DOI: 10.1002/ejoc.200900569

Hydrogen-Bond Accepting Strength of Five-Membered N-Heterocycles: The Case of Substituted Phenylpyrrolines and Myosmines

Virginie Arnaud,[a] Michel Berthelot,[a] François-Xavier Felpin,[b] Jacques Lebreton,[a] Jean-Yves Le Questel,[a] and Jérôme Graton*[a]

Keywords: Density functional calculations / IR spectroscopy / Nitrogen heterocycles / Hydrogen-bond basicity / pK_{BHX} scale

The hydrogen-bond (HB)accepting strengths of a series of five-membered N-heterocycles have been measured in CCl_4 solution and/or calculated by theoretical methods. These molecules present a great chemical versatility, ranging from very weak π bases up to strongly HB acceptors, imines and amines. Among these compounds, special attention has been paid to myosmines, which are bifunctional molecules containing two very similar pyridinic and pyrrolinic sp^2 nitrogen atoms. Infrared measurements provided the global HB basicities of these molecules, but the individual accepting strength of each nitrogen atom could not be achieved experimentally and had to be determined by theoretical calculations. Owing to their flexibility, the geometries of their different isomers were optimized and their basicities weighted by the calculated relative populations. To accurately estimate the individual HB strength of a nitrogen site, it was necessary to take into account a specific halogen bond between the second nitrogen atom and a solvent molecule. 1-Pyrroline is a significantly stronger base than pyridine, but irrespective of the substituent on the pyridine ring, the pyrrolinic site is always the weakest HB acceptor in the myosmine molecules.

Introduction

The frequent occurrence of several heteroatoms acting as potential hydrogen-bond (HB) accepting groups in the structures of biological macromolecules (proteins, nucleic acids) and their ligands has made the determination of the individual hydrogen-bond basicities of polybasic organic compounds a recurrent and challenging problem.[1] The measurement of the HB basicity of monobasic molecules may be obtained with a good accuracy by monitoring the remaining intensity of the free OH vibration of a phenol in ternary phenol/base/CCl_4 solutions of known initial concentrations of donor and acceptor. More than one thousand molecules corresponding to various classes of organic compounds have already been studied with the reference donor 4-fluorophenol (pFP) in CCl_4 at 25 °C, leading to the general pK_{BHX} scale initiated by Arnett and Taft under the acronym pK_{HB},[2–4] developed by Berthelot and Laurence's group[5] and compiled recently in the pK_{BHX} database[6] that can be accessed from the CEISAM laboratory.[7] However, when the acceptors hold more than one basic site, B_1, B_2, ..., several 1:1 associations consume the free phenol so that the only equilibrium constant accessible by monitoring the free hydroxy intensity is a global equilibrium constant $K_t = K_{B_1} + K_{B_2} + ...$ [Equations (1), (2) and (3)], and the different individual equilibrium constants K_{B_1}, K_{B_2}, ... cannot be achieved by this method.

$$4\text{-}FC_6H_4OH + B_1{<>}B_2 \underset{K_{B_1}}{\rightleftharpoons} 4\text{-}FC_6H_4OH\cdots B_1{<>}B_2 \quad (1)$$

$$4\text{-}FC_6H_4OH + B_2{<>}B_1 \underset{K_{B_2}}{\rightleftharpoons} 4\text{-}FC_6H_4OH\cdots B_2{<>}B_1 \quad (2)$$

$$K_t = \frac{[4\text{-}FC_6H_4OH\cdots B_1{<>}B_2] + [4\text{-}FC_6H_4OH\cdots B_2{<>}B_1] + \cdots}{[4\text{-}FC_6H_4OH][B_1{<>}B_2]} = K_{B_1} + K_{B_2} \quad (3)$$

When the secondary sites are relatively weak HB acceptors, for example, the π clouds in aromatic rings,[8] ethylenic/acetylenic derivatives[8] or halogen atoms,[9] they can be neglected because the important thermodynamic quantity is the logarithm of the constant K_t, an algebraic function that seriously minimizes the importance of the additional minor terms K_{B_2}, K_{B_3}. Note that this approximation is limited to a diluted ternary solution in which only 1:1 complexes coexist and that the secondary basic sites are no more negligible when the donor is in excess.[10] On the other hand, when the secondary sites are strictly equivalent to the first one, for example, in pyrimidine or trioxane, a simple

[a] Université de Nantes, UMR CNRS 6230, Chimie et Interdisciplinarité: Synthèse, Analyse, Modélisation (CEISAM), UFR Sciences & Techniques,
2, rue de la Houssinière, B. P. 92208, 44322 Nantes Cedex 3, France
Fax: +33-2-51125567
E-mail: Jerome.Graton@univ-nantes.fr
[b] Université Bordeaux 1, UMR CNRS 5255, Institut des Sciences Moléculaires,
351 Cours de la Libération, 33405 Talence Cedex, France

division of the total (experimental) equilibrium constant by the number of sites gives the individual equilibrium constant. To the best of our knowledge there is only one example in the literature in which the two individual equilibrium constants K_{B_1} and K_{B_2} of a dibasic compound situated between the latter two extreme situations have been measured separately.[1] In most cases, the only direct quantitative information are the total constants and various indirect methods have been proposed for their separation into individual association constants. These methods involve (i) experimental Δν(OH) frequency shifts,[11,12] (ii) substituent effects,[13,14] (iii) molecular fragment models[15] or (iv) theoretical descriptors.[12,16,17]

In a recent paper[18] we set up an equation based on theoretical descriptors computed at the B3LYP/6-31+G(d,p) level of theory aimed at calculating the equilibrium constant of pFP association with a nitrogen atom in carbon tetrachloride [Equation (4)]. In this equation, $V_{s,min}$ is the local minimum electrostatic potential value at the molecular surface of the monomeric base and $D_0^{(HF)}$ is the variation of the electronic energy of the model association equilibrium between hydrogen fluoride and the base [equilibrium (5)], corrected from the zero-point vibrational energy. The substitution of the HB donor pFP by HF drastically decreases the computation time owing to the reduction in the size of the molecule, but also because the axial geometry of HF limits the number of possible stereoisomeric structures of the complex.

$$pK_{BHX} = -0.0612D_0^{(HF)} - 0.0102V_{s,min} - 2.829 \quad (4)$$

r (correlation coefficient) = 0.993; s (standard error) = 0.07; n (number of points) = 59

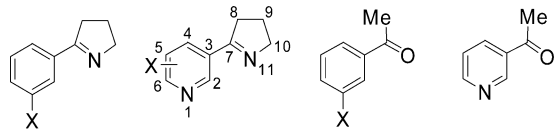
$$B + HF \rightleftharpoons B\cdots HF \quad (5)$$

However, if the application of the DFT method to equilibrium (5) appears rather straightforward and rapid for the determination of the pK_{BHX} values of monofunctional bases with rigid structures, we have shown that additional calculations are necessary for the most general solutes.[18] First, for flexible monomers, the $D_0^{(HF)}$ and $V_{s,min}$ parameters of each isomer must be calculated and weighted according to their Boltzmann population. Secondly, the solvent–base halogen-bond interaction must be explicitly taken into account when the base possesses a significant second basic site B_2 so that Equation (5) is replaced by Equations (6) and (7) for the calculations of dibasic $B_1<>B_2$ compounds.

$$B_1<>B_2\text{---Cl-CCl}_3 + HF \rightleftharpoons FH\cdots B_1<>B_2\text{---Cl-CCl}_3 \quad (6)$$

$$Cl_3C\text{-Cl---}B_1<>B_2 + HF \rightleftharpoons Cl_3C\text{-Cl---}B_1<>B_2\cdots HF \quad (7)$$

The situation can be even more complicated when the various HB accepting centres of polyfunctional molecules have strong chemical similarities. This is, for example, the case in the substituted myosmines **1d**–**f** (Scheme 1), in which the two sp^2 nitrogen basic sites possess very similar HB features, making the experimental separation of the individual complexation constants at the two sites rather difficult. Indeed, the overlapping of the characteristic vibrations of the two rings prevents the use of a spectroscopic probe specific to each site. Moreover, the C=N absorption is known to be very insensitive to HB formation.[19] In these compounds, an additional complication arises from the direct conjugation between the two sites (see below) so that the association at one site influences the basicity of the second site more strongly than in the nicotinic analogues in which conjugative interactions cannot occur.[14]



Scheme 1. Numbering of myosmine and the model compounds studied.

