Hydrogen bonding and steric effects on rotamerization in 3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxy-2-thienyldi(*tert*-butyl)-methanols: an NMR, IR and X-ray crystallographic study †

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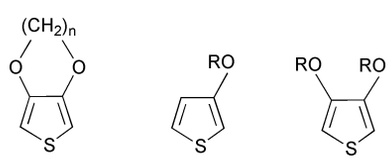
Received (in Cambridge, UK) 22nd October 2001, Accepted 26th November 2001
First published as an Advance Article on the web 10th January 2002

The equilibrium constant for the *anti* ↔ *syn* rotamerization (*anti*: intramolecularly hydrogen-bonded hydroxy group; *syn*: "free" hydroxy group) of 3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxy-2-thienyldi(*tert*-butyl)methanols depends on the 3,4-alkylenedioxy or alkoxy group(s) and the solvent, hydrogen-bonding solvents such as DMSO and pyridine favouring the *syn* isomer. Equilibrium constants ([*syn*]/[*anti*]) in chloroform and benzene decrease in the order: 3,4-OCH_2O-, 3,4-$O(CH_2)_2O$-, 3-OMe, 3-OEt, 3,4-$(OMe)_2$ ≈ 3-O*i*-Pr, 3,4-$(OEt)_2$, ranging over about 2.5 orders of magnitude. Variations in the IR OH stretching frequencies and the NMR OH proton shifts for the *anti* isomer indicate that intramolecular hydrogen bonding increases in roughly the same order. The *syn* ⟶ *anti* rotation barrier in DMSO increases with substituent size and number. The 3,4-methylenedioxythienyl derivative has a rather lower barrier (17.5 kcal mol^{-1}) than all the others (21.0–22.3 kcal mol^{-1}). The *syn* ⟶ *anti* rotation barrier is largely determined by steric effects but intramolecular hydrogen bonding in the *anti* isomer contributes to the variation of the *anti* ⟶ *syn* rotation barrier. A single crystal X-ray diffraction study of the *anti*-3,4-diethoxy derivative shows that the orientation of the 3-alkoxy group is very different from that in *anti*-3-methoxy-2-thienyldi-(1-adamantyl)methanol. Molecular mechanics and quantum mechanical calculations are used in an attempt to rationalize the equilibrium data.

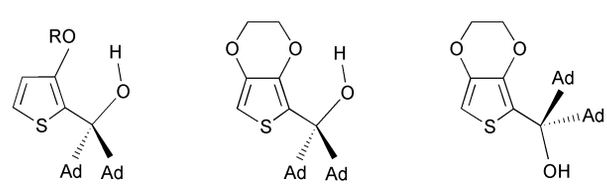
Introduction

3,4-Ethylenedioxythiophene (EDOT), **1** (*n* = 2), and its derivatives have been and continue to be the subject of many studies devoted almost exclusively to their polymerization and to the optoelectronic properties of the materials obtained.[1–3] Other thiophenes with oxygen functions at the 3- or 3- and 4- positions, such as 3,4-alkylenedioxythiophenes, **1** (*n* = 1, 3, 4),[2,4,5] 3-alkoxythiophenes, **2-R**,[6] and 3,4-dimethoxythiophene, **3-Me**,[6c,7] have been less studied, the qualities of the polymers being poorer than those of polyEDOT (PEDOT).



1(n) **2-R** **3-R**

Addition of 3-alkoxy-2-thienyl-lithium compounds to a highly congested ketone, di(1-adamantyl) ketone, gives the *anti* rotamers (sulfur remote from the OH group), **4A-R** (R = Me, Et and *i*-Pr), in which the hydroxy proton is hydrogen-bonded to the alkoxy oxygen.[8] However, the corresponding EDOT derivative, **5**, exists in two readily interconvertible forms, **5A** and **5S**, the equilibrium constant for *anti* ↔ *syn* rotamerization depending on the solvent, hydrogen-bonding solvents favouring the *syn* isomer.[9] The rotation barrier, about 26 kcal mol^{-1} (1 cal = 4.184 J), is too small for the *syn* isomer to be isolated free of *anti*.



4A-R **5A** **5S**

The 3-alkoxythienyl derivatives, **4-R**, can also adopt the *syn* form but the rotation barriers are much higher and the equilibrium constant favours the *anti* isomer.[10] This must reflect differences in hydrogen bonding and steric interactions in the 3-alkoxythienyl and EDOT systems. When the adamantyl groups are replaced by the smaller, less rigid *tert*-butyl groups *anti* ↔ *syn* rotamerization becomes fast at room temperature. This offers us the opportunity to compare 3,4-alkylenedioxythiophenes, 3-alkoxythiophenes and 3,4-dialkoxythiophenes from a chemical standpoint. It was hoped that the results would give useful insights into the difference between EDOT and the other oxygen-substituted thiophenes.

Results and discussion

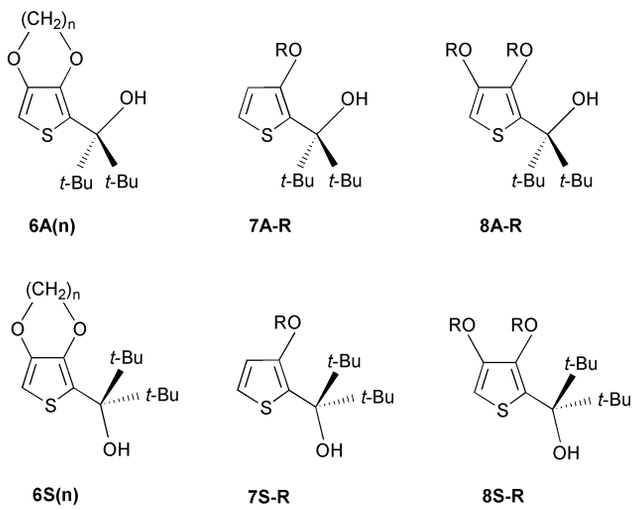
Synthesis

Apart from EDOT, **1** (*n* = 2), 3,4-alkylenedioxythiophenes with *n* = 3 and 4 have been described.[2,4] Electropolymerization of the

† Electronic supplementary information (ESI) available: NMR data; activation parameters for rotation; MMFF94 steric energies and alkoxy group geometries; thermodynamic data; quantum mechanical calculations of geometries; bond lengths, bond angles and torsion angles of **8A-Et**; NMR and IR data on new compounds. See http://www.rsc.org/suppdata/p2/b1/b109612p/

 DOI: 10.1039/b109612p

methylene derivative, **1** (*n* = 1), has been reported[5] but the preparation and characteristics of the monomer were not published. The pentylene derivative, **1** (*n* = 5), has not been reported. 3,4-Diethoxythiophene, **3-Et**, another new compound, was prepared as 3,4-dimethoxythiophene, **3-Me**.[11] All alcohols [**6** (*n* = 1–5), **7-R** (R = Me, Et and *i*-Pr) and **8-R** (R = Me and Et)] were prepared by lithiation of the 3-alkoxy-,[12] 3,4-dialkoxy- or 3,4-alkylenedioxythiophene by *n*-butyllithium–TMEDA in diethyl ether at room temperature, followed by reaction with di(*tert*-butyl) ketone.



IR Spectroscopy

The IR spectra of the various alcohols were determined in carbon tetrachloride. With the notable exception of the 3,4-methylenedioxythienyl and EDOT derivatives, **6** (*n* = 1) and **6** (*n* = 2), (*vide infra*) there is a strong, structure-dependent OH absorption at around 3500 cm^{-1}, due to the intramolecularly hydrogen-bonded *anti* form, and weaker absorptions at higher wavenumbers, close to 3606 and 3628 cm^{-1} regardless of structure, due to the *syn* isomer. The considerable difference between the frequencies for the *anti* forms of **6** (*n* = 2) (3568 cm^{-1}) and of all the others indicates weaker hydrogen bonding in the former case.

