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Hydrogen-bond basicity of solutes in hydroxylic solvents from octanol–water partition coefficients

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epoc ABSTRACT: Hydrogen-bond acceptor strengths of numerous bases can be extracted from octanol–water partition coefficients after subtraction of a hydrophobic-cavity term proportional to the molecular volume of the solutes. A stepwise correlation analysis is carried out to compare these basicities in hydroxylic solvents with the $\mathrm{p}K_x(\mathrm{HB})$ hydrogen-bonding basicity scale determined for the 1:1 association of 4-fluorophenol in carbon tetrachloride. Within a family of bases, hydrogen-bond acceptor ability in hydroxylic solvents is found to be predicted by the $\mathrm{p}K_x(\mathrm{HB})$ scale and the overall basicity of bifunctional and trifunctional solutes is precisely calculated by an exact summation $\sum \mathrm{p}K_x(\mathrm{HB})$ of the strengths of the individual basic sites. Plots of octanol–water partition coefficients against $\sum \mathrm{p}K_x(\mathrm{HB})$ present classical family-dependent relationships separating the amines, pyridines and ethers from the other bases. This separation can be accounted for by a simple multiplicative term λ restoring the additivity of the basicity strengths. Careful dissection of the overall basicities of bifunctional compounds into their individual components reveals the considerable levelling effect of the hydroxylic solvents on the relative strengths of the different basic groups present in the same solute. A two-parameter equation involving the molecular volume and the corrected summation for all basic sites $\sum \lambda \mathrm{p}K_x(\mathrm{HB})$ is proposed to predict partitioning between octanol and water. Significant deviations from the equation are found when one of the basic centres of the solute is hindered by bulky substituents. Copyright © 2002 John Wiley & Sons, Ltd.
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KEYWORDS: hydrogen bonding; lipophilicity; basicity scales; solvation

INTRODUCTION

Octanol–water partition coefficients (log *P*) have found wide application in quantitative structure–activity relationships (QSARs), where they have proved useful as empirical parameters for the analysis of the biological activity of solutes and the design of new active molecules.[1] Many sources provide partition coefficients, and the several thousand data critically collected by Hansch *et al.*[2] may serve as a reference table. However, even more compounds are missing, and a great many attempts have been made to develop programs or equations devoted to the prediction of these coefficients. The log *P* values are readily estimated by the summation of fragment values or by linear energy solvation relationships (LSERs) relating the partition coefficient of a solute to its molecular properties.[3] The former method necessitates the calculation of empirically or statistically determined incremental values for molecular fragments and the evaluation of interaction factors. The effort is limited, however, to the evaluation of the partition coefficient, and no other use of the fragmental coefficients can be made. In the LSER approach, the empirical determinations[4–9] and the theoretical calculations[10,11] of the parameters used in the equations may unravel the molecular interactions involved, both in the partitioning of a solute and in other important physicochemical processes, such as solubility.[12] Moreover, Abraham and Chadha[13] showed that many biological activities of molecules could be quantified solely by the physico-chemical parameters obtained from different partition coefficients or chromatographic capacity factors, stressing the importance of the decomposition of the bulk physico-chemical property or the biological activity into unambiguously defined and easily determined parameters.

The two main terms governing the partitioning of a solute between water and immiscible organic phases are a hydrophobic-cavity formation term and an opposing

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hydrogen-bond acceptor ability hydrophilic term.[4–9] It is generally agreed that the contributions of polarity/polarizability effects are of secondary importance in the distribution between wet octanol and water, and that the solvation differential between the two solvents cancels the hydrogen-bond acidity effect of the solute.[14] Since the cavity term, which is directly related to the size of the molecule, can readily be subtracted, the log P values constitute a unique collection of thousands of experimental data. These are mainly related to the basicity of organic solutes in water, the most biologically relevant solvent where direct measurements are difficult to obtain by standard methods.[15] This paper is devoted to the analysis of the hydrogen-bond contribution to the octanol–water partition coefficient. It explores the relationships between these effective basicities observed in hydroxylic solvents and the basicities determined from the 1:1 complexation of 4-fluorophenol in carbon tetrachloride (CCl_4):

$$\text{4-FC}_6\text{H}_4\text{OH} + \text{B} \rightleftharpoons \text{4-FC}_6\text{H}_4\text{OH}\cdots\text{B} \qquad (1)$$

$$K_x(25\ ^\circ\text{C, CCl}_4) = x_{[4-\text{FC}_6\text{H}_4\text{OH}\cdots\text{B}]}/x_{[\text{B}]}x_{[4-\text{FC}_6\text{H}_4\text{OH}]}$$

$$\text{p}K_x(\text{HB}) = \log K_x : K_x \text{ is expressed in terms of molar fraction}$$

The pK_x(HB) scale has the same definition as the pK_{HB} scale pioneered by Taft *et al.*[16] three decades ago, but it has been recalculated with equilibrium constants expressed in terms of molar fractions instead of molar concentrations. This has the practical advantage that the sum of two (or more) pK values is always greater than the individual pK values, since pK_x(HB) is positive even for the weakest base ever measured with 4-fluorophenol in CCl_4.[17] The molar volume of CCl_4 is 10.3 dm^3 mol^{-1}, so that pK_x(HB) can easily be calculated from pK_{HB} by the simple equation: pK_x(HB) = 1.01 + pK_{HB}. This shift gives an origin to the pK_x(HB) scale very close to the zero point of the β_2^{H} basicity scale statistically calculated by Abraham *et al.*[18] from linear free energy relationships involving different hydrogen-bond donors in CCl_4. The pK_x(HB) or pK_{HB} scale has now been published for more than 1000 bases belonging to a wide variety of neutral accepting groups, including carbon, nitrogen, oxygen, sulfur and halogen bases.[19] Throughout this work, priority has been given to the analysis of the effect of fine structural variations of the solutes, so that the data are deliberately limited to *(i)* the most representative compounds of the different families, in order to prevent any overfilling of the data sets by lengthening the hydrocarbon chains around the basic functional group, and *(ii)* the solutes for which the pK_x(HB) values have been determined experimentally. The data set that has been found to fulfil these requirements contains more than 300 bases. The complete data set used in this paper is available as supplementary material at http://www.wiley.com/epoc/.

