Hydrogen Bond Structural Group Constants

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The ability of functional groups to act as hydrogen bond acids and bases can be obtained from either equilibrium constants for 1:1 hydrogen bonding or overall hydrogen bond constants. Either method leads to structural constants for hydrogen bonding that in some way are analogous to substituent constants. Extensive lists of these functional group constants are reported. It is shown that those derived from overall hydrogen bond constants are the more useful in analyses of physicochemical and biochemical properties.

Introduction

The first substituent constants were devised by Hammett[1] and later extended by Taft[2] to include steric effects. There are now available numerous sets of substituent constants that relate to electronic and steric effects,[1−5] and the use of substituent constants has been widely reviewed.[6−9] However, in view of the importance of hydrogen bonding, it is very surprising that no similar-type constants have been formulated for either hydrogen bond acidity or hydrogen bond basicity of solutes. It is our aim in this paper to set out scales that reflect the propensity of functional groups to act as hydrogen bond acids and hydrogen bond bases and to show how these functional group structural constants can be used as substituent constants.

The use of substituent constants in organic chemistry is often to correlate free energy related quantities, such as equilibrium constants (as log K or $\Delta G°$) or rate constants (as log k or $\Delta G^{\ddagger}$). In pharmaceutical chemistry, the dependent variable may also be a concentration, as log C or log(1/C), the latter again being a free energy related quantity. It is therefore logical that independent variables used in the correlation of these quantities should also be free energy related. We therefore deliberately set out[10] to construct hydrogen bond scales that were derived from free energy related quantities, namely equilibrium constants, as log K values. Other thermodynamic quantities such as enthalpy were not considered, and neither were nonthermodynamic quantities such as UV/visible solvatochromic shifts.

Even with this restriction to free energy scales, it should still be recognized that two separate types of scale of solute hydrogen bond acidity and two separate types of scale of solute hydrogen bond basicity have been published. These are scales of hydrogen bond acidity and hydrogen bond basicity that refer to 1:1 acid:base complexation, and scales that refer to the overall or summation hydrogen bond acidity and hydrogen bond basicity that are properties of the whole molecule. We summarize these scales in turn.

Results

1:1 Hydrogen Bond Acidity and Basicity. The defining property for this type of hydrogen bonding is log K at 298 K for 1:1 hydrogen bond complexation, eq 1, in tetrachloromethane between monomeric acids and monomeric bases:

$$\mathrm{A-H + {:}B = A-H\text{---}{:}B} \qquad (1)$$

It was found[11,12] that when log K values were obtained for a set of acids against a given reference base, the log K values were linearly related to the log K values for the set of acids against any other reference base. This observation could be generalized by defining a scale of hydrogen bond acidity, log K^{H}_{A}, such that log K values for acids against any given base were linearly related to log K^{H}_{A}. Some examples are as follows:[12]

$$\log K(\text{acids against } Et_3N) = 1.0486 \log K^{H}_{A} + 0.0517 \qquad (2)$$

$$N = 23,\ R^2 = 0.991,\ SD = 0.085$$

$$\log K(\text{acids against DMSO}) = 1.2399 \log K^{H}_{A} + 0.2656 \qquad (3)$$

$$N = 51,\ R^2 = 0.989,\ SD = 0.096$$

In the above, N is the number of data points (the number of acids), R is the correlation coefficient, and SD

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is the standard deviation in the dependent variable. Forty-five such equations were obtained that possessed the interesting property of all intersecting at the point (−1.1, −1.1) when equilibrium constants were expressed on the molar scale. This "magic point" then provided an automatic origin for a scale of 1:1 hydrogen bond acidity, denoted as α_2^H:

$$\alpha_2^{H} = (\log K^{H}_{A} + 1.1)/4.636 \qquad (4)$$

The factor 4.636 in eq 4 serves only to provide a reasonable length of the scale. By definition, all non-hydrogen bond acids have $\alpha_2^H = 0$. The α_2^H scale represented the first general scale of hydrogen bond acidity, in terms of free energy, that had been reported.[11,12]

In a similar way,[13,14] log K values for series of bases against reference acids could be combined into a general scale of hydrogen bond basicity, log K^H_B, that was used to generate equations for log K values against 34 reference acids,[14] for example:

$$\log K(\text{bases against methanol}) = 0.582 \log K^{H}_{B} - 0.459 \qquad (5)$$

$$N = 49,\ SD = 0.090$$

$$\log K(\text{bases against 4-fluorophenol}) = 1.000 \log K^{H}_{B} + 0.000 \qquad (6)$$

$$N = 74,\ SD = 0.089$$

The 34 equations again all intersected at the point (−1.1, −1.1), which again provided a natural origin for the scale of 1:1 hydrogen bond basicity, defined as

$$\beta_2^{H} = (\log K^{H}_{B} + 1.1)/4.636 \qquad (7)$$

The coefficients in eq 7 are not arbitrary, but were chosen because Taft et al.[15,16] had previously used 4-fluorophenol as the reference acid in the hydrogen bond basicity scale pK_{HB}. The scope of the pK_{HB} scale was limited in that it had no origin and so it was impossible to assign a value of pK_{HB} to solutes that had no hydrogen bond basicity at all.

The analysis of 1:1 complexation in tetrachloromethane was further developed[17] through the general equation that correlated 1312 log K values with an SD of only 0.09 log unit:

$$\log K\ (\text{in } CCl_4) = 7.354\ \alpha_2^{H}\beta_2^{H} - 1.094 \qquad (8)$$

$$N = 1312,\ R^2 = 0.991,\ SD = 0.093$$

A similar equation for complexation in the gas phase was later promulgated by Abboud et al.,[18] and one for complexation in 1,1,1-trichloroethane (TCE) has recently been derived:[19]

$$\log K(\text{in the gas phase}) = 9.13\ \alpha_2^{H}\beta_2^{H} - 0.87 \qquad (9)$$

$$N = 23,\ R^2 = 0.974,\ SD = 0.20$$

$$\log K(\text{in TCE}) = 6.856\ \alpha_2^{H}\beta_2^{H} - 1.144 \qquad (10)$$

$$N = 84,\ R^2 = 0.960,\ SD = 0.16$$

Equations 8−10 can be used to determine either α_2^H or β_2^H from a log K value when the other parameter is known. In this way, a number of new α_2^H and β_2^H values were obtained[19] from 1:1 complexation constants in TCE.

