater negative slope for the $pK_a(\text{aq})$ vs σ plot ($\rho_{\text{aq}} = -8.6$ and -9.0 at the MP2/6-31G* and B3LYP/6-31G* levels, respectively, in contrast to the experimental slope of $\rho_{\text{aq}} = -5.8$). The model predicts a linear correlation between the theoretical (IPCM) ρ values in solution and the Onsager dielectric function $(\epsilon - 1)/(2\epsilon + 1)$. The estimate of ion solvation free energy for H^+ in acetonitrile ($G_s^\circ = -250.4 \text{ kcal mol}^{-1}$) indicates that there is a constant pK_a difference of $\Delta pK_a (= pK_a(\text{AN}) - pK_a(\text{W})) = 7.7$. This is due solely to the H^+ ion solvation free energy difference of $10.5 \text{ kcal mol}^{-1}$ between acetonitrile and water with near unity (1.02) slope for the $\delta pK_a(\text{AN})$ vs $\delta pK_a(\text{W})$ plot. The π donor effect of strong para π acceptors (*p*-CN, *p*-NO₂, etc.) on the pK_a values of pyridinium ions was found in the gas phase as well as in solution.

Introduction

The acid dissociation equilibria of a wide range of substituted pyridinium ions have been measured in the gas phase (ΔG_g°) by Taagepera et al.¹ and in aqueous solution (pK_a) by Fischer et al.² The STO-3G level calculations of the effects of substituents on pyridinium ion acidities ($-\Delta E_g^\circ$) were also reported by Taagepera et al.¹ These studies have shown that strong acceptor substituents, e.g., *p*-CN, *p*-NO₂, etc., exhibit large positive deviations from the otherwise linear pK_a vs σ plots. For these substituents the measured pK_a values are greater than those expected from the σ values, indicating that the electron-withdrawing power of these substituents has deteriorated. The exalted basicities of pyridines with these π acceptor substituents are also reflected in their enhanced nucleophilic reactivities, leading to large positive deviations in the Hammett plots of the reactivities of bimolecular nucleophilic substitution ($\text{S}_{\text{N}}2$) reactions.³ In contrast to these deviations of the π acceptors in the Hammett plots, however, perfectly normal Brønsted plots are observed without any anomalous behavior.³ This difference in the application of linear free energy relationships involving σ and pK_a of the π acceptors in the pyridinium ions originates from resonance electron donation from the π acceptor substituents to the positively charged functional center azonium ion ($>\text{N}^+=$) in the pK_a measurement, which is absent in the determination of σ constants. This π donor effect of strong acceptors is absent in the acid dissociations of anilinium ions or phenols, etc., and is observed only in the acidities of pyridinium ions.^{1b}

In this work we examine theoretically the effect of substituents on the basicities of pyridines in the gas phase at the HF/6-31G*, MP2/6-31G*, and B3LYP/6-31G*⁵ levels and in solutions using the isodensity surface-polarized continuum model (IPCM).⁶ We aim to clarify the origin of the π donor effect of π acceptor substituents and examine the influence of solvent medium on the basicities and transmission efficiency of substituent effect by calculating ρ values of the ΔpK_a versus σ plots (eq 1). The pK_a value is related to the standard free energy change, ΔG° , of pyridinium ion dissociation by eq 2 so that ΔG° is directly proportional to the basicity of pyridine or inversely related to the acidity ($-\Delta G^\circ$) of the pyridinium ion. Thus, in terms of ΔG° , the Hammett plot of the basicity (eq 1) can be expressed as eq 3 at 298 K.

$$\Delta pK_a = \rho \sigma \quad (1)$$

$$pK_a = \frac{\Delta G^\circ}{2.303RT} \quad (2)$$

$$(\Delta pK_a) = \frac{\delta \Delta G^\circ}{1.364} = \rho \sigma \quad (3)$$

Currently various computational schemes for predicting solvation energies are under development. These models, inter alia continuum solvation models,^{6,7} are widely used and are found to be useful in examining solvent effects on intramolecular as well as intermolecular reactions. However, before we can predict solvent effect by application of these models at least semiquantitatively, if not quantitatively, it is necessary to calibrate and test these models against experimental data. Thus, assessment of the performance of the solvation model (IPCM) is one of the more important goals of the present study.

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TABLE 1: Calculated Relative Gas-Phase Basicities ($\delta\Delta G_g^\circ$) of Pyridines (in kcal mol⁻¹ at 25.0 °C)

| X | σ^b | $\delta\Delta G_g^{\text{calc}}$ | | | exptl | STO-3G ^c |
|-----------------------------|------------|----------------------------------|------------|--------------|----------------------|---------------------|
| | | HF/6-31G* | MP2/6-31G* | B3LYP/6-31G* | | |
| <i>p</i> -NH ₂ | -0.66 | 13.34 | 12.17 | 13.92 | | 16.1 |
| <i>p</i> -OCH ₃ | -0.27 | 7.57 | 6.92 | 8.18 | 7.2 | 9.3 |
| <i>p</i> -CH ₃ | -0.17 | 3.73 | 3.74 | 4.44 | 4.3 | 5.0 |
| H | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | | (219.70) | (214.83) | (218.29) | (213.7) ^d | (277.8) |
| <i>p</i> -Cl | 0.23 | -5.53 | -4.52 | -4.09 | -3.3 | |
| <i>m</i> -CONH ₂ | 0.28 | -5.35 | -3.61 | -3.40 | | |
| <i>m</i> -CHO | 0.35 | -8.19 | -7.30 | -7.68 | | -3.6 |
| <i>p</i> -CONH ₂ | 0.36 | -4.18 | -2.02 | -1.81 | | |
| <i>p</i> -CHO | 0.42 | -7.14 | -5.88 | -6.47 | -6.1 | -2.9 |
| <i>m</i> -CN | 0.56 | -14.91 | -13.43 | -13.51 | -12.0 | -12.4 |
| <i>p</i> -CN | 0.66 | -13.91 | -11.84 | -11.83 | -11.2 | -11.4 |
| <i>m</i> -NO ₂ | 0.71 | -17.30 | -14.33 | -14.87 | -13.5 | -17.4 |
| <i>p</i> -NO ₂ | 0.78 | -17.64 | -12.90 | -14.28 | -12.7 | -16.7 |

