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Direct NMR measurement of rotation rates: solvent effects on rotation barriers

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ABSTRACT: 2,2,4,4-Tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)]thienyl}pentan-3-ols self-associate both in the solid state and in solution. The IR spectra of the solids display a broad OH absorption at 3320 cm^{-1}, corresponding to an intermolecularly hydrogen-bonded *syn* rotamer, probably a dimer, as well as absorptions around 3500 cm^{-1} of the intramolecularly hydrogen-bonded *anti* form. Well-crystallized samples of these derivatives go into solution in the *syn* form but undergo rotation to the *anti* rotamer at a rate which can be measured directly by proton Nuclear Magnetic Resonance (NMR) spectroscopy. The diethoxy derivative was studied in a wide variety of solvents. The activation energy for *syn*→*anti* rotation is practically solvent-independent, whereas that of the reverse reaction falls in hydrogen-bonding solvents, by more than 2 kcal mol^{-1} on going from chloroform or benzene to dimethylsulfoxide (DMSO). By combining direct measurements at low temperature and Dynamic Nuclear Magnetic Resonance (DNMR) results at high temperature, rotation rates were evaluated over a range of more than 100 K, and significantly large negative activation entropies determined. Copyright © 2007 John Wiley & Sons, Ltd.
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KEYWORDS: hydrogen bonding; NMR; IR; dimers; rotation; activation entropy

INTRODUCTION

There has been little systematic work on the solvent dependence of rotation barriers, probably because they are generally so small that the choice of solvents is severely restricted to those, often halohydrocarbons, which do not freeze at the low temperatures required for the measurements. The most notable exception to this statement concerns rotation about the C—N bond in amides and thioamides,[1] where activation energies increase with concentration and are much greater in polar than non-polar solvents. The positive activation entropies found in the more polar solvents are attributed to transition state desolvation. In contrast, rotation in 9-(2-methoxy-1-naphthyl)fluoren-9-ol is easier in DMSO than in hexachlorobutadiene, and activation entropies are negative in both solvents.[2] These results indicate contrasting patterns in the relative importance of reactant and transition state solvation.

In previous work from this laboratory[3–7] on rotation about sp^2-sp^3 carbon-carbon bonds in congested alcohols, it has been found: (a) that rotation barriers can range from about 15 to 45 kcal mol^{-1} (1 cal = 4.184 J), (b) that the rotation barrier is strongly directional, that is, equilibrium constants can be far from unity, in which case there are two different barriers, depending on whether the rotation is considered to start from one extremum or the other, and (c) that equilibrium constants and rotation barriers are solvent-dependent. Feature (a) is simply of matter of steric hindrance, sterically demanding rotors turning more slowly than smaller ones. Feature (b) may also depend on steric factors but in several cases both (b) and (c) are related to the presence of the OH group and the possibility of intramolecular hydrogen bonding.

We recently reported that 2,2,4,4-tetramethyl-3-{2-[3,4-alkylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ols, **1a** and **1b**, self-associate both in the solid and in solution.[8] The corresponding 3,4-dialkoxy derivatives, **1c** and **1d**, are found to behave in the same way but, because they are more sterically hindered, it becomes possible to measure rotation barriers directly at room temperature over a complete range of solvent character, without recourse to dynamic NMR. This unusual opportunity results from the convenient magnitude of the barriers and the fact that these alcohols crystallize in a self-associated form of the *syn* rotamer, which is the less stable in most solvents.

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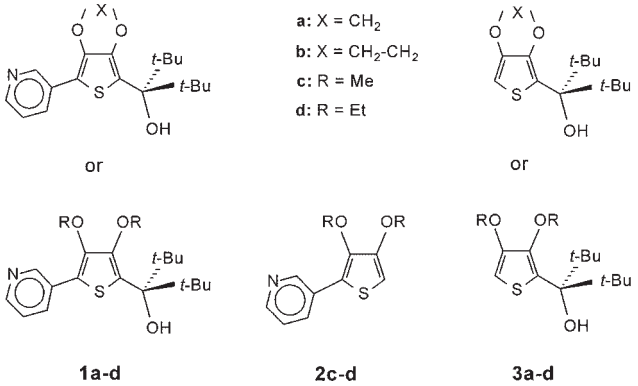
In some cases it is possible to complement the room-temperature data with measurements based on dynamic NMR at much higher temperatures. Analogous examples of direct measurement of rotation barriers involve isolation of the less stable rotamer as a lithium salt[9] or solvent change.[10]

RESULTS AND DISCUSSION

Synthesis, NMR and IR Spectroscopy

Two 2,2,4,4-tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)]-thienyl}pentan-3-ols, where the alkoxy group is methoxy (**1c**) or ethoxy (**1d**), were synthesized from the corresponding 2-(3-pyridyl)-3,4-dialkoxythiophenes, **2c** and **2d**, prepared by methods described previously.[8] Routine ^{1}H NMR spectra of equilibrated solutions of these compounds in chloroform at room temperature indicate that they are primarily in the *anti* form, with *syn*/*anti* ratios somewhat greater than those of analogues which lack the 5-(3-pyridyl) substituent, **3c** and **3d**.[10] Full details concerning the characterization of the *syn* and *anti* rotamers, as well as an X-ray diffraction study of the *syn* dimer of **1b** are given in the previous paper.[8] The relationship between the rotamers and the dimer is depicted in the Scheme below.



