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Self- and hetero-association of sterically hindered tertiary alcohols

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ABSTRACT: Self-association constants for 2,2,4,4-tetramethyl-3-alkylpentan-3-ols are so small as to be negligible in comparison with hetero-association constants for the same alcohols with a moderately strong base. Equilibrium constants were determined by the NMR titration method for the hydrogen bonding association of this and two other series of sterically hindered alcohols with pyridine, in benzene as solvent. Steric effects are small even when the 3-alkyl substituent is very bulky. The acidity of the OH hydrogen in 2,2,4,4-tetramethyl-3-phenylpentan-3-ols increases slightly with the electron-withdrawing ability of the *para* substituent (Hammett reaction constant, 0.3). The *syn* rotamer of a 2-methyl derivative, where the methyl and OH groups are close, has a lower association constant than the *anti* rotamer. In the case of 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols a second approach, based on the variation of the *syn*/*anti* ratio with the pyridine concentration, gives results concordant with those of the NMR method. The association constants predict accurately *syn*/*anti* ratios and *syn* OH proton chemical shifts in neat pyridine. The unusually large temperature coefficients of OH proton shifts in pyridine are due in part to the variation of the association constant. Copyright © 2005 John Wiley & Sons, Ltd.
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KEYWORDS: alcohols; pyridine; NMR; association constants; rotamers

INTRODUCTION

Non-covalent interactions underlie all aspects of supramolecular chemistry, including molecular recognition, host–guest chemistry and self-assembly, of both synthetic and natural, especially *in vivo*, systems.[1] One such interaction, hydrogen bonding,[2] has attracted particular attention because of its ubiquity, magnitude, specificity and directionality. Physicochemical investigation of self-association and hetero-association due to hydrogen bonding in rather simple systems involving small molecules dates back to the 1930s, and a very wide variety of donors and acceptors has been studied, mainly by IR spectroscopy and calorimetry, but also by NMR spectroscopy and many other techniques. In particular, numerous IR and calorimetric studies have been devoted to the association of alcohols and phenols as hydrogen bond donors with a wide range of acceptors.[3–7] Much of this work related to the once controversial topic of the Badger–Bauer relation,[8] i.e. the relationship between enthalpies of hydrogen bond formation, $-\Delta H^\circ$, and the change in the OH stretching frequency upon hydrogen bonding, $\Delta\nu$. This work has been reviewed[9] and references to further studies will be found in more recent reports.[10] The self-association of alcohols is another long-standing research topic, to which NMR was applied even in its infancy,[11] and questions regarding the existence of dimers, trimers, tetramers, etc., and concerning the open and/or cyclic structure of these species have been much investigated.[12–21]

Steric effects on hydrogen bonding have been discussed almost exclusively in the context of *ortho* substitution in phenols.[22–27] However, the hetero- and self-association of 2,2,4,4-tetramethylpentan-3-ol [di(*tert*-butyl)methanol], **1a**,[28–31] and, to a lesser extent, of a few other more or less sterically hindered aliphatic alcohols has been investigated.[32–35] There are scattered reports on the self-association of 3-substituted 2,2,4,4-tetramethylpentan-3-ols but no systematic study of their hetero- or self-association. 2,4-Dimethyl-3-ethylpentan-3-ol is reported to be weakly self-associated,[33] whereas 2,2,3,4,4-pentamethylpentan-3-ol, **1b**, is very slightly[28] and 2,2,4,4-tetramethyl-3-isopropylpentan-3-ol, **1d**, not at all according to some workers,[32–34] while another group finds evidence for a monomer–dimer equilibrium.[36] Alcohol **1e** is a monomer in the solid state[37] and can therefore be presumed to be a monomer in solution also. Early NMR studies[7,14] indicated that association constants for the hydrogen bonding of **1d** and 2,4-dimethyl-3-ethylpentan-3-ol with various

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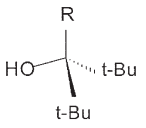
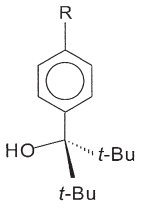
donors are low, although the $-\Delta H^{\circ}$ values are normal. In other systems also variations in association constants have been related in part or predominantly to changes in the reaction entropy.[23,25,38]

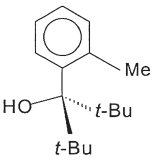


1a: R = H
1b: R = Me
1c: R = Et
1d: R = i-Pr
1e: R = t-Bu
1f: R = neoPen

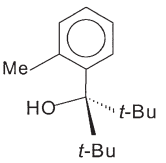
In a search for polar and steric effects on hydrogen bonding in sterically hindered alcohols by ^{1}H NMR we have now re-examined some 2,2,4,4-tetramethyl-3-alkylpentan-3-ols, **1**, and extended this study to substituted 2,2,4,4-tetramethyl-3-phenylpentan-3-ols, [aryldi(*tert*-butyl)methanols], **2**,[39–41] and 2,2,4,4-tetramethyl-3-(2-thienyl)-pentan-3-ols, {2-[di(*tert*-butyl)hydroxymethyl]thiophenes}, **3**.[42–43]



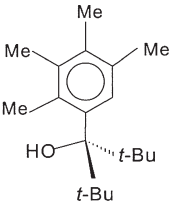
2a: R = CF_3
2b: R = Cl
2c: R = H
2d: R = Me
2e: R = OMe



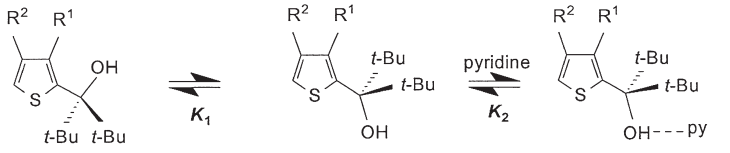
2f



2g



2h



anti ***syn*** ***syn-py***

3a: R^1, R^2 = OCH_2O
3b: R^1, R^2 = $O(CH_2)_2O$
3c: R^1, R^2 = $O(CH_2)_3O$
3d: R^1 = OMe; R^2 = H
3e: R^1 = R^2 = OMe

The relative merits of different solvents for association studies have been discussed,[5,6] some workers advising against the use of carbon tetrachloride, albeit the most widely used solvent in IR spectroscopy, because of its interaction with bases.[44] Our own choice was motivated by practical and economic considerations: cyclohexane, the most neutral solvent, is very expensive in its perdeuteriated form; carbon tetrachloride requires a cosolvent for NMR locking; chloroform, the cheapest NMR solvent, is highly unsuitable for use with bases.[4] Finally, benzene, which is the most convenient NMR solvent for differentiating the *syn* and *anti* isomers of alcohols **3**, was adopted for the major part of this work. An added advantage is that self-association of alcohols is suppressed by solvent–solute interactions.[17] Deuteriopyridine was chosen as a suitably strong acceptor.

An independent determination of the association constants for some of the thiophene derivatives, **3**, based solely on the concentration dependence of the *syn*/*anti* ratio, gave results in satisfactory agreement with those from the NMR shift method.

