Rotational isomerism in 3,4-alkylenedioxy-2,5-bis[di(*tert*-butyl)hydroxymethyl]thiophenes

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ABSTRACT: In 3,4-ethylenedioxy-2,5-bis[di(*tert*-butyl)hydroxymethyl]thiophene there are three rotational isomers, *syn,syn* (**SS**), *anti,syn* (**AS**) and *anti,anti* (**AA**) (*syn*, free; *anti*, hydrogen-bonded), differing in the number (zero, one or two) of alcohol hydrogen atoms intramolecularly hydrogen bonded to the oxygen atoms of the bridge. When a methyl group is introduced into the bridge the **AS** rotamer can be distinguished from **SA** [where the first character indicates the orientation of the —C(*t*-Bu)$_2$OH group closer to the substituent] by means of a ^{1}H NOESY experiment. Forms with 'free' OH groups are favoured by hydrogen-bonding solvents, but the **AS:SA** ratio for the methyl derivative is solvent independent, slightly favouring the **AS** isomer. Whatever the solvent, the methyl group has no significant effect upon the equilibrium rotamer ratios. Rotation barriers for the various equilibria are of the order of 20 kcal mol^{-1}. Copyright © 2003 John Wiley & Sons, Ltd.
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INTRODUCTION

2-Alkoxyphenyl(α,α-dialkyl)methanols and the 3-alkoxythiophene analogues exist in two forms, with the OH hydrogen either 'free' or intramolecularly bonded to the alkoxy oxygen.[1–4] When the alkyl groups are bulky, such as *tert*-butyl, the rotamers can be distinguished on the NMR time-scale at room temperature[2,3] and in some cases physically separated.[1] The equilibrium constant for rotational isomerization depends not only on the structure but also on the solvent, hydrogen bond acceptor solvents favouring the form in which the OH hydrogen is not intramolecularly bonded. In the thiophene series, alkoxy substituents at the 3- and 4-positions, including 3,4-alkylenedioxy bridges, as in 3,4-ethylenedioxythiophene (EDOT), have a very marked effect upon the equilibrium isomer ratio, short bridges and small substituents favouring the *syn* isomer at the expense of the intramolecularly hydrogen-bonded *anti* isomer.[4]

We have now examined 3,4-alkylenedioxythiophene derivatives where both the 2- and 5-positions are occupied by di(*tert*-butyl)hydroxymethyl substituents. This results in a system with two rotors which can be oriented so that the OH group is either intramolecularly hydrogen bonded or free. This leads to four rotamers,

AA, **AS**, **SA** and **SS** (**A** for *anti*, **S** for *syn*), but if the alkylene bridge is symmetrical **AS** and **SA** are degenerate, reducing the number to three. In what follows, unless stated otherwise, '**AS/SA**' denotes **AS** and **SA**, i.e. all species which are neither **AA** nor **SS**. The **AS** and **SA** rotamers can be distinguished by introducing a substituent on the alkylene bridge, this giving rise to an unusual case of conformational isomerism.

1 (R = H, Me)

2   **3**
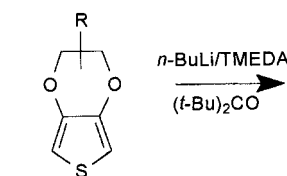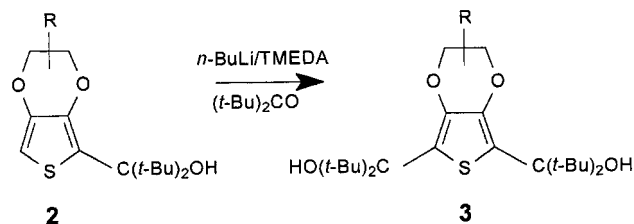
RESULTS AND DISCUSSION

Synthesis

Lithiation of **2-H**[3] by 2 equiv. of *n*-butyllithium–TMEDA

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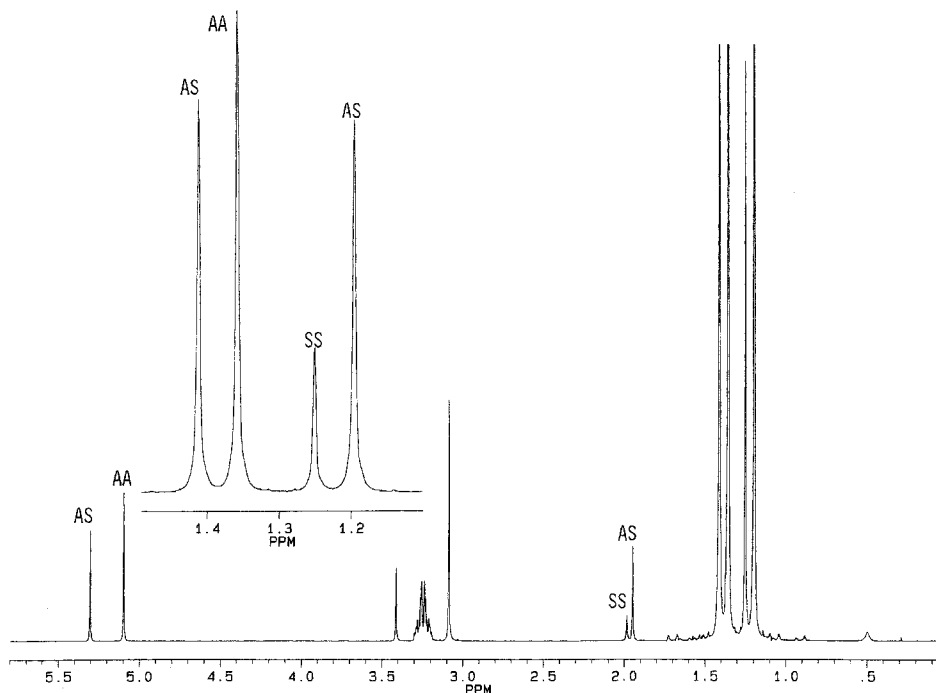E-mail: lomas@itodys.jussieu.fr

