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Complete Thermodynamic Analysis of the Hydration of Thirteen Pyridines and Pyridinium Ions. The Special Case of 2,6-Di-*tert*-butylpyridine

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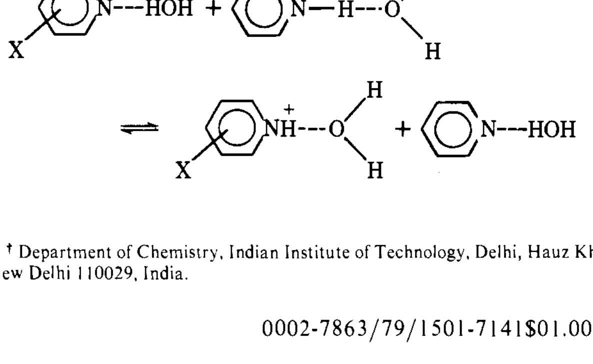
Abstract: An apparatus is described for measuring vapor pressures and deriving Henry's Law constants at a series of temperatures in order to obtain standard free energies and enthalpies and entropies of solution from the gas phase to water for a number of substituted pyridines. The results agree well with comparable published values. In view of its low volatility and low solubility, special strategies were required to study 2,6-di-*tert*-butylpyridine. By using these data for solution of the pyridine bases from the gas phase to water, and published values for the thermodynamics of protonation in the gas phase, a complete analysis of the ionization in water is presented for all 13 pyridines. The most interesting new data are those for the solvation of the 13 pyridinium ions. In terms of all these properties (and also the infrared hydrogen-bonding spectra of its salts presented here), 2,6-di-*tert*-butylpyridine is differentiated sharply from the rest of the series. All of the results support the proposal that steric hindrance to hydration of the 2,6-di-*tert*-butylpyridinium ion is largely responsible for the very low relative basicity in water in contrast to its high basicity in the gas phase.

Introduction

Recent advances in gas-phase chemistry provide a large fund of information about the intrinsic acidities and basicities of several hundred organic compounds in the absence of solvents.[1] Combinations of thermodynamic values for proton transfer processes in the gas phase with the corresponding data in solution can lead to exact relative values for solvation of the acidic cation (BH^+) or basic anion (A^-) provided that thermodynamic data for solution of the neutral conjugate base (B) or acid (AH) are available.[2] This type of analysis has been applied to yield solvation energies (and in some cases entropies) for a number of ammonium,[3-7] oxonium, sulfonium, and phosphonium ions in water and HSO_3F[8] and a variety of organic anions in water and Me_2SO.[9]

Analysis of the enthalpies of ionization of a series of pyridines in water[10] showed that the principal effect of substituents on pyridine protolysis is through hydrogen bonding of water to the neutral pyridines and of the pyridinium ions to water.



(1)

The experimental results in this case agreed remarkably well with STO-3G calculations of the substituent effects on the hydrogen-bonded systems.

For most purposes, free energy differences are ipso facto a more definitive measure of chemical driving force than are enthalpies, although variations in ΔG are often proportional to or equal to variations in ΔH. However, water is a notoriously poor solvent for relating enthalpies to free energies because of the large temperature-dependent effects caused by the influence of solutes on water structure.[11-15] It is therefore especially important to have free energies of solvation available for rigorous comparison of pK_a values in water with those in the gas phase.

The chief obstacle at present to developing an extensive catalogue of free energies of hydration for organic cations is a dearth of reliable Henry's Law constants for the equilibrium distribution of the neutral bases between the gas phase and water. A complete dissection into the 12 relevant (ΔG, ΔH, and ΔS) parameters for protolysis and hydration has been reported by Aue[4,15] and ourselves[3] for aliphatic and alicyclic amines for which Henry's Law constants and enthalpies of solution were known. We are now interested in broadening the analysis to other bases.

The present article describes a simple apparatus for measurement of Henry's Law constants with high precision. This is used to get the necessary free energy data to complete the analysis of the hydration thermodynamics for 13 pyridines.

This study includes data and estimates of thermodynamic parameters for 2,6-di-*tert*-butylpyridine (DTBP). There is considerable evidence that this base and its conjugate acid pyridinium ion are precluded from the types of hydrogen-

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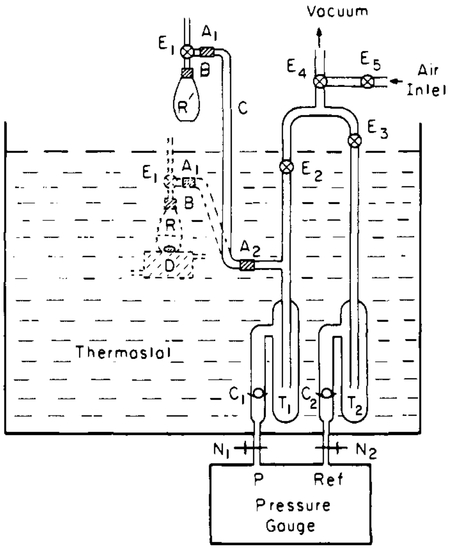


Figure 1. Vapor pressure apparatus.

bonding interactions with water which we have shown are the chief factors in regulating the ionization of other pyridines in water. Comparison of its solvating behavior with that of the other pyridines is therefore interesting.