The IR spectra of **1c** and **1d**, deposited from dichloromethane solution onto a KBr plate, show strong absorptions at 3497 and 3489 cm^{-1}, respectively, corresponding to the *anti* isomer (Figure 1). Compounds **3c** and **3d**, which lack the 3-pyridyl substituent, absorb at 3502 and 3486 cm^{-1}, respectively, in solution in carbon tetrachloride.[5b] However, **1c** and **1d** also show broad

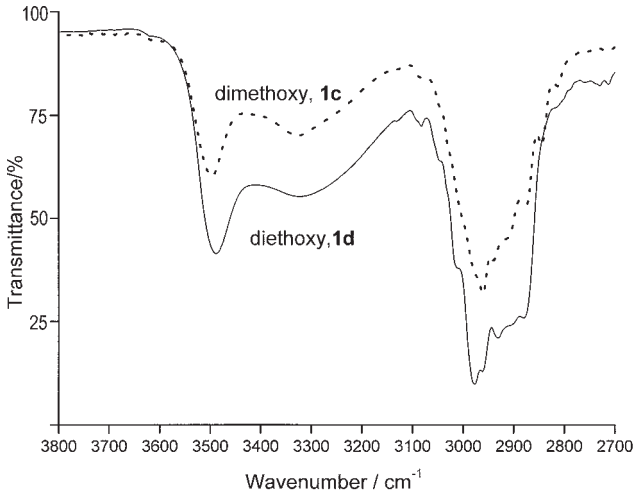


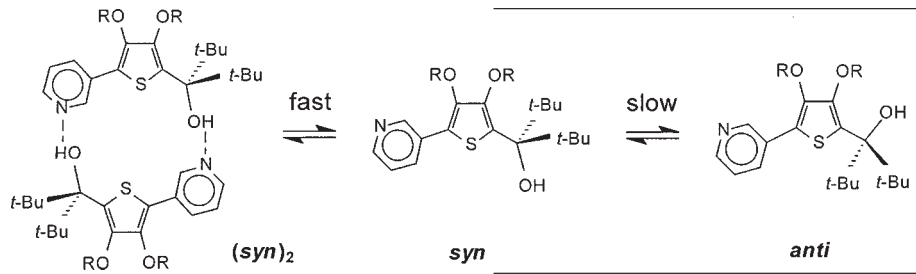
Figure 1. IR spectra of **1c** and **1d**, cast from CH_2Cl_2 solution onto KBr plates

absorptions at about 3320 cm^{-1}, associated with an intermolecularly hydrogen-bonded species. The free *syn* isomers of **3c** and **3d** have OH absorptions at 3606/3626 and 3605/3629 cm^{-1}, respectively,[5b] which means that the absorptions of the associated forms of the *syn* rotamer (which we assume, by analogy with **1b**,[8] to be dimers) of **1c** and **1d** are red-shifted by about 370 cm^{-1}.

Direct NMR measurement of rotation barriers

The first aim was to extend our study of self-association[8] to the 3,4-dimethoxythiophene derivative, **1c**, though the low equilibrium *syn*/*anti* ratio would be expected to make self-association of the *syn* rotamer more difficult to investigate. However, a solution of the alcohol in benzene was found to evolve rapidly: the *syn*/*anti* ratio is high immediately after dissolution of the solid but falls at the same time as does the shift of the *syn* OH proton. Both reach stable values after about 4 hours at 298 K (Figure 2). The well-crystallized samples used for the NMR work are very predominantly *syn*, in agreement with the single-crystal X-ray diffraction study on the 3,4-ethylenedioxythiophene (EDOT) derivative, **1b**,[8] whereas the IR samples, prepared by evaporation of a solution, are clearly much less homogeneous.

The overall rate constant, k_{glob}, is 9.7×10^{-4} s^{-1} and the equilibrium constant 0.14 ($K_1 = [syn]/[anti]$), which give activation energies of 21.6 kcal mol^{-1} and



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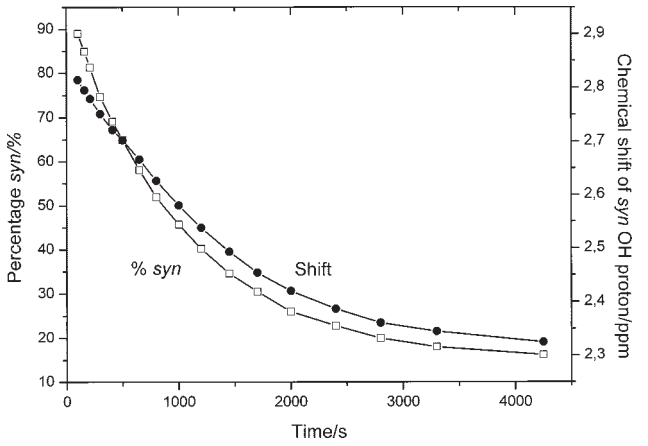