^a The absolute values (ΔG_g°) for X = H are shown in parentheses. $\Delta G_g^\circ = G_g^\circ(\text{Py}) + G_g^\circ(\text{H}^+) - G_g^\circ(\text{PyH}^+)$ where $G_g^\circ(\text{H}^+) = -6.28$ kcal mol⁻¹ is calculated using a statistical thermodynamic relationship. ^b Taken from the following: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. ^c Relative gas-phase deprotonation energies, $\delta\Delta E_g^\circ$, taken from ref 1. ^d Reference 1b.

Calculations

The Gaussian 94 program package⁸ with standard Pople-type basis sets was used throughout in this work. The nature of all stationary points was verified by calculation of the vibrational frequencies at all theoretical levels used with no application of scaling factors. The gas-phase energies (E_g°) were obtained at three levels: HF/6-31G*/HF/6-31G*, MP2/6-31G*/MP2/6-31G*, and B3LYP/6-31G*/B3LYP/6-31G*.⁴ The solvation energies (ΔG_s°) were calculated using the isodensity surface-polarized continuum model, IPCM/MP2/6-31G* and IPCM/B3LYP/6-31G*. The gas-phase geometries were used in the IPCM calculations. The isodensity level was kept to 0.001 electrons per cubic bohr. Recently, Zhan and Chipman have shown that the isodensity level of 0.001 electrons per cubic bohr has an adequate accuracy in the IPCM calculation.^{7c} The total gas-phase standard free energy changes, ΔG_g° in kcal mol⁻¹, were obtained by applying zero-point energy (ZPE) and thermal energy corrections and entropy changes, ΔS° .

Results and Discussion

Gas-Phase Basicities. The calculated relative gas-phase standard free energy changes ($\delta\Delta G_g^\circ$) at three levels of theory are summarized in Table 1 together with the available experimental results. The corresponding values ($\delta\Delta E_g^\circ$) at the STO-3G level¹ are also compared in the table. The ΔG_g° value for the unsubstituted pyridinium ion (X = H) is slightly higher than the experimental value by 1.1, 4.6, and 6.0 kcal mol⁻¹ at the MP2, B3LYP, and RHF levels, respectively. The STO-3G value¹ is higher than the experimental value by as much as 64 kcal mol⁻¹.

The π donor effect of para π acceptor substituents, *p*-CN, *p*-NO₂, *p*-CO₂CH₃, and *p*-COCH₃, was confirmed by the relatively large positive deviations from the otherwise linear experimental gas-phase $\text{p}K_a$ (eq 2) vs σ plot. This π donor effect of the strong π acceptor groups is manifest only in the basicities of pyridines but not in those for other acid systems such as anilinium ions, phenols, etc.^{1b} In these latter systems, the π acceptor groups show large negative deviations, requiring the use of σ^- scale in the gas-phase $\text{p}K_a$ vs σ correlations.⁹ Clearly, the π donor effect of the π acceptor groups in the basicities of the pyridines is due to (i) the presence of a strong cationic charge center, the azonium ion ($>\text{N}^+=$), which has a much stronger π acceptor ability ($\sigma_R = 0.30$) than any other substituents, *p*-CN,

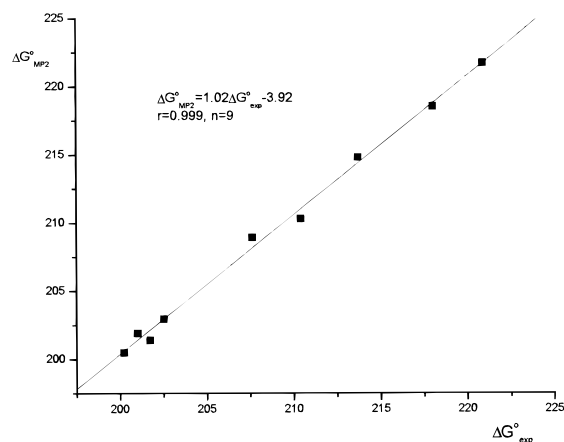


Figure 1. Plot of theoretical (MP2) vs experimental absolute gas-phase basicities (ΔG_g°) of pyridines.

p-NO₂, etc. ($\sigma_R \leq 0.1$)¹⁰ and (ii) the orthogonality of the ring π orbital to the lone-pair electrons on the nitrogen atom (n_N). This prevents the through conjugative interaction between n_N and the acceptor substituents (in contrast to the through conjugations found in the basicities of anilines and phenolate anions).

