The Relationship between Nonaqueous Hydrogen Bonding and Aqueous Acidities

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The relationship between formation of hydrogen bonds in nonaqueous solvents and the aqueous acidities of the donor and the acceptor conjugate acid is described by a multi-step phase-transfer pathway in which the reactants are transferred to water for formation of the hydrogen bond followed by transfer back to the nonaqueous phase. The explicit dependence of the hydrogen bond formation constant on aqueous acidity K_a values and nonaqueous–aqueous partition coefficients is tested with a large body of literature data. The slope of the resultant linear free energy plots is related to how change in acidity free energy is divided between nonaqueous hydrogen bond free energy and the free energy for aqueous hydrogen bond formation from ionized hydrogen donor and acceptor. Analysis of the intercept leads to a proposed new constant, the standard hydrogen bonding constant, which permits comparison of hydrogen bonding tendencies for donor–acceptor classes with no common members, with quite different acidities, and which were studied in different solvents.

The relationship between hydrogen bond formation equilibrium constants K_{HB} and the acidity of the hydrogen donors and acceptors has been extensively studied.[1] Although the problem is complicated by the fact that K_{HB} is commonly determined in nonaqueous solvents, while the acidities are determined in water, numerous workers have reported linear correlations between nonaqueous log K_{HB}, or a related quantity, and the aqueous pK_a of either the donor or the conjugate acid of the acceptor.[2–17] Such plots can be viewed as examples of linear free energy relationships.[18] However, a rigorous thermodynamic basis for interpretation of the slope and intercept of such plots has not been published. A step in this direction was taken when Zeegers-Huyskens and Huyskens[1d,8] described the transfer constant K_t for formation of a proton-transfer complex from a hydrogen-bonded complex in terms of a multi-step phase-transfer pathway, in which the proton-transfer complex and the hydrogen-bonded complexes were transferred between the aqueous and nonaqueous solvents. An explicit relationship was obtained relating *aqueous* K_{HB}, the aqueous K_a values, the solvent partition coefficients of the complexes, and other equilibria. Thus, a linear relationship between *aqueous* log K_{HB} and ΔpK_a for a series of donors or a series of acceptors was predicted if the other equilibrium constants and partition coefficients are invariant through the series.

We propose to analyse nonaqueous hydrogen bonding in terms of a multi-step phase-transfer pathway similar to but different in some key respects from that proposed by Zeegers-Huyskens and Huyskens.[1d] Our approach leads to an explicit and thermodynamically rigorous statement of the relationship between *nonaqueous* K_{HB} and aqueous K_a values. Furthermore, with the aid of an extrathermodynamic assumption which has been experimentally established,[19] the product of the partition coefficients in our proposed pathway can be estimated. The only equilibrium constant in the pathway that cannot be independently determined corresponds to hydrogen bond formation between the ionized donor and the protonated acceptor in water. We designate this the ion hydrogen bonding constant K_{IHB}. K_{IHB} is simply calculable given experimental K_{HB} and K_a values, and using the extrathermodynamic partition coefficient.

Hydrogen bonding data from 18 studies taken from the literature are reanalysed according to our phase-transfer model. The slopes of our linear free energy plots are related to how a change in acidity free energy is divided between changes in nonaqueous hydrogen bonding and aqueous ion hydrogen bonding free energies. The intercepts of the linear free energy plots are interpreted in terms of a proposed new constant, the standard hydrogen bonding constant K_{std}. K_{std} permits comparison of hydrogen bonding tendencies for donor–acceptor classes, even when the classes: (1) have no members in common; (2) represent molecules with quite different acidity ranges; and (3) are studied in different solvents.

The Phase-transfer Model.—Consider hydrogen bond formation in a nonaqueous solvent:

$$\mathrm{HA(nonaq) + B(nonaq)} \xrightarrow{K_{HB}} \mathrm{AHB(nonaq)} \qquad (1)$$

How K_{HB} depends on the *aqueous* acidities of HA and BH^+ is shown by the alternate pathway (2)—(7) for the same reaction.

$$\mathrm{HA(nonaq)} \xrightarrow{K_1} \mathrm{HA(aq)} \qquad (2)$$

$$\mathrm{B(nonaq)} \xrightarrow{K_2} \mathrm{B(aq)} \qquad (3)$$

$$\mathrm{HA(aq)} \xrightarrow{K_3} \mathrm{A^-(aq) + H^+(aq)} \qquad (4)$$

$$\mathrm{B(aq) + H^+(aq)} \xrightarrow{K_4} \mathrm{BH^+(aq)} \qquad (5)$$

$$\mathrm{A^-(aq) + BH^+(aq)} \xrightarrow{K_5} \mathrm{AHB(aq)} \qquad (6)$$

$$\mathrm{AHB(aq)} \xrightarrow{K_6} \mathrm{AHB(nonaq)} \qquad (7)$$

Because the net reactions are identical, we have equations (8a) and (8b). K_3 and K_4 correspond to aqueous acidity reactions: $K_3 = K_{a.HA} \equiv K_{HA}$; $K_4 = 1/K_{a.BH^+} \equiv 1/K_{BH^+}$. K_1, K_2, and K_6

$$\Delta G^\circ_{HB} = \sum_{i=1}^{6} \Delta G_i^\circ \ (8a) \qquad K_{HB} = \prod_{i=1}^{6} K_i \qquad (8b)$$

correspond to solvent-distribution partition coefficients, P_i, for transfer of species i from a nonaqueous to an aqueous phase: $K_1 = P_{HA}$, $K_2 = P_B$, $K_6 = 1/P_{AHB}$. K_5 corresponds to hydrogen bonding by the aqueous ions, and is designated K_{IHB}, the ion hydrogen bonding constant.

