Hydrogen-bond basicity pK_{HB} scale of six-membered aromatic N-heterocycles

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Using 4-fluorophenol as a reference hydrogen-bond donor, equilibrium constants, K_f, for the formation of 1:1 hydrogen-bonded complexes have been obtained by FTIR spectrometry for 65 six-membered N-heteroaromatics of widely differing structures, in CCl_4 at 298 K. The pK_{HB} scale shows that most N_{sp^2} bases are weaker hydrogen-bond bases than many oxygen bases. This scale extends from the hypobasic pentafluoropyridine, illustrating the electron-withdrawing field effect of fluoro substituents, to push–pull 4-NR_2-pyridines, illustrating the resonance effect of the 4-NR_2 substituents which donate electrons in the order NH_2 < piperidino < NMe_2 < NEt_2 < pyrrolidino. A spectroscopic scale is constructed from the IR frequency shift $\Delta\nu$(OH) of methanol hydrogen-bonded to N-heteroaromatics. The thermodynamic pK_{HB} scale correlates with the $\Delta\nu$(OH) scale, but 2-substituted pyridines deviate markedly. These deviations are attributed to, and allow the semi-quantitative determination of: (i) steric effects, most important in 7,8-benzoquinoline; (ii) lone pair–lone pair repulsions, most important in 1,2-diazines; and (iii) lone pair–bond pair repulsions, most important in 2,6-difluoropyridine. IR spectra show the fixation of 4-fluorophenol to the nitrile nitrogen of 2-, 3- and 4-cyanopyridines, to the carbonyl oxygen of 3-COOMe, 3-COPh and 4-COMe-pyridines, and to the ether oxygen of 2-methoxypyridine, in addition to the fixation to the pyridine nitrogen. A cyclic complex, with both NH · · · O and OH · · · N hydrogen bonds, is formed with 2-amino- and 2-methylamino-pyridines.

Since the work of Gurker and Taft[1] and Arnett *et al.*,[2] 4-fluorophenol has proved to be an excellent reference hydrogen-bond donor for the establishment of a thermodynamic hydrogen-bond basicity scale of organic bases B. This scale, denoted by pK_{HB}, is defined as the logarithm of the formation constant K_f of the 1:1 hydrogen-bonded complex 4-$F_6H_4OH \cdots B$ in CCl_4 at 25 °C [eqns. (1)–(3)].

$$B + 4\text{-}FC_6H_4OH \rightleftharpoons 4\text{-}FC_6H_4OH \cdots B \quad (1)$$

$$K_f = [\text{hydrogen-bonded complex}]/[B][4\text{-}FC_6H_4OH] \quad (2)$$

$$pK_{HB} = -\log_{10}(\text{dissociation constant of the complex}) = \log_{10} K_f \quad (3)$$

The choice of these standard conditions allows the accurate determination of K_f over a wide basicity range, by measuring equilibrium concentrations from various signals such as the ^{19}F NMR shifts,[1] the $\pi \longrightarrow \pi^*$ transition UV absorbances at 281 nm or the O–H stretching IR absorbances[2] at 3614 cm^{-1}. The lowest published[3] K_f value is 0.14 $dm^3\ mol^{-1}$ (pK_{HB} = −0.85) for the very weakly basic 2,3-dimethylbut-2-ene and linear free energy relationships indicate[4] that the lowest limit of the pK_{HB} scale measurable in CCl_4 is *ca.* −1.1. The highest measured K_f values are 4570 $dm^3\ mol^{-1}$ (pK_{HB} = 3.66)[5] for the neutral base Ph_3AsO and 120 000 $dm^3\ mol^{-1}$ (pK_{HB} = 5.08)[6] for the tetrabutylammonium cyanate ion pair $NBu_4^+\ OCN^-$. For neutral bases we have indications[5] that the pK_{HB} scale can be extended to *ca.* 6. Thus this basicity scale extends over a 7 pK units range and 40 kJ mol^{-1} Gibbs energy range.

The building of the pK_{HB} scale contributes not only to the increasing efforts towards a quantitative description of the hydrogen bond but also to the difficult and unachieved task of measuring quantitatively the strength of organic Lewis bases. We have already measured pK_{HB} for amidines,[7] alcohols,[8] amides,[9] esters,[10] nitriles,[11] nitro compounds,[12] thioamides,[13] π bases[3] and sulfonyl derivatives.[14] We present here a wide-range pK_{HB} scale for: (i) pyridines very diversely substituted at the *ortho*, *meta* and *para* positions; (ii) pyridines with one or two fused benzene rings; (iii) diazines; and (iv) *s*-triazine. We have been able to gather 65 values extending over 3.4 pK units (19 kJ mol^{-1}) from pentafluoropyridine (pK_{HB} *ca.* −0.45) to 4-pyrrolidinopyridine (pK_{HB} = 2.93). The case of 1,10-phenanthrolines, which are still more basic (pK_{HB} > 3),[5] will be studied in a future paper. In addition to this thermodynamic scale of HB basicity, we have measured the lowering of the O–H stretching wavenumber of methanol, $\Delta\nu$(OH), on going from the free to the hydrogen-bonded OH group. This wavenumber shift is generally considered to be a spectroscopic scale of HB basicity, and, within a family of bases, the thermodynamic and spectroscopic scales are often well correlated.[3,7–14]

These properties and this large and diverse sample of six-membered N-heterocycles allow us to study: (i) the position of N-heteroaromatics on the pK_{HB} scale; (ii) the pK_{HB}–$\Delta\nu$(OH) relationship in the pyridine family; (iii) the field-inductive and resonance effects in *meta*- and *para*-substituted pyridines; (iv) the steric and the lone pair–lone pair repulsion in *ortho*-substituted pyridines; and (v) the hydrogen-bonding site in pyridines containing a second basic centre (*e.g.* cyanopyridines).