Excluding these para π acceptors, the slope (eqs 1 and 3) of the experimental gas-phase $\text{p}K_a$ vs σ plot was $\rho_g = -14.6$ ($r = 0.950$, $n = 16$) at 25.0 °C. The corresponding theoretical slopes were $\rho_g = -17.1$ (RHF, $r = 0.994$, $n = 9$), $\rho_g = -16.2$ (B3LYP, $r = 0.991$, $n = 9$), and $\rho_g = -15.0$ (MP2, $r = 0.991$, $n = 9$). Thus, the relative as well as absolute gas-phase basicities of pyridines at the MP2/6-31G* level are in good agreement with the corresponding experimental results. We have shown correlations between the experimental and theoretical basicities in Figures 1 and 2. We note that the MP2 results give a straight line of near-unity slope (1.02) passing through a point quite near the origin (off only by -3.9 kcal mol⁻¹) in Figure 1, demonstrating a much better agreement with experiment than the B3LYP results (slope = 1.10 and intercept = -17.2 kcal mol⁻¹) in Figure 2.

Basicities in Solution. *Experimental Basicities of Pyridines in Water at 25.0 °C.* The experimental $\text{p}K_a$ values for the acid dissociation equilibria of pyridinium ions in water at 25.0 °C are converted to their free energy changes, $\Delta G_{\text{aq}}^\circ$ (eq 4), which

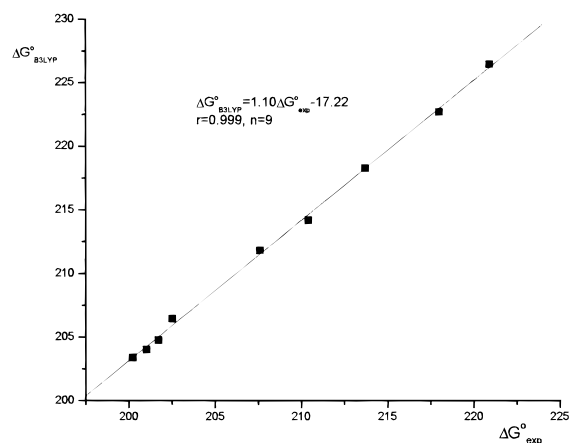


Figure 2. Plot of theoretical (B3LYP) vs experimental absolute gas-phase basicities (ΔG_g°) of pyridines.

TABLE 2: Dissection of Experimental Relative Basicities ($\delta\Delta G_{aq}^\circ$ in kcal mol⁻¹) of Pyridines in Water at 25.0 °C

| $XPyH^+ \rightleftharpoons XPy + H^+$ | | | | |
|--|-------------------|-----------------------------|--------------------------|------------------------------|
| X | pK_a^a | $\delta\Delta G_{aq}^\circ$ | $\delta\Delta G_g^\circ$ | $\delta\Delta G_{sol}^\circ$ |
| <i>p</i> -N(CH ₃) ₂ | 9.78 ^b | 6.25 | 15.6 | -9.3 |
| <i>m</i> -N(CH ₃) ₂ | 6.45 ^b | 1.71 | 9.5 | -7.8 |
| <i>p</i> -OCH ₃ | 6.58 | 1.86 | 7.2 | -5.4 |
| <i>m</i> -OCH ₃ | 4.78 | -0.59 | 3.0 | -3.6 |
| <i>p</i> -CH ₃ | 6.03 | 1.11 | 4.3 | -3.2 |
| <i>m</i> -CH ₃ | 5.67 | 0.62 | 2.9 | -2.3 |
| H | 5.21 | 0.0 | 0.0 | 0.0 |
| | | (7.09) | (213.7) ^f | (-206.6) (54.3) ^g |
| <i>p</i> -CHO | 4.53 | -2.07 | -6.1 | 5.2 |
| <i>m</i> -F | 2.97 | -3.05 | -7.0 | 3.9 |
| <i>p</i> -Cl | 3.83 | -1.88 | -3.3 | 1.4 |
| <i>m</i> -Cl | 2.81 | -3.27 | -6.2 | 2.9 |
| <i>p</i> -CO ₂ CH ₃ | 3.49 | -2.34 | -2.3 | 0.0 |
| <i>m</i> -CO ₂ CH ₃ | 3.09 | -2.89 | -2.8 | -0.1 |
| <i>p</i> -COCH ₃ | 3.51 | -2.32 | -3.7 | 1.4 |
| <i>m</i> -COCH ₃ | 3.26 | -2.66 | -3.9 | 1.2 |
| <i>p</i> -CN | 1.86 | -4.56 | -11.2 | 6.6 |
| <i>m</i> -CN | 1.35 | -5.25 | -12.0 | 6.7 |
| <i>p</i> -NO ₂ | 1.39 | -5.20 | -12.7 | 7.5 |
| <i>m</i> -NO ₂ | 1.18 | -5.49 | -13.5 | 8.0 |

^a Taken from ref 2. ^b Estimated values by $\Delta G_{aq}^\circ = 2.303RT \log pK_a = 1.364 pK_a$. ^c Taken from ref 1. ^d Solvation free energy changes, $\Delta G_{sol}^\circ = \Delta G_{aq}^\circ - \Delta G_g^\circ$. ^e Solvation free energy differences: $\Delta G_s^\circ = G_s^\circ(XPy) - G_s^\circ(XPyH^+) = \Delta G_{sol}^\circ - G_s^\circ(H^+)$. ^f Reference 1b.^g On the basis of aqueous ion solvation energy for H⁺ of $G_s^\circ(H^+) = -260.9$ kcal mol⁻¹.¹²

are then dissected into the gas phase (ΔG_g°) and solvation free energy (ΔG_{sol}°) components.