RESULTS AND DISCUSSION

Self-association: ^{1}H NMR study

Despite evidence from IR spectroscopy, dielectric permittivity and other techniques that *n*-alcohols and even branched secondary and tertiary alcohols self-associate not only as dimers but also as trimers, tetramers and possibly even higher polymers,[12,16–18,20,35,45] certain authors of NMR studies assume only dimerization to occur, even at high concentration. Thus, with this assumption Luo *et al*.[46] measured self-association constants for 2,4-dimethylpentan-3-ol and 3-methylpentan-3-ol and found them to decrease in the order cyclohexane > carbon tetrachloride ≫ chloroform. The difference (expressed in units of molality, kg mol^{-1}) between the first two solvents is less than a factor of two, but in the last solvent, the values are 10–20 times lower than in CCl_4. Our preliminary experiments with 2,4-dimethylpentan-3-ol in benzene gave values similar to those in chloroform. As association constants and solubilities are smaller for more hindered alcohols, it proves to be impossible to reach that part of the NMR vs concentration plot where significant curvature appears. We therefore determined the self-association constants of the smaller alcohols in our series, **1a–c**, in carbon tetrachloride, and estimated the values in benzene by applying a factor based on work on the previous authors' alcohols. For alcohols as hindered as **1a–c** it is generally agreed that no polymers higher than cyclic or open dimers are formed by self-association.[28–31]

In the NMR titration method, advantage is taken of the fact that the ^{1}H NMR shift of an NH or OH proton which is hydrogen bonded in the associated form is different,

generally higher, than that of the same hydrogen in the non-associated form.[47] In the simple case where alcohol self-association gives only dimer, the observed chemical shift, δ_{obs}, is related to the chemical shifts, δ_M and δ_D, of the monomer and dimer species by the following equation, where K is the equilibrium constant and $[ROH]_0$ the analytical alcohol concentration (Chen–Shirts equation):[48]

$$\delta_{obs} = \delta_M + (\delta_D - \delta_M)\frac{(1 + 8K[ROH]_0)^{1/2} - 1}{(1 + 8K[ROH]_0)^{1/2} + 1} \quad (1)$$

Graphical iterative procedures have been described for the solution of this equation,[48,49] but it is more conveniently handled by the the non-linear least-squares curve-fitting option of the Origin program (Microcal Software, now OriginLab, Northampton, MA, USA), which uses the Levenberg–Marquardt algorithm.

The value we find for 2,2,4,4-tetramethylpentan-3-ol, **1a**, in carbon tetrachloride (with 5% cyclohexane) at 298 K, 0.15 kg mol^{-1} (Table 1), is smaller than that which is obtained by applying the Chen–Shirts equation to early data for this alcohol in carbon tetrachloride at 298.6 K, 0.26 kg mol^{-1}.[30] We cannot explain this difference. That for the methyl derivative, **1b**, is the same as that for **1a**, whereas the ethyl derivative, **1c**, has a slightly lower self-association constant, 0.09 kg mol^{-1}. Significant changes are found in the shift of the associated form, δ_D, which is 4.08, 2.27 and 1.63 ppm for **1a**, **1b** and **1c**, respectively. A similarly small value, 3.07 ppm, was reported for 2,3,4-trimethylpentan-3-ol at the same temperature, 298 K.[46]

Procedures have been proposed for the determination of hetero-association constants when both hetero-association and dimerization occur.[50] However, if we take a reasonable estimate of the conversion factor for going from carbon tetrachloride to benzene, say 5, then the self-association constants for **1a** and **1b** are going to be of the order of 0.02 M^{-1}, which means that at the concentrations where we shall study hetero-association (0.15–0.2 M) only about 0.8% of the alcohol is self-associated even in the absence of pyridine; this is clearly negligible. Alcohol **1c** and the other more crowded alcohols will self-associate even less.

Hetero-association

2,2,4,4-Tetramethyl-3-alkylpentan-3-ols. Successive additions of pyridine to a solution of an alcohol increase the shift, δ_{obs}, of the OH proton very markedly, those of the other protons much less. This corresponds to the formation of a hydrogen-bonded species in fast equilibrium with alcohol and pyridine, the shift of the OH proton in the complex, δ_{Mpy}, being greater than that in the free alcohol, δ_M. The 1:1 stoichiometry of the association was first checked by means of a Job plot (Fig. 1) where the mole fraction of 2,2,4,4-tetramethyl-3-(*tert*-butyl)pentan-3-ol, **1e**, is varied from 0.1 to 0.9 while the total concentration (alcohol plus pyridine) is maintained constant.[51] Although the overall change in the shift of the OH proton is only 0.35 ppm, the plot of (mole fraction) $\times \Delta\delta$ vs mole fraction shows a clear maximum at 0.5. For the *tert*-butyl proton shift, which varies by only 0.03 ppm, the mole fraction at the maximum is less well defined but is again close to 0.5.

If the association constant is K, we have[52]

$$\delta_{obs} = \delta_M + (\delta_{Mpy} - \delta_M)\frac{\left\{B - (B^2 - 4[ROH]_0[py]_0)^{1/2}\right\}}{2[ROH]_0} \quad (2)$$

where $B = [ROH]_0 + [py]_0 + 1/K$, and $[ROH]_0$ and $[py]_0$ are the analytical concentrations of alcohol and pyridine. The association constant and δ_{Mpy} are found by fitting the experimental values of δ_{obs} to the above equation using the non-linear least-squares curve fitting option of Origin. This procedure can be applied to the shift variation of other protons but, since these are not directly involved in hydrogen bonding, the range of variation is much smaller and the results are consequently less reliable, although of the same order of magnitude. It cannot be excluded that part of their variation is not due to hydrogen bonding. We shall therefore refer to values based on OH proton shifts throughout this work.

Preliminary experiments were run on 2,2,4,4-tetramethyl-3-(*tert*-butyl)pentan-3-ol, **1e**, to determine the effects of solvent on the association constant with pyr-

Table 1. Self-association constants (kg mol^{-1}) and OH proton chemical shifts, δ_M and δ_D (ppm), for some sterically hindered alcohols at 298 K[a]

Compound	K (C_6D_{12})	K ($CDCl_3$)	K (C_6D_6)	K (CCl_4)	δ_M (CCl_4)	δ_D (CCl_4)
3-Methylpentan-3-ol	2.24	0.05	0.20 ± 0.03	1.24	0.16	4.49
2,4-Dimethylpentan-3-ol	1.05	0.056[b]	0.07 ± 0.01	0.67	0.56	4.74
2,3,4-Trimethylpentan-3-ol	—	—	0.07 ± 0.01	0.42	0.53	3.07
1a	—	—		0.15 ± 0.02	1.22 ± 0.01	4.08 ± 0.25
1b	—	—		0.15 ± 0.01	0.90 ± 0.01	2.27 ± 0.05
1c	—	—		0.09 ± 0.01	1.06 ± 0.01	1.63 ± 0.03

[a] Data from Ref. 46 are quoted without standard deviations; all others, this work.
[b] 0.07 ± 0.02 (this work).

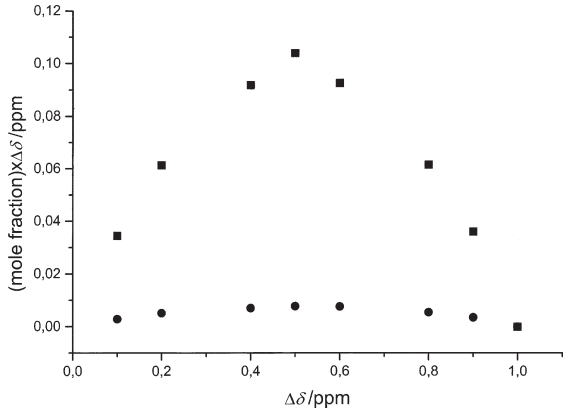


Figure 1. Job plot for 2,2,4,4-tetramethyl-3-(*tert*-butyl)-pentan-3-ol, **1e**, and pyridine in benzene at 298 K: total concentration = 0.286 M (OH, ■; *tert*-butyl, ●)

idine. The values are highest in cyclohexane, a neutral solvent, somewhat lower in carbon tetrachloride (with 5% deuteriocyclohexane) and lower still with 5% or 50% benzene (Table 2). With neat benzene the association constant is again slightly smaller, and is further depressed by the addition of 5% of deuteriochloroform. This last result is explained by the association of chloroform itself with pyridine,[4] which reduces the availability of pyridine for association with the alcohol. In neat chloroform there is a small (0.25 ppm for a 1.3 M change), rectilinear increase in the OH shift with the pyridine concentration, which means that no association constant can be extracted from the data. This dependence of the association constant on the solvent corresponds qualitatively with what has been observed for other associations. Self-association constants for alcohols follow the order $C_6D_{12} > CCl_4 \gg CDCl_3$, values being particularly small for the last,[46] and hydrogen bond enthalpies of 3-fluorophenol with various bases, including pyridine, decrease in the order $C_6D_{12} > CCl_4 > C_6H_6$.[6b]

