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NMR Method for the Determination of Solute Hydrogen Bond Acidity

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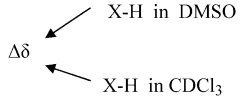
Received December 22, 2005



It is shown that the difference in the ^{1}H NMR chemical shift of a protic hydrogen in DMSO and $CDCl_3$ solvents is directly related to the overall, or summation, hydrogen bond acidity for a wide range of solutes. This provides a new and direct method of measuring the hydrogen bond acidity. For 54 compounds, the observed shifts for 72 protic hydrogens could be correlated to the Abraham solute hydrogen bond acidity parameter, *A*, with a correlation coefficient squared, R^2, of 0.938 and a standard deviation, SD, of 0.054 units in *A*. A training equation that used half the data could predict *A* values for the remaining data with an average error of 0.001 and a standard deviation, SD, of 0.053 units, thus demonstrating the predictive power of the method. Unlike any previous method for the determination of solute hydrogen bond acidities, the NMR method allows the determination of *A* values for individual protic hydrogens in multifunctional solutes.

Introduction

The solvent dependence of ^{1}H chemical shifts has been investigated since the beginning of high-resolution NMR. In a seminal paper, Buckingham et al.[1] defined four interactions responsible for solvent effects. These were hydrogen bonding, the anisotropy of the solvent molecules, and polar and van der Waals effects; this analysis has formed the basis for all subsequent investigations. The relative importance of these four contributions can vary considerably. When hydrogen bonding occurs with protic solutes, this is a major interaction with solvent effects of up to 5 ppm for the protic hydrogen.[1] Large anisotropy contributions of ca. 1 ppm have also been observed for nonpolar anisotropic solvents such as benzene and carbon disulfide.[1,2] Solvent shifts due to the electric field of the polar solute molecule haves been calculated using variations of the Onsager reaction field model[1−4] despite its many limitations. van der Waals effects have been shown to be significant in gas to solvent shifts even for nonpolar molecules in nonpolar solvents.[5] This early work has been well summarized.[6−8] The effect of solvent on chemical equilibria has been investigated in depth recently by both molecular modeling and quantum theory,[9−12] and Barone et al.[11,12] have employed the polarizable continuum model (PCM) solvation routine[13,14] to calculate ^{1}H and ^{13}C chemical shifts in solution via the quantum mechanical GIAO approach in the Gaussian suite.[15] However, this model is the quantum mechanical formulation of the Onsager reaction field model and does not include any solvent hydrogen bonding, van

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10.1021/jo052631n CCC: $33.50
Published on Web 03/31/2006

der Waals, or anisotropy contributions. Thus, there is still no general treatment of solvent effects on the ^{1}H chemical shifts of organic solutes. The problems involved in the quantitative calculation of the four contributions given for a polar, anisotropic, protic solvent are prohibitive. There is not even any empirical correlation of solvent effects vs any other molecular quantity.

In the course of an investigation into the effect of DMSO vs $CDCl_3$ solvent on ^{1}H NMR chemical shifts,[16] it was realized that the solvent shift for any protic hydrogen may be related to the solute hydrogen bond acidity. It is the purpose of this work to demonstrate that there is a direct correlation of this solvent shift with the hydrogen bond acidity and that this provides a new experimental method for the measurement of the hydrogen bond acidity of a solute. We compare results from the NMR method with the various "overall" scales of solute hydrogen bond acidity, A, $\Lambda\alpha$, $\epsilon\alpha$, α_2^{Ca}, and Ax, as detailed later.

The first scale of solute hydrogen bond acidity was constructed[17,18] from 1:1 equilibrium constants for a series of hydrogen bond acids against a given hydrogen bond base; see eq 1.

$$\text{A-H} + :\text{B} \xrightarrow{K^H_A} \text{A-H} \text{ --- } :\text{B} \qquad (1)$$

Values of K^H_A were transformed into a general hydrogen bond acidity scale through eq 2, where the constant 1.1 serves to define the origin of the scale, and the factor 4.636 simply scales α^H_2 values to a convenient range.

$$\alpha^H_2 = (1.1 + \log K^H_A)/4.636 \qquad (2)$$

Raevsky et al.[19] then devised an entirely equivalent scale, which they denoted as C_A, and further work has been carried out to extend the α^H_2 scale to a number of alkynes[20] and to 1:1 equilibrium constants in 1,1,1-trichloroethane[21,22] and in cyclohexane.[23] Although the 1:1 scales of Abraham et al.[17,18] and of Raevsky et al.[19] represent a fundamental chemical property, they are not particularly useful in systems in which the hydrogen bond acid is surrounded by a number of hydrogen bond base molecules, not just complexed by one molecule as in eq 1. For many monofunctional acids, the distinction may not be very important, but it does become important for polyfunctional acids.