$$\Delta G_{aq}^\circ = \Delta G_g^\circ + \Delta G_{sol}^\circ \quad (4)$$

By use of the solvation free energy changes ΔG_{sol}° thus determined, the aqueous solvation free energy (G_s°)¹¹ differences between pyridines and pyridinium ions, $\Delta G_s^\circ = G^\circ(XPy) - G^\circ(XPyH^+)$, can then be calculated using the experimental aqueous ion solvation free energy for H⁺ of $G_s^\circ(H^+) = -260.9$ kcal mol⁻¹ (eq 5).

$$\Delta G_s^\circ = G_s^\circ(XPy) - G_s^\circ(XPyH^+) = \Delta G_{sol}^\circ - G_s^\circ(H^+) = \Delta G_{sol}^\circ + 260.9 \quad (5)$$

The results of energy dissection are summarized in Table 2.¹¹ Since $G_s^\circ(H^+)$ is a constant, the relative values (to X = H) of ΔG_s° will be identical to those of ΔG_{sol}° , i.e., $\delta\Delta G_s^\circ = \delta\Delta G_{sol}^\circ$. We note that the pyridinium ions (XPyH⁺) are more stabilized

by solvation (by ca. 55 ± 7 kcal mol⁻¹) than the neutral pyridine (XPy) molecules. The donor substituents ($\delta\sigma_x < 0$) delocalize the cationic charge, leading to lesser solvation, whereas the acceptor groups ($\delta\sigma_x > 0$) lead to stronger charge and stronger solvation. As a result, the difference of ca. 8.6 pyridinium ion pK_a units results in ca. 17 kcal mol⁻¹ solvation energy difference. Another interesting feature is that the π donor effect of π acceptors, e.g., *p*-NO₂, is present still in aqueous solution but with somewhat reduced extent. For example, in the gas-phase *p*-NO₂ and *p*-CN have greater basicity of $\delta\Delta G_g^\circ = 0.8$ kcal mol⁻¹ than the corresponding meta substituents, but in aqueous solution the difference reduces to 0.29 and 0.69 kcal mol⁻¹ for NO₂ and CN, respectively. This is due to solvation energies, $\delta\Delta G_{sol}^\circ$, which partially offset the $\delta\Delta G_g^\circ$ values (eq 4).

The experimental $pK_a(aq)$ vs σ plot gives a slope of $\rho_{aq} = -5.8$ ($r = 0.996$, $n = 14$) with exclusion of π acceptors. This ρ_{aq} is the net sum of ρ_g ($= -14.6$) and $\rho_{sol} \approx +8.6$ in accordance with eq 4. Thus, the transmission efficiency of substituent effects in the gas phase is reduced to less than half in water by charge dispersion due to solvation, $\rho_{aq}/\rho_g = 0.40$.

Theoretical Basicities of Pyridines in Water at 25.0 °C. The solvation free energy changes, ΔG_{sol}° , were calculated using eq 5 by first calculating $\Delta G_s^\circ (= G_s^\circ(XPy) - G_s^\circ(XPyH^+))$, where G_s° is the free energy of solvation of the individual species, and then applying the experimental free energy of solvation of a proton, $G_s^\circ(H^+)$, of -260.9 kcal mol⁻¹.¹² The relative basicities of pyridines in water at 25.0 °C ($\delta\Delta G_{aq}^\circ$) were then estimated by adding the theoretical gas-phase values ($\delta\Delta G_g^\circ$) to the computed solvation free energy changes ($\delta\Delta G_{sol}^\circ$) (eq 4). The results are summarized in Table 3. First of all, the theoretical (MP2 and B3LYP) solvation free energy differences for X = H, $\Delta G_s^\circ (= G^\circ(Py) - G^\circ(PyH^+))$, are in excellent agreement with the experimental value in Table 2; i.e., the theoretical ΔG_s° values are overestimated only by 0.7 and 0.5 kcal mol⁻¹ at the MP2 and B3LYP levels, respectively. The differences between the experimental and theoretical results are due to slight overestimation of the solvation energies of the pyridinium ions ($G_s^\circ(XPyH^+)$) by the theoretical continuum solvation energy model (IPCM) (vide infra). The experimental G_s° values of the pyridinium ion and neutral pyridine are -58.0 and -3.7 kcal mol⁻¹,¹² respectively, whereas the theoretical G_s° values are -58.8 and -3.8 kcal mol⁻¹ at the MP2 level and -58.7 and -3.9 kcal mol⁻¹ at the B3LYP level. Thus, the theoretical $G_s^\circ(PyH^+)$ values are slightly overestimated, leading to larger theoretical ΔG_s° values. We note that the theoretical solvation energy of the neutral pyridine ($G_s^\circ(Py)$) is in excellent agreement with experimental results.