Results for the other 2,2,4,4-tetramethyl-3-alkylpentan-3-ols (Table 3) indicate that increasing the size of the third substituent to the C—OH carbon tends to reduce the association constant, the lowest and highest values being of the order of 0.3 and 0.9 M^{-1}, respectively. Also included in this and subsequent tables are the experimental and calculated (see below) OH proton shifts in neat pyridine, and also the temperature coefficients of the chemical shift in this solvent. In prevous work,[42,53] shifts were referenced to the pyridine signal at 8.71 ppm but it became apparent in the course of this work that, for compatibilty with the measurements in benzene, TMS should be used as the reference, since the shift of this pyridine signal decreases with increasing temperature.

The major difficulty and source of error in the determination of small hetero-association constants by NMR titration is that if association is not studied over a sufficiently large concentration range the shift of the associated form and, consequently, the value of the association constant, are likely to be ill-defined.[47b–e] However, in the present work, by taking relatively high final values of the pyridine concentration we obtain δ_{Mpy} values with low standard deviations.

Moreover, if we assume that the change in solvent from predominantly benzene to totally pyridine has no effect on the association constant or on the shifts of the alcohol and the alcohol–pyridine complex, the values of δ_M, δ_{Mpy} and K can be used to calculate those of δ_{OH} in neat pyridine. The difference between the optimized value of δ_{Mpy} and that of the latter is due to the fact the association constants are so low that the various alcohols are not fully associated even in the pure base. Calculated values of the OH proton shift are remarkably close to those observed at the same temperatures (Table 3). Either this means that our original assumption is correct, or that compensatory changes occur in the values of δ_{Mpy} and K on going from benzene to pyridine. Good agreement between the calculated and experimental values of the OH proton shift is found for the other alcohols studied, the mean deviation on 46 data being only 0.037 ppm, the greatest deviations being almost systematically at the higher temperatures. This may indicate that the temperature dependences of the association constant and of δ_{Mpy} are slightly different in pyridine and in benzene. These results establish that the remarkably large upfield displacement of the OH proton signal when the temperature increases is due to changes both in the association constant, K, and in the shift of the associated form, δ_{Mpy}.

2,2,4,4-Tetramethyl-3-phenylpentan-3-ols. A 2,2,4,4-tetramethyl-3-phenylpentan-3-ol (not *ortho*-substituted) has a rotation barrier of about 21 kcal mol^{-1} (1 kcal = 4.184 kJ),[39,40] which means that the two *meta*

Table 2. Pyridine association constants and OH proton chemical shifts, δ_M and δ_{Mpy}, for alcohol **1e** at 298 K

Solvent	δ_M (ppm)	δ_{Mpy} (ppm)	K (M^{-1})
Cyclohexane	1.196	4.172 ± 0.010	1.104 ± 0.008
Carbon tetrachloride (5% v/v cyclohexane)	1.076	4.246 ± 0.020	0.484 ± 0.005
Carbon tetrachloride (5% v/v benzene)	1.063	4.263 ± 0.039	0.456 ± 0.009
Carbon tetrachloride/benzene (50:50 v/v)	1.108	4.729 ± 0.021	0.409 ± 0.004
Benzene	1.105	4.884 ± 0.027	0.400 ± 0.004
Benzene (5% v/v chloroform)	1.119	5.117 ± 0.035	0.324 ± 0.004

Table 3. Pyridine association constants and OH proton chemical shifts for 2,2,4,4-tetramethyl-3-alkylpentan-3-ols, **1a**–**f**, and substituted 2,2,4,4-tetramethyl-3-phenylpentan-3-ols, **2a**–**h**, in benzene at 298 K

Compound	R	σ_p[a]	δ_M (ppm)	δ_{Mpy}(ppm)	K (M^{-1})	δ_{OH} (ppm)[b]	δ_{OH} (ppm)[c]	$-\Delta\delta/\Delta T$ (ppb K^{-1})	$-\Delta H^\circ$ (kcal mol^{-1})	$-\Delta S^\circ$ (cal mol^{-1} K^{-1})
1a	H		1.102	6.068 ± 0.035	0.875 ± 0.012	5.716	5.647	19.8 ± 0.1	4.3 ± 0.1	14.7 ± 0.1
1b	Me		0.826	5.308 ± 0.023	0.545 ± 0.005	4.729	4.726	18.7 ± 0.1	4.1 ± 0.1	15.0 ± 0.3
1c	Et		1.032	4.712 ± 0.046	0.322 ± 0.006	3.942	3.971	17.2 ± 0.1		
1d	*i*-Pr		1.039	4.883 ± 0.050	0.312 ± 0.006	4.003	4.089	17.5 ± 0.1		
1e	*t*-Bu		1.105	4.884 ± 0.027	0.400 ± 0.004	4.199	4.246	17.6 ± 0.1	3.5 ± 0.2	13.5 ± 0.6
1f	*neo*-Pe[d]		1.108	4.513 ± 0.051	0.284 ± 0.006	3.743	3.756	17.2 ± 0.1		
2a	4-CF_3	0.551	1.519	5.898 ± 0.018	0.908 ± 0.006	5.558	5.538	16.4 ± 0.1	4.3 ± 0.1	14.5 ± 0.2
2b	4-Cl	0.226	1.485	5.833 ± 0.031	0.778 ± 0.009	5.398	5.422	17.0 ± 0.1		
2c	H	0.000	1.581	5.720 ± 0.033	0.583 ± 0.008	5.220	5.214	18.0 ± 0.1		
2d	4-Me	−0.170	1.598	5.762 ± 0.048	0.533 ± 0.010	5.154	5.168	18.3 ± 0.1		
2e	4-OMe	−0.268	1.591	5.780 ± 0.065	0.524 ± 0.012	5.155	5.217	18.3 ± 0.1	3.7 ± 0.2	13.8 ± 0.5
2f	2-Me (*anti*)		1.571	5.890 ± 0.034	0.684 ± 0.009	5.363	5.431	18.8 ± 0.1		
2g	2-Me (*syn*)		1.581	5.225 ± 0.073	0.364 ± 0.010	4.536	4.561	17.2 ± 0.1	3.5 ± 0.2	13.9 ± 0.5
2h	Prehn.[e]		1.637	5.318 ± 0.049	0.364 ± 0.007	4.623	4.647	19.1 ± 0.1		

[a] Hammett substituent constant.
[b] OH proton shift measured in pyridine.
[c] OH proton shift in pyridine, calculated from δ_M, δ_{Mpy} and K.
[d] Neopentyl.
[e] 2,3,4,5-Tetramethylphenyl (*syn*).