More extreme is the 3,4-methylenedioxythienyl derivative, **6** (*n* = 1), whose IR absorption consists of a broad band peaking at about 3623 cm^{-1} with a shoulder to lower wavenumbers. Decomposition of this band into Lorentzian components is not unambiguous. Three-peak decomposition gives strong bands at 3624 and 3608 cm^{-1}, with a very weak band (about 3% of the integrated intensity) at 3554 cm^{-1}. However, it can be represented equally well by four bands: 3624 (62%), 3605 (21%), 3612 (11%) and 3561 cm^{-1} (4%), though only three are expected for *syn* (two) and *anti* (one) isomers. Comparison with data for the other 3,4-alkylenedioxythienyl derivatives suggests that the two strongest bands can be associated with the *syn* isomer, that at 3612 cm^{-1} with the *anti*, and the weakest band unattributed.

NMR spectroscopy: non-hydrogen-bonding solvents

In chloroform or benzene, the hydroxy proton shift for the *syn* rotamer ranges from 2.0 to 2.2 ppm, while that for the *anti* isomer is at much lower field. Within the 3-alkoxy-2-thienyl series, **7-R**, there is a small increase in the shift as methoxy is replaced by ethoxy and then isopropoxy (0.3 ppm overall). Shifts for the 3,4-dialkoxythienyl derivatives, **8-R**, are similar to those for **7-R**. In the 3,4-alkylenedioxythienyl series, **6**(*n*), the OH proton shift for the *anti* isomer varies from 2.7 ppm (*n* = 1) to about 6.0 ppm (*n* = 5). The former value is particularly low for an intramolecularly hydrogen-bonded proton. The NMR and the IR data for the 3,4-alkylenedioxythienyl and 3-alkoxythienyl derivatives can be correlated by a second-order polynomial, which goes through the points for the *syn* isomers (Fig. 1). Previous IR–NMR correlations of this type have been linear.[13,14] Both data reveal small differences in hydrogen bonding in the 3-alkoxy, 3,4-dialkoxy and long-chain 3,4-alkylenedioxy (*n* ≥ 3) derivatives, weaker bonding in the EDOT compound and very weak bonding in the 3,4-methylenedioxythienyl analogue.

Table 1 Equilibrium constants ([*syn*]/[*anti*]) for 3,4-alkylenedioxy-, **6**(*n*), 3-alkoxy-, **7-R**, and 3,4-dialkoxy-2-thienyldi(*tert*-butyl)methanols, **8-R**, in hydrogen-bonding and non-hydrogen-bonding solvents at 298 K

Compound	*K*($CDCl_3$)	*K*(benzene)	*K*(pyridine)	*K*(DMSO)
6 (*n* = 1)	9.2	7.7		
6 (*n* = 2)	0.91[a](0.94)	0.87[a](0.84)	9.2	25[a](18)
6 (*n* = 3)	0.24	0.22	2.5	5.45
6 (*n* = 4)	0.18	0.20	2.3	5.2
6 (*n* = 5)	0.18	0.15	1.6	4.8
7-Me	0.18	0.20	1.85	4.0
7-Et	0.14	0.15	1.3	3.3
7-*i*-Pr	0.071	0.078	0.64	1.5
8-Me	0.069	0.090	0.88	2.1
8-Et	0.032	0.037	0.41	1.0

[a] This work; other data for **6** (*n* = 2), ref. 9.

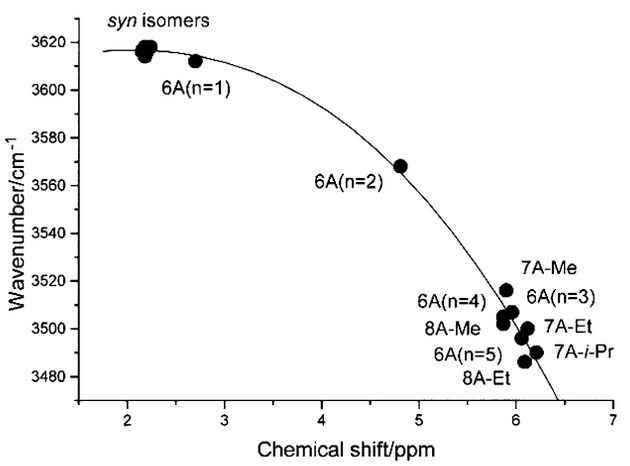


Fig. 1 Non-linear correlation between IR absorption frequency, ν_{OH} (CCl_4/cm^{-1}) and ^{1}H NMR hydroxy proton shift δ_{OH} ($CDCl_3$/ppm).

NMR spectroscopy: hydrogen-bonding solvents

In non-hydrogen-bonding solvents the ^{1}H NMR OH proton signal in the *syn* rotamer is considerably upfield of that in the *anti* isomer. However, DMSO and pyridine hydrogen-bond strongly with the *syn* hydroxy proton, causing marked downfield displacement of this signal; pyridine brings it to within 0.2–0.3 ppm of the signal for the *anti* isomer while in DMSO it is at about 4.7 ppm regardless of the structure (Supplementary Material Table S1). The temperature dependence (Table S1) of the shift indicates whether the proton corresponding to a given signal is intramolecularly hydrogen-bonded (low coefficient) or is hydrogen-bonded to the solvent (high coefficient).[14]

The most important effect of transferring these alcohols to a hydrogen-bonding solvent is the increase in the equilibrium concentration of the *syn* isomer. This will be discussed in the following paragraph.

Rotamer equilibria at room temperature

These di(*tert*-butyl) derivatives equilibrate rapidly at room temperature in solution (Table 1). In DMSO, the stronger

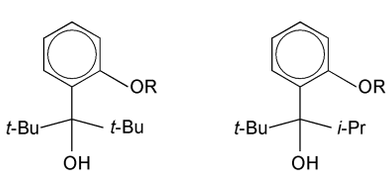
hydrogen-bonding solvent, the equilibrium lies further in favour of the *syn* rotamer than in pyridine. New measurements on the EDOT derivative, **6** (*n* = 2), in DMSO at lower temperatures than in the previous study[9] give a slightly higher value for the equilibrium constant, ([*syn*]/[*anti*]), and a revised free energy *vs.* temperature correlation in better agreement with data for the other derivatives (*vide infra*).

As the size of the alkoxy group in the 3-alkoxythienyl series, **7-R**, increases the proportion of *anti* rotamer rises. In the same way, in the 3,4-alkylenedioxythienyl series, **6**(*n*), the proportion of the *anti* isomer increases markedly from **6** (*n* = 1) to **6** (*n* = 2) to **6** (*n* = 3) and then remains practically constant. For the 3,4-methylenedioxythienyl derivative, **6** (*n* = 1), even in chloroform or benzene the major isomer is *syn* and in the hydrogen-bonding solvents no *anti* isomer can be detected at all. The values of the equilibrium constant are not very different from that for 2-thienyldi(1-adamantyl)methanol (7.0),[14] a further indication that intramolecular hydrogen bonding to oxygen in the *anti* isomer, **6A** (*n* = 1), is very weak.

