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A Theoretical Evaluation of the pK_{HB} and ΔH°_{HB} Hydrogen-Bond Scales of Nitrogen Bases

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Abstract: The experimental pK_{HB} hydrogen-bond (HB) basicity scale and the corresponding ΔH°_{HB} enthalpic scale of nitrogen compounds are extended and analysed in light of simple theoretical descriptors using the B3LYP density functional method and a medium-size basis set (6-31+G(d,p)). The selected training set includes 59 monofunctional unhindered nitrogen bases for which homogeneous and accurate experimental pK_{HB} and ΔH°_{HB} data have been determined by means of the association equilibrium of the bases with a reference hydrogen-bond acid, 4-fluorophenol, in CCl_4. The three hybridisation states encountered in the nitrogen atom, sp, sp^2 and sp^3, are equally represented in this data set. A proper estimation of their experimental enthalpy (ΔH°_{HB}) is directly attainable from the theoretical enthalpy of the complexation reaction with hydrogen fluoride ($\Delta H^{\circ(HF)}$). However, a second parameter is required to calculate with good accuracy the experimental free energy of association represented by pK_{HB}. About 99% of the variance of the pK_{HB} scale is described by a bilinear equation using the minimum electrostatic potential ($V_{s,min}$) of the monomer in addition to the interaction energy ($D_0^{(HF)}$). The equations are tested for an external set of 99 additional compounds including very different nitrogen bases such as *ortho*-substituted pyridines, polyazines and azoles. Theoretical calculations give a reliable estimation of hydrogen-bond basicity provided that the populations of the different isomers of the bases are taken into account by using the Boltzmann law, and that a specific halogen-bond interaction with the solvent CCl_4 is considered for polybasic molecules. The pK_{HB} scale can thus be extended to important classes of species experimentally inaccessible in CCl_4, to polynitrogen compounds and to molecules of biological significance.

Keywords: density functional calculations · hydrogen bonds basicity · nitrogen bases · pK_{HB} scale

Introduction

The literature devoted to the experimental determination of hydrogen-bond thermodynamic parameters is voluminous. Thirty years ago, Joesten and Schaad could already examine and gather the results of several thousand references[1] and, since that date, numerous additional data have appeared so that the hydrogen-bond strength of the association between any possible hydrogen-bond donor–acceptor couples may appear to have been fully characterised. From an exhaustive compilation of the complexation constants of various series of hydrogen-bond acids and bases in inert solvents, Abraham et al.[2,3] constructed two hydrogen-bond acidity and basicity scales, called α_2^H and β_2^H, respectively, which are very useful in the interpretation of numerous physicochemical or biological processes.[4] However, although these parameters have proven their value in identifying the role of the hydrogen-bond interaction in very different processes and in quantifying their relative importance, they cannot be used for the analysis of the minute structural variations that modulate the hydrogen-bond acidity or basicity of a solute. The two most important failures of a general statistical survey of the literature data were pointed out early on by Taft and coworkers[5,6] who set up with Arnett et al.[7] the first reliable scale of hydrogen-bond (HB) basicity, named pK_{HB}, from the equilibrium constants of the association between the reference donor 4-fluorophenol (pFP) and about 80 oxygen and nitrogen bases. On examining the linear free-energy relationships between different donors and pFP on the one

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hand,[8] and between different solvents and CCl_4 on the other hand,[9] they highlighted the fundamental family-dependent (FD) character of the hydrogen-bond free energies. In the donor versus donor or solvent versus solvent diagrams, the amines, pyridines and carbonyl bases may form well-separated lines precluding the transfer of data by means of a single general regression line. On the contrary, different families depending on the nature of the accepting atom must be established to calculate the data for a reference hydrogen-bond donor in a reference solvent. Due to the narrowness of the scale, which only spans 6 to 7 pK units for the neutral organic bases, two additional reasons prevent the construction of a precise scale from a statistical treatment of the literature data. First, the quality of the experiment is of utmost importance, eliminating a great number of data that have not been obtained in rigorous conditions of concentration and temperature on accurate instruments. Second, the numerous and most attractive polyfunctional bases require special attention because their secondary site may not have a negligible weight in the apparent equilibrium constant, and cannot be easily subtracted.[10] Hence, we have followed the second possible route to establish a reference scale of solute hydrogen-bond basicity. Starting from the pioneering work of the Arnett and Taft groups,[5–7] we have measured by means of infrared spectroscopy the thermodynamic parameters of about one thousand solutes[11] under the same rigorous experimental conditions [Eqs. (1)–(4); in which B = base, K_c and K_x = complexation equilibrium constant, C = equilibrium molar concentration, x = equilibrium molar fraction].

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

$$K_c = C_{complex}/(C_{base}C_{pFP}); \quad K_x = x_{complex}/(x_{base}x_{pFP}) \quad (2)$$

$$pK_{HB} = \log K_c; \quad \Delta G^{\circ}_{HB} = -RT\ln K_x \quad (3)$$

$$\Delta H^{\circ}_{HB} = RT^2\,(\partial \ln K_x/\partial T)_P \quad (4)$$

In these studies, more than twenty different families have been characterised, extending the pK_{HB} scale of neutral compounds from the very weak π or halogen bases up to the strong amine or phosphine oxides. The experimental determination of a single pK_{HB} or ΔH°_{HB} value is a rather long process requiring a full day of spectroscopic work after careful purification and desiccation of the reactants and solvents. Moreover, many families among the most important for the biochemical applications of the scale, primary and secondary amides, azoles and so forth, are definitely excluded because they are not soluble and/or strongly self-associated at the concentrations required for a proper determination of the equilibrium constant. Hence, it is tempting to check whether hydrogen-bond basicity parameters could be satisfactorily predicted with theoretical descriptors. Based on our experimental data, few studies have appeared with the objective of modelling the pK_{HB} scale. Owing to the original Pauling description of the hydrogen-bond interaction,[12] the first efforts to interpret and predict hydrogen-bond affinity were devoted to producing adequate electrostatic parameters.[13–15] However, it soon appeared that the predictive power of the correlations between the pK_{HB} values and the minimum electrostatic potential on the molecular surface ($V_{s,min}$), the most elaborate descriptor, remained unsatisfactory. When all families of bases were mixed,[15] or even when the set was restricted to homogeneous families,[16] the statistical error of the predicted pK_{HB} was about 0.3, corresponding to an error of about 100 % on the equilibrium constant. Semiempirical AM1 calculations were proposed to evaluate the pK_{HB} data of series of substituted pyridines and nitriles. Hennemann et al.[17] defined no fewer than four descriptors of the base to unravel the different structural effects in the pyridine series. However, using the AM1-calculated enthalpies of hydrogen-bond formation between pFP and 22 substituted nitriles, Le Questel et al.[18] found an encouraging correlation with a standard error of 0.17 pK units. Lamarche and Platts[19] developed ab initio density functional theory (DFT) calculations on a model of the equilibrium shown in Equation (1), in which the donor pFP is replaced by hydrogen fluoride. They found a fair correlation between the calculated Gibbs energy and the pK_{HB} values for a series of 40 solutes pertaining to well-diversified accepting atoms. The authors correctly judged the 0.3 pK unit error of the fit as unacceptable but attributed the deviations to pollution of the experimental values by complexations of higher order, rather than to an inadequate model. In their subsequent papers,[20,21] they re-examined more successfully the same data set by a multivariate analysis including the minimum electrostatic potential, $V_{s,min}$, of the base and the bond order or the energy density calculated at the bond critical point of the most stable complex with HF. They also improved their model by considering a second stereoisomer for the complexes of HF with the oxygen and sulphur bases so that they reached a final standard error of 0.15 pK units.

In our view, these analyses of the pK_{HB} scale are either too limited or too ambitious. On the one hand, the study of a single family evidently masks the family dependence (FD), which is one of the important characteristics of the hydrogen-bond interaction and, on the other hand, the calculations on all kinds of acceptors are limited by the lack of knowledge of the association geometry between the acceptor and the donor in CCl_4. In this preliminary work, we have therefore limited our training data set to 59 monofunctional sp, sp^2 and sp^3 nitrogen bases. The objective is to simplify the theoretical modelling with accepting groups containing a single lone pair, but without losing any important structural information because these three series present the strongest FD behaviour of our pK_{HB} database.[11,22] Along with the theoretical calculations, we have completed the measurements of the experimental enthalpies (ΔH°_{HB}) of the association between the bases and pFP, to make the first comparison between theoretical and experimental enthalpies in substituted series of bases. We started our analysis with an additional simplification, introducing in the training data set the maximum number of rigid or quasi-rigid acceptors such as

nitriles, pyridines and quinuclidines. However, to preserve a correct balance between the three families, it was necessary to examine a small number of flexible primary, secondary and tertiary amines. The training set showed such good correlations between theoretical and experimental data that an external set was selected including more complex structures in which the nitrogen lone pair is disturbed by proximity and/or cyclisation effects such as in *ortho*-substituted pyridines, polyazines and azoles. Finally, the robustness of these correlations enabled the pK_{HB} and ΔH°_{HB} scales to be extended to a great number of important nitrogen bases that cannot be experimentally evaluated either because they are insoluble, self-associated or react with CCl_4, or simply because they are very difficult to handle. For polyfunctional bases, it provides the opportunity to calculate the basicities of the individual sites, whereas the experimental results are limited to the evaluation of a global basicity constant and can hardly be separated into their different components.[10,23] Finally, the significant disruptive effect of the solvent is revealed by the differences between the experimental and the calculated global basicities. The specific halogen-bond interaction of CCl_4 with the basic centres is taken into account for these polybasic compounds.