Interpretation of the Slope of log K_{HB} versus *pK_a Plots.*—The basis for linearity of the conventional plots of log K_{HB} *versus* pK_a can be seen by rewriting equation (8b) as (9). Thus, a plot of

$$\log K_{HB} = \log(K_{IHB}\, P_{HA}\, P_B/P_{AHB}) + pK_{BH^+} - pK_{HA} \qquad (9)$$

log K_{HB} *versus* pK_a for either donor or acceptor, or *versus* ΔpK_a, should be linear and have unit slope *if* the product of K_{IHB} and the partition coefficients is constant. The y-intercept would be $\log(K_{IHB}P_{AH}P_{B}/P_{AHB}) + pK_{BH^+}$ if, for example, pK_{HA} were the abscissa. How can the fact that experimental data commonly give linear plots but with slopes between 0.2 and 0.7[1d] be reconciled with the absence of a variable coefficient in front of the pK_a term(s) in equation (9)? In general, if the $K_{IHB}P_{HA}P_{B}/P_{AB}$ product is not constant, a *curved* plot is expected. However, if $\log(K_{IHB}P_{HA}\,P_{B}/P_{AHB})$ happens to vary linearly with pK_a, it can be shown that a linear plot of $\log K_{HB}$ *versus* pK_a is still predicted. A rationale for such linearity and interpretation of the slope is as follows.

First we make the extrathermodynamic assumption that the product of the partition coefficients, $P_{HA}P_{B}/P_{AHB}$, is expected to be approximately constant. The principle that a partition coefficient is well approximated by the product of partition coefficients of the atoms and/or molecular fragments composing the molecule has been experimentally established.[19-22] Application of this principle to the partition coefficient product reduces the product to simply the partition coefficient of the hydrogen bond itself.

$$P_{HA}P_{B}/P_{AHB} = \mathrm{P}_{HB} \qquad (10)$$

The P_{HB} has been evaluated experimentally for *intra*molecular hydrogen bonds by comparing the partition coefficients of pairs of molecules that are very similar (*e.g. o*- and *p*-nitrophenol), one of which is capable of hydrogen bonding while the other is not.[19] P_{HB} is found to be a surprisingly well-defined quantity. It is largely independent of the structure of the rest of the molecule and is constant for a given solvent, at least within the rather large experimental error bounds of the measurements.[19,20] Furthermore, it is reasonable to expect that P_{HB} would be most well defined for partition into non-hydrogen-bonding solvents, such as are our concern. Literature values for P_{HB} in a variety of solvents are given in Table 1. We make the further assumption that these are reasonable approximations to the *inter*molecular P_{HB}.

Let us consider, for discussion's sake, the case in which a family of donors of varying pK_{HA} is studied with the same acceptor. The slope m of the conventional $\log K_{HB}$ *versus* pK_{HA} plot is defined by equation (11). A slope of -1 occurs if the

$$m \equiv \frac{\mathrm{d}\log K_{HB}}{\mathrm{d}\,pK_{HA}} = -\frac{\mathrm{d}\,(\Delta\,G^\circ{}_{HB})}{\mathrm{d}\,(\Delta\,G^\circ{}_{HA})} \qquad (11)$$

change in free energy of aqueous acid ionization is exactly matched by an identical change in free energy of nonaqueous hydrogen bond formation. The slope is that fraction of a change in aqueous acidity free energy that is propagated into the nonaqueous hydrogen bonding free energy. The common experimental situation of slope <1 can be viewed as less than 100% of a change in acidity free energy propagated into hydrogen bond free energy. Because the total free energy for alternative pathways between two given states must be the same, the only way less than 100% of a change in $\Delta G^\circ{}_{HA}$ can be propagated into $\Delta G^\circ{}_{HB}$ is if there is simultaneously a change in ΔG° of opposite sign for one of the other steps in the phase-transfer pathway. Assuming that the extrathermodynamic approximation in equation (11) produces a constant P_{HB}, and recalling that we are considering the case of constant acceptor, the ion hydrogen bonding reaction is the only step in the pathway whose free energy can change and thereby be responsible for a non-unit slope. Equation (12) shows the explicit dependence of the slope on how $\Delta G^\circ{}_{IHB}$ changes when ΔG_{HA} is changed.

Table 1. Partition coefficients of the hydrogen bond.

