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# $\pi$-DEFICIENT N-HETEROAROMATICS AS PROTON ACCEPTORS IN HYDROGEN-BONDING

## INFRARED SPECTRAL SHIFTS VS. p*Ka*'s AS MEASURES OF "BASICITY"[1]

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**Abstract** IR spectral shifts ($\Delta\nu$) due to hydrogen-bonding between a common proton donor, methanol, and a wide variety of $\pi$-deficient N-heteroaromatics, including pyridine, alkylpyridines, halo- and cyano-pyridines, benzologues of pyridine, and related molecules containing two N atoms were determined With 3- and 4-cyanopyridines as proton acceptors, two methanol bonded OH peaks were observed, corresponding to hydrogen-bonding to the nitrile nitrogen and to the pyridine nitrogen, all other compounds gave symmetrical bonded OH peaks The $\Delta\nu$'s obtained were compared with the p*Ka*'s of the bases and the equilibrium constants (log *K*'s) for the associations phenol + base $\rightleftarrows$ hydrogen-bonded complex p*Ka* and log *K* as well as log *K* and $\Delta\nu$ for all bases correlated reasonably well. A good linear relation between $\Delta\nu$ and p*Ka* for the limited class of alkyl pyridines also was found, but when all bases were considered, this correlation was not as successful However, the compounds which deviated most significantly were probably exceptional cases whose behavior could be understood in terms of special structural features present. The abnormally high p*Ka* of 1,10-phenanthroline was attributed to a strong intramolecular hydrogen-bond in the protonated base, while the high p*Ka*'s found with azines with adjacent N atoms were similarly ascribed to intermolecular hydrogen-bonding These exceptions illustrate the essential difference between p*Ka* and $\Delta\nu$ as a measure of the "basicity" of molecules 2,6-Di-t-butylpyridine did not associate with methanol, even at high concentration Solvation effects in this molecule must also be very much inhibited

THE distribution of electrons in a proton acceptor should be perturbed relatively slightly by the formation of a hydrogen-bond. Such an interaction is relatively weak, for a proton has only partially been transferred to the hydrogen-bonding base For this reason the OH stretching frequency shift ($\Delta\nu$, best determined in an "inert" solvent) of a standard proton donor resulting from an intermolecular hydrogen-bond with such a proton acceptor should be an approximate measure of its "ground state" basicity [3] The constant most frequently employed to designate the "basicity" of such bases is the p*Ka*, i.e. the negative logarithm of the acid dissociation constant of $BH^+$, usually determined in aqueous solution p*Ka*'s are dependent not only on ground state basicity, but also on the stability of the protonated form, as well as on solvation effects on both the base and its conjugate acid This gives rise to several interesting questions, the answers to which will be discussed in the present paper In what ways do these two criteria of basicity, p*Ka* and $\Delta\nu$, differ? For what types of compounds can $\Delta\nu$ and p*Ka* be linearly related? What are possible reasons for the deviations of some compounds from the $\Delta\nu$-p*Ka* relationships established for other bases of the same "type"?

Gordy and Stanford[4] were the first to attempt to correlate $\Delta\nu$ and p*Ka* Direct proportionality between $\Delta\nu$ and p*Ka* with a number of bases was observed Tamres *et al* [5] later found a linear p*Ka*-$\Delta\nu$ relationship for a few pyridine-type molecules, but observed a distinctly different one for aliphatic amines. They concluded that linear p$Ka$-$\Delta\nu$ correlations would be expected only when the bases compared were of the same type.

Both of theses studies are subject to the criticism that the pure base was used as solvent. The magnitude of $\Delta\nu$ depends significantly on the solvent used (Fig. 1).[6,7] For valid comparisons of $\Delta\nu$'s, a constant and inert environment should be maintained.[8] A dilute solution of proton donor and acceptor in an "inert" solvent, generally $CCl_4$, eliminates environmental differences, especially when the measurements are extrapolated to infinite dilution.[8] Using such experimental conditions, we undertook a reexamination of the relation of $\Delta\nu$ to p$Ka$ for $\pi$-deficient N-heteroaromatics ("pyridine-like" compounds), materials which might be expected to be of the same "type".

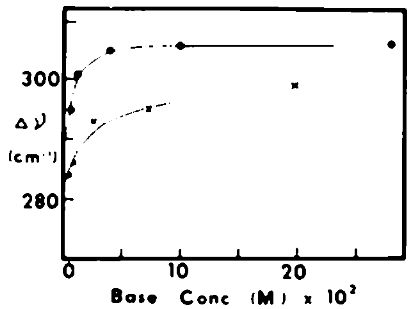



FIG. 1 Effect of Concentration of 2-picoline (●) and 3-picoline (×) on $\Delta\nu$ methanol in $CCl_4$ solution

Several papers[9–11] are pertinent to the present work. The association of phenol with a number of pyridine bases has been studied, and spectral shifts,[9] association constants,[9,10] and thermodynamic parameters[9,10b] reported. Although a number of correlations involving these data were established by the various authors, only one group examined the relationship between p$Ka$ and $\Delta\nu_{phenol}$.[9b] Eq. 1

$$\Delta\nu = 27{\cdot}9\,\mathrm{p}Ka + 330\,(\text{in cm}^{-1}) \tag{1}$$

was found to hold for pyridine and eight of its derivatives, mostly those with electron withdrawing substituents. Spectral shifts between pyridine and phenol are large; the bonded peak is shifted nearly into the C—H absorption region where interference is marked. For this reason, the spectral shifts with pyridines substituted with electron releasing substituents are hard to measure with confidence. Perhaps for this reason attempts to correlate p$Ka$ and $\Delta\nu$ have not been more widely reported.

