Analysis of hydrogen-bond complexation constants in 1,1,1-trichloroethane: the $\alpha_2^H\beta_2^H$ relationship

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Hydrogen-bond complexation constants determined by Taylor and co-workers using 1,1,1-trichloroethane (TCE) solvent have been analysed through the $\alpha_2^H\beta_2^H$ relationship; α_2^H and β_2^H are the solute hydrogen-bond acidity and basicity parameters obtained from complexation constants in tetrachloromethane. Constants for three alcohol/*N*-methylpyrrolidinone complexations have been determined in TCE, and if these are used instead of the original alcohol/*N*-methylpyrrolidinone complexation constants, a good relationship is obtained, eqn. (i). The slope in eqn. (i) is smaller than that for the $\alpha_2^H\beta_2^H$ relationship in tetrachloromethane, but the intercept is the same.

$$\log K = 6.856\,\alpha_2^H\beta_2^H - 1.144 \qquad \text{(i)}$$

$$n = 84,\ r^2 = 0.9604,\ \text{sd} = 0.16,\ F = 1993$$

Eqn. (i) has been used to obtain 25 new α_2^H values for acids; these include acetanilides, sulfonamides, triazoles and tetrazoles. The latter two types of compound have very large α_2^H values; that for 5-phenyl-1,2,3,4-tetrazole (0.88) being near the value for dichloroacetic acid (0.90). Values of β_2^H for 31 hydrogen-bond bases have also been calculated using eqn. (i). These include bases with heterocyclic moieties to which β_2^H values had not previously been assigned, *e.g.* oxazole, isoxazole, triazoles and a tetrazole.

The majority of hydrogen-bond complexation constants, eqn. (1), have been determined with tetrachloromethane as

$$B + HA = B\cdots HA \qquad (1)$$

solvent; this is why most scales of solute hydrogen-bond acidity or hydrogen-bond basicity refer to complexation in this solvent. Of reasonably general scales that are related to Gibbs energy, rather than to enthalpy, the first was due to Taft and co-workers.[1–3] They defined a scale of solute hydrogen-bond basicity, pK_{HB}, using log K values for complexation of bases against the standard acid, 4-fluorophenol, in tetrachloromethane, eqn. (2).

$$\mathrm{p}K_{HB} = \log K \text{ in } CCl_4 \text{ for eqn. (1); HA = 4-fluorophenol} \qquad (2)$$

The pK_{HB} scale has subsequently been extended very considerably by Laurence, Berthelot and co-workers,[4–11] so that now some 700 bases are included.

Some years after the pK_{HB} scale had been introduced, Abraham and co-workers developed scales of solute hydrogen-bond acidity[12,13] and solute hydrogen-bond basicity,[14,15] again using log K values for eqn. (1) in tetrachloromethane. These workers noticed that if values of log K for a series of acids against a given reference base were plotted *vs.* values of log K for a series of acids against any other reference base there were obtained a set of lines that all intersected at a point corresponding to log $K = -1.10$ when the units of K were dm^3 mol^{-1}. This enabled log K values for acids against any reference base all to be placed on the same general scale of hydrogen-bond acidity, denoted as log K_A^H. Forty five equations of the form of eqn. (3) were set

$$\log K^i(\text{series of acids against base B}) = L_B \log K_A^H + D_B \qquad (3)$$

up, where L_B and D_B are characteristic of the given reference base, and some 190 values of log K_A^H were thus calculated. Because all the 45 equations intersected at log $K = -1.10$, this enabled a hydrogen-bond acidity scale to be defined with a lower limit of zero. The constant 4.636 in eqn. (4) serves only to

$$\alpha_2^H = (\log K_A^H + 1.1)/4.636 \qquad (4)$$

define a convenient range of α_2^H. In addition to the 190 solutes for which values of log K_A^H, and hence α_2^H, could be calculated, a very large number of non-acidic solutes could be incorporated into the hydrogen-bond acidity scale simply by assigning α_2^H as zero.