Raevsky et al.[20] have also analyzed 1:1 complexation constants in tetrachloromethane and have derived scales of hydrogen bond acidity and basicity in a way analogous to that of Abraham et al.[11−14] In addition, Raevsky et al.[20] have obtained hydrogen bond scales based on enthalpies of complexation.

In their original work, Abraham et al.[12,14] obtained α_2^H values for 190 solutes and β_2^H values for some 500 solutes. Since then, Laurence et al. have made a very large number of new measurements on nitrogen,[21] sulfur,[22] and π bases[23] and on a wide variety of oxygen bases, including esters,[24] amides,[25] aldehydes and ketones,[26] nitro bases,[27,28] sulfonyl bases,[29] amidates,[30a] ethers,[30b] and peroxides,[30b] as well as on haloalkanes[31] and on six-membered aromatic N-heterocycles.[32a]

Laurence and Berthelot[32] pointed out that for a base with two functional groups X and Y, XRY, the observed K value in eq 1 will be given by $K = K_X + K_Y$ where K_X and K_Y are the 1:1 equilibrium constants for separate complexation with the X and Y functionalities in XRY. Thus, even if the functional groups X and Y in XRY do not interact at all, $\beta_2^H(XRY) \neq \beta_2^H(X) + \beta_2^H(Y)$, and $pK_{HB}(XRY) \neq pK_{HB}(X) + pK_{HB}(Y)$, so that the β_2^H, pK_{HB}, and also the α_2^H scale are not additive.

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Table 1. Some Values of α_2^H and β_2^H for Aliphatic Homologues

solute	α_2^H	β_2^H	solute	α_2^H	β_2^H
BuC≡CH		0.17	$PeNH_2$	0.00	0.70
PeC≡CH	0.13	0.20	$HexNH_2$	0.00	0.69
HexC≡CH		0.22	$HeptNH_2$	0.00	0.69
EtCHO	0.00	0.39	$OctNH_2$	0.00	0.71
PrCHO	0.00	0.40	MeOH	0.37	0.41
HeptCHO	0.00	0.39	EtOH	0.33	0.44
nonylCHO	0.00	0.40	PrOH	0.32	0.45
$PrNH_2$	0.00	0.70	BuOH	0.33	0.46
$BuNH_2$	0.00	0.71	OctOH		0.46

In Table 1 are given some values of α_2^H and β_2^H for a number of aliphatic homologous series. It can be seen that, except perhaps for the first member of the series, values of α_2^H and β_2^H are constant along any series. These values can then be regarded as aliphatic structural constants and are collected in Table 2.[12,14,33] In a few cases, only a value for the substituted methane was available; these are indicated as (Me)- in Table 2. From an analysis of multiple determinations of log *K* values by different workers, the error in α_2^H and β_2^H was found to range from 0.01 to 0.05, with an average error of 0.02 units,[14] and we can take the latter as the expected general error of the 1:1 aliphatic structural constants in Table 2.

Aromatic 1:1 hydrogen bond acidity structural constants can be treated in exactly the same way as the aliphatic constants, because benzene has no hydrogen bond acidity. Thus, the aromatic acidity 1:1 structural constant for the −OH group is 0.60; see Table 3. However, the hydrogen bond basicity constants require a somewhat different treatment because the standard solute, benzene, is itself a hydrogen bond base. In the case of styrene, we can take the basicity structural constant as 0.04 if we assume that the basicity of the aromatic ring in styrene is the same as that in benzene. But for chlorobenzene, the difference in basicity of −0.05 is not due to a direct effect of the basicity of the chlorine atom, but to a diminution of the basicity of the benzene ring through withdrawal of electrons by the chlorine atom. Similarly, for nitrobenzene, the basicity difference of 0.20 will reflect both the basicity of the nitro group and the reduction in basicity of the benzene ring. This is not entirely correct, because of the nonadditivity of β_2^H values, but with this proviso, we assign 1:1 aromatic structural constants, $\Delta\beta_2^H$, as (β_2^H −0.14). These are assembled in Table 4.[12,14,33] Laurence et al.[23] have determined 1:1 hydrogen bond basicities of a number of π-bases; their β_2^H value for benzene is 0.13, rather than 0.14, but for consistency we have calculated the constants for the other π-bases also as (β_2^H −0.14).

Overall Hydrogen Bond Acidity and Basicity This refers to the situation in which a solute is surrounded by solvent molecules, so that all acid and basic functional groups in the solute are potentially involved in acid−base interactions at the same time. There are two reasons why this differs from 1:1 hydrogen bonding. First, a basic functional group with several lone pairs of electrons may interact with more than one acidic solvent molecule, but (by definition) will only be involved with one molecule of the reference acid in 1:1 complexation. Second, if there are two functional groups in the same molecule, XRY, then both X and Y will simultaneously interact with solvent molecules, but in 1:1 complexation (again by definition) X can only interact when Y does not interact, and vice versa. The overall solute hydrogen bond acidity and overall hydrogen bond basicity were denoted[10] as $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$, respectively, but more recently, the simpler notation **A** and **B** has been used.[34]

