Relationships between the Thermodynamics of Protonation in the Gas and Aqueous Phase for 2-, 3-, and 4-Substituted Pyridines

Donald H. Aue,*,† Hugh M. Webb,† William R. Davidson,† Pogban Toure,†
Harry P. Hopkins, Jr.,*,‡ S. P. Moulik,‡ and D. V. Jahagirdar‡

Contribution from the Department of Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106, and the Department of Chemistry, Georgia State University, Atlanta, Georgia 30303.
Received March 2, 1990.
Revised Manuscript Received October 15, 1990

Abstract: The gas- and aqueous-phase basicities have been determined for an extensive series of 2-, 3-, and 4-substituted pyridines, quinoline, and isoquinoline. Gibbs free energies and enthalpies of aqueous protonation, heats of vaporization, and heats of solution have been measured for many of the substituted pyridines, where reliable data were not available from the literature. This combination of gas- and solution-phase data makes possible a complete thermodynamic analysis of basicities and solvation energies for a large number of pyridines via the thermodynamic cycle in Scheme I. The gas- and aqueous-phase free energies of protonation correlate roughly with one another, but with an approximate 2-fold attenuation of the gas-phase substituent effects in the aqueous basicities. The correlations for the free energies and enthalpies of protonation show a 2.4–2.5-fold attenuation factor for the 3- and 4-substituted pyridines. The 2-substituted pyridines give correlations for the free energies and enthalpies with attenuation factors of 1.4 and 1.7, respectively. Only the 2- and 4-aminopyridines, 2,6-di-*tert*-butylpyridine, 2-phenylpyridine, methylnicotinate, and methylisonicotinate deviate substantially from the correlations. The aminopyridines exhibit anomalously high aqueous basicities as a result of increased solvation at the high charge densities on the resonance-stabilizing 2- and 4-amino groups of the pyridinium ions, an effect not observed for the 3-amino group or dimethylamino groups. Analysis of the data here permits a separation of Hepler's intrinsic and extrinsic (solvation) effects in the aqueous equilibria for proton transfer. The solvation effects for the pyridines and pyridinium ions have been separated into terms for cavity formation, van der Waals interactions and solvent structure-making by alkyl groups, dipole–solvent interactions, and charge–solvent interactions. The changes in solvation of substituted neutral pyridines are mainly due to changes in the dipolar solvation term, which correlates with the dipole moment. The primary solvation term responsible for the attenuation of the gas-phase basicity differences on passing into aqueous solution is the charge–solvent interaction term. This term decreases with increasing charge delocalization for charge-stabilizing substituents and increases with increasing charge density at the ring NH for inductively destabilizing substituents. These electrostatic charge solvation terms correlate closely with stabilization energies and semiempirical and ab initio calculated charge densities at the ring NH.

Some years ago the only reliable thermodynamic data on the ionization of acids or the protonation of bases were those that had been determined in the solution phase.[1] The interpretation of the variations observed in these data was limited, because there was no way to experimentally separate the changes due to purely internal effects from those due to solute–solvent interactions. Hepler[2] and others[3] did recognize, however, that substituent effects on the thermodynamic parameters for protonation in a series of organic molecules could be divided, in principle, into intrinsic (gas-phase) and environmental (solute–solvent interactions) contributions. With the advent of current technology, the thermodynamic parameters for the transfer of a proton from one base to another can be determined in the gas phase by several different techniques with a high degree of precision and accuracy.[4] Very little real advancement in our understanding of the protonation process occurred before the appearance of these gas-phase data. These data are appropriate for the analysis of the intrinsic factors affecting the energetics of protonation and for comparison with theoretical calculations. Furthermore, when appropriate thermodynamic parameters for dissolution, aqueous protonation, and vaporization are available, Hepler's environmental component for protonation in the aqueous phase can be experimentally determined, and individual solvation terms for the ions involved can be calculated from the thermodynamic cycle shown in Scheme I.

Such analyses have been reported for a large number of alkyl amines,[5] a few phenols,[6] thiophenol,[6] and a limited number of substituted pyridines.[7a,b] In this paper, we present an analysis of this type using gas-phase basicities[8] for a large number of substituted pyridines and aqueous solution parameters reported here and extracted from the literature. These data provide an extensive set of thermodynamic parameters for the transfer of

Scheme I. Thermodynamic Cycle for the Analysis of Proton Affinities, $-PA = \Delta H^\circ_{prot,g}$, and Aqueous Protonation of Pyridines

$$\begin{tikzcd}
B_g \arrow[d, "\Delta H^\circ_{g\to s}(B)"'] & + H^+_g \arrow[r, "\Delta H^\circ_{prot,g}"] \arrow[d, "\Delta H^\circ_{g\to s}(H^+)"] & BH^+_g \arrow[d, "\Delta H^\circ_{g\to s}(BH^+)"] \\
B_s & + H^+_s \arrow[r, "\Delta H^\circ_{prot,s}"] & BH^+_s
\end{tikzcd}$$

$$\Delta H^\circ_{prot,s} = -PA + \Delta H^\circ_{g\to s}(BH+) - \Delta H^\circ_{g\to s}(B) - \Delta H^\circ_{g\to s}(H+)$$

---

† University of California, Santa Barbara.
‡ Georgia State University.

[1] Larson, J. W.; Hepler, L. G. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Dekker: New York, 1969.

[2] (a) Hepler, L. G.; O'Hara, W. F. *J. Phys. Chem.* **1961**, *68*, 811. (b) Larson, J. W.; Hepler, L. G. *J. Org. Chem.* **1968**, *33*, 3961. (c) Sayer, W. F. In *Progress in Physical Organic Chemistry*; Wiley: New York, 1969; Vol. 2. (d) Hepler, L. G.; Wooley, E. M. In *Water: A Comprehensive Treatise*; Frank, F., Ed.; Plenum: New York, 1973; Vol. 3.

[3] (a) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1940. (b) Gurney, R. *Ionic Processes in Solution*; McGraw-Hill, New York, 1953. (c) Bell, R. P. *The Proton in Chemistry*; Cornell University Press: Ithaca, NY, 1959. (d) King, E. J. *Acid-Base Equilibria*; Pergamon Press: New York, 1965.

[4] (a) Aue, D. H.; Bowers, M. T. *Gas-Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2. (b) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. No. 1. (c) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.

[5] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 318.

[6] McIver, R. T.; Silvers, J. H. *J. Am. Chem. Soc.* **1976**, *95*, 8462.

[7] (a) Arnett, E. M.; Chawla, B.; Bell, L.; Taagepera, M.; Hehre, W. H.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5729. (b) Arnett, E. M.; Chawla, B. *J. Am. Chem. Soc.* **1979**, *101*, 7141.

0002-7863/91/1513-1770$02.50/0

neutral and protonated pyridines from the gas to the aqueous phase. We have looked for correlations within the data, carried out an analysis of the data in terms of the concepts of environmental effects of Hepler, and explored the applicability of solvation effects such as hydrogen bonding between solute and solvent, van der Waals and dipolar interactions of the solute with the solvent, hydrophobicity, cavity formation, and electrostatic interactions of the cations with the solvent.

Experimental Section

All substituted pyridines included in this study, except 3-(dimethylamino)pyridine, were purchased from Aldrich Chemical Co. or Pfaltz and Bauer Inc. The commercial samples were vacuum distilled or vacuum sublimed and stored under nitrogen until use. We prepared 3-(dimethylamino)pyridine by methylation[9] of 3-aminopyridine and purified it by recrystallizing the picrate several times from an alcohol–water mixture. The purified 3-(dimethylamino)pyridine was recovered by extraction into CH_2Cl_2 from an aqueous NaOH solution and vacuum distilled to give the material employed in the thermodynamic measurements.

Calorimetric measurements were performed either in a Tronac Model 450 titration calorimeter or in a 200-mL isoperibol solution calorimeter previously described.[10] All voltage measurements, including those related to the temperature variations, were made with a Hewlett-Packard digital voltmeter (Model 3450A). Enthalpies of protonation were determined by introducing aqueous $HClO_4$ into a $1-5 \times 10^{-3}$ M aqueous solution of the substituted pyridine being studied. Calculations and corrections were performed by procedures previously described.[10] The enthalpies of dissolution for the pyridines into aqueous HCl were determined by introducing the liquid or solid directly into an aqueous solution, where a sufficient excess of HCl was present to ensure complete protonation. Uncertainties associated with all the calorimetric determinations are 0.10 kcal mol^{-1} or less.

The pK_a values for the 2- and 3-(dimethylamino)-substituted pyridines were determined by a spectrophotometric method with a Beckman Acta V UV-visible spectrophotometer. Values of the pK_a were determined by a procedure designed by Bates and Gary[11] at five different ionic strengths in standard phosphate buffers.

The vapor pressures for several pyridines were measured by the Knudsen effusion method with a specially constructed cell which has been previously described.[12] The measurements for each compound were made in the −40 to 50 °C temperature range in an interval in which the mean free path of the molecule in the gas phase was as large as possible to minimize the number of collisions in the hole in the top of the cell as the molecules effuse out of the cell.

Gas-phase basicity measurements were made by using equilibrium ICR techniques and high-pressure mass spectrometric reactant ion monitoring and metastable ion techniques.[8]

Results

We have listed in Table I thermodynamic parameters for the four processes shown in Scheme I for an extensive set of substituted pyridines. The Gibbs free energy changes are given in the first four columns, the enthalpy changes are in the next four columns, and the corresponding entropy components are recorded in the remaining columns. In the gas phase, the standard state is the ideal one atmosphere, but the infinite dilution one molar standard state is used in the aqueous phase.

Values for the negative of the Gibbs free energy change for the protonation of the pyridines in the gas phase, or gas-phase basicity (GB), $-\Delta G^\circ_{\text{prot,g}}$ = GB, have been measured by using ion cyclotron resonance and mass spectrometric techniques.[8] The GB values measured compare well with the GB differences given by Arnett and Taft et al.[7,8] for substituted pyridines. Except for the 2- and 3-(dimethylamino)pyridines, the corresponding Gibbs free energy changes for the protonation process in the aqueous phase, $\Delta G^\circ_{\text{prot,s}}$, were calculated from pK_a values found in the literature. Our pK_a values determined at several ionic strengths for the 2- and 3-(dimethylamino)pyridinium ions were extrapolated to infinite dilution by means of the Debye–Huckel relationship to yield 7.03 and 6.65 for the true thermodynamic pK_a values, respectively. Gibbs free energy changes, $\Delta G^\circ_{g\to s}(B)$, for the transfer of the alkyl-substituted pyridines were calculated from vapor pressure measurements over aqueous solutions.[13] Similar measurements by Arnett and Chawla[7b] were used to calculate these parameters for the 2- and 3-chloropyridines.