THE NON-BASIC SOLUTE SET: EVALUATION OF THE CAVITY FORMATION ENERGETIC TERM

Taft and Murray[14] have shown that, among the different parameters available, the molecular volume V_x of the solute calculated by the Abraham–McGowan equation[20] can measure the magnitude of the complex energy differences arising from the creation of cavities and from the dispersive interactions involved in the two partitioning solvents. Indeed, Eqn. (2) gives a good relationship for the range of eight log P units covered by the 50 compounds given in Table 1. These are either non-basic or very weak bases, such as rare gases, straight-, branched- and cyclic-chain aliphatic hydrocarbons, small diatomic molecules (O_2, N_2, H_2) and perhalogenated compounds:

$$\log P = 3.885(\pm 0.049)V_x/100 + 0.043(\pm 0.045) \qquad (2)$$

for which the correlation coefficient $R = 0.996$, the number of points $n = 50$, the standard error $s = 0.17$, Fisher statistic $F = 6260$ and the numbers in parentheses are the 95% confidence intervals. V_x is expressed in cubic centimeters per mole and is scaled by the factor 1/100 to give relatively comparable coefficients for the different parameters used in the subsequent correlations. As expected, the intercept of the line corresponding to a hypothetical molecule with a zero volume, which should distribute equally between the two solvents, is not significant. We have thus forced the line through the origin and the cavity term is obtained from the simpler least-squares Eqn. (3) without significant loss of precision:

$$\log P = 3.926(\pm 0.026)V_x/100 \qquad (3)$$

BASICITY OF AMINES AND PYRIDINES: THE EXACT ADDITIVITY OF THE pK_x(HB) VALUES

The determination of the pK_x(HB) value by the FTIR method is based on the measurement of the decrease in absorbance of the free phenol absorption with the formation of the hydrogen-bond complex on the base. If the base contains several basic sites, and if the concentration of the phenol is kept sufficiently low to prevent complexes of higher stoichiometries, the measured experimental equilibrium constant K_{t} is the sum of all possible 1:1 equilibria formed on all basic sites:

$$K_{x\text{t}} = \sum K_{x\text{i}} \quad \text{and} \quad \text{p}K_x(\text{HB})_{\text{t}} = \log\left(\sum K_{x\text{i}}\right) \qquad (4)$$

Then, a simple statistical correction factor of log n is

Table 1. Partition coefficients for non-basic compounds

No. Molecule	Formula	$V_x/100^a$	log P^b	$3.926V_x/100$	Residuals[c]
1 Helium	He	0.068	0.28	0.27	0.01
2 Neon	Ne	0.085	0.28	0.33	−0.05
3 Argon	Ar	0.190	0.74	0.75	−0.01
4 Krypton	Kr	0.246	0.89	0.97	−0.08
5 Xenon	Xe	0.329	1.28	1.29	−0.01
6 Radon	Rn	0.384	1.51	1.51	0.00
7 Dihydrogen	H_2	0.109	0.45	0.43	0.02
8 Dioxygen	O_2	0.183	0.65	0.72	−0.07
9 Dinitrogen	N_2	0.222	0.67	0.87	−0.20
10 Methane	CH_4	0.250	1.09	0.98	0.11
11 Ethane	C_2H_6	0.390	1.81	1.53	0.28
12 Propane	C_3H_8	0.531	2.36	2.08	0.28
13 Butane	C_4H_{10}	0.672	2.89	2.64	0.25
14 Pentane	C_5H_{12}	0.813	3.39	3.20	0.20
15 Hexane	C_6H_{14}	0.954	3.90	3.75	0.15
16 Heptane	C_7H_{16}	1.095	4.66	4.30	0.36
17 Octane	C_8H_{18}	1.236	5.18	4.86	0.33
18 Nonane	C_9H_{20}	1.377	5.65	5.41	0.24
19 Undecane	$C_{11}H_{24}$	1.659	6.54	6.51	0.03
20 Dodecane	$C_{12}H_{26}$	1.799	6.80	7.06	−0.26
21 Tridecane	$C_{13}H_{28}$	1.940	7.56	7.62	−0.06
22 Tetradecane	$C_{14}H_{30}$	2.081	8.00	8.17	−0.18
23 2-Methyl propane	C_4H_{10}	0.672	2.76	2.64	0.12
24 2,2-Dimethylpropane	C_5H_{12}	0.813	3.11	3.19	−0.08
25 3-Methylpentane	C_6H_{14}	0.954	3.60	3.75	−0.15
26 2,2-Dimethylbutane	C_6H_{14}	0.954	3.82	3.75	0.07
27 2,3-Dimethylbutane	C_6H_{14}	0.954	3.42	3.75	−0.33
28 3,3-Dimethylheptane	C_9H_{20}	1.377	5.19	5.41	−0.22
29 Methylcyclohexane	C_7H_{14}	0.986	3.61	3.87	−0.26
30 Methylcyclopentane	C_6H_{12}	0.845	3.37	3.32	0.05
31 Cyclopropane	C_3H_6	0.423	1.72	1.66	0.06
32 Cyclopentane	C_5H_{10}	0.705	3.00	2.77	0.23
33 Cyclohexane	C_6H_{12}	0.845	3.44	3.32	0.12
34 Cycloheptane	C_7H_{14}	0.986	4.00	3.88	0.13
35 Cyclo-octane	C_8H_{16}	1.127	4.45	4.42	0.03
36 Carbon tetrachloride	CCl_4	0.739	2.83	2.90	−0.08
37 Carbon tetrafluoride	CF_4	0.320	1.18	1.26	−0.08
38 Carbon tetrabromide	CBr_4	0.950	3.42	3.73	−0.31
39 Hexachloroethane	C_2Cl_6	1.125	4.14	4.42	−0.28
40 Hexafluoroethane	C_2F_6	0.497	2.00	1.95	0.05
41 Tetrachloroethylene	C_2Cl_4	0.837	3.40	3.29	0.11
42 Hexachlorobenzene	C_6Cl_6	1.451	5.73	5.70	0.03
43 Sulfur hexafluoro	SF_6	0.464	1.68	1.82	−0.14
44 Carbon disulfide	CS_2	0.491	1.94	1.93	0.01
45 Trichlorofluoromethane	$CFCl_3$	0.634	2.53	2.49	0.04
46 Bromotrifluoromethane	$CBrF_3$	0.478	1.86	1.88	−0.02
47 Chlorotrifluoromethane	$CClF_3$	0.425	1.65	1.67	−0.02
48 Dichlorodifluoromethane	CCl_2F_2	0.530	2.16	2.08	0.08
49 1,2-Dichlorotetrafluoroethane	$C_2Cl_2F_4$	0.706	2.82	2.77	0.05
50 1,1,2-Trichlorotrifluoroethane	$C_2F_3Cl_3$	0.811	3.16	3.19	−0.02