Solvent	P_{HB}[a]	a[a]	b[a]
Chloroform	10.01	1.276 ± 0.14	0.171 ± 0.17
Octan-1-ol	4.47 ± 1.26		
Carbon tetrachloride	3.68	1.207 ± 0.27	−0.219 ± 0.37
Benzene	1.67	1.223 ± 0.19	−0.573 ± 0.20
Toluene	0.97	1.398 ± 0.22	−0.922 ± 0.37
Cyclohexane	0.91	1.063 ± 0.12	−0.734 ± 0.25
Heptane	0.095	1.848 ± 0.44	−2.223 ± 0.93

[a] Partition coefficients of the hydrogen bond P_{HB} calculated using 'solvent regression equation' in ref. 19: $\log P_{HB} = a(\log P_{HB},\text{octanol}) + b$. The coefficients a and b in the regression equation are from least-squares fits of experimental data for several partitioned species in the same class as the intramolecular hydrogen bond, The uncertainties of a and b are the 95% confidence limits as stated in ref. 19. The uncertainty stated for P_{HB} in octan-1-ol is the uncertainty, given in ref. 19, based on the averate deviation obtained from an unstated number of solutes with the required structure.

$$m = -\frac{\mathrm{d}(\Delta G^\circ{}_{HB})}{\mathrm{d}(\Delta G^\circ{}_{HA})} = -\frac{\mathrm{d}(\Delta G^\circ{}_{IHB} + \Delta G^\circ{}_{HA} + \sum_{i\neq 3.5} \Delta G^\circ{}_{i})}{\mathrm{d}(\Delta G^\circ{}_{HA})} = -\left[\frac{\mathrm{d}(\Delta G^\circ{}_{IHB})}{\mathrm{d}(\Delta G^\circ{}_{HA})} + 1\right] \qquad (12)$$

It is evident from equation (12) that a slope of magnitude <1 corresponds to $\Delta G^\circ{}_{IHB}$ changing in opposite direction to a change in $\Delta G^\circ{}_{HA}$. That is, increasing aqueous acidity must decrease the strength of the aqueous ion hydrogen bonding reaction. This is reasonable, because the ion hydrogen bonding reaction itself has an acid–base aspect, namely, after the ions come together there is a partial give-back of the proton to form the hydrogen bond. It is expected that a stronger acid would be less likely to accept back the proton during the ion hydrogen bonding reaction.

Significance of K_{IHB}.—K_{IHB} can be simply calculated from equations (9) and (10) using the extrathermodynamic P_{HB} and experimental K_{HB}, K_{HA}, and K_{BH^+} values for a given donor–acceptor pair, but what is its significance? Unfortunately, the price we have paid for an explicit relationship between K_{HB} and the aqueous K_a values is to be left with this K_{IHB} which is probably more difficult to interpret than the original, nonaqueous K_{HB}. Probably the most intractable aspect of the ion hydrogen bonding reaction is understanding the hydration changes. This complexity is illustrated by thinking of the reaction as occurring in three substeps. The ions first come together to form an ion pair, then they partially dehydrate and fall closer together to form the proton-transfer complex, and finally the proton is transferred to form the hydrogen-bonded species. One possible use of the $\Delta G^\circ{}_{IHB}$ values is to help sort out the thermodynamics of these three substeps by comparison with data from other systems where only one or two of the substeps occur.

Significance of the Intercept and Definition of the Standard Hydrogen Bonding Constant.—If a $\log K_{HB}$ *versus* pK_{HA} plot is linear with unit slope, equation (9) shows that the intercept must be $\log K_{IHB}P_{HA}P_{B}/P_{AHB} + pK_{BH^+}$. A fixed value of K_{IHB} is implied. What then is the significance of the intercept of a linear plot with non-unit slope, since we have shown that K_{IHB} is not constant for such a plot?

One approach is to note that the intercept is equal to the log K_{HB} value predicted when $pK_{HA} = 0$, that is, when $K_{HA} = 1$. Thus, comparison of intercepts for various homologous series of donors with the same acceptor would provide information about the interaction of the acceptor with hypothetical donors of $K_{HA} = 1$ from each homologous series.

We suggest that a more informative approach to realise fully all the information provided by a K_{HB} *versus* pK_a study is to analyse the data according to a rearrangement of equation (9), such that the only unknown, K_{IHB}, is isolated. Granting the notion of a constant P_{HB}, we have equation (13).

$$\log K_{HB} = \log K_{IHB} + \log (P_{HB}K_{HA}/K_{BH^+}) \qquad (13)$$

The intercept of a log K_{HB} *versus* log ($P_{HB}K_{HA}/K_{BH^+}$) plot is the value of log K_{HB} predicted when log ($P_{HB}K_{HA}/K_{BH^+}$) = 0, or, when $P_{HB}K_{HA} = K_{BH^+}$. Although the above is true even if the plot is non-linear, the fact of experimentally observed linearity permits evaluation by extrapolation and interpretation of the intercept even when the data do not cross the ordinate. The virtue of knowing log K_{HB} when $P_{HB}K_{HA} = K_{BH^+}$ is that one can then calculate a proposed useful new quantity, the standard hydrogen bonding constant, K_{std}.

We define the standard hydrogen bonding constant as the hydrogen bond formation equilibrium constant that is characteristic of a donor–acceptor *class* when (1) the donor and conjugate acid of the acceptor have equal aqueous acidities; (2) the hydrogen bond is formed in a hypothetical solvent for which $P_{HB} = 1$; and (3) only one of either the donor or acceptor is varied.

