

Proton NMR and IR study of self-association in pyridylalkanols: open or cyclic dimers? higher polymers?

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ABSTRACT: ^1H NMR measurements indicate that (X-pyridyl)alkanols of the general formula $(\text{C}_5\text{H}_4\text{N})(\text{CH}_2)_n\text{OH}$, where $n = 1, 2$ or 3 , self-associate as open dimers, cyclic dimers, trimers and tetramers, with considerable variations depending on the position of the alkyl chain and its length. 2-(X-Pyridyl)propan-2-ols behave like the corresponding pyridylmethanols with, however, somewhat lower association constants. The IR spectra of 3-(X-pyridyl)-2,2,4,4-tetramethylpentan-3-ols ($X = 3$ or 4) in carbon tetrachloride suggest weak association, while the 2-pyridyl derivative occurs mainly as the intramolecularly hydrogen-bonded rotamer. The OH NMR shifts for the 3- and 4-pyridyl derivatives in benzene are concentration-dependent, but neither the equilibrium constants nor the degree of association can be evaluated. Benzyl alcohol in benzene associates as an open dimer and a cyclic tetramer, as does 2-phenylpropan-2-ol, only more weakly. Rotation barriers for 3-(X-pyridyl)-2,2,4,4-tetramethylpentan-3-ols ($X = 2, 3$ or 4) in DMSO or nitrobenzene are 20–21 kcal mol $^{-1}$. Copyright © 2006 John Wiley & Sons, Ltd.

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KEYWORDS: pyridine; alcohols; hydrogen bonds; NMR; IR; self-association constants; dimers; trimers; tetramers; rotamers

INTRODUCTION

Whether the hydrogen bond in water is classified as weak, moderate, or strong appears to be largely a matter of where the limits are placed. The calculated value, 1 5 kcal mol $^{-1}$, puts it just on the “strong” side of Desiraju and Steiner’s “weak-strong” classification. 2 What really distinguishes the water molecule is the number of hydrogen bonds in which it can participate, both as a donor and as an acceptor. It is this feature which makes self-association between water molecules such a highly important phenomenon. When it comes to organic derivatives, in which one hydrogen has been replaced by a hydrocarbon group, the possibilities for extensive hydrogen-bonded networks are much reduced, but low-molecular-weight alcohols such as methanol, ethanol, and other 1-alkanols, for example, self-associate as dimers, trimers, tetramers, and even higher n -mers, $^{3-24}$ phenols as dimers, trimers and tetramers. $^{23a,24-29}$ However, when the hydrocarbon group is bulky, $^{30-37}$ steric hindrance to the approach of like molecules offsets the advantage of hydrogen bonding, and not only does the extent of association fall but also the number of molecules

associated: thus 2,2,4,4-tetramethylpentan-3-ol, otherwise known as di(*tert*-butyl)methanol, dimerizes weakly, $^{31-33,36}$ and tertiary alcohols derived from this alcohol have very low self-association constants. 30,31,34,35b,37 Tri(*tert*-butyl)-methanol is a monomer even in the solid state. 38

In simple alcohols the OH group is both the acceptor and the donor, but more interesting are species in which there is a chemically distinct acceptor. The biologically most important hydrogen bonds involve hydrogen atoms covalently bound to oxygen or nitrogen, and the acceptor atoms are commonly nitrogen or oxygen. In this study we shall consider the particular case of O—H \cdots N bonding in pyridine-substituted alcohols. Previous work appears to be limited to three studies. $^{39-41}$ The NMR chemical shift of the OH hydrogen in (2-pyridyl)alkanols in chloroform increases with concentration, indicating intermolecular hydrogen bonding, despite the proximity of the OH group and the nitrogen atom. 39 In contrast, (2-pyridyl)di(1-adamantyl)methanol was isolated as the *syn* rotamer with an intramolecular hydrogen bond. 40 Intramolecular hydrogen bonding in (2-pyridyl)alkanols was also investigated by IR spectroscopy. 41

The aim of this work is to determine as far as possible by NMR and IR spectroscopies the nature and degree of the apparent association in (2-pyridyl)alkanols and to extend this study to 3- and 4-substituted derivatives. Steric effects

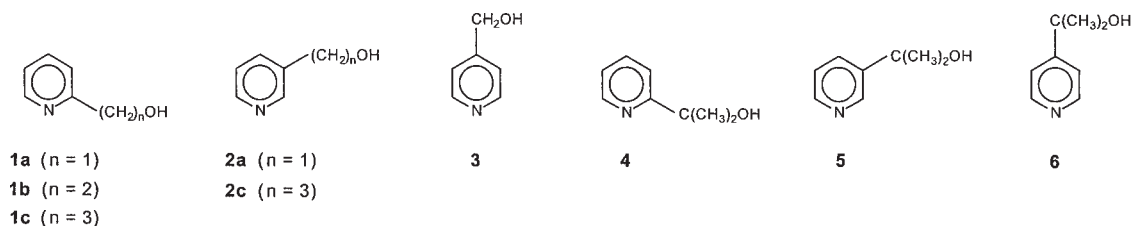
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on association will be investigated by replacing the CH₂ hydrogens of the (X-pyridyl)methanols by, firstly, methyl groups [2-(X-pyridyl)propan-2-ols] and then by *tert*-butyls [3-(X-pyridyl)-2,2,4,4-tetramethylpentan-3-ols]. Though the latter are somewhat less hindered than the di(1-adamantyl) derivative previously studied,⁴⁰ they prove to be difficult to study, because of their low solubility and the presence, in the 2- and 3-pyridyl derivatives, of *syn* and *anti* rotamers in equilibrium. Results concerning the rotational isomerism of these compounds are included in this paper.

RESULTS AND DISCUSSION

2-(X-Pyridyl)propan-2-ols and (X-pyridyl)alkanols

About 35 years ago a series of (2-pyridyl)alkanols, **1a–c**, was investigated by IR⁴¹ and NMR³⁹ spectroscopies. In the first part of this study we seek, by means of IR spectroscopy, qualitative information concerning both intra- and intermolecular hydrogen bonding in **1a–c** and some 3- and 4-pyridyl derivatives, **2a**, **2c**, and **3**. The related 2-(X-pyridyl)propan-2-ols, **4–6**, are also considered.⁴² In the second part we shall attempt to determine association constants for the formation of the various possible *n*-mers by NMR spectroscopy.



(i) IR spectroscopy

Dilute solutions of alcohols **1** in carbon tetrachloride show free and intramolecularly H-bonded OH absorptions close to those previously reported.⁴¹ At higher concentration alcohol **1a** has a clear association band at 3270 cm⁻¹, which increases relative to the bands for the free (3622/3641 cm⁻¹) and intramolecularly bonded (3440 cm⁻¹) forms as the concentration is raised (Fig. 1). Further details of the IR spectra are given in Supplementary Material Table S1.

Alcohol **1b** shows only a relatively weak association band at about 3300 cm⁻¹, while the presence of a second low-wavenumber band for **1c** at all concentrations suggests a higher degree of association. For **1c** the relative intensities of the two bands, already observed in dilute solution at about 3275 and 3380 cm⁻¹, change slightly, the latter increasing with the concentration.