Because these parameters relate to the solute surrounded by solvent, they have to be obtained through experiments that reflect this situation. Furthermore, consideration has to be taken of other solute−solvent interactions as well as just hydrogen bonding, and so various solvation parameters have had to be devised. A number of processes have been used in the determination of solvation parameters, including gas−liquid chromatography,[35,36] water−solvent partitions,[37−39] HPLC,[40] and even solubilities.[41] Detailed accounts have been given of the determination of solvation descriptors[38−42] including, of course, **A** ($\Sigma\alpha_2^H$) and **B** ($\Sigma\beta_2^H$). In brief, a number of equations of the general form of eq 11 or eq 12 are set up, where SP is a solute property for a series of solutes in a given system; note the new notation in these equations.

$$\log \mathrm{SP} = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + v\mathbf{V} \qquad (11)$$

$$\log \mathrm{SP} = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + l\mathbf{L} \qquad (12)$$

The independent variables are solute descriptors as follows:[10] **E** is an excess molar refraction, **S** is the dipolarity/polarizability, **A** and **B** are as above, **V** is the McGowan characteristic volume, and **L** is the logarithm of the solute gas−liquid partition coefficient on hexadecane at 298 K. **E** and **V** can be calculated easily, so that if a number of equations of the type of eq 11 and eq 12 are available, for which values of log SP are known for a given solute, then **S**, **A**, **B**, and **L** can be assigned as the “best fit” values that reproduce the observed log SP data. All of the processes used to determine values of **A** and **B** are equilibrium processes, and so these overall hydrogen bond constants[10,37−45] are again free energy related.

Because **A** and **B** are defined as zero for alkanes, the overall hydrogen bond structural constants for aliphatic compounds can be obtained exactly as for the 1:1 constants and are listed in Table 2. There is one complica-

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Table 2. Aliphatic Hydrogen Bond Structural Constants[a]

substituent	α_2^H	β_2^H [b]	(s**A**)	(s**B**)[c]	substituent	α_2^H	β_2^H [b]	(s**A**)	(s**B**)[c]
$-H$	0.00	0.00	0.00	0.00	$-NH{\cdot}NO_2$	0.57			
$-F$	0.00	0.19 (0.23)[31]	0.00	0.10	$-NHCOMe$	0.38	0.73	0.40	0.74
$-Cl$	0.00	0.15 (0.15)[31]	0.00	0.10	$-N(Me)COMe$	0.00	0.76	0.00	0.78
$-Br$	0.00	0.17 (0.16)[31]	0.00	0.12	$-CONH_2$			0.55	0.68
$-I$	0.00	0.18 (0.15)[31]	0.00	0.15	$-CONHMe$	0.38	0.72[25]	0.40	0.71
$-CHCl_2$		0.15[31]	0.10	0.10	$-CONMe_2$	0.00	0.75[25]	0.00	0.78
$-CHBr_2$			0.10	0.16	$-CONEt_2$	0.00	0.77[25]	0.00	0.80
$-CCl_3$	0.00	0.09[31]	0.00	0.09	$-CON(CH_2)_5$	0.00	0.71	0.00	
$-C{=}CH_2$	0.00	0.02 (0.05)[23]	0.00	0.07	$-CON(CH_2)_6$	0.00	0.72	0.00	
$-C{\equiv}CH$	0.13	0.20 (0.19)[23]	0.12	0.10	$(Pr^i)CO{\cdot}N^-N^+Me_3$		0.95[30a]		
$-C{\equiv}CEt$	0.00	0.21[23]	0.00	0.15	$-OCONH_2$			0.35	0.64
$-OMe$	0.00	0.43	0.00	0.44	$-OCONHEt$			0.24	0.61
$-OEt$	0.00	0.46	0.00	0.45	$-OCONMe_2$	0.00	0.63[25]	0.00	0.64
$(Me)\text{-}OBu^t$	0.00	0.49[30b]	0.00		$-OCONEt_2$	0.00	0.66[25]	0.00	0.68
$(Me)\text{-}OCH(CF_3)_2$	0.00	0.15[30b]	0.00		$-N{=}C(H)NMe_2$		0.80		
$-OCH{=}CH_2$	0.00	0.26[30b]	0.00	0.41	$-SH$	0.00	0.16	0.00	0.24
$-OCH_2CH{=}CH_2$	0.00		0.00	0.45	$-SEt$	0.00	0.29	0.00	0.32
$-CHO$	0.00	0.40	0.00	0.45	$-SBu$	0.00	0.29	0.00	0.32
$-COMe$	0.00	0.49[26]	0.00	0.51	$-SSEt$	0.00		0.00	0.28
$-COEt$	0.00	0.48[26]	0.00	0.51	$(Me)\text{-}C(S)NHMe$		0.48[22]		
$(Me)\text{-}COCF_3$	0.00	0.22[26]	0.00		$-C(S)NMe_2$	0.00	0.49 (0.52)[22]	0.00	
$(Me)\text{-}COCCl_3$	0.00	0.24[26]	0.00		$-OSO_2OEt$	0.00	0.41[29]	0.00	
$(Me)\text{-}COCHCl_2$		0.29[26]			$-SOMe$	0.00	0.78	0.00	0.97(0.76)
$(Me)\text{-}COCH_2Cl$		0.38[26]			$-SOBu$	0.00	0.78	0.00	0.97(0.75)
$-CO_2Me$	0.00	0.40	0.00	0.45	$-SO_2Me$	0.00		0.00	0.76
$-CO_2Et$	0.00	0.45	0.00	0.45	$-SO_2Et$	0.00		0.00	0.76
$-O{\cdot}COH$	0.00	0.40	0.00	0.38	$-SO_2Bu$	0.00	0.57[29]	0.00	0.76
$-O{\cdot}COMe$	0.00	0.45	0.00	0.45	$(Me)\text{-}SO_2Me$	0.00	0.54	0.00	0.76
$-O{\cdot}COEt$	0.00	0.45	0.00	0.45	$(Me)\text{-}S(O)NMe_2$	0.00	0.74	0.00	
$-O{\cdot}COPr^i$	0.00	0.47[24]	0.00	0.47	$(Me)\text{-}SO_2NHMe$		0.51		
$-O{\cdot}COBu^t$	0.00	0.46[24]	0.00	0.45	$(Me)\text{-}SO_2NMe_2$	0.00	0.52 (0.52)[29]	0.00	
$-O{\cdot}COCH_2F$	0.00	0.40[24]	0.00		$-SO_2N^-N^+NMe_3$		0.85[29]		
$-O{\cdot}COCH_2Cl$	0.00	0.38[24]	0.00		$-SCN$	0.00	0.37	0.00	0.37
$-O{\cdot}COCF_3$	0.00	0.25[24]	0.00		$(Me)\text{-}SCN$	0.00	0.39[21]	0.00	
$-O{\cdot}COCCl_3$	0.00	0.27	0.00	0.36	$-NCS$	0.00	0.22	0.00	0.22
$-O{\cdot}COC{\equiv}CH$		0.37	0.19		$-P(O)(OMe)_2$	0.00	0.81	0.00	1.08
$-O{\cdot}CO{\cdot}OEt$	0.00	0.43[24]	0.00	0.55	$-P(O)(OEt)_2$	0.00	0.83	0.00	1.15
$-C(O)F$	0.00	0.21	0.00		$-OP(OEt)_2$	0.00		0.00	1.06
$-CN$	0.00	0.44 (0.43)[21]	0.00	0.36	$-SeEt$	0.00	0.27	0.00	
$-NH_2$	0.00	0.70	0.16	0.61	$-OH$ (1°)	0.33	0.45	0.37	0.48
$-NHEt$	0.00	0.70	0.08	0.69	$-OH$ (2°)	0.32	0.47	0.33	0.56
$-NMe_2$	0.00	0.66	0.00	0.64	$-OH$ (3°)	0.32	0.49	0.31	0.60
$-NEt_2$	0.00	0.67	0.00	0.79	$-CO_2H$	0.54	0.42	0.60	0.45
$-NO_2$	0.00	0.25 (0.31)[27]	0.00	0.31					