The magnitude of the slope of the plot of theoretical basicities (MP2 and B3LYP) of pyridines in aqueous solution at 25.0 °C vs σ is somewhat larger with $\rho_{aq} = -8.6$ ($r = 0.981$, $n = 9$) and $\rho_{aq} = -9.0$ ($r = 0.978$, $n = 9$) at the MP2 and B3LYP levels, respectively, than the corresponding experimental value of $\rho_{aq} = -5.8$. This larger negative theoretical ρ_{aq} value is caused by (i) a larger theoretical ρ_g ($= -15.0$ and -16.2 by MP2 and B3LYP, respectively) and (ii) a smaller positive theoretical $\rho_{sol} = +6.5$ ($r = 0.94$, $n = 9$) by MP2 and $\rho_{sol} = +7.3$ ($r = 0.94$, $n = 9$) by B3LYP in the relation required by eq 4, $\rho_{aq} = \rho_g + \rho_{sol}$. The smaller ρ_{sol} value is due mainly to the abnormally small solvation free energy for X = NH₂, leading to a narrower range of the $\delta\Delta G_{sol}^\circ$ values for a nearly constant range of σ values ($\delta\sigma$). This solvation energy for X = *p*-NH₂ by the IPCM model may be less reliable. The $\delta\Delta G_{sol}^\circ$ values for X = *p*-NH₂ are smaller than those for X = *p*-OCH₃, though

TABLE 3: Dissection of Theoretical Relative Basicities ($\delta\Delta G_{\text{aq}}^{\circ}$ in kcal mol⁻¹) of Pyridines in Water ($\epsilon = 78.5$) at 25.0 °C

| X | $\text{XPyH}^+ \rightleftharpoons \text{XPy} + \text{H}^+$ | | | | | |
|-----------------------------|--|-----------------------|--------------------------------------|---------------------|---|-----------------------|
| | $\delta\Delta G_{\text{g}}^{\circ}$ | | $\delta\Delta G_{\text{aq}}^{\circ}$ | | $\delta\Delta G_{\text{sol}}^{\circ} (\delta\Delta G_{\text{s}}^{\circ})$ | |
| | MP2 | B3LYP | MP2 | B3LYP | MP2 | B3LYP |
| <i>p</i> -NH ₂ | 12.17 | 13.92 | 6.5 | 8.1 | -5.7 | -5.8 |
| <i>p</i> -OCH ₃ | 6.92 | 8.18 | 0.7 | 1.7 | -6.2 | -6.5 |
| <i>p</i> -CH ₃ | 3.74 | 4.44 | -0.3 | 0.2 | -4.0 | -4.2 |
| H | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | (214.83) ^a | (218.29) ^a | (8.9) ^c | (12.2) ^c | (-205.9) ^d | (-206.1) ^d |
| | | | | | (55.0) ^d | (54.8) ^d |
| <i>p</i> -Cl | -4.52 | -4.09 | -4.9 | -4.6 | -0.4 | -0.5 |
| <i>m</i> -CONH ₂ | -3.61 | -3.40 | -3.8 | -2.9 | -0.2 | 0.5 |
| <i>m</i> -CHO | -7.30 | -7.68 | -6.2 | -5.8 | 1.1 | 0.7 |
| <i>p</i> -CONH ₂ | -2.02 | -1.81 | -1.3 | -0.6 | 0.8 | 1.2 |
| <i>p</i> -CHO | -5.88 | -6.47 | -5.4 | -5.8 | 0.5 | 0.7 |
| <i>m</i> -CN | -13.43 | -13.51 | -9.4 | -8.9 | 4.0 | 4.6 |
| <i>p</i> -CN | -11.84 | -11.82 | -7.1 | -7.0 | 4.8 | 4.8 |
| <i>m</i> -NO ₂ | -14.33 | -14.87 | -8.9 | -8.1 | 5.5 | 6.8 |
| <i>p</i> -NO ₂ | -12.90 | -14.28 | -6.4 | -6.2 | 6.5 | 8.2 |

^a The $\Delta G_{\text{g}}^{\circ}$ values for X = H. ^b Based on the experimental aqueous ion solvation free energy for H⁺ of -260.9 kcal mol⁻¹.¹² $\delta\Delta G_{\text{sol}}^{\circ} = \delta\Delta G_{\text{s}}^{\circ}$.
^c The $\Delta G_{\text{aq}}^{\circ}$ value for X = H. ^d The $\Delta G_{\text{sol}}^{\circ}$ and $\Delta G_{\text{s}}^{\circ}$ values for X = H.

TABLE 4: Theoretical (B3LYP) Relative Solvation Energy Difference ($\delta\Delta G_{\text{s}}^{\circ}$) and Relative Basicities ($\delta\Delta G_{\text{AN}}^{\circ}$, $\delta\Delta G_{\text{DM}}^{\circ}$, $\delta\Delta G_{\text{CH}}^{\circ}$) at 25.0 °C (in kcal mol⁻¹)

