Competing inter- and intramolecular hydrogen bonding: solvent-driven rotamerization in 3,4-(ethylenedioxy)-2-thienyldi(*tert*-alkyl)methanols

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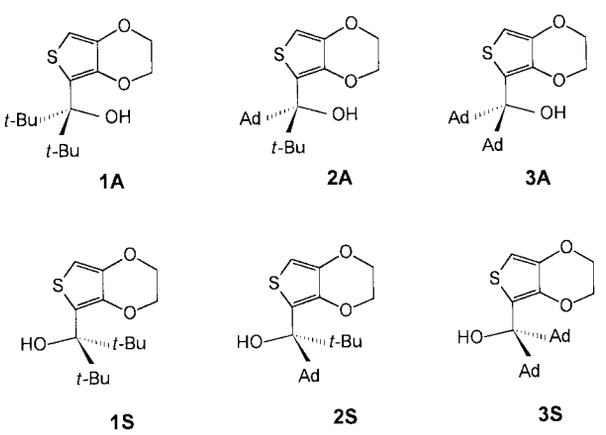
3,4-(Ethylenedioxy)-2-thienyldi(*tert*-alkyl)methanols exist in two rotameric forms, the equilibrium constant for the *anti*⇌*syn* rotamerization depending on the solvent. The equilibrium constant ([*syn*]/[*anti*]) is close to unity in benzene and chloroform, regardless of the *tert*-alkyl groups (*tert*-butyl or 1-adamantyl). This rises to about 10 in pyridine and 20 in DMSO (both at 25 °C), where intermolecular hydrogen bonding clearly prevails over intramolecular. For the di(*tert*-butyl) derivative there is a good correlation between the equilibrium constant (log *K*) and the hydrogen bond basicity parameter (β_2^H). The temperature dependence of the rotamer ratio in strongly hydrogen-bonding solvents indicates that the enthalpy term favours the *syn* isomer and the entropy term the *anti*. Rotation barriers have been measured in both hydrogen-bonding and non-hydrogen-bonding solvents. The differences in the equilibrium constants reflect the solvent effect upon the *anti*→*syn* isomerization, which is shown to be "solvent-driven" in the case of the di(1-adamantyl) derivative in pyridine.

Introduction

Aryl- and heteroaryldi(*tert*-alkyl)methanols exist in two rotameric forms which can be distinguished on the NMR time-scale and can in some cases, particularly when the *tert*-alkyl group is a bulky substituent, such as 1-adamantyl, be separated by column chromatography.[1–3] To date, however, when there is an alkoxy group close to the OH group, as in 2-anisyl- and 3-alkoxy-2-thienyldi(1-adamantyl)methanols, only the intramolecularly hydrogen-bonded rotamer has been found.[4,5] The existence of the hydrogen bond and favourable steric effects would appear to be an adequate explanation for this phenomenon. Nevertheless, 2-anisyl(alkyl)methanols and 2-anisyldi(alkyl)methanols, with alkyl groups as large as *tert*-butyl, are reported to occur as hydrogen-bonded and "free" forms in equilibrium at room temperature, the latter form being favoured by hydrogen-bonding solvents.[6]

Our interest in the structure and reactivity of heteroaryldi(1-adamantyl)methanols[2–4] led us to synthesize a series of alcohols (**1**–**3**) by reaction of the organolithium derivative of 3,4-(ethylenedioxy)thiophene (EDOT)[7] with di(*tert*-butyl) ketone, 1-adamantyl *tert*-butyl ketone and di(1-adamantyl) ketone, respectively. EDOT has for many years been the subject of extensive study, since its polymerization yields materials with interesting optical and electronic properties,[8] but little work has been done on the monomer as such, considered simply as a disubstituted thiophene.



These alcohols are found to exist in two rotameric forms, the *anti* rotamer having a relatively weak intramolecular hydrogen bond. Equilibrium constants in hydrogen-bonding and non-hydrogen-bonding solvents are reported, as well as rotation barriers in certain solvents. The temperature dependence of the ^{1}H NMR shift of the OH protons in the *syn* and *anti* rotamers is compared in pyridine and DMSO.