Computational Methods

All DFT calculations were performed using either the Gaussian 03[24] or Spartan[25] packages. Geometries of the molecular systems were optimised with the B3LYP functional, also used to evaluate the harmonic vibrational frequencies and their total energies.[26,27] The 6-31+G(d,p) Pople basis set was selected as the minimum basis set recommended to give accurate geometries and vibrational frequencies of the monomers[28,29] and realistic relative estimations of the hydrogen-bond energies of the complex formation[19,30,31] without the cost of MP2 calculations. Structures were confirmed as energetic minima through harmonic frequency calculations. The zero point energy (ZPE) corrections were scaled by the empirical factor 0.9804 proposed by Scott and Radom.[32] Correction for the basis set superposition error (BSSE) is expected to be below the intrinsic error limits in the calculations[30] and to be approximately constant in this data set. It has therefore not been included in these calculations.

Monomer conformations: Some of the bases under study are generally present under several conformations in CCl_4 and the conformers may have different basicities. Thus, theoretical calculations must take into account the flexibility of the monomer not only to improve the correlation statistics but also to gain a better insight of the structural dependence of the hydrogen-bond basicity. The major difficulty is then to estimate the actual populations of the conformers from the theoretical parameters. In a recent work,[33] we have shown that a weighting of the electrostatic potentials by a Boltzmann function based on the electronic energies of the different conformers provides satisfactory descriptions of the experimental hydrogen-bond basicities of the alcohol, carbonyl and amine families including both rigid and flexible molecules. In the present work, we suggest that the method can be extended to the different theoretical descriptors. Owing to the large number of compounds studied, the potential energy surface cannot be fully explored for all flexible bases and we have therefore limited our calculations to the most stable conformers.

Complex conformations: Following the work of Lamarche and Platts,[19,21] we have recently confirmed that[10,23,34] if a separate treatment is carried out for different families of bases, hydrogen fluoride (HF) can be selected as a convenient model of hydrogen-bond donor with the double benefit that it requires the minimum of computing time and limits the number of stereoisomeric complexes around the accepting centre. In the initial geometries of the complexes, the HF molecule was placed in the direction of the nitrogen lone pair and the interaction energetics—the interaction energy ($D_0^{(HF)}$), the theoretical enthalpy of the complexation reaction with hydrogen fluoride ($\Delta H^{\circ(HF)}$) and the free energy of the complexation reaction with hydrogen fluoride ($\Delta G^{\circ(HF)}$)—were calculated from Equations (5)–(7), in which E_{el} = the electronic energy and ΔE_{tr}, ΔE_{rot}, $\Delta E_{vib,therm}$ = the changes in the translational, rotational and vibrational energies, respectively, and $\Delta S^{\circ(HF)}$ = the entropy of the complexation reaction with hydrogen fluoride:

$$D_0^{(HF)} = E_{el(B\cdots HF)} - (E_{el(B)} + E_{el(HF)}) + ZPE_{(B\cdots HF)} - (ZPE_{(B)} + ZPE_{(HF)}) \quad (5)$$

$$\Delta H^{\circ(HF)} = D_0^{(HF)} + \Delta E_{tr} + \Delta E_{rot} + \Delta E_{vib,therm} - RT \quad (6)$$

$$\Delta G^{\circ(HF)} = \Delta H^{\circ(HF)} - T\Delta S^{\circ(HF)} \quad (7)$$

Electrostatic potentials: Since the original work of Murray and Politzer,[13,15,35,36] it has been consistently shown that FD relationships exist between the hydrogen-bond basicity and the minimum electrostatic potential in the vicinity of the nitrogen atom of N-heterocycles,[14,23] nitriles[37] and amines.[16,38] The so-called $V_{s,min}$ values are calculated at the molecular surface, as defined by the 0.001 e Bohr^{-3} contour of the electronic density,[39] with the Spartan program. Using the wave functions from Gaussian, systematic greater values of (5 ± 0.5) kJ mol^{-1} are found with the Molden interface,[40] and the results are therefore not merged.

Natural bond orbital (NBO) analysis: To compare the charge-transfer component of hydrogen-bond complexes between the different nitrogen hybridisation states, a NBO analysis[41] was carried out. The populations of the nitrogen lone pair and the HF antibonding σ* orbital are estimated at the B3LYP/6-31+G(d,p) level, as well as their interaction energy ($E^{(2)}_{n\rightarrow\sigma*}$) evaluated from the second-order perturbation theory.

Experimental Section

Complexation equilibrium constants: These were defined by using Equation (2) (see above) relative to concentration units in which the equilibrium concentration ($C_{complex}$) was obtained from the IR intensity decrease of the free OH vibration of pFP in carbon tetrachloride. Temperature was maintained at (25.0 ± 0.2) °C with a Peltier thermoelectric device. This method of determination has already been described elsewhere.[42] From repetitive determinations with different operators working with different spectrometers, on different solutions of donors and acceptors, the mean accuracy of the equilibrium constants may be estimated to be around ±10%, corresponding to ±0.04 pK units. A mean error of 0.03 pK units was generally found when the constant K was in the range 2–1000 and this error gradually increases for the weakest and strongest complexes with the increasing experimental difficulty of achieving the ideal acceptor concentration range.[43]

Enthalpies and entropies: The enthalpy variation of the equilibrium in Equation (1) (see above) was measured by using the single solution method. We adapted the procedure described by Joesten and Drago[44] for their UV determinations to IR measurements in which the extraction of the relevant intensities is greatly simplified because the absorption bands of the free and hydrogen-bonded donor are resolved. Enthalpies and entropies were calculated from the slopes and intercepts of van't Hoff plots. The OH intensities of pFP were recorded at five different temperatures from −5 to 55 °C for a solution of known concentration of hydrogen-bond donor and acceptor. As described in our previous papers,[23,45] the errors in ΔH°_{HB} and ΔS°_{HB} were estimated to be around ±0.8 kJ mol^{-1} and ±6 J mol^{-1} K^{-1}, respectively. In this study, the pK_{HB} scale is reported on the molar concentration scale, but all the thermodynamic functions ΔG°_{HB}, ΔH°_{HB} and ΔS°_{HB} are relative to equilibrium constants calculated in mole fraction units.[45]

Chemicals: These were generally commercially available and purified by using standard methods. The synthesis and purification of some original super-basic nitriles (**60** and **61**) have already been described in previous

papers.[46–48] Substituted benzyl dimethylamines (**48** and **49**) were prepared by methylation of the corresponding benzyl chlorides by using the procedure recommended by Lee and Srinivasan.[49]

Some amines react with CCl_4[50,51] and were therefore analysed in C_2Cl_4. The differences between the data obtained in the two solvents are small[16] and no correction was attempted to scale the values obtained in tetrachloroethylene. The spectroscopic grade solvents CCl_4 and C_2Cl_4 were dried over freshly activated 4 Å molecular sieves before use. The hydrogen-bond donor pFP was sublimed over P_2O_5 under reduced pressure at 60 °C.

Results and Discussion

Experimental results: A first training data set of 18 sp, 19 sp^2 and 22 sp^3 nitrogen bases was selected and is presented in Table 1. The pK_{HB} values come from our earlier studies, and are the average of several equilibrium constants resulting from experiments in which the base concentration variation modifies the equilibrium position. The thermodynamic values ΔH°_{HB} and ΔS°_{HB}, obtained from the van't Hoff plots in which the equilibrium position is altered by the temperature variation, are also reported in Table 1. The resulting free-energy values ΔG°_{HB} and pK'_{HB} are calculated at 298 K. It can be seen that the agreement between the two series of data, pK_{HB} (concentration variation) and pK'_{HB} (temperature variation), is excellent, and we thus use the more recent and more complete pK'_{HB} scale in all the subsequent calculations and refer to it as pK_{HB}. For these compounds, the methanol OH frequency shifts upon complexation are specified in Table 1. They are preferred to pFP OH frequency shifts because they are much more accurate for amine[16] and pyridine[52] families and because a single linear family-independent relationship holds between the two spectroscopic OH scales.