(3 and 5) and the two *ortho* protons (2 and 6) are magnetically non-equivalent at room temperature. In particular, in chloroform the *ortho* proton closest to the OH group (2) resonates 0.14–0.25 ppm downfield of the other (6).[39] When there is a 2-substituent, such as a methyl group, the rotation barrier is considerably enhanced and the two rotamers are readily separated chromatographically, the *syn* isomer (that with the OH group close to the 2-methyl group) being less strongly adsorbed than the other.[41] This difference in the adsorption properties of the two isomers suggests that a similar difference in hydrogen bonding ability might be observed. A substituent in the *meta* position (3) does not enhance the rotation barrier but the two rotamers, present in approximately equal amounts, are distinct on the NMR timescale.[39,41c] This leads to complex spectra and for this reason such derivatives were not examined in this study. A short series of 2- and 4-substituted compounds was investigated. The ^{1}H NMR spectra of compounds **2a**–**h** were determined in benzene and the aromatic proton signals completely assigned by spectrum simulation using the gNMR program (version 4.1) (Adept Scientific, Letchworth, UK).

A satisfactory Job plot indicating 1:1 stoichiometry was obtained for the 4-trifluoromethyl derivative, **2a** (Fig. S1 in the supplementary material, available in Wiley Interscience). Association constants (Table 3), determined from the variation of the OH proton shift with pyridine concentration, for the 4-substituted derivatives correlate relatively well with Hammett's substituent constant, σ_p,[54] giving a reaction constant, ρ, of 0.32 ± 0.04, electron-withdrawing substituents slightly increasing the acidity of the OH proton (Fig. S2). The closest comparison that we can find concerns the Hammett correlation of hydrogen bond enthalpies, ΔH°, for phenols with pyridine in cyclohexane, where $\rho = 2.01$.[55] If our association constants are converted to free energies, ΔG°, the reaction constant falls to 0.19 ± 0.02. However, this difference is only partly due to the fact that there is a carbon atom between the OH group and the ring in these alcohols. We shall show later that ΔG° differences are also reduced by concomitent variation of ΔH° and ΔS°.

The 2-methyl derivatives, **2f**–**h**, give different association constants, depending on whether the group is close to (*syn*) or remote from (*anti*) the OH group. In the former case, **2g** and **2h**, steric hindrance reduces the association constant, whereas for the *anti* rotamer, **2f**, the value is slightly greater than for the unsubstituted derivative. These results are qualitatively consistent with the chromatographic behaviour of the *syn* and *anti* rotamers.[41]

2,2,4,4-Tetramethyl-3-(2-thienyl)pentan-3-ols. 2,2,4,4-Tetramethyl-3-(2-thienyl)pentan-3-ols with a 3-alkoxy substituent or a 3,4-alkylenedioxy bridge exist in two rotameric forms separated by rotation barriers of about 17–23 kcal mol^{-1}: *anti*, with an intramolecular hydrogen bond, and *syn*, with the OH group 'free'.[42,43] Structural analogues with different substituents in the 3- and 4-positions show variations in the equilibrium constant corresponding to free energy differences spanning 3.3 kcal mol^{-1}.[43] When these compounds are transferred from a non-hydrogen-bonding solvent, such as benzene, to a hydrogen-bonding solvent, such as pyridine or DMSO, the *syn*/*anti* ratio at 298 K increases systematically by factors of about 10 and 30, respectively.[43] The OH proton signals are temperature-dependent in hydrogen-bonding solvents, that of the *syn* rotamer moving upfield, as the temperature increases, much more than that of the *anti* rotamer.[42] The temperature coefficient for

the *syn* rotamer OH is much higher (ca -17 ppb K^{-1}) in pyridine than in DMSO (ca -6 ppb K^{-1}).[42] The values for alcohols **1** and **2**, even when the OH is close to a methyl group, as in **2g** and **2h**, are in the same range (see Table 3).

It is convenient to present first the results for the EDOT derivative, 2,2,4,4-tetramethyl-3-[2-(3,4-ethylenedioxythienyl)]pentan-3-ol, **3b**, as these illustrate the main features of this part of the study. Successive additions of pyridine to a benzene solution of **3b** increase the shift of the *syn* OH proton very markedly, whereas that of the *anti* OH proton varies by less than 0.012 ppm as the concentration is raised from zero to 1.3 M at 298 K. For the same concentration variation the *syn*/*anti* ratio, *R*, determined by integration, rises from 0.86 (the value of the equilibrium constant, K_1, for the *syn* ⇌ *anti* equilibrium) to 1.76 (Table 4). The fact that a variable amount of the alcohol is in the *syn* form, the only one able to associate with pyridine, means that it is impossible to run a Job plot on this compound.

The association constant of the *syn* isomer, K_2, can be obtained both from the variation of the *syn* OH proton shift and from that of the *syn*/*anti* ratio. In the first case (method A) we have, by analogy with Eqn (2) for simple alcohols, the equation

$$(\delta_{obs})^{syn} = \delta_S + \frac{(\delta_{Spy} - \delta_S)}{2[S]_0}\left\{B - (B^2 - 4[S]_0[py]_0)^{1/2}\right\} \quad (3)$$

where $B = [S]_0 + [py]_0 + 1/K_2$, δ_S and δ_{Spy} being the chemical shifts of the free and associated forms of the *syn* rotamer, $[S]_0$ and $[py]_0$ the analytical concentrations of the *syn* rotamer and pyridine; $[S]_0$ is determined from the *syn*/*anti* ratio and the analytical concentration of the alcohol, $[ROH]_0$. The values of K_2 and δ_{Spy} are found by fitting the experimental values of $(\delta_{obs})^{syn}$ to the above equation (Table 5).

For this alcohol, **3b**, a further experiment was performed at 298 K: additional points with pyridine concentrations ranging from 2.5 to 12.5 M (neat pyridine) were added to the usual range (0–1.3 M) and K_2 and δ_{Spy} were recalculated. The values obtained, 0.852 ± 0.003 M^{-1} and 6.360 ± 0.003 ppm, are in very good agreement with those, 0.849 M^{-1} and 6.375 ppm, for the shorter range (Fig. S3). This establishes two points, that the association constant is virtually the same in pyridine as in benzene and that there is no serious error in measuring association constants over the shorter range.

In the second case (method B), we have

$$[S] = K_1[A] \quad \text{and} \quad [Spy] = K_2[S][py] = K_1K_2[A][py]$$

where [A] and [S] are the concentrations of the *anti* and free *syn* rotamers, respectively.

$$[py] = [py]_0 - K_1K_2[A][py]$$

$$[ROH]_0 = [A] + K_1[A] + K_1K_2[A][py] = [A](1 + K_1 + K_1K_2[py])$$

then

$$[py] = [py]_0 - K_1K_2[ROH]_0[py]/(1 + K_1 + K_1K_2[py])$$

Rearranging this and solving the quadratic equation gives [py], whence the *syn*/*anti* ratio, R ($= K_1 + K_1K_2[py]$) is expressed by the equation

$$R = K_1 + \left(\left\{B^2 + 4K_1K_2(1 + K_1)[py]_0\right\}^{1/2} - B\right)\Big/2 \quad (4)$$

where $B = 1 + K_1 + K_1K_2([ROH]_0 - [py]_0)$. K_1 is the value of R when $[py]_0 = 0$, and K_2 is again calculated by the non-linear least-squares procedure. This gives results in good agreement with method A as applied to the *syn* OH shift data (Table 5), with the *R*-derived values on average within 3% of those calculated from the shift data. Full details of the temperature and concentration dependence of *R* are given in Table S1.