As pointed out before,[13] there were a few acid–base combinations for which a modified α_2^H value had to be used; none of these combinations are encountered in the present work, however.

In an exactly similar way, a scale of solute hydrogen-bond basicity, log K_B^H, could be defined through eqn. (5); 34 such

$$\log K^i(\text{series of bases against acid A}) = L_A \log K_B + D_A \qquad (5)$$

equations all intersecting at log $K = -1.1$, as before. Then a hydrogen-bond basicity scale with a lower limit of zero could be obtained, as eqn. (6). Again, the constant in eqn. (6) serves only

$$\beta_2^H = (\log K_B^H + 1.1)/4.636 \qquad (6)$$

to provide a convenient range for the scale. Because any reference acid (A) could be used in eqn. (5), it was possible to obtain β_2^H values for a huge number of bases, around 500. In addition, any non-basic solute such as an alkane or a cycloalkane could be assigned a β_2^H value of zero, and hence incorporated into the scale.

The two scales could be combined[16] into a general equation for the correlation and prediction of log K values for eqn. (1) in tetrachloromethane, eqn. (7). Here, n is the number of data

$$\log K(\text{in } CCl_4) = 7.354\, \alpha_2^H \beta_2^H - 1.094 \qquad (7)$$

$$n = 1312,\ r^2 = 0.9912,\ sd = 0.09,\ F = 147882$$

points (log K values), r is the correlation coefficient, sd is the regression standard deviation and F is the F-statistic. This equation was subsequently used[17] to re-analyse hydrogen-bond complexation constants that had been obtained by Hine and co-workers,[18] and to extend the α_2^H scale to a series of acetylenes.[19] Raevsky and co-workers[20] have also used a multiplicative approach to complexation constants, and have obtained hydrogen-bond parameters for 163 acids and 195 bases.[21] Thus, two comprehensive analyses of complexation constants in terms of hydrogen-bond acidity and basicity in solvent tetrachloromethane are available.[16,21] Although this is the most common solvent used in the determination of hydrogen-bond complexation constants, it suffers from the disadvantage that many compounds, especially those of pharmaceutical interest, are of low solubility. More polar solvents are needed to study these compounds, and 1,1,1-trichloroethane, TCE, is of special interest. Taylor and co-workers[22] chose this solvent, not only because of its good solubility properties, but also because it has no (or little) hydrogen-bond properties, and because it has a relative permittivity (7.53) that might make it a suitable mimic for biological membranes.

In this paper, we use the log K values obtained by Taylor and co-workers[22] in TCE to develop a relationship of the type given as eqn. (7), and we show that the relationship can be used to obtain additional α_2^H and β_2^H values for compounds, many of which are difficult to study in tetrachloromethane.

Table 1 Some values of log K, α_2^H and β_2^H

Solute	log K^a	$\alpha_2^{H\,b}$
Acids *vs.* *N*-methylpyrrolidinone		
Methanol	1.48	0.367
Ethanol	1.21	0.333
Propan-1-ol	1.11	0.316
Hexan-1-ol	1.20	0.328
Propan-2-ol	0.91	0.325
tert-Butyl alcohol	0.78	0.320
2-Chloroethanol	1.08	0.383^c
Chloroform	0.40	0.197
2,6-Dichlorophenol	0.98	0.321
MeNHCO-Bu^t	0.70	0.380^d
Methanol	0.71^e	0.387
tert-Butyl alcohol	0.40^e	0.320
2-Chloroethanol	0.93^e	0.383^c

Solute	log K^a	$\beta_2^{H\,f}$
Bases *vs.* 4-nitrophenol		
1,3-Dioxolane	0.70	0.399^g
Pentan-3-one	1.50	0.460^h
Methyl isopropyl ketone	1.52	0.487^h
Bu^{t}CON (Me)-Bu^t	2.53	0.680^g
PhOCONMe$_2$	2.09	0.600^i
3,4-Dimethylpyridine	3.06	0.718^j
Benzothiazole	1.76	0.528^j
1-Methylpyrazole	2.22	0.634^j
Me$_2$NCN	2.00	0.574^k
Chloroacetonitrile	0.61	0.321^k
4-Chlorobenzonitrile	0.92	0.390^j

