Solvent effects on hydrogen bonding and rotation barriers in α-alkyl-substituted 2-alkoxybenzyl alcohols †

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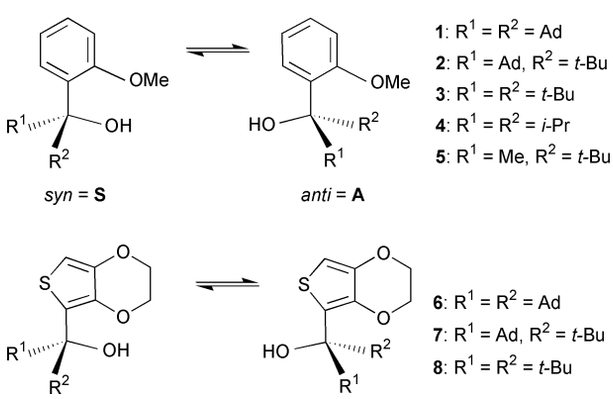
2-Alkoxyphenyl(α,α-dialkyl)methanols exist in two conformations, where the hydroxy hydrogen is either intramolecularly hydrogen-bonded to the alkoxy oxygen (*syn* rotamer) or is remote from the alkoxy group (*anti* rotamer) and therefore "free". The *anti* and *syn* rotamers of 2-anisyldi(*tert*-butyl)methanol, and of derivatives where one or both *tert*-butyls are replaced by 1-adamantyl, can be separated by chromatography. The activation energy for *anti*→*syn* rotation of 2-anisyldi(*tert*-butyl)methanol (about 28 kcal mol^{-1} at 373 K) varies insignificantly with the solvent, while that for the reverse reaction decreases in the order: chloroform ≈ toluene > pyridine > DMSO. Stabilization of the *anti* rotamer and the rotation transition state by hydrogen-bonding solvents would appear to be of equal importance, whereas the *syn* rotamer has no requirement for solvation of the polar OH group. Very similar solvent effects on equilibrium constants and rotation barriers are found for 2-anisyl(isopropyl)(*tert*-butyl)methanol, the rotamers of which are separable on the NMR time-scale. The free energy differences for the rotamers of this alcohol in a variety of solvents correlate with those for 3,4-(ethylenedioxy)-2-thienyldi(*tert*-butyl)methanol and with solute hydrogen bond basicity parameters.

Introduction

Intramolecular hydrogen bonds stabilize the three-dimensional structures of biological and other molecules. These hydrogen bonds may be in competition with intermolecular hydrogen bonds to solvent molecules, of which water is the most important for biological systems. Consequently, structure depends on solvent. In extreme cases change of solvent may result in complete structural change; in less extreme cases the equilibrium between different conformations may be modified.

In heteroaryl(α,α-dialkyl)methanols the balance between intermolecular and intramolecular hydrogen bonding is a function of the heteroaryl group and of the solvent, two conformers being readily distinguished by IR and NMR spectroscopy.[1] Similar behaviour is expected of species where the heteroatom is in a substituent close to the OH group. The product isolated from the reaction of 2-anisyllithium with di(1-adamantyl) ketone has the *syn* structure, **1S**, with the hydroxy hydrogen intramolecularly hydrogen-bonded to the methoxy oxygen.[2] This conformation is clearly favoured in that it also minimizes steric interactions between the methoxy group and the adamantyls, whereas the *anti* isomer, **1A**, would not only lose the benefit of hydrogen bonding but also suffer greater steric strain. However, recent work on 3,4-ethylenedioxythiophene (EDOT) analogues, **6**–**8**,[3] has shown that these can exist in both *anti* and *syn* forms, and that the isomer with the "free" OH group can be stabilized by solvation in a hydrogen-bonding solvent such as DMSO or pyridine.

It has been reported that for 2-anisyl(α-alkyl)methanols and 2-anisyl(α,α-dialkyl)methanols, with rather smaller alkyl substituents [up to di(*tert*-butyl)], both forms occur and that they are in equilibrium at 293–323 K.[4–6] From the temperature dependence of the IR spectra in carbon tetrachloride Ito and Hirota[5] determined "enthalpies of hydrogen bond formation"



(*i.e.* $\Delta H°$ for the equilibrium between the free and hydrogen-bonded forms). In this and more recent work[6] molecular mechanics calculations were used to determine the steric energy profile for rotation about the sp^2–sp^3 bond in these alcohols, the main conclusions being that the α,α-dialkyl derivatives adopt stable conformations in which the C–OH bond is close to the plane of the benzene ring, while in the rotation transition state it is approximately orthogonal to this plane. These conclusions agree with crystallographic studies[2,7,8] and previous calculations[9] on analogues without the 2-methoxy group.

According to a dynamic ^{1}H NMR study of α,α-dialkyl-3,4,5-trimethoxybenzyl alcohols in DMSO the rotation barrier for the di(*tert*-butyl) derivative is substantially higher than that for the (isopropyl)(*tert*-butyl) analogue: 21 and 13 kcal mol^{-1}, respectively.‡[10] Now, that for 2-anisyl(isopropyl)(*tert*-butyl)-methanol, **4**, is about 18 kcal mol^{-1},[6] which suggests that, if the above difference were reproduced in the 2-anisyl derivatives, 2-anisyldi(*tert*-butyl)methanol, **3**, would be in the range where the rotamers can be separated by chromatography or crystallization. If this were the case it would be difficult to understand how they could be in equilibrium at 293–323 K.

† Electronic supplementary information [ESI] available: Tables 4 and 5 with ^{13}C NMR spectral data and details of the hydroxy proton shift in solvents other than chloroform. See http://www.rsc.org/suppdata/p2/b1/b102416g/

‡ 1 cal = 4.184 J.

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Table 1 Rate constants (s^{-1}) and rotation barriers (kcal mol^{-1}) for 2-anisyldi(*tert*-butyl)methanol, **3**, in various solvents

Solvent	Temp./K	10^6k_S	10^6k_A	$\Delta G_S^{\ddagger}$	$\Delta G_A^{\ddagger}$
Chloroform	358	3.84	63.0	29.99	27.99
	372	18.6	253	30.01	28.08
	385	76.3	900	30.08	28.18
	401	299	3260	30.17	28.27
Toluene	348	1.40	17.2	29.80	28.07
	358	4.31	49.6	29.88	28.14
	373	22.8	249	29.93	28.15
	383	61.2	604	30.00	28.25
Pyridine	348	4.45	19.5	29.00	27.98
	358	12.6	60.9	29.11	27.99
	373	61.4	294	29.19	28.03
	383	153	795	29.30	28.04
DMSO	348	8.29	18.4	28.57	28.02
	358	25.0	58.2	28.63	28.03
	373	109	279	28.76	28.07
	388	433	1190	28.89	28.11

We now report the separation of the *syn* and *anti* rotamers of alcohols **1**–**3**. The kinetics of the interconversion of the rotamers of **3** have been studied in several solvents. Some less congested 2-alkoxyphenyl(α,α-dialkyl)methanols, which are separable on the NMR time-scale, will also be discussed.

