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The pK_{BHX} Database: Toward a Better Understanding of Hydrogen-Bond Basicity for Medicinal Chemists

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1. Introduction

The hydrogen bond (HB[a]) is one of the fundamental noncovalent interactions between a drug molecule and its local environment. For drug molecules, this local environment may be a biological target, a biological off-target, aqueous solution, a lipid membrane, or even a crystalline solid. Consequently, hydrogen bonding impacts a wide range of molecular properties critical to drug design including potency,[1,2] selectivity,[1,3,4] and permeability and solubility.[5−7] Despite its importance, it is the authors' experience that in general the medicinal chemistry community has a poor intuition for the relative basicity (i.e., strengths) of hydrogen-bond acceptors. In an attempt to assess the relative hydrogen-bond basicities of functional groups, it is common practice to resort to a simple correlation with pK_{BH^+},[8] which is generally incorrect and holds true only for closely related compounds in a series (i.e., a family dependent relationship). There is also a tendency to view hydrogen-bond acceptors as atomic sites and to consider them equivalent while disregarding the effects of organic functions and substituents that define the local molecular environment. This is evident in the lack of consideration for exploring hydrogen-bond basicity as an SAR parameter, as is commonly done to establish preferred steric, polar, basic, and acidic moieties. This poor intuition may partly stem from the lack of experimentally observable physical properties that are directly attributed to relative hydrogen-bond basicities. Furthermore, despite the well-known role of hydrogen bonds in protein−ligand interactions and the fact that hydrogen bonds are qualitatively well understood, it is generally admitted that quantitative data are needed.[9]

In the second section of this paper we review hydrogen-bond basicity scales in general and introduce the pK_{BHX} scale with a brief thermodynamic discussion on the treatment of polyfunctional compounds. In section 3 we discuss the effects of a medium more polar than the definition solvent CCl_4 and changes in the reference HB donor on the pK_{BHX} scale. In section 4, we present the pK_{BHX} database and describe the fields of each entry, which correspond to three main categories of data: HBA identification, thermodynamic, and spectroscopic. In section 5 we show that the pK_{BHX} scale of HB basicity differs considerably from the pK_{BH^+} scale of proton transfer basicity. This is important for medicinal chemists who have a good knowledge of Brønsted proton basicity scales and incorrectly consider HB basicity and proton basicity scales as equivalent. Section 6 reviews the hydrogen-bond basicities of functional groups relevant to medicinal chemistry while considering factors that modulate these values. Section 7 extends this medicinal chemistry discussion by providing examples of the role of hydrogen-bond basicity in properties of interest for drug design and briefly reviews computational approaches for addressing hydrogen bonding.

2. Introduction to Hydrogen-Bond Basicity Scales

The hydrogen bond is an attractive interaction between a hydrogen-bond donor (HBD) XH and a hydrogen-bond acceptor (HBA). A natural bond orbital analysis[10] of the hydrogen bond shows that charge transfer from nonbonding or π-bonding electron pairs of the HBA to the antibonding orbital σ^* of the X−H bond is a characteristic feature of hydrogen bonding. Therefore, in the enlarged Lewis definition of acidity and basicity, where acids accept and bases donate electron density, the HBD is a Lewis acid because it accepts electron density and the HBA is a Lewis base since it donates electron density. Hydrogen bonding can thus be considered a special class of Lewis acid−base interaction. The hydrogen-bond basicity of a substance must therefore be defined in terms similar to those of the IUPAC (International Union of Pure and Applied Chemistry) definition of Lewis basicity,[11] that is, as "its thermodynamic tendency to act as a [HBA]. Comparative measures of this property are provided by the equilibrium constants K for [1:1 hydrogen-bonded complex] formation for a series of [HBAs] with a common reference [HBD]."

In this way, two 1:1 hydrogen-bond basicity scales have been constructed from $\log K$ values for a series of bases against a reference HBD, the pK_{HB} scale[12] against 4-fluorophenol, and the $\log K_\beta$ scale[13] against 4-nitrophenol. In contrast, the $\log K_B^H$ (and its linear transform β_2^H) scale[14] has been built against a great number of reference HBDs. Unfortunately, the combination of many reference acids requires a statistical treatment of $\log K$ values within the literature so that the determination of new values is not straightforward.

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[a] Abbreviations: HB, hydrogen bond; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; IUPAC, International Union of Pure and Applied Chemistry; FTIR, Fourier transform infrared; PDE, phosphodiesterase; CYP, cytochrome P-450; LFER, linear free energy relationship.

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The B scale[15] (formerly denoted $\sum\beta_2^{\mathrm{H}}$)[16] refers to the situation in which a solute with *n* HBA groups, a polyfunctional hydrogen-bond base, is surrounded by an excess of HBD groups such that a hydrogen-bonded complex of 1(HBA):*n*(HBD) stoichiometry can potentially be formed. B values are calculated mostly from partition coefficients and chromatographic retention parameters which are equilibrium processes. While they are still log *K* related, they do not obey the IUPAC definition of basicity. For polyfunctional bases, they evidently differ from 1:1 scales, since they correspond to 1:*n* complexation.

It has been claimed[15] that "overall hydrogen-bond basicity" constants B are more useful than 1:1 scales such as $\mathrm{p}K_{\mathrm{HB}}$ in analyses of physicochemical and biochemical properties. Indeed the B scale is the most quoted hydrogen-bond basicity scale for "property-based design" in drug discovery.[5] The $\mathrm{p}K_{\mathrm{HB}}$ and $\log K_\beta$ scales are generally not considered by medicinal chemists, despite the latter having been "explicitly targeted to the needs of the medicinal chemist in the context of potential drug–receptor interactions".[13] There are possibly two reasons for this lack of interest. First, the number of data in each set (117 $\mathrm{p}K_{\mathrm{HB}}$ values, 90 $\log K_\beta$ values) is very limited compared to the number of potential hydrogen-bond acceptors that results from the combination of atomic sites, functional groups, and substituents. Consider the atomic HBA sites (mainly O and N, but also Cπ, S, F, and even P, As, Cl, Br, I, Se, Te) multiplied by the number of organic functional groups and their possible substituents. For example, nitrogen bases may correspond to nitriles, amines, imines, amidines, pyridines, etc., and a review[17] of Hammett substituent constants lists 530 parameters. Second, these scales do not treat the problem of bases with multiple HBA sites. The logarithm of a global equilibrium constant is assigned to the whole molecule, whereas each site should be characterized by an individual equilibrium constant. This drawback is serious for medicinal chemists, since almost all drugs have more than one HBA site. In the library of 2245 compounds used for establishing the Lipinski "rule of five",[6] 12% of compounds have even more than 10 nitrogen and oxygen HBA sites.

Over the years 1988–2008,[18,19] we have measured in Nantes a large collection of hydrogen-bond formation constants with the objective of keeping the simplicity of the $\mathrm{p}K_{\mathrm{HB}}$ and $\log K_\beta$ definitions and to include the B advantage of treating polyfunctionality. We have assembled these values in a numerical database called the $\mathrm{p}K_{\mathrm{BHX}}$ database, where $\mathrm{p}K_{\mathrm{BHX}}$ has been defined as described below.

For historical[12] and technical reasons, 4-fluorophenol is chosen as the reference HBD. Thus, the hydrogen-bond basicity of a series of bases B is measured by the 1:1 complexation constant *K* of the equilibrium 1

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

in $\mathrm{CCl_4}$ at 25 °C, where the notation $\cdots$ indicates a hydrogen bond and $4\text{-}\mathrm{FC_6H_4OH}\cdots\mathrm{B}$ is the hydrogen-bonded complex of 1:1 stoichiometry. From this set of equilibrium constants, the hydrogen-bond basicity scale $\mathrm{p}K_{\mathrm{BHX}}$ (where X stands for $4\text{-}\mathrm{FC_6H_4O}$) is defined as

$$\mathrm{p}K_{\mathrm{BHX}} = -\log_{10} K_{\mathrm{BHX}} = +\log_{10} K \qquad (2)$$

In this manner, a strong HBA will form a hydrogen-bonded complex with a large association constant (*K*), that is, a low dissociation constant ($K_{\mathrm{BHX}} = 1/K$), and will correspond to a large positive value of $\mathrm{p}K_{\mathrm{BHX}}$. The 4-fluorophenol basicity scale was formerly denoted as $\mathrm{p}K_{\mathrm{HB}}$, but from now on, the clearer notation $\mathrm{p}K_{\mathrm{BHX}}$ is used. Indeed, the symbol $\mathrm{p}K_{\mathrm{BHX}}$ is homogeneous to the notation $\mathrm{p}K_{\mathrm{BH^+}}$ commonly used for the scale of proton basicity toward the reference acid $\mathrm{H^+}$, and clears up the ambiguity of the subscript HB, which can designate HB acidity as well as HB basicity.