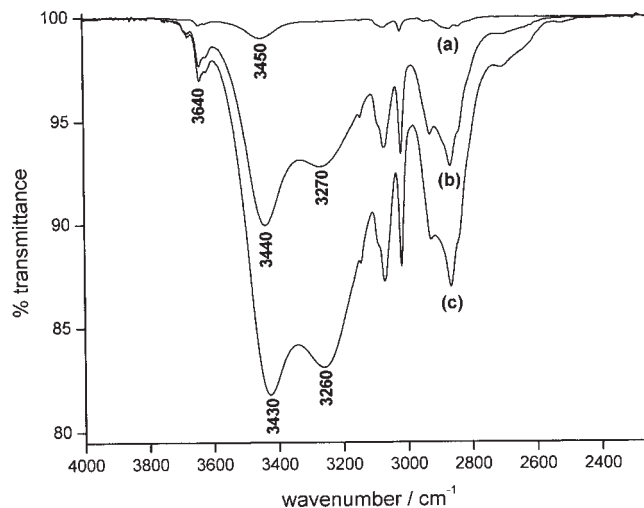


Figure 1. Concentration dependence in the OH stretching region of the IR spectrum of (2-pyridyl)methanol, **1a**, in carbon tetrachloride: (a) 0.016 M; (b) 0.16 M; (c) 0.31 M

Alcohols **2a**, **2c**, and **3** show free OH absorptions at 3617/3629, 3639, and 3618/3635 cm⁻¹, respectively, and broad association bands at 3280, 3315, and 3245 cm⁻¹, respectively, all these latter with ill-defined shoulders to higher wavenumbers (3395, 3420, and 3400 cm⁻¹, respectively). Since the relative heights of the principal and secondary absorptions seem to vary little with change in concentration, it is not possible to attribute them to specific types of association. It seems more likely that

they are due to different conformations of the association complexes.⁴¹

Alcohols **4–6** were synthesized by the reaction of methyl-lithium with the appropriate acetylpyridine. Certain aspects of their IR (in carbon tetrachloride) and NMR (in benzene) spectra differ from what was previously reported in chloroform.⁴² Whereas the OH vibration wavenumbers in the IR spectrum are stated to be 3450 (neat), 3200, and 3200 cm⁻¹ for **4**, **5**, and **6**, respectively, we find for **4** in carbon tetrachloride a broad band at 3430 cm⁻¹ and a weak absorption at 3612/3621 cm⁻¹, not previously mentioned. This latter obviously corresponds to the *anti* rotamer, with a free OH group. For **5** there are moderately strong free OH absorptions at 3606/3618 cm⁻¹ and two association bands at 3400 and 3250 cm⁻¹. The free OH absorptions are relatively stronger when the solution is diluted. For **6**,

which is very poorly soluble in CCl_4 , the free OH absorptions are at the same wavenumbers and there is a very weak, broad association band at about 3290 cm^{-1} . Reinvestigation of **5** and **6** in chloroform reveals that the strongest absorption at low concentration is in fact that of free OH at about 3600 cm^{-1} , while the 3200 cm^{-1} band is clearly due to association.

(ii) NMR spectroscopy

The ^1H NMR chemical shift of a NH or OH proton which is hydrogen-bonded in an associated form is higher than that of the same hydrogen in the non-associated form. One signal is observed for a proton in fast exchange between the two (or more) species, its shift being the weighted average of the shifts of these species. Consequently, the observed shift is concentration-dependent and, from the so-called NMR titration curve, association constants can be determined. This approach has been much used in a wide variety of fields to determine association constants and stoichiometries, particularly those concerned with biologically important species or their analogs, and in supramolecular chemistry in general.⁴³

(a) *Concentration dependence of NMR shifts.* All alcohols were studied in benzene. Although attention is normally focused on the OH proton shift, the other proton shifts are also concentration-dependent, though to a lesser extent. A particularly clear example is provided by **3**, where the H3/5 and CH_2 protons move downfield as the concentration increases, while H2/6 move upfield (Fig. 2).

These variations correspond to changes in the electron density: decrease at sites close to the OH group; increase at sites close to nitrogen. In **2a** H2 is sandwiched between nitrogen and the CH_2OH group and therefore hardly

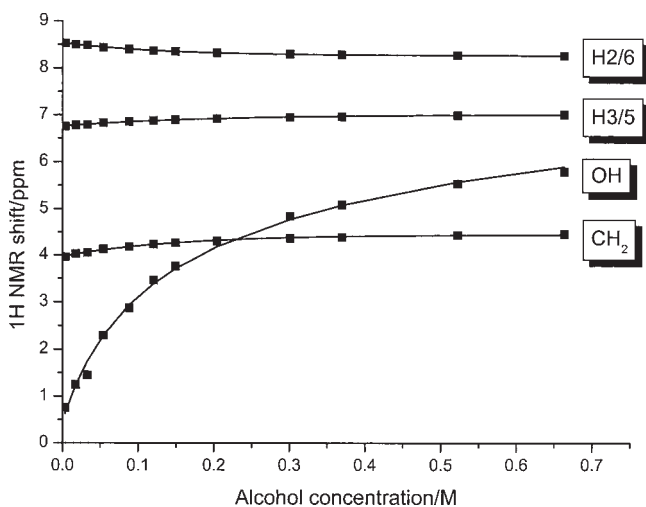


Figure 2. Concentration dependence of proton shifts in (4-pyridyl)methanol, **3**, in benzene at 298 K

moves, whereas H6 goes slightly upfield. Proton H4 moves downfield and H5 is little affected (Supplementary Material Fig. S1). The situation in **1a** is somewhat anomalous: proton H6, though close to nitrogen, goes downfield (Supplementary Material Fig. S2). However, since intramolecular hydrogen bonding is replaced by intermolecular bonding, the overall effect on the electron density is less predictable.

(b) *Association constants.* The NMR data for the variation of the OH proton shift with concentration were analyzed in terms of several models by means of WinEQNMR,⁴⁴ the R-factor (see Experimental section) being taken as the criterion of goodness-of-fit. Generally a cyclic trimer or tetramer appears to be accompanied by a dimer which is usually cyclic, though in some cases the fit was not disimproved by assuming it to be open. In Table 1 are listed association constants for the best models for each compound studied. In Supplementary Material Table S2 the R-factors and the chemical shifts of the free and hydrogen-bonded OH protons are listed. An example of the application of several models to a single data set is given in Supplementary Material Table S3.

For (2-pyridyl)methanol, **1a**, three models describe the data almost equally well: cyclic dimer-trimer; cyclic dimer-tetramer; open dimer-tetramer. For the corresponding 2-(2-pyridyl)ethanol, **1b**, and 3-(2-pyridyl)propan-1-ol, **1c**, there are four possibilities which all satisfy the data very well: cyclic dimer-trimer; open dimer-trimer; open dimer-tetramer; cyclic dimer-tetramer. The major difference between these compounds is that **1b** has much lower association constants, whatever the model. For **2a**, **2c**, and **3**, in each case there are at least three possibilities, but generally the best fit is with an open dimer-tetramer.

Free and intramolecularly hydrogen-bonded monomer are not distinguished. The value of δ_{B} , the chemical shift of the hydrogen-bonded OH hydrogen in the polymer, whatever it is, refers to intermolecular hydrogen bonding only (mean values for **2a**, **2c**, and **3** are 7.24, 6.65, and 7.45 ppm, respectively). The value of the chemical shift of the monomer, δ_{M} , on the other hand, represents both free and intramolecularly hydrogen-bonded monomer and is therefore high for the 2-pyridyl derivatives, **1a–c**, 3.62, 4.07, and 2.95 ppm, respectively. The highest value of δ_{M} , for **1b**, is associated with a very small constant for the formation of polymers. If association constants in the same models are compared for **1a** and **1c**, it is seen that they are always greater for **1c**, which has the lowest value of δ_{M} of this series. If δ_{M} can be taken as a measure of the hydrogen bond strength, this means that the formation of association complexes is modulated by the strength of the intramolecular hydrogen bond. For the other pyridylalkanols, **2** and **3**, where the side-chain is in the 3 or 4 position, and intramolecular hydrogen bonding is absent or very weak, the values of δ_{M} are much smaller (mean values for **2a**, **2c**, and **3** are 0.66, 0.36, and 0.64 ppm, respectively) and the association constants considerably higher.

