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Diols as hydrogen bond acids: ^{1}H NMR study of the hetero-association of pyridine with sterically hindered EDOT diols

John S. Lomas[a]* and Christine Cordier[a]

The hetero-association of pyridine with the *cis* and *trans* methyl-3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophenes (Me-EDOT alcohols), 3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene (EDOT diol) and methyl-3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene (Me-EDOT diol) has been studied by ^{1}H nuclear magnetic resonance (NMR) spectroscopy in benzene at 298 K. Self-consistent association constants for the *syn* (S), *anti-syn* (AS) and *syn-syn* (SS) rotamers are determined from the variation of the OH proton chemical shift and of the rotamer composition with the pyridine concentration. The bridge methyl group has no effect upon the association constant of a *syn* OH group. Association constants are the same for the *syn* OH groups in the AS and *syn-anti* (SA) rotamers of the diols, being slightly higher than for the alcohols. In contrast, values for a single *syn* OH group in the SS rotamers of the diols are significantly lower. Hydrogen bond acidity *A* values, determined for some congested alcohols and diols by the NMR method of Abraham, confirm that the *syn* OH protons of SS rotamers are less acidic than the single *syn* OH proton of an AS or SA rotamer. *A* values, with the notable exceptions of those for propan-1,3-diol and butan-1,4-diol, correlate with pyridine hetero-association constants. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: EDOT; NMR; hydrogen bonding; pyridine; benzene; *A* values

INTRODUCTION

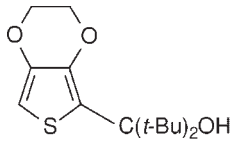
Cooperativity, the enhancement of a first hydrogen bond between a proton-donor group, X—H, and a proton-acceptor B, when a third partner, Y—H, forms another H-bond with the atom X, requires that X should also be an acceptor,[1–6] which explains why it is frequently invoked, together with its antithesis, anti-cooperativity, in the context of water and alcohols.[1–11] Carbohydrates constitute another noteworthy class of compounds where OH groups are abundant and determine molecular recognition, crystallization, self-assembly and other structural features. Intramolecular hydrogen bonding (IHB), when X—H and Y—H are parts of the same molecule, and cooperative effects in sugars and model compounds, often diols, have been much studied by both experimental and theoretical means.[12–25] The theoretical criteria for IHB are not satisfied in vicinal diols, including ethan-1,2-diol,[12,13,26–32] (in contrast to 2-aminoethanol)[33–35] and it has been suggested that the formation of such bonds in some cases is an opportunistic consequence of close proximity rather than a major conformational driving force.[20] Cooperativity in even the simplest polyol systems is still not well understood. The hydrogen bond capabilities of diols (and glycerol), as expressed by Abraham's scale of effective or overall solute hydrogen bond acidities, $\Sigma\alpha_2^H$ or A,[36–39] are slightly lower than expected on the basis of additivity, *i.e.* anti-cooperative. This was attributed to IHB, apparently confirmed by infrared spectroscopic red-shifts for several alkan-1,ω-diols, notably butan-1,4-diol.[40] However, red-shifts are not necessarily diagnostic of hydrogen bonding,[28] and the vaporization enthalpies of such diols show that it is thermodynamically unimportant, both in the liquid and gas phases.[41] The enthalpies of atomization of alkan-1,n-diols (n = 2 to 5) do not reveal IHB.[23] Paradoxically, the enhancement of the 1:1 association constant of butan-1,4- and propan-1,3-diols with pyridine was taken as evidence for cooperativity. Donors were found to be independent when sufficiently far apart, as in cyclohexan-1,4-, pentan-1,5- and hexan-1,6-diols but also, surprisingly, when on neighbouring carbons in 1,2-diols.[42]

In order to further examine the interdependence of hydrogen bond donor groups, we have now investigated diols where the two donors are separated by five atoms, where self- and intramolecular associations are ruled out by steric hindrance but where, nevertheless, there is *prima facie* evidence for non-additivity of hydrogen bond acidity.[43,44] The monohydric alcohol, 3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, **1**, and related compounds exist in *syn* and *anti* forms,[45,46] while the diol, 3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, **2**, and its analogues with other substituents at the 3 and 4 positions, exist as mixtures of

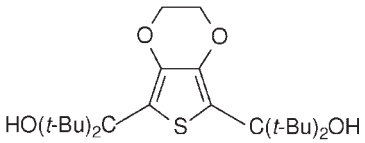
* *Correspondence to: J. S. Lomas, ITODYS, Université de Paris-Diderot, Bâtiment Lavoisier, 15 rue Jean de Baïf, 75205 Paris Cedex 13, France.*
E-mail: lomas@itodys.univ-paris-diderot.fr

a *J. S. Lomas, C. Cordier*
ITODYS (Interfaces, Traitements, Organisation et, Dynamique des Systèmes), Université Paris Diderot (Paris 7), CNRS UMR 7086, Bâtiment Lavoisier, 15 rue Jean de Baïf, 75205 Paris Cedex 13, France

three rotamers, where the two OH groups are oriented either both *anti* to the sulfur atom (**AA**), both *syn* to this atom (**SS**) or one *anti* and one *syn* (**AS** and **SA**). For diol **3** there are formally four rotamers, since **AS** and **SA** are distinct (as shown below, R = Me). When the distinction between the two is unimportant, **AS** will be used to designate both rotamers. The OH groups in the *anti* orientation are hydrogen-bonded to the oxygen atoms of the bridging group.[43,44]



1



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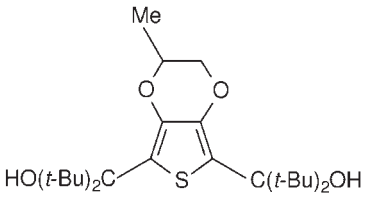
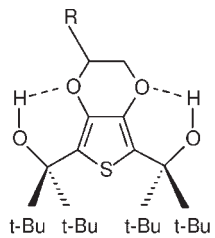