[a] Molecular volume in $cm^3 \, mol^{-1}$.

[b] Ref. 2.

[c] Difference between experimental and calculated log *P*.

applied to the experimental values of polyfunctional bases with *n* identical functional groups in order to obtain the basicity of a single site. In the general case, however, the molecule possesses different functional groups and the $pK_x(HB)_i$ values of the individual groups are calculated from the family-dependent relationships between the $pK_x(HB)$ values and the frequency shifts of a phenol or an alcohol[21] or the minimum electrostatic potential.[22]

When the polyfunctional acceptor molecule is surrounded by an excess of donor, all basic centres form simultaneous associations with the donor molecules. In the simplified case of a bifunctional F_1—F_2 molecule, the stepwise addition of the donor is represented by the equilibria in Eqns (5) and (6). The overall equilibrium constant K'_t is then the product of the individual equilibrium constants K'_1 and K'_2 corresponding to the associations on both sites of the acceptor in ROH as solvent:

$$\mathrm{ROH} + \mathrm{F_1F_2} \rightleftharpoons \mathrm{ROH\cdots F_1F_2} \qquad K'_1 \quad (5)$$

$$\mathrm{ROH\cdots F_1F_2} + \mathrm{HOR} \rightleftharpoons \mathrm{ROH\cdots F_1F_2\cdots HOR} \qquad K'_2 \quad (6)$$

$$2\mathrm{ROH} + \mathrm{F_1F_2} \rightleftharpoons \mathrm{ROH\cdots F_1F_2\cdots HOR} \qquad K'_t \quad (7)$$

$$K'_t = K'_1 K'_2 \text{ and } pK'_x(\mathrm{HB})_t = pK'_x(\mathrm{HB})_1 + pK'_x(\mathrm{HB})_2 \qquad (8)$$

Eqn. (8) can be extended for a molecule containing n non-interacting sites to:

$$pK'_x(\mathrm{HB})_t = \sum_{i=1}^{n} pK'_x(\mathrm{HB})_i \qquad (9)$$

Therefore, the problem is to check whether the second term of Eqn. (9) is a simple function f of the pK corresponding to the 1:1 associations of a phenol on the same sites in apolar solvents:

$$pK'_x(\mathrm{HB})_t = f\left[\sum_{i=1}^{n} pK_x(\mathrm{HB})_i\right] \qquad (10)$$

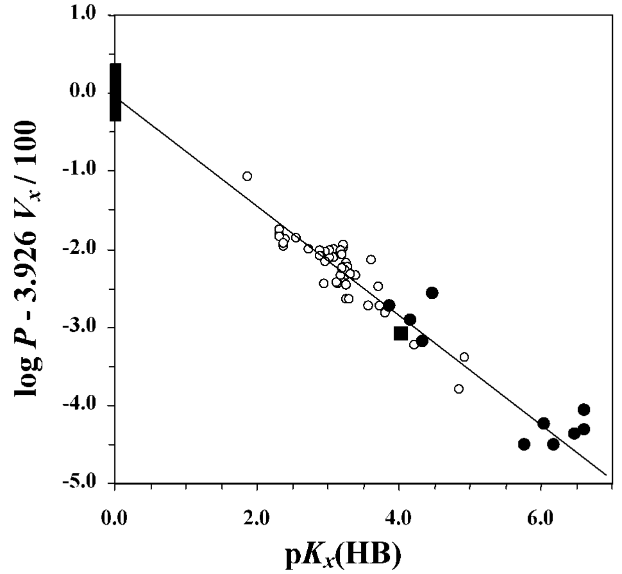

Figure 1. Relationship between the HB term of the partition coefficient and the pK_x(HB) scale for monofunctional N-sp^2 and N-sp^3 bases (regression line and ○). The pK_x(HB) values of the diamines and diazines (●) are multiplied by a factor of two. The pK_x(HB) values of 1,3,5-triazine (■) is multiplied by a factor of three. The segment on the y axis represents the non-basic compounds

This additivity rule of the pK_x(HB) values was first tested on a series of nitrogen molecules, where the presence of a single lone pair on the basic site limits the possibility of formation of higher-order complexes. When corrected from the cavity term, the log P values of a series of 22 *monofunctional* primary,[22] secondary[23] and tertiary amines[24] and 30 *monofunctional* imines or meta- and para-substituted pyridines[21] define a linear relationship with pK_x(HB) (open circles and straight line of Fig. 1). In Table 2, we have collected the experimental pK_x(HB)$_t$ of 11 *bifunctional* and *trifunctional* amines and pyridines and calculated their basicity parameters $\sum$pK_x(HB) in the situation where all nitrogen atoms are hydrogen bonded, for instance when the molecules are dissolved in hydroxylic solvents. It can be seen in Fig. 1 that the corresponding points (closed circles) are nicely distributed along the line drawn for monofunctional

Table 2. Additivity of the pK_x(HB) values for the evaluation of the octanol–water partition coefficients