Results and discussion

IR and NMR spectroscopy

All alcohols were readily prepared by lithiation of EDOT by means of *n*-butyllithium–TMEDA in diethyl ether at room temperature, followed by reaction with the appropriate ketone. The IR spectra of the various alcohols were determined in carbon tetrachloride. The di(1-adamantyl) derivative, **3**, shows only a single broad OH absorption, at 3569 cm^{-1}. The less encumbered derivatives show a strong signal at approximately the same wavenumber but also weaker absorptions at higher wavenumber, at around 3606 and 3628 cm^{-1}. The single broad signal can be attributed to the intramolecularly hydrogen-bonded *anti* form of the alcohols,[6] with the OH directed towards the neighbouring –OCH_2– group, and the two smaller signals to the *syn* isomer. The difference between the frequencies for the *anti* forms of the EDOT derivatives and those for the 3-alkoxythienyl analogues (3486–3511 cm^{-1}, depending on the alkoxy group)[4] would appear to suggest weaker hydrogen bonding in the former case, probably because the oxygen atom is restrained and withdrawn from the OH.

The ^{1}H NMR spectrum of **3** confirms that this alcohol has the *anti* conformation, and the lower chemical shift of the OH proton signal (4.70 ppm in $CDCl_3$) is again consistent with the idea that hydrogen bonding is weaker than in the 3-alkoxy

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derivatives (5.80–6.09 ppm).[4] Intramolecularly hydrogen-bonded alcohol rotamers can be readily distinguished from those which are hydrogen-bonded to the solvent by the temperature dependence of the chemical shift in pyridine.[2] For **3**, $\Delta\delta/\Delta T$ is -1.97 ± 0.03 ppb per °C, which is as low as for the 3-alkoxy-2-thienyl(diadamantyl)methanols.[4] However, heating the alcohol in pyridine leads to partial isomerization to the *syn* isomer, with an equilibrium *syn–anti* ratio at 70 °C of about 5. The *syn* isomer has in pyridine a much higher temperature coefficient, -17.1 ± 0.1 ppb per °C, and in chloroform a much lower shift for the OH proton (2.20 ppm), indicating loss of the intramolecular hydrogen bond. Heating the *syn–anti* mixture in chloroform at 150 °C for 2 h gives an equilibrium mixture with a *syn–anti* ratio of 1.3. Treating the original intramolecular hydrogen-bonded *anti* alcohol in the same way gives the same result, which indicates, rather surprisingly, that this alcohol is merely the kinetic product of the addition reaction and that there is little difference in the thermodynamic stabilities of the two rotamers. Since the initally formed alcohol is only weakly hydrogen-bonded but is poorly solvated by pyridine, isomerization to a highly solvated rotamer is energetically favourable, despite the somewhat, but obviously not prohibitively, enhanced interactions between the adamantyl substituents and the methyleneoxy substituent.

The other two EDOTdi(*tert*-alkyl)methanols, **1** and **2**, show similar behaviour, except that the times and temperatures required for equilibration are substantially less than for the di(1-adamantyl) derivative. In pyridine the *anti* rotamers give $\Delta\delta/\Delta T$ values close to -1.9 ppb per °C whereas the *syn* isomers are associated with values near -17 ppb per °C. For the *anti* rotamers values in DMSO (-1.14 to -1.35 ppb per °C) are slightly smaller than in pyridine but for the *syn* rotamers they are about one-third (-5.6 to -5.8 ppb per °C) of those in pyridine.

Table 1 Equilibrium constants for *anti*⇌*syn* isomerization of EDOT-di(*tert*-alkyl)methanols in hydrogen-bonding solvents ($K = [syn]/[anti]$)

T/K	**1S–1A**[a]	**1S–1A**[b]	**2S–2A**[a]	**3S–3A**[a]
298	9.2	(18.0)[c]	10.0	(11.3)[c]
303	8.0		9.6	
308	7.1		8.1	
313	6.3		7.7	
318	5.7		6.7	
323	5.2		6.0	6.9
328	4.7	11.5	5.3	6.1
336				5.4
338		10.2		
343				4.8
348		9.4		
353				4.1
358		8.0		
368		7.2		
378		6.6		