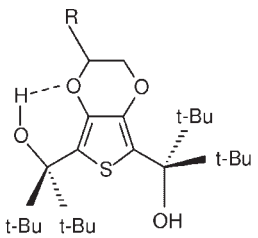
3

The rotamer distribution depends on the temperature and, more importantly, on the solvent, hydrogen bond base solvents favouring the *syn* orientation of the OH groups. There are two association constants to consider:

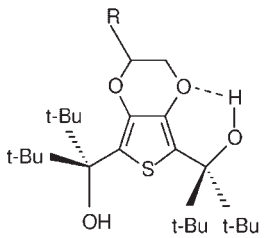
AA ⇌ **AS** $K_1 = [AS]/[AA]$
and **AS** ⇌ **SS** $K_2 = [SS]/[AS]$



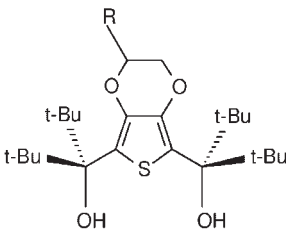
AA



AS



SA



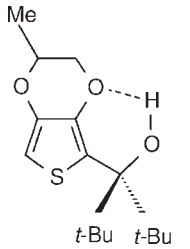
SS

The latter, K_2, is less sensitive to change in solvent basicity than K_1, and it was suggested that in **SS** the two OH groups lie too close together, despite the intervening atoms, to be efficiently solvated by an acceptor solvent.[44] In order to put this observation on a more quantitative footing, we have now measured the hetero-association constants of the **AS** and **SS** forms of **2** and **3** with pyridine. Compound **3** is particularly interesting in that the methyl group marker leads to distinct ^{1}H NMR signals for the two donor group OH protons (as well as for those of the *anti* OH groups in the **AA** rotamer)[43] but has no effect upon their association with pyridine. This was first established by determining the association constants of the isomeric Me-EDOT derivatives, ***4-cis*** and ***4-trans***, for comparison with those of the EDOT alcohol, **1**.

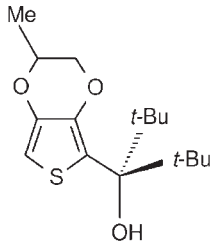
RESULTS

Methyl-3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophenes, 4

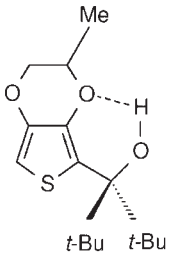
The product, **4**, obtained from Me-EDOT by lithiation followed by addition of a single —C(*t*-Bu)$_2$OH function, consists of a 1:5 mixture of the *cis* and *trans* isomers [referring to the proximity or remoteness, respectively, of the Me and —C(*t*-Bu)$_2$OH groups] in their *anti* and *syn* forms, making a total of four NMR-distinct isomers.



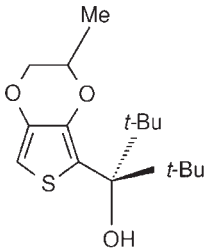
4-*trans*, *anti*



4-*trans*, *syn*



4-*cis*, *anti*



4-*cis*, *syn*

The isomers were identified and the signals attributed by comparison with compounds **1**, **2** and **3**. The assignments were confirmed by a ^{1}H NOESY NMR experiment (Fig. 1), which shows a dipolar contact only between the most upfield methyl doublet and the more downfield *anti* OH proton signal; this associates the smaller signals unambiguously with the *cis* isomer. As is usual for EDOT derivatives,[45,46] the *syn*/*anti* rotamer ratio is close to unity (0.81 and 0.86, respectively) for both the *cis* and *trans* isomers.

The ^{1}H NMR spectrum of a dilute solution of ***4-cis*** and ***4-trans*** in deuteriated solvent mixtures ranging from pure benzene to

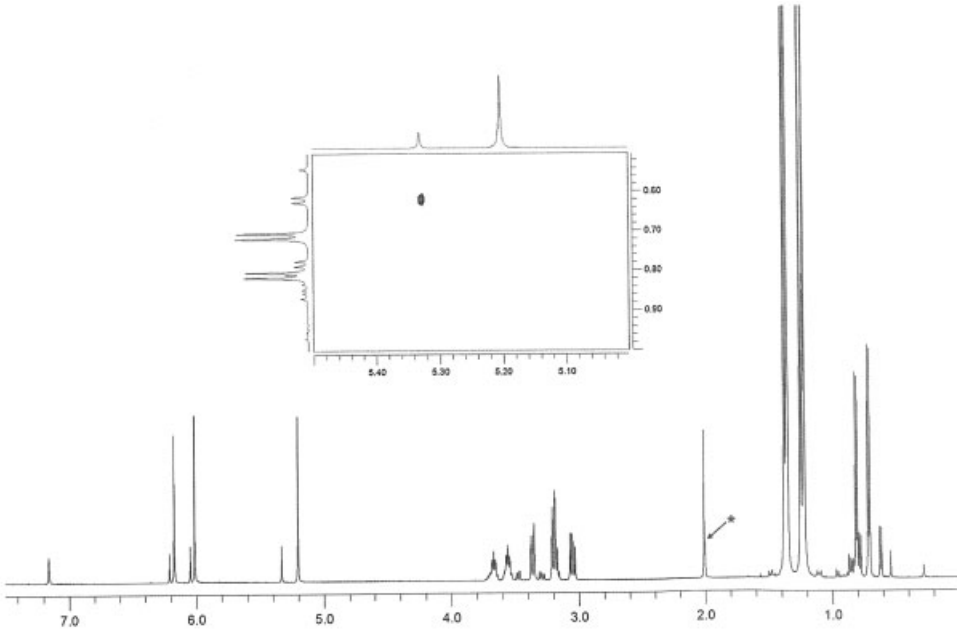


Figure 1. ^{1}H NMR spectrum of alcohols **4** in benzene at 299 K. Inset: NOESY experiment showing dipolar correlation between the OH proton and the methyl group in the *cis, anti* isomer. The *cis, syn* OH signal at 2.00 ppm is starred*

