# Rate and equilibrium effects of *tert*-alkyl groups on rotamerization in 3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxy-2-thienyl(di-*tert*-alkyl)methanols: an IR, NMR, kinetics and MM study †

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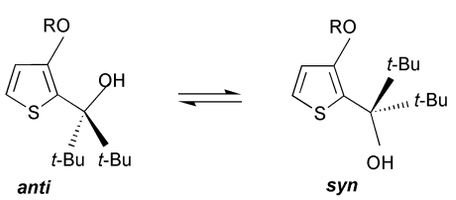
Di-1-adamantyl and (1-adamantyl)(*tert*-butyl) analogues are compared with the previously studied 3- or 3- and 4-substituted 2-thienyl(di-*tert*-butyl)methanols. The equilibrium constants for *syn–anti* rotamerization ([*syn*]/[*anti*]) are slightly greater than for the smaller di-*tert*-butyl derivatives. In the intramolecularly hydrogen-bonded *anti* rotamers, neither the $^1$H NMR shift of the hydroxy proton nor the OH stretching frequency, both indicators of intramolecular hydrogen bond strength, is greatly affected by a change in the *tert*-alkyl group; these changes in the equilibrium constants must, therefore, be attributed to variations in steric effects. The rotation barriers for the compounds with the larger *tert*-alkyl groups are much enhanced and better differentiated. In all three sets the *syn*⟶*anti* and *anti*⟶*syn* rotation barriers are linearly correlated, and either can be correlated with the free energy difference. Nevertheless, the data do not meet the criteria for a classical Leffler–Grunwald-type rate-equilibrium relationship. Molecular mechanics calculations (MMFF94 force field) account fairly well for the variation in the free energy difference for rotamer pairs of the di-1-adamantyl, (1-adamantyl)(*tert*-butyl) and di-*tert*-butyl derivatives, but slightly overestimate the small differences in the equilibrium constants for the three series. The calculated rotation barriers for the di-*tert*-butyl compounds are about 7 kcal mol$^{-1}$ higher than those observed. Those for 2-anisyl-, phenyl- and 2-tolyldialkylmethanols are increasingly overestimated as the rotation barrier rises, but a good correlation ranging over 20 kcal mol$^{-1}$ is obtained; this correlation is not coincident with that for the thiophene derivatives.

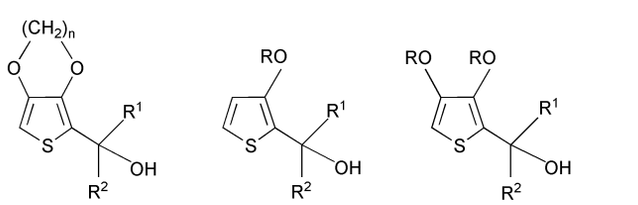
## Introduction

In previous work[1] it was shown that varying the ring size in 3,4-alkylenedioxy-2-thienyl(di-*tert*-butyl)methanols, **1**(*n*), or the substituent size in the 3-alkoxy, **2-R**, and 3,4-dialkoxy, **3-R**, analogues has marked effects upon the equilibrium constant between the *syn* ("free" OH group) and *anti* (intramolecularly hydrogen-bonded OH group) rotamers.




Increasing the chain length or the substituent size favours the *anti* isomer, the equilibrium constants spanning about 2.5 orders of magnitude, equivalent to a change in the free energy difference of 3.3 kcal mol$^{-1}$ (1 cal = 4.184 J) at 298 K. Apart from the 3,4-methylene derivative, **1** (*n* = 1), which has an unusually low rotation barrier, the *syn*⟶*anti* barriers range over only 1.3 kcal mol$^{-1}$.

The replacement of a *tert*-butyl group by the more rigid 1-adamantyl group has been shown to enhance rotation barriers.[2] In pursuing our study of these thiophene derivatives we thought it interesting to attempt to amplify the steric contribution to the differences in rotation rates and equilibria. It turns out that the rotation barriers are considerably increased by the more sterically demanding *tert*-alkyl group and that the magnitude of this increase depends on the bulk of the substituted thiophene moiety. Equilibrium constants, on the other hand, are little affected by change in the *tert*-alkyl group size.




**1:** $R^1 = R^2$ = t-Bu; **2:** $R^1 = R^2$ = t-Bu; **3:** $R^1 = R^2$ = t-Bu
**4:** $R^1$ = Ad; $R^2$ = t-Bu; **5:** $R^1$ = Ad; $R^2$ = t-Bu; **6:** $R^1$ = Ad; $R^2$ = t-Bu
**7:** $R^1 = R^2$ = Ad; **8:** $R^1 = R^2$ = Ad; **9:** $R^1 = R^2$ = Ad

n = 1, 2, 3 or 4; R = Me, Et or i-Pr; R = Me or Et

## Results and discussion

### Synthesis and spectroscopy

All new alcohols **4** (*n* = 1 and 4), **7** (*n* = 1, 3 and 4), **5** and **8** (R = Me, Et and *i*-Pr), **6** and **9** (R = Me and Et) were prepared by lithiation of the 3-alkoxy-, 3,4-dialkoxy- or 3,4-alkylenedioxythiophene by means of *n*-butyllithium–TMEDA in diethyl ether at room temperature,[1] followed by reaction with (1-adamantyl)(*tert*-butyl) ketone (**4**–**6**) or di-1-adamantyl ketone (**7**–**9**).