Our $\mathrm{p}K_{\mathrm{BHX}}$ scale has a meaning similar to the $\mathrm{p}K_{\mathrm{HB}}$, $\log K_\beta$, and $\log K_{\mathrm{B}}^{\mathrm{H}}$ hydrogen-bond basicity scales. An important difference, however, is that we used a Fourier transform infrared (FTIR) spectrometry methodology instead of ^{19}F NMR, UV, and dispersive IR techniques mostly used for $\mathrm{p}K_{\mathrm{HB}}$, $\log K_\beta$, and $\log K_{\mathrm{B}}^{\mathrm{H}}$, respectively. As a consequence of the IR spectrometry time scale, bandwidths, and the ability of FTIR to deconvolute overlapping bands, it is often possible to observe the significant multiple HBA sites of polyfunctional bases and to attribute a $\mathrm{p}K_{\mathrm{BHX}}$ value to each site. This FTIR advantage is decisive for characterizing properly the hydrogen-bond basicity of drugs and drug candidates. Moreover, the FTIR technique allows the measurement of $\Delta\nu(\mathrm{OH})$, the IR shift to lower wavenumbers of the OH stretching vibration of 4-fluorophenol (and/or methanol) upon hydrogen bonding. On the assumption that this shift is dominated by the strength of the hydrogen bond, $\Delta\nu(\mathrm{OH})$ can be considered a spectroscopic estimate of "basicity".[20] The main attraction of $\Delta\nu(\mathrm{OH})$ is the ease with which it can be measured. Its usefulness arises from the existence of family dependent relationships between $\mathrm{p}K_{\mathrm{BHX}}$ and $\Delta\nu(\mathrm{OH})$, which can be applied to the study of steric effects on hydrogen-bond basicity,[21] the detection of three-centered hydrogen bonds,[22] the calculation of secondary values, and the assignment of an individual $\mathrm{p}K_{\mathrm{BHX}}$ value to each HBA site of bases with multiple HBA groups.

As highlighted above, a great number of organic compounds, and the vast majority of drugs, bear more than one possible HBA site. They are polyfunctional bases, or polybases. For instance, *N*,*N*-diethylnicotinamide may be hydrogen-bonded on the pyridine nitrogen and/or on the carbonyl oxygen. In order to measure the 1:1 HB basicity of such polyfunctional compounds, it is necessary to determine the relative stability of the various possible isomeric 1:1 complexes. Surprisingly, the issue of polyfunctionality has not been addressed in the construction of 1:1 HB basicity scales such as $\mathrm{p}K_{\mathrm{HB}}$,[12] $\log K_\beta$,[13] and $\log K_{\mathrm{B}}^{\mathrm{H}}$.[14] For example, a single value, 2.177 in the $\log K_{\mathrm{B}}^{\mathrm{H}}$ scale and 2.76 in the $\log K_\beta$ scale, is given for measuring the HB basicity of the two HBA sites of *N*,*N*-diethylnicotinamide. We show below that not only does this single value give no useful information, but more seriously, it is thermodynamically incorrect.

Consider, as the simplest example, the hydrogen bonding of 4-fluorophenol with a bifunctional HBA, B. Two 1:1 complexes can be formed by the hydrogen bonding of 4-fluorophenol at either of the HBA sites, giving the isomeric 1:1 complexes $\mathrm{C_1}$ and $\mathrm{C_2}$ of equilibrium constants K_1 and K_2 (eqs 3 and 4).

$$K_1 = \frac{[\mathrm{C_1}]}{[\mathrm{B}][4\text{-}\mathrm{FC_6H_4OH}]} \qquad (3)$$

$$K_2 = \frac{[\mathrm{C_2}]}{[\mathrm{B}][4\text{-}\mathrm{FC_6H_4OH}]} \qquad (4)$$

A base/phenol complex with a 1:2 ratio may be formed by the addition of a second molecule of 4-fluorophenol to either of the 1:1 complexes. This possibility can be ruled out if the initial concentration of base is chosen in excess of the initial concentration of 4-fluorophenol.

Most experimental methods are not able to determine separately the equilibrium concentrations [C_1] and [C_2], and they furnish only the sum [C_1] + [C_2]. It follows that these methods yield only the total equilibrium constant K_t (eq 5)

$$K_t = \frac{[C_1]+[C_2]}{[B][4\text{-}FC_6H_4OH]} \qquad (5)$$

whose relationship to the individual constants K_1 and K_2 is given by eq 6.

$$K_t = K_1 + K_2 \qquad (6)$$

This can be generalized to any number of isomeric 1:1 complexes.

$$K_t = \sum_{i=1}^{n} K_i \qquad (7)$$

The logarithm of K_t lacks any thermodynamic significance, since no thermodynamic function can be calculated from it. The term $-RT\ln K_t$ is not simply related to the ΔG_i ($-RT\ln K_i$), since the logarithm of a sum is not equal to the sum of logarithms. From this point of view, it is illustrative to compare the thermodynamic data that can be calculated from the $\log K_B^H$ and pK_{BHX} scales on the three polyfunctional HBAs of Table 1, since $\log K_B^H$ has been scaled to 4-fluorophenol as the reference HBD. Whereas no Gibbs energy values can be calculated from the $\log K_B^H$ scale, which corresponds to $\log K_t$, the comparison of the $pK_{BHX}(i)$ values and their variation from the value of a parent compound do allow one to calculate, on a Gibbs energy scale, the selectivity in and the substituent effects on HB basicity toward 4-fluorophenol. For example, in nicotine, the N sp^2 site is calculated to be a better HBA than the N sp^3 site by 5.3 kJ mol^{-1}, and the electron-withdrawing and steric effects of the pyridyl group are calculated to weaken the 4-fluorophenol basicity of *N*-methylpyrrolidine by 6.2 kJ mol^{-1}.[23]

3. Domain of Validity of the pK_{BHX} Scale

Delimitation of the range of validity of the pK_{BHX} scale is a crucial problem for its use in hydrogen bonding studies. Both the solvent and the reference HBD validity ranges need to be specified.

Carbon tetrachloride has been selected for pK_{BHX} measurements by means of the FTIR method because it is devoid of significant HBA ability and is transparent to IR light in the OH stretching zone. This solvent has a relative permittivity ε of 2.23 and its Onsager function, $(\varepsilon - 1)/(2\varepsilon + 1)$, which ranks the strength of the solvent reaction field, is 0.23. However, chemical and biological surroundings of relevance for HB interactions can range all the way from the gas phase ($\varepsilon = 1$) to the aqueous phase ($\varepsilon = 78$), corresponding to values of the Onsager function from 0 to 0.49. It is necessary to address the question of how the ranking order of HBA strength may be affected by such variations. The study[24] of the hydrogen bonding of 4-fluorophenol in several solvents of relative permittivity ranging from 2.02 (cyclohexane) to 10.36 (1,2-dichloroethane) (Onsager function from 0.2 to 0.43) shows that linear free energy relationships ($\log K$ in a given solvent versus pK_{BHX} in CCl_4) are always obeyed by oxygen and sp-hybridized nitrogen bases. However, sp^2 and sp^3 nitrogen bases gain basicity relative to oxygen and sp nitrogen bases as the reaction field rises. This has been explained[24] by an increased extent of proton sharing in hydrogen-bonded complexes permitted by the action of polar solvents. However, the resulting increase in basicity does not exceed 4 kJ mol^{-1}.

Table 1. Comparison of the $\log K_B^H$ and pK_{BHX} Scales for Selected Polybases

polybase	$\log K_B^H$	pK_{BHX} 1	pK_{BHX} 2
nicotine	2.087	2.03 (Nsp^2)	1.11 (Nsp^3)
N,*N*-diethylnicotinamide	2.177	1.98 (O)	1.63 (N)
1,3-dimethyluracil	1.760	1.74 (O4)	0.76 (O2)

The pK_{BHX} database has been scaled to 4-fluorophenol, but other HBDs are chemically and biochemically relevant. It is important to know if CH, NH (and even NH$^+$), and other OH donors rank the bases in the same or in a different order than 4-fluorophenol. The study[12,14,19] of the existence of linear free energy relationships between pK_{BHX}, or a very similar quantity, and $\log K$ for the complexes of various hydrogen-bond donors shows that (i) OH donors (phenols, alcohols, and water), (ii) NH$^+$ donors such as n-Bu_3NH^+, and (iii) strong NH donors such as amides and imides rank all the bases in the same way. However, CH donors such as chloroform and alk-1-ynes and weak NH donors such as aliphatic amines, anilines, and pyrroles rank only the oxygen and the sp nitrogen bases in the same order. The sp^2 and sp^3 nitrogen bases lose basicity relative to oxygen bases as the hydrogen-bond acidity of the hydrogen-bond donor falls.