Methanol is a weaker proton donor than phenol, the spectral shifts to a given base are generally about half as large, and no interference with the C—H absorptions is experienced. Accordingly, we have employed methanol as the standard proton donor. While our investigation was in progress, Kitao and Jarboe[11] reported that p$Ka$ and $\Delta\nu_{methanol}$ were linearly related for pyridine and a number of alkyl pyridines. However, alkyl substituents have a comparatively small effect on the basicities. We report here a study covering a much wider range of compounds, a range including not only pyridine derivatives, but also benzopyridines and several N-heteroaromatics with two ring N atoms The p$Ka$'s of some of the latter class of compounds are often hard to determine due to competitive hydration of the molecule,[12] and it seemed possible that indirect estimation using the hydrogen-bonding method might be made, provided a relationship between p$Ka$ and $\Delta\nu$ could be established

The association constant $K$ for the hydrogen-bonding equilibrium, A—H + B $\rightleftarrows$ A—H···B, should also be dependent on the "ground state" basicity of B Except for sterically hindered bases, linear p$Ka$ – log $K$ relationships have been found previously for pyridine-like compounds.[9-11] Using a compilation of all available literature values, we have examined such correlations further

## RESULTS

IR spectral shifts ($\Delta\nu$'s) of the OH stretching vibration due to hydrogen-bonding are generally concentration dependent[8] (Fig. 1) Nevertheless, $\Delta\nu$'s usually have been determined at only one set of proton donor and acceptor concentrations. Discrepancies between $\Delta\nu$'s reported in the literature are often not due to experimental error but are a result of the different concentrations employed by different investigators. It has been proposed that $\Delta\nu$ be determined by extrapolating proton acceptor (and if possible proton donor) concentrations to infinite dilution to obtain a concentration independent measurement [8] This procedure has been applied to the determination of the $\Delta\nu_{MeOH}$'s listed in Table 1. For all compounds studied, $\Delta\nu$ decreased as the proton acceptor solution was diluted (see examples in Fig 1).

The $\Delta\nu_{MeOH}$'s reported by Kitao and Jarboe[11] are from 20-30 cm$^{-1}$ higher than those found here (Table 1). Although no explicit details were given,[11] it appears likely that these earlier $\Delta\nu$ values were not determined by extrapolation to infinite dilution.

Aromatic π-electrons and N atoms normally are both proton acceptors.[3] However, when π-deficient N-heteroaromatics without basic substituents formed intermolecular hydrogen-bonds with hydroxylic proton donors, only a single symmetrical bonded OH peak was observed. Because of the large $\Delta\nu$'s (Table 1) associated with these peaks, they were assigned to OH···N hydrogen-bonds. Association of methanol to the π-electrons of benzene rings substituted with electron withdrawing groups generally result in $\Delta\nu$'s of about 20 cm$^{-1}$.[13] The π-electrons in such benzene derivatives and in pyridine-like molecules should have comparable proton acceptor abilities Despite this, bonded OH peaks with $\Delta\nu$'s of this magnitude were not observed for compounds **1–27**. Even π-deficient N-heteroaromatics with weakly basic substituents, e g **13–15** with bromine atoms and a vinyl group, showed no experimental evidence for the presence of two proton acceptor sites. Evidently the N atom is so much more basic than the other potential sites that OH···N hydrogen-bonding takes place almost exclusively.

In contrast to all other proton acceptors studied here, 3-cyano and 4-cyanopyridines produced two well resolved bonded OH peaks The high frequency bonded peaks ($\Delta\nu$'s ~ 60 cm$^{-1}$) are attributed to nitrile···HO hydrogen-bonds and the low frequency bonded peaks ($\Delta\nu$ ~ 200 cm$^{-1}$) to pyridine···HO associations. $\Delta\nu$'s from 60-80 cm$^{-1}$ have been reported for other aromatic nitriles: *o*-toluonitrile (77 cm$^{-1}$), benzonitrile (73 cm$^{-1}$), *m*-bromobenzonitrile (64 cm$^{-1}$), *m*-chlorobenzonitrile (64 cm$^{-1}$), and *o*-chlorobenzonitrile (65 cm$^{-1}$).[14] In this instance the alternative sites, the CN groups, form sufficiently strong hydrogen-bonds to furnish observable competition with the ring nitrogen

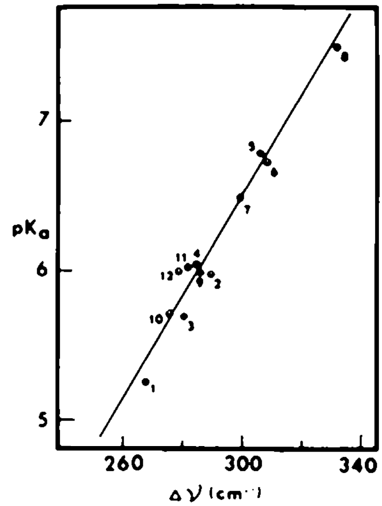



FIG. 2 Correlation between p*Ka* and Δν methanol for pyridine and alkyl substituted pyridines as proton acceptors

*Correlations*

We have confirmed the observations of Kitao and Jarboe that the $\Delta\nu_{methanol}$'s and the p*Ka*'s of alkyl pyridines show a good linear correlation (Fig. 2). When all compounds we have studied are considered, the overall correlation is noticeably

