Hydrogen bonding and solvent effects in heteroaryldi(1-adamantyl)methanols: an NMR and IR spectroscopic study

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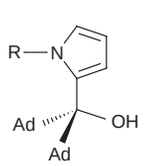
Received (in Cambridge) 17th August 1998, Accepted 23rd September 1998

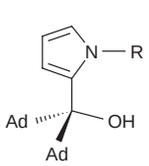
Reaction of the organolithium derivatives of certain heteroaromatics [2-furanyl, 2-thienyl, 2-thiazolyl, 2-pyridyl and 2-(3-methylpyridyl)] with di(1-adamantyl) ketone gives potentially rotameric tertiary alcohols. With 2-pyridyl- and 2-(3-methylpyridyl)lithium only the *syn* isomer is obtained. The *syn* isomer makes up 85–100% of (2-furanyl)diadamantylmethanol and 80–90% of the 2-thienyl derivative, depending on the NMR solvent. In chloroform or benzene the 2-thiazolyl derivative is a 2:1 mixture, the isomer with the sulfur atom *syn* to the OH group predominating; in DMSO or in the solid state this is the sole species. The IR absorption frequency for OH stretching correlates with the corresponding proton NMR shift in chloroform and with its temperature dependence, $\Delta\delta/\Delta T$. In pyridine $\Delta\delta/\Delta T$ is either large (−20 ppb/°C) or small (−1 to −2 ppb/°C) for intermolecular and intramolecular hydrogen-bonded species, respectively. Semi-empirical calculations (AM1 and PM3) suggest that the *anti* alcohols should be the more stable in the gas phase, but solvent effects and hydrogen bonding, in the case of the pyridyl derivatives, appear to reverse this situation, making the isomer with OH *syn* to the heteroatom the principal, and sometimes the only, species observed in solution.

Introduction

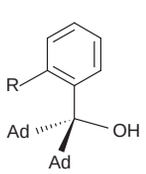
It was shown recently that 2-lithio-*N*-alkylpyrroles (alkyl = Me or Et), **1**, are sufficiently nucleophilic to attack the very congested carbonyl group in di(1-adamantyl) ketone, with the formation of the thermodynamically less stable *anti* isomer of [2-(*N*-alkylpyrrolyl)]di(1-adamantyl)methanol, **1A**.[1] Rotation about the sp^2–sp^3 C–C bond has an activation energy of about 31 kcal mol^{-1} † and gives the *syn* isomer, **1S**, which according to AM1 and *ab initio* calculations is more stable by about 5 kcal mol^{-1}. Although there are some minor quantitative differences, doubtless due to the smaller size of the aromatic ring, the properties of **1A** and **1S** are closely analogous to those of *o*-tolyldiadamantylmethanols, **3A** and **3S**,[2] the chemistry being to a large extent controlled by the *N*-methyl substituent. It was of interest, therefore, to examine a series of heteroaryldiadamantylmethanols without this dominant feature (with one exception), in order to study structural and spectroscopic properties more characteristic of the heterocycle. The systems studied here were chosen essentially for the accessibility of the appropriate organolithium derivatives and the proximity of the heteroatom to the OH group in the target alcohols.



1A: R = Me or Et

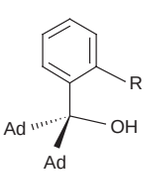


1S: R = Me or Et



2: R = H

3A: R = Me



3S: R = Me

† 1 cal = 4.184 J.

Results and discussion

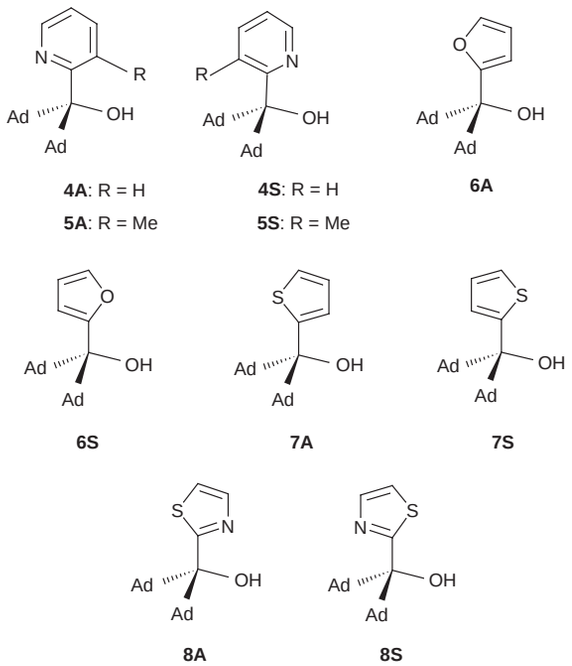
Alcohol synthesis

Treatment of 2-bromopyridine,[3] 2-bromo-3-methylpyridine,[4] 2-bromothiophene[5] or 2-bromothiazole[6] with *n*-butyl- or *tert*-butyllithium under various conditions gave the corresponding lithio compounds. 2-Lithiofuran was prepared directly by treatment of furan with *n*-butyllithium in the presence of TMEDA.[7] Starting materials were used in excess, in order to avoid dilithiation. Generally, a large excess of organolithium reagent over di(1-adamantyl) ketone was used. No attempt was made to optimize yields by systematic variation of the conditions, but progress of the reaction was monitored by sampling the reaction mixture from time to time after addition of the ketone to the organolithium compound.