Figure 1. ^{1}H NMR spectrum of **3-H** in benzene at 298 K. Expansion: *tert*-butyl group region, 1.10–1.49 ppm

in hexane–diethyl ether under argon at room temperature followed by reaction with 1 equiv. of di(*tert*-butyl) ketone gave **3-H** (yield 64%). 2-Methyl-2,3-dihydro-thieno[3,4-*b*][1,4]dioxine (EDOT-Me, **1-Me**) was synthesized by a modification of the method described by Kumar *et al.*[5] By the same procedure as for **3-H**, **3-Me** was prepared in 40% overall yield from **1-Me**.

IR stretching modes at about 3569 cm^{-1} and 3608/3624 cm^{-1} (mean values for **3-H** and **3-Me**) are characteristic of intramolecularly hydrogen-bonded and free OH groups, respectively.[2–4] More detailed information about the rotamers present and their relative concentrations can only be obtained by NMR spectroscopy.

^{1}H NMR spectroscopy

3-H. This compound presents three isomers in similar amounts. The proton NMR spectrum in benzene (Fig. 1) shows two signals in the downfield OH region (5.09 and 5.30 ppm) and two in the upfield region (1.94 and 1.98 ppm). One of the downfield signals (5.30 ppm) has the same integral as one of the upfield signals (1.94 ppm): these clearly belong to the *anti,syn* isomer, denoted in what follows as **3-H(AS)**. Obviously, no distinction can be made between **AS** and **SA**. The remaining upfield (1.98 ppm) and downfield (5.09 ppm) signals correspond to the *syn,syn* and *anti,anti* isomers [denoted **3-H(SS)** and **3-H(AA)**], respectively. The bridging methylene groups are represented by two singlets, corresponding to the

symmetrical isomers (**AA** 3.08 and **SS** 3.41 ppm), and to a multiplet corresponding to the **AS/SA** isomer. The *tert*-butyl groups are well resolved, it being possible to distinguish those corresponding to the symmetrical isomers (**AA** 1.36 and **SS** 1.25 ppm) and to the two types in the non-symmetrical isomer (1.41 and 1.19 ppm, corresponding to the *anti* and *syn* groups, respectively).

3-Me. The proton NMR spectrum in benzene (Fig. 2) now shows four signals in the upfield OH region (1.94, 1.96, 1.98 and 1.99 ppm) and four in the downfield region (5.15, 5.27, 5.35 and 5.47 ppm). The two upfield signals (1.94 and 1.96 ppm) which have the same integrals as two of the downfield signals (5.35 and 5.47 ppm) correspond to **3-Me(AS)** and **3-Me(SA)**, where the first character inside the parentheses indicates the orientation of the —C(*t*-Bu)$_2$OH group closest to the substituent.