For all these reasons, myosmines represent an interesting challenge to check the validity of our model. Furthermore, it is rather surprising to observe that the HB basicity of simple molecules such as pyrroles and pyrrolines, which are the basic units of the biologically essential porphyrins and hemes, has not been the subject of a systematic evaluation so far. Finally, note that myosmine, as a specific tobacco alkaloid, is commonly present in very low concentration in many fruits and vegetables.[20] Despite its low affinity towards nicotinic acetylcholine receptors (nAChRs), it presents some interesting biological properties. It was evaluated as a moderate inhibitor of cytochrome P450 2A6 implicated in the metabolism of nicotine,[21] and so it may help in smoking cessation by maintaining a significant concentration of nicotine in the blood. As a modest inhibitor of acetylcholinesterase (AChE), it also regulates the acetylcholine synaptic concentration with positive effects against neurodegenerative diseases.[22]

Among the numerous papers devoted to HB strength prediction, Gilli et al. established recently in an impressive work[23] the pK_a slide rule based on an "approximate graphical evaluation of ΔpK_a for any donor–acceptor couple, so allowing empirical prediction of the H-bond strengths in terms of pK_a matching". This rule is indeed of great interest for a quick but approximate evaluation of HB strength for a given donor–acceptor couple. For more quantitative predictions, further approaches are needed. Furthermore, the pK_a slide rule appears restricted to monofunctional donor–acceptor couples. Our methodology leads to more quantitative estimates and is suitable for polyfunctional molecules. In this work we apply our methodology to the example of five-membered N-heterocycles and to bifunctional compounds from the myosmine family.

We therefore present a combined theoretical and experimental study of a series of five-membered rings containing a nitrogen heteroatom to locate the place of the 1-pyrroline

family as the myosmines **1d**–**f** can be considered as *ortho*-substituted 1-pyrrolines. We report the different methods used to achieve the HB basicities of the pyridine and imine sites of three substituted myosmines and we compare them to their global equilibrium constants that have been measured experimentally in carbon tetrachloride. These synthetic precursors of nicotines have been isolated and analysed because they present, in addition to the above-mentioned features, the two essential difficulties that have been claimed to be surmounted when a correct application of Equation (4) is carried out. First, they show in significant amounts two well-defined isomers in CCl_4 solution in which each nitrogen site shows a significant basicity. Secondly, in both isomers, each nitrogen site shows a significant but different basicity. Therefore, in a ternary diluted solution of myosmine and pFP in CCl_4, four different associations can be found, and the only experimentally accessible value is the weighted sum of the equilibrium constants. To confirm the importance of the halogen-bond interaction at the second site, we have also analysed the thermodynamic, spectroscopic and theoretical parameters of the closely related substructures and models represented in Scheme 1: (i) 2-substituted pyrrolines **1a**–**c** as monofunctional *ortho*-phenyl-substituted pyrrolines, (ii) substituted acetophenones **2a**–**c** as oxygen homologues of phenylpyrrolines and (iii) 3-acetylpyridine **2d** as a model of myosmine.

Results and Discussion

HB Affinity of the Monofunctional Bases

Variation of HB Acceptor Strength in Five-Membered N-Heterocyclic Compounds

Much of the experimental and theoretical data on mono- and polyheteroatomic five-membered rings, such as substituted imidazoles, pyrazoles, oxazoles and thiazoles, has already been analysed in our preliminary work on the HB basicity of nitrogen bases.[18] Hence, the data in Table 1 is limited to the experimental and/or calculated pK_{BHX} values of a few diverse five-membered N-heterocyclic compounds. The basicity range of these compounds appears to be extremely large because the nitrogen atoms belong to very different families depending on the number and positions of the double bonds.

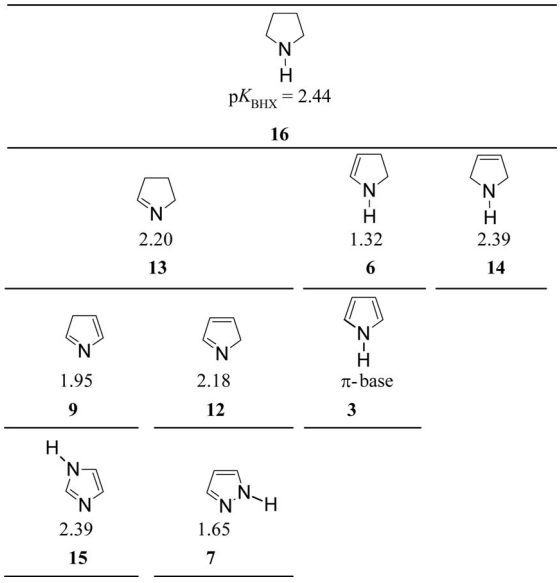
In Scheme 2, the saturated frame of pyrrolidine (**16**) was used as a starting point for comparison. One can introduce the first double bond into three possible positions. The nitrogen HB basicity decreases systematically, but the position of the double bond strongly influences the nitrogen accepting strength. In 1-pyrroline (**13**), the change in the hybridization of the nitrogen atom results in a decrease in the equilibrium constant by about 40% compared with that of pyrrolidine. This loss of basicity, in line with the diminution of p character, has been attributed to a reduction of the charge transfer between the nitrogen lone-pair and the anti-bonding XH orbital of the HB donor.[18] The nitrogen basicity of 3-pyrroline (**14**) is only slightly weakened by the small electron-withdrawing effect of the unsaturation[26] when the nitrogen and the double bond are separated by a methylene group. The most severe fall in basicity is observed for 2-pyrroline (**6**), in which the double bond induces an important delocalization of the nitrogen lone-pair leading to a reduction of about 90% in the equilibrium constant. On the electrostatic potential map of this compound (Figure 1), a very weak secondary minimum may be detected on the C3 π electrons. Moreover, considering the complex of HF at this site, geometry optimization [B3LYP/6-31+G(d,p)] leads to an effective energetic local minimum. Pyrrole (**3**) is obtained by the introduction of a second double bond into the frame of 2-pyrroline (**6**). The nitrogen lone-pair is now totally delocalized on the π cloud, as clearly seen in Figure 1, in which the most negative (red) electrostatic potential region is located on the C3 and C4 carbon atoms rather than on the nitrogen. Hence, pyrrole is no more a nitrogen base, but rather a π HB acceptor.[27] Note that pyrrole (**3**) and *N*-methylpyrrole (**4**) are, by far, the strongest π HB acceptors ever measured (Table 1) as the upper limit of the pK_{BHX} scale for π bases was 0.02 with hexamethylbenzene.[8] This limit has not been overcome in the arylamine series[12] because in these molecules the nitrogen lone-pair is only partially delocalized on the benzene ring and a residual basicity remains on the nitrogen atom. A second unsaturation added to the structure of 1-pyrroline (**13**) provides either 2*H*-pyrrole (**12**) or 3*H*-pyrrole (**9**) N_{sp^2} bases. In the latter, the N_{sp^2} nitrogen is linked to two C_{sp^2}-hybridized atoms and presents a HB accepting strength (pK_{BHX} = 1.95) comparable to that of pyridine (pK_{BHX} = 1.86).[11] From compounds **9** and **12**, the substitution of the remaining methylenic carbon by an amino nitrogen atom yields the structures of imidazole (**15**) and pyrazole (**7**), respectively. The important nitrogen HB basicity might be predicted for imidazole owing to the strong resonance electron-donating effect of the introduced nitrogen atom. This electron-donor nitrogen is, in turn, totally deactivated from its HB accepting potential, as shown in the electrostatic potential map of **15** in Figure 1, and stands as a non-basic

