Ion Thermochemistry of Low-Volatility Compounds in the Gas Phase. 2. Intrinsic Basicities and Hydrogen-Bonded Dimers of Nitrogen Heterocyclics and Nucleic Bases

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Received August 28, 1978

Abstract: The number densities (N_{B_2}) of low-volatility samples (B_2) in the ion source of a pulsed high-pressure mass spectrometer were determined on the basis of the proton-transfer rates from t-$C_4H_9^+$ to B_2. Subsequently, proton-transfer equilibria between B_2 and reference compounds B_1 were observed and equilibrium constants $K = (I_{B_2H^+}N_{B_1}/I_{B_1H^+}N_{B_2})$ were measured. The proton affinities (PA) of aromatic nitrogen heterocyclics decrease with increasing number of nitrogen atoms in the ring (all PA values related to PA(NH_3) = 207 kcal mol^{-1}): pyridine (PA = 222.0 kcal mol^{-1}), 1,2-diazine (218.3), 1,3-diazine (215.5), 1,4-diazine (210.8), 1,3,5-triazine (203.3). The addition of one or two fused benzene rings each increases the PA by ca. 6 kcal mol^{-1} as seen in the series pyridine (PA = 222.0), quinoline (227.6), and acridine (233.0); 1,4-diazine (210.8), quinoxaline (217.1), phenazine (224.8); and 1,2-diazine (218.3), cinnoline (224.3). The effects of the fused rings are due mainly to electrostatic stabilization of the charge. Linear correlation is observed between the IPs and PAs of the di- and triazines. The hydrogen affinities (HA) of the radical ions ($B^{+}\cdot$) of these compounds are lower by 10–15 kcal mol^{-1} than those of the monoazines; however, the HAs of all the nitrogen heterocyclics fall in the general range of amines and are quite distinct from carbon bases such as polycyclic aromatics. Solvent effects in H_2O attenuate the basicities of the aromatic nitrogen bases, compared with NH_3, by up to 32 kcal mol^{-1}. Solvent-effected attenuation of basicity increases with molecular size of BH^+, owing to inefficient ion solvation, and with increasing polarity of the neutral B, owing to efficient solvation of B. PAs of nucleic bases were measured as follows: adenine (224.6), cytosine (224.9), and thymine (210.9). Thermodynamics of association equilibria $BH^+ + B \rightleftarrows BH^+\cdot B$ were measured as follows ($-\Delta H°$, kcal mol^{-1}; $-\Delta S°$, cal mol^{-1} K^{-1}); pyridine (23.7, 28), adenine (30.3, 39), thymine (30.1, 37), cytosine (38.3, 37). The enthalpies and entropies of association indicate two hydrogen bonds in (adenine)$_2H^+$ and (thymine)$_2H^+$ and three hydrogen bonds in (cytosine)$_2H^+$.

Introduction

Measurements of the proton affinities of nitrogen bases by gas-phase proton-transfer equilibria afforded a detailed analysis of the intramolecular structural effects on the intrinsic basicities of these compounds.[1] In conjunction with heats of protonation in solution and with heats of solution of the neutral bases, detailed information was obtained on the thermodynamics of solvation of the ammonium ions.[2,3] While most of the work concentrated on aliphatic amines, the understanding of the basicities of substituted anilines[4] and pyridines[5,6] also benefited from gas-phase studies. For example, it was observed that the difference between gas-phase and solution basicities of substituted pyridines results mostly from substituent effects on the hydrogen bond between the protonated pyridines and H_2O.[6]

It is expected that heterocyclic aromatic chemistry may benefit similarly from measurements of gas-phase basicities of this class of compounds. For example, the effects of increased annelation on the basicities of pyridine and the diazines are irregular both in sign and in magnitude in aqueous solution.[7] In alkylamines, gas-phase studies revealed that the irregular order of solution basicities pK_a(CH_3NH_2) < pK_a($(CH_3)_2NH$) > pK_a($(CH_3)_3N$) is due to the interference of methyl groups with the solvation of the ammonium ions, and the intrinsic basicities increase with increasing alkyl substitution.[2,3,8,9] Similarly, one may expect that the order pK_a(pyridine) > pK_a(quinoline) < pK_a(acridine) is due to solvent effects, and that gas-phase measurements will reveal the true intrinsic relative basicities of these compounds. In addition, the intrinsic, solvent-free basicities of some nitrogen heterocyclics may be of biological interest. For example, nucleic bases exist both in environments open to solvation as well as in regions from which the aqueous solvent is excluded in biological systems.

Recently, we developed a technique which relies on gas-phase proton-transfer kinetics to measure the partial pressure of involatile samples in the ion source of a pulsed high-pressure mass spectrometer.[10] Using this technique, we measured the gas-phase basicities of several α-amino acids and found that α substitution by -COOH on an aliphatic amine lowers the PA of the amine by 2-3 kcal mol^{-1}. In the present work we extended similar measurements to the gas-phase basicities of electron-deficient aromatic heterocyclics, including three nucleic bases. In the course of the measurements on the nucleic bases we observed the formation of (adenine)$_2H^+$, (thymine)$_2H^+$, and (cytosine)$_2H^+$, and noted that the latter was significantly more stable than the other two dimers. The bonding in these dimers is of interest in relation to the chemistry of nucleic bases in acid environments and also in radiation biochemistry, since the protonated nucleotides may be formed by ionizing radiation. We therefore measured the strength of bonding in these dimers; the results give some clues to the structure of the dimers. These results will also be presented in this paper.

Experimental Section

The measurements were performed on the Rockefeller University Chemical Physics Mass Spectrometer, using pulsed high-pressure techniques.[11]

Low-volatility compounds whose melting points are above about 100 °C were introduced to the ion source via a direct insertion probe. The reactant gas used in these studies was i-C_4H_{10}, and the protonated sample molecules were formed by the reaction

$$t\text{-}C_4H_9^+ + B_2 \rightarrow B_2H^+ + C_4H_8 \qquad (1)$$

The pressure of B_2 (P_{B_2}) in the source was always lower by about three orders of magnitude than that of i-C_4H_{10}. As a result, P_{B_2} (or N_{B_2}) could not be determined accurately by direct measurement. To circumvent this problem, we measured the rate of the reaction 1 (r_1) and found N_{B_2} from $N_{B_2} = r_1/k_1$. k_1 is the second-order rate constant for reaction 1, and we assume that k_1 is equal to the collision rate calculated from ADO theory.[12] This assumption is based on the observations that exothermic proton transfer reactions between t-$C_4H_9^+$ ions and bases proceed at collision efficiencies of 0.8–1.0.[13,14] After N_{B_2} has been thus determined, a reference base B_1 whose proton affinity (PA) is known was added to the gas mixture in the ion source. In most cases B_1 was a moderately volatile liquid which was expanded in a

