Hydrogen-bond basicity pK_{HB} scale of secondary amines

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Using 4-fluorophenol as a reference hydrogen-bond donor, equilibrium constants K for the formation of 1 : 1 hydrogen-bonded complexes have been obtained by FTIR spectrometry for 33 secondary amines in CCl_4 and/or C_2Cl_4 at 298 K. A spectroscopic scale of hydrogen-bond basicity is constructed from the IR frequency shift $\Delta\nu$(OH) of methanol hydrogen-bonded to secondary amines. The comparison of the pK_{HB} (log K), $\Delta\nu$(OH), and pK_a scales points to the sensitivity of pK_{HB} to steric effects, and of $\Delta\nu$(OH) to the p character of the nitrogen lone pair. The pK_{HB} scale of secondary amines extends from 2.59 for pyrrolidine to −0.45 for $(Me_3Si)_2NH$. The main effects explaining the pK_{HB} variations are (*i*) the opposite polarizability and steric effects in alkylamines, (*ii*) field-inductive effects (*e.g.* N≡CCH_2NHMe), (*iii*) intramolecular hydrogen bonding, *e.g.* in $(MeOCH_2CH_2)_2NH$, and (*iv*) the ring size giving the order: pyrrolidine = azetidine > piperidine > 2-methylaziridine > azepane. IR spectra show the attachment of 4-fluorophenol to the nitrile nitrogen of N≡CCH_2NHMe and N≡CCH_2CH_2NHMe, to the oxygen of morpholine and $(MeOCH_2CH_2)_2NH$, and to the sulfur of thiomorpholine and thiazolidine, in addition to attachment to the amino nitrogen. The correlation of pK_{HB} with the minimum electrostatic potential on the nitrogen lone pair is used for unravelling the basicity of each nitrogen of 1-methyl-1,4-diazepane.

Introduction

Early work by Taft *et al.*[1–3] and Arnett *et al.*[4] established 4-fluorophenol as an excellent reference hydrogen-bond donor for the construction of a thermodynamic hydrogen-bond basicity scale for organic bases B. This scale, denoted pK_{HB}, is defined as the logarithm of the formation constant K of the 1 : 1 hydrogen-bonded complex 4-$FC_6H_4OH\cdots B$ in CCl_4 at 298 K [eqns. (1)–(3)].

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

$$K/dm^3\ mol^{-1} = [complex]/[4\text{-}FC_6H_4OH]\ [B] \qquad (2)$$

$$pK_{HB} = \log_{10} K \qquad (3)$$

There are two main reasons for building the pK_{HB} scale of organic bases. Firstly, hydrogen bonding is known to play a crucial role throughout chemistry,[5,6] biology,[7] and materials science.[8,9] However, hydrogen bond energies remain difficult quantities to measure precisely. The pK_{HB} scale allows quantitative comparison of hydrogen bond Gibbs energies. Secondly, while the Brønsted basicity is quantitatively well defined through the pK_a scale[10] in water or the GB scale[11] in the gas phase, the measurement of the Lewis basicity remains unachieved. Since most hydrogen bonds are mainly electrostatic[12] in origin, the pK_{HB} scale might provide the electrostatic term of Lewis acid–base interactions.[13]

We have already measured pK_{HB} for a wide variety of nitrogen, oxygen, sulfur, halogen, and π bases.[14] In the case of nitrogen bases, nitriles,[15,16] amidines,[17–19] pyridines[20] and primary amines[21] have been studied. We present here the pK_{HB} scale for secondary amines.

We have determined the pK_{HB} values of 33 aliphatic secondary amines including alkylamines of different chain length and chain branching, cyclic amines of increasing ring size, heterocyclic amines, amines substituted with various electron-withdrawing groups ($CH{=}CH_2$, Ph, MeO, Cl, HC≡C, C≡N), one acyclic diamine and one silylamine. We have found that the pK_{HB} scale of secondary amines extends over *ca.* 3 pK units (17 kJ mol^{-1}) from pyrrolidine (pK_{HB} = 2.59) to $(Me_3Si)_2NH$ (pK_{HB} = −0.45) and the main effects governing these variations are discussed.

We have used FTIR spectrometry in this work since this technique has many advantages. Firstly, the high photometric accuracy of FTIR spectrometers allows the measurement of the equilibrium concentrations of the species in eqn. (1) with a higher precision than ^{19}F NMR,[1] UV[22] or calorimetric techniques.[4] Secondly, infrared gives the opportunity of measuring the methanol O–H stretching wavenumber shifts upon complexation with amines. These shifts are considered[23] as a spectroscopic scale of hydrogen-bond basicity and their comparison with the thermodynamic pK_{HB} scale reveals interesting structural effects. Lastly, for hetero-substituted amines, the appearance of an additional broad O–H band in the IR spectra of the complexes reveals the existence of a second hydrogen-bond acceptor site, in addition to the sp^3 nitrogen site. By using relationships between pK_{HB} and IR shifts, the true amine basicity can be calculated from the overall measured complexation constant (*vide infra*).