Results

(i) 2-Anisyldi(*tert*-butyl)methanol, 3

Rotamer equilibria. 2-Anisyldi(*tert*-butyl)methanol, **3**, was synthesized by reaction of 2-anisyllithium (from anisole, *n*-butyllithium and TMEDA in diethyl ether at room temperature) with di(*tert*-butyl) ketone. Distillation of the product at reduced pressure gives a mixture of two isomers in a ratio of about 10 : 1, the major component being the *syn* isomer, **3S**. They were separated by column chromatography on alumina, the *syn* isomer being eluted first in light petroleum–diethyl ether mixtures. The less stable, *anti* isomer, **3A**, held at the highest temperature used by Ito and Hirota,[5] 320 K, for several hours in chloroform or in hydrogen-bonding solvents, such as DMSO and pyridine, gives no *syn* isomer. Samples of this material were heated for 2 h at 423 K in tubes sealed under vacuum either neat or with a deuteriated solvent: chloroform, benzene, DMSO or pyridine. The neat sample and those in chloroform or benzene show about 9% of the *anti* isomer, while those in pyridine and DMSO contain rather more (16 and 26%, respectively).

Rotation barriers. Rates of equilibration of the alcohol, starting with the *anti* isomer, **3A**, were determined in several solvents. In all cases the activation energy for *anti*→*syn* rotation (associated with k_A) is high, about 28 kcal mol^{-1}, as it must be for separation to be possible at room temperature. A remarkable feature is that for four very different solvents the *anti*→*syn* barriers are closely similar, averaging 28.1, 28.2, 28.0 and 28.1 kcal mol^{-1} for chloroform, toluene, pyridine and DMSO, respectively (Table 1). The differences in the equilibrium constants are due almost entirely to differences in the barrier for the *syn*→*anti* reaction (associated with k_S), these decreasing in the order: chloroform (30.1 kcal mol^{-1}) ≈ toluene (29.9 kcal mol^{-1}) > pyridine (29.15 kcal mol^{-1}) > DMSO (28.7 kcal mol^{-1}). It is therefore possible to speak of the *syn*→*anti* reaction as being "solvent-driven", insofar as it is accelerated by hydrogen-bonding solvents.

These results are consistent with the idea that in the *anti*→*syn* reaction the initial and the transition states are similarly solvated, whereas in the reverse reaction (*via* the same transition state) the polar OH group in the initial state is intramolecularly hydrogen-bonded and has no specific requirement for solvation.[6] The solvent is therefore much more important in the *syn*→*anti* than in the *anti*→*syn* reaction. A similar result has been reported for the rotamerization of EDOTdi(1-adamantyl)methanol, **6**, in toluene and pyridine.[3]

Inspection of the activation enthalpies and entropies, despite their relative imprecision, reveals some significant features. For toluene and chloroform the activation entropies for the two reactions are similar and average about −5 cal mol^{-1} K^{-1}, the greater stability of the *syn* isomer residing almost totally in the enthalpy term. Conversely, for pyridine and toluene hydrogen bonding favours the *anti* isomer by a little over 1 kcal mol^{-1} in both cases, whereas the activation entropies are now quite different, about 6 cal mol^{-1} K^{-1} more negative for the *syn*→*anti* reaction than for *anti*→*syn*. The overall result is that, because of this entropy term, at room temperature the *syn* rotamer still predominates. Analogous findings for the EDOT derivative, **6**, were attributed to solvent structuring in the rotation transition state.[3]

(ii) 2-Anisyl(1-adamantyl)(*tert*-butyl)methanol, 2

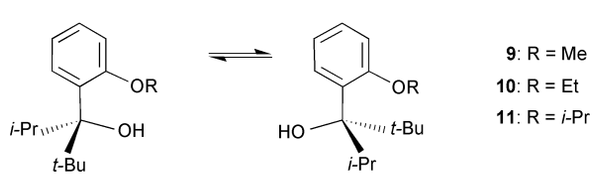
Rotamer equilibria and rotation barriers. The alcohol, as isolated by column chromatography, is the *syn* isomer, **2S**. Samples were equilibrated in various solvents at 423 K, the equilibrium constants being little different from those for the previous alcohol, **3**, the *anti* isomer, **2A**, representing 12, 16 and 23% for toluene, pyridine and DMSO, respectively.

Rotation barriers, measured in toluene, are 33.9 and 32.2 kcal mol^{-1} for the *syn*→*anti* and *anti*→*syn* reaction, respectively, both values being 4 kcal mol^{-1} higher than for the corresponding reactions of the less crowded 2-anisyldi(*tert*-butyl)-methanol, **3**. This is closely similar to the effect (4.1 kcal mol^{-1} at 473 K) of replacing one *tert*-butyl by 1-adamantyl in the *anti*→*syn* reaction of 2-tolyldi(*tert*-butyl)methanol.[9b]

(iii) 2-Anisyldi(1-adamantyl)methanol, 1

Rotamer equilibria. An attempt to attain rotamer equilibrium by heating the *syn* isomer, **1S**, in DMSO at 473 K led to no product which could be identified as the *anti* rotamer. It is possible that in this solvent a carbocation is formed and that this undergoes a 1,5-hydride shift, with the formation of a carboxonium ion and subsequent reaction with a nucleophile.[11] This reaction was not investigated further. On the other hand, equilibration in toluene and pyridine proceeds normally to give mixtures in which the *anti* isomer represents about 13.5 and 14%, respectively. That these figures should be so similar is explained in part by the fact that the amount of the less stable isomer increases with temperature in toluene, whereas it decreases in pyridine, as can be seen from the data on 2-anisyldi(*tert*-butyl)methanol, **3**. A small amount of the *anti* isomer, **1A**, was isolated by reaction of the *syn* in a xylene mixture in a sealed tube at 473 K, followed by alumina chromatography. No attempt was made to study the kinetics of its rotation.

(iv) 2-Alkoxyphenyl(isopropyl)(*tert*-butyl)methanols, 9–11



Rotamer equilibria. 2-Anisyl(isopropyl)(*tert*-butyl)methanol, **9**, was previously investigated by Suezawa *et al.*[6] In contrast to its more congested analogues, in this case the rotamers cannot be separated by chromatography or crystallization, but the

Table 2 Free energy differences and MMFF94-calculated steric energy differences (both in kcal mol^{-1}) for 2-anisyl(α,α-dialkyl)methanols: solvent effects

Compound	Solvent	[*anti*]/[*syn*]	$\Delta G°$ [a,e]	ΔSE [b]	Δsolv. [c]	ΔΔsolv. [d]
2-Anisyl(isopropyl)(*tert*-butyl)methanol, **9** (298 K)						
	Chloroform	0.17	1.04	1.65	0.61	0
	Benzene	0.23	0.88	1.65	0.77	0.16
	Toluene	0.24	0.85	1.65	0.80	0.19
	Acetonitrile	0.52	0.40	1.65	1.25	0.64
	Methanol	0.67	0.24	1.65	1.41	0.80
	Acetone	0.68	0.22	1.65	1.43	0.82
	THF	1.03	−0.02	1.65	1.67	1.06
	Pyridine	1.35	−0.16	1.65	1.81	1.20
	DMSO	2.93	−0.64	1.65	2.29	1.68
2-Anisyldi(*tert*-butyl)methanol, **3** (348 K)						
	Chloroform	0.050[f]	2.07 (2.17)	2.64	0.57	0 (0)
	Toluene	0.081	1.73 (1.69)	2.64	0.91	0.34 (0.48)
	Pyridine	0.23	1.02 (0.74)	2.64	1.62	1.05 (1.43)
	DMSO	0.45	0.55 (0.28)	2.64	2.09	1.52 (1.89)