The standard hydrogen bonding constant K_{std} can be calculated from the intercept of a plot according to equation (13) as follows. We must first determine the value of K_{HB} in the experimental solvent when $K_{HA} = K_{BH^+}$, and then determine K_{HB} in a hypothetical 'standard' solvent for which $P_{HB} = 1$ and when also $K_{HA} = K_{BH^+}$. We denote as K'_{HB} the value of K_{HB} predicted in the experimental solvent when $K_{HA} = K_{BH^+}$. Using the experimental slope m and intercept b from the log K_{HB} *versus* log ($P_{HB}K_{HA}/K_{BH^+}$) plot, and the extrathermodynamic P_{HB} value, K'_{HB} can be calculated for the case $K_{HA} = K_{BH^+}$ as equation (14).

$$\log K'_{HB} = m \log P_{HB} + b \qquad (14)$$

It can be shown using thermodynamic cycles that K_{std} can then be calculated for a hypothetical solvent in which $P_{HB} = 1$ as equation (15) where the P_{HB} in equation (15) is the value for the actual experimental solvent–water partition coefficient.

$$K_{std} = K'_{HB}/P_{HB} \qquad (15)$$

K_{std} represents a *hypothetical* standard reaction because it is in an imaginary solvent for which $P_{HB} = 1$, and because the condition $K_{HA} = K_{BH^+}$ cannot be met by real members of some donor–acceptor classes. The reaction is not completely unrealistic, however, because the real P_{HB} values (Table 1) cluster about unity, and in some cases (see Figure 1) donor–acceptor acidities bracket the $K_{HA} = K_{BH^+}$ condition. Note that a unique value for the intercept, and K_{std}, obtains only when either the donor or acceptor is held constant. So, for example, a well defined K_{std} is expected for the donor–acceptor class, phenol with various substituted pyridines, but not for the larger class, various substituted phenols with various substituted pyridines. Also, the range of substituents used must be such as to maintain homology. For our purposes, a series is homologous if it produces a linear log K_{HB} *versus* log ($P_{HB}K_{HA}/K_{BH^+}$) plot. When these conditions are met, comparison of K_{std} values provides a convenient, non-arbitrary way to compare hydrogen-bonding tendencies of compounds whose aqueous acidities are known, even when the classes do not share a common reference species, are of widely varying aqueous acidities, and are studied in different solvents.

Comparison with Experiment.—We have analysed 18 different hydrogen-bonding studies in terms of our phase-transfer model. These studies used phenols and aliphatic alcohols as donors, and aliphatic amines, pyridines, anilines, acetone, and an amide as acceptors. The data were plotted according to equation (13) as log K_{HB} *versus* log ($P_{HB}K_{HA}/K_{BH^+}$), using the values of P_{HB} given in Table 1 and aqueous K_a values taken from the literature.[23] In all cases, the plots, although sometimes scattered, appeared linear to the eye. Linear least-squares analyses were performed to determine the slopes, intercepts, and correlation coefficients. The 95% confidence limits of the slopes and intercepts were calculated using a standard algorithm,[24] requiring the additional assumption that the experimental points are normally distributed about the least-squares line. Values of K'_{HB} and K_{std} were calculated according to equations (14) and (15), respectively. The results of this analysis are presented in Table 2, where the data are arranged with similar classes grouped together and in order of decreasing K_{std}. For the duplicate studies, agreement was generally within experimental error. Not all of the cases are strictly comparable, because of temperature differences. Also, for those hydrogen-bonding studies not done at 25 °C, there will be an additional error due to the use of 25 °C pK_a values. Table 3 and Figure 1 represent additional efforts to discern trends in the data. In Table 3 the data are grouped by donor–acceptor class and arranged in order of decreasing slope. Representative plots for nine different donor–acceptor classes are shown in Figure 1. For clarity, only the least-squares lines are indicated. The extrapolations (dashed lines) to the y-intercept give an approximate indication of how far K'_{HB}, K_{std}, and the condition $K_{HA} = K_{BH^+}$ are from the experimental data. [Note that y-intercept ≈ log K'_{HB} ≈ log K_{std}, in accord with equations (14) and (15).]