No. Polyfunctional compound	pK_x(HB)$_t$[a] Exp. CCl$_4$	$\sum$pK_x(HB)[b] Calc.	log P Exp.[c]	log P Calc.[d]	Δlog P[e]
51 Pyrimidine	2.38	4.16	−0.40	−0.42	0.02
52 Phenazine	2.53	4.47	2.84	2.22	0.62
53 Pyrazine	2.23	3.86	−0.23	−0.21	−0.02
54 Triazine	1.81	4.01	−0.73	−0.47	−0.26
55 2,2′-Bipyridine	2.46	4.32	1.73	1.83	−0.10
56 1,2-Diaminoethane	3.56	6.47	−2.04	−2.20	0.16
57 1,3-Diaminopropane	3.63	6.61	−1.43	−1.76	0.33
58 Piperazine	3.43	6.24	−1.50	−1.37	−0.13
59 *N,N*′-Dimethylethylene diamine	3.61	6.60	−0.62	−1.20	0.58
60 *N,N*′-Dimethylpiperazine	3.19	5.76	−0.40	0.05	−0.45
61 *N,N,N*′,*N*′-Tetramethylenediamine	3.33	6.04	0.30	0.28	0.02

[a] K_x(HB)$_t$ is the measured equilibrium constant obtained by IR spectroscopy in CCl$_4$.[21–24]

[b] $\sum$pK_x(HB) = n[pK_x(HB)$_t$ − log n]; n is the number of identical basic sites (see text).

[c] Experimental log P from Ref. 2.

[d] Calculated log P from Eqn. (11).

[e] Δ log P = log P(exp) − log P(calc).

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solutes. Therefore, all the data corresponding to the mono- and poly-functional amines, imines and pyridines may be gathered with the non-basic compounds to give the biparametric regression in Eqn. (11), where the basicity parameter is now the exact summation term $\sum \mathrm{p}K_x(\mathrm{HB}) = n[\mathrm{p}K_x(\mathrm{HB})_t - \log n]$:

$$\begin{aligned}\log P = {} & 3.870(\pm 0.051)V_x/100 \\ & - 0.699(\pm 0.010)\sum \mathrm{p}K_x(\mathrm{HB}) \\ & + 0.037(\pm 0.047) \qquad (11)\end{aligned}$$

for which $R = 0.994$, $n = 113$, $s = 0.20$ and $F = 4850$. This equation shows both the remarkable robustness of the cavity coefficient and that no bias has been introduced by the basicity term, since the intercept again has a zero value, corresponding to an equal partitioning for solutes of zero basicity and volume. The log P range covered by Eqn. (11) is now greater than ten log units, and the standard error of 0.2 log units gives to this regression line a satisfactory predictive power.

THE FAMILY DEPENDENCE AND THE FACTOR λ

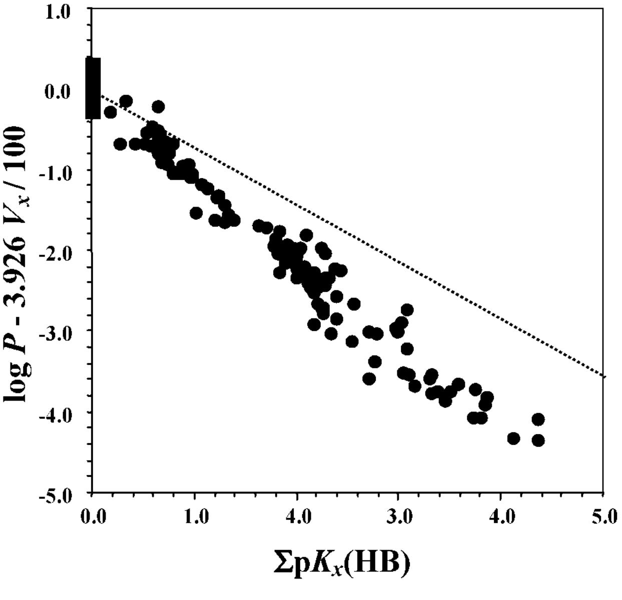

Figure 2. Relationship between the HB term of the octanol–water partition coefficient and the pK_x(HB) scale of hydrogen-bond acceptor strength of π bases, halogens, carbonyl, phosphoryl and sulfuryl compound groups and nitriles. The dashed line corresponds to the amine and pyridine families

Table 3. Family dependence to the $\sum \mathrm{p}K_x$(HB) parameter

Set	Family	$-\lambda$[a]	n[b]	s[c]
1	Amines	0.69	28	0.23
1	Pyridines	0.72	35	0.20
	Set 1	**0.703**	**63**	**0.22**
2	π bases	1.17	26	0.15
2	Nitriles	1.08	18	0.14
2	Carbonyls	1.10	59	0.22
2	Halogens	1.02	14	0.18
2	Alcohols	1.09	8	0.16
2	NO and SO bases	1.01	14	0.29
2	Thioethers	1.11	3	0.07
	Set 2	**1.07**	**142**	**0.22**
3	**Ethers (set 3)**	**0.87**	**11**	**0.15**

[a] Slope of the regression line: log $P - 3.926V_x/100 = \lambda \sum pK_x$(HB).
[b] Number of points.
[c] Standard deviation.

Figure 2 represents the relationship obtained between the hydrogen-bonding part of the octanol–water partition coefficient and the $\sum \mathrm{p}K_x$(HB) scale for a large series of families of bases containing one or two identical basic sites. In these series, the usual basic functional groups are represented, such as aromatic and aliphatic nitriles, aromatic and aliphatic carbonyl groups (esters, aldehydes, ketones and amides), pyridine N-oxides, nitro compounds, sulfoxides and sulfones, thioethers and aliphatic alcohols. Their individual sensitivities λ to the parameter pK_x(HB) reported in Table 3, differ significantly from the values found for the pyridines and the amines, but they remain approximately constant in a narrow range from 1.01 to 1.17. In the same set we have also found two important families of bases considered as weak or very weak in CCl_4 but that appear to contribute significantly to the partition process. The first one is the π bases family containing aromatic and polyaromatic derivatives for which a statistical factor corresponding to the number of aromatic sextets is applied.[17] This family also includes a few ethylenic and acetylenic compounds. The second family of bases corresponds to the aliphatic halogen derivatives (fluoro-, chloro-, bromo- and iodo-derivatives). Their basicity has only recently been introduced into a quantitative scale in CCl_4.[25] When these seven different families are gathered in a single set (set 2), a good relationship [Eqn. (12)] is obtained with V_x and $\Sigma \mathrm{p}K_x$(HB):

$$\begin{aligned}\log P = {} & 3.823(\pm 0.040)V_x/100 \\ & - 1.062(\pm 0.012)\Sigma \mathrm{p}K_x(\mathrm{HB}) \\ & + 0.066(\pm 0.040) \qquad (12)\end{aligned}$$

for which $R = 0.993$, $n = 192$, $s = 0.20$ and $F = 7089$. Direct comparison with Eqn. ((11)) shows that the cavity term remains essentially the same, but that the coefficient of the basicity term for all these families of compounds is about 50% greater than the coefficient corresponding to amines and pyridines. No simple molecular property, such as the polarity of the solute families or the number of available lone pairs allowing higher degrees of complexation, can definitively explain this difference between the two sets of families. Indeed, both sets contain compounds with a wide range of dipolarity, and set 2