Despite the wide structural diversity of the nitrogen bases analysed in this study, the difference in enthalpies of complexation (ΔH°_{HB}) with pFP does not exceed 22 $kJ\,mol^{-1}$ on going from 4-chlorobenzonitrile (**2**) to quinuclidine (**59**). In such a situation, the accuracy of measurements becomes a prerequisite for a relevant analysis of the fine structural parameters influencing the interaction strength. With our method, the statistical errors on the van't Hoff slopes always appear excellent (mean standard error lower than 1%) with an excellent reproducibility on the replicates. Nevertheless, the accuracy of enthalpies determined by the present method of the single solution can only be tested in light of measurements carried out by calorimetry. We have compared six compounds also studied by Arnett et al.[7,53] on exactly the same ternary systems. Table 2 shows the good calibration of our measurements since the individual differences never exceed the sum of the estimated errors of the two methods.

In Figure 1, we have represented the relationships between the three thermodynamic functions characterising the association reaction of pFP with the nitrogen bases and the frequency shift of methanol ($\Delta\nu_{(OH)}$) by association on the same bases. Although all the possible $x-y$ planes that can be drawn with these four parameters exhibit similar FD lines, we have selected the spectroscopic scale as the reference abscissa to prevent all bias due to the possible compensation effects between thermodynamic scales.[54,55] Much important information can be obtained from this figure. The first concerns the validity of the so-called "Badger–Bauer correlation"[56,57] between the enthalpy of the association and the frequency shift, which has been the object of many controversies in the literature over several decades.[7,45,60–62] On the basis of our own experimental determinations, we have recently shown[22] that, even within the apparently homogeneous amine family, ammonia, primary, secondary and tertiary amines behave differently. We have also highlighted the large deviations due to the steric hindrance of the basic site. Figure 1A, which does not include any sterically hindered base, confirms the significant FD of the Badger–Bauer relationship. Second, a family trend is also apparent in the plot of the entropy variations versus the frequency shifts (Figure 1B). The mean values of the entropies ($\Delta S^{\circ}_{HB} = -24$, -44 and $-53\,J\,K^{-1}\,mol^{-1}$) and the frequency shifts ($\Delta\nu_{(OH)} = 90$, 299 and 372 cm^{-1}) regularly increase with the hydrogen-bond strength of nitriles, pyridines and amines, respectively, whereas the individual entropies are more or less constant within these families. It must be stressed that, although Figure 1A and B suggest a similar family split for enthalpy and entropy data, the large experimental error of the entropies ($\pm 6\,J\,mol^{-1}\,K^{-1}$) does not allow a detailed analysis. A rapid survey of the literature on this issue shows that, as soon as the precision of the enthalpic measurements is sufficient, this FD isoentropic character of the hydrogen-bond interaction appears distinctly when related donors[63–65] or acceptors[7,53,66] or both[67] are investigated. In the three series analysed here, the enthalpy and entropy behaviour is strikingly different. Clearly, the proposal of Pimentel and McClellan[68] that the strongest complexes (most negative ΔH°_{HB}) have the most restricted structure and hence the most unfavourable entropies (most negative ΔS°_{HB}) only holds for a modification of the nature of the accepting group. Once the latter is set constant, no more variation in the entropy with the nature of the substituent can be detected unless steric effects occur.[22] Finally, the partition into different families observed in Figure 1A for the enthalpy ΔH°_{HB} is also apparent for the entropic term $T\Delta S^{\circ}_{HB}$, which separates the three families in the same direction. The result is the wide scatter shown on plot Figure 1C between the free-energy scale pK_{HB} and the spectroscopic scale $\Delta\nu_{(OH)}$. On this plot, six families of bases are now clearly apparent so that no general correlation holds between the two scales.

Theoretical results: The calculated electrostatic potential values of the monomers and the thermodynamic data of their complexation with hydrogen fluoride are reported in Table 3. Table 4 illustrates, using the example of piperidine (**47**), the gain in statistical and chemical precision obtained when the population of the different isomers of the bases is taken into account. For this compound, the theoretical re-

Table 1. Experimental thermodynamic and spectroscopic scales of hydrogen-bond basicity.

No.	Compound	pK_{HB}[a]	Ref.	pK'_{HB}[a]	$-\Delta G^{\circ}_{HB}$[b]	$-\Delta H^{\circ}_{HB}$[b]	$-\Delta S^{\circ}_{HB}$[c]	Ref.	$\Delta\nu(OH)$[d]
1	chloroacetonitrile	0.39	[58]	0.42	8.2	16.3	27	–	49
2	4-chlorobenzonitrile	0.66	–	0.68	9.7	15.8	21	–	68
3	acrylonitrile	0.70	[58]	0.71	9.9	17.5	26	–	67
4	methylthiocyanate	0.73	[58]	0.73	9.9	16.6	22	–	69
5	benzonitrile	0.80	[8]	0.80	10.3	17.5	24	–	73
6	2,6-dimethylbenzonitrile	–	–	0.86	10.7	18.1	25	–	77
7	allylcyanide	–	–	0.87	10.8	17.8	24	–	78
8	acetonitrile	0.91	[58]	0.89	10.9	19.3	28	–	76
9	propionitrile	0.96	[58]	0.93	11.1	18.2	24	–	79
10	isobutyronitrile	1.00	[58]	0.98	11.4	18.1	23	–	81
11	4-methoxybenzonitrile	0.97	[58]	0.99	11.4	18.1	23	–	84
12	trimethylacetonitrile	0.99	[e]	0.99	11.4	18.5	24	–	83
13	4-dimethylaminobenzonitrile	1.25	–	1.26	13.0	20.5	25	–	100
14	dimethylcyanamide	1.56	[47]	1.51	14.4	22.4	27	–	118
15	1-piperidinecarbonitrile	1.58	[47]	1.58	14.8	21.7	23	–	122
16	diethylcyanamide	1.63	[47]	1.61	14.9	21.9	23	–	124
17	*trans*-3-dimethylaminoacrylonitrile	1.70	[47]	1.70	15.5	23.5	27	–	129
18	N^1,N^1-dimethyl-N^2-cyanoformamidine	2.09	[47]	2.03	17.4	24.5	24	–	150
19	3,5-dichloropyridine	0.85	[52]	0.81	10.4	23.9	45	[23]	200
20	3-chloropyridine	1.31	[52]	1.30	13.2	27.2	47	[23]	239
21	3-bromopyridine	1.31	[52]	1.35	13.5	24.8	38	–	241
22	3-fluoropyridine	1.35	[52]	1.35	13.5	25.4	40	[23]	240
23	pyridine	1.86	[52]	1.86	16.4	29.6	44	[23]	286
24	quinoline	1.89	[52]	1.90	16.6	30.1	45	–	296
25	isoquinoline	1.94	[52]	1.93	16.7	29.7	43	–	291
26	2-methylpyridine	2.03	[52]	2.01	17.2	30.5	45	–	315
27	3-methylpyridine	2.00	[52]	2.03	17.4	30.0	43	[23]	300
28	4-methylpyridine	2.07	[52]	2.10	17.8	30.8	44	–	304
29	3,5-dimethylpyridine	2.21	[52]	2.18	18.2	31.9	46	[23]	314
30	2,4-dimethylpyridine	–	–	2.21	18.4	31.8	45	–	330
31	4-aminopyridine	2.56	[52]	2.52	20.2	32.7	42	–	347
32	4-methylaminopyridine	–	–	2.69	21.0	33.5	42	–	354
33	4-*N*,*N*-dimethylaminopyridine	2.80	[52]	2.77	21.6	34.1	42	–	366
34	4-pyrrolidinopyridine[f]	2.93	[52]	2.93	22.6	36.3	43	–	372
35	2-methylpyrroline	–	–	2.56	20.4	34.2	46	–	344
36	5-bromo-1-methylimidazole	–	–	2.22	18.4	30.5	41	–	272
37	1-methylimidazole	–	–	2.70	21.2	34.0	43	–	313
38	3,5-difluorobenzylamine[f]	–	–	1.28	12.9	29.0	50	–	286
39	3-fluorobenzylamine[f]	–	–	1.58	14.7	29.6	50	–	306
40	benzylamine[f]	1.88	[59]	1.88	16.4	31.1	49	[22]	324
41	3-methylbenzylamine[f]	–	–	1.97	16.9	31.7	50	–	326
42	*tert*-butylamine[f]	2.19	–	2.23	18.4	34.2	53	[22]	359
43	ethylamine[f]	2.17	[59]	2.28	18.6	33.8	51	[22]	349
44	1,2,3,6-tetrahydropyridine	–	–	2.16	18.1	32.1	47	–	383
45	dimethylamine[f]	2.26	[16]	2.23	18.4	35.1	56	[22]	388
46	*N*-methylethylamine	2.25	–	2.26	18.5	34.7	54	[22]	394
47	piperidine	2.38	[16]	2.34	19.2	36.0	56	–	404
48	pyrrolidine[f]	2.59	[16]	2.56	20.3	36.1	53	[22]	406
49	azetidine	2.59	[16]	2.57	20.3	35.7	51	[22]	402
50	*N*,*N*-dimethylbenzylamine	1.59	[38]	1.61	14.7	31.9	58	–	387
51	*N*,*N*-dimethylpropargylamine	1.60	[38]	1.63	15.0	30.3	51	[22]	367
52	*N*,*N*-dimethylallylamine	1.92	[38]	1.93	16.8	32.8	54	[22]	399
53	3-chloroquinuclidine	1.97	[38]	1.96	16.9	34.1	58	[22]	394
54	1-methyl-1,2,3,6-tetrahydropyridine	–	–	1.98	17.1	32.5	52	–	399
55	*N*-methylpiperidine	2.11	[38]	2.11	17.8	34.0	54	[22]	421
56	trimethylamine	2.13	[38]	2.11	17.8	33.5	52	[22]	409
57	*N*,*N*-dimethylethylamine	2.17	[38]	2.17	18.2	34.5	55	[22]	418
58	*N*-methylpyrrolidine	2.19	[38]	2.25	18.5	34.8	55	[22]	423
59	quinuclidine	2.71	[38]	2.67	21.1	37.7	56	[22]	444