Experimental

Materials

All the compounds used in this study are commercially available. Their purity was checked by gas chromatography and, when necessary, the compounds were distilled. Bis(2-chloroethyl)amine and (methylamino)acetonitrile were liberated from their hydrochlorides by reaction with excess sodium hydroxide. All were dried over activated 4 Å molecular sieves and/or basic aluminium oxide. Spectroscopic-grade CCl_4 and C_2Cl_4 were passed through a column of freshly activated 4 Å molecular sieves before use. Spectroscopic-grade methanol was kept over 3 Å molecular sieves. 4-Fluorophenol was sublimed over P_2O_5 at 60 °C and 13 Pa.

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Infrared spectra

IR spectra were recorded with Bruker IFS 48 or Vector 22 instruments at a resolution of 1 cm^{-1}. An Infrasil quartz cell of pathlength 1 cm was used. The cell temperature was maintained at 25 ± 0.2 °C by means of a Peltier thermoelectric device.

Equilibrium constants

The formation constant of 1 : 1 complexes (c) of 4-fluorophenol (a) with amines (b) is defined as $K = C_c/C_aC_b = (C^\circ_a - C_a)/C_a(C^\circ_b - C^\circ_a + C_a)$, where the concentrations are on a molar scale. The initial concentration of 4-fluorophenol, C°_a, was kept under the limit of 4×10^{-3} mol dm^{-3} in order to discount self-association. The initial concentration of the amine, C°_b, was adjusted so that 20 to 80% of 4-fluorophenol was hydrogen-bonded. This was fulfilled with C°_b/C°_a ratios ranging from 2–4 for the more basic amines **1** and **2** to 3–25 for the amine **31** (50–360 for **32** which is of exceptionally low basicity). The equilibrium concentration C_a was obtained from the absorbance of the 3614 cm^{-1} band of 4-fluorophenol (ε = 237 dm^3 mol^{-1} cm^{-1} in CCl_4 at 25 °C). In the case of diamines, we maintained the diamine concentration in fivefold excess in order to favour the formation of 1 : 1 complexes over 2 : 1 complexes. The constancy of K, determined at different amine concentrations on the basis of 1 : 1 complexation, indicates that the 1 : 1 complex is the primary species formed. The maximum error in pK_{HB} is estimated to be ±0.03. All operations, including the filling of the cell, were conducted in the dry atmosphere of a glove-box.

Infrared shifts

The wavenumber shift of the OH band of methanol is defined as $\Delta\nu$(OH) = ν(free OH) − ν(complex OH) = 3644 − ν(OH · · · N). It is measured on ternary solutions of methanol (1 mmol dm^{-3}), amine (from 0.018 to 0.18 mol dm^{-3} according to the amine basicity), and CCl_4. It is generally known to ±3 cm^{-1} but the accidental presence of the amine ν(NH) band near the maximum of the broad ν(OH · · · N) band causes larger errors. This is the case of amines having extinction coefficients for the ν(NH) band higher than 2 dm^3 mol^{-1} cm^{-1} (**4**, **15**, **20**, **22**, **26**–**29**, **30**).

Calculation methods

Ab initio calculations were performed using Spartan 4.0,[24] Gaussian 94 or Gaussian 98[25] running respectively on a Silicon Graphics Indy workstation, a 300 MHz bi-pentium II personal computer, or the IDRIS computational facility. The geometries of the free amines were optimised at the HF/6-31G** level. We have not fully explored the conformational space of the molecules but, where it was deemed necessary, we have optimised the geometries of various input conformations. Moreover, the calculated geometries always agree with the experimental gas-phase conformation found in the Mogadoc database[26] for compounds **1**–**3**, **7**–**9**, **17**, **19**, **20**, **23**, **25**–**27** and **30**–**32** (*i.e.* 16 compounds of 33). The electrostatic potential was then computed for the most stable conformation. We have calculated $V_{S,\min}$, the minimum electrostatic potential on the molecular surface defined[27] by the 0.001 electron $bohr^{-3}$ contour of the electronic density, at the HF/6-31G** level.