Abraham et al.[24−26] then devised an alternative solute hydrogen bond acidity scale that they referred to as "overall" or "effective" hydrogen bond acidities, $\Sigma\alpha^H_2$, and which represented the hydrogen bond acidity of a solute surrounded by hydrogen bond bases, as, for example, a solute in a solvent that is a hydrogen bond base. The effective hydrogen bond acidity for solutes was originally obtained from gas liquid chromatographic retention data.[24,25] However, the experimental method for the determination of $\Sigma\alpha^H_2$, or A, as it is now denoted, has been considerably expanded, as described in detail.[27] Briefly, equations along the lines of eqs 3 and 4 are set up for a number of processes.

$$\text{SP} = c + eE + sS + aA + bB + vV \qquad (3)$$

$$\text{SP} = c + eE + sS + aA + bB + vL \qquad (4)$$

Equation 3 is used for processes within condensed phases and eq 4 is used for gas to condensed phase processes. In eqs 3 and 4 the dependent variable, SP, is a set of solute properties in a given system; for example, SP in eq 3 could be log P_{oct}, where P_{oct} is the water to octanol partition coefficient for a series of solutes. The independent variables in eqs 3 and 4 are solute descriptors as follows.[27] E is the solute excess molar refractivity in units of (dm^3 mol^{-1})/10, S is the solute dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, V is the McGowan characteristic volume in units of (dm^3 mol^{-1})/100, and L is the logarithm of the gas to hexadecane partition coefficient at 298 K.

Of the independent variables, or descriptors, in eqs 3 and 4, E can be obtained from the solute refractive index or can easily be calculated and V is trivially calculated. Then for any given solute four descriptors remain to be determined (or three, if only eq 3 is considered). Various equations on the lines of eqs 3 and 4 are set up for particular systems using solutes with known descriptors. Then for any new solute, determination of the dependent variable in four or more systems will enable all the descriptors S, A, B (and L) to be obtained.[27] An example is the determination of descriptors, including A, for the alkylcarboxylic acids.[28]

Both Liu et al.[29] and Leo[30] have used a variation on this method to obtain solute hydrogen bond acidities from partition coefficients in just two systems. Liu et al.[29] use the water to di-*n*-butyl ether (bue) and water to cyclohexane (cyc) systems and derive eq 5, where we denote their determined hydrogen bond acidity as $\Lambda\alpha$.

$$\log P(\text{bue}) - \log P(\text{cyc}) = 3.85\Lambda\alpha + 0.15 \qquad (5)$$

$$N = 41,\ R^2 = 0.982,\ \text{SD} = 0.129$$

Here, N is the number of data points (or solutes), R is the correlation coefficient, and SD is the standard deviation. The method of Leo[30] is very similar, except that he uses partition coefficients in the water to octanol (oct) and water to chloroform (chl) systems and derives the hydrogen bond acidity, $\epsilon\alpha$, through eq 6.

$$\epsilon\alpha = (\log P_{oct} - \log P_{chl} + V + 0.03)/3.2 - 0.04\text{XAA} \qquad (6)$$