Figure 2. Rotation and dissociation of **1c** in benzene at 298 K

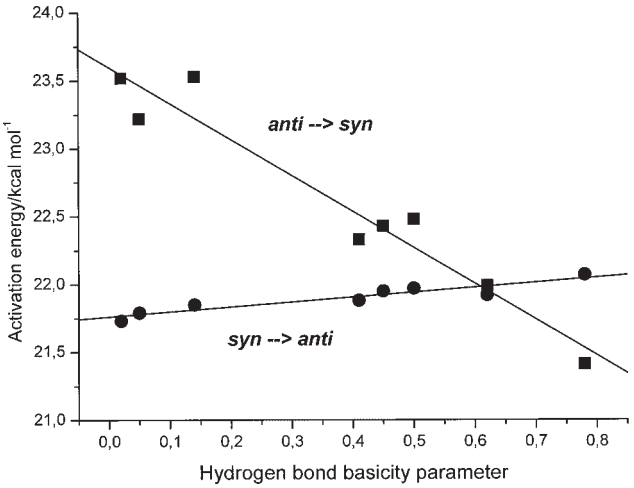

Figure 3. Solvent dependence of rotation barriers for **1d**

22.8 kcal mol^{-1} for the *syn*→*anti* and *anti*→*syn* rotations, respectively. The reaction is slightly faster in chloroform, 1.26×10^{-3} s^{-1}, and the equilibrium constant about the same, giving activation energies of 21.5 and 22.7 kcal mol^{-1}. Corresponding values for the reaction in pyridine are 2.6 10^{-3} s^{-1} and 2.08 (activation energies 21.6 and 21.2 kcal mol^{-1}). According to our previous findings,[5a,6] the *syn*→*anti* barrier should be solvent-independent, whereas the *anti*→*syn* barrier should decrease in the more hydrogen-bonding solvent. These expectations are satisfied by the data obtained at 298 K.

The slightly less reactive 3,4-diethoxy derivative, **1d**, was studied in a much wider variety of solvents. The activation energies for the *syn*→*anti* rotation range from 21.7 kcal mol^{-1} in chloroform to about 22.1 kcal mol^{-1} in DMSO, whereas that for *anti*→*syn* rotation goes from 23.5 to 21.4 kcal mol^{-1} in the same solvents (Table 1). Where values can be compared, they are slightly higher for **1d** than for **1c**, following the same trend as for the parent compounds without the 3-pyridyl substituent, **3c** and **3d**.[5c] The activation energies for **1d** correlate roughly with Abraham's hydrogen bond basicity parameters,[11] the slopes being 0.36 ± 0.06 and -2.65 ± 0.28 for *syn*→*anti* and *anti*→*syn*, respectively (Figure 3). For such a simple one-parameter approach the correlations are remarkably good. Only for dimethylthioacetamide has a greater solvent effect been reported, the rotation barrier going from 20.3 kcal mol^{-1} in decalin to 23.4 kcal mol^{-1} in DMSO.[1b]

An attempt to run analogous experiments on the EDOT derivative **1b** failed because the material cannot be dissolved quickly enough. It is initially in the *syn* form, as witnessed by the X-ray diffraction and IR studies,[8] but the *syn*⇌*anti* equilibrium is established more quickly than for **1c**. This is expected, since the rotation barriers for **3b** in DMSO are about 1.6 kcal mol^{-1} lower than for **3c**.[5c]

The question arises as to why simpler derivatives have not been investigated in the same way, e.g. 2,2,4,4-

Table 1. Solvent dependence of *syn*⇌*anti* rotation barriers in 2,2,4,4-tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)]thienyl}-pentan-3-ols, **1c** and **1d**, at 298 K

Compound	Solvent	K_1 [*syn*]/[*anti*]	[$10^4 k_{glob}$] s^{-1}	$\Delta G^{\neq}$ *syn*→*anti* kcal mol^{-1}	$\Delta G^{\neq}$ *anti*→*syn* kcal mol^{-1}	K_1(**3c** or **3d**) [*syn*]/[*anti*]
1c	Chloroform	0.13	12.6	21.47	22.68	0.069[a]
1c	Benzene	0.14	9.7	21.6	22.8	0.090[a]
1c	Pyridine	2.1	26.0	21.6	21.2	0.88[a]
1c	DMSO	5.9	—	(21.7)[b]	(20.6)[b]	2.1[a]
1d	Chloroform	0.048	7.6	21.73	23.52	0.032[a]
1d	Benzene	0.055	6.3	21.85	23.53	0.037[a]
1d	CD_2Cl_2	0.090	7.0	21.79	23.22	0.048
1d	Acetone	0.42	6.8	21.97	22.48	0.16
1d	Dioxan[c]	0.45	7.1	21.95	22.43	—
1d	Methanol	0.47	8.2	21.88	22.33	0.14
1d	Pyridine	0.88	9.9	21.92	21.99	0.41[a]
1d	DMF[d]	1.4	12.5	21.92	21.72	0.51
1d	DMSO	3.1	16.4	22.07	21.41	1.02[a]

[a]Reference 5b.
[b]Estimated value.
[c]Hydrogen bond basicity parameter taken as 0.45 (ether) for Figure 3.
[d]Not included in Figure 3.