[a] α_2^H and β_2^H from refs 12, 14, and33 except where noted; **A** and **B** from refs 10, 37, 43, and 44 and this work. [b] Values in parentheses are alternative values of β_2^H. [c] Values in parentheses in the final column refer to **B**°.

Table 3. Hydrogen Bond Acidity and Basicity for Some Aromatic Solutes

solute	α_2^H	β_2^H	**A**	**B**
benzene	0.00	0.14	0.00	0.14
styrene	0.00	0.18	0.00	0.16
chlorobenzene	0.00	0.09	0.00	0.07
nitrobenzene	0.00	0.34	0.00	0.28
benzoic acid	0.59	0.42	0.59	0.40
phenol	0.60	0.22	0.60	0.30
4-fluorophenol	0.63	0.21	0.63	0.23

tion, as follows. Taylor et al.[46] used partition coefficients in four particular water−solvent systems to set up a scale of solute hydrogen bond basicity denoted as β. For most solutes, values of β could be obtained as averages from data in the four systems. However, for a few solutes, notably sulfoxides and some bases containing the P=O group, this was not possible because no constant basicity was obtained. Abraham[37] encountered a similar problem in an analysis of partition coefficients in 16 different systems but was able to include the "difficult" solutes in a general analysis by defining an alternative hydrogen bond basicity, B° ($\Sigma\beta_2°$). This basicity was required only for the "difficult" solutes in certain partition systems. The solutes were sulfoxides (but not sulfones and not sulfonamides), alkylanilines, and alkylpyridines; subsequently, a number of heterocyclic nitrogen solutes were included. The systems include partitions from water to solvents that are partly miscible with water (e.g., octanol, ethyl acetate, ether) and also RP-HPLC. In the aliphatic series to date, only sulfoxides fall into this category, and structural constants based on **B**° values are shown in parentheses in Table 2.

Aromatic structural constants can be assigned on exactly the same basis as for the 1:1 constants. Because **A** for benzene is zero, the acidity structural constant is taken as equal to **A**; but since **B** for benzene is 0.14 unit, the basicity structural constant is taken as s**B** = (**B** −0.14). The aromatic overall hydrogen bond structural constants are in Table 4; for a few solutes, the alternative **B**° value is shown in parentheses.

Hydrogen Bond Structural Constants for Heterocyclic Compounds There are only a few heterocyclic moieties for which it is possible to list a reasonable number of overall hydrogen bond constants, and even here, there are practically no acidic substituents at all.

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[46] Leahy, D. E.; Morris, J. J.; Taylor, P. J.; Wait, A. R. *J. Chem. Soc., Perkin Trans. 2* **1992**, 705−722.

Table 4. Aromatic Hydrogen Bond Structural Constants[a]