The enthalpies of vaporization, $\Delta H^\circ_{\text{vap}}$, were derived for several compounds from a least-squares analysis of a van't Hoff plot of the vapor pressures from −40 to 50 °C and have associated statistical uncertainties of 0.1–0.3 kcal mol^{-1}. Enthalpies of vaporization determined by us for 2- and 3-chloropyridine are, within experimental error, in accord with those reported by Arnett and Chawla.[7b] For the 2-fluoro, 3-fluoro, 3-bromo, and 2-methoxy-substituted pyridines, the vapor pressures were above 1 Torr at 25 °C; thus, the $\Delta H^\circ_{\text{vap}}$ values for these compounds are more uncertain than the other values reported here. The values for the (dimethylamino)pyridines are from the thesis of Kasudia.[14]

Enthalpies for protonation in the gas phase, $-\Delta H^\circ_{\text{prot,g}}$ = PA, were derived from the GB values by assuming that the entropy change in the gas phase can be calculated by statistical mechanical procedures. The translational and rotational contributions to the entropy changes are near zero because the molecular weights and moments of inertia of the neutral and protonated pyridines are virtually identical.[15] Contributions to the entropy change due to symmetry changes are also expected to be zero, since the symmetries of the base and the cation are expected to be the same. All but two of the enthalpies of protonation in the aqueous phase, $\Delta H^\circ_{\text{prot,s}}$, were taken from work of Hopkins et al.[16] or what we judged to be the best literature values derived from calorimetric data.

Because we needed the enthalpies for the transfer of the neutral pyridines from the pure state to the infinite dilution standard state in the aqueous phase, we determined the enthalpy change for the dissolution of the pure substituted pyridines into aqueous HCl, where the HCl concentration was large enough to ensure complete protonation. For those pyridines whose pK_a is greater than 2, the concentration of the HCl was 0.1 M to ensure that better than 99% of the pyridine was protonated in solution. In those cases in which the pK_a values were lower than 2, higher concentrations were used to approach the 99% protonation level. To convert these values to the infinite dilution standard-state values, we need the enthalpy of dilution for the pyridines, the corresponding pyridinium chloride salts, and HCl. The latter is known, but the first two are not. Actually, differences between the enthalpies of dilution for the pyridinium chlorides and HCl appear in the calculations, but these differences should be small. The enthalpy of dilution for the neutral pyridine is also expected to be small; therefore, the experimental values are taken to be the $\Delta H^\circ_s(\text{HCl})$ values. This appears to be a reasonable assumption, since the $\Delta H^\circ_s(\text{HCl})$

---

[8] (a) Aue, D. H.; Webb, H. W.; Toure, P. Unpublished results. (b) Aue, D. H.; Toure, P. Unpublished results. The GB scale used here is from equilibrium ICR measurements. GB's agree within 0.5 kcal mol^{-1} with equilibrium ICR values of R. W. Taft (private communication) except that Taft has expanded the GB scale by 7% to compensate for a possible 20° systematic temperature error. (See ref 4c.) This adjustment makes the scale more compatible with scales from high-pressure mass spectrometric studies and recent MP2/6-31+G(d,p)//6-31G* calculated PA's of ours on pyridines and other bases and might be used to correct our GB data, as well, but we use our experimental data directly, at this point. A 10% adjustment of our scale would leave the GB of pyridine nearly unchanged and would not change any chemical conclusions, except to make the observed effects on pyridinium solvation energies 10% larger.

[9] Glam, C. S.; Houch, A. E. *Org. Prep. Proced. Int.* **1977**, *9*, 9.

[10] (a) Hopkins, H. P., Jr.; Ali, S. Z. *J. Am. Chem. Soc.* **1977**, *99*, 2069. (b) Liotta, C. L.; Perdue, E. M.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7981.

[11] Bates, R. G.; Gary, R. *J. Res. Natl. Bur. Stand., Sect. A* **1961**, *65*, 495.

[12] Jackson, W.; Hung, T. S.; Hopkins, H. P., Jr. *J. Chem. Thermodyn.* **1971**, *3*, 347.

[13] Hopkins, H. P.; Jahagirdar, D. V.; Moulik, S. P.; Aue, D. H.; Webb, H. M.; Davidson, W. R.; Pedley, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 4341.

[14] Kasudia, P. T. Masters Thesis, Georgia State University, Atlanta, GA, 1974.

[15] Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311. Frequency calculations on most of the substituted pyridines and pyridinium ions at the AM1 level show that the ions generally have larger entropies, but by less than 1–2 cal mol^{-1} K^{-1} in all cases. Ab initio frequency calculations, in the several cases looked at, show entropies comparable to the AM1 values. See ref 8b.

[16] Hopkins, H. P., Jr.; Perdue, E. M.; Liotta, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 7308.

Table I. Thermodynamic Data for Protonation in the Gas and Aqueous Phase and Transfer from the Gas to the Aqueous Phase for Substituted Pyridines at 25 °C[a]

	GB[h]	$-\Delta G^\circ_{\mathrm{prot,s}}$[c]	$-\Delta G^\circ_{g\to s}(\mathrm{B})$[d]	$-\Delta G^\circ_{g\to s}$-($\mathrm{BH^+}$)[d,e]	$\Delta H^\circ_{\mathrm{vap}}$[f]	PA[g]	$-\Delta H^\circ_{\mathrm{prot,s}}$[c]	$-\Delta H^\circ_{s}(\mathrm{HCl})$	$-\Delta H^\circ_{g\to s}(\mathrm{B})$[d]	$-\Delta H_{g\to s}$-($\mathrm{BH^+}$)[d]	$-\Delta H^\circ_{g\to s}$-($\mathrm{BH^+}$)[c,l]	$\Delta S^\circ_{\mathrm{prot,s}}$	$-\Delta S^\circ_{g\to s}(\mathrm{B})$[d]	$-\Delta S^\circ_{g\to s}$-($\mathrm{BH^+}$)[d]
pyridine	212.6	7.11	2.80[h]	57.8		220.4	4.80[i]		11.65[h]	65.9	54.2	7.8	29.7	27.2
2-CH_3	215.9	8.13	2.74[h]	55.5		223.7	6.22[j]		12.64[h]	65.0	52.4	6.4	33.2	31.8
3-CH_3	215.0	7.68	2.88[h]	56.1		222.8	5.87[i]		12.60[h]	65.5	52.9	6.1	32.6	31.5
4-CH_3	215.9	8.15	3.04[h]	55.9		223.7	6.13[i]		12.82[h]	65.1	52.3	6.8	32.8	30.9
2-CH_2CH_3	217.1	8.04	2.44[h]	53.9		224.9	6.58[k]		13.31[h]	64.8	51.5	4.9	36.4	36.5
3-CH_2CH_3	216.1	7.58	2.71[h]	54.7		223.9	5.96		12.78[h]	64.6	51.8	5.4	33.7	33.2
4-CH_2CH_3	216.8	8.04	2.84[h]	54.6		224.6	6.22		12.48[h]	63.9	51.4	6.1	32.3	31.2
2,3-diCH_3	218.4	8.96	2.93[h]	54.0		226.2	7.5[l]		13.79[h]	64.9	51.1	4.9	36.4	36.6
2,4-diCH_3	219.3	9.04	2.97[h]	53.2		227.1	7.17[m]		14.02[h]	63.9	49.9	6.3	37.0	35.9
2,5-diCH_3	218.4	8.73	2.82[h]	53.7		226.2	6.82[m]		14.00[h]	65.4	51.4	6.4	37.4	35.9
2,6-diCH_3	219.3	9.16	2.71[h]	53.1		227.1	7.24[m]		14.44[h]	64.4	50.0	6.4	39.3	37.9
3,4-diCH_3	218.2	8.81	3.33[h]	54.4		226.0	7.40[m]		13.54[h]	64.7	51.2	4.7	34.2	34.6
3,5-diCH_3	217.8	8.39	2.95[h]	54.0		225.6	6.37[m]		13.45[h]	64.0	50.6	6.8	35.2	33.6
2-NH_2	216.0	9.15			12.6	223.8	8.17	6.10	10.5	64.7	54.2	3.3		
3-NH_2	217.6	8.24[n]			20.3	225.4	6.41[i]	3.17	17.0	67.9	50.9	5.9		
4-NH_2	223.2	12.44[n]			21.5	231.0	11.27[i]	7.10	17.3	67.4	50.1	3.9		
2-N(Me)$_2$	221.4	9.59[o]			12.9	229.2	7.08[k]	9.42	15.2	62.9	47.7	8.4		
3-N(Me)$_2$	222.1	9.07[o]			16.9	229.9	7.18[o]	8.41	18.1	65.3	47.2	6.3		
4-N(Me)$_2$	227.9	12.92			19.5	235.7	11.73[k]	8.52	16.6	62.4	45.8	4.0		
2-F	203.3	−0.6			10.4	211.1		0.74		69.8				
3-F	207.0	4.05			10.8	214.8		3.18		69.0				
4-F	209.4					217.2								
2-Cl	207.0	0.67[j]	2.48[p]	56.7	11.3[p]	214.8	0.25[k]	1.34	12.4	67.6	55.2	1.4	33.2	36.6
3-Cl	207.9	3.83[n]	2.12[p]	58.6	10.4[p]	215.7	2.60[i]	3.78	11.6	67.9	56.7	4.1	31.8	32.6
4-Cl	210.0	5.24[n]				217.8	3.58[i]				55.4	5.6		
2-Br	207.8	0.97[j]			12.2	215.6	0.47[k]	0.54	12.3	66.9	54.7	1.7		
3-Br	208.5	3.89[n]			10.8	216.3	2.78[i]	3.83	11.8	68.1	56.3	3.7		
4-Br	210.1	5.12[n]				217.9	3.51[i]				55.4	5.4		
2-CF_3	203.8					211.6								
3-CF_3	205.0	3.36[q]				212.8	2.0[q]					4.6		
4-CF_3	205.3	3.59[q]			9.98[q]	213.1	2.22[q]		11.66[q]	70.6	59.0	4.6	−1.37	
2-OCH_3	213.5	4.17			10.0	221.3	3.88[k]	5.45	11.6	64.0	52.4	1.0		
3-OCH_3	214.7	6.52[n]				222.5								
4-OCH_3	219.0	8.98[n]			12.6	226.8	6.85[i]		14.1[q]	64.0	49.9	7.1		
2-CN	201.1	−0.35[j]			18.3	208.9	−0.91[k]	−0.24	19.0	79.0	60.0	1.8		
3-CN	201.8	1.84[m]			15.0	209.6	0.88[i]	0.41	14.5	75.6	61.1	3.4		
4-CN	202.5	2.54[n]			12.9	210.3	1.26[i]	−1.90	9.7	70.5	60.8	4.5		
2-SCH_3	214.2	4.94				222.0								
4-SCH_3	217.7	8.14				225.5								
3-OH	212.5	6.55[j]				220.3	3.92[j]				53.4	8.8		
2-Cl,6-CH_3	208.1	−0.18				215.9								
3-CO_2CH_3	212.5	4.22[n]				218.3								

