Tetrahedron. Vol. 29, pp. 2115 to 2118. Pergamon Press 1973. Printed in Great Britain

INVESTIGATIONS OF DITHIENYLGLYCOLIC ESTERS—IV

SOLVENT EFFECTS ON THE CHEMICAL SHIFT DIFFERENCES OF THE DIASTEREOTOPIC THIENYL PROTONS IN AN ASYMMETRIC 2,2'-DITHIENYLGLYCOLIC ESTER

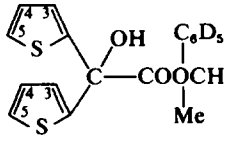
B. ÖSTMAN
Research Institute of National Defence, Dept 1, S-172 04 Sundbyberg, Sweden

(*Received in the UK* 6 *December* 1972; *Accepted for publication* 21 *February* 1973)

Abstract—The chemical shift differences ($\Delta\nu$) of the diastereotopic thienyl protons of 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate have been measured for different solvents and at different temperatures. The solvent dependence of the $\Delta\nu$'s are interpreted as being due mainly to solvent shifts of the diastereotopic protons.

The chemical shift differences of diastereotopic groups of protons in esters of α-hydroxy acids with an asymmetric centre have been reported.[1-3] Thus, for a given solvent, the magnitude of the chemical shift difference, $\Delta\nu$, "will be influenced by the specific differences in the averaged environments of the two groups including the type and anisotropy of the other portions of the molecule, the distances between the groups and the portion of the molecule responsible for the diastereomerism of the environments, . . .".[4]

In the present work the solvent induced changes in the magnitude of the $\Delta\nu$'s of the thienyl protons of 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate,



have been investigated at different temperatures. The dependence of each of the $\Delta\nu$'s (*i.e.* for the thienyl protons 3, 4 and 5) on solvents at +36° is shown in Table 1, which has been arranged according to decreasing $\Delta\nu$'s. The choice of solvents is somewhat arbitrary but an attempt was made to cover a fair range of solvent dielectric constants.

RESULTS

The proton resonance spectra (at 60 MHz) of the thienyl protons are treated, for the solvents and the temperatures considered, as two separate three spin systems I and II, since in none of the spectra could splittings be detected which were due to coupling to the protons of the other thiophene ring. No crossing over was found to occur; *i.e.* the $\Delta\nu$'s of Table 1 are all of the same sign, which hold for the entire temperature regions investigated. The determinations of the $\Delta\nu$'s are judged to be reliable within 0·1 Hz. Fig 1 provides an example of the type of spectra encountered in this work.

In Fig 2 are given the temperature dependences of $\Delta\nu_3$ of the solutions listed in Table 1. The type of dependences reveal that the temperature ranges do not include the low temperature limit in which cases sigmoid plots should be obtained. The

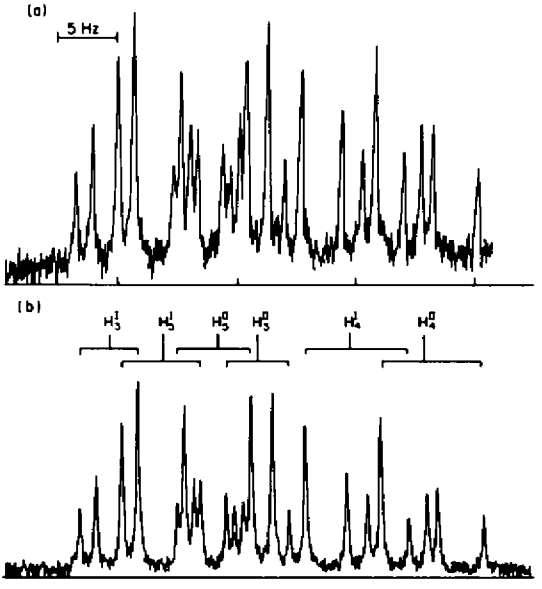


Fig 1. Proton resonance spectrum of the thienyl protons of 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate in 0·11 molar cyclohexane solution at +36°C.
a) Observed 60 MHz spectrum
b) XY recorder plot[14] of the computed (LAOCOON 3) spectrum