[a] In pyridine. **1** (Pyridine, 298–328 K): $\Delta G^\circ = (4.3 \pm 0.1) - (10.1 \pm 0.3)T$. **2** (Pyridine, 298–328 K): $\Delta G^\circ = (4.2 \pm 0.2) - (9.4 \pm 0.7)T$. **3** (Pyridine, 328–353 K): $\Delta G^\circ = (3.8 \pm 0.2) - (8.0 \pm 0.4)T$. [b] In DMSO. **1** (DMSO, 328–378 K): $\Delta G^\circ = (2.8 \pm 0.1) - (3.7 \pm 0.4)T$. [c] Extrapolated.

Rotamer equilibria

For all three alcohols, **1**–**3**, the equilibrium rotamer ratios are close to unity in benzene or chloroform but the *syn* rotamer is favoured in pyridine or DMSO. Alcohol **1** was studied in several additional NMR solvents, intermediate in hydrogen-bonding ability. Values of the *syn–anti* ratio for THF, acetone, acetonitrile and methanol cluster in the 3–4 range, with no obvious order. A plot of the 8 data-points, expressed as log K, where K is the equilibrium constant for the *syn*⇌*anti* isomerization, against the solute hydrogen bond basicity parameter, β_2^H,[9] is approximately linear (intercept -0.22 ± 0.08; gradient 1.82 ± 0.18; correlation coefficient 0.9732).

Whereas the rotamer ratio is virtually temperature-independent in chloroform or aromatic solvents such as benzene and toluene, in a hydrogen-bonding solvent such as pyridine the proportion of the intermolecularly hydrogen-bonded, *syn* isomer (hydrogen-bonded to solvent) falls as the temperature is increased (Table 1).

Although 1-adamantyl is generally reckoned to be more sterically demanding than *tert*-butyl, there is a small *increase* in the *syn–anti* ratio on going from **1** to **2** to **3**, but the total variation in the free energy difference, ΔG°, at 25 °C is less than 0.15 kcal mol^{-1}. Plotting ΔG°(*anti* − *syn*) against the temperature gives the enthalpy and entropy contributions, ΔH° and ΔS°. For alcohols **1**, **2** and **3** in pyridine, values are 4.3, 4.2 and 3.9 kcal mol^{-1} and 10.1, 9.4 and 8.3 cal mol^{-1} K^{-1}, respectively. This indicates that the *anti* rotamer is enthalpically less favoured but entropically more favoured. The first result is consistent with the idea that hydrogen bonding by the solvent in the *syn* form is much stronger than the internal hydrogen bond in the *anti* isomer. However, hydrogen bonding in the *anti* isomer might be expected to cause a loss of rotational freedom and to be also entropically unfavourable. That this is not the case suggests that the solvent is structured by hydrogen bonding. Measurements on **1** in DMSO indicate that both terms are substantially smaller than in pyridine, but the *syn–anti* ratio is so high that data in this solvent are somewhat less reliable.

Gellman *et al.*,[10] comparing the internally hydrogen-bonded and non-hydrogen-bonded forms of a diamide in dichloromethane by IR and NMR spectroscopy, found that the closed form was enthalpically preferred by about 1.5 kcal mol^{-1} but entropically disfavoured by some 8 cal mol^{-1} K^{-1}. However, in this case the open form was not hydrogen-bonded by the solvent.

Rotamerization kinetics

It would have been desirable to study the kinetics of the *anti* to *syn* rotation of alcohols **1**–**3** in both hydrogen-bonding and non-hydrogen-bonding solvents. However, practical difficulties make this impossible. The di(*tert*-butyl) derivative, **1**, can only be studied by dynamic NMR which means, paradoxically, that it has to be investigated at higher temperatures than the less reactive analogues, and the equilibrium is so much in favour of the *syn* isomer in hydrogen-bonding solvents that even this is not feasible. Alcohol **2** occurs mainly as the *syn* isomer, **2S**, which means that it cannot be studied kinetically in hydrogen-bonding solvents, where this is the major component of the equilibrium mixture. Only with alcohol **3**, isolated as **3A**, can both types of solvent be studied.