Table 1. Association constants (M^{-1} , M^{-2} or M^{-3}) for pyridylalkanols and benzyl alcohols in benzene at 298 K, calculated according to various dimer, trimer, and/or tetramer models

Cpd.	Open dimer K/M^{-1}	Cyclic dimer K/M^{-1}	Cyclic trimer K/M^{-2}	Cyclic tetramer K/M^{-3}
1a		0.18 ± 0.04	0.82 ± 0.10	
1a		0.36 ± 0.01		1.61 ± 0.09
1a	0.68 ± 0.04			3.55 ± 0.15
1b		0.22 ± 0.01	0.20 ± 0.03	
1b	0.34 ± 0.02		0.30 ± 0.04	
1b		0.32 ± 0.01		0.35 ± 0.06
1b	0.64 ± 0.03			1.03 ± 0.11
1c		0.99 ± 0.03	1.45 ± 0.18	
1c	1.52 ± 0.01		3.93 ± 0.22	
1c		1.30 ± 0.03		5.16 ± 0.67
1c	2.90 ± 0.16			37.8 ± 1.0
2a		1.26 ± 0.15	20.6 ± 1.4	
2a		2.46 ± 0.10		155 ± 10
2a	4.67 ± 0.21			536 ± 17
2c		1.21 ± 0.21	9.31 ± 1.30	
2c		2.11 ± 0.11		53.4 ± 5.2
2c	4.30 ± 0.32			235 ± 17
3		1.70 ± 0.18	25.0 ± 1.9	
3		3.08 ± 0.16		231 ± 20
3	6.00 ± 0.37			866 ± 36
4		0.066 ± 0.027		
4	0.14 ± 0.07			
5		1.35 ± 0.17	10.4 ± 1.5	
5	1.85 ± 0.27		18.0 ± 1.1	
5	4.45 ± 0.41			287 ± 22
6		1.26 ± 0.66	5.71 ± 13.3	
6		1.46 ± 0.19		46.1 ± 18.2
6	3.22 ± 1.44			159 ± 222
9	1.08 ± 2.11		0.60 ± 5.16	
9	1.20 ± 1.72			2.25 ± 12.4
10		0.25 ± 0.01		1.26 ± 0.03
10	0.46 ± 0.01			2.16 ± 0.04
11		0.17 ± 0.01		0.31 ± 0.01
11	0.32 ± 0.01			0.53 ± 0.01

2-(3-Pyridyl)propan-2-ol, **5**, behaves very much like **2a** ($\delta_M = 0.89$ ppm; $\delta_P = 6.96$ or 7.42 ppm). However, alcohols **4** and **6** are poorly soluble in benzene, and measurements could be made over only a very limited concentration range. The OH proton shift of alcohol **4** in benzene at 298 K increases only slightly and almost linearly with concentration, by about 0.1 ppm on going from near-zero to 0.3 M. If we assume that the value of δ_P is 7.5 ppm, this would indicate a dimerization constant of 0.14 or $0.066 M^{-1}$, depending on whether the dimer is taken as open or cyclic, and that intramolecular hydrogen bonding prevails over association ($\delta_M = 4.91$ ppm). Trimer and tetramer species were rejected by the optimization procedure. For alcohol **6**, with the same assumption, the data are well described by three models, albeit with very high standard deviations, particularly on the higher n -mer association constants. Models with an open or cyclic dimer accompanied by a tetramer are the best ($\delta_M = 0.90$ ppm).

The OH proton signal in the 1H NMR spectrum in chloroform is reported to be at 5.0, 6.1, and 4.1 ppm for **4**,

5, and **6**, respectively.⁴² While the limiting value, δ_M , for **4** in benzene, 4.91 ppm, is similar to that quoted, the much smaller values for **5** and **6**, both about 0.9 ppm, indicate that there is considerable self-association at the presumably higher concentrations used for the early measurements.

(c) *OH NMR shifts in almost neat alcohols.* Curve-fitting gives not only association constants but also the related shifts of the monomer and polymer species, δ_M and δ_P , respectively (Table S2). While the former is relatively well defined by measurements made at low concentration and varies little with the model, the latter shows considerable fluctuations. It is therefore important to consider whether these values correspond in any way to the shift of the OH proton in the neat compound, bearing in mind however that even this will not be completely associated. Several compounds [**1a–c**, **2a**, **2c**, and **10** (see below)] were therefore examined in the presence of the minimum amount (5%) of deuteriated benzene for locking.

Equation (1) was solved numerically:

$$[\text{alcohol}] = [\text{monomer}] + 2K_2[\text{monomer}]^2 + nK_n[\text{monomer}]^n \quad (1)$$

where $n=3$ or 4 , and K_2 and K_n are the association constants for formation of dimer and n -mer, respectively. The OH shift was then calculated from Eqn (2) or (3):

$$[\text{alcohol}]\delta_{\text{calc}} = [\text{monomer}]\delta_{\text{M}} + 2K_2\delta_{\text{P}}[\text{monomer}]^2 + nK_n\delta_{\text{P}}[\text{monomer}]^n \quad (2)$$

or:

$$[\text{alcohol}]\delta_{\text{calc}} = [\text{monomer}]\delta_{\text{M}} + K_2(\delta_{\text{M}} + \delta_{\text{P}})[\text{monomer}]^2 + nK_n\delta_{\text{P}}[\text{monomer}]^n \quad (3)$$

when the dimer is open (Supplementary Material Table S4).

For the pyridylalkanols the calculated shifts are in all but one case (**2c** in the cyclic dimer-trimer model) lower than observed, by an average for all models and compounds of 0.09 ppm. In all cases the calculated shift is within 0.2 ppm of that observed, the greatest deviations concerning the cyclic dimer-tetramer model. The question arises as to whether results based on relatively low concentrations of alcohols in benzene are compatible with those where the "solvent" represents only 5% of the solution. In previous work it was found that alcohol hetero-association behaved consistently from low concentrations of pyridine in benzene right up to neat pyridine.³⁷ In the present case it is reassuring to find that there is good agreement between the calculated and observed shifts, but this can hardly be used as a test to determine which of the models is the most appropriate. At the high concentrations of these experiments it is possible that higher n -mers are present, or that the trimer and tetramer shifts are greater than that of dimer.