[a] Free energy difference (*anti* − *syn*). [b] Steric energy difference (*anti* – *syn*).[13] [c] "Solvation effect". [d] Relative solvation effect, referenced to chloroform. [e] Data in parentheses are extrapolated to 298 K from data at higher temperatures. [f] Extrapolated from data at higher temperatures.

exchange rate at room temperature is low on the NMR timescale. Equilibrium constants ([*anti*]/[*syn*]) at 298 K are about 0.7 in acetone and methanol,[6] and 0.2, 0.2, 0.5, 1 and 1.3 in chloroform, toluene, acetonitrile, THF and pyridine, respectively. In DMSO the (*Z*)–(*E*) (*syn*–*anti*) ratio is not 77 : 23 (OCH_3) or 72 : 28 (*i*-PrC*H*),[6] but the inverse, the *anti* isomer, **9A**, being preferred in this solvent. A plot of the 8 data-points, expressed as log *K*, where *K* is the equilibrium constant for the *syn*⇌*anti* reaction, against the solute hydrogen bond basicity parameter, β_2^H,[12] is approximately linear (intercept −0.84 ± 0.08; gradient 1.58 ± 0.16; correlation coefficient 0.9716). These data are also well correlated with those for EDOTdi(*tert*-butyl)methanol, **8**, in the same solvents (intercept –0.64 ± 0.05; gradient 0.85 ± 0.07; correlation coefficient 0.9794).[3]

For the four solvents for which we have comparable data, the equilibrium constants are about 5 times lower (*i.e.* there is a preference for the *syn* isomer) for the di(*tert*-butyl), **3**, than for the (isopropyl)(*tert*-butyl) derivative, **9** (Table 2). Extrapolating the data for **9** to 298 K gives $\Delta G°$ values which can be compared with those for **3**: the average difference is 0.96 ± 0.12 kcal mol^{-1} which is very close to the variation (0.99 kcal mol^{-1}) in the *anti* − *syn* steric energy difference on going from **3** to **9**, calculated on the basis of the MMFF94 force field in Sybyl.[13]

Two other alkoxy derivatives were examined: the 2-ethoxy and 2-isopropoxy analogues, **10** and **11**, respectively. Regardless of the solvent (chloroform, benzene, pyridine or DMSO), increasing the size of the alkoxy group lowers the *anti*–*syn* ratio. The corresponding free energy differences at 298 K, compared to the 2-methoxy derivative, **9**, are about 0.1 and 0.4 kcal mol^{-1} for **10** and **11**, respectively. There are two possible explanations for the increase in the relative stability of the *syn* rotamer. The first is that increasing the bulk of the alkoxy group destabilizes the *anti* more than the *syn* isomer. This can be tested by molecular mechanics calculations.[13] These indicate that the difference between the steric energies of the *anti* and *syn* rotamers varies very little as the size of the alkoxy group is increased and that, contrary to expectation, it is 0.1 kcal mol^{-1} less for **10** and **11** than for **9**, *i.e.* by this token the *anti*–*syn* ratio should be higher for **10** and **11**. A second possibility is that in the *syn* isomer hydrogen bonding is stronger because the oxygen atom bears a more electron-donating alkyl group. This latter possibility would appear to be supported by the increasingly downfield shift of the hydroxy proton in the NMR spectrum, whatever the solvent, and the concomitant change in the IR frequency of the OH stretching vibration to lower wavenumbers (3528, 3517 and 3493 cm^{-1} for **9**, **10** and **11**, respectively). If no other factors have been overlooked, after correction for the steric energy increment, these changes correspond to hydrogen bond energy increments of about 0.2 and 0.5 kcal mol^{-1}.

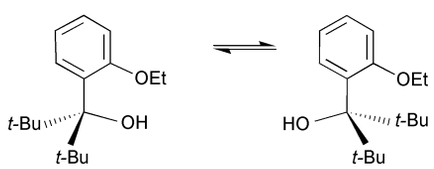
Correlation of the free energy differences between the rotamers in DMSO against temperature gives very similar $\Delta H°$ and $\Delta S°$ values for alcohols **9**–**11**. The enthalpy term (1.5–1.7 kcal mol^{-1}) is close to that for **3** in the same solvent (1.5 kcal mol^{-1}), while the entropy term is somewhat smaller, being 3–5 cal mol^{-1} K^{-1} in favour of the *syn* isomer as compared to 5.7 cal mol^{-1} K^{-1} for **3**. This difference presumably reflects structural dependence of the solvation of the various species involved in rotamerization.

Rotation barriers. Dynamic ^{1}H NMR was used to determine rotation barriers for 2-anisyl(isopropyl)(*tert*-butyl)methanol, **9**, the exchange rates being calculated by gNMR simulation[14] of the spectra at different temperatures. Values for the *anti*→*syn* reaction are 17.4, 17.7 and 17.3 kcal mol^{-1} for chloroform (308–343 K), toluene (328–353 K) and pyridine (303–333 K), respectively, while the corresponding values for the *syn*→*anti* reaction are 18.3, 18.5 and 17.3 kcal mol^{-1}. In DMSO the hydroxy proton signal of *anti*-2-anisyl(isopropyl)(*tert*-butyl)methanol, **9A**, moves into the region of the methoxy signals as the temperature is increased, making it difficult to determine the rotation barrier, though Suezawa *et al*. reported a value of 17.8 kcal mol^{-1} for the *anti*→*syn* reaction.[6,15] By ^{13}C DNMR we obtain 17.6 kcal mol^{-1}, in good agreement with the ^{1}H NMR value, and 17.0 kcal mol^{-1} for the *syn*→*anti* reaction (298–328 K). The variation in the *anti*→*syn* rotation barriers, though greater than for **3**, is of the same order of magnitude as the experimental error on their determination, while the *syn*→*anti* reaction barrier is again much reduced in the hydrogen-bonding solvents, such as pyridine and DMSO, as compared to chloroform and toluene.