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tetramethyl-3-(2-thienyl)pentan-3-ols, **3a-d**. However, these are mainly in the intramolecularly hydrogen-bonded *anti* form in the solid state.[5b] Compound **3a** is very predominantly *syn* in solution but the rotation barrier is so low that dynamic NMR is required to measure it even at room temperature.[5b] Alcohol **3b** has a slightly higher barrier but insufficient for direct measurement at room temperature. Equilibration of **3c** and **3d** is slower but in benzene would correspond to only about 8% (**3c**) or 3% (**3d**) reaction. Hydrogen-bonding solvents are potentially more interesting, as they favor the *syn* rotamer, but the rotation rates are higher and difficult to measure at 298 K even using single-scan NMR spectra. However, compound **3d** goes into solution in the *anti* form, and in DMSO ($K_1 = 1.0$) has an overall rate constant of $1.3 \pm 0.1 \times 10^{-3}\,s^{-1}$, whence a rotation barrier of 21.8 kcal mol^{-1}.

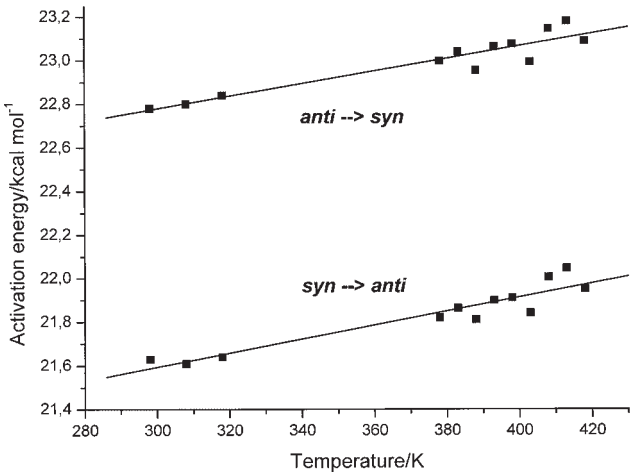

Figure 4. Rotation barriers for **1c** in benzene/toluene

Dynamic NMR measurement of rotation barriers

It is notoriously difficult to measure activation enthalpies and entropies of rotation by dynamic NMR,[12] but in many cases activation entropies are small enough to be neglected,[13] which means that the activation energy, $\Delta G^{\neq}$, can be used for discussion in the place of the activation enthalpy, $\Delta H^{\neq}$. However, in hydrogen-bonding solvents the equilibrium constant for alcohols such as **1a-d** and **3a-d** varies very considerably with the temperature, the *anti* rotamer tending to predominate as the temperature increases and hydrogen bonding of the *syn* rotamer by the solvent weakens.[5b] This means that while $\Delta S^{\neq}$ may be negligible for one rotation it certainly cannot be for the reverse rotation, the difference between the two activation entropies being the reaction entropy, ΔS°. For these and related alcohols in pyridine or DMSO this latter is of the order of 10 cal mol^{-1} K^{-1}.[5b]

In the present work we use $\Delta G^{\neq}$ values, which can be measured accurately at close to room temperature, in order to ''anchor'' rotation barriers measured by conventional dynamic NMR at relatively high temperatures. The errors on rates determined by dynamic NMR are least close to coalescence or beyond this point but, in our experience, when the rotamer populations are unequal, relative concentrations and chemical shifts and, consequently, activation energies become unreliable in this range. Moreover, in some cases which we investigated coalescence occurs considerably above the boiling point of the solvent, and experiments had to be curtailed to avoid explosion. Except in the most favorable cases, a scatter of data points is obtained in the high-temperature range, with a poorly defined temperature dependence. Nevertheless, all points must be assumed to lie in the general area of the true activation energy, even if individual points are unreliable. A valid correlation can therefore be drawn through these points and the one or several points at lower temperature(s).

The dimethoxy derivative, **1c**, was studied in benzene at room temperature and in toluene (sealed tube) at temperatures around 400 K. Combining the data gives plots which extend over a range of more than 100 K (Figure 4, Supplementary Material Table S1). Activation entropies for both the *anti*→*syn* and the *syn*→*anti* rotations are small, -2.9 ± 0.3 and -3.2 ± 0.4 cal mol^{-1} K^{-1}, respectively (Table 2). These are not very different from those reported by Oki (-3.2 and -6.6 cal mol^{-1} K^{-1}) for 9-(2-methoxy-1-naphthyl)fluoren-9-ol in hexachlorobutadiene, another system where one rotamer has an OH group hydrogen-bonded to an ether oxygen.[2] In pyridine the contrast is much more pronounced, the corresponding values being -11.0 ± 0.1 and -2.6 ± 0.2 cal mol^{-1} K^{-1}, respectively (Figure 5,

Table 2. Activation enthalpies and entropies for rotations in 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols

		syn→*anti*		*anti*→*syn*	
Compound	Solvent	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal mol^{-1} K^{-1}	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal mol^{-1} K^{-1}
1c	Benz/tol	20.64 ± 0.14	-2.9 ± 0.3	21.91 ± 0.13	-3.2 ± 0.4
1c	Pyridine	20.86 ± 0.07	-2.6 ± 0.3	17.95 ± 0.05	-11.0 ± 0.1
1c	DMSO	20.75 ± 0.21	-3.4 ± 0.6	17.38 ± 0.27	-11.1 ± 0.7
1d	DMSO	21.54 ± 0.30	-1.9 ± 0.8	18.36 ± 0.24	-10.3 ± 0.6
3d	DMSO	20.13 ± 0.17	-5.5 ± 0.4	18.14 ± 0.15	-12.2 ± 0.4