The 2-lithio derivatives of the selected heteroaromatic systems react with diadamantyl ketone giving satisfactory yields of the corresponding alcohols. The aromatic carbon or hydrogen NMR signals were inspected to determine whether one or two isomers are formed. In the case of (2-pyridyl)diadamantylmethanol, **4**, and the 3-methyl derivative, **5**, the product is a single isomer. Attempts to generate a second rotamer or modify the rotamer ratio by heating at 150 °C resulted in 10–17% conversion of **4**, depending on the solvent, while **5** decomposed under these conditions. The corresponding 2-furanyl compound, **6**, is apparently a single isomer in DMSO or pyridine but two isomers in a ratio of about 9:1 or 6:1 in benzene or chloroform, respectively. In the same way, the 2-thienyl compound, **7**, is a mixture of two isomers in a ratio of about 9:1 or 4:1, depending on the NMR solvent. According to its NMR spectra in chloroform or benzene the 2-thiazolyl derivative, **8**, is a 2:1 isomer mixture; the proton NMR spectrum in pyridine indicates about 4% of the second isomer and in DMSO only one isomer can be detected. Alcohol **8** slowly decomposed to diadamantyl ketone when heated in chloroform at 150 °C.

Structure determination by NMR

The ^1H and ^{13}C NMR spectra of all the new alcohols could be fully attributed on the basis of the proton–proton coupling



constants,[8] spectrum simulation by means of the gNMR program[9] and heteronuclear correlation. ^{1}H NMR NOE experiments in chloroform were used in some cases to determine spatial relationships and thereby to establish the conformation of the isomeric alcohols. They consisted essentially in irradiating the various peaks of the adamantyl group signal and observing the effects on the other proton signals. Since ^{13}C NMR shifts are much less solvent-sensitive than proton shifts they were used systematically to identify rotamers in solvents other than chloroform.

NOE study of the 2-pyridyl, 2-(3-methylpyridyl), 2-furanyl and 2-thienyl alcohols (**4, 5**, **6** and **7**) indicates that the sole or major product (in chloroform) is the *syn* isomer. NOE cannot be used to differentiate the isomers of the 2-thiazolyl derivative, **8**, since there is no aromatic hydrogen close to the adamantyls. However, the high chemical shift (5.22 ppm) of the OH proton in the minor component, by analogy with the 2-pyridyl compound, **4**, strongly suggests that it is the isomer with nitrogen close to the OH group, that with sulfur *syn* to the OH group (2.57 ppm) predominating.‡ In DMSO only one isomer is found; the similarity of the ^{13}C NMR spectra, particularly the C2 and C4 shifts, in this solvent and chloroform indicates that it is the *syn* isomer, **8S**.

Hydrogen bonding in constrained alcohols

Among the many methods for the detection of hydrogen bonding,[11] either inter- or intramolecular, the best established is doubtless IR spectroscopy[12] but in certain areas of chemistry ^{1}H NMR spectroscopy[13] is increasingly used either alone or in conjunction with IR. Hydrogen bonding is typically associated with IR absorptions at lower-than-usual frequencies and higher-than-usual NMR shifts. Linear correlations between these two types of data have been reported.[14]

Benzyl alcohol and many related structures show two IR absorptions in the OH stretching region separated by 10–30 cm^{-1}, that at the lower frequency being attributed to a species in which there is hydrogen bonding to the π-electron system.[12] A relationship was established between this frequency and the C_{ar}–C_{ar}–C–O torsion angle,[15] orthogonality with the benzene ring being clearly advantageous.[16] Nevertheless, there are some doubts as to the reality of this type of hydrogen bonding which must in any case be very weak. Similar two-fold absorptions in sterically constrained dialkylbenzyl alcohols, such as **2** and **3A**, where the C–O bond is almost coplanar with the benzene ring, are better attributed to different conformations with respect to the C_{ar}–C–O–H torsion angle.[17] There are no crystallographic data on any of the compounds in the present study but the related [2-(*N*-methylpyrrolyl)]di(1-adamantyl)methanols, **1A** and **1S** (R = Me),[1] are structurally similar to the congested dialkylbenzyl methanols.[18] Molecular mechanics and semi-empirical quantum chemical calculations (*vide infra*) indicate small C_{ar}–C–O–H torsion angles.

In this work the IR spectra of the alcohols (Table 1) were measured in carbon tetrachloride, except for the 2-thiazolyl mixture, **8A** and **8S**, which was insufficiently soluble and was therefore studied in chloroform. The 2-furanyl and 2-thienyl derivatives, **6S** and **7S**, show strong absorptions at 3620 and 3624 cm^{-1}, respectively, with a strong shoulder at 3608 cm^{-1}. The 2-pyridyl analogue, **4S**, has a single peak at 3313 cm^{-1}, consistent with intramolecular hydrogen bonding. Treatment at 150 °C, giving presumably the *anti* isomer, **4A**, is associated with the appearance of a very weak absorption at 3637 cm^{-1}. This is a clear indication that any hydrogen bond formed in the *syn* isomer is specific to the nitrogen atom rather than to the π-electron system as a whole. The 2-(3-methylpyridyl) derivative, **5S**, absorbs at even lower frequency, 3165 cm^{-1}. Alcohol **8** has absorptions at 3619 and 3608 cm^{-1} and at 3427 and 3378 cm^{-1}; these can be attributed to the **8S** and **8A** rotamers, respectively, the latter low-frequency absorption being characteristic of hydrogen bonding to nitrogen, as in **4S**. This absorption is absent when the spectrum is run in KBr, suggesting that in the solid, as in DMSO, the stable species is the *syn* isomer.