Results

Table 1 summarizes the pK_{HB} scale constructed from the hydrogen-bonding complexation of 4-FC_6H_4OH with 32 amines in CCl_4 (or C_2Cl_4) at 25 °C. Also given are (*i*) the $\Delta\nu$(OH) scale constructed from the IR OH shifts of methanol hydrogen-bonded to the amines and (*ii*) the pK_a values in water (generally at 25 °C).[10] A few secondary amines (*e.g.* pyrrolidine or $PhCH_2NHMe$) react[28] or are complexed[29] with CCl_4. Their complexation constants with 4-FC_6H_4OH have then been measured in C_2Cl_4. In order to check whether the values measured in CCl_4 and C_2Cl_4 combine, we have compared them for 32 nitrogen bases: 12 primary amines (from previous work),[21] 8 secondary amines, 9 tertiary amines, and 3 pyridines (this work). Through the correlation coefficient r, the standard deviation s, and the Fisher test F, eqn. (4) shows that $K(C_2Cl_4)$

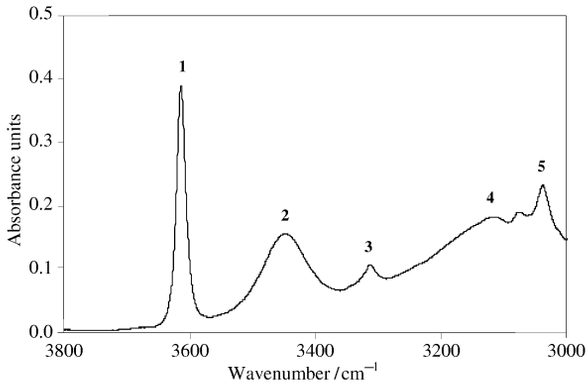


Fig. 1 IR spectrum of the association of 4-fluorophenol (0.004 M) with 3-(methylamino)propiononitrile (0.049 M) in CCl_4 showing (1) the ν(OH) band of free 4-fluorophenol, (2) the ν(OH · · · N≡C) band of the first 1 : 1 complex (3) the ν(NH) band of 3-(methylamino)propiononitrile, (4) the ν(OH · · · Nsp^3) band of a second 1 : 1 complex and (5) the ν(CH) bands of 4-fluorophenol.

$$\log K(C_2Cl_4) = 0.999\ (\pm 0.013)\ pK_{HB}(CCl_4) + 0.05\ (\pm 0.03) \quad (4)$$

$$n = 32,\ r = 0.998,\ s = 0.05,\ F = 6083$$

is strongly correlated to $K(CCl_4)$. Moreover the regression coefficient and the intercept demonstrate that the solvent change does not bring about any significant variation of the complexation constant.

In addition to the broad ν(OH · · · NH) band, we observe (Fig. 1) for amines with a second potential hydrogen-bond acceptor site, $(MeOCH_2CH_2)_2NH$, morpholine, thiomorpholine, thiazolidine, N≡CCH_2CH_2NHMe, and N≡CCH_2NHMe, the presence of a second band in the IR spectra of their complexes with 4-fluorophenol and methanol. We attribute this new band to ν(OH · · · O) for oxygen compounds, ν(OH · · · S) for sulfur compounds, and ν(OH · · · N≡C) for nitriles. This shows that two 1 : 1 complexes are formed in solution (in preference to a 2 : 1 complex because the amine is in excess). In this case, the measured complexation constant is a total constant corresponding to the sum of the constants of two 1 : 1 complexes.[14] In eqn. (5) K(X) stands for K(O), K(S), or K(C≡N). In order to

$$K(\text{total}) = K(X) + K(NH) \quad (5)$$

obtain the true amino basicity, K(NH), we have to subtract K(X) from K(total). K(O), K(S) and K(C≡N) can be evaluated by using the relationships between pK_{HB} and $\Delta\nu$(OH) previously established in the families of ethers,[30] thioethers[31] and nitriles[15] respectively. The calculations are summarized in Table 2. In the same way K(total) = 2K(NH) for the diamines **5** and **17**, if we assume that the two nitrogens have the same basicity. In order to refer to the basicity of one nitrogen, we must apply a −log 2 statistical correction to pK_{HB}.

Discussion

Comparison of the pK_{HB}, pK_a and $\Delta\nu$(OH) basicity scales

The parent compound of secondary amines, dimethylamine, has a pK_{HB} of 2.26, which shows that secondary amines are slightly stronger hydrogen-bond bases than primary amines (pK_{HB} = 2.17 for ethylamine).[21] In the absence of significant

Table 1 pK_{HB}, $\Delta\nu$(OH)/cm^{-1}, and pK_a basicity scales of secondary amines