Experimental Section

Vapor-Pressure Technique. Figure 1 shows the essential features of the apparatus used for vapor-pressure measurements. Most of the equipment is completely submerged in a constant-temperature bath, but easy access to the vessel containing the solution is maintained so that outgassing and the addition of increments of solute can be accomplished conveniently. Vapor pressures were measured with a fused quartz pressure gage manufactured by Texas Instruments Inc., Houston, Texas. Bath temperature was controlled by a Tronac 1040 precision temperature controller with a long term stability of better than ±0.006 °C, as demonstrated by a Hewlett-Packard Model 2801 A quartz thermometer. A mercury diffusion pump (not shown) provided evacuation down to 10^{-3} to 10^{-4} Torr.

For a typical measurement, the sample vessel was cleaned, dried, and capped with a rubber septum after flushing with dry argon for about 0.5 h. Concurrently, the apparatus was flushed repeatedly as follows. Valves E_1 and E_3 were closed and the system was evacuated. Then valve E_4 was closed and dry argon was flushed in through valve E_1 while the rotatable arm C was in the *up* position (shown with solid lines). Evacuation and flushing were repeated several times. The sample vessel was then filled with 2-5 mL of the liquid compound of solution sample and connected to the setup through glass tapered joint, B. The sample was outgassed by repeated freeze-thaw cycles using dry ice-acetone mixture, and the pressure gauge was zeroed after evacuating the apparatus when valves E_2 and E_3 were open. Valve E_2 was closed and the sample vessel was slowly lowered into the constant-temperature water bath to the *down* position (dotted lines) over the water-driven magnetic stirrer, D. This was accomplished without loss of vacuum by rotation around spring-loaded ₮ joints A_1 and A_2. The water-driven stirring motor was started and the sample vessel was allowed to stand in the bath for about 20-30 min until thermal equilibrium was reached and then the gauge reading was recorded and converted to pressure (mmHg) by multiplying by the tube constant provided with the gauge. For each sample, the measurements were repeated at least four to eight times.

Purification of Compounds. The commercially available liquid pyridines, including 2,6-di-*tert*-butylpyridine (Chemical Samples Co.), were distilled over solid KOH and stored overnight over activated molecular sieves before their use. Piperidine was distilled twice and dried over activated molecular sieves. Purity of compounds was established by boiling points and gas chromatography.

Infrared spectra of the pyridinium salts were measured, as before,[16] as hexachlorobutadiene mulls by using a Perkin-Elmer 247 spectrometer. All salts were handled in a drybox under argon, but the fluoride salts were so hygroscopic that absorbed water probably caused poor elemental analyses. The microanalyses were performed by Galbraith Laboratories (Table V).

Solubility of 2,6-Di-*tert*-butylpyridine (DTBP) in Water. A saturated solution of DTBP in water was obtained by stirring a mixture of DTBP (~0.4 mL) and water (50 mL) in a 60-mL separatory funnel overnight at ambient temperature (23.5 ± 1.0 °C). The aqueous layer was separated and examined by ultraviolet spectroscopy. Since the $\pi-\pi^*$ absorbance was too large for direct concentration measurement, the saturated aqueous solution was diluted 10 times and 100 times for two separate spectral comparisons. For Beer's law calibration, ten aqueous solutions of different concentrations over the range of 9.71×10^{-6} to 9.76×10^{-4} M were prepared, and the absorbance of the $\pi-\pi^*$ band was recorded with a Cary 15 spectrophotometer. The concentrations of the solutions from the saturation experiments were obtained from a plot of absorbance vs. concentration, and then the solubility of DTBP in water was calculated, yielding a value of 9.4×10^{-3} M at 23.5 ± 1.0 °C.