Table 1. Calculated and/or experimental HB basicities of five-membered N-heterocycles.

	Compound	$pK_{BHX(exp)}$[a]	$pK_{BHX(calcd.)}$[b]	Family
3	pyrrole	0.15		π base
4	*N*-methylpyrrole	0.23		π base
5	*N*-methyl-2-pyrroline		1.13	enamine
6	2-pyrroline		1.32	enamine
7	pyrazole		1.65[c]	imine
8	*N*-methylpyrazole	1.82	1.84	imine
9	3*H*-pyrrole		1.95	imine
10	*N*-methyl-3-pyrroline		2.04	amine
11	*N*-methylpyrrolidine	2.25[d]	2.15[c]	amine
12	2*H*-pyrrole		2.18	imine
13	1-pyrroline		2.20	imine
14	3-pyrroline		2.36	amine
15	imidazole	2.47[c]	2.39[c]	imine
16	pyrrolidine	2.56[e]	2.44[c]	amine
17	*N*-methylimidazole	2.70[c]	2.63[c]	imine

[a] Experimental value determined in CCl_4 or C_2Cl_4. [b] Calculated from Equation (4). [c] Ref.[18] [d] Ref.[24] [e] Ref.[25]

"pyrrole-like" nitrogen.[28] When the second nitrogen atom is in the α position of the first one, such as in pyrazole (**7**), its HB basicity is also completely lost, as illustrated by the



Scheme 2. Chemical structures and calculated pK_{BHX} values of the five-membered N-heterocycles investigated. The pK_{BHX} value of pyrrole **3**, being a π base, cannot be determined from Equation (4) established for nitrogen acceptors.

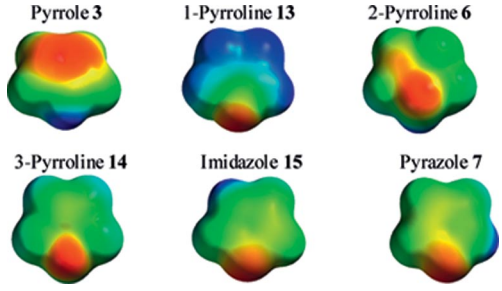


Figure 1. Electrostatic potential at the molecular surfaces of pyrrole, pyrrolines, imidazole and pyrazole. The orientations of the heterocycles are as shown in Scheme 2.

electrostatic potential map (Figure 1). Conversely, its electron-withdrawing inductive effect strongly reduces the basicity of the imine nitrogen [pK_{BHX}(**12**) = 2.18 and pK_{BHX}(**7**) = 1.65].

The methylation of the endocyclic nitrogen, whenever possible, is also very interesting to consider. On the one hand, it leads to a regular decrease in the HB accepting strength when the methylation occurs at an amino site, as in *N*-methylpyrrolidine (**11**), *N*-methyl-3-pyrroline (**10**) and *N*-methyl-2-pyrroline (**5**). This general trend has been explained by the predominance of the steric effect over the polarisability effect of the methyl group.[24] On the other hand, when the HB acceptor site is not the methylated nitrogen, as in *N*-methylpyrrole (**4**), *N*-methylpyrazole (**8**) and *N*-methylimidazole (**17**), the steric effect does not operate anymore and the basicity of the site is strengthened. This is the case for the π cloud of **4** and the N_{sp^2} nitrogen atoms of **8** and **17**. The most important rise in basicity is found for *N*-methylimidazole, in which the internal electronic push–pull effect confers on this N_{sp^2} base a HB affinity equivalent to the most basic amine (quinuclidine: pK_{BHX} = 2.71).[24]

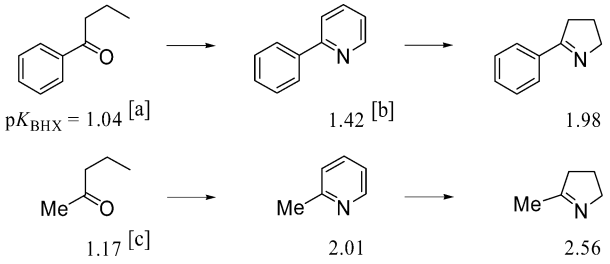
2-Phenylpyrrolines and Acetophenones

2-Phenylpyrrolines and acetophenones are monofunctional structural models of myosmine. The thermodynamics for their HB complexation and their spectroscopic parameters are summarized in Table 2. With the help of Scheme 3, the HB accepting strength of the 1-pyrroline nitrogen can be positioned in the general pK_{BHX} scale, revealing the important HB affinity of the 1-pyrroline family. 2-Phenyl-1-pyrroline (**1a**) is thus more basic than its carbonyl homologue butyrophenone[29] by about 1 p*K* unit and it is 0.56 p*K* units more basic than 2-phenylpyridine.[11] As revealed in the second line of Scheme 3, a similar increase in the HB affinity is observed when the phenyl group is replaced by a methyl group, a less bulky substituent without any electron-withdrawing effect. In addition, the comparison between the pK_{BHX} values of the two series collected in Table 2

Table 2. Thermodynamic and spectroscopic parameters of the HB association of pFP and methanol with the reference compounds in CCl_4.

Compound	pK_{BHX}	$-\Delta G^{\circ}_{BHX}$[a] [kJ mol^{-1}]	$-\Delta H^{\circ}_{BHX}$[a] [kJ mol^{-1}]	$-\Delta S^{\circ}_{BHX}$[a] [J K^{-1} mol^{-1}]	$\Delta\nu_{(OH)}$[b] [cm^{-1}]	$\nu_{(C=X)}$ [cm^{-1}]
Pyrrolines						C=N
2-Phenyl-1-pyrroline	1.98	17.0	31.0	46.7	314	1617.1[c]
2-(3-Fluorophenyl)-1-pyrroline	1.66	15.2	29.0	46.3	297	1619.5[c]
2-[3-(Trifluoromethyl)phenyl]-1-pyrroline	1.52	14.4	28.0	45.6	287	1623.0[c]
Acetophenones						C=O
Acetophenone	1.11[d]	12.1	20.8	28.7	92[c]	1690.8
3-Fluoroacetophenone	0.83[d]	–	–	–	–	1695.9
3-(Trifluoromethyl)acetophenone	0.72[d]	–	–	–	68[c]	1697.8

[a] Measured relative to concentrations expressed in mol fractions. [b] Frequency shift of methanol upon association of the base. [c] Doublet. [d] Ref.[13]