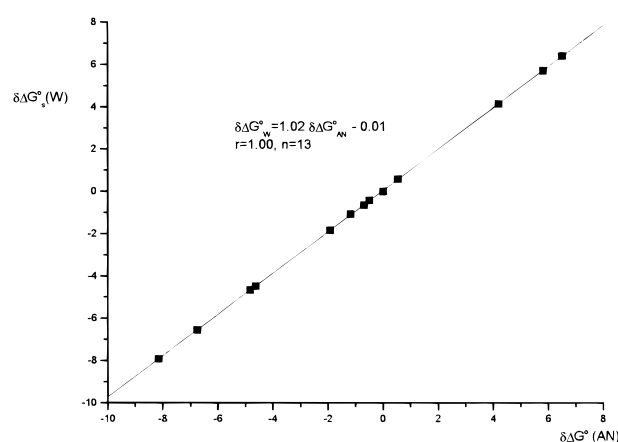
| X | CH ₃ CN (AN, $\epsilon = 37.5$) | | CH ₂ Cl ₂ (DM, $\epsilon = 8.9$) | | C ₆ H ₁₂ (CH, $\epsilon = 2.0$) | |
|-----------------------------|---|--------------------------------------|---|--------------------------------------|--|--------------------------------------|
| | $\delta\Delta G_{\text{s}}^{\circ}$ | $\delta\Delta G_{\text{AN}}^{\circ}$ | $\delta\Delta G_{\text{s}}^{\circ}$ | $\delta\Delta G_{\text{DM}}^{\circ}$ | $\delta\Delta G_{\text{s}}^{\circ}$ | $\delta\Delta G_{\text{CH}}^{\circ}$ |
| <i>p</i> -NH ₂ | -5.7 | 8.2 | -5.0 | 8.9 | -2.5 | 11.5 |
| <i>p</i> -OCH ₃ | -6.4 | 1.8 | -5.8 | 2.4 | -3.2 | 5.0 |
| <i>p</i> -CH ₃ | -4.1 | 0.3 | -3.7 | 0.7 | -2.0 | 2.4 |
| H | 0.0 | 0.0 | 0.0 | 0.0 ^c | 0.0 | 0.0 ^d |
| | (54.0) | (21.9) ^b | (49.2) | | (27.6) | |
| <i>p</i> -Cl | -0.6 | -4.7 | -0.8 | -4.9 | -0.8 | -4.9 |
| <i>m</i> -CONH ₂ | 0.4 | -3.0 | -0.1 | -3.5 | -0.8 | -4.2 |
| <i>m</i> -CHO | 1.9 | -5.9 | 1.3 | -6.4 | 0.1 | -7.6 |
| <i>p</i> -CONH ₂ | 1.1 | -0.7 | 0.5 | -1.4 | -0.6 | -2.4 |
| <i>p</i> -CHO | 0.6 | -5.8 | 0.4 | -6.1 | -0.2 | -6.7 |
| <i>m</i> -CN | 4.5 | -9.0 | 3.7 | -9.8 | 1.2 | -12.3 |
| <i>p</i> -CN | 4.7 | -7.2 | 3.7 | -8.1 | 1.0 | -10.8 |
| <i>m</i> -NO ₂ | 6.5 | -8.3 | 5.4 | -9.4 | 2.0 | -12.9 |
| <i>p</i> -NO ₂ | 7.9 | -6.4 | 6.5 | -7.7 | 2.4 | -11.9 |

^a Solvation energy difference, $\Delta G_{\text{s}}^{\circ} = G_{\text{s}}^{\circ}(\text{XPy}) - G_{\text{s}}^{\circ}(\text{XPyH}^+)$. ^b Experimental value is 16.8 kcal mol⁻¹.¹³ Thus, experimental $\Delta G_{\text{sol}}^{\circ} = \Delta G_{\text{AN}}^{\circ} - \Delta G_{\text{g}}^{\circ} = 16.8 - 213.7 = -196.9$ kcal mol⁻¹. ^c The absolute value is not known. $\Delta G_{\text{DM}}^{\circ}(\text{X} = \text{H}) = [264.7 + G_{\text{s}}^{\circ}(\text{H}^+)_{\text{DM}}]$ kcal mol⁻¹. ^d The absolute value is not known. $\Delta G_{\text{CH}}^{\circ}(\text{X} = \text{H}) = [245.7 + G_{\text{s}}^{\circ}(\text{H}^+)_{\text{CH}}]$ kcal mol⁻¹.

the *p*-NH₂ substituent is a much stronger electron-donating substituent ($\sigma = -0.66$) than *p*-OCH₃ ($\sigma = -0.27$). The theoretical ρ_{sol} values excluding X = NH₂ are +7.9 ($r = 0.96$, $n = 8$) and +9.0 ($r = 0.97$, $n = 8$) by MP2 and B3LYP, respectively. These values are in much better agreement with the experimental $\rho_{\text{sol}} = +8.6$.

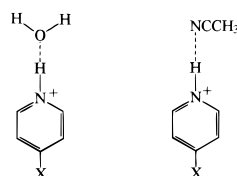
Theoretical Basicities in Acetonitrile (AN, $\epsilon = 37.5$), Dichloromethane (DM, $\epsilon = 8.9$), and Cyclohexane (CH, $\epsilon = 2.0$). The calculated (B3LYP) relative solvation free energy differences ($\delta\Delta G_{\text{s}}^{\circ}$) and relative basicities in acetonitrile ($\delta\Delta G_{\text{AN}}^{\circ}$), dichloromethane ($\delta\Delta G_{\text{DM}}^{\circ}$), and cyclohexane ($\delta\Delta G_{\text{CH}}^{\circ}$) are summarized in Table 4. Since the experimental solvation free energies for H⁺, $G_{\text{s}}^{\circ}(\text{H}^+)$, in other solvents (than in water) are not available, $\Delta G_{\text{sol}}^{\circ}$ in eq 5 cannot be calculated from $\Delta G_{\text{s}}^{\circ}$. However, the $G_{\text{s}}^{\circ}(\text{H}^+)$ value in acetonitrile can be estimated as follows. Comparison of the two columns of $\delta\Delta G_{\text{s}}^{\circ}$ in water (Table 3) and in acetonitrile (Table 4) reveals that the two are remarkably similar. In fact, there is a difference in the absolute value of only 0.8 kcal mol⁻¹ for X = H, 54.8 (H₂O), and 54.0 kcal mol⁻¹ (CH₃CN), with the excellent correlation between the two relative values (eq 6 and Figure 3).

$$\delta\Delta G_{\text{s}}^{\circ}(\text{W}) = 1.02 \delta\Delta G_{\text{s}}^{\circ}(\text{AN}) - 0.01 \quad (r = 1.00, n = 13) \quad (6)$$

**Figure 3.** Theoretical (IPCM/B3LYP/6-31G*) correlation between relative basicities of pyridines in water and in acetonitrile.