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TABLE 1. Differences in ^{1}H NMR Chemical Shifts, $\Delta\delta$, the Indicator Variable IS, and Observed and Calculated Values of *A*

compd (proton measured)	*A* obsd	*IS*	$\Delta\delta$	*A* calcd	compd (proton measured)	*A* obsd	*IS*	$\Delta\delta$	*A* calcd
pentane (Me)	0.00	0	−0.01	0.01	styrene (=CH)	0.00	0	0.03	0.01
hexane (Me)	0.00	0	−0.01	0.01	phenylethyne (≡CH)	0.12	0	1.13	0.16
cyclohexane	0.00	0	−0.03	0.00	acetophenone (Me)	0.00	0	−0.02	0.00
cis-pent-2-ene (Me)	0.00	0	0.00	0.01	aniline (NH_2)	0.13	0	1.34	0.18
dichloromethane	0.10	0	0.49	0.07	aniline (NH_2)	0.13	0	1.34	0.18
trichloromethane	0.15	0	1.06	0.15	*N*-methylaniline (NH)	0.17	0	1.86	0.25
1-chlorobutane (Me)	0.00	0	−0.05	0.00	benzamide (NH_2)	0.25	0	1.55	0.21
isopropyl acetate (MeCO)	0.00	0	−0.06	0.00	benzamide (NH_2)	0.25	0	1.55	0.21
pentylamine (NH_2)	0.08	0	0.22	0.04	formanilide (NH)	0.50	0	3.00	0.41
pentylamine (NH_2)	0.08	0	0.22	0.04	phenol (OH)	0.60	0	4.69	0.63
diethylamine (NH)	0.08	0	0.49	0.07	2-cyanophenol (OH)	0.78	0	5.36	0.72
triethylamine (Me)	0.00	0	−0.10	−0.01	4-cyanophenol (OH)	0.80	0	5.31	0.71
formamide (NH_2)	0.32	0	1.64	0.22	2-nitrophenol (OH)	0.05	0	0.33	0.05
formamide (NH_2)	0.32	0	1.64	0.22	4-nitrophenol (OH)	0.82	0	5.64	0.76
acetamide (NH_2)	0.27	0	1.57	0.22	resorcinol (OH)	0.55	0	4.41	0.59
acetamide (NH_2)	0.27	0	1.57	0.22	resorcinol (OH)	0.55	0	4.41	0.59
trimethylacetamide (NH_2)	0.28	0	1.41	0.19	hydroquinone (OH)	0.53	0	4.20	0.56
trimethylacetamide (NH_2)	0.28	0	1.41	0.19	hydroquinone (OH)	0.53	0	4.20	0.56
N-methylformamide (NH)	0.40	0	2.20	0.30	2-pyrrolidinone (NH)	0.30	0	2.16	0.29
N-methylacetamide (NH)	0.40	0	2.17	0.30	camphor (CH_2)	0.00	0	−0.04	0.00
methanol (OH)	0.43	0	3.20	0.43	phenanthridinone (NH)	0.35	0	2.48	0.34
ethanol (OH)	0.37	0	3.21	0.43	diphenylamine (NH)	0.30	0	2.42	0.33
propan-1-ol (OH)	0.37	0	3.09	0.42	benzotriazole (NH)	0.62	0	3.80	0.51
propan-2-ol (OH)	0.33	0	3.05	0.41	halothane (CH)	0.15	0	1.40	0.19
2-methoxyethanol (OH)	0.30	0	2.66	0.36	*p*-toluenesulfonamide (NH_2)	0.28	0	2.59	0.35
ethane-1,2-diol (OH)	0.29	0	2.69	0.36	*p*-toluenesulfonamide (NH_2)	0.28	0	2.59	0.35
ethane-1,2-diol (OH)	0.29	0	2.69	0.36	*p*-aminophenol (OH)	0.53	0	4.16	0.56
propane-1,3-diol (OH)	0.38	0	2.43	0.33	*p*-aminophenol (NH2)	0.07	0	1.13	0.16
propane-1,3-diol (OH)	0.38	0	2.43	0.33	*p*-aminophenol (NH2)	0.07	0	1.13	0.16
butane-1,4-diol (OH)	0.36	0	2.48	0.34	4-aminobenzyl alcohol (OH)	0.37	0	2.88	0.39
butane-1,4-diol (OH)	0.36	0	2.48	0.34	4-aminobenzyl alcohol (NH2)	0.13	0	1.22	0.17
pentane-1,5-diol (OH)	0.36	0	3.10	0.42	4-aminobenzyl alcohol (NH2)	0.13	0	1.22	0.17
pentane-1,5-diol (OH)	0.36	0	3.10	0.42	dodecanethiol (SH)	0.00	1	0.86	−0.01
dimethyl sulfoxide	0.00	0	0.00	0.01	butylthiol (SH)	0.00	1	0.86	−0.01
benzene	0.00	0	0.01	0.01	isobutylthiol (SH)	0.00	1	0.87	−0.01
toluene (Me)	0.00	0	−0.06	0.00	thiophenol (SH)	0.12	1	1.96	0.14

XAA is the count of all sp^3 carbon atoms in a molecule, except those connected to an aromatic ring or to a heteroatom, and functions as an empirical correction term.