Scheme 3. Comparison of the basicities of the 2-substituted-pyrrolines and their pyridine and carbonyl homologues. [a] Ref.[29] [b] Ref.[11] [c] Ref.[13]

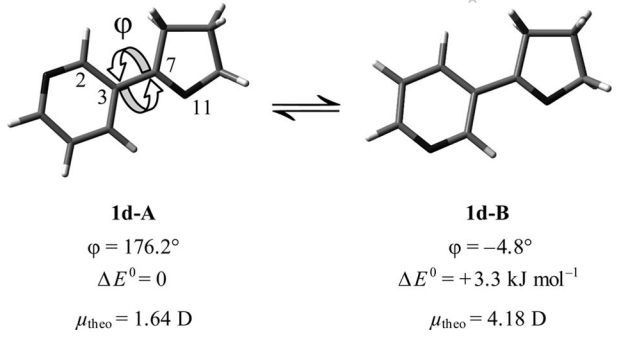


Figure 2. Structural parameters of the two A and B stable isomers of myosmine calculated at the B3LYP/6-31+G(d,p) level of theory.

shows a significantly greater sensitivity of the phenylpyrroline family to the substituent effect, as illustrated by the slope of Equation (8).

$$pK_{BHX(2\text{–phenyl-1-pyrrolines})} = 1.172\,pK_{BHX(acetophenones)} + 0.681 \quad (8)$$

$r = 0.9997$; $s = 0.008$; $n = 3$

Rotational Isomerism of the Bases

The only significant degree of freedom of myosmine, acetylpyridine and their models, phenylpyrrolines and acetophenones, is the rotation around the C3–C7 single bond presented in Figure 2 for myosmine (**1d**). The corresponding rotational profile for myosmine calculated by using a relaxed scan shows two minima named A and B by analogy with the denomination adopted by Elmore and Dougherty for nicotine.[30] Both isomers are quasi-planar and their energies differ by 3.5 kJ mol^{-1} in favour of the less polar isomer A in which the lone-pair vectors of the two nitrogen atoms are in opposition. The barrier height was found to be 26 kJ mol^{-1} and the transition states correspond to structures with two orthogonal rings.

The theoretical dihedral angle ϕ and dipole moment μ_{theo} are gathered in Table 3 for each isomer of the studied compounds. Their relative populations p were calculated by a Boltzmann function using the electronic energies corrected from the zero-point energies of the two structures A and B. The dipole moment of each molecule was then estimated by considering the molar polarization additivity of its isomers, and scaled to benzene solution by using the calibration line published in a previous work.[1] All the available experimental dipole moments are in fairly good agreement with the calculated values, despite the different approximations made in the calculations. With the two molecules of myosmine (**1d**) and 3-acetylpyridine (**2d**), for instance, one obtains a ratio of 70:30 for the A/B populations from a back calculation starting from the experimental dipole moment, whereas the values obtained from the theoretical calculations are 80:20.

An important observation that can be extracted from Table 3 is the specificity of the endocyclic nitrogen aza substituent effect on the isomeric equilibrium. Although the calculated populations of the two A and B isomers are approximately equal for all the six substituted phenylpyrrolines and acetophenones, the pyridyl group notably dis-

Table 3. Estimated relative populations, dihedral angles and dipole moments of isomers A and B for the series of pyrrolines and acetophenones [estimated at the B3LYP/6-31+G(d,p) level of theory].

Compound	Isomer A				Isomer B		Molecule	
	$\Delta E°_{(A/B)}$[a] [kJ mol^{-1}]	p[b] [%]	ϕ[c] [°]	μ_{theo}[d] [D]	ϕ[c] [°]	μ_{theo}[d] [D]	μ_{calc}[e] [D]	μ_{exp} [D]
Pyrrolines								
2-Phenyl-1-pyrroline	0.0	50	175.8	1.86	–4.0	1.86	1.72	
2-(3-Fluorophenyl)-1-pyrroline	0.2	48	176.3	1.41	–3.3	3.60	2.58	
2-(3-Trifluoromethylphenyl)-1-pyrroline	–1.2	62	177.6	2.40	–3.7	5.00	3.37	
Myosmine	–3.3	79	176.2	1.64	–4.8	4.18	2.23	2.42[f]
5-Bromomyosmine	–2.3	72	176.3	3.08	–7.4	3.73	3.04	
6-Methylmyosmine	–3.1	77	176.8	0.92	–4.2	3.75	1.82	
Acetophenones								
Acetophenone	0.0	50	180.0	3.28	0.0	3.28	3.05	2.95[g]
3-Fluoroacetophenone	0.4	46	180.0	1.51	0.0	4.13	2.97	2.86[g]
3-(Trifluoromethyl)acetophenone	–1.3	63	179.9	0.37	–0.7	5.03	2.86	3.01[g]
3-Acetylpyridine	–3.4	80	180.0	0.97	–0.3	4.58	2.06	2.33[h]

[a] Energy difference between the A and B isomer corrected from the zero-point vibrational energy. [b] Boltzmann population of isomer A calculated from $\Delta E°_{(A/B)}$. [c] Dihedral angle C2–C3–C7–N11. [d] Theoretical dipole moment of the isomer. [e] Estimated value of the molecule dipole moment weighted by the isomer relative population and calculated in benzene by using Equation (12) of ref.[1]: $\mu_{calc} = 0.931\mu_{theo} - 0.007$. [f] This work; solvent: C_2Cl_4. [g] Ref.[31,32]; solvent: benzene. [h] Ref.[33]; solvent: benzene.

places the equilibrium in favour of the less polar rotamer A. This effect is partly confirmed by the experimentally determined dipole moments of myosmine and acetylpyridine, which correspond to populations of about 72% of isomer A.

HB Affinity of the Polyfunctional Bases

Experimental Analysis

As shown in Table 4, 3-acetylpyridine is the only compound for which it has been possible to separate the total equilibrium constant experimentally. For these polyfunctional molecules, we analysed the equilibrium constant over widely different concentration ratios C_a°/C_b° (pFP/base) in order to vary significantly the apparent equilibrium constant K_{app}, as shown in Table 5 for 6-methylmyosmine (**1f**). Despite these important variations, the numerical methods proposed by Clotman et al.[34] or Roland,[35] which have been successfully adapted for polyfunctional compounds in the cases of nicotine, nornicotine[14] or cotinine,[1] yield inconsistent values for the individual basicities of the imine and pyridine sites of the myosmines. The approximation of the independence of the two sites on which these equations are built (the association at one site does not alter appreciably the HB affinity of the other site) is clearly inappropriate for myosmine derivatives. Indeed, whereas the two rings were found to be quasi-perpendicular for nicotine and substituted phenylpyrrolidines,[36] we have shown that they are very nearly co-planar for myosmines and phenylpyrrolines (Table 3). This conformation causes a π-electron delocalization from one nitrogen ring to the other, which involves the non-independence of the two nitrogen sites. Moreover, in our sample of molecules, the mean length of the pivotal C3–C7 bond (1.478 Å), which is 0.04 Å shorter than in the nicotine derivatives, confirms the stronger interaction between their two nitrogen rings. We have therefore limited our selection of data to experiments carried out with a large excess of base in which the 1:2 (base/pFP) complexation is negligible. Within these conditions, the precision of the total equilibrium constants K_t (Table 4), which corresponds to the exact sum of the two 1:1 individual equilibrium constants, is estimated to be at around 10%. For the unique case of 3-acetylpyridine (**2d**), however, we were able to measure independently the equilibrium constant of the pyridinic nitrogen by using the ν1 pyridinic vibration located at 1022 cm^{-1} (molar extinction coefficient, ε = 22.2 $dm^3 mol^{-1} cm^{-1}$; half band width = 4.4 cm^{-1}), which undergoes a blueshift of 7 cm^{-1} on association with the phenol. The method, which requires the simultaneous evaluation of the total concentration of the complex and the individual concentration of the phenol associated with the pyridinic nitrogen site, has been described in a previous paper.[1] Furthermore, an indirect but independent and precise estimation of the basicity of the carbonyl group can also be made from the frequency of the carbonyl absorption [$\nu_{(C=O)}$ = 1695.3 cm^{-1}] by using the calibration frequencies of the acetophenones given in Table 2, with the fluorine and trifluoromethyl substituents being selected to surround the endocyclic aza substituent.[36] This approach cannot be used for myosmines because, as already mentioned, the corresponding $\nu_{(C=N)}$ vibrations of the three derivatives **1d**–**f** at around 1619 cm^{-1} are insensitive to the association[19] and are strongly coupled with other C=C vibrations so that no further information can be gained from the IR spectra of this series of molecules.

