

Hydrogen-bond acceptor properties of nitriles: a combined crystallographic and *ab initio* theoretical investigation

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ABSTRACT: The hydrogen-bond ability of nitrogen in X—C≡N···HO—R systems was investigated using crystallographic data retrieved from the Cambridge Structural Database and via *ab initio* calculations. The classification of hydrogen-bond geometries by the nature of the donor shows that the strength of the interaction increases in the order water ≈ alcohols < phenols. If the hydrogen-bond geometries are classified according to the nature of the acceptor inside each sample of donor, the strongest hydrogen bonds are always observed for ‘push–pull’ nitriles, as observed in solution on the p*K*_{HB} scale for such molecules. *Ab initio* molecular orbital calculations are then used to compute descriptors of hydrogen-bond basicity (enthalpy Δ*H*^o, hydrogen-bond length and minimum electrostatic potential of the base) for hydrogen-bond formation between water and 18 nitriles embracing a wide range of structure and basicity. Correlations between the hydrogen-bond basicity scale p*K*_{HB} and these quantum mechanical descriptors allow the calculation of p*K*_{HB} values for experimentally inaccessible bases and the treatment of polyfunctional nitriles. They also confirm the super-basicity of the nitrile group of cimetidine, a well known antiulcer drug. This property might be relevant in the molecular recognition of cimetidine by the H₂ receptor. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen-bond basicity; nitriles; Cambridge Structural Database analysis; *ab initio* calculations; cimetidine

INTRODUCTION

Since the pioneering work of Taft's group,^{1,2} the hydrogen-bond (HB) basicity scale p*K*_{HB} [Eqns (1)–(3)] has been found especially useful in solution chemistry. It is defined as log *K*_f for the complexation of organic bases B with a reference HB donor, 4-fluorophenol, in CCl₄ at 298 K.



$$K_f / 1\text{mol}^{-1} = [\text{complex}] / [\text{base}][4\text{-FC}_6\text{H}_4\text{OH}] \quad (2)$$

$$pK_{\text{HB}} = \log K_f = (\Delta G^\circ / \text{kcal mol}^{-1}) / 1.36 \quad (3)$$

Although the p*K*_{HB} scale has been extended to various families of organic bases such as nitrogen,³ oxygen,^{4–7} sulfur⁸ and carbon⁹ bases, its generalization comes up against various experimental difficulties. For example, practical matters such as solubility and lack of quantitative measurements for very weak or very strong hydrogen bonds limit the number of experimental data

available. Furthermore, in the case of molecules bearing several hydrogen-bond acceptor sites, the various methods used for p*K*_{HB} determination (IR,¹⁰ UV¹¹ or ¹⁹F NMR¹) give only a global value and not the individual basicity of each function.

In this work, we calculated secondary p*K*_{HB} values for experimentally inaccessible bases by establishing correlations between p*K*_{HB} and *ab initio* quantum-mechanical descriptors of hydrogen-bond basicity. We chose three descriptors already selected in a previous study devoted to the estimation of secondary p*K*_{HB} values with semi-empirical calculations,¹² namely thermochemical, geometrical and electronic descriptors. The first descriptor of base strength is the enthalpy of the hydrogen-bond complex formation, Δ*H*^o. In order to save computational time, we replaced 4-fluorophenol in reaction (1) by H₂O to calculate Δ*H*^o. Such a replacement is possible since various studies¹³ have shown the existence of linear free energy relationships between hydrogen-bond basicity scales based on 4-fluorophenol and water. The second descriptor is the hydrogen bond length *d*(BH) and the third is the most negative value of the electrostatic potential on the molecular surface of the base, *V*_{s,min}.

Theoretical calculations have proved to be useful tools for structural studies of hydrogen bonding systems and calculations of their interaction energies¹⁴ A reliable

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absolute calculation of ΔH° , $d(\text{BH})$ and $V_{s,\text{min}}$ by *ab initio* methods requires the use of a large basis set, taking account of electron correlation and correcting the basis set superposition error. Despite the dramatic progress made in *ab initio* computational chemistry in the last decade and the advent of larger and faster computing machines, this seems unlikely to be realized for extended sets of relatively large molecules. For such an investigation, the single determinant Hartree–Fock level of theory combined with one of the most widely used augmented 6–31G basis set, 6–31G**,¹⁵ can be a reasonable compromise. This basis set has proven to produce reliable and consistent data on hydrogen bonding previously.¹⁶ In a hydrogen bond $\text{AH}\cdots\text{B}$, the strength of interaction depends on the proton donor ability of AH and on the hydrogen-bond acceptor ability of B. Etter and Reutzel¹⁷ tried to rank the relative proton-accepting abilities of various functional groups by analyzing molecular packing in crystalline systems. These studies showed that hydrogen-bond accepting properties of functional groups clearly depend on their local intramolecular environment. This is the reason why we divided the bases into families bearing a common hydrogen-bond acceptor function. The present work was devoted to nitriles because a great number of experimental data are available for $\text{X}-\text{C}\equiv\text{N}$ systems.

First, nitriles are well characterized on the $\text{p}K_{\text{HB}}$ scale^{18–20} and their hydrogen-bonding basicity extends over a range of 3.50 pK units. For the present work, we selected 18 nitriles with very diversified X substituents, the first atom being as different as C_{sp^3} , C_{sp^2} , C_{sp} , N_{sp^3} , N_{sp^2} , Si, S, O and Cl.

Second, theoretical studies^{21,22} and gas-phase experimental structures²³ have both shown that the sp nitrogen lone pair is the hydrogen-bond acceptor site and that the geometry of the $\text{X}-\text{C}\equiv\text{N}\cdots\text{H}-\text{A}$ complexes is quasi-linear.²³ Such a geometry of interaction eliminates steric interferences between the X substituents and the hydrogen-bond donor approaching the nitrogen lone pair which should avoid abnormal entropy contributions to ΔG° and permit a linear $\text{p}K_{\text{HB}}$ vs ΔH° relationship.

Finally, many physical properties of nitriles are known and will be helpful in the calculations and the analysis of the results. From a thermodynamic point of view, the enthalpy ΔH° of reaction (1) has been determined in our group for several nitriles (unpublished data). Furthermore, numerous nitrile dipole moments^{24,25} have been measured. Finally, the gas-phase²⁶ and crystalline structures of many nitriles are known. In a recent study devoted to the HB accepting power of isocyanides, high-level theoretical calculations and structural investigations in the solid state have shown the strong structural and hydrogen bonding similarities between hydrogen isocyanide, $\text{H}-\text{N}\equiv\text{C}$, and its cyanide isomer, $\text{H}-\text{C}\equiv\text{N}$.²⁷ In this work, we first used the Cambridge Structural Database (CSD, October 1997 release)²⁸ to analyze the geometric characteristics of inter $\text{ROH}\cdots\text{N}\equiv\text{C}-\text{X}$

hydrogen bonds formed on the nitrile nitrogen. These data show that the shortest hydrogen bonds observed in the solid state correspond to strong hydrogen-bond bases as measured by the $\text{p}K_{\text{HB}}$ scale. We then computed ΔH° , $d(\text{NH})$ and $V_{s,\text{min}}$ for 18 nitriles at the HF/6–31G** level of theory. These computed properties were correlated with the experimental $\text{p}K_{\text{HB}}$ and used in a second step to calculate $\text{p}K_{\text{HB}}$ values of the gaseous nitriles $\text{HC}\equiv\text{N}$, $\text{FC}\equiv\text{N}$, $\text{N}\equiv\text{C}-\text{C}\equiv\text{N}$ and $\text{CF}_3\text{C}\equiv\text{N}$, of the insoluble and self-associated cyanamide $\text{H}_2\text{NC}\equiv\text{N}$ and of the polyfunctional 4-cyanopyridine which accepts hydrogen bonding not only on the nitrile nitrogen but also on the pyridine nitrogen.²⁹ We also analyzed HF/6–31G** calculations on cimetidine, an important antihistaminic molecule, bearing several hydrogen-bond acceptor groups including a nitrile.