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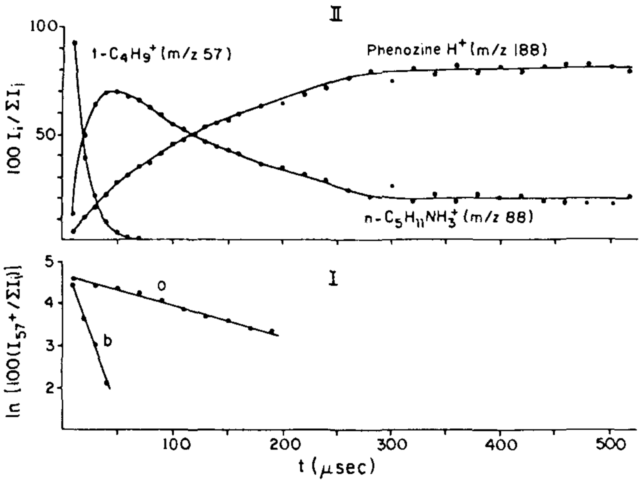


Figure 1. A typical experiment consisting of the measurements of the number density of a low-volatility sample B_2, the density of the sample plus the reference compound B_1, and the observation of proton transfer equilibrium $B_1H^+ + B_2 \leftrightarrows B_2H^+ + B_1$. For the example in this figure B_2 = phenazine and B_1 = n-pentylamine. (I) The decay of the t-$C_4H_9^+$ reactant ion intensity in the presence of (a) only phenazine, (b) phenazine + n-$C_5H_{11}NH_2$. The slopes of (a) and (b) yield decay rates of 0.5×10^4 and 6.3×10^4 s^{-1}. Using $k_1 = 1.7 \times 10^{-9}$ and 1.4×10^{-9} for the reactions of t-$C_4H_9^+$ with phenazine and n-$C_5H_{11}NH_2$, respectively, we obtain $N_{\text{phenazine}} = 0.30 \times 10^{13}$ and $N_{n\text{-}C_5H_{11}NH_2} = 5.4 \times 10^{13}$ cm^{-3}. (II) The evolution of normalized ion intensities as a function of reaction time. The decay of t-$C_4H_9^+$ due to proton transfer to phenazine and to n-$C_5H_{11}NH_2$ is followed by the reaction n-$C_5H_{11}NH_3^+$ + phenazine $\rightleftarrows$ phenazine H^+ + n-$C_5H_{11}NH_2$, which reaches equilibrium after about 300 μs reaction time. Using the equilibrium ion ratio and the densities obtained above we obtain $K = (I_{\text{phenazine H}^+}/I_{n\text{-}C_5H_{11}NH_3^+})(N_{n\text{-}C_2H_5NH_2}/N_{\text{phenazine}}) = (81/19)(5.4/0.3) = 76.7$ and $\Delta G = -4.4$ kcal mol^{-1}. Experimental conditions: source temperature = 514 K, total source pressure = 0.82 Torr, probe temperature = 493 K.

heated bulb and mixed with i-C_4H_{10}, and the mixture was then allowed to flow to the ion source. N_{B_1} could thus be directly calculated. In addition N_{B_1} was also measured by measuring the combined rate of proton transfer from t-$C_4H_9^+$ to B_2 and B_1, thereby determining $N_{B_1} + N_{B_2}$; then the difference between $N_{B_1} + N_{B_2}$ and N_{B_2} as determined before yielded N_{B_1}. With both B_1 and B_2 in the source, the equilibrium

$$B_1H^+ + B_2 \rightleftarrows B_2H^+ + B_1 \qquad (2)$$

was measured. Subsequently, B_1 was removed and N_{B_2} was measured again to ascertain that its value was constant during the equilibrium measurement. A typical experiment which includes the determination of N_{B_2}, N_{B_1} and K_2 is described in Figure 1.

The temperature of the insertion probe could be varied independently of that of the source. The pressure of B_2 in the source was controlled by the probe temperature, which was set so that r_1 was in the range $5-50 \times 10^3$ s^{-1}. This is the observable range of r_1 with our method, and it in turn defines the measurable range of N_{B_2}. In general the probe temperature was different, usually by up to ±50 K from that of the source, which was 500–650 K in the present experiments. However, the probe was at a distance of 6–10 mm from the reaction zone in the source, and one can calculate that, at our source pressures of 0.5–1.0 Torr, a molecule evaporating from the probe collides 150–300 times with isobutane molecules in transit to the reaction zone. The sample molecules will thus be thermalized at the temperature of the isobutane reactant gas. Furthermore, the B_2H^* and B_1H^+ ions formed in the reaction zone will undergo several thousand collisions with isobutane molecules during the 150–200-μs time during which reaction 2 is observed, and thus they too should be thermalized at the temperature of the isobutane gas. The temperature of isobutane is that of the source, and thus all the reactants in equilibrium 2 are thermalized at the source temperature.

Since the probe which is in direct contact with the gas in the source may constitute a cold or hot spot in the source, it is important to establish that the gas temperature in the reaction zone is not affected by the probe temperature. In order to check this point, we observed an equilibrium which is sensitive to temperature, at a constant source temperature but with varying probe temperatures. We selected the clustering equilibrium

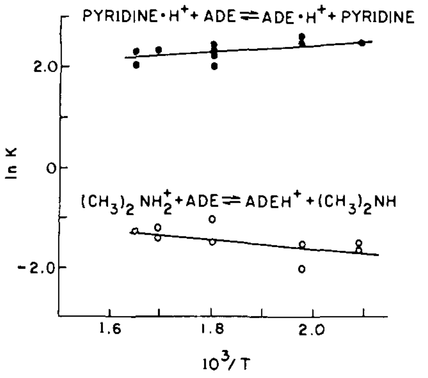


Figure 2. van't Hoff plots for the proton transfer equilibria indicated in the figure.

$$(CH_3NH_2)_2H^+ + CH_3NH_2 \rightleftarrows (CH_3NH_2)_3H^+ \qquad (3)$$

The reactant for this equilibrium, CH_3NH_2, could be introduced to the source as a gas mixture with i-C_4H_{10}, without using the solid insertion probe. We measured for reaction 3 $\Delta H°_3 = -15.6$ kcal mol^{-1}, $\Delta S°_3 = -23.1$ cal mol^{-1} K^{-1}. Based on this data, a variation of the gas temperature by 4 K, from 348 to 352 K, should change K_3 from 5.2×10^4 to 4.1×10^4 atm^{-1}. Nevertheless, as we varied the probe temperature between 330 and 570 K, while the source temperature was kept at 350 K, we saw no observable variation in K_3 within the experimental accuracy of ±10%. We thus conclude that varying the probe temperature by 240 K does not affect the gas temperature in the source by more than ±2 K.

Some of the samples we measured have melting points about or below 100 °C. In these cases we prepared liquid mixtures of the samples with reference bases, and introduced these mixtures to the source via the heated bulb, without using the probe techniques.

