PERKIN 2

Can semi-empirical calculations yield reasonable estimates of hydrogen-bonding basicity? The case of nitriles

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Descriptors of hydrogen-bond basicity (enthalpy of hydrogen-bond formation, hydrogen-bond length and minimum electrostatic potential of the base) have been calculated by the AM1 and PM3 methods for hydrogen-bond formation between 4-fluorophenol and numerous nitriles embracing a large range of structures and basicity. The AM1 method heavily underestimates the enthalpy of hydrogen-bond formation and the hydrogen-bond length compared to PM3, but, from a relative point of view, correlations between the hydrogen-bond basicity scale pK_{HB} and quantum-mechanical descriptors calculated with AM1 have a better predictive power. These correlations allow the extension of the pK_{HB} scale and the treatment of polyfunctional nitriles. The subtle effects of alkyl groups in alkyl cyanides, cyanamides and cyanoguanidines are correctly predicted. The antiulcer drug cimetidine is found to possess a super-basic nitrile group which could be hydrogen-bonded to an hydrogen-bond donor site of the H_2 receptor.

The development of a new basicity scale,[1,2] pK_{HB} [eqns. (1)–(3)],

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

$$K_f/\mathrm{dm^3\ mol^{-1}} = [\mathrm{Complex}]/[\mathrm{Base}][\mathrm{4\text{-}F\ C_6H_4OH}] \qquad (2)$$

$$\mathrm{p}K_{HB} = \log K_f = (\Delta G^0/\mathrm{kcal\ mol^{-1}})/1.36 \qquad (3)$$

related to the Gibbs energy ΔG^0 of formation of the hydrogen-bonded complexes in CCl_4 at 298 K, comes up against various experimental difficulties. Bases not commercially available, gaseous, insufficiently soluble in CCl_4 and/or self-associated cannot be easily studied. Moreover, in the case of polyfunctional bases, the IR,[3] UV[4] or ^{19}F NMR[1] methods used for the pK_{HB} measurements give only a global value and not the individual basicity of each function.

About 500 primary pK_{HB} values are now available for nitrogen,[5] oxygen,[6–9] sulfur[10] and carbon[11] bases. In this paper we calculate secondary pK_{HB} values for experimentally inaccessible bases by establishing correlations between pK_{HB} and quantum-mechanical descriptors of hydrogen-bond basicity. We have selected three descriptors: thermochemical, geometrical and electronical, respectively. The first descriptor of base strength is the enthalpy ΔH^0 [eqn. (4)] of the simple bimolecular hydrogen-bond reaction (1).

$$\Delta H^0 = \Delta H_f^0(\mathrm{complex}) - \Delta H_f^0(\mathrm{base}) - \Delta H_f^0(\mathrm{4\text{-}FC_6H_4OH}) \qquad (4)$$

Strong bases form strong *i.e.* short hydrogen bonds and we expect that the hydrogen bond length $R(\mathrm{B\cdots H})$, might be another useful descriptor of hydrogen-bond basicity. The well-established importance of the electrostatic component in hydrogen bonding gives the base electrostatic potential for the last descriptor; following one of us,[12] we have selected $V_{s,min}$, the most negative value of the electrostatic potential on the molecular surface of the base.

A reliable absolute calculation of ΔH^0, $R(\mathrm{B\cdots H})$ and $V_{s,min}$ by *ab initio* methods requires the use of a large basis set, taking account of electron correlation and, for energies, correcting the basis set superposition error and introducing zero-point energies and thermal corrections. This seems unlikely to be realized for extended sets of relatively large molecules. As an alternative to *ab initio* methods we have turned to semi-empirical quantum-mechanical methods which dramatically reduce the computational time. In many cases it has been established that errors due to the approximate nature of quantum-mechanical methods are largely transferable within structurally related series and that relative values of calculated descriptors can be meaningful even though their absolute values are not directly applicable. This is the reason why we have divided the bases into families with a common hydrogen-bond acceptor function *e.g.* ethers, pyridines, ketones, sulfoxides or nitriles. This first paper is devoted to nitriles [equilibrium (5)] because this family

$$\mathrm{X{-}C{\equiv}N + 4\text{-}FC_6H_4OH \rightleftharpoons 4\text{-}FC_6H_4OH\cdots N{\equiv}C{-}X} \qquad (5)$$

present numerous advantages for determining whether semi-empirical calculations have definite utilities for estimating the hydrogen-bond basicity.

Firstly, primary pK_{HB} values have been measured[13–15] for a great number of nitriles covering a wide range of basicity from the weak $CCl_3C{\equiv}N$ (−0.26) to the strong zwitterionic base $Bu_3N^+N^-C{\equiv}N$ (3.24). In this set we have been able to select 22 nitriles bearing very diversified X substituents with the first atom as different as C_{sp^3}, C_{sp^2}, C_{sp}, N_{sp^3}, N_{sp^2}, Si, S, O and Br.

Secondly, it is well-established[13–15] that the sp nitrogen lone pair is the hydrogen-bond acceptor site and that the geometry of the $\mathrm{X{-}C{\equiv}N\cdots H{-}A}$ complexes is quasi-linear. Such a structure guarantees that the X substituents will not sterically interfere with the hydrogen-bond donor approaching the nitrogen lone pair. This should prevent abnormal entropy contributions to ΔG^0 and permit a linear pK_{HB} *vs.* ΔH^0 relationship for equilibrium (5).