substituent	α_2^H	$\Delta\beta_2^H$ [b]	s**A**	s**B**[c]	substituent	α_2^H	$\Delta\beta_2^H$ [b]	s**A**	s**B**[c]
−H	0.00	0.00	0.00	0.00	−NMe$_2$	0.00	0.21	0.00	0.27(0.33)
−Me	0.00	0.00 (0.02)[23]	0.00	0.00	−NEt$_2$	0.00	0.27	0.00	0.27(0.36)
−Et	0.00	0.01 (0.02)[23]	0.00	0.01	−CH$_2$NMe$_2$	0.00	0.46	0.00	0.55
−Pr^i	0.00	0.01 (0.02)[23]	0.00	0.02	−NH·CO·H			0.50	0.36
−Bu	0.00		0.00	0.01	−NH·CO·Me			0.50	0.53
−Bu^i	0.00		0.00	0.01	−NH·CO·Et	0.48		0.46	0.55
−Bu^s	0.00		0.00	0.02	−NH·CO·OEt	0.36		0.36	0.41
−Bu^t	0.00	0.01 (0.03)[23]	0.00	0.04	−NH(Me)CO·H		0.47[25]		
−CH═CH$_2$	0.00	0.04 (0.02)[23]	0.00	0.02	−NH(Me)CO·Me		0.57[25]		
−CH═CHMe (trans)	0.00	0.04[23]	0.00	0.04	−NH·CO·NH$_2$			0.77	0.63
−C(Me)═CH$_2$	0.00	0.03[23]	0.00	0.05	−NH·CO·NHMe			0.70	0.66
−C≡CH	0.12	0.05 (0.05)[23]	0.12	0.10	−NH·CO·NMe$_2$			0.36	0.83
−C≡CMe	0.00	0.09[23]	0.00		−N(Me)·CO·NH$_2$			0.40	0.87
−cyclopropyl	0.00	0.01	0.00	0.01	−O·CO·NH$_2$			0.50	0.55
−cyclohexyl	0.00	0.03[23]	0.00	0.03	−NO$_2$	0.00	0.20 (0.16)[27]	0.00	0.14
− 1-adamantyl	0.00	0.04[23]	0.00		−CONH$_2$			0.49	0.53
−F	0.00	−0.04	0.00	−0.04	−CONHMe		0.54[25]	0.40	0.57
−Cl	0.00	−0.05	0.00	−0.07	−CONHEt			0.39	0.58
−Br	0.00	−0.05	0.00	−0.05	−CONMe$_2$	0.00	0.53 (0.58)[25]	0.00	0.84
−I	0.00	−0.05	0.00	−0.02	−CONEt$_2$	0.00	0.56 (0.58)[25]	0.00	0.96
−CF$_3$	0.00		0.00	−0.03	−CON(Me)Bu	0.00	0.56	0.00	0.83
−CH$_2$Cl	0.00	0.04	0.00	0.19	−CON(cyclohexyl)$_2$	0.00	0.58	0.00	0.93
−CHCl$_2$			0.10	0.08	−CON(CH$_2$)$_5$	0.00	0.56	0.00	0.80
−CCl$_3$	0.00		0.00	0.09	−CH$_2$CONH$_2$			0.44	0.75
−CH$_2$Br	0.00		0.00	0.06	−CH$_2$CH$_2$CONH$_2$			0.52	0.66
−CH$_2$I	0.00		0.00	0.07	−CH$_2$NH·CO·Me			0.32	0.61
−OMe	0.00	0.12	0.00	0.15	−N═CHNMe$_2$		0.51		
−OEt	0.00	0.13	0.00	0.18	−CH═NMe		0.36		
−CH$_2$OMe	0.00		0.00	0.34	−C(NMe$_2$)═NMe	0.00	0.66	0.00	
−CHO	0.00	0.27	0.00	0.25	−SH	0.11[d]		0.09	0.02
−CH═CH·CHO	0.00	0.35	0.00	0.45	−Sme			0.00	0.19
−COMe	0.00	0.34	0.00	0.34	−CH$_2$SH			0.00	0.23
−COEt	0.00		0.00	0.37	−NCS			0.00	−0.03
−COPr^i	0.00		0.00	0.36	−C(S)NH$_2$			0.46	0.27
−COC≡CH			0.19	0.46	−C(S)NMe$_2$	0.00	0.34 (0.32)[22]	0.00	
−CH$_2$COMe	0.00		0.00	0.52	−NHC(S)NH$_2$			0.49	0.64
−CH═CH·COMe	0.00	0.39[25]			−SOMe	0.00	0.56	0.00	0.83(0.61)
−CO$_2$Me	0.00	0.28 (0.29)[24]	0.00	0.32	−SO$_2$Me	0.00		0.00	0.62
−CO$_2$Et	0.00	0.28 (0.30) [24]	0.00	0.32	(Me)SO$_2$OEt	0.00	0.46	0.00	
−CO$_2$Pr^i	0.00		0.00	0.34	−SO$_2$NH$_2$			0.55	0.66
−CO$_2$Bu^t	0.00	0.31[24]	0.00	0.38	−SO$_2$NHMe			0.30	0.68
−CH$_2$CO$_2$Me	0.00		0.00	0.44	−SO$_2$NMe$_2$	0.00	0.39 (0.35)[29]	0.00	0.72
−CH$_2$CO$_2$Et	0.00	0.32[24]	0.00	0.43	−SO$_2$N═CHNMe$_2$		0.49[29]		
−CH═CHCO$_2$Me	0.00		0.00	0.44	−SONMe$_2$	0.00	0.54	0.00	0.72
−CH═CHCO$_2$Et		0.34[24]	0.00	0.44	−P(O)Me$_2$	0.00	0.78	0.00	
−CH$_2$OCOMe	0.00		0.00	0.51	−OP(O)Pr$_2$	0.00	0.66	0.00	
−OCOH	0.00	0.17[24]	0.00		−OH	0.60	0.08	0.60	0.16
−OCOMe	0.00		0.00	0.40	−CH$_2$OH	0.39	0.28	0.39	0.42
−C(O)F	0.00	0.03	0.00		−CH$_2$CH$_2$OH		0.31	0.30	0.50
−CN	0.00	0.28	0.00	0.19	−(CH$_2$)$_3$OH			0.30	0.53
−CH$_2$CN	0.00	0.27 (0.27)[21]	0.00	0.31	−(CH$_2$)$_4$OH			0.33	0.56
−CH$_2$CH$_2$CN	0.00		0.00	0.37	−(CH$_2$)$_5$OH			0.33	0.58
−NH$_2$	0.26	0.24	0.26	0.27 (0.36)	−(CH$_2$)$_6$OH			0.33	0.58
−NHMe	0.17		0.17	0.29 (0.34)	−CO$_2$H	0.59	0.31	0.59	0.26
−NHEt			0.17	0.29 (0.37)	−CH$_2$CO$_2$H			0.60	0.47

[a] α_2^H and $\Delta\beta_2^H$ from refs 12, 14, and 33 except where noted; **A** and **B** from refs 10, 37, 43, 44, and this work. [b] Values in parentheses are alternative values. [c] Values in parentheses in the final column refer to **B**°. [d] From data by Gramstad,T.; Olsen,T. *Spectrochim. Acta* **1974**, *30A*, 2121−2131.