Determining the rate constants for the equilibration of alcohol **3** in pyridine at different temperatures allows the ΔH° and ΔS° terms given above to be broken down. The *anti*→*syn* isomerization is associated with a much lower activation enthalpy, 20.2 kcal mol^{-1}, and a much more negative activation entropy, -13.9 cal mol^{-1} K^{-1}, than the *syn*→*anti* isomerization (24.1 kcal mol^{-1} and -5.6 cal mol^{-1} K^{-1}). In work on related systems[1,3] slow rotations in non-hydrogen-bonding solvents have been generally associated with activation entropies ranging from about -5 to -10 cal mol^{-1} K^{-1}, indicative of a transition state which is not only more strained but also more ordered than the initial state. The unusually large value for **3S→3A** in a hydrogen-bonding solvent suggests that solvent structuring is important in the transition state. The entropic cost of solvent ordering associated with intermolecular hydrogen bonding has been discussed in the context of "proton sponges".[11]

In toluene the activation enthalpies are virtually the same (25.4 kcal mol^{-1}) and the activation entropies very small and similar (-1.8 and -1.2 cal mol^{-1} K^{-1}). In the case of the *syn*→

anti isomerization of alcohol **3** the activation parameters are approximately compensated in the temperature range studied, and the rate constants are almost independent of solvent. This means that the change in the equilibrium constants on going from toluene to pyridine is almost entirely due to an increase in the rates of the *anti*→*syn* isomerization. In this respect it would be appropriate to refer to this rotation as being "solvent-driven".

In previous work, on *o*-tolyldi(*tert*-alkyl)methanols, the rotation barrier was found to increase markedly as one then two *tert*-butyl groups were replaced by 1-adamantyls.[1a] The same trend is observed in this work, despite the fact that the rotation barriers are smaller and the increase much less dramatic. In the non-hydrogen-bonding solvents, nitrobenzene, benzene and toluene, mean activation energies are 20.8 (365–400 K), 22.8 (298–318 K) and 25.9 kcal mol^{-1} (333–353 K) for alcohols **1**, **2** and **3**, respectively. These relatively large differences contrast with the very small variation in the ΔG° values for the rotamer pairs, and underline the fact that it is steric interactions in the transition state which are the major factor in determining the rotation barrier.

Conclusions

In previous work[4] it was shown that the addition of 3-alkoxy-2-thienyllithium compounds to a highly congested ketone, di(1-adamantyl) ketone, gives tertiary alcohols in which the hydroxy proton is hydrogen-bonded to the alkoxy oxygen, corresponding to the *anti* rotamer (sulfur remote from the OH group). This conformation would appear to have the added advantage of reducing steric interactions between the alkoxy and adamantyl groups which would occur in the *syn* rotamer.

Even in the most congested alcohol of the present series, **3**, it is easy to observe the rotation of the *anti* rotamer, the normal reaction product, when it is treated with pyridine or DMSO. Depending on the solvent, the *syn* isomer, which lacks an intramolecular hydrogen bond, is almost as stable or is significantly more stable than the *anti* form. This is the mirror image of recent work in which the *syn–anti* rotamerization of 2-(2′-pyridyl)-1*H*-indole is solvent-induced by alcohols.[12]

The question is then: why was this phenomenon not observed in the 3-alkoxy-2-thienyldi(1-adamantyl)methanols? The answer would appear to be that (a) the intramolecular hydrogen bond is substantially stronger than in the EDOT derivative, (b) the rotation barriers are higher, and (c) the greater steric interaction between the alkoxy group and the adamantyls favours the *anti* isomer. This analysis is based on preliminary experiments[13] which show that the same phenomena do occur in the 3-alkoxy-2-thienyldi(*tert*-alkyl)methanols but that the equilibrium and rate constants are rather different from those reported here.