TABLE 1. BASICITIES OF π-DEFICIENT N-HETEROAROMATICS AS INDICATED BY Δν, LOG *K* AND p*Ka*.

| Cmpd No | Proton acceptor | $\Delta\nu_{MeOH}$[a] | $\Delta\nu_{PhOH}$ | log *K*[b] | p*Ka*[d] |
|---|---|---|---|---|---|
| 1 | Pyridine | 268 (287)[11,d] | 492[9a,e] | 1·76[c] | 5·25 |
| 2 | 2-Methylpyridine | 290 (317)[11] | 520[9a] (496)[9b] | 1·87[e] (1·71)[h] | 5·97 |
| 3 | 3-Methylpyridine | 281 | 491[9a] (481)[9b] | 1·86,[9a] 1·81[10b] (1·70)[h] | 5·68 |
| 4 | 4-Methylpyridine | 285 | 500[9a] (501)[9b] | 1·90,[9a] 1·91[10b] (1·84)[h] | 6·02 |
| 5 | 2,6-Dimethylpyridine | 308 (338)[11] | 535[9a] | 1·98[9a] (1·80)[i] | 6·77 |
| 6 | 2,4-Dimethylpyridine | 309 | 516[9a] | 2·02[9a] (1·93)[i] | 6·72 |
| 7 | 2,5-Dimethylpyridine | 300 | | | 6·47 |
| 8 | 2,4,6-Trimethylpyridine | 333 (356)[9a] | 531[9a] | 2·14[9a] | 7·48 |
| 9 | 2-Ethylpyridine | 286 (315)[11] | | | 5·99 |
| 10 | 3-Ethylpyridine | 276 | | | 5·70 |
| 11 | 4-Ethylpyridine | 282 | 510[9c] | 1·89[10b] | 6·02 |
| 12 | 4-t-Butylpyridine | 279 | | 1·92[10b] | 5·99 (25°) |
| 13 | 2-Vinylpyridine | 269 | | | 4·98 (25°) |
| 14 | 2-Bromopyridine | 174 | | (0·82)[h] | 0·8 (25°)[m] |
| 15 | 3-Bromopyridine | 228 | | 1·18[10b] (1·08)[h] | 2·91 |
| 16 | 3-Cyanopyridine | 64[e] 202 | | 1·15[10b] | 1·39 (24°)[m] |
| 17 | 4-Cyanopyridine | 56[e] 213 | | 1·08[10b] | 1·90[m,e] |
| 18 | Isoquinoline | 276 | 529[9a] | 1·79[9a] | 5·42 |
| 19 | Quinoline | 284 | 498[9a] | 1·76[9a] | 4·92 |
| 20 | Phenanthridine | 280 | | | 4·61 |
| 21 | Acridine | 282 | 520[9a] | 1·83[9a] | 5·58 |
| 22 | Pyrazine | 189 | | | 0·51[h,p] |

TABLE 1 - *continued*

| Cmpd No | Proton acceptor | $\Delta\nu_{MeOH}$[a] | $\Delta\nu_{PhOH}$ | Log *K*[b] | p*K*a[c] |
|---|---|---|---|---|---|
| 23 | Pyridazine | 196 | 390[e] | 1.42[h,p] | 2.24[p] |
| 24 | Pyrimidine | 208 | 385[e] | 1.0[h,p] | 1.23[o,p] |
| 25 | Quinoxaline | 201 | | | 0.53[p] |
| 26 | Phthalazine | 224 | | | 3.45[p] |
| 27 | 1,10-Phenanthroline | 221 | | | 5.01[p] |
| 28 | 2-Isopropylpyridine | (311)[11] | | | (4.82)[11,q] |
| 29 | 2-t-Butylpyridine | (295)[11] | | | (4.68)[11,q] 5.76 (25°) |
| 30 | 2-Ethyl-6-methylpyridine | (339)[11] | | | |
| 31 | 2,6-Diethylpyridine | (339)[11] | | | |
| 32 | 2,6-Diisopropylpyridine | (329)[11] | | | (5.34)[11,q] |
| 33 | 2,6-Di-t-butylpyridine | | | (0.41)[j] | (3.58)[24,q] |
| 34 | 3,5-Dimethylpyridine | | 511[9c] | (1.94)[j] | (5.2)[10a,q] |
| 35 | 2-Methylquinoline | | 520[9c] | 1.90[9c] | 5.83 |
| 36 | 4-Benzylpyridine | | | 1.89[9c] | |
| 37 | 2-Chloropyridine | | 346[9c] | (0.87)[k] | 0.6 (25°)[m] |
| 38 | 3-Chloropyridine | | 416[9c] | (1.07)[k] | 2.84 (25°) |
| 39 | 4-Chloropyridine | | | (1.23)[k,r] | 3.84 |
| 40 | 2-Methoxypyridine | | 423[9c] | (0.80)[k,s] | 3.33 |

[a] Solvent, $CCl_4$; methanol concentration, 0.5 μl/ml, measured from the "free" OH band of methanol at 3643 cm$^{-1}$. Δν values extrapolated to infinite dilution (see text and Fig 1); the uncertainty introduced by this procedure is probably ± 3 cm$^{-1}$.

[b] Logarithm of the association constant for the equilibrium B + phenol ⇌ phenol····B, solvent, $CCl_4$, determined at 20°.

[c] D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths, London (1965). Perrin divided the p*K*a's of literature into two categories, *approximate* (estimated uncertainty ≤ ± 0.04 p*K*a units) and *uncertain* (estimated uncertainty of > ± 0.04 p*K*a units). p*K*a's are of *approximate* accuracy and were measured at 20° in aqueous solution, unless otherwise noted. In cases where more than one determination was available, the average was taken.