The compounds used in the present studies were purchased from commercial suppliers (Aldrich, Frinton Laboratories, MCB, and Matheson), with purities of 98% or higher, and were used as purchased. No impurities, pyrolysis products, or ionic decomposition products were observed in the mass spectra in more than trace quantities in any of the equilibrium measurements. If impurities, such as isomers of the sample B, on the order of 1–2% of the sample concentration are present, their low concentration in the source would make the rates of their reaction too low to affect the results in observable reaction times. For example, under typical source conditions the number density of a 1% impurity in the source would be $N = 10^{11}$ cm^{-3}; a proton-transfer reaction to this impurity would have a half-life of $t_{1/2} = 0.69/10^{11} \times 10^{-9}$ s $= 6.9 \times 10^3$ μs, compared with observation times of $\approx 10^2$ μs.

Results

The majority of proton-transfer equilibria which we observed were measured at a single temperature, which was between 500 and 570 K. These high temperatures were chosen to avoid interference by the formation of cluster ions. In addition to the single-temperature measurements we performed temperature studies (Figure 2) on two proton-transfer equilibria and obtained the following results:

$$\text{pyridine} \cdot H^+ + \text{adenine} \rightleftarrows \text{adenine} \cdot H^+ + \text{pyridine} \qquad (4)$$

$$\Delta H° = -1.6 \pm 0.5 \text{ kcal mol}^{-1}$$

$$\Delta S° = 1.6 \pm 1.0 \text{ cal mol}^{-1} \text{ K}^{-1}$$

$$(C_2H_5)_2NH_2^+ + \text{adenine} \rightleftarrows \text{adenine} \cdot H^+ + (C_2H_5)_2NH \qquad (5)$$

$$\Delta H° = 2.6 \pm 0.5 \text{ kcal mol}^{-1}$$

$$\Delta S° = 1.6 \pm 2.4 \text{ cal mol}^{-1} \text{ K}^{-1}$$

(Error estimates are based on standard deviations of slope and intercept of plots in Figure 2).

Previous studies of proton-transfer equilibria in our laboratory[10] and by other workers[15,16] showed that the entropy change in most proton transfer reactions can be adequately represented by $\Delta S°_{\text{rot sym}} = R \ln [\sigma_{B_1H^+}\sigma_{B_2})/(\sigma_{B_2H^+}\sigma_{B_1})]$ where σ are the rotational symmetry numbers. For the low-symmetry reactants involved in the present measurements, $\Delta S°_{\text{rot sym}}$ is always between +2 and −2 cal mol^{-1} K^{-1}. It was also observed by us[10] and by Yamdagni and Kebarle[17] that small rotational entropy changes in proton-transfer reactions are often within the error limits of temperature studies by pulsed high-pressure techniques. The entropy changes measured in reactions 4 and 5 conform to these previous observations.

In most of the reactions we measured, internal hydrogen bonding in the protonated species can be excluded on the basis of the structure, and $\Delta S°_{\text{rot sym}}$ is thus expected to adequately represent $\Delta S°$ of the reaction. The only ion in the present study where internal hydrogen bonding is plausible is protonated adenine, where hydrogen bonding could occur between the amine group and the $-\text{N}=$ group in the imidazole ring. However, significant entropy changes are not observed even in this case, as is evident from the results for reactions 4 and 5. Consequently, we shall use $\Delta H° = \Delta G° + T\Delta S°_{\text{rot sym}} = \Delta G° + RT \ln [(\sigma_{B_1H^+}\sigma_{B_2})/(\sigma_{B_1H^+}\sigma_{B_1})]$ to calculate the PA of the sample compounds from the measured $\Delta G°$ values.

We employed several checks to assure that our results represent equilibrium measurements, and that our data are consistent with relative PA values of the reference bases as published by other authors.[15,17] The primary proof of equilibrium is the attainment of constant $I_{B_2H^+}/I_{B_1H^+}$ ion ratios as illustrated in Figure 1. The invariance of K_{obsd} when the relative concentrations of B_1 and B_2 are varied is also often used as an equilibrium test. In the present case, owing to the involatile nature of the samples, N_{B_2} could not be conveniently varied at will. However, we varied N_{B_2}/N_{B_1} by up to a factor of 3 in several test equilibria by varying N_{B_1}. K_{obsd} was independent of N_{B_2}/N_{B_1} within experimental error limits in each case.

To compare our measurements with other published PA data, we measured each of our samples against at least two reference bases. In all cases the measured PA values agreed with each other within ±1 kcal mol^{-1}. Consequently, the relative PA of the two reference bases as obtained from these measurements also agreed with the published values within ±1 kcal mol^{-1}. We also measured directly the proton-transfer equilibrium between two of our reference compounds, aniline and 3-aminopropionitrile, and obtained ΔPA = 4.3 kcal mol^{-1}, in very good agreement with the published value of 4.4 kcal mol^{-1}.[27] Also, the ladder created by the present measurements (Table I) between the two reference compounds with the extreme PA values yields $\text{PA}((C_2H_5)_3N) - \text{PA}(C_3H_7OC(O)CH_3) = 30.6$ kcal mol^{-1}, in good agreement with the value obtained from Kebarle's tabulation,[27] 30.5 kcal mol^{-1}.

Errors in the present measurements result from three sources. The first is uncertainties in the values of k_1. Proton transfer rate constants are usually within 20% of theoretical (ADO) rate constants.[18] For most reactions in the present set ADO rates can be calculated; in a few cases dipole moments or polarizabilities had to be estimated by comparison with similar molecules. For the nucleic bases $k_1 = 1.5 \times 10^{-9}$ kcal mol^{-1} was used, and these rate constants may be inaccurate by ±50%. The second is errors in the measurement of r_1. Usually, reaction rates can be measured with an accuracy of ±20% by pulsed high-pressure techniques. An uncertainty by an unrealistically high factor of 2 in N_{B_1}/N_{B_2}, resulting from cumulative errors in the rate measurements and in the rate-constant estimates, would cause an uncertainty of $\pm RT \ln 2 = \pm 0.7$ kcal mol^{-1} in the measured PA values. The third is scatter of the measured $\Delta G°$ values. The average precision of measured $\Delta G°$ values, in 12 sets of duplicate measurements on different equilibria, was 0.34 kcal mol^{-1}.

As a result of these considerations, we estimate the error in our relative PA values conservatively as ±1 kcal mol^{-1}. The agreement between our PA values and published reference PA values, as discussed above, is also consistent with an error estimate of ±1 kcal mol^{-1}. It should be noted that all the measurements and discussions in this paper concern relative basicities and proton affinities. The absolute values refer to $\text{PA}(NH_3) = 207$ kcal mol^{-1},[27b] and the accuracy of the absolute PA values depends on the accuracy of this reference standard.