The number of compounds for which 1:1 structural constants are available in heterocyclic systems is very small indeed.

In furan, there are two possible sites of substitution, and a number of **B** values are known for the 2- and 3-positions. Values of s**B** based on **B** = 0.13 for furan are in Table 5; the very few **A** values are given in parentheses.

Pyridine is the only heterocycle for which both sets of hydrogen bond basicity parameters are available for a reasonable number of substituents. A few hydrogen bond acidity values are also available, and details of both acid and basic structural values are in Table 6. The situation here is a little complicated because for pyridine itself, **B** = 0.52 and **B**° = 0.47 units. Hence, s**B** = (**B** −0.52) and s**B**° = (**B**° −0.47).

A number of overall structural constants can be calculated for pyrazine derivatives. The situation is much simpler than for pyridine, because there is only one monosubstituent in pyrazine, and because for the latter **B** = **B**° = 0.52 units. Details are in Table 7.

Discussion

We have denoted **A** and **B** as “structural” constants because they are not substituent constants in the sense of, e.g., Hammett substituent constants. In an aromatic system, a substituent, X, will refer to some functional

Table 5. Furan Overall Hydrogen Bond Structural Constants[a]

substituent	s**B** 2-sub	s**B** 3-sub
−H	0.00	0.00
−Me	0.01	0.01
−Et	0.01	0.01
−Pe	0.01	
−Br		−0.09
−OMe	0.12	
−CHO	0.31	0.26
−COMe	0.46	
$-CO_2Me$	0.37	0.33
$-CO_2Et$	0.37	0.33
$-CONH_2$	0.70 (**A** = 0.10)	0.54 (**A** = 0.40)
−CONHMe	0.63 (**A** = 0.36)	0.69 (**A** = 0.36)
−CONHEt	0.68 (**A** = 0.36)	0.72 (**A** = 0.36)
$-CONMe_2$	0.76	0.85
−CN	0.20	
$-CH_2OH$	0.50 (**A** = 0.50)	

[a] Based on **A** = 0.00 and **B** = 0.13 for furan. The **A** values are in parentheses.

group, G, in a compound XC_6H_4G where G is a reaction center. However, neither type of hydrogen bond “structural” constants involves a reaction center at all. As we shall show, however, the **A** and **B** parameters can be used as though they were substituent constants, with certain provisos.

We now address the question of the relationship between the 1:1 and the overall hydrogen bond parameters. As regards monosubstituted acids, there is very little difference between α_2^H and **A** values, and so structural constants will be largely the same. For monosubstituted bases, the general trend in the constants is similar, but there are occasional substantial differences that prevent the two sets of structural constants from being interchangeable.

As regards difunctional compounds, it is clear from the work of Laurence et al.[32] that β_2^H values in compounds such as XRY are not additive, even when the groups X and Y do not interact. There is no theoretical reason to indicate if **B** (or **A**) values are similarly nonadditive, and it is not easy to identify test compounds in which two functional groups are definitely noninteractive. However, values of **A** and **B** are available for α,ϖ-diols, Table 8, from which it can be seen that as the two OH groups become further separated, both **A** and **B** approach the value expected for two independent primary alcohol groups. It therefore appears that for noninteractive groups, **A** and **B** are indeed additive.

Table 6. Pyridine Hydrogen Bond Structural Constants[a]