[d] Other literature values are 300,[9c] 267[e] and 304.[f]

[e] J. Braudmuller and K. Seevogel, *Spectrochim. Acta* **20**, 453 (1964).

[f] L. Henry in *Hydrogen Bonding* (Edited by D. Hadži), p. 163. Pergamon Press, London (1959).

[g] Other literature values are 471,[9f] 444,[e] 465,[h] 465 (M. D. Joesten and R. S. Drago, *J. Am. Chem. Soc.* **84**, 3817 (1962), and T. D. Epley and R. S. Drago, *Ibid.* **89**, 5770 (1967)) and 468.[f]

[h] H. Dunken and H. Fritzshe, *Z. Chem.* **2**, 345 (1962).

[i] Average of literature values 1.78,[9c] 1.77[10a] and 1.72.[h] By employing a ΔH of − 7.40 kcal/mole,[j] the following values for log $K_{25°}$ were evaluated from measurements conducted at other temperatures: 1.79 (from $K_{25°}$ cited in Ref *j*), 1.55 (from $K_{25°}$ cited in Ref 9*b*) and 1.42 (from $K_{25}$ cited in Ref *e*).

[j] E. M. Arnett, E. J. Mitchell, T. S. S. R. Murty, P. von R. Schleyer and L. Joris, *J. Am. Chem. Soc.* **89**, 5955 (1967).

[k] Estimated from data given in Refs 9*b* and 9*c*.

[l] Estimated from data given in Refs 9*c* and 10*a*.

[m] Measurement of uncertain accuracy.

[n] Hydrogen bonding to the nitrile group.

[o] The temperature of the determination was not stated.

[p] For meaningful comparisons between mono and dinitrogen bases, a statistical correction of 0.3 (log 2) should be subtracted from log *K* and added to p*K*a of bases with two ring nitrogens. Such corrections have been made in the figures but not in this Table.

[q] Determined in 50% aqueous ethanol at 25°.

[r] A ΔH for **39** was not given and the ΔH for **38** was used instead.

[s] ΔH for **40** was not given and the ΔH for **14** was used instead.

poorer, but this is due in part to several points (especially 27) which deviate significantly (Fig. 3). Moreover, the least square correlation lines for all the π-deficient N-heteroaromatic compounds and for just the alkyl pyridines do not have the same slope (Fig. 3). This emphasizes the dangers inherent in generalizing from the results of

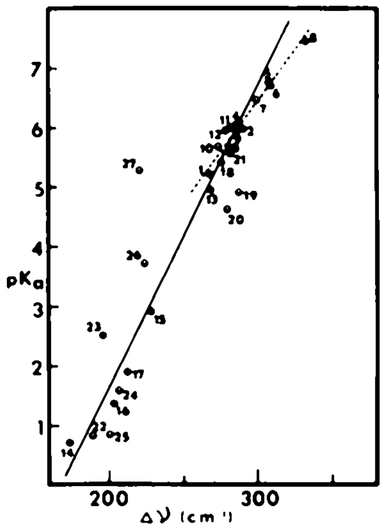



FIG. 3 Correlations between p$K_a$ and Δν methanol for π-deficient N-heteroaromatics ( ) and pyridine and alkyl substituted pyridines ( )

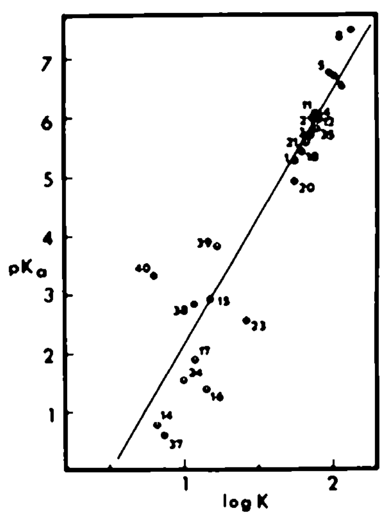



FIG. 4 Correlation between p$K_a$ and log $K$ for π-deficient N-heteroaromatics

limited series of closely related compounds. However, the rather broader class of substituted pyridines and benzopyridines gives reasonably good p$Ka$ – $\Delta\nu$, p$Ka$ – log $K$ (Fig. 4) and log $K$ – $\Delta\nu$ (Fig. 5) correlations (Eqs 2-4).

$$\Delta\nu_{\text{methanol}} = 19{\cdot}6\, \mathrm{p}Ka + 169\,(\text{in cm}^{-1}) \tag{2}$$

$$\mathrm{p}Ka = 4{\cdot}23 \log K_{\text{phenol}} - 2{\cdot}05 \tag{3}$$

$$\log K_{\text{phenol}} = 0{\cdot}00959\, \Delta\nu_{\text{methanol}} - 0{\cdot}904 \tag{4}$$

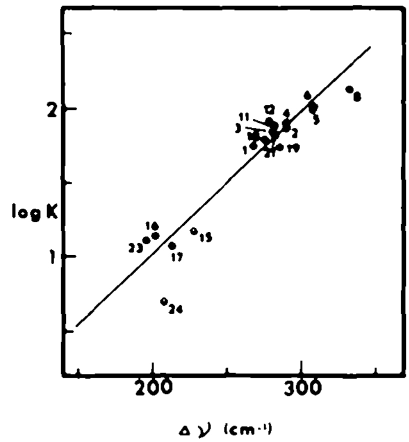



FIG. 5 Correlation of log $K$ and $\Delta\nu$ methanol for $\pi$-deficient N-heteroaromatics