37% pyridine (4.6 M) in benzene was recorded at 298 K. The chemical shifts of the *anti* OH protons, which are intramolecularly hydrogen-bonded to the oxygens of the bridge, vary by no more than 0.025 ppm over the whole pyridine concentration range, whereas the *syn* OH proton shifts go from about 2 ppm to over 5.4 ppm. Association constants are derived from this system in two ways, from the variation of the chemical shifts of the OH protons and from that of the rotamer ratios determined by integration of suitable peaks. The difference between the chemical shifts of the two *syn* OH protons, 0.01 ppm, was constant throughout the entire run, indicating that the association constants are identical. To determine this value, therefore, the isomer mixture was treated as though it were a single compound and the mean *syn* OH proton shift used in calculations.

Shift variation

For a *syn* rotamer, the association constant, K_3, is given by Eqn (1)[47,48]

$$\delta_{OH} = \delta_S + \frac{(\delta_{Spy} - \delta_S)}{2[S]_o}\left\{B - \left(B^2 - 4[S]_o[py]_o\right)^{1/2}\right\} \qquad (1)$$

where δ_{OH} is the chemical shift of the *syn* OH proton, with $B = [S]_o + [py]_o + 1/K_3$, $[S]_o$ the analytical *syn* alcohol concentration, $[py]_o$ that of pyridine and δ_S and δ_{Spy} the chemical shifts of the *syn* OH proton in free *syn* and in pyridine-complexed *syn*, respectively. $[S]_o$ is determined from the *syn*/*anti* ratio, *R*, and the analytical concentration of the alcohol, $[ROH]_o$.

Values of K_3 [0.778 ± 0.004 (molar scale, standard state 1 M)], δ_S (1.974 ± 0.003 ppm) and δ_{Spy} (6.375 ± 0.007 ppm) are determined by fitting the experimental values for δ_{OH} to $[py]_o$ and $[S]_o$ 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). These results are not tabulated. Full data on shifts, and rotamer and isomer distributions are given in Supplementary Material Table S1.

Variation of rotamer distribution

We showed previously that association constants can be determined from the *syn*/*anti* ratio by Eqn (2)[49]

$$R = K_4 + \{(B^2 + 4K_3K_4(1 + K_4)[py]_o)^{1/2} - B\}/2 \qquad (2)$$

where $B = 1 + K_4 + K_3K_4([ROH]_o - [py]_o)$. K_4 is the value of *R* when $[py]_o = 0$, *i.e.* the equilibrium, constant for the *syn* ⇌ *anti* equilibrium and K_3 is again calculated by the non-linear least-squares procedure. Applied to the total *syn*/*anti* ratio, this approach gives an association constant ($K_3 = 0.778 \pm 0.009$) in complete agreement with that determined by the first method, where the K_4 value (0.858 ± 0.007) is essentially that of the predominant *trans* isomer (results not tabulated).

For comparison, the association constant for the EDOT alcohol, **1**, was re-determined under exactly the same conditions, and was found to be slightly lower (by 8 or 2%, depending on the method) than previously reported.[49] Values obtained by the two methods are in better agreement than previously: 0.783 ± 0.003 from the shifts ($\delta_S = 1.981 \pm 0.002$ ppm; $\delta_{Spy} = 6.385 \pm 0.004$ ppm) and 0.791 ± 0.008 from the rotamer distribution ($K_4 = 0.861 \pm 0.006$), respectively, and are indistinguishable from those of the Me-EDOT alcohols, **4** (results not tabulated).

3,4-Ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, 2

The ^{1}H NMR spectrum of 3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, **2**, was recorded under the same conditions as for the monohydric alcohols **1** and **4**, except that the initial diol concentration was lower and the final pyridine

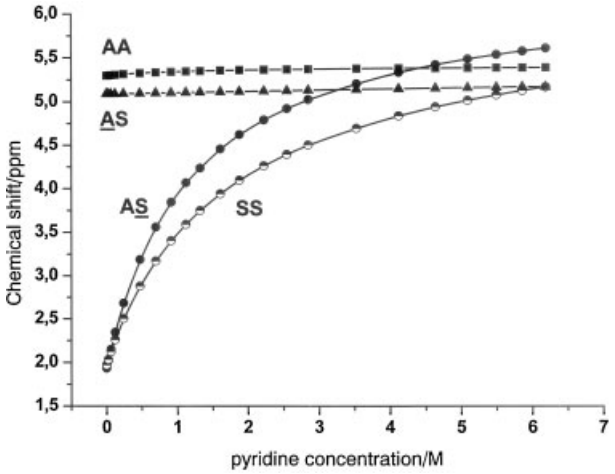


Figure 2. Variation of the ^{1}H NMR chemical shifts of the OH protons in diol **2** with pyridine concentration

concentration higher, 6.2 M. The variation of the chemical shifts of the different OH protons with pyridine concentration is presented in Fig. 2. Full data on shifts and rotamer distributions are given in Supplementary Material Table S2.

Shift variation

For the **AS** rotamer, the association constant, K_3, is given by the simplified equation for a monohydric alcohol[50]

$$\delta_{OH} = \delta_{AS} + K_3[py]_o \frac{(\delta_{ASpy} - \delta_{AS})}{1 + K_3[py]_o} \quad (3)$$

where $[py]_o$ is the analytical pyridine concentration, and δ_{AS} and δ_{ASpy} the chemical shifts of the *syn* OH proton in free **AS** and in **ASpy**, pyridine-complexed **AS**.