Table 1. Chemical shift differences ($\Delta\nu$ Hz), chemical shifts (δ ppm rel. internal TMS) and coupling constants (J Hz) of the thienyl proton spin systems I and II (*cf.* text) of 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate measured for different solvents at + 36°

Solvent	Conc mol l^{-1}	$\Delta\nu_3$	$\Delta\nu_4$ Hz	$\Delta\nu_5$	δH_3 I	δH_3 II	δH_4 I	δH_4 II	δH_5 I	δH_5 II	J_{34} I	J_{34} II	J_{35} I	J_{35} II	J_{45} I	J_{45} II
C_6H_{12}	0·11*	12·4	6·3	4·6	7·19	6·98	6·85	6·75	7·11	7·03	3·69	3·70	1·22	1·27	5·19	5·14
CCl_4	0·40	11·8	5·8	4·2	7·16	6·97	6·91	6·81	7·19	7·12	3·90	3·67	1·31	1·30	4·85	5·19
$CDCl_3$	0·47	11·4	5·7	4·1	7·22	7·03	6·95	6·85	7·25	7·19	3·70	3·84	1·27	1·45	5·24	4·96
$MeNO_2$	0·47	9·2	4·3	3·3	7·28	7·13	7·01	6·93	7·37	7·31	3·68	3·67	1·40	1·53	4·92	4·83
MeOH	0·39	8·4	4·3	3·2	7·18	7·04	6·94	6·87	7·33	7·27	3·82	3·67	1·43	1·48	4·98	4·93
MeCN	0·48	7·7	3·7	2·7	7·20	7·07	6·96	6·90	7·34	7·29	3·87	3·67	1·48	1·53	4·83	4·93
Me_2CO	0·49	7·7	3·7	2·7	7·24	7·11	6·97	6·90	7·36	7·32	3·56	3·72	1·38	1·43	5·04	4·98

*The cyclohexane solution had to be more diluted than the other solutions due to low solubility of ester.

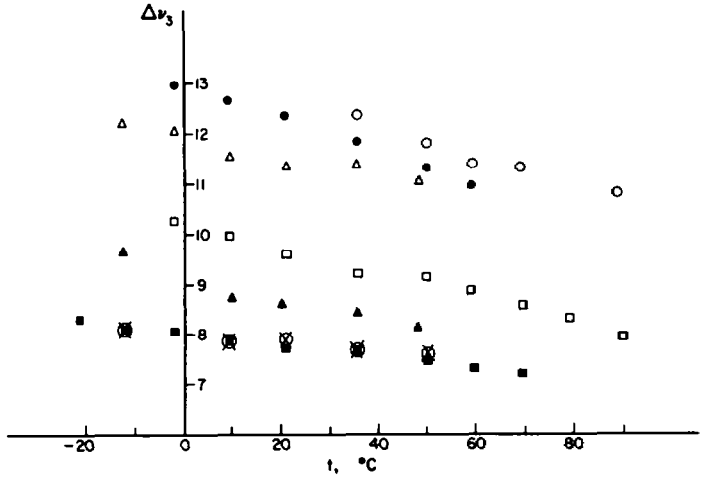


Fig 2. Temperature dependences of $\Delta\nu_3$ (Hz) of 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate for different solvents. (○ C_6H_{12}, ● CCl_4, △ $CDCl_3$, □ CH_3NO_2, ▲ CH_3OH, ■ CH_3CN, ⊠ $(CH_3)_2CO$).

changes of $\Delta\nu_4$ and $\Delta\nu_5$ with temperature are within the ±0·1 Hz error, but decreasing trends with temperature increase could be noticed for these cases as well.