METHODOLOGY

Crystal structure data

All crystallographic data were retrieved from the October 1997 (175 093 entries) release of the CSD.²⁸ Searches for bonded substructures and intermolecular non-bonded $\text{R}-\text{OH}\cdots\text{N}\equiv\text{C}-\text{X}$ contacts were carried out using the program QUEST3D (CSD, 1994). Data analyses were performed with VISTA (CSD, 1995).

Three subfiles of data were selected containing either alcoholic, phenolic hydroxyl groups or water molecules as donor and N_{sp} of nitrile groups as acceptors. Substructures were only located in entries that (a) were organic compounds within CSD chemical classes definitions, (b) had error-free coordinate sets in CSD check procedures, (c) exhibited no crystallographic disorder, (d) contained no polymeric connections and (e) had a crystallographic R factor ≤ 0.10 . All H atoms involved in non-bonded contact searches were placed in normalized positions, i.e. they were repositioned along their x-ray determined O–H vectors at a distance from O equal to the appropriate mean bond length established from neutron studies.³⁰

Non-bonded contact searches and geometric analyses of interactions involving the three different O–H hydrogen-bond donors and N_{sp} acceptors were carried out in the form of the parameters indicated in Fig. 1 with $d(\text{HN})$ in Å and the hydrogen-bond angles θ_1 ($\text{CN}\cdots\text{H}$)

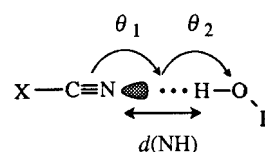


Figure 1. Definition of geometric parameters describing hydrogen-bonding interactions on the nitrogen atom of nitriles $\text{X}-\text{C}\equiv\text{N}$

and θ_2 ($\text{NH}\cdots\text{O}$) with the condition $\text{N}\cdots\text{H}$ distances $< 2.65 \text{ \AA}$ (sum of van der Waals radii with 1.55 \AA for N and 1.10 \AA for H).³¹

Calculations

All calculations were performed using the Spartan 4.0 program package (Wavefunction, Irvine, CA, USA) running on a Silicon Graphics Indy workstation. The geometries of both monomers (nitriles and water) were fully optimized at the HF/6-31G** level starting from the experimental structures given by microwave³² or x-ray spectroscopy, when available. The geometries of the hydrogen-bonded complexes were completely optimized. The starting geometry of complexation is illustrated schematically in Fig. 1: in each case, the θ_1 ($\text{C}\equiv\text{N}\cdots\text{H}$) and θ_2 ($\text{N}\cdots\text{HO}$) angles were set to 180° and the starting $d(\text{NH})$ distance was fixed at 2 \AA . In all cases frequency analyses were performed at the HF/6-31G** level to verify that the computed structures were local minima on the various potential energy surfaces. The hydrogen-bond complex enthalpies ΔH° were computed as the difference between the energy of the complex and the sum of the energies of the monomers according to Eqns ((4)–(6)) after evaluation of zero-point vibrational energies and thermal corrections:

$$\Delta E^\circ = E(\text{complex}) - [E(\text{base}) + E(\text{H}_2\text{O})] \quad (4)$$

$$\Delta E^\circ = \Delta E_{\text{elec}} + \Delta E_{\text{ZPVE}} + \Delta E_{\text{vib.therm}} + \Delta E_{\text{trans}} + \Delta E_{\text{rot}} \quad (5)$$

$$\Delta H^\circ = \Delta E^\circ - RT \quad (6)$$

where ΔE° is the full thermodynamic interaction energy. It includes the variation of the different energetic components: electronic ΔE_{elec} , the zero-point vibrational energies ΔE_{ZPVE} and the thermal energies which comprise the effects of molecular translation ΔE_{trans} , rotation ΔE_{rot} , and vibration $\Delta E_{\text{vib.therm}}$, at 298.15 K and 1 atm . A scaling factor of 0.9135 ³³ was used to correct approximately for vibrational anharmonicity and for overestimation of the force constants at the SCF level due to the lack of proper consideration of electron correlation.

Calculations of electrostatic potential energy surfaces were performed using HF/6-31G** geometry-optimized structures. These surfaces were mapped on to the electron density surfaces (0.001 e/au : electron/atomic units isosurface) at high resolution.

RESULTS AND DISCUSSION

Cambridge Structural Database

An obvious use of the CSD is to derive molecular

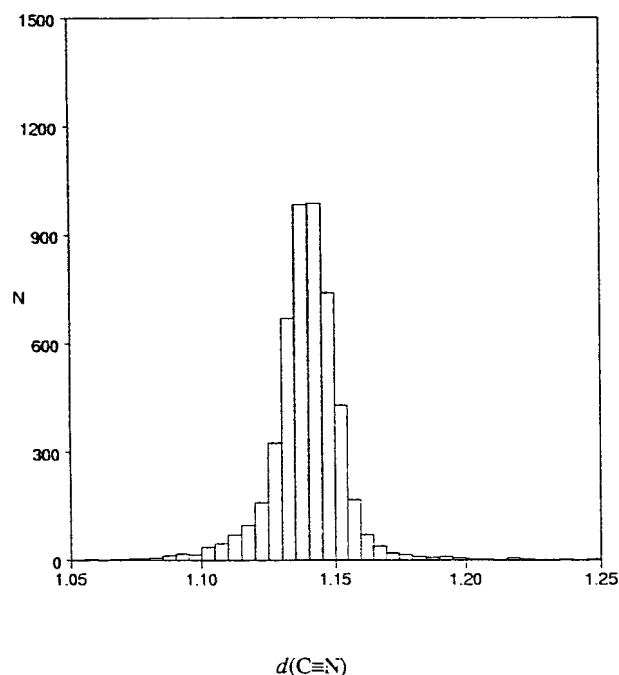


Figure 2. Histogram of $\text{C}\equiv\text{N}$ bond lengths in $\text{X}-\text{C}\equiv\text{N}$ systems

dimensions of functional groups in a very wide range of chemical environments. In this part, we therefore first use the CSD to derive standard values for the $\text{C}\equiv\text{N}$ bond lengths and $\text{X}-\text{CN}$ valence angles. In a second step, the CSD is used to analyze the geometric characteristics of $\text{R}-\text{OH}\cdots\text{N}\equiv\text{C}-\text{X}$ intermolecular hydrogen bonds.

Observed $\text{C}\equiv\text{N}$ geometry. A total of 5059 nitriles groups corresponding to 2634 entries were found in the CSD. The overall distribution of the $\text{C}\equiv\text{N}$ bond lengths shown in Fig. 2 seems near normal with a mean $\text{C}\equiv\text{N}$ bond length of $1.14(2) \text{ \AA}$. The $\text{X}-\text{CN}$ angle is quasi-linear with an average value of $177(3)^\circ$.

