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Self-association in {2-[3,4-alkylenedioxy-5-(3-pyridyl)]-thienyl}alkanols: an NMR, IR, and single-crystal X-ray study

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ABSTRACT: *syn*-2,2,4,4-Tetramethyl-3-{2-[3,4-alkylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ols self-associate both in the solid state and in solution. Single-crystal X-ray diffraction study of the 3,4-ethylenedioxythiophene (EDOT) derivative shows that it exists as a centrosymmetric head-to-tail, *syn* dimer in the solid state. The IR spectra of the solids display only a broad OH absorption around 3300 cm^{-1}, corresponding to a hydrogen-bonded species. ^{1}H Nuclear Overhauser Effect Spectroscopy (NOESY) NMR experiments in benzene reveal interactions between the *tert*-butyl groups and the H2 and H6 protons of the pyridyl group. Two approaches have been used to determine association constants of the EDOT derivative by NMR titration, based on the concentration dependence of (i) the *syn*/*anti* ratio and (ii) the OH proton shift of the *syn* rotamer. Reasonably concordant results are obtained from 298 to 323 K (3.6 and 3.9 M^{-1}, respectively, at 298 K). Similar values are obtained from the *syn* OH proton shift variation for the 3,4-methylenedioxythiophene (MDOT) derivative. Concentration-dependent variation of the *anti* OH proton shift in the latter suggests that the *anti* isomer associates in the form of an open, singly hydrogen-bonded dimer, with a much smaller association constant than the *syn* rotamer. Self-association constants for 3-pyridyl-EDOT-alkanols with smaller substituents vary by a factor of 4 from $(i\text{-Pr})_2$ up to $(\mathrm{CD}_3)_2$, while the hetero-association constants for the same compounds with pyridine vary slightly less. Copyright © 2007 John Wiley & Sons, Ltd.
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KEYWORDS: hydrogen bonding; rotamers; self-association; hetero-association

INTRODUCTION

The hydrogen bond is a non-covalent force arising from the electrostatic interaction between an electronegative donor group, D, consisting of a hetero-atom, usually oxygen or nitrogen, bearing a covalently bound hydrogen atom, and an electron-acceptor, A, again O or N, in another or the same molecule. This type of bonding, albeit much weaker than covalent bonding, is one of the most important factors determining the three-dimensional structures of supramolecular assemblies in chemical and biochemical systems.[1] The very simplest bonding situation is that where two different molecules carry a single donor and a single acceptor, and interact in a 1:1 ratio: A···D. Such 1:1 hydrogen-bonded complexes are intrinsically unstable, because of the weakness of the hydrogen bond, and are easily disrupted by solvation of the acceptor and/or donor sites. Multiplication of the number of hydrogen bonds by the inclusion of several sites leads to more complicated bonding patterns and enhanced stability.[2] The extreme situation is that of water, where the entire molecular surface consists of donor and acceptor groups, the cooperative effect of which leads to stability out of all proportion to the strength of the hydrogen bond in the water dimer.[3]

In this work we shall consider O—H···N bonding in species where the donor and the acceptors are present in the same molecule, giving rise potentially to a centrosymmetric array. This is a key step towards the construction of supramolecular architectures based on a relatively uncommon type of hydrogen bonding. Previous work on self-association by O—H···N bonding in pyridine-substituted alcohols is limited to three stu-

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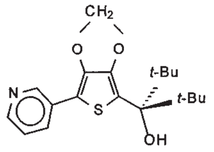
dies.[4–6] Early NMR[4] and IR[5] spectroscopic studies on (2-pyridyl)alkanols reveal intermolecular as well as intramolecular hydrogen bonding due to the proximity of the OH group and the nitrogen atom. More generally, pyridyl derivatives of simple alkanols, X-pyridyl $(CH_2)_nOH$, where $X = 2$, 3, or 4 and $n = 1$, 2, or 3, corresponding to methanol, ethanol, or propanol, respectively, form hydrogen-bonded self-association complexes, probably open and/or cyclic dimers as well as cyclic trimers and tetramers.[6] In the sterically hindered 2,2,4,4-tetramethyl-3-(X-pyridyl)pentan-3-ols, the pyridyl group and the encumbered OH hydrogen are paradoxically too close for cyclic dimers or higher n-mers to be formed, though NMR studies are consistent with association (not $X = 2$), presumably as open dimers or n-mers.[6] Our aim was to find a rigid spacer which would prevent intramolecular O—H···N hydrogen bonding, at the same time as it reduced the impact of steric hindrance and would thereby allow self-association of such alcohols. A suitable system was suggested by work on the 3-alkoxy,[7] 3,4-dialkoxy,[7] and 3,4-alkylenedioxy[7–10] derivatives of 2,2,4,4-tetramethyl-3-(2-thienyl)pentan-3-ols, which exist in two rotameric forms, where the hydroxy hydrogen is either intramolecularly hydrogen-bonded (*anti*) or 'free' (*syn*). Hydrogen-bond-acceptor solvents such as pyridine and DMSO favor the *syn* form in which the OH group is hydrogen-bonded to the solvent (A···D hetero-association). If an acceptor group is introduced into such a molecule with a suitable geometry, self-association should occur. To test this prediction we have synthesized two 5-(3-pyridyl) derivatives of 2,2,4,4-tetramethyl-3-[2-(3,4-alkylenedioxy)thienyl]pentan-3-ols, **1** and **2a**. Their IR and NMR spectroscopic behavior has been investigated and the single-crystal X-ray diffraction structure of **2a** determined. Equilibrium constants for self- and hetero-association (with pyridine) of **2a** and less encumbered species **2b–d** (t-Bu replaced by i-Pr, Et, or Me), determined by NMR titration, establish that steric effects on association are small.



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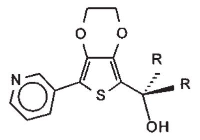
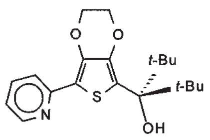


2a-d

a: R = *t*-Bu
b: R = *i*-Pr
c: R = Et
d: R = Me
e: R = H



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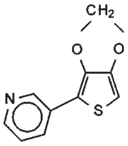

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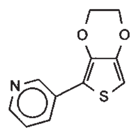

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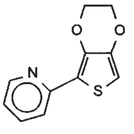

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RESULTS AND DISCUSSION

Synthesis

2-(X-Pyridyl)-3,4-alkylenedioxythiophenes, **4–6** ($X = 2$ or 3), were prepared by reaction of the appropriate 2-(tri-n-butylstannyl)thiophene with X-bromopyridine in DMF at 120 °C catalyzed by bis(triphenylphosphine)palladium(II) chloride (Stille reaction).[11] The 3,4-substituted 2,2,4,4-tetramethyl-3-{2-[5-(3-pyridyl)]thienyl}pentan-3-ols, **1**, **2a**, and **3**, were synthesized from the above by lithiation with n-BuLi/TMEDA in diethyl ether at room temperature followed by reaction with 2,2,4,4-tetramethylpentan-3-one. Less encumbered derivatives **2b–d** (R = i-Pr, Et, or Me) were synthesized in the same way from **5** at −75 °C.

Single-crystal X-ray diffraction structure of *syn*-2-2,4,4-tetramethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 2a

The unit cell of compound **2a** contains a centrosymmetric pair of molecules associated by two hydrogen bonds between the OH hydrogens and the pyridine nitrogens, the distance between the oxygen and nitrogen atoms being 2.86 Å. The —C(t-Bu)$_2$OH group is in the *syn* orientation, and the pyridine ring is at about 20° to the thiophene ring (Fig. 1). Selected bond lengths, bond angles, and torsion angles are given in Supplementary Material Table S1 with a labeled CAMERON diagram.