Experimental

Materials

All compounds were purchased from Aldrich, Fluka or Reilly, except 4-piperidinopyridine and *N*-methyl-*N*-pyridin-4-ylhydrazine which were synthesized by Dr D. G. Morris (Glasgow). Liquids were distilled, then chromatographed on basic aluminium oxide and stored over molecular sieves. Their purity was checked by gas chromatography. Solids were recrystallized from the appropriate solvent, then dried on P_2O_5 under high vacuum. Their purity was established by thin-layer chromatography. 4-Fluorophenol was sublimed over P_2O_5 at

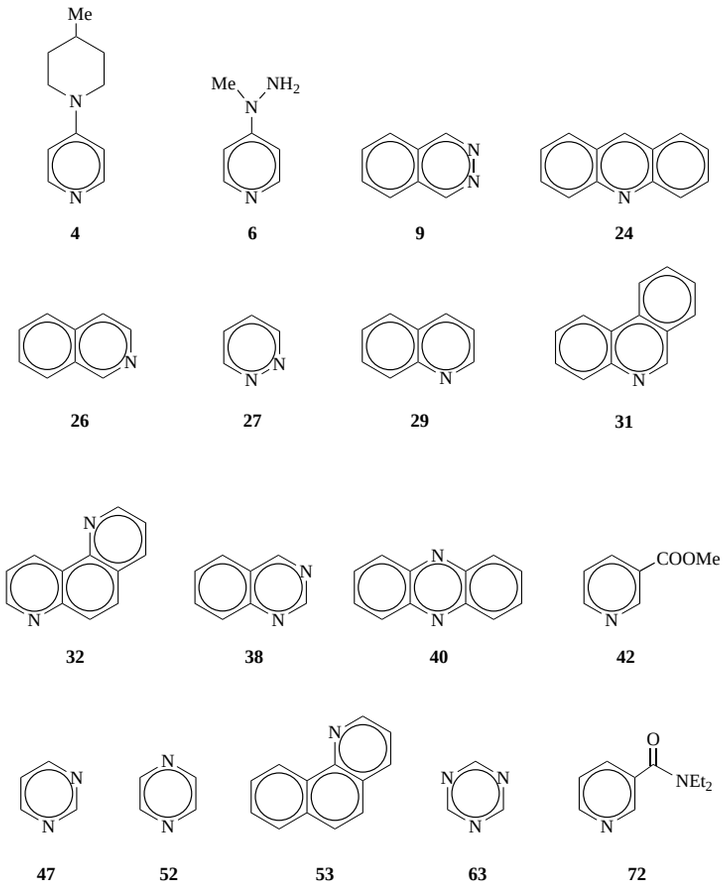


Fig. 1 Structures of some of the **N**-heteroaromatic molecules listed in Table 1

60 °C and 13 Pa. Spectroscopic grade CCl_4 was passed before use through a column of freshly activated 4 Å molecular sieves. Spectroscopic grade absolute methanol was kept over 3 Å molecular sieves.

IR spectra

IR measurements were carried out on a Bruker IFS 48 or a Nicolet 510 M Fourier transform spectrometer, by selecting a 1 cm^{-1} resolution and 256 accumulations. The 1 cm and 5 cm quartz infrasil cells were thermostatted at 25 ± 0.2 °C. All operations, including the filling of the cell, were conducted in a desiccated glove box.

Equilibrium constants

The formation constant of 1 : 1 HB complexes (c) of 4-fluorophenol (a) with bases (b) is defined as $K_f = C_c/C_aC_b$. K_f is based on molar standard states and activity coefficients are taken to be unity. The initial molar concentration of 4-fluorophenol C_a^0 was kept below 3×10^{-3} mol dm^{-3} in order to prevent self-association, while the initial molar concentration of base, C_b^0, was adjusted so that the complexation of 4-fluorophenol was not less than 20% and not more than 80%. For example, for 4-phenylpyridine ($K_f = 90.8$ dm^3 mol^{-1}), C_b^0 was varied from 7×10^{-3} mol dm^{-3} (34% of complex) to 2×10^{-2} mol dm^{-3} (60% of complex). The equilibrium concentration C_a was obtained from the absorbance of the 3614 cm^{-1} peak of 4-fluorophenol ($\varepsilon = 237$ dm^{-3} mol^{-1} cm^{-1}) and the equilibrium concentrations were deduced: $C_b = C_b^0 - (C_a^0 - C_a)$ and $C_c = C_a^0 - C_a$. If we took care to avoid the addition of a second 4-fluorophenol molecule to the 1 : 1 complex by maintaining the base in excess, the K_f values did not depend on concentration. From the standard deviation of 5 to 10 separate determinations and from the comparison of mean results obtained in our laboratory by various operators on different FTIR apparatus, the maximum error in pK_{HB} is estimated to be ±0.04.

IR shifts

We have used methanol, instead of 4-fluorophenol, as the standard hydrogen-bond donor for the measurement of IR OH spectral shifts. With 4-fluorophenol, shifts are difficult to measure with confidence because the bonded OH band is broad and irregularly shaped and interferes with the C–H absorptions. Methanol is a weaker HB donor than 4-fluorophenol, the shifts are about half as large and no interference with the C–H bands is experienced. Moreover, the band shape is quasi Gausso-Lorentzian. The $\Delta\nu$ values are generally base concentration-dependent and it has been proposed[15] that they be determined by extrapolating base concentrations to infinite dilution. Because of the uncertainty introduced by this procedure, we have preferred working on highly diluted solutions by using a long path cell (5 cm) and accumulating 256 spectra. $\Delta\nu$ values are believed to be accurate to within ±2–5 cm^{-1}.

Results

Table 1 summarizes the pK_{HB} scale constructed from the hydrogen-bonding formation of 4-FC_6H_4OH with 65 different six-membered aromatic N-heterocycles in CCl_4 solution at 25 °C. Also given are the corresponding values of $\Delta\nu$(OH), the ν(OH) wavenumber shift between complexed and uncomplexed methanol.

