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Water and alcohol(s): what's the difference? A proton NMR and DFT study of hetero-association with pyridine

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Hetero-association of water and some simple aliphatic alcohols with pyridine in benzene has been studied by ^{1}H nuclear magnetic resonance (NMR) spectroscopy at very low donor concentration, where self-association is negligible. Association constants for the formation of 1:1 and 2:1 pyridine:water complexes can then be determined without recourse to *ad hoc* computer programmes. That for association of a second pyridine with water is about 10 times lower than for the first. Reaction parameters for the first association with water are very similar to those for the alcohols, whereas the reaction enthalpy for the second association is somewhat smaller. The chemical shift of the OH protons and the H—C—O—H coupling constants for alcohols at high dilution in benzene are almost identical with gas-phase data. The change in chemical shift upon association with pyridine correlates with the free energy of the reaction. Quantum mechanical calculations [BPE0 functional, 6-311+G(d,p) basis set and a polarized continuum model of the solvent (IEFPCM)] have been run on complexes of pyridine with water, both 1:1 and 2:1, and with four alcohols. Calculated reaction enthalpies are in qualitative and, in some cases, almost quantitative agreement with the experimental data. The association constants for 1:1 complexation of pyridine with alcohols follow a rough Taft correlation in terms of polar substituent constants. Substituent size, even in the case of very bulky groups, seems to be unimportant. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Water is the prime example of the importance of hydrogen bonding in determining the structure and properties of molecular species. Recent work sees liquid water as consisting of hydrogen-bonded chains or large rings embedded in a weakly hydrogen-bonded disordered network,[1–4] replacing the conventional view of it as a tetrahedrally coordinated random network.[5] However, regardless of the exact structure, bulk water remains highly self-associated, but this does not prevent it from behaving as a monomolecular species in its interactions with other molecules. Water has obviously two hydrogen bond donor sites and is not infrequently found as a bridging species. A ConQuest search of the Cambridge Crystallographic Data Centre (CCDC) database (ConQuest v. 1.9, CCDC, Cambridge, UK) reveals about 160 crystallographic structures where water is in most cases hydrogen-bonded to two or three oxygens in crown ethers or linear polyethers, often in association with metal ions complexed by other ligands as well as the bridging water molecule. Structures where nitrogen atoms are the acceptors are somewhat less common but the same database contains about 80 such species, of which some 10% involve two sites in the same molecule.

The association of water with hydrogen bond acceptors, such as aza-heterocycles, in particular pyridine, has been a subject of continued interest for over 80 years. A wide variety of techniques, including infrared (IR) and Raman spectroscopy,[6–36] solution thermodynamics,[37–46] calorimetry[47–51] and others,[52–54] has been applied to binary mixtures and to solutions of the donor and the acceptor in an inert solvent. The fundamental datum established by IR spectroscopic[7,10,15] and solubility[41] studies is that complexes with a 1:1 and 2:1 ratio of base to water are formed. The 2:1 complex has also been postulated in the context of studies on the calorimetry[50] and compressibility[52] of dilute solutions of water in pyridines. In systems containing substantial amounts of water, species consisting of pyridine associated with two or more solvent molecules become important.[21,35,41]

Organic solvents used in nuclear magnetic resonance (NMR) spectroscopy generally contain traces of adventitious water.[55] This means that when association constants are measured by the NMR titration method in a nominally dry solvent, even when stored over molecular sieve, a water peak is always present alongside those of the product under study. This is no problem provided that the amount of water remains small and that it is not strongly associated with the product. The present work takes advantage of this water at very low concentration to re-investigate its hetero-association with pyridine in benzene.

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For comparison, some small aliphatic alcohols are also studied under the same conditions. Quantum mechanical calculations have been performed on 1:1 and 2:1 pyridine–water complexes as well as on some pyridine–alcohol complexes.

RESULTS AND DISCUSSION

NMR titration of water and alcohols: hetero-association constants

The chemical shift of the OH proton, δ_{OH}, of an alcohol associated with pyridine is given by Eqn (1):[56,57]

$$\delta_{OH} = \delta_M + \frac{(\delta_{Mpy} - \delta_M)}{2[M]_0}\{B - (B^2 - 4[M]_0[py]_0)^{1/2}\} \qquad (1)$$

with $B = [M]_0 + [py]_0 + 1/K$, where K is the association constant, $[M]_0$ the analytical alcohol concentration, $[py]_0$ that of pyridine, and δ_M and δ_{Mpy} the chemical shifts of the OH proton in the free alcohol and in the pyridine-complexed alcohol, respectively. In order to minimize the effect of self-association, measurements were made at very low alcohol concentration. However, under these conditions, that of pyridine will always be much greater, and it is possible to simplify Eqn (1) by assuming that the amount of pyridine associated with the alcohol is negligible compared to the overall pyridine concentration, to give Eqn (2), which is independent of $[M]_0$:

$$\delta_{OH} = \delta_M + K[py]_0 \frac{(\delta_{Mpy} - \delta_M)}{1 + K[py]_0} \qquad (2)$$