The IR and NMR spectra of the various alcohols were determined in carbon tetrachloride and chloroform, respectively. The most important features of the spectra are the OH

† Electronic supplementary information (ESI) available: additional experimental data. See http://www.rsc.org/suppdata/p2/b2/b203714a/

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**Table 1** IR ($\nu_{OH}$/cm$^{-1}$ in carbon tetrachloride) and $^1$H NMR ($\delta_{OH}$/ppm in chloroform) data for *anti*-3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxy-2-thienyl(di-*tert*-alkyl)methanols

| | Di-*tert*-butyl[a] | | (1-Adamantyl)(*tert*-butyl) | | Di-1-adamantyl | |
|---|---|---|---|---|---|---|
| RO | IR | NMR | IR | NMR | IR | NMR |
| 3,4-Methylenedioxy | 3612 | 2.7 | 3614 | 2.67 | 3616 | 2.63 |
| 3,4-Ethylenedioxy[b] | 3568 | 4.81 | 3570 | 4.76 | 3569 | 4.7 |
| 3,4-Propylenedioxy | 3507 | 5.96 | — | — | 3503 | 5.84 |
| 3,4-Butylenedioxy | 3505 | 5.87 | 3505 | 5.8 | 3504 | 5.75 |
| 3-Methoxy | 3516 | 5.9 | 3513 | 5.85 | 3511 | 5.80[c] |
| 3-Ethoxy | 3500 | 6.12 | 3497 | 6.06 | 3486 | 6.02[c] |
| 3-Isopropoxy | 3490 | 6.21 | 3488 | 6.15 | 3486 | 6.09[c] |
| 3,4-Dimethoxy | 3502 | 5.87 | 3499 | 5.81 | 3499 | 5.76 |
| 3,4-Diethoxy | 3486 | 6.09 | 3484 | 6.01 | 3482 | 5.96 |

[a] Ref. 1. [b] Ref. 4. [c] Ref. 5.

**Table 2** Free energy differences and MMFF94 steric energy differences for 2-thienyl(di-*tert*-butyl)methanols, 2-thienyl(1-adamantyl)(*tert*-butyl)-methanols and 2-thienyl(di-1-adamantyl)methanols [$\Delta G°$(*anti* − *syn*) and steric energies, ΔSE/H(*anti* − *syn*) in kcal mol$^{-1}$ at 298 K]

| | Di-*tert*-butyl | | (1-Adamantyl)(*tert*-butyl) | | Di-1-adamantyl | |
|---|---|---|---|---|---|---|
| RO | $\Delta G°$(**1**–**3**) benzene[a] | ΔSE/H(**1**–**3**) | $\Delta G°$(**4**–**6**) benzene | ΔSE/H(**4**–**6**) | $\Delta G°$(**7**–**9**) toluene | ΔSE/H(**7**–**9**) |
| 3,4-Methylenedioxy | 1.21 | 1.84 | 1.35 | 2.12 | 1.44 | 2.40 |
| 3,4-Ethylenedioxy | −0.08[b] | 0.66 | 0.05[b] | 1.12 | 0.17[b] | 1.31 |
| 3,4-Propylenedioxy | −0.90 | 0.46 | — | 0.98 | −0.69 | 1.22 |
| 3,4-Butylenedioxy | −0.95 | 0.12 | −0.72 | 0.77 | −0.58 | 0.98 |
| 3-Methoxy | −0.95 | 0.21 | −0.78 | 0.62 | −0.58 | 0.81 |
| 3-Ethoxy | −1.12 | 0.40 | −0.97 | 0.91 | −0.72 | 1.16 |
| 3-Isopropoxy | −1.51 | 0.29 | −1.39 | 1.02 | −1.28 | 1.26 |
| 3,4-Dimethoxy | −1.43 | −0.04 | −1.31 | 0.38 | −1.11 | 0.57 |
| 3,4-Diethoxy | −1.95 | −0.28 | −1.80 | 0.26 | −1.63 | 0.47 |

[a] Ref. 1. [b] Ref. 4.

stretching frequency in the IR spectrum and the chemical shift of the OH proton in the $^1$H NMR spectrum. In all cases these are similar to those for the di-*tert*-butyl analogues previously reported (Table 1).[1] Both data reveal small differences in hydrogen bonding in the 3-alkoxy, 3,4-dialkoxy and long-chain 3,4-alkylenedioxy ($n \geq 3$) derivatives, weaker bonding in the 3,4-ethylenedioxythiophene (EDOT) compounds and very weak in the 3,4-methylenedioxythiophene analogues. The replacement of *tert*-butyl by 1-adamantyl leads to somewhat contradictory effects on the IR and NMR values. Whereas the bulkier group reduces the NMR shift by up to 0.13 ppm on going from di-*tert*-butyl to di-1-adamantyl, suggesting slightly weaker hydrogen bonding, the very small decreases (up to 4 cm$^{-1}$) in the IR frequencies, for all except **7** ($n$ = 1) and **7** ($n$ = 2), would suggest the opposite. Clearly, as indicators of hydrogen bond strength, IR and NMR data are not perfectly correlated.[3]

## Equilibrium constants

Equilibrium constants for the di-*tert*-butyl compounds, **1**–**3**, in various solvents at 298 K were reported in previous work.[1] Those for compounds **4**–**6** in DMSO and benzene or toluene were either measured directly at 298 K or were extrapolated from measurements at higher temperatures. For alcohols **7**–**9**, all except that for the 3,4-methylenedioxythienyl compound, **7** ($n$ = 1), were extrapolated from data at higher temperatures. Values of $\Delta G°$(*anti* − *syn*) are listed in Table 2. The activation entropies for rotation in toluene show some rather surprising variations, ranging from −0.4 to −7.3 cal mol$^{-1}$ K$^{-1}$, for the *anti*⟶*syn* barrier [not including **7** ($n$ = 1)], the highest values being situated at the extremes, where the equilibrium constant is the most difficult to measure (Supplementary Information, † Table S1). However, the difference between the activation entropies for the *syn*⟶*anti* and *anti*⟶*syn* reactions is generally small, 2 cal mol$^{-1}$ K$^{-1}$ or less.