There have been in the past many measurements of the formation constant K for 1 : 1 hydrogen-bonded complexes between substituted pyridines and various hydrogen-bond donors under other conditions of temperature and solvent.[16–25] Comparison of ten literature sets with our pK_{HB} scale has been made *via* linear free energy relationships (4) and the results are presented in Table 2.

$$pK_{HB} = a \log K + b \qquad (4)$$

Table 1 Hydrogen-bond basicity of six-membered N-heteroaromatics: the thermodynamic pK_{HB} scale and the spectroscopic $\Delta\nu$(OH) (cm^{-1}) scale

No.	Compound	pK_{HB}[a]	$\Delta\nu$(OH)[b]
1	4-Pyrrolidinopyridine	2.93	373
2	4-*N*,*N*-Diethylaminopyridine	2.89	370
3	4-*N*,*N*-Dimethylaminopyridine	2.80[d]	366
4	4-(4-Methylpiperidino)pyridine[c]	2.68	359
5	4-Piperidinopyridine	2.68	359
6	*N*-Methyl-*N*-pyridin-4-ylhydrazine[c]	2.58	354
7	4-Aminopyridine	2.56	~347
8	2,4,6-Trimethylpyridine (2,4,6-collidine)	2.29	349
9	Phthalazine[c]	2.27 (1.97)[e]	239
10	3,4-Dimethylpyridine (3,4-lutidine)	2.24	314
11	3,5-Dimethylpyridine (3,5-lutidine)	2.21	316
12	3-Aminopyridine	2.20	
13	2,6-Dimethylpyridine (2,6-lutidine)	2.14	331
14	4-Methoxypyridine	2.13[f]	312
15	2-Aminopyridine	2.12	~320
16	4-*tert*-Butylpyridine	2.11	303
17	2-Methylaminopyridine	2.11	
18	4-Methylpyridine (4-picoline)	2.07[g]	304
19	4-Ethylpyridine	2.07	306
20	2-Methylpyridine (2-picoline)	2.03	315
21	3-Ethylpyridine	2.01	305
22	3-Methylpyridine (3-picoline)	2.00	300
23	4-Phenylpyridine	1.96	293
24	Acridine[c]	1.95	312
25	4-Vinylpyridine	1.95	293
26	Isoquinoline[c]	1.94	291
27	Pyridazine[c]	1.95[h] (1.65)[e]	218
28	2-Ethylpyridine	1.94	316
29	Quinoline[c]	1.89[i]	296
30	2-Butylpyridine	1.88[f]	
31	Phenanthridine[c]	1.87	292
32	1,7-Phenanthroline[c]	1.87[j]	289
33	Pyridine	1.86[k]	286
34	2-Aminopyrimidine	1.85[l]	
35	2-Isopropylpyridine	1.76	307
36	2-Vinylpyridine	1.65	287
37	2-*N*,*N*-Dimethylaminopyridine	1.61	294
38	Quinazoline[c]	1.55[j]	235
39	4-Chloropyridine	1.54	255
40	Phenazine[c]	1.52 (1.32)[e]	248
41	4-Acetylpyridine	1.50[m]	255 (75)[t]
42	Methyl nicotinate[c]	1.49[m]	250 (75)[t]
43	3-Benzoylpyridine	1.49[m]	248 (77)[t]
44	2,2′-Bipyridine	1.45 (1.15)[e]	267
45	2-Phenylpyridine	1.43	270
46	2-*tert*-Butylpyridine	1.42	285
47	Pyrimidine[c]	1.37[n] (1.07)[e]	213
48	3-Iodopyridine	1.37	245
49	3-Fluoropyridine	1.35	240
50	3-Chloropyridine	1.31	237
51	3-Bromopyridine	1.31[o]	241
52	Pyrazine[c]	1.22[p] (0.92)[e]	205
53	7,8-Benzoquinoline[c]	1.16	270
54	2-Chloropyridine	1.05	192
55	4-Cyanopyridine	1.05[m]	214 (53)[t]
56	3-Cyanopyridine	1.00[m]	203 (61)[t]
57	2-Methoxypyridine	0.99[m]	232 (74)[t]
58	2-Fluoropyridine	0.95	167
59	2-Bromopyridine	1.03[q]	192
60	5-Bromopyrimidine	0.89 (0.59)[e]	171
61	2-Cyanopyridine	0.85[m]	157 (64)[t]
62	3,5-Dichloropyridine	0.85[r]	200
63	*s*-Triazine[c]	0.80 (0.32)[s]	147
64	2,6-Difluoropyridine	0.14	87
65	Pentafluoropyridine	~−0.49	~40

[a] This work unless specified. [b] This work. [c] Formula in Fig. 1. [d] 2.81 in ref. 1. [e] Statistically corrected by $-\log 2$. [f] Ref. 43. [g] 2.03 in ref. 1. [h] 1.90 in ref. 44. [i] 1.85 in ref. 1. [j] Two non-equivalent nitrogens: $pK_{HB} = \log [K_f(N_1) + K_f(N_2)]$. [k] 1.88 in ref. 1. [l] 1.73 in ref. 44. [m] IR spectra show the formation of a second 1 : 1 complex on the substituent X: $pK_{HB} = \log [K_f(X) + K_f(pyr\ N)]$. [n] 1.35 in ref. 1 and 1.36 in ref. 44. [o] 1.31 in ref. 2 and 1.30 in ref. 43. [p] 1.11 in ref. 44. [q] 0.94 in ref. 1. [r] 0.80 in ref. 43. [s] Statistically corrected by $-\log 3$. [t] IR shift of the OH group hydrogen-bonded to the X substituent.