This equation gives the same values of K, δ_M and δ_{Mpy} as the more exact treatment. In both cases, these are determined by fitting the experimental values for δ_{OH} to $[py]_0$ {and $[M]_0$ in the case of Eqn (1)} by means of the non-linear least-squares curve-fitting option of the Origin programme (Microcal Software Inc., now OriginLab Corporation, One Roundhouse Plaza, Northampton, MA01060, USA), which uses the Levenberg–Marquardt algorithm. The zero-point in the titration ($[py]_0 = 0$) is not used, since this reflects the extent to which the alcohol is self-associated or associated with residual water, though the calculated δ_M is generally close to the shift value in the absence of pyridine.

Hetero-association constants at 298 K and the reaction enthalpies and entropies, ΔH° and ΔS°, for some alkanols and benzyl alcohol, based on data at 298–348 K, and for methanol at 278–338 K, are given in Table 1. Full details are given in the Supplementary Material Tables S1–S8. The parameters cover very small ranges, 0.9 kcal mol^{-1} (1 cal = 4.184 J) for ΔH° and 3 cal mol^{-1} K^{-1} for ΔS°, rather smaller than those found by IR spectroscopic measurements on propanols and butanols in carbon tetrachloride,[58] where association constants are slightly higher.

If water is assumed to form only a 1:1 complex with pyridine, Eqns (1) and (2) must be modified, since we now have:

$$2[M]_0\delta_{OH} = 2([M]_0 - [Mpy])\delta_M + [Mpy](\delta_N + \delta_{Mpy})$$

where $[M]_0$ is now the analytical concentration of water, Mpy is 1:1 pyridine-complexed water, the chemical shift of the non-associated proton of water being denoted δ_N, and that of the associated proton δ_{Mpy}. This leads to Eqns (1a) and (2a) developed in the Supplementary Material. It is not possible to determine δ_N and δ_{Mpy} separately, only their sum, and application of these equations to the water data leads to absurd values of $(\delta_N + \delta_{Mpy})$ and δ_M, as do the simpler, but equivalent equations [Eqns (1b) and (2b) in the Supplementary Material] where it is assumed that $\delta_N = \delta_M$ (*i.e.* association of one proton does not affect the chemical shift of the non-associated proton). Neither gives a good fit for the variation of the NMR OH shift of water. We consider, therefore, that there are two equilibria involving pyridine and water, where:

$$\begin{aligned} &M + py \rightleftharpoons Mpy && K_1 = [Mpy]/[M][py] \\ &Mpy + py \rightleftharpoons Mpy_2 && K_2 = [Mpy_2]/[Mpy][py] \\ &\text{and}: [M]_0 = [M] + [Mpy] + [Mpy_2] && \end{aligned}$$

Table 1. Equilibrium constants and OH proton chemical shifts for hetero-association of water and alcohols with pyridine in benzene at 298 K; reaction enthalpies and entropies (at 298–348 K unless stated)

Cpd.	δ_M/ppm	δ_{Mpy}/ppm	K/molar scale	ΔH°/kcal mol^{-1}	ΔS°/cal mol^{-1} K^{-1}
NeopOH[a]	0.666 ± 0.007	6.26 ± 0.02	1.42 ± 0.01	-4.22 ± 0.04	-13.5 ± 0.1
Et_2CHOH	0.674 ± 0.013	6.03 ± 0.07	0.632 ± 0.019	-4.26 ± 0.05	-15.1 ± 0.2
t-BuOH[b]	0.591 ± 0.014	5.85 ± 0.07	0.787 ± 0.025	-3.65 ± 0.03	-12.7 ± 0.1
i-BuOH[c]	0.521 ± 0.008	6.26 ± 0.03	1.34 ± 0.02	-4.25 ± 0.05	-13.6 ± 0.2
i-PrOH[d]	0.571 ± 0.011	5.98 ± 0.04	1.02 ± 0.02	-3.64 ± 0.05	-12.2 ± 0.2
EtOH	0.407 ± 0.004	6.05 ± 0.01	1.22 ± 0.01	-3.84 ± 0.07	-12.5 ± 0.2
MeOH[e]	-0.019 ± 0.008	5.90 ± 0.02	1.53 ± 0.02	-4.37 ± 0.05	-13.8 ± 0.1
BzOH	0.775 ± 0.016	6.95 ± 0.04	2.46 ± 0.04	-4.54 ± 0.09	-13.4 ± 0.3
Water[e]	0.353 ± 0.009	5.73 ± 0.02	2.33 ± 0.03 (K_1)	-4.11 ± 0.11	-12.2 ± 0.4
Water[f]	0.353 ± 0.009	5.73 ± 0.02[g]	0.201 ± 0.005 (K_2)	-3.47 ± 0.11	-14.9 ± 0.3

[a] 2,2-Dimethylpropan-1-ol.