Although O—H···N hydrogen bonding occurs in a large number of structures determined by X-ray diffraction – a search for crystallographic data with ConQuest (v. 1.8, CDDC, Cambridge, UK) gave about 1200 hits with H···N distances between 1.5 and 2.5 Å – only two other structures appear to involve similar centrosymmetric pairs joined through weak hydrogen bonds, with N···O distances of 3.03 and 2.95 Å.[12] One of these involves a pyridine ring and a phenolic OH,[12a] the other an imidazole ring and an alcoholic OH.[12b]

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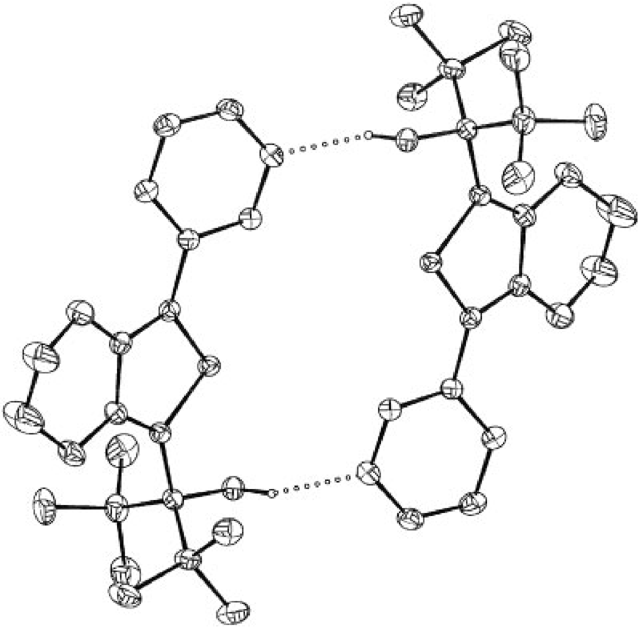

Figure 1. CAMERON diagram for *syn*-2-2,4,4-tetramethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl} pentan-3-ol, **2a**, showing 30% probability displacement ellipsoids. Hydrogen atoms, except OH, have been omitted for clarity

^{1}H NOESY NMR experiments on 2,2,4,4-tetramethyl-3-{2-[3,4-alkylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ols

As compound **1** exists very predominantly as the *syn* rotamer, no cross-peaks corresponding to the *anti* isomer are detected. The 2D ^{1}H Nuclear Overhauser Effect Spectroscopy (NOESY) NMR spectrum of **1** in benzene displays correlations between the *tert*-butyl groups of the *syn* rotamer and the {H2, H6} pyridine protons, the correlations with H6 being stronger. This correlation is particularly significant, since H6 is the most remote from the *tert*-butyl groups of the same sub-unit in both rotamers, regardless of the orientation of the pyridyl group. Furthermore, there are also correlations between the *syn* OH proton and the same pyridyl protons, though that with H6 is weak (Fig. 2). According to the X-ray crystallographic structure of **2a** there are four small distances between *tert*-butyl group protons and the pyridyl H6 (2.45, 3.53, 3.73, and 3.91 Å); there is only one similar distance for H2 (3.50 Å). Crystallography indicates that for **2a** the OH···H2 distance (3.05 Å) is greater than OH···H6 (2.88 Å). Nevertheless, in **1**, which would be expected to have a very similar structure, the correlation peak for OH···H2 appears to be more intense than that for OH···H6. These contacts are consistent with the presence of an associated species in which the *tert*-butyl groups of one sub-unit are brought close to the pyridyl substituent of a second sub-unit.

The NOESY experiment on **2a** is complicated by the fact that the effective concentration of the self-associated species is small, owing to the low solubility, the presence of about 45% of the *anti* rotamer, and the apparently low association constant (Supplementary Material Figure S1). Weak correlations are observed for the *tert*-butyl signal of the *anti* rotamer with the {H2, H4} pyridyl protons. For the *syn* isomer of **2a** there are correlations between the *tert*-butyl group and only the {H2, H6} protons. An unexpected feature of the NOESY spectrum is a cross-peak corresponding to the *tert*-butyl group of the *syn* isomer and the OH group of the *anti* isomer. This is attributed to fast chemical exchange of the OH group protons between the different rotamers during the mixing time, an explanation confirmed by a 1D homonuclear decoupling experiment, in which irradiation at either OH proton frequency leads to a marked reduction in the signal of the other OH proton (Supplementary Material Figure S2).

IR Spectroscopy

On the basis of their wavenumbers and shapes, ν_{OH} bands are assigned to the different alcohol isomers in carbon tetrachloride (**1** and **2a–d**) and to solid samples deposited from solution onto a KBr plate (**1**, **2a**, and **3**) (Table 1). The strong, very broad signals at low wavenumbers for **1** and **2a** in the solid state are consistent with a structure in which the OH group is hydrogen-bonded to the pyridyl nitrogen in an associated form of the *syn* rotamer. For the 2-pyridyl-EDOT derivative, **3**, there is no association band whatsoever in the cast spectrum, simply two absorptions, corresponding to the *syn* and *anti* rotamers.

Previous work[7] on analogs lacking the 3-pyridyl substituent facilitates the assignment of the free *syn* and intramolecularly hydrogen-bonded *anti* OH vibrations in **1**, **2a**, and **3** around 3600 cm^{-1}, but for **2b–c** the wavenumber differences are smaller and the assignments less reliable. Alcohol **2d** gives only a single broad absorption in this region. For alcohol **1** there is a very broad band at 3310 cm^{-1}, with a red-shift of about 310 cm^{-1} relative to the free *syn*, while for **2a** the red-shifts of the two weak bands are 410 and 330 cm^{-1}. That both are weak is due to the poor solubility of this material and the fact that nearly half is in the *anti* form (for **1** there is only 10% which is not *syn* – see below). For **2b–d** the absorptions of the free *syn* and *anti* rotamers are accompanied in all cases by strong bands attributed to an associated form of the *syn* rotamer, with the red-shift increasing from about 330 to 350 to 370 cm^{-1} as the substituent becomes smaller.

Self-association constants for {2-[3,4-alkylenedioxy-5-(*X*-pyridyl)]thienyl}-alkanols

^{1}H NMR titration. Benzene solutions of 2,2,4,4-tetramethyl-3-{2-3,4-alkylenedioxy-5-(3-pyridyl)]thienyl} pentan-3-ols, **1** and **2a**, and of 2,2,4,

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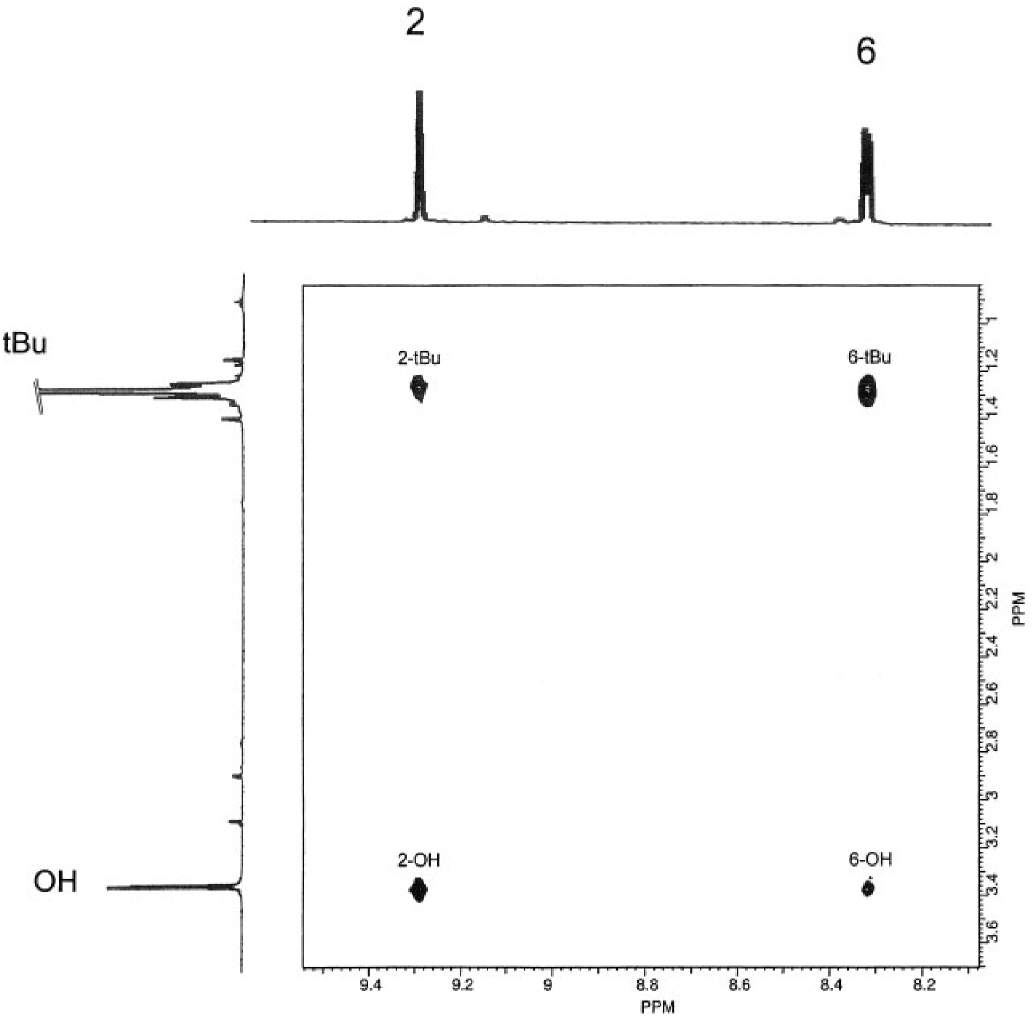