Intramolecular hydrogen bonding has been claimed for (2-pyridyl)-substituted alcohols,[19] though the IR frequency shifts are substantially smaller than found here, of the order of 190 cm^{-1} for 2-pyridylmethanol, for example. Later work has shown that the NMR shift of the hydroxy proton is highly concentration-dependent, moving upfield with increasing dilution.[20] Clearly, both inter- and intramolecular hydrogen bonding are involved. The IR absorption for **4S** is almost 100 cm^{-1} lower than for the intramolecular hydrogen-bonded species (about 80–90% of the total) in the related (2-pyridyl)-arylmethanols[21] and about 150 cm^{-1} lower than in some quinoxaline diols of similar geometry.[22] 2,3-Di(2-pyridyl)-butane-2,3-diols and related compounds also show large ν_{OH} shifts and high δ_{OH}, but the crystallographic evidence[20] indicates that the hydrogen bonding involves a six-membered rather than a five-membered ring, which occurs in compounds examined here (**4S**, **5S** and **8A**).

A good IR–NMR correlation [$\delta_{OH} = (50 \pm 2) - (0.0135 \pm 0.0006)\nu_{OH}$; $r = 0.9945$] is found for alcohols **2**–**8** with, however, marked dispersion at the low shift/high frequency end (weighted means were taken for the IR values). This means that, while there is clear evidence for hydrogen bonding in the nitrogen-containing compounds, for the derivatives where sulfur or oxygen would be involved the situation is much less clear, the IR absorption being virtually indistinguishable from that of phenyldiadamantylmethanol, **2**. The NMR data, but not the IR, argue in favour of very weak H-bonding in **7S** and **8S**, but not in **6S**. Such small deshielding effects could, however, have causes other than hydrogen bonding. It should be noted that the *anti* isomer of the 2-thienyl derivative, **7A**, is associated with a proton signal at 2.17 ppm (that of **7S** is at 2.40 ppm) but it is impossible to locate the corresponding IR absorption.

Generally speaking, although changing the solvent from chloroform to benzene modifies considerably the aromatic proton spectrum the effect on the hydroxy proton shift is small, there being a modest upfield or downfield change (0.0–0.4 ppm) (Table 1). Going to DMSO, on the other hand, has marked

‡ Since S has priority over N the 2-thiazolyl isomer with OH close to nitrogen is denoted *anti*, whereas this situation for the 2-pyridyl derivatives corresponds to the *syn* isomer, N having priority over C.[10]

Table 1 Solvent dependence of hydroxy proton NMR chemical shifts (in ppm) in heteroaryldi(1-adamantyl)methanols; temperature coefficient (25–55 °C) of chemical shift in chloroform (*ca.* 0.05 M; in ppb/°C); OH stretching frequencies in carbon tetrachloride (*ca.* 0.01 M)

Compound	$\delta(CDCl_3)$[a]	$-\Delta\delta/\Delta T$	$\delta(C_6D_6)$[a]	$\delta(C_5D_5N)$	$-\Delta\delta/\Delta T$	δ(DMSO-d_6)[b]	ν_{OH}
2	1.97	0.13 ± 0.02	1.66	4.93	21.5 ± 0.1	3.81	3636, 3610
6S	1.85	0.47 ± 0.04[c]	1.93	5.17	21.5 ± 0.7	3.87	3620, 3608
7S	2.40	0.40 ± 0.01	2.14	5.67	20.7 ± 0.4	4.31	3624, 3608
7A	2.17	0.24 ± 0.01	—[d]	5.27	20.7 ± 0.3	4.10	—[e]
8S	2.57	0.57 ± 0.04	2.25	6.18	19.9 ± 0.3	4.99	3619,[f] 3608[f]
8A	5.22	1.86 ± 0.08	5.63	5.66	3.0 ± 0.1	—[g]	3429,[f] 3378[f]
4S	6.51	2.68 ± 0.10	6.78	6.74	1.7 ± 0.1	6.30	3313
4A	—[d]		1.79	4.52	20.5 ± 0.1	3.93	3637
5S	8.14	3.08 ± 0.02	8.32	8.30	1.9 ± 0.1	7.90	3165
Water				4.94	19.6 ± 0.1		

[a] 25 °C. [b] 60 °C. [c] −8 to 32 °C. [d] The signal fell in the range of the adamantyl protons (1.6–2.1 ppm) but could not be located unambiguously. [e] See text. [f] In chloroform. [g] The species is not detected in this solvent.

Table 2 Experimental free energy differences in various solvents and theoretical gas phase heat of formation differences (kcal mol^{-1}) for heteroaryldiadamantylmethanols (*anti* − *syn*)

Compound	$\Delta\Delta G°(CDCl_3)$	$\Delta\Delta G°(C_6D_6)$	$\Delta\Delta G°(C_5D_5N)$	$\Delta\Delta G°$(DMSO-d_6)	$\Delta\Delta H_f$(AM1)	$\Delta\Delta H_f$(PM3)
6[a]	1.0	1.3	>2.7	>2.7	−0.1	—
7[a]	1.2	1.0	1.3	0.8	−2.0	0.2
8[a]	0.4	0.5	1.9	>2.7	−2.1	−1.7
4[b]	1.8	1.7	1.5	1.4	−0.7	—

[a] At 25 °C. [b] At 150 °C.

effects on the phenyl, *syn*-2-furanyl, *syn*-2-thienyl, *syn*-2-thiazolyl and *anti*-2-pyridyl derivatives (**2**, **6S**, **7S**, **8S** and **4A**), the downfield displacement being 1.9–2.4 ppm. Changes of this magnitude are consistent with intermolecular bonding of the hydroxy hydrogen to the oxygen of DMSO. However, the two *syn*-pyridyl derivatives, **4S** and **5S**, move slightly upfield. This suggests that in these two alcohols the OH hydrogen is so strongly intramolecularly bonded to nitrogen that bonding with the solvent presents no thermodynamic advantage. In the case of the thiazolyl derivative the hydrogen bond in the *anti* isomer, **8A**, is too weak to make this isomer the more stable in chloroform or benzene, and in DMSO it disappears completely, as does **6A**. In pyridine, chosen as a potentially powerful hydrogen bonding solvent, the shifts of the hydroxy protons are about 30% higher than in DMSO, except for **4S** and **5S** which again do not move significantly.