Results

Vapor Pressures and Enthalpies of Vaporization. Many methods have been described for the measurements of vapor pressures of pure liquids[17-20] and their aqueous solutions.[21-24] Also, enthalpies of vaporization may be determined from the temperature coefficient of the vapor pressure or calorimetrically.[25] Enthalpies of solvation of neutrals, such as the pyridines, from the gas phase to high dilution in water can be determined exactly by subtracting the enthalpies of vaporization of the pure neutrals from their enthalpies of solution in water.[10] For the work presented here, we have chosen to use vapor-pressure measurements primarily since they can provide the complete hydration data for the neutrals: free energies, $\Delta G_s{}^{\circ g \rightarrow H_2O}(B)$, Henry's Law constants, enthalpies, $\Delta H_s{}^{\circ g \rightarrow H_2O}(B)$ from temperature coefficients of Henry's Law constants, and entropies, $\Delta S_s{}^{\circ g \rightarrow H_2O}(B)$ by combination of the other two hydration properties.

Before attempting to study binary systems, we confirmed the ability of our equipment to determine accurate vapor pressures and enthalpies of vaporization through comparison with reliable standard data. Table I presents our results including some new data for the pyridines. Enthalpies of vaporization were obtained by two methods that are frequently used for treatment of temperature coefficients of vapor pressure. Column "a" in Table I presents the results from using the exact Clapyron equation and column "b" shows results using the more complex Antoine equation.[26] For the three cases which permit comparison with published values, there is no reason to prefer one treatment over the other.

Standard Free Energies and Enthalpies of Solution. Having demonstrated that this approach provides reliable thermodynamic data for vaporization of pure liquids, we next turned to the study of aqueous solutions. Following Cabani et al.,[23] we determined the activity coefficient of the solute at infinite dilution (f_∞) by extrapolating a plot of $\log f'$ vs. X_B as $X_B \rightarrow 0$ where

$$f' = \frac{(P_T - X_W P_W{}^\circ)}{X_B P_B{}^\circ} \qquad (2)$$

and P_T is the total vapor pressure, $P_W{}^\circ$ and $P_B{}^\circ$ are vapor pressures of pure water and pure base, and X_W and X_B are the corresponding concentrations (in mole fractions) in solution.

The standard free energies of solution $[\Delta G_S{}^\circ(B)]$ and hydration $[\Delta G_s{}^{\circ g \rightarrow H_2O}(B)]$ (Table II) were calculated through the following equation.[20]

$$\Delta G_s{}^\circ = RT \ln f_\infty \qquad (3)$$

and

$$\Delta G_s{}^{\circ g \rightarrow H_2O} = RT \ln f_\infty + RT \ln P_B{}^\circ \qquad (4)$$

Table I. Vapor Pressures (mmHg) at Various Temperatures

compd	temp, °C						ΔH_{vap} (25 °C), kcal/mol		
	10.29	15.29	20.29	25.29	30.00	40.00	*a*	*b*	lit. values
pyridine	8.794 ± 0.032	11.866 ± 0.016	15.767 ± 0.029	20.986 ± 0.006			9.69	9.69	9.61[c], 9.60[d] 9.66[e]
4-methylpyridine	2.193 ± 0.006	3.101 ± 0.015	4.271 ± 0.006	5.773 ± 0.016			10.86	10.87	10.83[f]
3-chloropyridine	1.863 ± 0.014	2.592 ± 0.021	3.591 ± 0.014	4.693 ± 0.011			10.44	10.38	
2-chloropyridine	0.701 ± 0.019	1.054 ± 0.010	1.469 ± 0.007	1.922 ± 0.020			11.27	11.06	
4-*tert*-butylpyridine	0.165 ± 0.007	0.255 ± 0.003	0.360 ± 0.004	0.506 ± 0.009	0.720 ± 0.011 (30.35 °C)		12.4	12.2	
2,6-di-*tert*-butylpyridine			0.177 ± 0.004 (20.00 °C)	0.255 ± 0.003 (25.00 °C)	0.407 ± 0.006 (30.00 °C)	0.765 ± 0.004 (40.00 °C)	13.5	13.7	
water	9.20 ± 0.05 (10.00 °C)	12.65 ± 0.03 (15.00 °C)	17.56 ± 0.04 (20.00 °C)	23.763 ± 0.006 (25.00 °C)			10.61	10.50	10.58[d]
water[d]	9.20[d] (10.00 °C)	12.78[d] (15.00 °C)	17.53[d] (20.00 °C)	23.76[d] 23.752[g] (25.00 °C)					

[a] By integrated Clausius Clapyron equation. [b] By Antoine equation.[26] [c] McCollough, J. P.; et al. *J. Am. Chem. Soc.* **1957,** *79,* 4289. [d] Ref 18. [e] Andon, R. J. L.; et al. *Discuss. Faraday Soc.* **1953,** *15,* 168. [f] Scott, D. W.; et al. *J. Phys. Chem.* **1963,** *67,* 685. [g] Miller, W. J.; Grunwald, E. *J. Phys. Chem.* **1964,** *68,* 1285.

where $P_B°$ (in atm) is the vapor pressure of pure amine. The usual negative sign on the right of the equation is omitted since that would refer to the vaporization process rather than to solution.

