A Simple Relation between ^{1}H NMR Data and Mixing Enthalpy for Systems with Complex Formation by Hydrogen Bonding

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A simple explicit relation linking ^{1}H NMR chemical shifts and mixing enthalpy has been found for systems that form 1:1 complexes by hydrogen bonding. Starting from relatively general assumptions, we have derived two forms of this relation. The first form is represented by proportionality between the solution enthalpy of the proton donor and the chemical shift change of its active hydrogen atom. The second form is mediated by the relative extent of hydrogen bond formation, $\eta_{1,\text{rel}}$, a quantity that can be directly evaluated from measurements of either the ^{1}H NMR chemical shift or the mixing enthalpy. The validity of both relation forms has been convincingly demonstrated for 12 systems formed by a strong proton donor (halothane [1-bromo-1-chloro-2,2,2-trifluoroethane] or trichloromethane) and an oxygen- or nitrogen-containing proton acceptor (aliphatic or alicyclic ether, piperidine).

1. Introduction

Formation of molecular complexes by hydrogen bonding greatly affects thermodynamic, spectroscopic, and some other properties of respective systems, causing their behavior to differ considerably from that exhibited by systems with interactions of the purely van der Waals type. During the past decade, we have systematically studied some model systems with distinct formation of complexes consisting of strong proton donors, halothane (1-bromo-1-chloro-2,2,2-trifluoroethane) or trichloromethane, and oxygenated solvents as efficient proton acceptors.[1−5] In these studies, data on excess thermodynamic functions (G^E, H^E, C_P^E) or ^{1}H NMR chemical shifts or both for these systems were analyzed by several models of associated solution. The criterion of model adequacy was, apart from physically reasonable values of the adjustable parameters, the capability of fitting various system properties simultaneously, that is, with a single set of parameter values. It has long been known that ^{1}H NMR spectroscopy can be used for quantitative studies of complex formation by hydrogen bonding. Such studies, although quite frequent in the literature, only rarely confront their results with thermodynamic data.[5−8] The relations between thermodynamic properties and the NMR chemical shifts mediated by associated solution models are generally complex and implicit. Nevertheless, as we have found, these relations can take a simple and explicit form in some special cases. In this work, we deal with one such case, examining the interrelation between information yielded by ^{1}H NMR spectroscopy and data on mixing enthalpy.

2. Theory

Consider binary liquid mixtures of which the components, proton donor (1) + proton acceptor (2), do not self-associate

but extensively form a 1:1 complex by hydrogen bonding. A number of the systems, which we have lately studied, pertain demonstrably to this type (halothane or trichloromethane with aliphatic or alicyclic monoethers).[1,3,4]

The formation of a hydrogen bond causes a change of the chemical shift of the resonance signal corresponding to the proton involved. This change, $\Delta\delta_1$, is proportional to the relative size of the "bound" proton population ($n_1^{(b)}/n_1$) and to the difference, D_1, between the chemical shifts of the "bound" and "free" protons

$$\Delta\delta_1 = (n_1^{(b)}/n_1)D_1 \tag{1}$$

As we have shown previously,[5] upon scaling $\Delta\delta_1$ by the span of its values, we obtain a newly defined quantity

$$\eta_{1,\text{rel}} \equiv \frac{\Delta\delta_1}{\Delta\delta_1^{\infty}} \tag{2}$$

which we denote as the relative change of the chemical shift. The value of $\Delta\delta_1^{\infty} = \Delta\delta_1(x_1{\rightarrow}0)$ is determined by the extrapolation of data in the dilute region of proton donor. The relative change of the chemical shift is a dimensionless quantity normalized to the interval $\langle 0,1 \rangle$ and can be directly evaluated from the observed chemical shifts. The major advantage of defining $\eta_{1,\text{rel}}$ lies in the physical significance of this quantity, which follows from combining eqs 1 and 2

$$\eta_{1,\text{rel}} = \frac{(n_1^{(b)}/n_1)}{(n_1^{(b)}/n_1)^{\infty}} \tag{3}$$

Equation 3 indicates that $\eta_{1,\text{rel}}$ expresses the relative extent of hydrogen bonding compared with its maximum value occurring at infinite dilution of the proton donor.