No.	Compound	Formula	pK_{HB}	$\Delta\nu$(OH)	pK_a
1	Pyrrolidine	$CH_2CH_2CH_2CH_2NH$	2.59	406	11.31
2	Azetidine	$CH_2CH_2CH_2NH$	2.59	402	11.29
3	Piperidine	$CH_2CH_2CH_2CH_2CH_2NH$	2.38	404	11.12
4	Bis(2-methoxyethyl)amine	$(MeOCH_2CH_2)_2NH$	2.35 (2.31)[b]	396	
5	*N*,*N*′-Dimethylethylenediamine	$MeHN(CH_2)_2NHMe$	2.60 (2.29)[c]	407	10.24 (9.94)[c]
6	2-Methylaziridine	$MeCHCH_2NH$	2.28	327	
7	Dimethylamine	Me_2NH	2.26	388	10.78
8	*N*-Methylethylamine	EtNHMe	2.25	394	
9	Diethylamine	Et_2NH	2.25	398	11.02
10	*N*-Methylcyclohexylamine	*c*-HexNHMe	2.24	402	11.04
11	*N*-Methylbutylamine	*n*-BuNHMe	2.24	395	10.90
12	Azepane	$CH_2CH_2CH_2CH_2CH_2CH_2NH$	2.24	400	11.10
13	*N*-Methyl-*tert*-butylamine	*t*-BuNHMe	2.21	406	
14	*N*-Methylisopropylamine	*i*-PrNHMe	2.20	395	
15	*N*-Methylphenethylamine	$PhCH_2CH_2NHMe$	2.14	394	10.08
16	Dibutylamine	*n*-Bu_2NH	2.11	401	11.25
17	Piperazine	$CH_2CH_2NHCH_2CH_2NH$	2.42 (2.11)[c]	386	9.73 (9.43)[c]
18	1,2,3,4-Tetrahydroisoquinoline	[a]	2.04	376	9.41
19	Diisopropylamine	*i*-Pr_2NH	2.00	396	11.20
20	*N*-Methylallylamine	$H_2C{=}CHCH_2NHMe$	2.00	374	10.11
21	2,2,6,6-Tetramethylpiperidine	$Me_2CCH_2CH_2CH_2C(Me_2)NH$	1.88	422	11.07
22	*N*-Methylbenzylamine	$PhCH_2NHMe$	1.82	359	9.56
23	Morpholine	$CH_2CH_2OCH_2CH_2NH$	1.86 (1.78)[b]	360	8.49
24	Diallylamine	$(H_2C{=}CHCH_2)_2NH$	1.70	356	9.24
25	Thiomorpholine	$CH_2CH_2SCH_2CH_2NH$	1.69 (1.67)[b]	364	
26	*N*-Methylpropargylamine	$HC{\equiv}CCH_2NHMe$	1.64	336	
27	3-(Methylamino)propiononitrile	$N{\equiv}CCH_2CH_2NHMe$	1.50 (1.37)[b]	337	8.10
28	Dibenzylamine	$(PhCH_2)_2NH$	1.34	344	8.52
29	Bis(2-chloroethyl)amine	$(ClCH_2CH_2)_2NH$	1.19	330	
30	Thiazolidine	$CH_2SCH_2CH_2NH$	1.17 (1.10)[b]	282	6.22
31	(Methylamino)acetonitrile	$N{\equiv}CCH_2NHMe$	1.03 (0.66)[b]	270	
32	1,1,1,3,3,3-Hexamethyldisilazane	$(Me_3Si)_2NH$	−0.45	175	

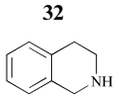
[a]  [b] Value corrected for the presence of a second hydrogen-bond acceptor site. [c] Statistically corrected.

Table 2 Evaluation of the amine hydrogen-bond basicity *K*(NH) in the case of amines with a second basic centre X

No.	Compound	*K*(total)[a,b]	$\Delta\nu$(OH···X)[c]	*K*(X)[a,d]	*K*(NH)[a,e]
4	$(MeOCH_2CH_2)_2NH$	225.0	147	9.8	215.2
23	Morpholine	71.9	149	12.6	59.3
25	Thiomorpholine	48.1	161	2.2	45.9
27	$N{\equiv}CCH_2CH_2NHMe$	31.7	81	8.6	23.1
30	Thiazolidine	14.4	152	2.1	12.3
31	$N{\equiv}CCH_2NHMe$	10.8	76	6.2	4.6

[a] dm^3 mol^{-1}. [b] Experimental value. [c] cm^{-1}. $\Delta\nu(OH\cdots X) = 3644 - \nu(OH\cdots X)$. [d] Calculated from the pK_{HB} *vs.* $\Delta\nu(OH\cdots X)$ relationships in the families of ethers,[30] thioethers,[31] or nitriles.[15] [e] $K(NH) = K(total) - K(X)$.

steric effects (*vide infra*), the passage from primary amines[21] XNH_2 to the corresponding secondary amines XNHMe (*e.g.* X = $N{\equiv}CCH_2CH_2$, $HC{\equiv}CCH_2$, $H_2C{=}CHCH_2$ or Et) increases pK_{HB} by +0.06 to +0.09 p*K* units (see Table 2 of ref. 21 and Table 1). However, the hydrogen-bond basicity, unlike the Brønsted basicity, remains weaker for secondary amines than for the oxygen base $(Me_2N)_3PO$ ($pK_{HB} = 3.56$,[1] $pK_a = -0.97$[32]).