DISCUSSION

The values of $\Delta\nu$ measured for the present compound must be considered to be relatively large in view of the fact that the diastereotopic protons are separated from the asymmetric centre with 5–7 bonds (Table 1). However, according to the quotation[4] above, the distance between the pertinent groups is not the only factor responsible for the magnitude of $\Delta\nu$, also the magnetic properties of these groups are important. Thus in the present case the combined effects of the strongly anisotropic phenyl and thienyl groups ("the magnetic field gradients"[5]) are believed to be responsible for the unexpectedly high $\Delta\nu$ values.

The progression of $\Delta\nu$ values "through the thiophene ring" (Table 1) is in the same sense for the solvents listed and demonstrates clearly, other things being equal, the distance dependence of $\Delta\nu$. Solvent induced changes in $\Delta\nu$ (*cf* Table 1) have been suggested[6] to be due to solvent induced conformational changes, which in the present case should imply that the relative orientation of the dithienyl and the 1-phenyl ethyl groups should not be the same in all solvents. Accordingly there should then also be some changes in the distances between the different thiophene protons and the 1-phenyl ethyl group. Some solvent dependence of the ratios between $\Delta\nu_3$, $\Delta\nu_4$ and $\Delta\nu_5$ should then be expected. Log log plots of *e.g.* $\Delta\nu_3$ and $\Delta\nu_4$ against $\Delta\nu_5$ yield, however, slopes of near unity for the solvents of Table 1. Thus (at + 36°C), the equations $\Delta\nu_3 = 3\cdot\Delta\nu_5^{(0\cdot95\pm0\cdot01)}$ and $\Delta\nu_4 = 1\cdot3\cdot\Delta\nu_5^{(1\cdot04\pm0\cdot01)}$ are obtained from the least squares fits of the log log plots. Hence, $\Delta\nu_i/\Delta\nu_j$ = constant is approximately valid which implies that the ratios of the $\Delta\nu$'s are nearly solvent independent at constant temperature. Consequently different solvents can not pos-

sibly induce significant variations in the relative orientations of the diastereotopic dithienyl group and the asymmetric 1-phenyl ethyl group.

In discussing the solvent dependence of the $\Delta\nu$'s it is pertinent to observe that for cyclohexane solution the shift difference $\delta H_5 - \delta H_3$ changes sign in going from spin system I to II (*cf* Fig 1). According to Table 1 this occurs for cyclohexane solution only; for the other solvents listed the shift difference in question has the same sign for the two spin systems. This fundamental difference between the cyclohexane and the other solvents with respect to the behavior of the thienyl proton shifts prevails at all temperatures and concentrations investigated.

In the present context cyclohexane is the only one of the solvents which can be assumed to be inert with respect to the solute molecules. Accordingly, the observed difference in the relative shieldings of protons 3 and 5 in the spin system I and II must presumably be due only to the long range shielding effect of the anisotropic phenyl group at the asymmetric centre with no interference whatsoever of the solvent cyclohexane. The result implies a preferred conformation[3] in which the phenyl group is closer to one of the thienyl rings than to the other. The solvent independence of the ratios $\Delta\nu_3/\Delta\nu_5$ and $\Delta\nu_4/\Delta\nu_5$ strongly suggest that the preferred conformation found in cyclohexane solution is then also the same for the other solvents. The fact that the particular spectral appearence of the relative thienyl proton shifts in cyclohexane solution is not shown for the other solvents, suggest that the concept of specific solvent shifts[7] applies for these solutions. Solvent shifts arise principally from the formation of collision complexes between the solvent and the solute.[7] Thus if the solvent molecules form collision complexes with the thienyl rings the shifts of the thienyl protons will be modified and, bearing in mind the spatial requirements of such complexes,[7] the closer proximity of one of the rings to the phenyl group will then result in net contributions to the shift differences $\Delta\nu$.