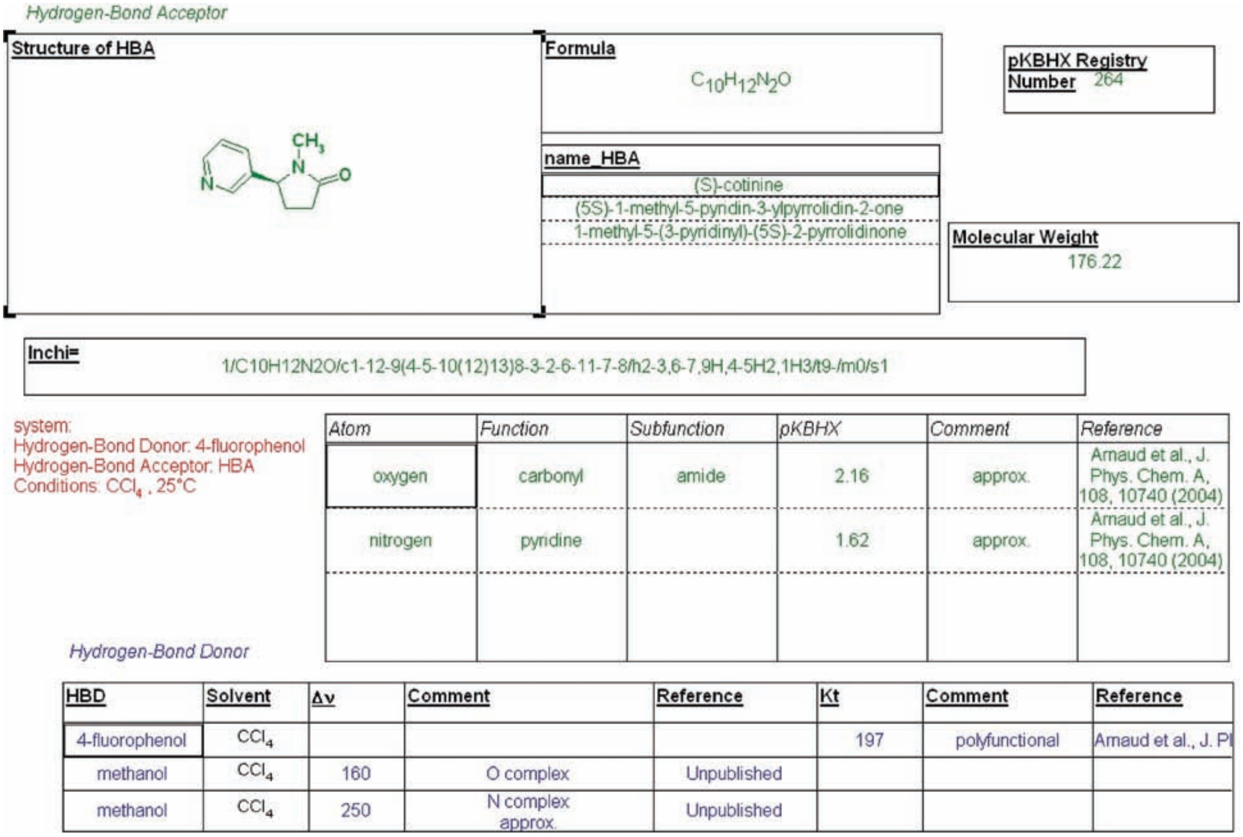
Although not quite general toward all HBDs in all solvents, the pK_{BHX} scale is a reasonably general scale toward many OH, NH, and NH$^+$ hydrogen-bond donors in a large range of medium polarity. In particular the pK_{BHX} scale may be applied to the hydrogen-bonded complexes of (i) water, (ii) the OH group of SER, THR, and TYR residues, (iii) the NH group(s) of ASN, GLN, ARG, and HIS residues, and (iv) the NH group of the peptide backbone of proteins, all of which are frequently observed as hydrogen-bond donors in protein–ligand complexes. The calculation of absolute $\log K$ of complexation of OH and strong NH donors with the 1000 HBAs contained in the pK_{BHX} database can be performed through the LFERs ($\log K$ vs $\log K_B^H$) listed by Abraham and co-workers.[14] These LFERs can be safely used because the $\log K_B^H$ values are scaled to 4-fluorophenol and therefore similar to pK_{BHX} for monofunctional bases.

4. Description of the pK_{BHX} Database

The software used to build the database is MDL ISIS/Base, version 2.5.[25] This graphics-based software allows the storage and retrieval of HBAs and their corresponding data, with substructure search capability. The information offered by the database is contained in a number of fields, as displayed in Figure 1 for the example of cotinine.

The HBA identification is described in five fields. They contain (i) its 2D structure, (ii) its empirical formula, (iii) its name, systematic and/or common, (iv) its molecular weight, and (v) its IUPAC International Chemical Identifier (InChI), which represents the 2D chemical structure as a unique string of characters.

Seven fields are devoted to the thermodynamics of hydrogen bonding. The main field, “pKBHX”, containing the pK_{BHX} value ($\log_{10}$ of the equilibrium constant of reaction 1 in L mol^{-1}), is preceded by the fields “Atom”, describing the atomic site to which 4-fluorophenol is hydrogen-bonded, “Function”, the functional group containing the HBA atomic site, and “Subfunction”, to define more precisely the function.



Hydrogen-Bond Acceptor

Structure of HBA

Formula $C_{10}H_{12}N_2O$

pKBHX Registry Number 264

name_HBA

(S)-cotinine
(5S)-1-methyl-5-pyridin-3-ylpyrrolidin-2-one
1-methyl-5-(3-pyridinyl)-(5S)-2-pyrrolidinone

Molecular Weight 176.22

Inchi= 1/C10H12N2O/c1-12-9(4-5-10(12)13)8-3-2-6-11-7-8/h2-3,6-7,9H,4-5H2,1H3/t9-/m0/s1

system:
Hydrogen-Bond Donor: 4-fluorophenol
Hydrogen-Bond Acceptor: HBA
Conditions: CCl_4, 25°C

Atom	Function	Subfunction	pKBHX	Comment	Reference
oxygen	carbonyl	amide	2.16	approx.	Arnaud et al., J. Phys. Chem. A, 108, 10740 (2004)
nitrogen	pyridine		1.62	approx.	Arnaud et al., J. Phys. Chem. A, 108, 10740 (2004)

Hydrogen-Bond Donor

HBD	Solvent	Δν	Comment	Reference	Kt	Comment	Reference
4-fluorophenol	CCl_4				197	polyfunctional	Arnaud et al., J. Pl
methanol	CCl_4	160	O complex	Unpublished			
methanol	CCl_4	250	N complex approx.	Unpublished			

Figure 1. Screenshot of the pK_{BHX} database showing the cotinine entry.

The field "Comment" specifies whether the value is approximate, secondary, or statistically corrected, and the "Reference" field comprises published journal articles, Ph.D. theses, and unpublished research reports of the Nantes laboratory. The polyfunctional HBAs require a field "Kt" (with associated "Comment" and "Reference" fields). Indeed, within the conditions used for measuring by FTIR spectrometry the complexation constants of compounds with n HBA sites, n 1:1 complexes are formed through equilibria of individual constants K_i. With this method only the sum of the K_i values, the global or total constant K_t, can be usually measured (see section 2).

The other fields give IR spectroscopic information on the hydrogen bonding of 4-fluorophenol and/or methanol with the HBA. The field "$\Delta\nu$" contains the shift to lower wavenumbers of the stretching vibration of the O−H bond upon hydrogen bonding, calculated from eq 8,

$$\Delta\nu(\mathrm{OH})/\mathrm{cm}^{-1} = \nu(\text{free OH}) - \nu(\text{hydrogen-bonded OH}) \quad (8)$$

where ν(free OH) is 3644 cm^{-1} for methanol and 3614 cm^{-1} for 4-fluorophenol in CCl_4. The field "HBD" specifies whether the $\Delta\nu$(OH) values refer to 4-fluorophenol or methanol. In fact, 4-fluorophenol hydrogen-bonded to strong HBAs yields OH shifts that are too large to be measured easily. In this situation the weaker HBD methanol is more appropriate than 4-fluorophenol. The field "Comment" is important for polyfunctional bases that usually show multiple hydrogen-bonded OH bands. These bands can be assigned to the various 1:1 complexes that are formed, since the value of $\Delta\nu$(OH), as well as the band shape, often allows one to discriminate the potential HBA sites. For example, the comments "O complex" and "N complex" for cotinine in Figure 1 mean that $\Delta\nu$(OH) values correspond to the hydrogen bonding of methanol with the amide oxygen and the pyridine nitrogen, respectively.

Table 2. Occurrence of HBA Sites in the pK_{BHX} Database

group 14	n	group 15	n	group 16	n	group 17	n
carbon	119	nitrogen	516	oxygen	624	fluorine	10
		phosphorus	1	sulfur	96	chlorine	38
		arsenic	2	selenium	4	bromine	18
		antimony	1	tellurium	1	iodine	17

The pK_{BHX} database (version 08.05) contains 1338 pK_{BHX} values related to 1164 HBAs. Table 2 lists the frequency of occurrence of the elements comprising HBA sites in the database and thus provides an initial estimate of the database diversity. The spread of the pK_{BHX} values over the pK_{BHX} scale is shown graphically (Figure S1 of the Supporting Information), arranged by functional groups and structural modifications that modulate the hydrogen-bond basicity. Oxygen and nitrogen atoms are by far the most encountered sites in the database. This observation might appear to validate the Lipinski measurement[6] of the HB basicity as the sum of nitrogens and oxygens. However the shortcomings of this approximation are discussed in section 7. The diversity of HBAs can be further assessed by the variety of the related functions and subfunctions. The frequency of those corresponding to nitrogen and oxygen HBA sites is given in Table 3. The most frequent functions are the carbonyl group, followed by five- and six-membered aromatic N-heterocycles and ethers.

As a consequence of the large and varied selection of entries in the database, the pK_{BHX} scale covers an extended energetic

Table 3. Functions and Subfunctions Corresponding to Oxygen and Nitrogen HBA Sites