Alcohols **10** and **11** also were studied by ^{13}C DNMR in an attempt to determine the effect, if any, of the size of the alkoxy group. In fact, increasing the size of the alkyl group merely raises both barriers slightly, the effect being slightly greater for the *syn*→*anti* (17.0, 17.3 and 17.9 kcal mol^{-1} for **9**, **10** and **11**, respectively) than for the *anti*→*syn* reaction (17.6, 17.7 and 18.1 kcal mol^{-1}). This result contrasts with the much greater effects of 3-alkoxy groups on the rotation of *anti*-3-alkoxy-2-thienyldi(1-adamantyl)methanes, a total variation of 2.3 kcal mol^{-1} on going from methoxy to isopropoxy.[8] This suggests that in the transition state for rotation of the 2-alkoxyphenyl(isopropyl)(*tert*-butyl)methanols the smaller group, isopropyl, is brought the closer to the alkoxy group (though not eclipsed with it; conformations with either alkyl group eclipsed with the

benzene ring do not constitute maxima on the rotation energy profile). Since isopropyl has a sterically undemanding orientation, strain can be minimized by turning the CH bond towards the alkoxy group, which means that the nature of this group is of less importance than when both α-alkyl substituents are sterically demanding in all orientations, as is 1-adamantyl.

It would have been interesting to compare 2-alkoxyphenyldi-(*tert*-butyl)methanols with the same alkoxy groups, but only the 2-ethoxy derivative, **12**, is readily accessible. The yield of the 2-isopropoxy compound is poor (less than 2%) and the equilibrium concentration of the *anti* rotamer, even in DMSO, will be lower than that of **12** and, therefore, too low for the synthesis of adequate amounts of this material for kinetic investigation. The *anti–syn* ratios for **12** in various solvents at 423 K, as for **9** and **10**, are lower than for **3**, corresponding to a relative free energy difference of 0.55 ± 0.07 kcal mol^{-1}. The increase in steric energy on going from **12S** to **12A** is 0.3 kcal mol^{-1} higher than for **3S** to **3A**, which suggests that a small part of this difference can be attributed to stronger hydrogen bonding in **12S** than in **3S**, again correlated with a downfield shift in the OH proton NMR signal and a lower IR OH stretching frequency for **12S** as compared to **3S**.



12S **12A**

Comparison of the activation energies for the rotation of **12** in DMSO with those for **3** at 358–388 K reveals again a small effect on the *anti*→*syn* reaction (0.1 kcal mol^{-1}) and a rather greater effect upon the *syn*→*anti* reaction (0.6 kcal mol^{-1}). This increase is greater than for the corresponding (isopropyl)-(*tert*-butyl) derivatives, and is consistent with the fact that *tert*-butyl has no sterically undemanding orientation, but is less demanding than 1-adamantyl.

Discussion

Solvent effects on equilibrium constants

According to molecular mechanics calculations (MM3 or MMFF94) the *anti* rotamer of 2-anisyl(α,α-dialkyl)methanols has a higher steric energy than the *syn* form, the difference increasing with the size of the alkyl groups.[6] Since these force fields do not take intramolecular hydrogen bonding into account explicitly, the preference for the *syn* form should be even greater than that indicated by MM. In fact, the data for alcohols **3** and **9** show that, even in non-hydrogen-bonding solvents, the *syn* form is somewhat less favoured than expected. Given that MM calculates gas-phase energies, it may be argued that this is a solvation effect, whether the solvent be hydrogen-bonding or not. However, it is possible that the difference is due to inadequacies in the force field. The data in Table 2 have been organized to show the magnitude of any such solvation effect or error, neglecting, however, the contribution of the intramolecular hydrogen bond. The relative solvation effects (which are free of any error in the force field) follow the same trend for the two alcohols considered. The values for the second set, **3**, are slightly higher, but since these data are extrapolated from higher temperatures and the precision on the thermodynamic parameters, particularly the activation entropy, is low, the difference is not significant. Data on the equilibrium constants for the EDOT derivatives, **7** and **8**, in chloroform, pyridine and DMSO at 298 K give relative solvation effects averaging 1.3 and 1.7 kcal mol^{-1} for pyridine and DMSO, respectively, closely similar to the values for alcohol **9** at the same temperature (Table 3).

Table 3 Free energy differences (kcal mol^{-1}) for EDOT(α,α-dialkyl)-methanols: solvent effects[3]

Compound	Solvent	[*syn*]/[*anti*][a]	ΔG°[b]	ΔΔsolv.[c]
EDOTdi(*tert*-butyl)methanol, **8** (298 K)				
	Chloroform	0.94	−0.04	0
	Benzene	0.84	−0.10	−0.06
	Acetonitrile	3.3	0.70	0.74
	Methanol	3.85	0.80	0.84
	Acetone	3.4	0.73	0.77
	THF	4.1	0.84	0.88
	Pyridine	9.2	1.31	1.35
	DMSO	18	1.71	1.75
EDOT(1-adamantyl)(*tert*-butyl)methanol, **7** (298 K)				
	Chloroform	1.08	0.12	0
	Benzene	1.22	0.05	−0.07
	Pyridine	10	1.36	1.24
	DMSO	21	1.80	1.68

[a] According to the Cahn–Ingold–Prelog rules,[16] the *syn* and *anti* designations are reversed with respect to those for the 2-anisyl derivatives. [b] Free energy difference (*syn* − *anti*). [c] Relative solvation effect, referenced to chloroform.

The equilibrium between two conformers in a given solvent reflects several factors, including the difference in the steric energies, the strength of the intramolecular hydrogen bond, general solvation phenomena and the specific effect of the solvent on the "free" hydroxy group. The first two factors may be considered to be independent of solvation, and the major effect of replacing one solvent by another clearly lies in the last of these factors, differences in the solvation of the rest of the molecule being apparently negligible for the closely related species considered in this work.

Rotamer equilibria and IR measurements

The data given above indicate that the rate of equilibration of the two 2-anisyldi(*tert*-butyl)methanol rotamers, **3A** and **3S**, in chloroform would be very slow at 293–323 K. The half-life for equilibration at 293 K would be something over a year, and about a week at 323 K. It seems unlikely that in the IR spectroscopic work[5] the system was allowed to equilibrate several weeks or years between spectra. Moreover, our data indicate that there would be less than 4% of the *anti* isomer at 323 K whereas Hirota's data suggest a higher figure. Insofar as chloroform is a solvent very similar to carbon tetrachloride, it is difficult to believe that the reported changes in the IR spectrum are due to variations in the equilibrium constant.

The question is whether the intensities of the bands can be taken as a measure of conformer populations. In our hands, distillation of **3** affords a mixture containing about 9% of the *anti* isomer, according to the NMR measurement. The isomer ratio based on the IR measurement, with the simple assumption that the peak height is proportional to concentration and that the two isomers have the same extinction coefficient, gives a somewhat higher value, about 15%. For the di(isopropyl) derivative, **4**, the IR measurement in carbon tetrachloride indicates 15% of the *anti* isomer at 293 K, whereas NMR in chloroform gives 17% at 223 K.[15] Since our data show that the *anti* isomer fraction increases with temperature in chloroform, the IR measurement this time underestimates the amount of *anti*. Finally, for the (isopropyl)(*tert*-butyl) derivative, **9**, there is good agreement between Hirota's IR and our NMR data (15% *anti* in both cases). On the basis of this evidence the IR intensities do not appear to be a reliable guide to rotamer ratios.