Because systems with intensive complex formation are considered, the contribution of complex formation to excess thermodynamic quantities is dominant; the contribution of van

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der Waals interactions is, on the other hand, relatively small, and we will neglect it in further considerations. The enthalpic change resulting from the formation of hydrogen bonds can be expressed for 1 mol of the solution as follows

$$H^E = n_1^{(b)}\Delta_b H^\circ/(n_1 + n_2) = x_1(n_1^{(b)}/n_1)\Delta_b H^\circ \qquad (4)$$

where H^E denotes the excess molar enthalpy and $\Delta_b H^\circ$ is the standard molar enthalpy of hydrogen bond formation. If we rewrite this equation into the form

$$\Delta_{sol}H_1 = H^E/x_1 = (n_1^{(b)}/n_1)\Delta_b H^\circ \qquad (5)$$

it is clearly seen that the solution enthalpy of the proton donor, $\Delta_{sol}H_1$, likewise the change of the chemical shift $\Delta\delta_1$, is directly proportional to the relative size of the "bound" proton population. Hence, on combining eqs 1 and 5, we disclose proportionality between the solution enthalpy of the proton donor and the change of chemical shift

$$\Delta_{sol}H_1 = (\Delta_b H^\circ/D_1)\Delta\delta_1 = k\Delta\delta_1 \qquad (6)$$

Furthermore, from eqs 3 and 5, it follows that enthalpic measurements can be readily used to express also the relative extent of hydrogen bond formation, $\eta_{1,rel}$

$$\eta_{1,rel} = \frac{\Delta_{sol}H_1}{\Delta_{sol}H_1^\infty} = \frac{H^E/x_1}{\bar{H}_1^{E,\infty}} \qquad (7)$$

where $\Delta_{sol}H_1^\infty = \bar{H}_1^{E,\infty}$ denote the infinite dilution values of the solution enthalpy and partial molar excess enthalpy of the proton donor, respectively.

The link between ^{1}H NMR spectroscopic data and enthalpic quantities represented by the proportionality relation of eq 6 or by the simultaneous validity of eqs 2 and 7 has been verified in this work for 12 binary mixtures of halothane (1) or trichloromethane (1) with dipropyl ether (2), diisopropyl ether (2), methyl *tert*-butyl ether (2), tetrahydrofuran (2), tetrahydropyran (2), and piperidine (2). For this purpose, experimental data on excess enthalpies were taken from previous publications of ours[9-11] or from Becker and Kiefer[12] and the ^{1}H NMR spectroscopic measurements were carried out in this work except for tetrahydropyran systems for which they were done in a specialized study.[13]

3. Experimental Section

Materials. Trichloromethane of analytical-reagent grade (Lachema, Czech Republic) stabilized with 1% of ethanol was first washed with water to remove the stabilizer and then dried with calcium chloride. The substance was further refluxed with a small portion of 2,4-dinitrophenylhydrazine acidified with hydrogen chloride and then fractionally distilled under nitrogen twice on 1 and 1.5 m columns packed with ceramic saddles. Tetrahydropyran, puriss (Fluka), which was first distilled on a 0.5 m packed column, halothane of medical grade without a stabilizer (Léčiva, Czech Republic), piperidine, puriss (Fluka), dipropyl ether, 99% (Aldrich), diisopropyl ether, 99.9% (Aldrich), and methyl *tert*-butyl ether, 99.9% (Aldrich), were all dried with 4 Å molecular sieves and stored in the dark in sealed ampules, while trichloromethane was purified and used immediately for measurements because of its rapid decomposition. Tetrahydrofuran, anhydrous, 99.9% (Aldrich), was used as purchased.
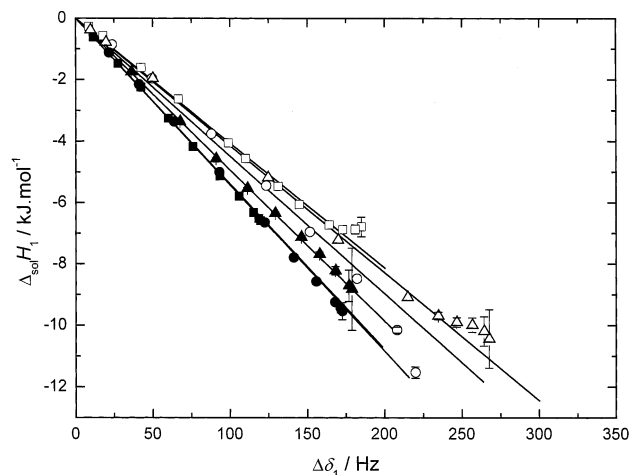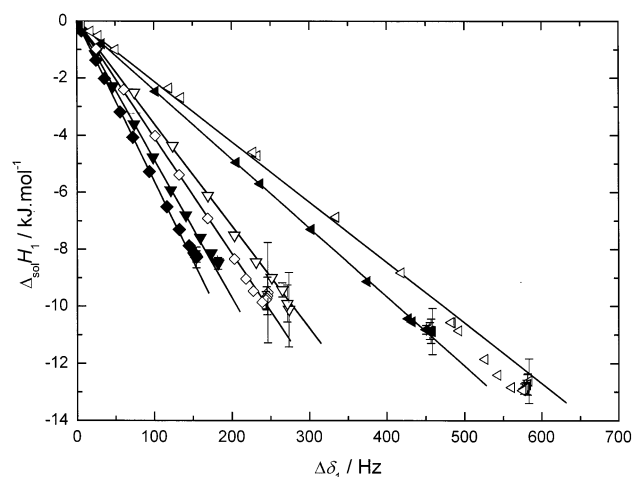