atom	function	subfunction	*n*
nitrogen			4
nitrogen	amidine		24
nitrogen	amidine	acetamidine	11
nitrogen	amidine	benzamidine	12
nitrogen	amidine	formamidine	35
nitrogen	amidine	guanidine	4
nitrogen	amine		34
nitrogen	amine	primary amine	28
nitrogen	amine	secondary amine	39
nitrogen	amine	tertiary amine	56
nitrogen	diazene		2
nitrogen	heteroarene		19
nitrogen	heteroarene	imidazole	7
nitrogen	heteroarene	isoxazole	2
nitrogen	heteroarene	oxazole	4
nitrogen	heteroarene	phenanthroline	7
nitrogen	heteroarene	pyrazole	1
nitrogen	heteroarene	pyridine	91
nitrogen	heteroarene	pyrimidine	2
nitrogen	heteroarene	pyrrole	3
nitrogen	heteroarene	thiazole	2
nitrogen	imine		14
nitrogen	imine	oxime	2
nitrogen	nitrile		91
nitrogen	nitrile	cyanamidate	1
nitrogen	nitrile	cyanamide	7
nitrogen	nitrile	cyanate	1
nitrogen	nitrile	thiocyanate	1
nitrogen	pyridine		12
oxygen			6
oxygen	alcohol		21
oxygen	amine *N*-oxide		4
oxygen	arsine *N*-oxide		2
oxygen	carbonyl		6
oxygen	carbonyl	acid anhydrid	2
oxygen	carbonyl	aldehyde	9
oxygen	carbonyl	amide	64
oxygen	carbonyl	carbamate	8
oxygen	carbonyl	carbonate	5
oxygen	carbonyl	carboxamidate	10
oxygen	carbonyl	ester	60
oxygen	carbonyl	imide	8
oxygen	carbonyl	ketone	125
oxygen	carbonyl	lactam	4
oxygen	carbonyl	lactone	7
oxygen	carbonyl	thiocarbamate	1
oxygen	carbonyl	urea	8
oxygen	ether		95
oxygen	nitro		5
oxygen	nitro	nitramidate	2
oxygen	nitro	nitramide	1
oxygen	nitro	nitroalkane	5
oxygen	nitro	nitroalkene	5
oxygen	nitro	nitroaromatic	9
oxygen	nitroso		2
oxygen	nitroso	nitrosamine	3
oxygen	peroxide		6
oxygen	phenol		5
oxygen	phosphoryl		15
oxygen	phosphoryl	phosphate	8
oxygen	phosphoryl	phosphinate	7
oxygen	phosphoryl	phosphine oxide	11
oxygen	phosphoryl	phosphonate	31
oxygen	phosphoryl	phosphoramide	2
oxygen	pyridine *N*-oxide		8
oxygen	seleninyl	selenoxide	2
oxygen	siloxane		1
oxygen	sulfinyl		1
oxygen	sulfinyl	sulfinamide	3
oxygen	sulfinyl	sulfite	5
oxygen	sulfinyl	sulfoxide	14
oxygen	sulfonyl		6
oxygen	sulfonyl	sulfate	2
oxygen	sulfonyl	sulfonamidate	4
oxygen	sulfonyl	sulfonamide	6
oxygen	sulfonyl	sulfonate	2
oxygen	sulfonyl	sulfone	8

range. For monofunctional neutral HBAs, pK_{BHX} values span from -0.96 (1,1,1,3,3,3-hexafluoro-2-propanol) to $+5.46$ (trimethylamine *N*-oxide). This range of 6.42 p*K* units corresponds to a Gibbs energy change of 37 kJ mol^{-1} ($\Delta\Delta G° = -RT\ln 10\,\Delta pK_{BHX} = -5.708\,\Delta pK_{BHX}$ at 298 K). A histogram of the 1338 pK_{BHX} values in the database approaches a normal distribution (Figure 2). This distribution provides numerical criteria for a classification of HBAs as "very weak", "weak", "medium", "strong", and "very strong". Table 4 shows the limits of the five HBA classes, calculated from the average value of 1.17, the range of 6.42, and the class width of 1.28.

The spectroscopic data $\Delta\nu(OH)$ refer to 4-fluorophenol and/or methanol. The 409 $\Delta\nu(OH)$ values of 4-fluorophenol are generally limited to medium, weak, and very weak HBAs, while the 790 $\Delta\nu(OH)$ values for methanol span from 3 cm^{-1} for $CHCl_3$, a very weak chloro base, to 488 cm^{-1} for Oct_3NO, a very strong oxygen base. There is a statistically significant correlation between pK_{BHX} and $\Delta\nu(OH,CH_3OH)$ ($n = 594$, $r = 0.722$, $P < 0.001$). However, only 52% of the variance of pK_{BHX} is explained by $\Delta\nu(OH)$. This is not due to the difference of the reference HBD in the thermodynamic and spectroscopic scales, since $\Delta\nu(OH,CH_3OH)$ is well correlated to $\Delta\nu(OH,4\text{-}FC_6H_4OH)$ ($n = 164$, $r = 0.979$, $P < 0.001$), but is a consequence of the different sensitivities of the two properties to the various forces contributing to a hydrogen bond.[20] Therefore, the correlation between pK_{BHX} and (OH, CH_3OH) is not useful to predict new pK_{BHX} values. Nevertheless, useful family dependent $pK_{BHX}-\Delta\nu(OH, CH_3OH)$ relationships do hold.[20] In this context, a family is defined as a set of bases that possess the same HBA atomic site within the same function and subfunction with almost constant steric

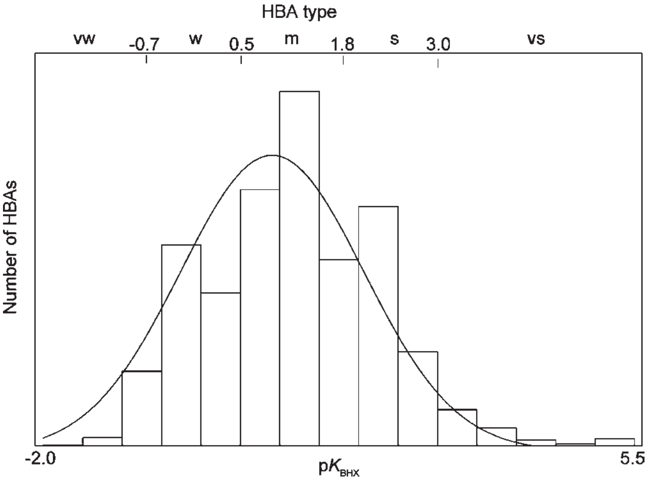


Figure 2. Distribution of the pK_{BHX} values in the pK_{BHX} database.

requirements. The pK_{BHX} versus $\Delta\nu(OH)$ plot of Figure 3 shows some data that could be resolved into separate lines corresponding to the families of amides, substituted imidazoles, 3- and 4-substituted pyridines, primary amines, and unhindered tertiary amines.

A more detailed description of the database, as well as the contact for its appropriate access (free of charge for academic affiliates), is available on the Web site of the CEISAM laboratory (http://www.sciences.univ-nantes.fr/CEISAM/en_lhmin.php). The database will be updated once a year. The version 09 will contain a 100 new compounds, among them anions, amines, amides, and alkaloids. A significant representative sample of the data contained in the database (about one-third) is provided as Supporting Information.

5. Lack of Correlation between the pK_{BHX} and pK_{BH^+} Basicity Scales

Previous comparisons of the 1:1 HB basicity scales pK_{HB}, $\log K_\beta$, and $\log K_B^H$ with the aqueous Brønsted proton basicity scale pK_{BH^+} have suggested that there is no quantitative general relationship between HB basicity and proton basicity.[12−14] Only limited family dependent relationships can be established. In the absence of other intuitive measures, many chemists extend these family dependent relationships beyond a reasonable scope and incorrectly use the order of proton basicity to approximate HB basicity between families. In the literature, one may find sentences such as "an order of acidity and basicity based on hydrogen bonding would not differ radically from one based on acid/base equilibria in aqueous or nonaqueous solution"[26] or "insofar as a hydrogen bond reflects partial transfer of a proton, it would seem logical for the hydrogen bond energy to correlate closely with [proton] basicity."[27] A "pK_a slide rule" has recently been proposed[28] to predict the hydrogen-bond strength from the pK_a of the hydrogen-bond donor and the pK_{BH^+} of the hydrogen-bond acceptor. This section presents a comparison of the pK_{BH^+} and pK_{BHX} scales for a sample of bases not presented in previous studies and highlights the wide variability between these two scales. Examples are given where the relationship between pK_{BH^+} and pK_{BHX} scales breaks down for simple druglike molecules and becomes of little predictive value.

We have been able to collect a set of 232 bases for which reliable values of both pK_{BH^+} and pK_{BHX} are known (available in the Supporting Information). N sp^2 and N sp^3 bases represent the main group of bases (164 compounds), followed by oxygen bases (60), and eight miscellaneous N sp, C, and S bases. The pK_{BH^+} values cover a range of more than 28 pK units, whereas the pK_{BHX} range is more restricted and spans less than 5 pK units. As shown by Figure 4, there is no relationship between the 4-fluorophenol basicity scale pK_{BHX} and the aqueous proton basicity scale pK_{BH^+}. Only 22% of the variance of pK_{BHX} can be explained by pK_{BH^+}. A worse correlation ($n = 55$, $r^2 = 0.14$, $P < 0.01$) and a complete scatter diagram is obtained when using the pK_{BH^+} data set supporting

Table 4. pK_{BHX} Classification of HBAs

HBA type	pK_{BHX} range	examples	pK_{BHX}
very weak	$pK_{BHX} < -0.7$	cyclohexene	−0.82
weak	$-0.7 < pK_{BHX} < 0.5$	fluorocyclohexane	−0.07
medium	$0.5 < pK_{BHX} < 1.8$	acetone	1.18
strong	$1.8 < pK_{BHX} < 3.0$	imidazole	2.41
very strong	$3.0 < pK_{BHX}$	trimethylamine *N*-oxide	5.46

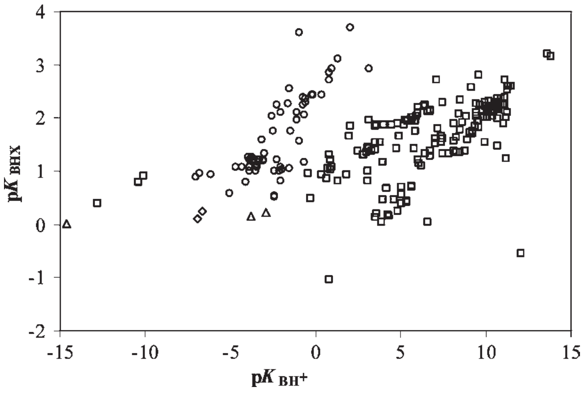


Figure 4. Lack of general relation between pK_{BHX} and pK_{BH^+} for 232 nitrogen (□), oxygen (○), sulfur (◇), and carbon (△) bases.