[a] Values from ref. 22, unless shown otherwise. [b] Values from ref. 13, unless shown otherwise. [c] P. Goralski, M. Berthelot, J. Rannou, D. Legoff and M. Chabanel, *J. Chem. Soc.*, *Perkin Trans. 2*, 1994, 2337. [d] Estimated by analogy with similar compounds. [e] Log K values, this work. [f] Values from ref. 15, unless shown otherwise. [g] M. H. Abraham and D. V. Prior, unpublished work. [h] M. H. Abraham, D. V. Prior, R. A. Schulz, J. J. Morris and P. J. Taylor, *J. Chem. Soc.*, *Faraday Trans.*, in the press. [i] Ref. 6. [j] M. Berthelot and C. Laurence, unpublished work. [k] Ref. 8.

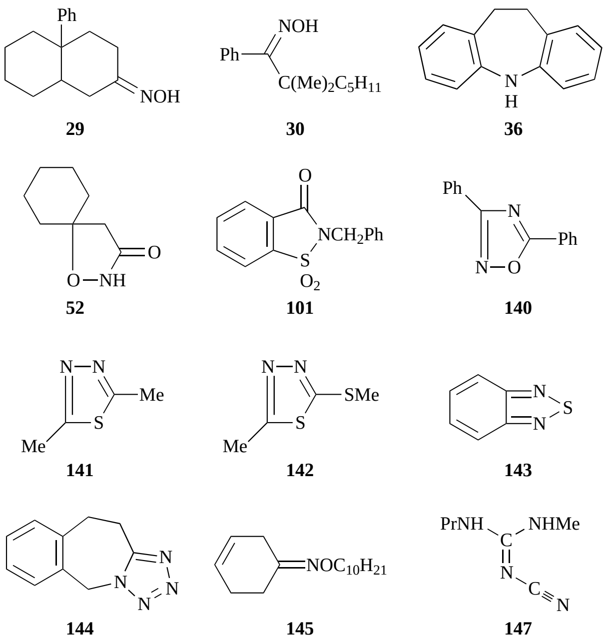

Fig. 1 The structures of the numbered compounds in Tables 2–5

Experimental

Materials

The solvent 1,1,1-trichloroethane (Aldrich) and *N*-methylpyrrolidinone (99%, Aldrich), anhydrous and packaged under nitrogen, were used as such. For preparing solutions they were dispensed with a cylinder-outlet valve in a dry glove box. Methanol, *tert*-butyl alcohol, and 2-chloroethanol were carefully distilled and dried over molecular sieves.

Measurement of *K*-values

Spectra were run on a Bruker IFS-48 FTIR spectrometer at 1 cm^{-1} resolution and 256 scans. A path length of 5 mm was selected, the longest one compatible with the IR transparency of TCE. Temperature was maintained at 25 ± 0.2 °C using a Peltier system.

The measurement of K relies on the measurement of the OH stretching absorbance of hydrogen-bond acids as a function of the concentration of *N*-methylpyrrolidinone, as previously described.[8] The absorptivity coefficients of 2-chloroethanol at 3620 cm^{-1}, methanol at 3636 cm^{-1}, and *tert*-butyl alcohol at 3612 cm^{-1} are, respectively, 41.4, 79.6 and 77.3 dm^3 mol^{-1} cm^{-1}. They allow the use of alcohol concentrations of 10^{-2} mol dm^{-3}. At this concentration there is no significant alcohol self-association in TCE, and the Beer–Lambert law is obeyed. The concentration of *N*-methylpyrrolidinone ranged from 0.02 to 0.30 mol dm^{-3}.