Figure 1. Proportionality between the proton-donor solution enthalpy, $\Delta_{sol}H_1$, and the change of its chemical shift, $\Delta\delta_1$, at 298.15 K for halothane (closed symbols) or trichloromethane (open symbols) with aliphatic monoethers: (□) dipropyl ether; (○) diisopropyl ether; (△) methyl *tert*-butyl ether. Mixing enthalpy data were taken from refs 9, 10, and 12.

Apparatus and Procedure. Samples for ^{1}H NMR measurements were prepared by weighing from pure components, which were spiked before with a small volume (0.001 v/v) of tetramethylsilane (TMS). Relatively large sample volumes (1 mL) were used to minimize the volume of the vapor phase in the sample tube and to decrease the influence of inaccuracy in weighing. Measurements of chemical shifts were carried out using a Varian Mercury Plus 300BB spectrometer with the operating frequency at 300.075 MHz. The magnetic field homogeneity was adjusted on a sample tube with deuterated trichloromethane, and then the measurements were performed without lock. Each sample was measured three times with one scan after 20 min of temperature stabilization. The temperature was stable to within ± 0.1 K and was calibrated using methanol as a temperature calibration sample. The chemical shift of halothane or trichloromethane was determined from the NMR spectra, TMS being used as an internal standard. The ^{1}H NMR signal of halothane is a quartet due to the ^{1}H–^{19}F spin–spin coupling. The signals of trichloromethane and TMS are singlets. The uncertainty of the measurement of the chemical shift is estimated to be within 0.5 Hz.

4. Results and Discussion

The measured changes in ^{1}H NMR chemical shifts of the active halothane or trichloromethane proton, along with the values of the relative extent of hydrogen bonding evaluated from eq 2, are deposited as Supporting Information. The values of $\Delta\delta_1^\infty$ needed for the evaluation of $\eta_{1,rel}$ were obtained by straight-line or second-order polynomial extrapolations of the $\Delta\delta_1 - x_1$ data.

The solution enthalpy, $\Delta_{sol}H_1$, plotted as a function of the observed change of chemical shift, $\Delta\delta_1$, is shown for the examined systems in Figures 1 and 2. To construct these plots, $\Delta_{sol}H_1$ values corresponding to $\Delta\delta_1$ were calculated at NMR experimental compositions from $H^E(x_1)$ dependences smoothed by Redlich–Kister polynomial. The experimental uncertainty shown was estimated using the error propagation law from the standard deviation of fit of H^E data; the uncertainty in the NMR measurement has a negligible effect. The straight lines are fits obtained by the weighted least-squares method. Results of this correlation are summarized in Table 1. This table and Figures

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Figure 2. Proportionality between the proton-donor solution enthalpy, $\Delta_{sol}H_1$, and the change of its chemical shift, $\Delta\delta_1$, at 298.15 K for halothane (closed symbols) or trichloromethane (open symbols) with alicyclic monoethers or piperidine: ($\triangledown$) tetrahydrofuran; ($\diamond$) tetrahydropyran; (tilted triangle) piperidine. Mixing enthalpy data were taken from refs 9, 11, and 12.