(d) *Temperature coefficients of OH NMR shifts.* The signal of an OH or NH proton usually goes upfield when

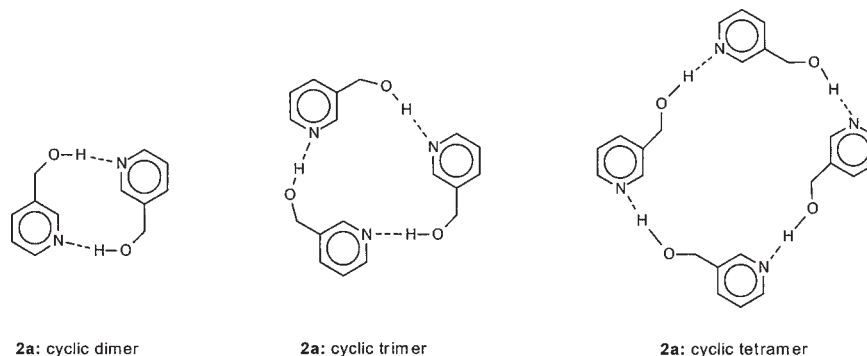
the temperature is raised, the variation being approximately linear with temperature and depending on the solvent and the nature of the group.⁴⁵ Hydrogen-bonded protons are associated with higher negative values of the temperature coefficient, in the ppb K^{-1} range, than those which are not hydrogen-bonded.

Our data on the association of **2a**, **3**, and **5** (Supplementary Material Tables S5 and S6) confirm that δ_{M} varies little with temperature.³⁷ The temperature coefficients for δ_{P} , on the other hand, are model- and alcohol-dependent, ranging from 22.5 (**5**, open dimer-trimer) to -19 (**3**, open dimer-tetramer) ppb K^{-1} . The latter figure is of the same order of magnitude as values for the hetero-association of pyridine with hindered alcohols.³⁷ For low-molecular-weight alcohols in cyclohexane, values based on a 1-2- n association model range from -4 to -8 ppb K^{-1} .²³ Large positive values are, therefore, anomalous. However, since the data for alcohol **5** are more scattered than for **2a** and **3** (R-factors $>1\%$), the results are less reliable. It may simply be that the open dimer-trimer model is incorrect, although the R-factors are as good as for cyclic dimer-trimer and open dimer-tetramer.

(e) *Thermodynamic parameters and molecular mechanics calculations.* In the three cases where we have determined the dimer and n -mer association constants at a range of temperatures (Supplementary Material Table S5), the van't Hoff plots show a significant difference in the reaction enthalpies and entropies (Table 2). Dimers, whether they be open or cyclic, are associated with small values of reaction enthalpies, ranging from -2 to -5 kcal mol^{-1} (1 cal = 4.184 J). Trimers and tetramers have much greater ΔH° , from -10 to -15 kcal mol^{-1} , tetramers being associated with slightly higher values than trimers. The dimerization enthalpies are less than would be expected for even one O—H...N hydrogen bond, which suggests that hydrogen bonding is partially offset by the increase in steric energy caused by bringing the two systems together. Dimer reaction entropies

Table 2. Reaction enthalpies (kcal mol^{-1}) and entropies (cal $\text{mol}^{-1} \text{K}^{-1}$) for selected pyridylalkanols in benzene, calculated according to various dimer, trimer, and/or tetramer models

Cpd.	Model	Open dimer		Cyclic dimer		Cyclic trimer		Cyclic tetramer	
		ΔH°	ΔS°	ΔH°	ΔS°	ΔH°	ΔS°	ΔH°	ΔS°
2a	Cyclic dimer-trimer			-3.8 ± 1.6	-12.1 ± 5.2	-10.4 ± 0.8	-28.9 ± 2.5		
2a	Cyclic dimer-tetramer			-4.8 ± 0.8	-14.1 ± 2.5			-13.8 ± 0.9	-36.4 ± 3.0
2a	Open dimer-tetramer	-4.6 ± 1.0	-12.2 ± 3.2					-14.3 ± 1.2	-35.4 ± 3.7
3	Cyclic dimer-trimer			-2.5 ± 0.4	-7.3 ± 1.4	-10.3 ± 0.9	-27.9 ± 2.7		
3	Cyclic dimer-tetramer			-3.7 ± 0.2	-10.3 ± 0.8			-13.1 ± 0.8	-33.0 ± 2.7
3	Open dimer-tetramer	-3.4 ± 0.3	-7.9 ± 1.0					-12.4 ± 0.2	-28.1 ± 0.7
5	Cyclic dimer-trimer			-3.1 ± 0.2	-10.0 ± 0.5	-14.6 ± 0.5	-44.2 ± 1.6		
5	Open dimer-trimer	-2.2 ± 0.2	-6.2 ± 0.7			-12.8 ± 0.4	-37.3 ± 1.1		
5	Open dimer-tetramer	-4.2 ± 0.1	-11.1 ± 0.4					-15.4 ± 0.1	-40.6 ± 0.4



average about $-10 \text{ cal mol}^{-1} \text{ K}^{-1}$ as against $-35 \text{ cal mol}^{-1} \text{ K}^{-1}$ for the higher polymers. These differences, though perfectly reasonable, do not allow us to discriminate between the various models. Neither do our results provide any information about the cooperativity effect.

Molecular mechanics calculations (MMFF94 in Sybyl 7.0 from Tripos, St. Louis, MO)⁴⁶ were run on all the monomers and on some of the possible polymers, from open dimers to cyclic tetramers (Table 3, further details in Supplementary Material Table S7). In almost all cases there is a reduction in steric energy on going from n monomer molecules to one n -mer species (ΔSE). The calculations find open dimers to be several kcal mol^{-1} more strained than the cyclic equivalents. Schematic representations of the dimer, trimer and tetramer of alcohol **2a** are shown above.

For alcohols **2a**, **3**, **5** and **6**, dimers, trimers, and tetramers should be formed with increasing ease: the larger the ring, the greater the strain relief. Values for **1a** follow the same order but are much smaller. If these values were correct, and if there were no compensatory reaction entropy changes,⁴⁷ only tetramers would be found in solutions of these alcohols. In fact, in the cases

where ΔH° has been measured (**2a**, **3** and **5**), ΔSE values for formation of the open dimer, cyclic dimer, trimer, and tetramer exceed the corresponding reaction enthalpies, ΔH° , by an average of 4.4, 9.0, 11.7, and 21.3 kcal mol^{-1} , respectively. If these figures are divided by the number of hydrogen bonds in the various species, we find excess energies of 4.4, 4.5, 3.9, and 5.3 kcal mol^{-1} , respectively, which indicates that MM overestimates the strength of one hydrogen bond by about 4.5 kcal mol^{-1} . This means that the cyclic dimers for compounds **1–6** are no less strained than the open dimers. Of the force fields available in Sybyl, the only other one which accepts these molecules is Tripos, and this gives even higher values of ΔSE .

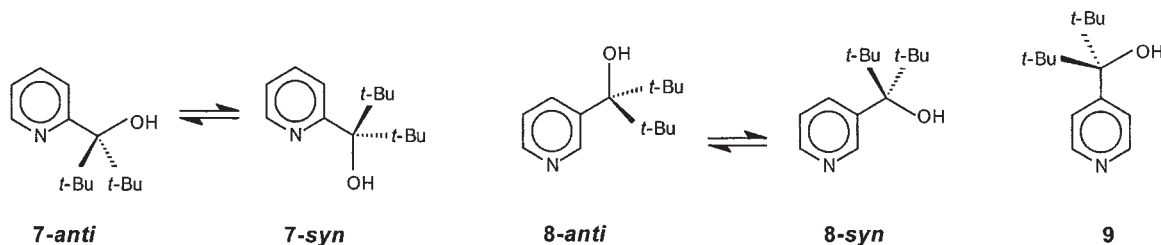
3-(X-Pyridyl)-2,2,4,4-tetramethylpentan-3-ols

The three previously unreported 3-(X-pyridyl)-2,2,4,4-tetramethylpentan-3-ols, **7–9**, were synthesized by reaction of the appropriate X-pyridyl-lithium with 2,2,4,4-tetramethylpentan-3-one in diethyl ether at -75°C , and were purified by column chromatography.