A reasonable assumption is that the downfield signals with the lower shifts (5.15 and 5.35 ppm), i.e. closer to the values in **3-H**, can be attributed to the hydrogen-bonded OH protons of the —C(*t*-Bu)$_2$OH group remote from the methyl substituent on the bridge. Calculation suggests that the hydroxy proton of the group with the *anti* orientation closest to the methyl substituent should be about 3.5 Å from one or two of the methyl hydrogens. At such a distance it should be possible to observe NOE in the ^{1}H NMR spectrum. The methyl groups appear as four well defined doublets ($J = 6.4$ Hz) upfield of the *tert*-butyls. A NOESY experiment (Fig. 3) does indeed show correlation peaks for the signals attributed to the **AS**
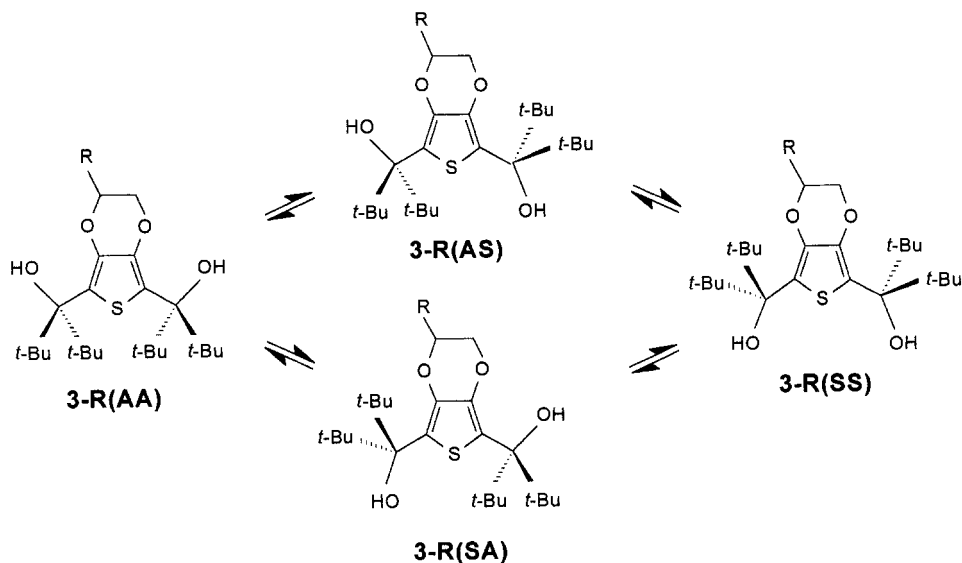
hydroxy proton (5.47 ppm) and to the corresponding methyl group, and also for one of the **AA** hydroxy protons (that at 5.27 ppm) and its associated methyl group, but not for the **SA** and **SS** rotamers. This confirms that the signals at 1.94 and 5.35 ppm correspond to **3-Me(SA)** and those at 1.96 and 5.47 ppm to **3-Me(AS)**. The remaining pairs of upfield and downfield signals are associated with the *syn,syn* and *anti,anti* isomers, **3-Me(SS)** and **3-Me(AA)**, respectively.

The bridging methylene and methine groups are represented by a complex multiplet ranging from 2.9 to 3.7 ppm. In benzene the *tert*-butyl signals fall into two batches, centred on 1.25 and 1.40 ppm, corresponding to isomers with —C(*t*-Bu)$_2$OH groups in the *syn* and *anti* conformations, respectively. These were assigned to the various isomers by simulation of the 1D spectrum, taking the relative concentrations from the hydroxy proton integrals (gNMR, version 4.1; Adept Scientific, Letchworth, UK). The strong cross peaks in the NOESY plot correspond to contacts between the *anti* OH protons and the *tert*-butyl groups on the same carbons; their positions are consistent with the assignments made by simulation. The same is true for the *syn* —C(*t*-Bu)$_2$OH groups (not shown).

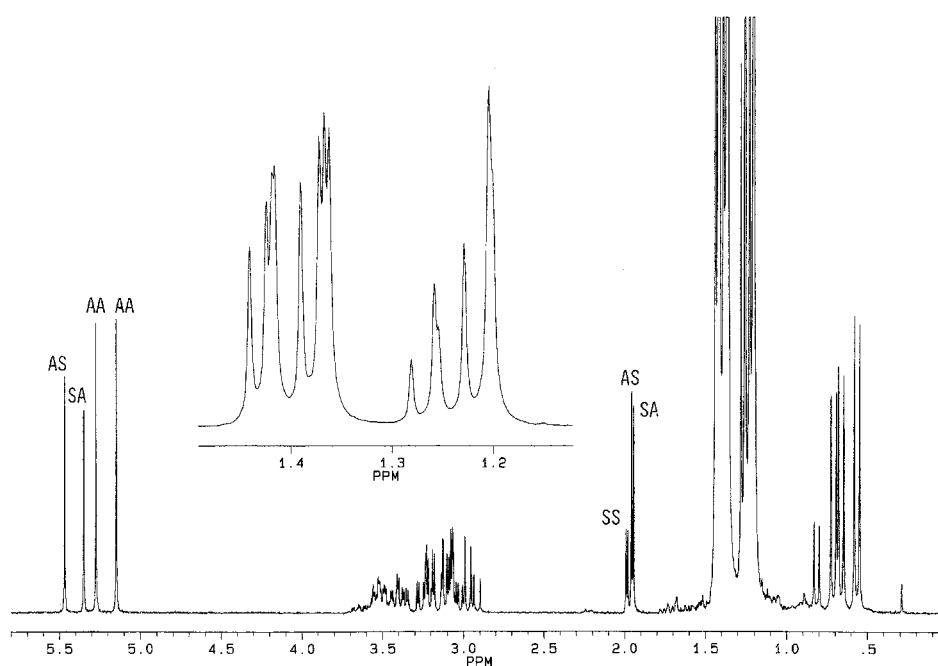**Figure 2.** ^{1}H NMR spectrum of **3-Me** in benzene at 298 K. Expansion: *tert*-butyl group region, 1.12–1.49 ppm
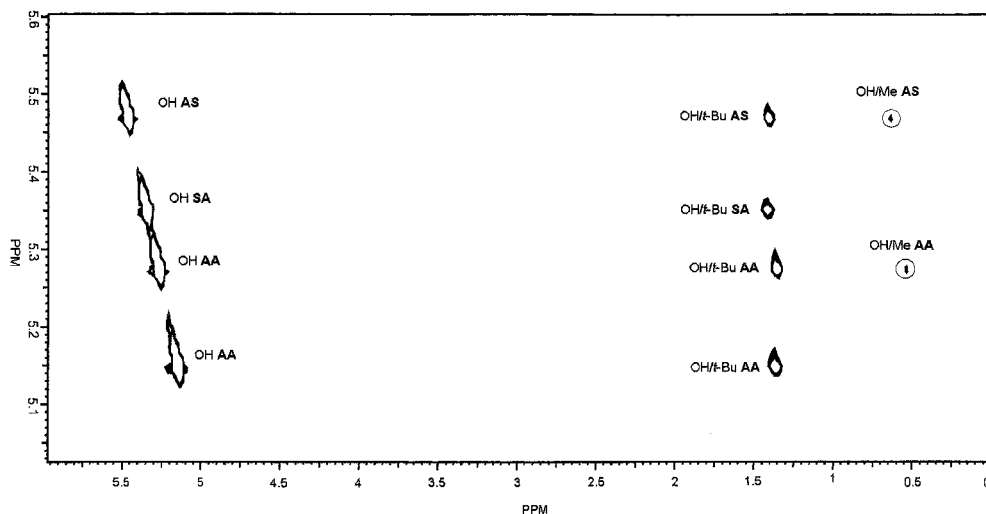
Figure 3. [1]H NOESY experiment on **3-Me**, showing dipolar correlation (ringed) between the **AS** *anti* OH proton and the corresponding methyl group, and between the downfield OH proton of the **AA** rotamer and its methyl group. The much stronger cross peaks concern the *anti*-oriented —C(*t*-Bu)$_2$OH groups