The effective electronegativity of nitrogen in nitriles can be increased by conjugative interactions between $\text{C}\equiv\text{N}$ and the lone pair of one N substituent. Table 1 compares the mean geometries of nitriles for X being an N_{sp^3} or C_{sp^3} in $\text{X}-\text{CN}$ systems. The average $\text{C}\equiv\text{N}$ bond length of $1.15(4) \text{ \AA}$ in $\text{N}_{\text{sp}^3}-\text{C}\equiv\text{N}$ is not significantly longer than that in $\text{C}_{\text{sp}^3}-\text{C}\equiv\text{N}$ [$1.13(2) \text{ \AA}$] in the light of the estimated standard deviations (e.s.d.) obtained.

Table 1. Comparison of the mean geometries of the $\text{X}-\text{C}\equiv\text{N}$ fragment for cyanamides ($\text{X}=\text{N}_{\text{sp}^3}$) and aliphatic nitriles as observed in the Cambridge Structural Database

X	N_{obs}	$\text{X}-\text{C} (\text{\AA})$	$\text{C}\equiv\text{N}$
N	28	1.32(4)	1.15(4)
C	1634	1.47(3)	1.13(2)
N^a	9282	1.47(2)	

^a Mean geometry of the $\text{N}-\text{C}$ bond length in tertiary amines.

Table 2. Mean values of geometric descriptors (Fig. 1) with e.s.d's for intermolecular hydrogen bonds to nitrile nitrogen ($N_{\text{obs}} = 95$)^a

	$d(\text{NH})$ (Å)	$d(\text{NO})$ (Å)	θ_1 (°)	θ_2 (°)
Minimum	1.74	2.72	74	96
Maximum	2.64	3.50	179	179
Mean	2.05	2.94	145	156
SD sample	0.20	0.14	23	18

^a CSD refcodes: ALZFR, BIVNEZ, BOHVUP, BUYTIY10, CESKOA, CHSECN, CHTDED, CIMBOP, CIMGUA, CITXUY10, CNADMT, CPRPCY, DAHFAT, DIKFAE, DIZPEH, DOKSIF, DOYHOO, DUMDIY, DUZXEB, EACPAZ, FANNIR, FAVKAO, FAZBEN, FEGBEY, FIRPIF, FITWAG, FUHFIX10, GAVPUO, HACTIO, HATLAP, HEXGAS, HQUACN01, HYCYAN, JAPDEJ, JATLIZ, JECFIG, JEGWAT, JEYKED, JIXBAT, JOTBID, JUXLIX, KCNCRN, KENMIZ, KENMUL, KOBSOJ, LAGMUB, LAVPAZ, LILKEW, MSACTZ10, NADTER, PABDOL, PCYPOL, PECBII, PIGTAA, RAGMUH, RAGNAO, SAVDAU, SIRWOF, SOYHOD, SUKNER, TAGZAC, TAHFIR, TAYBIE, TEDTUR, TEXPOB, TEXPUH, TICRUS, TIPJIL, TOZPAZ, TUCGED, TUCGUT, VOBTUB, VUNNUN, WANWUD, WANXAK, WEJVUC, WISGEK, YEGMIG, YEMMAE, ZIDKOM, ZOZVUF, ZUFPU, ZZZAVV10.

However, a shortening of the $N_{\text{sp}^3}\text{—C}$ single bond in $N_{\text{sp}^3}\text{—C}\equiv\text{N}$ can be pointed out by comparing the mean value observed in nitriles [1.32(4) Å] with the average value of the $N_{\text{sp}^3}\text{—C}$ bond length in aliphatic tertiary amines [1.47(2) Å]. This shortening can be partially attributed to conjugative interactions in the case of cyanamides but also to the field/inductive and resonance effects of the nitrile group.

Intermolecular hydrogen bonding to $\text{C}\equiv\text{N}$ acceptors. Searches and geometrical results for hydrogen-

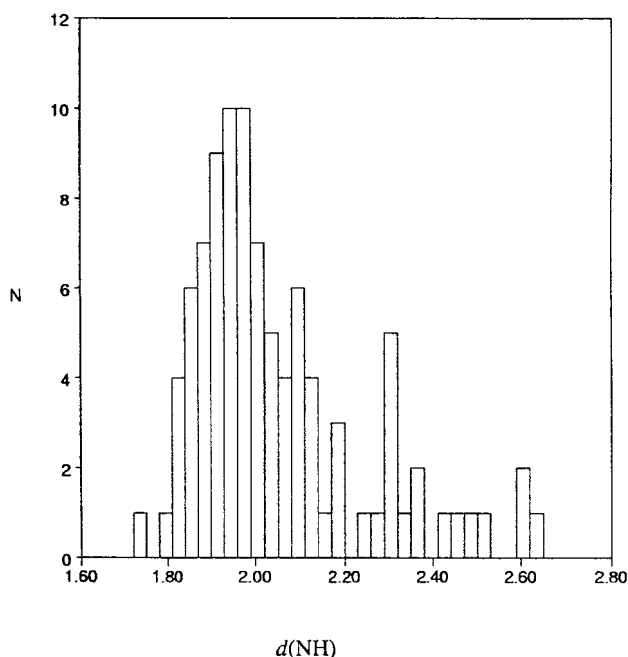


Figure 3. Histogram of $d(\text{NH})$ distances in $\text{X—C}\equiv\text{N}\cdots\text{HOR}$ hydrogen-bonded systems

bonded systems. The resulting subfile contains 83 crystal structures with 95 nitrile–hydrogen bond interactions. Mean values of the geometric descriptors (defined in Fig. 1 and in the Methodology section) for hydrogen bonds to the nitrogen atom of nitriles are collected in Table 2 together with the relevant CSD reference codes. The mean values of the $\text{N}\cdots\text{H}$ hydrogen bond and $\text{O—H}\cdots\text{N}$ angle are 2.05(20) Å and 156(18)°, respectively. Their respective histograms are shown in Figs 3 and 4(a). The distribution of the valence angle $\text{O—H}\cdots\text{N}$ is replotted in Fig. 4b after correction for geometric factors³⁴ to show that $\text{C}\equiv\text{N}\cdots\text{H—O}$ interactions have a strong tendency to linearity.