The following treatment of the **SS** rotamer can be applied to any symmetrical diol with identical OH groups. Consider a diol, HOC′-X-C″OH, with the carbons bearing the OH groups labelled C′ and C′. X is an undefined spacer; the other substituents at C′ and C″ are not indicated. We have then

$$\begin{array}{lrcll} & HOC' - X - C''OH + py & \rightleftharpoons & py \ldots HOC' - X - C''OH & K_5 \\ \text{and} & HOC' - X - C''OH + py & \rightleftharpoons & HOC' - X - C''OH \ldots py & K_5 \\ \text{then} & py \ldots HOC' - X - C''OH + py & \rightleftharpoons & py \ldots HOC' - X - C''OH \ldots py & K_6 \\ \text{and} & HOC' - X - C''OH \ldots py + py & \rightleftharpoons & py \ldots HOC' - X - C''OH \ldots py & K_6 \end{array}$$

In this case the analytical diol concentration, $[D]_o$, is expressed by

$$[D]_o = [D] + [pyD] + [Dpy] + [pyDpy] = [D](1 + 2K_5[py] + K_5K_6[py]^2)$$

pyD (and **Dpy**) and **pyDpy** are 1:1 and 2:1 pyridine-complexed diol. The free pyridine concentration, [py], is taken as $[py]_o$; this is a valid approximation as long as the diol concentration and, consequently, the concentrations of associated species are much lower than $[py]_o$. Then δ_{OH}, the OH proton shift, is given by

$$2[D]_o\delta_{OH} = 2[D]\delta_D + ([pyD] + [Dpy])(\delta_D + \delta_{Dpy}) + 2[pyDpy]\delta_{Dpy2}$$

where δ_D, δ_{Dpy} and δ_{Dpy2} are the chemical shifts of the OH protons in the free diol and of the associated protons in 1:1 and 2:1 pyridine-complexed diol, respectively. Whence

$$\delta_{OH} = (\delta_D + K_5[py]_o(\delta_D + \delta_{Dpy}) + K_5K_6[py]_o^2\delta_{Dpy2})/(1 + 2K_5[py]_o + K_5K_6[py]_o^2) \quad (4)$$

To a first approximation we might consider that the two OH groups are independent, *i.e.* the first association does not affect the second. In this case, $K_5 = K_6$, and the equation simplifies to:

$$\delta_{OH} = (\delta_D + K_5[py]_o(\delta_D + \delta_{Dpy}) + K_5^2[py]_o^2\delta_{Dpy2})/(1 + 2K_5[py]_o + K_5^2[py]_o^2) \quad (5)$$

We now apply these equations to the **SS** rotamer, δ_D, δ_{Dpy} and δ_{Dpy2} being replaced by δ_{SS}, δ_{SSpy} and δ_{SSpy2}, the chemical shifts of the OH protons in the free rotamer and of the associated protons in 1:1 and 2:1 pyridine-complexed **SS** rotamer, respectively. The same assumptions are made as in a previous publication:[50] (i) association of one proton does not affect the chemical shift of the non-associated proton; (ii) association of the second proton does not affect the chemical shift of that already complexed, and the shift of the second associated proton is the same as that of the first: $\delta_{SSpy} = \delta_{SSpy2}$.

For the **SS** rotamer Eqn (4) gives: $K_5 = 0.61 \pm 0.01$, $K_6 = 0.46 \pm 0.01$, $\delta_{SS} = 1.971 \pm 0.001$ ppm and $\delta_{SSpy} = 6.22 \pm 0.01$ ppm, which suggests that the second association is affected by the existence of the first one. By Eqn (5), we obtain: $K_5 = 0.58 \pm 0.01$, $\delta_{SS} = 1.987 \pm 0.006$ ppm and $\delta_{SSpy} = 6.04 \pm 0.01$ ppm. This is not an altogether satisfactory result in that the value of δ_{SS} is rather higher than the observed zero value of 1.971 ppm. This is a constant feature of the application of Eqn (5) to all systems so far investigated.

Variation of rotamer distribution

For the **AS** and **SS** rotamers we have

$$[AS]_o = [AS] + [ASpy] = [AS] + K_3[AS][py]_o = [AS](1 + K_3[py]_o)$$

and

$$[SS]_o = [SS] + [SSpy] + [SSpy_2] = [SS] + 2K_5[SS][py]_o + K_5K_6[SS][py]_o^2 = [SS](1 + 2K_5[py]_o + K_5K_6[py]_o^2)$$

or

$$[SS]_o = [SS] + [SSpy] + [SSpy_2] = [SS] + 2K_5[SS][py]_o + K_5^2[SS][py]_o^2 = [SS](1 + 2K_5[py]_o + K_5^2[py]_o^2)$$

depending on whether the first association affects the second or not. Since the **AA** isomer does not associate with pyridine,

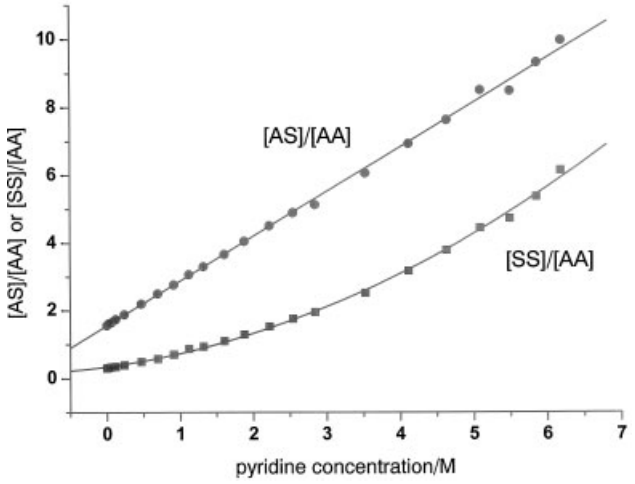


Figure 3. Variation of the rotamer ratios for diol **2** with pyridine concentration