2-Anisyl(isopropyl)(*tert*-butyl)methanol has a rotation barrier of about 18 kcal mol^{-1},[6c] substantially higher than that for a phenyl analogue lacking the 2-methoxy group, *i.e.* 3,4,5-trimethoxyphenyl(isopropyl)(*tert*-butyl)methanol, 13 kcal mol^{-1}.[13] As that for 3,4,5-trimethoxyphenyldi(*tert*-butyl)-methanol is so much higher, 21.4 kcal mol^{-1},[14] this result suggests that the barrier for 2-anisyldi(*tert*-butyl)methanol could be 8 kcal mol^{-1} or more higher than that for the (isopropyl)-(*tert*-butyl) compound. This puts it in the range where the rotamers can be separated, in which case they cannot be in equilibrium at room temperature.[6b] In a subsequent paper we shall report separation of the rotamers of 2-anisyldi(*tert*-butyl)methanol.[13]

Experimental

General methods have been described in previous papers.

Alcohol synthesis

To a mixture of 3,4-(ethylenedioxy)thiophene (Bayer, redistilled) (5 mmol) and TMEDA (0.75 cm^3, 5 mmol) in diethyl ether (15 cm^3) under argon at room temperature was added a solution of *n*-butyllithium in hexane (1.6 M, 3.2 cm^3, 5 mmol). After 30 min stirring di(*tert*-butyl) ketone, 1-adamantyl *tert*-butyl ketone or di(1-adamantyl) ketone (1–2 mmol) was added. The mixture was stirred for a further 30 min, then quenched with water and the organic materials extracted with diethyl ether. Washing with water, drying and evaporation of solvent gave an oily residue from which the alcohol was isolated by chromatography on silica gel in light petroleum (petroleum ether 35–60 °C)–dichloromethane mixtures.

***anti*-3,4-(Ethylenedioxy)-2-thienyldi(*tert*-butyl)methanol, 1A.** Isolated as a mixture with the *syn* isomer (0.51 g, 91%) from di(*tert*-butyl) ketone (0.28 g, 2 mmol): mp 55–56 °C; ν_{OH}/cm^{-1} (CCl_4) 3568; δ_C (chloroform) 29.1 (6 CH_3), 42.9 (2 C_q), 64.0 (CH_2), 64.7 (CH_2), 86.8 (COH), 96.3 (C5), 121.9 (C2), 138.4 (C3 or C4) and 139.7 (C3 or C4); δ_H (chloroform) 1.14 (*t*-Bu), 4.19 (CH_2), 4.81 (OH) and 6.20 (H5) (Found: C, 63.2; H, 8.4; S, 11.3. $C_{15}H_{24}O_3S$ requires C, 63.35; H, 8.51; S, 11.27%).

***syn*-3,4-(Ethylenedioxy)-2-thienyldi(*tert*-butyl)methanol, 1S.** ν_{OH}/cm^{-1} (CCl_4) 3608, 3627; δ_C (chloroform) 29.1 (6 CH_3), 42.6 (2 C_q), 63.9 (CH_2), 64.1 (CH_2), 85.8 (COH), 96.4 (C5), 128.3 (C2), 134.7 (C3) and 141.0 (C4); δ_H (chloroform) 1.14 (*t*-Bu), 2.18 (OH), 4.15 (CH_2) and 6.21 (H5).

***anti*-3,4-(Ethylenedioxy)-2-thienyl(1-adamantyl)(*tert*-butyl)-methanol, 2A.** Isolated as a mixture with the *syn* isomer (0.47 g, 87%) from 1-adamantyl *tert*-butyl ketone (0.33 g, 1.5 mmol) by trituration with pentane: mp 124 °C; ν_{OH}/cm^{-1} (CCl_4) 3570; δ_C (chloroform) 29.1 (3 CH_3), 29.4 (3 CH), 37.0 (3 CH_2), 38.3 (3 CH_2), 43.2 (C_q), 46.1 (C_q), 64.0 (CH_2), 64.8 (CH_2), 87.1 (COH), 96.3 (C5), 121.2 (C2), 138.8 (C3 or C4) and 139.7 (C3 or C4); δ_H (chloroform) 1.15 (*t*-Bu), 1.61 and 1.8–2.1 (br m, Ad), 4.19 (CH_2), 4.76 (OH) and 6.21 (H5) (Found: C, 69.7; H, 8.1; S, 8.9. $C_{21}H_{30}O_3S$ requires C, 69.58; H, 8.34; S, 8.84%).