[a] Relative to concentrations expressed in mol dm^{-3}; pK_{HB} is obtained from a base concentration variation, whereas pK'_{HB} comes from a temperature variation. pK'_{HB} will be used in the correlations throughout the paper. [b] In kJ mol^{-1}. Relative to concentrations expressed in mole fractions. [c] In J K^{-1} mol^{-1}. Relative to concentrations expressed in mole fractions. [d] Frequency shift [cm^{-1}] of methanol upon association on the base: $\Delta\nu_{(OH)} = 3644 - \nu_{(OH\cdots)}$. [e] A typing error occurs in ref. [58]. [f] The thermodynamic properties have been measured in C_2Cl_4.

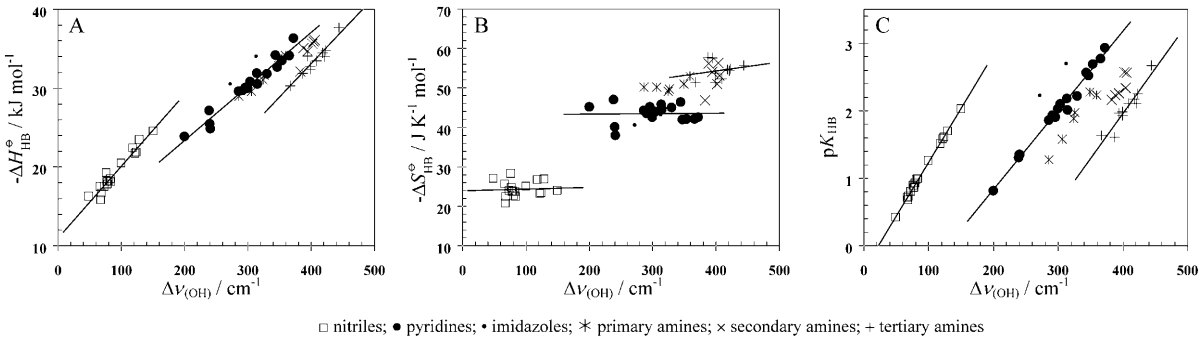


Figure 1. Family-dependent relationships between thermodynamic and spectroscopic scales of hydrogen-bond basicity. For the sake of clarity, regression lines are only drawn for the nitrile, pyridine and tertiary amine families.

Table 2. Hydrogen-bond complexation enthalpies determined by calorimetric[a] and van't Hoff[b] methods.

No.	Compound	$-\Delta H^{\circ}_{HB}$ [a]	$-\Delta H^{\circ}_{HB}$ [b]
8	acetonitrile	17.6	19.3
19	3,5-dichloropyridine	22.6	23.9
21	3-bromopyridine	25.9	24.8
23	pyridine	29.7	29.6
26	4-methylpyridine	30.5	30.8
30	4-dimethylaminopyridine	32.6	34.1

[a] In kJ mol^{-1}. Refs. [7,53]. [b] In kJ mol^{-1}. This work.

sults in vacuo are in good agreement with the IR[69] and NMR[70] spectroscopic experiments showing that the axial (ax) and equatorial (eq) isomers co-exist in CCl_4 and C_2Cl_4 and that their population ratio is around 2:1 (eq/ax) at 25 °C. Whereas the axial conformer is slightly less stable, its basicity is significantly stronger. Such a population weighting leads to a significant correction of the estimated basicity of piperidine (201 dm^3 mol^{-1}, Table 4) in better agreement with the mean experimental value ((230 ± 20) dm^3 mol^{-1}). A further example illustrating the quality of this weighting method will be developed later for the 3(5)-methylpyrazole tautomers.

The relationships between theoretical and related experimental thermodynamic parameters are illustrated in Figure 2. The statistics of the calculated versus experimental enthalpy correlation (Figure 2A) are exceptionally good [Eq. (8), in which r = correlation coefficient, s = standard error and n = number of points].

$$\Delta H^{\circ}_{HB} = 0.616\,\Delta H^{\circ(HF)} + 3.400 \quad (8)$$

$r = 0.992$, $s = 0.85$ kJ mol^{-1}, $n = 59$

Indeed, more than 98 % of the variance ($=100r^2$) of the experimental enthalpy is explained by a single theoretical parameter and the standard error of the estimate is almost identical to the experimental error. Although limited to nitrogen compounds without any significant steric effect, these results yield a robust equation including a large number of points over an enthalpy scale range of 22 kJ mol^{-1}. Hence, owing to the computer time required at this level of theory and with this basis set, the calculations on these systems are thought to become competitive with the experimental determinations. On the other hand, the entropies estimated by the calculation in the harmonic approximation are also quite well correlated to the experimental entropies (Figure 2B). Thus, the solvation entropy term present in the experimental data in CCl_4 is either constant or proportional to the calculated values in vacuo. The standard error of the estimation is about 4 J mol^{-1} K^{-1}, much better than the experimental error, and the variance explained by the theory is 91 % [Eq. (9)].

$$\Delta S^{\circ}_{HB} = 1.28\,\Delta S^{\circ(HF)} - 104 \quad (9)$$

$r = 0.955$, $s = 4$ J mol^{-1} K^{-1}, $n = 59$

It should also be mentioned that the calculations reproduce well the invariance of the entropy inside each family and the regularity of the entropy variation between the three families of nitrogen bases. A deeper investigation of the entropy calculations shows that the entropy variation is controlled by the vibrational term because the masses and the moments of inertia of the different species are very similar for the whole set of molecules. With these two family-independent correlations between the enthalpies and the entropies presented in Figure 2A and B [Eqs. (8) and (9), respectively], one would have expected a linear plot between the experimental and theoretical free energies. On the contrary, Figure 2C shows that the corresponding plot is family-dependent. In our view, this proportionality breakdown between experiment and theory could be partly the consequence of the harmonic approximation in the frequency calculations. The anharmonicity correction of the calculated entropies would increase the difference between the nitrile and amine families because the latter, which are more basic, give more anharmonic complex vibrations. Depending on the importance of the correction, the FD of the ΔG plot of Figure 2C would be reduced.

In the absence of a straightforward relationship between theoretical and experimental free energies of complexation, a multilinear correlation has been applied between the pK_{HB} values and the theoretical descriptors $V_{s,min}$ and $D_0^{(HF)}$. Both

Table 3. Theoretical results and thermodynamic scales of hydrogen-bond basicity.