[b] 2-Methylpropan-2-ol.

[c] 2-Methylpropan-1-ol.

[d] Propan-2-ol.

[e] 1:1 complex; reaction parameters at 278-338 K.

[f] 2:1 complex: reaction parameters at 278–338 K.

[g] $\delta_{Mpy} = \delta_{Mpy2}$.

Mpy$_2$ is 2:1 pyridine-complexed water with OH shift δ_{Mpy2}. Shifts δ_M, δ_N and δ_{Mpy} are defined above. We have then:

$$2[M]_0\delta_{OH} = 2[M]\delta_M + [Mpy](\delta_N + \delta_{Mpy}) + 2[Mpy_2]\delta_{Mpy2}$$

As above, taking $[py]_0$ as the free pyridine concentration, and making the same assumption as for Eqn (2), we obtain Eqn (3):

$$\delta_{OH} = \frac{(2\delta_M + K_1[py]_0(\delta_N + \delta_{Mpy}) + 2K_1K_2[py]_0^2\delta_{Mpy2})}{2(1 + K_1[py]_0 + K_1K_2[py]_0^2)} \qquad (3)$$

However, when five parameters [K_1, K_2, δ_M, $(\delta_N + \delta_{Mpy})$ and δ_{Mpy2}] are optimized the van't Hoff plots are poor, and the ΔH° values (Supplementary Material Table S9) are not supported by previous work[15,16,47–49] or DFT calculations (see below). We assume then that $\delta_N = \delta_M$ and that $\delta_{Mpy2} = \delta_{Mpy}$ (*i.e.* association of the second proton does not affect the chemical shift of that already complexed, and the shift of the second associated proton is the same as that of the first), and optimize only four parameters (Table 1 and Supplementary Material Table S10) in Eqn (4):

$$\delta_{OH} = \frac{(2\delta_M + K_1[py]_0(\delta_M + \delta_{Mpy}) + 2K_1K_2[py]_0^2\delta_{Mpy})}{2(1 + K_1[py]_0 + K_1K_2[py]_0^2)} \qquad (4)$$

This is equivalent to the 'two-state approximation' commonly used in the treatment of molecular clusters of water or alcohols: only free and bonded OH groups are distinguished.[59]

The association constant K_1 at 298 K, 2.3 (all association constants are on the molar scale, standard state 1 M), is in full agreement with the value of 2.3 determined by solubility studies,[41] but K_2 (0.2) is substantially lower than the rather ill-defined value of 1.2 ± 0.9.[41] Good linear van't Hoff plots are obtained for both K_1 and K_2, with ΔH° −4.1 and −3.5 kcal mol^{-1}, respectively, the corresponding ΔS° values being −12.2 and −14.9 cal mol^{-1} K^{-1}. The over 10-fold difference in the first and second association constants is therefore almost equally shared between the enthalpy and entropy terms. The reaction enthalpy for the first association is consistent with the previous values of -4.1 ± 0.4 kcal mol^{-1} from IR spectroscopy[15] and −3.9 and −4.3 kcal mol^{-1} from calorimetry,[47–49] and is slightly below the gas-phase IR spectroscopic value of -4.7 ± 0.5 kcal mol^{-1}.[16]

Figure 1 shows the variation of the mole fraction of the different species present in solution as the pyridine concentration is raised from 0 (neat benzene) to 12.4 M (neat pyridine) at 298 K.

The 1:1 and 2:1 hetero-association constants for water with pyridine, about 2.3 and 0.2 at 298 K, are higher and lower, respectively, than for any alkanol investigated here. Only for benzyl alcohol it is higher than the 1:1 water association constant. The range of values for pyridine hetero-association with aliphatic alcohols is very small, the lowest values previously reported being around 0.3 for the 2,2,4,4-tetramethyl-3-alkylpentan-3-ols, **1c, d** and **f**.[60] The hetero-association constant for *tert*-butanol with pyridine, about 0.78 at 298 K, is only twice that for 2,2,4,4-tetramethyl-3-(*tert*-butyl)pentan-3-ol, **1e**, where each methyl group has been replaced by a *tert*-butyl, 0.4.[60]

R(*t*-Bu)$_2$COH **1** (**a:** R = H; **b:** Me; **c:** Et; **d:** *i*-Pr; **e:** *t*-Bu; **f:** neopentyl)

Chemical shift changes and association constants

The chemical shifts of the OH protons of aliphatic alcohols, including those of this study and the more encumbered ones of a previous study,[60] do not have any simple rationale. Gauge-including atomic orbital (GIAO) calculations have been applied to ethanol,[61] and magnetic shieldings for ^{1}H, ^{13}C and ^{17}O in methanol have been compared with the theoretical calculations.[62] An extensively parametrized modified neglect of diatomic overlap (MNDO) approach, including several simple alkanols, has been published.[63] The quantum cluster equilibrium (QCE) method has been used to investigate the self-association of some liquid alcohols and to explain the concentration and temperature dependence of the OH proton NMR shift.[64–69] The extended real-associated solution (ERAS) model has been applied to butanol–cyclohexane and *n*-butanol–pyridine mixtures.[70]