Li et al.[31] and Weckwerth et al.[32] have both used gas liquid chromatographic, GLC, retention data (effectively gas to liquid partition coefficients) to obtain scales of solute hydrogen bond acidities, denoted as α_2^{Ca} and Ax, respectively. The method of Weckwerth et al.[32] is of further interest in that it is claimed that the various descriptors, including Ax, are "pure" descriptors not contaminated with other effects. Quite how this can be demonstrated is not obvious—indeed it is none too clear what is the meaning of a "pure" descriptor. In the case of hydrogen bond acidity, the α^H_2 descriptor derived from equilibrium constants for eq 1 might be considered to be a "pure" descriptor. However, the energy of a hydrogen bond is itself usually regarded as a combination of effects,[33,34] and since the relative proportions can change with the actual hydrogen bond, the concept of a "pure" hydrogen bond descriptor seems not very helpful.

The *A* descriptor has proved to be very useful indeed, as shown by the number of theoretical calculations of *A*,[35−40] and so it is a little surprising that no further experimental methods for the determination of *A* exist beyond those based on equilibrium measurements.[29−32]

Results and Discussion

The obtained differences in chemical shift, $\Delta\delta = \delta(\text{DMSO}) - \delta(CDCl_3)$, are collected in Table 1 for 54 compounds. There are actually 72 shifts because in the NMR method the differences in chemical shifts are due to all of the active protons. Thus, in 4-aminophenol, separate signals for the OH and NH_2 protons could be observed, and for the diols, the dihydroxyphenols, and compounds containing the NH_2 group the signals refer to both the protons. From partition coefficients we can only obtain the overall hydrogen bond acidity for a solute, and not individual values for the various protic hydrogens. For the diols, the dihydroxyphenols, and the NH_2 groups we take the individual values of *A* as half the observed values. For 4-aminophenol, $A = 0.65$, and we assign values of 0.12 and 0.53 to the amino and phenolic functions by analogy with monofunctional compounds; the amino group is itself composed of two protic hydrogens each of which is assigned a value of $A = 0.06$ units. 4-Aminobenzyl alcohol is treated similarly.

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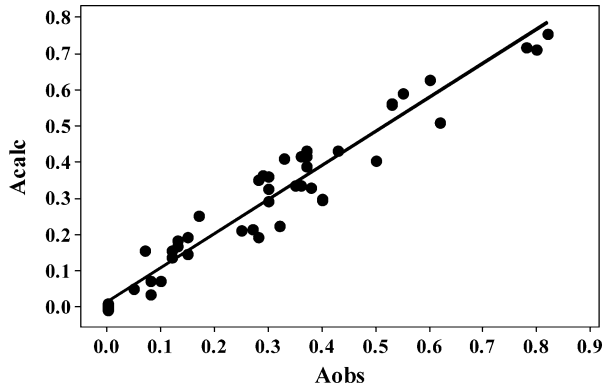

FIGURE 1. Plot of calculated values of *A* on eq 7 against observed values of *A*.

We then have NMR shifts, $\Delta\delta$, for 72 protic hydrogens. We first studied the correlation of $\Delta\delta$ with the five descriptors in eq 3. It is no coincidence that these five descriptors encode the various solute−solvent interactions suggested by Buckingham et al.[1] in their analysis of solvent effects on chemical shifts, because eq 3 was designed specifically as a general equation for solute−solvent interactions. We also included a sixth descriptor, *IS*, that we shall discuss later. A linear regression of $\Delta\delta$ against the six descriptors yielded an equation with $N = 72$, $R^2 = 0.957$, SD = 0.326, and F (the F-statistic) = 242. However, the descriptors in eq 3 were not very significant, except for the *A* descriptor, and a linear regression of $\Delta\delta$ against *A* and IS gave an equation with $N = 72$, $R^2 = 0.935$, SD = 0.391, and $F = 496$. Hence, the difference in chemical shift depends almost entirely on hydrogen bond acidity. Solute−solvent interactions that involve solute hydrogen bond basicity, polarizability, dipolarity, and general dispersion interactions are absent, or at least very small. If the regression is "turned round" so as to provide an equation that can be used for the prediction of further values of *A*, eq 7 results.