Comparison of the $\Delta G°$(*anti* − *syn*) data for the di-*tert*-butyl, **1**–**3**, (1-adamantyl)(*tert*-butyl), **4**–**6**, and di-1-adamantyl series, **7**–**9**, in benzene or toluene at 298 K reveals a small but fairly regular trend in favour of the *syn* isomer as *tert*-butyl is replaced by 1-adamantyl. The difference between the extremes ranges from 0.21–0.40 kcal mol$^{-1}$. The data for alcohols **7**–**9** can be correlated with those for **1**–**3** with a slope of 0.97 ± 0.03 (corr. coeff. 0.9973). The fact that the data for alcohols **7**–**9** were obtained in toluene and those for the di-*tert*-butyl analogues **1**–**3** in benzene is not considered important. Data for the (1-adamantyl)(*tert*-butyl) derivatives, **4**–**6**, correlate well with those for **1**–**3**, both in benzene, (slope 1.00 ± 0.01, corr. coeff. 0.9993).

Since the IR data indicate that the intramolecular hydrogen bond energies in the *anti* isomers are closely similar for the three series of compounds, this identifies the small change in the equilibrium constant, if it is significant, as a steric phenomenon. The somewhat unexpected conclusion is that the larger *tert*-alkyl groups at the COH carbon slightly favour the *syn* form.

## Rotation barriers

**(i) Barrier enhancement.** Because of the wide range of values, rotation barriers for the various derivatives (Table 3) had to be determined by several techniques in different solvents and temperatures ranges: dynamic $^1$H NMR, *in situ* NMR monitoring of the rotation or sealed-tube experiments followed by NMR analysis. Since dynamic $^1$H NMR requires relatively high temperatures to measure quite low barriers, those for the di-*tert*-butyl derivatives, **1**–**3**, were measured in DMSO. Most of those for alcohols **4**–**6** were also measured in DMSO but at temperatures close to ambient. One compound, **5-Me**, was insufficiently soluble in DMSO and was therefore studied in pyridine. For the two smallest 3,4-alkylenedioxythienyl derivatives, **4** ($n$ = 1) and **4** ($n$ = 2), the equilibrium constant is unfavourable in hydrogen-bonding solvents and these had to be

**Table 3** Rotation barriers for 2-thienyl(di-*tert*-butyl)methanols, 2-thienyl(1-adamantyl)(*tert*-butyl)methanols and 2-thienyl(di-1-adamantyl)-methanols [$\Delta G^{\neq}$ in kcal mol$^{-1}$ at 298 K], ΔSE/H(max – *syn*) for 2-thienyl(di-*tert*-butyl)methanols calculated by MMFF94 (in kcal mol$^{-1}$)

| | *anti*⟶*syn* | | | *syn*⟶*anti* | | | |
|---|---|---|---|---|---|---|---|
| RO | $\Delta G^{\neq}$(**1**–**3**) DMSO[a] | $\Delta G^{\neq}$(**4**–**6**) DMSO | $\Delta G^{\neq}$(**7**–**9**) toluene | $\Delta G^{\neq}$(**1**–**3**) DMSO[a] | ΔSE/H(**1**–**3**) | $\Delta G^{\neq}$(**4**–**6**) DMSO | $\Delta G^{\neq}$(**7**–**9**) toluene |
| 3,4-Methylenedioxy | 14.4[b] | 16.2[b] | 19.4 | 17.4[c] | 24.3 | 19.3[d] | 20.7 |
| 3,4-Ethylenedioxy | 19.2 | 20.9[b] | 25.78 | 20.7 | 27.4 | 22.82[c] | 25.95 |
| 3,4-Propylenedioxy | 20.9 | — | 27.98 | 21.8 | 28.4 | — | 27.29 |
| 3,4-Butylenedioxy | 21.0 | 23.30 | 27.83 | 21.8 | 28.7 | 24.34 | 27.25 |
| 3-Methoxy | 20.5 | 22.72 | 27.38 | 21.2 | 28.3 | 23.63 | 26.80 |
| 3-Ethoxy | 21.05 | 23.67 | 28.59 | 21.9 | 28.3 | 24.33 | 27.87 |
| 3-Isopropoxy | 21.5 | 24.68 | 30.17 | 21.6 | 28.7 | 25.02 | 28.89 |
| 3,4-Dimethoxy | 21.9 | 23.5[e] | 28.25 | 22.3 | 28.7 | 23.97[f] | 27.14 |
| 3,4-Diethoxy | 21.9 | 24.56 | 29.65 | 21.7 | 29.2 | 24.69 | 28.02 |

[a] Ref. 1. [b] Correction of 1.9 kcal mol$^{-1}$ to convert data for chloroform, benzene or toluene to DMSO (ref. 6). [c] In benzene. [d] In toluene. [e] Correction of 0.5 kcal mol$^{-1}$ to convert data for pyridine to DMSO (ref. 6). [f] In pyridine.

studied in benzene or toluene. Finally, the di-1-adamantyl derivatives, **7**–**9**, were all studied in toluene, at temperatures ranging from 298 to 418 K.

Data for two of the di-1-adamantyl derivatives, **8-Me** and **8-Et**, in solvents other than toluene (Supplementary Information,† Table S1) confirm our previous observation[1] that *syn*⟶*anti* rotation barriers are virtually solvent-independent whereas the reverse reaction is accelerated by hydrogen-bonding solvents. This implies that the OH group is similarly solvated in the *syn* rotamer and the rotation transition state. (In the corresponding 2-anisyl derivatives,[6] because of nomenclature rules, it is the *anti*⟶*syn* rotation barrier which is solvent-independent.)