4-CO_2Me	212.5[u]	4.78[n]	218.3[u]			
4-CHO	207.4	6.17[n]	215.2	4.92[r]	59.5	4.2
4-NO_2	201.1[s]	1.68	208.9	−1.10[l]	59.2	9.3
4-vinyl	215.4	7.67	223.1			
4-CH_3CO	209.6	4.79	217.4	3.17	55.6	5.0
quinoline	218.0	6.54	225.8	5.37	49.4	3.9
isoquinoline	217.9	6.92	225.7	5.93	50.0	3.3

[a] Enthalpy and Gibbs free energy changes are in kilocalories per mole, entropy changes are in calories per degree per mole and unreferenced values are from this work. [b] GB values, $-\Delta G°_{prot,g}$, are on a scale where $GB(NH_3) = 196.4$ kcal mol^{-1} and $PA(NH_3) = 205.0$ kcal mol^{-1}. [c] Unless stated otherwise, $\Delta G°_{prot,s}$ and $\Delta H°_{prot,s}$ values from Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965. And/or: Christensen, J. J.; Hansen, L. D.; Izatt, R. M. *Handbook of Proton Ionization, Heats and Related Thermodynamic Quantities*; Wiley-Interscience: New York, 1976. Or *Handbook of Biochemistry and Molecular Biology. Physical Chemical Data*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, OH, 1976; Vol. 1. [d] Symbols such as $\Delta G°_{g\rightarrow s}$ refer to standard thermodynamic properties for transfer from the gas to the aqueous phase. [e] Calculated by using $\Delta G°_{g\rightarrow s}(H^+) = -260.5$ kcal mol^{-1} (Noyes, R. M. *J. Am. Chem. Soc.* **1962**, *84*, 513) and $\Delta H°_{g\rightarrow s}(H^+) = -269.8$ kcal mol^{-1} (Friedman, H.; Krishnan, C. V. *Water: A Comprehensive Treatise*; Franks, F. F., Ed.; Plenum Press: New York, 1973; Vol. 3, Chapter 1). [f] Enthalpy change for vaporization process; unless stated otherwise, determined by us as described under Experimental Section. [g] PA values, $\Delta H°_{prot,g}$, calculated from GB values by using the entropy of H^+ (Altschuller, A. P. *J. Am. Chem. Soc.* **1955**, *77*, 3480) and the assumption that symmetry of neutral and protonated pyridines are the same. See ref 15. [h] Andon, R. J. L.; Cox, J. D.; Herington, E. F. G. *J. Chem. Soc.* **1954**, 3188. [i] Reference 16. [j] Christensen, J. J.; Smith, D. E.; Slade, M. D.; Izatt, R. M. *Thermochim. Acta* **1972**, *5*, 35. [k] Reference 18. [l] Berthon, G.; Enea, O.; M'Foundou, E. *Bull. Soc. Chem. Fr.* **1973**, 2967. [m] Sacconi, L.; Paoletti, P.; Ciampolini, J. *J. Am. Chem. Soc.* **1960**, *82*, 3831. [n] Fischer, A.; Galloway, W. J.; Vaughn, J. *J. Chem. Soc.* **1964**, 3591. [o] Determined in this work by a procedure similar to the one described in: Hopkins, H. P., Jr.; Ali, Z. *J. Am. Chem. Soc.* **1977**, *99*, 2069. [p] Reference 7b. [q] Reference 7a. [r] Reference 31. [s] Unpublished data of R. Taft from: Lias, S.; Liebman, J.; Levin, R. D. *J. Phys. Chem. Ref Data* **1984**, *13*, 695. [t] Bellobono, I. R.; Diani, E. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1707. [u] Estimated from 3-CO_2Me-pyridine and ab initio calculations, ref 8.

values for 3-aminopyridine and 4-aminopyridine are in excellent agreement with the values calculated from the independently measured enthalpies of protonation and solution.[14] The enthalpy of solution of 4-aminopyridine into aqueous HCl at infinite dilution reported by Hepler and Burchfield[17] agrees within 0.1 kcal mol^{-1} with our value.

Our values for $\Delta H°_s$(HCl) were combined with available values for $\Delta H°_{prot,s}$ and $\Delta H°_{vap}$ to yield the enthalpy changes, $\Delta H°_{g\rightarrow s}$(B), for the transfer of the neutral pyridines from the gas to the aqueous phase. For the alkyl-substituted pyridines, we chose values[13] from the temperature dependence of the pressure above the aqueous solution.

For each step in the cycle in Scheme I for which we have $\Delta G°$ and $\Delta H°$ values, we have calculated the corresponding entropy changes. This $\Delta S°_{prot,g}$ is expected to be −26 cal mol^{-1} deg^{-1} in the gas phase for all the substituted pyridines[15] and is not listed in Table I.

Discussion

Substituent Effects. Application of Hepler's Model. Before the appearance of gas-phase data on protonation reactions, Hepler introduced a scheme which, in principle, could be used to dissect the thermodynamic parameters for the proton-transfer process

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

into internal or intrinsic components and external or environmental components.[2c,3d]

$$\Delta H°_l = \Delta H°_{inl} + \Delta H°_{exl} \qquad (2)$$

$$\Delta S°_l = \Delta S°_{inl} + \Delta S°_{exl} \qquad (3)$$

For most systems of organic acids or bases, $\Delta S°_{inl}$ is negligible;[2a,5,15] therefore, Hepler set $\Delta S°_l$ equal to $\Delta S°_{exl}$ and suggested that $\Delta H°_{exl}$ is proportional to $\Delta S°_{exl}$. Originally, the proportionality constant, β, was thought to be nearly equal to the temperature at which the data were derived. Using these assumptions, Hepler concluded that $\Delta G°_l$ for proton-transfer reaction 1 was approximately equal to the then unknown intrinsic enthalpy change, $\Delta H°_{inl}$.

$$\Delta G°_l = \Delta H°_{inl} + (\beta - T)\Delta S°_{exl} \approx \Delta H°_{inl} \qquad (4)$$

Hepler later stated that $\Delta H°_{exl}$ was not exactly equal to $T\Delta S°_{exl}$, and he modified his equation by adding a second term proportional to $\Delta H°_{inl}$, yielding[2b,d]

$$\Delta G°_l = (1 + \gamma)\Delta H°_{inl} + (\beta - T)\Delta S°_{exl} = (1 + \gamma)\Delta H°_{inl} \qquad (5)$$

To better fit available experimental data, simplify the analysis, and have one free of the dubious assumption that β is equal to T, we have proposed[5] that the environmental enthalpy and entropy terms are proportional to the intrinsic enthalpy term in

$$\Delta H°_{exl} = h\Delta H°_{inl} \qquad (6)$$

$$-\Delta S°_{exl} = s\Delta H°_{inl} \qquad (7)$$

where h and s are the proportionality constants. Combining these equations with eqs 2 and 3, the previous assumption that $\Delta S°_{inl} = 0$, and the standard equation for the Gibbs free energy, we find two general equations that depend simply on the assumed proportionalities of $\Delta H°_{exl}$ and $\Delta S°_{exl}$ to $\Delta H°_{inl}$.

$$\Delta H°_l = (1 + h)\Delta H°_{inl} \qquad (8)$$

$$-T\Delta S°_l = Ts\Delta H°_{inl} \qquad (9)$$

$$\Delta G°_l = (1 + h + Ts)\Delta H°_{inl} \qquad (10)$$

These equations have been found previously to be valid, at least approximately, for a variety of acids and bases for which both gas-phase and solution-phase data are available.[5] The data in this paper[18] can be used to test these proposed assumptions and this

---

(17) Hepler, L. G.; Burchfield, T. E. *J. Chem. Thermodyn.* **1981**, *13*, 513.

(18) For a preliminary communication of these results see: Aue, D. H.; Webb, H. M.; Bowers, M. T.; Liotta, C. L.; Alexander, C. J.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 854.

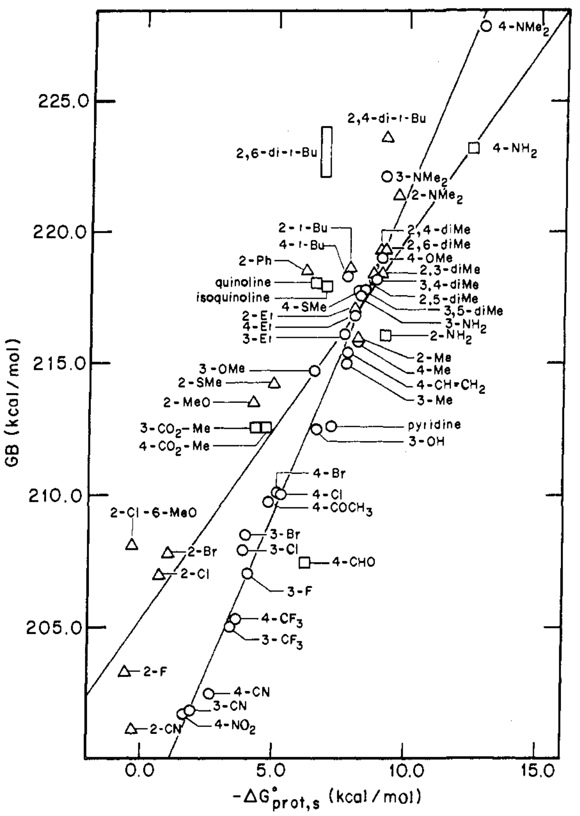

Figure 1. Plot of PA vs $-\Delta G^\circ_{prot,s}$ for substituted pyridines at 25 °C. Correlation lines are for the 2-substituted (△) and 3- and 4-substituted pyridines (○), but exclude certain anomalous cases (□).