Table 3. Molecular mechanics calculations on selected pyridylalkanol and benzyl alcohols (MMFF94, steric energy differences in kcal mol^{-1})

Cpd.	ΔSE open d.	ΔSE cyc. d.	ΔSE tri.	ΔSE tetra.	$\text{N}\cdots\text{O}/\text{\AA}$ (a)	$\text{N}\cdots\text{H}-\text{O}/^\circ$ (a)
1a	-1.06	3.79	9.79	16.19	2.646	123.9
1b	2.63	6.79	16.03		2.799	138.3
1c	1.54				2.810	158.8
2a	8.08	13.51	24.44	34.90		
2c	4.62	7.06				
3	7.33	11.50	22.83	35.29		
4	-1.09	2.10	3.42		2.605	125.4
5	8.33	11.35	25.02	35.92		
6	8.20	12.58	22.68	36.98		
7-syn					2.518	128.5
8-anti	8.66					
8-syn	8.29	4.04				
9	8.24	7.01	20.65			
10	18.58	32.46				
11	10.15		22.59	37.37		

(a) Dimensions for 2-pyridyl-substituted alcohols.



(i) Rotation barriers

It has been known since the early 1970s that a $-\text{C}(\text{t-Bu})_2\text{OH}$ group attached to a benzene ring rotates slowly on the NMR time-scale with a barrier of about 20 kcal mol^{-1} .^{48,49} Barriers to rotation of the same rotor attached to hetero-aromatic groups vary from about 14 to 22 kcal mol^{-1} .⁵⁰ Replacing the *tert*-butyl groups by the more rigid 1-adamantyl substituent raises the rotation barrier by $5\text{--}10 \text{ kcal mol}^{-1}$, depending on the group to which the rotor is attached.⁵¹ This makes it possible to isolate both members of a rotamer pair on the bench,⁵² whereas the *tert*-butyl derivatives can only be distinguished in solution, most conveniently by NMR spectroscopy.

(a) *3-(2-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol*, **7**. In chloroform or benzene, alcohol **7** occurs very predominantly (*ca.* 95%, estimated from the magnitude of a second peak in the *tert*-butyl region and, in benzene, of peaks in the aromatic region) as the intramolecularly hydrogen-bonded *syn* isomer. Molecular mechanics calculations give steric energies of 89.5 and $85.8 \text{ kcal mol}^{-1}$ for the *anti* and *syn* rotamers, respectively (Table S7), the difference of $3.7 \text{ kcal mol}^{-1}$ being rather greater than the free energy difference of about $1.8 \text{ kcal mol}^{-1}$ at 298 K. In pyridine and DMSO the *anti/syn* ratio rises to 0.24 and 0.57, respectively. This corresponds to the familiar situation where the equilibrium between two rotamers, one with an intramolecular hydrogen bond and the other without, is strongly affected by the hydrogen bond basicity of the solvent.⁵³ The slope of a plot of $\log(K)$ for a set of seven solvents against the corresponding hydrogen bond basicity parameters⁵⁴ is 1.49 ± 0.09 , which is similar to values found in other systems.⁵³

Mean rotation barriers measured in DMSO at 348–378 K are 20.2 and $19.7 \text{ kcal mol}^{-1}$ for *syn* \rightarrow *anti* and *anti* \rightarrow *syn, respectively, the temperature dependence being very low for both reactions, that is, the activation entropies are close to zero. Small, mainly negative, activation entropies have been reported for other rotations of this type.^{53,55}*

(b) *3-(3-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol*, **8**. The ^1H NMR spectrum of **8** in benzene was resolved, that is, the various signals were associated with the H2, H4, H5, and H6 protons in the major and minor isomers, by gNMR simulation of the two sets of peaks, the ^{13}C NMR peaks

attributed by XHCORR and the rotamers identified by 2D-NOESY experiments (Supplementary Material Fig. S3). The *anti* and *syn* rotamers are characterized by the presence of strong cross-peaks for correlations between the *tert*-butyl groups and H2 and H4, respectively. Nevertheless, the *tert*-butyl groups are so voluminous that there are clear correlations, albeit weaker, with H4 and H2, respectively. Very weak correlations between the *anti* and *syn* OH groups and H4 and H2, respectively, are also observed.

Alcohol **8** occurs as a mixture of *anti* and *syn* forms in a ratio of 1.41:1 in benzene at 298 K. Molecular mechanics calculations give steric energies of 77.0 and $77.4 \text{ kcal mol}^{-1}$ for the *anti* and *syn* rotamers, respectively (Table S7), the difference of $0.4 \text{ kcal mol}^{-1}$ being in good agreement with the free energy difference of $0.2 \text{ kcal mol}^{-1}$. Values for chloroform, pyridine, and DMSO are (based on the assumption that relative peak positions are not solvent-dependent; NOE experiments were not performed in these solvents) slightly lower, at 0.15, 0.00, and $-0.05 \text{ kcal mol}^{-1}$, respectively, the *anti* isomer being slightly less favored as solvent basicity increases.

Mean rotation barriers measured in DMSO at 343–388 K are $20.6 \text{ kcal mol}^{-1}$ for both the *syn* \rightarrow *anti* and *anti* \rightarrow *syn rotations, the temperature dependence being very low for both reactions, that is, the activation entropies are again close to zero.*

(c) *3-(4-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol*, **9**. Since there is no dissymmetric element this derivative exists as a single species, that is, there are no rotamers. The NMR spectra clearly distinguish four CH groups in the pyridine ring, and the mean rotation barrier in DMSO at 363–408 K is $20.7 \text{ kcal mol}^{-1}$ and in nitrobenzene at 368–393 K is $20.9 \text{ kcal mol}^{-1}$.

The rotation barriers found here for the X-pyridyl derivatives are similar to that reported by Baas *et al.*⁴⁹ for the corresponding 3,4,5-trimethoxybenzene derivative in DMSO at a coalescence temperature of 421 K ($21.4 \text{ kcal mol}^{-1}$), which agrees with that calculated from the data of Gall *et al.*⁴⁸ Values for the 2-, 3- and 4-pyridyl derivatives at 421 K would be 19.5/20.2, 20.7, and $20.8 \text{ kcal mol}^{-1}$, respectively.

(ii) Association studies

IR spectra of near-saturated solutions of **8** and **9** in carbon tetrachloride show broad bands for the OH stretching

modes around 3370 cm^{-1} , consistent with self-association. Alcohol **7** already absorbs in this region (3330 cm^{-1}) even at low concentration, due to intramolecular hydrogen bonding; no further absorption is detected at high concentration.

The self-association of alcohols **7–9** was further investigated by determining the concentration dependence of the NMR shift of the OH protons in benzene (Table 4). In the case of the 2-pyridyl derivative, **7**, the chemical shift of neither the *syn* nor the *anti* OH proton changes significantly. The *syn* OH proton is hydrogen-bonded intramolecularly, as shown by its high NMR shift and the low OH stretching wavenumber. The fact that the *anti* rotamer is at very low concentration argues against self-association.