Results and discussion

The log K values used are those of Taylor and co-workers;[22] the α_2^H and β_2^H values were mostly from our previous compilations.[13,15] In Table 1 are given a number of other values of α_2^H and β_2^H, as well as details of some outlying complexes (see below), and results obtained in this work. Compound numbers of Taylor and co-workers[22] correspond to the structures shown in Fig. 1. (Note that two compounds were entered as 147 in ref. 22; the correct structure is in Fig. 1). For all the 90 combinations for which the $\alpha_2^H\beta_2^H$ product is known, there is found a reasonable (but not good) relationship, eqn. (8). However, a

$$\log K = 6.248\, \alpha_2^H \beta_2^H - 0.834 \qquad (8)$$

$$n = 90,\ r^2 = 0.9351,\ sd = 0.20,\ F = 1268$$

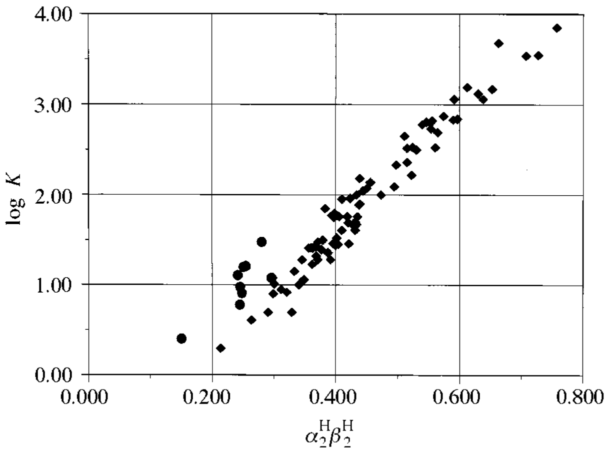

Fig. 2 A plot of log *K vs.* $\alpha_2^H\beta_2^H$ for the 90 complexes in eqn. (8); the nine outlying points are shown as ●

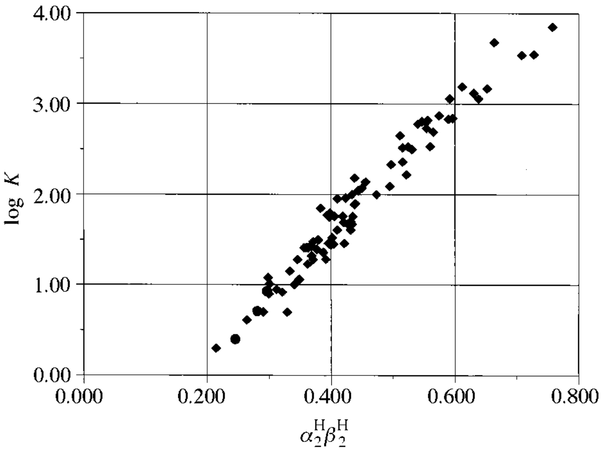

Fig. 3 A plot of log *K vs.* $\alpha_2^H\beta_2^H$ for the 84 complexes in eqn. (10); the points corresponding to the three new log *K* values for alcohol/NMP complexation are shown as ●

plot of log *K vs.* $\alpha_2^H\beta_2^H$ shows that there is no random scatter about the line of identity, see Fig. 2. There are nine outlying acid/*N*-methylpyrrolidinone (NMP) complexes, all with rather low values of log *K*, that are systematically above the line. Repeating the regression without these points, which correspond to the first nine entries in Table 1, leads to the much better eqn. (9).

$$\log K = 6.824\,\alpha_2^H\beta_2^H - 1.128 \qquad (9)$$
$$n = 81,\ r^2 = 0.9573,\ \mathrm{sd} = 0.16,\ F = 1766$$