***syn*-3,4-(Ethylenedioxy)-2-thienyl(1-adamantyl)(*tert*-butyl)-methanol, 2S.** ν_{OH}/cm^{-1} (CCl_4) 3605, 3626; δ_C (chloroform) 29.2 (3 CH_3), 29.3 (3 CH), 37.0 (3 CH_2), 38.6 (3 CH_2), 42.9 (C_q), 45.1 (C_q), 63.9 (CH_2), 64.1 (CH_2), 86.1 (COH), 96.5 (C5), 127.7 (C2), 134.9 (C3) and 141.0 (C4); δ_H (chloroform) 1.15 (*t*-Bu), 1.61 and 1.8–2.1 (br m, Ad), 2.19 (OH), 4.16 (CH_2) and 6.22 (H5).

***anti*-3,4-(Ethylenedioxy)-2-thienyldi(1-adamantyl)methanol, 3A.** Isolated as a white solid (0.367 g, 83%) from di(1-adamantyl) ketone (0.3 g, 1 mmol): mp 201 °C (hexane); ν_{OH}/cm^{-1} (CCl_4) 3569; δ_C (chloroform) 29.2 (6 CH), 37.1 (6 CH_2), 38.6 (6 CH_2), 46.1 (2 C_q), 64.1 (CH_2), 64.8 (CH_2), 87.3 (COH), 96.4 (C5), 120.5 (C2), 139.3 (C3 or C4) and 139.8 (C3 or C4); δ_H (chloroform) 1.61 and 1.8–2.1 (br m, Ad), 4.19 (CH_2), 4.70 (OH) and 6.21 (H5) (Found: C, 73.5; H, 8.4; S, 7.5. $C_{27}H_{36}O_3S$ requires C, 73.60; H, 8.23; S, 7.28%).

***syn*-3,4-(Ethylenedioxy)-2-thienyldi(1-adamantyl)methanol, 3S.** By rotation of **3A** in pyridine at 70 °C for 2 h, extraction with water and hexane, the organic phase being washed several times with dilute acid, dried ($MgSO_4$) and the solvent evaporated; *syn–anti* ratio 4.8. ν_{OH}/cm^{-1} (CCl_4) 3604, 3626; δ_C (chloroform) 29.3 (6 CH), 37.1 (6 CH_2), 38.8 (6 CH_2), 45.6 (2 C_q), 63.8 (CH_2), 64.2 (CH_2), 86.3 (COH), 96.5 (C5), 127.2 (C2), 135.1 (C3) and 141.0 (C4); δ_H (chloroform) 1.61 and 1.8–2.1 (br m, Ad), 2.20 (OH), 4.17 (CH_2) and 6.22 (H5).

Temperature dependence of OH proton NMR shift

Temperature coefficients were measured from 25 to 50 °C in pyridine and from 25 to 65 °C in DMSO [solvent (alcohol, δ_H(25 °C, ppm), $\Delta\delta/\Delta T$(ppb per °C)]: pyridine (**1A**, 5.16, −1.92 ± 0.09; **2A**, 5.19, −1.86 ± 0.04; **3A**, 5.24, −1.88 ± 0.02; **1S**, 5.67, −17.1 ± 0.1; **2S**, 5.82, −16.9 ± 0.1; **3S**, 6.00, −16.8 ± 0.2); DMSO (**1A**, 4.93, −1.00 ± 0.03; **2A**, 4.88, −1.14 ± 0.02; **3A**, 4.83, −1.35 ± 0.03; **1S**, 4.67, −5.8 ± 0.1; **2S**, 4.56, −5.7 ± 0.1; **3S**, 4.43, −5.6 ± 0.1).