Some 3-alkoxythienyl(di-1-adamantyl)methanes have been studied in chloroform.[5] Values of the *syn*⟶*anti* rotation barrier at 298 K for the OMe, OEt and O*i*-Pr derivatives are 27.7, 28.8 and 30.0 kcal mol$^{-1}$, respectively, very close to the values found for the corresponding alcohols, **8-Me**, **8-Et** and **8-*i*-Pr**, in toluene (27.4, 28.6 and 30.2 kcal mol$^{-1}$). It will be remarked also that the barrier for **7** ($n$ = 1) is very close to that for 2-thienyl-(di-1-adamantyl)methanol in DMSO at 350–420 K (21.1 kcal mol$^{-1}$).[7]

The rotation barriers are considerably enhanced by replacing *tert*-butyl groups by 1-adamantyl, the *syn*⟶*anti* barrier being increased by 3.3 (3,4-methylenedioxythienyl) to 7.3 (3-isopropoxythienyl) kcal mol$^{-1}$ on going from di-*tert*-butyl to di-1-adamantyl. It is interesting to note that the barriers are not only greater but that the magnitude of the increase depends on the bulk of the substituted thiophene moiety. The *syn*⟶*anti* rotation barriers for sets **1**–**3** and **7**–**9** (all recalculated for 298 K) are roughly correlated (slope 1.52 ± 0.20, corr. coeff 0.9462) (Supplementary Information,† Fig. S1a), the two outlying points probably being due to uncertainties in the entropy terms. No correction need be made for the difference between toluene (used for **7**–**9**) and DMSO [used for **1**–**3**, except for **1** ($n$ = 1) which was examined in benzene and chloroform]. Data for the *anti*⟶*syn* rotation barriers can be correlated similarly (slope 1.35 ± 0.10, corr. coeff. 0.9919) (Supplementary Information,† Fig. S1b), but here a correction of 1.9 kcal mol$^{-1}$ was applied to the datum for **7** ($n$ = 1) to allow for the change in solvent from benzene and chloroform, in which the measurements were made, to DMSO.[5]

**(ii) Rate equilibrium relationships.** There is a good linear correlation between the *syn*⟶*anti* and *anti*⟶*syn* rotation barriers for the di(adamantyl) series, **7**–**9**, in toluene (slope 1.33 ± 0.05, corr. coeff. 0.9945) (Fig. 1). To compare the various (1-adamantyl)(*tert*-butyl) derivatives, **4**–**6**, in a common solvent, DMSO, some data have again been corrected for the solvent effect on the *anti*⟶*syn* barrier, the *syn*⟶*anti* barrier being treated as solvent-independent. With this approximation we

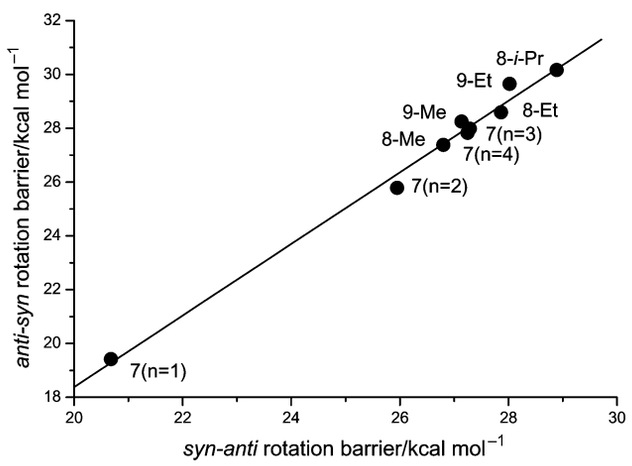


**Fig. 1** Correlation of *anti*⟶*syn* and *syn*⟶*anti* rotation barriers for 2-thienyl(di-1-adamantyl)methanols, **7**–**9**.

obtain again a good correlation (slope 1.48 ± 0.07, corr. coeff. 0.9934) (Supplementary Information,† Fig. S2a). Finally, the corresponding data for the di-*tert*-butyl derivatives, **1**–**3**, with the datum for **1** ($n$ = 1) corrected to bring it to DMSO, show a similar trend, but the smaller range and the lesser precision of the values, all measured by dynamic NMR, make the quality of the correlation poorer (slope 1.56 ± 0.11, corr. coeff. 0.9835) (Supplementary Information,† Fig. S2b).

The rationale behind these correlations is fairly obvious. If the equilibrium constant did not vary within a given series then we would obtain a correlation with unit slope. Any random variation in the equilibrium constant would be manifested as scatter about the regression line. In the present case, however, the quality of the correlations and the fact that the slopes are not unity suggest that $\Delta G^{\circ}$ and $\Delta G^{\neq}$ are linearly related, *e.g.*

$$\Delta G^{\circ}(syn - anti) = \Delta G^{\neq}(anti) - \Delta G^{\neq}(syn) = \alpha\Delta G^{\neq}(syn) + \beta \quad (1)$$

where α and β are constants. In other words, the free energy difference between the rotamers increases in parallel with the rotation barrier. This gives an equation of the form observed:

$$\Delta G^{\neq}(anti) = (1 + \alpha)\Delta G^{\neq}(syn) + \beta \quad (2)$$

It should be noted that though eqn. (1) is formally a rate-equilibrium relationship, it in no way respects the Leffler–Grunwald (L–G) criteria for such relationships.[8] In their formulation, the reaction is the faster the more the equilibrium favours the product(s), and the coefficient, which may be taken to express the degree of advancement of the transition state, lies

between zero and unity. The L–G approach requires in the present case:

$$\Delta G^{\neq}(syn) = \alpha' \Delta G^{\circ}(anti - syn) + \beta' \quad (3)$$

in which for alcohols **7**–**9** we obtain $\alpha' = -2.45 \pm 0.36$ and $\beta' = 25.3 \pm 0.4$ (corr. coeff. 0.9307). In our series we have clearly variations in the steric effects and hydrogen bonding which both raise the rotation barrier and favour the *anti* isomer as we progress from the 3,4-alkylenedioxy compounds to the 3-alkoxy and 3,4-dialkoxy derivatives.