$$\mathbf{A} = 0.0066 - 0.128IS + 0.133\Delta\delta \qquad (7)$$

$$N = 72,\ R^2 = 0.938,\ \mathrm{SD} = 0.054,\ F = 523.9$$

Compounds with the −SH group could only fit the general correlation if we assigned an "indicator variable" to them. Solutes with an −SH group were assigned an indicator variable $IS = 1$. All other solutes had $IS = 0$. The indicator variable was significant at the 99.8% level. A plot of calculated values of *A* on eq 7 against observed values of *A* is in Figure 1 and shows random scatter around the regression line.

The idea of family dependencies of compounds with particular functional groups is not new. Maria et al.[41] have shown that basicity scales in general exhibit family dependencies, and Abraham et al.[42] have found the same for hydrogen bond basicity scales in particular. The effect of family dependency is shown, for example, in plots of one set of basicity values against another set. If there is no family dependency, all points will lie on the same line, but with family dependency a series of parallel lines are obtained, each line corresponding to compounds with the same functional group. There is much less data on hydrogen bond acids than on hydrogen bond bases, and this is probably why family dependency in hydrogen bond scales of acidity is not so evident. However, in setting up their α^{H}_2 scale, Abraham et al.[2] noted that a number of weak hydrogen bond acids, including alkylthiols, required a special scale for complexation with amine and ether bases.

Equation 7 is only a fitting equation, and the statistics give no information as to the predictive ability of the equation. We therefore ordered the data in increasing values of $\Delta\delta$ and selected every other data point to use as a training set. This procedure ensures that the training set and the test set cover the same range of values. The training set led to the following equation.

$$A = 0.0065 - 0.134IS + 0.133\Delta\delta \qquad (8)$$

$$N = 36,\ R^2 = 0.940,\ \mathrm{SD} = 0.055,\ F = 258.7$$

The coefficients in eq 8 are reasonably close to those in eq 7, suggesting that the training set is a representative sample from the total set. Equation 8 can then be used to predict the remaining 36 values in the test set that have not been used to construct eq 8. We found the average error, AE, = 0.001, the absolute average error, AAE = 0.041, and the standard deviation, SD = 0.053, between the observed and predicted values for the test set. The average error shows that there is no bias in the predictions, and the values of AAE and SD, both measures of predictive ability, indicate that eq 8 and by implication eq 7 can be used to obtain new values of the solute hydrogen bond acidity descriptor, *A*, to within about 0.05 unit.

Some of the scales of hydrogen bond acidity mentioned in the Introduction include so few solutes that hydrogen bond acidities are available for only a proportion of the solutes listed in Table 1. However, results of correlation equations between the various scales and $\Delta\delta$ are as follows.

$$\Lambda\alpha = -0.0816 + 0.056IN + 0.133\Delta\delta \qquad (9)$$

$$N = 15,\ R^2 = 0.767,\ \mathrm{SD} = 0.162,\ F = 20$$

$$\epsilon\alpha = -0.0404 + 0.317IS + 0.136\Delta\delta \qquad (10)$$

$$N = 43,\ R^2 = 0.851,\ \mathrm{SD} = 0.117,\ F = 59$$

$$\alpha_2^{Ca} = -0.0124 + 0.116\Delta\delta \qquad (11)$$

$$N = 24,\ R^2 = 0.896,\ \mathrm{SD} = 0.057,\ F = 189$$

$$\mathrm{Ax} = -0.0176 + 0.107\Delta\delta \qquad (12)$$

$$N = 14,\ R^2 = 0.834,\ \mathrm{SD} = 0.081,\ F = 60$$

Equations 9−12 are all statistically quite reasonable, thus showing that the NMR chemical shifts do, indeed, reflect the hydrogen bond acidic strength of the solutes. This is the first time that a procedure not based on partition coefficients has been shown to yield solute hydrogen bond acidities.