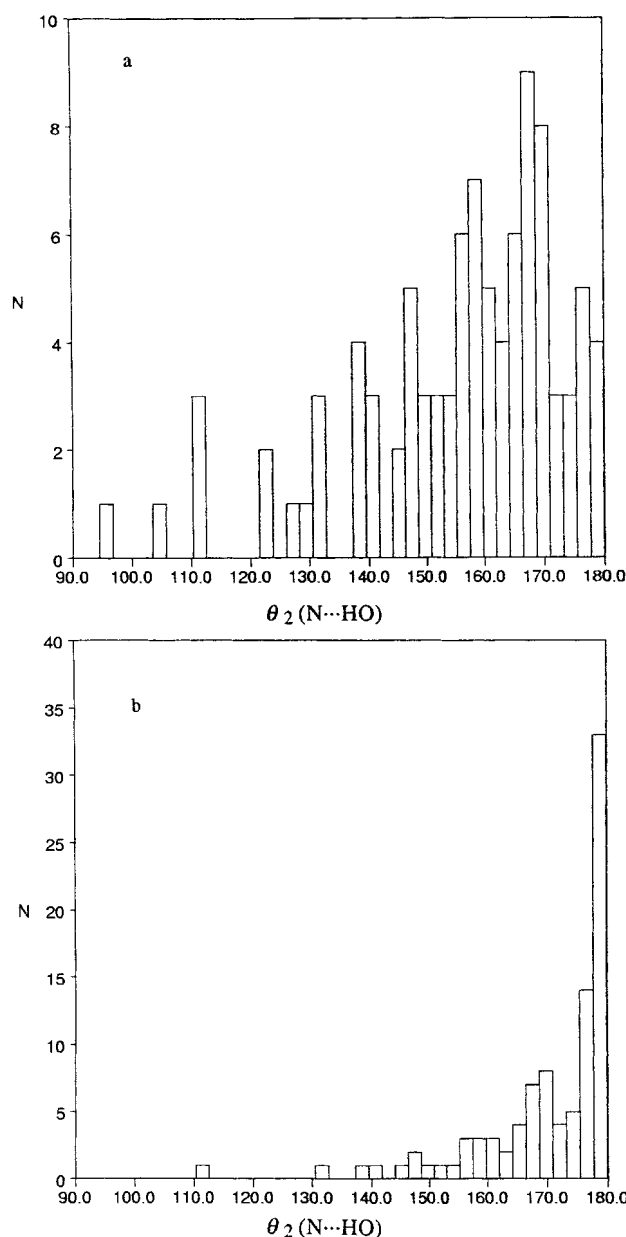


Figure 4. Histogram of $\theta_2(\text{OH}\cdots\text{N})$ valence angles in $\text{X—C}\equiv\text{N}\cdots\text{HOR}$ hydrogen-bonded systems: (a) observed values; (b) after correction for geometric factors³⁴

Table 3. Mean values of geometric descriptors (Fig. 1) with e.s.d.'s for intermolecular hydrogen bonds to nitrile nitrogen classified by the nature of the donor

Donor	N_{obs}		$d(\text{NH})$ (Å)	$d(\text{NO})$ (Å)	θ_1 (°)	θ_2 (°)
Phenolic OH	25	Minimum	1.74	2.72	93	111
		Maximum	2.61	3.11	176	179
		Mean	1.99	2.87	150	154
		SD sample	0.21	0.09	23	19
Alcoholic OH	42	Minimum	1.78	2.77	74	104
		Maximum	2.64	3.50	179	178
		Mean	2.06	2.95	146	155
		SD sample	0.20	0.16	23	18
H_2O	28	Minimum	1.86	2.79	96	97
		Maximum	2.60	3.30	179	175
		Mean	2.09	2.99	159	138
		SD sample	0.17	0.12	18	23

The strength of the hydrogen-bond interactions in $\text{X}-\text{C}\equiv\text{N}\cdots\text{HOR}$ systems can be strongly influenced by the nature of both the R and X substituents. We therefore classified the different hydrogen-bonding interactions according to the nature of the donor and according to the nature of the acceptor.

Hydrogen-bond geometries classified according to the nature of the donor. A search of the various OH groups inside the total set of hydrogen-bond interactions led to 19 phenols, 41 alcohols and 23 water-type of donors. Table 3 shows the geometric parameters observed for these different subfiles. By considering the acidity of the various OH donors, one would expect that the mean donor-acceptor separation would follow the sequence $\text{PhOH} < \text{C}_{\text{sp}^3}\text{-OH} \approx \text{H}_2\text{O}$. Owing to the low number of data in each sample, the three subsets cannot be statistically separated but the evolution of the $d(\text{NO})$ distances follows the expected chemical order: phenols 2.87 (0.09) Å < alcohols 2.95 (0.16) Å \approx water 2.99 (0.12) Å.

The examination of the relation between the $\text{OH}\cdots\text{N}$ angles and the $d(\text{HN})$ hydrogen-bond distances obtained for the three data sets might help to indicate the respective strengths of interactions of the various donors, the tendency for the shorter (strongest) hydrogen bonds to become more nearly linear being well known.³⁵ Figure 5 shows the scatterplots of the $\text{OH}\cdots\text{N}$ angles versus the $d(\text{HN})$ distances with their regression lines for (a) phenols, (b) alcohols and (c) water-type of donors. A higher correlation coefficient is actually obtained for phenols (-0.879) relative to alcohols (-0.674) and water (-0.660). Owing to the linearity of the $\text{X}-\text{C}\equiv\text{N}$ fragment, the directionality of approach of the donors cannot be analyzed through the classical spherical polar angles θ and Φ . Nevertheless, the use of the $\text{C}\equiv\text{N}\cdots\text{H}$ valence angle can give information on the acceptor directionality. The mean values observed for the different subfiles (Table 3) of 150 (23), 146 (23), and 159 (18), respectively, do not reveal a specific behavior of the various donors owing to the e.s.d. obtained. These data

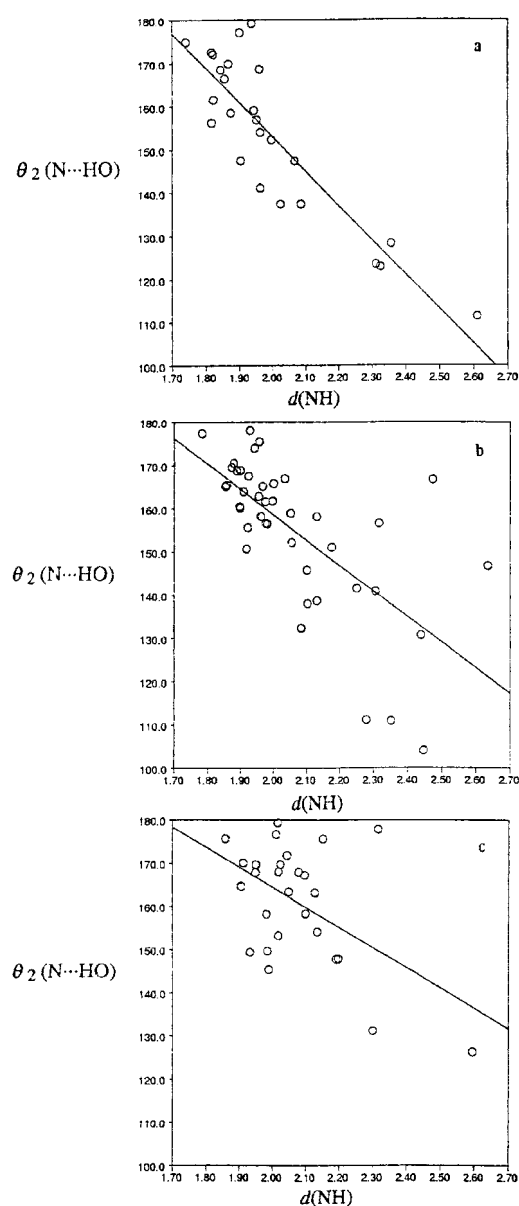
**Figure 5.** Scatterplots of θ_2 ($\text{OH}\cdots\text{N}$) valence angles versus $d(\text{NH})$ hydrogen-bond distances together with their regression lines for (a) phenols, (b) alcohols and (c) water

Table 4. Mean values of geometric descriptors (Fig. 1) with e.s.d.'s for intermolecular hydrogen bonds to nitrile nitrogen classified by the nature of the acceptor X—C≡N inside each sample of hydrogen bond donor