Table 1 also summarizes literature data for $\Delta\nu_{\text{phenol}}$ with a number of pyridine bases. We regard these values to be much less reliable than the $\Delta\nu_{\text{MeOH}}$'s we have determined, for reasons already mentioned. The variations in the reported $\Delta\nu_{\text{phenol}}$ to pyridine—from 444 to 492 cm$^{-1}$!—illustrate the possible error range of these values. The highest value, 492 cm$^{-1}$, is due to Gramstad,[9a] who has contributed data for a number of compounds. Unfortunately, an older low resolution infrared spectrometer, equipped with a NaCl prism, was used for these measurements, and their accuracy is especially poor. More recent determinations give values for $\Delta\nu$ phenol pyridine in a narrow range, 465-471 cm$^{-1}$, but this agreement is probably fortuitous, since the various investigators did not extrapolate to infinite dilution (cf., Fig. 1).

One would expect a good $\Delta\nu_{\text{MeOH}}$–$\Delta\nu_{\text{phenol}}$ plot with a series of similar pyridine bases, but, in fact, the results are mediocre (the correlation coefficient is only 93% and the plot does not go through the origin), probably due to the unreliability of the $\Delta\nu_{\text{phenol}}$ data. For this reason, it is also not surprising that p$Ka$ correlates more poorly with $\Delta\nu_{\text{phenol}}$ than with $\Delta\nu_{\text{MeOH}}$ (Fig. 3), when the same range of compounds are compared (data from Table 1). However, Eq. 5, describing the relationship found, agrees well with that from the literature[9b] (cf. Eq. 1).

$$\Delta\nu_{\text{phenol}} = 29{\cdot}0\, \mathrm{p}Ka + 343\,(\text{in cm}^{-1}) \tag{5}$$

One can have divergent opinions regarding the success of the plots (Figs 3–5). Certainly hydrogen bonding equilibrium constants and spectral shifts, measured in $CCl_4$, might be expected to provide quite different information about the basicity of molecules than their p*Ka*'s, determined in aqueous solution. That any relationships at all are found, albeit not excellent ones, is quite remarkable. The various measures of "basicity", log *K*, p*Ka*, and $\Delta\nu$, are perhaps not so different as first appears.

$$B \cdots HOH + H_3O^+ \rightleftarrows B^+\!-H \cdots OH_2 + H_2O \quad \text{in } H_2O \quad pKa \quad (6)$$

$$B \cdots HOR \quad \text{in } CCl_4 \quad \Delta\nu \quad (7)$$

$$B + HOR \rightleftarrows B \cdots HOR \quad \text{in } CCl_4 \quad \log K \quad (8)$$

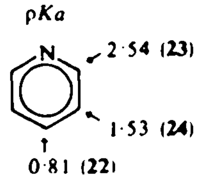
In the p*Ka* equilibrium (Eq. 6) both free base and its conjugate acid will be hydrogen bonded in hydroxylic solvents. Although the extent of this hydrogen-bonding (and of other, less specific solvation effects) in both protonated and unprotonated forms will help to determine the p*Ka*, the magnitudes of those effects may be related. The stronger the base, the stronger will be the association with the solvent in the unprotonated form (Eq. 6). However, the conjugate acids of such strong bases will be weaker proton donors. For the weaker bases, the situation should be reversed, and hydrogen-bonding of the "free" base should be less important than that of the conjugate acid (Eq. 6). If the extents of hydrogen bonding of unprotonated and protonated forms of bases are related, then $\Delta\nu$ and log *K* (Eqs 7 and 8) may provide an index of the solvation effects on p*Ka*.

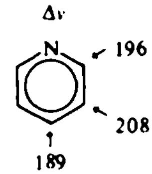
In one important particular—the effect of steric hindrance—solvation effects should not be similar in water (p*Ka*) and in $CCl_4$ ($\Delta\nu$ and log *K*). Besides the specific, hydrogen-bonding solvation shown in Eq. 6, less specific or "bulk" solvation should also be quite important in water. Solvation of this type is probably minor in $CCl_4$, a so-called "inert" solvent with a low dielectric constant. Steric hindrance of the basic site might well influence p*Ka* and log *K* more than $\Delta\nu$. Differences in solvation effects undoubtedly are contributing to the scatter observed in Fig. 3. We will discuss steric hindrance in greater detail later.

Resonance and inductive effects also play a major role in determining basicity,[12] both in the unprotonated (but hydrogen-bonded) base and in its protonated form (also hydrogen-bonded) (Eq. 6). $\Delta\nu$'s are influenced by resonance and inductive effects in the hydrogen-bonded base only (Eq. 7). In hydrogen bonding, the proton is only partially transferred from proton donor to acceptor. In a p*Ka* measurement, there is complete proton transferal to the base. If resonance effects differ markedly in going from unprotonated to the protonated form of a base, then correlation of p*Ka* with $\Delta\nu$ would not be expected. In general, this does not appear to be the case, at least in the series of compounds we have studied here (Fig. 3). The p*Ka*'s of a number of these compounds, e.g. **14**, **21**, **22**, have been interpreted by invoking specific resonance effects in their protonated forms.[12] Since their p*Ka*'s and spectral shifts correlate, it does not appear to be necessary to invoke such specific resonance effects in the conjugate acids. Whatever resonance and inductive influences are present, these are already manifest in the hydrogen-bonded base, before complete proton transfer has taken place. This may not, of course, always be the case. For this reason the measurement of $\Delta\nu$ for a base is a potentially revealing adjunct to the determination of its p*Ka*.