Isomer ratios and molecular mechanics calculations

The isomer ratio **AA:AS/SA:SS** for **3-H** in benzene at 298 K is 1.26:2.00:0.39. That for **3-Me (AA:AS:SA:SS)** in the same solvent is 1.27:1.00:0.92:0.35, very close to that for **3-H** if the contributions from the **AS** and **SA** rotamers are summed (Table 1). Very similar results are obtained in benzene.

Molecular mechanics calculations (MMFF94 force field,[6,7] gas phase) on **3-H** suggest that the stability order should be **SS** > **AS** = **SA** > **AA**, with the **SS** isomer more stable than **AS** or **SA** by 0.6 kcal mol^{-1} (1 cal = 4.184 J) and **AS** or **SA** more stable than **AA** by 0.4 kcal mol^{-1}. The reality is somewhat different, in that the order is reversed and the differences are smaller than calculated: **SS** is the least stable by 0.6 kcal mol^{-1} relative to **AS** or **SA** and **AA** the most stable by 0.2 kcal mol^{-1}, again relative to **AS** or **SA**. This means that, relative to the **AA** isomer, the errors for the **AS** or **SA** and **SS** isomers are

about 0.6 and 1.2 kcal mol^{-1}, respectively, i.e. approximately 0.6 kcal mol^{-1} for each —C(*t*-Bu)$_2$OH group in the *syn* conformation. This may be considered as a very satisfactory performance for a force field not specifically parametrized for this type of molecule. There are two possibilities: either these calculations underestimate the strain in *syn* conformations or overestimate that in *anti* conformations. The former would occur if the interactions between the *tert*-butyl groups and the ethylenedioxy bridge were slightly too weak, the latter if the strength of the intramolecular hydrogen bonds was underestimated. It should be noted, however, that force field calculations refer to the gas phase, and that our experimental data relate to solution, even if we have selected solvents of low hydrogen-bonding ability.

Results in various solvents (Table 1) indicate that there is always a slight preference for the **AS** rotamer in **3-Me**: [**AS**]/[**SA**] ≈ 1.1. MM calculations find **3-Me(SA)** 0.16 kcal mol^{-1} more stable than **3-Me(AS)**, whereas in fact the former is slightly less stable than the latter, by

Table 1. Solvent effects on equilibrium constants for 3,4-ethylenedioxy-2,5-bis[di(*tert*-butyl)hydroxymethyl]thiophenes, **3-H** and **3-Me**, at 298 K: $K_1 = ([\mathbf{AS}] + [\mathbf{SA}])/[\mathbf{AA}]$; $K_2 = [\mathbf{SS}]/([\mathbf{AS}] + [\mathbf{SA}])$[a]

Compound	Solvent	**AA** (%)	**AS** (%)	**SA** (%)	**SS** (%)	Log K_1	Log K_2
3-H[b]	Chloroform	37	26	26	10	0.15	−0.70
3-H[b]	Benzene	34	27	27	11	0.21	−0.69
3-H[b]	Pyridine	3	24	24	49	1.22	0.00
3-H[b]	DMSO	1	15	15	69	1.53	0.36
3-Me	Chloroform	39	27	25	9	0.12	−0.75
3-Me	Benzene	36	28	26	10	0.18	−0.74
3-Me	Pyridine	3	25	23	49	1.18	0.01
3-Me	DMSO	1	15	15	69	1.58	0.36

[a] Percentage compositions have been rounded to the nearest integer value: total = 100 ± 1%.
[b] For **3-H** the **AS** and **SA** isomers are degenerate.