Donor	X	N_{obs}		$d(\text{NH})$ (Å)	$d(\text{NO})$ (Å)	θ_1 (°)	θ_2 (°)
Phenolic OH	C_{sp^3}	8	Minimum	1.74	2.72	114	111
			Maximum	2.61	3.11	176	179
			Mean	2.06	2.90	146	148
			SD sample	0.29	0.14	25	23
	N_{sp^3} or O_{sp^3} —C=C ^a	14	Minimum	1.82	2.75	93	124
			Maximum	2.31	2.97	174	173
			Mean	1.94	2.85	152	157
			SD sample	0.13	0.06	23	14
			Minimum	1.86	2.82	111	104
			Maximum	2.45	3.17	179	178
Alcoholic OH	C_{sp^3}	20	Mean	2.04	2.93	152	156
			SD sample	0.17	0.09	19	17
			Minimum	1.90	2.82	107	138
			Maximum	2.18	3.07	165	169
	N_{sp^3} or O_{sp^3} —C=C ^a	7	Mean	2.01	2.92	142	156
			SD sample	0.12	0.10	19	11
			Minimum	1.78	2.77	158	111
			Maximum	2.28	2.79	162	177
			Mean	2.03	2.78	160	144
			SD sample	0.35	0.02	3	47
H_2O	C_{sp^3}	4	Minimum	1.95	2.92	128	158
			Maximum	2.15	3.13	168	177
			Mean	2.05	3.02	151	170
			SD sample	0.09	0.09	17	8
	N_{sp^3} or O_{sp^3} —C=C ^a	6	Minimum	1.86	2.82	135	149
			Maximum	2.02	2.99	175	176
			Mean	1.95	2.89	159	161
			SD sample	0.06	0.06	15	11
			Minimum	1.95	2.92	97	154
			Maximum	2.13	3.08	122	168
N_{sp^3} or O_{sp^3} —C=N	4	Mean	2.06	3.01	110	163	
		SD sample	0.09	0.07	12	7	

^a The functional group between N_{sp^3} or O_{sp^3} and the nitrile function must be an unsaturated carbon system such as a phenylene or a vinyl group.

show that values close to 150° are favored over the more linear angles, the population density always being largest for values of the $\text{C}\equiv\text{N}\cdots\text{H}$ angle between 140 and 180° .

Hydrogen-bond geometries classified according to the nature of the acceptor. In cyanamides, $\text{R}_2\text{N}-\text{C}\equiv\text{N}$, conjugative interactions between the lone pair of the amino nitrogen N_{sp^3} and the cyano group can lead to a shortening of the $\text{N}-\text{C}$ single bond and a lengthening of the $\text{C}\equiv\text{N}$ triple bond. The importance of the resonance structures $\text{R}_2\text{N}-\text{C}\equiv\text{N} \leftrightarrow \text{R}_2\text{N}^+=\text{C}=\text{N}^-$ is thought to be the main cause of the increased hydrogen bonding of cyanamides compared to other nitriles.¹⁹ These effects are general to 'push-pull' nitriles, in which a 'pushing' substituent is directly (cyanamides) or indirectly conjugated with the $\text{C}\equiv\text{N}$ group. In the latter case, the 'transmitter' between the 'pushing' substituent and the nitrile function can be a phenylene, a vinyl or an imino group. The relative order of hydrogen-bond basicity of the nitrile nitrogen is well characterized in solution on the $\text{p}K_{\text{HB}}$ scale for such systems.¹⁸ These interactions are similar to those involved in resonance-assisted hydrogen

bonding, originally pointed out in the solid state and in solution for intramolecular hydrogen bonding in R_1COR_2 systems^{36,37} and generalized for intermolecular hydrogen bonding in heteroconjugated systems such as amide, R_1NHCOR_2 ,³⁶ and, more recently, thioamide and thiourea, $\text{R}_1\text{R}_2\text{C}=\text{S}$, acceptors.³⁸ In order to verify such effects on the crystal data of nitriles, we divided each set of hydrogen-bond donors into different subsets corresponding to the nature of the X substituent in $\text{X}-\text{C}\equiv\text{N}$. Four different subsearches were made for: (i) X being an N_{sp^3} (cyanamides), (ii) X being an N_{sp^3} or O_{sp^3} separated of the nitrile group by an unsaturated system such as a phenylene or a vinyl group, (iii) X corresponding to an N_{sp^3} or O_{sp^3} —C=N group and (iv) X being a C_{sp^3} , the latter subfile representing our reference set. Table 4 presents the results obtained for each data set. Owing to the small number of compounds in each sample, conclusions must be drawn carefully from these results. In particular, it is worth noting that the shortest hydrogen bonds are generally observed, inside each sample of donor, for 'push-pull' nitriles. This is not true for the phenolic data set, in which the strongest hydrogen bond is observed for an aliphatic nitrile (ALZFLR 2.721 Å) to be

Table 5. Experimental pK_{HB} scale of nitriles and the HF/6–31G** calculated descriptors of the nitrile hydrogen-bond basicity: ΔH° , $d(\text{NH})$ and $V_{\text{s,min}}$

No.	Compound	Formula	pK_{HB}^a	$-\Delta H^\circ$ (kcal mol ⁻¹) ^b	$d(\text{NH})$ (Å) ^c	$d(\text{NO})$ (Å) ^c	$d(\text{C}\equiv\text{N})$ (Å) ^c	$-V_{\text{s,min}}$ (kcal mol ⁻¹) ^b
1	Cyanogen chloride	ClCN	0.19	2.10	2.318	3.253	1.134	33.68
2	Ethynyl cyanide	HC≡CCN	0.30	2.26	2.314	3.245	1.136	35.93
3	Chloroacetonitrile	ClCH ₂ CN	0.39	2.22	2.282	3.221	1.134	36.71
4	4-Chlorobenzonitrile	4-ClC ₆ H ₄ CN	0.66	2.62	2.252	3.191	1.136	39.94
5	Acrylonitrile	H ₂ C=CHCN	0.70	2.76	2.249	3.186	1.136	42.23
6	Methyl thiocyanate	MeSCN	0.73	2.57	2.256	3.198	1.137	40.03
7	Benzonitrile	PhCN	0.80	3.12	2.243	3.179	1.136	43.10
8	Acetonitrile	MeCN	0.91	2.86	2.249	3.186	1.135	42.95
9	Trimethylsilylcyanide	Me ₃ SiCN	0.93	2.95	2.247	3.182	1.139	43.57
10	4-Methoxybenzonitrile	4-MeOC ₆ H ₄ CN	0.97	3.10	2.233	3.163	1.137	45.30
11	Trimethylacetone nitrile	t-BuCN	0.99 ^d	3.10	2.228	3.165	1.136	44.68
12	Cyclopropylcyanide	c-PrCN	1.03	3.05	2.229	3.168	1.136	44.71
13	4-Dimethylaminobenzonitrile	4-Me ₂ NC ₆ H ₄ CN	1.25 ^e	3.33	2.226	3.156	1.138	48.17
14	Dimethylcyanamide	Me ₂ NCN	1.56	3.59	2.205	3.139	1.140	48.29
15	<i>trans</i> -3-Dimethylaminoacrylonitrile	Me ₂ NCH=CHCN	1.70	3.83	2.190	3.126	1.139	51.39
16	<i>N</i> ¹ , <i>N</i> ¹ -Dimethyl- <i>N</i> ² -cyanoformamidine	Me ₂ NCH=NCN ^f	2.09	4.34	2.164	3.107	1.141	54.74
17	<i>N</i> ¹ , <i>N</i> ¹ -Dimethyl- <i>N</i> ² -cyanoacetamidine	Me ₂ NCMe=NCN ^f	2.24	4.49	2.143	3.096	1.141	54.87
18	Trimethylammoniocyanamidate	Me ₃ N ⁺ -N ⁻ CN	3.24 ^g	7.90	2.137	3.064	1.149	67.16

^a Refs. 17 and 18.^b 1 Å = 10⁻¹⁰^c 1 cal = 4.184^d There was a typing error in Ref. 17.^e Ref. 12.^f Stereoisomer E.^g Ref. 19 value for Bu₃N⁺N⁻CN.

compared with a mean N···O distance of 2.90 (0.14) Å for the subset of reference. However, in this sample, six strong hydrogen bonds (shorter than 1.90 Å) are observed on the total of 14 interactions of phenols with ‘push–pull’ nitriles. For the alcohols data set, the shortest hydrogen bond is observed for a cyanamide (DUMDIY 2.77 Å) to be compared with a mean N···O distance of 2.93 (0.09) Å. If the hydrogen bond donor is water, the strongest hydrogen bond is observed for a vinylogue (FAZBEN 2.82 Å) to be compared with a mean N···O distance of 3.02 (0.09) Å.