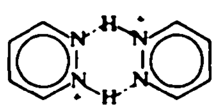
Three bases with two ring nitrogen atoms, **23**, **26**, and **27**, have larger p*Ka*'s than their spectral shifts would suggest, even after statistical corrections are made This point is brought out in the comparison below

The arrows show the location of the second nitrogen atom.



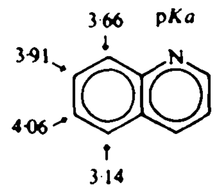




On the basis of resonance arguments,[12] one would expect 1,2 and 1,4 arrangements of two nitrogens to produce similar basicity effects, relative to 1,3 dispositions This is in fact the case for the spectral shifts, since both pyrazine (**22**) and pyridazine (**23**) give smaller Δν's than pyrimidine (**24**). The p*Ka*'s of the same compounds do not follow the same pattern. The high p*Ka* of pyridazine (**23**) (and other dinitrogen heterocycles (e.g. **26**) with vicinal N atoms) has been attributed to hydrogen bonding dimer formation of the protonated forms, (I)[12] Such dimers cannot form during the association of **23** and **26** with methanol; the Δν's of these compounds, therefore, are normal (Fig 3)




I

The arrows show the location of the second N atom.

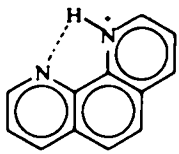



II

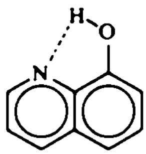
By far the largest deviation from the p*Ka*-Δν plot (Fig 3) is produced by 1,10-phenanthroline (**27**); its p*Ka* of 5·30 is 2·7 units larger than would be expected on the basis of its spectral shift Of course, some special effect on either p*Ka* or Δν or both could be responsible for this deviation, but comparison of the p*Ka* of **27** with that of model compounds possessing two nitrogen atoms in separate rings indicates that the p*Ka* certainly seems to be too large. For example, 1,5-, 1,7-, and 4,7-phenanthroline all have statistically corrected p*Ka*'s near 4·3 and the values for the quinoline derivatives, shown in II, are from 3·1 to 4·1[15] A p*Ka* for 1,10-phenanthroline (**27**) in this range would be in more reasonable agreement with the one (p*Ka* = 2·6) estimated from the spectral shifts (Fig 3)

It seems likely to us that a strong (but still asymmetrical)* intramolecular hydrogen-bond in the protonated form of 1,10-phenanthroline (III) is responsible for the abnormal p*Ka* of this compound. Such an intramolecular hydrogen-bond obviously would not be possible in the other phenanthroline isomers and the other model compounds (II) IV[17,18] and V,[19] with chelate rings of geometry similar to that of III, have been shown by IR spectroscopy to have strong intramolecular hydrogen-bonds.

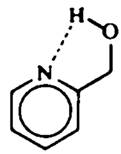
* Symmetrical hydrogen-bonds are usually found only in the strongest cases when the proton acceptor sites have appreciable negative charge.[16]



III



IV

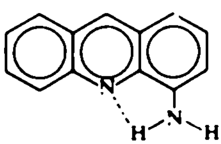


V[19]

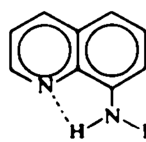
$\nu_f$ 3431,[17] 3415[18] cm$^{-1}$ $\nu_f$ 3641 cm$^{-1}$
$\nu_b$ 3450 cm$^{-1}$

We have been unable to find in the literature previous suggestions of intramolecular hydrogen-bonding in protonated 1,10-phenantholine (**27**).* This is surprising to us, in view of the well-known ability of **27** to form metal chelates,[21] and the rather ideal geometry found in III. This emphasizes a point we would like to stress. The p*Ka* alone of **27** does not reveal its exceptional character clearly. In comparison with other model compounds, the p*Ka* of **27** seems somewhat high, but one can never be completely sure that the models chosen are suitable ones. The hydrogen-bonding – p*Ka* comparison of Fig 3 shows rather dramatically the abnormal behavior of **27**. Such hydrogen bonding studies provide useful information helpful to the interpretation of the p*Ka*'s of acids and bases.

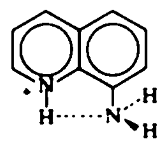
Chelation, as shown in III, IV, V, 8-aminoquinoline (VII) and 1-amino-acridine (VI), has often been postulated to affect p*Ka*.[12] The p*Ka* of 8-hydroxyquinoline (IV) is about one unit higher than expected by comparison with other hydroxyquinoline and isoquinoline analogs,[12] incapable of intramolecular association. In contrast to this behavior, and the parallel behavior of III (both are weaker *acids*, due to hydrogen-bonding), both 8-aminoquinoline (VII) and 1-aminoacridine (VI) are weaker *bases*



VI



VII



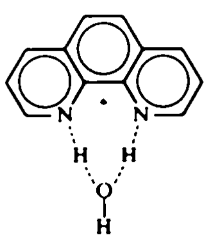
VIII

than normal.[12] Since both VI and especially VII would appear to be good di-nitrogen models for III, their disparate behavior requires comment.

The conventional explanation for the weaker basicity of VI and VII is that hydrogen bonding is possible in both neutral species, as illustrated in the structures.[12] This

* However, Beattie[20] suggested that *A* may be the structure of the monohydrate monohydrochloride of 1,10-phenantroline.