The temperature dependence of the amide proton NMR shift in strongly hydrogen bonding solvents, usually DMSO, has been used as a criterion of hydrogen bonding in peptides,[13] model amides[23] and other compounds.[24] Small values ($-\Delta\delta/\Delta T \leq 3$ ppb/°C) are associated with protons involved in intramolecular hydrogen bonds or otherwise shielded from the medium, while exposed hydrogens exhibit larger values ($-\Delta\delta/\Delta T > 4$ ppb/°C). To the best of our knowledge, there has been no work on N···H–O bonding.

The temperature dependence of the hydroxy proton chemical shift in pyridine, measured from 25 to 50 °C on approximately 0.05 M solutions (shifts were not significantly concentration-dependent), is striking. For all those alcohols (as well as water) which are hydrogen-bonded to the solvent the coefficient, $\Delta\delta/\Delta T$, is of the order of −20 ppb/°C, while for the two pyridyl derivatives the value is barely a tenth of this, −1.7 and −1.9 ppb/°C for **4S** and **5S**, respectively. Here we would appear to have a clear-cut distinction between intramolecular and intermolecular hydrogen-bonded species. Only one structure, *anti*-(2-thiazolyl)diadamantylmethanol, **8A**, shows what appears to be an anomalous value, −3.0 ppb/°C. A reasonable interpretation would be that there is an equilibrium between intra- and intermolecular H-bonded species of this rotamer, and that the greater temperature dependence is due in part to a change in the equilibrium constant, as has been observed in certain diamides and triamides.[23]

Small amide $\Delta\delta/\Delta T$ values in non-hydrogen-bonding solvents have been taken to mean that the proton is entirely free of hydrogen bonding or completely locked in an intramolecular hydrogen bond, though Gellmann has shown that small values are not incompatible with equilibrium between intramolecularly hydrogen-bonded and non-hydrogen-bonded states.[23a] Given that these hypotheses appear to cover the complete range of possibilities, the interpretation of small $\Delta\delta/\Delta T$ values in such solvents would appear to be a hopeless task. For the alcohols examined in the present work, in chloroform the temperature coefficients range from −0.1 ppb/°C for phenyldiadamantylmethanol, **2**, to −3.1 ppb/°C for the 2-(3-methylpyridyl) derivative, **5S**. These values are all small, regardless of whether the hydroxy hydrogen is H-bonded or not, and there is an approximately linear dependence on the shift at 25 °C (Table 1) [$\Delta\delta/\Delta T = (0.68 \pm 0.12) - (0.48 \pm 0.03)\delta_{OH}$; $r = 0.9906$]. In this case, therefore, all that can be said is that $\Delta\delta/\Delta T$ correlates with the strength of intramolecular hydrogen bonding, insofar as it is expressed by the NMR shift data and the IR absorption frequencies.

Molecular mechanics and semi-empirical quantum chemical calculations

No detailed structural information was available for any of these compounds, but it was interesting to see to what extent the relative stabilities within the various rotamer pairs were reproduced by molecular mechanics and/or semi-empirical AM1 or PM3 calculations (Table 2). The most commonly used force field, MMP2,[25] has not been parametrized for substituted five-membered heteroaromatics, and even for pyridine derivatives two torsion angles have to be parametrized *ad hoc*. Both types of calculation gave well defined minima corresponding to the two rotamers, with the C–O bond generally within 10–12° of the ring plane.

According to MMP2 calculations on (2-pyridyl)diadamantylmethanol, **4**, the *anti* isomer is about 1.2 kcal mol^{-1} less strained than the *syn*. This is consistent with the intuitive idea that the nitrogen atom is less bulky than the cyclic CH, and can be taken as an indication of the relative stabilities in the absence of non-steric interactions. The fact that the *syn* is in reality the more stable, by 1.4–1.8 kcal mol^{-1} (depending on the solvent,

Table 2) indicates that there is a stabilizing interaction, equivalent to 2.6–3.0 kcal mol^{-1}. However, the solvent-dependence of the equilibrium shows that this quantity cannot be entirely attributed to hydrogen bonding but also includes solvation energy differences. For the 3-methyl-substituted derivative, **5S**, the steric energy difference is substantially greater, 7.6 kcal mol^{-1} in favour of the isomer with nitrogen *anti* to the OH group. This is slightly more than the difference between the corresponding *o*-tolyldiadamantylmethanols, **3A** and **3S** (7.0 kcal mol^{-1}). Since **5S** decomposes upon heating rather than rotates, and also fails to rotate in the presence of an organolithium reagent,[2b] it is not possible to estimate either the equilibrium constant or the contribution of hydrogen bonding to the stability of this isomer. Calculated distances between the N and O atoms in **4S** and **5S** are 2.55 and 2.45 Å, respectively; between N and H, 2.18 and 2.09 Å, respectively. The distances between the heteroatoms are well within the limit, the sum of their van der Waals radii (3.07 Å), below which a hydrogen bond can occur,[11,26] though the N···H···O bond angles are far from ideal.