substituent	α_2^H	$\Delta\beta_2^H$ [b]	s**A**	s**B**[c]
−H	0.00	0.00	0.00	0.00
2-Me	0.00	0.01 (0.04)[32]	0.00	0.06 (0.01)
2-Et	0.00	−0.02 (0.02)[32]	0.00	0.07 (0.02)
2-Bu	0.00	0.01 (0.00)[32]	0.00	
2-Pr^i	0.00	−0.12 (−0.02)[32]	0.00	
2-Bu^t	0.00	−0.13 (−0.09)[32]	0.00	
$2-CH=CH_2$	0.00	−0.05[32]	0.00	0.08 (0.03)
2-F	0.00	−0.19 (−0.20)[32]	0.00	−0.16 (−0.11)
2-Cl	0.00	−0.17 (−0.17)[32]	0.00	−0.14 (−0.09)
2-Br	0.00	−0.19 (−0.18)[32]	0.00	−0.16 (−0.11)
2-I	0.00		0.00	−0.14 (−0.09)
2-OMe	0.00	−0.17 (−0.19)[32]	0.00	−0.05 (0.00)
2-COMe	0.00		0.00	0.15 (0.20)
2-CN	0.00	−0.21 (−0.22)[32]	0.00	−0.01 (0.04)
$2-NH_2$		0.04 (0.05)[32]	0.32	0.11 (0.12)
2-NHMe		0.05[32]		
$2-NMe_2$	0.00	−0.05	0.00	0.10 (0.10)
$2-NO_2$	0.00		0.00	0.02 (0.07)
3-Me	0.00	0.00	0.00	0.02 (−0.03)
3-Et	0.00		0.00	0.05 (0.00)
$3-CH=CH_2$	0.00		0.00	0.06 (0.06)
3-F	0.00	−0.11[32]	0.00	−0.09 (−0.04)
3-Cl	0.00	−0.14 (−0.12)[32]	0.00	−0.12 (−0.07)
3-Br	0.00	−0.12 (−0.12)[32]	0.00	−0.14 (−0.09)
3-I	0.00	−0.10 (−0.11)[32]	0.00	−0.15 (−0.10)
3-OMe	0.00		0.00	0.01 (0.06)
3-COMe	0.00		0.00	0.38 (0.39)
3-CHO	0.00		0.00	0.24 (0.22)
3-CN	0.00	−0.19 (−0.19)[32]	0.00	0.10 (0.15)
$3-NH_2$		0.07	0.35	− (0.21)
$3-NMe_2$	0.00	0.12[32]	0.00	− (0.17)
$3-NO_2$	0.00		0.00	0.02 (0.07)
4-Me	0.00	0.03 (0.06)[32]	0.00	0.02 (0.04)
4-Et	0.00	0.03 (0.04)[32]	0.00	0.00 (0.00)
4-Pr^i	0.00	0.03	0.00	
4-Bu^t	0.00	0.03 (0.05)[32]	0.00	0.14 (0.09)
$4-CH=CH_2$	0.00	0.02[32]	0.00	0.01 (0.01)
4-F	0.00		0.00	−0.09 (−0.04)
4-Cl	0.00	−0.07[32]	0.00	−0.12 (−0.07)
4-Br	0.00		0.00	−0.14 (−0.09)
4-I	0.00		0.00	−0.15 (−0.10)
4-COMe	0.00	−0.08[32]	0.00	0.32 (0.28)
4-CHO	0.00		0.00	0.18 (0.14)
4-OMe	0.00	0.07 (0.06)[32]	0.00	0.01 (0.06)
4-CN	0.00	−0.15 (−0.17)[32]	0.00	0.07 (0.12)
$4-NH_2$		0.15	0.41	0.25 (0.15)
$4-NMe_2$	0.00	0.23 (0.20)[32]	0.00	− (0.19)
$4-NEt_2$	0.00	0.22[32]	0.00	
$4-NO_2$	0.00		0.00	0.13 (0.18)

[a] Values for pyridine are β_2^H = 0.625 (0.638),[32] **B** = 0.52, and **B**° = 0.47. [b] Values in parentheses are alternative values. [c] Values in parentheses refer to **B**°, based on **B**° = 0.47 for pyridine itself.

Table 7. Pyrazine Overall Hydrogen Bond Basicity Constants[a]

substituent	s**B**	substituent	s**B**
−H	0.00	−COMe	0.12
−Me	0.04	$-CO_2Me$	0.17
−Et	0.05	$-CO_2Et$	0.20
−Bu^i	0.04	$-CONMe_2$	0.65
−F	−0.10	−CN	0.06
−Cl	−0.15	$-NMe_2$	0.65
−OMe	−0.06	−SMe	−0.09
−OEt	−0.04		

[a] Values for pyrazine are **B** = **B**° = 0.61.

The additive nature of the structural constants is of importance if they are to be regarded in any sense as substituent constants. Because structural constants based on 1:1 equilibrium constants are certainly not additive,[32] they cannot be regarded as substituent constants in the sense of, e.g., Hammett substituent constants. However, the structural constants based on overall hydrogen bonding do have the property of additivity provided that the functional groups are noninteractive. In Table 9 are compared observed values of **B** for a series of substituted acetophenones with those calculated from the s**B** structural constants in Table 4. For many substituents there is reasonable agreement, even for ortho-substitution, but the calculated values for the −OMe and −OH substituted acetophenones are much too large. This is a general manifestation of the “push−pull” effect[32b,47] shown by electron-withdrawing and electron-attracting groups together in an aromatic ring; the calculated hydrogen bond basicity is always larger than that observed. In addition to the “push−pull” effect, there will be large nonadditivity in ortho-substituted derivatives in which intramolecular

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(47) Bradshaw, J.; Taylor, P. J. *Quant. Struct.-Act Relat.* **1989**, *8*, 279−287.

Table 8. Values of A and B for α,ϖ- Diols

diol	A	B
$HO(CH_2)_2OH$	0.58	0.78
$HO(CH_2)_3OH$	0.77	0.85
$HO(CH_2)_4OH$	0.72	0.90
$HO(CH_2)_5OH$	0.72	0.91
$HO(CH_2)_6OH$	0.75	0.92
$HO(CH_2)_7OH$	0.75	0.92
2*(primary alcohol)	0.74	0.96

Table 9. Observed and Calculated Values of B for Substituted Acetophenones Using the Structural Constants in Table 4

substituent	**B** (obsd)	**B** (calcd)	substituent	**B** (obsd)	**B** (calcd)
o-Me	0.51	0.48	*o*-I	0.47	0.46
m-Me	0.51	0.48	*m*-I	0.43	0.46
p-Me	0.52	0.48	*p*-I	0.44	0.46
o-F	0.46	0.44	*o*-NO_2	0.64	0.62
m-F	0.46	0.44	*m*-NO_2	0.63	0.62
p-F	0.47	0.44	*p*-NO_2	0.59	0.62
o-Cl	0.47	0.41	*o*-OMe	0.50	0.60
m-Cl	0.40	0.41	*m*-OMe	0.53	0.60
p-Cl	0.44	0.41	*p*-OMe	0.53	0.60
o-Br	0.47	0.43	*o*-OH	0.47	0.64
m-Br	0.43	0.43	*m*-OH	0.55	0.64
p-Br	0.45	0.43	*p*-OH	0.44	0.64

hydrogen bonds can form, for example 2-chloro- and 2-nitrophenol, but difficulties with ortho derivatives are, of course, inherent in substituent constants of the Hammett type.