Finally, the knowledge of many of the physical properties of the molecules involved in equilibrium (5) will help in the calculations and the analysis of the results. An important thermochemical property, ΔH^0_{298}, has been determined.[19] From an electrical point of view, the dipole moments of many nitriles[20,21] and of their complexes with 4-fluorophenol[22] are known. As far as the geometry is concerned, the gas-phase structure of many nitriles[23] and the crystalline structure of 4-cyanophenol[24] have been found in the literature. In this crystal, hydrogen bonds form infinite chains $\mathrm{\cdots N{\equiv}CC_6H_4OH\cdots N{\equiv}CC_6H_4OH\cdots}$,

Table 1 The experimental pK_{HB} scale of nitriles, and the AM1 and PM3 calculated descriptors of the nitrile hydrogen-bond basicity: ΔH^0_{298} /kcal mol^{-1}[a] R(N···H)/Å[b] and $V_{s,min}$/kcal mol^{-1}[a]

				$-\Delta H^0_{298}$		R(N···H)		$-V_{s,min}$	
No.	Compound	Formula	pK_{HB}[c]	AM1	PM3	AM1	PM3	AM1	PM3
1	Trichloroacetonitrile	CCl_3CN	−0.26	1.15	1.92	2.7707	1.8397	35.02	46.83
2	Cyanogen bromide	BrCN	0.19	1.43	2.91	2.7486	1.8281	40.86	55.55
3	Ethynyl cyanide	HC≡CCN	0.30	1.70	2.96	2.7296	1.8279	44.57	56.11
4	Chloroacetonitrile	$ClCH_2CN$	0.39	1.67	2.78	2.7232	1.8303	44.58	54.97
5	4-Chlorobenzonitrile	4-ClC_6H_4CN	0.66[d]	1.84	3.21	2.7145	1.8247	46.87	58.00
6	Acrylonitrile	H_2C=CHCN	0.70	1.97	3.31	2.7073	1.8240	49.70	59.71
7	4-Fluorobenzonitrile	4-FC_6H_4CN	0.72	1.84	3.11	2.7138	1.8255	46.88	57.04
8	Methylthiocyanate	MeSCN	0.73	1.85	2.92	2.7100	1.8279	47.90	55.49
9	Phenyl cyanate	PhOCN	0.77	1.75	3.21	2.7186	1.8265	44.99	59.31
10	Benzonitrile	PhCN	0.80	1.99	3.39	2.7075	1.8229	49.45	59.78
11	3-Toluonitrile	3-MeC_6H_4CN	0.85	2.02	3.44	2.7058	1.8224	49.94	60.28
12	Acetonitrile	MeCN	0.91	2.02	3.38	2.7023	1.8238	50.73	60.45
13	Trimethylsilylcyanide	Me_3SiCN	0.93	2.01	4.30	2.6929	1.8110	49.98	64.28
14	4-Methoxybenzonitrile	4-$MeOC_6H_4CN$	0.97	2.07	3.57	2.7016	1.8209	50.67	61.18
15	Trimethylacetonitrile	Bu^tCN	0.99[e]	2.11	3.51	2.6968	1.8219	51.79	61.19
16	Cyclopropylcyanide	c-PrCN	1.03	2.04	3.42	2.6999	1.8229	51.07	60.88
17	4-Dimethylaminobenzonitrile	4-$Me_2NC_6H_4CN$	1.25[d]	2.28	3.73	2.6901	1.8192	53.91	62.67
18	Dimethylcyanamide	Me_2NCN	1.56	2.22	3.70	2.6898	1.8209	52.73	63.10
19	*trans*-3-Dimethylaminoacrylonitrile	Me_2NCH=CHCN	1.70	2.49	4.07	2.6713	1.8158	57.95	65.86
20	N^1,N^1-Dimethyl-N^2-cyanoformamidine	Me_2NCH=NCN[g]	2.09	2.52	4.26	2.6685	1.8150	57.06	66.71
21	N^1,N^1-Dimethyl-N^2-cyanoacetamidine	Me_2NCMe=NCN[g]	2.24	2.62	4.45	2.6619	1.8129	58.40	67.82
22	Trimethylammoniocyanamidate	Me_3N^+–N^-CN	3.24[f]	3.65	6.31	2.5917	1.7968	73.83	82.55

[a] 1 cal = 4.184 J. [b] 1 Å = 10^{-10} m. [c] Refs. 13 and 14. [d] This work. [e] There was a typing error in ref. 13. [f] Ref. 15; value for Bu_3N^+–N^-CN. [g] Stereoisomer *E*.

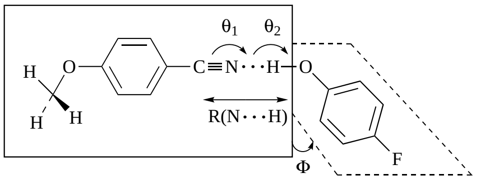


Fig. 1 The AM1 geometry minimisation procedure for the 4-methoxybenzonitrile–4-fluorophenol hydrogen-bond complex. Starting from the optimised AM1 geometry of 4-methoxybenzonitrile (quasi C_s) and 4-fluorophenol (quasi C_s) and from $\theta_1 = \theta_2 = 180°$, R(N···H) = 2 Å and Φ = 0, 90 or 180° a minimum value of ΔH^0_{298} is found for $\theta_1 = 165.6°$, $\theta_2 = 174.6°$, R(N···H) = 2.70 Å and $\Phi = 94.8°$.

giving a guess as to the starting geometry of the fragment $-C_6H_4OH$···N≡C– in the geometry optimisation procedure. Moreover, IR frequency shifts of the OH stretching upon complexation have been studied,[13–15] allowing a quantitative estimate of the –OH lengthening upon hydrogen-bond formation.