Figure 2. 2D NOESY spectrum of 2,2,4,4-tetramethyl-3-{2-[3,4-methylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, **1**, in benzene at 293 K

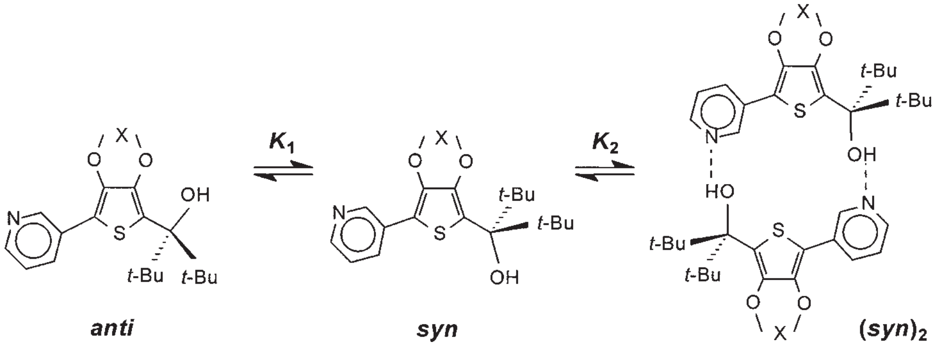
4-tetramethyl-3-{2-[3,4-ethylenedioxy-5-(2-pyridyl)]thienyl}pentan-3-ol, **3**, at various concentrations were studied by NMR spectroscopy. For compound **1** the shifts of the OH proton, the methylene, and the *tert*-butyl group protons in the very predominant *syn* isomer (*ca*. 91%) increase with concentration; that of the *anti* OH proton increases very slightly, but the other signals of the *anti* isomer are difficult to differentiate and, depending on the temperature, are partially or totally coalesced with those of the *syn* isomer (Supplementary Material Table S2). For **2a** the shifts of the OH proton and the *tert*-butyl group protons of the *syn* isomer also increase with concentration, while the corresponding shifts for the *anti* isomer are virtually constant within the experimental error (Supplementary Material Table S3).

Table 1. IR OH stretching vibrations (ν_{OH} in cm^{-1}) for {2-[3,4-alkylenedioxy-5-(*X*-pyridyl)]thienyl}alkanols **1**, **2a–d**, and **3**

Cpd.	ν_{OH} Free *syn*	ν_{OH} Bound *anti*	ν_{OH} Bound *syn* *n*-mer
1[a]	—	—	3300
2a[a]		3562	3280
3[a]	3605	3570	—
1	3624	3613	3310
2a	3604, 3627	3576	3220, 3300
2b	3619	3598	3285
2c	3610	3601	3250
2d	3600	3600	3235

[a] Solid deposited onto KBr plate from CH_2Cl_2 solution; all others in CCl_4.

The variations in the shifts of certain protons in compounds **1** and **2a** are consistent with the formation of a self-associated species of the *syn* conformer. While the *anti*$\rightleftharpoons$*syn* rotation (equilibrium constant K_1) is slow on the NMR time-scale and, consequently, gives rise to well defined peaks for each rotamer, the free$\rightleftharpoons$associated interconversion (equilibrium constant K_2) is rapid and does not give separate signals but a single somewhat broadened signal (Scheme 1). In view of the results of the X-ray diffraction study it seems



Scheme 1

reasonable to assume that in solution the associated species is also a cyclic dimer.

In what follows, S, A, and SS refer to the *syn* rotamer, the *anti* rotamer, and the *syn* dimer, respectively; $[\mathrm{ROH}]_\mathrm{o}$ is the analytical concentration of the alcohol. Taking $(\delta_{\mathrm{OH}})^{\mathrm{syn}}$, the chemical shift of the *syn* OH, as the weighted average of the shifts of the monomer, δ_S, and of the dimer, δ_{SS}, following Chen and Shirts,[13] we have Equation (1):

$$(\delta_{\mathrm{OH}})^{\mathrm{syn}} = \delta_\mathrm{S} + (\delta_{\mathrm{SS}} - \delta_\mathrm{S})\frac{(1+8K_2[\mathrm{S}]_\mathrm{o})^{1/2}-1}{(1+8K_2[\mathrm{S}]_\mathrm{o})^{1/2}+1} \quad (1)$$

where $[\mathrm{S}]_\mathrm{o}$ is the analytical concentration of the *syn* rotamer. If R is the *syn*/*anti* ratio, $[\mathrm{S}]_\mathrm{o}/[\mathrm{A}]_\mathrm{o}$, where $[\mathrm{S}]_\mathrm{o} = [\mathrm{S}] + 2[\mathrm{SS}]$, and $[\mathrm{A}]_\mathrm{o}$ is the concentration of the *anti* rotamer, Equation (2) applies:

$$[\mathrm{S}]_\mathrm{o} = \frac{R[\mathrm{ROH}]_\mathrm{o}}{1+R} \quad (2)$$

Since measurements are only possible at low monomer and, therefore, low dimer concentration, the value of the chemical shift of the OH proton in the associated form, δ_{SS}, is poorly defined by parameter optimization through Equation (1).[14] This difficulty is overcome by determining the hetero-association constant with pyridine in benzene and, at the same time, δ_{Spy} by means of Equation (3):[15]

$$(\delta_{\mathrm{OH}})^{\mathrm{syn}} = \delta_\mathrm{S} + \frac{(\delta_{\mathrm{Spy}} - \delta_\mathrm{S})}{2[\mathrm{S}]_\mathrm{o}}\left\{B - (B^2 - 4[\mathrm{S}]_\mathrm{o}[\mathrm{py}]_\mathrm{o})^{1/2}\right\} \quad (3)$$

where $B = [\mathrm{S}]_\mathrm{o} + [\mathrm{py}]_\mathrm{o} + 1/K$; $[\mathrm{py}]_\mathrm{o}$ is the analytical pyridine concentration. In order to minimize the effect of self-association these measurements were made at low alcohol concentration: at the lowest pyridine concentration not more than 1% of the alcohol is self-associated. Values of K, δ_{Spy}, and δ_S are determined by fitting the experimental values of $(\delta_{\mathrm{OH}})^{\mathrm{syn}}$ to those of $[\mathrm{S}]_\mathrm{o}$ and $[\mathrm{py}]_\mathrm{o}$ by means of the non-linear least-squares curve fitting option of the Origin program (Microcal Software, Inc., now OriginLab Corporation, One Roundhouse Plaza, Northampton, MA01060, USA), which uses the Levenberg–Marquardt algorithm.

We then assume that hetero-association of the alcohol with the solvent mimics self-association in benzene, that the effects of inter- and intramolecular hydrogen bonding are similar, that is, that δ_{Spy}, the OH proton shift in the pyridine complex, can be taken as δ_{SS}. The self-association constant, K_2, is then found by fitting the experimental values of $(\delta_{\mathrm{OH}})^{\mathrm{syn}}$ *versus* $[\mathrm{S}]_\mathrm{o}$ to the Chen–Shirts equation [Equation (1)]. Results are listed in Tables 2 and 3. The very small standard deviations on δ_S and K_2 indicate that the Chen–Shirts equation fits the data very well with this approximation.