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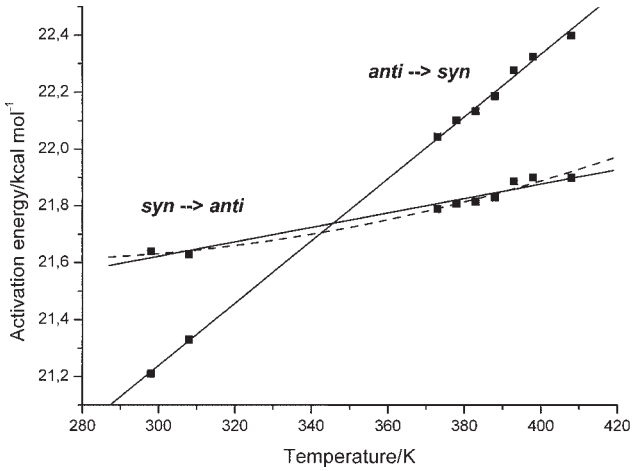

Figure 5. Rotation barriers for **1c** in pyridine

Supplementary Material Table S2). The first figure is close to those found for either rotation of Oki's system in DMSO.[2] Strictly speaking, since the plot of ΔG° against T for **1c** in pyridine is not perfectly rectilinear (Supplementary Material Figure S1), that is, it does not follow the van't Hoff model, a polynomial should be drawn through the data for *syn→anti* rotation (dashed line in Figure 5).

The reaction of **1c** in DMSO at 298 K is fast and gives only 14% of the *anti* isomer; therefore, the rotation barrier cannot be determined directly but, by comparison with **1d**, activation energies of 20.6 and 21.7 kcal mol^{-1} can be estimated for the *anti→syn* and *syn→anti* rotations, respectively. The high-temperature data lie on roughly straight lines which are, however, somewhat skewed with respect to the low-temperature point. Nevertheless, the overall activation entropy values are similar to those for pyridine, -11.1 ± 0.7 and -3.4 ± 0.6 cal mol^{-1} K^{-1}, respectively (Supplementary Material Figure S2 and Table S3). The outstanding result is that both the activation entropy and the activation enthalpy for *syn→anti* rotation are virtually solvent-independent. In contrast, the activation entropy for *anti→syn* rotation is much more negative for the hydrogen-bonding solvents than for benzene/toluene, while the activation enthalpy is much lower (Table 2).

The high-temperature DNMR data for **1d** in DMSO (only the pyridyl region can be used) show considerable scatter but, when taken with the experimental datum at 298 K, give activation entropies, -10.3 ± 0.6 and -1.9 ± 0.8 cal mol^{-1} K^{-1}, for the *anti→syn* and *syn→anti* rotations, respectively, similar to those for the dimethoxy derivative, **1c** (Supplementary Material Figure S3 and Table S4). The activation enthalpies for **1d** are about 1.0 kcal mol^{-1} higher in both cases, which means that the difference in the rotation rates of **1c** and **1d** is essentially enthalpic.

For compound **3d** in DMSO once again the datum at 298 K can be used to anchor the high-temperature data (Supplementary Material Figure S4 and Table S5), and the activation parameters are not very different from those obtained from the high-temperature data alone. For both rotations the activation enthalpies are lower for **3d** than for **1d**, whereas the activation entropies are more negative. The greatest differences are for the *syn→anti* rotation, but these compensate in the high-temperature region. Comparison of **1c** and **1d** with **3c** and **3d**,[5b] respectively, reveals that the *syn→anti* rotation barrier in DMSO is virtually unchanged whereas the *anti→syn* barrier falls by about 0.5 kcal mol^{-1} when the 3-pyridyl substituent is introduced. This corresponds to a particularly high *syn*/*anti* ratio in DMSO, more pronounced than in the other solvents examined, and this is reflected in the unusually high slope of the Abraham plot, that is, greater overall sensitivity to solvent variation. A plot of log(*syn*/*anti*) for **1d** against values for **3d** in seven solvents at 298 K (Table 1) has a slope of 1.18 ± 0.08. Likewise, for **1c** and **3c** a slope of 1.14 ± 0.04 is found (4 solvents). There is no obvious explanation for this difference.

The differences in the activation entropies are consistent with a rotation transition state which has less freedom than the *anti* isomer but is similar to the *syn* isomer in this respect. Given the difference in the solvent dependence of the two rotations, it is reasonable to assume that solvent ordering is the most important factor. The small but significantly positive activation entropies found in rotation about the C—N bond in amides and thioamides[1b] were attributed to an increase in freedom owing to desolvation of the rotation transition state, the transition state being less polar than the reactants. The small negative activation entropies associated with *syn→anti* rotation in the present study must be related to loss of internal freedom, since solvent effects (see above) suggest that the *syn* rotamer is slightly more solvated than the transition state. Low or near-zero activation entropies are to be expected for rotations where interactions between the solvent and the rotor group(s) are inconsequential or are similar for the transition state and both rotamers. This is the case for rotations in non-polar solvents, as illustrated here by the data for **1c** in benzene and toluene.