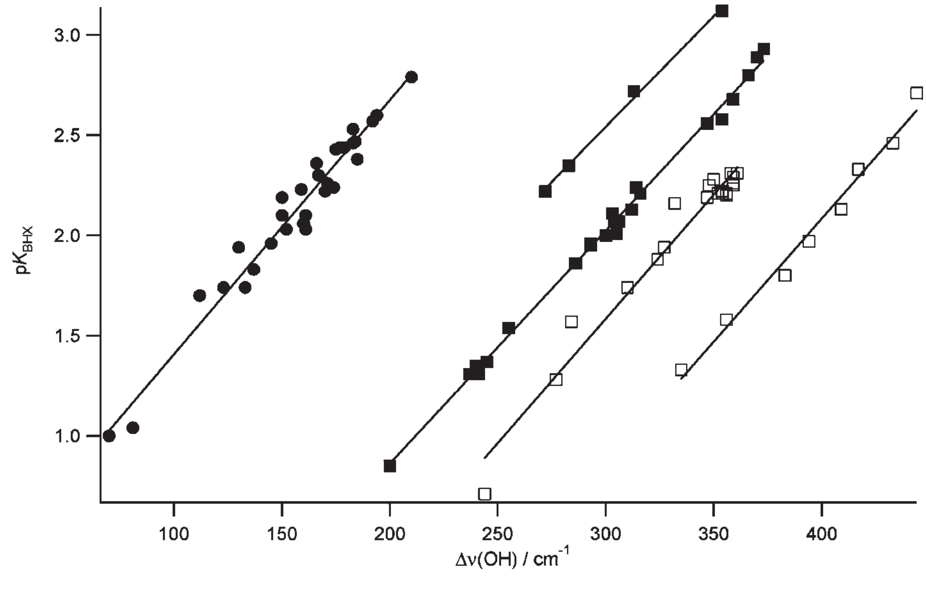


Figure 3. Plot of pK_{BHX} versus $\Delta\nu(OH)$ showing from left to right the families of amides, substituted imidazoles, 3- and 4-substituted pyridines, primary amines, and unhindered tertiary amines.

the "pK_a slide rule". We acknowledge that family dependent relationships do hold, as illustrated in Figure 5, for 3- and 4-substituted pyridine *N*-oxides ($n = 8$, $r^2 = 0.998$, $P < 0.001$), 3- and 4-substituted pyridines ($n = 24$, $r^2 = 0.975$, $P < 0.001$), or primary amines ($n = 20$, $r^2 = 0.976$, $P < 0.001$). However, such families must be carefully chosen. For example, starting from the 20 primary amines, r^2 falls to 0.897 when four primary amines with intramolecular hydrogen bonds are added, to 0.657 when secondary, tertiary, and primary amines are mixed, and to 0.371 when all nitrogen bases are considered. A priori selection of appropriate family members, in the absence of measured pK_{BH^+} and pK_{BHX} values, is not easily achieved.

The differences between the hydrogen bonding and proton basicity scales can be so large that in many polyfunctional bases the preferred site of hydrogen bonding differs from the first aqueous protonation site. For instance, in nicotine (**1**) and nornicotine (**2**) (Scheme 1) the first aqueous protonation site occurs on the pyrrolidine nitrogen whereas the pyridine nitrogen is the main site of hydrogen bonding.[23] In cotinine (**3**), hydrogen bonding occurs preferentially on the oxygen and aqueous protonation on the pyridine nitrogen.[29] In inert solvents, lobeline (**4**) has an intramolecular hydrogen bond as depicted in Scheme 1. The incipient proton transfer in this strong intramolecular OH$\cdots$N hydrogen bond raises the HB basicity of the hydroxyl oxygen so that this atom becomes the preferred site of hydrogen bonding.[30] In water, the intramolecular hydrogen bond is broken and the protonation occurs on the nitrogen. These examples illustrate the challenges of using pK_{BH^+} to predict pK_{BHX}, even for qualitative applications. Thus, the reader is cautioned to attempt to establish a family dependent relationship between pK_{BH^+} and pK_{BHX} for their system of interest before using this as a predictive method.

6. HB Basicities of Common Functional Groups

Figure 6 provides a graphical representation of the hydrogen-bond basicities for functional groups commonly encountered in medicinal chemistry. The scale covers 4 pK units starting with the unconventional weak acceptor benzene (π-system) to the strong acceptor 1-methylimidazole. While this depiction is useful for providing general guidance, substituent effects can be quite pronounced and alter these relative orderings. The following section reviews in greater detail the hydrogen-bond basicities of functional groups relevant to medicinal chemistry. In addition to placing these groups within the framework of the pK_{BHX} hydrogen-bond scale, factors that are important for tuning the relative hydrogen-bond strengths will be presented. We begin with the carbonyl hydrogen-bond acceptors which include amides, esters, ureas, carbamates, and ketones. This is followed by alcohols, ethers, nitriles, sulfones, sulfoxides, and sulfonamides. We close with a discussion on five- and six-membered heterocycles. This is not intended to be a comprehensive review but rather a useful medicinal chemistry-oriented synopsis of the data and trends contained within the pK_{BHX} database.

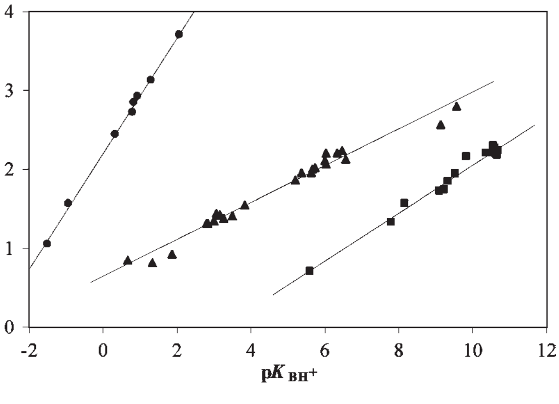
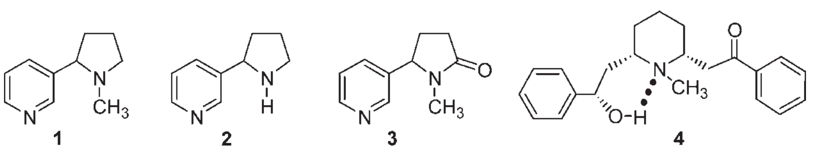


Figure 5. Limited family dependent relations between pK_{BHX} and pK_{BH^+} established for pyridine *N*-oxides (●), pyridines (▲), and primary amines (■).

Amides (Figure 6A). The amide carbonyl of *N*-methylacetamide is a strong hydrogen-bond acceptor (p$K_{BHX} = 2.30$), as expected given the essential role of the peptide group in stabilizing protein secondary structure. Methyl acetate, the ester analogue of *N*-methylacetamide, is considerably weaker (p$K_{BHX} = 1.0$). This trend is also observed for carbamates relative to amides. In the case of esters and carbamates, both the alkoxy and carbonyl moieties may in principle be hydrogen-bond acceptors. However, the FTIR data are consistent with the carbonyl as the major acceptor. These observations agree with the preferences observed in crystalline environments and rationalized through ab initio based energy calculations.[31] The data within the pK_{BHX} database are somewhat sparse for ureas; however, in general acyclic ureas have approximately the same basicity as the analogous amide. Only cyclic ureas are more basic than the analogous cyclic amides (lactams). Cyclization of amides to lactams also increases basicity so that the sequence of basicity is as shown in Scheme 2. It is interesting to observe that the aromatic analogue, 1-methyl-2-pyridone (pK_{BHX} = 2.50) has a similar hydrogen-bond basicity to the simple lactam 1-methyl-2-piperidone. Thus, resonance stabilization intrinsic to the amide functional group already enhances the hydrogen-bond basicity and further π-conjugation within an aromatic ring has no significant effect.

N-Phenylbenzamide is among the most common molecular frameworks present for compounds entering phase I clinical trials or beyond.[32] This is a good system to illustrate substituent effects on hydrogen-bond basicity. Consider the analogues of *N*,*N*-dimethylbenzamide (pK_{BHX} = 2.23) shown in Table 5. Substitution on the phenyl ring can alter the hydrogen-bond basicity of the amide carbonyl by up to ±0.3 pK_{BHX} units. Electron-withdrawing groups, such as 4-nitro or 4-trifluoromethyl, reduce the hydrogen-bond basicity to 1.90 and 1.97, respectively. Electron-donating groups such as 4-methoxy or 4-dimethylamino enhance the hydrogen-bond basicity to 2.31 and 2.49, respectively.