Temperature increase reduces the intensity of the OH absorption for the hydrogen-bonded, *syn* isomer, while that of the free OH changes very little, the sum of the intensities

decreasing as the temperature increases.[5] This is wrongly attributed to a slight increase in the proportion of the *anti* isomer. The data presented do not allow us to determine whether or not the integrated peak area remains the same. An interesting feature of the IR spectra, not previously reported for 2-alkoxybenzyl alcohols, is that the free hydroxy group is always associated with two bands of similar intensity and separated, for the alcohols examined here, by an average of 34 cm^{-1}. This is a common phenomenon with aryl(dialkyl)methanols and has been attributed to the existence of two conformations with respect to rotation about the C-O bond.[1,9a,17]

Solvent effects on rotation barriers

Our values for the rotation barriers in alcohols **3** and **9** clearly show that solvent hydrogen bonding has little or no effect on the *anti*→*syn* reaction but marked effects on the reverse reaction, where the initial and transition states have very different solvation characteristics. In previous work rotational barriers and free energy differences for 2-anisyl(methyl)(*tert*-butyl)-methanol, **5**, in acetone–chloroform mixtures were studied.[6] The listed activation energy relates to the *syn*→*anti* reaction,[15] and that for the *anti*→*syn* reaction is obtained by subtracting the free energy difference. There is a very small decrease (0.14 kcal mol^{-1}) in the *anti*→*syn* barrier on going from acetone to 90% chloroform, while that for *syn*→*anti* increases by about 1.5 kcal mol^{-1}, at temperatures which decrease from about 265 to 255 K.[15] While these results are consistent with the general pattern indicated above, the magnitude of the effect upon the *syn*→*anti* reaction for the change from a moderately hydrogen-bonding solvent, acetone, to chloroform is surprisingly large. For **9** at 298 K the corresponding change in ΔG° is only 0.8 kcal mol^{-1}. This may again reflect a structural dependence of solvation. On the other hand, it should be noted that in the cited work:[6] (i) the temperatures are 30–40 K lower, which will increase the importance of hydrogen bonding (the *anti*–*syn* ratio in hydrogen-bonding solvents increases as the temperature falls); (ii) the equilibrium constants were measured at an even lower temperature, 223 K,[15] which apart from the effect on the ΔG° value, must have complicated the evaluation of the exchange rate.

Rotation barriers in *ortho*-substituted aryldi(*tert*-butyl)-methanols

Only three data are available, the *ortho* substituent being hydrogen, methoxy or methyl. For the first, values for several solvents were determined by Sternhell *et al*.,[18] but these values vary as much with the method of determination as with the solvent. Baas *et al*. give for the 3,4,5-trimethoxy derivative in DMSO a value of 21.4 kcal mol^{-1} at a coalescence temperature of 421 K.[10] For the *o*-tolyl derivative, only the *anti*→*syn* barrier has been determined,[9a] the equilibrium constant lying so far in the direction of the *syn* rotamer that the reverse reaction cannot be detected. Molecular mechanics calculations indicate a steric energy difference of about 7 kcal mol^{-1} [9a,b,d] but this has never been verified by measuring the heats of formation. However, acid-catalysed solvolysis rates for the two rotamers in acetic acid at 298 K differ by a factor of about 10^4,[19] which corresponds to 5.5 kcal mol^{-1}, in fair agreement with theory. The *anti*→*syn* rotation barrier in dodecane at 373 K is 29 kcal mol^{-1},[9a,b] which makes the *syn*→*anti* barrier about 35 kcal mol^{-1}. To complete the set, we have the results of the present work in toluene or chloroform: *anti*→*syn*, 28 kcal mol^{-1}; *syn*→*anti*, 30 kcal mol^{-1}.

These results show a fairly smooth progression in the value of the *syn*→*anti* barrier as hydrogen (21.4 kcal mol^{-1}) is replaced by methoxy (30 kcal mol^{-1}) and then by methyl (35 kcal mol^{-1}). However, the reverse reaction has very similar values for methyl (29 kcal mol^{-1}) and methoxy (28 kcal mol^{-1}), and a much smaller one for hydrogen (21.4 kcal mol^{-1}). Intuitively it is hard to understand why there is not a more regular variation. This brings us back to the problem of the discrepancy between the calculated steric energy difference, which neglects intramolecular hydrogen bonding, and the experimental free energy difference for the 2-anisyldi(*tert*-butyl)methanol and 2-anisyl(isopropyl)(*tert*-butyl)methanol rotamers. High-level *ab initio* calculations with a good solvation model could help to resolve this problem.

Conclusion

The *syn* and *anti* rotamers, with intramolecularly hydrogen-bonded and "free" hydroxy groups, respectively, of 2-anisyldi(*tert*-butyl)methanol, **3**, are readily separated at room temperature. The *anti*→*syn* rotation barrier is of the order of 28 kcal mol^{-1}, independent of the nature of the solvent, whether it be hydrogen bonding or not. In hydrogen-bonding solvents the *syn*→*anti* conversion can be spoken of as "solvent-driven". Replacing one or both of the *tert*-butyl groups by 1-adamantyl makes the rotation barrier even higher. Other less encumbered alcohols with lower rotation barriers and, therefore, not physically separable, behave in the same way. The general interpretation is that the *anti* isomer and the transition state are similarly solvated whereas the *syn* isomer has quite different solvation characteristics, insofar as the hydrogen of the polar OH group is intramolecularly hydrogen-bonded to the 2-methoxy oxygen. The fact that the rotamerization of **3** is slow casts doubt upon the interpretation of IR studies where the intensities of the absorption bands of the *syn* and *anti* isomers of this and other alcohols are found to be temperature-dependent.[5] Though we have not re-examined the series fully, the fact that all the alcohols show the same temperature dependence of the IR spectra as **3** suggests that this phenomenon is in no case attributable to variations in the equilibrium constant, despite the fact that rotation is much faster for the less congested alcohols.

Experimental

General methods have been described elsewhere (see supplementary information and ref. 8).

Alcohol synthesis

All *syn* alcohols were synthesized by the reaction of the appropriate 2-alkoxyphenyllithium (prepared by the reaction of 2-alkoxybenzene with TMEDA and *n*-butyllithium in diethyl ether or TFA at room temperature under argon) with the appropriate ketone. After aqueous work-up and extraction into light petroleum (boiling range 35–60 °C), drying and evaporation of the solvents, the product was purified either by distillation or by column chromatography on alumina in light petroleum–diethyl ether mixtures containing up to 20% of diethyl ether. The *anti* rotamers are either in equilibrium with the *syn* rotamer at room temperature (alcohols **9**–**11**) or are obtained by partial rotation of the *syn* isomer in a suitable solvent at higher temperature, followed by chromatographic separation on alumina (alcohols **1**–**3**, **12**).

2-Anisyldi(*tert*-butyl)methanol, 3. Di(*tert*-butyl) ketone was added to 2-anisyllithium in diethyl ether. The as-synthesized alcohol is the *syn* isomer, **3S**. Distillation (165 °C/20 mmHg; lit.[4] 155 °C/5 mmHg) gave the alcohol as a 10 : 1 mixture of the *syn* and *anti* isomers, which were separated by column chromatography, the *syn* isomer being eluted first: ν_{OH}/cm^{-1} (CCl_4) 3510 (lit.[5] 3508); δ_H (chloroform) 1.12 (*t*-Bu), 3.87 (CH_3), 6.60 (OH), 6.92 (H5, *J* 1.4, 7.2 and 8.1), 6.94 (H3, *J* 0.3, 1.4 and 8.3), 7.19 (H4, *J* 1.7, 7.2 and 8.3) and 7.56 (H6, *J* 0.3, 1.7 and 8.1).