The positions of the 3,4-dimethoxy and 3,4-diethoxy derivatives, **8-Me** and **8-Et**, between **7-Et** and **7-*i*-Pr** and beyond the 3-isopropoxy compound, **7-*i*-Pr**, respectively, are somewhat surprising. The NMR shifts of the hydroxy protons in these compounds are similar to those for the corresponding 3-alkoxy compounds and, if this is taken as an indicator of hydrogen bond strength, there is no reason for the *anti* isomer to be favoured. However, part of the variation of the equilibrium constant is due to changes in the relative steric energies of the two rotamers as the effective bulk of the 3-substituent is varied. This may be increased by the buttressing effect of the 4-alkoxy group on the 3-alkoxy, and be decreased when the methylene group is more or less tied back by a short alkylene chain (*n* = 1 or 2). Molecular mechanics and quantum mechanical calculations on the energies and structures of **6**(*n*), **7-R** and **8-R** will be presented below.

Correlation of the equilibrium constants [log *K*(1) *vs.* log *K*(2)] for the 9 or 10 compounds in the different solvents taken pairwise gives gradients not far from unity in all cases, indicating that the solvent effect is virtually structure-independent. Not surprisingly, the best correlations are those for solvents of the same type: chloroform *vs.* benzene (Fig. 2a, slope 1.07 ± 0.04; corr. coeff. 0.9956) and pyridine *vs.* DMSO (Fig. 2b, slope 0.97 ± 0.04; corr. coeff. 0.9935).

In previous work[15] it was found that there was a good correlation between solvent effects (8 solvents) on rotamer equilibria of 2-anisyl(isopropyl)(*tert*-butyl)methanol, **10-Me**, and EDOT-di(*tert*-butyl)methanol, **6** (*n* = 2). For the set of alcohols considered in this work mean solvent effects on the free energy difference, $\Delta G°$, relative to chloroform are: benzene (0.03 ± 0.09 kcal mol^{-1}); pyridine (1.38 ± 0.08 kcal mol^{-1}); DMSO (1.92 ± 0.09 kcal mol^{-1}). These values are quite similar to those for both 2-anisyldi(*tert*-butyl)methanol, **9-Me**, and 2-anisyl(isopropyl)(*tert*-butyl)methanol, **10-Me**, at the same temperature (298 K).[15]



9-R **10-R**

Temperature dependence of equilibrium constants in hydrogen-bonding solvents

In pyridine or DMSO as the temperature is increased the amount of *anti* isomer increases at the expense of the *syn*. The free energy difference $\Delta G°$(*anti* − *syn*) varies linearly with temperature, allowing the evaluation of $\Delta H°$ and $\Delta S°$. Data for all

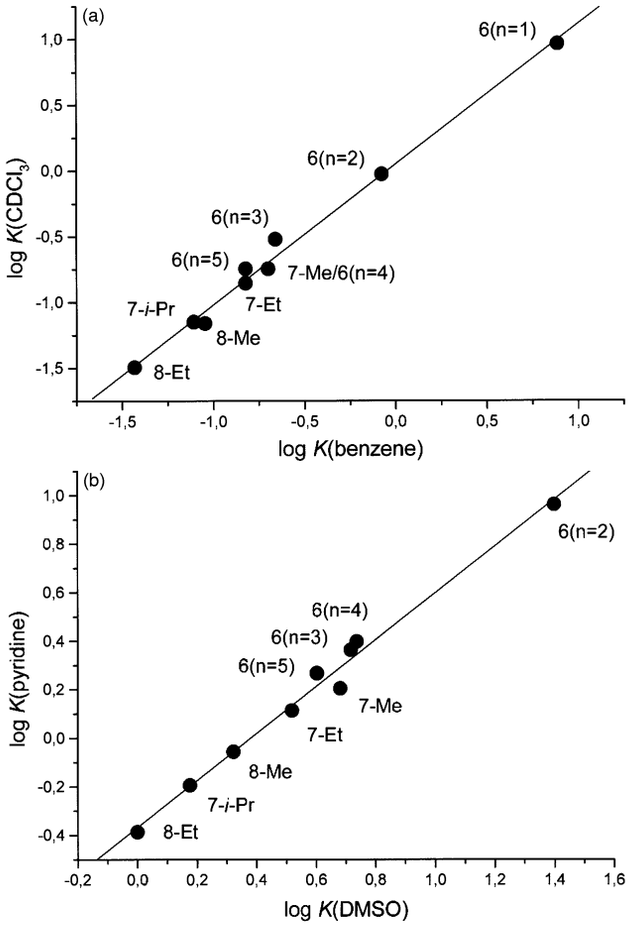


Fig. 2 (a) log–log correlation of equilibrium constants for alcohols in chloroform and benzene; (b) log–log correlation of equilibrium constants for alcohols in pyridine and DMSO.

alcohols except **6** (*n* = 1) are listed in Table 2. The enthalpy term favours the *syn* isomer but the entropy term the *anti*. This indicates that the *syn* rotamer is favoured by hydrogen bonding to the solvent but that this involves a more ordered structure, presumably due to solvent organization.[9,16] For pyridine the entropy terms are very similar for all the compounds investigated, covering a rather narrower range than for DMSO. In particular, for the 3-alkoxythienyl derivatives, **7-R**, the entropy terms are virtually identical, the change in the equilibrium constant being due to the progressive fall in the enthalpy term on going from methoxy to ethoxy to isopropoxy.

Rotamerization kinetics

The rotation barriers (Table 3) for most of the various substituted 2-thienyldi(*tert*-butyl)methanols fall in a range where they can only be studied by dynamic ^{1}H NMR in DMSO, the only solvent which has a high boiling point and where the rotamer ratio is sufficiently close to unity for reliable measurement. The EDOT derivative, **6** (*n* = 2), was previously studied in nitrobenzene[9] but we have now succeeded in obtaining data in DMSO. The 3,4-methylenedioxythienyl derivative, **6** (*n* = 1), was studied in chloroform and benzene, the only solvents where a detectable amount of the *anti* isomer is present. Simulation of the exchange spectra using the gNMR programme[17] provides rate constants for the *syn* ⟶ *anti* and *anti* ⟶ *syn* interconversion processes, from which are calculated the rotation barriers. Estimates based on different parts of the spectra for the 3-alkoxythienyl derivatives, **7-R**, give closely similar results.

Nevertheless, the derived thermodynamic data (Supplementary Material Table S2) cannot be considered very reliable. In particular, there is considerable scatter in the activation entropies, which for the *syn* ⟶ *anti* reaction in DMSO range from 3

Table 2 Temperature dependence of equilibrium constants ([*syn*]/[*anti*]) for 3,4-alkylenedioxy-, **6**(*n*), 3-alkoxy-, **7-R**, and 3,4-dialkoxy-2-thienyldi(*tert*-butyl)methanols, **8-R**, in hydrogen-bonding solvents [$\Delta G°(anti - syn) = \Delta H° - T\Delta S°$; $\Delta H°$ in kcal mol^{-1}; $\Delta S°$ in cal mol^{-1} K^{-1}]

	Pyridine			DMSO		
Compound	Temp. range/K	$\Delta H°$	$\Delta S°$	Temp. range/K	$\Delta H°$	$\Delta S°$
6 (n = 2)	298–328 [a]	4.31 ± 0.08	10.1 ± 0.3	298–348	4.77 ± 0.10	9.6 ± 0.3
6 (n = 3)	298–348	3.21 ± 0.11	9.0 ± 0.3	298–383	3.15 ± 0.09	7.2 ± 0.3
6 (n = 4)	298–343	3.78 ± 0.04	11.0 ± 0.1	298–358	3.64 ± 0.06	8.9 ± 0.2
6 (n = 5)	298–333	3.51 ± 0.08	10.9 ± 0.2	298–358	3.71 ± 0.05	9.3 ± 0.2
7-Me	298–348	3.12 ± 0.06	9.3 ± 0.2	298–358	3.09 ± 0.02	7.6 ± 0.1
7-Et	298–368	2.89 ± 0.05	9.2 ± 0.2	298–358	3.57 ± 0.09	9.6 ± 0.3
7-*i*-Pr	298–368	2.45 ± 0.05	9.2 ± 0.1	298–388	2.35 ± 0.04	7.1 ± 0.1
8-Me	298–368	2.42 ± 0.08	8.5 ± 0.2	298–388	2.55 ± 0.03	7.1 ± 0.1
8-Et	298–368	2.37 ± 0.11	9.7 ± 0.3	298–388	2.30 ± 0.02	7.7 ± 0.1

[a] Ref. 9.