Association constants

As shown by the IR spectroscopic and X-ray crystallographic (for **1b**) studies,[8] the solid alcohols are essentially in the *syn* form, favored by self-association. In solution the association equilibrium is established very rapidly but that between the *anti* and *syn* rotamers is reached much more slowly. This means that the association constant can be obtained from a single sample by correlating the *syn* OH proton shift, $(\delta_{OH})^{syn}$, with the analytical concentration of the *syn* rotamer, $[S]_o$, as determined from the analytical concentration of the alcohol, $[ROH]_o$, and the *syn*/*anti* ratio, R. Equations (1)

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and (2) are well-known.[14,15]

$$(\delta_{OH})^{syn} = \delta_S + (\delta_{SS} - \delta_S)\frac{(1 + 8K_2S]_o)^{1/2} - 1}{(1 + 8K_2[S]_o)^{1/2} + 1} \quad (1)$$

where $[S]_o = R[ROH]_o/(1+R)$. The shifts of the monomer and of the dimer are δ_S and δ_{SS}, respectively. Because of the low solubility of these alcohols in benzene we use the approximation that δ_{SS} can be taken as the value, δ_{Spy}, for hetero-association with pyridine, as detailed in a previous paper.[8]

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

where $B = [S]_o + [py]_o + 1/K$, K being the equilibrium constant for hetero-association with pyridine in benzene. The self-association constant, K_2, is found by fitting the experimental values of $(\delta_{OH})^{syn}$ *vs.* $[S]_o$ to Equation (1). With these assumptions, the association constants for **1c** and **1d** in benzene at 298 K are 2.53 and 2.28 M^{-1}, respectively, very similar to those for the slightly less encumbered 3,4-methylenedioxythiophene (MDOT) and EDOT derivatives, **1a** and **1b**, 2.57 and 3.88 M^{-1}, respectively.[8]

It is noteworthy that in no solvent except benzene and the chlorohydrocarbons, dichloromethane and chloroform, is there any variation in the *syn* OH proton shift. This clearly indicates that association is negligible in hydrogen-bonding solvents. For the chlorohydrocarbons, there are indications of weak association. In dichloromethane, as the concentration of the *syn* isomer falls from 0.097 to 0.008 M the OH proton shift goes from 2.67 to 2.47 ppm. For chloroform the decrease on going from a *syn* concentration of 0.095 to 0.005 M is only 0.15 ppm. Comparable data for benzene are 3.23 ppm at 0.078 M *syn* and 2.46 ppm at 0.004 M (Supplementary Material Tables S6–S8). As there is no way of estimating δ_{SS} in these solvents it is not possible to determine the association constants but it is clear that, unless δ_{SS} were very much lower than in benzene, which seems unlikely, they must be substantially smaller than for benzene. This can be attributed to solvent interaction with the pyridyl nitrogen.[16]

Systems where there is an observable interplay of self-association and slow rotation are uncommon, but the NH chemical shift of the *Z* form of (5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone in chloroform falls as its concentration decreases when the *Z*/*E* ratio drops upon slow equilibration.[17] This is consistent with a change from the *Z* form, able to form intermolecular hydrogen bonds by self-association, to the *E* form, which is stabilized by intramolecular hydrogen bonds.

CONCLUSION

In the solid state 2,2,4,4-tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)thienyl}pentan-3-ols are predominantly or completely associated,[8] and go into solution as the *syn* form which equilibrates to give a mixture with the *anti* rotamer, in proportions which depend on the nature of the solvent, the temperature and, in some cases, the concentration. Rotation occurs at a rate which can be followed by ^{1}H NMR at room temperature, without recourse to dynamic NMR, making it possible for the first time to study rotation barriers in a very wide range of solvents. The rate of rotation from the form with a ''free'' OH group is virtually solvent-independent, whereas in the other direction it depends markedly on the hydrogen-bonding character of the solvent, confirming previous work on 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols[5] and 2,2,4,4-tetramethyl-3-(2-anisyl)pentan-3-ols.[6] The rationale of this result is that the solvation energy of the rotation transition state is similar to, or slightly less than, that of the rotamer with a ''free'' OH group, while that of the intramolecularly hydrogen-bonded OH in the other rotamer is much weaker.

We have measured activation entropies over exceptionally wide temperature ranges by combining direct and dynamic NMR rate measurements. These are strongly directional in hydrogen-bonding solvents, those for *anti*→*syn* rotations being much more negative than for the reverse reaction. Nevertheless, in no case, not even for *syn*→*anti* rotation in non-polar aromatic solvents, can the activation entropy be said to be zero. The popular assumption that this is a valid approximation would probably prove to be unfounded if rotation rates could be measured over 100 K rather than over 15-25 K, as is often the case.

EXPERIMENTAL

General methods have been described elsewhere.[8] Precursor 2-(3-pyridyl)thiophenes, **2c** and **2d**, and the derived alcohols, **1c** and **1d**, were prepared as for the MDOT and EDOT analogues.[8]

Synthesis

2-(3-Pyridyl)-3,4-dimethoxythiophene, 2c. Yield 59%; mp 45 °C (Found: C, 59.7; H, 5.1; N, 6.3. $C_{11}H_{11}NO_2S$ requires C, 59.71; H, 5.01; N, 6.33%). δ_C 57.3 (CH_3), 60.4 (CH_3), 95.3 (C5-th), 121.7 (C2-th), 123.4 (C5-py), 129.4 (C3-py), 133.7 (C4-py), 144.4 (C3-th), 147.8 (C2-py), 148.1 (C6-py) and 151.4 (C4-th); δ_H 3.85 (s, CH_3), 3.88 (s, CH_3), 6.22 (s, H5-th), 7.29 (H5-py, *J* 0.9, 4.8, 8.0), 7.98 (H4-py, *J* 1.6, 2.3, 8.0), 8.49 (H6-py, *J* 0.3, 1.6, 4.8) and 8.94 (H2-py, *J* 0.3, 0.9, 2.3).