Scheme 1. Structures of Nicotine(**1**), Nornicotine(**2**), Cotinine(**3**), and Lobeline(**4**)



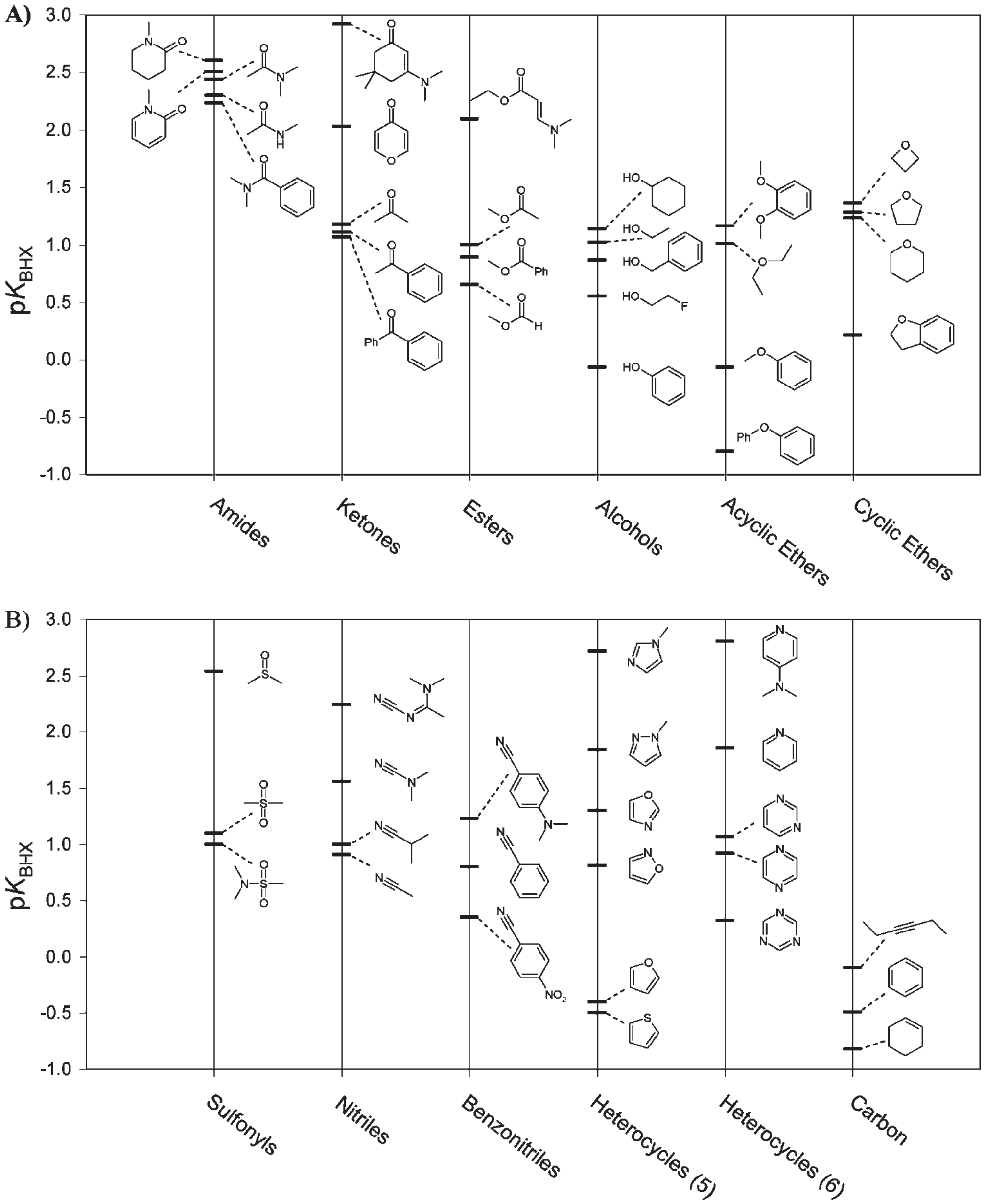
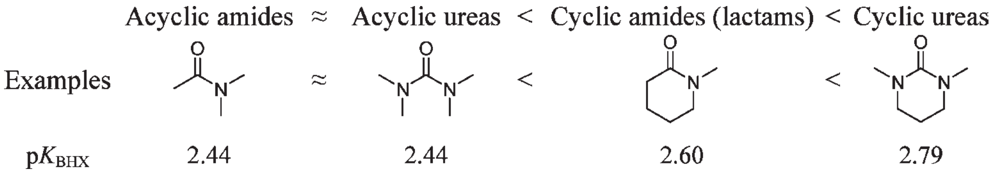


Figure 6. Plot of measured pK_{BHX} values for functional groups commonly encountered in medicinal chemistry revealing their relative hydrogen-bond basicities. Members of the same functional group family are grouped along the *x*-axis: (A) amides, ketones, esters, alcohols, acyclic and cyclic ethers acceptors; (B) sulfonyls, nitriles, benzonitriles, heterocycles, and carbon acceptors.

Scheme 2. Effects of Cyclization on Amide and Urea Hydrogen-Bond Basicities



Substituents capable of intramolecular hydrogen bonding can have an even greater effect on the measured hydrogen-bond basicity. Comparing 2-methoxy (pK_{BHX}=2.48) versus 2-hydroxy (pK_{BHX} = 1.27) substituted *N*,*N*-dimethylbenzamide reveals a change of −1.21 pK_{BHX} units. It is clear that the carbonyl hydrogen-bonding capacity is largely satisfied by the neighboring hydroxyl of the phenol. These examples illustrate the ability to specifically probe and tune hydrogen-bond basicity as a variable during an SAR analysis.

Ketones and Esters (Figure 6A). Ketones and esters are medium hydrogen-bond acceptors and have pK_{BHX} values close to 1. Of the two, esters are generally weaker hydrogen-bond acceptors than the analogous ketones by ~0.2 pK_{BHX} units. For example, methyl acetate (pK_{BHX}=1.00) and acetone (pK_{BHX} = 1.18) differ by 0.18 pK_{BHX} units. Similarly, acetophenone (pK_{BHX} = 1.11) and methyl benzoate (pK_{BHX} = 0.89) differ by 0.22 pK_{BHX} units. As observed for amides, cyclization of ketones and esters increases the hydrogen-bond basicity of the carbonyl oxygen. This effect is quite pronounced for esters, which have a strong preference for an s-trans geometry when acyclic. Cyclization to the lactone forces an s-cis ester conformation, further enhancing the hydrogen-bond basicity by ~0.4 pK_{BHX} units. As an example of these effects, compare cyclohexanone (pK_{BHX} = 1.39) and δ-valerolactone (pK_{BHX}=1.57) to acetone and methyl acetate, respectively. Benzophenone, a very common scaffold in drugs, has a pK_{BHX} = 1.07 which is quite close to that of acetone. Acetophenone behaves similarly to benzamide in response to substitutions on the aromatic ring, thus allowing one to adjust the hydrogen-bond basicity by ±0.5 pK_{BHX} units (Table 5). Electron-donating groups increase while electron-withdrawing groups decrease hydrogen-bond basicity. The measured pK_{BHX} of 2.50 for 2,6-dimethyl-γ-pyrone is quite exceptional and represents a significant deviation from other ketones or esters. An examination of electron density from X-ray crystallography and ab initio quantum mechanical calculations reveals extensive delocalization of the π-system electrons.[33] It is this delocalization that presumably enhances the hydrogen-bond basicity of the γ-pyrone carbonyl.

Alcohols and Ethers (Figure 6A). It is common dogma to consider aliphatic ethers and alcohols as weaker hydrogen-bond acceptors than ketones or the carbonyl oxygen of esters. However, experimental measurements are consistent with these groups being equivalent with pK_{BHX} values of ~1. For example, diethyl ether (pK_{BHX} = 1.01) has a pK_{BHX} quite close to those of methyl acetate and acetone. Cyclic ethers such as tetrahydrofuran (pK_{BHX} = 1.28) and tetrahydropyran (pK_{BHX} = 1.23) are commonly encountered in natural products and are more basic than their acyclic counterparts. The strained four-membered ring of oxetane (pK_{BHX} = 1.36) is still a stronger HBA and can be used to improve the solubility of a molecule without compromising its metabolic stability. It is important to recognize the impact of phenyl substitution through π-conjugation and inductive-field effect, as aromatic ethers and alcohols are weak hydrogen-bond acceptors. Anisole and phenol have the same hydrogen-bond basicity (pK_{BHX} = −0.07). This is consistent with the observation that tyrosine is predominantly a hydrogen-bond donor in protein structures and rarely accepts a hydrogen bond.[34]

Table 5. Substituent Effects on Measured pK_{BHX} Values for Selected Aromatic Systems

substituent	*N*,*N*-dimethylbenzamide	acetophenone	benzonitrile
2-OH	1.27	0.56	
4-NO_2	1.90	0.57	0.35
4-CF_3	1.97	0.78	0.54
H	2.23	1.11	0.80
4-OMe	2.31	1.33	0.97
2-OMe	2.48	1.34	
4-NMe_2	2.49	1.76	1.23

Diphenylmethane is the most common molecular core found in drugs[35] and often can be replaced with diphenyl ether (pK_{BHX} = −0.80). While these two cores have somewhat different conformational preferences, the unusually low hydrogen-bond basicity of the diphenyl ether oxygen helps rationalize its bioisostere complementarity to diphenylmethane. As an aside, benzophenone should not be considered a bioisostere of either diphenyl ether or diphenylmethane given its stronger hydrogen-bond basicity and considerable conformational differences.[32] At the other end of the spectrum, 1,2-dimethoxybenzene (pK_{BHX} = 1.16) is an unusually strong hydrogen-bond acceptor compared to other aromatic ethers. The catechol functionality participates in a three-centered hydrogen bond, as can be observed in both small molecule X-ray structures and protein−ligand complexes. Figure 7 shows two example crystal structures, one from the Cambridge Structural Database[36] (code MAXDUL) and another from the Protein Data Bank[37] (code 1XM4), depicting these three-centered hydrogen bonds. X-ray structures of the catalytic domains of PDE4B, PDE4D, and PDE5A in complex with 10 different inhibitors including rolipram and piclamilast reveal a conserved three-centered hydrogen bond between the catechol scaffold and an invariant glutamine (Gln 443 in PDE4B).[38] This functionality is also found in the kinase inhibitors gefitinib and erlotinib, presumably to enhance the solubility of the planar aromatic systems while maintaining potency.