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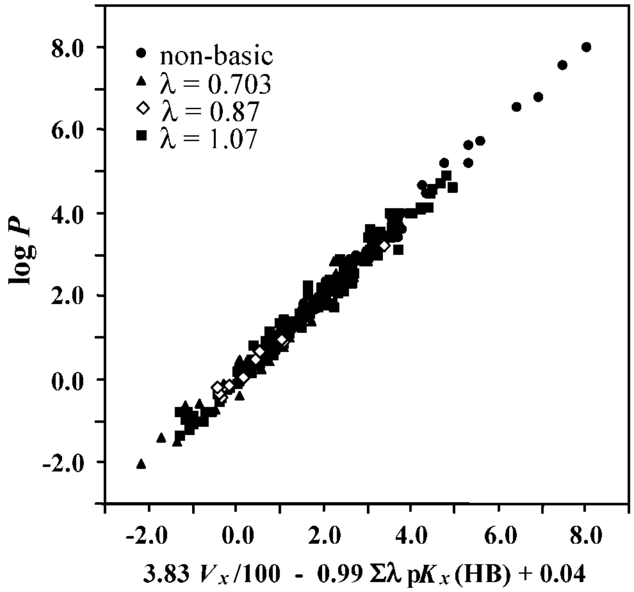

Figure 3. Relationship between experimental and calculated log *P* [Eqn. (13)]

includes the nitrile family with a single lone pair on the basic atom together with other families containing basic centres with several lone pairs. Therefore, this behaviour must rather be explained by the family dependence generally observed when different basicity-dependent properties are analysed with various donors and/or in different solvents.[19,26–29] Moreover, a third family is observed with the ether-oxides, for which an intermediary λ coefficient of the pK_x(HB) parameter is found necessary, in spite of the few members of this family. Such a gain in the basicity strength of amines, pyridines and ethers from all other functional groups when the solvent polarity increases is the main obstacle to the definition of a fully generalized single parameter scale of hydrogen-bonding basicity.[18,30] However, in this analysis, it appears possible to take into account only three different sensitivities ($\lambda = 0.703$, 0.87 and 1.07) corresponding to the three sets presented on Table 3, so that a general and very simple relationship [Eqn. (13)] ranging over ten log *P* units (Fig. 3) may be set up to estimate the partition coefficients from the equilibrium constants of the 1:1 associations measured in CCl_4:

$$\log P = 3.827(\pm 0.036)V_x/100 - 0.988(\pm 0.010)\Sigma\lambda pK_x(\mathrm{HB}) + 0.046(\pm 0.037) \qquad (13)$$

for which $R = 0.993$, $n = 266$, $s = 0.20$ and $F = 9220$. In his analysis of numerous partitioning systems, Abraham[31] found it necessary to set up two basicity parameters for the amine and pyridine families depending on whether water was substantially miscible or not in the organic phase. This strongly suggests that the family-dependence parameter λ is not transferable to all organic–water systems.

ADDITIVITY OF THE $\Sigma\lambda pK_x$(HB) VALUES

It is necessary to check whether the additivity of the basicities of the different sites remains valid for molecules containing several basic sites belonging to different families. This question is of particular significance here, since: (*i*) the structures of molecules of biological importance are generally polyfunctional and their basic centres belong to the three different λ groups; (*ii*) substituents that are considered as negligibly active in the solute scale of basicity in apolar solvents may become an important source of interaction with the hydroxylic solvents by virtue of the scaling λ factor.

Since the relative precision of an equilibrium constant measured in CCl_4 [Eqn. (1)] is *ca* 5–10%, the estimation of the strength of a secondary basic site in the pK_x(HB) scale can only be carried out in a few favourable cases, where the relative HB abilities of the two basic sites are not too far apart and where the two 1:1 associations give different absorptions in the IR spectra.[21,23,24] Some instructive examples are given in Tables 4 and 5. When the molecules are treated as monofunctional solutes (Table 4), with a basicity taken as the experimental equilibrium constant $K_x(\mathrm{HB})_t$ determined in CCl_4 and attributed in totality to the 'main' function—ether, pyridine or amine—very large deviations are obtained for all the compounds selected. On the contrary, when the basicity of the 'substituent' is evaluated accurately, scaled by the factor λ, and added to the corrected basicity of the functional group, the partition coefficients of the bifunctional compounds are calculated with a good precision. The determining influence of the substituent on the total basicity in water is worth noticing here. For 3-cyanopyridine, the experimental basicity measured in CCl_4 is $pK_x(\mathrm{HB})_t = 2.01$ and, after evaluation of the equilibrium constant on the cyano group,[21] the basicity of the pyridine is calculated as $pK_x(\mathrm{HB})_N = 1.83$. Thus, the presence of a basic nitrile substituent increases the basicity of the molecule by a modest factor of 10%. In octanol–water, on the contrary, the calculated overall basicity is $\Sigma\lambda pK_x(\mathrm{HB})_t = 2.94$, whereas the actual basicity of the pyridine nitrogen of 3-cyanopyridine is $\lambda pK_x(\mathrm{HB})_N = 1.29$. The presence of a nitrile substituent has thus increased the basicity by a factor of 130% and the 'substituent' has become more basic than the functional group. The examples of Tables 4 and 5 reveal the tremendous levelling effect operated by the hydroxylic solvents on the relative hydrogen-bonding abilities of the different basic sites present in polyfunctional molecules. In anisole and dimethylaniline, the phenyl group contributes to about 50% of the overall basicity, in morpholine the ether oxygen and the amine nitrogen are equally basic, and in the substituted pyridines the