Table II. Parameters Derived from Linear Least-Squares Treatment of the Data in Figures 1-3

	3- and 4-subst pyr[a]	2-subst pyr[b]
GB vs $\Delta G^\circ_{prot,s}$ (Figure 1)		
slope = atten factor	2.43	1.42
corr coeff	0.977	0.901
PA vs $\Delta H^\circ_{prot,s}$ (Figure 2)		
slope = atten factor	2.47	1.73
corr coeff	0.958	0.911
h[c]	−0.59	−0.42
PA vs $-T\Delta S^\circ_{prot,s}$ (Figure 3)		
corr coeff	0.001	0.475
Ts[d]	0.002 ± 0.020	0.10 ± 0.04

[a] Correlation includes all 3- and 4-substituted pyridines in Table I and Figures 1-3 except 4-NH$_2$-, 3-CO$_2$Me-, and 4-CHO-pyridine and the quinolines. [b] Correlation includes all 2-substituted pyridines in Table I and Figures 1-3 except for 2-NH$_2$-pyridine and the *tert*-butylpyridines in Figures 1 and 2. [c] Proportionality constant h from eq 6, slope in Figure 2 = $1/(1 + h)$. [d] Proportionality constant Ts from eq 7, slope in Figure 3 = $1/Ts$.

method of analysis for a series of pyridines with a large variety of substituents. Therefore, we have constructed the plots shown in Figure 1 ($\Delta G^\circ_{prot,s}$ vs GB), Figure 2 ($\Delta H^\circ_{prot,s}$ vs PA), and Figure 3 ($T\Delta S^\circ_{prot,s}$ vs PA) to test, respectively, eqs 10, 8, and 9.[19] The slopes and correlation coefficients for the least-squares lines drawn in Figures 1-3 are summarized in Table II and were used to calculate the proportionality constants Ts and h.

The ΔG° plot in Figure 1 for the 3- and 4-substituted pyridines shows linearity, but with substantial scatter for several points. This linearity is in agreement with the predictions of both Hepler's modified theory (eq 5) and our theory (eq 10). The slope (2.43) of the line for 3- and 4-substituted pyridines is very different from the slope of 1.0 predicted from Hepler's original theory (eq 4). For the 2-substituted pyridines, the least-squares line has a slope (1.42) that is significantly smaller than that found for the other pyridines. The 2- and 4-aminopyridines, *tert*-butylpyridines,[20] 4-formylpyridine, methylnicotinate, methylisonicotinate, 2-phenylpyridine, and quinolines were not included in the calculation of the least-squares lines in any of the three plots, because these pyridines appear to be anomalous.

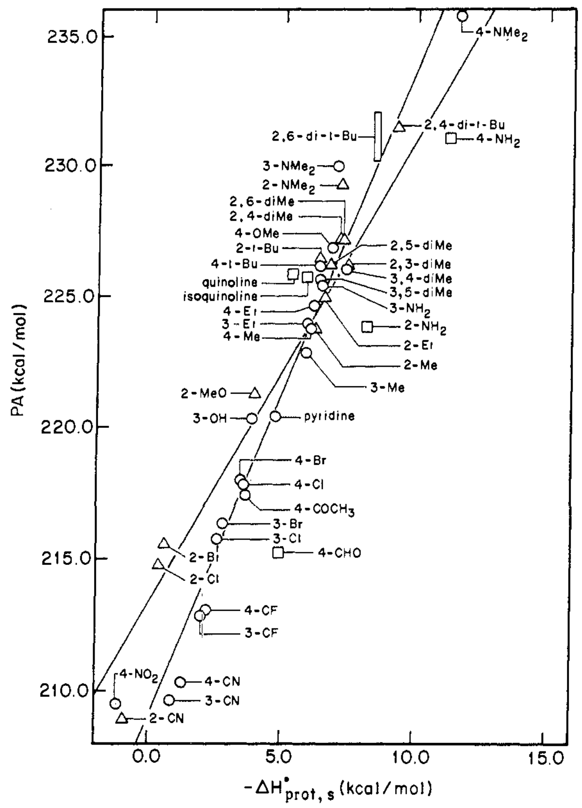

Figure 2. Plot of PA vs $-\Delta H^\circ_{prot,s}$ for substituted pyridines at 25 °C. Correlation lines are for the 2-substituted (△) and 3- and 4-substituted pyridines (○), but exclude certain anomalous cases (□).

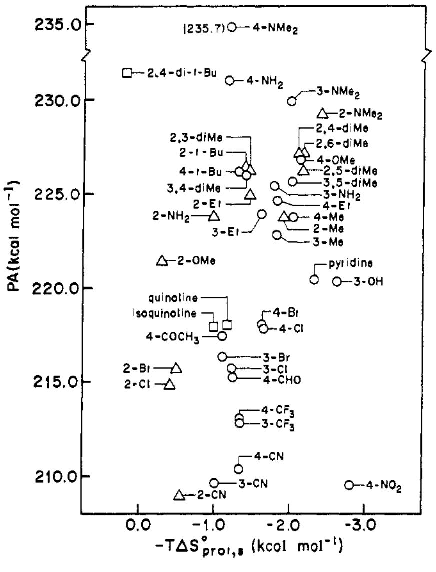

Figure 3. Plot of PA vs $-T\Delta S^\circ_{prot,s}$ for substituted pyridines at 25 °C.

In Figure 2, the $\Delta H^\circ_{prot,s}$ values show a linear correlation with PA similar (slope = 2.47) to that found in Figure 1 between $\Delta G^\circ_{prot,s}$ and GB. For the 3- and 4-substituted pyridines all the points, except those for the anomalous pyridines, are very close to the least-squares line. The 2-substituted pyridines are fit to

---

(19) For graphical convenience, the PA (or GB, since $\Delta S^\circ_{int} = 0$) values are plotted as equivalent to the ΔH°_{int} parameter vs differences in the $\Delta X^\circ_{prot,s}$ parameters, which are equivalent to the ΔX°_{I} parameters, where X is any state function for reaction 1.

(20) For a complete discussion of the results for *tert*-butylpyridines, see ref 13.

a line with a smaller slope (1.73). These linear enthalpy relationships are predicted by our eq 8 but could not be expected from Hepler's treatments. The correlation coefficients are good (0.90–0.98) and average deviations remarkably small (<1 kcal mol^{-1}).

Because both $\Delta G^\circ_{\mathrm{prol,s}}$ and $\Delta H^\circ_{\mathrm{prol,s}}$ are linearly related to $\Delta H^\circ_{\mathrm{inl}}$, which is equal to changes in PA, the corresponding $\Delta S^\circ_{\mathrm{prol,s}}$ values might also be expected to be linearly related to the PA values (eq 7). The correlation for entropy parameters in Figure 3, however, is much poorer than the correlations found in Figures 1 and 2, and, in fact, shows the entropy terms for the 3- and 4-substituted pyridines to correlate with zero correlation coefficient with PA and to be largely constant to within ±0.5 kcal mol^{-1}. The irregularities in the entropy changes could be, in part, due to experimental uncertainties, but, in many cases, the deviations from the linear correlation are large enough to be significant. These irregularities in the entropy terms cause the free energy correlation in Figure 1 to differ somewhat from the enthalpy correlation in Figure 2, particularly for the 2-substituted pyridines. The variation of the entropy terms for the 2-substituted pyridines has the sign (Ts positive, opposite the enthalpy of solvation term) expected from electrostatic theory. The small magnitude of the changes in the entropy terms ($-T\Delta S^\circ_{\mathrm{prol}}$ varies overall by less than 15% of the variation in $\Delta H^\circ_{\mathrm{inl}}$, $Ts/h = 0.002$ and 0.10) is also expected from electrostatic theory (predicted $Ts/h = 0.017$) and from known solvation parameters for alkali metal ions ($Ts/h = 0.13$) (vide infra). For the 3- and 4-substituted pyridines, in fact, this predicted electrostatic variation in $-T\Delta S^\circ_{\mathrm{prol}}$ is apparently too small to be discernible within the experimental data, which are, in fact, constant within 1 kcal mol^{-1}.

With the solvation effects separated from intrinsic effects, the origin of these solvation effects on the pyridinium ions and their conjugate bases can now be explored in more detail. As we shall see, these effects and the demonstrated correlations in eqs 6 and 7 will be found to be largely understandable in terms of simple electrostatic theories.

Electrostatic Solvation Effects. From the thermodynamic cycle in Scheme I, one can derive the solvation terms, e.g., $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$, required for the analysis of the effect of solvent on the proton-transfer equilibria for the pyridinium ions. This calculation requires that all of the other energies in the cycle, including $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{B})$, have been determined experimentally. We have given the required experimental data in Table I and calculated $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$ and $\Delta G^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$ and $\Delta S^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$, where possible. Direct interpretation of these basic solvation data is, however, complicated by the fact that the solvation effects are made up of a large number of terms: (1) the formation of a cavity in the solvent, (2) the van der Waals dispersion interactions between the solute and the solvent and any associated solvent structure making, (3) the dipolar interactions between the solute and the solvent, and (4) electrostatic charge–solvent interactions for ions.[21] The first two terms are nonpolar solvation terms associated with the hydrophobic effect.[21b] Even though the hydrophobic effect may not be entirely understood theoretically, we will consider the relevant solvation terms for nonpolar groups to be identical with the cavity and van der Waals (and structure making) terms above for aqueous solvation throughout this discussion. The first three terms operate for the neutral base and may be considered to affect the ionic solvation as well.[5]

We have devised a method to separate these factors from one another that has been successful in the analysis of both the neutral and ionic solvation. We have defined an electrostatic charge–solvent interaction term,[5] $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})^{\mathrm{el}}$, that is derived simply by subtraction of the solvation parameters for the neutral pyridines from the solvation parameters for the corresponding cations, e.g.

$$\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})^{\mathrm{el}} = \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+}) - \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{B}) \qquad (11)$$

This term has been called an electrostatic solvation parameter for ionic solvation, since it gives just the effect of the proton and positive charge on the solvation of the ion. While this treatment can be justified as a reasonable *definition* of electrostatic solvation effects, it will be most effective if one can establish that the solvation effects on the neutral base operate as well for the ion, but with the additional electrostatic interactions. These electrostatic parameters should then be free of effects caused merely by creating a cavity in the solvent for the solute species and the solvent structure-making or van der Waals interactions of the neutral base or ion with the solvent. If present in both the neutral and cationic species, these factors will tend to cancel in the calculation of the $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})^{\mathrm{el}}$ term, leaving only the effect of placing a charge on the pyridine in the solvent cavity in the electrostatic term. Justification for this approach can be seen in the parallel behavior of the entropies of solvation for B and BH$^+$ in Table I for the limited number of cases where data are available, particularly for pyridines with increasing alkylation. A more complete set of data for alkyl amines[5] shows that the entropies of solvation for alkyl groups are closely correlated for B and BH$^+$. This suggests that the nonpolar solvation of the ion from the cavity and van der Waals factors should be similar to those for the neutral base in the $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$ and $\Delta G^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$ parameters as well. Thus, the subtraction of $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{B})$ from $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})$ to remove the cavity and van der Waals terms in BH$^+$ seems reasonable and does lead to electrostatic terms for alkyl amines that fit expectations from electrostatic theory reasonably well.[5] The extension of this approach to treat dipolar solvation terms in the neutral bases in a similar fashion has not been well tested, and its effectiveness will be explored in detail here.