Discussion

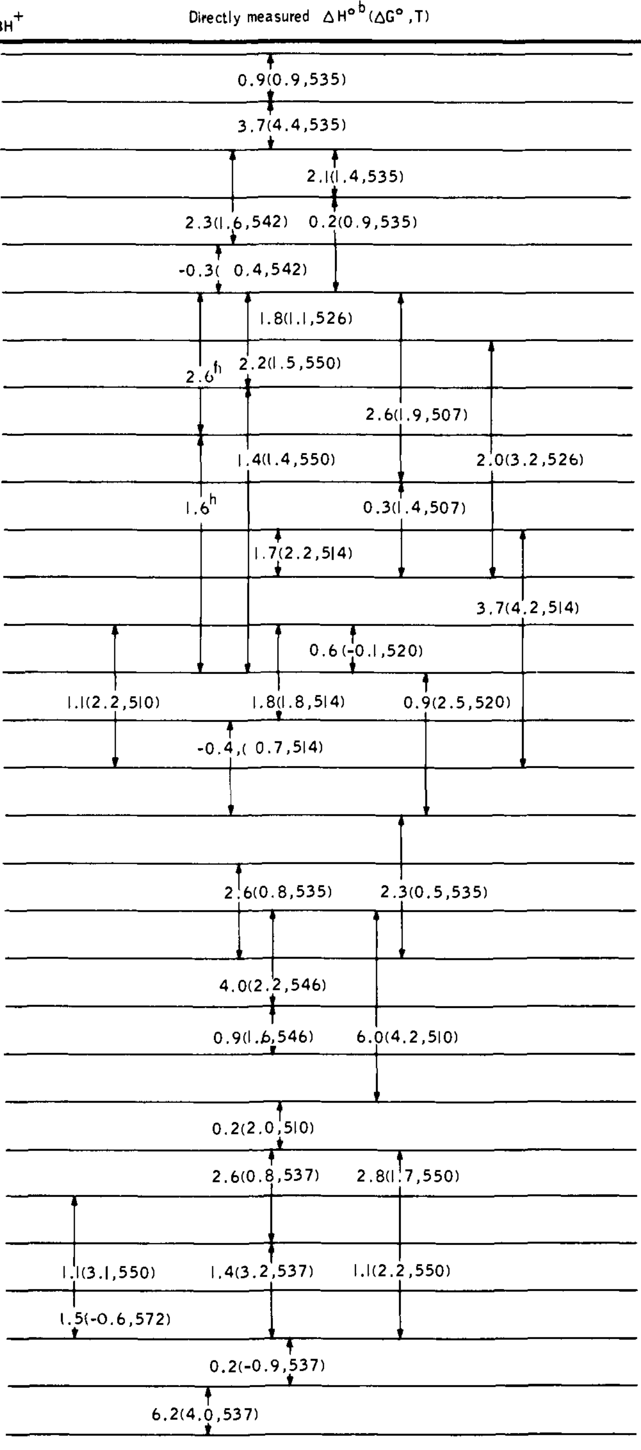
A. Effects of Nitrogen Substitution and Annelation on Proton Affinities. The effects of substitution of nitrogen for carbon atoms in the pyridine ring on the proton affinities can be observed by the inspection of Table II. The addition of one nitrogen atom decreases the proton affinity by 3.7, 6.5, and 11.2 kcal mol^{-1} for 1,2-, 1,3-, and 1,4-diazine, respectively. The addition of a further nitrogen atom further reduces the proton affinity significantly, rendering the PA of 1,3,5-triazine lower than that of ammonia, and thus lower than any other sp^2 or sp^3 nitrogen base measured so far.

As opposed to the effects of nitrogen substitution, increased annelation increases the PA of aromatic heterocyclics. The effects of annelation are similar in all the molecules we measured and additive upon the addition of the first two fused-ring substituents. Thus we observe that the addition of both the first and the second fused benzene ring to the original aromatic moiety each increases the PA by about 5–6 kcal mol^{-1}. This is true for the benzologs of pyridine and for the benzologs of the two diazines we investigated, as is seen in the series pyridine (PA = 222.0), quinoline (227.6), acridine (233.0), in the series 1,4-diazine (210.8), quinoxaline (217.1), and phenazine (224.8), as well as in comparing 1,2-diazine (218.3) and cinnoline (224.3). By a detailed analysis of the proton affinities of alkylamines, Bowers and co-workers[1] showed that the effects of alkyl substituents can be interpreted on the basis of the stabilization of the charge on the protonated nitrogen by electrostatic interactions with induced dipoles on the alkyl groups. It is of interest to examine whether in the present molecules π interactions of the annelated substituents contribute to further stabilization of the protonated bases. In order to investigate the effects of these interactions, we compare the proton affinities of the annelated pyridines with those of the alkyl-substituted pyridines. To do so we note that the proton affinities of 4-*tert*-butylpyridine and quinoline are approximately equal (227[5] and 227.6 kcal mol^{-1}, respectively). From the point of view of electrostatic effects, these compounds are derived from pyridine by the addition of the rough equivalent of four methylene units. Again, the proton affinities of 2,6-di-*tert*-butylpyridine and acridine are quite close (232[5] and 233.0 kcal mol^{-1}, respectively); in these compounds, the rough equivalents of eight methylene units are added to pyridine. We made an estimate of the relative electrostatic stabilization of the charge on the protonated pyridine nitrogen group by interaction with the polarizable bonds in the 2-*tert*-butyl substituent and in the fused benzene substituent (as in quinoline). The energy of interaction between the charge and the substituents may be computed from

$$U = \sum \alpha_i q^2 / 2\epsilon r_i^4 \qquad (6)$$

where α_i are the bond polarizabilities, r_i are the distances from the charged nitrogen function to the bond centers, q is the proton charge, and ϵ is the local dielectric constant, and the summation is over all the bonds in the substituent. The relative

Table I. Enthalpies and Free Energies of Proton Transfer between Nitrogen Heterocyclics and Reference Bases, Proton Affinities, Hydrogen Atom Affinities of B^+, and N^+–H Homolytic σ Bond Dissociation Energies[a]