In this paper, we have computed ΔH^0_{298}, R(N···H) and $V_{s,min}$ for the 22 nitriles in Table 1 with the AM1 and PM3 methods, since there is no general agreement for deciding which method provides the best description of hydrogen-bonded systems.[25,26] However, the AM1 computed properties give significantly better correlations with the experimental pK_{HB} (*vide infra*) and this method has therefore been selected for the correlation applications. These applications concern firstly the pK_{HB} calculations of the gaseous nitriles HC≡N, FC≡N, N≡C–C≡N and CF_3C≡N, of the insoluble and self-associated cyanamide H_2NC≡N and of the polyfunctional 4-cyanopyridine which accepts hydrogen-bonding not only on the nitrile nitrogen but also on the pyridine nitrogen. We will also show that AM1 calculations are able to reproduce very subtle effects of alkyl groups in the alkyl cyanides Alk–C≡N, the alkylcyanamides $(Alk)_2N$–C≡N and the cyanoamidines Me_2N–C(Alk)=N–C≡N. We will also analyse AM1 calculations on the cyanoguanidines $(R_2N)_2C$=N–C≡N, in order to throw light on the hydrogen-bond basicity of an important antihistaminic molecule, cimetidine.

Calculations

All calculations were performed using the Spartan 4.0 program package[27] running on a Silicon Graphics Indy workstation.

The geometries of both monomers (nitriles and 4-fluorophenol) were fully optimised starting from the experimental structures given by microwave[28] or X-ray spectroscopy, when available. The geometries of the hydrogen-bonded complexes were completely optimised. The starting geometry of complexation is schematically illustrated in Fig. 1 for the complex of 4-fluorophenol with 4-methoxybenzonitrile. In each case the θ_1 (C≡N···H) and θ_2 (N···HO) angles were set to 180°, whereas the starting R(N···H) distance was fixed at 2 Å, according to the structure of the 4-cyanophenol homodimer. When necessary we have tried various Φ angles (0, 90 and 180°), adapted to the C_s, C_{2v} or C_{3v} nitrile symmetry, but we have not explored the potential energy surface in detail. Calculations of electrostatic potential energy surfaces were performed using AM1 or PM3 geometry optimised structures. These surfaces were mapped onto the electron density surfaces (0.001 e/ua isosurface) at high resolution.

AM1 and PM3 are parametric methods including finite temperature effects and zero point energy. They consequently give gas-phase ΔH^0_{298} values.

Results and discussion

The 22 nitriles selected for this investigation are shown in Table 1, together with the ΔH^0_{298} of hydrogen-bond formation [eqn. (4)], the hydrogen-bond length R(N···H) and the minimum electrostatic potential, $V_{s,min}$. This minimum is always found on the nitrogen of the nitrile function.

Reliability of the AM1 and PM3 methods for calculating molecular properties of nitriles and their hydrogen-bonded complexes

This section studies the accuracy of the AM1 and PM3 methods in calculating the nitrile bond lengths R(C≡N) in the free bases, the dipole moments μ(XC≡N) of the free nitriles, the enthalpies of hydrogen formation ΔH^0_{298}, the dipole moments of the complexes μ(XC≡N···HOC_6H_4F), the hydrogen-bond length R(N···H) and the lengthening ΔR(OH) of the OH bond length upon hydrogen bonding.

***R*(C≡N).** If we except the case of MeSC≡N and Me_3SiC≡N, all the calculated distances are too long with AM1 (Table 2).

Table 2 Experimental[a] and AM1, PM3 calculated C≡N distances/Å

No.	Compound	AM1	PM3	Exp.
23	HCN	1.1602	1.1557	1.153
24	CF_3CN	1.1587	1.1551	1.154
12	MeCN	1.1634	1.1594	1.156
2	BrCN	1.1638	1.1547	1.157
25	FCN	1.1651	1.1585	1.157
6	$H_2C{=}CHCN$	1.1640	1.1600	1.157
10	PhCN	1.1635	1.1597	1.158
26	NC–CN	1.1625	1.1591	1.158
15	Bu^tCN	1.1622	1.1585	1.159
27	H_2NCN	1.1696	1.1633	1.160
3	HC≡CCN	1.1646	1.1608	1.161
16	c-PrCN	1.1631	1.1591	1.161
8	MeSCN	1.1698	1.1649	1.170
13	Me_3SiCN	1.1649	1.1600	1.170

[a] Ref. 23.

Table 3 Experimental[a] and AM1, PM3 calculated dipole moments (D) of nitriles

No.	Compound	AM1	PM3	Exp.[b]
24	CF_3CN	0.03	0.32	1.26 (gas)
1	CCl_3CN	1.17	1.74	2.00 (alkane)
25	FCN	1.21	1.63	2.17 (gas)
5	$4\text{-}ClC_6H_4CN$	2.10	2.77	2.64 (C_6H_6)
7	$4\text{-}FC_6H_4CN$	1.78	1.99	2.70 (CCl_4)
2	BrCN	2.07	3.46	2.94 (gas)
23	HCN	2.36	2.70	2.95 (gas)
4	$ClCH_2CN$	2.45	2.75	3.00 (alkane)
3	HC≡CCN	3.04	3.33	3.60 (gas)
15	Bu^tCN	3.02	3.32	3.70 (CCl_4)
16	c-PrCN	3.04	3.31	3.78 (C_6H_6)
6	$H_2C{=}CHCN$	3.00	3.25	3.90 (gas)
12	MeCN	2.89	3.21	3.92 (gas)
9	PhOCN	3.35	3.64	3.93 (C_6H_6)
8	MeSCN	3.05	3.40	4.00 (gas)
13	Me_3SiCN	2.68	3.69	4.06 (CCl_4)
10	PhCN	3.34	3.61	4.14 (gas)
11	$3\text{-}MeC_6H_4CN$	3.51	3.79	4.21 (C_6H_6)
27	H_2NCN	3.37	3.49	4.30 (gas)
28	$CH_2(CH_2)_3CH_2NCN$	3.77	3.97	4.61 (CCl_4)
29	Et_2NCN	3.64	3.89	4.63 (CCl_4)
14	$4\text{-}MeOC_6H_4CN$	3.95	4.20	4.76 (CCl_4)
18	Me_2NCN	3.55	3.72	4.77 (gas)
30	$CH_2(CH_2)_2CH_2NCN$	3.88	3.98	4.85 (C_6H_6)
19	$Me_2NCH{=}CHCN$	5.09	4.79	6.12 (C_6H_6)
17	$4\text{-}Me_2NC_6H_4CN$	5.35	4.91	6.39 (CCl_4)
20	$Me_2NCH{=}NCN$	5.96	5.64	6.59 (C_6H_6)
21	$Me_2NC(Me){=}NCN$	6.06	5.71	7.04 (C_6H_6)