The increase in the *syn*⟶*anti* rotation barriers on going from the small-ring bridged compounds to the dialkoxy compounds is a reflection of the increasing steric interaction between the thiophene system and the *tert*-alkyl groups in the ground state. Any interaction of this sort is magnified in the transition state and for this reason barriers are always higher for the more strained compounds.[2a] The *anti*⟶*syn* rotation barriers, however, include also a contribution from the breaking of the intramolecular hydrogen bond. This contribution is low for the small-ring bridged compounds, increases with ring-size and is large for the 3-alkoxy and 3,4-dialkoxy derivatives, there being little difference between these latter. The contribution depends slightly on the alkoxy group size, increasing from OMe to OEt to O*i*-Pr. In a previous paper[1] we expressed the two rotation barriers as follows,

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

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:

$$\Delta G^{\neq}(syn) = \mathrm{SE(TS)} - \mathrm{SE}(syn) \quad (5)$$

For rotation in the other direction, we have:

$$\Delta G^{\neq}(anti) = \mathrm{SE(TS)} - \mathrm{SE}(anti) - \mathrm{SHB(TS)} + \mathrm{IHB}(anti) \quad (6)$$

where IHB(*anti*) is the intramolecular hydrogen bond energy and SE(*anti*) the steric energy of the *anti* isomer. Assuming that SHB(TS) is negligible for non-hydrogen-bonding solvents gives:

$$\Delta G^{\neq}(anti) = \mathrm{SE(TS)} - \mathrm{SE}(anti) + \mathrm{IHB}(anti) \quad (7)$$

whence:

$$\Delta G^{\circ}(anti - syn) = \mathrm{SE}(anti) - \mathrm{SE}(syn) - \mathrm{IHB}(anti) \quad (8)$$

Unfortunately, the steric energy terms cannot be determined independently of the hydrogen bond term, but we can estimate IHB(*anti*) from the IR spectroscopy data, assuming that the Bagler–Bauer relationship[9] applies with a suitable coefficient and that this term is equivalent to $\Delta H$, the hydrogen bond formation enthalpy. For the di-*tert*-butyl derivatives, **1**–**3**, we showed[1] that if the coefficient is taken as 0.01 kcal mol$^{-1}$ cm,[10] then the contribution of hydrogen bonding accounts for about 50% of the overall change in the equilibrium constant on going from **1** ($n = 1$) to **3-Et**. Since the equilibrium constant range is virtually the same for **1**–**3**, **4**–**6** and **7**–**9**, whereas the IR spectra are practically unchanged, the differential interaction of the various substituted thiophene motifs with the *tert*-alkyl groups appears to be independent of the group size, apart from a small general shift in favour of the *syn* isomer.

## Molecular mechanics calculations

**(i) Equilibrium constants.** In a previous paper an attempt was made to understand the equilibrium constant variation in terms of molecular mechanics and quantum mechanical calculations. The MMFF94 force field[11] in the Sybyl package[12] gave better results than the latter and for vastly shorter calculation times, even when compared to the semi-empirical approach with the AM1 parametrization. Under the circumstances we have restricted our treatment of the larger molecules of the present study to molecular mechanics. Unfortunately, reexamination of the previously calculated di-*tert*-butyl structures, **1**–**3**, revealed that in a number of cases the true energy minimum had not been found. In the Supplementary Information, † Table S2, are listed revised values for these derivatives and corresponding data for the analogues, **4**–**6** and **7**–**9**, in the same conformations (see also Table 2). The revision of the data for **1**–**3** considerably improves the quality of the correlation of free energy difference (in benzene) against the MMFF94 energy difference, ΔSE/H(*anti* − *syn*), (corr. coeff. 0.9529) but the slope remains high, 1.46 ± 0.18 (Fig. 2), expressing the fact that the equilibrium

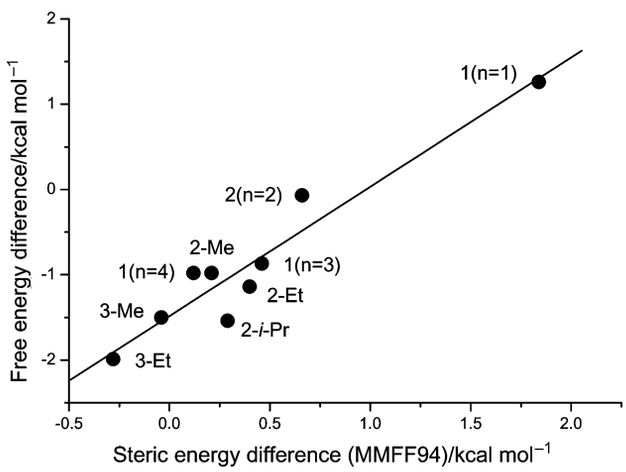


**Fig. 2** Correlation of free energy difference against MMFF94-calculated steric energy difference for 2-thienyl(di-*tert*-butyl)methanols, **1**–**3**.

constant varies more than the steric energy calculations would suggest. Moreover, the calculations almost always make the *anti* isomer less stable than the *syn*, whereas the reverse is true except for **1** ($n = 1$) and **1** ($n = 2$).

The MMFF94 energy difference, ΔSE/H(*anti* − *syn*), is systematically higher for the (1-adamantyl)(*tert*-butyl), **4**–**6**, and di-1-adamantyl derivatives, **7**–**9**, than for di-*tert*-butyl compounds, **1**–**3**, by mean values of 0.5 and 0.7 kcal mol$^{-1}$, respectively These differences are in accord with the observation that there is a shift in favour of the *syn* isomer as 1-adamantyl replaces *tert*-butyl, but the changes in ΔSE/H are always greater than those for the free energy difference. Correlations of $\Delta G^{\circ}$ against ΔSE/H for **4**–**6** and **7**–**9** are poorer than for **1**–**3**, mainly because the 3-alkoxy compounds are badly handled, ΔSE/H increasing from OMe to OEt to O*i*-Pr, whereas the $\Delta G^{\circ}$ values fall. Added to this is the possibility of extrapolation errors, particularly in **7**–**9**. The results are then, for **4**–**6**: slope 1.56 ± 0.30, corr. coeff. 0.9068 (Supplementary Information, † Fig. S3a) and for **7**–**9**: slope 1.36 ± 0.26, corr. coeff. 0.8938 (Supplementary Information, † Fig. S3b).

