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Downfield γ -*gauche* and γ -antiperiplanar Effects on ^{13}C NMR Chemical Shifts Exerted by Thiophene Sulphur

J. W. de Haan,* M. E. van Dommelen, L. J. M. van de Ven and A. Corvers

Laboratories of Instrumental Analysis and Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands

The γ -effects of sulphur on ^{13}C NMR chemical shifts have been measured in a series of steroidal compounds containing the thiophene ring in different configurations with respect to the rest of the molecule. The data constitute the first example of downfield effects exerted by sulphur on both *gauche* and antiperiplanar γ -carbons. The γ -*gauche* effect of sulphur amounts to 1.6–1.8 ppm, the γ -antiperiplanar effect from practically zero to almost 1 ppm.

INTRODUCTION

Recently several papers have appeared concerning the influence on ^{13}C NMR chemical shifts exerted by hetero atoms in γ -position with respect to the carbon atom under consideration.¹ For second row elements a general rule seems to emerge that both in *gauche* fragments and in antiperiplanar fragments the shifts are upfield with respect to systems containing only all-carbon interactions.[†] The difference is larger in antiperiplanar fragments.^{1a}

It seems clear that third row elements like chlorine and sulphur (as in chlorides and thioethers respectively) cause only very small upfield effects on an antiperiplanar γ -carbon: c. -1 ppm.^{1a} Results reported later for 2,5-dialkyl-1,3-dithianes seem to suggest that 1,4-*gauche* effects by sulphur are larger: c. -1 to -3 ppm per sulphur atom. It should be kept in mind that accompanying effects on C-2 substituents, as well as on axial and equatorial protons at the 2- and 5-positions of 1,3-dithianes and 1,3-dioxanes, are still largely unexplained.²

Independently, Barbarella *et al.* demonstrated that antiperiplanar shifts caused by sulphur depend markedly on the electronegativity of the sulphur atom.³ Values of -2.1 to -4.2 ppm for γ -effects in 6-membered rings were explained as changes in the δ -effects of the same relative magnitudes; the largest effect was observed with an S^+-Me group.

In conformationally mobile systems the weighted average of *gauche* and antiperiplanar effects is practically constant at -3 ppm. This could be due, as

suggested by the authors, to changing conformational equilibria or to progressively downfield *gauche* effects with increasing positive charge on sulphur.³ At present it seems impossible to distinguish between these two possibilities, or a combination of both, without data pertaining to *gauche* interactions exerted by 'charged' sulphur in rigid systems.

In view of the above it would be of interest to investigate the influence of sulphur embedded in a thiophene ring in which an electron from sulphur may be dispersed within the ring. Here, we present results obtained with steroidal compounds containing the thiophene ring in different configurations with respect to the rest of the molecule. In these systems (3–8), as well as in a pair of models (1, 2), some methylene carbons are held in fixed *anti* configurations with respect to the sulphur atom of the thiophene ring, while, in the 'odd members' of this series another methylene or a methyl group within the same molecule occupies a γ -*gauche* position with respect to the sulphur atom.

EXPERIMENTAL

Compounds 1 and 2 were prepared from 2-methyl-5-(3-thienyl)pent-2-ene and 2-methyl-5-(2-thienyl)pent-2-ene, respectively.⁴ The structures of these precursors were verified in the usual way from their chemical and physical properties.⁴ The stereochemical relationships between the sulphur atoms and the methyl groups in 1 and 2 are established unequivocally by the syntheses from the respective precursors.⁴

The steroidal compounds 3 and 4 were prepared in a similar manner. Subsequently, these were converted to the epoxides 7 and 8 and thence to the ketones 5

* Author to whom correspondence should be addressed.