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2-(3-Pyridyl)-3,4-diethoxythiophene, 2d. Yield 60%; mp 32°C (Found: C, 62.3; H, 6.1; N, 5.6. $C_{13}H_{15}NO_2S$ requires C, 62.62; H, 6.06; N, 5.62%). δ_C 14.7 (CH_3), 15.5 (CH_3), 65.6 (CH_2), 68.6 (CH_2), 95.6 (C5-th), 121.5 (C2-th), 123.3 (C5-py), 129.7 (C3-py), 133.7 (C4-py), 143.7 (C3-th), 147.7 (C2-py), 147.8 (C6-py) and 150.6 (C4-th); δ_H 1.30 (CH_3, *J* 7.0), 1.45 (CH_3, *J* 7.0), 4.06 (CH_2, *J* 7.0), 4.12 (CH_2, *J* 7.0), 6.19 (s, H5-th), 7.29 (H5-py, *J* 0.9, 4.8, 8.0), 8.01 (H4-py, *J* 1.7, 2.3, 8.0), 8.47 (H6-py, *J* 0.3, 1.7, 4.8) and 8.97 (H2-py, *J* 0.3, 0.9, 2.3).

2,2,4,4-Tetramethyl-3-{2-[3,4-dimethoxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 1c. Yield 36%; mp 128 °C; IR (cast/cm^{-1}) 3330, 3497 (Found: C, 66.3; H, 8.1; N, 3.8. $C_{20}H_{29}NO_3S$ requires C, 66.08; H, 8.04; N, 3.85%). *anti*: δ_C 29.2 (CH_3), 42.6 (C_q), 60.4 (CH_3), 61.1 (CH_3), 87.0 (COH), 118.4 (C5-th), 123.4 (C5-py), 128.7 (C2-th or C3-py), 128.8 (C2-th or C3-py), 133.3 (C4-py), 146.0 (C4-th), 147.4 (C2-py), 147.5 (C3-th) and 148.0 (C6-py); δ_H 1.18 (s, 6 CH_3), 3.81 (s, CH_3), 3.95 (s, CH_3), 5.74 (s, OH), 7.29 (H5, *J* 0.7, 4.9, 8.0), 7.96 (H4, *J* 1.6, 2.4, 8.0), 8.48 (H6, *J* 0.7, 4.9) and 8.95 (H2, *J* 0.7, 2.4).

2,2,4,4-Tetramethyl-3-{2-[3,4-diethoxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 1d. Yield 29%; mp 100 °C; IR (cast/cm^{-1}) 3320, 3488 (Found: C, 67.5; H, 8.6; N, 3.4. $C_{22}H_{33}NO_3S$ requires C, 67.48; H, 8.49; N, 3.58%). *anti*: δ_C 15.4 (CH_3), 15.4 (CH_3), 29.1 (CH_3), 42.6 (C_q), 68.9 (CH_2), 69.7 (CH_2), 86.9 (COH), 118.7 (C5-th), 123.2 (C5-py), 128.3 (C2-th or C3-py), 128.9 (C2-th or C3-py), 133.1 (C4-py), 145.0 (C4-th), 147.0 (C3-th), 147.4 (C2-py) and 147.7 (C6-py); δ_H 1.14 (s, 6 CH_3), 1.25 (CH_3, *J* 7.0), 1.38 (CH_3, *J* 7.0), 3.96 (CH_3, *J* 7.0), 4.19 (CH_3, *J* 7.0), 5.90 (s, OH), 7.25 (H5, *J* 0.8, 4.8, 8.0), 7.95 (H4, *J* 1.6, 2.3, 8.0), 8.43 (H6, *J* 0.2, 1.6, 4.8) and 8.96 (H2, *J* 0.2, 0.8, 2.3).

Determination of self-association constants and rotation rates. To a known amount (10–20 mg) of **1c** or **1d** in an NMR tube was added 0.5 ml of deuteriated solvent. The tube was quickly sonicated or shaken to dissolve the material and then placed in the NMR spectrometer (Bruker AC 200). Ten to twenty single-scan spectra were recorded at convenient time intervals over about three reaction half-lives, and a final spectrum was recorded after 10 half-lives or more. The *syn*/*anti* ratio was determined by integration of suitable signals, with the help of gNMR (version 4.1, Adept Scientific, Letchworth, UK) in some cases. A plot of $\ln[\%syn(t) - \%syn(\infty)]$ vs. time (t) gives the sum of the rate constants, k_{glob}, for the *syn*→*anti* and *anti*→*syn* rotations. Rate constants are reproducible to ±3%, activation energies to ±0.02 kcal mol^{-1}. The standard deviation on a single run is 1–3% of the rate constant ($R \geq 0.995$), except for **1d** in DMSO (5%, $R = 0.985$). Specimen kinetic runs for **1d** in three solvents are given in Tables S6-8. Activation energies for rotation are listed in Table 1. New measurements were made on the equilibrium composition of **3d** at 298 K in CD_2Cl_2, methanol, acetone and DMF (Table 1).