Sulfones and Sulfonamides (Figure 6B). Sulfones and sulfonamides are prominent in drugs and have comparable pK_{BHX} hydrogen-bond basicities near 1.0. While the data are sparse for these functional groups, the most simple analogues dimethylsulfone (pK_{BHX} = 1.10) and *N*,*N*-dimethylmethanesulfonamide (pK_{BHX} = 1.00) exemplify the trend. The similar pK_{BHX} values for sulfones and sulfonamides may be a somewhat unexpected finding given the difference in hydrogen-bond basicity between ketones and amides. By analogy, one may expect that sulfonamides would be stronger hydrogen-bond acceptors than sulfones. However, it is important to recognize that the nitrogen atom of the sulfonamide is sp^3 hybridized and has a pyramidal geometry. It does not participate in a resonance structure as is the case for amides and thus is largely reduced to the role of a spectator. In contrast, sulfoxide is a strong hydrogen-bond acceptor and dimethyl sulfoxide (DMSO) has a pK_{BHX} = 2.54. The

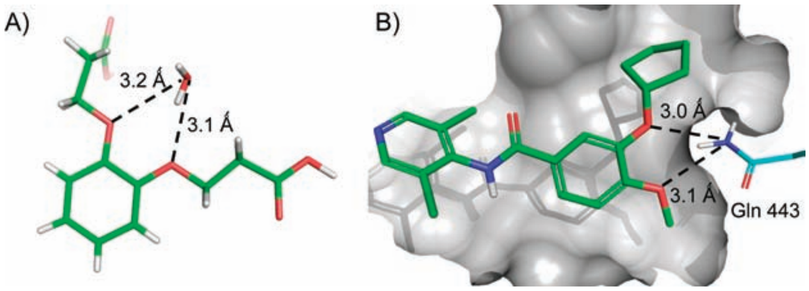
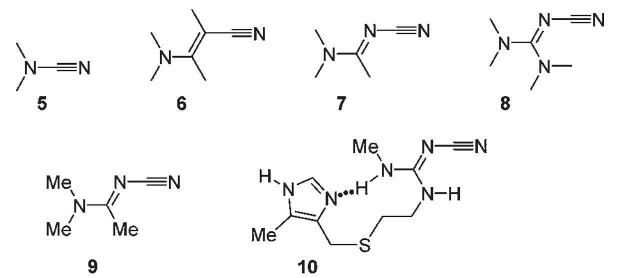


Figure 7. Crystal structures of three-centered hydrogen bonds observed for a catechol core: (A) Cambridge Structural Database entry MAXDUL, showing a bound water molecule bifurcating the two catechol oxygen atoms; (B) protein structure 1XM4 of the catalytic domain of PDE4B in complex with the inhibitor piclamilast. The two catechol oxygen atoms form a three-centered hydrogen bond to Gln 443, a highly conserved binding motif for all inhibitors of the PDE family.

Scheme 3. Structures of Superbasic Nitriles



solubilizing properties of DMSO are well-known, and it is common to dissolve organic compounds with poor aqueous solubility in a DMSO solution prior to dilution in an aqueous buffer for biological screening. Undoubtedly the strong hydrogen-bonding ability of the sulfoxide contributes to these unique properties.

Nitriles (Figure 6B). Simple aromatic and aliphatic nitriles are medium to weak hydrogen-bond acceptors. Acetonitrile and benzonitrile have pK_{BHX} values of 0.91 and 0.80, respectively. Nitriles are particularly sensitive to substituent effects, and the more basic nitriles are cyanamides (**5**), vinylogous cyanamides (**6**), cyanoamidines (**7**), and cyanoguanidines (**8**) (Scheme 3). Their pK_{BHX} values span from 1.56 (*N*,*N*-dimethylcyanamide) to 2.24 (N^2-cyano-N^1,N^1-dimethylacetamidine **9**).[39] It is worth noting that this relative order of HB basicity, attributed to the increase of conjugative interactions between the lone pair of the amino substituent and the nitrile group, has been observed in small organic crystal structures and in the analysis of theoretical calculations at the DFT level.[40] The strong HB basicity of the cyanoguanidine moiety of cimetidine (**10**) suggests a role for the nitrile group in hydrogen-bonding to the H_2 receptor.[19] As observed for aromatic amides and ketones, benzonitrile (pK_{BHX} = 0.80) can be made more basic with the introduction of 4-methoxy (pK_{BHX} = 0.97) or 4-dimethylamino (pK_{BHX} = 1.23) substitutions. Conversely, 4-nitrobenzonitrile (pK_{BHX} = 0.35) is considerably less basic (Table 5). Perhaps of academic interest rather than directly applicable to medicinal chemistry, pentafluorobenzonitrile has a pK_{BHX} = 0.01. The inductive effects of each fluorine atom are roughly additive, resulting in almost complete loss of hydrogen-bond accepting ability of the nitrile group. While the data are not available, one can speculate that a similar trend would be observed for other acceptors such as a benzamide.

Heterocycles (Figure 6B). Aromatic heterocycles are fundamental to medicinal chemistry and can impart desirable properties to a molecule such as improved solubility. It is common for medicinal chemists to take into consideration potential hydrogen-bonding interactions when deciding which heterocycle to synthesize. However, rarely is there an appreciation of the significant differences in relative hydrogen-bond basicity that can occur upon the introduction of different heteroatoms in different positions. The hydrogen-bond basicities of a set of simple nitrogen-containing six-membered heterocycles are included in Figure 6B. Pyridine (pK_{BHX} = 1.86), with a single nitrogen atom, is the most basic. Introduction of a second nitrogen atom reduces the hydrogen-bond basicity to different degrees depending on the substitution pattern. Of these, the most pronounced change is for pyrazine with a pK_{BHX} of only 0.92. Extending this trend with the addition of a third nitrogen atom, as in 1,3,5-triazine (pK_{BHX} = 0.32), attenuates the hydrogen-bond basicity even further.

Pyridine is particularly sensitive to aromatic substitutions, and the changes in hydrogen-bond basicity are best described by a combination of inductive-field and resonance Hammett/Taft σ descriptors.[17,21] Polarizability, which is important for describing proton transfer basicity, is not significant for describing the hydrogen-bond basicity of pyridine analogues. Similar to the benzamide case, 4-dimethylaminopyridine (pK_{BHX} = 2.80) is a considerably stronger hydrogen-bond acceptor than pyridine. Steric effects are also important for hydrogen-bonding atoms within a ring. Substitution or annulation adjacent to the HBA site can reduce the hydrogen-bond basicity. However, these steric effects are often counterbalanced by favorable electronic contributions and can be difficult to predict.

Five-membered heterocycles cover a wide range of hydrogen-bond basicities. Furan (pK_{BHX} = −0.40) and thiophene (pK_{BHX} = −0.50) are weak hydrogen-bond acceptors. They have both nonbonding and π-bonding pairs and give *n* and/or π complexes.[41] In general they should be considered analogues of benzene (pK_{BHX} = −0.49) with different steric and geometric properties. Isoxazole (pK_{BHX} = 0.81) and oxazole (pK_{BHX} = 1.30) are hydrogen-bond acceptors of medium strength, comparable to esters. Indeed, these rings are often successfully used as bioisosteres of esters with the benefit of enhanced metabolic stability. For heterocycles containing both oxygen and nitrogen atoms, a question often arises as to which atom is the preferred HBA. In the case of aromatic heterocycles, there is no ambiguity and the nitrogen atom is overwhelmingly preferred. This trend is supported by a statistical analysis, complemented by in vacuo ab initio calculations, of HB interactions observed in the X-ray structures of organic molecules compiled within the Cambridge Structural Database.[42,43] The strongest hydrogen-bond acceptors in this series are 1-methylpyrazole (pK_{BHX} = 1.84), 1-methylimidazole (pK_{BHX} = 2.72), and 1,5-dicyclohexylimidazole (pK_{BHX} = 3.12). These are comparable in hydrogen-bond basicity to amides and vinylogous amides (3-dimethylamino-5,5-dimethyl-2-cyclohexen-1-one, pK_{BHX} = 2.92).

7. Relevance of HB Basicity to Medicinal Chemistry

Drug discovery is an extremely complex multidimensional optimization problem, and there is an increasing awareness in the pharmaceutical industry that optimizing independent properties, such as potency, absorption, metabolic stability, etc., requires a parallel approach.[44] Hydrogen bonding is well recognized as one of the major noncovalent forces involved in protein−ligand binding and hence is important for ligand affinity. Indeed, nature often utilizes the variable strength of hydrogen bonds from strong to weak to achieve specificity and control function.[45] Equally well recognized, yet less often put into practice, is the understanding that hydrogen bonds also strongly influence the physicochemical and transport properties of a molecule. Despite its importance, medicinal chemists rarely probe the strength of hydrogen bonds in a systematic manner, as is often done for other properties such as steric bulk, hydrophobicity, and proton basicity or acidity. While this shortcoming was recognized by Morris et al. nearly 2 decades ago[46] and attributed to a lack of suitable hydrogen-bond scales, very little has changed following the development of such scales. One of our objectives in this Perspective is to raise awareness and to provide access to the required data to effect a change in this status quo with the introduction of the pK_{BHX} database.

While there is a recognition that parallel optimization of properties is desirable or even essential to success, the lure of the perceived benefits of high potency is difficult to resist such that potency and specificity are still at the forefront of most lead optimization campaigns. In structure-based design, existing protein−ligand hydrogen bonds or new sites for hydrogen bonding are easily identified within a binding pocket directly from the atomic coordinates. It is common for medicinal chemists to gravitate toward these interactions in an attempt to design more potent or selective analogues. When presented with a scale such as the pK_{BHX}, it is tempting to take a simplistic view that strengthening the HB basicity of a critical HBA in a ligand will lead to an increase in affinity. However, the relationship between ligand affinity and number or strength of hydrogen bonds is often complex and not predictable. A recent study of hydrogen bonds at the interface of protein−ligand complexes[47] found that multicentered hydrogen bonds (e.g., bifurcation and trifurcation) are ubiquitous, further complicating attempts to relate hydrogen bonds directly with ligand affinity.