AM1 calculations[27] on **4A** and **4S** find a difference in the heats of formation similar to that of the MMP2 steric energies and in the same direction, **4A** being the more stable by 0.7 kcal mol^{-1}, making the possible contribution of hydrogen bonding and differential solvation 2.1–2.5 kcal mol^{-1}. The geometry, however, is rather different, with the N···O and N···H distances 2.70 and 2.47 Å, respectively. For **5**, where the energy difference is dominated by steric interactions between the *ortho*-methyl group and the adamantyls, the *anti* rotamer is calculated to be 9.0 kcal mol^{-1} more stable than the *syn*; the N···O and N···H distances in **5S** are 2.58 and 2.35 Å, respectively. Despite the marked differences between the MMP2 and semi-empirical calculations, the N···O distance is clearly well inside the range required for hydrogen bonding. The effect of the *ortho*-methyl group is simply to push the two heteroatoms slightly closer.

AM1 calculations on the gas-phase stabilities of the other alcohol pairs generally predict the *anti* isomer to be the more stable, by 0.1 kcal mol^{-1} for **6A**, 2.0 kcal mol^{-1} for **7A** and 2.1 kcal mol^{-1} for **8A**, in contradiction with the solution results. On the other hand, PM3, which is better parametrized for sulfur, makes **7S** 0.2 kcal mol^{-1} more stable than **7A**, but **8S** still 1.7 kcal mol^{-1} less stable than **8A**. **8A** is calculated (AM1, PM3) to have N···O and N···H distances of 2.77, 2.70 and 2.56, 2.54 Å, respectively, obviously slightly greater than for the six-membered pyridine heterocycles but still well within the limit. In none of these calculations is there any explicit indication of hydrogen bonding, such as lengthening of the O–H bond, for example.

If we consider the "best" values for the gas-phase energy differences, in chloroform and benzene the calculations err in favour of the *anti* isomer by about 1 kcal mol^{-1} (Table 2). The free energy difference in favour of the *syn* isomer is rather greater for DMSO and pyridine; since **6A** is not seen at all in these solvents, we can only say that $\Delta\Delta G^\circ$ is greater than about 2.7 kcal mol^{-1}, assuming (somewhat optimistically, perhaps) that 1% of **6A** could have been detected. In the case of **8** the *anti* isomer is absent in DMSO and just detectable (*ca.* 4%) in pyridine, making the free energy difference >2.7 and 1.9 kcal mol^{-1}, respectively. There is no simple way of rationalizing the fact that, in contrast to the behaviour of the closely related compounds **6** and **8**, where the stability of the *syn* isomer is enhanced by hydrogen-bonding solvents, the level of **7A** is slightly greater in DMSO than in the other solvents examined.

Preliminary calculations on **6** and **7** using the AM1/SM2 model for hypothetical solvation by water, taken as a polar solvent, give rather surprising results. According to this model both **6A** and **6S** are destabilized by solvation, to the extent of 1.3 and 0.9 kcal mol^{-1}, respectively. This now makes the *syn* isomer the more stable. On the contrary, solvation of **7A** and **7S** appears to stabilize both isomers, but by very different amounts, 0.4 and 2.3 kcal mol^{-1}, respectively. This reduces the difference to 0.1 kcal mol^{-1}, still in favour of **7A**, but tends to run counter to the observation that **7A** is enhanced in DMSO. However, the opposed effects of pyridine and DMSO serve to underline the specificity of solvation phenomena and suggest that this treatment of solvent effects is inadequate to explain such relatively small free energy differences. In conclusion, the observation that isomer ratios are sensitive to the NMR solvent used clearly indicates that there are differential solvation effects upon the relative stabilities of the isomers, and it is quite likely that the solvation energies involved are of the same order of magnitude as the differences in the gas-phase heats of formation (albeit with their own degree of approximation) calculated by the semi-empirical methods.

Conclusions

The NMR spectra of most of the tertiary alcohols synthesized here (not the pyridyl derivatives) indicate that they exist in two rotameric forms, which interconvert rapidly on the laboratory time-scale and show a significant thermodynamic preference for the *syn* isomer, that in which the heteroatom and the OH group are closest. The IR and NMR spectra of the 2-pyridyl derivatives, which are synthesized as the *syn* isomers, and one isomer of the 2-thiazolyl derivative show that intramolecular hydrogen bonding is important; the data for the other alcohols indicate little or no hydrogen bonding. In the 2-thiazolyl derivative, the hydrogen bonding in the *anti* isomer is not strong enough to make it the more stable species, though semi-empirical calculations suggest that it should be, even without hydrogen bonding. Semi-empirical calculations systematically give the *anti* alcohol as the more stable in the gas phase. This disagreement with the experimental (solution) results may be due to deficiencies in the parametrization or to the neglect of solvation. The solvent-dependent variations in the isomer ratios show that the solvation energies of the two rotamers of a given alcohol can differ by at least 2 kcal mol^{-1}.