***anti*-2-Anisyldi(*tert*-butyl)methanol, 3A.** Distilled 2-anisyldi-(*tert*-butyl)methanol (2 g) was dissolved in dry DMSO (20 cm^3) and held at 150 °C for 30 min. After cooling, the alcohol was extracted into pentane and the organic phase thoroughly

washed with water, then dried and the solvent evaporated. Chromatography yielded **3A** (oil, 0.42 g, 21%): ν_{OH}/cm^{-1} (CCl_4) 3613, 3648 (lit.[5] 3616); δ_H (chloroform) 1.16 (*t*-Bu), 1.90 (OH), 3.80 (CH_3), 6.88 (H3, *J* 0.5, 1.3 and 8.1), 6.98 (H5, *J* 1.3, 7.3 and 8.1), 7.26 (H4, *J* 1.8, 7.3 and 8.1) and 7.90 (H6, *J* 0.5, 1.8 and 8.1) (Found: C, 76.9; H, 10.6. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%).

***syn*-2-Anisyl(1-adamantyl)(*tert*-butyl)methanol, 2S.** (1-Adamantyl) (*tert*-butyl) ketone was added to 2-anisyllithium in diethyl ether. The crude alcohol, identified as the *syn* isomer, was purified by column chromatography (yield 71%): mp 84 °C; ν_{OH}/cm^{-1} (CCl_4) 3503; δ_H (chloroform) 1.15 (*t*-Bu), 1.59 and 1.8–2.1 (Ad), 3.87 (CH_3), 6.56 (OH), 6.93 (H5, *J* 1.4, 7.2 and 8.2), 6.94 (H3, *J* 0.2, 1.4 and 8.3), 7.20 (H4, *J* 1.7, 7.2 and 8.3) and 7.53 (H6, *J* 0.2, 1.7 and 8.2) (Found: C, 80.4; H, 9.8. $C_{22}H_{32}O_2$ requires C, 80.44; H, 9.82%).

***anti*-2-Anisyl(1-adamantyl)(*tert*-butyl)methanol, 2A.** By treating **2S** (1.47 g) in DMSO (100 cm^3) at 150 °C for 4 h, followed by extraction into pentane, thorough washing with water, evaporation of the solvent and alumina chromatography **2A** was obtained (yield 0.282 g, 19%): mp 96 °C; ν_{OH}/cm^{-1} (CCl_4) 3611, 3643; δ_H (chloroform) 1.14 (*t*-Bu), 1.58 and 1.7–2.1 (Ad), 1.88 (OH), 3.78 (CH_3), 6.85 (H3, *J* 0.2, 1.3 and 8.1), 6.94 (H5, *J* 1.3, 7.2 and 8.1), 7.22 (H4, *J* 1.8, 7.2 and 8.1) and 7.81 (H6, *J* 0.2, 1.8 and 8.1) (Found: C, 80.5; H, 9.8. $C_{22}H_{32}O_2$ requires C, 80.44; H, 9.82%).

***anti*-2-Anisyldi(1-adamantyl)methanol, 1A.** Di(1-adamantyl) ketone was added to 2-anisyllithium, as previously described,[2] to give the *syn* isomer, **1S**. Treatment of this material (0.39 g) in a xylene mixture (5 cm^3) in a sealed tube at 200 °C for 5 h, followed by evaporation of the solvent and alumina chromatography gave **1A** (yield 48 mg, 12%): mp 190 °C; ν_{OH}/cm^{-1} (CCl_4) 3606, 3640; δ_H (chloroform) 1.62 and 1.8–2.1 (Ad), 1.94 (OH), 3.81 (CH_3), 6.88 (H3, *J* 0.4, 1.2 and 8.1), 6.95 (H5, *J* 1.2, 7.2 and 8.0), 7.24 (H4, *J* 1.7, 7.2 and 8.1) and 7.81 (H6, *J* 0.4, 1.7 and 8.0) (Found: C, 82.6; H, 9.5. $C_{28}H_{38}O_2$ requires C, 82.71; H, 9.42%).

2-Anisyl(isopropyl)(*tert*-butyl)methanol, 9. By the reaction of 2-anisyllithium with (isopropyl) (*tert*-butyl) ketone in diethyl ether: bp 147 °C/20 mm (lit.[4] 133 °C/5 mm); **9S**: ν_{OH}/cm^{-1} (CCl_4) 3528 (lit.[5] 3532); δ_H (chloroform) 0.79 (CH_3, *J* 6.6), 0.97 (*t*-Bu), 1.15 (CH_3, *J* 6.6), 2.52 (CH, *J* 1.6 and 6.6), 3.87 (CH_3), 5.97 (OH, *J* 1.6), 6.92 (H3, *J* 0.4, 1.3 and 8.1), 6.94 (H5, *J* 1.3, 7.3 and 8.0), 7.19 (H4, *J* 1.7, 7.3 and 8.1) and 7.21 (H6, *J* 0.4, 1.7 and 8.0); **9A**: ν_{OH}/cm^{-1} (CCl_4) 3606, 3639 (lit.[5] 3603.5); δ_H (chloroform) 0.61 (CH_3, *J* 6.8), 0.96 (*t*-Bu), 1.14 (CH_3, *J* 6.8), 1.65 (OH), 3.31 (CH, *J* 6.8), 3.77 (CH_3), 6.83 (H3, *J* 8.0), 6.94 (H5), 7.19 (H4) and 7.69 (H6, *J* 1.8 and 7.8).

2-Ethoxyphenyl(isopropyl)(*tert*-butyl)methanol, 10. Compound **10** was obtained by the reaction of 2-ethoxyphenyllithium with (isopropyl) (*tert*-butyl) ketone in diethyl ether: mp 49 °C; **10S**: ν_{OH}/cm^{-1} (CCl_4) 3517; δ_H (chloroform) 0.80 (CH_3, *J* 6.7), 0.98 (*t*-Bu), 1.16 (CH_3, *J* 6.7), 1.47 (CH_3, *J* 7.0), 2.52 (CH, *J* 1.5 and 6.7), 4.06 (CH, *J* 7.0 and 9.2), 4.14 (CH, *J* 7.0 and 9.2), 6.21 (OH, *J* 1.5), 6.90 (H3, *J* 0.2, 1.3 and 8.1), 6.92 (H5, *J* 1.3, 7.2 and 8.1), 7.14 (H4, *J* 1.7, 7.2 and 8.1) and 7.21 (H6, *J* 0.2, 1.7 and 8.1); **10A**: ν_{OH}/cm^{-1} (CCl_4) 3606, 3642; δ_H (chloroform) 0.62 (CH_3, *J* 6.8), 0.98 (*t*-Bu), 1.14 (CH_3, *J* 6.8), 1.43 (CH_3, *J* 7.0), 1.64 (OH), 3.42 (CH, *J* 6.8), 3.97 (CH, *J* 6.7 and 8.8), 4.04 (CH, *J* 6.7 and 8.8), 6.79 (H3, *J* 8.2), 6.92 (H5), 7.14 (H4) and 7.69 (H6, *J* 1.7 and 7.9) [Found (*anti* + *syn*): C, 76.6; H, 10.6. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%].