As above, the values of δ_{Spy}, K_1 and K_2 can be used to calculate those of $(\delta_{OH})^{syn}$ in neat pyridine. Calculated values of the *syn* OH proton shift are on average 0.07 ppm lower than those observed at the same temperatures. Values of *R* can also be calculated. The data in Table 6 indicate a very satisfactory degree of agreement between

Table 4. Dependence of chemical shifts (ppm) and *syn*/*anti* ratio (*R*) for 2,2,4,4-tetramethyl-3-[2-(3,4-ethylenedioxythienyl)]-pentan-3-ol, **3b**, on pyridine concentration in benzene at 298 K

$[py]_0$	$[\mathbf{3b}]_0$	$(\delta_{H\text{-}5})^{syn}$	$(\delta_{OH})^{syn}$	$(\delta_{t\text{-}Bu})^{syn}$	$(\delta_{H\text{-}5})^{anti}$	$(\delta_{OH})^{anti}$	$(\delta_{t\text{-}Bu})^{anti}$	*R*
0.000	0.150	6.187	1.990	1.216	6.013	5.165	1.349	0.86
0.123	0.149	6.194	2.384	1.245	6.017	5.165	1.347	0.94
0.244	0.147	6.201	2.711	1.270	6.024	5.167	1.346	1.02
0.362	0.146	6.208	2.983	1.289	6.030	5.167	1.344	1.10
0.478	0.145	6.213	3.216	1.305	6.036	5.169	1.343	1.16
0.704	0.142	6.222	3.584	1.331	6.048	5.171	1.340	1.35
0.921	0.139	6.231	3.871	1.345	6.059	5.173	1.339	1.46
1.130	0.137	6.236	4.097	1.365	6.069	5.175	1.336	1.60
1.332	0.134	6.242	4.280	1.376	6.078	5.177	1.334	1.76

Table 5. Pyridine association constants for 2,2,4,4-tetramethyl-3-[2-(3,4-ethylenedioxythienyl)]pentan-3-ol, **3b**

Solvent	Temperature (K)	K_1	K_2 (M^{-1})[a]	K_2 (M^{-1})[b]
Cyclohexane	298	0.73	2.35 ± 0.24	
Carbon tetrachloride[c]	298	0.82	0.891 ± 0.007	0.812 ± 0.009
Benzene	298	0.86	0.849 ± 0.003	0.803 ± 0.019
Benzene	308	0.86	0.667 ± 0.002	0.660 ± 0.007
Benzene	318	0.86	0.538 ± 0.005	0.517 ± 0.007
Benzene	328	0.85	0.421 ± 0.004	0.411 ± 0.006
Chloroform	298	0.89		0.330 ± 0.022

[a] From concentration dependence of *syn* OH proton shift.
[b] From concentration dependence of the *syn*/*anti* ratio (R).
[c] With 5% deuteriocyclohexane.

the calculated and observed values of R: if the *syn*/*anti* ratio is expressed as *%syn*, then the difference is $<1\%$ at temperatures ranging from 298 to 328 K. From these data we obtain ΔH° and ΔS° values of -4.6 ± 0.1 kcal mol^{-1} and -10.9 ± 0.4 cal mol^{-1} K^{-1}, respectively, close to the reported values of -4.3 ± 0.1 kcal mol^{-1} and -10.1 ± 0.3 cal mol^{-1} K^{-1}.[43] The data based on the *syn*/*anti* ratio (method B) give slightly higher values for R. The caveat concerning the possible compensation of changes in the values of δ_{Mpy} and K (K_2 in the present case), mentioned above, clearly does not apply here. These results, therefore, confirm that the association constant determined at low pyridine concentration in benzene is valid in neat pyridine.

For alcohols **3c** and **3d**, similar agreement is obtained between association constants determined by the two methods. Calculated *syn* OH proton shifts in neat pyridine are on average 0.04 and 0.06 ppm, respectively, lower than observed, and the mean error on the amount of *syn* at equilibrium is about 2%, the results for **3d** being somewhat less satisfactory than those for **3b** and **3c** (full details are given in Table S2).

As mentioned above, method A can be applied to the *syn* H-5 and *tert*-butyl shifts, for which the range of variation is much smaller and the results consequently less reliable. In contrast to the *anti* OH proton shift, which is virtually constant, the *anti* H-5 and *tert*-butyl shifts vary for reasons which are apparently unrelated to hydrogen bonding to pyridine, such as solvation, nonideality and unspecific shielding.[47e] For **3a**, method B, based on the variation of the *syn*/*anti* ratio, could only be used at 298 K; at higher temperatures R, which is already high at 298 K even in the absence of pyridine, increases and becomes more and more difficult to determine accurately. This does not significantly affect the values based on the chemical shifts alone.

The rotation barrier of the 3,4-dimethoxy derivative, **3e**, is rather higher (22.1 and 22.0 kcal mol^{-1} for *anti* $\rightarrow$ *syn* and *syn* $\rightarrow$ *anti*, respectively, in DMSO) than those of the other derivatives,[43] and for this reason the *anti* $\rightleftharpoons$ *syn* equilibrium is only slowly established at room temperature. However, the *syn*/*anti* ratio is measured at the same time as the shift of the *syn* OH proton and is allowed for in the calculation of the association constant. Results for alcohols **3a–e** are summarized in Table 7.

Alcohol **3b** in carbon tetrachloride has an association constant only slightly higher than that in benzene, consistent with what was found for 2,2,4,4-tetramethyl-3-(*tert*-butyl)pentan-3-ol, **1e**. The value based on the variation of R is about 10% low. In the case of cyclohexane, the association constant determined by method A is greater than those in benzene and CCl_4 by a factor of about 2.5, but method B gave only a ragged line, possibly due to slow *anti* $\rightleftharpoons$ *syn* equilibration. For **3b** in chloroform the shift of no signal except that of the *syn* OH proton changes by more than 0.05 ppm as the pyridine concentration is raised from 0 to 1.3 M. That of the *syn* OH, however, goes downfield by 1.0 ppm, while the *syn*/*anti* ratio increases from 0.89 to 1.26 (Table S3). Application of Eqn (4) to the R data gives values of K_1 and K_2 of 0.89 ± 0.01 and 0.33 ± 0.02 M^{-1}, respectively. Method A [Eqn (3)] fails to converge to plausible values of K_2 and δ_{Spy}. As stated above, the low K_2 in chloroform is attributable to association between the solvent and pyridine.[4]

The *anti* OH proton shift in **3a** is pyridine concentration dependent, rising by 0.43 ppm as that for the *syn* OH proton rises by 2.4 ppm (Table S4). This small increase could be due to hydrogen bonding to pyridine of the weakly intramolecularly hydrogen-bonded proton.[43] The variation is almost rectilinear and curve fitting gives an association constant of 0.070 ± 0.013 M^{-1} with an

Table 6. Temperature dependence of *syn* OH proton chemical shift (ppm) and *syn* content for 2,2,4,4-tetramethyl-3-[2-(3,4-ethylenedioxythienyl)]pentan-3-ol, **3b**, in pyridine

Temperature (K)	δ_S(OH)	δ_{Spy}	δ_{OH}[a]	δ_{OH}[b]	*%syn*[c]	*%syn*[d]	*%syn*[e]
298	1.990	6.376 ± 0.007	5.999	5.993	90.2	90.8	90.4
308	1.989	6.242 ± 0.008	5.839	5.776	87.7	88.7	88.6
318	1.992	6.108 ± 0.026	5.671	5.556	85.1	86.5	86.0
328	1.995	6.081 ± 0.024	5.584	5.400	83.7	83.6	83.3

[a] *syn* OH proton shift measured in pyridine.
[b] *syn* OH proton shift in pyridine, calculated from δ_S, δ_{Spy} and K_2 (method A).
[c] Measured in pyridine.
[d] For pyridine, calculated from K_1 and K_2 (method A).
[e] For pyridine, calculated from K_1 and K_2 (method B).