No.	Compound	$-V_{s,min}$[a]	$-D_0^{(HF)}$[a]	$-\Delta H^{\circ(HF)}$[a]	$-\Delta S^{\circ(HF)}$[b]	$-\Delta G^{\circ(HF)}$[a]
1	chloroacetonitrile	138.6	26.0	27.9	100	−2.1
2	4-chlorobenzonitrile	154.6	31.1	32.9	100	3.0
3	acrylonitrile	159.1	30.7	32.7	101	2.6
4	methylthiocyanate	157.2	30.3	32.3	101	2.3
5	benzonitrile	164.9	32.4	34.3	101	4.1
6	2,6-dimethylbenzonitrile	167.1	34.3	36.2	102	5.7
7	allylcyanide	165.3	32.2	34.2	100	4.2
8	acetonitrile	164.4	32.2	34.3	101	4.1
9	propionitrile	168.5	33.0	35.0	102	4.6
10	isobutyronitrile	170.8	33.7	35.9	103	5.2
11	4-methoxybenzonitrile	175.6	34.9	36.8	101	6.7
12	trimethylacetonitrile	171.6	34.7	36.6	101	6.5
13	4-dimethylaminobenzonitrile	190.3	38.0	40.0	106	8.5
14	dimethylcyanamide	187.9	38.7	40.4	97	11.7
15	1-piperidinecarbonitrile	193.5	39.8	41.8	103	11.0
16	diethylcyanamide[c]	190.4	39.6	41.7	101	11.5
17	*trans*-3-dimethylaminoacrylonitrile	202.9	41.5	43.4	98	14.2
18	N^1,N^1-dimethyl-N^2-cyanoformamidine	213.7	43.4	45.9	104	14.8
19	3,5-dichloropyridine	123.2	40.5	43.1	114	9.0
20	3-chloropyridine	141.3	45.4	48.1	115	13.9
21	3-bromopyridine	140.8	45.0	47.7	115	13.3
22	3-fluoropyridine	143.2	45.9	48.6	115	14.3
23	pyridine	160.8	50.8	53.6	116	19.2
24	quinoline	153.4	51.7	54.6	120	18.8
25	isoquinoline	163.0	52.0	54.7	114	20.5
26	2-methylpyridine	159.5	52.8	55.8	120	20.0
27	3-methylpyridine	167.3	52.7	55.3	113	21.5
28	4-methylpyridine	168.8	52.9	55.7	116	21.0
29	3,5-dimethylpyridine	170.8	53.8	56.7	115	22.3
30	2,4-dimethylpyridine	166.5	54.9	57.8	119	22.3
31	4-aminopyridine	182.2	57.4	60.0	115	25.6
32	4-methylaminopyridine	188.2	59.6	62.0	111	29.0
33	4-*N*,*N*-dimethylaminopyridine	191.1	59.7	62.3	113	28.6
34	4-pyrrolidinopyridine	195.3	60.5	63.4	120	27.7
35	2-methylpyrroline	176.8	57.3	60.1	114	26.1
36	5-bromo-1-methylimidazole	176.8	51.4	54.1	116	19.6
37	1-methylimidazole	196.0	56.2	59.0	115	24.6
38	3,5-difluorobenzylamine[c]	113.1	48.6	52.2	124	15.3
39	3-fluorobenzylamine[c]	127.7	51.4	55.0	123	18.3
40	benzylamine[c]	142.9	54.3	57.8	122	21.4
41	3-methylbenzylamine[c]	146.8	55.2	58.6	119	23.0
42	*tert*-butylamine	162.3	56.8	60.6	125	23.2
43	ethylamine[c]	167.9	55.9	59.7	119	24.0
44	1,2,3,6-tetrahydropyridine[c]	155.6	57.2	60.6	122	24.3
45	dimethylamine[c]	155.0	56.6	60.3	120	24.5
46	*N*-methylethylamine[c]	153.7	57.4	61.0	122	−24.7
47	piperidine[c]	152.4	58.5	61.8	122	24.0
48	pyrrolidine[c]	160.0	59.4	62.7	119	27.1
49	azetidine	163.9	59.9	63.4	120	27.7
50	*N*,*N*-dimethylbenzylamine[c]	110.7	54.1	57.4	126	19.9
51	*N*,*N*-dimethylpropargylamine[c]	131.6	52.0	55.4	125	18.3
52	*N*,*N*-dimethylallylamine[c]	131.4	55.4	58.9	126	21.2
53	3-chloroquinuclidine	134.0	55.6	58.7	123	22.0
54	1-methyl-1,2,3,6-tetrahydropyridine	140.6	55.5	58.7	123	21.9
55	*N*-methylpiperidine	135.5	57.6	60.9	125	23.7
56	trimethylamine	140.7	56.5	59.8	121	23.7
57	*N*,*N*-dimethylethylamine[c]	138.4	57.1	60.4	125	23.2
58	*N*-methylpyrrolidine	138.5	58.4	61.4	120	25.6
59	quinuclidine	157.7	62.0	65.0	122	28.7

[a] In $kJ\,mol^{-1}$. [b] In $J\,K^{-1}\,mol^{-1}$. [c] Thermodynamic properties correspond to average weighted values for the different stable isomers of the monomer.

electrostatic potential and electronic energies of complexation with HF have already been claimed to be related to the pK_{HB} scale[13–21] and the family dependences of the relationships are well documented. For our training set, the two parameters are quasi-orthogonal ($r=0.14$, $n=59$) allowing a statistical multilinear analysis. Figure 3 illustrates the rela-

Table 4. Weighting of the energetic parameters for the two isomers of piperidine (**47**).

Piperidine conformer	Relative energy[b]	Relative population[b]	$-V_{s,min}$[a]	$-D_0^{(HF)}$[a]	K[c]
equatorial NH	0.00	0.76	149.7	57.99	176[d]
axial NH	2.92	0.24	161.4	60.07	311[d]
weighted parameters	–	–	152.4	58.48	201[e]

[a] In kJ mol^{-1}. [b] Determined using the Boltzmann law. [c] In dm^3 mol^{-1}. [d] Equilibrium constant of complexation with pFP in CCl_4 estimated by using Equation (10). [e] Experimental values found on independent runs are $K = 240$ and $K' = 219$ dm^3 mol^{-1} (see Table 1).

tionships between pK_{HB} and $V_{s,min}$ (Figure 3A), pK_{HB} and $D_0^{(HF)}$ (Figure 3B) and finally pK_{HB} and ($V_{s,min}$, $D_0^{(HF)}$) (Figure 3C), revealing important features never previously analysed.

As expected, the electrostatic potential is well correlated to the pK_{HB} values (Figure 3A), provided that the different nitrogen families are identified and calibrated. Although this descriptor allows an accurate prediction inside the pyridine or nitrile hydrogen-bond basicities, the case of the sp^3 nitrogen base is obviously more complicated and this family must be separated into three sub-families: primary, secondary and tertiary amines. This is clearly unsatisfactory when the aim is to contribute to the definition of a single general relationship for hydrogen-bond basicity prediction. Within each family, the increase of $-V_{s,min}$ due to electron-donating substituents is regularly followed by a rise in the pK_{HB} value in agreement with the largely electrostatic nature of the hydrogen-bond interaction. This is illustrated in Table 5 for the three substituted pyridines **22**, **23** and **33**. However, the behaviour between each family is totally different. For the three parent compounds, acetonitrile (**8**), pyridine (**23**) and trimethylamine (**56**), the strongest negative electrostatic potential corresponds to the weakest hydrogen-bond base as shown in Table 5.

An NBO analysis carried out on these base···HF systems is presented in the last columns of Table 5 to interpret this behaviour. The $n \rightarrow \sigma^*$ charge transfer is clearly dependent on the hybridisation state of the nitrogen atom.[71,72] Indeed, the estimated decrease in the lone pair occupancy ($n_{(N)}$), from acetonitrile to pyridine and to trimethylamine, is followed by a significant increase in the HF antibonding σ* population ($\sigma^*_{(HF)}$), due to the increase in the interaction energy ($E^{(2)}_{n \rightarrow \sigma^*}$). On the other hand, when the nature of the accepting group is kept constant, such as in the substituted pyridines **22**, **23** and **33**, there is a good proportionality between the electrostatic and the covalent contributions to the hydrogen-bond attractive energy as previously suggested by Maria et al.[73]

As shown in Figure 3B, the plot between pK_{HB} and $D_0^{(HF)}$ values also presents separate lines corresponding to families but with slightly better statistics. The marked difference

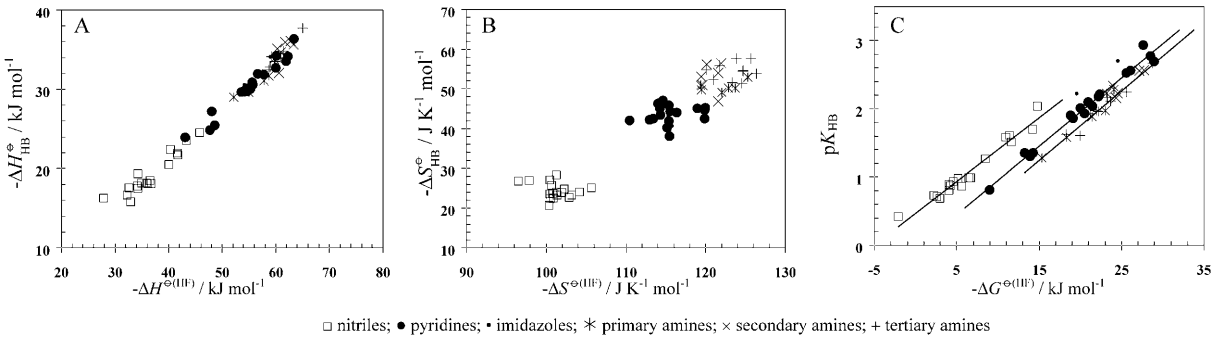


Figure 2. The relationship between the experimental thermodynamic parameters of the association equilibrium with 4-fluorophenol and the corresponding theoretical parameters of the association equilibrium with hydrogen fluoride.