Of these outliers, we believe that for the 2,6-dichlorophenol/NMP complex and the chloroform/NMP complex there is probably experimental error in log *K* (or in the α_2^H value for the former complex). The remaining outliers are seven alcohol/NMP complexes. Now the determination of log *K* values for alcohol/NMP complexes is difficult; the log *K* values are rather low and this leads to the problem of self-association of the alcohols. We felt that the alcohol/NMP data could be in error, and so we determined complexation constants for a number of alcohol/NMP systems. By using a long-path cell we were able to work with alcohol concentrations as low as 10^{-2} mol dm^{-3}, so avoiding self-association. The log *K* values we have obtained are in Table 1 as entries 11–13. Our values are appreciably lower than those obtained before, *viz* 0.71 for methanol/NMP and 0.40 for *tert*-butyl alcohol/NMP as opposed to the original values[22] of 1.48 and 0.78, respectively. The new log *K* values agree exactly with eqn. (9), and together with the 81 data points used in eqn. (9) yield our preferred $\alpha_2^H\beta_2^H$ relationship, eqn. (10); the sd values for the coefficients are also given. A plot

$$\log K = 6.856(\pm 0.153)\,\alpha_2^H\beta_2^H - 1.144(\pm 0.070) \qquad (10)$$
$$n = 84,\ r^2 = 0.9604,\ \mathrm{sd} = 0.16,\ F = 1993$$

of log *K vs.* $\alpha_2^H\beta_2^H$ is given in Fig. 3, with the three new data points shown separately. The alcohol/NMP data are now no longer outliers, and we feel that these results confirm our suggestion that the original alcohol/NMP data are in error.

Although eqn. (10) is reasonable, there is still some scatter that might be due to different sets of bases giving rise to slightly different lines, *i.e.* to family dependencies. We can test this by omitting pyridine, amine and heterocyclic amine bases from the correlation. The result is eqn. (11), in which there is no

$$\log K = 6.769(\pm 0.180)\,\alpha_2^H\beta_2^H - 1.118(\pm 0.080) \qquad (11)$$
$$n = 63,\ r^2 = 0.9580,\ \mathrm{sd} = 0.16,\ F = 1407$$

statistical difference in the slope and intercept from those in eqn. (10). We conclude that within the statistical error of the correlations, sd = 0.16 in log *K*, there is no family dependency as between log *K* values in TCE and in tetrachloromethane. This is in line with the analysis of Taylor and co-workers[22] who showed that for log K_β the Maria–Gal[23,24] θ-value was between 65–69° against the reference acid 4-nitrophenol in TCE. This is the same as the value of 68° for the β_2^H scale itself,[25] so that any family dependence between log K_β and β_2^H is very unlikely; log K_β is the solute hydrogen-bond basicity scale of Taylor and co-workers.[22]

The slope and intercept in the $\alpha_2^H\beta_2^H$ relationship are of interest. Leahy and co-workers[26] have suggested that for more polar solvents than tetrachloromethane, the intercept should be more positive than −1.1, possibly being *ca.* −0.6 in TCE. However, the intercept in eqn. (10) is −1.144 with an sd value of 0.070, so that it is essentially the same as that in tetrachloromethane, −1.094. The $\alpha_2^H\beta_2^H$ relationship has been applied by Abboud and co-workers[27] to complexation constants in the gas phase, yielding eqn. (12). The difference in value for the

$$\log K(\mathrm{g}) = 9.13(\pm 0.32)\,\alpha_2^H\beta_2^H - 0.87(\pm 0.11) \qquad (12)$$
$$n = 23,\ r^2 = 0.974,\ \mathrm{sd} = 0.20,\ F = 787$$

intercepts in eqn. (10) and eqn. (12) is only just significant, but is in the opposite direction to that suggested by Leahy and co-workers.[26] More work is needed to resolve the problem of the intercept. The value of this slope is easier to interpret; the lower slopes in TCE (6.856) and tetrachloromethane (7.354) by comparison to the gas phase (9.13) show the well-known attenuation effect on transfer from the gas phase to solvents.