Table 7. Pyridine association constants and OH proton shifts (ppm) for substituted 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols, **3**, in benzene at 298 K

Compound	δ_S	δ_{Spy}	K_2 $(M^{-1})^a$	K_2 $(M^{-1})^b$	$\delta_{OH}{}^c$	$\delta_{OH}{}^d$	$-\Delta\delta/\Delta T$ (ppb K^{-1})	$-\Delta H^\circ$ (kcal mol^{-1})	$-\Delta S^\circ$ (cal mol^{-1} K^{-1})
3a	1.939	6.356 ± 0.019	0.948 ± 0.009	0.899 ± 0.068	6.038	6.009	17.7 ± 0.1		
3b	1.990	6.376 ± 0.007	0.849 ± 0.007	0.803 ± 0.019	5.999	5.993	17.8 ± 0.1	4.5 ± 0.1	15.5 ± 0.4
3c	1.985	6.378 ± 0.011	0.864 ± 0.004	0.701 ± 0.067	6.017	6.003	18.0 ± 0.2	4.4 ± 0.1	15.1 ± 0.3
3d	2.036	6.338 ± 0.010	0.777 ± 0.004	0.743 ± 0.015	5.965	5.932	18.1 ± 0.1	4.3 ± 0.1	14.9 ± 0.4
3e	2.013	6.411 ± 0.025	0.759 ± 0.006		5.977	5.989	18.1 ± 0.3		

[a] From concentration dependence of *syn* OH proton shift.
[b] From concentration dependence of the *syn*/*anti* ratio (R).
[c] OH proton shift measured in pyridine.
[d] OH proton shift in pyridine, calculated from δ_S, δ_{Spy}, K_1 and K_2 (method A).

improbably high and uncertain δ_{Apy} of 8.10 ± 0.85 ppm. Unfortunately, K_1 is so high that it is impossible to measure the shift of the *anti* OH proton in neat pyridine.

Thermodynamic parameters and molecular mechanics calculations. Thermodynamic parameters were measured for selected compounds at 298–328 K. Since the range of association constants is small, those of the standard reaction enthalpy and entropy terms are also (Tables 3 and 7; full details are given in Table S5). There is a rough correlation (correlation coefficient 0.93488) between the two terms, both increasing in magnitude as the association constant increases (Figure S4). This means that the stronger hydrogen bonds in the less sterically hindered compounds, for example, are partially compensated by greater reaction entropy terms, a phenomenon which is well known in molecular association processes.[1c,g,h,10c,47d,56] The reaction enthalpy values, ranging from -3.5 to -4.5 kcal mol^{-1}, place the pyridine-alcohol hydrogen bond at the admittedly arbitrary limit between weak and strong hydrogen bonds.[2e,57] These are of the same order of magnitude as values found mainly by IR spectroscopic measurements in carbon tetrachloride, which range from 2.7 kcal mol^{-1} for pentan-1-ol and nonan-1-ol to 6.1 kcal mol^{-1} for propan-2-ol.[10]

Molecular mechanics calculations (MMFF94[58] in Sybyl 6.9 from Tripos, St. Louis, MO, USA) were run in order to determine the steric energies of the starting alcohols and their complexes with pyridine (Table S6). Attempted correlation of the various association constants, expressed as ΔG° $[-RT\ln(K)]$ indicates that the data for the alkyl (**1b–f**) and aryl (**2c**, **f**, **g** and **h**) derivatives fall on the same area of the graph, with slopes of 0.44 ± 0.19 and 0.30 ± 0.04, respectively (Fig. 2). The thiophene derivatives (**3a–e**) lie apart, with a similar slope of 0.37 ± 0.15, but clearly have association constants higher than their steric energy changes would suggest, in comparison with the aryl and alkyl derivatives. The only secondary alcohol, **1a**, lies on no correlation.

The calculations refer to reaction enthalpies while the experimental ΔG° values include variable entropy contributions. A plot of $T\Delta S^\circ$ against ΔH° for a temperature of 298 K has a slope of 0.48 ± 0.07, which means that for every kcal mol^{-1} increase in ΔH° about 50% of the effect on K is cancelled by the increase in $T\Delta S^\circ$. This could explain, in part, why the slopes of the correlations are so small. A further possibility is that the relative differences in association constants between more and less strained alcohols are reduced by the use of a slightly basic solvent, benzene, and that a neutral solvent, such as cyclohexane, would give higher slopes. If the steric energy of pyridine, 15.52 kcal mol^{-1}, is taken into account, association is accompanied by a fall in the overall steric energy of 5.8–7.5 kcal mol^{-1}, which is substantially higher than the $-\Delta H^\circ$ values determined above. These deviations, the underestimation of the slope, the anomalous correlation of the thiophene set, and the deviation of **1a**, must be due to deficiences in the force field and/or the failure to account for polar effects.

Temperature dependence of the OH proton shift in pyridine. As can be seen from Eqn (2), the shift of the OH proton in neat pyridine depends on δ_{Mpy}, δ_M and K. The value of δ_M is almost independent of temperature whereas that of δ_{Mpy} generally falls slightly as the temperature is increased. Numerical simulation was performed by generating sets of association constants using ΔH° values from -3.5 to -4.5 kcal mol^{-1} and ΔS° from -13 to -16 cal mol^{-1} K^{-1}, and then calculating δ_{OH} at

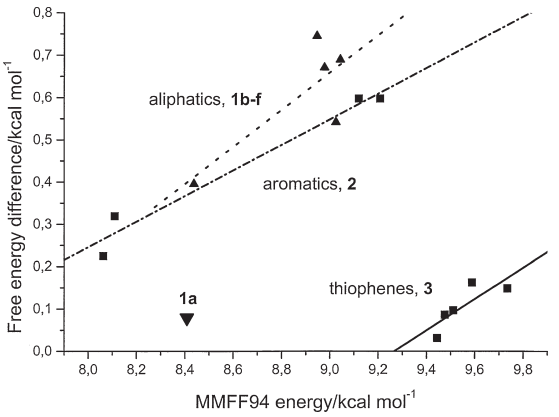


Figure 2. Correlation of free energy differences against steric energy changes

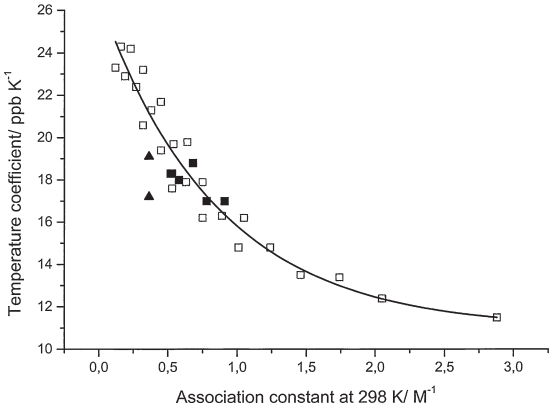


Figure 3. Exponential relationship between temperature coefficient in pyridine and association constant with pyridine in benzene (synthetic data, □; **2a–f**, ■; **2g–h**, ▲)

temperatures from 298 to 328 K, assuming that δ_M has a temperature coefficient of $+1$ ppb K^{-1} (1.56 ppm at 298 K), and that δ_{Mpy} (5.81 ppm at 298 K) has a coefficient of -8 ppb K^{-1}. For a given value of K at 298 K, the higher are $-\Delta H^\circ$ and $-\Delta S^\circ$, the higher is the temperature coefficient. This results in a fuzzy exponential curve where the temperature dependence of δ_{OH} decreases as K increases (Fig. 3). These values were chosen to match the data for the substituted 2,2,4,4-tetramethyl-3-phenylpentan-3-ols, **2a–f**, which naturally fall close to the calculated curve. However, the points for both of the *syn ortho*-substituted alcohols, **2g** and **2h**, lie below the curve, because the corresponding δ_{Mpy} values are lower than for **2a–f**. The other two sets, for alcohols **1** and **3**, also lie off this curve, and those for set **1** show a reverse trend in the relationship between temperature dependence and association constant, the coefficients for the least associated alcohols being the lowest.