A number of sets agree reasonably well ($r \geqslant 0.990$) with the pK_{HB} scale. Among them, set no. 7 contains interesting compounds which were not available to us. From this data set and eqn. (4), we have therefore calculated secondary pK_{HB} values which are collected in Table 3.

Discussion

The place of pyridines on the pK_{HB} scale

If we class, somewhat arbitrarily, hydrogen-bond bases as hypobases ($pK_{HB} < 0$), weak bases ($0 < pK_{HB} < 1$), medium bases

Table 2 Results[a] of the correlations $pK_{HB} = a \log K + b$ between the equilibrium constants for the association of N-heteroaromatics with 4-fluorophenol (pK_{HB}) and other hydrogen-bond donors (log K)

Set no.	Hydrogen-bond donor, T/K, solvent	a ($\pm sa$)	b ($\pm sb$)	n[b]	r[c]	s[d]	Ref.
1	Phenol, 298, CCl_4	1.049 (±0.077)	0.12 (±0.14)	7	0.987	0.05	16
2	Phenol, 293, CCl_4	1.108 (±0.077)	−0.06 (±0.14)	9	0.984	0.03	17
3	Phenol, 293, CCl_4	1.254 (±0.083)	−0.31 (±0.14)	8	0.987	0.08	18
4	Phenol, 300, CCl_4	1.118 (±0.037)	−0.01 (±0.05)	10	0.996	0.05	19
5	Methanol, 298, CCl_4	1.353 (±0.248)	1.34 (±0.10)	6	0.939	0.10	20
6	Methanol, 298, CCl_4	2.533 (±0.166)	0.84 (±0.07)	13	0.977	0.12	21
7	Phenol, 298, CCl_4	1.198 (±0.040)	−0.13 (±0.07)	6	0.998	0.04	22
8	Phenol, 298, CCl_4	1.065 (±0.044)	0.10 (±0.07)	17	0.988	0.09	23
9	Phenol, 298, CCl_4	0.900 (±0.136)	0.37 (±0.26)	5	0.967	0.05	24
10	4-Nitrophenol, 298, CCl_3CH_3	0.759 (±0.026)	−0.01 (±0.06)	19	0.990	0.08	25

[a] The large differences in the regression coefficients and intercepts corresponding to identical systems are partly due to the restricted and different samples of bases. [b] Number of common bases in the set and in Table 1. [c] Correlation coefficient. [d] Standard deviation.

Table 3 Secondary pK_{HB} values[a]

No.	Compound	pK_{HB}
66	3-(*N*,*N*-Dimethylamino)pyridine	2.43
67	2-(*N*,*N*-Dimethylamino)pyrimidine	1.40
68	4-(*N*,*N*-Dimethylamino)pyrimidine	2.11
69	5-(*N*,*N*-Dimethylamino)pyrimidine	1.88
70	4-(*N*,*N*-Dimethylamino)quinoline	2.43
71	9-(*N*,*N*-Dimethylamino)acridine	2.31

[a] Calculated from the equation: $pK_{HB} = 1.198 \log K - 0.126$. K is the formation constant of the phenol–pyridine complex at 298 K in CCl_4.

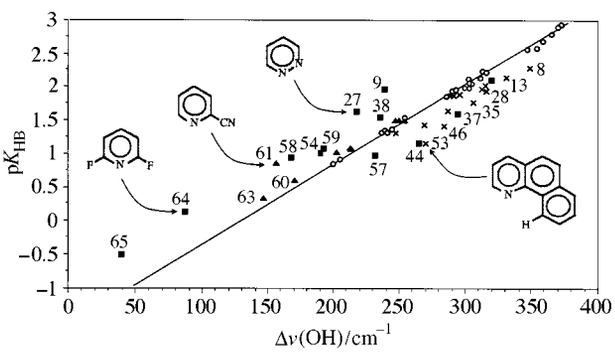
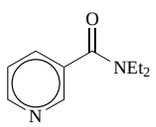


Fig. 2 Relationship between the thermodynamic scale pK_{HB} and the spectroscopic scale $\Delta\nu$(OH). (○) *meta* and *para* substituents; (×) *ortho* substituents without a lone pair; (■) *ortho* substituents bearing lone pair(s); (▲) pyridines containing a secondary basic site or interacting lone pairs. The line of eqn. (6) is drawn. Numbers refer to Table 1.

$$pK_{HB} = 1.139\ (\pm 0.012)\ (\Delta\nu_{OH}/100) - 1.384\ (\pm 0.036) \quad (5)$$
$$n\ \text{(number of points)} = 31 \quad r\ \text{(correlation coefficient)} = 0.998$$
$$s\ \text{(standard deviation)} = 0.040$$

(1 < pK_{HB} < 2), strong bases (2 < pK_{HB} < 4) and super-bases (pK_{HB} > 4), we can qualify the lead compound, pyridine, (pK_{HB} = 1.86) as a medium base on the hydrogen-bond scale. In fact, unlike the Brønsted basicity, many oxygen bases such as amides,[9] sulfoxides[1] or phosphoryl compounds,[1] are stronger hydrogen-bond bases than pyridine. For example, *N*,*N*-diethylacetamide (pK_{HB} = 2.47) is more basic than pyridine (pK_{HB} = 1.86). As a consequence, the behaviour of *N*,*N*-diethylnicotinamide **72** has been shown[26] to accept quite differently



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hydrogen-bond donors (*e.g.* phenols) and proton donors (*e.g.* HCl) in solution: this molecule is protonated on the pyridine nitrogen whereas phenols are hydrogen-bonded to the oxygen atom.