TABLE 1: Correlation of $\Delta_{sol}H_1$ with $\Delta\delta_1$, Proportionality Constant, k, in the Relation $\Delta_{sol}H_1$ (J mol^{-1}) = $k\Delta\delta_1$ (Hz), Standard Deviation $s(k)$, and Coefficient of Determination, r^2

system	k	$s(k)$	r^2
halothane (1) + dipropyl ether (2)	−40.67	0.51	0.9991
trichloromethane (1) + dipropyl ether (2)	−54.23	0.25	0.9997
halothane (1) + diisopropyl ether (2)	−44.89	0.96	0.9965
trichloromethane (1) + diisopropyl ether (2)	−53.92	0.33	0.9997
halothane (1) + methyl *tert*-butyl ether (2)	−41.48	0.36	0.9988
trichloromethane (1) + methyl *tert*-butyl ether (2)	−49.36	0.21	0.9992
halothane (1) + tetrahydrofuran (2)	−35.90	0.32	0.9988
trichloromethane (1) + tetrahydrofuran (2)	−48.52	0.15	0.9997
halothane (1) + tetrahydropyran (2)	−40.74	0.20	0.9995
trichloromethane (1) + tetrahydropyran (2)	−56.07	0.19	0.9996
halothane (1) + piperidine (2)	−21.17	0.19	0.9973
trichloromethane (1) + piperidine (2)	−24.19	0.04	0.9999

1 and 2 convincingly demonstrate that the proportionality between $\Delta_{sol}H_1$ and $\Delta\delta_1$ holds very well. The coefficient of determination attains values of $r^2 \geq 0.9965$. Deviations are noticeable only in the region of dilute proton donor (i.e., for the largest enthalpic effects and the largest changes of chemical shift), and they correspond mostly to strongly propagated experimental uncertainty in this region. The systematic trend of the deviations or their enhancement or both as compared to the estimated errors for $x_1 \rightarrow 0$ is a consequence of smoothing and extrapolating calorimetric data (Redlich−Kister polynomial) and of their higher experimental error in the dilute region. Note that the calorimetric information was mostly obtained by conventional flow mixing microcalorimetry without focusing to dilute regions.
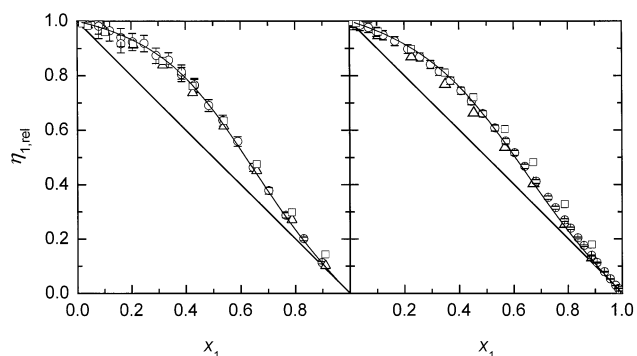
Figures 3−5 show the relative extent of hydrogen bonding, $\eta_{1,rel}$, as a function of system composition for six of the systems studied. The values of $\eta_{1,rel}$ were calculated both from the ^{1}H NMR spectroscopy (eq 2) and from the measurement of mixing enthalpies (eq 7). Let us mention that in both cases extrapolation of measured data to infinite dilution of proton donor was required. Reliable determination of $\Delta\delta_1^\infty$ from NMR spectroscopic measurement presented no special problems, in particular, because of the aimed experiment that accented the proton-donor dilute region. In case of enthalpic measurements, the extrapolation is less certain. The values of $\bar{H}_1^{E,\infty}$ were determined by linear or quadratic extrapolation of H^E/x_1x_2 vs x_1 using several data points at the lowest proton-donor concentration that we had at disposal. The error propagation analysis for $\eta_{1,rel}$ indicates
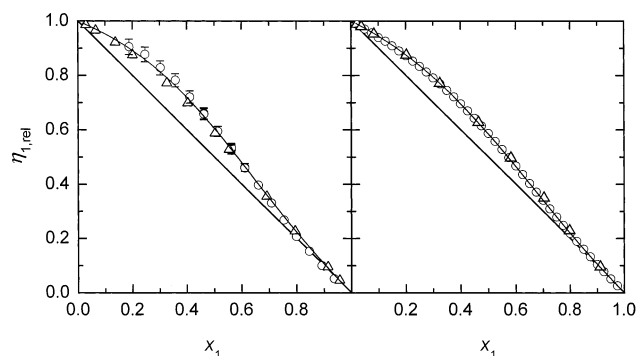
Figure 3. Relative extent of hydrogen bond formation, $\eta_{1,rel}$, as a function of system composition for (left) halothane (1) + dipropyl ether (2) and (right) trichloromethane (1) + dipropyl ether (2): ($\triangle$) from ^{1}H NMR spectroscopy (eq 2); ($\bigcirc$) from calorimetric measurements of mixing enthalpy^{9,12} (eq 7). Curves are fits of the $\eta_{1,rel}$−x_1 data by the ideal association model (eq 8) with (left) $K_{AB} = 1.36$ and (right) $K_{AB} = 0.98$.
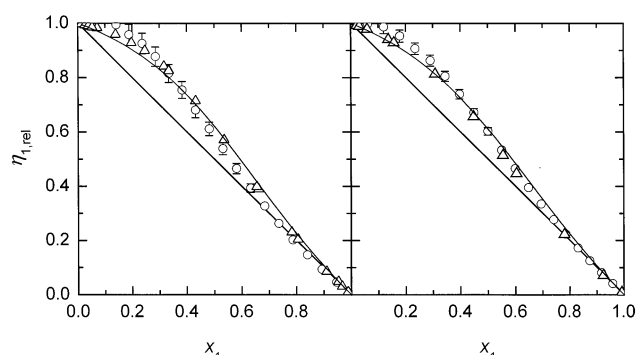
Figure 4. Relative extent of hydrogen bond formation, $\eta_{1,rel}$, as a function of system composition for (left) halothane (1) + piperidine (2) and (right) trichloromethane (1) + piperidine (2): ($\triangle$) from ^{1}H NMR spectroscopy (eq 2); ($\bigcirc$) from calorimetric measurements of mixing enthalpy^{11} (eq 7). Curves are fits of the $\eta_{1,rel}$−x_1 data by the ideal association model (eq 8) with (left) $K_{AB} = 1.70$ and (right) $K_{AB} = 1.47$.