Equilibrium constants

Samples of the various alcohols (*ca.* 10 mg) were made up in deuteriated solvents (0.5 cm^3). The rotation barrier for the di(*tert*-butyl) derivative, **1**, is so low that an equilibrium mixture is obtained immediately upon dissolution. The (1-adamantyl)-(*tert*-butyl) derivative, **2**, equilibrates somewhat more slowly. Equilibrium constants for **3** were taken from the "infinity" measurements on the kinetic runs. Values of *syn–anti* ratios [alcohol (solvent, temperature/ °C, *K*)]: **1** (benzene, 25, 0.84; chloroform, 25, 0.94; acetonitrile, 25, 3.3; acetone, 25, 3.4; methanol, 25, 3.9; THF, 25, 4.1; pyridine, 25, 9.2; DMSO, 25, 18); **2** (benzene, 25, 1.08; chloroform, 25, 1.22; pyridine, 25, 10.0; DMSO, 25, 21); **3** (benzene, 150, 1.30; toluene, 60–80, 1.33; pyridine, 25, 11.4). For details of the temperature dependence in hydrogen-bonding solvents, see Table 1.

Rotation kinetics

Dynamic NMR was used for alcohol **1**. The ^{1}H NMR spectrum of a solution of the compound in pentadeuterionitrobenzene was determined at 298–400 K. Shifts and line-widths for the *tert*-butyl group signals optimized by gNMR [15] at "low" temperature were used with the exchange option to estimate the exchange rate constant, k_{exch}, at 365–400 K. The *syn–anti* ratio was sufficiently close to unity (1.03) for the forward and reverse rate constants to be taken as equal (T/K, k_{exch}/s^{-1}) (365, 4.40; 370, 6.03; 375, 7.73; 380, 8.65; 385, 12.3; 390, 15.6; 395, 19.8; 400, 25.7). The activation energy varies from 20.44 to 21.07 kcal mol^{-1} (average value 20.77 kcal mol^{-1}) which implies an anomalously high value for the activation entropy, of the order of −19 cal mol^{-1} K^{-1}. However, the spectra were not of very good quality and it seems likely that this is an artefact of the optimization procedure.

Alcohol **2** as isolated is essentially in the *syn* conformation, and the rate constant (sum of k_A and k_S for the *anti*→*syn* and *syn*→*anti* isomerizations, respectively) of attainment of the *anti–syn* equilibrium in benzene can be determined directly in the probe, the ^{1}H NMR spectrum being scanned at convenient intervals. The rotamerization of alcohol **3A** in toluene or pyridine was followed in the same way. Rate data [alcohol, solvent (T/K, $(k_A + k_S)/s^{-1}$, percentage *anti* at equilibrium)]: **2**, benzene (298, $2.41 \pm 0.04 \times 10^{-4}$, 48.1; 304, $4.90 \pm 0.05 \times 10^{-4}$, 48.4; 311, $1.22 \pm 0.01 \times 10^{-3}$, 48.7; 318, $2.56 \pm 0.03 \times 10^{-3}$, 49.0); **3**, toluene (333, $1.39 \pm 0.02 \times 10^{-4}$, 42.8; 343, $4.26 \pm 0.04 \times 10^{-4}$, 42.7; 353, $1.30 \pm 0.02 \times 10^{-3}$, 42.9); **3**, pyridine (323, $1.70 \pm 0.01 \times 10^{-4}$, 12.6; 336, $5.57 \pm 0.04 \times 10^{-4}$, 15.6; 343, $1.18 \pm 0.02 \times 10^{-3}$, 17.2; 353, $2.89 \pm 0.06 \times 10^{-3}$, 19.5). Thermodynamic parameters [alcohol, solvent, (reaction, $\Delta H^{\ddagger}$/kcal mol^{-1}, $\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}, mean $\Delta G^{\ddagger}$/kcal mol^{-1})]: **2**, benzene, (*anti*→*syn*, 21.7 ± 0.5, −3.6 ± 1.6, 22.81; *syn*→*anti*, 22.0 ± 0.4, −2.7 ± 1.4, 22.84); **3**, toluene, (*anti*→*syn*, 25.4 ± 0.4, −1.8 ± 1.2, 26.03; *syn*→*anti*, 25.4 ± 0.4, −1.2 ± 1.2, 25.83); **3**, pyridine, (*anti*→*syn*, 20.2 ± 0.4, −13.9 ± 1.1, 24.85; *syn*→*anti*, 24.1 ± 0.3, −5.6 ± 1.0, 25.96).

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