Equations 7 and 8 are especially significant, in that they indicate that *A* values can be determined by the NMR method to around 0.05 units. One disadvantage of the NMR method is that it is difficult to apply to solutes that are strongly dimerized in trichloromethane. This is why we have left out carboxylic acids from our analysis. Since solutes such as propanoic acid exist as dimers in trichloromethane but as monomers in DMSO, the difference in the NMR chemical shifts will refer to neither

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of these species. In addition, great care has to be taken when dealing with strong proton bases, such as the alkylamines, because traces of acids will disrupt the measurements.

It is not surprising that the methods based on partitions in two systems yield hydrogen bond acidities that are comparable to those obtained by more elaborate methods. Testa et al.[43] pointed out many years ago that differences between water−solvent partition coefficients in a number of systems were roughly proportional to the solute hydrogen bond acidity. Of the above two methods based on partitions in two water−solvent systems, that of Leo[14] seems statistically rather better than that of Liu et al.,[13] but of course the equation for the calculation of $\epsilon\alpha$ has two extra terms as compared to the equation of Liu et al. Neither of these equations, with SD values of 0.16 and 0.12, is likely to yield hydrogen bond acidities as reliably as the NMR method. The two methods based on the determination of GLC retention data give hydrogen bond acidities that correlate very well with the NMR shift data, although for rather simple solutes. Neither of the GLC methods have been applied to compounds with active $-NH_2$ groups or $-SH$ groups, and hence, eqs 10 and 11 contain no term with the indicator variable, *IS*. Unfortunately, neither of the GLC methods is at all general. In the procedure of Li et al.,[15] retention data on 19 specified GLC stationary phases were used in order to obtain solute dipolarity/polarizability, *S*, and solute hydrogen bond acidity as α_2^{Ca}. The method of Weckworth et al.[16] uses retention data on five specified stationary phases under specific experimental conditions. Thus, the two GLC methods, as such, are quite difficult to apply by other workers. However, there seems no reason why similar GLC methods could not be used to determine values of *A* in the future.

The NMR method has advantages of experimental convenience and accuracy and also it gives the hydrogen bond acidity of a particular proton in the molecule. This could be of particular importance for multifunctional molecules, provided the particular hydrogen atoms considered are not interconverting rapidly on the NMR time scale. In this connection, it is important to note that the various scales of hydrogen bond acidity which we have compared to the NMR shifts refer to "overall" or "summation" hydrogen bond acidity. This is the observed hydrogen bond acidity when a solute is surrounded by hydrogen bond base molecules, as is the case for a solute dissolved in DMSO. We have suggested that this type of acidity, in terms of *A* values, is "additive" in that if a molecule possesses two functional groups that do not interact intramolecularly the *A* values for the two separate solutes can be added to give the *A* value for the bifunctional molecule.

This is not at all the situation for solute hydrogen bond acidity or solute hydrogen bond basicity derived from 1:1 complexation constants, usually in tetrachloromethane, and denoted as α^H_2 and β^H_2, respectively; see eqs 1 and 2. Suppose we have a molecule with two hydrogen bond acidic groups that undergo no intramolecular interaction, denoted as A1-XY-A2. That is, the 1:1 complexation constant for the group A1 in the molecule A1-XY-A2 is the same as that in the molecule A1-X, and the complexation constant for A2 in A1-XY-A2 is the same as that in Y−A2. Then log K^H_A (A1) and log K^H_A(A2) are the respective experimental 1:1 complexation constants for the solutes A1-X and Y-A2. The observed 1:1 complexation constant for A1-XY-A2 in an experiment in which A1-XY-A2 is allowed to complex with an equimolar hydrogen bond base is given by[44]

$$K^H_A(A1 + A2) = K^H_A(A1) + K^H_A(A2) \quad (13)$$

Then, from eq 2

$$\alpha^H_2(\text{total}) = \{1.1 + \log[K^H_A(A1) + K^H_A(A2)]\}/4.636 \quad (14)$$