[a] Refs. 20 and 21. [b] When μ has been measured in several physical states we have selected our value in the order: gas > alkane > CCl_4 > C_6H_6.

Table 4 Experimental[a] and AM1, PM3 calculated hydrogen bond enthalpies $-\Delta H^0_{298}$ /kcal mol^{-1} for the interaction of 4-fluorophenol with nitriles

No.	Compound	AM1	PM3	Exp.
5	$4\text{-}ClC_6H_4CN$	1.84	3.21	3.82
4	$ClCH_2CN$	1.67	2.78	3.90
10	PhCN	1.99	3.39	4.18
6	$H_2C{=}CHCN$	1.97	3.31	4.21
14	$4\text{-}MeOC_6H_4CN$	2.07	4.33	3.57
12	MeCN	2.02	4.64	3.38
15	Bu^tCN	2.11	3.51	4.76
17	$4\text{-}Me_2NC_6H_4CN$	2.28	3.73	4.90
18	Me_2NCN	2.22	3.70	5.35
19	$Me_2NCH{=}CHCN$	2.49	4.07	5.62
20	$Me_2NCH{=}NCN$	2.52	4.26	5.95

[a] In CCl_4. Ref. 19. $\Delta H^0_{298} = RT^2$ (d log K_c/dT) $- \alpha RT^2$. The last term involves the thermal coefficient of CCl_4 α.

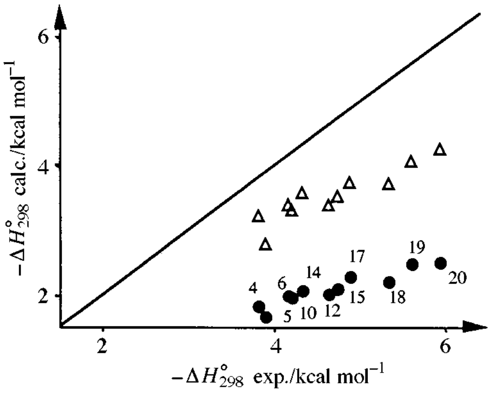


Fig. 2 Relationship between the AM1 (●) and PM3 (△) calculated hydrogen-bond enthalpies $-\Delta H^0_{298}$ for the interaction of 4-fluorophenol with nitriles and their experimental values (ref. 19). The numbers refer to Table 4. The line of slope 1 is indicated.

The mean absolute error is 0.005 Å. With PM3, the calculated distances are closer to the experimental values, the mean absolute error being of 0.0002 Å.

μ(XC≡N). We have been able to collect (Table 3) 28 dipole moments of nitriles ranging from 1.2–7 Debyes (1 D = 3.336 × 10^{-30} Cm). AM1 values are always too low with a mean absolute error of 0.87 D, but 97.5% of the variance of μ is correctly explained by AM1 calculations [eqn. (6)]. If we except the case

$$\mu(\text{exp}) = 0.885 + 0.994\,\mu\,(\text{AM1}) \qquad (6)$$
$$n = 28 \quad r^2 = 0.975 \quad s = 0.22\ \text{D}$$

of 4-ClPhC≡N and BrC≡N, the dipole moments calculated with PM3 are also too low but closer to the experimental values, the mean absolute error being 0.60 D. The predictive power of PM3 is, however, inferior to AM1 since only 91.2% of the variance is correctly explained by this method [eqn. (7)]. In eqns. (6) and

$$\mu(\text{exp}) = 0.794 + 1.151\,\mu\,(\text{PM3}) \qquad (7)$$
$$n = 28 \quad r^2 = 0.918 \quad s = 0.40\ \text{D}$$

(7), n, r and s are, respectively, the number of data, the correlation coefficient and the standard deviation.

ΔH^0_{298} [for reaction (5)]. We have determined elsewhere[19] accurate enthalpies for the hydrogen-bond formation of 11 nitriles with 4-fluorophenol, in CCl_4, a poorly solvating medium. Table 4 and Fig. 2 show that the AM1 hydrogen bond enthalpies are seriously underestimated; however, 89% of the variance of ΔH^0_{298} is correctly predicted by the AM1 method [eqn. (8)]. The hydrogen bond enthalpies calculated by PM3 are

$$-\Delta H^0_{298}(\text{exp}) = -0.728 + 2.574\,(-\Delta H^0_{298},\ \text{AM1}) \qquad (8)$$
$$n = 11 \quad r^2 = 0.890 \quad s = 0.25\ \text{kcal mol}^{-1}$$

much closer to the experimental values (Fig. 2), but, relatively, the predictive power of this method is inferior to AM1 since 84% of the variance of ΔH^0_{298} is predicted [eqn. (9)].