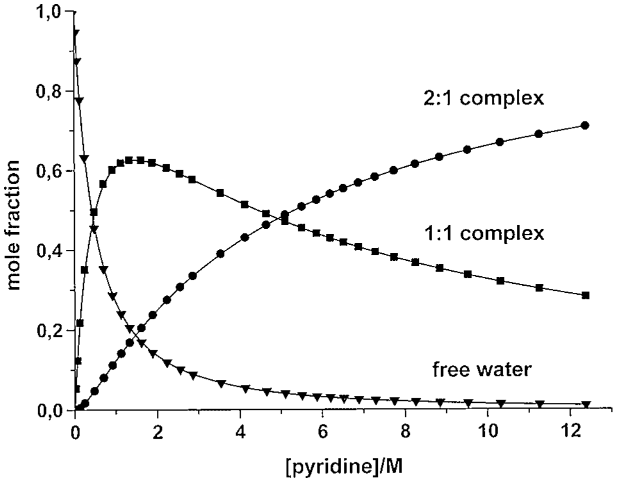

Figure 1. Distribution of free water, and 1:1 and 2:1 pyridine–water complexes in benzene at 298 K as a function of pyridine concentration

The more encumbered alcohols have δ_M values of about 1 ppm, whereas the less bulky ones range down from about 0.7 ppm for neopentanol to −0.02 ppm for methanol (Supplementary Material Table S11). Water, with a δ_M of 0.35 ppm at 298 K, lies roughly in the middle of this range. If we assume that it is present only as monomer and dimer at 4×10^{-3} M concentration in benzene at 298 K, where the shift is 0.385 ppm, and that δ_D, the dimer shift, is 5 ppm, we obtain a plausible self-association constant of about 1, which means that about 0.8% is in dimer form (or less if δ_D is higher). In this respect NMR is more sensitive than vibrational spectroscopy.[71,72]

For all the alcohols previously investigated in a gas-phase study at 100 torr and 422 K[73] there is a good correlation (correlation coefficient, $r = 0.9885$; slope: 0.98 ± 0.05) between the OH proton chemical shifts and those measured in benzene at very low concentration, or extrapolated to zero concentration, at 298 K (δ_M values have been supplemented with high-dilution values for some alcohols; there are no gas-phase data for Et$_2$CHOH). The H—C—O—H coupling constants are also very similar in the two studies. The high-dilution chemical shifts tend to be slightly lower than the gas-phase values, especially for primary alcohols and water. More detailed studies of water[74] and methanol[62] diluted with fluoromethanes in the gas phase give much higher values at 300 K than those reported by Chauvel and True.[73]

Hydrogen bonding of the OH or NH proton to an acceptor is associated with an increase in shift, to δ_{Mpy} in the present case, but the magnitude of this change does not appear to have received much attention. On the basis of the available data for 22 alcohols [(i) six bulky alcohols and (ii) eight 2,2,4,4-tetramethyl-3-arylpentan-3-ols, Ar(*t*-Bu)$_2$COH, all from

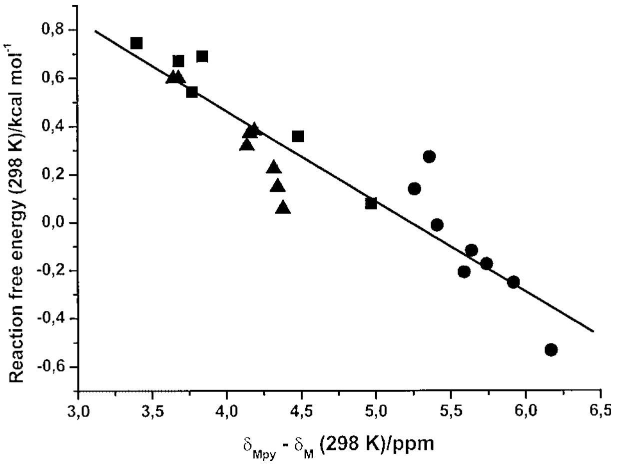

Figure 2. Relationship between reaction free energy (298 K) and change in OH proton chemical shift in hetero-association: ● this work; ■ **1a–f**, Reference 60; ▲ aromatics, Reference 60

our previous work[60] and (iii) the seven alkanols and benzyl alcohol from the present study] a plot of ΔG° (298 K) against $\delta_{Mpy}-\delta_M$ (298 K) ($\Delta G^\circ = -RT\ln K$) gives a roughly linear correlation ($r = 0.9302$) with slope, -0.38 ± 0.03 kcal mol^{-1} ppm^{-1}, the reaction free energy increasing with the magnitude of the change in the chemical shift of the OH proton (Fig. 2). It should be noted, however, that each set can be taken separately to give correlations for (i) -0.42 ± 0.05 kcal mol^{-1} ppm^{-1} ($r = 0.9691$); (ii) -0.64 ± 0.09 kcal mol^{-1} ppm^{-1} ($r = 0.9444$) and (iii) -0.76 ± 0.12 kcal mol^{-1} ppm^{-1} ($r = 0.9273$). There is *a priori* no reason why the different types of alcohol should show the same relationship between hydrogen bond strength and the chemical shift change.