0.06 kcal mol^{-1}. Again, the agreement is remarkably good, even if the relative energy has the wrong sign.

Solvent effects

Naturally, in hydrogen bond acceptor solvents the equilibria for both **3-H** and **3-Me** shift towards isomers in which the —C(t-Bu)$_2$OH group is in the *syn* conformation. Data for rotamer distributions and equilibrium constants in chloroform, benzene, pyridine and DMSO are listed in Table 1. The methyl substituent has no significant effect on the overall isomer ratio. For these solvents, there is little difference between Abraham's solute hydrogen bond basicity parameters[8] and the solvent parameters of Kamlet and Taft.[9] Both give fair correlations of log K_1 and log K_2 with gradients of about 1.9 ± 0.1 and 1.4 ± 0.2, respectively. The former value is in keeping with data on 3,4-ethylenedioxy-2-[di(*tert*-butyl)hydroxymethyl]thiophene in a greater variety of solvents (1.82 ± 0.18).[3] Another way of appreciating the difference in behaviour of the two equilibria is to plot log K_2 against log K_1, which gives a linear correlation with slope 0.75 ± 0.03 (correlation coefficient 0.99668). It is not clear why K_2 should be less sensitive to solvent variation than K_1. One possibility is that in the **SS** isomer the two OH groups are too close together to be efficiently solvated by a hydrogen bond acceptor solvent. With catechols and 1,8-naphthalenediols, where the two OH groups are intramolecularly hydrogen bonded, DMSO forms 1:1 complexes, and 1:2 complexes (diol–DMSO) may be formed at high DMSO concentrations in carbon tetrachloride.[10] However, no information is available concerning the equilibrium constants for the formation of the latter. Solvent effects on equilibrium constants for **3-H**, **3-Me** and other analogous diols will be investigated in detail in further work.

Rotation barriers

In pyridine and DMSO the *syn* OH proton signals move into much the same region of the NMR spectrum as those of the *anti* OH protons. In these solvents, as the temperature is raised, all the OH signals move upfield, the displacement being about 10 times higher for *syn* than for *anti*. This effect is 2–3 times greater in pyridine than in DMSO.[3,11] Since there are three isomers, no protons in the 5-position and a complex pattern of overlapping *tert*-butyl group signals in **3-Me** and for **3-H** in some solvents, only the OH proton signals were used to measure rotation barriers. For **3-H** in toluene and dioxane the *anti* and *syn* OH protons are downfield and upfield, respectively, of the bridging protons, and in pyridine all the OH signals remain downfield of the these protons.

The activation entropies (Supplementary Material, Table S3) for the **AA** $\rightleftharpoons$ **AS/SA** equilibrium in DMSO follow the usual pattern, with the value for the **AS/SA** $\rightarrow$ **AA** interconversion close to zero (0.8 cal mol^{-1} K^{-1}) and that for **AA** $\rightarrow$ **AS/SA** about 7 cal mol^{-1} K^{-1} lower (-6.0 cal mol^{-1} K^{-1}). This difference in the activation entropies is very similar to that observed for the *anti* $\leftrightarrow$ *syn* equilibrium of 2-[di(*tert*-butyl)hydroxymethyl]thiophenes (5.7 cal mol^{-1} K^{-1}),[2] the rotation of a —C(t-Bu)$_2$OH group from *anti* to *syn* in hydrogen bond acceptor solvents always being associated with the more negative activation entropy.

In previous work, it was found that the 'free' $\rightarrow$ 'hydrogen-bonded' rotation barrier was virtually independent of the solvent, the change in equilibrium constant on going to a hydrogen-bonding solvent resulting almost entirely from a decrease in the barrier for the reverse reaction.[1,3] In the present case this would imply that the **AS/SA** $\rightarrow$ **AA** and **SS** $\rightarrow$ **AS/SA** barriers should be solvent independent whereas those for **AA** $\rightarrow$ **AS/SA** and **AS/SA** $\rightarrow$ **SS** should decrease as the hydrogen-bonding capacity of the solvent increases. This expectation is roughly borne out by the results in Table 2.