This means that solvation free energy differences between XPyH⁺ and XPy are almost identical in water and in acetonitrile. Thus, the experimental value of $\Delta G_{\text{s}}^{\circ}(\text{AN})$ can be given by 53.5 kcal mol⁻¹, which is obtained by 54.3 (experimental value in water) - 0.8 (difference in theoretical value). On the other hand, the experimental value of $\Delta G_{\text{AN}}^{\circ}$ is 16.8 kcal mol⁻¹ 13a so that the experimental solvation free energy change for the pyridinium

CHART 1



(X = H) ion ionization in acetonitrile, $\Delta G_{\text{sol}}^{\circ}$, is $\Delta G_{\text{sol}}^{\circ} = \Delta G_{\text{AN}}^{\circ} - \Delta G_{\text{g}}^{\circ} = 16.8 - 213.7 = -196.9 \text{ kcal mol}^{-1}$. Thus, the experimental $G_{\text{s}}^{\circ}(\text{H}^{+})$ in acetonitrile becomes $G_{\text{s}}^{\circ}(\text{H}^{+})_{\text{AN}} = \Delta G_{\text{sol}}^{\circ} - \Delta G_{\text{s}}^{\circ} = -196.9 - 53.5 = -250.4 \text{ kcal mol}^{-1}$. This experimental solvation free energy for H^{+} in acetonitrile is numerically smaller than that in water ($-260.9 \text{ kcal mol}^{-1}$) by $10.5 \text{ kcal mol}^{-1}$. In terms of $\text{p}K_{\text{a}}$ units, this difference in the $G_{\text{s}}^{\circ}(\text{H}^{+})$ value corresponds to 7.7. This result provides a theoretical basis for the experimentally established constant difference in $\text{p}K_{\text{a}}$, $\Delta \text{p}K_{\text{a}} = \text{p}K_{\text{a}}(\text{AN}) - \text{p}K_{\text{a}}(\text{W}) = 7.7 \pm 0.3$, for structurally similar amines.^{13,14} The plot of theoretical (B3LYP) $\text{p}K_{\text{a}}$ values in acetonitrile vs those in water gave an excellent correlation (eq 7) with a $\Delta \text{p}K_{\text{a}}$ value of ~ 7.0 , which is in good agreement with the experimental correlation (eq 8) with $\Delta \text{p}K_{\text{a}} \cong 7$ with 22 amines including various alkyl and alicyclic amines and pyridine.^{13a} Correlations between $\text{p}K_{\text{a}}(\text{AN})$ and $\text{p}K_{\text{a}}(\text{W})$ have also been reported by Leffek and co-workers.^{13c} It is interesting to note that quite similar experimental correlations between $\text{p}K_{\text{a}}(\text{AN})$ and $\text{p}K_{\text{a}}(\text{MeOH})$ are reported¹⁴ (eq 9) so that $\text{p}K_{\text{a}}$ values of amines including pyridines in methanol should be almost the same as those in water with the $\Delta \text{p}K_{\text{a}} = \text{p}K_{\text{a}}(\text{W}) - \text{p}K_{\text{a}}(\text{MeOH}) \cong 0.0$.

$$\text{p}K_{\text{a}}(\text{AN}) = (1.02 \pm 0.004) \text{p}K_{\text{a}}(\text{W}) + 6.89 \pm 0.03$$

$$(r = 1.00, n = 13) \quad (7)$$

$$\text{p}K_{\text{a}}(\text{AN}) = (1.05 \pm 0.06) \text{p}K_{\text{a}}(\text{W}) + 7.20 \pm 0.58$$

$$(r = 0.972, n = 22) \quad (8)$$

$$\text{p}K_{\text{a}}(\text{AN}) = (1.05 \pm 0.03) \text{p}K_{\text{a}}(\text{MeOH}) + 7.12 \pm 0.21$$

$$(r = 0.997, n = 10) \quad (9)$$

The near-unity slope of the $\text{p}K_{\text{a}}(\text{AN})$ vs $\text{p}K_{\text{a}}(\text{W})$ plot (eq 7) provides a justification for correlating experimental rate data in acetonitrile ($\log k(\text{AN})$) with $\text{p}K_{\text{a}}(\text{W})$, as have often been reported.^{13b,15} Another important aspect of our theoretical analysis is that the constant difference in $\text{p}K_{\text{a}}$, $\Delta \text{p}K_{\text{a}}$ (~ 7.0), between acetonitrile and water is *solely* due to the difference in the solvation free energy of the H^{+} ion in the two media (corresponding to $\Delta \text{p}K_{\text{a}} = 7.7$). In other words the solvation free energy differences between pyridinium ions (XPyH^{+}) and neutral pyridines (XPy) are nearly the same in acetonitrile and in water. This is rather surprising at first glance in that a protic solvent, water, and an aprotic solvent, acetonitrile, show the same solvation energy differences. However, it must be due to the apparent lack of a specific hydrogen-bonding component to the solvent effects on the two species involved, pyridinium ions and neutral pyridines, in the IPCM model. In the IPCM model, a specific (acceptor) hydrogen bond type shown in Chart 1 is neglected. It should be noted that the pyridinium ion is a cationic species so that water cannot act as a hydrogen bond donor. Thus, there is no difference between a protic and an aprotic solvent as far as specific hydrogen-bond-donating solvation of the pyridinium ion is concerned. A similar type of structure as shown in Chart 1 can be envisaged with the acetonitrile molecule. The slope of near-unity in eq 7 predicts