$$\alpha^H_2(A1) = \{1.1 + \log K^H_A(A1)\}/4.636 \quad (15)$$

$$\alpha^H_2(A2) = \{1.1 + \log K^H_A(A2)\}/4.636 \quad (16)$$

That is, for 1:1 complexation

$$\alpha^H_2(A1) + \alpha^H_2(A2) \neq \alpha^H_2(\text{total}) \quad (17)$$

In the case of A1 = A2, for example, pentane-1,5-diol, it follows from eqs 2 and 14 that

$$\alpha^H_2(\text{total}) = \{1.1 + \log[2K^H_A(A1)]\}/4.636 \quad (18)$$

$$\alpha^H_2(\text{total}) = 0.065 + \alpha^H_2(A1) \quad (19)$$

Similar equations apply to hydrogen bond basicity, where there is much more data to confirm the equations experimentally. For two identical base groups in a molecule, the corresponding equation to eq 19 is eq 20

$$\beta^H_2(\text{total}) = 0.065 + \beta^H_2(B1) \quad (20)$$

Laurence et al.[45] have measured 1:1 complexation constants for amines. They find that $\beta^H_2 = 0.714$ for *n*-butylamine and that $\beta^H_2 = 0.779$ for 1,4-diaminobutane, exactly the value calculated from eq 20. Laurence et al.[44] have also described a method for the determination of 1:1 basicity (not overall basicity) of individual functional groups in a molecule through a combination of FTIR measurements, coupled with various family dependent relationships that are used to assign the FTIR shifts to specific functional groups.

We can investigate multifunctional solutes through our NMR method, which, for the first time, allows the overall hydrogen bond acidities to be determined for individual functional groups. This is a direct method which gives the overall hydrogen bond acidity of the functional groups straight away, without the requirement of having to assign NMR shifts. We chose 4-aminobenzyl alcohol as an example because the two functional groups are separated by the "benzyl" group and so interaction between them will be small. For aniline and benzyl alcohol, *A* values are 0.26 and 0.39, respectively, leading to a total *A* value of 0.65 if there is no intramolecular interaction at all. The NMR method yields a total value of 0.55, so there is perhaps a small amount of interaction between the groups. The diols are a simpler example, because the two groups are the same. A primary alcohol has $A = 0.37$ and so for an α,ω-diol such as butane-1,4-diol or pentane-1,5-diol, we expect an *A* value of 0.74, as compared to experimental values of 0.72 for butane-1,4-diol and pentane-1,4-diol, and 0.75 for the higher α,ω-diols,

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and the NMR values of 0.68 for butane-1,4-diol and 0.84 for pentane-1,5-diol.

Conclusion

It is shown that the measurement of the NMR chemical shift difference of a proton in DMSO vs $CDCl_3$ solvent is directly related to the hydrogen bond acidity of the solute molecule. This provides a convenient and accurate measurement of the overall, or summation, hydrogen bond acidity of a solute, which could be of particular use for complex multifunctional molecules.

Experimental Section

All the compounds and solvents were obtained commercially. The $CDCl_3$ and DMSO solvents were stored over molecular sieves of 3 Å pore size and used without further purification. Solutions of ~10 mg/mL concentration were run with TMS as internal standard except for the alcohols and phenols in $CDCl_3$ solvent in which to remove intermolecular hydrogen-bonding shifts; in this solvent, the OH chemical shift was obtained for ca. 1 mg/mL concentration. The ^1H spectra were obtained on a 400 MHz NMR spectrometer operating at 400.13 MHz. Typical running conditions were 128 transients, spectral width 3300 Hz and 32 K data points, giving an acquisition time of 5 s. The FIDs were zero-filled to 64 K. The spectra were first order, and the assignments were straightforward. Full details of the assignments and chemical shifts have been given previously.[16]

Acknowledgment. We thank Astra/Zeneca for an industrial research studentship (J.J.B) and EPSRC for a grant toward the purchase of a 400 MHz NMR spectrometer. We thank Dr. Mehdi Mobli for the data on phenol and the cyano and nitrophenols, and Dr. Paul Leonard for the data on resorcinol, hydroquinone, and isobutylthiol.

JO052631N