Experimental

General methods

NMR measurements were performed on a Bruker AS 200 FT instrument operating at 200 MHz (proton) or 50 MHz (carbon). Chemical shifts are given in ppm and *J* values in Hz. Unless otherwise noted all measurements were made in hexadeuteriobenzene, deuteriochloroform, pentadeuteriopyridine or hexadeuteriodimethyl sulfoxide at 25 °C (internal scaling/TMS: δ_H = 7.16, 7.26, 8.71 and 2.50; δ_C = 128.0, 77.0, 149.9 and 39.5). Carbon and hydrogen shifts of the heterocyclic system are numbered: C2, C3, *etc*. Generally, the proton signals were assigned on the basis of coupling constants[8] and spectrum simulation by the gNMR program (Cherwell Scientific).[9] The corresponding ^{13}C signals were identified by 2D heteronuclear correlation experiments using the XHCORR sequence. Samples for NOE experiments were solutions in deuteriochloroform degassed by several freeze–pump–thaw cycles before sealing under vacuum. Measurements were made on a Bruker AM-500 spectrometer at 500 MHz using the NOEMULT pulse sequence. NOE difference spectra were obtained by subtraction of the off-resonance control FID (16 K) from the on-resonance FID. The signal of interest was selectively saturated for 4 s. A cycle of 16 cycles of 16 scans was chosen with a relaxation delay of 2 s between each irradiation. Free induction decays were processed using exponential multiplication with a line broadening of 3 Hz before Fourier transformation. IR spectra were measured in carbon tetrachloride, chloroform or KBr on a Nicolet 60SX FTIR spectrometer with 2 cm^{-1} resolution. Lorentzian deconvolution was used to locate shoulders and to resolve broad absorptions. Gas chrom-

atography was performed on a 30 cm 10% SE30 on Chrompack column. Column chromatography was performed on silica gel 60 (Merck) in light petroleum (boiling range 35–60 °C)–dichloromethane mixtures. Melting points were determined in capillary glass tubes on a Mettler FP5 instrument with a heating rate of 3 °C min^{-1}.

Synthesis of heteroaromatic di(1-adamantyl)methanols

(2-Pyridyl)di(1-adamantyl)methanol, 4. 2-Bromopyridine (1 cm^3, 10.3 mmol) was stirred in sodium–dry diethyl ether (10 cm^3) under argon at −75 °C. A solution of *n*-butyllithium in cyclohexane (2 M, 5 cm^3, 10 mmol) was added dropwise in about 5 min. After stirring for 30 min, a solution of di(1-adamantyl) ketone (0.5 g, 1.7 mmol) in diethyl ether (40 cm^3) was added in about 15 min, the cooling bath removed and the mixture allowed to warm to about 0 °C. It was then quenched with water, and the organic product was extracted with a mixture of hexane and dichloromethane and twice rinsed with water. After drying ($MgSO_4$) the volatile solvents were largely evaporated at reduced pressure until solid started to appear. At this point the solution was refrigerated to complete crystallization. Filtration and washing with cold hexane gave a light brown product, identified by NOE, ν_{OH} and the chemical shift of the OH proton as **4S**, which was further purified by column chromatography (0.34 g, 54%): mp 215 °C; ν_{OH}/cm^{-1} (CCl_4) 3313, (KBr) 3277; δ_C (chloroform) 29.2 (6 CH), 37.1 (6 CH_2), 39.3 (6 CH_2), 44.5 (2 C_q), 82.2 (COH), 121.8 (C5), 124.0 (C3), 134.4 (C4), 145.7 (C6) and 161.0 (C2); δ_H (chloroform) 1.58 (br s, Ad), 1.6–2.0 (br m, Ad), 6.51 (OH), 7.21 (H5, *J* 1.0, 5.5 and 7.6), 7.58 (H3, *J* 1.0, 1.0 and 8.0), 7.65 (H4, *J* 1.3, 7.6 and 8.0) and 8.49 (H6, *J* 1.0, 1.3 and 5.5) (Found: C, 82.8; H, 9.4; N, 3.6. $C_{26}H_{35}NO$ requires C, 82.71; H, 9.34; N, 3.71%).

Heating a solution of the alcohol in $CDCl_3$ in a sealed tube for 2 h at 150 °C gave about 10% of an isomeric material, presumably the *anti* rotamer, **4A**, revealed by its IR spectrum and ^{13}C NMR (chloroform) peaks at 39.1 (CH_2), 44.9 (C_q), 120.7 (CH), 122.7 (CH), 134.8 (CH) and 146.3 (CH) ppm; signals corresponding to two of the aromatic protons were detected at *ca*. 7.05 and 8.6 ppm; ν_{OH}/cm^{-1} (CCl_4) 3637, (KBr) 3624. Replacing the solvent by benzene for NMR analysis greatly improved the separation of two of the aromatic proton signals. **4S**: δ_H 6.60 (H5), 7.05 (H4), 7.33 (H3) and 8.20 (H6); **4A**: δ_H 6.65 (H5), 7.21 (H4), 7.74 (H3) and 8.51 (H6). The same isomerization experiment run in benzene, pyridine and DMSO gave **4A** to the extent of 11, 14 and 17%, respectively.