It was hoped that the temperature coefficient, since it can be measured with greater precision than a series of association constants, would give some information about the reaction entropy, ΔS°, but it is clear now that this is impossible since the shifts in pyridine depend on both K and on the values and temperature dependence of δ_{Mpy} and δ_M, and that these latter are not only unpredictable but also follow no clear pattern.

CONCLUSION

Systems with very small association constants ($K < 1$ M^{-1}) do not satisfy the Weber,[59] Person[60] and Deranleau[61] criteria for accurate determination, insofar as the fraction of the guest which is complexed by the host tends to be small and that, consequently, δ_{Mpy} is ill defined.[1c,g,h,10c,56] In the present work, however, when relatively high pyridine concentrations (up to 1.3 M) are used the standard deviations on the values of δ_{Mpy} calculated by curve fitting are rarely more than 0.05 ppm. Moreover, there is good agreement between the experimentally determined OH proton chemical shifts in neat pyridine and those calculated from δ_{Mpy} (or δ_{Spy}), δ_M (or δ_S) and the equilibrium constant(s), which suggests that association constants are the same in benzene and pyridine. For some of the thiophene derivatives it has been possible to determine the association constant by a second method, based on the variation of the *syn*/*anti* ratio, with satisfactory agreement between the two methods. We conclude, therefore, that variations in the association constants determined by the NMR titration method are significant.

There is a small polar effect of substituents in the *para* position on the hydrogen bonding of 2,2,4,4-tetramethyl-3-phenylpentan-3-ols with pyridine. A methyl group in the *ortho* position has little effect when it is *anti* to the OH group but significantly reduces the association constant when it is *syn*. Hydrogen bonding is virtually independent of the substituents at the 3- and 4-positions in 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols.

Whereas small alcohols form a variety of polymers by self-association, in the case of bulky alcohols only dimers appear to be formed. Whether they are brought together by one (open structure) or two (cyclic structure) hydrogen bonds, and to what extent, are questions which have not been fully resolved after many years of, albeit sporadic, research. However, it is clear that association constants are reduced by increasing the size of the 3-substituent in 2,2,4,4-tetramethylpentan-3-ols, and that these alcohols are less associated than their smaller homologues, although quantitative comparison with the latter is difficult because of the different degrees of polymerization.

The situation is somewhat different as regards heteroassociation. The important fact which emerges from this study is that steric crowding in the donor species of a hydrogen-bonded complex, such as a 3-substituted 2,2,4,4-tetramethylpentan-3-ol, does not have much impact on the association constant or the strength of the hydrogen bond with a relatively unencumbered species, such as pyridine, the overall range from the least to the most associated being only a factor of three. While increasing the size of the 3-substituent has dramatic effects on the steric energy of the alcohol itself, its interaction with the rather remote hydrogen bond acceptor species is little changed. This means that the outer envelope of the alcohol, as perceived by the pyridine molecule, is not very sensitive to the 3-substituent. It would be possible to make the alcohols more discriminating by increasing the size of the acceptor with *ortho* substituents, but this would further decrease the association constants.

A very common feature of biological systems is that donors and acceptors are in the same molecule, and binding occurs between complementary pairs in the two or several components. A simple way to mimic such a situation in the context of our work would be to incorporate a pyridyl substituent into an alcohol and thereby to study self-association. Early IR[62] and NMR[63] studies on hydroxyalkylpyridines focused on intramolecular

hydrogen bonding and its dependence on chain length. Experiments designed to eliminate or drastically reduce this and to favour intermolecular bonding by means of a rigid spacer are in hand. More elaborate systems with upwards of two hydrogen bonds can be envisaged.[64]

EXPERIMENTAL

All compounds except **1a** were synthesized by addition of 2,2,4,4-tetramethylpentan-3-one to the appropriate organolithium compound in diethyl ether under argon at room temperature, as described in the cited work, and were purified by column chromatography on alumina. Alcohol **1a** was synthesized by $LiAlH_4$ reduction of the same ketone. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer with a spectral resolution of 0.001 ppm. Shifts in deuteriated benzene and pyridine are referenced to TMS at 0.000 ppm, those in cyclohexane to the residual solvent signal at 1.380 ppm and those in chloroform or carbon tetrachloride–cyclohexane mixtures to HMDS at 0.060 ppm. Aromatic proton signals in **2** were assigned by spectrum simulation using the gNMR program; coupling constants (*J* in Hz) involving methyl groups are not signed. The 2-position is that closest to the hydroxyl group, except in **2f**; *syn* indicates proximity of the OH and the 2-methyl group (**2g**–**h**) and *anti* the opposite (**2f**).

^{1}H NMR spectra (in benzene)

2,2,4,4-Tetramethylpentan-3-ol, ***1a***. NMR, δ_H (0.028 M): 0.970 (2 *tert*-butyl), 1.064 (OH, *J* 5.7) and 2.757 (CH, *J* 5.7).

2,2,3,4,4-Pentamethylpentan-3-ol, ***1b***. NMR, δ_H (0.028 M): 0.791 (OH), 0.979 (CH_3) and 1.015 (2 *tert*-butyl).

2,2,4,4-Tetramethyl-3-ethylpentan-3-ol, ***1c***. NMR, δ_H (0.028 M): 0.862 (CH_3, *J* 7.6), 1.002 (2 *tert*-butyl), 1.022 (OH) and 1.532 (CH_2, *J* 7.6).

2,2,4,4-Tetramethyl-3-isopropylpentan-3-ol, ***1d***. NMR δ_H (0.229 M): 1.040 (OH), 1.093 (2 *tert*-butyl), 1.139 (2 CH_3, *J* 7.3) and 2.301 (CH, *J* 7.3).

*2,2,4,4-Tetramethyl-3-(*tert*-butyl)pentan-3-ol,* ***1e***. NMR, δ_H (0.208 M): 1.106 (OH) and 1.233 (3 *tert*-butyl).

2,2,4,4-Tetramethyl-3-neopentylpentan-3-ol, ***1f***. NMR, δ_H (0.192 M): 1.015 (2 *tert*-butyl), 1.108 (OH), 1.157 (1 *tert*-butyl) and 1.600 (CH_2).

2,2,4,4-Tetramethyl-3-[(4-trifluoromethyl)phenyl]pentan-3-ol, ***2a***. NMR, δ_H: 0.894 (2 *tert*-butyl), 1.519 (OH), 7.291 (H5, *J* 0.5, 2.2, 8.6), 7.337 (H6, *J* 0.6, 2.1, 8.6), 7.476 (H3, *J* 0.5, 2.2, 8.4) and 7.740 (H2, *J* 0.5, 2.1, 8.4).

2,2,4,4-Tetramethyl-3-(4-chlorophenyl)pentan-3-ol, ***2b***. NMR, δ_H: 0.923 (2 *tert*-butyl), 1.481 (OH), 7.056 (H5, *J* 0.4, 2.5, 8.7), 7.198 (H6, *J* 0.4, 2.6, 8.7), 7.219 (H3, *J* 0.4, 2.5, 8.6) and 7.581 (H2, *J* 0.4, 2.6, 8.6).