$[AA]_o = [AA]$, and we can write

$$[AS]_o/[AA]_o = K_1(1 + K_3[py]_o) \quad (6)$$

and $$[SS]_o/[AA]_o = K_1K_2(1 + 2K_5[py]_o + K_5K_6[py]_o^2) \quad (7)$$

or $$[SS]_o/[AA]_o = K_1K_2(1 + 2K_5[py]_o + K_5^2[py]_o^2) \quad (8)$$

Values of K_1 and K_2 ($K_1 = 1.56$; $K_2 = 0.199$) are most reliably taken from the rotamer distribution in the absence of pyridine; K_3 is determined by plotting $[AS]_o/[AA]_o$ *versus* $[py]_o$, and K_5 and K_6 by curve-fitting $[SS]_o/[AA]_o$ to $[py]_o$ (Fig. 3). In practice it was found better to take logarithmic versions of Eqns (7) and (8), failing which the optimization is biased

$$\log([SS]_o/[AA]_o) = \log(K_1K_2) + \log(1 + 2K_5[py]_o + K_5K_6[py]_o^2) \quad (9)$$

or

$$\log([SS]_o/[AA]_o) = \log(K_1K_2) + \log(1 + 2K_5[py]_o + K_5^2[py]_o^2) \quad (10)$$

The results are listed in Table 1.

Methyl-3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, 3

When the two alcohol functions are differentiated by introducing a substituent, such as a methyl group into the bridge, as in **3**, the two *anti-syn* rotamers are distinguished as **AS** and **SA**, the first character indicating the orientation of the —C(*t*-Bu)$_2$OH group closer to the substituent.[43] The **AS** rotamer is slightly more stable than **SA**. The two *anti* OH protons in **AA** and the two *syn* protons in **SS** are non-identical, and give different signals in the ^{1}H NMR spectrum.[43] Given that the shift for the **AS** *syn* OH proton is slightly higher than that for the **SA** rotamer, and that the shift of the **AS** *anti* OH proton is substantially higher than for the **SA** rotamer, it seems reasonable to assume that the higher shifts in the **SS** and **AA** rotamers are associated with the groups *cis* to the bridge methyl group. Association constants are determined for the *syn* OH group in the **AS** and **SA** forms by means of the simplified equation (Eqn (3)). If the **SS** signals are lumped together and the data treated by Eqns (4) and (9) [or by Eqns (5) and (10)] the results for diol **3** are very like those for **2** (Table 1). Treating the **SS** rotamer as two monohydric alcohols, **S**S and **S**S, by Eqn (3) implies the same assumption as Eqn (5), and gives for the two *syn* OH groups closely similar values of K_3 ($\equiv K_5$), δ_{SS} and

Table 1. Hetero-association constants (molar scale, standard state 1 M) and chemical shifts for association of EDOT diol, **2**, and Me-EDOT diol, **3**, with pyridine in benzene at 298 K

Cpd.	Equation	K_3	δ_{AS} or δ_{SA}/ppm	δ_{ASpy} or δ_{SApy}/ppm	K_5	K_6	δ_{SS}/ppm	δ_{SSpy}/ppm
2-AS	3	0.845 ± 0.002	1.935 ± 0.002	6.31 ± 0.01				
2-AS	6	0.846 ± 0.008						
3-AS	3	0.840 ± 0.001	1.946 ± 0.001	6.32 ± 0.01				
3-AS	6	0.843 ± 0.006						
3-SA	3	0.823 ± 0.001	1.934 ± 0.001	6.30 ± 0.01				
3-SA	6	0.833 ± 0.009						
2-SS	4				0.610 ± 0.001	0.463 ± 0.004	1.971 ± 0.001	6.22 ± 0.01
2-SS	9				0.576 ± 0.016	0.482 ± 0.029		
3-SS[a]	4				0.597 ± 0.001	0.465 ± 0.003	1.976 ± 0.001	6.20 ± 0.01
3-SS	9				0.569 ± 0.012	0.467 ± 0.021		
2-SS	5				0.584 ± 0.007	—	1.987 ± 0.006	6.04 ± 0.01
2-SS	10				0.544 ± 0.003	—		
3-SS[a]	5				0.574 ± 0.006	—	1.990 ± 0.006	6.03 ± 0.01
3-SS	10				0.533 ± 0.002	—		
3-SS[b]	3	0.578 ± 0.006					1.995 ± 0.005	6.04 ± 0.01
3-SS[b]	3	0.570 ± 0.006					1.985 ± 0.006	6.02 ± 0.01

[a] Mean value.
[b] Treated as a monohydric alcohol; $K^3 \equiv K^5$.

δ_{SSpy}, which are averaged by the latter equation. Full data on shifts and rotamer distributions are given in Supplementary Material Table S3.

1,4-Bis(hydroxymethyl)benzene, 5, propan-1,3-diol, 6, and butan-1,4-diol, 7

For comparison with the encumbered diols, a simple aromatic diol with a six-atom spacer, 1,4-bis(hydroxymethyl)benzene, **5**, propan-1,3-diol, **6**, and butan-1,4-diol, **7**, were examined under similar conditions, except that the concentrations were further reduced to minimize self-association (Table 2). Here again, the shift data can be treated by Eqns (4) and (5), where δ_D is the shift of a non-associated OH proton and δ_{Dpy} that of an associated proton, regardless of whether the diol is singly or doubly associated. The latter equation gives a poorer fit in all cases. For 1,4-bis(hydroxymethyl)benzene, **5**, the value of δ_D is distinctly anomalous at 0.90 ppm, while δ_{OH}, in the absence of pyridine and extrapolated to zero diol concentration, is 0.82 ppm. The values of δ_D and δ_{Dpy} (0.81 and 7.01 ppm, respectively) in Eqn (4) are close to those for benzyl alcohol, 0.78 and 6.95 ppm, respectively, and K_5 (2.30) is practically the same as the association constant (2.46) for the one —CH_2OH group in benzyl alcohol;[50] K_6 is 1.72, suggesting a small effect of the first association on the second, *i.e.* the two —CH_2OH functions are not completely independent.