If self-association involved only a single hydrogen bond, then the *syn* dimer could be assumed to contain one hydrogen-bonded OH group, with shift δ_{SS}, and one free OH group with the same shift, δ_S, as in the monomer, which gives:

$$[\mathrm{SS}] = K_3[\mathrm{S}]^2 \text{ and } [\mathrm{S}]_\mathrm{o} = [\mathrm{S}] + 2K_3[\mathrm{S}]^2$$

whence: $[\mathrm{S}] = (B^{1/2} - 1)/4K_3$, where: $B = 1 + 8K_3[\mathrm{S}]_\mathrm{o}$. This leads to Equation (4):

$$(\delta_{\mathrm{OH}})^{\mathrm{syn}} = \delta_\mathrm{S} + 0.5(\delta_{\mathrm{SS}} - \delta_\mathrm{S})\frac{(1+8K_3[\mathrm{S}]_\mathrm{o})^{1/2}-1}{(1+8K_3[\mathrm{S}]_\mathrm{o})^{1/2}+1} \quad (4)$$

Solving this equation for δ_S and K_3, using as δ_{SS} and δ_{Spy} values determined for hetero-association, gives for alcohol **2a** the data listed in Supplementary Material Table S4, corresponding to reaction enthalpy and entropy of −11.6 kcal mol^{-1} and −34 cal mol^{-1} K^{-1}, respectively (1 cal = 4.184 J). Both terms are unusually high for the formation of a single O—H···N hydrogen bond. For **2a** a second approach to the determination of the association constant, described below, makes it possible to eliminate the eventuality of an open dimer.

The use of an extended Chen–Shirts equation with terms for both open and cyclic dimers [Equation (5)] leads to particularly ill-defined association constants, one of which becomes negative at the highest temperatures

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Table 2. Hetero- and self-association constants for 2,2,4,4-tetramethyl-3-{2-[3,4-methylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, **1**, in benzene

T/K	$\delta_{Spy}{}^{a}$/ppm	K^{a}/M^{-1}	$\delta_{S}{}^{b}$/ppm	$K_2{}^{b}$/M^{-1}	$\delta_{A}{}^{c}$/ppm	$K_6{}^{c}$/M^{-1}
298	6.548 ± 0.045	1.10 ± 0.03	1.969 ± 0.008	2.57 ± 0.05	3.010 ± 0.002	0.28 ± 0.01
303	6.508 ± 0.013	0.99 ± 0.01	1.963 ± 0.008	2.08 ± 0.03	3.012 ± 0.001	0.26 ± 0.01
308	6.480 ± 0.016	0.88 ± 0.01	1.958 ± 0.007	1.69 ± 0.03	3.016 ± 0.001	0.24 ± 0.01
313	6.468 ± 0.013	0.76 ± 0.01	1.958 ± 0.007	1.38 ± 0.03	3.020 ± 0.001	0.21 ± 0.01
318	6.375 ± 0.013	0.71 ± 0.01	1.958 ± 0.006	1.17 ± 0.02	3.023 ± 0.001	0.21 ± 0.01
323	6.323 ± 0.015	0.64 ± 0.01	1.960 ± 0.005	0.98 ± 0.02	3.025 ± 0.002	0.20 ± 0.02

[a] Hetero-association with pyridine.
[b] Self-association, from concentration dependence of *syn* OH proton shift, taking δ_{Spy} as δ_{SS}.
[c] Self-association, from concentration dependence of *anti* OH proton shift.

Table 3. Hetero- and self-association constants for 2,2,4,4-tetramethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, **2a**, in benzene

T/K	$\delta_{Spy}{}^{a}$/ppm	K^{a}/M^{-1}	$\delta_{S}{}^{b}$/ppm	$K_2{}^{b}$/M^{-1}	$K_1{}^{c}$	$K_2{}^{c}$/M^{-1}
298	6.518 ± 0.009	1.03 ± 0.01	2.008 ± 0.012	3.88 ± 0.11	1.064 ± 0.006	3.55 ± 0.20
303	6.477 ± 0.010	0.93 ± 0.01	2.007 ± 0.010	3.01 ± 0.08	1.061 ± 0.004	2.88 ± 0.14
308	6.445 ± 0.009	0.83 ± 0.01	2.009 ± 0.007	2.37 ± 0.06	1.052 ± 0.007	2.54 ± 0.21
313	6.400 ± 0.010	0.74 ± 0.01	2.013 ± 0.005	1.89 ± 0.04	1.037 ± 0.004	2.43 ± 0.12
318	6.296 ± 0.012	0.68 ± 0.01	2.016 ± 0.003	1.55 ± 0.02	1.043 ± 0.005	1.78 ± 0.15
323	6.296 ± 0.011	0.59 ± 0.01	2.019 ± 0.002	1.24 ± 0.02	1.042 ± 0.003	1.59 ± 0.08

[a] Hetero-association with pyridine.
[b] Self-association, from concentration dependence of *syn* OH proton shift, taking δ_{Spy} as δ_{SS}.
[c] From concentration dependence of the *syn*/*anti* ratio (R).

(Table S4). This is not, therefore, a convincing model.

$$(\delta_{OH})^{syn} = \delta_S + 0.5(\delta_{SS} - \delta_S)\frac{(1 + 8K_4[S]_o)^{1/2} - 1}{(1 + 8K_4[S]_o)^{1/2} + 1} + (\delta_{SS} - \delta_S)\frac{(1 + 8K_5[S]_o)^{1/2} - 1}{(1 + 8K_5[S]_o)^{1/2} + 1} \qquad (5)$$

The *syn*/*anti* ratio. In the case of the EDOT derivative, **2a**, where the *syn*/*anti* ratio is not far from unity and the rotation barrier sufficiently high, R can be measured in benzene with an accuracy of 1–2% by integration of the *tert*-butyl group signals. This is also concentration-dependent, increasing with the concentration (Supplementary Material Tables S2 and S5). We have then:

$$[S] = K_1[A]$$

and, assuming that SS is any sort of dimer:

$$[SS] = (K_1)^2 K_2 [A]^2$$

whence:$[ROH]_o = [A] + K_1[A] + 2(K_1)^2 K_2 [A]^2$. Putting $R = ([ROH]_o - [A])/[A]$ and rearranging give Equation (6):

$$R^2 + R(1 - K_1) = K_1 + 2[ROH]_o (K_1)^2 K_2 \qquad (6)$$

The values of K_1 and K_2 are obtained by solving the quadratic equation for R and using the non-linear least-squares procedure to fit the curve of R *versus* $[ROH]_o$. The similarity of the two sets of K_2 values for **2a** (Table 3) indicates that our estimate, based on the assumption that **2a** forms a cyclic dimer in which the OH shift is approximately the same as in the corresponding association complex with pyridine, is satisfactory. The greatest discrepancies occur at the highest temperatures, where both methods are less reliable, the changes in both R and $(\delta_{OH})^{syn}$ being smaller than at low temperatures. Mean K_2 values for the whole temperature range are 2.46 M^{-1} (based on the *syn*/*anti* ratio) and 2.32 M^{-1} (based on $(\delta_{OH})^{syn}$), whereas for an open dimer it would be 6.92 M^{-1} (Table S4). This second approach involves no prior assumption about the shift of the associated *syn* form, nor about the structure of the dimer. However, it is limited to situations where the signals of the *syn* and *anti* rotamers are well separated, and the *syn*/*anti* ratio can be measured accurately. For **1** only NMR titration could be used.