Table 3 Activation energies for *syn* ⟶ *anti* and *anti* ⟶ *syn* rotation in 3,4-alkylenedioxy-, **6**(*n*), 3-alkoxy-, **7-R**, and 3,4-dialkoxy-2-thienyldi(*tert*-butyl)methanols, **8-R**, in DMSO [mean $\Delta G^{\neq}$ in kcal mol^{-1} at T(mean) in K]

Compound	Temp. range/K	T(mean)	$\Delta G^{\neq}(syn \longrightarrow anti)$	$\Delta G^{\neq}(anti \longrightarrow syn)$
6 (n = 1) [a]	298–323 [c]	311	17.4	16.3
6 (n = 1) [b]	298–328 [c]	313	17.5	16.1
6 (n = 2)	353–398 [d]	374	21.0 [g]	19.8 [g]
6 (n = 3)	378–423 [d]	401	22.0	21.7
6 (n = 4)	373–428 [d]	401	22.2	22.0
6 (n = 5)	383–428 [d]	406	22.0	22.0
7-Me	378–423 [d]	400	21.4	21.4
	378–408 [e]	391	21.5	21.35
7-Et	368–413 [d]	393	21.8	21.85
	368–398 [f]	384	21.9	21.9
7-*i*-Pr	368–403 [d]	388	21.9	22.3
	358–393 [e]	379	21.9	22.2
	358–393 [f]	377	21.95	22.3
8-Me	358–398 [c]	378	22.0	22.1
8-Et	378–428 [d]	404	22.3	23.05

[a] In chloroform. [b] In benzene. [c] Hydroxy group. [d] Aromatic(s). [e] Methyl group(s). [f] *tert*-Butyl. [g] In nitrobenzene at 365–400 K: 20.8 kcal mol^{-1}, ref. 9.

to −7 cal mol^{-1} K^{-1}, with that for the *anti* ⟶ *syn* reaction on average about 5 cal mol^{-1} K^{-1} more negative. The differences in the activation entropies are doubtless more reliable than the individual values but it should be noted that they are smaller than the $\Delta S°$ values for the same solvent, albeit in a lower temperature range. Likewise, the differences in the activation enthalpies are smaller than the $\Delta H°$ values. This implies that the $\Delta G°$ plot at high temperature deviates somewhat from that at lower temperature. Comparison of the two sets of $\Delta G°$ values suggests that they are parts of a continuous curve and that either the $\Delta C_p° = 0$ assumption [18] is incorrect or that there is a temperature-dependent change in the nature of the solvation of the OH group.

Structural effects on rotation barriers

In previous work [2,15,19] we have shown that the activation energy for rotation from the form with a "free" hydroxy group, through a transition state with again a "free" hydroxy group, to the form with an intramolecularly hydrogen-bonded hydroxy group, is virtually solvent-independent. For the reverse reaction, the barrier is solvent-dependent, falling for solvents in which the transition state is specifically solvated by hydrogen bonding with the hydroxy group.

The *syn* ⟶ *anti* rotation barrier for the 3,4-methylenedioxythienyl derivative, **6** (n = 1) (17.4 and 17.5 kcal mol^{-1} in chloroform and benzene, respectively) is much lower than that measured for the EDOT analogue, **6** (n = 2), in nitrobenzene (about 20.8 kcal mol^{-1}) [9] or DMSO (21.0 kcal mol^{-1}), and clearly shows the reduced steric effect of the tied-back oxygen atom at the 3-position; further lengthening of the chain results in only a modest increase to 22.0–22.2 kcal mol^{-1}. The three 3-alkoxythienyl compounds, **7-R**, give very similar rotation barriers, with a small increase on going from methoxy to ethoxy and isopropoxy. The 3,4-dialkoxy compounds, **8-R**, are associated with barriers about 0.5 kcal mol^{-1} higher than those of the corresponding 3-alkoxy derivatives.

The differences between the 3-alkoxy groups and between the 3,4-dialkoxy and 3-alkoxy derivatives are somewhat more marked for the *anti* ⟶ *syn* rotation barrier. The reason is that this reaction involves the breaking of an intramolecular hydrogen bond, whose strength varies significantly over the range of compounds studied, and the formation of a solvent-hydrogen-bonded transition state, the energetic contribution of which is relatively independent of structure.

There are few comparable data on rotation barriers involving thiophene derivatives: 2-thienyldi(1-adamantyl)methanes and -methanols have barriers ranging from about 20 (2-thienyldiadamantylmethane) to 38 kcal mol^{-1} (3-methyl-2-thienyldiadamantylmethane) [20] while values for *anti*-3-alkoxy-2-thienyldi(1-adamantyl)methanes rise from 28.4 to 30.7 kcal mol^{-1} on going from methoxy to isopropoxy.[8] For 2-alkoxyphenyl(isopropyl)(*tert*-butyl)methanols, **10-R**, the span is only 0.5 or 0.9 kcal mol^{-1}, depending on the direction of rotation.[16] Similar small effects are observed when methoxy is replaced by ethoxy in 2-alkoxyphenyldi(*tert*-butyl)methanols, **9-R**.[15] These results suggest that the effect of varying the alkoxy group is conditioned by the size of the alkyl substituents to the C–OH carbon. 1-Adamantyl groups, whose rigidity reduces their ability to distort,[21] enhance rotation barriers much more than *tert*-butyls, which means that rotation barrier differences should be amplified in the corresponding 3- or 3,4-substituted 2-thienyldi(1-adamantyl)- and 2-thienyl(1-adamantyl)(*tert*-butyl)methanols. This will be the subject of further work.

Separation of hydrogen bonding and steric effects

The variations in the equilibrium constants and the rotation barriers clearly result from the interplay of steric and hydrogen bonding effects, which appear to vary approximately in parallel, and the question arises as to their relative importance. There is no reliable basis in the literature for quantifying the IR and NMR spectroscopic data in terms of energy changes. Correlations between hydrogen bond formation enthalpies and IR frequency shifts, the Badger–Bauer rule,[22] mainly for intermolecular hydrogen bonding, have gradients ranging from 0.004–0.04 kcal mol^{-1} cm,[13d,e,23] with a preference for values around 0.01 kcal mol^{-1} cm.[23] It is clear from the variation of the *syn* ⟶ *anti* rotation barrier that the steric effect of the substituted thienyl group increases through the different series, but it is not obvious how much this contributes to the equilibrium constants. The rotation barrier is the difference between the ground state and rotation transition state energies, and though it generally increases with steric strain in the ground state,[21a] it says nothing about the difference in the steric energies of the two rotamers.