[2-(3-Methylpyridyl)]di(1-adamantyl)methanol, 5. 2-Bromo-3-methylpyridine (0.25 cm^3, 2.2 mmol) was stirred in sodium–dry diethyl ether (10 cm^3) under argon at −75 °C. A solution of *tert*-butyllithium in pentane (1.7 M, 2.5 cm^3, 4.2 mmol) was added dropwise in about 2 min. After stirring for 30 min at the same temperature, a solution of di(1-adamantyl) ketone (0.15 g, 0.5 mmol) in diethyl ether (20 cm^3) was added in about 15 min. The reaction mixture was allowed to rise slowly to room temperature over a period of about 2 h, then quenched with water. The organic phase was washed with water, then dried over $MgSO_4$ and the solvent evaporated under vacuum to give a yellowish paste. Chromatography on silica gel gave a white solid (179 mg, 91%) consisting of **5S** (as shown by NOE, ν_{OH} and δ_H of the OH proton): mp 131 °C, decomp.; ν_{OH}/cm^{-1} (CCl_4) 3165; δ_C (chloroform) 26.4 (Me), 29.3 (6 CH), 37.1 (6 CH_2), 39.4 (6 CH_2), 45.4 (2 C_q), 86.5 (COH), 121.4 (C5), 132.4 (C3), 141.6 (C4), 142.2 (C6) and 160.7 (C2); δ_H (chloroform) 1.5–2.1 (br m, Ad), 2.74 (Me), 7.12 (H5, *J* 4.6 and 7.5), 7.52 (H4, *J* 0.6, 1.75 and 7.5), 8.14 (OH) and 8.37 (H6, *J* 0.6, 1.75 and 4.6); homonuclear decoupling experiments indicate that H4 and H6 are coupled with the methyl group (Found: C, 83.0; H, 9.6; N, 3.4. $C_{27}H_{37}NO$ requires C, 82.81; H, 9.52; N, 3.58%).

Attempts to convert this material to the *anti* isomer by heating resulted only in decompostion to diadamantyl ketone. The alcohol was unchanged by treatment with *tert*-butyllithium in pentane for 1 h.

(2-Furanyl)di(1-adamantyl)methanol, 6. Furan (0.36 cm^3, 5 mmol) was lithiated by treatment with *n*-butyllithium (1.6 M in hexanes, 3.1 cm^3, 5 mmol) in the presence of TMEDA (0.68 cm^3, 5 mol) in diethyl ether (10 cm^3) under argon at room temperature. After 30 min a solution of di(1-adamantyl) ketone (0.15 g, 0.5 mmol) in diethyl ether (20 cm^3) was added in about 10 min. After 1 h the mixture was quenched with water, the organic phase washed with water, then dried over $MgSO_4$ and the solvent evaporated to yield a light brown solid which was purified by silica gel chromatography and crystallization from hexane (0.153 g, 83%; mp 178 °C); by NOE the major constituent was identified as **6S**: ν_{OH}/cm^{-1} (CCl_4) 3620, 3608sh; δ_C (chloroform) 29.4 (6 CH), 37.1 (6 CH_2), 38.7 (6 CH_2), 44.5 (2 C_q), 82.6 (COH), 107.9 (C3), 109.2 (C4), 140.1 (C5) and 160.0 (C2); δ_H (chloroform, −8 °C) 1.6–2.1 (br m, Ad), 1.84 (OH), 6.17 (H3, *J* 1.0 and 3.2), 6.32 (H4, *J* 1.8 and 3.2) and 7.38 (H5, *J* 1.0 and 1.8). A minor component, *ca.* 15% of the total, gave ^1H NMR peaks, located in part by gNMR simulation, at 6.15 (H3), 6.42 (H4) and 7.36 (H5) ppm and ^{13}C signals at 105.5, 110.8 and 138.5 ppm. These were attributed to the *anti* isomer, **6A**; this isomer was not found in DMSO at 25 or 60 °C (Found: C, 81.7; H, 9.3. $C_{25}H_{34}O_2$ requires C, 81.92; H, 9.35%).

(2-Thienyl)di(1-adamantyl)methanol, 7. 2-Bromothiophene (0.95 cm^3, 9.9 mmol) was stirred in sodium–dry diethyl ether (10 cm^3) under argon at 0 °C. A solution of *n*-butyllithium in cyclohexane (2 M, 5 cm^3, 10 mmol) was added dropwise in about 5 min. After stirring for 30 min, a solution of di(1-adamantyl) ketone (0.50 g, 1.7 mmol) in diethyl ether (30 cm^3) was added in about 15 min. After a further 30 min the reaction mixture was quenched with water, and the organic phase was washed with water, then dried over $MgSO_4$ and the solvent evaporated. Crystallization from *n*-hexane gave a solid (0.50 g, 78%; mp 205 °C) apparently containing two products in a ratio of 7:1. Major product, identified by NOE, **7S**: ν_{OH}/cm^{-1} (CCl_4) 3624, 3608sh; δ_C (chloroform) 29.0 (6 CH), 36.9 (6 CH_2), 38.8 (6 CH_2), 45.0 (2 C_q), 84.7 (COH), 121.6 (C5), 122.5 (C3), 126.3 (C4) and 151.4 (C2); δ_H (chloroform) 1.60 (br s, Ad), 1.7–2.1 (br m, Ad), 2.40 (OH), 6.92 (H3, *J* 1.0 and 3.6), 7.01 (H4, *J* 3.6 and 5.1) and 7.16 (H5, *J* 1.0 and 5.1). In DMSO at 60 °C the **7S/7A** isomer ratio is 4:1. Major product, **7S**: δ_C (DMSO) 28.3 (6 CH), 36.3 (6 CH_2), 38.6 (6 CH_2), 44.2 (2 C_q), 83.9 (COH), 121.6 (C5), 121.6 (C3), 126.7 (C4) and 152.1 (C2); δ_H (DMSO) 1.56 (br s, Ad), 1.7–2.1 (br m, Ad), 4.31 (br, OH), 6.90 (H3, *J* 1.0 and 3.6), 6.97 (H4, *J* 3.6 and 5.2) and 7.20 (H5, *J* 1.0 and 5.2); minor product, **7A**: δ_C (DMSO) 28.4 (6 CH), 36.4 (6 CH_2), 38.0 (6 CH_2), 43.6 (2 C_q), 84.6 (COH), 123.3 (CH), 123.7 (CH), 126.6 (CH) and 146.5 (C2); δ_H (DMSO) 1.56 (br s, Ad), 1.7–2.1 (br m, Ad), *ca*. 4.1 (br, OH), 6.93 (H4, *J* 3.6 and 5.1), 7.06 (H3, *J* 1.4 and 3.6) and 7.31 (H5, *J* 1.4 and 5.1) (Found: C, 78.6; H, 9.1; S, 8.3. $C_{25}H_{34}OS$ requires C, 78.48; H, 8.96; S, 8.38%).