B	σ_B/σ_{BH^+}	$-\Delta H°$ [c]	PA[d]	HA[e]	σD_{B^+-H}[f]
$(C_2H_5)_3N$	1	26.7	233.7		
acridine	1	26..	233.0	104	104
$(C_3H_7)_2NH$	1/2	22.4	229.4		
quinoline	1	20.6	227.6	113[g]	123
isoquinoline	1	20.5	227.5	111[g]	127
$(C_2H_5)_2NH$	1/2	20.4	227.4		
quinoline N-oxide	1	18.7	225.7		
cytosine	1	17.9	224.9		
adenine	1	17.6	224.6	117	
cinnoline	1	17.3	224.3	107	107
phenazine	2	17.8	224.8		
$t\text{-}C_4H_9NH_2$	1/3	16.5	223.5		
pyridine	1	15.0	222.0	124[g]	128
pyridine N-oxide	2	14.5	221.5		
purine	1	13.4	220.4	130	
$n\text{-}C_5H_{11}NH_2$	1/3	14.0	221.0		
$n\text{-}C_4H_9NH_2$	1/3	13.7	220.7		
$n\text{-}C_3H_7NH_2$	1/3	13.2	220.2		
$C_2H_5NH_2$	1/3	11.7	218.7		
1,2-diazine	2	11.3	218.3	110[g]	110
quinoxaline	2	10.1	217.1	111[g]	111
2-chloropyridine	1	9.5	216.5		
1,3-diazine	2	8.5	215.5	119[g]	119
$C_6H_5NH_2$	1/3	6.5	213.5		
thymine	1	3.9	210.9	115	
1,4-diazine	2	3.8	210.8	113[g]	116
pyrrole	2	3.4	210.4	85	
$NC\,CH_2CH_2NH_2$	1/3	2.1	209.1		
1,3,5-triazine	3	-3.7	203.3	122	
$C_3H_7C(O)OCH_3$	1	-4.8	202.2		

[a] All values in kcal mol^{-1}. For molecular structures see Table II. [b] Sign of $\Delta H°$ and $\Delta G°$ in ladder corresponds to reaction $B_1H^+ + B_2 \rightarrow B_2H^+ + B$, where B_1 is the upper and B_2 the lower base in the ladder. $\Delta H°$ obtained from $\Delta H° = \Delta G° + T\Delta S°_{\text{rot sym}}$. [c] For reaction $NH_4^+ + B \rightarrow BH^+ + NH_3$, based on proton affinities in next column. [d] For samples, values as measured in this work. For reference compounds, PAs from ref 27a. All PAs referred to $PA(NH_3) = 207$ kcal mol^{-1} (ref 27b). Samples are all nitrogen heterocyclics; other compounds and also 2-Cl pyridine are reference bases. [e] As calculated from eq 7, using lowest molecular IPs as selected by Rosenstock et al.,[28] unless indicated otherwise. [f] As calculated from eq 7, using IPs of nitrogen lone pair, as assigned in ref 22. [g] Using lowest molecular IPs as given by ref 22. [h] $\Delta H°$ obtained from temperature studies (reactions 4 and 5).

electrostatic charge stabilization is given by the ratio of the sums $\Sigma_i\alpha_i/r_i^4$ for the two substituents. We calculated this ratio using C–C and C–H bond polarizabilities as given by Denbigh,[19] and r_i as obtained from Dreiding models. The results show that the ratio [PA(quinoline) − PA(pyridine)]/[PA(2-*tert*-butylpyridine − PA(pyridine)] and also the ratio [PA(acridine) − PA(pyridine)]/[PA(2,6-di-*tert*-butylpyridine) − PA(pyridine)] should be 1.07 if only electrostatic charge stabilization is considered. The experimental value for the latter ratio is 1.13. The close agreement with the calculated value is probably fortuitous, but the similarity in the magnitude of stabilization by the aliphatic and aromatic substituents does

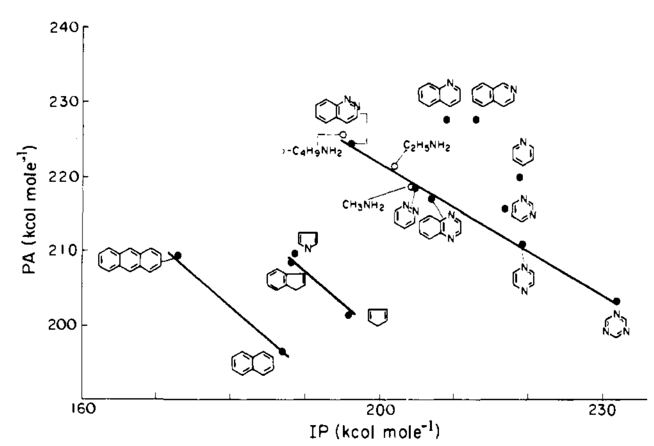


Figure 3. Proton affinities vs. lone-pair ionization potentials of aromatic nitrogen heterocyclics. For comparison, several alkylamines and several polycyclic aromatics are also indicated. Data for alkylamines from ref 1.

suggest that charge delocalization from the protonated nitrogen group via the aromatic system is not significant in protonated nitrogen heterocyclics. This result is not surprising, considering that the charge in the nitrogen bases is probably not significantly π delocalized.

B. Relation between Ionization Potentials and Proton Affinities. Linear correlation between ionization potentials and proton affinities was observed in aliphatic amines[1] and in nitriles.[20] The two quantities are also related by the thermodynamic cycle:

$$\begin{tikzcd}
B + H \arrow[r, "IP_B"] \arrow[d, "IP_H"'] & B^+ + H \arrow[d, "-HA"] \\
B + H^+ \arrow[r, "-PA"] & BH^+
\end{tikzcd}$$

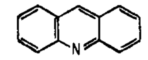
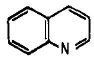
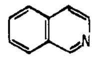
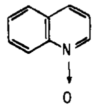
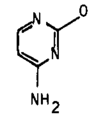
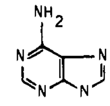
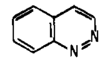
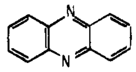
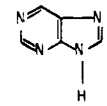
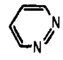
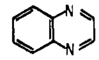
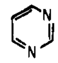
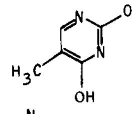
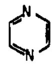
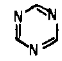
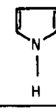
which leads to the relationship

$$HA = IP_B + PA - IP_H \tag{7}$$

If the lowest adiabatic molecular ionization potential is used in eq 7, HA will represent the exothermicity of addition of H· to $B^{+}\cdot$ when all reactants are in their ground states. Molecular hydrogen affinities (HA) of $B^{+}\cdot$ obtained in this manner are given in Table II. In the aromatic heterocyclics, however, ionization may involve removal of either a π or a nitrogen lone pair electron. If the nitrogen lone pair adiabatic IP is used in eq 7, the homolytic σ bond dissociation energy σD_{B^+-H} may be obtained.[20] For the azalogs of benzene and naphthalene IPs were assigned by Worley and Dewar;[22] σD_{B^+-H} values for these compounds are given in Table II.

In nitriles, as in the aromatic nitrogen heterocyclics, ionization may involve π as well as nitrogen electrons. Staley et al.[20] showed that in nitriles the proton affinities are linearly correlated with the nitrogen lone pair ionization potentials, rather than the (lower) cyanide π ionization potentials. In analogy, a linear correlation is expected and is indeed observed between the nitrogen lone pair σIPs and the PAs of the aromatic diazines (Figure 3). We also note that 1,3,5-triazine too fits on this correlation line, although the IP of this compound has not been assigned. The equation for the correlation line may be expressed as PA = −0.57IP + 336, and, using eq 7, σD_{B^+-H} = 0.43IP + 22. It is also interesting to note that the primary aliphatic amines fall on the same correlation line shown in Figure 3. The slopes of the PA vs. IP correlation lines for secondary and tertiary amines are also similar to those of the primary amines[7] and thus also to the slope of the line in Figure 3. Moreover, the equation of the correlation line for nitriles is PA = −0.58σIP + 357, again with a slope identical with that of the line in Figure 3.