*A*



explanation seems somewhat superficial The protonated form of VII can also form intramolecular hydrogen bonds, as shown in VIII. It is not only these intramolecular hydrogen-bonds which are important in helping to determine the p*Ka*, but also the intermolecular ones to the solvent, especially when the good proton acceptor, water, is used for this purpose Furthermore, for intramolecular hydrogen-bonds to be effective, they must be strong, stronger than those to the solvent. An infrared spectral study of VI and VII in both "inert" and proton acceptor solvents revealed that while little direct spectroscopic spectral shift evidence could be found for the chelation shown in VI and VII, both compounds showed abnormally low tendency to form intermolecular hydrogen-bonds [22] It would appear, then, that the chelation in VI and VII is important. But what about the potential chelation in VIII? If this is equally important as that in VII, then the p*Ka* would appear to be "normal", contrary to observation.

Although the intramolecular hydrogen-bonds in VIII and in III appear to be similar, there is a very significant difference between the two compounds In VII (and VI) the amino group should be coplanar or very nearly coplanar with the ring.* This would facilitate not only chelation, but also resonance interaction of the nitrogen lone-pair with the aromatic system [10] In VIII, chelation is possible only if the $NH_2$ group is twisted, so that the lone-pair is in the plane of the ring. In such a conformation, resonance is not possible Chelation in VIII must thus compete with resonance stabilization, and this is an unfavorable situation. In III, no such competition is present; the lone-pair on nitrogen is not involved in resonance, and a strong intramolecular hydrogen-bond is possible

*Steric effects*

2,6-*Di-t-butylpyridine*. There appear to be no significant deviations in the p*Ka* − log *K* plot (Fig 4) attributable to steric effects Steric effects may contribute to the scatter of the data points in Fig. 3 (p*Ka* vs Δν), but no definite conclusions can be drawn because of the inconsistency of behavior of compounds with 2- and 6-substituents (Table 1)- some compounds deviate, others do not However, the size of these substituents in the bases studied was small, and it appeared desirable to examine compounds with more bulky groups

A number of papers have considered the effects of hindering groups on the base strength of pyridine derivatives Halleux[11] claimed that even the single Me group of 2-methylpyridine caused a deviation from a p*Ka* − log *K* (phenol) plot However, insufficient compounds were examined to establish a reliable correlation line When enough data points are available (cf. Gramstad[9a] and Fig 4) it is seen that 2-methylpyridine and 2,6-dimethylpyridines do not behave abnormally Nevertheless, it is clear from Halleux's data that 2-t-butyl and 2,6-di-t-butylpyridine have very much lower log *K*'s than would be expected from the p*Ka*'s of these compounds On the other hand, Rubin and Panson[10b] found that the association constant of 2-t-butylpyridine with phenol was only slightly smaller than that for 4-t-butylpyridine, but 2,6-di-t-butylpyridine was extremely hindered With methanol as proton donor, a good p*Ka* − Δν correlation was found for a number of alkylpyridines, but there

* Aniline is not planar, but it does possess a partially flattened structure since ∠ HNH is about 114°[23] compared with a value of 106° for the corresponding angle in $CH_3NH_2$[23a]

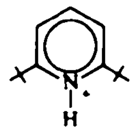
were serious deviations in the p$Ka$ – log $K$ plot for the same compounds.[11] An isopropyl or t-butyl group but not a Me or Et produced a significant steric effect, and the deviation was magnified in 2,6-di-isopropyl pyridine. Work of Brown and Kanner[24] has established the consistency of response of the p$Ka$ of pyridines when first a 2-substituent and then two 2,6-substituents are introduced. Interestingly, even 2-isopropyl-6-t-butylpyridine shows the regular behavior displayed by the other alkylpyridines. Only 2,6-di-t-butylpyridine was found to be abnormal; its p$Ka$ was estimated by extrapolation from the p$Ka$'s of pyridine and of 2-t-butylpyridine to be 1·4 units lower than expected.[24] Condon[25] argued that this procedure was insufficient, since 2-t-butylpyridine itself was hindered. He estimated that the deviation of p$Ka$ of 2,6-di-t-butylpyridine was 2·2 units on the basis of the expected inductive effects of the substituents.

In summary, then, log $K$ seems to be more sensitive to steric effects than either p$Ka$ or $\Delta\nu$. Two flanking t-butyl groups are needed to cause large deviations in the p$Ka$'s of alkyl pyridines. For this reason, we felt it desirable to examine the $\Delta\nu$ of 2,6-di-t-butylpyridine, which value is not available in the literature. Unfortunately, no OH $\cdots$ N bonded peak was observed with methanol, even with a 1 : 1 v : v solution of 2,6-di-t-butylpyridine in $CCl_4$. Very weak absorptions, which have $\Delta\nu$'s less than 130 cm$^{-1}$ would be obscured by the low intensity absorption of methanol dimer (about 10% as intense as the free OH absorption at the methanol concentration employed). For this reason methanol is a poor choice as a proton donor when spectral shifts for weak associations are desired. With p-fluorophenol as a stronger proton donor, only a very weak, ill defined absorption was seen at lower frequencies ($\Delta\nu$ = ca. 40 cm$^{-1}$). Perhaps this is an OH $\cdots$ $\pi$ bonded peak. However, the absorption might have been an artifact, since lack of material prevented a thorough study. It is clear that the nitrogen atom is effectively screened in this compound, and hydrogen bonding is completely or nearly completely inhibited.*