Table 1 shows that the hydrogen-bond basicity of the pyridine nitrogen is very sensitive to the molecular structure. We have been able to create an hypo-basic pyridine by means of five electron-withdrawing fluorine substituents (compound **65**) and strongly basic pyridines by means of electron-donating groups. Thus the 'push–pull' pyridines **1**–**7** (pK_{HB} = 2.56 to 2.93) become more basic than dimethylacetamide (pK_{HB} = 2.44)[9] and dimethyl sulfoxide (pK_{HB} = 2.53).[1] Nevertheless, the phosphoramide $(Me_2N)_3PO$ (pK_{HB} = 3.56)[1] and the phosphine oxide Ph_3PO (pK_{HB} = 3.16)[1] remain still more basic than 4-pyrrolidinopyridine **1** (pK_{HB} = 2.93).

The pK_{HB}–$\Delta\nu$(OH) relationship

If we plot pK_{HB} values *vs.* the IR shifts $\Delta\nu$(OH), it appears clearly in Fig. 2 that these two basicity scales are linearly related for the 3- and 4-substituted pyridines, but not for the 2-substituted ones. With all the 3- and 4-substituted pyridines the equation and statistics of the line are given by eqn. (5)

In spite of these very satisfactory statistics, it seems chemically judicious to exclude from our sample of pyridines those derivatives containing a secondary basic site (substituents 3-CN, 4-CN, 3-COPh, 3-COOMe and 4-COMe), and also those bearing interacting lone pairs (*s*-triazine and pyrimidines **47** and **60**). They all systematically deviate above the line of eqn. (5) and although these deviations are generally not statistically significant, we will show later that they are chemically significant. Therefore, we have selected eqn. (6) as the best chemical equation for correlating pK_{HB} and $\Delta\nu$(OH).

$$pK_{HB} = 1.167\ (\pm 0.015)\ (\Delta\nu_{OH}/100) - 1.476\ (\pm 0.047) \quad (6)$$
$$n = 24 \quad r = 0.998 \quad s = 0.037$$

The relationship between Gibbs energies of hydrogen-bond formation (*i.e.* pK_{HB}) and IR shifts has often been studied.[3,7–15,19,27] It is well known[27] that a general correlation does not hold for all functional groups, but that well-defined correlation lines do exist[3,7–15,19] (*i.e.* we have family-dependent relationships) if three conditions are met. Firstly, the site of hydrogen-bond fixation must remain unchanged within the family: this is the reason why the oxygen base *N*,*N*-diethylnicotinamide does not obey eqn. (6) for pyridines which are sp^2 nitrogen bases. Secondly, the steric requirements of this site must remain constant: this is the reason why sterically hindered 2-substituted pyridines deviate below the line of eqn. (6) (*vide infra*). Lastly, the hydrogen-bonding site must remain unique: this is why pK_{HB} values of diazines and triazine must be corrected by the statistical factors of, respectively, −log 2 and −log 3 before obeying eqn. (6) for monoazines, and also why the

Table 4 Quantitative analysis of the pK_{HB} values of X-substituted pyridines in terms of polarizability, field and resonance contributions. The ρ values[33] for gas-phase proton transfer are indicated between brackets.

Series	pK^0_{HB}	$-\rho_\alpha$	$-\rho_F$	$-\rho_R^+$	n^a	r	s	F
ortho	1.91 ± 0.18	−0.29 ± 0.27 (4.7)	2.14 ± 0.33 (19.9)	0.40 ± 0.33 (10.5)	16	0.886	0.26	14
meta	1.86 ± 0.02	0.10 ± 0.03 (3.1)	1.79 ± 0.04 (16.8)	1.14 ± 0.05 (12.0)	10	0.999	0.02	924
para	1.89 ± 0.06	−0.01 ± 0.11 (3.5)	1.62 ± 0.14 (15.8)	1.67 ± 0.10 (19.0)	13	0.990	0.09	151

[a] Some substituted pyridines from Table 1 are excluded from this analysis because their σ parameters are not given in ref. 45. These are **1**, **4**, **5** and **6** in the *para* series, **48** in the *meta* series and **44** in the *ortho* series.

pyridines with a second basic site stand above the line of eqn. (6) (see Fig. 2 and *vide infra*).

A rough physical interpretation of the family-dependent ΔG–$\Delta\nu$ correlations can be recalled here. They are the consequence of two often quoted,[28] and often debated,[29] empirical relationships, (i) the Badger–Bauer ΔH–$\Delta\nu$ relationship (roughly family-independent)[28,29] between enthalpies of hydrogen-bond formation and IR shifts, and (ii) the extrathermodynamic (isoequilibrium) ΔG–ΔH relationship (strongly family-dependent)[28,29] between the Gibbs energy and the enthalpy of hydrogen-bond formation. Because of their entropic consequences, steric effects are often considered to be an important cause of failure of this extrathermodynamic relationship.

In summary, the pK_{HB}–$\Delta\nu$(OH) relationships are important in hydrogen-bonding studies. They will allow us to study *ortho* effects in 2-substituted pyridines and to calculate the contribution of each site to the overall basicity of polysite pyridines (*vide infra*). They also add support to the existence, at least from the family-dependence point of view, of the disputed[28,29] Badger–Bauer and isoequilibrium relationships in hydrogen-bond formation.

Field-inductive and resonance effects on the hydrogen-bond basicity of pyridines

The influence of molecular structure on the aqueous and gas-phase Brönsted basicities of substituted pyridines has been extensively studied[30–33] by means of empirical σ substituent constants. This approach has also been used for hydrogen-bond formation constants.[18,19] Here we apply to the pK_{HB} scale the methodology developed by Taft and Topsom[34] for the interpretation and prediction of gas-phase basicities. Their linear additive model separates polarizability (α), field-inductive (F), and resonance (R) substituent effects according to eqn. (7)

$$pK_{HB} = pK^0_{HB} + \rho_\alpha\sigma_\alpha + \rho_F\sigma_F + \rho_R\sigma^+_R \qquad (7)$$

where each effect is represented by a $\rho\sigma$ product in which σ is a substituent constant and ρ a sensitivity coefficient to a given effect.