[†] The terms γ -*gauche* and γ -antiperiplanar refer to the conformations:

and **6**.⁴ ^{13}C NMR spectra were measured in the pulse mode in CDCl_3 solutions at 25.15 MHz on a Varian HA-100 spectrometer, interfaced with a Digilab FTS-NMR-3 Pulsing and Data system. Usually, about 500–1000 spectra were accumulated; pulse angles of about 90° were applied at 10 s intervals, 8 K data points were sampled using a bandwidth of 4544 Hz. Chemical shifts were measured with respect to TMS in $\text{C}_2\text{Br}_2\text{F}_4$, which served as an external ^{19}F lock.

SPECTRAL ASSIGNMENTS

The assignments of the signals of **1** and **2**, which serve as model compounds for the A and B rings of steroidal systems **3–8** were obtained as follows.

The thiophene rings yield two singlets and two doublets which may be assigned by means of the known substitution rules of thiophenes.¹ The signals of C-8 and C-10 are assigned based on signal multiplicities (off-resonance experiments) and/or signal areas. The allylic hydrogens at C-5 resonate at lower fields than those at C-6 and C-7 ($\delta = 2.5$ and $\delta = 1.7$ respectively). Therefore, the signals of C-5 can be located by means of selective decoupling experiments. The remaining two triplets near 21.5 ppm and 40.0 ppm are assigned by taking into account the known effects of geminal dimethyl substitution in a cyclohexane ring.

The thiophene signals of **3**, **5** and **7** are assigned by comparison with those of **1**, and, correspondingly, the signals of **4**, **6** and **8** with those of **2**.

The entire C and D part of **6** (C-7–C-17) can be analysed by comparison with the known assignments of estrone acetate; the discrepancies are generally smaller than 1.5 ppm with the exception of C-16 and C-17. Of the remaining two triplets, the one near 26 ppm was assigned by means of a selective decoupling experiment irradiating near $\delta = 2.7$ in the ^1H NMR spectrum. The same experiment also yielded additional evidence for the location of the C-15 signal at 36.83 ppm since the corresponding protons are known

to absorb at relatively low field. Finally the signal at 27.60 ppm was still considerably broadened, as is to be expected from the relatively high-field position of the corresponding protons.

A further and final verification was obtained from a selective decoupling experiment near $\delta = 1.55$ in the ^1H NMR spectrum. As expected, the other four triplets are now better decoupled. It is worth noting that the relative position of the signals of C-5 and C-6 in **6** is reversed with respect to that in estrone acetate. The analysis of the ^{13}C NMR spectrum of **5** is straightforward by comparing it with that of **6** and with the model compounds **1** and **2** in order to allow the distinction of the signals of C-6 and C-10.

Off-resonance decoupling at high field in the ^1H NMR spectra of **3** and **4** ($\delta = -1.2$) yielded relatively large residual splittings for three triplets which were, therefore, classified as being due to the allylic carbons C-5, C-11 and C-15. The triplets near 26.5 ppm in both **3** and **4** were assigned to C-5 by reference to **1**, **2** and **5**, **6** (see above). Moreover, the signals near

Table 1. Carbon-13 NMR chemical shifts of **1–8**

	1	2	3	4	5	6	7	8
C-1		125.94		126.03		126.06		126.50
C-2	122.19	122.46	122.63	122.72	123.16	123.22	122.98	123.07
C-3	127.88		128.14		128.92		128.76	
C-4	134.54	134.81	135.25	136.04	135.72	136.26	136.04	136.66
C-5	26.91	26.33	26.78	26.29	26.63	26.15	26.78	26.40
C-6	21.17	21.70	28.89	29.29	27.66	28.03	28.28	29.18
C-7	40.27	39.44	42.52	42.48	40.59	39.74	42.92	42.90
C-8	34.67	33.97	50.42	49.76	44.83	44.65	44.86	44.13
C-9	147.25	144.69	141.16	139.61	140.93	139.84	140.94	139.64
C-10	33.48	31.67	34.32	32.55	29.24	27.60	31.89	30.22
C-11			28.89	28.94	32.64	32.70	28.67	28.41
C-12			136.48	136.70	49.57	49.32	72.30	72.28
C-13			52.71	52.71	50.72	50.72	47.02	46.98
C-14			26.68	26.78	22.81	22.81	24.53	24.72
C-15			38.20	38.29	36.83	36.83	33.70	33.84
C-16			129.73	129.56	221.38	221.38	69.48	69.43
C-17			14.60	14.69	15.23	15.17	16.32	16.50