For highly insoluble compounds of low vapor pressure, Hine and Mookerjee[27] take C_w as the saturated aqueous solubility of the base in moles per liter and C_g as the vapor pressure. This approach permits calculation of the standard free energy of solution for the amine in water from the solubility and vapor pressure which we have determined. Thus, at 23.5 °C, $C_w = 9.4 \times 10^{-3}$ mol/L which must be nearly the same at 25 °C since the heat of solution of this compound is negligible. From this and the measured vapor pressure in Table I, we derive $\Delta G_s°^{g \rightarrow H_2O}(\text{DTBP}) = 1.364 (\log 9.4 \times 10^{-3} - \log 0.255 + 4.269) = 3.87$ kcal/mol. We have proposed[10] that the difference between the enthalpies of solution in water of similarly substituted pyridines and benzenes may be ascribed primarily to hydrogen bonding from water to the pyridine nitrogen atom. If 2,6-DTBP is not hydrogen bonded in this manner, we might expect that its $\Delta G_s°^{g \rightarrow H_2O}$ would be well modeled by that for 1,3-di-*tert*-butylbenzene. Using the group contributions of Hine and Mookerjee,[27] one may estimate a value of 4.3 kcal/mol for this compound. The near agreement with our values for DTBP lends support to all the assumptions on which the values are based.

Table III presents standard free energy data including some comparisons with published values. Agreement is excellent.

When enthalpies of solution[10] are combined with enthalpies of vaporization, the enthalpies of hydration from the gas phase $[\Delta H_s^{g \rightarrow H_2O}]$ are obtained. Comparison of our values derived in this manner[10] with those of Andon et al.,[21] which were obtained from temperature coefficients of vapor pressures, show good agreement on relative values of $[\delta \Delta H_s^{g \rightarrow H_2O}(B)]$ but a systematic difference of about 0.5 kcal/mol, the calorimetric values being more exothermic. Their vapor pressure work appears to be of high quality and is intuitively attractive since it approaches directly the thermodynamics of distribution between vapor and solution. The source of the discrepancy is not obvious to us, and we will beg the question of its origin since it is the relative values which are needed for our analysis, and they agree well. Data for a typical study of 2-chloropyridine are shown in Table II.

Table II. Calculation of Standard Free Energy of Hydration of 2-Chloropyridine[a]

$(X_B) \times 10^3$	P, mmHg	f'	$\log f'$
1.970	24.74	260.9	2.423
2.760	25.07	255.0	2.407
3.273	25.27	246.9	2.392
4.211	25.48	219.6	2.342

$f^{\infty} = 317.1$ (least-squares intercept)
$\Delta G_s = RT \ln f_\infty$
$\Delta G_h° = RT \ln f_\infty + RT \ln P_B°$

[a] See ref 23. Activity coefficients are based on the mole fraction concentration scale referred to a standard state of infinite dilution.

Table III. Free Energies of Solution of Various Bases in Water at 25 °C

system	$\Delta G_s°$, kcal mol^{-1}	
	this study	lit.
1. piperidine-water	1.09 ± 0.01	1.08 ± 0.01[a]
2. 3-chloropyridine-water	3.27 ± 0.01	
3. 2-chloropyridine-water	3.41 ± 0.02	
4. 4-methylpyridine-water	2.33 ± 0.01	2.24 ± 0.02[b]
5. pyridine-water	1.72 ± 0.01	1.71 ± 0.01[b]

[a] Reference 23. [b] Reference 21. Standard free energies refer to a standard state of infinite dilution in water and are derived from mole fraction activity coefficients.

Hine and Mookerjee[27] have recently tabulated most of the available data for distribution of organic compounds between the gas phase and aqueous solution. Furthermore, they have used them to develop an additivity scheme which can be used for calculation of unmeasured values. The difficulties of comparing such data are considerable,[11] both because of experimental problems and the subtle differences in defined standard states which may produce large (and purely formal) discrepancies in standard free energies and entropies of solution. The approach of Hine and Mookerjee is of considerable value for relating gas phase proton transfer to that in water. Accordingly, we adopt their convention of taking the Henry's Law constant as $\gamma_\infty = C_w/C_g$, where C_w and C_g represent moles per liter concentrations in aqueous solution and the gas phase, respectively. Since our activity coefficients at infinite dilution are based on a mole fraction extrapolation, we convert them to Hine's conventions by the expression

$$\log \gamma = \log f_\infty - \log 55.5 + \log P - 4.269 \qquad (5)$$

where the latter two terms convert vapor pressure into gas phase molarity.[27]

Because of its low solubility, the enthalpy of solution of 2,6-DTBP was not directly measurable by us despite many attempts. Qualitatively it was clear that the value was small, and this fact combined with the slow rate of solution precluded accurate measurement of the enthalpy of solution.