**(ii) Rotation barriers.** The calculation of rotation barriers by molecular mechanics has a long history, going back to early work on biphenyls by Westheimer.[13] More recent protagonists include Baas,[14] Anderson,[15,16] Lunazzi,[16,17] Mitchell[18] and ourselves.[2a,19] The great advantage over quantum mechanical calculations is that complete reaction profiles can be generated in a relatively short time. Moreover, insofar as the only observeable is the barrier height, it is really only necessary to establish the energy mimima and maxima. In the present case, one torsion angle is defined by attributing an arbitrarily high force constant

to its variation from the required value. For the di-*tert*-butyl derivatives, **1**–**3**, the torsion angle involving the sulfur atom and one of the quaternary *tert*-butyl group carbons or the OH oxygen was driven backwards and forwards through a series of values in the vicinity of the energy maximum in order to determine to lowest rotation pathway (Supplementary Information, † Table S2). Since the *anti*⟶*syn* rotation barrier is solvent-dependent, the calculated values were compared with experimental values for the *syn*⟶*anti* barrier; the former are 6–7 kcal $mol^{-1}$ too high (Table 3). However, somewhat fortuitously there is a fair correlation with almost unit slope (0.97 ± 0.09, corr. coeff. 0.9688) (Supplementary Information, † Fig. S4), which is determined largely by the point for **1** ($n$ = 1), all the other data except that for **1** ($n$ = 2) lying close to 21.8 (experimental) and 28.4 (calculated) kcal $mol^{-1}$. An attempt to calculate rotation barriers for the di-1-adamantyl compounds, **7**–**9**, was abandoned when it was found that for the 3,4-methylendioxy derivative, **7** ($n$ = 1), the result was about twice the measured value.

This seemed a good opportunity to test the ability of MMFF94 to predict or, at least, to correlate available data for rotation barriers in aryldialkylmethanols, and to compare the results with those for our thiophene derivatives. The oldest data, from Baas,[20] are activation energies measured at the necessarily variable temperature of coalescence. We have attempted to correct these to 298 K by assuming a value of the activation entropy of −8 cal $mol^{-1}$ $K^{-1}$ taken from our work on 2-tolyl(di-*tert*-butyl)methanol.[2a] We have made no correction for the probably small effect of the methoxy substituents on the rotation barrier. Some data for the *anti*⟶*syn* (this corresponds to *syn*⟶*anti* in the thiophene series) rotation of 2-anisyl derivatives are taken from Suezawa's work with no correction,[21] and those from our own work are extrapolated to 298 K.[5]

When the calculated barriers (Supplementary Information, † Table S3) are plotted against the experimental values (Fig. 3)

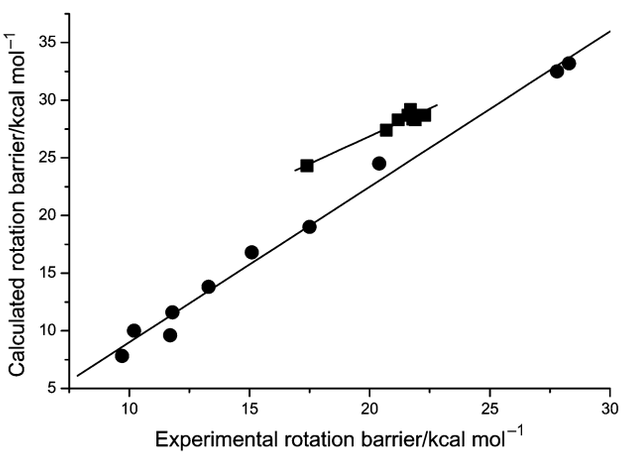


**Fig. 3** Correlation of MMFF94-calculated rotation barriers against experimental rotation barriers. Comparison of 2-thienyl(di-*tert*-butyl)-methanols, **1**–**3** (■) and aryldialkylmethanols (●).

we obtain a good correlation spanning some 20 kcal $mol^{-1}$ (slope 1.35 ± 0.05, corr. coeff. 0.9951). It will be noted that the barrier is increasingly overestimated as it become larger, *i.e.* the force field exaggerates the strain in the most congested species. Comparison with the thiophene derivatives shows that, apart from the difference in slope, all the points for **1**–**3** lie above the correlation for the benzenoid derivatives.

## Conclusion

Complementing previous work on 3,4-alkylenedioxy-, 3-alkoxy- and 3,4-dialkoxy-2-thienyl(di-*tert*-butyl)methanols, *syn*–*anti* equilibrium constants and rotation barriers have been determined for the corresponding (1-adamantyl)(*tert*-butyl) and di-1-adamantyl compounds. These show a small change in the equilibrium constant in favour of the *syn* isomer as the bulk of the *tert*-alkyl group is increased. Since the IR and NMR data for the *anti* rotamers, indicative of intramolecular hydrogen bonding, are virtually independent of the *tert*-alkyl groups, this can only be a steric phenomenon. The rotation barriers are considerably enhanced by replacing *tert*-butyl groups by 1-adamantyl, but to an extent which increases with the bulk of the substituted thiophene moiety. For each set of compounds the *syn*⟶*anti* and *anti*⟶*syn* rotation barriers and, consequently, the free energy differences are roughly correlated, but these correlations correspond in no way to a classical Leffler–Grunwald type rate-equilibrium relationship. Instead, increasing the steric bulk of the substituted thiophene moiety due to ring enlargement or the presence of larger substituents augments the rotation barriers at the same time as it favours the *anti* rotamer. The contribution of hydrogen bonding to stabilization of the *anti* isomer and, therefore, to the increase in the *anti*⟶*syn* rotation barrier rises in roughly the same order.