2,2,4,4-Tetramethyl-3-phenylpentan-3-ol, ***2c***. NMR, δ_H: 1.030 (2 *tert*-butyl), 1.578 (OH), 7.095 (H5, *J* 0.5,1.6, 7.5, 8.2), 7.108 (H4, *J* 1.2, 1.2, 7.4, 7.5), 7.261 (H3, *J* 0.6, 1.6, 7.4, 8.1), 7.467 (H6, *J* 0.6, 1.2, 2.2, 8.2) and 7.796 (H2, *J* 0.5, 1.2, 2.2, 8.1).

2,2,4,4-Tetramethyl-3-(4-methylphenyl)pentan-3-ol, ***2d***. NMR, δ_H: 1.062 (2 *tert*-butyl), 1.611 (OH), 2.173 (CH_3, *J* 0.5, 0.6), 6.944 (H5, *J* 0.3, 0.5, 2.1, 8.2), 7.093 (H3, *J* 0.1, 0.6, 2.1, 8.1), 7.404 (H6, *J* 0.1, 2.3, 8.2) and 7.711 (H2, *J* 0.3, 2.3, 8.1).

2,2,4,4-Tetramethyl-3-(4-methoxyphenyl)pentan-3-ol, ***2e.*** NMR, δ_H: 1.062 (2 *tert*-butyl), 1.590 (OH), 3.368 (CH_3), 6.740 (H5, *J* 0.1, 2.9, 8.9), 6.840 (H3, *J* 0.1, 2.9, 8.2), 7.374 (H6, *J* 0.1, 2.6, 8.9) and 7.721 (H2, *J* 0.1, 2.6, 8.2).

anti-2,2,4,4-Tetramethyl-3-(2-methylphenyl)pentan-3-ol, ***2f***. NMR, δ_H: 1.047 (2 *tert*-butyl), 1.581 (OH), 2.708 (CH_3, *J* 0.2, 0.4, 0.4, 0.6), 6.987 (H5, *J* 0.4, 1.9, 7.1, 8.3), 7.024 (H4, *J* 0.2, 1.4, 7.1, 7.7), 7.068 (H3, *J* 0.4, 0.6, 1.9, 7.7) and 7.465 (H6, *J* 0.4, 0.4, 1.4, 8.3).

syn-2,2,4,4-Tetramethyl-3-(2-methylphenyl)pentan-3-ol, ***2g***. NMR, δ_H: 1.076 (2 *tert*-butyl), 1.571 (OH), 2.478 (CH_3, *J* 0.3, 0.3, 0.3, 0.5), 7.031 (H3, *J* 0.3, 0.5, 1.6, 7.6), 7.070 (H4, *J* 0.3, 1.4, 7.2, 7.6), 7.181 (H5, *J* 0.5, 1.6, 7.2, 8.7) and 8.211 (H6, *J* 0.3, 0.5, 1.4, 8.7).

syn-2,2,4,4-Tetramethyl-3-(2,3,4,5-tetramethylphenyl)pentan-3-ol, ***2h***. NMR, δ_H: 1.163 (2 *tert*-butyl), 1.638 (OH), 2.039 (CH_3), 2.128 (CH_3), 2.179 (CH_3), 2.706 (CH_3-2) and 7.329 (H6).

2,2,4,4-Tetramethyl-3-[2-(3,4-methylenedioxythienyl)]pentan-3-ol, ***3a***. NMR, δ_H: *syn*, 1.153 (2 *tert*-butyl), 1.939 (OH), 5.334 (CH_2) and 5.692 (H5); *anti*, 1.244 (2 *tert*-butyl), 2.948 (OH), 5.308 (CH_2) and 5.551 (H5).

2,2,4,4-Tetramethyl-3-[2-(3,4-ethylenedioxythienyl)]pentan-3- ol, ***3b***. NMR, δ_H: *syn*, 1.216 (2 *tert*-butyl), 1.990 (OH), ca 3.41 (m, 2 CH_2) and 6.187 (H5); *anti*, 1.349 (2 *tert*-butyl), 5.165 (OH), *ca.* 3.24 (m, 2 CH_2) and 6.013 (H5).

2,2,4,4-Tetramethyl-3-[2-(3,4-propylenedioxythienyl)]pentan-3-ol, ***3c***. NMR, δ_H: *syn*, 1.203 (2 *tert*-butyl), ca 1.53 (m, CH_2), 1.987 (OH), ca 3.63 (m, 2 OCH_2) and 6.391 (H5); *anti*, 1.331 (2 *tert*-butyl), ca 1.39 (m, CH_2), ca 3.48 (m, 2 OCH_2), 6.184 (OH) and 6.231 (H5).

2,2,4,4-Tetramethyl-3-[2-(3-methoxythienyl)]pentan-3-ol, ***3d***. NMR, δ_H: *syn*, 1.205 (2 *tert*-butyl), 2.038 (OH), 3.260

(CH_3), 6.490 (H4, *J* 5.6) and 6.778 (H5, *J* 5.6). *anti*, 1.339 (2 *tert*-butyl), 3.142 (CH_3), 6.081 (OH), 6.302 (H4, *J* 5.6) and 6.595 (H5, *J* 5.6).

2,2,4,4-Tetramethyl-3-[2-(3,4-dimethoxythienyl)]pentan-3-ol, ***3e***. NMR, δ_H: *syn*, 1.207 (2 *tert*-butyl), 2.013 (OH), 3.243 (CH_3O), 3.764 (CH_3O) and 5.727 (H5); *anti*, 1.333 (2 *tert*-butyl), 3.178 (CH_3O), 3.612 (CH_3O), 5.539 (H5) and 6.131 (OH).

Determination of association constants

Self-association constants. Solutions of solids were prepared by adding solvent (or solvent mixture) to weighed amounts of the alcohol in NMR tubes. Solutions of liquids were made up by injecting successive amounts of the alcohol to the solvent (or solvent mixture). For ease of comparison with Luo *et al*.'s work,[46] concentrations are expressed on the molal scale, mol kg^{-1}, and association constants in kg mol^{-1} (Table 1). The alcohol concentration ranged from about 0.1 to 2 mol kg^{-1}. All measurements were made at 298 K.

Hetero-association constants. Samples (10–20 mg) were weighed directly into NMR tubes and solvent (0.5 ml) was syringed in. Successive amounts of deuteriated pyridine were injected, and after each addition the ^1H NMR spectrum was recorded at 298 or 298–328 K. In calculating the concentrations, allowance was made for the volume of pyridine and the cubical expansion of the solvent with temperature but not for the solute volume. The pyridine concentration ranged from 0 to 1.3 M, except for one experiment with alcohol **3b** at 298 K where further samples were prepared at 2.5–12.5 M. The *syn*/*anti* ratios, *R*, for alcohols **3a–e** were determined as far as possible by integration of the *tert*-butyl proton signals, but when these overlapped methyl group signals in appropriate compounds and/or H-5 and/or OH proton signals were used. Particular difficulty is experienced when *R* is very large or very small; errors in its determination have little effect on association constants determined by the NMR shift method (method A) but seriously affect those based on the variation of *R* alone (method B). It should be noted also that method B requires that the *syn* $\rightleftharpoons$ *anti* equilibrium be established at all times. For compounds with rotation barriers over about 21.5 kcal mol^{-1} this condition becomes excessively time consuming and this method is no longer applicable; method A, however, remains valid whether the *syn* $\rightleftharpoons$ *anti* equilibrium be established or not, provided that the association equilibrium is.

Molecular mechanics calculations

Molecular mechanics calculations were performed using the MMFF94 force field[58] with the MMFF94 charge model in the Sybyl 6.9 package. Steric energies (kcal mol^{-1}) for the most stable conformations of alcohols and the corresponding alcohol–pyridine complexes are given in Table S5.

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