Table IV. Thermodynamic Properties for Ionization and Hydration of Pyridines and Their Conjugate Acids[a]

						from ref 10							
substituted pyridines	$\Delta G_s^{g\to H_2O}$ (B)	$\delta\Delta G_i^\circ$ (g)	$\delta\Delta G_i^\circ$ (w)	$\delta\Delta G_s^{g\to H_2O}$ (B)	$\delta\Delta G_s^{g\to H_2O}$ (BH$^+$)	$\delta\Delta H_i^\circ$ (g)	$\delta\Delta H_i^\circ$ (w)	$\delta\Delta H_s^{g\to H_2O}$ (B)	$\delta\Delta H_s^{g\to H_2O}$ (BH$^+$)	$\delta(T\Delta S_i^\circ)$ (g)	$\delta(T\Delta S_i^\circ)$ (w)	$\delta(T\Delta S_s^\circ)$ (B)	$\delta(T\Delta S_s^\circ)$ (BH$^+$)
2,6-DTBP	3.87[c]	10.3	−0.41	4.29	15.0	10.3	1.9	−1.7	6.7	0	2.31	−5.99	−8.3
4-*tert*-butyl	−0.19[b]	5.2	0.96	0.23[b]	4.47	5.2	2.0	−1.9	1.3	0	1.04	−2.13	−3.17
2,6-(CH_3)$_2$	−0.33	8	2.18	0.09	5.91	8	2.44	−2.88	2.7	0	0.26	−2.98	−3.22
2,4-(CH_3)$_2$	−0.59	6.9	2.01	−0.17	4.72	6.9	2.37	−2.58	1.9	0	0.36	−2.41	−2.82
4-OCH_3		6.7	1.87			6.7	2.55	−2.20	2.0	0	0.68		
2,5-(CH_3)$_2$	−0.44	6.1	1.43	−0.02	4.65	6.1	2.02	−2.61	1.5	0	0.59	−2.59	−3.15
3,5-CH_3	−0.57	5.5	1.13	−0.15	4.24	5.5	1.59	−2.53	1.4	0	0.46	−2.39	−2.83
4-CH_3	−0.66	4.0	1.12	−0.24	2.64	4.0	1.30	−1.34	1.4	0	0.18	−1.10	−1.24
	−0.57			−0.16	2.72							−1.18	−1.32
2-CH_3	−0.36	3.5	1.09	0.08	2.49	3.5	1.40	−1.24	0.9	0	0.31	−1.31	−1.58
3-CH_3	−0.50	2.7	0.63	−0.08	1.99	2.7	0.91	−1.12	0.7	0	0.28	−1.04	−1.29
H	−0.42	(0.0)	(0.00)	(0.00)	(0.00)	(0.0)	(0.00)	(0.00)	(0.0)	0	(0.00)	(0.00)	(0.00)
	−0.41[c]												
3-Cl	0.26[c]	−5.8	−3.28	0.67	−1.85	−5.8	−2.44	0.88	−2.48	0	0.84	−0.21	−0.63
2-Cl	−0.18[c]	−6.3	−6.32	0.29	0.31	−6.3	−4.78	0.11	−1.41	0	1.54	−0.18	−1.10

[a] All values in kcal/mole relative to pyridine. [b] Ref 21. [c] This report. Solution terms refer to an extrapolated state of infinite dilution in water. Free energy terms were derived from the mole fraction concentration scale.

Indirect evidence was supplied from two experiments. The first was through thermometric titration of a solution of 0.01 M HCl, containing a known amount of 2,6-di-*tert*-butylpyridine, with 0.1 M NaOH. As neutralization of the 2,6-di-*tert*-butylpyridinium ion began, the amine appeared as a milky emulsion which subsequently separated as droplets. A control titration of an equivalent amount of the pure HCl solution with NaOH solution yielded, by difference, the enthalpy of neutralizing the 2,6-DTBPH$^+$ ion plus some part of its enthalpy of precipitation. This corresponds to ($\Delta H_i - \Delta H_s^\circ$) and is equal to 6.5 ± 0.3 kcal/mol. Now the enthalpy of solution of pure 2,6-DTBP was measured into 0.1 M HCl. This value (−6.7 ± 0.3 kcal/mol) represents the sum of the enthalpy of protonating the pyridine and its enthalpy of solution ($-\Delta H_i + \Delta H_s^\circ$). Since the two values for the different processes agree within experimental error, we conclude that the enthalpy of solution term ΔH_s° for this amine is nearly zero.