Figure 5. Relative extent of hydrogen bond formation, $\eta_{1,rel}$, as a function of system composition for (left) halothane (1) + tetrahydrofuran (2) and (right) trichloromethane (1) + tetrahydrofuran (2): ($\triangle$) from ^{1}H NMR spectroscopy (eq 2); ($\bigcirc$) from calorimetric measurements of mixing enthalpy^{6,9} (eq 7); ($\square$) from VLE measurements^{14,15} (eq 12). Curves are fits of the $\eta_{1,rel}$−x_1 data by the ideal association model (eq 8) with (left) $K_{AB} = 3.25$ and (right) $K_{AB} = 2.25$.

that appreciable uncertainty can typically occur in H^E-based $\eta_{1,rel}$ values; this uncertainty is therefore shown in Figures 3−5. It can be seen from Figures 3−5 that the dependences of $\eta_{1,rel}(x_1)$ determined from ^{1}H NMR and H^E measurements agree mutually very well. To appreciate the accord, it is worth stressing that the dependence $\eta_{1,rel}(x_1)$ sensitively reflects the nonparabolic nature of $H^E(x_1)$ of the systems in question; the parabolic course

of $H^E(x_1)$, corresponding to the strictly regular solution ($H^E = Ax_1x_2$), is represented in the $\eta_{1,\text{rel}}-x_1$ diagrams by the diagonal line shown. Curves in the diagrams are fits of the $\eta_{1,\text{rel}}-x_1$ data by the ideal association model

$$\eta_{1,\text{rel}} = \frac{K_{AB} + 1}{2K_{AB}x_1}[1 - \sqrt{1 - 4K_{AB}x_1x_2/(K_{AB} + 1)}] \quad (8)$$

Qualitatively, as the deflection of the curve in the $\eta_{1,\text{rel}}-x_1$ diagram from the diagonal line becomes greater, the value of the equilibrium constant of complex formation, K_{AB}, becomes higher.