Considering only steric energies and hydrogen bonding, we can write:

$$\Delta G^{\neq}(syn) = \mathrm{SE(TS)} - \mathrm{SE}(syn) - \mathrm{SHB(TS)} + \mathrm{SHB}(syn) \quad (1)$$

where SE(TS) is the steric energy of the transition state, SHB(TS) its hydrogen bonding solvation energy, and SE(*syn*) and SHB(*syn*) are the corresponding terms for the *syn* isomer.

If SHB(TS) ≈ SHB(*syn*) we obtain:

$$\Delta G^{\neq}(syn) = \mathrm{SE(TS)} - \mathrm{SE}(syn) \quad (2)$$

which expresses the fact that *syn* ⟶ *anti* rotation barriers are solvent-independent.

For rotation in the other direction, we have:

$$\Delta G^{\neq}(anti) = \mathrm{SE(TS)} - \mathrm{SE}(anti) - \mathrm{SHB(TS)} + \mathrm{IHB}(anti) \quad (3)$$

where IHB(*anti*) is the intramolecular hydrogen bond energy. Subtraction of (3) from (1) gives eqn. (4):

$$\Delta G^{\neq}(syn) - \Delta G^{\neq}(anti) = \mathrm{SE}(anti) - \mathrm{SE}(syn) + \mathrm{SHB}(syn) - \mathrm{IHB}(anti) \quad (4)$$

where the left hand side is, of course, the same as $\Delta G^{\circ}(anti - syn)$, whence:

$$\Delta G^{\circ}(anti - syn) = \Delta\mathrm{SE}(anti - syn) + \mathrm{SHB}(syn) - \mathrm{IHB}(anti) \quad (5)$$

If it can be assumed that SHB(*syn*) is a constant regardless of structure, which is supported by the equilibrium data, there are only two variables in this equation: the steric energy difference between the two rotamers and the intramolecular hydrogen bond energy for the *anti* rotamer. Unfortunately, in modern molecular mechanics force fields hydrogen bonding is treated as an electrostatic interaction, and its contribution is therefore included in the steric energy, so that we have:

$$\Delta G^{\circ}(anti - syn) = \Delta\mathrm{SE/H}(anti - syn) + \mathrm{SHB}(syn) \quad (6)$$

where ΔSE/H(*anti* − *syn*) includes the intramolecular hydrogen bonding term.

Insofar as the presence of this particular interaction determines in part, or even to a large extent (since it can represent several kcal mol^{-1}), the optimum geometry, it affects the magnitude of all other deformations and interactions. For these reasons, our previous attempt to correct for steric effects in 2-alkoxyphenyl(isopropyl)(*tert*-butyl)methanols[15] is a measure of the error in the MM calculations rather than of the variation in the hydrogen bond energy.

The steric energies of both rotamers of **6** (*n* = 1–4), **7-R** and **8-R** were calculated by means of the MMFF94 force field[24] contained in the Sybyl package:[25] data refer to gas-phase energies. In the 3,4-alkylenedioxythiophene derivatives, **6**(*n*), the orientation of the O–CH_2 bond at C3 is largely determined by the requirements of the chain connecting it to C4; however, the longer the chain the more difficult it is to determine its conformation. For the *syn* rotamers of **7-R** the C2–C3–O–C torsion angle is close to 180° regardless of R, *i.e.* the alkoxy carbon is practically in the plane of the thiophene ring. In the *anti* rotamers, it deviates by 12°, 15° and 38° as R goes from Me to Et to *i*-Pr. In the 3,4-dialkoxy derivatives, **8-R**, the 3-alkoxy carbon is about 15° and 67° from the plane in the *syn* and *anti* isomers, respectively, regardless of R. Details are given in Supplementary Material Table S3.

Except for the two 3,4-dialkoxythienyl derivatives, **8-R**, where the steric energies of the rotamers are very similar, the *syn* isomer is calculated to be the more stable, the difference, ΔSE/H, ranging from 0.6 (**7-*i*-Pr**) to 2.1 [**6** (*n* = 1)] kcal mol^{-1}. The data (Table 4) indicate that ΔSE/H overestimates the stability of the *syn* isomer of **6** (*n* = 1) and **6** (*n* = 2) by nearly 1 kcal mol^{-1}, and that of **7-Et**, **7-*i*-Pr** and **8-Et** by about 2 kcal mol^{-1}. Since ΔSE/H is always greater than ΔG° this would make SHB(*syn*) a negative quantity and variable, whereas we have defined it as positive and believe it to be constant. The correlation of the mean values of ΔG° for chloroform and benzene against ΔSE/H is rather poor (corr. coeff. 0.9140; slope 1.42 ± 0.24) (Fig. 3).

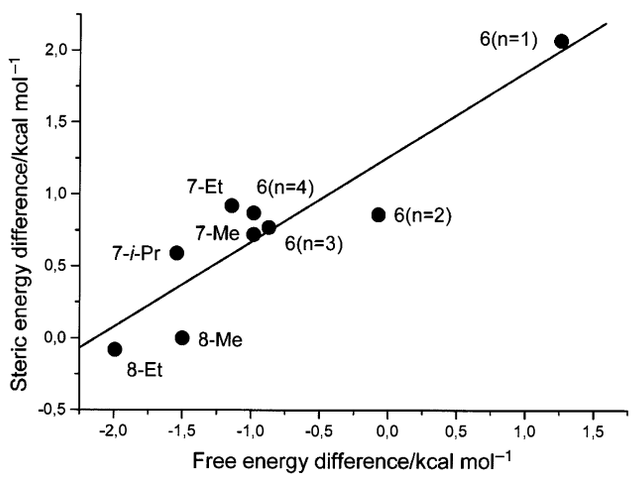


Fig. 3 Correlation of ΔG° for equilibrium in benzene and chloroform against ΔSE/H calculated by MMFF94 (both in kcal mol^{-1}).

The relative lack of success of this approach is not altogether surprising. Molecular mechanics force fields are not well parametrized for heteroatomic and particularly heterocyclic systems, and the parameter set for these thiophenes includes many lacunes which are filled with "default" and "estimated" parameters.[24] Since the number, the nature and the importance of these parameters differ from one set of compounds to another, **6**(*n*), **7-R** or **8-R**, considerable discrepancies are to be expected.

Another way of tackling this problem is to assume that the hydrogen bond enthalpy is correlated with the IR frequency shift relative to the mean value of 3617 cm^{-1} for the *syn* rotamers, IR being chosen rather than NMR for the simple reason that there are more data on this type of correlation. In particular, there is a range of values for the $\Delta H/\Delta\nu$ gradient.

The question arises as to whether it is legitimate to work with free energies, which are known with greater precision, rather than with enthalpies. The ΔS° values reported in Table 2 represent the entropy change associated with the equilibrium

Table 4 MMFF94 steric energy differences [ΔSE/H(*anti* − *syn*) in kcal mol^{-1}], free energy differences [Δ*G*°(*anti* − *syn*), mean for benzene and chloroform in kcal mol^{-1}], IR OH frequencies (*anti* in CCl_4/cm^{-1}) and hydrogen bond enthalpy contributions (in kcal mol^{-1})

Compound	ΔSE/H	Δ*G*°	ν_{OH}	Δ*H*[a]	ΔSE[a]	Δ*H*[b]	ΔSE[b]
6 (*n* = 1)	2.07	1.26	3612	0.05	1.31	0.07	1.33
6 (*n* = 2)	0.86	−0.07	3568	0.49	0.42	0.64	0.57
6 (*n* = 3)	0.77	−0.87	3507	1.10	0.23	1.43	0.56
6 (*n* = 4)	0.87	−0.98	3505	1.12	0.14	1.46	0.48
7-Me	0.72	−0.98	3516	1.01	0.03	1.31	0.33
7-Et	0.92	−1.14	3500	1.17	0.03	1.52	0.38
7-*i*-Pr	0.59	−1.54	3490	1.27	−0.27	1.65	0.11
8-Me	0.00	−1.50	3502	1.15	−0.35	1.50	0.00
8-Et	−0.08	−1.99	3486	1.31	−0.68	1.70	−0.29

[a] Gradient $\Delta H/\Delta\nu = 0.010$ kcal mol^{-1} cm. [b] Gradient $\Delta H/\Delta\nu = 0.013$ kcal mol^{-1} cm.