Again employing the thermodynamic cycle in Scheme I for any state function, one sees that the external parameters for the proton-transfer reaction 1 are simply equal to the differences in the solvation parameters for the transfer of each species, BH$^+$ and B and AH$^+$ and A, from the gas to the aqueous phase.

$$\Delta H^\circ_{\mathrm{exl}} = \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+}) - \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{B}) - [\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{AH^+}) - \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{A})] \qquad (12)$$

This leads to the conclusion that the external solvation effect on reaction 1 is simply equal to the difference between the solvation parameters that we have defined[5] as the electrostatic terms, $\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})^{\mathrm{el}}$.

$$\Delta H^\circ_{\mathrm{exl}} = \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{BH^+})^{\mathrm{el}} - \Delta H^\circ_{\mathrm{g\to s}}(\mathrm{AH^+})^{\mathrm{el}} \qquad (13)$$

The electrostatic enthalpy parameters for all of the pyridines in this study have been calculated and are shown in Table I. A discussion of these electrostatic solvation energies follows the discussion of the solvation of the neutral pyridines below. We will show that separation of the electrostatic term for ionic solvation and the different neutral solvation terms discussed in these sections provides a useful framework for analysis of solvation that is consistent with predictions of theory. Further support for this approach comes from the comparison with Bjerrum and Born theory below.

According to the simple Bjerrum and Born theory[3d,5,22] of electrostatic solvation, the parameters for transferring an ion from the gas to the solution phase are inversely proportional to the radius (r) of the ion. For ions in water at 25 °C and 1-atm pressure, these relationships are

$$\Delta G^\circ_{\mathrm{g\to s}}(\mathrm{M^+}) = -163.9\ (\mathrm{kcal\ \AA\ mol^{-1}})/r \qquad (14)$$

$$\Delta H^\circ_{\mathrm{g\to s}}(\mathrm{M^+}) = -166.8\ (\mathrm{kcal\ \AA\ mol^{-1}})/r \qquad (15)$$

$$\Delta S^\circ_{\mathrm{g\to s}}(\mathrm{M^+}) = -9.68\ (\mathrm{cal\ \AA\ mol^{-1}\ K^{-1}})/r \qquad (16)$$

Combining these equations with the above analysis, $\Delta H^\circ_{\mathrm{exl}}$ and

---

(21) (a) Barta, L.; Hepler, L. G. *J. Phys. Chem.* **1989**, *93*, 5588. (b) Marcus, Y. *Ion Solvation*; Wiley-Interscience: New York, 1985.

(22) (a) Born, M. *Phys. Z.* **1920**, *1*, 45. (b) Bockris, J. O. M.; Reddy, A. K. N. *Modern Electrochemistry*; Plenum Press: New York, 1970; Vol. 1, Chapter 2. (c) Friedman, H.; Krishnan, C. V. In *Water: A Comprehensive Treatise*; Franks, F. F., Ed.; Plenum Press: New York, 1973; Vol. 3, Chapter 1. (d) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; Wiley: New York, 1981. (e) Ben-Naim, A. *Hydrophobic Interactions*; Plenum Press: New York, 1980.

Table III. Component Solvation Terms for Transfer of Pyridines from Gas to Aqueous Phase at 25 °C[a]

	$\Delta G^\circ_{g\rightarrow s}$(B)	$\Delta G^\circ_{g\rightarrow s}$(PhR)[b]	ΔG°_{cav}(B)[c]	ΔG°_{vdw}(B)[d]	ΔG°_{dip}(B)[e]	μ(D)[f]
pyridine	−2.80	0.91	4.4	−3.5	−3.7	2.20
4-Me	−3.04	0.99	5.5	−4.5	−4.0	2.60
4-Et	−2.84	1.10	6.8	−5.7	−3.9	2.65
2-Cl	−2.53	0.99	5.5	−4.5	−3.5	3.25
3-Cl	−2.14	0.99	5.5	−4.5	−3.1	2.02
pyridine	−11.65	−7.72	0.9	−8.6	−3.9	2.20
4-Me	−12.82	−8.86	1.1	−10.0	−4.0	2.60
4-Et	−12.48	−9.77	1.4	−11.2	−2.7	2.65
2-Cl	−12.4	−8.86	1.1	−10.0	−3.5	3.25
3-Cl	−11.6	−8.86	1.1	−10.0	−2.7	2.02
	$-T\Delta S^\circ_{g\rightarrow s}$(B)	$-T\Delta S^\circ_{g\rightarrow s}$(PhR)[b]	$-T\Delta S^\circ_{cav}$(B)[c]	$-T\Delta S^\circ_{vdw}$(B)[d]	$-T\Delta S^\circ_{dip}$(B)[e]	
pyridine	8.9	8.6	3.5	5.1	0.3	
4-Me	9.8	9.9	4.4	5.5	−0.1	
4-Et	9.6	10.9	5.4	5.5	−1.3	
2-Cl	9.9	9.9	4.4	5.5	0.0	
3-Cl	9.5	9.9	4.4	5.5	−0.4	

[a] All energies in kilocalories per mole and are based on the infinite dilution one molar standard state. [b] Parameters are for aqueous solvation of benzene, toluene, and ethylbenzene, which are used as isostructural models for the ΔX°_{cav}(B) and ΔX°_{vdw}(B) terms for pyridines of corresponding molecular sizes; i.e., benzene models pyridine, toluene models methyl- and chloro-pyridines, and ethylbenzene models ethylpyridine. Taken from ref 23b, but the Henry's law standard-state values are converted to the one molar infinite dilution standard-state values; see: Castellan, G. W. *Physical Chemistry*, 3rd ed.; Addison-Wesley; Reading, MA, 1983. [c] Cavity term in water calculated from scaled particle theory by the method in refs 23b and c. [d] Van der Waals term derived from $\Delta X^\circ_{vdw}(B) = \Delta X^\circ_{g\rightarrow s}(PhR) - \Delta X^\circ_{cav}(B)$ by using data for isostructural models, see footnote b, column two minus column three, where X is any thermodynamic parameter. [e] Esimated from eq 17 by using data for isostructural models, see footnote b, column one minus column four. [f] Reference 25.

$T\Delta S^\circ_{exl}$ would be predicted to be related to each other, if both are indeed electrostatic in origin. The ratio of ΔH°_{exl} to $T\Delta S^\circ_{exl}$ is $-Ts/h$ from eqs 6 and 7. Using values of s and h determined from the least-squares analysis of the plots in Figures 2 and 3, $-Ts/h$ is found to be very small (<0.02) for the 3- and 4-substituted pyridines and 0.10 for the 2-substituted ones. This ratio is predicted to be 0.017 from eqs 15 and 16 taken from Born electrostatic theory, but this theory does not include effects due to dielectric saturation or the oblate shape of the pyridinium cations. In the analysis[2d,5,18,22] of the solvation data for alkali metal ions this ratio is found experimentally to be 0.13, which is close to the ratio (0.10) for the 2-substituted pyridinium ions. The fact that the ratios for the pyridinium ions and the alkali metal ions are of comparable magnitudes is consistent with evidence that electrostatic solvation is indeed the major contributor to the external components of the thermodynamic parameters.

Solvation of Neutral Pyridines. As discussed earlier, thermodynamic parameters for the transfer of a molecule from the gas to the aqueous phase can be divided into a term for the formation of a cavity in the solvent and two terms for the interaction of the solute with the solvent: the van der Waals dispersion (and associated solvent structure making) term and the dipolar electrostatic interaction term.

$$\Delta H^\circ_{g\rightarrow s}(B) = \Delta H^\circ_{cav}(B) + \Delta H^\circ_{vdw}(B) + \Delta H^\circ_{dip}(B) \qquad (17)$$

The terms for the formation of the cavity can be estimated from the scaled particle theory,[23] which is based on a hard sphere model for liquids, but several problems are associated with the application of this theory to pyridines in water: (1) water is definitely not closely related to a hard sphere liquid, (2) the cavity in which the substituted pyridine resides must be oblate and not spherical, and (3) the actual volume that the solute molecule occupies is not easily defined or calculated. Nevertheless, the thermodynamic parameters for formation of the cavity can be estimated from this theory to provide an indication of their magnitudes for the pyridines in this study. In Table III the terms for solvation of the neutral pyridines are summarized for a representative, but limited, number of pyridines for which a complete set of data are available.

For nonpolar molecules only the cavity and van der Waals terms are retained from eq 17. Any additional modification of solvent structure upon introduction of the solute into the cavity is included in the van der Waals term, since we know of no reliable method to separate the two. The cavity terms in column three of Table III have been estimated for the substituted pyridines from scaled particle theory calculations for benzene, toluene, and ethylbenzene, which are used as isostructural, but nonpolar, models for the corresponding pyridines.[23] Subtraction of the cavity terms from the experimental thermodynamic parameters for the substituted benzene models in column two gives values that we define as the van der Waals terms (column four) for the substituted benzenes, which we use as estimates of the van der Waals terms for the isostructural pyridines. As is always the case,[5,23] the cavity terms for the Gibbs free energy of transfer from gas to water are positive and primarily entropic, and, for the isostructural model benzenes, are opposed by favorable, but somewhat smaller, van der Waals terms that are mainly enthalpic. The enthalpic van der Waals terms are substantially negative, increasing regularly as the size of the solute increases, but the opposing entropic van der Waals terms are invariant for the limited data in Table III.

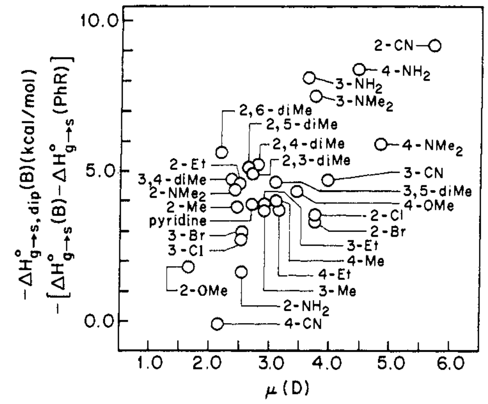

Figure 4. Plot of $-\Delta H^\circ_{g\rightarrow s}$(B) vs dipole moment, μ, at 25 °C.

Dipolar contributions (column five, Table III) to the thermodynamic parameters for solvation of the neutral pyridines can now be calculated by subtracting the cavity and van der Waals terms from the experimental values for transfer parameters from gas to water, i.e., by merely subtracting the experimental parameters in column two for the appropriate isostructural, nonpolar model compounds. The dipolar Gibbs free energies and enthalpies in Table III correlate only roughly with the dipole moments, but, as we note in the discussion that follows, the correlation of these polar solvation terms with dipole moment can be extended more

---

(23) (a) Pierotti, R. A. *J. Phys. Chem.* **1965**, *69*, 281. (b) Liabastre, A. A. Ph.D. Thesis, Georgia Institute of Technology, 1974. (c) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717.

successfully to the variety of substituted pyridines for which experimental data are available (Figure 4). The chloropyridines in Table III also show some improvement in correlation with dipole moment after effects of specific hydrogen bonding to the pyridine nitrogen are considered (vide infra). All of the entropic dipolar solvation terms are near zero, except that for 4-ethylpyridine, since the dipolar interaction presumably requires little structural change in the solvent. The ethylpyridine anomaly is relatively small and may be a result of experimental or modeling errors.