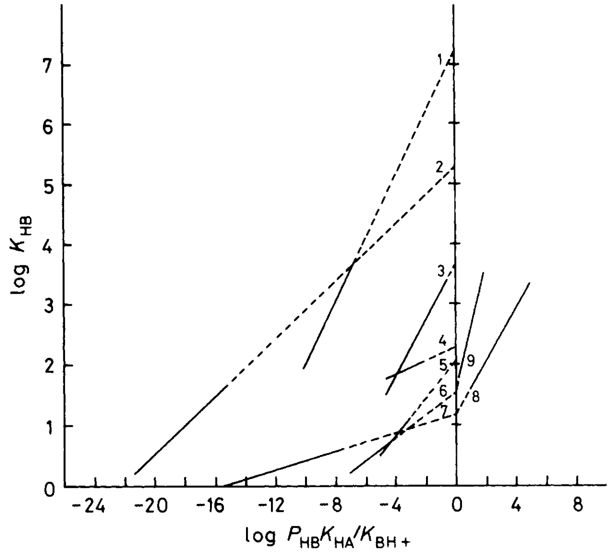

Figure 1. Representative plots, according to equation (13), for various donor–acceptor classes: 1, varying phenol derivatives–*NN*-dimethylacetamide;[36] 2, varying primary alcohols–acetone;[25] 3, varying phenol derivatives–pyridine;[11,32,34] 4, phenol–varying pyridine derivatives;[30] 5, varying phenol derivatives–aniline;[9] 6, phenol–varying aniline derivatives;[9] 7, methanol–varying pyridine derivatives;[10,31] 8, varying phenol derivatives–triethylamine;[13] 9, *p*-chlorophenol–varying aliphatic amines.[15] The solid line sements correspond to the range of the experimental data. The dashed segments illustrate the extrapolation necessary to obtain K'_{HB} and K_{std}. See Table 2 for least-squares parameters and confidence limits of slopes and intercepts. All data correspond to hydrogen bonding in CCl_4 except line 9, which was done in cyclohexane

It is evident from inspection of Table 2 and Figure 1 that there is no correlation between slope and K_{std} values for various

Table 2. Summary of parameters from all hydrogen bonding-data analysed by the phase-transfer model

Donor	Acceptor	Solvent	T/°C	$\log K_{HB}$[a] low, high	$\log \underset{i \neq 5}{\pi} K_i$[b] low, high	$\log K_{IHB}$[c] low, high	N[d]	r[e]	Slope[f]	Intercept[f]	$\log K'_{HB}$[G]	$\log K_{std}$[h]	Ref.
Phenol derivatives	*NN*-Dimethylacetamide	CCl_4	25	1.91, 3.42	−9.88, −6.78	10.2, 11.9	14	0.963	0.52 ± 0.09	7.20 ± 0.84	7.49	6.90	36
Primary alcohols	Acetone	CCl_4^1	25	0.06, 1.69	−21.6, −15.0	16.7, 21.6	5	0.998	0.24 ± 0.03	5.27 ± 0.49	5.41	4.84	25
Phenol derivatives	Pyridine	C_6H_{12}	25	1.86, 2.60	−5.18, −3.78	6.38, 7.04	5	0.992	0.53 ± 0.12	4.58 ± 0.54	4.55	4.59	14, 33, 35
Phenol derivatives	Pyridine	CCl_4	21	1.62, 2.24	−4.47, −3.28	5.52, 6.09	7	0.993	0.56 ± 0.07	4.13 ± 0.30	4.45	3.88	11
Phenol derivatives	Pyridine	CCl_4	21—25	1.53, 3.05	−4.59, −1.08	4.13, 6.12	13	0.989	0.47 ± 0.05	3.67 ± 0.17	3.94	3.37	11, 32, 34
Phenol derivatives	Pyridine	CCl_4	27	1.51, 2.34	−4.47, −2.54	4.88, 5.98	11	0.957	0.43 ± 0.10	3.51 ± 0.38	3.76	3.19	9
p-Fluorophenol	Pyridine derivatives	CCl_4	25	0.75, 2.61	−8.67, 1.55	2.37, 9.48	8	0.991	0.21 ± 0.03	2.68 ± 0.16	2.80	2.23	32
Phenol	Pyridine derivatives	CCl_4	20	1.08, 1.92	−7.99, −3.36	5.31, 9.14	8	0.983	0.19 ± 0.03	2.52 ± 0.19	2.63	2.06	29
Phenol	Pyridine derivatives	CCl_4	27	0.89, 1.92	−8.66, −3.36	5.28, 9.61	10	0.920	0.19 ± 0.07	2.42 ± 0.39	2.53	1.96	9
Phenol	Pyridine derivatives	CCl_4	20	1.76, 2.14	−4.50, −1.92	3.99, 5.96	10	0.926	0.12 ± 0.04	2.31 ± 0.14	2.38	1.81	30
Pentachlorophenol	Pyridine derivatives	CCl_4	25	1.03, 1.96	−3.34, 2.44	−2.45, 4.37	10	0.913	0.20 ± 0.07	1.55 ± 0.12	1.68	1.11	17
Phenol derivatives	Aniline	CCl_4	27	0.415, 1.13	−5.06, −3.13	4.26, 5.48	11	0.956	0.32 ± 0.07	2.07 ± 0.32	2.25	1.68	9
p-Chlorophenol	Aliphatic amines	C_6H_{12}	25	2.09, 3.43	0.49, 1.81	1.60, 2.19	6	0.900	1.11 ± 0.75	1.67 ± 0.91	1.62	1.66	15
o-Cresol	Aliphatic amines	C_6H_{12}	25	1.11, 2.01	−0.31, 1.01	0.86, 1.54	9	0.772	0.67 ± 0.49	1.42 ± 0.25	1.39	1.43	16
Phenol derivatives	Diethylamine	C_6H_{12}	30	1.85, 3.21	1.61, 6.83	−3.62, 0.32	6	0.787	0.22 ± 0.23	1.45 ± 1.06	1.44	1.48	37
Phenol	Aniline derivatives	CCl_4	27	0.286, 0.867	−6.78, −4.04	4.91, 7.10	12	0.968	0.19 ± 0.03	1.54 ± 0.19	1.65	1.08	9
Phenol derivatives	Triethylamine	CCl_4	30	1.42, 3.56	0.80, 3.97	−1.71, 0.72	17	0.967	0.47 ± 0.07	1.17 ± 0.19	1.14	0.87	13
Methanol	Pyridine derivatives	CCl_4	25	0.04, 0.52	−15.4, −7.50	8.02, 15.4	16	0.976	0.075 ± 0.01	1.14 ± 0.11	1.18	0.61	10, 31