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Table 4. Analysis of some bifunctional solutes with the general Eqn. (13) for solutes treated as monofunctional compounds

						log *P*		
No.	Compound	$V_x/100$[a]	$pK_x(HB)_t$[b]	$\lambda pK_x(HB)_t$[c]	Family	Exp.[d]	Calc.[e]	Δ log P[f]
62	Anisole	0.916	1.12	0.97	ether	2.11	2.59	−0.48
63	*N,N*-Dimethylaniline	1.098	1.50	1.05	amine	2.31	3.21	−0.90
64	2-Cyanopyridine	0.830	1.86	1.31	pyridine	0.40	1.93	−1.53
65	3-Cyanopyridine	0.830	2.01	1.41	pyridine	0.23	1.83	−1.60
66	4-Cyanopyridine	0.830	2.06	1.45	pyridine	0.46	1.79	−1.33
67	Methylnicotinate	1.032	2.51	1.76	pyridine	0.83	2.26	−1.43
68	4-Acetylpyridine	0.973	2.52	1.77	pyridine	0.48	2.02	−1.54
69	Morpholine	0.722	2.87	2.01	amine	−0.86	0.82	−1.68

[a] V_x is the molecular volume.[20]

[b] $K_x(HB)_t$ is the apparent equilibrium constant obtained by IR spectroscopy in CCl_4.

[c] λ is the family dependence parameter (see text).

[d] Data from Ref. 2.

[e] log *P* calculated from Eqn. (13).

Table 5. Analysis of some bifunctional solutes with the general Eqn. (13) for solutes treated as bifunctional compounds

						log *P*		
Compound	$\lambda pK_x(HB)_1$[a]	Family	$\lambda pK_x(HB)_2$[a]	Family	$\sum\lambda pK_x(HB)$	Exp.[b]	Calc.[c]	Δlog P[d]
Anisole	0.69	π	0.86	ether	1.55	2.11	2.02	0.09
N,N-Dimethylaniline	0.92	π	0.98	amine	1.90	2.31	2.37	−0.06
2-Cyanopyridine	1.73	nitrile	1.05	pyridine	2.78	0.40	0.47	−0.07
3-Cyanopyridine	1.65	nitrile	1.29	pyridine	2.94	0.23	0.31	−0.08
4-Cyanopyridine	1.59	nitrile	1.35	pyridine	2.94	0.46	0.31	0.15
Methylnicotinate	1.62	carbonyl	1.73	pyridine	3.35	0.83	0.68	0.15
4-Acetylpyridine	1.92	carbonyl	1.70	pyridine	3.62	0.48	0.19	0.29
Morpholine	1.93	ether	1.95	amine	3.88	−0.86	−1.03	0.17

[a] $K_x(HB)_1$ and $K_x(HB)_2$ are the equilibrium constants of the two basic sites of the molecule determined from IR frequency shifts.[21,23–24]

[b] Data from Ref. 2.

[c] log *P* calculated from Eqn. (13).

[d] Δ log $P = \log P$ (exp) − log P(calc).

basicities of the cyano and the carbonyl substituents can exceed the nitrogen basicity. This relative amplification of the hydrogen-bonding abilities of secondary sites in hydroxylic solvents by comparison with direct measurements in apolar solvents is an effective means to detect the polyfunctionality of solutes toward water. This step of hydrogen bonding in water also fills the gap between aqueous protonation and hydrogen bonding in apolar solvents that sometimes occurs at different sites.[32–34] For the molecules presented in Table 6, a clear frontier appears between the first four monofunctional compounds **70–73** and the remaining solutes **74–89**, which are at least bifunctional and, possibly, tri- or tetrafunctional. When the logarithm of the apparent equilibrium constant determined in CCl_4 is taken as the overall basicity of the compound, two situations arise for the difference Δ log *P* between the experimental and the calculated log *P*. In the first situation (compounds **70–73**), deactivation of the substituent by the strong electron-attracting inductive effect and/or resonance effect of the functional group appears sufficient to ruin the HB acceptor ability of the phenyl ring of benzonitrile and the amino nitrogen of dimethylcyanamide, diazabicyclononene or *N*-methylimidazole. In the second situation (compounds **74–82**), the sites are separated by a methylene group, which decreases the inductive effect of the functional group and eliminates the resonance effect. Both sites become active as HB acceptors and the deviations Δ log *P* exhibit important negative values related to the strengths of the second sites. For benzylcyanide **74**, the deviation corresponds to an excess of basicity of *ca* 0.44 due to the benzene ring, fully compatible with the presence of a benzene ring [$pK_x(HB) = 0.55$][17] deactivated by a field/inductive electron-withdrawing functional group CH_2CN ($\sigma_F = 0.32$).[39] In the same way, the increasing deviations observed in the series

allylamine **77**(−0.18) < diallylamine **78** (−0.75)
< triallylamine **79** (−0.98),
or 2-chloroethyl ethyl ether **80** (−0.99)
< bis-(2-chloroethyl)ether **81** (−1.40)

can be explained by the successive addition of new active secondary sites compatible with the known HB basicity

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Table 6. Analysis of potential polyfunctional molecules