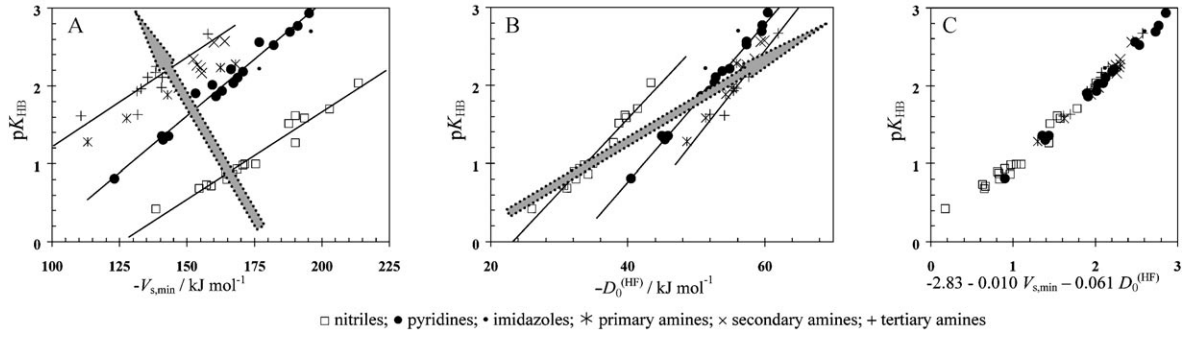


Figure 3. Relationships between the pK_{HB} scale and different theoretical parameters. For the sake of clarity, regression lines are only drawn for nitriles, pyridines and tertiary amines. The grey arrows indicate the evolution of the three parent compounds: acetonitrile, pyridine and trimethylamine.

Table 5. Comparison of the evolution of theoretical $V_{s,min}$ and $D_0^{(HF)}$ descriptors between nitrogen families and inside the pyridine family, and NBO analyses of the corresponding hydrogen-bonded complexes.

No.	Compound	pK_{HB}	$V_{s,min}$	$D_0^{(HF)}$	$n_{(N)}$[a]	$\sigma^*_{(HF)}$[b]	$E^{(2)}_{n\rightarrow\sigma^*}$[c]
8	acetonitrile	0.89	−164.4	−32.2	1.928	0.045	21.7
23	pyridine	1.86	−160.8	−50.8	1.846	0.087	41.5
56	trimethylamine	2.11	−140.7	−56.5	1.824	0.104	41.7
22	3-fluoropyridine	1.35	−143.2	−45.9	1.818	0.080	38.7
33	4-*N*,*N*-dimethylaminopyridine	2.80	−191.1	−59.7	1.848	0.099	46.2

[a] Nitrogen lone pair population. [b] H–F antibonding population. [c] Estimated interaction energy between the nitrogen lone pair and the HF antibonding orbital, in kcal mol^{-1}.

with the electrostatic potential is that this descriptor explains the evolution of pK_{HB} both *between* and *within* the families (Table 5). Therefore, the two independent theoretical descriptors $V_{s,min}$ and $D_0^{(HF)}$ carry substantially different information suggesting the possibility of a multilinear analysis of the whole experimental pK_{HB} scale. Indeed, a significant improvement in the pK_{HB} prediction of nitrogen compounds is provided by the resulting Equation (10). Although the standard error of the estimate is slightly larger than the experimental uncertainty of the pK_{HB} values, it enables the association equilibrium constant of pFP on a nitrogen base to be estimated with a precision of about 18%, an unprecedented level for a bi-parametric equation.

$$pK_{HB} = -0.0612\, D_0^{(HF)} - 0.0102\, V_{s,min} - 2.829 \qquad (10)$$

$r = 0.993$, $s = 0.07$, $n = 59$

Extension and applications: The validities of Equations (8) and (10) have been tested on 99 additional bases corresponding to a wide diversity of accepting nitrogen atoms for which published experimental basicities (pK_{HB} and/or ΔH°_{HB}) have already been measured or calculated through empirical relationships. New experimental results obtained for a few compounds have also been added when necessary. The whole extended data set (158 compounds) is reported in the Supporting Information, whereas the most important applications are only presented here for a limited series of molecules.

*Super-basic nitriles (compounds **60** and **61** in Table 6)*: In preceding papers, we have shown that a considerable increase in the hydrogen-bond basicity of different electron-withdrawing functional groups can be gained either by using new electron-donating substituents, such as the alkyl$_3$N$^+$N$^-$ group,[74] or by interposing more efficient transmitting fragments, such as the imino group,[47] between the substituent and the function. In the nitrile series, cyanoacetamidine (**60**) shows a stronger hydrogen-bond basicity than pyridine (**23**), and cyanamidate (**61**) exceeds quinuclidine (**59**) basicity and turns out to be the most basic compound of the present data set of neutral mono-nitrogen molecules. For these two compounds and by using Equation (10), the estimated pK_{HB} values perfectly match the experimental data (Table 6). Since both optimised structures correspond to the association of hydrogen fluoride specifically on the nitrile group, the theoretical calculations definitely rule out the possibility of a significant secondary association on the other nitrogen sites of these molecules.

*Steric effects (compounds **62–71** in Table 6)*: The selection of hydrogen fluoride as a model is an oversimplification restricting the structure of 4-fluorophenol to its OH bond. All the secondary interactions between the aromatic molecular frame and the acceptor are thus neglected. The results obtained on the training set [Table 3, Eqs. (8) and (10)] demonstrate that the model is satisfactory when the accepting nitrogen of the base can be freely accessed by the donor. In Table 6, we have presented the calculated and experimental results for some mono- and dialkylated pyridines on the ortho position. The increase in experimental entropy with the bulkiness of the alkyl group(s) is reasonably predicted by Equation (9), but the first noticeable difference between the enthalpies and free energies occurs for the very large *tert*-butyl group of **64**. In this case, the complexation enthalpy is underestimated by 3 kJ mol^{-1} and the pK_{HB} is overestimated by 0.19 pK units. The limit of this model is therefore not very severe and leaves a very large degree of freedom for the investigation of other nitrogen bases. We have overcome this limit and calculated the thermodynamic parameters of two more strongly hindered bases. Experimentally, 1,2,2,6,6-pentamethylpiperidine (**71**) possesses the highest

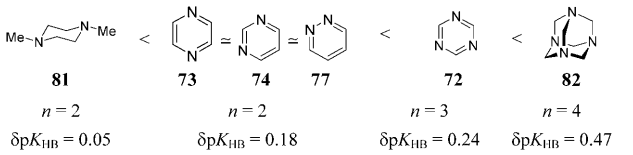
Table 6. Comparison of experimental and calculated data on an extended set containing super-basic nitriles and compounds with steric or proximity effects.

No.	Compound	Calculated			Experimental		
		pK_{HB}[a]	$-\Delta H^{\circ}_{HB}$[b]	$-\Delta S^{\circ}_{HB}$[c]	pK_{HB}	$-\Delta H^{\circ}_{HB}$	$-\Delta S^{\circ}_{HB}$
60	N^1,N^1-dimethyl-N^2-cyanoacetamidine	2.17	25.9	14	2.24[d]	–	–
61	tri-*n*-butylammonium cyanamidate	3.23	33.2	9	3.24[e]	–	–
62	2-ethylpyridine[f]	2.00	31.1	50	1.90	34.0	58
63	2-isopropylpyridine[f]	1.82	30.2	60	1.76	–	–
64	2-*tert*-butylpyridine[f]	1.60	28.7	57	1.41	31.7	60
65	2,6-dimethylpyridine	2.13	32.2	45	2.09	33.3	52
66	2,4,6-trimethylpyridine	2.29	33.2	54	2.28	35.3	55
67	2-fluoropyridine	1.14	22.3	41	0.94	24.5	45
68	2-chloropyridine	1.17	22.8	44	1.07	24.1	41
69	2-bromopyridine	1.13	22.6	44	1.04	23.7	40
70	2,6-di-*tert*-butylpyridine	0.40	21.5	75	−0.54[g]	–	–
71	1,2,2,6,6-pentamethylpiperidine	1.74	32.7	63	1.25[h]	34.0	71

[a] Calculated from Equation (10). [b] Calculated from Equation (8). [c] Calculated from Equation (9). [d] Ref. [47]. [e] Ref. [48]. [f] Weighted calculated values of different stable isomers. [g] Ref. [75]. [h] Ref. [22].

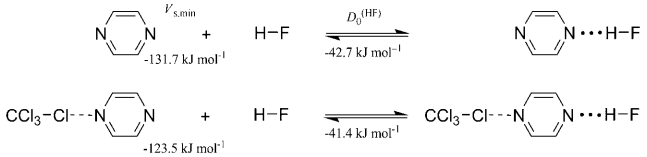
entropy of our data set, but the same enthalpy as its unhindered homologue 1-methylpiperidine (**55**). Whereas the predicted ΔH°_{HB} remains satisfactory, pK_{HB} is unacceptably overestimated ($\delta pK_{HB}=0.5$). The very high hydrogen-bond donating strength of hydrogen fluoride, combined with its tiny size, clearly allows the formation of stable complexes that are not accessible to the bulky pFP. It is then possible to find an energetic minimum corresponding to the association of HF on the nitrogen electron pair of 2,6-di-*tert*-butylpyridine (**70**), although we have previously shown experimentally that the complexation of pFP occurs exclusively on the π electrons of the pyridine ring.[75]

*Solvent effects: symmetric polyfunctional bases (compounds **72–82** in Table 7)*: In our experimental data set, numerous molecules possess *n* equivalent sites and statistical corrections, $-R\ln(n)$ and $-\log(n)$, are applied to ΔS°_{HB} and pK_{HB}, respectively, to put the results on a per nitrogen basis for a direct comparison with theoretical calculations. However, the analysis of these polyfunctional bases shows that calculations always overestimate their pK_{HB} values by a significant increasing amount depending approximately on the number (*n*) of equivalent nitrogen atoms (Scheme 1).