Molecular mechanics calculations (MMFF94), combining both steric and hydrogen bonding effects, give a fairly good account of the structural dependence of the equilibrium constants for the di-*tert*-butyl derivatives, though they tend to underestimate the overall range. They perform less well for systems with bulkier *tert*-alkyl groups. Rotation barriers calculated for the *syn*⟶*anti* reaction of the di-*tert*-butyl derivatives are systematically too high by 6–7 kcal $mol^{-1}$ but show the correct trend. Comparable data for benzene derivatives are better reproduced with, however, a tendency for calculation to overestimate the higher rotation barriers. These are clearly problems inherent in the force field and/or the driver routine (see Experimental section).

## Experimental

General methods have been described in previous papers.[5,7] IR spectra were measured in carbon tetrachloride. The spectra of **4** ($n$ = 1) and **7** ($n$ = 1) were decomposed using four Lorentzian peaks of which those at 3566 (16%) and 3551 $cm^{-1}$ (7%) for **4** ($n$ = 1) and **7** ($n$ = 1), respectively, could not be assigned. NMR chemical shifts of hydroxy protons in deuteriochloroform at 298 K are given in ppm (reference value of residual solvent protons: $\delta_H$ = 7.26 ppm with respect to TMS). Full details of the $^1H$ and $^{13}C$ NMR spectra of all new compounds in chloroform are given in Supplementary Information, † Table S4.

### 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 the appropriate ketone (2–3 mmol) was added. The mixture was stirred for a further 30 min, then quenched with water and the organic materials extracted with diethyl ether or dichloromethane. Washing with water, drying and evaporation of solvent gave an oily or solid residue from which the alcohol was isolated by chromatography on alumina in light petroleum (35–60 °C)–diethyl ether mixtures.

### Isolation of *syn* isomers

Pure or enriched samples of the *syn* isomers in the di-1-adamantyl series [not **7** ($n$ = 1)] were required for kinetics, and for **5-*i*-Pr** and **6-Et** in the (1-adamantyl)(*tert*-butyl) series for spectroscopic study. These were prepared by dissolving the *anti* alcohol in DMSO and holding it at a temperature depending on the rotation barrier for an appropriate time. Quenching the mixture in water and dichloromethane followed by several washes with water, drying ($MgSO_4$) and evaporation of solvent

at reduced pressure gave samples suitable for spectroscopy. Column chromatography of the di-1-adamantyl derivatives provided samples of the *syn* isomer either pure or sufficiently enriched for kinetics.

**3,4-Methylenedioxy-2-thienyl(1-adamantyl)(*tert*-butyl)-methanol, 4 (*n* = 1).** Yield 78%: mp 108 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$): *anti* 3614; *syn* 3603, 3623. Found: C, 68.9; H, 8.2; S, 9.6%. $C_{20}H_{28}O_3S$ requires: C, 68.93; H, 8.10; S, 9.20%.

**3,4-Butylenedioxy-2-thienyl(1-adamantyl)(*tert*-butyl)-methanol, 4 (*n* = 4).** Yield 23%: oil. $\nu_{OH}$/cm$^{-1}$($CCl_4$): *anti* 3505; *syn* 3603, 3627. Found: C, 70.9; H, 8.6%. $C_{23}H_{34}O_3S$ requires: C, 70.73; H, 8.77%.

**3-Methoxy-2-thienyl(1-adamantyl)(*tert*-butyl)methanol, 5-Me.** Yield 76%: mp 74 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$): *anti* 3513; *syn* 3604, 3627. Found: C, 71.7; H, 9.2; S, 9.4%. $C_{20}H_{30}O_2S$ requires: C, 71.81; H, 9.04; S, 9.59%.

**3-Ethoxy-2-thienyl(1-adamantyl)(*tert*-butyl)methanol, 5-Et.** Yield 81%: oil. $\nu_{OH}$/cm$^{-1}$($CCl_4$): *anti* 3497; *syn* 3604, 3627. Found: C, 72.1; H, 9.5%. $C_{21}H_{32}O_2S$ requires: C, 72.36; H, 9.25%.

**3-Isopropoxy-2-thienyl(1-adamantyl)(*tert*-butyl)methanol, 5-*i*-Pr.** Yield 67%: mp 60 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$) *anti* 3488; *syn* 3605, 3627. Found: C, 72.7; H, 9.8; S, 8.6%. $C_{22}H_{34}O_2S$ requires: C, 72.88; H, 9.45; S, 8.84%.

**3,4-Dimethoxy-2-thienyl(1-adamantyl)(*tert*-butyl)methanol, 6-Me.** Yield 58%: mp 104 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$) *anti* 3499; *syn* 3603, 3625. Found: C, 68.8; H, 9.1; S, 8.6%. $C_{21}H_{32}O_3S$ requires: C, 69.19; H, 8.85; S, 8.80%.

**3,4-Diethoxy-2-thienyl(1-adamantyl)(*tert*-butyl)methanol, 6-Et.** Yield 72%: mp 65 °C. $\nu_{OH}$/cm$^{-1}$ ($CCl_4$) *anti* 3484; *syn* 3604, 3625. Found: C, 70.2; H, 9.4; S, 8.3%. $C_{23}H_{36}O_3S$ requires: C, 70.36; H, 9.24; S, 8.17%.

**3,4-Methylenedioxy-2-thienyl(di-1-adamantyl)methanol, 7 (*n* = 1).** Yield 81%: mp 210 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$) *anti* 3616; *syn* 3602, 3623. Found: C, 73.2; H, 8.1; S, 7.6%. $C_{26}H_{34}O_3S$ requires: C, 73.20; H, 8.03; S, 7.52%.

**3,4-Propylenedioxy-2-thienyl(di-1-adamantyl)methanol, 7 (*n* = 3).** Yield 43%: mp 182 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$) *anti* 3503; *syn* 3600, 3624. Found: C, 73.8; H, 8.6; S, 7.1%. $C_{28}H_{38}O_3S$ requires: C, 73.96; H, 8.42; S, 7.05%.