In fact there are large differences[2] between the basicity orders given by the hydrogen-bond basicity scale pK_{HB} (or the similar log K_β scale)[33] and the Brønsted basicity scale pK_a. These have been attributed to the role of aqueous solvation on equilibrium (6)[34,35] and to differences in sensitivity of equilibria (1) and

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+ \qquad (6)$$

(6) to structural effects.[36] Family-dependent relationships have been suggested[2,33] between the pK_{HB} (or log K_β) and the pK_a scales. For the family of secondary amines, eqn. (7) shows that

$$pK_{HB} = 0.248\ pK_a - 0.473 \qquad (7)$$
$$n = 22,\ r = 0.862,\ s = 0.2,\ F = 58$$

only 74% (*i.e.* $100r^2$) of the pK_{HB} variance is explained by pK_a. The greatest deviations are observed downward for the hindered amines tetramethylpiperidine **21** and *i*-Pr_2NH **19**. They indicate that the pK_{HB} scale is more sensitive than the pK_a scale to the steric effects of the nitrogen substituents.

Comparison of the pK_{HB} and $\Delta\nu$(OH) scales [Fig. 2 and eqn. (8)] also points to the sensitivity of the pK_{HB} scale to the steric

$$pK_{HB} = 1.12\ [\Delta\nu(OH)/100] - 2.24 \qquad (8)$$
$$n = 32,\ r = 0.924,\ s = 0.24,\ F = 174$$

effects. We have already shown in the families of ethers[30] ROR′ and *ortho*-substituted pyridines[20] 2-RC_6H_4N that the pK_{HB}

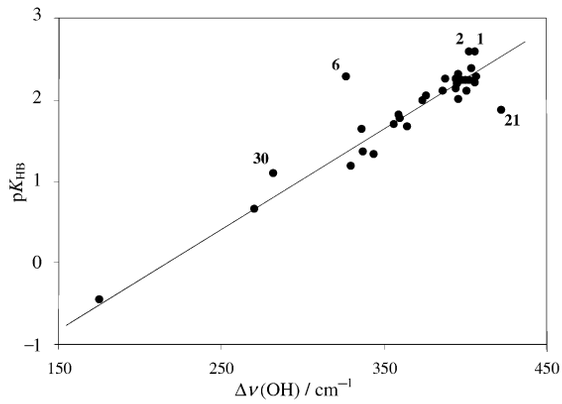


Fig. 2 Relationship between pK_{HB} and Δν(OH) showing the downward deviation of the hindered amine 2,2,6,6-tetraamethylpiperidine **21** and the deviation to the left of the strained amines 2-methylaziridine **6**, azetidine **2**, pyrrolidine **1**, thiazolidine **30**.

scale is more sensitive than the Δν(OH) scale to the steric effects of substituents R and R′. This is also the case for secondary amines RR′NH as illustrated by tetramethylpiperidine **21** (Fig. 2). This amine is the strongest hydrogen-bond base in the Δν(OH) scale (422 cm^{-1}) but is the weakest secondary alkylamine in the pK_{HB} scale (1.88). Clearly the frontal strain (steric hindrance in the complexes of hindered amines) between 4-fluorophenol and tetramethylpiperidine decreases markedly the equilibrium constant of reaction (1). Confirmation of this is given by *i*-Pr$_2$NH which has about the same Δν(OH) value (396 cm^{-1}) as Et$_2$NH (398 cm^{-1}) but a much weaker pK_{HB} value (2.00 instead of 2.25).

The strained cyclic amine 2-methylaziridine **6** also deviates significantly from the line of eqn. (8). This compound has a much lower Δν(OH) value (327 cm^{-1}) than expected from its pK_{HB} value (2.28). This deviation to the left of the pK_{HB} − Δν(OH) line (Fig. 2) has already been observed for strained cyclic ethers[30] and attributed to the greater sensitivity of Δν(OH) than pK_{HB} to the p character of the oxygen lone pairs. This explanation seems valid for cyclic amines since the deviations of strained cyclic amines to the left of the line of acyclic and six-membered cyclic amines increase in the order of the increasing s character of the nitrogen lone pair (*vide infra* for the calculation of the s character): 2-methylaziridine (Nsp$^{2.09}$) ⩾ azetidine (Nsp$^{4.43}$) > pyrrolidine (Nsp$^{5.16}$) > piperidine (Nsp$^{5.51}$) ~ 0.