Table 4. Experimental equilibrium constants and frequencies of the polyfunctional compounds in CCl_4.

Compound	K_t[a] [$dm^3 mol^{-1}$]	n[b]	$K_{pyridine}$ [$dm^3 mol^{-1}$]	$K_{carbonyl}$ [$dm^3 mol^{-1}$]
Myosmine	100	3		
5-Bromomyosmine	35	6		
6-Methylmyosmine	141	3		
3-Acetylpyridine	33	4	24.4[c]	8.0[d]

[a] Mean value of the n determination for which C_b°/C_a° is greater than 5. [b] Number of independent measurements. [c] Measured independently from the ν1 pyridine ring absorption at 1022 cm^{-1} for six independent determinations. [d] Calculated from the position of the carbonyl stretching vibration, $\nu_{(C=O)}$ = 1695.3 cm^{-1}.

Table 5. Variation of the apparent equilibrium constant between 6-methylmyosmine (**1f**) and pFP.

Solution	C_a°[a] [$mmol\,dm^{-3}$]	C_b°[b] [$mmol\,dm^{-3}$]	r[c]	C_a[d] [$mmol\,dm^{-3}$]	K_{app} [$dm^3 mol^{-1}$]
1	5.49	0.67	0.12	5.15	209.3
2	5.50	1.36	0.25	4.85	189.4
3	5.48	2.66	0.48	4.30	185.6
4	5.52	5.10	0.92	3.61	165.9
5	4.75	8.55	1.80	2.42	154.7
6	5.49	10.20	1.86	2.58	154.0
7	5.53	14.46	2.62	2.08	150.2
8	4.72	24.16	5.12	1.19	144.1
9	4.75	27.68	5.83	1.08	141.9
10	5.41	40.68	7.52	0.90	138.2

[a] Initial concentration of pFP. [b] Initial concentration of 6-methylmyosmine. [c] $r = C_b^\circ/C_a^\circ$. [d] Equilibrium concentration of uncomplexed pFP.

Theoretical Evaluation of the Individual Basicities

An accurate and cost-effective method of prediction of the HB basicity has been recently published in detail for nitrogen compounds.[18] To simulate the association equilibrium between a nitrogen base and pFP in CCl_4, we considered the complexation of this base with hydrogen fluoride in vacuo according to equilibrium (5) at the B3LYP/6-31+G(d,p) level of theory. Under these conditions, the experimental complexation enthalpies ΔH_{HB}° of numerous molecules containing sp-, sp^2- or sp^3-hybridized nitrogen atoms were evaluated with unprecedented precision from the theoretical enthalpies $\Delta H^{\circ(HF)}$ and the calibration Equation (9).[18]

$$\Delta H_{HB}^\circ = 0.616\Delta H^{\circ(HF)} + 3.400 \quad (9)$$

r = 0.992; s = 0.85; n = 59

On the contrary, the theoretical free energies calculated from this model reaction yielded family-dependent relationships with the experimental pK_{BHX} values. Any new acceptor family or unusual molecular environment of the ba-

sic atom should thus necessitate a preliminary calibration towards pK_{BHX}. Hence, we developed the biparameter Equation (4). This equation appeared to be very satisfactory for evaluating the free-energy pK_{BHX} scale of a great number of diverse nitrogen bases.[18] Simplification of the experimental model leads, however, to two possible limitations relevant for the molecules under study in this paper. First, the molecules with very large steric effects (front strain) around the accepting nitrogen group may appear more basic by theory with HF than in the experiment with the bulkier pFP. Indeed, a significant decrease in the HB basicity was found experimentally (0.58 pK_{BHX} units) when we compared either 2-methyl- and 2-phenylpyridine or 2-methyl- and 2-phenylpyrroline (Scheme 3), whereas the basicity gap is significantly lower (only 0.11 pK_{BHX} units) between 4-methyl- and 4-phenylpyridine[11] for which there is no steric effect. Considering the theoretical results, the case of substituted 2-phenylpyrrolines **1a**–**c** reveals that this effect is well taken into account by the selected theoretical model, HF, for the *o*-phenyl groups. Indeed, the first three rows of Table 6 give calculated parameters that perfectly match the corresponding experimental ΔH°_{HB} and pK_{BHX} data of Table 2, the larger error being 0.02 p*K* units on the free-energy scale. The neglect of the solvent effect in the calculation is the second cause of error in our model. By using Equation (4) for several polyfunctional molecules it rapidly became apparent that their global basicities were systematically overestimated by the calculations. We have shown[18] that this default indeed finds its origin in the fact that the interaction between the solvent and the secondary site of the molecule is not taken into account, the primary site being hydrogen-bonded to HF. Lamarche and Platts[37] definitely demonstrated recently that the inclusion of the solvent effect by the polarizable continuum model (PCM) did not offer any improvement in the statistics of the correlations. We therefore considered the specific association between the nitrogen lone-pair and the electrophilic moiety of one CCl_4 chlorine atom, as presented in Equations (6) and (7). Significant improvements in the predicted HB basicities were indeed found in all polyfunctional molecules in which this halogen bond was taken into account. Despite the multiplication of the necessary optimization processes and their corresponding computational time, this methodology has been applied to the studied myosmine derivatives. Thus, for each isomer, the structure of the complex corresponds to a myosmine frame with a CCl_4 molecule halogen-bonded to one site with the other site hydrogen-bonded to HF. The four corresponding optimized structures of myosmine (**1d**) interacting with HF and CCl_4 are shown in Figure 3. In the same way, two CCl_4 molecules have been bonded to the two putative lone-pairs of the carbonyl group of 3-acetylpyridine in the calculation of the pyridinic HB association of HF. The results are presented in the last four rows of Table 6.

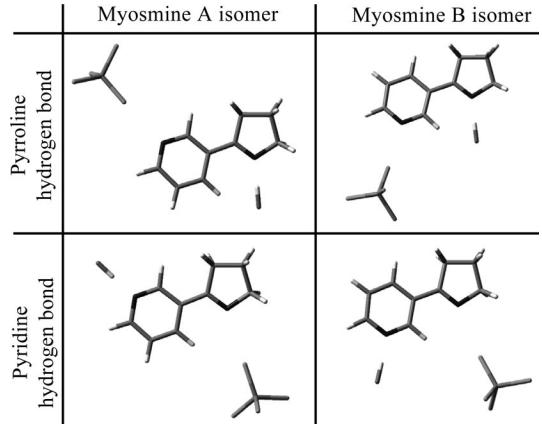


Figure 3. Optimized structures [B3LYP/6-31+G(d,p)] of myosmine (**1d**) with HF hydrogen-bonded either to the pyridine or the pyrroline site, and CCl_4 halogen-bonded to the other site.