Scheme 1. Symmetric polyfunctional bases showing the degree of overestimation of their pK_{HB} values (δpK_{HB}), which increases with increasing number of equivalent nitrogen atoms (*n*).

These systematic deviations from the correlation line and their regular evolution suggest that the interactions between the solvent CCl_4 and the non-hydrogen-bonded sites of the polyfunctional bases must be taken into account in the calculations. Nitrogen compounds are known to form weak electron donor–acceptor complexes with the polyhalogenated molecules,[76–79] which are now called halogen-bonded complexes.[80,81] As a first approximation, we have modelled this interaction by the association of one solvent molecule halogen-bonded to one or more nitrogen atoms. Geometry optimisations were therefore carried out on the $(CCl_4)_{n-1}$···base and $(CCl_4)_{n-1}$···base···HF systems, and these structures were used to replace the base monomer and the base···HF complex, respectively. In the example of pyrazine (**73**) (Scheme 1), the $n\rightarrow\sigma^*$ interaction, between the lone pair of a first nitrogen atom and the solvent Cl–C antibond, markedly decreases the electron density of the second one. The consequence is a significant perturbation of its $V_{s,min}$ and $D_0^{(HF)}$ parameters, which are used in Equation (10) to estimate the pK_{HB} for solvated pyrazine (Scheme 2). The predicted hydrogen-bond basicity of pyrazine ($pK_{HB}=0.97$) is thus significantly reduced in comparison with a hypothetical unsolvated molecule ($pK_{HB}=1.13$), and fits the experimental value better ($pK_{HB}=0.94$).



Scheme 2. Theoretical hydrogen-bond complexation (B3LYP/6-31+G-(d,p)) of pyrazine with hydrogen fluoride considering the influence of the solvent interaction with the base.

The results, reported in Table 7 for 11 compounds, show that the agreement between the calculated and the experimental values is, in general, much lower than the noise of the estimation. They give further support to the importance of the specific solute–solvent interaction recently analysed by Hunter et al.[82,83] The limit of this method is attained with the large underestimation (−0.16 p*K* units) of hexamethylenetetramine (**82**) basicity, which has been analysed here as a tri-solvated base in the absence of information on the number of specific interactions between CCl_4 and the base. It must be noted that the absolute deviation for the unsolvated molecule was far greater ($\delta pK_{HB}=0.45$) and that a bi-solvated model would give a correct agreement with the experiment. In the following, the unsymmetrical polyfunctional molecules will provide additional examples of this solvent influence on basicity.

*Extension to a new series of bases (compounds **83–94** in Table 8)*: A large number of important nitrogen compounds such as **83–94** are amphiprotic and their hydrogen-bond basicity cannot be measured with the

Table 7. Comparison of experimental and calculated data for symmetric polyfunctional molecules solvated by CCl_4.

No.	Compound	Calculated			Experimental		
		pK_{HB}[a]	$-\Delta H^{\circ}_{HB}$[b]	$-\Delta S^{\circ}_{HB}$[c]	pK_{HB}[d]	$-\Delta H^{\circ}_{HB}$	$-\Delta S^{\circ}_{HB}$[d]
72	[triazine–$(CCl_4)_2$]	0.30	19.2	35	0.31	19.8	40.9
73	[pyrazine–CCl_4]	0.97	23.8	52	0.94	22.6	38.4
74	[pyrimidine–CCl_4]	1.07	24.2	69	1.06	23.9	40.6
75	[5-bromopyrimidine–CCl_4]	0.62	21.3	42	0.59	–	–
76	[phenazine–CCl_4]	1.22	26.6	40	1.22	–	–
77	[pyridazine–CCl_4]	1.54	25.1	41	1.65	27.9	42.5
78	[phtalazine–CCl_4]	1.85	27.0	25	1.97	–	–
79	[2,5-dimethylpyrazine–CCl_4]	1.29	26.3	41	1.29	26.6	45.4
80	[4,6-dimethylpyrimidine–CCl_4]	1.46	27.3	46	1.47	27.8	45.9
81	[*N*,*N*′-dimethylpiperazine–CCl_4]	1.81	32.5	51	1.88[e]	–	–
82	[hexamethylenetetramine–$(CCl_4)_3$]	1.17	28.0	34	1.33[e]	–	–

[a] Calculated from Equation (10). [b] Calculated from Equation (8). [c] Calculated from Equation (9). [d] Experimental pK_{HB} and ΔS°_{HB} statistically corrected by the number of equivalent sites. [e] Ref. [22].

Table 8. Comparison of experimental and calculated data on amphiprotic molecules self-associated in CCl_4.

No.	Compound	Calculated			Secondary values	
		pK_{HB}[a]	$-\Delta H^{\circ}_{HB}$[b]	$-\Delta S^{\circ}_{HB}$[c]	pK_{HB}	$\log K_x$[d]
83	cyanamide	1.12	19.5	19.3	1.19[e]	–
84	imidazole	2.39	31.6	42.2	2.47[f]	–
85	4-methylimidazole	2.49	32.7	44.1	2.64[f]	–
86	3-methyl-4-bromopyrazole	1.31	25.7	37.0	–	4.06
87	pyrazole	1.65	27.1	38.8	–	4.47
88	4-methylpyrazole	1.81	28.0	37.2	–	4.69
89	3-methylpyrazole	1.81	28.7	39.4	–	–
90	5-methylpyrazole	1.91	28.7	38.8	–	4.84
91	3(5)-methylpyrazole[g]	1.85	28.7	39.1	–	–
92	3,5-dimethylpyrazole	2.05	30.2	39.3	–	5.03
93	3,4,5-trimethylpyrazole	2.17	31.0	41.1	–	5.16
94	2,4,5-trimethyloxazole	2.08	30.5	39.4	2.02[h]	–

[a] Calculated from Equation (10). [b] Calculated from Equation (8). [c] Calculated from Equation (9). [d] Logarithm of the equilibrium constant of the association with 3,5-dinitrophenol in cyclohexane, (expressed in molar fraction units).[84] [e] Calculated by substituent parameters with the updated Equation (11).[58] [f] Calculated from the association constants measured in dichloromethane with pFP. [g] Weighted calculated values of stable isomers. [h] Calculated from the association constants measured in CH_3CCl_3 with *p*-nitrophenol.[85]

standard methods because these compounds are too self-associated in carbon tetrachloride at the operating concentrations. Diverse techniques may be used to overcome this difficulty to get the true hydrogen-bond affinity of the monomer. Guiheneuf et al.[84] measured by UV spectroscopy the equilibrium constants of pyrazoles **86–93** in cyclohexane using the extremely strong donor 3,4-dinitrophenol to have very low concentrations of the base. Abraham et al.[85] used the couple 4-nitrophenol (a strong donor enabling a lower base concentration) and 1,1,1-trichloroethane (a polar solvent decreasing self-association) to obtain the association constants of numerous original bases. In our laboratory, we have been able to analyse about one hundred bases in dichloromethane keeping pFP as the donor. Unfortunately, in spite of the considerable effort made by Abraham[2,3] to gather and homogenise the literature data, the relationships between the different acids and the different solvents generate large errors in the secondary calculated pK_{HB} values. The examples presented in Table 8 show that the theoretical calculations might be an excellent alternative allowing the rationalisation of the experimental data since the precision of the correlations between the different acids or/and the different solvents are always limited by the absence of sufficient common points. To calculate a secondary value for cyanamide (**83**), we have used the regression line from Equation (11), which is an updated version of the equation found between the pK_{HB} values of 19 substituted nitriles X–CN and the resonance, field and polarisability constants of the substituents X.[58] The substituent parameters used for the amino group (NH_2) are $\sigma_r^+ = -0.52$, $\sigma_F = 0.14$ and $\sigma_\alpha = -0.16$.[86] The value 1.19 obtained by this equation perfectly matches the value taken from the theoretical calculation.

$$pK_{HB} = -1.42\,\sigma_r^+ - 1.95\,\sigma_F - 0.26\,\sigma_\alpha + 0.68 \quad (11)$$