In summary, the thermodynamic pK_{HB} and spectroscopic Δν(OH) scales of hydrogen-bond basicity give very similar basicity orders provided that the nitrogen lone pair keeps roughly the same hybridization state and is not too sterically hindered. By applying these conditions to our sample of 32 amines, *i.e.* by excluding strongly hindered amines **19** and **21** and strained cyclic amines **1**, **2**, **6** and **30**, the correlation coefficient between pK_{HB} and Δν(OH) rises to 0.986 (n = 26).

Field-inductive substituent effects

Alkyl groups have negligible field-inductive effects[37,38] (compared to hydrogen) and dimethylamine can be chosen as the parent compound for the study of field-inductive effects on the hydrogen-bond basicity of secondary amines. This basicity decreases strongly from dimethylamine (pK_{HB} = 2.26) to amines substituted by field-inductive electron-withdrawing groups such as N≡CCH$_2$NHMe (pK_{HB} = 0.66). Assuming the additivity of field-inductive effects, the hydrogen-bond base strengths of secondary amines are correlated by the field-inductive substituent parameter[37] σ_F (eqn. (9), Fig. 3). Dibenzylamine **28**, the diamine **5** and the methoxyamine **4** have not been included in this correlation. The downward deviation of dibenzylamine (Fig. 3) may be attributed to the steric effect of two benzyl groups. The upward deviations of **4** and **5** (Fig. 3) may be

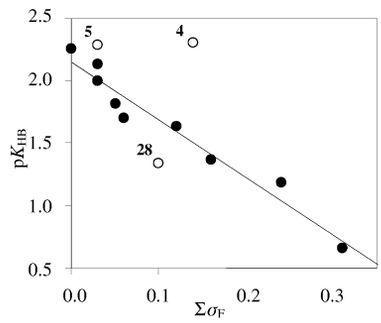


Fig. 3 Relationship between pK_{HB} and the field-inductive substituent constant σ_F showing the downward deviation of dibenzylamine **28** and the upward deviations of (MeOCH$_2$CH$_2$)$_2$NH **4** and MeNHCH$_2$-CH$_2$NHMe **5**.

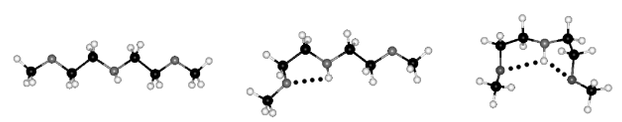
$$pK_{HB} = 2.16\ (\pm 0.06) - 4.63\ (\pm 0.39)\ \Sigma\sigma_F \qquad (9)$$
$$n = 9\ (\mathbf{7}, \mathbf{15}, \mathbf{20}, \mathbf{22}, \mathbf{24}, \mathbf{26}, \mathbf{28}, \mathbf{29}, \mathbf{31})$$
$$r = 0.976,\ s = 0.12,\ F = 141$$

explained by the formation of intramolecular hydrogen bonds NH · · · N in **5** and NH · · · O in **4**, which increase the hydrogen-bond basicity of the NH nitrogen. The next section is devoted to intramolecular hydrogen bonds.

Intramolecular hydrogen bonds

We have performed HF/6-31G** calculations in order to study the existence of intramolecular hydrogen bonds in our secondary amines. We have found that in the lowest electronic energy conformation of compounds **4**, **15**, **20**, **26**, **27**, and **31**, intramolecular hydrogen bonds NH · · · O (**4**), NH · · · π (Ph) (**15**), NH · · · π (C=C) (**20**), NH · · · π (C≡C) (**26**), and NH · · · π (C≡N) (**27**, **31**) are formed. Our calculations are supported by experimental results in the gas phase[39–42] and in CCl_4.[43] The phenyl, vinyl, and ethynyl groups are very weak hydrogen-bond acceptors[44] and the nitrile group is a significant hydrogen-bond acceptor only when the hydrogen-bond donor group points to the nitrogen lone pair.[45] So these N–H · · · π intramolecular hydrogen bonds do not perturb significantly the hydrogen-bond basicity of the amino nitrogen and the corresponding amines obey the pK_{HB} − σ_F correlation (*vide supra*).

Compound **4** can form zero (**4a**), one (**4b**), or two (**4c**) intramolecular hydrogen bonds. The form **4b** has the lowest electronic energy. The NH · · · O hydrogen-bond length of 2.44 Å is significantly shorter than the sum of the van der Waals radii of hydrogen (1.10 Å) and oxygen (1.52 Å). The hydrogen-bond cooperativity effect[46] predicts the nitrogen in **4b** to be a better intermolecular hydrogen-bond acceptor than in **4a**. Indeed the nitrogen electrostatic potential is more negative by 3.3 kcal mol^{-1} (1 cal = 4.184 J) in **4b** than in **4a** and the pK_{HB} value of **4** is the greatest of all the acyclic amines. It appears that the electron-withdrawing effect of the two MeOCH$_2$CH$_2$ groups ($\Sigma\sigma_F$ = +0.14) is overcompensated by the intramolecular hydrogen-bond cooperativity effect.