Finally, we can use eqn. (10) to determine α_2^H or β_2^H when one or the other is missing. In order to calculate possible errors in the determination, it is useful to restate eqn. (10) as eqn. (13). The sd value of 0.023 suggests that if an α_2^H value is calculated using $\beta_2^H = 0.765$ for NMP, the error will be *ca.* 0.03 units; this is also the case for a calculation of β_2^H using $\alpha_2^H = 0.824$ for 4-nitrophenol.

$$\alpha_2^H\beta_2^H = 0.1401(\pm 0.0031)\log K + 0.1778(\pm 0.0064) \qquad (13)$$
$$n = 84,\ r^2 = 0.9604,\ \mathrm{sd} = 0.023,\ F = 1993$$

In Table 2 are listed new values of α_2^H for 25 acids as calculated from eqn. (13) with NMP as the reference base. Where comparisons can be made, the new α_2^H values are reasonable. For example, the value of 0.58 for 3-isopropylphenol is in line with the value of 0.57 for 3-methylphenol. Important new α_2^H values are those for the triazoles and tetrazoles, known from their log K_α values to be very strong hydrogen-bond acids.[22] Thus, 5-phenyl-1,2,3,4-tetrazole on the α_2^H scale is as strong a hydrogen-bond acid as dichloroacetic acid. In Table 3 is given a selection of α_2^H values for some O–H and N–H acids to show how constitutional effects lead to a very

Table 2 Calculation of α_2^H values through eqn. (13)

Solute	α_2^H
3-Isopropylphenol	0.579
Compound **29**	0.412
Compound **30**	0.436
1,2,3,4-Tetrahydroquinoline	0.342
Compound **36**	0.342
4-Nitro-*N*-methylaniline	0.366
5-Nitroindoline	0.416
2-Aminobenzothiazole	0.434
Trifluoroacetamide	0.511
HexylNHCOHexyl	0.350
Acetanilide	0.478
4-(Diethylamino)acetanilide	0.320
3-Chloro-4-nitroacetanilide	0.687
3-(Trifluoromethyl)-4-nitroacetanilide	0.685
Thioacetanilide	0.511
Compound **52**	0.434
$(CF_3CO)_2NH$	0.714
Toluene-*p*-sulfonamide	0.443
N-Benzyltoluene-*p*-sulfonamide	0.397
N-(2-Naphthyl)toluene-*p*-sulfonamide	0.449
2-($CH_2CH_2CH_2OCOPh$)imidazole	0.452
3-($CH_2CH_2CH_2Ph$)-1,2,4-triazole	0.597
4-MeS-1,2,3-triazole	0.632
4-CF_3-1,2,3-triazole	0.729
5-Phenyl-1,2,3,4-tetrazole	0.883

Table 3 Values of α_2^H for some O–H and N–H acids

Solute	α_2^H
Alkylamines	0.000
Aniline	0.264
4-Nitro-*N*-methylaniline	0.366
N-Methylacetamide	0.383
Pyrrole	0.406
Acetanilide	0.478
Maleimide	0.497
Trifluoroacetamide	0.511
4-(MeS)-1,2,3-triazole	0.632
3-Chloro-4-nitroacetanilide	0.687
4-(CF_3)-1,2,3-triazole	0.729
5-Phenyl-1,2,3,4-tetrazole	0.883
3-Ethyl-2,4-dimethylpentan-3-ol	0.246
Ethanol	0.333
Acetic acid	0.550
2,2,2-Trifluoroethanol	0.567
Hexafluoropropan-2-ol	0.771
4-Nitrophenol	0.824
Dichloroacetic acid	0.899

Table 4 Calculation of β_2^H values through eqn. (13)