In view of the results for the less hindered pyridylalkanoles, the data for **9** (Table 4) were tentatively interpreted on the assumption that an open dimer and a larger cyclic polymer are formed. The choice of an open dimer was motivated by MM calculations, which indicate greater ΔSE than for a cyclic dimer. Again a value of δ_{p} ($=7.5\text{ ppm}$) was assumed. With these assumptions either a tetramer or, even better, a trimer completes the model adequately, but with very large uncertainties on the values of the association constants (Table 1). Both the K values for dimers of **9** (1.20 and 1.08 M^{-1} , respectively) appear to be higher than what was found for 2,2,4,4-tetramethylpentan-3-ol in carbon tetrachloride (0.15 M^{-1}), a solvent in which self-association constants are at least 5 times higher than in benzene.³⁷

In the 3-pyridyl derivative, **8**, both OH protons move downfield as the concentration increases, that for **8-anti** less than that for **8-syn**, while the *anti/syn* ratio is unchanged. If for the sake of simplicity we consider only open dimers, then we have potentially two homo-dimers (*anti-anti* and *syn-syn*), and two hetero-dimers (*anti-syn* and *syn-anti*). Systems where homo-association is accompanied by hetero-association can be handled if

the homo-association constants can be determined separately,⁵⁶ but this is not possible for alcohol **8**, which could, moreover, form homo- and hetero-polymers as well. Nevertheless, qualitative comparison of the concentration dependence of the OH NMR shifts for **8-anti** and **8-syn** with that for **9** (Table 4) suggests a similar degree of association at the same overall concentration.

In conclusion, the concentration dependence of the OH proton NMR shift indicates that the highly sterically hindered alcohols **8** and **9** associate at least as dimers. However, the situation is too complex to analyze in **8**, and the low solubility of **9** means that only very tentative values of the association constants can be given.

Calculations on the 2-pyridyl derivatives show clearly the steric effect of replacing hydrogen by methyl and by *tert*-butyl in the series **1a**, **4**, and **7**. As the substituent becomes more space-demanding the OH oxygen is forced closer to the nitrogen, and the $\text{N}\cdots\text{H}-\text{O}$ angle opens slightly (Table 3). This is mirrored by a progressive increase in the OH proton shift and a decrease in the degree of self-association. For the series comprising **1a–c**, where the chain-length increases, there is a rough correlation between the $\text{N}\cdots\text{O}$ distance and the $\text{N}\cdots\text{H}-\text{O}$ angle, but none with the shift of the OH proton, δ_{M} .

Despite the fact that we have not been able to analyze fully the data for **8** and **9**, it is instructive to compare series of molecules with decreasing substituent size: 2-substituted: **7**, **4**, **1a**; 3-substituted: **8**, **5**, **2a**. In alcohol **7** neither the *syn* nor the *anti* rotamer shows any tendency to associate, whereas **4**, though largely *syn*, associates slightly. The weaker intramolecular bond in **1a** allows both a dimer and a trimer or tetramer. The raw data for the two rotamers of alcohol **8** suggest a much greater degree of association than for **7**, somewhat less than that of **5**, which in turn differs from **2a** essentially in the magnitude of the trimer or tetramer association constant. It is difficult to be affirmative about the 4-substituted series: **9**, **6**, **3**, since association constants for alcohols **6** and **9** are so ill-defined. Alcohol **9**, with two *tert*-butyl substituents, appears to have a dimerization constant about a third of that of **6** and a fifth of that of **3**, where both bulky substituents have been replaced by hydrogens. Nothing can be said about the association constants for higher n -mers, except that they appear to fall rapidly with increasing substituent size.

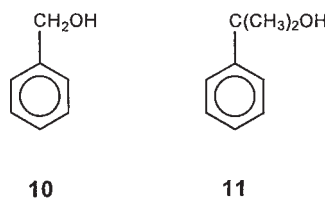
Benzyl alcohol and 2-phenylpropan-2-ol

Benzyl alcohol, **10**, has been the subject of several investigations,^{25,29,57–59} mainly by IR spectroscopy, various authors reaching quite different conclusions. According to early work²⁵ there are dimeric and high-order complexes in carbon tetrachloride, but another author reports that tetramers are the major species,⁵⁸ while multivariate resolution methods indicate open-

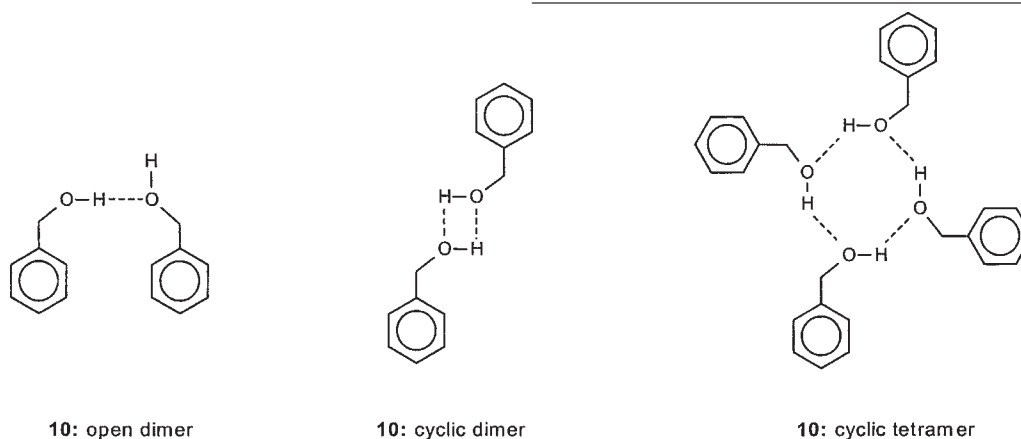
Table 4. Concentration dependence of OH NMR shifts (ppm) for 3-pyridyl-2,2,4,4-tetramethylpentan-3-ols, **7–9**, in benzene at 298 K

Cpd.	[M]	δ_{obs}	Cpd.	[M]	δ_{obs}
7-anti	0.0019	1.688	7-syn	0.0355	6.929
	0.0111	1.715		0.2101	6.918
8-anti	0.0013	1.466	8-syn	0.0009	1.487
	0.0064	1.508		0.0045	1.543
	0.0318	1.704		0.0226	1.789
	0.0596	1.895		0.0423	2.020
	0.1192	2.233		0.0845	2.390
9	0.0053	1.477			
	0.0159	1.537			
	0.0524	1.739			
	0.0987	1.963			
	0.2094	2.353			

chain aggregates and cyclic aggregates involving 4 and 7 monomers, respectively,⁵⁹ though the monomer is the major component throughout the range studied ($<0.2 \text{ mol kg}^{-1}$). According to heat capacity measurements in *n*-heptane, tetramers are the predominant species for 1-alkanols,²⁹ whereas for other alcohols (including **10** and 2-phenylpropan-2-ol, **11**) as the steric hindrance increases, the tetramer population is severely reduced.



Attempts to model cyclic dimers by molecular mechanics calculations failed, any preliminary closed structure opening automatically, whereas symmetrical cyclic trimer and tetramer species are well defined. For all three species, there is a considerable reduction in steric energy as compared to that of two, three or four monomers, respectively (Table 3). Schematic representations of the open dimer, closed dimer, cyclic trimer and cyclic tetramer of alcohol **10** are shown below.