$$-\Delta H^0_{298}(\text{exp}) = -0.910 + 1.585\,(-\Delta H^0_{298},\ \text{PM3}) \qquad (9)$$
$$n = 11 \quad r^2 = 0.839 \quad s = 0.30\ \text{kcal mol}^{-1}$$

$\mu(4\text{-}FC_6H_4OH\cdots N{\equiv}CX)$. The dipole moments of hydrogen-bonded complexes between 4-fluorophenol and 10 nitriles have been measured[22] in CCl_4 (Table 5). The reliability of these values is low since they strongly depend on the accuracy of the determination of the hydrogen-bonding formation constants required for the calculation of the concentrations of the different species of reaction (5). Both the absolute (Table 5) and relative [eqn. (10)] predictions seem unsatisfactory

Table 5 Experimental[a] and AM1, PM3 dipole moments (D) of hydrogen-bonded complexes between 4-fluorophenol and nitriles

No.	Compound	AM1	PM3	Exp.
1	CCl_3CN	3.28	5.03	2.50
31	C_6F_5CN	3.64	5.01	2.90
7	4-FC_6H_4CN	4.16	5.67	3.20
8	MeSCN	5.35	6.69	3.60
12	MeCN	5.14	6.62	4.00
32	c-PenCN	5.34	6.87	4.00
11	3-MeC_6H_4CN	5.91	7.51	4.10
10	PhCN	5.72	7.31	4.40
33	Ph_2PCN	5.48	7.63	4.70
13	Me_3SiCN	5.01	7.44	4.80

[a] In CCl_4. Ref. 22.

$$\mu(\text{exp}) = 0.335 + 0.711\,\mu\,(\text{AM1}) \qquad (10)$$
$$n = 10\ r^2 = 0.700\ s = 0.44\ \text{D}$$

with AM1. The dipole moments of the complexes calculated using PM3 are overestimated but 90% of the variance is correctly predicted with this method [eqn. (11)].

$$\mu(\text{exp}) = -0.943 + 0.724\,\mu\,(\text{PM3}) \qquad (11)$$
$$n = 10\ r^2 = 0.904\ s = 0.25\ \text{D}$$

***R*(N···H).** By comparing an experimental value of 1.97 Å found in the crystal of self-associated 4-cyanophenol[24] and the AM1 value of 2.70 Å calculated for the complex of 4-methoxybenzontrile with 4-fluorophenol, we can conclude that the AM1 overestimates the hydrogen-bond distance by *ca.* 0.70 Å. The same complex studied with PM3 gives a hydrogen-bond distance of 1.82 Å close to the experimental value.

Δ*R*(OH). Hydrogen bonding weakens the O–H bond of 4-fluorophenol and increases the distance between the oxygen and hydrogen nuclei. This increase can be deduced from the relative decrease of the OH stretching frequency with respect to the gas phase by means of the correlation (12):[28]

$$\Delta R(\text{OH})/\text{Å} = 0.28\ \Delta\nu(\text{OH})/\nu_g(\text{OH}) \qquad (12)$$

We have already measured[13–15] the frequency shifts Δν(OH) of 4-fluorophenol upon hydrogen bonding with nitriles. Thus we are able to estimate Δ*R*(OH) according to the correlation (12) and to compare, in Table 6, these 'experimental' values to the AM1 and PM3 calculated OH lengthening. We find AM1 OH lengthening to run one-tenth to one-fifteenth of the 'experimental' value. However, 90% of the variance of Δ*R*(OH) is explained by the AM1 method [eqn. (13)]. The lengthening of

$$\Delta R(\text{OH, estimated from IR}) =$$
$$-0.0098 + 18.856\,[\Delta R(\text{OH}),\text{AM1}] \qquad (13)$$
$$n = 19\ r^2 = 0.895\ s = 0.0021\ \text{Å}$$

the OH bond calculated by PM3 ranges from twice (CCl_3CN) to half (Me_3N^+N–CN) of the experimental value. However, the predictive power of this method is inferior since on the nineteen nitriles studied, 79% of the variance is explained by PM3 [eqn. (14)].

$$\Delta R(\text{OH, estimated from IR}) =$$
$$-0.0772 + 5.549\,[\Delta R(\text{OH}),\text{PM3}] \qquad (14)$$
$$n = 19\ r^2 = 0.789\ s = 0.0029\ \text{Å}$$

In summary, the AM1 method underestimates heavily the absolute strength of the hydrogen bond between 4-fluorophenol and nitriles, giving for example much too long hydrogen bonds and much too low hydrogen bond enthalpies. This is not the case with PM3, which gives absolute values of hydrogen bonds or hydrogen-bond enthalpies in better agreement with the experimental values. However, for all the correlations established, if we except those involving the dipole moments of the hydrogen bonded complexes, the predictive power of AM1 is significantly better. The satisfactory correlation coefficients of eqns. (6), (8) and (13) give hope of establishing good correlations between pK_{HB} and electrostatic [eqn. (6)], thermochemical [eqn. (8)] and geometrical [eqn. (13)] descriptors of hydrogen-bond basicity calculated by the AM1 method.