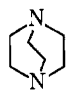
Table II. Free Energies of Proton Transfer $NH_4^+ + \rightarrow BH^+ + NH_3$ in the Gas Phase and in Water. Attenuation of the Basicity of B, Related to NH_3, by the Aqueous Solvent[a]

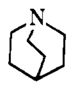
B		ΔG°_g [b]	$\Delta G^\circ_{H_2O}$ [c]	$\delta_{H_2O}\Delta G^\circ$ [d]
acridine		-26.8	5.1	31.9
quinoline		-21.4	6.0	27.4
isoquinoline		-21.3	5.3	26.6
quinoline N-oxide		-19.5		
cytosine		-18.7		
adenine		-18.4	7.1	25.5
cinnoline		-18.1	9.5	27.6
phenazine		-19.0	11.1	30.1
pyridine		-15.8	5.5	21.3
pyridine N-oxide		-15.7	11.7	27.4
purine		-14.2	9.6	23.8
1,2-diazine		-12.5	9.7	22.2
quinoxaline		-11.3	12.0	23.3
1,3-diazine		-9.7	11.0	20.7
thymine		-4.7		
1,4-diazine		-5.0	11.9	16.9
1,3,5-triazine		+2.2		
pyrrole		-4.6	18.0	22.6

[a] All values in kcal mol^{-1}. [b] ΔG°_g at 300 K, calculated from $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ_{\mathrm{rot\ sym}}$. ΔH values from Table I. [c] From dissociation constants. "CRC Handbook of Chemistry and Physics," 58th ed, CRC Press, Cleveland, Ohio, and from ref 7. [d] $\delta_{H_2O}\Delta G^\circ = \Delta G^\circ_{H_2O} - \Delta G^\circ_g$.

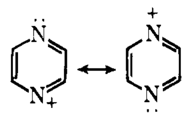
In nitriles, Staley et al.[20] interpreted the linear correlation between IP and PA on the basis that charge redistribution both in the protonated and radical ions involves the R-C-N-H (or R-C-N·) bond system. Similarly, σ bond polarization is responsible for the variation of PA with structure in primary aliphatic amines.[1] The similarity of the present correlation line to that of aliphatic amines and nitriles suggests that in the aromatic nitrogen heterocyclics too structure variations affect the σIPs and PAs primarily via the effects on σ bond polarization in $B^{+\cdot}$ and BH^+.

Inspection of Figure 3 shows that the monoazines deviate significantly from the correlation line of the diazines, i.e., σD_{B^+-H} is lower for the diazines than for monoazines. This effect is similar to the lowering of the σD_{B^+-H} energies in the aliphatic bicyclic compound diazabicyclooctane (a) by 14 kcal mol^{-1} as compared with quinuclidine (b), as observed by


a


b

Staley and Beauchamp.[21] These authors postulated that the lowering of σD_{B^+-H} results from the stabilization of the radical ion of (a) by two resonance structures which locate the charge on either of the two nitrogen lone pairs in (a). In analogy, the lower σD_{B^+-H} values in diazines, as compared with monoazines, can be attributed to stabilization of the diazine radical ions by resonance forms such as i and ii. We observe


i ii

that the σD_{B^+-H} energies are lower by 18, 9, and 12 kcal mol^{-1} in 1,2-, 1,3-, and 1,4-diazine, respectively, than in pyridine (Table II). To the extent that these values represent resonance stabilization by lone-pair interaction, the results show that this interaction is of similar magnitude in 1,4-diazine and in the aliphatic compound (a). The large reduction in σD_{B^+-H} for 1,2-diazine may reflect additional stabilization of the radical cation by through-space interactions between the lone-pair orbitals of the adjacent nitrogen atoms.

As noted above, the aromatic nitrogen heterocyclics fall in the same region in the PA vs. IP plot as other nitrogen bases, and quite distinct from carbon bases such as polycyclic aromatics (Figure 3). Indeed, the location of a particular base in the PA–IP diagram, or the hydrogen affinity of $B^{+\cdot}$, may be diagnostic of the site of protonation in aromatic nitrogen-containing heterocyclics. For example, the HA of pyrrole is 85 kcal mol^{-1}, and this nitrogen heterocyclic compound[1] falls on the correlation line of dienes, quite distinct from nitrogen bases (Figure 3). This confirms that, unlike pyridine and its deviatives, pyrrole is a carbon base.[7]

In conclusion of this section, we wish to summarize several similiarities between the gas-phase ion thermochemistry of aliphatic and of aromatic heterocyclic nitrogen bases.

(1) The correlation between IP and PA is similar in aliphatic amines, nitriles, and aromatic nitrogen heterocyclics.

(2) Lone-pair interactions stabilize the radical cation to a similar extent in aliphatic and aromatic dinitrogen bases.

(3) In addition, we note that aliphatic and fused aromatic substituents of similar polarizabilities affect the PA of pyridine to a similar extent.

All of these observations suggest that the thermochemistry of full ionization, or of partial ionization (by protonation) of the N lone pair in the aromatic heterocyclic bases is affected only by structural variations in the σ bond system. The absence of π-system effects on the ion thermochemistry can be assigned to the orthogonality of the σ and π bond systems in these molecules.

C. Comparison of the Gas-Phase and Solution Basicities. A detailed analysis of the comparative thermodynamics of protonation in solution and the gas phase can yield valuable insight into the effects of structure on ion-solvent interactions.[2,3] However, a detailed analysis is beyond the scope of this paper, in part because of the lack of an accurate, consistent set of solution data on the heats of protonation of the compounds of interest. The objective of this section will be to describe some interesting trends in the relation between gas-phase and solution basicities.

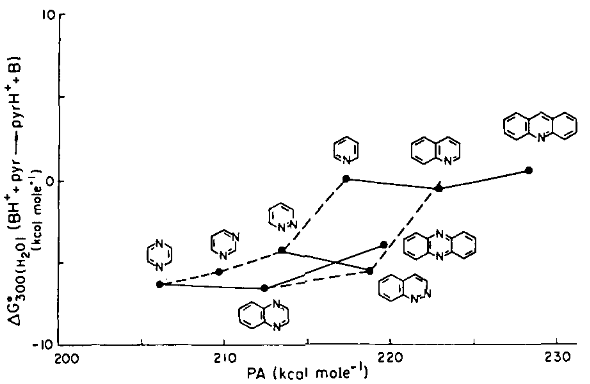


Figure 4. Relationship between proton affinities of nitrogen heterocyclics and the relative solution basicities of these compounds. The solution basicities are related to that of pyridine as reference.