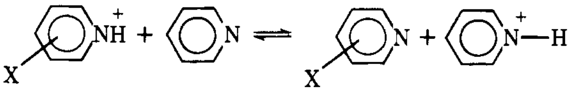
If we accept 6.6 kcal/mol as ΔH_i for 2,6-DTBPH$^+$ and ΔH_s° for the free base as zero, we may calculate the enthalpy of hydration of 2,6-DTBPH$^+$ ion relative to that for the unsubstituted pyridinium ion as we have done before in other cases[2-9] by the relations

$$\begin{aligned}\delta\Delta H_s^{g\to H_2O}(BH^+) &= \delta\Delta H_i^{g} - \delta\Delta H_i^{H_2O} + \delta\Delta H_s^{g\to H_2O}(B)\\ &= 10.3 - (1.9) + (-1.7) \qquad (6)\\ &= 6.7\ \text{kcal/mol (see Table V)}\end{aligned}$$

This represents how much less exothermic is the enthalpy of hydration of 2,6-DTBPH$^+$ from the gas phase than is that for the unsubstituted pyridinium ion.

Discussion

Table IV provides a complete analysis of the effect of substituents on the free energy, enthalpy, and entropy changes for ionization in the gas phase and in water and the thermodynamic properties for transfer from the gas phase to water for the neutral base. As before[10] all values are taken relative to those for unsubstituted pyridine for which the relative value is 0.00. Thus, $\delta\Delta G_i^\circ(g)$ represents the standard free energy of ionization for any substituted pyridine in the gas phase relative to that for unsubstituted pyridine and corresponds to the standard free energy change in the gas phase at 25 °C for the exchange

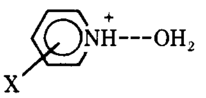

(7)

Correspondingly, $\delta\Delta G_s^{\circ g\to H_2O}(BH^+)$ is the standard free energy change for transfer of any substituted pyridinium ion from the gas phase to water at 25 °C minus that for unsubstituted pyridinium ion.

We will comment first on the general pattern of the variation of properties in response to changes in substitution and then discuss the singular behavior of 2,6-di-*tert*-butylpyridine.

All three properties for ionization of the pyridines in water [$\delta\Delta P_i^\circ$(w)], where $P = G^\circ, H^\circ, S^\circ$, have been discussed before.[10,28] Likewise, the gas phase ionization of many bases, including the pyridines, is currently a very lively area of research.[1-10] We have also given a complete analysis[10] of the enthalpy terms for all of the tabulated compounds except 2-chloropyridine, 4-*tert*-butylpyridine, and 2,6-di-*tert*-butylpyridine. The principal contributions which allow completion of the analysis are the free energies of hydration of the neutral bases, i.e., $\Delta G_s^{\circ g\to H_2O}(B)$. Some of these free energy terms come from published accounts and some have been determined in our laboratory by the method described herein. Combination of the free energy and enthalpy terms for hydration of the bases and their ions finally provides the entropies of hydration.

Free Energies of Hydration. The relative free energies of ionization for the pyridines in the gas phase are proportional to their values in water but are about twice (or maybe thrice) as sensitive to substituent changes.[10] The entire difference between the gas phase values and those in solution must perforce lie in the free energies of solvation of the neutral bases and their "onium ions". From the data for $\delta\Delta G_s^{\circ g\to H_2O}(B)$ and $\delta\Delta G_s^{\circ g\to H_2O}(BH^+)$, it is obvious that the free energies of hydration of the pyridinium ions vary in a manner which is closely parallel to the variation in relative free energy of ionization in water, $\delta\Delta G_i^\circ$(w). The corresponding variation in free energy of hydration $\Delta G_s^{g\to H_2O}(B)$ of the neutral pyridines is mostly notable for its near constancy, all values being small in magnitude (except for 2,6-DTBP). We, therefore, conclude that the entire source of the attenuation factor which halves the gas phase free energy of ionization for transfer to water must lie in the hydration of the pyridinium ions. For the enthalpy factors, we assigned this interaction primarily to variation of the hydrogen-bonding energy of the pyridinium ions to water:



The present results show a very similar trend consistent with progressively stronger hydrogen bonding as one descends the column. Variations in the relative free energies of hydration of the pyridines support the claim that they are participating as hydrogen-bond acceptors since $\delta\Delta G_s^{\circ g\to H_2O}(B)$ becomes