We suggest that our structural constants for hydrogen bonding acidity and basicity can be used as substituent constants with the proviso that care has to be taken with interactive functional groups. Formally, we can define structural constants for hydrogen bond acidity, s**A**, and hydrogen bond basicity, s**B**, as follows:

$$\mathrm{s}\mathbf{A} = \mathbf{A}\ \text{(aliphatic, aromatic, furan, pyridine and pyrazine series)} \quad (13)$$

$$\mathrm{s}\mathbf{B} = \mathbf{B}\ \text{(aliphatic series)} \quad (14)$$

$$\mathrm{s}\mathbf{B} = \mathbf{B} - 0.14\ \text{(aromatic series)} \quad (15)$$

$$\mathrm{s}\mathbf{B} = \mathbf{B} - 0.13\ \text{(furan series)} \quad (16)$$

$$\mathrm{s}\mathbf{B} = \mathbf{B} - 0.52\ \text{(pyridine series)} \quad (17)$$

$$\mathrm{s}\mathbf{B} = \mathbf{B} - 0.52\ \text{(pyrazine series)} \quad (18)$$

It is our experience that in multifunctional compounds there is little requirement for the special hydrogen bond basicity, **B**°, and so structural constants based on the **B** scale will generally be the most useful, as above. We have tabulated the alternative structural constants derived from **B**° for completeness, however. The following discussion is based entirely on s**A** and s**B** values.

There are comparatively few aliphatic s**A** values, the main ones being those for alcohols and carboxylic acids. However, amides such as $RCONH_2$ (0.55) and RCONHMe (0.40) are quite strong hydrogen bond acids, the former almost as strong as carboxylic acids. In the aliphatic series, many of the common functional groups, such as ethers, aldehydes, ketones, and esters have similar s**B** values, but there is a rather large selection of groups with enhanced hydrogen bond basicity (in increasing order): $-NH_2$, $-NMe_2$, $-CONH_2$, $-CONMe_2$, $-SO_2Me$, $-SOMe$ and $-P(O)(OMe)_2$. Both the aliphatic hydrogen bond acid and basic groups illustrate the point previously made[10−14,32b,48] that across families there is very little connection between hydrogen bond acidity (or basicity) and proton acidity (or basicity).

As might be expected, there are a number of differences between the aromatic and aliphatic structural constants. Thus, the aromatic $-OH$ and $-NH_2$ groups are both stronger acids and weaker bases than the aliphatic counterparts. Aromatic groups of the benzyl or 2-phenylethyl type, $-CH_2X$ and $-CH_2CH_2X$, however, are quite close to the aliphatic (R)-X values. As an example, for CN derivatives, aromatic s**B** values are $-CN$ (0.19), $-CH_2CN$ (0.31), and $-CH_2CH_2CN$ (0.37) as compared to the aliphatic structural constant of 0.36; see Tables 2 and 4.

Even though the hydrogen bond acidity of the $-NH_2$ (and the $-SH$) substituent differs quantitatively between the aromatic and aliphatic series, the qualitative sequence ($SH < CH{\equiv}CH < NH_2 < CH_2OH < NHCOMe < CONH_2 < CO_2H$) is almost the same. The one great difference is that the phenolic OH group is as strong a hydrogen bond acid as is CO_2H, whereas the alcoholic OH is much weaker. However, many hydrogen bond basic groups are quite strong both in the aliphatic and aromatic series.

There are comparatively few heterocyclic hydrogen bond constants that we have been able to collect; the number of acidic groups is so low that that we cannot usefully comment on these. An examination of Tables 5−7 suggests that there may be substantial differences between aromatic basic constants, and those for the heterocyclic compounds listed. Hence, the use of aromatic s**B** values in heterocyclic compounds would be a first approximation, only.

We conclude with some examples to show the potential use of our s**A** and **sB** constants. The solubility of liquids and especially solids in water at 298 K is of great practical importance in the pharmaceutical and agrochemical industries. Our recent equation for the prediction of solubilities, as log S_W with S_W in mol dm^{-3}, is a variant of eq 11, and is based on solubilities of 659 compounds[49]

$$\log S_W = 0.518 - 1.004\mathbf{E} + 0.771\mathbf{S} + 2.168\mathbf{A} + 4.238\mathbf{B} - 3.362\mathbf{A}{\cdot}\mathbf{B} - 3.987\mathbf{V} \quad (19)$$

$$N = 659,\ R^2 = 0.920,\ \mathrm{SD} = 0.557$$

For any series of functionally substituted compounds, the descriptors **E** and **V** can easily be calculated. The dipolarity/polarizability term is quite small, so that if s**A** and s**B** are used to obtain the group effects on hydrogen bond acidity and basicity, the effect of additional groups on solubility can be estimated quite simply just from structure.

Another crucial process in the pharmaceutical industry is human intestinal absorption, measured as % absorption (% Abs). We find that the % absorption can be

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[48] Abraham, M. H.; Duce, P. P.; Prior, D. V.; Barratt, D. G.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1355−1375.

[49] Abraham, M. H.; Le, J. *J. Pharm. Sci.* **1999**, *88*, 868−880.

described by the equations[50]

$$\% \text{ Abs} = 92 + 2.94\mathbf{E} + 4.10\mathbf{S} - 21.7\mathbf{A} - 21.1\mathbf{B} + 10.6\mathbf{V} \quad (20)$$

$$N = 169,\ R^2 = 0.740,\ \text{SD} = 14\%$$

$$\% \text{ Abs} = 96 - 20.0\mathbf{A} - 19.8\mathbf{B} + 13.9\mathbf{V} \quad (21)$$

$$N = 169,\ R^2 = 0.720,\ \text{SD} = 15\%$$

The statistics of eq 21 are very close to those of eq 20. Since **V** can be calculated, the effect of an additional group on a drug molecule can very easily be predicted through s**A** and s**B** constants applied to eq 21. As noted above, there is always the proviso that the additional group does not undergo any major intramolecular interaction with groups already present in the drug molecule.

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