Table 5 Semi-empirical (AM1) heats of formation differences [$\Delta\Delta H_f^\circ$(*syn* − *anti*) in kcal mol^{-1}], HF/3-21G and HF/6-31G* potential energy differences [Δ*E* in kcal mol^{-1}]; calculated H ··· O and O ··· O distances (in Å)

Compound	H ··· O[a]	O ··· O[a]	$\Delta\Delta H_f^\circ$[a]	H ··· O[b]	Δ*E*[b]	H ··· O[c]	Δ*E*[c]
6 (*n* = 1)	2.340	2.835	1.98	1.895	−0.05	2.132	−1.03
6 (*n* = 2)	2.196	2.59	2.92	1.749	1.97	1.894	−0.15
6 (*n* = 3)	2.139	2.55	4.48				
6 (*n* = 4)	2.089	2.62	4.62				
7-Me	2.160	2.51	3.53	1.699	2.52	1.831	−0.02
7-Et	2.145	2.53	4.18	1.774	4.10	1.886	1.82
7-*i*-Pr	2.130	2.66	4.83	1.768	4.43	1.883	2.39
8-Me	2.075	2.65	6.31	1.766	3.91	1.920	3.06
8-Et	1.980	2.66	6.24				

[a] AM1. [b] HF/3-21G. [c] HF/6-31G*.

between two conformers, where one has a hydrogen bond to solvent (if at all) and the other an intramolecular hydrogen bond. Given the similarity of the structures and the constancy of the solvation effects, it is reasonable to assume that the entropy of formation of the hydrogen bond to solvent is roughly constant. The fact that Δ*S*° values in DMSO and pyridine vary by little more than the experimental error suggests that the intramolecular hydrogen bond entropy is also constant. By the same reasoning, the fact that the equilibrium constants for **6** (*n* = 2) in non-hydrogen-bonding solvents are almost temperature-independent implies that intramolecular hydrogen bond entropies are moreover close to zero. This means that free energy changes correspond to enthalpy differences, *i.e.* IHB(*anti*) ≈ Δ*H*. We shall assume that SHB(*syn*) is negligible for chloroform and benzene.

We now need to choose the $\Delta H/\Delta\nu$ gradient according to the qualitative criteria that the steric effect as originally defined in eqn. (5), ΔSE(*anti* − *syn*), should decrease as we descend each family, **6**(*n*), **7-R** or **8-R**, and that the greatest Δ*H* value should be compatible with literature data for intramolecular hydrogen bonds of this type. These can be reasonably well satisfied, apart from a problem with **7-Me**, by using small values of the gradient between 0.010 and 0.013 kcal mol^{-1} cm, the lower of these values ordering **6(*n*)** the best but somewhat reducing the highest Δ*H* value below those for 1,ω-methoxy-alcohols (up to 2.7 kcal mol^{-1})[26a] and 1,ω-diols (up to 2.00 kcal mol^{-1}).[26b] At the lower limit we have 1.3 kcal mol^{-1} of the overall 3.27 kcal mol^{-1} of free energy variation due to change in hydrogen bond strength and 2.0 kcal mol^{-1} due to changes in steric effects; at the upper limit, 1.6 and 1.6 kcal mol^{-1}, respectively (Table 4).

Semi-empirical quantum mechanical calculations

Though quantum mechanics make no distinction between hydrogen bonding and steric effects, we thought it interesting to examine to what extent readily available and comparatively economical calculations are capable of describing our results. Fully optimized gas-phase heats of formation and geometries for all but one of the isomer pairs discussed in this work were calculated using the semi-empirical AM1 parametrization.[27] Calculations with the PM3 parametrization gave less satisfactory results and will not be discussed here. Some of the structures were also investigated by the *ab initio* approach with small basis sets.

In all cases the AM1 parametrization gives the *anti* rotamer as the more stable, to a much greater extent than is observed in even a non-hydrogen-bonding solvent. The results (Table 5 and Supplementary Material Table S4) show, however, sharp increases in the heat of formation difference, $\Delta\Delta H_f^\circ$, on going from **6** (*n* = 1) to **6** (*n* = 2) to **6** (*n* = 3, 4), and a steady increase through the 3-alkoxythiophene derivatives, **7-R**, while there is apparently little difference between **8-Me** and **8-Et**. The overall pattern is roughly consistent with the observed changes in the equilibrium constant, but the range of $\Delta\Delta H_f^\circ$ for rotamer pairs is substantially greater than that of Δ*G*° or Δ*H*°, and the correlation with Δ*G*° is poor (slope 1.32 ± 0.25; corr. coeff. 0.8957).

Because of the difficulty of locating the overall minimum in the case of the flexible 7- and 8-membered rings, *ab initio* calculations of the potential energies at the HF/3-21G and HF/6-31G* levels were run on a reduced selection of 6 structures. Though the Δ*E* values for **6** (*n* = 1) and **6** (*n* = 2) with the more extended basis set are close to the experimental values of Δ*G*° the overall Δ*E*/Δ*G*° correlation is again poor (slope 1.30 ± 0.38; corr. coeff. 0.8604). Surprisingly, for the smaller set the correlation is better but the energy range is even higher (slope 1.52 ± 0.21; corr. coeff. 0.9636).

The AM1-calculated H ··· O and O ··· O distances for the *anti* rotamer vary roughly as expected, decreasing through each series (Table 5 and Supplementary Material Table S5). The values of 1.98 and 2.66 Å for **8-Et** are in very good agreement with the crystallographic data (*vide infra*). Other aspects of this structure, in particular the disposition of the ethoxy groups, are also very well reproduced by the AM1 calculation. The H ··· O and O ··· O distances calculated by the *ab initio* approach are less satisfactory, those given by the smaller basis set being particularly low. A corollary of this strong interaction appears to be that in **7A-Me** and **7A-Et** the alkoxy group is swung out of the plane of the thiophene ring.