The NMR data on **10** and **11** in benzene at 298 K at concentrations up to 1.5 M are well satisfied by a dimer-tetramer model, regardless of whether the dimer is assumed to be open or cyclic (Table 1). Note, however, that the agreement between the OH shift observed for neat benzyl alcohol and that calculated according to the cyclic dimer-tetramer model is the worst of all (Supplementary Material Table S4). For **10**, tetramers predominate except below about 0.55 M, where the open dimer and tetramer levels are very similar. For **11**, which is more crowded than **10** in the vicinity of the OH group, the dimer constant is very similar and the tetramer constant about one quarter that of **10**. The association complex is predominantly tetramer above a concentration of about 0.9 M. The MM calculations suggest that **11** should be more associated than

10 (Table 3), in contradiction with what is observed. Again, these calculations overestimate the H-bond strength.

The analysis of the NMR titration curves for **1–3** and **5** in terms of a monomer-dimer-higher *n*-mer model gives no structural information about the associated species. Our mathematical model only requires that, except when the dimer is open, there be as many equivalent hydrogen bonds as there are monomers in the *n*-mer, but does not specify which atoms are involved in these bonds. It is important to note, however, that the degree of association of **10** and **11** is very much smaller than that of the 3- and 4-pyridyl analogs, **2a**, **3**, **5**, and **6**. This indicates that the pyridine nitrogen atom is directly implicated in the association of these latter, and of all the other pyridylalkanols investigated. While the pyridine nitrogen has an electron-withdrawing effect which makes the OH hydrogen more acidic, that is, a better donor, it must at the same time make the oxygen atom a weaker acceptor. The overall substituent effect of a pyridine nitrogen on association should therefore be small. The conclusion that we are dealing with O—H···N bonding is corroborated by the much lower wavenumbers for IR stretching associated with this as compared to O—H···O bonding, which is characterized by values of the order of 3500 cm^{-1} .^{12,14,15,30,31,32b,33,36,58–60}

CONCLUSION

NMR titration curves for pyridylalkanols in benzene are in most cases somewhat equivocal about the exact character of the self-association. The data can be interpreted in terms of models based on open or cyclic dimers coexisting with cyclic trimers or tetramers. The relative magnitudes of the association constants depend on the length and the position, with respect to the pyridyl nitrogen, of the alkanol chain. In particular, for (2-pyridyl)alkanols the extent of association is inversely proportional to the strength of the intramolecular hydrogen bond, as judged by the OH NMR shift in the alcohol monomer. Molecular mechanics calculations with the MMFF94 force field appear to exaggerate the enthalpic advantage of associ-

ations in pyridylalkanols by 4–5 kcal mol⁻¹ per hydrogen bond. Sterically hindered pyridylalkanols clearly self-associate but the mode and extent of association cannot be determined by NMR studies, particularly when associations between different rotamers are possible.

The literature on alcohol self-association reports studies by a multitude of techniques on a wide variety of alcohols in a considerable number of solvents at concentrations ranging from dilute to neat. It should be noted, moreover, that there are two schools of thought concerning the modelling of hydrogen bonding: chemical theory, which we have used here, where hydrogen bond formation is treated as a chemical reaction, and physical theory, in which hydrogen bonds are considered as strong physical interactions.²³ The latter approach tends to gloss over the differences between open and cyclic polymers and also between polymers of different sizes. The “best” model approach selects a few equilibria from a multitude of possible exchange processes between species, while the NMR data are the weighted averages of all the exchange processes. Each model treats only a part of a complex system of equilibria in solution, in such a way that the NMR data are compatible with several descriptions: all may therefore be valid. Other experimental approaches and high-level quantum mechanical calculations would no doubt help to overcome the intrinsic ambiguity of the NMR study.

EXPERIMENTAL

General methods

¹H NMR 1D spectra were recorded in deuteriated benzene at 298 K on a Bruker AC 200 spectrometer with a spectral resolution of 0.001 ppm/pt, ¹³C NMR spectra in deuteriochloroform at 298 K. Shifts (in ppm) are referenced to TMS at 0.000 ppm (¹H) or to solvent peak at 77.0 ppm (¹³C). Aromatic proton signals of the various alkanols at convenient concentrations were assigned by spectrum simulation using the gNMR program (version 4.1 from Adept Scientific, Letchworth, UK); coupling constants (*J* in Hz) are not signed. IR transmission spectra were recorded in carbon tetrachloride at 298 K on a Nicolet Magna 860 FTIR spectrometer with 4 cm⁻¹ resolution. Generally experiments were performed at a range of concentrations. The association bands are broad and concentration-dependent, both in intensity and in wavenumber, this latter tending to fall as the concentration increases. Values given are rounded to the nearest 5 or 10 cm⁻¹. In some cases, spectra were decomposed by curve-fitting with Voigt functions for the individual association bands, using the Origin program (Microcal Software, Inc., now OriginLab Corporation, MA), but we have not attempted to be exhaustive in decomposing these or the free OH bands. These latter are sharp, Lorentzian and constant, but generally consist

of two peaks separated by 5–20 cm⁻¹. Further details on the IR spectra are given in Supplementary Material Table S1.

Materials

Compounds **1–3**, **10**, and **11** were commercial materials (>99%) used as received. 2-(*X*-Pyridyl)propan-2-ols, **4–6**, were synthesized by the reaction of the appropriate acetylpyridine with methyl-lithium in ether at room temperature.⁴² NMR and IR spectra of these compounds are listed in the Supplementary Material section of this paper.

3-(2-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol, **7**.

To 2-bromopyridine in diethyl ether at -75°C was added an equivalent of *n*-butyl-lithium in hexane. After stirring for 30 min, a 10% excess of 2,2,4,4-tetramethylpentan-3-one was added and the mixture allowed to warm slowly to room temperature. Conventional work-up, followed by column chromatography on alumina in light petroleum (b. range 35–60°C)/diethyl ether mixtures gave the alcohol (mp 43°C; 15% yield), eluted in 1–2% diethyl ether. **7-syn**: IR (CCl₄)/cm⁻¹: 3330; δ_H (benzene, 0.0355 M) 1.159 (s, 2 *t*-Bu), 6.542 (H5, *J* 1.0, 4.9, 7.4), 6.929 (s, OH), 6.956 (H4, *J* 1.8, 7.4, 8.2), 7.285 (H3, *J* 1.0, 1.1, 8.2), and 8.131 (H6, *J* 1.1, 1.8, 4.9); δ_C (chloroform) 29.4 (*t*-Bu), 41.4 (C_q), 81.8 (COH), 121.7 (C5), 123.2 (C3), 134.9 (C4), 145.8 (C6), and 162.3 (C2). **7-anti**: IR (CCl₄)/cm⁻¹: 3643; δ_H (benzene, 0.0019 M) 1.18 (s, 2 *t*-Bu), 1.69 (s, OH), 6.62 (H5), 7.17 (H4), 7.70 (H3), and 8.40 (H6). (Found: C, 75.8; H, 10.1; N, 6.0. C₁₄H₂₃NO requires C, 75.97; H, 10.47; N, 6.33%).

3-(3-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol, **8**.