The relationship between gas-phase proton affinities of the unsubstituted nitrogen heterocyclics and between the free energies of protonation in aqueous solution (related to that of pyridine) is shown in Figure 4. Aue and co-workers[5] observed that for substituted pyridines a linear relationship exists between the PAs and the free energies of protonation in aqueous solution. Evidently, no such relationship exists in the present set of compounds (Figure 4). Only one subset of the present compounds, namely, the three diazines, exhibits a linear relation. A line drawn through these points shows that changes in the gas-phase PA in this series are attenuated by a factor of 3.5 in solution.

The series of one-ring compounds and of two-ring compounds are each connected by broken lines in Figure 4. Although no linear correlation exists within these series, both series illustrate that, if the molecular size is kept roughly constant, a monotonic relationship obtains between ΔPA and $\Delta\Delta G^\circ_{prot,H_2O}$. On the other hand, in all three series of benzologs indicated by solid lines in Figure 4 we observe a reversal of the order of gas-phase and solution basicities in going from one-ring to the two-ring compounds. Thus the solution basicity of quinoline is lower, though the gas-phase PA is higher, than that of pyridine; similar relations exist in the pairs quinoxaline–1,4-diazine and cinnoline–1,2-diazine. However, the addition of a third ring increases the solution basicity, as well as the gas-phase PA, in the benzologs both of pyridine and of 1,3-diazine. Since the gas-phase proton affinities increase regularly upon increasing annelation, the irregular order of solution basicities is obviously due entirely to solvent effects. Specifically, the inhibition of ion solvation by the bulky annelated benzene substituents is the most likely cause of the irregular order of basicities.

Taft and co-workers[3] calculated the effects of the aqueous medium on the reaction

$$NH_4^+ + B \rightleftarrows BH^+ + NH_3 \qquad (8)$$

in terms of the difference $\delta_{H_2O}\,\Delta G^\circ = \Delta G^\circ_{H_2O} - \Delta G^\circ_g$ where $\Delta G^\circ_{H_2O}$ and ΔG°_g are the free energies of reaction 8 in water and in the gas phase, respectively. Table II shows that the solvent effected attenuation of the basicity increases regularly by 5–6 kcal mol^{-1} upon the addition of each annelated ring. Thus $\delta_{H_2O}\Delta G^\circ$ increases by 6.1 kcal mol^{-1}, and then a further 4.5 kcal mol^{-1} in the series pyridine–quinoline–acridine; by 6.4 kcal mol^{-1} and then another 6.8 kcal mol^{-1} in the series 1,2-diazine–quinoxaline–phenazine; and by 5.4 kcal mol^{-1} in

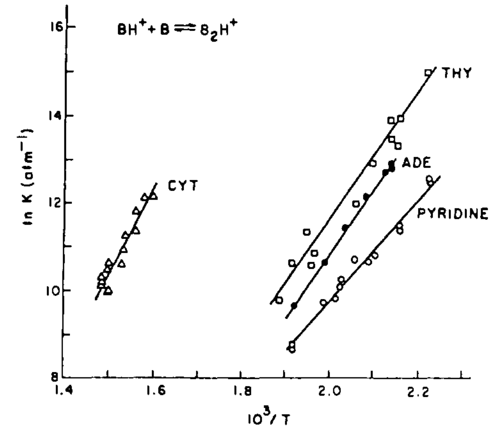


Figure 5. van't Hoff plots for association reactions $BH^+ + B \rightleftharpoons BH^+\cdot B$.

going from 1,2-diazine to cinnoline. These changes may be due in part to the increasing steric inhibition of solvation of the more bulky annelated ions. When the annelated substituent is added adjacent to the ring nitrogen, as in quinoline, $\delta_{\mathrm{H_2O}}\Delta G^\circ$ is somewhat higher than when it is added in a more remote position, as in isoquinoline, possibly also due to a steric effect in quinoline. Interestingly, the effect on solvent attenuation of adding an annelated ring to pyridine is similar in magnitude to adding two methyl substituents.[6]

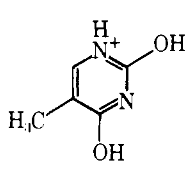
With increasing annelation the PA also increases, and thus PA and $\delta_{\mathrm{H_2O}}\Delta G^\circ$ are also correlated in each annelation series. Indeed, the changes of PA and $\delta_{\mathrm{H_2O}}\Delta G^\circ$ are similar in magnitude but opposite in sign to their effect on the solution basicity, thereby keeping the solution basicity nearly constant in each of the annelation series. Furthermore, increasing PA is also correlated to increasing $\delta_{\mathrm{H_2O}}\Delta G^\circ$ when the molecular size remains constant, i.e., in each of the series of one-, two-, and three-ring azalogs (Table II). Qualitatively, lower PA correlates with increased charge on H in $>N-H^+$, which leads to increased $BH^+\cdots OH_2$ hydrogen bond strength, and thus increased solution basicity of the compounds with lower PA. Indeed, Arnett et al.[6] showed that in substituted pyridines differential solvent attenuation of basicity resulted primarily from differential hydrogen bonding between BH^+ and H_2O.

We also observe that in the series of one-ring compounds the magnitude of solvent attenuation (Table II, column 3) is well correlated with increasing dipole moments of the neutral bases: 1,2-diazine (4.2 D) > 1,3-diazine (2.4 D) > pyridine (2.2 D) > 1,4-diazine (O D). We also note that the most strongly attenuated base, 1,2-diazine, is very strongly bonded (10 kcal mol^{-1}) by two hydrogen bonds to a solvent molecule.[29] These observations suggest that differential solvation of the neutral bases may also be important in determining the differential solvent attenuation: increasing solvation of B tends to push equilibrium 8 increasingly toward the neutral base and thus increases the attenuation of solution basicity.

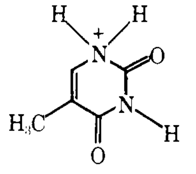
An especially interesting medium effect is observed in pyridine *N*-oxide. This compound is a very weak base in solution (pK_a = 0.8), while in the gas phase its PA is equal to that of pyridine. In this compound a large charge separation exists on the $N^{\delta+} \rightarrow O^{\delta-}$ groups, which should render the solvation of this neutral molecule very efficient. Thus the gas-phase results indicate that the low solution basicity of pyridine *N*-oxide is due entirely to solvent effects, probably primarily by the efficient solvation of the neutral base. With respect to this compound it is interesting to note that protonation must occur on the oxygen atom, thereby rendering pyridine *N*-oxide by far the strongest oxygen base reported so far.

D. Proton Affinities of Nucleic Bases. The proton affinities of adenine, cytosine, and thymine and of the parent structures purine and 1,3-diazine (pyrimidine) are reported in Table II. Guanine was not measured because of insufficient volatility.