Table 6 Δ*R*(OH), the OH lengthening of 4-fluorophenol (in Å) upon hydrogen bonding with nitriles, estimated from OH infrared shifts and AM1, PM3 calculated

No.	Compound	AM1	PM3	Exp.
1	CCl_3CN	0.0009	0.0153	0.0090
2	BrCN	0.0011	0.0164	0.0115
4	$ClCH_2CN$	0.0011	0.0162	0.0126
6	H_2C=CHCN	0.0014	0.0168	0.0148
7	4-FC_6H_4CN	0.0013	0.0166	0.0150
8	MeSCN	0.0013	0.0165	0.0150
9	PhOCN	0.0012	0.0164	0.0151
10	PhCN	0.0015	0.0169	0.0156
12	MeCN	0.0014	0.0168	0.0156
13	Me_3SiCN	0.0015	0.0185	0.0162
14	4-$MeOC_6H_4CN$	0.0015	0.0172	0.0171
15	Bu^tCN	0.0015	0.0170	0.0167
16	c-PrCN	0.0014	0.0170	0.0167
17	4-$Me_2NC_6H_4CN$	0.0016	0.0174	0.0191
18	Me_2NCN	0.0017	0.0171	0.0209
19	Me_2NCH=CHCN	0.0018	0.0178	0.0224
20	Me_2N CH=NCN	0.0017	0.0178	0.0250
21	Me_2N C(Me)=NCN	0.0017	0.0180	0.0264
22	$Me_3N^+N^-CN$	0.0023	0.0199	0.0361

[a] Calculated from the equation Δ*R*(OH) = 0.28 [3661 − ν(OH···)]/3661. 3661 cm^{-1} is the wavenumber of the OH stretching of free gaseous 4-fluorophenol. ν(OH···) is the wavenumber of the OH stretching of the hydrogen-bonded 4-fluorophenol in CCl_4, taken from refs. 13–15.

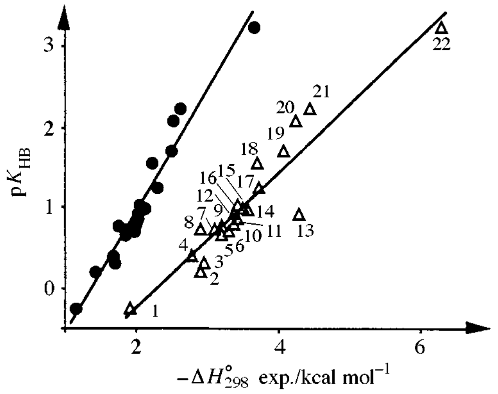


Fig. 3 Relationship between the thermodynamic hydrogen-bond basicity scale pK_{HB} and the AM1 (●), PM3 (△) calculated hydrogen-bond enthalpies. Numbers refer to Table 1.

Correlation of pK_{HB} with AM1 and PM3 descriptors of hydrogen-bond basicity

Eqns. (15)–(20) show that the experimental scale of hydrogen-bond basicity, pK_{HB}, is significantly better correlated with the AM1 calculated enthalpy of hydrogen-bond formation [eqn. (15) and Fig. 3], the AM1 calculated hydrogen-bond lengths

$$pK_{HB} = -2.072 + 1.511\,[(-\Delta H^0_{298}),\ \text{AM1}] \qquad (15)$$
$$n = 22\ r^2 = 0.951\ s = 0.17$$

[eqn. (16)] and the AM1 minimum electrostatic potential on the

$$pK_{HB} = 58.936 - 21.439\,[R(\text{N}\cdots\text{H}),\ \text{AM1}] \qquad (16)$$
$$n = 22\ r^2 = 0.944\ s = 0.18$$

nitrile nitrogen [eqn. (17)], than with the same theoretical

$$\mathrm{p}K_{\mathrm{HB}} = -3.888 + 0.098\,[(-V_{\mathrm{s,min}}),\ \mathrm{AM1}] \quad (17)$$
$$n = 22\ r^2 = 0.934\ s = 0.20$$

descriptors calculated using PM3 [eqns. (18)–(20) and Fig. 3].

$$\mathrm{p}K_{\mathrm{HB}} = -1.979 + 0.852\,[(-\Delta H^0_{298}),\ \mathrm{PM3}] \quad (18)$$
$$n = 22\ r^2 = 0.881\ s = 0.27$$

$$\mathrm{p}K_{\mathrm{HB}} = 151.888 - 82.802\,[R(\mathrm{N}\cdots\mathrm{H}),\ \mathrm{PM3}] \quad (19)$$
$$n = 22\ r^2 = 0.830\ s = 0.32$$

$$\mathrm{p}K_{\mathrm{HB}} = -5.587 + 0.109\,[(-V_{\mathrm{s,min}}),\ \mathrm{PM3}] \quad (20)$$
$$n = 22\ r^2 = 0.910\ s = 0.23$$

This reinforces us in the choice of the AM1 method for the remaining calculations.

The best descriptor of the nitrile hydrogen-bond basicity is the calculated hydrogen-bond enthalpy. This might mean that the large changes in pK_{HB} (*i.e.* ΔG^0) and ΔH^0_{298} are nearly independent of entropy changes in the nitrile family. This is not unexpected since Arnett has found[3] an isoentropic behaviour for several families of bases. Among electrostatic descriptors we have also tried the charge on the nitrile nitrogen, but we find that $V_{\mathrm{s,min}}$ ($r^2 = 0.934$) better predicts pK_{HB} than the Mulliken charge ($r^2 = 0.902$) or the charge calculated from electrostatic potentials ($r^2 = 0.740$).

Calculation of secondary pK_{HB} values. We can use eqn. (15) for the calculation of pK_{HB} values difficult to obtain experimentally. Table 7 shows the values calculated for $CF_3C{\equiv}N$, $N{\equiv}C{-}C{\equiv}N$, $FC{\equiv}N$, $H_2NC{\equiv}N$ and 4-cyanopyridine. The $CF_3C{\equiv}N$ value (−0.89) and the $FC{\equiv}N$ value (−0.11) seem rather low compared, respectively, to CCl_3CN (−0.26) and $BrC{\equiv}N$ (0.19), but lie in the right direction. The value of 0.68 for $HC{\equiv}N$ compares well with the value of 0.91 for $MeC{\equiv}N$ and with a pK_{HB} difference of 0.35 between HCOOMe and MeCOOMe.[7] The value of 1.12 for $H_2NC{\equiv}N$ seems slightly too low compared to another secondary value of 1.38 obtained from measurements in CH_2Cl_2.[29]

The value of 0.47 for the nitrile group of 4-cyanopyridine agrees with the value of 0.48 calculated from a correlation between pK_{HB} and the frequency shift of the OH band of 4-fluorophenol upon complexation.[14] 4-Cyanopyridine constitutes a good example of the usefulness of theoretical calculations for predicting the basicity of each site of polyfunctional molecules. As a matter of fact, the usual experimental methods of K_{f} determination yield only a global constant, since the equilibria (21) and (22) always occur simultaneously.