28.9 ppm are due to C-11 and those at c. 38.2 ppm to C-15 as is evident by comparison with C-2 in *exo*-methylenecyclohexane (taking into account the shielding by the (*Z*)-methyl-group) and with substituted cyclopentenes, respectively. An additional case in point is the similarity of these shifts in **3** and **4**; the differences are less than 0.1 ppm and these carbons are relatively far from the thiophene ring and should therefore not differ very much. Of the remaining three triplets the signal near 29 ppm is attributed to C-6 by comparison with **5** and **6**. The signals near 26.8 ppm (mutual difference 0.1 ppm) should be remote from the thiophene rings and agree with those of substituted cyclopentenes; they are therefore assigned to C-14.

In a similar way, high field CW decoupling of the epoxides **7** and **8** yielded large residual splittings for the triplets at 26.78 ppm and 33.70 ppm and for the triplets at 26.40 ppm and 33.84 ppm, respectively. The high field triplets were assigned to C-5 by analogy with the previous examples and the triplets near 33.8 ppm to C-15 which is β to the epoxy oxygen.

The signals due to C-14 were assigned with reference to the known upfield γ -effect of an epoxy ring with respect to a C=C bond. There is no unambiguous way in which the remaining three triplets for **7** and **8** can be assigned rigorously. The signals at 28.28 ppm and 29.18 ppm in **7** and **8**, respectively, could be assigned to C-6 since the mutual difference in chemical shifts is then similar to that in the previous pairs. The shifts near 28.5 ppm are relatively close together and are most probably due to C-11, leaving the signals at 31.89 ppm in **7** and at 30.22 ppm in **8** to be assigned to C-10. The assignments are summarized in Table 1.

DISCUSSION

The resulting shifts for C-10 in comparable 'odd' and 'even' compounds reflect the influence of the γ -*gauche*

sulphur atom: $\Delta\delta(1-2) = 1.81$ ppm, $\Delta\delta(3-4) = 1.77$ ppm, $\Delta\delta(5-6) = 1.64$ ppm and $\Delta\delta(7-8) = 1.67$ ppm. In the same way the γ -antiperiplanar shifts were found to range from practically zero (C-7 in **3**, **4** and in **7**, **8**) to almost 1 ppm (C-6 in **7**, **8**, C-7 in **1**, **2** and in **5**, **6**).

To our knowledge, the data given above constitute the first example of unambiguously determined combinations of *downfield* effects exerted by sulphur on *both gauche* and *antiperiplanar* γ -carbons. In the conformationally mobile system 2-*n*-butylthiophene an average *gauche* and *anti* effect on the γ -carbon is to be expected. Actually, C- β in 2-*n*-butylthiophene is deshielded by +1.1 ppm with respect to the comparable atom in 3-*n*-butylthiophene. Similar differences have been found in other 2- and 3-substituted thiophenes containing long side chains.⁶

Without going into details as to the exact nature of the observed effects we note that recent ASIS experiments suggest that the sulphur atom in thiophene is at the negative end of the molecular dipole.⁷ MO-calculations indicate donation of π -electrons by sulphur to the rest of the thiophene molecule with concurrent withdrawal of σ -electrons.⁸ In this respect sulphur in thiophene might well differ from that in other systems studied thus far. Further experimental data will be needed before more refined treatments can be given. In the meantime, detailed conformational analyses based on γ -sulphur-induced effects on ¹³C NMR shifts are to be considered with caution.

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