Although the fact that there are twice as many OH peaks in the ^{1}H NMR spectra of **3-Me** than in that of **3-H** makes it much more difficult to determine rotation barriers, the **AA** $\rightleftharpoons$ **AS** and **AA** $\rightleftharpoons$ **SA** equilibria could be examined in toluene. At a mean temperature of 381 K the barriers are almost identical at 20.8 kcal mol^{-1} for the **AA** $\rightarrow$ **AS** and **AA** $\rightarrow$ **SA** interconversions and less than 0.1 kcal mol^{-1} lower for the reverse. It is instructive to compare these values with those for the corresponding rotations in **3-H**, calculated for the same temperature. We

Table 2. Rotation barriers (kcal mol^{-1}) for 3,4-ethylenedioxy-2,5-bis[di(*tert*-butyl)hydroxymethyl]thiophenes, **3-H** and **3-Me**: $\Delta G^{\neq}$(**AA** $\rightarrow$ **AS/SA**), $\Delta G^{\neq}$(**AS/SA** $\rightarrow$ **SS**), $\Delta G^{\neq}$(**AS/SA** $\rightarrow$ **AA**) and $\Delta G^{\neq}$(**SS** $\rightarrow$ **AS/SA**)

Compound	Solvent	T_m (K)	$\Delta G^{\neq}$(**AA** $\rightarrow$ **AS/SA**)	$\Delta G^{\neq}$(**AS/SA** $\rightarrow$ **SS**)	$\Delta G^{\neq}$(**AS/SA** $\rightarrow$ **AA**)	$\Delta G^{\neq}$(**SS** $\rightarrow$ **AS/SA**)
3-H	Toluene	371	20.4 ± 0.1	21.1 ± 0.1^{a}	20.9 ± 0.1	20.2 ± 0.1^{a}
3-H	Dioxane	374	19.7 ± 0.2	20.4 ± 0.3	20.6 ± 0.2	20.0 ± 0.3
3-H	Pyridine	358	19.3 ± 0.1	20.0 ± 0.3	20.6 ± 0.1	19.5 ± 0.3
3-H	DMSO	379	19.1 ± 0.1	—	20.6 ± 0.1	—
3-Me	Toluene	381	20.8 ± 0.1^{b}	—	20.8 ± 0.1^{b}	—

[a] $T_m = 364$ K.
[b] Identical values for **AS** and **SA**.

would expect **AS/SA → AA** for **3-H** to have the same rotation barrier as **AS → AA** or **SA → AA** for **3-Me**, i.e. 20.8 kcal mol^{-1}. In fact it is 20.9 kcal mol^{-1}, which is the same to within the experimental error. However, for the **AA → AS/SA** interconversion of **3-H** there is a statistical factor of two, since either *anti* group can rotate to give the **AS** or **SA** isomer. This is equivalent to 0.5 kcal mol^{-1} at 381 K, which means that the corresponding barrier should be 20.3 kcal mol^{-1} (20.8 − 0.5), which agrees well with the experimental value of 20.4 kcal mol^{-1}. We have not introduced this statistical correction ('transmission coefficient') in the calculation of the rotation barriers listed in Table 2 (see the Experimental section for details). This is at variance with the practice of Lunazzi's group, where a transmission coefficient of 0.5 is used in such situations and the quoted rotation barrier is *RT*ln2 *less* than would be obtained with a unitary value.[12–14]

CONCLUSION

When there is a —C(*t*-Bu)$_2$OH group at the 2-position of the thiophene ring in EDOT it is possible to distinguish on the NMR time-scale at room temperature the situation where the OH hydrogen is intramolecularly bonded to a neighbouring oxygen atom in the 3,4-ethylenedioxy bridge (*anti*, **A**) from that where it is 'free' (*syn*, S).[3] Two such substituents, at the 2- and 5-positions, lead to only three isomers, since the **AS** and **SA** forms are degenerate. This degeneracy is removed by placing a substituent on one of the bridging carbon atoms.

Although there has been much work on systems with two or more identical rotors attached to a common stator, often benzene[12,15–20] or naphthalene[13,21–30] and, less frequently, a heteroaryl group,[31] studies of solvent effects on rotamer equilibria and kinetics have been notably lacking. This is no doubt due to the fact that the low temperatures required to measure generally small rotation barriers seriously restrict the range of solvents which can be used. Furthermore, in the absence of a polar 'handle,' such as an OH group, solvent effects may be unimportant.

A particularly interesting case is that of a highly hindered 1,5-naphthyl sulfoxide bearing two *t*-BuSO moieties where all 10 possible stereoisomers have been separated.[30b] In our system the introduction of chiral groups in the place of —C(*t*-Bu)$_2$OH would lead to seven stereoisomers for the EDOT derivative and 28 for the EDOT-Me analogue, where a further chiral centre is present. In principle, such a system could be easily achieved by the use of a non-symmetrical ketone instead of di(*tert*-butyl) ketone, but it remains to be seen whether it is possible to separate and characterize the various stereoisomers.

EXPERIMENTAL

IR spectra were recorded in carbon tetrachloride on a Nicolet Magna 860 FTIR spectrometer. All NMR measurements except the NOESY experiment (see below) were performed on a Bruker AS 200 FT instrument operating at 200 MHz (proton) or 50 MHz (carbon). Proton NMR chemical shifts in chloroform or benzene at 298 K are given in ppm (reference values of residual solvent protons: $\delta_H = 7.26$ and 7.16 ppm vs TMS, respectively) and J in hertz. Carbon NMR chemical shifts in chloroform or benzene at 298 K in ppm (reference values: $\delta_C = 77.0$ and 128.0 ppm vs TMS, respectively).