The reaction free energy is a more reliable experimental parameter than the reaction enthalpy and entropy, which are subject to greater errors, but the hydrogen bond strength (E_{HB}) which is calculated by quantum mechanics (see below) is closer to the reaction enthalpy, ΔH°. For the eight alcohols studied in the present work, the correlation of ΔH° is poorer than that of ΔG° ($r = 0.7588$) and the slope is higher (0.85 ± 0.30 kcal mol^{-1} ppm^{-1}). This difference is in part explained by the $T\Delta S^\circ$–ΔH° correlation of slope 0.56 ± 0.23 ($r = 0.7005$), which means that ΔH° varies more than ΔG°, the variations in ΔH° being attenuated by those in ΔS°.

Comparable data are hard to find, but for the self-association of six alkanols in carbon tetrachloride,[60] again at 298 K, there is a remarkably similar correlation between ΔG° and $\delta_D - \delta_M$, where δ_D is the shift of the dimer ($r = 0.8961$; slope $= -0.36 \pm 0.09$ kcal mol^{-1} ppm^{-1}). The variation of the association constant for a given acceptor with a range of hydrogen bond donors is therefore apparently related to the change in the chemical shift of the hydrogen-bonded proton. A qualitative explanation would be that the higher reaction free energy correlates with a strengthening of the hydrogen bond, that the hydrogen bond length decreases, the hydrogen atom is deshielded, and this results in a downfield change in the shift of the hydrogen-bonded proton.

Hartree-Fock, Møller-Plesset and DFT calculations on formic acid–formate anion and enol–enolate anion association show that hydrogen bond length and hydrogen bond strength are closely related, and give an excellent correlation between hydrogen bond strength and the predicted NMR shift of the hydrogen-bonded proton, with an average gradient of -1.5 kcal mol^{-1} ppm^{-1}.[75] For other classes of compounds, gradients of -0.9 and -1.7 kcal mol^{-1} ppm^{-1} are found.[76] While it is impossible to compare experimental (solution) and theoretical (gas-phase) data on such different systems, the calculations nevertheless support our finding of a correlation between the association constant and the change in the chemical shift (or the chemical shift itself) of the proton which is associated.

Density functional theory (DFT) calculations on pyridine–water and pyridine–alcohol complexes

Hydrogen bonding between aza-heterocycles and water to form 1:1 complexes has been the subject of many quantum mechanical and other theoretical calculations of various degrees of sophistication,[24–31,33,35,77–92] but other complexes have attracted little attention.[33]

There is general agreement between the various calculations that in the 1:1 complex the water molecule lies perpendicular to the plane of the pyridine, and that the hydrogen-bond angle, N. . .H—O, is close to 180° [C_s(perp) symmetry]. Nevertheless, there are considerable variations in the N. . .H distance and in the interaction energies, ΔE. Gas-phase values listed by Cai and Reimers[87] range from -4.5[78] to -8.2[80] kcal mol^{-1}; their own results range from 5.6 to 7.0 kcal mol^{-1}, after basis set superposition error (BSSE)[93] but not zero-point vibrational energy (ZPE) and thermal corrections. The most recent calculations[92] at the B3LYP/6-31+G** level give a value of 6.4 kcal mol^{-1}.

We have calculated reaction enthalpies, ΔH°, for the 1:1 and 2:1 complexes of pyridine and water, as well as for two alcohols corresponding almost to the extremes of the range of association constants, methanol and *tert*-butanol (Table 2). It is

Table 2. Electronic energies and enthalpies of reaction for pyridine with water and selected alcohols (kcal mol^{-1})