All experimental entropic terms listed in Table III include a cratic contribution that is present due to use of the hypothetical one molar infinite dilution standard state in the aqueous phase. This term (7.98 cal mol^{-1} K^{-1}) is entirely due to mixing 1 mol of solute with water; thus, the entropy of transfer from gas to solution phase can be dissected:

$$\Delta S^\circ_{g\rightarrow s}(\text{B, PhR, or cavity}) = \Delta S^\circ_{g\rightarrow s}(\text{interaction}) + \Delta S^\circ_{\text{cratic}} \quad (18)$$

One now realizes that the entropic contributions due to the solute–solvent interactions and perturbations on the solvent structure are actually more negative by 7.98 cal mol^{-1} K^{-1} than the experimentally derived entropies of solvation in columns two and three of Table III. This term is not present, however, in the parameters given in columns four and five of Table III, because these are calculated by difference.

For pyridines with polar substituents, subtraction of these nonpolar terms gives a set of polar terms for the solvation parameters that can be compared with predictions from electrostatic theory using the Onsager equation for polar molecules in a dielectric continuum.[24] This theory suggests that a relationship should exist between $\Delta G^\circ_{\text{dip}}(\text{B})$ or $\Delta H^\circ_{\text{dip}}(\text{B})$ and dipole moment, μ.[25] There is a complete set of data for alkylpyridines showing little variation in $\Delta G^\circ_{g\rightarrow s}(\text{B})$ as expected from the small variations expected for nonpolar solvation effects and from the small changes in dipole moment. Additional free energy data are only available for the chloropyridines. They have enthalpy parameters close to those for methylpyridines and entropy parameters that are somewhat more positive than expected. For 3-chloropyridine, the low dipole moment suggests its enthalpy should be comparable to those for methylpyridines, but the higher dipole moment of 2-chloropyridine is reflected in only a modest increase in exothermic solvation; again, consideration of specific hydrogen bonding effects described below would help improve the fit with dipole moment by making the dipolar free energy and enthalpy values for the chloropyridines more negative by about 0.5 kcal mol^{-1}. Among the most polar pyridines are the 3- and 4-aminopyridines from dipole moments measurements. The measurement of free energies of transfer from gas to solution for these bases gives values of ca. −9 kcal mol^{-1},[14] but the high solubilities make the measurements approximate without correction for activity coefficients. Nevertheless, these very polar pyridines show the large negative free energies and enthalpies expected for the polar solvation terms from the Onsager equation and approximate entropy terms close to normal.

For the polar enthalpy term, $\Delta H^\circ_{\text{dip}}(\text{B})$, from eq 17, we now have data for a large number of polar substituted pyridines that make the correlation with dipole moment in Figure 4 quite informative. There is a rough, general correlation (correlation coefficient = 0.60, standard deviation = 1.3 kcal mol^{-1}) that nicely confirms the effectiveness of electrostatic theory and the Onsager equation in explaining the major trends in neutral pyridine solvation. The enthalpy of solvation terms, $\Delta H^\circ_{g\rightarrow s}(\text{B})$, for alkylpyridines show a quite scattered correlation with dipole moment, but the corrections for nonpolar solvation terms give an improved clustering of these substituents in Figure 4 within the expected narrow range of enthalpy. The remaining scatter for the alkyl substituents may be due to experimental errors in the enthalpy terms, since the free energies show more regular variations. The proposed dipolar solvation enthalpies for most polar pyridines, however, correlate with dipole moment, as expected from the Onsager relationship.

Arnett and co-workers have suggested the use of an alternative scheme for the analysis of the solvation of pyridines.[7a] From a limited data base of enthalpies of solvation of eight 3- and 4-substituted pyridines, they proposed an analysis involving two primary terms—one a van der Waals term proportional to the enthalpies of vaporization and a second due to hydrogen bonding. From theoretical calculations and free energies of hydrogen bond formation with *p*-fluorophenol, they found the hydrogen bond energies to increase with increasing pyridine basicities and assumed this relationship would hold for the hydrogen-bonding term in bulk water solvent. While we expect that all pyridines will hydrogen bond at the ring nitrogen to a water molecule in bulk solvent and that hydrogen bond energy will likely show a general correlation with pyridine basicity, it is entirely clear from our much more extensive set of heats of solvation for a large variety of pyridines with polar substituents that Arnett's analysis fails to explain the most dramatic solvation energy changes, particularly for the amino- and cyanopyridines. This problem stems from the small set of substituted pyridines included in their analysis—four pyridines with polar substituents, but none with large dipole moments, and four with nonpolar substituents. For example, 2-cyanopyridine's heat of solvation is the highest we have studied, over 9 kcal mol^{-1} higher than that for 4-cyanopyridine, which has the lowest heat of solvation. Yet both would be predicted to be poorly solvated from Arnett's proposed correlation with gas-phase basicity. With our larger set of 28 different pyridines, 15 of them polar, a more critical test of solvation theories is now possible. Although there is some scatter in the correlation with dipole moment in Figure 4, the solvation enthalpies of the most polar substituents, such as the cyano and amino groups, correlate nicely with dipole moment. Consideration of an additional specific hydrogen bond component of $\Delta H^\circ_{\text{dip}}(\text{B})$ that is proportional to PA, as proposed by Arnett et al., rather than dipole moment does have the effect of improving the correlation with dipole moment for the remaining dipolar term. The maximum improvement (from correlation coefficient = 0.60, standard deviation = 1.34 kcal mol^{-1}, to correlation coefficient = 0.68, standard deviation = 1.16 kcal mol^{-1}) is found by varying the hydrogen-bonding term over a range of 2.6 kcal mol^{-1} (10% of ΔPA) for the pyridines in Figure 4. The magnitude of the hydrogen bond energies between the water molecule and the pyridine ring nitrogen is expected to vary with the proton affinity of the pyridine, as has been shown for the hydrogen bonding[26] of pyridines to phenol in CCl_4; however, the range of this interaction, measured by determining the Gibbs free energy change for the formation of the complexes, is only 2.7 kcal mol^{-1}. For water, which is intrinsically less acidic than phenol, the magnitude of the interaction and the variation due to the changes in proton affinity are expected to be smaller than 2.7 kcal mol^{-1}. Correction of the data in Figure 4 for a smaller and more realistic hydrogen-bonding term varying over only 1.3 kcal mol^{-1} (5% of ΔPA) still gives some, perhaps significant, improvement in the correlation with dipole moment (correlation coefficient = 0.65, standard deviation = 1.21 kcal mol^{-1}). The overall variation in $\Delta H^\circ_{\text{dip}}(\text{B})$ is over 9 kcal mol^{-1}, so the nonpolar and dipolar solvation terms defined and modeled above still explain the major variations found in the solvation enthalpies for the neutral pyridines. Inclusion of an additional small hydrogen-bonding term proportional to PA may be valid, but, in either case, the 4-(dimethylamino)-, 2,6-dimethyl-, 2-amino- and 2-halopyridines show slightly irregular behavior in the correlation with dipole moment, perhaps because of steric interference with hydrogen bonding to nitrogen in the last three cases. Thus, the simplest electrostatic theory for a continuous dielectric solvent

---

(24) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486. Pauling, J.; Bernstein, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 4353.

(25) McClellan, A. L. *Tables of Experimental Dipole Moments*; Freeman: San Francisco, 1963; Vol. 1 (1974; Vol. 2).

(26) Hopkins, H. P., Jr.; Ali, S. Z. *J. Phys. Chem.* **1978**, *82*, 1268. For calculations on monohydrated 2-substituted pyridines see: Del Bene, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7146. Del Bene, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5191.

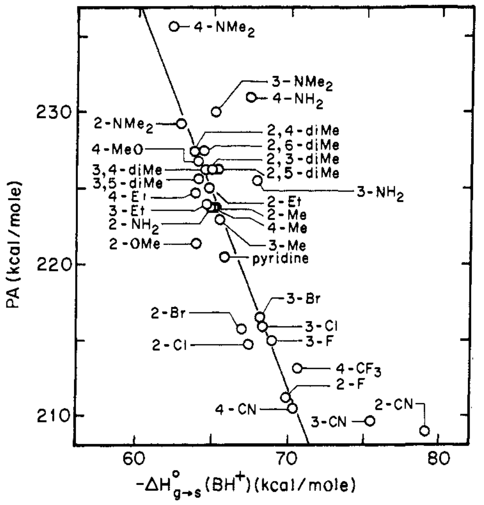

Figure 5. Plot of PA vs $-\Delta H^\circ_{g\to s}(BH^+)$ for substituted pyridines at 25 °C.

seems to do well in explaining pyridine solvation. A microscopic analysis in terms of individual hydrogen bonds to the pyridine nitrogen alone appears to be too simplistic at this stage, when the solvation can be affected by more remote solvent molecules and other sites of hydrogen bonding in many of the pyridines.

Solvation of Pyridinium Ions. With our understanding of neutral pyridine solvation and the electrostatic analysis scheme proposed for the analysis of proton-transfer reactions above, we are now in a position to discuss the solvation of pyridinium ions and evaluate the effectiveness and limitations of electrostatic theories in describing substituent effects in ionic solvation. One can analyze the raw $\Delta H^\circ_{g\to s}(BH^+)$ data for pyridinium ions by comparing the solvation enthalpies with the ability of the ion to act as an acid in hydrogen bonding with water. This is tested in Figure 5, where one sees a general correlation (correlation coefficient = 0.72), but with a number of pyridines, especially the amino-, (dimethylamino)-, methoxy, and cyanopyridines, as much as 8 kcal mol^{-1} more exothermically solvated than expected from the correlation line. These are just the same pyridines that have high dipole moments and large heats of solvation for the neutral bases. If we consider the heat of solvation of BH$^+$ to be made up of solvation terms with values identical with those for the corresponding neutral pyridines, as suggested earlier

$$\Delta H^\circ_{g\to s}(BH^+) = \Delta H^\circ_{cav}(BH^+) + \Delta H^\circ_{vdw}(BH^+) + \Delta H^\circ_{dip}(BH^+) + \Delta H^\circ_{chg}(BH^+) \quad (19)$$

then the first two nonpolar solvation terms and the dipole term can be subtracted out, leaving a term that we have defined to be the electrostatic solvation term

$$\Delta H^\circ_{g\to s}(BH^+)^{el} = \Delta H^\circ_{g\to s}(BH^+) - \Delta H^\circ_{g\to s}(B) = \Delta H^\circ_{chg}(BH^+) \quad (20)$$

in place of $\Delta H^\circ_{g\to s}(BH^+)$ in the analysis of the electrostatic charge–solvent interaction term for BH$^+$, $\Delta H^\circ_{chg}(BH^+)$. This procedure is consistent with the definition of the electrostatic term given earlier and considers the dipolar solvation term to be the same in the pyridinium ion as in the pyridine; i.e., the changes in the dipolar interactions caused by the charge are included in the electrostatic term. While this approach is arbitrary, it has been successful in handling nonpolar solvation for alkyl amines[5] and can be seen to be effective here in compensating for the nonpolar and dipolar solvation by noting the improved correlation (correlation coefficient = 0.88 for all substituents, higher for the 2-, 3-, and 4-substituent classes; see Table II) in the plot of the electrostatic heat of solvation vs PA in Figure 6. For the alkylpyridines, the correlation is improved a little, but the improvement is particularly noteworthy for the amino-, (dimethylamino)-, methoxy-, and cyanopyridines. The improved correlations in Figure 6 for these most polar pyridines provide evidence that our definition of electrostatic solvation is as empirically effective in the treatment of dipolar solvation as it has been for nonpolar solvation terms.[5]