Synthesized by reaction of 3-pyridyl-lithium with 2,2,4,4-tetramethylpentan-3-one as for **7**. The alcohol (mp 108°C; 29% yield) was eluted in 100% diethyl ether. The ¹H NMR spectrum was resolved by gNMR simulation of the two sets of peaks, the ¹³C NMR peaks attributed by XHCORR and the rotamers identified by NOESY. **8**: IR (CCl₄)/cm⁻¹: 3642, 3618, 3370. **8-syn**: δ_H (benzene, 0.0227 M) 0.911 (s, 2 *t*-Bu), 1.789 (s, OH), 6.688 (H5, *J* 0.8, 4.6, 8.2), 7.490 (H4, *J* 1.6, 2.5, 8.2), 8.547 (H6, *J* 0.4, 1.6, 4.6) and 9.322 (H2, *J* 0.4, 0.8, 2.5); δ_C (chloroform) 29.4 (*t*-Bu), 41.7 (C_q), 82.5 (COH), 120.6 (C5), 135.1 (C4), 140.3 (C3), 147.3 (C6) and 150.2 (C2). **8-anti**: δ_H (benzene, 0.0317 M) 0.920 (s, 2 *t*-Bu), 1.704 (s, OH), 6.893 (H5, *J* 0.9, 4.7, 8.1), 7.943 (H4, *J* 1.7, 2.4, 8.1), 8.490 (H6, *J* 0.4, 1.7, 4.7) and 9.061 (H2, *J* 0.4, 0.9, 2.4); δ_C (chloroform) 29.4 (*t*-Bu), 41.6 (C_q), 82.2 (COH), 122.8 (C5), 135.4 (C4), 141.4 (C3), 146.6 (C6), and 149.6 (C2). (Found: C, 76.2; H, 10.6; N, 6.1. C₁₄H₂₃NO requires C, 75.97; H, 10.47; N, 6.33%).

3-(4-Pyridyl)-2,2,4,4-tetramethylpentan-3-ol, 9. Synthesized by reaction of 4-pyridyl-lithium with 2,2,4,4-tetramethylpentan-3-one as for **7**. The alcohol (mp 152°C; 30% yield) was eluted in 100% diethyl ether. IR (CCl₄)/cm⁻¹: 3643, 3625, 3380; δ_H (benzene, 0.0524 M) 0.904 (s, 2 *t*-Bu), 1.739 (s, OH), 7.099 (H5, *J* 0.8, 2.2, 5.5), 7.506 (H3, *J* 0.7, 2.2, 5.3), 8.477 (H6, *J* 0.7, 5.5), and 8.668 (H2, *J* 0.8, 5.3); δ_C (chloroform) 29.3 (*t*-Bu), 41.2 (C_q), 82.5 (COH), 123.0 (C3), 123.2 (C5), 146.9 (C6), 149.4 (C2), and 154.7 (C4). (Found: C, 75.8; H, 10.6; N, 6.4. C₁₄H₂₃NO requires C, 75.97; H, 10.47; N, 6.33%).

¹H NOESY Experiment on 3-(3-pyridyl)-2,2,4,4-tetramethylpentan-3-ol, 8

For ¹H-¹H dipolar contact analysis, a NOESY spectrum was recorded in deuteriated benzene (degassed by several pump-freeze-thaw cycles and sealed under vacuum) on a Bruker DRX-500 spectrometer equipped with a Silicon Graphics workstation (Supplementary Material Fig. S3). A 5 mm broad-band probe with a shielded *z*-gradient was used. The temperature was monitored with a BCU 05 temperature unit and fixed at 300 K. Data were processed on a Silicon Graphics workstation with the help of GIFA (version 4.3).⁶¹ The 2D-NOESY experiment was acquired in the TPPI mode. It was recorded with 2 K points in *t*₂ over 6 kHz and 620 points in *t*₁. A 2.0 s relaxation delay and a mixing time of 600 ms were used for the 16 scans of each FID. Zero-filling was added in *F*₁. Squared-sine window functions were applied in both dimensions before Fourier transformation. Baselines were corrected using a polynomial function.

anti/syn Ratios for 3-(*X*-pyridyl)-2,2,4,4-tetramethylpentan-3-ols, 7 and 8

Small samples (*ca.* 10 mg) of alcohols **7** and **8** were dissolved in various solvents (0.5 ml) at 298 K and the *anti/syn* ratio (±0.01) determined by integration of the ¹H NMR spectra. Results were as follows. **7**: benzene, 0.06; chloroform, 0.04; methanol, 0.13; acetone, 0.13; pyridine, 0.24; DMSO, 0.57. **8**: benzene, 1.41; chloroform, 1.30; pyridine, 1.00; DMSO, 0.93.

Rotation kinetics on 3-(*X*-pyridyl)-2,2,4,4-tetramethylpentan-3-ols, 7-9

Dynamic ¹H NMR spectroscopy on solutions of alcohols **7-9** in DMSO and of **9** in nitrobenzene was used. Rate constants were determined by means of the gNMR program. Activation enthalpies (kcal mol⁻¹) and entropies (cal mol⁻¹ K⁻¹) determined from Eyring plots are as follows (compound, rotation direction, Δ*H*[‡], Δ*S*[‡]): **7**, *anti* → *syn*, 20.2 ± 0.1, 1.6 ± 0.3 (mean value

19.7 kcal mol⁻¹); **7**, *syn* → *anti*, 20.0 ± 0.2, -0.5 ± 0.4 (mean value 20.2 kcal mol⁻¹) (*T* = 348–378 K); **8**, *anti* → *syn*, 20.0 ± 0.2, -1.6 ± 0.6 (mean value 20.6 kcal mol⁻¹); **8**, *syn* → *anti*, 20.2 ± 0.2, -1.3 ± 0.6 (mean value 20.6 kcal mol⁻¹) (*T* = 343–388 K); **9**, -, 19.2 ± 0.2, -3.8 ± 0.4 (mean value 20.7 kcal mol⁻¹) (*T* = 363–408 K); **9**, nitrobenzene, -, 22.2 ± 0.6, 3.5 ± 1.4 (mean value 20.9 kcal mol⁻¹) (*T* = 368–393 K).

NMR titrations

Solutions of liquids were made up by injecting successive amounts of the alcohol into deuteriated benzene (0.5 ml) in an NMR tube. In calculating concentrations, volumes were taken as additive and the cubical expansion of the solution with temperature was assumed to be the same as that of the solvent. To a weighed amount of solid in an NMR tube was added solvent (0.5 ml); the volume was corrected by assuming a density of 1 g ml⁻¹ for the solid and additivity of volumes. ¹H NMR spectra were recorded at 298 K and in some cases at 298–328 K (Table S5). Reaction enthalpies (kcal mol⁻¹) and entropies (cal mol⁻¹ K⁻¹) were determined from van't Hoff plots (Table 2). Alcohols **1-3** were studied from about 0.01 to 2 M, **5** to 1.2 M. Highest concentrations of certain alcohols were severely limited by solubility: **4** to 0.3 M; **6** to 0.08 M; **7-9** to about 0.2 M.

Calculation of association constants

The general-purpose computer program, WinEQNMR,⁴⁴ optimizes association constants and the chemical shifts of the monomer, δ_M, and of the various associated species, δ_p. In practice we found that no more than three species could be handled (two association constants) and that it was advisable to make the simplifying assumption that all the hydrogen-bonded OH protons have the same chemical shift. Trimers and tetramers were assumed to be cyclic and to have three and four identical hydrogen-bonded OH protons, respectively. In the case of an open dimer we assumed that the shift of the free OH proton is the same as that of the monomer and that the hydrogen-bonded OH proton has the same shift as in a cyclic trimer or tetramer. The pertinence of the various models tested for each data set was judged according to the R-factor (defined in Supplementary Material Table S3), which was below 1% for the results quoted, except for alcohol **5**.

Molecular mechanics calculations

Molecular mechanics calculations were performed using the MMFF94 force field⁴⁶ with the MMFF94 charge model in the Sybyl 7.0 package. Steric energies (kcal mol⁻¹) for the most stable conformations of free alcohols and, where possible, the corresponding polymers are given in Table S7.

Acknowledgements

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