*2-Methyl-2,3-dihydrothieno[3,4-b][1,4]dioxine (EDOT-Me, **1-Me**).* This was prepared by a modification of the method described by Kumar *et al.*[5] allowing much shorter reaction times. 2,5-Dicarbethoxy-3,4-dihydroxy-thiophene (1 equiv.) was stirred under argon for 2 h at 110–120 °C with 1 equiv. of 1,2-dibromopropane and 3 equiv. of anhydrous potassium carbonate in anhydrous DMSO. The product was extracted into dichloromethane and washed with water several times, then dried (MgSO$_4$). After evaporation of the solvent, the product was purified by recrystallization from methanol. Hydrolysis by refluxing for 1 h with 4 equiv. of sodium hydroxide in 1:1 methanol–water, followed by filtration and acidification, gave the diacid, which, after drying in a desiccator overnight, was decarboxylated by heating for 2 h at 160–170 °C with copper chromite in freshly distilled quinoline. The product mixture was taken up in diethyl ether and water, the ether layer washed several times with 2 M hydrochloric acid, then filtered and dried (MgSO$_4$), and the solvent evaporated to leave an oil, which was purified by chromatography on alumina. Yield from dicarbethoxy-3,4-dihydroxythiophene: 17% (lit.[5] 13%). δ_C 16.2 (CH$_3$), 69.4 (CH$_2$), 70.0 (CH), 99.3 (CH), 141.4 (C3 or C4) and 142.1 (C3 or C4); δ_H 1.34 (CH$_3$, J 6.4), 3.82 (CH, J 8.6 and − 11.4), 4.13 (CH, J 2.0 and − 11.4), 4.27 (CH, J 2.0, 6.4 and 8.6), 6.30 (H2 or H5, J 3.7) and 6.32 (H2 or H5, J 3.7).

*Synthesis of **3-H** and **3-Me**.* To a mixture of the appropriate 2-[di(*tert*-butyl)hydroxymethyl]thiophene (5 mmol) and TMEDA (10 mmol) in diethyl ether (15 cm^3) under argon at room temperature was added a solution of *n*-butyllithium in hexane (1.6 M, 10 mmol). After 15 min of stirring, di(*tert*-butyl) ketone (5 mmol) was added. The mixture was stirred for a further 15 min, then quenched with water and the organic materials were extracted with diethyl ether. Washing with water, drying and evaporation of solvent gave an oil from which the alcohol was isolated by chromatography on alumina in light petroleum (boiling range 35–60 °C)–diethyl ether mixtures.

*3,4-Ethylenedioxy-2,5-bis[di(tert-butyl)hydroxy-methyl]thiophene, **3-H**.* Yield (from **2-H**) 64%; m.p. 180 °C; ν_{OH} (cm^{-1}) 3571, 3607, 3626 (found: C, 67.4; H, 10.1; S, 7.6. $C_{24}H_{42}O_4S$ requires C, 67.56; H, 9.92; S, 7.52%). **AA**: δ_C (benzene) 29.5 (CH$_3$), 42.7 or 43.3 (C$_q$), 63.9 (CH$_2$), 86.8 (COH), 118.7 (C2 and C5) and 136.9 (C3 and C4); δ_H (benzene) 1.36 (s, 4 *t*-Bu), 3.08 (s, 2 CH$_2$) and 5.09 (s, 2 OH). **AS/SA**: δ_C [benzene (the position of attachment of the *anti* motif is designated as C2)] 29.3 (CH$_3$), 29.7 (CH$_3$), 42.7 (C$_q$), 43.3 (C$_q$), 63.1 (CH$_2$), 63.9 (CH$_2$), 85.9 (COH), 86.8 (COH), 119.1 (C2), 124.8 (C5), 132.8 (C4) and 138.0 (C3); δ_H (benzene) 1.19 (s, 2 *t*-Bu), 1.41 (s, 2 *t*-Bu), 1.94 (s, OH), 3.22 (2 CH, *J* 2.3, 6.1 and − 15.4), 3.27 (2 CH, *J* 2.3, 6.1 and − 15.4) and 5.30 (s, OH). **SS**: δ_C (benzene) 29.5 (CH$_3$), 42.7 or 43.3 (C$_q$), 63.2 (CH$_2$), 85.8 (COH), 124.4 (C2 and C5) and 133.9 (C3 and C4); δ_H (benzene) 1.25 (s, 4 *t*-Bu), 1.98 (s, 2 OH) and 3.40 (s, 2 CH$_2$).