The effects of solvent, usually water, give rise to an often invoked oversimplification of the free energy changes during the ligand-binding process. In this simplified view, the non-complexed ligand and protein site are fully solvated, with solvent water fulfilling the full complement of hydrogen bonds for both species. Upon complex formation, water is displaced and new hydrogen bonds are formed between the ligand and protein with no net change in the total number of hydrogen bonds after the displaced waters form hydrogen bonds within the bulk solvent. This approximation ignores a multitude of variables that can strongly influence the energetics of hydrogen-bond formation including hydrogen-bond geometry, solvent accessibility, local polarity of the binding pocket, networks of hydrogen bonds, and differences in the properties of bulk, surface, and bound waters and the important contribution of conserved water molecules in mediating ligand protein contacts. A review of hydrogen bonds in protein−ligand complexes[2] lists a dozen studies investigating the enthalpy or free energy changes attributed to hydrogen-bond formation during ligand binding. The values range from 0 to −13 kJ/mol, with no convergence to a single value. This is not surprising, and it must be recognized that every binding pocket presents a unique environment and simplistic rules provide little guidance to the value of a specific hydrogen bond in a binding pocket.

A literature search was undertaken to identify case studies for which hydrogen-bond basicity is reported to be correlated with biological activity. While we do not claim to have completed an exhaustive search, there is a dearth of relevant examples, clearly suggesting that this is an area rarely systematically explored by medicinal chemists. Apparently, we do not hold this opinion alone. In a review, Williams and Ladbury state, “more data on ΔH, ΔG, and structural changes in series of similar complexes, categorized by type of hydrogen-bonding partners and local environmental change, are needed in order to provide a set of case histories from which it may be possible to predict the effect of a proposed change by similarity to a previous case.”[2] This may be too optimistic a view, and it is more likely that the hydrogen-bond SAR for a given site will be unique. Thus, it is imperative that the SAR be established early during a lead optimization campaign by systematically surveying the HB basicity landscape. The pK_{BHX} database can be useful during this endeavor.

The parallel optimization of physicochemical properties during the design of new analogues requires medicinal chemists to consider many factors that are tangentially related to hydrogen-bond basicity. For example, low aqueous solubility and high lipophilicity are often undesirable outcomes of a potency-driven lead optimization program and contribute to low intestinal absorption. One commonly employed strategy to reduce lipophilicity is to substitute phenyl rings with heterocycles to introduce polarity. The choice of heterocycle can be dictated to a large extent by the local environment within the binding pocket. If the phenyl ring is believed to be partially solvent exposed in the binding site, an ortho-substituted pyridine may be a good choice. The pyridine nitrogen atom is a strong HBA and will provide a polar interface to solvent, while the ortho-substitution can reduce undesirable binding to Cyp3A4.[48] However, in a hydrophobic environment or for central nervous system indications that require transport across the blood−brain barrier, this is perhaps one of the worst heterocycles to choose given its strong hydrogen-bond basicity. Instead, pyrazine or pyrimidine which form weaker hydrogen bonds are better alternatives.

Fluorine is often introduced at specific metabolically labile positions to reduce clearance or the formation of reactive intermediates.[49,50] During this process, the inductive effects of fluorine can also be used to exquisitely tune the hydrogen-bond basicity of a distal group. Consider pyridine and fluorine-substituted analogues: pyridine ($pK_{BHX} = 1.86$), 3-fluoropyridine ($pK_{BHX} = 1.35$), 2-fluoropyridine ($pK_{BHX} = 0.95$), 2,6-difluoropyridine ($pK_{BHX} = 0.14$), and pentafluoropyridine ($pK_{BHX} = -0.49$). Walking the fluorine atom(s) around the ring alters the hydrogen-bond basicity significantly. In a comprehensive study, a similar use of fluorine to modulate proton basicity has been reported.[51] For fluorine-substituted systems, the proton basicity and HB basicity are largely influenced by inductive-field effects. Therefore, it may be expected that the other trends reported for proton basicity will be transferable to hydrogen-bond basicity, although this is yet to be confirmed experimentally.

The importance of relative hydrogen-bond strengths long has been recognized within the field of computer-aided drug design. The initial focus was in developing descriptors for use in quantitative structure−activity relationship (QSAR) models. The complexity of these descriptors ranged from simplistic counts of donor and acceptor atoms to more sophisticated electronic properties derived from quantum mechanical methods and has been reviewed by Dearden and Ghafourian.[52] This remains an active area of research, and more recent reports reflect an attempt to apply these methods during the drug design process. A Web-based tool accessible to medicinal chemists for predicting hydrogen-bond basicities has been reported by Gancia et al.[53] Application of this tool to a series of IKK2 kinase inhibitors showed a useful correlation between the predicted hydrogen-bond strength and enzyme IC_{50}.[54] A similar tool based upon the electrostatic local minima ($V_{s,min}$) method[55−58] has been implemented at Roche Palo Alto. It is anticipated that the extensive data set contained within the pK_{BHX} database can be used to improve upon these descriptors and to refine the computational models of hydrogen bonding.

With improved computational models capable of predicting hydrogen-bond basicities, it is reasonable to consider refining the Lipinski “rule of 5” for intestinal absorption or permeation.[6] Lipinski et al. defined a set of rules targeted toward medicinal chemists and their inherent strengths in pattern and functional group recognition. As a consequence, the influence of hydrogen bonding on a molecule's intestinal absorption was reduced to a simple sum of NH and OH bonds for HBDs and the sum of N and O atoms for HBAs. At the time, it was recognized that this approximation for HBAs was poor given the considerable variability of HB basicities for a nitrogen or oxygen atom. Indeed, a sum of N and O atoms explains only 26% of the variance of the pK_{BHX} scale in a sample of 1094 values calculated to take into account polyfunctional HBAs (data not shown). Others have suggested the use of HB scales as the basis for an improved intestinal absorption model[5,7] and proposed structural group constants to rapidly predict hydrogen-bond basicities.[15] We continue research efforts in the development of robust prediction methods for drug molecules with 5−10 HBAs. It is anticipated that as these prediction methods mature, the Lipinski rule placing a limit of 10 N and O atoms may be replaced with a more meaningful maximum value derived from the pK_{BHX} scale.

8. Conclusions

The creation of the pK_{BHX} database is an incremental step that provides both a framework and the associated data to allow medicinal chemists the ability to develop an intuition for hydrogen-bond basicity. The hydrogen-bond basicity of a selected set of functional groups deemed to be particularly relevant to medicinal chemists was reviewed, with a focus on the effects of a few common substituents. Finally, a brief discussion highlighting the role of hydrogen-bond basicity in various aspects of drug design was intended to stimulate the curiosity of practicing medicinal chemists. It is the authors' hope that the data presented herein will provide the foundation for new experiments and inquiries that further improve our understanding of the hydrogen bond.

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Biographies

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Ken A. Brameld received his B.S. in Chemistry at the University of Washington in 1993. He earned his Ph.D. in Chemistry in 1998 from California Institute of Technology, under the supervision of Prof. William Goddard, III. In 1998 he began a postdoctoral fellowship at University of California, San Francisco, in the laboratory of Irwin "Tack" Kuntz and in 1999 was awarded an NIH postdoctoral fellowship. He joined the pharmaceutical industry in 2000 and is currently a Principal Research Scientist at Roche Palo Alto, where he is the computational chemistry group leader. He has contributed to research projects in multiple disease areas including oncology, immunology, and virology.

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Jean-Yves Le Questel received his Ph.D. in Physical Organic Chemistry in 1991 from the University of Nantes (France). After a postdoctoral period with Prof. James Milner White at Glasgow University, U.K., he carried on another postdoctoral appointment with Dr. Serge Perez at the French National Institute for Agricultural Research (INRA) of Nantes. He became a Lecturer at the University of Nantes in 1993 and a Professor in 2006. He is presently the head of the "Hydrogen Bonds and Neuroactive Molecules" group of the CEISAM laboratory of Nantes University. His research is focused on the elucidation of hydrogen-bond geometries and energies through experimental (IR spectrometry, structural database analyses) and computational chemistry, with a particular emphasis on the analysis of the hydrogen bonding of small-molecule biological ligands.

Eric Renault obtained his Ph.D. in Physical Chemistry in 1996 from the University Paris Descartes (France), under the supervision of Prof. M. Gardès-Albert and Dr. M.-P. Fontaine-Aupart. After postdoctoral research with L. Sanche at the University of Sherbrooke (Canada), he joined the Commissariat à l'Energie Atomique (Service des Photons, Atomes et Molécules) of Saclay (France) in M.-E. Couprie's Super-ACO FEL team. In 2001, he became Lecturer at the University of Nantes. A part of his research was devoted to time-resolved laser spectroscopy of biomolecular systems. Since his arrival in the laboratory of spectrochemistry, currently CEISAM, his current research interests include the application of computational chemistry, with a special emphasis on the molecular interactions.

Supporting Information Available: Graphic representation of the pK_{BHX} scale including the different functional groups encountered in the database; a table listing the pK_{BHX} and pK_{BH^+} values used for the comparison of the HB and proton basicity scales; a table listing a representative sample of the data contained in the pK_{BHX} database. This material is available free of charge via the Internet at http://pubs.acs.org.

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K_a of its conjugate acid BH^+, denoted pK_{BH^+} (Bagno, A.; Scorrano, G. *J. Am. Chem. Soc.*, **1998**, *110*, 4577−4582), clarifying the species for amphoteric compounds (anilines, phenols, primary and secondary amides and sulfonamides, etc). For example, the pK_{BH^+} of anilines refers to the acid−base pair $ArNH_3^+/ArNH_2$, that is, to their basicity, and not the pair $ArNH_2/ArNH^-$ (acidity).

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