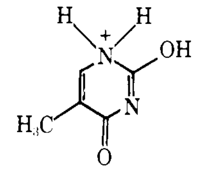
The PAs of the nucleic bases can be compared with the PA's of the parent structures. The PA of thymine is lower by 4.6 kcal mol^{-1} than 1,3-diazine. The lowered PA of thymine is not consistent with the tautomer (c), since in this structure all the substituents are electron donating. The PA of thymine thus suggests a tautomeric form such as (d), or at least one double-bonded oxygen as in (e), to be the dominant tautomer in the gas phase. In contrast, the PA of cytosine is higher by 9.4 kcal mol^{-1} than that of 1,3-diazine. This high PA is consistent with the enol tautomer shown in Table II. Indeed, the difference of 9.4 kcal mol^{-1} between the PA of cytosine and 1,3-diazine is similar to the difference between the PA of 4-aminopyridine and pyridine; in both cases an $-NH_2$ group is present para to the ring nitrogen in the substituted bases. Interestingly, the present tautomeric assignments are consistent with the gas-phase spectroscopic results of Beak et al.[30] They found in oxygen-substituted 1,3-diazines that with an oxygen substituent in the 2 position (structure (f), which is similar to cytosine) the hydroxy structure predominates in the gas phase, while in those with oxygen in the 4 position (structure g), which is similar to the thymine tautomer (e)), the amide form (g) predominates. Finally, the PA of adenine is somewhat higher than the PA of purine, which is consistent with a ring-protonated structure in (adenine)H^+, wherein the PA of the ring nitrogen is increased by the $-NH_2$ substituent.



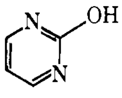
c



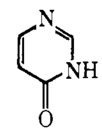
d



e



f



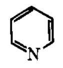
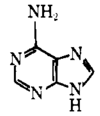
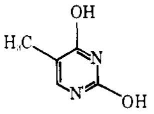
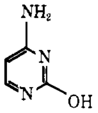
g

E. Hydrogen-Bonded Dimers of the Nucleic Bases. In the course of the measurements of proton affinities of nucleic bases we observed the formation of the dimers (adenine)$_2$H$^+$, (thymine)$_2$H$^+$, and (cytosine)$_2$H$^+$. The former two dimers were observed in significant concentrations only below ≈520 K, while the formation of the latter was observed up to 650 K. In order to understand the thermodynamic basis for the stabilities of these dimers we performed temperature studies on the association equilibria leading to the dimers. For reference, we also measured the analogous reaction in pyridine.

The introduction of the samples to the ion source and the determination of their partial pressures were done by the same techniques as in the proton-affinity measurements, except that, of course, no reference bases were introduced in the dimerization measurements. van't Hoff plots for the dimerization equilibria are shown in Figure 5. The thermodynamic results are summarized in Table III.

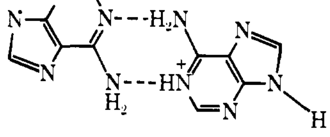
The enthalpies and entropies of association in pyridine are similar to the values observed in the formation of B_2H^+ dimers in alkylamines, as may be expected in a nitrogen base with one n-donor center. On the other hand, the bonding in both (Ade)$_2$H$^+$ and (Thy)$_2$H$^+$ is significantly stronger, and, at the same time, the entropy change in the nucleic base dimerizations is significantly more negative than in the dimerization of pyridine. A plausible explanation for strong bonding in the nucleic bases is the formation of two hydrogen bonds in the

Table III. Thermodynamic Values for Association Equilibria $BH^+ + B \rightleftarrows BH^+\cdot B$ in Pyridine and Nucleic Bases

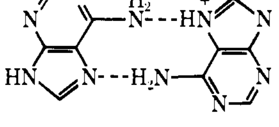
B		$-\Delta H^{\circ a,b}$	$-\Delta S^{\circ c,d}$
pyridine		23.7 ± 1	28 ± 2
adenine		30.3 ± 1	39 ± 3
thymine		30.1 ± 2	37 ± 5
cytosine		38.3 ± 3	37 ± 5

[a] All values in kcal mol^{-1}. [b] Error estimates from standard deviation of slopes of van't Hoff plots. [c] Error estimates from standard deviation of intercepts of van't Hoff plots. [d] In cal mol^{-1} K^{-1}.

protonated dimers. For example, in Ade_2H^+ structures (h) and (i) may be possible. Structure (i) may be preferable, since it is based on the protonation of, and hydrogen bonding to, the imidazole nitrogen, which has the highest negative charge density in purine.[7] The doubly hydrogen bonded structures also explain the large negative value of ΔS°_{assoc} as compared with pyridine since the double bonding eliminates the free internal rotation which is permitted about the N···H+···N bond in the pyridine dimers.

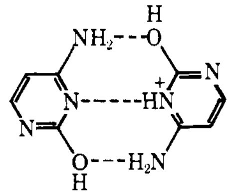


h

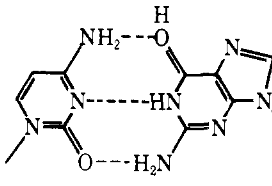


i

In going from $(Thy)_2H^+$ and $(Ade)_2H^+$ to $(Cyt)_2H^+$, $-\Delta H^\circ_{assoc}$ increases again by ≈7 kcal mol^{-1}. Again, the increase in bonding strength could result from an additional hydrogen bond, forming a triply bonded structure (j). The similarity of hydrogen bonding in (j) and in the cytosine–guanine pair (k) is evident.



j



k

While the bonding strength in $(Cyt)_2H^+$ is enhanced as compared with $(Ade)_2H^+$ and $(Thy)_2H^+$, there is no further decrease in ΔS°_{assoc} in going to $(Cyt)_2H^+$. This can be expected on the basis of structures (i) and (j) since the free rotation about the hydrogen bond is already inhibited in (i). Therefore, the introduction of the third hydrogen bond cannot have an entropy effect as the introduction of the second bond had in going from $(pyridine)_2H^+$ to $(Ade)_2H^+$ and $(Thy)_2H^+$. Since there is no entropy effect to compensate for the increased bonding in $(Cyt)_2H^+$, this dimer is more stable at higher temperatures than the other nucleic base dimers, as we noted in our qualitative observations.

Finally, we note that the degree of hydrogen bonding in the gas-phase ion dimers, as suggested by the thermodynamic data, is interestingly parallel to the degree of hydrogen bonding in DNA. In both cases thymine and cytosine are engaged by two hydrogen bonds, while cytosine is bonded by three hydrogen bonds. The similarity may be coincidental, but the resemblance between the hydrogen-bonded structures (k) and (j) links this analogy at least partially to the molecular structures.

Acknowledgments. I thank Mr. E. Hunter and Dr. P. Hamlet for carrying out some of the measurements, and Dr. F. H. Field for his interest in this work. This work was supported by NSF Grant CHE77-14617.

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