For the alkan-1,ω-diols, **6** and **7**, the first association constants, 3.0 and 2.9, respectively, are substantially higher than for related monohydric primary alcohols: 1.53, 1.22 and 1.42 for methanol, ethanol and 2,2-dimethylpropan-1-ol, respectively. For **6** and **7**, K_5 is a factor of about 1.9 and 1.6, respectively, higher than K_6. Again, Eqn (5) gives anomalous values for δ_D.

Determination of A values by the NMR method

Recently an NMR method has been proposed for determining *A* values, where the differences between the chemical shifts of solutes in DMSO and chloroform correlate linearly with values measured by other methods (gas-phase and high-pressure liquid chromatography, partition coefficients . . .).[51] For diols, dihydroxyphenols and NH_2 groups, individual values of *A* are taken as half the values observed by the conventional methods. An advantage of this method is that different protic hydrogens within a molecule, for example OH and NH_2, can be distinguished. We propose an interpretation of this approach in terms of the NMR titration technique for determining association constants used in the present work, wherein a hydrogen bond base is progressively added to a hydrogen bond acid solute in an inert solvent. The chemical shift of the protic hydrogen rises from a value where there is no association, δ_A, towards (but not reaching) a maximum corresponding to full association with the base, δ_{AB}, the shape of the curve depending on the association constant, *K*. The Abraham approach constitutes a two-point measurement, where the values in chloroform and in DMSO correspond roughly to δ_A and δ_{AB}, respectively. Given that $\delta_{AB} - \delta_A$ is linearly related to the hydrogen bond free energy ($-RT \ln K$),[50,52,53] it is not altogether surprising that $\delta_{DMSO} - \delta_{CDCl3}$ correlates with *A* values.

The *A* values for several highly congested alcohols were determined by the NMR method (Supplementary Material Table S4). These range from 0.24 for 2,2,4,4-tetramethyl-3-neopentylpentan-3-ol to 0.38 for 2,2,4,4-tetramethylpentan-3-ol;[49] for comparison, 1,4-bis(hydroxymethyl)benzene, **5**, has a value of 0.47. In the case of our diols, **2** and **3**, the values are 0.34 for a *syn* OH proton in an **AS** or **SA** rotamer, slightly lower at 0.31 for either one in an **SS** rotamer, and 0.00–0.02 for the *anti* OH protons in any rotamer. For the monohydric alcohols, **4**, values for the *syn* OH protons are 0.33 (*cis*) and 0.34 (*trans*); for the *anti* protons, 0.00 (*cis*) and 0.02 (*trans*). The values for the *syn* protons agree well with those for alkan-1,ω-diols, which range from 0.29 to 0.38. In this respect, therefore, sterically hindered diols,[49] though rather more elaborate in structure and bearing bulky groups in the vicinity of the alcohol functions, are akin to simple diols. The *anti* OH protons are very weak or not at all hydrogen bond acid functions. The OH protons in the **SS** rotamers are slightly less acidic than those in the **AS** or **SA** rotamers, and this is reflected in the lower pyridine association constants. A rough correlation ranging from 2,2,4,4-tetramethyl-3-neopentylpentan-3-ol to 1,4-bis(hydroxymethyl)benzene is found for log *K*, where *K* is the association constant with pyridine in benzene at 298 K, *versus A* values (Fig. 4); this is consistent with the history of hydrogen bond acidity. Abraham's first acidity scale, α_2^H, was defined on the basis of equilibrium constants for a series of hydrogen bond acids against a given hydrogen bond base.[36,37] Subsequently the *A* scale was defined, representing the acidity of a solute surrounded by hydrogen bond bases, such as a solvent.[38,39]

Statistically corrected, water fits on this correlation quite well. In fact, the data for water[50] are better treated in terms of Eqn (4) of the present paper, in which case the reported first association constants are divided by 2 and the second multiplied by the same factor. The activation enthalpies are unchanged at −4.11 and −3.47 kcal mol^{-1} but the activation entropies become −13.6 ± 0.4 and −13.5 ± 0.4 cal mol^{-1} K^{-1}, respectively.

Table 2. Hetero-association constants (molar scale, standard state 1 M) and chemical shifts for association of 1,4-bis(hydroxymethyl)benzene, **5**, and alkan-1,ω-diols, **6** and **7**, with pyridine in benzene at 298 K

Cpd.	Equation	K_5	K_6	δ_D/ppm	δ_{OH}[a] /ppm	δ_{Dpy}/ppm
5	4	2.30 ± 0.02	1.72 ± 0.01	0.812 ± 0.006	0.816	7.01 ± 0.01
5	5	2.00 ± 0.04	—	0.901 ± 0.023	0.816	6.89 ± 0.02
6	4	3.01 ± 0.09	1.62 ± 0.05	1.043 ± 0.019	1.081	5.95 ± 0.02
6	5	2.24 ± 0.10	—	1.194 ± 0.043	1.081	5.74 ± 0.04
7	4	2.86 ± 0.05	1.79 ± 0.03	1.052 ± 0.011	1.072	6.04 ± 0.01
7	5	2.27 ± 0.08	—	1.172 ± 0.029	1.072	5.89 ± 0.03

[a] $[py]_o = 0$; extrapolated to $[D]_o = 0$.