2-Isopropoxyphenyl(isopropyl)(*tert*-butyl)methanol, 11. Compound **11** was obtained by the reaction of 2-isopropoxyphenyllithium with (isopropyl) (*tert*-butyl) ketone in diethyl ether: oil; **11S**: ν_{OH}/cm^{-1} (CCl_4) 3493; δ_H (chloroform) 0.79 (CH_3, *J* 6.7), 0.98 (*t*-Bu), 1.15 (CH_3, *J* 6.7), 1.35 (CH_3, *J* 6.1), 1.43 (CH_3, *J* 6.1), 2.51 (CH, *J* 1.3 and 6.7), 4.69 (CH, *J* 6.1), 6.41 (OH, *J* 1.3), 6.90 (H5, *J* 1.3, 7.2 and 8.0), 6.91 (H3, *J* 0.4, 1.3 and 8.3), 7.14 (H4, *J* 1.7, 7.2 and 8.3) and 7.22 (H6, *J* 0.4, 1.7 and 8.0); **11A**: ν_{OH}/cm^{-1} (CCl_4) 3607, 3640; δ_H (chloroform) 0.61 (CH_3, *J* 6.8), 0.98 (*t*-Bu), 1.13 (CH_3, *J* 6.8), 1.35 (CH_3, *J* 6.1), 1.43 (CH_3, *J* 6.1), 1.61 (OH), 3.44 (CH, *J* 6.8), 4.69 (CH, *J* 6.1), 6.76 (H3, *J* 8.2), 6.90 (H5), 7.14 (H4) and 7.70 (H6, *J* 1.9 and 7.8) [Found (*anti* + *syn*): C, 77.4; H, 10.8. $C_{17}H_{28}O_2$ requires C, 77.22; H, 10.67%].

***syn*-2-Ethoxyphenyldi(*tert*-butyl)methanol, 12S.** Di(*tert*-butyl) ketone was added to 2-ethoxyphenyllithium in THF. The crude alcohol, identified as the *syn* isomer, was purified by column chromatography (yield 38%): mp 50 °C; ν_{OH}/cm^{-1} (CCl_4) 3493; δ_H (chloroform) 1.13 (*t*-Bu), 1.46 (CH_3, *J* 7.0), 4.12 (CH_2, *J* 7.0), 6.78 (OH), 6.90 (H5, *J* 1.4, 7.2 and 8.2), 6.92 (H3, *J* 0.3, 1.4 and 8.3), 7.16 (H4, *J* 1.7, 7.2 and 8.3) and 7.55 (H6, *J* 0.3, 1.7 and 8.2) (Found: C, 76.7; H, 10.7. $C_{17}H_{28}O_2$ requires C, 77.22; H, 10.67%).

***anti*-2-Ethoxyphenyldi(*tert*-butyl)methanol, 12A.** Compound **12A** was obtained by partial rotation of the *syn* isomer (0.74 g, 2.8 mmol) in dry DMSO (20 cm^3) at 150 °C for 5 h. Chromatography yielded **12A**: (96 mg, 13%): mp 44 °C; ν_{OH}/cm^{-1} (CCl_4) 3613, 3649; δ_H (chloroform) 1.14 (*t*-Bu), 1.48 (CH_3, *J* 7.0), 1.86 (OH), 4.08 (CH_2, *J* 7.0), 6.85 (H3, *J* 0.1, 1.3 and 8.1), 6.93 (H5, *J* 1.3, 7.1 and 8.1), 7.20 (H4, *J* 1.8, 7.1 and 8.1) and 7.89 (H6, *J* 0.1, 1.8 and 8.1) (Found: C, 77.2; H, 10.8. $C_{17}H_{28}O_2$ requires C, 77.22; H, 10.67%).

Equilibration experiments

Samples of **1S**, **2S**, **3S** and **12S** (10–15 mg) in a deuteriated solvent (0.5 cm^3) were sealed under vacuum in small tubes. The tubes were held at 150 or 200 °C for 2 or 5 h, then opened and the contents analysed by ^1H NMR spectroscopy. Results are given as percent *anti* in equilibrium with *syn*. **3S** (2 h at 150 °C): 9.5, 9, 16 and 26% for chloroform, benzene, pyridine and DMSO, respectively. No other product was detected. **2S** (5 h at 150 °C): 12, 16 and 23% for toluene, pyridine and DMSO, respectively. **1S** (5 h at 200 °C) 13.5 and 14% for toluene and pyridine, respectively. No *anti* isomer could be detected in the products of the reaction of this alcohol in DMSO. **12** (5 h at 150 °C): 5, 5, 9 and 15% for chloroform, benzene, pyridine and DMSO, respectively.

The other alcohols are equilibrium mixtures at room temperature. **10**: 11, 15, 51 and 70% *anti* and **11**: 7, 9, 39 and 61% *anti* for chloroform, benzene, pyridine and DMSO, respectively. Data for **9** are given in Table 2. *Anti–syn* ratios for alcohols **9**–**11** in DMSO were determined over 30–40 K and the corresponding $\Delta G°$ values plotted against temperature to estimate the $\Delta H°$ and $\Delta S°$ values. Results are as follows (alcohol, $\Delta H°$/kcal mol^{-1}, $\Delta S°$/cal mol^{-1} K^{-1}): **9**, 1.6 ± 0.2, 3.3 ± 0.5; **10**, 1.5 ± 0.3, 3.3 ± 0.8; **11**, 1.7 ± 0.2, 4.9 ± 0.4.

Rotation kinetics

Slow rotation. (i) From a solution of **3A** (*ca*. 30 mg) in deuteriochloroform (2 cm^3) 10 × 0.2 cm^3 aliquots were transferred to small tubes which were sealed under vacuum, the sample being frozen in liquid nitrogen. Batches of tubes were held in a thermostat, 8 samples being withdrawn at convenient intervals, the remaining two being used as "infinities" (*ca*. 10 half-lives). Each sample was made up in the same solvent to *ca*. 0.5 cm^3 for ^1H NMR spectroscopic analysis. The same procedure was employed to study the rotation of **2A** in deuteriated toluene.

(ii) A sample of **3A** (*ca.* 15 mg) in deuteriated toluene, pyridine or DMSO (0.5 cm^3) was placed in an NMR tube which was then introduced into the apparatus at an appropriate temperature. ^{1}H NMR spectra were then recorded at convenient time intervals over 2–3 half-lives and after approximately 10 half-lives. The same procedure was employed to study the rotation of **12A** in DMSO.