Solute	β_2^H
tert-Butyl methyl ether	0.464
1,2-Dimethoxyethane	0.503
1,4-Thioxane	0.396
Dihydro-2(3*H*)-thiophenone	0.440
N-Methyl-3-isoxazolidinone	0.620
N-Methylmaleimide	0.500
N-Methylquinol-4-one	0.896
$PhSO_2N(Me)CH_2Ph$	0.447
Compound **101**	0.384
Allylamine	0.663
1-Cyano-2-aminoethane	0.512
3-Fluoropyrridine	0.525
3-*N*,*N*-Diethylcarbamoylpyridine	0.685
4-Acetylpyridine	0.590
Isoxazole	0.396
Oxazole	0.500
2,4,5-Trimethyloxazole	0.666
1-Benzyl-1,2,4-triazole	0.620
1-Phenethyl-1,2,3-triazole	0.651
1-Methylbenzotriazole	0.585
4-Butyl-1,2,4-triazole	0.789
Compound **140**	0.313
Compound **141**	0.643
Compound **142**	0.552
Compound **143**	0.350
Compound **144**	0.554
Compound **145**	0.473
Me_2C:NOPh	0.403
Compound **147**	0.709
Methoxyacetonitrile	0.393
1-Methoxy-2-cyanoethane	0.433

Table 5 Values of β_2^H for some azoles and azines

Solute	Type	β_2^H	Ref.
Pyrrole	Azole	0.340	*a*
1-Methylpyrrole	Azole	0.294	*b*
Pyrazole	1,2-Diazole		
1-Methylpyrazole	1,2-Diazole	0.634	*c*
Imidazole	1,3-Diazole		
1-Methylimidazole	1,3-Diazine	0.805	*c*
1-Phenylethyl-1,2,3-triazole	1,2,3-Triazole	0.651	*d*
4-Butyl-1,2,4-triazole	1,2,4-Triazole	0.789	*d*
1-Benzyl-1,2,4-triazole	1,2,4-Triazole	0.620	*d*
Compound **144**	1,2,3,4-Tetrazole	0.554	*d*
Pyridine	Azine	0.625	*c*
Pyridazine	1,2-Diazine	0.636	*c*
Pyrimidine	1,3-Diazine	0.526	*c*
Pyrazine	1,4-Diazine	0.480	*c*

[a] From data in tetrachloromethane by M. Orban, A. Kiss and L. Barczo, *J. Chem. Soc.*, *Perkin Trans. 2*, 1987, 1815. [b] Obtained as described in ref. 15. [c] Table 1. [d] This work, Table 1.

large spread of values in each of the two series. It is quite clear that the practice of assigning an indicator variable to a hydrogen-bond acidic group (*i.e.* of taking all O–H or all N–H functional groups as having the same hydrogen-bond acidity) may often be a gross approximation. The acetanilides and sulfonamides in Table 2 are the first examples of these important classes for which α_2^H values have been assigned, and illustrate the advantage of a more polar solvent that can dissolve such solutes.

We can also calculate new β_2^H values for 31 bases, several of which are structurally quite different to any bases previously studied in this way. Results are in Table 4; no statistical corrections have been made for multifunctional bases. Where comparisons can be made, the calculated β_2^H values are chemically reasonable. Thus β_2^H is 0.464 for *tert*-butyl methyl ether, as compared to 0.419 for di-*n*-butyl ether, and the value of 0.525 for 3-fluoropyridine is in line with the β_2^H value for 3-chloropyridine (0.488). There are new values for a number of heterocyclic bases such as oxazole and isoxazole, but the β_2^H values for derivatives of azoles and azines are interesting, in that there is an almost complete set of azoles (though not of azines), as shown in Table 5. Taylor and co-workers[22] have already discussed the behaviour of many of these, especially in terms of the α-effect.

A number of polyfunctional bases, listed in Table 4, give two 1:1 complexes in presence of hydrogen-bond acids. 3-(*N*,*N*-Diethylcarbamoyl)pyridine possesses both an amide oxygen site ($\beta_2^H = 0.685$ for $PhCONEt_2$)[6] and a pyridine nitrogen site ($\beta_2^H = 0.625$).[15] Both sites deactivate each other and so it is not surprising to find the composite value of $\beta_2^H = 0.685$ for this compound. The UV method[22] of determination of log *K* values involves non-linear fitting, and if there are two products, might lead to a different composite log *K* value than the FTIR method. Further experimental work is needed here.

Acknowledgements

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