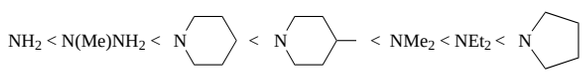
In this equation pK^0_{HB} refers to the unsubstituted pyridine. The intercept, regression coefficients ρ, and statistics of eqn. (7) are given in Table 4. It appears clearly that the following hold.

(i) Substituent effects on hydrogen-bonding are quite precisely described by eqn. (7) for 3- and 4-substituted pyridines, but not for 2-substituted pyridines.

(ii) Unlike proton transfer to pyridines in the gas phase,[32–34] polarizability effects are negligible for hydrogen bonding (proton sharing) to pyridines in solution. In particular, both the sign and magnitude of ρ_α are artefacts for 2-X substituents, since polarizability effects must stabilize ($\rho_\alpha < 0$) the hydrogen-bonded pyridines on one hand, and since there is a correlation between σ_α and steric parameters on the other hand (both depend on the substituent size).

(iii) Another fundamental difference between gas phase proton transfer and solution proton sharing is an attenuation by a factor of about ten of field and resonance contributions.

(iv) The resonance effect of π electron donors ($\sigma^+_R < 0$) is particularly efficient in the 4-position for increasing hydrogen-bond basicity. We gain 0.70 pK unit on going from pyridine to the 'push–pull' 4-aminopyridine. We increase basicity still further by alkylating and/or cyclizing the amino group in the order:



Thus, 0.37 supplementary pK unit is gained on going from 4-amino- to 4-pyrrolidino-pyridine, which is presently our strongest pyridine base on the pK_{HB} scale.

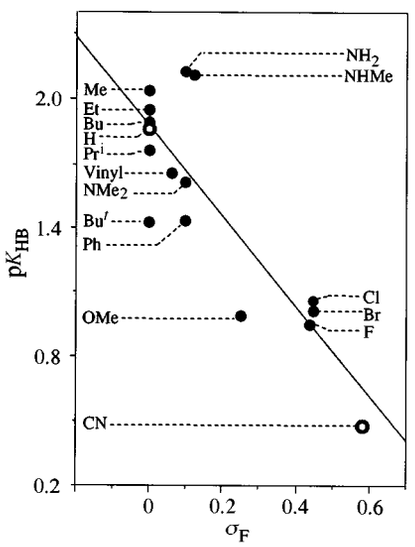


Fig. 3 Relationship between pK_{HB} and the field-inductive parameter σ_F for 2-substituted pyridines

Steric effects in 2-substituted pyridines

Whereas σ_α, σ_F and σ^+_R constants satisfactorily describe substituent effects on the gas-phase proton transfer to 2-substituted pyridines,[33] they only explain 80% of the pK_{HB} variance (*vide supra*). We therefore suspected that steric effects occur in hydrogen-bond formation and we added a steric term to eqn. (7) by means of the upsilon steric parameter υ.[35] This additional term did not significantly improve the fit and a stepwise regression procedure shows that σ_F is the only statistically significant parameter. The regression line of eqn. (8) (Fig. 3) passes

$$pK_{HB} = 1.87\ (\pm 0.09) - 2.06\ (\pm 0.34)\ \sigma_F \qquad (8)$$
$$n = 16 \quad r = 0.849 \quad s = 0.27$$

through the unsubstituted pyridine ($\sigma_F = \sigma^+_R = \upsilon = 0$) and close to the 2-cyano substituent which has the strongest σ_F value of our 16 substituents, a zero σ^+_R value and weak steric effects.

It might well represent the 'true' field-inductive line in the pK_{HB}, σ_F plane and might allow a safe chemical interpretation of residuals. Steric effects are expected to give negative residuals and we do observe that the bulky Pr^i, Ph and Bu^t substituents stand below the regression line. Electron-donor resonance effects must give positive residuals and indeed the NH_2 and NHMe substituents, which have strong σ^+_R values, are situated above the regression line. The position of other lone-pair bearing substituents (2-NMe_2, 2-OMe, 2-F, 2-Cl and 2-Br) is less

Table 5 Deviations ΔpK_{HB} of *ortho*-substituents from the line of *meta* and *para*-substituents [eqn. (6)] in the plot pK_{HB} *vs.* $\Delta\nu$(OH) (Fig. 2) and the upsilon steric parameter[35]

No.	Substituent or compound	ΔpK_{HB}	υ	No.	Substituent or compound	ΔpK_{HB}	υ
Substituents without a lone pair				Substituents with lone pair(s)			
33	H	0	0	**44**	2,2′-Bipyridine	−0.49[a]	*c*
53	7,8-Benzoquinoline	−0.52	*c*	**37**	2-NMe_2	−0.35	0.43
46	2-Bu^t	−0.43	1.24	**57**	2-OMe	−0.24	0.36
35	2-Pr^i	−0.35	0.76	**59**	2-Br	0.27	0.65
8	2,4,6-Me_3	−0.31	*d*	**54**	2-Cl	0.29	0.55
28	2-Et	−0.27	0.56	**58**	2-F	0.48	0.27
13	2,6-Me_2	−0.25	*d*	**65**	Pentafluoropyridine	~0.52	*d*
45	2-Ph	−0.25	0.57[e]	**27**	Pyridazine	0.58[a]	*c*
36	2-Vinyl	−0.22	0.57[e]	**64**	2,6-F_2	0.60	*d*
24	Acridine	−0.22	*c*	**9**	Phthalazine	0.66[a]	*c*
20	2-Me	−0.17	0.52	For comparison: polyazines			
40	Phenazine	−0.10[a]	*c*	**52**	Pyrazine	0[a]	*c*
29	Quinoline	−0.09	*c*	**60**	5-Bromopyrimidine	0.07[a]	*c*
31	Phenanthridine	−0.06	*c*	**47**	Pyrimidine	0.06[a]	*c*
				63	*s*-Triazine	0.08[b]	*c*

[a] After −log 2 correction. [b] After −log 3 correction. [c] υ is unknown. [d] Steric effects are generally not additive. [e] Upsilon is for the half thickness of this planar π-bonded group.

clear-cut: steric effects appear to overcome the resonance effect of 2-OMe, and the position of halogens should be more regular since their steric and resonance effects follow the same basicity order F, Cl, Br (*i.e.* F is the most electron-releasing substituent by resonance effect and the least steric).