	Water 1:1		Water 2:1		Methanol		*tert*-Butanol		Neopentanol		Benzyl alcohol	
Reaction	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent
ΔE (0 K)	−7.47	−6.16	−5.00	−4.05	−7.48	−6.17	−6.72	−5.26	−7.44	−5.77	−8.32	−6.70
ΔE (0 K) + ZPE	−5.69	−4.19	−3.88	−2.72	−6.32	−4.82	−5.60	−3.94	−6.48	−4.60	−7.36	−5.55
ΔH°(298 K)	−5.85	−4.42	−4.61	−2.92	−5.97	−4.52	−5.15	−3.51	−6.00	−4.16	−7.44	−5.11
ΔH° + BSSE	−5.29		−4.00		−5.35		−4.57		−5.46		−6.77	

convenient that the alkyl groups in these cases have simple C_{3v} symmetry, making the search for the most stable configurations that much easier. Benzyl alcohol is of special interest, since this is the only group in our study which is an electron-acceptor, whereas all the aliphatic groups are electron-donors. The calculations were run at the PBE0/6-311+G(d,p) level[94–97] with or without the solvent effect. The solvent, benzene, was represented by the integral-equation-formalism polarizable continuum model (IEFPCM).[98] The effect of the solvent, whose calculated contribution is mainly electrostatic in origin, is to weaken the interaction by about 1.6 kcal mol^{-1}, but at the same time to reduce the hydrogen bond length by 0.03–0.04 Å. Both the reactants and the association complex are stabilized by the solvent, but the reactants more than the complex, resulting in a diminution of the reaction enthalpy.

The gas-phase interaction energy for the 1:1 complex with water is about 1 kcal mol^{-1} lower (in absolute magnitude) than in the most recent study,[92] while the values for methanol and *tert*-butanol are about 0.4 kcal mol^{-1} higher than has been reported, or 0.2 kcal mol^{-1} lower and 0.9 kcal mol^{-1} higher, respectively, depending on which method is considered (B3LYP or MP2).[99]

The reaction enthalpies calculated for the formation of the two complexes of pyridine with water, and including the solvent effect, agree well with what is observed, except that the calculations slightly exaggerate the difference, the magnitude for the 1:1 complex being slightly too great (-4.42 as against -4.11 kcal mol^{-1}) and that for the 2:1 complex too small (-2.92 as against -3.47 kcal mol^{-1}). The calculations on benzyl alcohol, methanol, neopentanol and *tert*-butanol also correctly reproduce the differences in the experimental values, decreasing (in absolute magnitude) in the order given (-5.11, -4.52, -4.16 and -3.51 kcal mol^{-1}, respectively), while the corresponding experimental ΔH° values are -4.54, -4.37, -4.12 and -3.65 kcal mol^{-1}. For the last three alcohols, the agreement between the experimental and theoretical data is remarkably good. More important, however, than the numerical match, which could be in part fortuitous, is the very good correlation (Fig. 3) between experimental and calculated ΔH° values ($r = 0.9800$; gradient $= 0.52 \pm 0.05$). This indicates that the calculations tend to overestimate the overall variation in the reaction enthalpies.

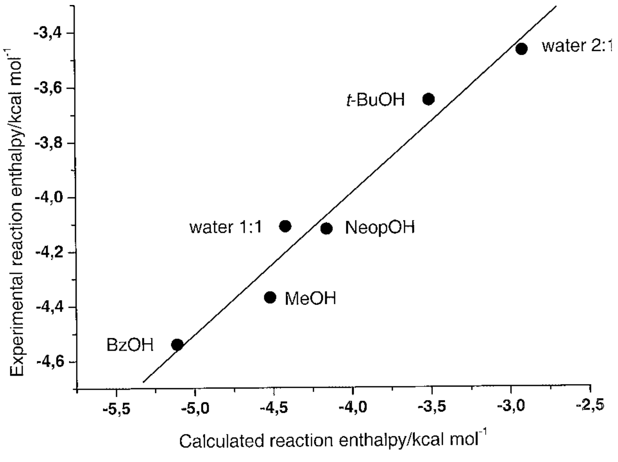

Figure 3. Correlation of experimental reaction enthalpies for association of water and alcohols with pyridine versus DFT-calculated values

The geometry calculated for the solvated 1:1 complex of water in the gas phase is consistent with the results of previous studies, though the H...N bond distance of 1.909 Å is rather shorter than previous estimates of 1.93 Å,[31,35,82] 1.94 Å[33] and 1.94–2.14 Å.[87] The H...N bond distances for the solvated alcohol complexes correlate qualitatively with the reaction enthalpies, falling from 1.905 Å for *tert*-butanol to 1.867, 1.859 and 1.831 Å for neopentanol, methanol and benzyl alcohol, respectively. Analogous bond length or hydrogen-bond distance correlations have been reported for the association of pyridines with water.[30,31] For the 1:1 complex with water in benzene, the hydrogen bond length (1.873 Å) is close to that for neopentanol but the 2:1 complex has two much longer hydrogen bonds at about 1.95 Å. The gas-phase value for the 2:1 complex is about 1.98 Å, again shorter than in previous calculations, 2.02 Å.[35] This complex is almost symmetrical with respect to the positions of the pyridines relative to the water molecule in the gas phase (*cf.* Reference[35]) but much less so when solvated, the major difference lying in the torsion angles about the O—H...N—C bonds, which are 133° and 119°, whereas the values for all the 1:1 complexes are close to 90°.