[a] Taken from the literature references. [b] Calculated from equation (13), where the extrathermodynamic assumption of P_{HB} has been made so that $\log \underset{i \neq 5}{\pi} K_i = \log (P_{HB} K_{HA}/K_{BH^+})$. Literature K_a values from ref. 23 were used. [c] Calculated from $\log K_{HB}$ and $\log \underset{i \neq 5}{\pi} K_i$ values according to equation (13). [d] N is number of data points (donor–acceptor pairs) in the set. [e] r is the correlation coefficient from the linear-least squares analysis of the $\log K_{HB}$ *versus* $\log (P_{HB}K_{HA}/K_{BH^+})$ plots. [f] The slope and intercept are the linear least-squares fits of the $\log K_{HB}$ *versus* $\log (P_{HB}K_{HA}/K_{BH^+})$ plots. The uncertainty is stated as ±95% confidence limits calculated according to algorithm given in ref. 24. [g] Calculated according to equation (14) using the slopes and intercepts from this Table and P_{HB} values from Table 1. [h] Calculated according to equation (15) using K'_{HB} from this Table and P_{HB} from Table 1.

Table 3. Donor–acceptor classes arranged by decreasing slope

Donor–acceptor class	Slope[a]	N[a]
Fixed phenol derivative–varying aliphatic amines	0.89, s = 0.31	2
Varying phenol derivatives–pyridine	0.50, s = 0.06	4
Varying phenol derivatives–*NN*-dimethylacetamide	0.52 ± 0.09	1
Varying phenol derivatives–triethylamine	0.47 ± 0.07	1
Varying phenol derivatives–aniline	0.32 ± 0.07	1
Varying phenol derivatives–diethylamine	0.22 ± 0.23	1
Varying primary alcohols–acetone	0.24 ± 0.03	1
Phenol–varying aniline derivatives	0.19 ± 0.03	1
Fixed phenol derivative–varying pyridine derivatives	0.18, s = 0.04	5
Methanol–varying pyridine derivatives	0.075 ± 0.010	1

[a] Average slopes of all log K_{HB} *versus* log ($P_{HB}K_{HA}/K_{BH^+}$) plots for a given donor–acceptor class. N is number of data sets for given donor–acceptor class. When $N = 1$, slope and 95% confidence limits are from Table 2. When $N > 1$, slope is average of Table 2 values, and standard deviation, s, of the Table 2 values is given.

donor–acceptor classes. That is, there is no simple relation between how efficiently acidity free energy is propagated into hydrogen bond free energy and the strength of the hydrogen bond under the standard conditions of equal donor and acceptor acidities. Furthermore, the magnitude of K_{IHB} is not correlated with either the slope or K_{std}. Also, there is no correlation between the magnitudes of the experimental K_{HB} and the K_{std} values; some donor–acceptor classes with similar K_{HB} have quite different K_{std}, while some classes with quite different K_{HB} have similar K_{std}.

The lack of correlation among the slope, K_{std}, and the magnitude-range of K_{IHB}, even though they are formally related by equations (14) and (15), suggests that these quantities are not all simply different manifestations of some single phenomenon such as donor–acceptor acidities, polarizabilities, or dipole moments, for example. Rather, we infer that these quantities represent different characteristic properties of the *class* of donor and acceptor interaction.

The various donor acceptor classes appear to fall into four groups when the slopes are considered (Table 3). All slopes were between zero and one, as predicted by the theory; note that the significance of the slope is identical whether plotting data according to equation (9) or (13). The largest slope was for the class, varying aliphatic amines with fixed substituted phenols. Although the error limits are large, *ca.* 90% of the change in acidity free energy appears in hydrogen bond free energy. In the next category, only 50% of the change in acidity free energy for varying substituted phenols is propagated into hydrogen bonds with pyridine, *NN*-dimethylacetamide, and triethylamine. Considering the confidence limits for the other two acceptors (aniline and diethylamine) studied with varying phenols, it is tempting to generalize that *ca.* 50% of varying phenol acidity free energy is propagated into nonaqueous hydrogen bonds, irrespective of the acceptor. 24% of varying primary aliphatic alcohol acidity is propagated into hydrogen bonding with acetone. Approximately 20% of varying pyridine or varying aniline acidity free energy is propagated into hydrogen bonding with fixed phenols. For five different studies of varying pyridines with fixed phenols the average slope was 0.18, standard deviation 0.036. With only 7.5% of the changing acidity free energy propagated into hydrogen bonding, the class, methanol with varying pyridines, is much lower than any other system studied.