If the chemical shift data of Table 1 are referred to those of the cyclohexane solution it is found that the shifts of spin system II are significantly more solvent sensitive than those of I. It is probable therefore that II represents the sterically more accessible one of the two thienyl groups, presumably the one farthest from the phenyl group. This is supported by the fact that for cyclohexane solution it is spin system I which is deviating from all the others (with respect to the $\delta H_5 - \delta H_3$ difference *cf* Table 1), which should be expected for an inert solvent if, in the time average, system I represents the thienyl group closest to the anisotropic phenyl group.

It is well known that α-hydroxy esters are both intra- and intermolecularly hydrogen bonded.[8-10] The intramolecular hydrogen bond obviously results in a highly preferred arrangement of the dithienylhydroxymethyl group relative to the carbonyl group. The intermolecular hydrogen bond between solute molecules has been shown[8] to persist down to *ca* 0·1 molar CCl_4 solution. Thus if there should be significant differences between the conformations representing inter- and intramolecular hydrogen bonding, this should be reflected in a concentration dependence of $\Delta\nu$ for solvents like cyclohexane, CCl_4 and $CDCl_3$. According to Table 2, however, the variations obtained are weak and inconsistent. Thus any regard to contributions from changes in intermolecular H-bonding is not warranted.

Table 2. $\Delta\nu_3$ values for different concentrations of l-phenyl (-d_5) ethyl 2,2'-dithienylglycolate

Solvent	Conc. mol l^{-1}	Temp. °C	$\Delta\nu_3$ Hz
C_6H_{12}	0·47	90	10·4
	0·22	90	10·8
	0·22	50	11·8
	0·11	50	11·2
CCl_4	0·40	36	11·8
	0·13	36	12·2
	0·07	36	12·1
$CDCl_3$	0·47	36	11·4
	0·13	36	10·9
	0·07	36	11·3

With respect to the intramolecular H-bond it is not possible to draw conclusions, from the present results, which are relevant to the imposed rotational barrier. The decrease of the $\Delta\nu$'s (Fig 2) with temperature is therefore interpreted as being due to the sum contributions of the equalization of the populations of the various conformers.[11]

In conclusion the present work is meant to show that solvent dependence of chemical shift differences of diastereotopic atoms or groups of atoms (magnetic non-equivalence) may be interpreted according to the current concepts of solvent shifts.[7] This approach has been feasible since diastereotopic spin systems have been studied rather than diastereotopic atoms or groups of equivalent atoms, which have hitherto been the subjects of several investigations.[12]

The present compound may further be regarded as a model substance for certain pharmacologically active esters of diarylglycolic acids.[13] Provided the spin systems I and II can be identified with certainty with each one of the two thienyl groups, the result pertaining to different complex forming capacity with solvent may conceivably be utilized in the research bearing on the understanding on the molecular level of the biological action of these drugs, since it has been found[13] that at least one aryl group is required for their activity on the CNS.

EXPERIMENTAL

The NMR spectra were obtained with a Varian A 60A Analytical Spectrometer equipped with the Varian V 6057 variable temperature system.

Preparation of 1-*phenyl* (-d_5) *ethyl* 2,2'-*dithienylglycolate*. The Grignard reagent of bromobenzene (-d_5) (Stohler Isotope Chemicals, Bern, Switzerland) was reacted with acetaldehyde to yield 1-phenyl (-d_5) EtOH, which was subsequently reacted with methyl 2,2'-dithienylglycolate[1] in a transesterification reaction to give 1-phenyl (-d_5) ethyl 2,2'-dithienylglycolate.* The synthetic product was purified on a silica gel column (Merck 0·05–0·2 mm) with benzene as eluant, m.p. 87–88·2°.

The mass-spectrum had its base peak at *m/e* 195 corresponding to the dithienylhydroxymethyl fragment characteristic of the fragmentation of dithienylglycolic esters.[14] The NMR spectrum ($CDCl_3$) had signals at (TMS reference) 1·55 ppm (d, Me), 4·65 ppm (OH), 6·00 ppm (sym. qu, CH), 6·8–7·33 ppm (m, thienyl), with relative intensities in the ratios 3 : 1 : 1 : 6.