Ab initio molecular orbital calculations

The 18 nitriles selected for the investigation of the relation between the pK_{HB} scale and *ab initio* theoretical descriptors of hydrogen-bond basicity [ΔH° , $d(\text{NH})$ and $V_{\text{s,min}}$] are shown in Table 5 together with their respective experimental and theoretical values. The computed intermolecular distances $d(\text{NO})$ between the nitrile nitrogen and the water oxygen atom engaged in hydrogen bonding and the calculated $d(\text{C}\equiv\text{N})$ bond lengths in the free bases are also indicated.

Before presenting the various correlations obtained, we discuss the accuracy of the HF/6–31G** method in calculating molecular properties of nitriles [nitrile bond lengths $d(\text{C}\equiv\text{N})$ and nitrile dipole moments $\mu(\text{XC}\equiv\text{N})$]

and of their hydrogen-bonded complexes [enthalpies of hydrogen bond formation ΔH° and intermolecular distances $d(\text{NO})$].

HF/6–31G calculations of molecular properties of nitriles.** $d(\text{C}\equiv\text{N})$. The *ab initio* optimized bond lengths at the 6–31G** level are close to the gas-phase data available (Table 6) and consistently too short, the mean absolute error being 0.024 Å. The pure $d(\text{C}\equiv\text{N})$ triple bond length in acetonitrile (1.135 Å) increases for

Table 6. Experimental (Ref. 25) and HF/6–31G** calculated C≡N distances (Å)

No.	Compound	HF/6–31G**	Exp.
19	HCN	1.133	1.153
20	CF ₃ CN	1.131	1.154
8	MeCN	1.135	1.156
21	FCN	1.132	1.157
5	H ₂ C=CHCN	1.136	1.157
7	PhCN	1.136	1.158
22	NC-CN	1.134	1.158
11	t-BuCN	1.136	1.159
23	H ₂ NCN	1.138	1.160
2	HC≡CCN	1.136	1.161
12	c-PrCN	1.136	1.161
6	MeSCN	1.137	1.170
9	Me ₃ SiCN	1.139	1.170

Table 7. Experimental (Ref. 25) and HF/6-31G** calculated dipole moments (D) of nitriles

No.	Compound	Calc.	Exp. ^a
20	CF ₃ CN	1.50	1.26 (gas)
21	FCN	2.32	2.17 (gas)
4	4-ClC ₆ H ₄ CN	2.85	2.64 (C ₆ H ₆)
1	ClCN	2.76	2.94 (gas)
19	HCN	3.20	2.95 (gas)
3	ClCH ₂ CN	3.40	3.00 (alkane)
2	HC≡CCN	4.08	3.60 (gas)
11	t-BuCN	4.22	3.70 (CCl ₄)
12	c-PrCN	4.43	3.78 (C ₆ H ₆)
5	H ₂ C=CHCN	4.26	3.90 (gas)
8	MeCN	4.07	3.92 (gas)
6	MeSCN	4.16	4.00 (gas)
9	Me ₃ SiCN	4.43	4.06 (CCl ₄)
7	PhCN	4.85	4.14 (gas)
23	H ₂ NCN	4.62	4.30 (gas)
10	4-MeOC ₆ H ₄ CN	5.81	4.76 (CCl ₄)
14	Me ₂ NCN	4.89	4.77 (gas)
15	Me ₂ NCH=CHCN	7.28	6.12 (C ₆ H ₆)
13	4-Me ₂ NC ₆ H ₄ CN	7.31	6.39 (CCl ₄)
16	Me ₂ NCH=NCN	8.11	6.59 (C ₆ H ₆)
17	Me ₂ NC(Me)=NCN	8.09	7.06 (C ₆ H ₆)

^a When μ was measured in several physical states we selected our value in the order gas > alkane > CCl₄ > C₆H₆.

dimethylcyanamide (1.140 Å) and 'push-pull' nitriles 15, 16, 17 and 18 (Table 5), the maximum lengthening being calculated for the cyanamidate 18 (1.149 Å).

$\mu(XC\equiv N)$. We were able to collect (Table 7) 21 dipole moments of nitriles ranging from 1.3 to 7 D (1 D = 3.336×10^{-30} C m). If we exclude ClC≡N, the computed values are always too high with a mean absolute error of 0.48 D, but 97.9% of the variance of μ is correctly explained at the 6-31G** level [Eqn. (7)]:

$$\mu(\text{exp.}) = 0.372 + 0.810\mu(\text{calc.}) \quad (7)$$

$$n = 21, r^2 = 0.979, s = 0.22 \text{ D}$$

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

Table 9. Correlations between the pK_{HB} scale and the AM1 and HF/6-31G** calculated descriptors of the nitrile hydrogen-bond basicity: ΔH° , $d(\text{NH})$ and $V_{s,\text{min}}$

Descriptor	AM1					HF/6-31G**				
	a	b	n	r^2	s	a	b	n	r^2	s
$-\Delta H^\circ$ (kcal mol ⁻¹)	1.545	-2.155	18	0.948	0.18	0.556	-0.711	18	0.906	0.24
$d(\text{NH})$ (Å)	-22.328	61.320	18	0.941	0.19	-13.836	31.969	18	0.965	0.15
$V_{s,\text{min}}$ (kcal mol ⁻¹)	0.103	-4.212	18	0.937	0.20	0.095	-3.171	18	0.979	0.11
$-\Delta H^\circ$ (kcal mol ⁻¹)	1.796	-2.653	17	0.934	0.16	0.843	-1.566	17	0.977	0.09
$d(\text{NH})$ (Å)	-25.332	69.446	17	0.912	0.18	-12.519	29.007	17	0.966	0.11
$V_{s,\text{min}}$ (kcal mol ⁻¹)	0.116	-4.821	17	0.901	0.19	0.094	-3.133	17	0.962	0.12

Table 8. Experimental hydrogen bond enthalpies $-\Delta H^\circ$ for the interaction of 4-fluorophenol with nitriles (unpublished data) and HF/6-31G** calculated enthalpies for the interaction of water with nitriles