Table 7 Secondary pK_{HB} values calculated from eqn. (15)

No.	Compound	Remark	$-\Delta H^0_{298}$ [a]	pK_{HB}
24	CF_3CN	gaseous	0.78	−0.89
26	NC–CN	gaseous	0.97	−0.61 [b]
25	FCN	gaseous	1.30	−0.11
23	HCN	gaseous	1.82	0.68
27	H_2NCN	insoluble	2.11	1.12
34	4-cyanopyridine	polyfunctional	1.68 [c]	0.47 [c]

[a] kcal mol^{-1}. Calculated by the AM1 method. [b] For one nitrile group. Add log 2 for the global basicity. [c] These values refer only to the basicity of the nitrile function.

$$4\text{-}FC_6H_4OH + NC_5H_4C{\equiv}N \rightleftharpoons 4\text{-}FC_6H_4OH\cdots NC_5H_4C{\equiv}N \quad (21)$$

$$4\text{-}FC_6H_4OH + NC_5H_4C{\equiv}N \rightleftharpoons 4\text{-}FC_6H_4OH\cdots N{\equiv}CC_5H_4N \quad (22)$$

We have found K_{f} (global) = K_{f} (21) + K_{HB} (22) = 11.4 $dm^3\ mol^{-1}$. The theoretical nitrile value $K_{\mathrm{f}}(22) = 10^{0.47} = 3\ dm^3\ mol^{-1}$ allows the determination of the pyridine basicity:

$$K_{\mathrm{f}}(21) = 11.4 - 3 = 8.4\ \mathrm{dm^{-3}\ mol^{-1}}.$$

Can AM1 calculations predict the subtle effects of alkyl groups on the hydrogen-bond basicity of cyanides, cyanamides and cyanoamidines?

The electrical effects of alkyl groups (field-inductive, polarizability and/or hyperconjugation) are long-standing topics of debate.[30–33] This debate probably stems from these effects being small and possibly outweighed by larger effects such as steric or solvation effects. In the field of hydrogen-bond basicity we have found indications[11,13,34] that for functions not sensitive to steric effects and in the poorly solvating medium CCl_4, alkyl groups are always electron-releasing relative to hydrogen and that the branching of methyl increases further the electron-donating mechanism in the order:

$$\text{1-Adam} > \mathrm{Bu}^t > \mathrm{Pr}^i > \mathrm{Et} > \mathrm{Me} > \mathrm{H}$$

However, many pK_{HB} differences between alkyl groups fall within experimental errors (±0.02 to ±0.05) and it seems important to obtain theoretical confirmations. Table 8 shows that AM1 semi-empirical calculations provide useful results for correcting, confirming and/or predicting pK_{HB} in various series of nitriles.

In the series of alkyl cyanides $RC{\equiv}N$, the theoretical order of basicity follows clearly the branching sequence:

$$\text{1-Adam} > \mathrm{Bu}^t > \mathrm{Pr}^i > \mathrm{Et} > \mathrm{Me} > \mathrm{H}$$

On the contrary, the pK_{HB} order[13] is less clear-cut:

$$\text{1-Adam} \sim \mathrm{Bu}^t = \mathrm{Pr}^i > \mathrm{Et} > \mathrm{Me} > \mathrm{H}$$

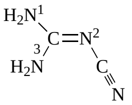
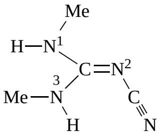
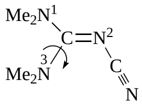
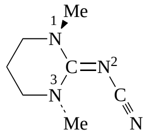
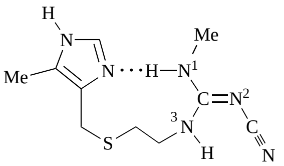
The theoretical order is confirmed by the spectroscopic shifts $\Delta\nu$(OH), a spectroscopic scale of basicity[13] reliable to within ±1–5 cm^{-1}, which shows the same regular branching sequence as ΔH^0_{298}.

Table 8 Electrical effects of alkyl substituents on the hydrogen-bond basicity of nitriles $RC{\equiv}N$, cyanamides $R_2NC{\equiv}N$ and cyanoamidines $Me_2NC(R){=}NC{\equiv}N$: comparison of experimental and AM1 theoretical results

	$RC{\equiv}N$			$R_2NC{\equiv}N$		$Me_2NC(R){=}N{-}C{\equiv}N$	
R	$\Delta\nu$(OH) [a]	pK_{HB}	$-\Delta H^0_{298}$(AM1) [b]	pK_{HB}	$-\Delta H^0_{298}$(AM1) [b]	pK_{HB}	$-\Delta H^0_{298}$(AM1) [b]
H	*c*	*c*	1.82	*c*	2.11	2.09	2.52 [f]
Me	157	0.91	2.02	1.56	2.22	2.24	2.62 [f]
Et	164	0.96	2.05	1.63 [d]	2.31	*e*	2.68 [f]
Pr^i	169	1.00	2.08	1.74 [d]	2.44	*e*	2.62 [f]
Bu^t	172	0.99	2.11	*e*	2.50		
1-Adam	180	1.00	2.15				

[a] cm^{-1}. $\Delta\nu$(OH) = ν(OH, free 4-fluorophenol) − ν(OH, hydrogen-bonded 4-fluorophenol). Ref. 13. [b] kcal mol^{-1}. [c] Experimentally difficult to obtain. [d] Refs. 14 and 30. [e] Not yet synthesized. [f] Stereoisomer *E*.