Table 6. Theoretical descriptors and predicted HB basicities of the reference phenylpyrrolines and the polyfunctional myosmines and acetylpyridine.

Compound	Site	Theoretical descriptors				Predicted HB basicities			
		Isomer A		Isomer B		Molecule			
		$-V_{s,min}$ [kJ mol^{-1}]	$-D_0^{(HF)}$ [kJ mol^{-1}]	$-V_{s,min}$ [kJ mol^{-1}]	$-D_0^{(HF)}$ [kJ mol^{-1}]	pK_{BHX}[a]	K_i[b] [dm^3 mol^{-1}]	K_t[c] [dm^3 mol^{-1}]	$-\Delta H^{\circ}_{HB}$[d] [kJ mol^{-1}]
2-Phenyl-1-pyrroline	N_{imine}	148.6	53.8	[e]	[e]	1.98	96	96	31.6
2-(3-Fluorophenyl)-1-pyrroline	N_{imine}	136.1	51.8	138.7	49.8	1.68	48	48	29.7
2-[3-(Trifluoromethyl)phenyl]-1-pyrroline	N_{imine}	124.7	50.9	132.9	47.2	1.51	32	32	28.9
Myosmine[f]	N_{imine}	123.0	51.7	135.9	46.7	1.56	36.0	103	29.7
	$N_{pyridine}$	151.0	50.6	166.3	49.5	1.82	66.6		29.2
5-Bromomyosmine[f]	N_{imine}	114.2	47.6	121.2	45.8	1.24	17.5	40	27.1
	$N_{pyridine}$	133.5	45.7	146.7	44.5	1.34	22.1		26.1
6-Methylmyosmine[f]	N_{imine}	130.4	52.8	144.0	47.7	1.71	50.7	127	30.3
	$N_{pyridine}$	146.9	52.3	162.5	50.8	1.88	76.6		30.3
3-Acetylpyridine[f]	$O_{carbonyl}$	140.7	35.0	145.2	35.5	0.80	(6.3)[g]	(32)	
	$N_{pyridine}$	130.3	46.5	146.4	45.5	1.41	25.7		26.7

[a] Calculated from Equation (4) with theoretical descriptors weighted by the relative populations found in Table 3. [b] $K_i = 10^{pK_{BHX}}$. [c] $K_t = K_{i(imine\ or\ carbonyl)} + K_{i(pyridine)}$. [d] Calculated from Equation (9) with theoretical descriptors weighted by the relative populations found in Table 3. [e] Isomers **A** and **B** are identical. [f] The other potential acceptor site is halogen-bonded to a CCl_4 molecule. [g] Approximate value because Equation (4) has not been calibrated for oxygen bases.

The excellent concordance between the calculated values presented in Table 6 and the experimental data of Tables 2 and 4 validates the theoretical method of basicity evaluation developed in our previous paper for nitrogen compounds.[18] All the calculated equilibrium constants, or the sum of the equilibrium constants, fit the experimental data with a maximum difference of 14%, or 0.06 pK units, in the case of the bifunctional 5-bromomyosmine (**1e**). For the three phenylpyrrolines **1a**–**c**, myosmine (**1d**) and 3-acetylpyridine (**2d**), the pK_{BHX} values are calculated to within 0.02, which is better than the experimental error. Therefore the data obtained for the monofunctional phenylpyrrolines show that the method properly estimates the basicity of flexible molecules present in two isomeric structures of different basicity in solution and substituted by a significantly steric group. When the solute is polyfunctional, the interaction of the solvent molecule with the secondary site decreases its electronic density so that it becomes more electron-withdrawing towards the primary HB donor site (and vice versa). This halogen-bond interaction is expected to reduce somewhat the basicity of the other site depending on the distance and the nature of the separating bonds between the two functions. We present in Table 7 the effect of the solvent interaction consideration for myosmine as an example. For both imine and pyridine sites, the equilibrium constant is significantly reduced when a specific interaction with the CCl_4 molecule is taken into account. The final calculated equilibrium constant matches exactly the experimental value, K_t = 100, whereas a large over-estimation of the whole HB basicity of myosmine, about 30%, is induced by the neglect of the solute–solvent interaction.

Table 7. Equilibrium constants of HF association with the imine and pyridine sites of myosmine in the presence and absence of a halogen bond with CCl_4 at the other site.

Reactants	HF complexation site		
	$K_{i(imine)}$[a] [dm^{3}mol^{-1}]	$K_{i(pyridine)}$[a] [dm^{3}mol^{-1}]	K_t[b] [dm^{3}mol^{-1}]
Myosmine-CCl_4 + HF	36	67	103
Myosmine + HF	49	82	131

[a] Weighted value for the A and B isomers. [b] $K_t = K_{i(imine)} + K_{i(pyridine)}$.

In these calculations, in which the sum of the two calculated equilibrium constants is the only result to be compared with the experimental data, no compensation between the two individual results was possible because they were carried out independently from different optimized reactants and products. Therefore, the individual basicities can be mixed with confidence with the results of the monofunctional derivatives. For instance, for 3-acetylpyridine (**2d**), the experimental complexation constant with the nitrogen group (24.4 dm^{3}mol^{-1}) was correctly estimated with a relative difference of around 5% (25.7 dm^{3}mol^{-1}). For myosmine, the predicted basicity of the pyridine site can be compared with the calculated value from the empirical substituent effects relationship [Equation (10)], established for a series of *meta*-substituted pyridines.[11] The σ values of the 1-pyrrolin-2-yl substituent (σ_α = –0.71, σ_F = 0.044, σ_R = 0.02) were calculated ab initio as described previously[14,36,38,39] and the empirical value [pK_{BHX} = 1.83, $K_{i(pyridine)}$ = 67.2 dm^{3}mol^{-1}] corroborates our theoretical value, $K_{i(pyridine)}$ = 66.6 dm^{3}mol^{-1} (Table 6). Considering the imine site of myosmine, its HB basicity (K = 36 dm^{3}mol^{-1}) was correctly estimated to be between the two values of compounds **1b** (K = 48) and **1c** (K = 32), which were specifically synthesized because the electronic effects of the 2-(3-fluorophenyl)- and 2-(3-trifluoromethylphenyl) substituents are known to bracket the 3-pyridyl group.[36]

$$pK_{BHX} = 1.86–0.10\sigma_\alpha – 1.79\sigma_F – 1.14\sigma_R \quad (10)$$

r = 0.998; s = 0.02; n = 10

Finally, we have compared the HB basicities of the two sites of the substituted myosmines **1d**–**f** with those of the corresponding 2-methylpyridine, pyridine and 3-bromopyridine (Figure 4).[11] Two conclusions may be drawn from this plot. First, the pyridinic site is always more basic than the pyrrolinic site despite the much greater HB basicity of pyrroline (pK_{BHX} = 2.20) compared with pyridine (pK_{BHX} = 1.86).[11] This is clearly due to the important steric effect that the 2-pyridyl group exerts on the imine nitrogen. Secondly, the substituent influences just slightly more the pyridinic nitrogen than the pyrrolinic one as could be expected by the relative distances between each functional group and the substituent.