No.	Compound	$-\Delta H^\circ$ (kcal mol ⁻¹)	
		Calc.	Exp.
4	4-ClC ₆ H ₄ CN	2.62	3.82
3	ClCH ₂ CN	2.22	3.90
7	PhCN	3.12	4.18
5	H ₂ C=CHCN	2.76	4.21
10	4-MeOC ₆ H ₄ CN	3.10	4.33
8	MeCN	2.86	4.64
11	t-BuCN	3.10	4.76
13	4-Me ₂ NC ₆ H ₄ CN	3.33	4.90
14	Me ₂ NCN	3.59	5.35
15	Me ₂ NCH=CHCN	3.83	5.62
16	Me ₂ NCH=NCN	4.34	5.95

HF/6-31G calculations of molecular properties of hydrogen-bonded nitriles.** ΔH° . Accurate enthalpies for the hydrogen-bond formation of 11 nitriles with 4-fluorophenol, in CCl₄, a poorly solvating medium, have been determined in our group (unpublished results). In order to save computational time, we selected water as the hydrogen bond donor of reference for the calculation of the hydrogen bond energies. As we indicated in the Introduction, the comparison of values obtained with these two different hydrogen-bond donors is possible since linear free energy relationships exist between hydrogen-bond basicity scales based on 4-fluorophenol and water.¹³ The experimental and theoretical values of hydrogen bond enthalpies are presented in Table 8. The results show that 88% of the variance of ΔH° is correctly predicted [Eqn. (8)] using HF/6-31G** *ab initio* calculations.

$$-\Delta H^\circ(\text{exp.}) = -0.197 + 1.064(-\Delta H^\circ) \quad (8)$$

$$n = 11, r^2 = 0.876, s = 0.26 \text{ kcal mol}^{-1}$$

$d(\text{NO})$. The computed intermolecular distances between the nitrogen atom of the nitrile function and the oxygen atom of the water molecule involved in hydrogen

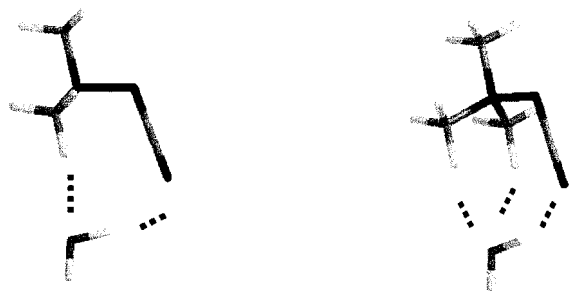


Figure 6. Geometry of the HF/6-31G** minimum found for the OH...C≡N and C—H...O hydrogen-bond interactions between trimethylammoniocyanamide 18 and water

bonding range from 3.253 Å for the weakest hydrogen-bond base ClC≡N to 3.064 Å for the strongest hydrogen-bond base Me₃N⁺—N[−]C≡N (Table 5). By comparing the mean value of 3.06 Å for these theoretical data with the mean *d*(NO) value of 2.99(12) Å (Table 3) observed for hydrogen bonding interactions of nitriles with water in the CSD, we verify the well known overestimation of hydrogen bonding parameters at the Hartree–Fock level.¹⁴

Correlation of p*K*_{HB} with HF/6-31G** descriptors of hydrogen-bond basicity

Table 9 compares the correlations obtained between the p*K*_{HB} scale and the three theoretical descriptors calculated at the HF/6-31G** level in this work and at the semi-empirical level with the AM1 method in a previous study.¹² These results show that the use of *ab initio* descriptors significantly improves the various correlations if we exclude that involving the thermochemical parameter Δ*H*[°]. We attribute it to the strong deviation of cyanamide 18 of the correlation between p*K*_{HB} and Δ*H*[°]. For this compound, the variation of enthalpy calculated at the HF/6-31G** level does not correspond only to the hydrogen bond interaction between the water molecule and the lone pair of the nitrile nitrogen, but also to the formation of two others hydrogen bonds between the hydrogen atoms carried by the Me₃N⁺ group and the lone pairs of the water

molecule (Fig. 6). This interaction can be explained by the acidic character of the hydrogens carried by the carbon atoms in this molecule owing to the presence of the positive charge on the trimethylammonio group. HF/6-31G** calculations of the Mulliken partial atomic charges on the C—H hydrogen atoms of trimethylamine (+0.12) and its protonated form (+0.20) confirm the enhanced positive character of such C—H hydrogen atoms. These secondary hydrogen bond interactions induce an increased stabilization of the complex giving rise to a much stronger variation of enthalpy than expected. As they also exert an obvious influence on the geometry of the interaction, we calculated the various correlations without including the cyanamide 18. These results, together with those obtained using AM1 calculations, are shown in Table 9. The *ab initio* HF/6-31G** descriptors are actually all significantly better correlated with p*K*_{HB} than the AM1 values. In agreement with our previous work using semi-empirical calculations, the best descriptor of the nitrile hydrogen-bond basicity is the thermochemical parameter Δ*H*[°]. These results confirm that the large changes observed in p*K*_{HB} (i.e. in Δ*G*[°]) and Δ*H*[°] are nearly independent of entropy changes in the nitrile family.

Calculation of secondary p*K*_{HB} values

We can use the fourth line of Table 9 [Eqn. (9)] for the calculation of p*K*_{HB} values that are difficult to obtain experimentally.

$$pK_{HB} = -1.566 + 0.843(-\Delta H^{\circ}) \quad (9)$$

$$n = 17, r^2 = 0.977, s = 0.09$$

Table 10 shows the values calculated from this equation for N≡C—C≡N, CF₃C≡N, FC≡N, H₂NC≡N and 4-cyanopyridine. The CF₃C≡N value (−0.58) seems low in comparison with the experimental p*K*_{HB} of CCl₃CN (−0.26), but lies in the right direction. The stronger value of FC≡N (0.28) compared with the experimental value of BrC≡N (0.19) is coherent with the electron-donating resonance effect of F relative to Br in this system. The value of 0.45 calculated for HC≡N is expectedly lower

Table 10. Secondary p*K*_{HB} values calculated from Eqn. (9)

No.	Compound	Remark	−Δ <i>H</i> [°] (kcal mol ^{−1}) ^a	p <i>K</i> _{HB}
22	NC-CN	Gaseous	0.99	−0.73
20	CF ₃ -CN	Gaseous	1.17	−0.58
21	FCN	Gaseous	2.19	0.28
19	HCN	Gaseous	2.39	0.45
23	H ₂ NCN	Insoluble	3.30	1.22
24	4-Cyanopyridine	Polyfunctional	2.34 ^b	0.41 ^b

^a Calculated at the HF/6-31G** level.

^b These values refer only to the basicity of the nitrile function.

Table 11. Hydrogen bond distances observed in the various crystal structures of cimetidine found in the CSD (the numbering of the atoms corresponds to that given in the text)

CSD refcode	$C\equiv N\cdots(H)Y^a$	$C=N\cdots(H)Y^a$	IHB ^b
<i>Crystal structures with an intramolecular hydrogen bond:</i>			
CIMETD	$N^4\cdots N^3$ 2.911	$N^2\cdots N^6$ 2.954	$N^5\cdots N^1$ 2.881
CIMETD02	$N^4\cdots N^3$ 2.909	$N^2\cdots N^6$ 2.941	$N^5\cdots N^1$ 2.874
CIMETD03	$N^4\cdots N^3$ 2.899	$N^2\cdots N^6$ 2.933	$N^5\cdots N^1$ 2.822
<i>Crystal structures without an intramolecular hydrogen bond:</i>			
CIMGUA	$N^4\cdots O^{w(c)}$ 3.080	$N^5\cdots O^{w(c)}$ 2.801	
CIMETD01	$N^4\cdots N^3$ 2.955 $N^4\cdots N^6$ 2.987	$N^5\cdots N^1$ 2.920	

^a Y = hydrogen bond donor.^b Intramolecular hydrogen bond.^c O^w = oxygen atom of a water molecule.

than the value of 0.91 for MeC≡N and agrees well with a pK_{HB} difference of 0.53 between HCOMe and Me-COMe.⁷ The calculated pK_{HB} of 1.22 for H₂NC≡N compares well with another secondary value of 1.38 obtained from unpublished measurements in CH₂Cl₂. Finally, the value of 0.41 for the nitrile group of 4-cyanopyridine is close to 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.¹⁸ By comparing these predicted pK_{HB} values with those obtained by using semi-empirical calculations,¹² it is clear that the use of *ab initio* descriptors increases significantly the predictive power of this approach.