Table 9 Hydrogen-bond basicity of cyanoguanidines: AM1 calculated hydrogen-bond enthalpies $-\Delta H^0_{298}$ (kcal mol^{-1}) for their interaction with 4-fluorophenol and electrostatic potentials V_s (kcal mol^{-1}) on their various nitrogen atoms

No.	Compound	$-\Delta H^0_{298}$ (AM1)	$-V_s$			
			N^1	N^3	N^2	C≡N
35		2.58	27.1	20.6	56.3	57.70
36		2.70	28.0	22.9	57.7	59.11
37		2.62	19.7	34.5	55.7	58.15
38		2.78	29.8	47.1	54.8	60.32
39		2.96	31.0	30.9	63.3	63.84

In the series of cyanamides $R_2NC{\equiv}N$ both experimental pK_{HB} values and theoretical ΔH^0_{298} reveal the regular influence of branching on the electron-donating resonance effect of NR_2 groups. Theoretical calculations predict that $N(Bu^t)_2$ must be a still better donor than $N(Pr^i)_2$.

In the series of cyanoamidines $Me_2NC(R){=}N{-}C{\equiv}N$, we had previously found[14] that the cyanoacetamidine (R = Me) is significantly more basic than the cyanoformamidine (R = H). AM1 calculations encourage us to synthesize the cyanopropianamide (R = Et), but not the cyanoisobutyramidine (R = Pr^i), if we want to obtain even more basic nitriles. In this series the optimum alkyl effect seems to be obtained with ethyl.

The case of cyanoguanidines and cimetidine

From literature results on N^2-cyano-N^1-methyl-N^3-propylguanidine,[14] we might consider that NR_2 on the functional carbon of the amidine skeleton possesses an ability similar—or superior—to that of alkyls for enhancing the hydrogen-bond basicity of the cyano group. So, we have performed AM1 calculations on the cyanoguanidines of Table 9, including cimetidine **39**, a famous antiulcer drug which antagonizes the histamine H_2 receptor.

The results in Table 9 show that the most negative electrostatic potential is always found on the nitrile nitrogen and consequently the nitrile group is the preferred hydrogen bonding acceptor site. This is not disproved in the crystal of cimetidine[35] since the $C{\equiv}N\cdots HN$ intermolecular hydrogen bonds are slightly shorter (2.15 Å) than the $C{=}N\cdots HN$ bonds (2.17 Å). If we compare the calculated ΔH^0_{298} of cyanoguanidines, (Table 9) and cyanoamidines (Table 8) we observe that cyanoguanidine **35**, its dimethyl **36** and its tetramethyl **37** derivatives have approximately the same basicity as the cyanoacetamidine **21**. However, AM1 modelling of the tetramethylcyanoguanidine **37** shows steric crowding which is relieved by rotation around the $C{-}N^3$ bond. Consequently the N^3 nitrogen lone pair is partly deconjugated with the $C{=}N{-}C{\equiv}N$ π system and becomes less efficient in enhancing the nitrile basicity. If we prevent rotation by cyclisation, we obtain the cyanoguanidine **38** which now becomes more basic than the cyanoacetamidine **21**.

However, the most basic nitrile group is found in cimetidine. This molecule is internally hydrogen bonded by an $N\cdots HN$ bond between the imidazole and the guanidine residue, forming a stable ten-membered ring system.[35–36] Intramolecular hydrogen bonding appears to be an effective factor for enhancing the nitrile basicity, if we compare cimetidine **39** to its analogue **36** without internal hydrogen bonding. We attribute this to the partial proton transfer accompanying this internal hydrogen bonding which causes the nitrogen N^1 to be more negative, *i.e.* more electron-donating to the cyano group.

The various structure–activity[37–39] studies of cimetidine and analogues have mainly focused attention on the hydrogen bonding between the N^3-H group and the hydrogen-bond acceptor site of the H_2 receptor. This study points out that the nitrile group of cimetidine is super-basic which allows us to conclude that its hydrogen bonding with an hydrogen-bond donor site of the receptor certainly contributes significantly to the recognition of cimetidine by the H_2 receptor.

Conclusions

In the first part of this work, we have tested the reliability of AM1 and PM3 methods for calculating the molecular properties of nitriles and their hydrogen-bonded complexes. This section has revealed that for all the properties investigated, PM3 gives values in much closer agreement with the experimental data than AM1, which heavily underestimates the same properties. However, the correlations established between the experimental data and the semi-empirical values calculated with AM1 and PM3 are all significantly better with AM1, except that involving the dipole moments of the hydrogen-bonded complexes. This superiority of AM1 over PM3, from a relative point of view, has been confirmed by the correlations between pK_{HB} and descriptors of hydrogen-bond basicity calculated with the two methods, pK_{HB} being always significantly better correlated with the descriptors computed with AM1. The AM1 method has therefore been selected in the second part to calculate secondary pK_{HB} values difficult to obtain experimentally, to predict the subtle effects of alkyl groups in alkyl-cyanides, -cyanamides, -cyanamidines and -cyanoguanidines. The study of cimetidine has pointed out that the nitrile group of this molecule is super-basic, showing that its hydrogen bonding with an hydrogen-bond acceptor site of the receptor might contribute significantly to the recognition of cimetidine by the H_2 receptor.

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