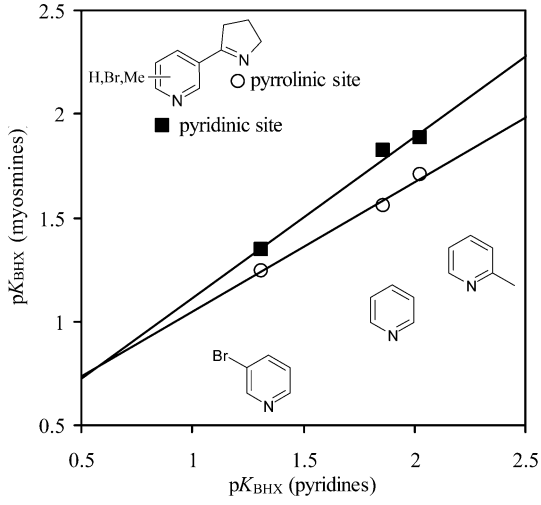


Figure 4. Influence of the pyridyl substitution on the HB strength of the substituted myosmines in comparison with the corresponding pyridines.

Conclusions

Experimental and theoretical HB accepting capacities of five-membered N-heterocycles have been determined. The introduction of one or two double bonds has a strong effect on their HB basicity, leading to a wide basicity range, from strong nitrogen HB bases to very weak π bases. This analysis gives quantitative guidelines for HB basicity modulation

in N-heterocycles, motifs recurrently encountered in molecules of biological significance.

The calibration line (4), developed recently for the prediction of the HB basicity of nitrogen compounds,[18] has been validated for polyfunctional compounds, showing acceptor sites with similar strengths. By using the cost effective B3LYP/6-31+G(d,p) level of theory, a careful consideration of each isomer of myosmine and of a specific halogen bond to the non-hydrogen-bonded site was carried out. This approach led to an accurate estimation of the individual HB basicity of the pyridinic and pyrrolinic sites of myosmine.

Experimental and Computational Details

Chemicals: Pyrrolines **1a**–**f** were synthesized following the protocol of Bleicher et al.[40] adapted to the reaction path proposed by Jacob.[41] They were sublimed over P_2O_5 and their purities checked by NMR and IR spectroscopy. All other compounds are commercial products purified by standard procedures and carefully dried. Carbon tetrachloride and tetrachloroethylene solvents were of spectroscopic grade and kept for several days over freshly activated 4 Å molecular sieves before use. 4-Fluorophenol was sublimed over P_2O_5. Solutions were prepared and cells were filled inside a dry glove box.

Dipole Moments: The dielectric permittivities in tetrachloroethylene solutions of myosmine (**1d**) were measured with a WTW dipolemeter DM 01 working at a frequency of 2 MHz. The DFL1 cell used in this work allowed high precision dielectric measurements ($\Delta\varepsilon/\varepsilon = 10^{-5}$) in the permittivity range of 1–3.4. It was calibrated with cyclohexane (ε = 2.0228), carbon tetrachloride (ε = 2.2326) and benzene (ε = 2.2825) at a temperature of 20 °C. The refractive indexes were obtained with an uncertainty of 2×10^{-5} on a Schmidt Haensch DNR-W2 refractometer thermostatted at 20 °C. The dielectric constant and the refractive index measurements were carried out on three solutions of weighted fractions (3.9×10^{-4}, 2.0×10^{-4} and 9.9×10^{-5}) and on the pure solvent. The experimental dipole moment was calculated with the Guggenheim–Smith[42,43] Equation (11) by using the slopes of the linear variations $a(\varepsilon)$ and $a(n^2)$ of the dielectric permittivity and of the square of the refractive index of the solution with the weight fraction of the solute:

$$\mu^2/D^2 = \frac{27kT}{4\pi N}10^{-38}\ \frac{M_2}{d_1}\left[\frac{a(\varepsilon)-a(n^2)}{(\varepsilon_1+2)^2}\right] = 0.144\ \frac{M_2}{d_1}\left[\frac{a(\varepsilon)-a(n^2)}{(\varepsilon_1+2)^2}\right] \quad (11)$$

In Equation (11), k is the Boltzmann constant, N the Avogadro number, M_2 is the molar mass of the solute and d_1 and ε_1 are, respectively, the measured density and dielectric permittivity of the solvent. The experimental slopes, $a(\varepsilon)$ = 8.71 and $a(n^2)$ = 0.459, yield a value μ_{1a} = 2.42 D (1 D = 3.336×10^{-3} C m) for the dipole moment of myosmine in C_2Cl_4, in excellent agreement with the value measured for its carbonyl model, 3-acetylpyridine, μ_{2d} (benzene, 25 °C) = 2.33 D.[33]

FTIR Spectrometry: The IR spectra were recorded in carbon tetrachloride solutions with a Fourier-transform spectrometer Bruker Tensor 27 at a resolution of 1 cm^{-1}. CaF_2 cells of 2, 1 and 0.1 mm path lengths were used for the study of the double bonds (C=N and C=O) and the pyridinic ν1 absorptions near 1650 cm^{-1} and 1020 cm^{-1}, respectively. By using the free pFP OH absorption at 3614 cm^{-1}, the measurement of the absorbance decrease leads to pK_{BHX} and ΔH°_{BHX} values. The 1 cm infrasil quartz cell used was thermostatted at 25.0 ± 0.2 °C by a Peltier effect regulation. The equilibrium constants of the polyfunctional bases such as myosmines **1d**–**f** and 3-acetylpyridine (**2d**) were analysed by using the methods described in a preceding article.[1] Accurate enthalpy measurements were carried out by following the absorbance of a single solution as a function of temperature.[44,45] In a typical measurement, the spectra of a solution containing approximately 4 mmol dm^{-3} of pFP and a base concentration adjusted so that about 50% of the phenol was complexed at 25 °C were recorded at five temperatures between –5 and +55 °C. The enthalpy ΔH°_{BHX} and the entropy relative to molar fractions and ΔS°_{BHX} were obtained through the van't Hoff equation.

Computational Methods: All geometries and energy calculations were performed at the B3LYP/6-31+G** level of theory by using the Gaussian 03[46] and Spartan 06[47] suites of programs. All stationary points were confirmed as true minima by harmonic vibrational frequency calculations.

Local minima of the electrostatic potential on the molecular surface around the nitrogen or carbonyl lone-pairs were calculated by using Spartan 06[47] with a grid mesh of 0.25 Bohr. The molecular surface was defined[48] as the 0.001 electron $Bohr^{-3}$ contour of the electronic density.

The geometries of all the different species, monomers and hydrogen- and halogen-bonded complexes have been fully optimized. Hydrogen fluoride was selected as the simplest HB donor with the lowest computational cost giving high quality relationships with the reference pK_{BHX} scale of hydrogen-bonding basicity.[18,37,49,50] In the initial geometries of complexes of the various hydrogen- and halogen-bond acceptors, denoted as B or $B_1 <> B_2$ in equilibria (5)–(7), the F–H bond of HF and one C–Cl bond of CCl_4 were placed in the direction of the lone-pair(s) of the acceptor at distances of 1.6 and 3 Å, respectively. The interaction energies $D_0^{(HF)}$ were computed as the difference between the electronic energy of the various complexes and the corresponding reactants [Equations (5)–(7)], corrected from the zero-point vibrational energy. The basis-set superposition error (BSSE) was not used to collect homogeneous data with the calibration line (4) used for the estimation of pK_{BHX} values.[18]

Acknowledgments

We thank Dr. Petr Nauš (Charles University, Prague) for the calculation of the σ_α value of the 1-pyrrolin-2-yl substituent and the Centre de Calcul Intensif des Pays de Loire (CCIPL), the Institut des Ressources en Informatique Scientifique (IDRIS) and the Centre Informatique National de l'Enseignement Supérieur (CINES) for granting computer time.