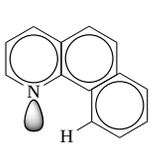
The departure of 2-substituents from the behaviour of 3- and 4-substituents in the pK_{HB} *vs.* $\Delta\nu$(OH) plot also throws light on the *ortho* effect. If we define their deviations as ΔpK_{HB} according to eqn. (9) we observe both positive and negative deviations

$$\Delta pK_{HB} = pK_{HB}\text{ (experimental)} - pK_{HB}\text{ [calculated from eqn. (6)]} \quad (9)$$

(Table 5). The interpretation of this plot in terms of a mainly enthalpic[28,29] $\Delta\nu$(OH) axis and of an enthalpic plus entropic pK_{HB} axis more sensitive to steric effects, allows the negative deviations to be partly or totally attributed to steric effects. Indeed the ΔpK_{HB} values of all the substituents without a lone pair (Table 5) agree with their ability to shield the nitrogen lone pair. This is shown by the correlation (10) between ΔpK_{HB} and the υ steric parameter.[35]

$$-\Delta pK_{HB} = 0.389\ (\pm 0.022)\ \upsilon \quad (10)$$
$$n = 7\text{ (H, Me, Et, Pr}^i\text{, Bu}^t\text{, vinyl, Ph)} \quad r = 0.990 \quad s = 0.04$$

This parameter is not known[35] for benzofusion, but molecular modelling clearly shows the steric effects of the peri hydrogen(s) of quinoline **29**, phenanthridine **31**, acridine **24** and phenazine **40**, and still more the strong shielding of the nitrogen of 7,8-benzoquinoline **53**. Conformational flexibility explains



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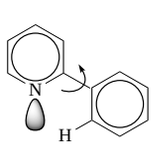


45

why 2-phenylpyridine **45** shows a smaller steric effect than the rigid heterocycle **53**.

At last, we are satisfied to observe that two *ortho* substituents give greater deviations than one (*cf.* acridine and quinoline and 2,6-lutidine and 2-picoline), but not additively, as is generally the case with steric effects.

Other *ortho* effects in 2-substituted pyridines

Since all substituents have almost the same size (the 2-aza pseudo-substituent) or a greater size than hydrogen, the positive deviations, in the pK_{HB} *vs.* $\Delta\nu$(OH) plot, of substituents bearing lone pairs cannot be explained by steric effects. In the same way, the lone-paired substituents 2-OMe and 2-NMe_2 deviate negatively, *i.e.* have a steric effect, but do not obey the steric eqn. (10), *i.e.* have another *ortho* effect. The example of pyridazine, which shows a large positive deviation, allows this second *ortho* effect to be attributed to an electrostatic repulsion between lone pair electrons.

Taft *et al.*[36] have already explained that pyridazine (1,2-diazine) is a stronger Brønsted base than pyrazine (1,4-diazine) because of the relief, upon protonation, of the electrostatic repulsion between adjacent nitrogen lone pairs. This is a differential effect between the adjacent NH^+-lone pair attraction in the protonated pyridazine and the adjacent lone pair–lone pair repulsion in the free pyridazine. Qualitatively the same explanation remains valid for proton sharing (hydrogen bonding) and we indeed find that pyridazine is a stronger hydrogen-bond base than pyrazine by 0.73 pK unit. Since $\Delta\nu$(OH) refers only to the hydrogen-bonded pyridazine, it ignores the lone pair–lone pair repulsion in the free pyridazine and $\Delta\nu$ values are roughly the same for pyridazine and pyrazine. In consequence pyrazine obeys the pK_{HB} *vs.* $\Delta\nu$(OH) relationship, whereas pyridazine shows a large positive deviation. Thus, these positive deviations reveal lone pair–lone pair repulsions, and the following order of deviations in diazines, and triazine, agrees qualitatively with the distance and angular dependences of the interaction energy between the lone pair dipole moments.

Phthalazine > Pyridazine ⩾ *s*-triazine ~ pyrimidine ~ 5-Br-pyrimidine > pyrazine (no deviation)
1,2-diazines ⩾ 1,3,5-triazine ~ 1,3-diazine > 1,4-diazine (no deviation)

The same explanation might apply to other positive deviations, if we take into account the adjacent lone pair–bond pair repulsion, in addition to non-adjacent lone pair–lone pair(s) repulsion. This last effect is pK_{HB} enhancing, not only for the pyridine nitrogen but also for the X substituent, and might explain why the gaseous 2-fluoro-, 2-chloro- and 2-methoxy-pyridines are able to accept a second hydrogen bond on the fluorine, chlorine and oxygen lone pairs respectively when they are adsorbed on silica.[37] We have also observed the presence of a ν(OH···O) band at 3450 cm^{-1}, in addition to the main ν(OH···N) band at 3190 cm^{-1} in the IR spectrum of the 2-methoxypyridine-4-fluorophenol complex. In the 4-methoxypyridine-4-fluorophenol complex we only

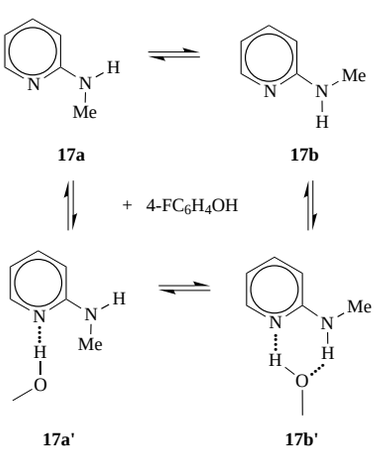
Table 6 Evaluation of the pyridine hydrogen-bond basicity K(N) in the case of pyridines with a second basic centre X