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Neither the shifts nor the R values for 2,2,4,4-tetramethyl-3-{2-[3,4-ethylenedioxy-5-(2-pyridyl)]-thienyl}pentan-3-ol, **3**, in benzene at 298 K show any great concentration dependence (Supplementary Material Table S6). The very slight variation of the *syn* OH shift corresponds to an association constant of $(1.7 \pm 0.2) \times 10^{-2}\,\mathrm{M}^{-1}$, the assumed δ_{SS} value being that of δ_{Spy} determined by hetero-association with pyridine.

anti-2,2,4,4-Tetramethyl-3-{2-[3,4-methylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 1. The OH proton shift of the *anti* rotamer of the MDOT derivative, **1**, is concentration-dependent in benzene (Table S2), whereas that for the EDOT derivative, **2a** (Table S3), is constant. This suggests that the weakly intramolecularly hydrogen-bonded OH hydrogen[7] in **1** is able to hydrogen-bond with the pyridine nitrogen of a second molecule, but this can only be an open dimer with a single hydrogen bond. In this case both homo- and hetero-dimers are possible where, in the latter, an *anti* 'head' (the OH group) is associated with a *syn* 'tail' (the pyridyl group). To simplify the mathematics it is assumed that the self-association of the *syn* form is unaffected, that is, that the association of the *syn* rotamer with the *anti* rotamer has an insignificant effect upon its concentration. The treatment, detailed in the Supplementary Material, assumes the same association constant, K_6, for the association of *anti* with *anti* or *syn*. Values of δ_{A}, the shift of the free *anti* rotamer, and K_6 are determined by non-linear curve fitting, the chemical shift of the dimer being attributed, for lack of a better estimate, the value of δ_{Spy} used for the *syn* isomer (Table 2). At 298 K K_6 is small ($0.31\,\mathrm{M}^{-1}$), about nine times lower than K_2 ($2.57\,\mathrm{M}^{-1}$). Because of the difference in the temperature dependence this ratio falls to about 5 at 323 K but, since the concentration of the *anti* rotamer is less than a tenth that of *syn*, the concentration of associated species involving the *anti* rotamer will never exceed 2% that of the *syn* dimer. This justifies *a posteriori* the assumption regarding the self-association of the *syn* isomer. The van't Hoff plot gives rough ΔH° and ΔS° values of $-2.7\,\mathrm{kcal\,mol^{-1}}$ and $-11.6\,\mathrm{cal\,mol^{-1}\,K^{-1}}$, respectively, rather smaller than those found for the singly hydrogen-bonded species obtained by hetero-association of encumbered alcohols with pyridine.[16]

Substituent effects on self-association. Steric effects on self-association are generally small.[16] In the context of the present work it was of interest to examine the effect of replacing the bulky *tert*-butyl groups in **2a** by isopropyl, ethyl, or methyl to give alcohols **2b–d** (R = *i*-Pr, Et, or Me). Hexadeuterioacetone was used in preference to unlabeled acetone so as to reduce the extent of hydrogen abstraction in the reaction with 3-pyridyl-EDOT-lithium and, thus, to improve the alcohol yield. The labeled methyl group is slightly smaller than the unlabeled one.[17] These alcohols have low rotation barriers for the —CR_2OH group, and the *syn* and *anti* isomers cannot be distinguished by 200 MHz ^{1}H NMR at 298 K. A simpler form of the Chen–Shirts equation[13] then applies [Equation (7)]:

$$\delta_{\mathrm{OH}} = \delta_{\mathrm{M}} + (\delta_{\mathrm{D}} - \delta_{\mathrm{M}})\frac{(1 + 8K_2[\mathrm{ROH}]_{\mathrm{o}})^{1/2} - 1}{(1 + 8K_2[\mathrm{ROH}]_{\mathrm{o}})^{1/2} + 1} \qquad (7)$$

where δ_{M} and δ_{D} are the shifts of the non-associated and associated forms of the alcohol, respectively. As described above for δ_{Spy} in the case of **1** and **2a**, the chemical shift of the dimer δ_{D} was attributed the value of δ_{Mpy} obtained by NMR titration of the alcohol against pyridine in benzene. Furthermore, in order to compare **2a** with alcohols **2b–d**, the weighted average OH shift was calculated from the shifts of the two rotamers and the *syn*/*anti* ratio, and was used with $[\mathrm{ROH}]_{\mathrm{o}}$ in Equation (7). This leads to association constants which are necessarily smaller than those based on the *syn* isomer alone. Incidentally, this treatment reduces the self-association constant for alcohol **3** in benzene at 298 K to zero (Table 4).

The results (Table 4; full details in Supplementary Material Table S7) show that the lowest hetero-association constant is for the *tert*-butyl derivative, **2a**, but that the isopropyl derivative, **2b**, is the least self-associated, there being a slight increase for the ethyl and deuteriomethyl compounds, **2c** and **2d**. The overall range is, however, very small, being a factor of 2.9 (**2d/2a**) for hetero-association at 298 K and a little higher, 3.8 (**2d/2b**) for self-association. A greater difference might have been expected, since two hydrogen bonds are involved in self-association and only one in hetero-association.

There is a marked increase in the shift of the associated form, δ_{Mpy}, at 298 K for **2c** and **2d**, 6.94 and 7.52 ppm, respectively, whereas **2a** and **2b** are very similar at 6.40 and 6.50 ppm, respectively (Table 4). The shift of the non-associated alcohols, on the other hand, falls in the series **2a–d**. Given that the value of 3.50 ppm for **2a** is the mean of the contributions of the *syn* and *anti* rotamers, this variation implies that intramolecular hydrogen bonding is less important for the alcohols with smaller substituents. Qualitative comparison of the IR spectra in carbon tetrachloride suggests an increase in the importance of the *syn* isomer on going from **2a** to **2c**; the single peak at $3600\,\mathrm{cm}^{-1}$ for **2d** makes it impossible to determine whether this trend continues for the smallest substituent, but overall the NMR data in benzene and the IR data in carbon tetrachloride are compatible.

Reaction enthalpies and entropies. In all cases, for both hetero- and self-association, the free energy difference, ΔG° ($= -RT^*\ln K$), varies linearly with the temperature. For self-association of the EDOT derivative, **2a**, the reaction enthalpy, ΔH°, and the reaction entropy, ΔS°, are $-8.7\,\mathrm{kcal\,mol^{-1}}$ and $-26\,\mathrm{cal\,mol^{-1}\,K^{-1}}$, respectively (Table 5). As expected, the enthalpy term

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Table 4. Hetero- and self-association constants for {2-[3,4-alkylenedioxy-5-(*X*-pyridyl)]thienyl}alkanols, **1**, **2a–d**, and **3** in benzene at 298 K

Cpd.	δ_{Mpy}[a] (ppm)	K[a]/M^{-1}	δ_{M}[b]/ppm	K_2[b]/M^{-1}
1	6.548 ± 0.045	1.10 ± 0.03	2.064 ± 0.007	2.14 ± 0.03
2a	6.402 ± 0.028	0.59 ± 0.01	3.498 ± 0.007	1.10 ± 0.01
2b	6.496 ± 0.021	0.83 ± 0.01	2.453 ± 0.002	0.76 ± 0.01
2c	6.943 ± 0.010	1.27 ± 0.01	2.082 ± 0.002	1.70 ± 0.01
2d	7.518 ± 0.025	1.72 ± 0.01	2.063 ± 0.009	2.90 ± 0.04
3	6.249 ± 0.080	0.46 ± 0.03	3.895 ± 0.002	-0.01 ± 0.01

[a] Hetero-association with pyridine.

[b] Self-association, from concentration dependence of OH proton shift, taking δ_{Mpy} as δ_{D}.

Table 5. Reaction enhalpies and entropies for hetero- and self-association of {2-[3,4-alkylenedioxy-5-(3-pyridyl)]thienyl}alkanols, **1** and **2a–d**

	Hetero-association		Self-association	
Cpd.	$-\Delta H^\circ$/kcal mol^{-1}	$-\Delta S^\circ$/cal mol^{-1} K^{-1}	$-\Delta H^\circ$/kcal mol^{-1}	$-\Delta S^\circ$/cal mol^{-1} K^{-1}
1[a]	4.18 ± 0.14	13.8 ± 0.5	7.37 ± 0.10	22.9 ± 0.3
1[b]	4.18 ± 0.14	13.8 ± 0.5	7.35 ± 0.10	23.2 ± 0.3
1[c]	—	—	2.69 ± 0.33	11.6 ± 1.1
2a[a]	4.22 ± 0.15	14.1 ± 0.5	8.66 ± 0.09	26.4 ± 0.3
2a[b]	5.02 ± 0.21	17.9 ± 0.7	10.42 ± 0.42	34.8 ± 1.3
2b[b]	4.21 ± 0.09	14.5 ± 0.3	5.30 ± 0.05	18.3 ± 0.2
2c[b]	4.30 ± 0.15	13.9 ± 0.5	6.11 ± 0.11	19.5 ± 0.3
2d[b]	4.61 ± 0.07	14.4 ± 0.2	7.05 ± 0.11	21.6 ± 0.4

[a] In terms of $[\mathrm{S}]_{\mathrm{o}}$.