No. Compound	Formula	V_x/100[a]	pK_x(HB)$_t$[b]	λ[c]	log P Exp.[d]	log P Calc.[e]	Δ log P[f]
70 Benzonitrile	PhCN	0.871	1.81	1.07	1.56	1.46	0.10
71 Dimethylcyanamide	Me_2NCN	0.645	2.57	1.07	−0.15	−0.21	0.06
72 Diazabicyclononene	$C_7H_{12}N_2$[g]	1.034	4.92	0.703	0.69	0.58	0.11
73 *N*-Methylimidazole	$C_4H_6N_2$	0.677	3.73	0.703	−0.06	0.04	−0.10
74 Benzylcyanide	$PhCH_2CN$	1.012	1.82	1.07	1.56	1.99	−0.43
75 Benzylamine	$PhCH_2NH_2$	0.957	2.85	0.703	1.09	1.72	−0.63
76 Phenethylamine	$PhCH_2CH_2NH_2$	1.098	3.17	0.703	1.41	2.04	−0.63
77 Allylamine	$H_2C{=}CHCH_2NH_2$	0.588	2.94	0.703	0.07	0.25	−0.18
78 Diallylamine	$(CH_2{=}CHCH_2)_2NH$	0.968	2.71	0.703	1.11	1.86	−0.75
79 Triallylamine	$(CH_2{=}CHCH_2)_3N$	1.348	2.35	0.703	2.59	3.57	−0.98
80 2-Chloroethyl ethyl ether	$ClCH_2CH_2OEt$	0.853	1.56	0.87	0.98	1.97	−0.99
81 Bis-(2-chloroethyl)ether	$(ClCH_2CH_2)_2O$	0.976	1.27	0.87	1.29	2.69	−1.40
82 Ethylchloroacetate	$ClCH_2COOEt$	0.869	1.68	1.07	0.94	1.59	−0.65
83 Hexamethylphosphotriamide	$(Me_2N)_3PO$	1.517	4.61	1.07	0.28	0.97	−0.69
84 Trimethylphosphate	$(MeO)_3PO$	0.971	3.51	1.07	−0.78	0.05	−0.83
85 Benzophenone	Ph_2CO	1.481	2.08	1.07	3.18	3.51	−0.33
86 Diphenylsulfoxide	Ph_2SO	1.546	3.04	1.07	2.06	2.74	−0.68
87 Triphenylphosphine oxide	Ph_3PO	2.195	4.17	1.07	2.83	4.03	−1.20
88 Nicotine	$C_{10}H_{14}N_2$[h]	1.371	3.11	0.703	1.17	3.13	−1.96
89 Nornicotine	$C_9H_{12}N_2$[i]	1.230	3.21	0.703	0.17	2.52	−2.35

[a] V_x is the molecular volume.[20]

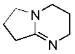
[b] K_x(HB)$_t$ is the measured equilibrium constant obtained by IR spectroscopy in CCl_4.[22–24,35–38]

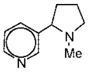
[c] λ is the family dependence parameter (see text).

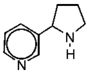
[d] Data from Ref. 2.

[e] log P calculated from Eqn. (13).

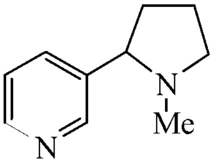
[f] Δ log P = log P(exp) − log P(calc).

[g] 

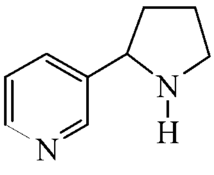
[h] 

[i] 

of an ethylenic bond[17] or a chlorine atom.[25] Deconjugation may also be provoked by stereochemical effects preventing the planarity of the molecule,[40,41] as shown by the deviations found for benzophenone **85**, or diphenylsulfoxide **86**, in line with the activity of one (or two) phenyl group(s) partially deconjugated with the carbonyl[42] or the sulfoxide[43] group. Similarly, the multiplication of very weakly active NMe_2, OMe and Ph substituents could be the origin of the significant overall basicity increase of hexamethylphosphoramide **83**, trimethylphosphate **84** and triphenylphosphine oxide **87** in hydroxylic solvents. This occurs in spite of the strong electron-withdrawing effect of the phosphoryl group,[39] since very low values of pK_x(HB) on the order of 0.36–0.40 per substituent are sufficient to cancel the deviations of the solutes. Here again, it must be stressed that the noticeable activity of substituents belonging to families that are different from the functional group may lead to non-constant overall basicity parameters for different partitioning phases if the λ parameter varies with the solvent systems, as observed by Leahy *et al.*[7] for some S=O or P=O solutes. As shown in Table 6, nicotine **88** and nornicotine **89** are definitely bifunctional hydrogen-bond donors in hydroxylic solvents.



88



89

Although the pyridine nitrogen appears to be the unique site of association in apolar solvents,[34] both the pyridine and the pyrrolidine nitrogen atoms are found to be active when the molecule is surrounded by an excess of hydroxylic solvent, in agreement with the dibasic character of nicotine towards the proton in water.[44]

STERIC EFFECTS ON THE SOLUTE HB STRENGTH

Manifestations of steric effects on the hydrogen-bond ability of a functional group are difficult or even

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Table 7. Analysis of the alkyl steric effect

No. Coumpound	Formula	$V_x/100$[a]	$pK_x(\mathrm{HB})_t$[b]	λ[c]	log *P*		Δ log *P*[f]
					Exp.[d]	Calc.[e]	
90 2,4-Dimethyl-pentan-3-one	*i*-Pr_2CO	1.111	2.09	1.070	1.86	2.08	−0.22
91 3,3-Dimethylbutan-2-one	MeCO*t*Bu	0.970	2.18	1.070	1.20	1.45	−0.25
92 2,2,4,4-Tetramethyl-pentan-3-one	*t*-BuCO*t*Bu	1.392	1.97	1.070	3.00	3.29	−0.29
93 Adamantane-1-(*N*,*N*-dimethylcarboxamide)	$C_{13}H_{21}ON$[g]	1.730	3.31	1.070	2.55	3.16	−0.61
94 2,2,5,5-Tetramethyl-tetrahydrofuran	$C_8H_{16}O$	1.186	2.44	0.870	2.06	2.48	−0.42
95 *tert*-Butylmethyl ether	$C_5H_{12}O$	0.872	2.20	0.870	0.94	1.49	−0.55
96 1,8-Cineole	$C_{10}H_{18}O$[h]	1.359	2.39	0.870	2.50	3.19	−0.69
97 Diisopropylether	$C_6H_{14}O$	1.013	2.12	0.870	1.52	2.10	−0.58
98 2-Methylpyridine	C_6H_7N	0.816	3.04	0.703	1.11	1.05	0.06
99 2-Ethylpyridine	C_7H_9N	0.957	2.95	0.703	1.69	1.66	0.03
100 2,6-Dimethylpyridine	C_7H_9N	0.957	3.15	0.703	1.68	1.52	0.16
101 2,4,6-Trimethylpyridine	$C_8H_{11}N$	1.098	3.30	0.703	1.88	1.95	−0.07
102 2-*tert*-Butylpyridine	$C_9H_{13}N$	1.239	2.43	0.703	2.40	3.10	−0.70
103 Diisopropylamine	*i*-Pr_2NH	1.054	2.99	0.703	1.40	2.01	−0.60
104 2,2,6,6-Tetramethylpiperidine	$C_9H_{19}N$	1.368	2.88	0.703	2.15	3.29	−1.13
105 Triethylamine	Et_3N	1.054	2.98	0.703	1.45	2.01	−0.56
106 Tripropylamine	*n*-Pr_3N	1.477	2.46	0.703	2.79	3.99	−1.20
107 Hexamethylbenzene	$C_{12}H_{18}$	1.562	1.03	1.070	4.61	4.93	−0.32
108 2-Methyl-2-chloropropane	*t*-BuCl	0.795	0.73	1.070	1.82	2.31	−0.49
109 2,6-Di-*tert*-butylpyridine	$C_{13}H_{21}N$	1.803	0.47	1.070	4.14	6.45	−2.31