Table V. Stoichiometry[a] and Hydrogen-Bonding Data[b] for Salts of 2,6-Di-*tert*-butylpyridine (2,6-DTBP) and Pyridine

acid salt	2,6-DTBP	pyridine	$\nu_{N^+-H--X^-}$, cm^{-1} 2,6-DTBP	$\nu_{N^+-H--X^-}$, cm^{-1} pyridine
trifluoroacetic acid (TFAH)	$DTBPH^+$ $TFA^- \cdot TFAH$	PyH^+ TFA^-	3275	2050 and 2460
HF	*c*	*c*	3380	2880[e]
HCl	$DTBPH^+ \cdot ClHCl$	Py^+HCl^-	3360	2443[e]
HBr	$DTBPH^+ \cdot Br^-$	Py^+HBr^-	3370	2791[f]
HI	$DTBPH^+ \cdot I^-$	Py^+HI^-	3350	2833[f]

[a] From C, H, N elemental analysis of purified salts. [b] For mull of salt in hexachloro-1,3-butadiene. [c] Poor analyses indicating the presence of several molecules of HF or water in the salt were obtained for these compounds. They are very hygroscopic. [d] Johnson, S. L.; Rumon, K. A. *J. Phys. Chem.* **1965,** *69,* 74. [e] Our data. [f] Cook, D. *Can. J. Chem.* **1961,** *39,* 2009.

less negative as we descend the column for compounds that are not sterically hindered.

Entropies of Hydration. The last three columns of Table IV show that the small variation in entropies of ionization $[\delta T \Delta S_{\mathrm{i}}^{\circ}(\mathrm{w})]$ for most of the series is the consequence of large and nearly compensatory variations in the entropies of hydration of the pyridines and their ions. Since most of the compounds listed here are alkylpyridines and their entropies of hydration increase roughly in proportion to the carbon number of the substituent groups, we suggest that this is a manifestation of the hydrophobic effect[4,11,14] which typically leads to a loss in entropy as a result of enhanced mutual interactions between water molecules in the vicinity of the hydrocarbon functions.[15] Here the effect is of nearly equal magnitude in the neutrals and in the ions but always a little larger in the latter.

2,6-Di-*tert*-butylpyridine. Ever since its anomalously low basicity was first noted by Brown and Kanner,[29] the question of proton transfer and hydration of this base and its conjugate acid has been a matter of interest.[30-37] Comparison of its hydrogen-bonding behavior[16,37] and volume of ionization[32] with other pyridines suggests strongly that the neutral base is unable to accept a hydrogen bond from hydroxylic solvents. The behavior of the hydrochloride salt and the trifluoroacetate ion pair[16] suggests that the 2,6-DTBPH$^+$ cation is virtually precluded from hydrogen bonding to its counterions. Further support for this notion comes from the remarkable correlation of Taft et al.[38] which shows that the solvation behavior of this ion is more like that of resonance-stabilized carbonium ions than of ammonium ions.

Conclusive evidence that the low basicity of 2,6-DTBP in solution is due to solvation factors rather than some inherent steric hindrance to the proton itself came from gas phase proton affinity measurements.[10,28] These showed that in the gas phase this is *an unusually basic* pyridine. Recently, Hopkins and his colleagues[39] have studied the thermodynamics of ionization of this base and a number of other pyridines in aqueous alcoholic solutions and conclude that steric hindrance to solvation of the cation cannot be the whole story but that solvation of the neutral is also abnormal. An abnormally slow rate of proton transfer[40] to 2,6-DTBP implies that steric hindrance to solvation of the ion is important.

Table IV shows that 2,6-DTBP differs markedly from the other pyridine bases in terms of all 12 properties for ionization and hydration. Although the hydration properties for the cation are most dramatically different from the other members of the series, the hydration of the neutral base also is sharply at variance with most of the trends shown by the other pyridines. In all cases the differences are in the direction to be expected if both the base and the ion are excluded from hydrogen-bonding interactions with water in the manner that is feasible for the other pyridines, namely, through restricted access to the nitrogen atom or to a proton attached to it.

Finally, Table V compares the hydrogen-bonding frequencies of several salts of 2,6-DTBP with those of pyridine. Although the hydrogen-bonding bands for the pyridine salts are broad and variable, those for 2,6-DTBPH$^+$ salts are sharp in every case and are nearly independent of the anion. This again supports the notion that 2,6-DTBPH$^+$ is a poor hydrogen-bond donor relative to pyridinium ion.