Equation 6 (or alternatively eq 7 together with eq 2) can serve to predict the complete $H^E(x_1)$ course from ^{1}H NMR chemical shift measurements, if just one point of $H^E(x_1)$ dependence (preferably the infinite-dilution solution enthalpy $\Delta_{\text{sol}}H_1^\infty$) is known. The simple relations linking ^{1}H NMR chemical shifts and H^E data could possibly find a greater use for interpretation of the behavior of complexing mixtures. In this context, we point out that eqs 1−7 are not restricted to the ideal or Flory−Huggins athermal associated solution model. The validity of these relations is more general because no particular model was specified for their derivation. Strictly speaking, the only essential assumption required is the negligibility of the contribution of van der Waals interactions to mixing enthalpy. In fact, eqs 1−7 are not limited to the 1:1 complex formation, but they can be theoretically valid even for the multiple solvation of proton acceptor by the proton donor (n:1 type); in this case, all hydrogen bonds formed between the proton donor and the proton acceptor must be described by uniform values of $\Delta_b H^\circ$ and D_1.

In practice, the derived relations between ^{1}H NMR chemical shifts and H^E can be obeyed quite well in still more complicated situations. An example is provided by the studied mixtures of halothane or trichloromethane with piperidine. Although their dependences of G^E, H^E, and δ_1 on composition would correspond to 1:1 complexation, the S-shape courses of $C_P^E(x_1)$ that we have measured recently indicate a much more complicated association mechanism.

The existence of simple explicit relations between ^{1}H NMR chemical shifts and H^E data provokes a question whether there are similar relations between ^{1}H NMR chemical shifts and vapor−liquid equilibrium (VLE) data. As we have found, the analogous links exist but under more restrictive conditions. Assuming the ideal associated solution model, the activity coefficient of proton donor in a 1:1 complexing mixture is given by

$$\gamma_1 = x_A/x_1 \quad (9)$$

where x_A is the proton-donor monomer mole fraction. This equation can be rewritten in terms of ξ

$$\gamma_1 = \frac{x_1 - \xi}{x_1(1 - \xi)} \quad (10)$$

where ξ is the molar amount of the complex formed per 1 mol of the original mixture, which is closely related to the relative size of the "bound" proton population as follows

$$\xi = x_1\frac{n_1^{(b)}}{n_1} \quad (11)$$

On combining eqs 10, 11, and 1, one reveals that a quantity $G_1 = (1 - \gamma_1)/(1 - \gamma_1x_1)$ is proportional to $\Delta\delta_1$, the proportionality

constant being $1/D_1$. Furthermore, by inserting this result into eq 2, we obtain a straightforward relation to calculate the relative extent of hydrogen bonding from VLE data

$$\eta_{1,\text{rel}} = \frac{1 - \gamma_1}{(1 - \gamma_1^\infty)(1 - \gamma_1x_1)} \quad (12)$$

In Figure 5 for halothane or trichloromethane with tetrahydrofuran, values of $\eta_{1,\text{rel}}$ determined from VLE data[14,15] are plotted along with those from ^{1}H NMR chemical shifts and H^E, and their mutual agreement appears to be very good. Nevertheless, VLE-based $\eta_{1,\text{rel}}$ values should be considered, in general, to be less reliable because eq 12 was obtained under more restrictive assumptions than eqs 2 and 7.

5. Conclusion

In this work, a simple straightforward relation linking ^{1}H NMR chemical shifts and mixing enthalpy has been found for systems with a strong complex formation by hydrogen bonding. Rather than through fitting parameters of a particular model, two forms of this relation have been established only on the assumption that the 1:1 complex formation gives the prevailing contribution to both thermodynamic excess properties and ^{1}H NMR chemical shifts. The first form is represented by proportionality between the solution enthalpy of the proton donor and the chemical shift change of its active hydrogen atom. The second form is mediated by the relative extent of hydrogen bond formation, a quantity which can be directly evaluated from measurements of either the ^{1}H NMR chemical shift or the mixing enthalpy. The validity of both relation forms has been convincingly demonstrated on 12 systems formed by a strong proton and an oxygen- or nitrogen-containing proton acceptor.

Supporting Information Available: Measured changes of ^{1}H NMR chemical shifts, $\Delta\delta_{1,\text{obs}}$, and relative extent of hydrogen bonding, $\eta_{1,\text{rel}}$, for proton donor (1) + proton acceptor (2) mixtures at 298.15 K. This material is available free of charge via Internet at http://pubs.acs.org.

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