The strongest standard hydrogen bond shown in Table 2 (log K_{std} = 6.9) is that between *NN*-dimethylacetamide and a hypothetical substituted phenol of the same acidity as the acidity of the amide's conjugate acid. There follows, in order of decreasing K_{std}, bonds between: aliphatic primary alcohol derivative with acetone, log K_{std} = 4.84; a phenol derivative with pyridine, average log K_{std} = 3.76; and a specific substituted phenol (non di-*ortho*) with a pyridine derivative, average log K_{std} = 2.02. Most of the remaining donor–acceptor classes, involving phenols with anilines and aliphatic amines, have log K_{std} values between 1.0 and 2.0. The lowest log K_{std} value, 0.61, is for methanol with a substituted pyridine.

The standard hydrogen-bonding constant is useful because it permits comparison of hydrogen bond strengths for different donor–acceptor classes under as comparable conditions as possible. As is clear from equation (9), hydrogen bond strengths depend on donor–acceptor acidities, and more importantly, according to equation (13), on the acidity ratio of K_{HA}/K_{BH^+}. Thus, when the hydrogen bonds formed by molecules from different donor–acceptor classes are compared, the question arises, to what extent are differences due to: (1) gross differences in acidities of the classes, (2) differences of acidity ratios of the pairs, and (3) other properties of the molecules? Use of the standard hydrogen-bonding constant removes the acidity variable from the comparison; all K_{std} values correspond to equal donor–acceptor acidities within a given class, and, as shown by equation (13), gross differences in acidities between classes are irrelevant if the *ratios* of acidities for the pairs are identical (all equal unity, in this case). For example, Figure 1 shows that hydrogen bonds between methanol and pyridine derivatives are typically much weaker than bonds between phenol derivatives and triethylamine. However, these two classes have nearly the same K_{std} values. We conclude that the experimentally observed difference in hydrogen bond strength can be entirely attributed to different acidity ratios for typical donor–acceptor pairs in the two classes. By contrast, the hydrogen bonds are about equally strong when phenol derivatives bond with pyridine as when they bond with triethylamine. But, K_{std} with pyridine is over 100-fold larger than with triethylamine. That is, a phenol derivative of acidity equal to pyridine would form a much stronger hydrogen bond than a phenol derivative of acidity equal to triethylamine. The similarity in experimental hydrogen bond strengths can be viewed as the 'fundamentally' weaker phenol–triethylamine bond being enhanced by higher K_{HA}/K_{BH^+} ratios. Another instructive comparison to draw is of donor–acceptor classes with similar K_{HA}/K_{BH^+} ratios but different K_{std} values. The largest and smallest K_{std} values reported belong to two such classes: phenols–*NN*-dimethylacetamide and methanol–pyridines. In this case, the wide difference in K_{HB} values and the even wider difference in K_{std} values suggest some fundamental difference in the hydrogen bonds unrelated to the acidities of the participants. A similar situation requiring a more subtle explanation is comparison of phenols–pyridine with phenol–pyridines. As expected, the K_{HB} values and the K_{HA}/K_{BH^+} ratios heavily overlap for these two classes, yet pyridine forms a stronger bond with a derivative of equal acidity than phenol forms with a pyridine derivative of equal acidity.

More theoretical work is necessary to explain the trend in free energy partitioning represented by the slopes, and the trend in the acidity and solvent-corrected standard hydrogen bond strengths calculated from the intercepts.

The Importance and Reliability of P_{HB}.—The extrathermodynamic assumption leading to our use of P_{HB} is not an essential feature of the phase-transfer model. The model, as represented by equations,[1–9] is thermodynamically rigorous. Also, interpretation of the slope as the fraction of acidity free energy propagated into hydrogen bond free energy [equation (11)] is rigorous. However, varying degrees of extrathermodynamic approximation are required for further quantitative interpretation of the hydrogen bonding–acidity relationship in terms of the phase-transfer model. For some purposes, it is only necessary to assume that the partition coefficient product $P_{HA}P_B/P_{AHB}$ for a particular donor–acceptor class is some constant, the actual value of which is irrelevant and which may vary for different donor–acceptor classes. On the other hand, the most extreme assumption we make is that the partition coefficient product reduces to P_{HB} [equation (10)], where P_{HB} is the same in a given solvent for all donor–acceptor classes, and is adequately approximated by the *intra*molecular P_{HB} value.

Analysis of the slope in terms of how acidity free energy propagates into ion hydrogen bonding free energy [equation (12)], or, how the acidity free energy partitions between hydrogen bonding and ion hydrogen bonding, requires the assumption that the ion hydrogen bonding reaction is the only other step in the phase-transfer pathway that is affected when the donor or acceptor acidity is changed. The partition product is therefore assumed to be constant for the donor–acceptor class being plotted, but the actual value is irrelevant and may even be different for other donor–acceptor classes.

The definition of K_{IHB} [equation (5)] does not require any extrathermodynamic assumption. However, in order to calculate K_{IHB} [from equation (9)] an extrathermodynamic approximation is needed because the partition coefficient of the hydrogen-bonded adduct P_{AHB} is not experimentally accessible. Therefore, equation (10) approximation along with the assumption of intra–intermolecular equivalence for P_{HB} is necessary to calculate the K_{IHB} values presented in Table 2.