Hydrogen-bonding, because of the small size of the probing atom, the proton, is usually relatively insensitive to steric hindrance. Bulky groups in the proton donors and acceptors produce a decrease in the association constant, but the $\Delta\nu$'s are generally affected much less. In these crowded situations, the hydrogen bonds which are able to form despite the hindrance seem to have normal distances. A situation in which all hydrogen bonding is inhibited is extreme, but some analogous instances are known. 2,6-Di-t-butyl-4-methylphenol gives only a free OH peak in solution in ether or in triethylamine, and evidence for hydrogen-bonding was only found with the uncrowded bases, tetrahydrofuran and pyridine.[26] In this phenol, the proton is held away from the ring by the intervening oxygen atom, and still the steric inhibition due to the two ortho t-butyl groups is great. In the protonated pyridine X, the proton is

* Three groups who studied the "association" of phenol with 2,6-di-t-butylpyridine[9b, 10a] and with 4-methyl-2,6-di-t-butylpyridine[10b] did not report specific evidence of hydrogen-bonding, e.g. the appearance of a bonded OH peak. Very low association constants, 3 and 0·65, respectively, were estimated by observing the behavior of the free phenol OH peak in the IR.[10] A calorimetric measurement gave $-\Delta H$ = 3·26 kcal/mole for the association of phenol with 2,6-di-t-butylpyridine.[9b] We regard these values as suspect in the absence of specific evidence for a hydrogen-bonding interaction; perhaps other effects are influencing the measurements.

completely encased by the t-butyl groups, and no hydrogen bonding is possible.* Since 2,6-di-t-butylpyridine itself also should not be able to hydrogen-bond with water or with ethanol, the p*Ka* of this compound should be independent of specific solvation (i.e. hydrogen-bonding) factors.



X

The abnormally low p*Ka* of such hindered bases as 2,6-di-t-butylpyridine is generally attributed to two possible factors: inhibition of solvation[24, 26] or steric strain.[24] The first explanation required the assumption that solvation due to hydrogen-bonding is greater in the protonated base than in the free one. Hence, when solvation is inhibited, the preferential stabilization of the protonated form is removed, and an increase of acidity results. The steric explanation assumes that the steric strain in the crowded base increases upon protonation, i.e. the effective "size" of a proton attached to nitrogen is greater than that of a lone pair of electrons without an attached nucleus.† Strained acids, such as IX, should therefore have enhanced acidities, since part of the strain is relieved on ionization.

Condon[25] has attributed the enhanced acidity of 2,6-di-t-butylpyridine (and of other hindered bases) to steric hindrance to hydration. On the basis of an electrostatic model, he calculated that the increase in hydrogen-bonding in going from trimethylamine to trimethylammonium ion amounted to 5·2 p*Ka* units. For reasons not made clear, this value was adopted as the "calculated" one for 2,6-di-t-butylpyridine. Since agreement with the "observed" $\delta$ p*Ka* = 2·2 (see above) was rather poor, Condon took this to mean that steric hindrance to hydration was not 100% "effective" in 2,6-di-t-butylpyridine. Since the direct evidence for hydrogen bonding in both this base and in its conjugate acid suggests nearly 100% "effectiveness", the approximate nature of Condon's estimates is brought out.

The choice of trimethylamine as a model for pyridine also seems inappropriate. It is well known that pyridine, a weaker base, forms weaker hydrogen bonds than does trimethylamine. However, the trimethylammonium ion is a weaker acid than is the pyridinium ion, and the former should form weaker hydrogen-bonds than the latter. The difference in hydrogen bonding energies between pyridine and the pyridinium ion therefore should be considerably larger than the difference between trimethylamine and trimethylammonium ion. This being the case, then the discrepancy between the "observed" $\delta$ p*Ka* and the "calculated" value must be very much greater, and one wonders about the accuracy of Condon's estimates of hydration energies.[25]

It should be possible to obtain experimental values for the hydrogen-bonding or solvation energies not only of free bases but also of their protonated forms. Until this is done, one cannot be certain to what extent the increase of acidity observed

* An IR study of solid, zwitterionic 2,6-di-t-butylpyridine-3-sulfonic acid showed only a free N—H absorption band, and no evidence for hydrogen-bonding.[27]

† The "size" of the lone pair of electrons on nitrogen is a subject of controversy.[28]

for the conjugate acids of hindered bases is due to inhibition of solvation or to steric strain

## EXPERIMENTAL

*Sources of Compounds* The alkyl pyridines and vinylpyridine were donated by the Reilly Tar and Chemical Co Professor R W Taft, Jr, supplied compounds 15 17, and 33 was provided by Professor H C Brown We would like to express our thanks for these materials The remaining compounds were commercially available The liquids were distilled from BaO and the solids were recrystallized The physical constants checked with those reported in the literature

Ir spectroscopic techniques were essentially the same as those previously described[8] The concentration of MeOH was 0·5 µl per ml of soln to keep dimerization at a minimum The proton acceptor concentration was varied between 0·5 2·0 mg ml, and the Δν's determined by extrapolation to infinite dilution of proton acceptor A least squares computer program was used to determine the correlation lines

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[b] Dr. E. Ōsawa has measured $\Delta\nu_{MeOH}$ for two pyridine bases of widely different basicities. As a test of Eq. 2 values of $\Delta\nu$ calculated from the known pKa's were compared with the experimental ones. 4-dimethylaminopyridine (pKa 9·59, $\Delta\nu_{MeOH}$ 357 (calc), 352 (obs)), 3,5-dichloropyridine (p*Ka* 0·67, $\Delta\nu_{MeOH}$ 182 (calc), 175 (obs)).