To determine the association constants of **1c** and **1d** in benzene the shift of the *syn* OH proton was plotted against $[S]_o$ and treated as in a previous paper[8] to obtain δ_S and K_2 (see text). Data for **1c**: $\delta_{Spy} = 6.507 \pm 0.010$ ppm; $K = 1.15 \pm 0.01\ M^{-1}$; $\delta_S = 2.167 \pm 0.008$ ppm; $K_2 = 2.53 \pm 0.06\ M^{-1}$. Data for **1d**: $\delta_{Spy} = 6.539 \pm 0.011$ ppm; $K = 1.11 \pm 0.01\ M^{-1}$; $\delta_S = 2.340 \pm 0.005$ ppm; $K_2 = 2.28 \pm 0.03\ M^{-1}$.

Dynamic ^{1}H NMR on 2,2,4,4-tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)]thienyl}-pentan-3-ols, 1c and 1d. The ^{1}H NMR spectra of solutions of 2,2,4,4-tetramethyl-3-{2-[3,4-dialkoxy-5-(3-pyridyl)]thienyl}pentan-3-ols, **1c** and **1d**, were recorded from 298 to 423 K (DMSO), 418 K (toluene, sealed tube) or 408 K (pyridine, sealed tube). Full line-shape analysis of the *tert*-butyl (**1c**), methyl (**1c**) or pyridyl (**1d**) proton signals by gNMR gives the exchange rate and the relative concentrations of the two species from which rate constants and rotation barriers (± 0.05–0.1 kcal mol^{-1}) are calculated. Temperature calibration and errors associated with temperature uncertainties have been discussed elsewhere.[7b] Full data for **1c** in toluene, pyridine and DMSO, and for **1d** and **3d** in DMSO are given in Tables S1–5. Summary data on **3d** have been published.[5b]

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REFERENCES

1. (a) Rabinovitz M, Pines A. *J. Am. Chem. Soc.* 1969; **91**: 1585–1589; (b) Neuman RC, Jonas V. *J. Org. Chem.* 1974; **39**: 928–931.
2. Nakamura M, Kihara H, Oki M. *Tetrahedron Letters* 1976; 1207–1210.
3. (a) Lomas JS, Luong PK, Dubois JE. *J. Org. Chem.* 1977; **42**: 3394–3399; (b) Lomas JS, Dubois JE. *Tetrahedron* 1981; **37**: 2273–2278; (c) Lomas JS, Bru-Capedeville V. *J. Chem. Soc., Perkin Trans. 2* 1994; 459–466; (d) Lomas JS, Anderson JE. *J. Org. Chem.* 1995; **60**: 3246–3248.
4. Lomas JS, Lacroix JC, Vaissermann J. *J. Chem. Soc., Perkin Trans. 2* 1999; 2001–2010.
5. (a) Lomas JS. *J. Chem. Soc., Perkin Trans. 2* 2001; 754–757; (b) Lomas JS, Adenier A, Gao K, Maurel F, Vaissermann J. *J. Chem. Soc., Perkin Trans. 2* 2002; 216–224; (c) Lomas JS, Adenier A. *J. Chem. Soc., Perkin Trans. 2* 2002; 1264–1270.
6. Lomas JS, Adenier A. *J. Chem. Soc., Perkin Trans. 2* 2001; 1051–1057.
7. (a) Lomas JS, Cordier C. *J. Phys. Org. Chem.* 2003; **16**: 361–368; (b) Lomas JS, Vaissermann J. *J. Phys. Org. Chem.* 2004; **17**: 102–112.

DOI: 10.1002/poc

8. Lomas JS, Cordier C, Adenier A, Maurel F, Vaissermann J. *J. Phys Org. Chem. in press*
9. Nakamura M, Nakamura N, Oki M. *Bull. Chem. Soc. Jpn.* 1977; **50**: 2986–2990.
10. Nakamura M, Nakamura N, Oki M. *Chem. Letters* 1980; 605–606.
11. Abraham MH. *Chem. Soc. Rev.* 1993; **22**: 73–83.
12. Allerhand A, Gutowsky HS, Jonas J, Meinzer R. *J. Am. Chem. Soc.* 1966; **88**: 3185–3194.
13. Mazzanti A, Lunazzi L, Minzoni M, Anderson JE. *J. Org. Chem.* 2006; **71**: 5474–5481.
14. Chen JS, Shirts RB. *J. Phys. Chem.* 1985; **89**: 1643–1646.
15. (a) Pineau P, Fuson N, Josien ML. *J. Chim. Phys.* 1958; **55**: 464–469; (b) Johnston MD, Gasparro FP, Kuntz ID. *J. Am. Chem. Soc.* 1969; **91**: 5715–5724.
16. Slejko FL, Drago RS, Brown DG. *J. Am. Chem. Soc.* 1972; **94**: 9210–9216.
17. (a) Markovic R, Shirazi A, Džambaski Z, Baranac M, Minic D. *J. Serb. Chem. Soc.* 2003; **68**: 1–7; (b) Markovic R, Shirazi A, Džambaski Z, Baranac M, Minic D. *J. Phys. Org. Chem.* 2004; **17**: 118–123.

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