Single crystal X-ray diffraction study of *anti*-3,4-diethoxy-2-thienyldi(*tert*-butyl)methanol, 8A-Et

Insofar as *tert*-butyl and 1-adamantyl have the same symmetry and despite the fact that the latter is more rigid and, consequently, more space-demanding, it is instructive to compare the structure of this new product with that previously determined for *anti*-3-methoxy-2-thienyldi(1-adamantyl)methanol, **4A-Me**.[8] In the diethoxy compound the hydroxy proton is 1.91 Å from the 3-ethoxy oxygen, the O ··· O distance 2.66 Å and the O–H ··· O angle 138°. The distances are somewhat greater than those for the 3-methoxy derivative (1.78 and 2.62 Å, respectively) and the angle somewhat smaller (156°). Such O ··· O distances are associated with much stronger hydrogen bonding in the methanol and acetic acid dimers.[28] It is interesting to note that the two ethoxy groups adopt the TGG′ conformation, that which is preferred in 1,2-dimethoxyethane.[29] All other features (Fig. 4, Supplementary Material Table S6) are

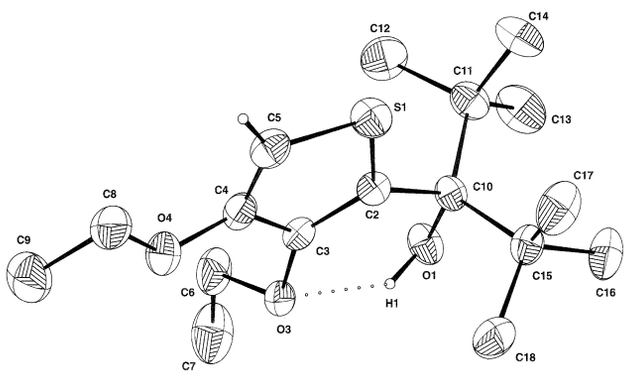


Fig. 4 CAMERON diagram for *anti*-3,4-diethoxy-2-thienyldi(*tert*-butyl)methanol, **8A-Et**, showing 30% probability displacement ellipsoids. Hydrogen atoms have been omitted for clarity.

typical of aryl- and heteroaryldiadamantylmethyl derivatives previously studied.[30] The major difference between **4A-Me** and **8A-Et** is in the orientation of the 3-alkoxy group, the O–CH_2 bond being at about 70° to the thiophene plane (relative to C2) in **8A-Et**, whereas in the 3-methoxy derivative the methyl group is almost coplanar (10°). These values are close to those calculated by MMFF94 [68 and 12°, respectively, both for the di(*tert*-butyl) derivative] and by AM1 (69 and 7°, respectively). The 4-ethoxy group, on the other hand, is in the plane of the ring, whereas the MM calculation puts it at about 60° to the plane.

Conclusion

In solution at room temperature 2-thienyldi(*tert*-butyl)-methanols, with alkoxy substituent(s) at the 3- or 3- and 4-positions or with 3,4-alkylenedioxy chains, exist as a mixture of two conformers in equilibrium. As the size and number of the substituent(s) or the length of the alkylene chain is increased the equilibrium favours the *anti* rotamer, that in which there is intramolecular hydrogen bonding between the oxygen at the 3-position and the hydroxy proton. Much the same trend is followed by the activation energies for the interconversion of the two rotamers, the barrier height increasing in the same order as the equilibrium constant. IR and NMR spectroscopic evidence indicates that hydrogen bond strength increases on going from 3,4-methylenedioxy to longer chains and through the 3-alkoxy series, increasing with the size of the alkoxy group, but that the 3,4-dialkoxy derivatives differ little from the 3-alkoxy compounds.

The failure of the Badger–Bauer rule[22] for intramolecular hydrogen bonding has been attributed to "conformation" and "geometric" effects, meaning that changes in conformational energy associated with hydrogen bonding tend to obscure the intrinsic contribution of this bond. Neither molecular mechanics nor quantum mechanics distinguishes intramolecular hydrogen bonding from other electrostatic interactions, making the separation of steric and hydrogen bonding effects not only difficult but to a certain extent artificial. Our attempt to do so, in spite of this observation, suggests that in the oxygen-substituted thiophene series investigated these two factors are of roughly equal importance. Quantum mechanical calculations, whether semi-empirical or *ab initio*, tend to overestimate the difference between the extremes. The AM1 parametrization accurately reproduces the hydrogen bond geometry of **8A-Et** in the solid state, *ab initio* calculations suggesting much tighter hydrogen bonds.

The reason for the popularity of EDOT as a monomer for electrochemical and chemical polymerization lies in the fact that it is readily available on a large scale and that its polymers are electrochemically stable, highly conductive, transparent in the doped form and have a low band gap. Early studies showed that **1** (*n* = 3) gave shorter, more soluble chains, presumably because of steric hindrance to coupling.[2] If this is the case, one cannot but wonder why more attention has not been paid to **1** (*n* = 1). However, the effective conjugation length is shorter in PMDOT than in PEDOT, possibly because of ring strain.[5] From a chemical standpoint, as probed by studying the equilibria between intramolecularly hydrogen-bonded and solvent-hydrogen-bonded 2-thienyldi(*tert*-butyl)methanol rotamers, EDOT is situated on a continuum between 3,4-methylenedioxythiophene and other 3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxythiophenes.

Experimental

General methods have been described in previous papers.[8,20,30f] NMR chemical shifts of hydroxy protons in deuteriochloroform at 298 K are given in ppm (reference value: δ_H = 7.26 ppm with respect to TMS). NMR data for hydroxy proton shifts in other solvents and temperature coefficients are given in Supplementary Material Table S1. Full details of the ^1H and ^{13}C NMR spectra of all new compounds in chloroform are given in Supplementary Material Table S7.

3,4-Alkylenedioxythiophenes, 1

Prepared from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate by reaction with 1,ω-dibromoalkanes in DMF at 90–100 °C in the presence of potassium carbonate,[4a,31] hydrolysis to the diacid, followed by decarboxylation and purification as for 3,4-diethoxythiophene (*vide infra*).[11]

3,4-Methylenedioxythiophene, 1 (*n* = 1). Yield, from the dicarboxylate, 13%; oil (Found: C, 46.8; H, 3.3; S, 24.5. $C_5H_4O_2S$ requires C, 46.86; H, 3.15; S, 25.02%).

3,4-Propylenedioxythiophene, 1 (*n* = 3). Yield, from the dicarboxylate, 20%; mp 81–82 °C (lit.[4a] 82–84 °C).

3,4-Butylenedioxythiophene, 1 (*n* = 4). Yield, from the dicarboxylate, 21%; oil.

3,4-Pentylenedioxythiophene, 1 (*n* = 5). Yield, from the dicarboxylate, 4%; oil (Found: C, 58.8; H, 6.7. $C_9H_{12}O_2S$ requires C, 58.67; H, 6.56%).

3,4-Diethoxythiophene, 3-Et

Prepared from the dipotassium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate by reaction with diethyl sulfate in toluene catalysed by [18]crown-6, as for 3,4-dimethoxythiophene, **3-Me**,[11] followed by hydrolysis to the diacid and subsequent decarboxylation in quinoline for 2 h at

170 °C with copper chromite as catalyst; purified by chromatography on alumina in light petroleum (b. range 35–60 °C)–diethyl ether mixtures (yield, from the dipotassium salt, 30%): mp 42 °C (Found: C, 55.6; H, 7.2; S, 19.1. $C_8H_{12}O_2S$ requires C, 55.78; H, 7.02; S, 18.62%).

Alcohol synthesis

To a mixture of the appropriate thiophene derivative (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 (0.78 g, 5.5 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 and excess ketone gave an oily or solid residue from which the alcohol was isolated by chromatography on alumina in light petroleum (b. range 35–60 °C)–diethyl ether mixtures.

3,4-Methylenedioxy-2-thienyldi(*tert*-butyl)methanol, 6 (*n* = 1). Yield 64%: mp 64 °C (Found: C, 62.2; H, 8.4; S, 11.9. $C_{14}H_{22}O_3S$ requires C, 62.19; H, 8.20; S, 11.86%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) see text; δ_{OH} 2.70. ***syn***: ν_{OH}/cm^{-1} (CCl_4) see text; δ_{OH} 2.18.

3,4-Propylenedioxy-2-thienyldi(*tert*-butyl)methanol, 6 (*n* = 3). Yield 31%: mp 81 °C (Found: C, 64.6; H, 8.8; S, 10.8. $C_{16}H_{26}O_3S$ requires C, 64.39; H, 8.78; S, 10.74%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3507; δ_{OH} 5.96. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3606, 3628; δ_{OH} 2.19.