[a] V_x is the molecular volume.[20]

[b] $K_x(\mathrm{HB})_t$ is the equilibrium constant obtained by IR spectroscopy in CCl_4.

[c] λ is the family dependence parameter (see text).

[d] Data from Ref. 2.

[e] log *P* calculated from Eqn. (13).

[f] Δ log *P* = log *P*(exp) − log *P*(calc).

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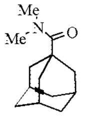

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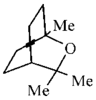

impossible to quantify, since: *(i)* all groups containing unsaturations or heteroatoms must *a priori* be excluded from the analysis, since they are potential hydrogen-bond acceptors leading to negative deviations Δ log *P* that cannot be quantitatively corrected for (*vide infra*); *(ii)* the steric effect takes very different forms depending on the environment of the functional group[45] (*i.e.* on the family). Thus, cyclic species (pyridines, π bases), molecules with functional atoms included (amines, ethers) in the carbon chain or outside the skeleton (carbonyl, phosphoryl, sulfonyl, etc.) and basic atoms with different numbers of lone pairs are not equally sensitive to the shielding effect of a neighbouring atom. In Table 7, the log *P* values of a few bases bearing alkyl substituents in α positions of the basic atom and belonging to different families are calculated from Eqn. (13). The negative deviations of the last column show that the differential between octanol and water gives to the sterically hindered basic groups a weak but significant excess of hydrophilic character. This is in accordance with the reduced steric requirement of the donor water compared with the reference donor 4-fluorophenol of the $\mathrm{p}K_x(\mathrm{HB})$ scale. It is satisfying to note that the hydrophilic effect is greater for the ethers, where the basic atom is part of the skeleton, in comparison with the similar but less hindered ketones:

$$^i\mathrm{PrO}^i\mathrm{Pr}(-0.58) > {}^i\mathrm{PrCO}^i\mathrm{Pr}(-0.22)$$

and that lengthening the chains around the basic nitrogen of tertiary amines increases significantly the deviation:

$$\mathrm{Me_3N}(0.00) < \mathrm{Et_3N}(-0.56) < n\text{-}\mathrm{Pr_3N}(-1.20)$$

The pyridine nitrogen remains unaffected by the presence of one or two methyl groups in the ortho position and in the absence of a log *P* value for 2-isopropylpyridine the first significant deviation is observed for 2-*tert*-butylpyridine (Δ log *P* = −0.71). The hydration of neutral 2,6-di-*tert*-butylpyridine (DTBP) has been the subject of controversy.[46,47] In a recent IR study[48] conducted in CCl_4, we have shown that the associations of water, methanol and 4-fluorophenol stand exclusively on the π cloud of DTBP, and we have measured a basicity

$pK_x(HB)$ value comparable to that of benzene basicity: $pK_x(HB) = 0.47$. This absence of a hydrogen bond on the pyridine nitrogen was further confirmed by ^{15}N NMR studies.[49] When this value is introduced into Eqn. (13) a very large deviation of -2.31 units of log P is observed. Such a large negative value cannot be interpreted by steric effects on the π cloud, and suggests unambiguously that the nitrogen atom is an HB acceptor site in pure water. Interestingly, the apparent HB basicity in the octanol–water partition pK_x^{ow} (HB) calculated by means of Eqn. (13)

$$pK_x^{ow}(HB) = (\log P - 3.83V_x/100 - 0.04)/-0.99$$

yields the following sequence:

pyridine: 2.02$\langle$2-*tert*-butylpyridine: 2.45 $<$ DTBP: 2.88

which corresponds to an additive increment on the basicity of the nitrogen group of 0.43 units due to the 2-*tert*-butyl substituent.

CONCLUSION

A comparison can be carried out between the apparent driving hydrophilic force obtained from octanol–water partition coefficients by subtraction of a simple cavity term and the basicities of solutes measured in CCl_4 solutions. The main features shown in this analysis are that: *(i)* all unsaturations and heteroatoms present in the solute are hydrogen-bonded to the solvent(s) unless they are deactivated by resonance push–pull effects; *(ii)* apparent basicities in hydroxylic solvents can be calculated by exact addition of the strengths measured in CCl_4 for the different sites; (*iii*) relationships between both scales show family-dependent lines. Bulk or effective solute basicity parameters $\Sigma\beta_2^H$ as determined by Abraham[31] from partition coefficients have proved their usefulness for the analysis of numerous solvation-related properties in the field of chemical and biochemical processes.[50] It is another task to analyse the apparent hydrogen-bond basicity of a solute in hydroxylic media. This work shows the transferability of the $pK_x(HB)$ scale to such media, and thus affords a much simpler reference process for the estimation of the basicity of solutes by computational chemistry[51] than the apparent basicity expressed as $\Sigma\beta_2^H$.

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