Calculation of K_{std} requires the assumption that P_{HB} is both constant and known. However, the absolute accuracy of the P_{HB} values is most important when comparing data gathered in different solvents. For any given solvent, a systematic error in P_{HB} would shift *all* points plotted according to equation (13) by the same amount to the left or right. All log K_{std} values would thus be changed by the same additive constant, and the relative sequence left unchanged.

An attempt was made to test the reliability and internal consistency of the published P_{HB} values.[19] According to the phase-transfer model, when equation (13) is plotted using data for a given donor–acceptor class but gathered in different solvents, the data should all fall on the same line. This is tested in Figure 2 for the class of substituted phenols with pyridine. Sets of data were available for cyclohexane and CCl_4, and a few points were available for benzene, heptane, and chloroform. Although the data are grouped, and cyclohexane and CCl_4 plots have the same slope, they are not collinear as predicted. We believe that this deviation from collinearity corresponds to error in the hydrogen bond partition coefficient(s). The error includes the considerable experimental error in the intramolecular P_{HB} values (Table 1), and whatever error results from equating intra- and inter-molecular P_{HB} values. The vertical distance between the two lines corresponds to a difference in log K_{std} of 0.7, and therefore we have to assume that the uncertainty in log K_{std} values reported in Table 2 is at least as large. Note, however, that the fact the plots are parallel is consistent with the assumption of *constant* P_{HB}, at least for a given homologous series in a given solvent. Also, the magnitude of the displacement of the plots is consistent with the published experimental error in the P_{HB} values.[19] Recalculation of the cyclohexane and CCl_4 data using limiting P_{HB} values based on the published error limits shows that the two lines are within experimental error of each other. Clearly, more experimental work is necessary to obtain improved values of P_{HB} and to improve the accuracy of K_{IHB} and K_{std} values obtained from the phase-transfer model analysis.

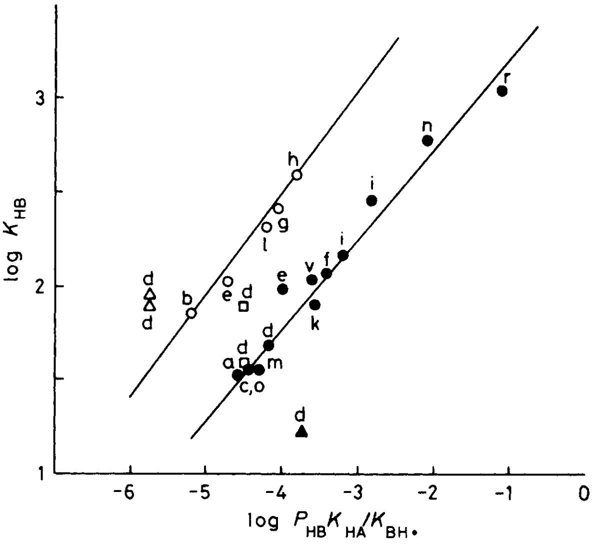

Figure 2. Hydrogen bonding of phenol derivatives with pyridine, in various solvents: ○, cyclohexane;[14,33,35] ●, carbon tetrachloride;[28,32,34] △ heptane;[26,27] ▲, chloroform;[29] □, benzene.[27,30] The least-squares lines are shown for the cyclohexane and carbon tetrachloride data, and correspond to data presented in Table 2. Key: a, *o*-cresol; b, *p*-t-butylphenol; c, *p*-cresol; d, phenol; e, *p*-fluorophenol; f, *p*-iodophenol; g, *m*-fluorophenol; h, *m*-trifluoromethylphenol; i, 3,4-dichlorophenol; j, *m*-chlorophenol; k, *p*-bromophenol; l, *p*-chlorophenol; m, *m*-cresol; n, 3,5-bis(trifluoromethyl)phenol; o, *p*-methoxyphenol

Conclusions.—We suggest that the phase-transfer model provides a uniquely useful framework in which to seek an understanding of the relationship between nonaqueous hydrogen bonding and aqueous acidities. An explicit functional dependence is derived. The slope of the relevant linear free energy plot is interpreted in terms of the partition of acidity free energy between the nonaqueous hydrogen bonding and the hydrogen bonding by the ionized aqueous forms of the donor and acceptor. The equilibrium constant of the ion hydrogen bonding reaction can be calculated with the aid of an extrathermodynamic partition coefficient. The intercept of the linear free energy plot leads to the standard hydrogen bonding constant, which permits comparison of hydrogen-bonding tendencies of donor–acceptor classes, even when (1) the classes do not share a common reference species, (2) are of widely varying acidities, and (3) are studied in different solvents. A wide variety of literature data have been analysed according to the phase-transfer model.

The phase-transfer model is, in principle, applicable to any nonaqueous adduct formation that is expected to correlate with aqueous acidity. The quantitative application of the model requires that the relevant partition coefficient for the *adduct bond* be known. To our knowledge the partition coefficient is currently available only for the hydrogen bond, but it should be possible to determine values for other adduct bonds in the same manner. We note the caveats that the fundamental significance of *aqueous* acidities has been questioned,[38] and that an ultimate understanding of the hydrogen bond will come from modern gas-phase studies[39] and quantum mechanical calculations.[40]

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