3,4-Butylenedioxy-2-thienyldi(*tert*-butyl)methanol, 6 (*n* = 4). Yield 56%: oil (Found: C, 65.3; H, 8.9; S, 10.5. $C_{17}H_{28}O_3S$ requires C, 65.34; H, 9.03; S, 10.26%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3505; δ_{OH} 5.87. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3605, 3628; δ_{OH} 2.15.

3,4-Pentylenedioxy-2-thienyldi(*tert*-butyl)methanol, 6 (*n* = 5). Yield 61%: mp 57 °C (Found: C, 66.2; H, 9.1; S, 10.0. $C_{18}H_{30}O_3S$ requires C, 66.22; H, 9.26; S, 9.82%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3496; δ_{OH} 6.06. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3606, 3629; δ_{OH} 2.16.

3-Methoxy-2-thienyldi(*tert*-butyl)methanol, 7-Me. Yield 64%: oil (Found: C, 65.4; H, 9.6; S, 12.4. $C_{14}H_{24}O_2S$ requires C, 65.58; H, 9.43; S, 12.50%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3516; δ_{OH} 5.90. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3607, 3630; δ_{OH} 2.24.

3-Ethoxy-2-thienyldi(*tert*-butyl)methanol, 7-Et. Yield 79%: oil (Found: C, 66.4; H, 9.9; S, 12.0. $C_{15}H_{26}O_2S$ requires C, 66.62; H, 9.69; S, 11.86%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3500; δ_{OH} 6.12. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3606, 3630; δ_{OH} 2.24.

3-Isopropoxy-2-thienyldi(*tert*-butyl)methanol, 7-*i*-Pr. Yield 59%: oil (Found: C, 67.6; H, 10.0; S, 11.4. $C_{16}H_{28}O_2S$ requires C, 67.56; H, 9.92; S, 11.27%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3490; δ_{OH} 6.21. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3606, 3630; δ_{OH} 2.24.

3,4-Dimethoxy-2-thienyldi(*tert*-butyl)methanol, 8-Me. Yield 52%: mp 112 °C (Found: C, 62.9; H, 9.3; S, 11.5. $C_{15}H_{26}O_3S$ requires C, 62.90; H, 9.15; S, 11.19%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3502; δ_{OH} 5.87. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3606, 3626; δ_{OH} 2.20.

3,4-Diethoxy-2-thienyldi(*tert*-butyl)methanol, 8-Et. Yield 47%: mp 101 °C (Found: C, 64.8; H, 9.8; S, 10.0. $C_{17}H_{30}O_3S$ requires C, 64.93; H, 9.62; S, 10.20%). ***anti***: ν_{OH}/cm^{-1} (CCl_4) 3486; δ_{OH} 6.09. ***syn***: ν_{OH}/cm^{-1} (CCl_4) 3605, 3629; δ_{OH} 2.20.

Equilibrium constants for *anti* ↔ *syn* rotamerization

Samples of the various alcohols (*ca.* 10 mg) were made up in deuteriated chloroform, benzene, pyridine or DMSO (0.5 cm^3). Except in the case of **6** (*n* = 1) and **6** (*n* = 2), the first two solvents were studied only at 298 K, the others over a temperature range depending on the boiling point of the solvent. Free energy plots were linear over the temperature ranges indicated for each compound in a given solvent. The further the equilibrium constant from unity, the lower the accuracy of its measurement: at the extremes values estimated from different parts of the ^{1}H NMR spectrum may vary by up to 20%, which represents 0.08 l.u. or 0.11 kcal mol^{-1} at 298 K.

The temperature dependence of the equilibrium constant for **6** (*n* = 2) was also studied in chloroform and benzene. Variations in chloroform (298–328 K) were random and no greater than 1%; in benzene (298–343 K) the variation was greater (3%), [*syn*]/[*anti*] tending to increase slightly with temperature. Chloroform: $\Delta G°(anti - syn) = 0.028 \pm 0.042 - (0.3 \pm 0.1)T$; benzene: $\Delta G°(anti - syn) = 0.088 \pm 0.026 - (0.6 \pm 0.1)T$.

Rotation kinetics

Dynamic NMR was used. The ^{1}H NMR spectrum of a solution of the compound in DMSO-d_6 was recorded at temperatures ranging from 298 to over 400 K. Exchange generally occurred at a significant rate from about 350 K onwards. The 3,4-methylenedioxythienyl derivative, **6** (*n* = 1), was studied in chloroform and benzene up to 328 K only. Simulation of the *tert*-butyl, methyl, hydroxy or aromatic proton signals by gNMR [17] gives the exchange rate and the relative concentrations of the two species from which rate constants and the rotation barriers are calculated. To obtain an Eyring plot with the points all within 0.02 kcal mol^{-1} of the line the rate constants must be known to better than ±3%. The activation energies ($\Delta G^{\neq}$ in kcal mol^{-1}) listed are the means of 6–12 self-consistent data points (*i.e.* following a roughly linear Eyring plot) for the mean temperature (in K) at which the corresponding rate data were recorded (Table 3). Activation enthalpies and entropies are listed in Supplementary Material Table S2. These data are somewhat sensitive to errors in the assumed line-width for spectra in the absence of exchange.

Molecular mechanics calculations

Molecular mechanics calculations were performed using the MMFF94 force field with the MMFF94 charge model in the Sybyl 6.7 package.[25] Steric energies (kcal mol^{-1}) and torsion angles for the alkoxy substituents in the most stable conformations are given in Supplementary Material Table S3.

Quantum chemical calculations

Energies and geometries of the *syn* and *anti* rotamers of all alcohols except **6** (*n* = 5) were determined by fully optimized semi-empirical AM1 quantum mechanical calculations, using the Spartan package.[27] Data for the most stable conformations are reported (Supplementary Material Tables S4 and S5). *Ab initio* calculations (HF/3-21G and HF/6-31G*) were run on **6** (*n* = 1, 2), **7-R** and **8-Me** only.

X-Ray crystallography ‡

***anti*-3,4-Diethoxy-2-thienyldi(*tert*-butyl)methanol.** $C_{17}H_{30}O_3S$, **8A-Et.** *Crystal data.* M = 314.5. Monoclinic, a = 12.367(3), b = 11.139(2), c = 14.127(3) Å, β = 112.72(7)°, V = 1795(7) Å^3 (by least squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.71069 Å), space group $P2_1/c$, Z = 4, D_x = 1.16 g cm^{-3}. Colourless prismatic crystals, ν(Mo-Kα) = 1.8 cm^{-1}.

Data collection and processing. At 295 K, Enraf-Nonius MACH-3 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.8 + 0.345 tan θ, graphite-monochromated Mo-Kα radiation. 3898 reflections measured ($1 \leq \theta \leq 26°$), 3523 unique, giving 2271 with $I > 3\sigma(I)$.

‡ CCDC reference number 172908. See http://www.rsc.org/suppdata/p2/b1/b109612p/ for crystallographic files in .cif or other electronic format.

Structure analysis and refinement. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic; hydrogens placed in geometrically calculated positions and refined with one overall isotropic thermal parameter (192 refinable parameters). No absorption correction. Final R and R_w (Chebyshev series) values are 0.055 and 0.074. Programmes used were the PC version of CRYSTALS [32] for refinements and CAMERON [33] for views. Selected bond lengths, bond angles and torsion angles are listed in Supplementary Material Table S6.

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors' (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 172908.

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