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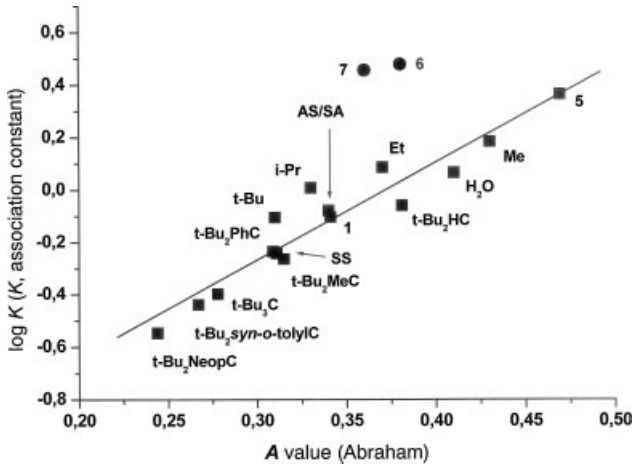


Figure 4. Correlation between log *K* (*K*, the pyridine association constant at 298 K) and *A* values. **SS** and **AS/SA** refer to both diols, **2** and **3**

DISCUSSION

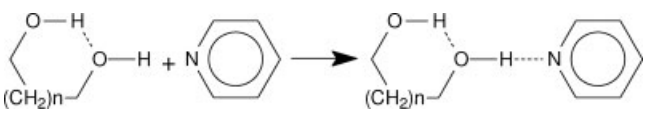
The two methods for determining the association constants for the **AS** and **SS** isomers of diols **2** and **3** give results in fairly good agreement. Values of K_5 determined from rotamer composition are, however, slightly lower than the more precise values based on chemical shifts. This is consistent with a very small variation of the **AA** concentration with that of pyridine. It is noticeable that the shifts of the *anti* OH protons rise rather more with increase in the pyridine concentration, by about 0.09 ppm overall, in the diols than in the alcohols, and that the *A* values are not quite zero. There are no significant differences between the various association constants for **2** and **3**. Given the similarity of the alcohols, **1** and **4**, this was to be expected. The presence of a —C(*t*-Bu)$_2$OH substituent in the *anti* conformation at the 5-position of the thiophene ring appears to slightly enhance the association constant of the *syn* group at the 2-position. The hetero-association constant, K_3, for the **AS** or **SA** rotamer is about 8% higher than that found (0.78) for the *syn* isomer of the corresponding EDOT alcohol, 3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, **1**. The chemical shift values, δ_{AS} and δ_{ASpy}, are very close to those, δ_S and δ_{Spy}, of the alcohol. Conversely, the presence of a substituent in the *syn* conformation at the 5-position significantly reduces the association constant of the *syn* group at the 2-position. The first association constant for the **SS** rotamers, K_5, is about 0.6, lower than for alcohols **1** and **4**, and the second, K_6, is a further 20% lower at 0.48.

The low values of the association constant for the **SS** rotamer are compatible with what was observed earlier for a range of solvents, *i.e.* K_2 is less sensitive to solvent basicity than K_1.[44] The relevant information upon which the solvent correlations were based is contained in Eqns (6) and (7). Ideally we should have association constants for the full range of solvents, but how this result comes about can be seen by looking at benzene and pyridine. The value of $[AS]_o/[AA]_o$ increases by a factor of 11.5 on going from benzene to pyridine, whereas $[SS]_o/[AA]_o$ is multiplied by about 60. Consequently, the value of $[SS]_o/[AS]_o$ varies less with solvent change than $[AS]_o/[AA]_o$, increasing by a factor of only 5.2. In previous work on diol **2** in a range of solvents,[44] correlations of log K_1 and log K_2 against Abraham's hydrogen bond basicity parameter, β_2^H,[39] had gradients of 1.8 and 1.3, respectively, the ratio, 0.72, being close to that we obtain from the two-point correlation here: log (5.2)/log (11.5) = 0.68. In Fig. 2 of the reference[44] the pyridine and DMSO labels were inadvertently permuted.

The alternative treatment in terms of a single association constant, K_5 [Eqns (5), (8) and (10)], which assumes that the two sites are equivalent and independent *i.e.* association of one site has no effect upon that of the other, tends to round down the former and raise the latter. The explanation of the different solvent dependencies of K_1 and K_2 is, however, unchanged. It lies in the fact that the association constants for the *syn* OH protons in an **SS** rotamer are lower than in an **AS** or **SA** rotamer.

Two questions remain: (i) Why is the association constant for a *syn* OH group reduced by the presence of another? One would have thought that the distance between the two groups—the oxygen atoms are approximately 5.4 Å apart—was sufficient for them to act independently. Why then is the acidity of the *syn* OH proton sensitive to the orientation, *anti* or *syn*, of the substituent at the 5-position? Is there an anti-cooperative through-bond or through-space interaction, either direct or via a perturbation of the cybotactic region, which reduces the acidity? At present this problem does not seem to be amenable to theoretical treatment, but clearly indicates that caution must be exercised in assuming that groups 'sufficiently' far apart are independent. (ii) Does the association of a first *syn* OH proton affect that of the second one? The fact that better fits are obtained when Eqn (4) is used to handle the NMR titration data, rather than Eqn (5), suggests that this is the case. For diols **2** and **3** there is a small effect of the first association on the second. Even for 1,4-bis(hydroxymethyl)benzene, **5**, the second association seems to be affected by the first, though acetylation of **5**, a much more drastic reaction, gave product compositions in good agreement with an independent functional groups model.[54,55]

The case of propan-1,3-diol, **6**, and butan-1,4-diol, **7**, is intriguing. The *A* values of alkan-1,ω-diols are slightly less than twice the values for similar monohydric alcohols; this non-additivity Plass and Kolbe attributed to IHB.[40] Curiously, in a subsequent paper,[42] they found that the association constants of these diols with pyridine in dichloromethane were substantially higher than those of similar alkanols, that of butan-1,4-diol being particularly high. Our preliminary measurements confirm this result, though the difference between **6** and **7** appears much smaller than reported.[42] The corresponding points lie significantly above the correlation in Fig. 4, indicating that for these compounds the *A* values and the hetero-association constants do not reflect the same phenomenon. The enhancement of the association constants of these two diols is consistent with the formation of an intramolecularly hydrogen-bonded complex and a consequent cooperative effect.