For the diamine **5**, the intramolecular hydrogen-bonded conformation **5b** is more stable (ΔE = 6.0 kJ mol^{-1}) than the zigzag conformation **5a**. Thus we also attribute the upward deviation of **5** in Fig. 3, *i.e.* the enhanced pK_{HB} value of the diamine, to the cooperativity effect of the intramolecular NH · · · N hydrogen bond. Indeed the electrostatic potential on N_1 in **5b** is more negative by 3.2 kcal mol^{-1} than in **5a**.

5a 5b

Polarizability and steric effects of alkyl groups

Because of their nearly zero field-inductive substituent constants,[37] alkyl groups are expected to influence the hydrogen-bond basicity mainly by their polarizability and steric effects. These two effects cause pK_{HB} to vary in two opposite directions.

The polarizability effect increases the hydrogen-bond basicity, possibly through the contribution of dispersion and induction forces to the hydrogen-bond energy. This effect is generally measured by the Hehre–Taft polarizability substituent constant[47] σ_α determined from polarization potential *ab initio* calculations: minus σ_α increases with the alkyl chain length and chain branching.

The steric effect is well-known to decrease the hydrogen-bond basicity, through the front-strain mechanism. Another steric mechanism could be the opening of the CNC angle caused by the repulsion of the alkyl substituents of nitrogen. Consequently, the p character of the nitrogen lone pair and therefore the nitrogen basicity should decrease. The steric effect can be measured roughly by the Taft[48] E_S or Charton[49] υ steric parameters, which are significantly correlated.

A dual substituent parameter equation $\rho_\alpha \sigma_\alpha + sE_S$ cannot unravel the two opposite effects because the parameters σ_α and E_S are mutually correlated: both increase with the size of the alkyl group. We can only say which effect prevails from the sign of the regression coefficient in a one-parameter equation. For example, a positive variation of pK_{HB} with $-\sigma_\alpha$ was found[21] for primary alkylamines and attributed to the predominance of polarizability effects.

The correlations of pK_{HB} and $\Delta\nu$(OH) with σ_α, represented in Fig. 4A and 4B, can be interpreted on this basis. For small alkyl groups, the pK_{HB} of secondary amines remains almost constant, because steric effects compensate for the polarizability effect, but for the more bulky groups, pK_{HB} falls because steric effects prevail in the end. The lesser sensitivity of $\Delta\nu$(OH) to steric effects is illustrated by the increase of $\Delta\nu$(OH) with $-\sigma_\alpha$ for most secondary amines, except the most hindered one, *i*-Pr_2NH **19**.

1,1,1,3,3,3-Hexamethyldisilazane

Fast scan FTIR spectrometry provides a good experimental pK_{HB} value for $(Me_3Si)_2NH$ in spite of the slow reaction with 4-fluorophenol. In agreement with the low Lewis basicity of silylamines,[50] we find a very low pK_{HB} value of -0.45. Since the concept of significant d-orbital participation in the Si–N bonding [51] has been abandoned,[52] the low hydrogen-bond basicity may be due to steric factors rather than to delocalization of the nitrogen lone pair. Indeed the steric substituent constant of $SiMe_3$ is exceptionally high ($\upsilon = 1.40$ compared to $\upsilon = 0.76$ for *i*-Pr)[49] and the substitution of the nitrogen by two $SiMe_3$ groups causes (*i*) severe steric hindrance toward 4-fluorophenol, and (*ii*) opening of the SiNSi angle (131.3°)[53] leading to a higher s character and lower basicity of the nitrogen lone pair.

Cyclic amines

The pK_{HB} of cyclic amines does not vary monotonically with the ring size, being maximum for pyrrolidine (five-membered ring) and azetidine (four-membered ring). This might be the result of two opposite effects, the steric and the hybridization effect. When the CNC angle (Table 3) decreases with the ring size, the steric hindrance of the nitrogen lone pair by the α-methylene groups must decrease, and consequently pK_{HB} increases. In contrast, the closure of the CNC angle decreases the p character of the nitrogen lone pair, reducing pK_{HB}. Table 3 contains our results of a nitrogen lone pair orbital analysis by the Natural Bond Orbital procedure.[55] The rehybridization of the nitrogen lone pair is significant mainly in 2-methylaziridine and this explains that the three-membered ring structure causes a definite decrease in $\Delta\nu$(OH) (327 cm^{-1} instead of *ca.* 400 cm^{-1} for other cyclic amines), the hydrogen-bond property most sensitive to the nitrogen hybridization (*vide supra*).