$r = 0.997$, $s = 0.03$, $n = 19$

The results for imidazole (**84**) and 4-methylimidazole (**85**) are comparable to secondary values obtained from dichloromethane measurements, which are imprecise because the diagram between CCl_4 and CH_2Cl_2 is FD.[8] On the contrary, there is a single relationship[85] between the log*K* values measured in 1,1,1-trichloroethane with 4-nitrophenol and pK_{HB} values, and the experiment confirms the proposed value for the substituted oxazole **94**. In the absence of any reference compound, it is not possible to directly test the substituted pyrazoles **86–93**. However, the consistency of the results is revealed by the excellent statistics of Equations (12) and (13) relating the calculated pK_{HB} values to the logarithm of the association constant between the pyrazoles **86–90** and 3,4-dinitrophenol in cyclohexane or with pK_a in water, respectively.

$$\log K_x = 1.30\,pK_{HB} + 2.35 \quad (12)$$

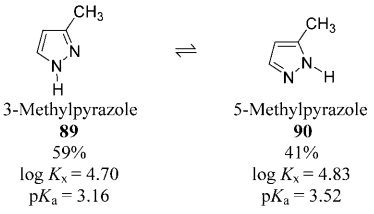
$r = 0.999$, $s = 0.02$, $n = 5$

$$pK_a = 3.66\,pK_{HB} - 3.47 \quad (13)$$

$r = 0.997$, $s = 0.12$, $n = 5$

With these equations, the individual values of $\log K_x$ and pK_a corresponding to the two tautomeric forms 3- and 5-methylpyrazole can be evaluated (Scheme 3). By comparison with the experimental results, $\log K_x = 4.84$ and $pK_a = 3.27$,[84] we quantitatively show that the tautomeric equilibrium is significantly influenced by the solvent. In cyclohexane, 5-methylpyrazole is clearly the only tautomeric form present, whereas the intermediate experimental value found in water strongly suggests that the two tautomers co-exist in approximately equal proportions.

Analysis of polyfunctional bases (Table 9): The experimental measurement of hydrogen-bond basicity is generally limited to the analysis of monofunctional bases because the standard methods of determination of the equilibrium constants



3-Methylpyrazole
89
59%
$\log K_x = 4.70$
$pK_a = 3.16$

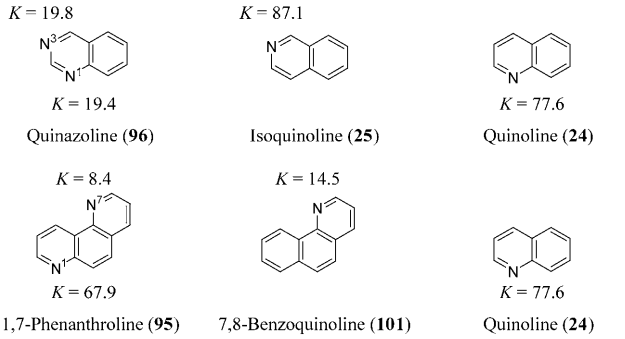
5-Methylpyrazole
90
41%
$\log K_x = 4.83$
$pK_a = 3.52$

Scheme 3. Evaluation of $\log K_x$ and pK_a values corresponding to the tautomeric forms of methylpyrazole.

Table 9. Individual basicities of nitrogen polyfunctional bases.

No.	Compound	Theoretical					Exptl.
		site	K_i[a]	site	K_i[a]	pK_t[b]	pK_t
95	1,7-phenanthroline	N^1	67.9	N^7	8.4	1.88	1.87[c]
96	quinazoline	N^1	19.4	N^3	19.8	1.59	1.55[c]
97	2-cyanopyridine	N_{sp}	3.9	N_{sp^2}	4.0	0.89	0.85[c]
98	3-cyanopyridine	N_{sp}	2.7	N_{sp^2}	6.7	0.97	1.00[c]
99	4-cyanopyridine	N_{sp}	1.8	N_{sp^2}	8.8	1.03	1.05[c]
100	*N*,*N*-dimethylaminoacetonitrile[d]	N_{sp}	4.8	N_{sp^3}	5.7	1.02	1.02[e]

[a] $K_c = 10^{pK_{HB}}$, calculated from Equation (10) with compounds halogen-bonded to a molecule of CCl_4 on their second site. [b] $pK_t = \log(\Sigma K_i)$. [c] Ref. [52]. [d] Weighted values of two stable monomers. [e] Ref. [38].



Scheme 4. Comparison of the equilibrium constants of the polyfunctional bases.

cannot distinguish between the associations of the donor on the different sites and thus yield a global equilibrium constant $K_t = \Sigma K_i$ corresponding to the sum of the individual K_i constants.[10] Since the corresponding $pK_t = \log(\Sigma K_i)$ is algebraically different from $\Sigma\log(K_i)$, the pK_t is of no thermodynamic interest. There are, however, two important exceptions. The first occurs when the molecule has *n* equivalent sites; then $pK_t = \log(nK_i) = \log(K_i) + \log(n)$ and the individual association constants are easily calculated as shown previously. The second is related to the numerous molecules in which the secondary sites have a much weaker basicity than the functional group so that their equilibrium constants are negligible. In all the other situations, the individual constants must be evaluated by different empirical relationships using, for instance, the frequency shifts or the substituent constants inside series of related compounds.[52] Hence the pK_{HB} values predictions from the theoretical calculations find here their utility since they refer to the association on the individual sites. However, as shown above, the solvent acidity plays a non-negligible part in the hydrogen-bond affinity of the functional group when it is linked to the basic substituent. Therefore, all the calculations reported in Table 9 were carried out with a CCl_4 molecule halogen-bonded to the substituent.

Whatever the nature of the accepting site, the theoretical calculations allow the total equilibrium constant to be determined with the same precision as the experimental error despite the error propagation due to the summation of two constants. To our knowledge, the separation between the two N_{sp^2} sites of 1,7-phenanthroline (**95**) and quinazoline (**96**) has never been carried out before. Both sites of quinazoline strongly deactivate each other in comparison with quinoline (**24**) and isoquinoline (**25**) (Scheme 4), but their basicities are nearly equivalent in agreement with the nearly identical values of **24** and **25**. On the contrary, the two nitrogen atoms of **95** differ significantly and the equilibrium constants of the two sites can be compared to the monofunctional models available: 7,8-benzoquinoline (**101**) and quinoline (**24**). Scheme 4 shows the large steric effect occurring on the N^7 nitrogen of **95** as well as the small mutual deactivation of the two nitrogen atoms in **95**.

The separations carried out for three cyanopyridines **97**–**99** confirm that the halogen-bond interaction of the solvent molecule to a secondary site is also significant when the accepting centre is a nitrile nitrogen atom. In these molecules, the reduction in basicity of the pyridine nitrogen is found to be around 20% in comparison with the unsolvated cyanopyridines and decreases with the distance between the two sites. Lastly, in dimethylaminoacetonitrile (**100**), it is very satisfying to find a perfect match between the theoretically and experimentally[38] predicted equilibrium constants of the nitrile group. However, the superiority of the theoretical method lies in the fact that the basicity of the amino group can also be evaluated independently and is not simply estimated by difference with the experimental K_t.

Model validation: As a final point, the whole data set presented in the supporting information can be considered for an ultimate validation of the model. The regression Equation (14) may be set up for the 142 nitrogen compounds for which the pK_{HB} values are available. It is reassuring that all regression coefficients are comparable to those of Equation (10), which shows its robustness. Although the statistical parameters are of slightly poorer quality, they are still satisfying when we keep in mind that this external set contains not only strongly hindered and solvent-sensitive polyfunctional bases but also many bases showing distorted negative zones around the lone pairs (*ortho*-halogeno pyridines for instance). This anisotropy of the lone pair is partly accommodated by the complementary anisotropy of the positive isopotential surface of the hydroxyl hydrogen of pFP but cannot be fully taken into account when HF is the model for the donor.

$$pK_{HB} = -0.0608\,D_0^{(HF)} - 0.0111\,V_{s,min} - 2.96 \qquad (14)$$

$r = 0.991$, $s = 0.096$, $n = 142$

Conclusion

The analysis and the development of the pK_{HB} and ΔH°_{HB} scales of hydrogen-bond basicity of nitrogen bases have been achieved with a density functional method coupled with the 6-31+G** basis set. Hydrogen fluoride may gener-

ally be used as a cost-effective model in place of 4-fluorophenol. The evaluation of the pK_{HB} scale requires the calculation of the minimum electrostatic potential at the molecular surface around the nitrogen lone pair and the variation in electronic energy of the reaction of association between the base and HF. This analysis shows that, provided that relative values of basicities are to be compared, the effort to understand and develop the hydrogen-bond basicity scale is not primarily a matter of the sophistication of the theoretical method or of the level of the basis set. Once a sufficient level of precision in the predicted values is attained, the real complexity of the modelling process appears. The calculations must appreciate and weight the basicities of the different monomers present in solution and quantify the specific interactions between carbon tetrachloride and the molecules when the latter have a secondary basic site.

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