**3,4-Butylenedioxy-2-thienyl(di-1-adamantyl)methanol, 7 (*n* = 4).** Yield 67%: mp 218 °C. $\nu_{OH}$/cm$^{-1}$($CCl_4$) *anti* 3504; *syn* 3600, 3625. Found: C, 74.3; H, 8.7; S, 6.8%. $C_{29}H_{40}O_3S$ requires: C, 74.31; H, 8.60; S, 6.84%.

***syn*-3-Methoxy-2-thienyl(di-1-adamantyl)methanol, 8-Me.** mp 143 °C; $\nu_{OH}$/cm$^{-1}$($CCl_4$) 3602, 3625. Found: C, 75.6; H, 8.8; S, 7.8%. $C_{26}H_{36}O_2S$ requires: C, 75.68; H, 8.79; S, 7.77%.

***syn*-3-Ethoxy-2-thienyl(di-1-adamantyl)methanol, 8-Et.** mp 160 °C; $\nu_{OH}$/cm$^{-1}$($CCl_4$) 3602, 3625. Found: C, 75.8; H, 9.2; S, 7.5%. $C_{27}H_{38}O_2S$ requires: C, 76.01; H, 8.98; S, 7.50%.

***syn*-3-Isopropoxy-2-thienyl(di-1-adamantyl)methanol, 8-*i*-Pr.** mp 141 °C; $\nu_{OH}$/cm$^{-1}$($CCl_4$) 3601, 3625. Found: C, 76.2; H, 9.3; S, 7.4%. $C_{28}H_{40}O_2S$ requires: C, 76.32; H, 9.16; S, 7.26%.

**3,4-Dimethoxy-2-thienyl(di-1-adamantyl)methanol, 9-Me.** Yield 31%; *anti*: mp 254 °C; $\nu_{OH}$/cm$^{-1}$($CCl_4$) 3499; *syn* 3600, 3624. Found: C, 73.3; H, 8.6; S, 7.4%. $C_{27}H_{38}O_3S$ requires: C, 73.26; H, 8.65; S, 7.24%.

**3,4-Diethoxy-2-thienyl(di-1-adamantyl)methanol, 9-Et.** Yield 86%; *anti*: mp 201 °C; $\nu_{OH}$/cm$^{-1}$($CCl_4$) 3482; *syn* 3600, 3624. Found: C, 73.8; H, 9.3; S, 7.0%. $C_{29}H_{42}O_3S$ requires: C, 74.00; H, 8.99; S, 6.81%.

### Rotation kinetics

**(i) Fast rotation.** Dynamic NMR was used only for the 3,4-methylenedioxythienyl derivatives, **4** (*n* = 1) and **7** (*n* = 1). The $^1$H NMR spectrum of a solution of **4** (*n* = 1) in deuteriated toluene was recorded at temperatures ranging from 298 to 353 K. Simulation of the *tert*-butyl or the methylene and aromatic proton signals by gNMR [22] gives the exchange rate and the relative concentrations of the two species from which rate constants and the rotation barriers are calculated. For **7** (*n* = 1) the solution was sealed in air at atmospheric pressure, and measurements were taken up to 393 K. The methylene and aromatic proton signals were used to determine the exchange rates. The activation energies given here ($\Delta G^{\neq}$ in kcal mol$^{-1}$) are the means of about 10 self-consistent data points (*i.e.* following a roughly linear Eyring plot) for the mean temperature ($T_m$/K) at which the corresponding rate data were recorded: **4** (*n* = 1): *tert*-butyl: $\Delta G^{\neq}$(*syn*) 19.3, $\Delta G^{\neq}$(*anti*) 18.2, $T_m$ 333, methylene and aromatic: $\Delta G^{\neq}$(*syn*) 19.2, $\Delta G^{\neq}$(*anti*) 18.1, $T_m$ 334; **7** (*n* = 1): methylene and aromatic: $\Delta G^{\neq}$(*syn*) 21.7, $\Delta G^{\neq}$(*anti*) 20.5, $T_m$ 373. Thermodynamic parameters are listed in Supplementary Information, † Table S1.

**(ii) Slow rotation. Di-1-adamantyl derivatives.** From a solution of the *syn* isomer, either pure or enriched, (*ca.* 20 mg) in a deuteriated solvent (1 cm$^3$) ten 0.1 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, eight samples being withdrawn at convenient intervals, the remaining two being used as "infinities" (*ca.* 10 half-lives). Each sample was made up in chloroform to *ca.* 0.5 cm$^3$ for $^1$H NMR spectroscopic analysis.

**(1-Adamantyl)(tert-butyl) derivatives.** A sample of compound (*ca.* 15 mg) in deuteriated 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. Because of the low solubility of **6-Me** in DMSO this compound was studied in pyridine.

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 [%*syn*($t$) − %*syn*($\infty$)] *vs.* time. Rate constants are listed in Supplementary Information, † Table S5, and the thermodynamic parameters in Supplementary Information, † Table S1.

### Molecular mechanics calculations

Molecular mechanics calculations were performed using the MMFF94 force field with the MMFF94 charge model [11] in the Sybyl 6.8 package.[12] Rotation barriers were calculated by driving one S–C–C–C (largest alkyl) or the S–C–C–O angle, using a blocking force constant of 7.5 kcal mol$^{-1}$/(°)$^2$. The exact value of this constant is unimportant to the result. The rotation profile was taken to be determined by the lowest energy conformation for each value of the torsion angle. In, for example, phenyl(di-*tert*-butyl)methanol, a pointed profile with no real transition state results from the crossing of two rising energy curves, followed by catastrophic drops as the torsion angle is pushed further. These are due to drastic reorientation of the *tert*-butyl (or other) groups and are probably artefacts resulting from the inadequacy of the driver routine,[23,14d] though other authors apparently believe they correspond to a molecular phenomenon.[24] Steric energies (kcal mol$^{-1}$) of the most stable

conformations and the maxima for thiophene derivatives are given in Supplementary Information,† Table S2. Corresponding data for aryldialkylmethanols and experimental rotation barriers are given in Supplementary Information,† Table S3.

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