[1] V. Arnaud, J.-Y. Le Questel, M. Mathe-Allainmat, J. Lebreton, M. Berthelot, *J. Phys. Chem. A* **2004**, *108*, 10740–10748.
[2] D. Gurka, R. W. Taft, *J. Am. Chem. Soc.* **1969**, *91*, 4794–4801.
[3] R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, J. W. Rakshys, *J. Am. Chem. Soc.* **1969**, *91*, 4801–4808.
[4] E. M. Arnett, L. Joris, E. Mitchell, T. S. S. R. Murty, T. M. Gorrie, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1970**, *92*, 2365–2377.
[5] C. Laurence, M. Berthelot, *Perspect. Drug Discovery Des.* **2000**, *18*, 39–60.
[6] C. Laurence, K. A. Brameld, J. Graton, J.-Y. Le Questel, E. Renault, *J. Med. Chem.* **2009**, ACS ASAP.

[7] http://www.sciences.univ-nantes.fr/CEISAM/lhmin.php.
[8] F. Besseau, C. Laurence, M. Berthelot, *Bull. Soc. Chim. Fr.* **1996**, *133*, 381–387.
[9] C. Ouvrard, M. Berthelot, C. Laurence, *J. Phys. Org. Chem.* **2001**, *14*, 804–810.
[10] M. Berthelot, J. Graton, C. Ouvrard, C. Laurence, *J. Phys. Org. Chem.* **2002**, *15*, 218–228.
[11] M. Berthelot, C. Laurence, M. Safar, F. Besseau, *J. Chem. Soc. Perkin Trans. 2* **1998**, 283–290.
[12] E. Marquis, J. Graton, M. Berthelot, A. Planchat, C. Laurence, *Can. J. Chem.* **2004**, *82*, 1413–1422.
[13] F. Besseau, M. Lucon, C. Laurence, M. Berthelot, *J. Chem. Soc. Perkin Trans. 2* **1998**, 101–108.
[14] J. Graton, M. Berthelot, J.-F. Gal, C. Laurence, J. Lebreton, J.-Y. Le Questel, P.-C. Maria, R. Robins, *J. Org. Chem.* **2003**, *68*, 8208–8221.
[15] J.-Y. Le Questel, G. Boquet, M. Berthelot, C. Laurence, *J. Phys. Chem. B* **2000**, *104*, 11816–11823.
[16] J.-Y. Le Questel, M. Berthelot, C. Laurence, *J. Phys. Org. Chem.* **2000**, *13*, 347–358.
[17] C. Ouvrard, M. Lucon, J. Graton, M. Berthelot, C. Laurence, *J. Phys. Org. Chem.* **2004**, *17*, 56–64.
[18] F. Besseau, J. Graton, M. Berthelot, *Chem. Eur. J.* **2008**, *14*, 10656–10669.
[19] P. Migchels, T. Zeegers-Huyskens, D. Peeters, *J. Phys. Chem.* **1991**, *95*, 7599–7604.
[20] S. Tyroller, W. Zwickenpflug, E. Richter, *J. Agric. Food Chem.* **2002**, *50*, 4909–4915.
[21] T. T. Denton, X. Zhang, J. R. Cashman, *Biochem. Pharmacol.* **2004**, *67*, 751–756.
[22] N. Karadsheh, P. Kussie, D. S. Linthicum, *Toxicol. Lett.* **1991**, *55*, 335–342.
[23] P. Gilli, L. Pretto, V. Bertolasi, G. Gilli, *Acc. Chem. Res.* **2009**, *42*, 33–44.
[24] J. Graton, F. Besseau, M. Berthelot, E. D. Raczynska, C. Laurence, *Can. J. Chem.* **2002**, *80*, 1375–1385.
[25] J. Graton, M. Berthelot, C. Laurence, *J. Chem. Soc. Perkin Trans. 2* **2001**, 2130–2135.
[26] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
[27] M. A. Munoz, M. Galan, L. Gomez, C. Carmona, P. Guardado, M. Balon, *Chem. Phys.* **2003**, *290*, 69–77.
[28] C. A. Matuszak, A. J. Matuszak, *J. Chem. Educ.* **1976**, *53*, 280–284.
[29] A. Locati, M. Berthelot, M. Evain, J. Lebreton, J.-Y. Le Questel, M. Mathe-Allainmat, A. Planchat, E. Renault, J. Graton, *J. Phys. Chem. A* **2007**, *111*, 6397–6405.
[30] D. E. Elmore, D. A. Dougherty, *J. Org. Chem.* **2000**, *65*, 742–747.
[31] A. L. McClellan, *Tables of Experimental Dipole Moments*, W. H. Freeman and Co., San Francisco and London, **1963**, vol. 1.
[32] A. L. McClellan, *Tables of Experimental Dipole Moments*, Rahara Enterprises, El Cerrito, **1974**, vol. 2.
[33] J. Barassin, M. H. Lumbroso, *Bull. Soc. Chim. Fr.* **1959**, 1947–1952.
[34] D. Clotman, D. Van Lerberghe, T. Zeegers-Huyskens, *Spectrochim. Acta Part A* **1970**, *26*, 1621–1631.
[35] G. Roland, *Spectrochim. Acta Part A* **1969**, *25*, 1135–1153.
[36] J. Graton, M. Berthelot, J.-F. Gal, S. Girard, C. Laurence, J. Lebreton, J.-Y. Le Questel, P.-C. Maria, P. Naus, *J. Am. Chem. Soc.* **2002**, *124*, 10552–10562.
[37] O. Lamarche, J. A. Platts, *Chem. Phys. Lett.* **2003**, *367*, 123–128.
[38] O. Exner, M. Ingr, P. Carsky, *THEOCHEM* **1997**, *397*, 231–238.
[39] P. Carsky, P. Naus, O. Exner, *J. Phys. Org. Chem.* **1998**, *11*, 485–488.
[40] L. S. Bleicher, N. D. P. Cosford, A. Herbaut, J. S. McCallum, I. A. McDonald, *J. Org. Chem.* **1998**, *63*, 1109–1118.
[41] P. Jacob III, *J. Org. Chem.* **1982**, *47*, 4165–4167.
[42] E. A. Guggenheim, *Trans. Faraday Soc.* **1949**, *45*, 714–720.
[43] J. W. Smith, *Trans. Faraday Soc.* **1950**, *46*, 394–399.
[44] B. Illien, K. Evain, M. Berthelot, C. Laurence, *J. Phys. Org. Chem.* **2003**, *16*, 608–614.
[45] J. Graton, M. Berthelot, F. Besseau, C. Laurence, *J. Org. Chem.* **2005**, *70*, 7892–7901.
[46] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, J. T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Gaussian, Inc., Wallingford, CT, **2003**.
[47] *Spartan 06*, Wavefunction, Inc., Irvine, CA.
[48] R. F. W. Bader, M. T. Carroll, J. R. Cheeseman, C. Chang, *J. Am. Chem. Soc.* **1987**, *109*, 7968–7979.
[49] O. Lamarche, J. A. Platts, *Chem. Eur. J.* **2002**, *8*, 457–466.
[50] O. Lamarche, J. A. Platts, *Phys. Chem. Chem. Phys.* **2003**, *5*, 677–684.

Received: May 22, 2009
Published Online: September 3, 2009