Theoretical and experimental studies concur as to the existence of IHB in the isolated butan-1,4-diol molecule,[40,57,58] and propan-1,3-diol has been used as a model to analyse hydrogen bond cooperativity in sugars.[14] This molecule satisfies the 'bond critical point' criterion for IHB, even though the net interaction energy is close to zero.[28]

CONCLUSION

Association constants of the **AS** and **SS** isomers of 3,4-ethylenedioxy-2,5-bis[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophene, **2**, and its bridge-methyl derivative, **3**, with pyridine in benzene at 298 K, have been determined by analysing the variation of the shift or of the rotamer distribution with the pyridine concentration. The **AS** and **SA** rotamers can be treated as simple monohydric alcohols, whereas the **SS** rotamers are akin to water in that two donor sites are available for association, but more isolated than in water. In all cases a 4-parameter equation, based on the assumption that the first and second associations have different association constants, gives more satisfactory results than a 3-parameter equation where it is assumed that the two OH groups are totally independent. The outstanding feature of this system is that the hydrogen bond acidity of a donor group is affected by a remote substituent of the same type.

Further experimental and theoretical work will be devoted to bis(hydroxymethyl) benzenes and alkan-1,ω-diols, in an attempt to clarify a rather complex situation as regards the interdependence of donor groups and the contribution of IHB and cooperativity.

EXPERIMENTAL

Synthesis

EDOT alcohol, **1**, EDOT diol, **2** and Me-EDOT diol, **3**, were prepared as described previously.[43,45] Methyl-3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophenes, **4**, were prepared as follows. Lithiation of Me-EDOT with 1.5 equivalent of *n*-butyllithium in diethyl ether at room temperature under argon, followed by addition of 1.5 equivalent of 2,2,4,4-tetramethylpentan-3-one, and separation from unreacted Me-EDOT and the diol by column chromatography on alumina in petroleum ether (bp 35–60°C)/diethyl ether mixtures gave a 1:5 mixture of the *cis* and *trans* isomers [referring to the proximity or remoteness, respectively, of the Me and —C(*t*-Bu)$_2$OH groups] of **4**, in their *anti* and *syn* forms. The *syn*/*anti* rotamer ratio is close to unity (0.81 and 0.86, respectively) for both isomers. Isomers were identified and the signals attributed by comparison with compounds **1**, **2** and **3**, and by a ^{1}H NOESY experiment. The methine and methylene signals (3.0–3.8 ppm) were not attributed. Two of the *tert*-butyl signals of the minor, *cis*, isomer are masked by those of the major, *trans*, isomer. δ_H (benzene, 500 MHz, 299 K): ***cis, anti*:** 0.62 (d, Me, $J = 6.4$ Hz), 1.36 (s, *t*-Bu), 5.33 (s, OH), 6.05 (s, H5); ***cis, syn*:** 0.78 (d, Me, $J = 6.4$ Hz), 1.23 (s, *t*-Bu), 2.00 (s, OH), 6.21 (s, H5); ***trans, anti*:** 0.71 (d, Me, $J = 6.4$ Hz), 1.35 and 1.38 (s, *t*-Bu), 5.21 (s, OH), 6.01 (s, H5); ***trans, syn*:** 0.82 (d, Me, $J = 6.4$ Hz), 1.22 and 1.25 (s, *t*-Bu), 2.01 (s, OH), 6.17 (s, H5).

^{1}H NOESY NMR experiment on methyl-3,4-ethylenedioxy-2-[3-(2,2,4,4-tetramethylpentan-3-ol)]thiophenes

For ^{1}H-^{1}H dipolar contact analysis, a 2D NOESY spectrum of the alcohol mixture **4** was recorded in deuteriated benzene on a Bruker DRX-500 spectrometer equipped with a Silicon Graphics workstation (Fig. 1). A 5 mm broad-band probe with a shielded z-gradient was used. The temperature, fixed at 299 K, was monitored with a BCU 05 temperature unit. Data were processed on a Silicon Graphics workstation with the help of GIFA (version 4.3).[59,60] The 2D NOESY spectrum was acquired in the TPPI mode. It was recorded with 2 K points in t_2 over 5.0 kHz and 512 points in t_1. A 3.0 s relaxation delay and mixing time of 1.6 s were used for the 32 scans of each free induction decay curve. Zero-filling was added in F_1 prior to Fourier transformation. Unshifted squared sine-bell window functions were applied in both dimensions. Baselines were corrected using a polynomial function.

Determination of association constants

Deuteriated benzene (99.6% D, Euriso-top) and pyridine (99.5% D, Euriso-top) were stored over molecular sieve. ^{1}H NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer at 298 K, and are referenced to internal tetramethylsilane at 0.000 ppm. Samples were prepared by progressively adding pyridine (0.001 to 0.3 or 0.5 ml) to a solution of alcohols **1** or **4** (7 mg, 5×10^{-2} M), diols **2** or **3** (5 mg, 2×10^{-2} M), 1,4-bis(hydroxymethyl)benzene, **5** (*ca.* 5×10^{-3} M), propan-1,3-diol, **6** (*ca.* 2×10^{-3} M), or butan-1,4-diol, **7** (*ca.* 2×10^{-3} M), in benzene (0.5 ml) in an NMR tube. Runs were performed in duplicate, and mean values of the shifts (varying by less than 0.02 ppm) and rotamer compositions, for **1**-**4** (varying by less than 1% for any component), at each pyridine concentration used to evaluate the results. Full details for alcohol **4** and for diols **2** and **3** are given in Supplementary Material Tables S1–3.

Determination of A values by the NMR method

^{1}H NMR shifts were determined for the OH protons of a number of alcohols and diols in dilute solutions in $CDCl_3$ and DMSO, following the procedure of Abraham *et al.*[51] *A* values were calculated from the equation: $A = 0.0066 + 0.133\Delta\delta$, where $\Delta\delta$ is the difference in chemical shift, expressed in ppm. Details are given in Supplementary Material Table S4. Other *A* values used in Fig. 4 are taken from the literature.[38–40,51]

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