The case of cimetidine

The various correlations of Table 9 can be used to evaluate the hydrogen bonding basicity of nitriles in drugs. We will illustrate this on the example of cimetidine (**25**), a well known anti-ulcer drug which antagonizes the histamine H₂ receptor.

Cimetidine carries several potentially hydrogen-bond acceptors heteroatoms. On the basis of the pK_{HB} scale, the thioether sulfur atom and the nitrogens of the guanidine function can be ruled out owing to their too weak hydrogen-bonding basicity.³⁹ The nitrogen atom of the imidazole ring and the nitrile nitrogen of the side-chain remain the last candidates for the interaction with hydrogen-bond donor sites of the H₂ receptor. Of these, the nitrile group seems particularly important since in one crystalline form of cimetidine the lone pair of the imidazole ring nitrogen is already engaged in an intramolecular hydrogen bond.⁴⁰

Among the various theoretical descriptors chosen in this study, we selected the electrostatic potential $V_{s,min}$ to

investigate the hydrogen-bond basicity of the nitrile group of cimetidine since this property is the most accessible in terms of computational time. In order to have reasonable starting geometries for our computations, we searched the crystal structures of cimetidine in the CSD. The hydrogen-bond interactions observed in each of the five entries^{40–43} found have also been analyzed, their distances being reported in Table 11 together with the corresponding refcodes. These data show that the hydrogen bonds involving the nitrile group are always the shortest for the crystalline form of cimetidine with an intramolecular hydrogen bond. When the imidazole ring nitrogen is not engaged in an internal hydrogen bond, it becomes the atom involved in the shortest interactions. These data are coherent with the respective ranges of the pK_{HB} scale for N_{sp} and N_{sp²} hydrogen-bond bases.³⁹

In order to investigate the influence of the conformation on the hydrogen bond basicity of the nitrile group of cimetidine, the $V_{s,min}$ values were calculated starting from the CIMETD⁴⁰ (internally hydrogen bonded) and the CIMETD01⁴¹ (without internal hydrogen bond) crystal structures. Owing to the size of the cimetidine molecule, the positions of the hydrogens atoms were first optimized at the semi-empirical level with the PM3 method and HF/6–31G** single-point calculations were applied to the resulting structures. The most negative value of $V_{s,min}$ of the internally hydrogen-bonded form of cimetidine is indeed found on the nitrile nitrogen (−59.76 kcal mol^{−1}), the value of V_s on the imino nitrogen N² being about 20 kcal mol^{−1} higher (−42.10 kcal mol^{−1}). The comparison of this value with those obtained for the various nitriles in Table 8 confirms the super-hydrogen-bonding basicity of the cimetidine nitrile group already pointed out at the semi-empirical level¹² and are coherent with the crystallographic data.

The comparison of the electrostatic potentials calculated on the nitrile nitrogen of the conformations of cimetidine with ($-59.76 \text{ kcal mol}^{-1}$) and without an intramolecular hydrogen bond ($-54.55 \text{ kcal mol}^{-1}$) confirms the efficiency of internal hydrogen bonding for enhancing the nitrile basicity. The secondary values of pK_{HB} calculated from these two electrostatic potentials using the sixth line of Table 9 are 2.48 and 2.00, respectively. It is worth noting that despite the obvious differences in terms of three-dimensional structures between the two cimetidine conformations studied, the nitrile nitrogen remains a strong hydrogen-bond acceptor site. This strongly suggests its involvement during the molecular recognition process of cimetidine to the H_2 receptor. The quantitative structure–activity relationship study of Nakayama on derivatives of cimetidine⁴⁴ which pointed out the relation between electrostatic properties of histamine H_2 antagonist side-chains and biological activity supports this hypothesis.

CONCLUSION

In the first part of this study, a statistical analysis of hydrogen-bond interactions on the nitrile nitrogen in $X-C\equiv N\cdots HO-R$ systems was made using crystallographic data retrieved from the CSD; 83 crystal structures with 95 nitrile hydrogen-bond interactions were found with mean values of $N\cdots H$ hydrogen-bond length and $OH\cdots N$ angle of 2.05 (20) Å and 156 (18°). In order to investigate the influence of the R and X substituents on the hydrogen-bond strengths, the hydrogen-bond geometries were classified by the nature of the donor and by the nature of the acceptor. The examination of the relations between the $OH\cdots N$ angles and the $N\cdots H$ hydrogen-bond distances for the 19 phenols, the 41 alcohols and the 23 water-type donors found shows that a higher correlation coefficient is found for phenols (-0.879) relatively to alcohols (-0.674) and water (-0.660). These results indicate that the strength of the $X-C\equiv N\cdots HO-R$ hydrogen bonds observed in the solid state follows the order of hydrogen-bond donor acidity: water \approx alcohols $<$ phenols. Within each subset of donor, a search of various substructures in which conjugative interactions are possible between a 'pushing' substituent and the 'pulling' nitrile group was made. Despite the small number of data in each data set, these results show that the strongest (shortest) hydrogen bonds are always observed for 'push-pull' nitriles, as observed experimentally in solution on the pK_{HB} scale for such systems.

Ab initio molecular orbital calculations were used in the second part to compute the molecular properties of the free nitriles [$d(C\equiv N)$ bond lengths, dipole moments $\mu(XC\equiv N)$] and of the hydrogen-bonded complexes [enthalpies of hydrogen bond formation ΔH° , intermolecular distances $d(NO)$ between the nitrile nitrogen and the water oxygen atoms involved in

hydrogen bonding]. These theoretical data confirmed the well known overestimation of molecular and hydrogen bonding parameters at the Hartree–Fock level. Nevertheless, from a relative point of view, reasonable correlations are found between the theoretical and the experimental data available. Descriptors of hydrogen-bond basicity [enthalpy ΔH° , hydrogen-bond length $d(NH)$ and minimum electrostatic potential of the base $V_{s,\min}$] calculated at the HF/6–31G** level for hydrogen-bond formation between water and 18 nitriles embracing a wide range of structure and basicity were then correlated with the experimental pK_{HB} values. All the correlations are significantly better than these obtained using the same quantum mechanical descriptors calculated at the semi-empirical level by the AM1 method, provided that cyanamide is excluded. This approach allows the calculation of secondary pK_{HB} values for experimentally inaccessible bases and the treatment of polyfunctional nitriles. It can also be used to evaluate the hydrogen bond basicity of the nitrile group in drugs. The illustration of this method on the example of cimetidine confirms the super-hydrogen bond basicity of the cimetidine nitrile group and strongly suggests its implication during the molecular recognition process of this well known anti-ulcer drug to the H_2 receptor.

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