In both cases suitable peaks of the *anti* and *syn* isomers were integrated to determine the relative composition, and the overall rate constant ($k_A + k_S$) was calculated by plotting log [%*anti*(t) − %*anti*(∞)] *vs.* time.

Rate constants for **3A** are as follows [solvent (T/K, ($k_A + k_S$)/s^{-1}, *syn–anti* ratio at equilibrium)], the error limits being the standard deviations on single runs: chloroform (358.3, $6.68 \pm 0.03 \times 10^{-5}$, 16.4; 372.2, $2.72 \pm 0.01 \times 10^{-4}$, 13.6; 385.1, $9.76 \pm 0.03 \times 10^{-4}$, 11.8; 400.9, $3.56 \pm 0.02 \times 10^{-3}$, 10.9); toluene (348, $1.86 \pm 0.01 \times 10^{-5}$, 12.3; 358, $5.39 \pm 0.02 \times 10^{-5}$, 11.5; 373, $2.72 \pm 0.02 \times 10^{-4}$, 10.9; 383, $6.65 \pm 0.03 \times 10^{-4}$, 9.9); pyridine (348, $2.39 \pm 0.01 \times 10^{-5}$, 4.4; 358, $7.35 \pm 0.05 \times 10^{-5}$, 4.8; 373, $3.55 \pm 0.02 \times 10^{-4}$, 4.8; 383, $9.48 \pm 0.06 \times 10^{-4}$, 5.2); DMSO (348, $2.67 \pm 0.03 \times 10^{-5}$, 2.2; 358, $8.31 \pm 0.04 \times 10^{-5}$, 2.3; 373, $3.88 \pm 0.06 \times 10^{-4}$, 2.6; 388, $1.62 \pm 0.02 \times 10^{-3}$, 2.7). Thermodynamic parameters [solvent (reaction, $\Delta H^{\ddagger}$/kcal mol^{-1}, $\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}, mean $\Delta G^{\ddagger}$/kcal mol^{-1})]: chloroform (*anti*→*syn*, 25.7 ± 0.1, −6.3 ± 0.2, 28.13; *syn*→*anti*, 28.4 ± 0.3, −4.4 ± 0.7, 30.06); toluene (*anti*→*syn*, 26.5 ± 0.2, −4.6 ± 1.2, 28.15; *syn*→*anti*, 28.0 ± 0.2, −5.1 ± 0.6, 29.90); pyridine (*anti*→*syn*, 27.3 ± 0.1, −1.9 ± 0.2, 28.01; *syn*→*anti*, 26.3 ± 0.3, −8.0 ± 0.8, 29.15); DMSO (*anti*→*syn*, 27.2 ± 0.1, −2.4 ± 0.3, 28.06; *syn*→*anti*, 25.7 ± 0.1, −8.1 ± 0.4, 28.71).

Rate constants for **2A** in toluene are as follows [T/K, ($k_A + k_S$)/s^{-1}, *syn–anti* ratio at equilibrium]: 409.1, $6.26 \pm 0.04 \times 10^{-5}$, 8.6; 423.1, $2.35 \pm 0.02 \times 10^{-4}$, 7.8; 438.0, $8.62 \pm 0.10 \times 10^{-4}$, 6.8; 451.6, $2.33 \pm 0.02 \times 10^{-3}$, 6.5. Thermodynamic parameters (reaction, $\Delta H^{\ddagger}$/kcal mol^{-1}, $\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}, mean $\Delta G^{\ddagger}$/kcal mol^{-1}): (*anti*→*syn*, 30.2 ± 0.6, −4.8 ± 1.4, 32.24; *syn*→*anti*, 32.5 ± 0.8, −3.3 ± 1.9, 33.94). Rate constants for **12A** in DMSO are as follows [T/K, ($k_A + k_S$)/s^{-1}, *syn–anti* ratio at equilibrium]: 358, $6.08 \pm 0.06 \times 10^{-5}$, 4.6; 373, $2.86 \pm 0.03 \times 10^{-4}$, 5.0; 388, $1.18 \pm 0.03 \times 10^{-3}$, 5.4; 398, $2.69 \pm 0.09 \times 10^{-3}$, 5.7. Thermodynamic parameters (reaction, $\Delta H^{\ddagger}$/kcal mol^{-1}, $\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}, mean $\Delta G^{\ddagger}$/kcal mol^{-1}): *anti*→*syn*, 26.4 ± 0.3, −4.8 ± 0.8, 28.22; *syn*→*anti*, 24.9 ± 0.3, −12.1 ± 0.9, 29.46.

Fast rotation. (i) Rotation barriers for **9** in chloroform, toluene and pyridine were determined by dynamic ^{1}H NMR, the part of the spectrum associated with the methoxy group being simulated by the gNMR program.[14] A low-temperature spectrum (no exchange) was first simulated to determine shifts and line-widths. Variations in the latter parameter at higher temperatures were neglected, but shifts and relative concentrations are temperature-dependent and were, therefore, optimized at each temperature at the same time as the exchange rate, which was divided by the species concentrations to obtain rate constants for the *anti*→*syn* and *syn*→*anti* reactions, k_A and k_S, respectively. The activation energies are not sufficiently regular for activation enthalpies and entropies to be determined; the values listed are mean activation energies based on 4–7 measurements at 5 or 10 °C intervals in the ranges indicated. Results are as follows (solvent, temperature range/K, $\Delta G_A^{\ddagger}$/kcal mol^{-1}, $\Delta G_S^{\ddagger}$/kcal mol^{-1}): (chloroform, 308–343, 17.4 ± 0.1, 18.3 ± 0.1); (toluene, 328–353, 17.7 ± 0.1, 18.5 ± 0.1); (pyridine, 303–333, 17.3 ± 0.1, 17.3 ± 0.1).

(ii) Rotation barriers for alcohols **9**–**11** in DMSO were determined by dynamic ^{13}C NMR, the part of the spectrum associated with the isopropyl group being simulated by the gNMR program. Relative concentrations were determined at each temperature by integration of the *tert*-butyl group peaks. Shifts were optimized at each temperature at the same time as the exchange rate. Results are as follows [alcohol (temperature range/K, $\Delta G_A^{\ddagger}$/kcal mol^{-1}, $\Delta G_S^{\ddagger}$/kcal mol^{-1})]: **9** (298–328, 17.6 ± 0.1, 17.0 ± 0.1); **10** (298–333, 17.7 ± 0.1; 17.3 ± 0.1); **11** (298–338, 18.1 ± 0.2, 17.9 ± 0.1).

Molecular mechanics

Molecular mechanics calculations were performed using the MMFF94 force field in the Sybyl 6.7 package.[13] Values for **3** and **9** are considerably higher than those reported previously.[16] Steric energies (kcal mol^{-1}) of the most stable conformations are: **3A**, 90.60; **3S**, 87.96; **9A**, 70.01; **9S**, 68.36; **10A**, 67.32; **10S**, 65.82; **11A**, 71.82; **11S**, 70.34; **12A**, 88.25; **12S**, 85.32. There is no obvious reason why steric energies are lower for the 2-ethoxy than for the corresponding 2-methoxy derivatives.

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