TABLE 5: Correlations of $\Delta G_{\text{s}}^{\circ}$ ($=G_{\text{s}}^{\circ}(\text{Py}) - G_{\text{s}}^{\circ}(\text{PyH}^{+})$) and ρ_{s} (plots of $\text{p}K_{\text{a}}$ vs σ) Values in Various Solvents at the B3LYP/6-31G* Level with Onsager Dielectric Function

| ϵ | $(\epsilon - 1)/(2\epsilon + 1)$ | $\Delta G_{\text{s}}^{\circ} (\text{kcal mol}^{-1})^a$ | ρ_{s}^b |
|------------|----------------------------------|--|---------------------|
| 1.0 | 0.00 | 0 | -16.0 |
| 2.0 | 0.20 | 27.6 | -13.4 |
| 8.9 | 0.42 | 49.2 | -9.9 |
| 37.5 | 0.48 | 54.0 | -9.1 |
| 78.5 | 0.49 | 54.8 | -8.9 |

^a $\Delta G_{\text{s}}^{\circ} = 110.0[(\epsilon - 1)/(2\epsilon + 1)] + 2.1$, $r = 0.996$, $n = 5$. ^b $\rho_{\text{s}} = 14.6[(\epsilon - 1)/(2\epsilon + 1)] - 16.1$, $r = 0.999$, $n = 5$.

(and indeed found) that the $\text{p}K_{\text{a}}(\text{AN})$ vs σ plot should give the same slope as found for the $\text{p}K_{\text{a}}(\text{W})$ vs σ plot, $\rho_{\text{AN}} \cong \rho_{\text{W}} \cong -9$ (at the B3LYP level).

In dichloromethane ($\epsilon = 8.9$) and cyclohexane ($\epsilon = 2.0$) the solvation energy difference, $\Delta G_{\text{s}}^{\circ}$, decreases further to 49.2 and 27.6 kcal mol^{-1} , respectively. In all the solvent media, the $\text{p}K_{\text{a}}$ values for *p*-CN and *p*-NO₂ substituted pyridinium ions are greater than the corresponding meta-substituted ions, indicating the π donor effect of the π acceptors is effective. Since there is very little, if any, specific hydrogen-bonding solvation effect in water, a satisfactory correlation of $\Delta G_{\text{s}}^{\circ}$ with the Onsager dielectric function $(\epsilon - 1)/(2\epsilon + 1)$, including water, is expected. In Table 5, we summarized the $\Delta G_{\text{s}}^{\circ}$ and ρ_{s} values (the slope of the plot of $\text{p}K_{\text{a}}$ vs σ excluding π donor substituents) in various solvents. We note that the correlations of the two, $\Delta G_{\text{s}}^{\circ}$ and ρ_{s} , with the Onsager dielectric function are good, albeit they are based on only five media. This again confirms that the specific hydrogen-bonding solvation component is not important in the solvation effect on the ionization equilibria of pyridinium ions in water. In addition, the predictions of the solvent effect by the IPCM model appear to be satisfactory for the systems studied, although absolute accuracies of the calculated $\text{p}K_{\text{a}}$ values in solutions were somewhat poor (the calculated $\text{p}K_{\text{a}}$ values in water and acetonitrile were 1–4 $\text{p}K_{\text{a}}$ units larger than the experimental values).

In summary, the theoretical gas-phase basicities of pyridines at the MP2/6-31G* level agree quite well with the experimental results. The IPCM model overestimates the free energy of solvation of the pyridinium ion ($G_{\text{s}}^{\circ}(\text{PyH}^{+})$) only by 0.7–0.8 kcal mol^{-1} . The estimate of the H^{+} ion solvation free energy in acetonitrile shows that the constant $\text{p}K_{\text{a}}$ difference, $\Delta \text{p}K_{\text{a}} = \text{p}K_{\text{a}}(\text{AN}) - \text{p}K_{\text{a}}(\text{W}) = 7.7$, is solely due to the H^{+} ion solvation free energy difference of 10.5 kcal mol^{-1} between acetonitrile and water. The IPCM model predicts a linear correlation between the ρ values for the $\text{p}K_{\text{a}}$ vs σ plots in various solvents including water and the Onsager dielectric function $(\epsilon - 1)/(2\epsilon + 1)$, indicating that there is very little specific hydrogen bonding effect on the pyridinium ion dissociation. The π donor effect of strong π acceptor substituents on the basicities of pyridines is found in the gas phase as well as in solution.

Acknowledgment. We thank Inha University for support of this work. One of us (I. S. Han) also thanks Inha University for a postdoctoral fellowship. We also thank the Korea Research Foundation for financial support (1998-015-D00159) in the program year of 1998.

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