(2-Thiazolyl)di(1-adamantyl)methanol, 8. 2-Bromothiazole (0.5 cm^3, 5.6 mmol) was stirred in sodium–dry diethyl ether (10 cm^3) under argon at −75 °C. A solution of *n*-butyllithium in hexanes (1.6 M, 3 cm^3, 4.8 mmol) was added dropwise. After stirring for 1 h at the same temperature, a solution of di(1-adamantyl) ketone (0.15 g, 0.5 mmol) in diethyl ether (20 cm^3) was added in about 10 min. The reaction mixture was allowed to warm slowly to room temperature and was left overnight. It was then quenched with water and a mixture of light petroleum and dichloromethane, an abundant black precipitate filtered off, the organic phase washed with water, then dried over $MgSO_4$ and the solvent and other volatiles evaporated. After chromatography ^1H NMR showed the product to consist of a 2:1 mixture [167 mg, 87%; mp 199 °C; ν_{OH}/cm^{-1} ($CHCl_3$) 3619, 3608sh and 3429, 3378, (KBr) 3588, 3581] of isomeric

alcohols. Major product, *syn* with respect to sulfur, **8S**: δ_C (chloroform) 29.0 (6 CH), 36.9 (6 CH_2), 38.7 (6 CH_2), 45.1 (2 C_q), 85.2 (COH), 117.5 (C5), 141.6 (C4) and 178.3 (C2); δ_H (chloroform) 1.5–2.2 (br m, Ad), 2.57 (OH), 7.21 (H5, *J* 3.3) and 7.78 (H4, *J* 3.3); δ_C (DMSO) 28.4 (6 CH), 36.6 (6 CH_2), 38.0 (6 CH_2), 44.3 (2 C_q), 84.5 (COH), 118.3 (C5), 141.3 (C4) and 178.8 (C2); δ_H (DMSO) 1.5–2.2 (br m, Ad), 4.99 (OH), 7.47 (H5, *J* 3.3) and 7.74 (H4, *J* 3.3); minor product, **8A**: δ_C (chloroform) 29.0 (6 CH), 37.0 (6 CH_2), 38.6 (6 CH_2), 44.4 (2 C_q), 85.3 (COH), 119.2 (C5), 137.9 (C4) and 172.8 (C2); δ_H (chloroform) 1.5–2.2 (br m, Ad), 5.22 (OH), 7.33 (H5, *J* 3.2) and 7.70 (H4, *J* 3.2). **8A** was not found in DMSO (Found: C, 74.6; H, 8.6; N, 3.9; S, 8.1. $C_{24}H_{33}ONS$ requires C, 75.15; H, 8.67; N, 3.65; S, 8.36%).

Alcohol **8** (65 mg) in chloroform (1.5 cm^3) was heated in a sealed tube at 150 °C for 5 h. Evaporation of the solvent followed by chromatography on alumina in light petroleum–diethyl ether gave di(1-adamantyl) ketone (42 mg, 83%).

Temperature coefficient of the ^{1}H NMR chemical shift

Approximately 0.05 M solutions of the various alcohols in deuteriochloroform or pentadeuteriopyridine (chosen in preference to DMSO because of the low solubility of the alcohols in the latter) were examined at 5 °C intervals in the 25–50 °C range (Table 1). The temperature variation of the hydroxy proton shift is based on the assumption that the solvent reference is constant. Values of $\Delta\delta/\Delta T$ are expressed in ppb/°C.

Molecular mechanics and semi-empirical quantum mechanical calculations

To handle pyridyl derivatives with MMP2(85),[25] parameters for two torsion angles (types 1-1-2-37 and 6-1-2-37) have to be supplied. The steric energies (kcal mol^{-1}) are based on the assumption that they can be treated as types 1-1-2-2 and 6-1-2-2, respectively. **4A** 58.6; **4S** 59.8; **5A** 61.8; **5S** 69.4.

The Spartan package[27] with AM1 and PM3 (for sulfur-containing species) was used for semi-empirical calculations. Preliminary calculations with the AM1/SM2 model for solvation by water were run on **6** and **7**. The heats of formation ($\Delta\Delta H_f$/kcal mol^{-1}) listed are those for the lowest-energy conformations within the different conformers: **4A** (AM1) −58.2; **4S** −57.5; **5A** (AM1) −60.1; **5S** −51.1; **6A** (AM1) −91.6; **6S** −91.5; **7A** (AM1, PM3) −66.2, −48.4; **7S** −64.2, −48.6; **8A** (AM1, PM3) −54.3, −38.4; **8S** −52.2, −36.7. AM1/SM2 results: **6A** −90.2; **6S** −90.6; **7A** −66.6; **7S** −66.4.

Acknowledgements

We are indebted to Ms Claire Mangeney for helpful discussions.

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Paper 8/06485G