[b] In terms of $[\mathrm{ROH}]_{\mathrm{o}}$.

[c] Association of *anti* isomer.

is favorable, corresponding to the formation of two hydrogen bonds, but this is to a large extent compensated by the entropy term which reflects the difficulty of bringing together two molecules into a single unit. For comparison, corresponding ΔH° and ΔS° values for the hetero-association of **2a** with pyridine are very close to half of those for self-association (see also Ref. 16). For both the hetero- [Equation (3)] and self-association [Equation (6)] of **2a**, replacing the treatment of the *syn* OH proton shift in terms of $[\mathrm{S}]_{\mathrm{o}}$ by that of the average OH proton shift in terms of $[\mathrm{ROH}]_{\mathrm{o}}$ results in greater ΔH° and ΔS° values which, nevertheless, still follow the same ratio. Given that hetero- and self-association involve one and two hydrogen bond(s), respectively, this appears to show that enthalpy and even entropy terms are additive: two A···D pairs contribute twice as much as one, and cooperativity is negligible since the pairs are effectively isolated by the intervening structure. However, further inspection of the data suggests that this result may be fortuitous.

Values of ΔH° and ΔS° for the MDOT derivative, **1**, are somewhat less than double the values for hetero-association. For the hetero-association of **2b–d** with pyridine the reaction enthalpy varies from −4.2 to −4.6 kcal mol^{-1}, apparently increasing as the steric demand of the substituent falls (Table 5). All these values are surprisingly slightly smaller than for **2a** when calculated on the basis of $[\mathrm{ROH}]_{\mathrm{o}}$ rather than $[\mathrm{S}]_{\mathrm{o}}$. However, the '$[\mathrm{ROH}]_{\mathrm{o}}$' data for **2a** are considerably less reliable than the '$[\mathrm{S}]_{\mathrm{o}}$' set, and the exceptionally high ΔS° value may be an artefact. Reaction enthalpies and entropies for the less encumbered alcohols, **2b–d**, are much smaller than for **1** and **2a**, increasing in absolute magnitude as substituent size decreases, and bearing no simple relationship to the hetero-association values. This suggests that entropic factors, related to conformational changes involved in self-association or solvation phenomena, are very different in this set, and that they are correlated with changes in the reaction enthalpy. For **1** and **2a–d**, ΔH° is a linear function of ΔS° with an isokinetic temperature of 292 ± 26 K. Early IR spectroscopic work by Findlay and Kidman[18] on the hetero-association of the two propanols and two butanols with pyridine in carbon tetrachloride shows comparable variations in reaction enthalpy (−4.1 to −6.1 kcal mol^{-1}) 1) and reaction entropy (−11.9 to −18.9 cal mol^{-1} K^{-1}) and a similar $\Delta H^\circ - \Delta S^\circ$ correlation. The ΔH° values and the ΔH°–ΔS° correlations showed the same scatter in the IR and NMR spectroscopic data of simple alcohols cited by Kluk *et al.* [19] It is, therefore, not clear whether such compensation is significant at the molecular level or is the result of statistical artefacts and/or experimental error.[20]

Quantum mechanical DFT/ONIOM calculations

Quantum mechanical calculations on large molecules can be facilitated by treating different parts of the molecule at different levels. In the present case, the entire molecule was treated by DFT but a more extensive basic set was used for the interacting COH and pyridine systems than for the rest of the molecule (ONIOM).[21] Preliminary tests were successfully run on monomer species of {2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}methanol, 3-py-EDOT-CH_2OH, **2e**, to check that this approximation has no serious effects on the relative energies of the *anti* and *syn* rotamers. Full *ab initio* calculations at the B3LYP/6-311+G(d) level on **2e** for the four conformers, taking into account the orientations of both the pyridyl ring and the CH_2OH group, give values ranging over 0.3 kcal mol^{-1}. The ONIOM values for **2e** at the B3LYP/6-311+G(d):B3LYP/3-21G level differ from the *ab initio* values by no more than 0.2 kcal mol^{-1} (Supplementary Material Table S8). For **2a**, conformations with the pyridyl ring in the *anti* orientation are favored by about 1 kcal mol^{-1}, whereas the opposite is true for **2d** (for simplicity calculations were run with $R = CH_3$). For **2a** the *anti-syn* and *anti-anti* conformations differ by less than 0.2 kcal mol^{-1}, which is in good agreement with the equilibrium constant of close to unity (K_1 in Table 2) found in a non-hydrogen-bonding solvent, such as benzene or chloroform.

The dimers of **2a** and **2d** give, after correction for the basis set superposition error,[22] interaction energies of −9.4 and −10.6 kcal mol^{-1}, respectively (Supplementary Material Table S9). The former is of the same order of magnitude as the experimental reaction enthalpy, −10.4 kcal mol^{-1}. That the value for the dimethyl compound, **2d**, should be greater is intuitively appealing, but unfortunately conflicts with the experimental data, which appear to indicate that the small enhancement of association in **2d** as compared to **2a** is due to a much more favorable entropy factor. A possible explanation is that the less encumbered monomer is more solvated, even in benzene, and that dimer formation is accompanied by release of solvent molecules, resulting in smaller reaction enhalpy and entropy terms. Nevertheless, it is not clear how **2b** and **2c** fit into this scheme, since the substituents are bigger than in **2d** but the reaction enhalpy and entropy terms even smaller.

The geometry of the dimer of *syn* **2a**, as determined by ONIOM calculations (Supplementary Material Figure S3), despite the difference in phase, is not very different from that determined by X-ray crystallography. The distance between the oxygen and nitrogen atoms is 2.82 Å, as against the measured 2.86 Å, and the pyridine ring is at 10° to the thiophene ring, as against 20° in the crystal. A more general comparison of selected internal coordinates from the gas-phase calculations and the solid-state X-ray data is given in the Supplementary Material Table S1. Overall the root mean square deviations in bond lengths, bond angles, and torsion angles for this selection are 0.038 Å, 1.4°, and 12°, respectively. The bond length deviation is to a large extent due to overestimation of the C—S and C—O distances in the calculations, no doubt due to the use of a small basis set for the relevant parts of the molecule. Corresponding rms values from a molecular mechanics calculation (MMFF94 in Sybyl 7.0 from Tripos, St. Louis, MO, USA)[23] are 0.016 Å, 1.8°, and 10°, respectively, but the N···O distance is seriously overestimated at 3.12 Å (details not given). Interaction energies are similar to those found by the ONIOM approach: 10.5 and 11.4 kcal mol^{-1} for **2a** and **2d**, respectively.

CONCLUSION

In the solid state 2,2,4,4-tetramethyl-3-{2-[3,4-alkylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ols, **1** and **2a**, occur as the *syn* rotamer and are predominantly or completely associated, as demonstrated by IR spectroscopy and a single-crystal X-ray diffraction study of **2a**. In solution *anti* and *syn* rotamers are in equilibrium, and in benzene the *syn* rotamers self-associate with relatively small equilibrium constants for the formation of cyclic dimers. The concentration dependence of the *syn/anti* ratio in the case of the EDOT derivative confirms this model. For these alcohols the rotation barrier about the C—C(*t*-Bu)$_2$OH bond is so low that the *syn→anti* conversion accompanying dissolution is imperceptible. We shall report in a subsequent paper on slightly more sterically hindered analogs, where the rate of this conversion can be measured directly.

In one isolated case, **2a**, the reaction enthalpy and entropy for self-association (involving two hydrogen bonds) are close to twice the values for hetero-association (involving only one hydrogen bond) of the same alcohol with pyridine, but such a simple relationship does not exist for the other alcohols, possibly due to solvation effects. In a series comprising *tert*-butyl, isopropyl, ethyl, and deuteriomethyl substituents, **2a–2d**, self-association constants vary slightly more than hetero-association constants, but the total range is very small in both cases. There is nothing which can be attributed to a cooperative effect.