Table 3 CNC angles and % p character of the nitrogen lone pair of cyclic amines, calculated at the HF/6-31G** level

Amine no.	**6**	**2**	**1**	**3**	**12**
Ring size	3	4	5	6	7
CNC/°	61.0 (60.3)[a]	91.1 (91.2)[a]	105.6 (105.2)[a]	112.9 (109.8)[a]	114.2
% p[b]	67.5	81.5	83.7	84.6	85.0
pK_{HB}	2.28	2.59	2.59	2.38	2.24

[a] Experimental value.[54] [b] Calculated by the Natural Bond Orbital procedure.[55]

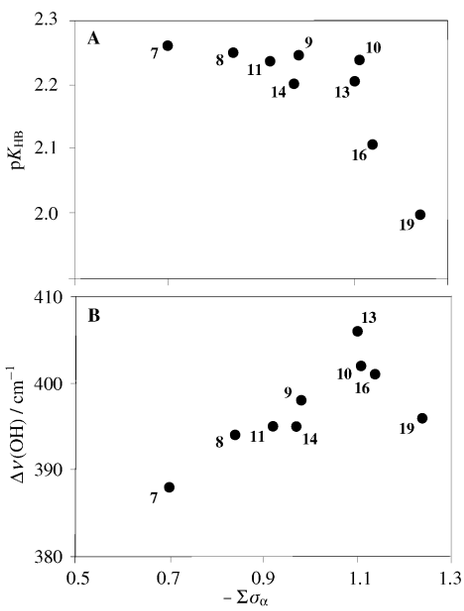


Fig. 4 Relationships between pK_{HB} (A) or $\Delta\nu$(OH) (B) and the polarizability substituent constant σ_α. Numbers refer to Table 1.

pK_{HB} prediction from electrostatic potentials

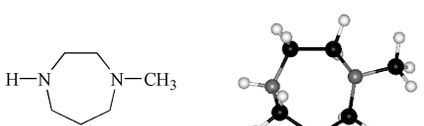
It would be useful to predict the pK_{HB} scale for experimentally inaccessible amines and for the treatment of polyfunctional ones. Today a reliable absolute calculation of the Gibbs energy of reaction (1) seems unlikely to be achieved. However Politzer *et al.*[56] have shown that approximate pK_{HB} values can be obtained from their relationships with $V_{S,\,min}$, the minimum electrostatic potential on the molecular surface defined by the 0.001 electron $bohr^{-3}$ contour of the electronic density. For 33 oxygen, nitrogen, sulfur, and π-bases, the correlation coefficient is 0.902 with $V_{S,\,min}$ calculated at the HF/6-31G*//HF/6-31G* level. By restricting the sample of base to the nitrile family ($n = 18$) but keeping a wide pK_{HB} range from ClC≡N (0.19) to Me_3N^+–N^-C≡N (3.24), Le Questel *et al.*[45] found a much higher correlation coefficient (0.989). In the same way, for 23 aromatic *N*-heterocycles Kenny[57] obtained $r = 0.981$ between log K_β and V_{min} calculated at the HF/6-31G*//HF/3-21G* level.

We have calculated $V_{S,\,min}$ in the region of the nitrogen lone pair at the HF/6-31G**//HF/6-31G** level for our 32 amines

and obtained the correlation (10). The correlation is less satisfactory for secondary amines than for nitriles [45] and aromatic *N*-heterocycles.[57] A possible explanation arises from the great conformational flexibility of aliphatic amines and the sensitivity of $V_{S,\ min}$ to the molecular conformation. $V_{S,\ min}$ is computed from the most stable conformation *in vacuo* at 0 K, while pK_{HB} corresponds to the mean basicity of the various amine conformers existing in CCl_4 at 298 K.

$$pK_{HB} = 0.081\ (-V_{S,\ min}) - 1.06 \qquad (10)$$
$$n = 32,\ r = 0.890,\ s = 0.28,\ F = 114$$

The usefulness of $V_{S,\ min}$ calculations can be illustrated by the example of 1-methyl-1,4-diazepane **33**. For an excess of **33**, the measured complexation constant of this diamine with 4-fluorophenol (263 $dm^3\ mol^{-1}$) corresponds to the sum of the two 1 : 1 equilibrium constants for the complexation of the phenol to NH and NMe. There is no spectroscopic means to unravel the two complexation constants *K*(NH) and *K*(NMe) because the broad and close *v*(OH · · · NH) and *v*(OH · · · NMe) IR bands of the two 1 : 1 complexes overlap. The calculation of $V_{S,\ min}$ (NH) and the good $pK_{HB}/V_{S,\ min}$ correlation for the six- and seven-membered alicyclic secondary amines of Table 1 (**3**, **12**, **17**, **21**, **23** and **25**) ($n = 6$, $r = 0.985$) provide a value of 116 $dm^3\ mol^{-1}$ for *K*(NH) which compares well with the value for piperazine (129).



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