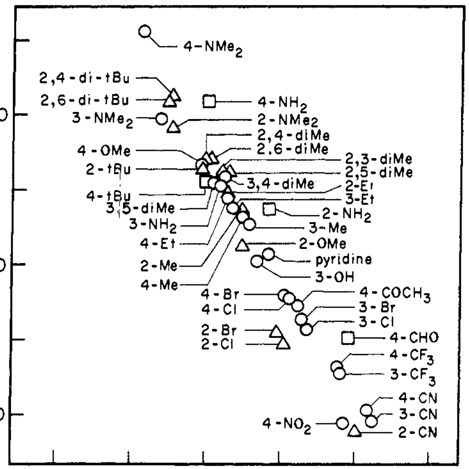

Figure 6. Plot of PA vs $-\Delta H^\circ_{g\to s}(BH^+)^{el}$ for substituted pyridines at 25 °C.

From the thermodynamic cycle in Scheme I, one can see that the differences between gas- and solution-phase basicities result from differences between the corresponding solvation parameters for the neutral base and the ion. This difference, due to solvation, is then merely equal to the term we have defined in eq 11 as the electrostatic solvation term, and differences in these electrostatic terms are equal to ΔX°_{exl} for parameters from eq 13 for proton-transfer equilibria. If the electrostatic solvation effects on enthalpies, for example, are indeed proportional to changes in PA, or ΔH°_{inl}, from eq 8, then the $\Delta H^\circ_{g\to s}(BH^+)^{el}$ terms, or ΔH°_{exl}, from eq 8, must be proportional to PA as confirmed in Figure 6.[27]

Enthalpies of transfer from the gas to the aqueous phase for the substituted pyridinium ions, $\Delta H^\circ_{g\to s}(BH^+)$, vary over a range of 17 kcal mol^{-1}, which is nearly twice as large as the 9 kcal mol^{-1} spread for the neutral pyridines. These variations oppose one another in $\Delta H^\circ_{g\to s}(BH^+)^{el}$, which varies over 12 kcal mol^{-1} in a remarkably regular manner to give a very good linear relationship with PA. The changes in $\Delta H^\circ_{g\to s}(BH^+)^{el}$ vary with PA such that they oppose the PA changes in solution leading to the linear attenuation of the gas-phase basicities on passing into the aqueous phase, as seen in Figures 1 and 2. The conjugate acids of the least basic pyridines are the most exothermically solvated, whereas the most basic pyridines form cations that are the least exothermically solvated. These correlations are consistent with the principles of the Born theory for electrostatic interactions of a charged molecule in a dielectric continuum. For example, the decrease in positive charge density expected at the ring NH$^+$ in the aminopyridinium ions should cause a decrease in the solvation enthalpy. Similarly, electron-withdrawing substituents should lead to an increased concentration of positive charge near the ring nitrogen. Such charge density effects have been noted previously to correlate more or less well with gas and solution basicities.[5,8,28] In the above analysis, changes in PA values have been anticipated to be accompanied by variations in the charge density at the ring nitrogen, and we have carried out molecular orbital calculations at the CNDO/2, AM1, and ab initio STO-3G, 3-21G, and 6-31G* levels[8,29] to test for such a correlation. In Figure 7, the PA's, which correlate with $\Delta H^\circ_{g\to s}(BH^+)^{el}$ values, are seen to be linearly related

---

(27) The correlation in Figure 6 is, in fact, equivalent to that in Figure 2 in accord with the cycle in Scheme I.

(28) Catalan, J.; De Paz, J. L. G.; Yanez, M.; Elguero, J. *J. Am. Chem. Soc.* **1984**, *106*, 6552. Catalan, J.; Mo, O.; Perez, P.; Yanez, M. *J. Am. Chem. Soc.* **1979**, *101*, 6520.

(29) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

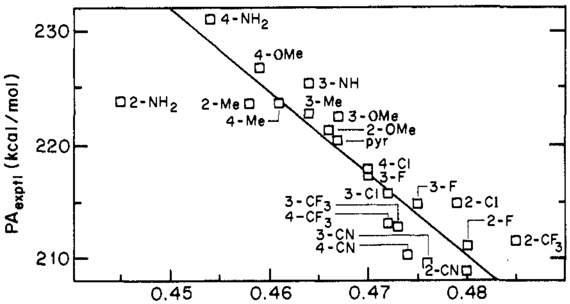

Figure 7. Plot of PA vs charge density at H of NH$^+$ from 6-31G*//3-21G ab initio calculations for substituted pyridines.

(correlation coefficient = 0.84, standard deviation = 2.5 kcal mol^{-1} for all substituents but 2-NH$_2$) to the Mullikan charge density at the NH$^+$ hydrogen from 6-31G*//3-21G calculations. Charges calculated at AM1//AM1, STO-3G//STO-3G, 3-21G//3-21G, and 6-31G*//6-31G* (for the 4-substituted pyridines) consistently show comparable correlations as do plots of $\Delta H°_{g\to s}(BH^+)^{el}$ vs charge density. Some variation in charges at the NH$^+$ H were noted as the geometry optimization method was changed. Much larger changes in charge are observed for the total charge on the CHNHCH group of the pyridinium ring, which correlates very well with PA and $\Delta H°_{g\to s}(BH^+)^{el}$ for the 3- and 4-substituted pyridines. These charges are not so sensitive to geometry optimization, and the changes appear clearly significant, but the charges on the NH$^+$ H were plotted in Figure 7 to get a full set of data for all pyridines, including the 2-substituted ones.[30] The observed correlations, attenuation effects in Figures 1, 2, and 6, and the derived relationships in eqs 6 and 7, are now readily explained by the simple electrostatic charge solvation arguments and charge density correlations described above.

Most 3- and 4-substituents in the correlations in Figures 1, 2, and 6 fall within 0.5 kcal mol^{-1} of the correlation lines and most 2-substituents within 1 kcal mol^{-1}, but a few are anomalous. The 2- and 4-aminopyridines appear to have abnormally large solvation energies and enthalpies by ca. 2 kcal mol^{-1}, but not the (dimethylamino)- or 3-aminopyridines. This suggests that the 2- and 4-aminopyridinium ions enjoy especially strong hydrogen bond stabilization at the amino groups as well as at the ring NH$^+$, since considerable positive charge should be concentrated at the amino hydrogens. The 3-aminopyridine would, of course, not show such a strong resonance interaction and behaves normally. Charge densities from the theoretical calculations of the 2- and 4-aminopyridinium ions confirm this argument by showing increased charge densities at the amino NH$_2$ hydrogens, when compared to 3-aminopyridinium ion, the neutral amines, or the CH$_3$ H's of corresponding methylpyridines. An alternative explanation for the amino substituent anomaly could have been that the subtraction of the $\Delta H°_{dip}(B)$ term to compensate for $\Delta H°_{dip}(BH^+)$ is not appropriate and distorts the amino solvation data, but this explanation does not explain why the 3-amino substituent or the cyano substituents, which all show large $\Delta H°_{dip}(B)$ terms, behave normally in Figures 2 and 6.

The 4-formyl substituent appears to show abnormally strong ionic solvation also, but an explanation of this effect may depend upon a more complete analysis of the degree of hydration of the carbonyl group in the neutral and ionic species.[31] Quinoline and isoquinoline show weaker solvation of their conjugate acid ions, but only by about 1 kcal mol^{-1}. Similarly, 2-phenylpyridine's solution basicity is unusually low. While the enthalpy of solvation of 2,6-di-*tert*-butylpyridine is normal, these substituents lead to a large, 3.5 kcal mol^{-1}, deviation from the $\Delta G°$ plot in Figure 1. This effect has been analyzed in detail[20] and found to result from the entropy terms due to reduced rotational freedom in the *tert*-butyl groups and perhaps waters of the hydrated 2,6-di-*tert*-butylpyridinium ion. The 3- and 4-(methoxycarbonyl)-pyridines, methylnicotinate and methylisonicotinate, show 1–2 kcal mol^{-1} deviation from the $\Delta G°$ plot, indicating an abnormally low solvation free energy for reasons that are, as yet, unclear.[32]

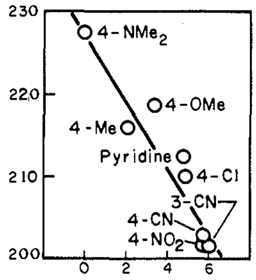

Figure 8. Plot of GB vs $-\Delta G°_{400K}$ for the attachment of a single water molecule to BH$^+$ for substituted pyridines at 25 °C.

Arnett et al. have argued that the variation in the solvation enthalpies of the pyridinium cations is due to differences in hydrogen bonding of the pyridinium ion to a water molecule in the solvent. Kebarle and Davidson[33] have, in fact, measured the Gibbs free energy change for the attachment of one water molecule to substitued pyridinium ions and estimated the corresponding enthalpy values.

$$BH^+ + H_2O \rightarrow BH{\cdot}OH_2^+ \tag{21}$$

They found an approximate linear correlation between these enthalpies and the gas-phase basicities (Figure 8). This linear correlation can, of course, be viewed as a result of an increased interaction energy for the first water of attachment as the charge density at the NH$^+$ of the cation increases and the GB decreases, in parallel with the electrostatic arguments above. The variation in this single water attachment energy is about 6 kcal mol^{-1} compared to a variation of 17 kcal mol^{-1} for $\Delta H°_{g\to s}(BH^+)$ and 12 kcal mol^{-1} for $\Delta H°_{g\to s}(BH^+)^{el}$. Thus, the interaction with the bulk water is about as important as the first water of hydration to the total solvation effect. It is, therefore, clear that hydrogen bonding does occur between the pyridinium ions and water and will vary with the PA of the pyridine. Since the variations in hydrogen bonding of the first water and the variations in electrostatic interactions with the bulk water both seem to correlate with PA and charge density at the ring NH$^+$, however, an explanation based solely on electrostatic interactions with the positive charge has the advantage of simplicity, in the Occam's razor sense.