EXPERIMENTAL

Routine ^1H and ^{13}C NMR spectra of all new compounds were determined in chloroform-*d* at 298 K on a Bruker AC 200 spectrometer with a spectral resolution of 0.001 ppm/point. Chemical shifts (in ppm) are referenced to TMS at 0.000 ppm (^1H) or to solvent peak at 77.0 ppm (^{13}C). Wherever the NMR data are not fully assigned, this is because signals overlap. The pyridine ^1H NMR signals were assigned and coupling constants (*J* in Hz, not

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signed) determined by spectrum simulation using gNMR (version 4.1, Adept Scientific, Letchworth, UK). Most ^{1}H NMR shifts in alcohols, particularly those of the OH protons, are concentration-dependent. The corresponding ^{13}C signals were assigned by XHCORR experiments; C_q's were identified by comparison with spectra of 3,4-alkylenedioxythiophenes,[7] pyridylthiophenes,[24] and 2,2,4,4-tetramethyl-3-(3,4-alkylenedioxythienyl)pentan-3-ols,[7] it being assumed that substituent effects are additive. IR transmission spectra were recorded on a Nicolet Magna 860 FTIR spectrometer with 4 cm^{-1} resolution (Table 1). Drops of saturated solutions of alcohols **1**, **2a**, and **3** in dichloromethane were allowed to evaporate on KBr plates and the spectra recorded at 298 K. Solutions of **1** and **2a–d** in carbon tetrachloride were examined in 1 mm glass cells. Details on how the 2D NOESY NMR spectra were recorded and the association constants measured are given in the Supplementary Material.

Synthesis of pyridylthiophenes, 4–6

2-(Tri-*n*-butylstannyl)thiophenes were prepared by reaction of tri-*n*-butyltin chloride with the organolithium reagent prepared by reaction of the parent thiophene with *n*-butyl-lithium/TMEDA in diethyl ether under argon at room temperature, followed by aqueous work-up. Treatment of the appropriate 2-(tri-*n*-butylstannyl) thiophene with 2- or 3-bromopyridine in DMF at 115–125°C under argon for 2–5 h in the presence of bis(triphenylphosphine)palladium(II) chloride gave 2- or 3-pyridylthiophene.[11] The crude product was first extracted into 1 N aqueous HCl, the aqueous layer rinsed with diethyl ether to remove neutrals, and the bases regenerated by treatment with 1 N NaOH, followed by diethyl ether extraction. The residue after solvent evaporation was purified by chromatography on alumina in light petroleum-diethyl ether mixtures.

2-(3-Pyridyl)-3,4-methylenedioxythiophene, 4. Yield 45%; mp 119 °C (Found: C, 58.5; H, 3.4. $C_{10}H_7NO_2S$ requires C, 58.52; H, 3.44%). δ_C 91.5 (C5-th), 106.8 (C2-th), 109.4 (CH_2), 123.6 (C5-py), 128.3 (C3-py), 132.1 (C4-py), 145.5 (C3-th), 146.0 (C2-py), 147.3 (C6-py), and 148.3 (C4-th); δ_H 6.07 (s, H5-th), 6.32 (s, CH_2), 7.27 (H5-py, *J* 0.9, 4.8, 8.0), 7.80 (H4-py, *J* 1.6, 2.4, 8.0), 8.45 (H6-py, *J* 0.3, 4.8), and 8.82 (H2-py, *J* 0.3, 0.9, 2.4).

2-(3-Pyridyl)-3,4-ethylenedioxythiophene, 5. Yield 61%; mp 63 °C (Found: C, 60.3; H, 4.2. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14%). δ_C 64.0 (CH_2), 64.4 (CH_2), 98.5 (C5-th), 113.1 (C2-th), 123.0 (C5-py), 129.1 (C3-py), 132.3 (C4-py), 138.9 (C3-th), 141.9 (C4-th), 146.4 (C2-py), and 146.8 (C6-py); δ_H 4.25 (CH_2, *J* 2.2, 6.2, 13.2), 4.32 (CH_2, *J* 2.2, 6.2, 13.2), 6.36 (s, H5-th), 7.26 (H5-py, *J* 0.9, 4.8, 8.1), 7.97 (H4-py, *J* 1.6, 2.4, 8.1), 8.43 (H6-py, *J* 0.3, 1.6, 4.8), and 8.94 (H2-py, *J* 0.3, 0.9, 2.4).

2-(2-Pyridyl)-3,4-ethylenedioxythiophene, 6. Yield 25%; mp 79 °C (Found: C, 60.0; H, 4.1. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14%). δ_C 64.3 (CH_2), 64.9 (CH_2), 101.2 (C5-th), 118.6 (C2-th), 120.2 (C3-py), 120.9 (C5-py), 136.3 (C4-py), 139.9 (C3-th), 142.0 (C4-th), 149.1 (C6-py), and 151.5 (C2-py); δ_H 4.24 (CH_2, *J* 2.2, 6.1, 11.6), 4.35 (CH_2, *J* 2.2, 6.1, 11.6), 6.42 (s, H5-th), 7.05 (H5-py, *J* 1.1, 4.9, 7.5), 7.64 (H4-py, *J* 1.9, 7.5, 8.1), 7.92 (H3-py, *J* 1.0, 1.1, 8.1), and 8.51 (H6-py, *J* 1.0, 1.9, 4.9).

Synthesis of 2,2,4,4-tetramethyl-3-{2-[5-(*X*-pyridyl)]thienyl}pentan-3-ols

To a mixture of the appropriate 2- or 3-pyridylthiophene (*x* mmol, *x* generally 2–5) and TMEDA (*x* mmol) in diethyl ether (10–15 ml) under argon at room temperature was added a solution of *n*-butyl-lithium in hexane (1.6 M, *x* mmol). After 30 min stirring, 2,2,4,4-tetramethylpentan-3-one (*x* mmol) was added. The mixture was stirred for a further 30 min, then quenched with water, and the organic materials extracted with diethyl ether. Washing with water, drying and evaporation of solvent gave a residue from which the alcohol was isolated by chromatography on alumina or by trituration in light petroleum-diethyl ether mixtures. Less encumbered alcohols, **2b–d**, were synthesized by the same procedure except that *n*-BuLi and ketone were added successively at −75 °C, after which the reaction mixture was allowed to warm slowly to room temperature before work-up.

2,2,4,4-Tetramethyl-3-{2-[3,4-methylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 1. Yield 25%; mp 178 °C (dec.). (Found: C, 65.9; H, 7.3; N, 3.9. $C_{19}H_{25}NO_3S$ requires C, 65.68; H, 7.25; N, 4.03%). *syn:* δ_C 28.9 (CH_3), 42.7 (C_q), 85.0 (COH), 104.5 (C5-th), 107.3 (CH_2), 121.3 (C2-th), 123.4 (C5-py), 128.5 (C3-py), 131.7 (C4-py), 140.3 (C3-th), 144.2 (C4-th), 146.1 (C2-py), and 146.8 (C6-py); δ_H 1.17 (s, 6 CH_3), 2.71 (s, OH), 6.20 (s, CH_2), 7.23 (H5, *J* 0.8, 4.9, 8.0), 7.79 (H4, *J* 1.7, 2.4, 8.0), 8.38 (H6, *J* 0.7, 1.7, 4.9), and 8.82 (H2, *J* 0.7, 0.8, 2.4).