Analysis of the changes in charge distribution on the various atoms involved in hydrogen bonding does not give a very clear picture of the relationship between charge and hydrogen bond energy. The increase in the negative charge on the pyridine nitrogen tends to correlate with the calculated reaction enthalpy, being greater for water (1:1 complex), benzyl alcohol, methanol and neopentanol, in that order, than for *tert*-butanol, but the charge distribution on the oxygen and hydrogen atoms follows no discernable pattern. The relationship between the overall increase in the positive charge, ΔR^+, on the alcohol or water and the reaction enthalpy is rather simpler. When the second pyridine is associated with the 1:1 water complex the charge on the first pyridine goes from -0.039 to -0.030 but this is accompanied by electron transfer to the second pyridine which goes to -0.033. The total charge on the water molecule, 0.063, can be considered as associated with the sum of the two reaction enthalpies, -7.34 kcal mol^{-1}. With the other data this gives a correlation of the form: $\Delta H^\circ = -0.64 - 100 \times \Delta R^+$ ($r = 0.9596$). Full details are given in Supplementary Material Tables S12–13.

Polar and steric substituent factors

Quantum mechanical calculations do not answer the classical question: are the variations in the association constants due to polar, steric and/or hyperconjugative factors? The fact that the variation is very small makes it hard to explain. The much greater variations in the acidity of aliphatic alcohols in the gas phase have been discussed in terms of dipolar, polarizability and hyperconjugation effects, while in aqueous solution solvation effects are all- important.[100–106] In the present case, the differences can be analysed in terms of Taft's two-parameter equation, which distinguishes the polar and steric effects of alkyl groups.[107] Hancock-type parameters derived from Taft steric constants by means of a hyperconjugative correction term have been shown to be unnecessary.[108]

Although the gas-phase acidities clearly show that methyl groups, for instance, stabilize anions, the Taft parameters rank alkyl groups as electron-donors.[107] Replacement of the hydrogens in methanol by alkyl groups would, according to

Taft's model, tend to reduce the acidity of the OH proton, and therefore make it less prone to hydrogen bond. On the other hand, the larger alkyl groups might be expected to reduce the association constants slightly, due to their steric effect. Both lines of reasoning predict the same trend, that which is observed, for the *t*-BuOH, *i*-PrOH, EtOH, MeOH series, where the E_s and σ^* parameters are correlated. For the very bulky alcohols, **1a-f**, examined in a previous study,[60] there are no σ^* parameters and only one experimentally determined E_s value (strictly speaking, E_s', a revised steric parameter),[109,110] −6.97, for the 2,2,4, 4-tetramethylpent-3-yl group of **1a**, for which a polar constant of −0.33 has been calculated by an additive procedure (see Supplementary Material for Discussion and Table S14). Including **1a** with 2,2-dimethylpropan-2-ol (NeopOH), 2-methylpropan-2-ol (*i*-BuOH), pentan-3-ol (Et_2CHOH), benzyl alcohol (BzOH) and the four alcohols named above gives a poor correlation ($r = 0.7978$) with reaction constants of 1.03 ± 0.24 and −0.01 ± 0.02 for σ^* and E_s', respectively. The correlation is slightly different but no better without alcohol **1a** ($r = 0.7983$; reaction constants: 0.95 ± 0.29 and 0.03 ± 0.06, respectively). This means that electron-donating substituents disfavour association, while bulky substituents hardly affect it. In fact, a better correlation ($r = 0.8862$), including **1a**, is obtained with σ^* alone (reaction constant: 0.94 ± 0.19). To include previous data on highly hindered alcohols, tentative polar substituent constants have also been calculated for the bulky alkyl groups in **1b–f**. The association constants of the six alcohols, **1a–f**, are roughly correlated ($r = 0.7941$) but give a rather higher reaction constant (2.67 ± 1.02) than the smaller alcohols. This may indicate that steric effects are significant at this level of congestion (no E_s or E_s' values are available), as was suggested by molecular mechanics calculations (MMFF94 force field).[60] These calculations were, however, on the whole rather unsatisfactory, and the introduction of the less encumbered alcohols results in a scatter plot (not shown). A better approach is to ignore steric effects altogether and to correlate the entire set with σ^* alone; this gives the best correlation of all ($r = 0.9263$) with a reaction constant of 1.32 ± 0.15 (Fig. 4).

This should not be taken as a general conclusion to the effect that steric effects on the hetero-association of pyridines are always small. Calorimetric[51] and compressibility[52] studies on the association of methanol and *tert*-butanol with *ortho*-substituted pyridines show clear steric effects.