No.	Compound	K_f (total)[a,b]	K_f (X)[a]	K_f (N)[a,c]	pK_f (N)[d]
61	2-Cyanopyridine	7.08	4.05[e]	3.03	0.48
56	3-Cyanopyridine	10.00	3.39[f]	6.61	0.82
55	4-Cyanopyridine	11.22	2.98[g]	8.24	0.92
42	Methylnicotinate	31.20	3.16[h]	28.04	1.45
43	3-Benzoylpyridine	30.90	5.25[i]	25.65	1.41
41	4-Acetylpyridine	31.92	6.03[j]	25.89	1.41

[a] dm^3 mol^{-1}. [b] $K_f = 10^{pK_{HB}}$. [c] K_f (N) = K_f (total) − K_f (X). [d] pK_{HB} (N) = log K_f (N). [e] Calculated from the pK_{HB} *vs.* $\Delta\nu$(OH) relationship in the nitrile family: pK_{HB} = 0.0102 $\Delta\nu$(OH) − 0.79 = 0.0102 × 137 − 0.79 = 0.607. [f] Measured value for 3-CF_3 benzonitrile: pK_{HB} = 0.53. [g] Calculated from the pK_{HB} *vs.* $\Delta\nu$(OH) relationship in the nitrile family: pK_{HB} = 0.0102 × 124 − 0.79 = 0.475. [h] Estimated value for 3-CF_3 methyl benzoate: pK_{HB} (3-$CF_3C_6H_4COOMe$) = pK_{HB} (C_6H_5COOMe) − CF_3 increment = 0.89 − 0.39 = 0.50. [i] Estimated value for 3-CF_3 benzophenone: pK_{HB} (3-$CF_3C_6H_4COPh$) = pK_{HB} (C_6H_5COPh) − CF_3 increment = 1.07 − 0.39 = 0.72. [j] Measured value for 4-CF_3 acetophenone: pK_{HB} = 0.78.

observe the ν(OH···N) band. This peculiar behaviour of 2-methoxypyridine testifies to an unexpectedly significant hydrogen-bond formation constant to the ether oxygen in the *ortho* position.

A last *ortho* effect seems to be present in 2-amino- and 2-methylamino-pyridines. These two pyridines are more basic than 2-(*N*,*N*-dimethylamino)pyridine by *ca*. 0.50 pK unit. This difference cannot be explained merely by a greater steric effect of NMe_2: we observe a difference of only 0.27 pK_{HB} unit between 2-picoline and 2-isopropylpyridine, sterically similar to 2-amino- and 2-(*N*,*N*-dimethylamino)-pyridine respectively. As indicated by the STO-3G structure of the 2-aminopyridine–water complex,[38] we attribute a part of the 0.50 difference to a NH···O hydrogen bond in a cyclic complex. IR spectroscopy confirms the NH···O interaction. The IR spectrum of free 2-methylaminopyridine shows two ν(NH) bands at 3466 and 3446 cm^{-1}, attributed[39] to conformers **17a** and **17b** respectively.



When we add 4-fluorophenol to a CCl_4 solution of **17**, the band at 3446 cm^{-1} is shifted to lower wavenumbers by 12 cm^{-1}, proving the structure **17b′**, whereas the band at 3466 cm^{-1}, is shifted to higher wavenumbers by 1 cm^{-1}, as expected for **17a′**.

Pyridines with a second basic centre

We have already mentioned that *N*,*N*-diethylnicotinamide and 2-methoxypyridine can accept hydrogen bonding to their oxygen atom instead (3-$CONEt_2$) of or in addition (2-OMe) to their pyridine nitrogen atom. The presence of a ν(OH···X) band, in addition to the ν(OH···N) band, in the IR spectra of X-substituted pyridine–4-fluorophenol complexes shows that the following X substituents:

2-CN, 3-CN, 4-CN, 4-COMe, 3-COOMe, 3-COPh

are also hydrogen-bond acceptors.[40] Two 1:1 hydrogen-bond complexes are simultaneously formed in solution and it is easy to show that the measured formation constant K_f (with the substituted pyridine in excess, in order to avoid 1:2 complexes) is a global constant corresponding to the sum of the formation constants of two 1:1 complexes:

$$K_f\,(\text{total}) = K_f\,(\text{X}) + K_f\,(\text{N}) \qquad (11)$$

In the same way eqn. (12) applies to polyazines.

$$K_f\,(\text{total}) = \sum_{i=1}^{n} K_f\,(N_i) \qquad (12)$$

Eqns. (11) and (12) show that N-heteroaromatics with a second basic centre are expected to give positive deviations in the pK_{HB} *vs.* $\Delta\nu$(OH) or pK_{HB} *vs.* σ relationships when pK_{HB} (total) is used and that these deviations will disappear if we are able to calculate K_f (N) or K_f (N_i). For polyazines with n equivalent nitrogens, it is easy to refer to the basicity of one nitrogen by applying the statistical correction $-\log n$ to pK_{HB} (total). In the case of eqn. (11) we have to subtract K_f (X) from the experimental constant. K_f (X) may be evaluated by assuming that the aza pseudo-substituent and the CF_3 substituent have comparable effects[41,42] on the basicity of benzonitriles, acetophenones, benzophenones and methyl benzoates. For 2-cyano- and 4-cyano-pyridines, an accurate value of $\Delta\nu$(OH) for the OH···N≡C complex can be measured, and we have preferred using the pK_{HB} *vs.* $\Delta\nu$(OH) relationship already established[11] in the nitrile family. The results are presented in Table 6.

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