2,2,4,4-Tetramethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 2a. Yield 42%; mp 176 °C (dec.). (Found: C, 66.4; H, 7.6; N, 3.9. $C_{20}H_{27}NO_3S$ requires C, 66.45; H, 7.53; N, 3.87). *anti:* δ_C 29.1 (CH_3), 42.9 (C_q), 63.6 (CH_2), 64.6 (CH_2), 87.0 (COH), 110.0 or 110.2 (C5-th), 121.5 (C2-th), 123.3 (C5-py), 129.0 or 129.7 (C3-py), 132.5 (C4-py), 137.3 (C4-th), 139.0 (C3-th), 146.9 (C2-py), and 147.1 (C6-py);

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δ_H 1.18 (s, 6 CH_3), 4.30 (m, 2 CH_2), 4.76 (s, OH), 7.25 (H5, *J* 0.9, 4.8, 8.1), 7.95 (H4, *J* 1.6, 2.4, 8.1), 8.41 (H6, *J* 0.2, 1.6, 4.8), and 8.95 (H2, *J* 0.2, 0.9, 2.4). *syn:* δ_C 29.1 (CH_3), 42.6 (C_q), 64.2 (CH_2), 64.3 (CH_2), 86.0 (COH), 110.0 or 110.2 (C5-th), 123.2 (C5-py), 128.2 (C2-th), 129.0 or 129.7 (C3-py), 132.4 (C4-py), 135.1 (C4-th), 138.7 (C3-th), 146.6 (C6-py), and 146.9 (C2-py); δ_H 1.17 (s, 6 CH_3), 2.50 (s, OH), 4.23 (m, 2 CH_2), 7.22 (H5, *J* 0.9, 4.8, 8.1), 7.97 (H4, *J* 1.6, 2.4, 8.1), 8.37 (H6, *J* 0.2, 1.6, 4.8), and 8.97 (H2, *J* 0.2, 0.9, 2.4).

2,4-Dimethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 2b. Yield 41%; mp 170 °C. (Found: C, 65.1; H, 7.0; N, 4.1. $C_{18}H_{23}NO_3S$ requires C, 64.84; H, 6.95; N, 4.20%). δ_C 16.6 (CH_3), 17.8 (CH_3), 34.5 (CH), 64.2 (CH_2), 64.5 (CH_2), 82.3 (COH), 110.6 (C5-th), 121.8 (C2-th), 123.3 (C5-py), 129.5 (C3-py), 132.4 (C4-py), 136.8 (C3-th), 138.6 (C4-th), and 146.8 (C2-py and C6-py); δ_H 0.92 (2 CH_3, *J* 6.8), 0.96 (2 CH_3, *J* 6.8), 2.36 (2 CH, *J* 6.8), 2.75 (br s, OH), 4.21 (CH_2, *J* 2.2, 6.1, 11.3), 4.30 (CH_2, *J* 2.2, 6.1, 11.3), 7.23 (H5, *J* 0.9, 4.8, 8.0), 7.95 (H4, *J* 1.6, 2.4, 8.0), 8.38 (H6, *J* 1.6, 4.8), and 8.94 (H2, *J* 0.9, 2.4).

3-{2-[3,4-Ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 2c. Yield 9%; mp 141 °C. (Found: C, 63.0; H, 6.5; N, 4.6. $C_{16}H_{19}NO_3S$ requires C, 62.93; H, 6.27; N, 4.59%). δ_C 8.0 (CH_3), 33.6 (CH_2), 64.3 (CH_2), 64.6 (CH_2), 77.2 (COH), 110.1 (C5-th), 123.3 (C5-py), 123.7 (C2-th), 129.6 (C3-py), 132.4 (C4-py), 136.1 (C3-th), 139.0 (C4-th), and 146.7 (C2-py and C6-py); δ_H 0.92 (2 CH_3, *J* 7.4), 1.83 (2 CH, *J* 7.4, 13.9), 1.97 (2 CH, *J* 7.4, 13.9), 2.87 (br s, OH), 4.23 (CH_2, *J* 2.2, 6.1, 10.9), 4.30 (CH_2, *J* 2.2, 6.1, 10.9), 7.23 (H5, *J* 0.9, 4.8, 8.0), 7.95 (H4, *J* 1.6, 2.4, 8.0), 8.38 (H6, *J* 1.6, 4.8), and 8.93 (H2, *J* 0.9, 2.4).

2-{2-[3,4-Ethylenedioxy-5-(3-pyridyl)]thienyl}propan-2-ol-d_6, 2d. Yield 20%; mp 148 °C. (Found: C, 59.2; N, 4.9; S, 11.5. $C_{14}H_9D_6NO_3S$ requires C, 59.34; N, 4.94; S, 11.31%). δ_C 64.4 (CH_2), 64.6 (CH_2), 70.9 (COH), 109.6 (C5-th), 123.3 (C5-py), 125.5 (C2-th), 129.5 (C3-py), 132.6 (C4-py), 136.4 (C3-th), 139.2 (C4-th), and 146.9 (C2-py and C6-py); δ_H 2.80 (br s OH), 4.28 (CH_2, *J* 2.2, 6.1, 11.5), 4.31 (CH_2, *J* 2.2, 6.1, 11.5), 7.24 (H5, *J* 0.9, 4.8, 8.1), 7.94 (H4, *J* 1.6, 2.4, 8.1), 8.40 (H6, *J* 1.6, 4.8), and 8.921 (H2, *J* 0.9, 2.4).

2,2,4,4-Tetramethyl-3-{2-[3,4-ethylenedioxy-5-(2-pyridyl)]thienyl}pentan-3-ol, 3. Yield 42%; mp 138 °C (dec.). (Found: C, 66.3; H, 7.6; N, 3.8. $C_{20}H_{27}NO_3S$ requires C, 66.45; H, 7.53; N, 3.87%). *anti:* δ_C 29.2 (CH_3), 42.9 (C_q), 64.4 (CH_2), 64.5 (CH_2), 87.2 (COH), 120.6 (C3-py), 120.8 (C5-py), 136.3 (C4-py), and 149.2 (C6-py); *syn:* δ_C 29.1 (CH_3), 42.5 (C_q), 63.6 (CH_2), 64.4 (CH_2), 86.0 (COH), 120.4 (C3-py), 120.4 (C5-py), 136.2 (C4-py), and 149.2 (C6-py). C_q's at 114.9, 115.2, 124.1, 130.8, 134.9, 138.1, 138.8, 139.4, 151.4, and 152.0 not assigned; *anti* and *syn:* δ_H 1.17 (*syn*), 1.19 (*anti*) (s, 6 CH_3), 2.25 (s, 0.4H, *syn*-OH), 4.2–4.4 (m, CH_2), 4.79 (s, 0.6H, *anti*-OH), 7.01–7.08 (m, H5), 7.60–7.68 (m, H4), 7.87–7.94 (m, H3), and 8.49–8.53 (m, H6).

X-Ray crystallography: *syn*-2,2,4,4-Tetramethyl-3-{2-[3,4-ethylenedioxy-5-(3-pyridyl)]thienyl}pentan-3-ol, 2a, $C_{20}H_{27}NO_3S$

Crystal data. $M = 361.51$. Triclinic $a = 8.074(1)$ Å, $b = 8.694(1)$ Å, $c = 13.748(2)$ Å. $\alpha = 80.73(1)$, $\beta = 87.50(1)$, $\gamma = 79.34(1)$, $V = 935.9(2)$ Å^3 (refined from 75 reflections, $4 < \theta < 24°$), space group *P*-1, $Z = 2$, $D_x = 1.28\ \mathrm{g\,cm^{-3}}$. Colorless prismatic crystals, $\mu(\mathrm{Mo\,K}\alpha) = 0.191\ \mathrm{mm^{-1}}$.

Data collection and processing. At 295 K, Enraf-Nonius Kappa CCD diffractometer, ω mode, graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). 7706 reflections measured ($2.4 \leq \theta \leq 27.5°$), 4089 unique, giving 2614 with $I > 3\sigma(I)$.

Structure analysis and refinement. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic; hydrogen H11 located from Fourier difference map and not refined; all other hydrogens placed in geometrically calculated positions; only one overall isotropic thermal parameter refined (227 refinable parameters). Absorption corrections were determined using DIFABS.[25] Final *R* and R_w (Chebyshev series) values are 0.056 and 0.64. Programs used were the PC version of CRYSTALS[26] for refinements and CAMERON[27] for views. Selected bond lengths, bond angles, and torsion angles are listed in Supplementary Material Table S1.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 289515). Any request to the CCDC for this material should quote the full literature citation and the reference number.

Quantum mechanical DFT/ONIOM calculations

Details of this approach along with data (Tables S1, S8, and S9), structure diagrams for the dimers of **2a** and **2e** (Figure S3), and full references are given in the Supplementary Material.

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