*Methyl-3,4-ethylenedioxy-2,5-bis[di(tert-butyl)hy-droxymethyl]thiophene, **3-Me**.* Yield (from **1-Me**) 40%; m.p. 101 °C; ν_{OH} (cm^{-1}) 3568, 3609, 3622 (found: C, 68.0; H, 10.2; S, 7.2. $C_{25}H_{44}O_4S$ requires C, 68.14; H, 10.06; S, 7.28%). **AA**: δ_H (benzene) 0.56 (CH$_3$, *J* 6.4), 1.36, 1.37, 1.37 and 1.39 (s, 4 *t*-Bu), 5.15 (s, OH) and 5.27 (s, OH). **AS**: δ_H (benzene) 0.66 (CH$_3$, *J* 6.4), 1.21, 1.23, 1.42 and 1.42 (s, 4 *t*-Bu), 1.96 (s, OH) and 5.47 (s, OH). **SA**: δ_H (benzene) 0.71 (CH$_3$, *J* 6.4), 1.20, 1.20, 1.42 and 1.44 (s, 4 *t*-Bu), 1.94 (s, OH) and 5.35 (s, OH). **SS**: δ_H (benzene) 0.81 (CH$_3$, *J* 6.4), 1.25, 1.26, 1.26 and 1.28 (s, 4 *t*-Bu), 1.98 (s, OH) and 1.99 (s, OH). The methine (3.3–3.7 ppm) and methylene (2.9–3.3 ppm) signals could not be attributed. The ^{13}C NMR spectrum consists largely of multiplets which could not be resolved or assigned except to carbon type.

*^{1}H NOESY Experiment on **3-Me**.* For ^{1}H–^{1}H dipolar contact analysis in **3-Me**, a NOESY spectrum was recorded in benzene (degassed by several pump–freeze–thaw cycles and sealed under vacuum) on a Bruker DRX-500 spectrometer equipped with a Silicon Graphics workstation. A 5 mm broadband probe with a *z*-gradient was used. The temperature was monitored with a BCU 05 temperature unit and fixed at 299 K. Data were processed on a Silicon Graphics station with the help of GIFA (version 4.3).[32] The 2D NOESY experiment was acquired in the TPPI mode. It was recorded with 2K points in t_2 over 3.13 kHz and 448 points in t_1. A 2.0 s relaxation delay and a mixing time of 600 ms were used for the 16 scans of each FID. Zero-filling was added in F_1. Shifted sine-bell window functions were applied in both dimensions before Fourier transformation. Baselines were corrected using a poly-nomial function.

Equilibrium constants for anti $\rightleftharpoons$ syn rotamerization. Samples of the alcohols (ca 20 mg) were made up in deuterated solvents (0.5 cm^3). Rotamer ratios (Table 2) were determined by ^{1}H NMR spectroscopy, integration of the OH proton signals being used in most cases. However, for **3-H** the bridging methylene signals were in some cases sufficiently well separated to be used as well.

Rotation kinetics. Dynamic NMR was used. For **3-H**, both sets of OH protons could be studied in toluene, dioxane and pyridine. In DMSO the signals of the *anti* OH protons in the **AA** and **AS/SA** isomers as well as those of the *syn* OH protons in the **AS/SA** and **SS** rotamers are widely separated. Moreover, the *syn* OH proton signals move upfield as the temperature increases and become confused with those of the bridge protons. This means that only **AA** $\rightleftharpoons$ **AS/SA** exchange can be studied. Simulation of the OH proton signals by gNMR gives the exchange rate and the relative concentrations of the two species from which rate constants and the rotation barriers are calculated. However, since the program requires that one proton exchange with one proton in another molecule (and not with two), the two equivalent protons in the **AA** and **SS** isomers of **3-H** have to be represented by one, which means that the apparent concentration of **AA** or **SS** exchanging with **AS/SA** is doubled. This must be corrected before calculation of the rotation barriers. This does not apply to **3-Me** where the **AA** isomer is represented by two peaks. No statistical correction or transmission coefficient has been intro-duced (see text). In dioxane and pyridine there was considerable scatter of the activation energies ($\Delta G^{\neq}$ in kcal mol^{-1}) and anomalously high activation entropies. The values listed (Table 2) are the means of 6–12 self-consistent data points (i.e. following a roughly linear Eyring plot) for the mean temperature at which the corresponding rate data were recorded. The temperature was checked by calibration against a Bruker 80% ethylene glycol in DMSO-d_6 standard and corrected temperatures used for the calculation of activation energies. Standard deviations of the activation energies over the temperature range studied are given in Table 2 and activation parameters in the Supplementary Material, Table S1.

Molecular mechanics calculations. Molecular mechan-ics calculations were performed using the MMFF94 force field[6,7] with the MMFF94 charge model in the Sybyl 6.8 package (Tripos, St. Louis, MO, USA). Calculated energies (kcal mol^{-1}) are as follows: **3-H(AA)** 134.23, **3-H(AS or SA)** 133.84, **3-H(SS)** 133.25, **3-Me(AA)** 136.06, **3-Me(AS)** 135.65, **3-Me(SA)** 135.49, **3-Me(SS)** 134.88. Internal coordinates (critical torsion angles) for all fully optimized structures are listed in the Supple-mentary Material, Tables S2 and S3, based on the numbering system in the Supplementary Material, Fig. S1.

Acknowledgement

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