NMR measurements. The solvents used for the measurements were either of spectroquality (Merck or Eastman) or analytical (Merck), and were used without further purification from freshly opened bottles. Ordinary NMR tubes were used, they were, however, matched. The tubes were acid washed, rinsed and finally dried in an oven. Samples of the ester were weighed in the dried tubes, the solvent was pipetted (0·5 or 0·6 ml) down in the tubes and these were finally sealed off. The temperature of the NMR probe was determined by means of the internal shift differences of standard ethyleneglycol and methanol samples for high and low temperatures, respectively.

For the determination of the shift differences ($\Delta\nu_3$, $\Delta\nu_4$, $\Delta\nu_5$) spectra were run at 50 Hz sweep width at optimum conditions, usually with a sweep rate of 0·1 Hz/second.

Spectral assignments. The shifts and coupling constants were extracted from the spin systems I and II by means of the common ABX procedure.[15] The calculations involved were facilitated by using a FOCAL program. Since several of the bands of I and II coincided in the AB regions of the spectra of the cyclohexane, chloroform and carbontetrachloride solutions, the ABX parameters of these spectra were adjusted with the iterative LAOCOON 3 program to give a fit within 0·1 rms error of the calculated frequencies to the corresponding experimental lines. These calculated spectra were plotted[14] and compared with the experimental. Fig 1b is an example of the kind of plots which were used. The adjusted shift parameters deviated from 0·1 to 0·7 Hz from the ABX shift assignments. The probable errors of the adjusted shifts and coupling constants are in general given by the program as ±0·05. The iterative procedure was not considered necessary for the spectra of the solutions from the other solvents, since these were almost completely resolved making even first order assignments in close agreement with the ABX treatment.

*The compound was kindly supplied by Mrs. Gun Wallerberg.

Acknowledgements—The stimulating discussions with Docent Johan Santesson as well as his valuable assistance in the programming work and the valuable comments by Professor Jan Sandström, Department of Organic Chemistry, University of Lund are gratefully acknowledged. The author is further indebted to Dr. Stefan Sjöberg, Institute of Chemistry, University of Uppsala, for exploratory measurements and to Dr. Torbjörn Drakenberg, Division of Physical Chemistry, The Lund Institute of Technology for the provision of the program deck of the LAOCOON 3 program.

REFERENCES

[1]K. Nyberg, B. Östman and G. Wallerberg, *Acta Chem. Scand.* **24**, 1590 (1970)
[2]C. van der Vlies, *Rec. Trav. Chim.* **84**, 1289 (1965)
[3]N. S. Bowman, D. E. Rice and B. R. Switzer, *J. Am. Chem. Soc.* **87**, 4477 (1965)
[4]K. Mislow and M. Raban, *Topics in Stereochemistry* (Edited by N. L. Allinger & E. L. Eliel) Vol. 1, p. 25. Interscience, New York (1967)
[5]E. I. Snyder, *J. Am. Chem. Soc.* **85**, 2624 (1963)
[6]G. M. Whitesides, J. J. Grocki, D. Holtz, H. Steinberg and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 1058 (1965)
[7]L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, (2nd Ed.) p. 246. Pergamon Press (1969)
[8]L. Larsson, G. Wallerberg and B. Östman, *FOA 1 Rapport C 1291–31*, (1968)
[9]N. Mori, S. Omura, O. Yamamoto, T. Suzuki and Y. Tsuzuki, *Bull. Chem. Soc. Japan* **36**, 1401 (1963)
[10]R. J. Piffath and S. Sass, *Appl. Spectr.* **26**, 92 (1972)
[11]J. A. Pople, *Mol. Phys.* **1**, 3 (1958)
[12]See *e.g.* Ref. 4 and Ch. 5-2 of Ref. 7
[13]L. G. Abood and J. H. Biel, *Int. Rev. Neurobiology* **4**, 217 (1962)
[14]J. Santesson. To be published
[15]J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance*, Vol. 1, p. 357. Pergamon Press (1966)