Conclusions

The gas- and solution-phase basicities of an extensive set of 2-, 3-, and 4-substituted pyridines show good corelations for both $\Delta G°$ and $\Delta H°$ over a 27 kcal mol^{-1} range of gas-phase basicity. These remarkable correlations result from large, but regular, solvation terms that have the effect of partially canceling the intrinsic substituent effects. Combination of gas- and solution-phase data makes possible a complete thermodynamic analysis of these basicities and solvation energies using the thermodynamic cycle in Scheme I as expressed in the $\Delta G°$, $\Delta H°$, and $\Delta S°$ data in Table I. The primary conclusions from a detailed analysis of these data follow:

(1) The gas- and aqueous-phase free energies of protonation for 3- and 4-substituted pyridines correlate with a 2.43-fold attenuation factor and a correlation coefficient of 0.977, while the attenuation factor for the enthalpies of protonation is 2.47 and the correlation coefficient 0.958. Since these slopes are about the same, the entropies of protonation are nearly constant throughout

---

(30) Correlations with the sum of charges at N and its attached hydrogen were less satisfactory, however, with correlation coefficients of 0.24 for 2-, 0.25 for 3-, and 0.79 for 4-substituted pyridines. For details of the correlations, see: Toure, P. Ph.D. Thesis, University of California, Santa Barbara, and ref 8.

(31) Cabani, S.; Conti, G.; Giannio, P. *J. Chem. Soc. A* **1969**, 1363. Cabani, S.; Conti, G. *Gazz. Chim. Ital.* **1965**, *45*, 533.

(32) Anomalous entropy effects could be responsible for this effect.

(33) Davidson, W. R.; Sunner, J.; Kebarle, P. *J. Am. Chem. Soc.* **1979**, *101*, 1257. See also: Moet-ner, M. *J. Am. Chem. Soc.* **1984**, *106*, 1265.

the series of 3- and 4-substitued pyridines.

(2) The 2-substituted pyridines fit on a somewhat different correlation line for free energies and enthalpies with smaller attenuation factors of 1.4 and 1.7, respectively. The correlation coefficients are poorer (0.901 and 0.911) and the attenuation factors smaller than for the 3- and 4-substituents. One explanation for the smaller attenuation by the solvent for the 2-substituents can be found within the framework of Bjerrum and Kirkwood–Westheimer electrostatic treatments of charge–dipole interactions,[3d] where the effect of dipolar solvent intervention would decrease as the distance of separation between the substituent and positive charge decreases.

(3) For the 2-substituted pyridines, the larger attenuation factor for the enthalpies vs the free energies of protonation is the result of a weak correlation (Table II) between the entropies of protonation and PA. The small variation (1–2 kcal mol^{-1}) in $T\Delta S^\circ_{\text{prot,s}}$ is of a magnitude expected on the basis of simple electrostatic theory and known experimental data for alkali metal ions.

(4) The 2- and 4-aminopyridines, 2,6-di-*tert*-butylpyridine, methylnicotinate, and methylisonicotinate deviate substantially from the correlations. The aminopyridines exhibit anomalously high (by 2–3 kcal mol^{-1}) aqueous basicities as a result of increased solvation at the sites of high positive charge densities on the resonance-stabilizing 2- and 4-amino groups of the pyridinium ions, an effect not observed for the 3-amino or (dimethylamino) groups. The anomalous entropy effects in 2,6-di-*tert*-butylpyridine solvation have been described by us previously.[13] The reason(s) for the 1–2 kcal mol^{-1} deviation in free energy by methylnicotinate and methylisonicotinate is (are) not known.[32]

(5) Analysis of the data here permits a separation of Hepler's intrinsic and extrinsic (solvation) substituent effects in the aqueous equilibria for proton transfer.[2] The extrinsic, or solvation, effects for the pyridines and pyridinium ions have been further separated here into terms for cavity formation, van der Waals interactions and solvent structure making by alkyl groups, dipole–solvent interactions, and charge–solvent interactions.

(6) The linearity of the ΔG° plots in Figure 1 for the 3- and 4-substituted pyridines agrees with the predictions of Hepler's theory. The slope of about 2 for the lines is very different from the slope of 1.0 predicted from Hepler's original theory (eq 4) but can be accommodated by Hepler's modified theory (eq 5). The linear correlation of $\Delta H^\circ_{\text{prot,s}}$ values in Figure 2, however, is not contemplated in Hepler's theories, leading us to propose a new analysis expressed in eqs 6–10 that is consistent with known experimental data in gas and solution phases for substituted pyridines and other classes of acids and bases.[5] This new analysis is based on an expectation, from simple electrostatic theories, that the external (solvation) enthalpy and entropy changes with changing substituents will generally be proportional to the intrinsic changes in proton affinity. This expectation will be realized when the substituents act by inductive destabilization or resonance stabilization of the ion, since these inductive (or field) and resonance effects cause the positive charge density in the ion to increase or decrease, respectively, in proportion to the change in PA. This is confirmed by theoretical calculations summarized in Figure 7.

(7) Simple electrostatic theories suggest correlations between charge density and entropy of solvation.[5] The correlation for entropy parameters in Figure 3, however, is much poorer than the correlations found in Figures 1 and 2 (see Table II).

(8) The changes in solvation of substituted neutral pyridines are mainly due to changes in the dipolar solvation term which correlates with dipole moment (Figure 4). Terms for cavity formation and van der Waals interactions and solvent structure making may be separated from the dipolar term as shown in Table III. Specific N·HOH hydrogen-bonding terms may be present as well, as suggested by Arnett et al.,[7a] but these terms must be small (1–2 kcal mol^{-1}).

(9) We have proposed the empirical definition of an "electrostatic" solvation term for ions,[5] which is equal to the change in solvation energy induced by attachment (or detachment) of a proton and the associated charging of the neutral molecule. It is just this critical electrostatic solvation term that is responsible for the attenuation of the gas-phase basicity differences on passing into aqueous solution. Analysis of solvation data for ammonium ions shows that the nonpolar solvation terms—cavity, van der Waals, and solvent structure making—are felt in the ion as well as the neutral and may be conveniently separated to leave the electrostatic charge–solvent interaction term.[5] In this analysis, the dipolar solvation terms for the pyridines are subtracted from the total solvation energy of the pyridinium ions as well. This leaves an electrostatic term defined, attractively, as equal to the change in solvation due to protonation. Unlike the nonpolar solvation terms, which are expected to remain about the same in the ion and neutral, the *dipolar* terms in the ion and neutral need not be the same. This treatment, however, significantly improves the empirical correlations in Figure 6 vs Figure 5. We have attributed this electrostatic term to the charge–solvent interaction and then, as expected, find that this term decreases with increasing charge delocalization for charge-stabilizing substituents and increases with increasing charge density at the ring NH for inductively destabilizing substituents. Empirically, these electrostatic charge solvation terms correlate closely with gas-phase stabilization energies, PA's (Figure 6), and semiempirical and ab initio calculated charge densities at the ring NH (Figure 7). The success of the correlation with PA is precisely the origin of the close correlation of gas and solution basicities. This helps justify the attribution of our electrostatic term to the charge–solvent interaction term, but leaves unclear why these correlations are better than those with the total solvation energies of the pyridinium ions in Figure 5, in which the neutral dipolar terms have not been subtracted. Resolution of this problem will have to await more complete theoretical treatment of the solvation of the ion and neutral.

The analysis proposed here for substituted pyridinium ions should be generally applicable to the analysis of substituent effects and solvent effects in other acid–base reactions and for solvents other than water. This set of substituted pyridines provides the largest body of data now available for testing such an analysis for any class of acid–base reaction. Where other tests are available, the resulting understanding of the experimental solvation data using only the most simple electrostatic theoretical concepts is gratifying, at this point.[34] It is hoped this work will stimulate further experimental tests and development of more sophisticated solvation theories.[35]

Registry No. Pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 2-ethylpyridine, 100-71-0; 3-ethylpyridine, 536-78-7; 4-ethylpyridine, 536-75-4; 2,3-dimethylpyridine, 583-61-9; 2,4-dimethylpyridine, 108-47-4; 2,5-dimethylpyridine, 589-93-5; 2,6-dimethylpyridine, 108-48-5; 3,4-dimethylpyridine, 583-58-4; 3,5-dimethylpyridine, 591-22-0; 2-aminopyridine, 504-29-0; 3-aminopyridine, 462-08-8; 4-aminopyridine, 504-24-5; 2-(dimethylamino)pyridine, 5683-33-0; 3-(dimethylamino)pyridine, 18437-57-5; 4-(dimethylamino)pyridine, 1122-58-3; 2-fluoropyridine, 372-48-5; 3-fluoropyridine, 372-47-4; 4-fluoropyridine, 694-52-0; 2-chloropyridine, 109-09-1; 3-chloropyridine, 626-60-8; 4-chloropyridine, 626-61-9; 2-bromopyridine, 109-04-6; 3-bromopyridine, 626-55-1; 4-bromopyridine, 1120-87-2; 2-(trifluoromethyl)pyridine, 368-48-9; 3-(trifluoromethyl)pyridine, 3796-23-4; 4-(trifluoromethyl)pyridine, 3796-24-5; 2-methoxypyridine, 1628-89-3; 3-methoxypyridine, 7295-76-3; 4-methoxypyridine, 620-08-6; 2-cyanopyridine, 100-70-9; 3-cyanopyridine, 100-54-9; 4-cyanopyridine, 100-48-1; 2-(methylthio)pyridine, 18438-38-5; 4-(methylthio)pyridine, 22581-72-2; 3-pyridinol, 109-00-2; 2-chloro-6-methylpyridine, 18368-63-3; 3-pyridylcarboxylic acid, 93-60-7; 4-pyridylcarboxylic acid, 2459-09-8; 4-pyridylcarboxaldehyde, 872-85-5; 4-nitropyridine, 1122-61-8; 4-vinylpyridine, 100-43-6; 1-(4-pyridyl)-ethanone, 1122-54-9; quinoline, 91-22-5; isoquinoline, 119-65-3.

---

(34) Structural effects which do not operate by stabilization or destabilization of the ion, but by effects on the neutral, e.g., resonance stabilization of the neutral, that do not cause changes in ionic charge density clearly will not follow the patterns discussed here; see ref 5.

(35) See, for example: Singh, U. C.; Brown, F. K.; Bash, P. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 1607. Jorgensen, W. L.; Briggs, J. M.; Gao, J. *J. Am. Chem. Soc.* **1987**, *109*, 6857.