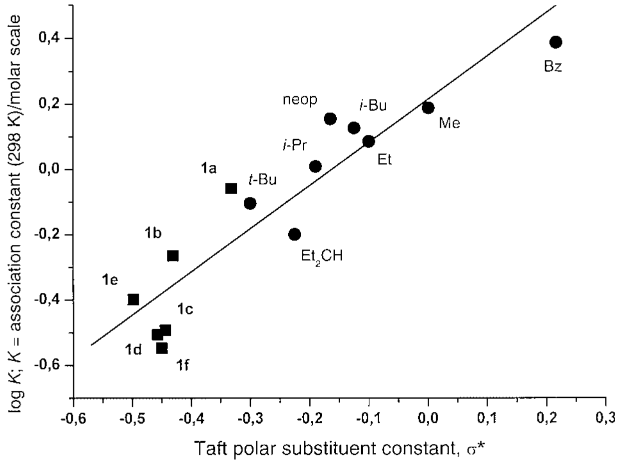

Figure 4. Correlation of association constants [log K(298 K)] with Taft's polar substituent constants, σ^*. ● this work; ■ **1a–f**, Reference 60

CONCLUSION

Compared to the vast amount of work which has been and continues to be devoted to every aspect of the association of water with nitrogen-based acceptors, little has been performed on that of alcohols, only a few fragmentary studies,[49,58,99,111–120] and one devoted entirely to highly congested alkanols,[60] which could be atypical. The debate as to whether water is, as a proton-donor, like phenol or alcohols was never pursued.[13,46]

The present work shows that the hetero-association of water with pyridine in benzene, when the amount of water is vanishingly small, can be described in terms of 1:1 and 2:1 pyridine:water complexes, the association constant for the latter being about 10 times less than that of the former. Under the conditions of this study, self-association of water is unimportant and the question of higher hydrates of pyridine with the possibility of cooperative hydrogen bonding does not arise. In the case of the monohydric alcohols, for the same reasons, only 1:1 complexes with pyridine need to be considered. For the 1:1 association of water with pyridine, the association constants, as well as the reaction enthalpy and entropy are very similar to those for aliphatic alcohols. DFT calculations with a continuum solvent model give reaction enthalpies in remarkably good agreement with experimental values for both complexes of water, and for the 1:1 complexes of methanol, *tert*-butanol, neopentanol and benzyl alcohol. Analysis of available data on the association of pyridine with alcohols by the Taft polar and steric parameter approach suggests that polar effects are much more important than steric factors, even when highly hindered substituents are considered.

EXPERIMENTAL

General

Alcohols were high-purity commercial samples used as received. Deuteriated benzene (99.6% D, Euriso-top) and pyridine (99.5% D, Euriso-top) were stored over molecular sieve. All ^1H NMR spectra (see Supplementary Material for ^1H NMR spectra of dilute solutions of alcohols and water in benzene at 298 K) were recorded on a Bruker AC 200 with a spectral resolution of 0.001 ppm/point, and are referenced to internal tetramethylsilane (TMS) at 0.000 ppm.

Determination of association constants

Samples were prepared by mixing appropriate amounts (total volume: 0.5–1 ml) of deuteriated pyridine and benzene in an NMR tube, together with 1 μl of cyclohexane and a trace of TMS. The water (considered as H_2O) concentration, determined by the integration of the cyclohexane and water signals in the ^1H NMR spectrum, varied typically from 4×10^{-3} to 14×10^{-3} M as pyridine was added, and was 5–5000 times less than that of pyridine. Alcohols [concentration, $(2–5) \times 10^{-3}$ M] were introduced directly by means of a microsyringe or in solution in cyclohexane (*t*-BuOH, NeopOH). In calculating pyridine concentrations, allowance was made for the cubical expansion of the solvents with temperature. Shifts of the OH protons were measured at 278–348 K. The NMR data were processed using Eqns (1–4). For the alcohols, values of K, δ_M and δ_{Mpy} in Eqn (1) were determined by fitting the experimental values of δ_{OH} to those of $[py]_0$; Eqn (2) gave exactly the same results. Full details are given in Supplementary Material Tables S1–S8. For water, Eqn (4) was used. (Supplementary Material Table S10).

DFT calculations

All calculations were carried out using the Gaussian 03 suite of programmes.[121] The geometry of each species was optimized in the framework of DFT using the PBEPBE1 (PBE0)[94,95] functional and 6-311+G(d,p) basis set. This parameter-free functional is based on the Perdew-Burke-Ernzerhof pure functional,[96] in which the exchange is weighted (75% DFT/25% HF) according to a theoretical rationale,[97] *i.e.* absolutely no experimental input has been used to design PBE0. For those molecules or complexes which have more than one possible conformation, the conformation with the lowest electronic energy was singled out and used for the subsequent calculations. Harmonic frequency calculations were carried out to characterize the overall minimum of each optimized geometry and to determine the ZPEs and thermal vibrational corrections to the enthalpy, ΔH° (298 K). BSSE was calculated for the hydrogen bonding energy using the full counterpoise procedure.[93]

To model bulk solvent effects, a continuum description of the solvent based on the self-consistent reaction field (SCRF) method at the PBE0/6-311+G(d,p) level was used. The polarized continuum model (IEFPCM) developed by Tomasi *et al.*[98] was employed.

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