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Molecular Orbital Theory of the Hydrogen Bond. 21. 2-Monosubstituted Pyridines as Proton Acceptors

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Abstract: Ab initio SCF calculations with the STO-3G basis set have been performed to investigate substituent effects on the hydrogen bonding ability of 2-R-pyridines as proton-acceptor molecules, with the substituents including CH_3, NH_2, OH, F, C_2H_3, CHO, and CN. The equilibrium water-2-R-pyridine dimers generally have open structures stabilized by the formation of a linear hydrogen bond through the nitrogen lone pair of electrons, except for the water-2-aminopyridine dimer, which is cyclic, and the water-2-hydroxypyridine dimer, which has 2-hydroxypyridine as the proton donor. The relative orientation of the pyridine ring and the water molecule in an equilibrium dimer is determined by secondary substituent effects which include long-range interactions and the alignment of the dipole moment vectors of the proton-donor and proton-acceptor molecules. The hydrogen bonds in the water-2-R-pyridine dimers are weaker than in the water-pyridine dimer in all cases except the water-2-aminopyridine dimer. Primary substituent effects alter the electronic environment at the nitrogen, and are reflected in the n orbital energies of the pyridine bases. These energies are linearly related to the hydrogen-bond energies of a particular set of dimers in which the pyridine ring is perpendicular to the plane of the water molecule. Secondary substituent effects also influence the relative stabilities of the equilibrium water-2-R-pyridine dimers.

Introduction

Recent developments in experimental methods for studying organic ion-molecule equilibria in the gas phase have provided valuable new data on the gas-phase basicities of molecules toward acids such as H^+ and Li^+.[1-4] A comparison of these data with basicities measured in solution has emphasized the mediating influence of the solvent on molecular basicity.[1,5-7] Paralleling these experimental developments and contributing to a better understanding of the factors which influence gas-phase and solution basicities has been the application of ab initio molecular orbital theory to the fundamental acid-base reactions of protonation, lithium ion complexation, and hydrogen-bond formation.[8-17]

An important series of organic compounds for which experimentally determined basicities in the gas phase and in aqueous solution are now available are the substituted pyridines.[6] The results of ab initio molecular orbital calculations of the association energies of some of these bases with H^+ and H_2O have also been reported.[6,18-20] However, there has not yet been a thorough and systematic study to determine the equilibrium structures of these acid-base complexes, nor a detailed analysis of substituent effects on their structures and energies. Therefore, such an investigation has been initiated in this laboratory. The structures and stabilization energies of a set of hydrogen-bonded complexes containing HF or H_2O as proton donors and pyridine or one of the diazines as proton acceptors have already been reported.[21,22] This investigation has now been extended to include another series of dimers which has water as the proton donor and a monosubstituted pyridine (2-R-pyridine) as the proton acceptor, with R including the isoelectronic saturated groups CH_3, NH_2, OH, and F and the unsaturated groups C_2H_3 (vinyl), CHO, and CN.

Owing to the particular geometry of the proton acceptor 2-R-pyridines and the structures of the water-2-R-pyridine complexes, particular rotations of the substituted pyridines are possible which leave the hydrogen bond intact, but which change the position of the substituent with respect to the water molecule. As a result, this series of dimers provides a unique opportunity to separately evaluate primary and secondary substituent effects on dimer structures and stabilities. The primary substituent effects are those which result from the influence of the substituent on the electronic environment at the nitrogen, and specifically on the availability of the nitrogen lone pair for hydrogen-bond formation. Secondary substituent effects arise from other long-range and dipole interactions which are due to the presence of the substituent in the 2 position of pyridine. The importance of such secondary substituent effects has long been recognized from the failure of the Hammett substituent constants for ortho-substituted aromatic rings to correlate with rate or equilibrium processes, presumably because ortho substituents are close enough to the reaction site to exert a significant proximity effect. The results of this present study may therefore provide a more detailed and quantitative insight into such ortho effects. The twofold aim of this investigation is to determine the equilibrium structures and stabilization energies of the water-2-R-pyridine dimers and to examine in detail primary and secondary substituent effects on these structures and stabilities.

Method of Calculation

Wave functions for the closed-shell ground states of the monomers and the hydrogen-bonded complexes have been expressed as single Slater determinants Ψ

$$\Psi = |\psi_1(1)\bar{\psi}_1(2) \ldots \psi_n(2n-1)\bar{\psi}_n(2n)|/\sqrt{(2n)!}$$

consisting of a set of doubly occupied molecular orbitals. These orbitals ψ_i are expressed as linear combinations of atomic basis functions ϕ_μ (the LCAO approximation)

$$\psi_i = \sum_\mu c_{\mu i}\phi_\mu$$

with the expansion coefficients $c_{\mu i}$ determined from the

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