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Nuclear Magnetic Resonance of Aromatic Heterocyclics

IV. The ^1H and ^{19}F Spectra of Substituted Fluorothiophenes. An Experimental Study

SÖREN RODMAR,[a] LUIS MORAGA,[a]* SALO GRONOWITZ[b] and ULF ROSÉN[b]

[a]*Institute of Physics, University of Uppsala, Box 530, S-751 21 Uppsala 1, and* [b]*Chemical Center, Division of Organic Chemistry, University of Lund, P.O. Box 740, S-220 07 Lund 7, Sweden*

The NMR spectra of nineteen 5-substituted 2-fluorothiophenes, thirteen 4-substituted 2-fluorothiophenes and fourteen 5-substituted 3-fluorothiophenes have been analysed. The relative signs of the spin couplings between the fluorine nucleus and the ring protons have been determined by double resonance. In 5-substituted 3-fluorothiophenes J_{F-4} is of opposite sign to J_{F-2} which is assumed to be positive as are the other pairs of H–F couplings. If possible the signs of the couplings between a side-chain proton and the fluorine nucleus have been determined, and are all positive except for J_{C-H3} in 3-fluoro-5-methylthiophene. The intervals for the fluorine chemical shifts and H–F couplings in 5-substituted 2-fluorothiophenes are: δ_F 23.6–46.3 ppm downfield from C_6F_6, J_{F-3} 1.17–3.46 Hz, J_{F-4} 3.02–4.29 Hz; in 4-substituted 2-fluorothiophenes: δ_F 29.5–36.8 ppm, J_{F-3} 0.61–2.04 Hz, J_{F-5} 3.13–3.97 Hz; in 5-substituted 3-fluorothiophenes: δ_F 31.7–41.1 ppm, J_{F-2} 0.58–2.00 Hz, J_{F-4} −0.54 to −1.16 Hz.

1. INTRODUCTION

In the preceding papers [1,2] of this series, the ^1H and ^{19}F spectra of mono- and difluorothiophenes were discussed. We have now extended our study to include nineteen 5-substituted 2-fluorothiophenes, thirteen 4-substituted 2-fluorothiophenes and fourteen 5-substituted 3-fluorothiophenes, in order to obtain information on substituent effects on NMR parameters. The synthesis of the fluorothiophenes is described in Ref. 3. In the present paper the analysis of the NMR spectra is given, and in the following paper [4] the substituent effects on the NMR parameters will be discussed.

* Present address: Faculty of Science, University of Chile, Santiago de Chile, Chile.

2. RESULTS

The NMR spectra of the compounds in this paper are of the types ABX, ABM_3X, ABM_2X and ABMX. A and B stand for the ring protons and M stands for a side-chain proton that couples either with the ring protons or with the fluorine nucleus, which is denoted X.

The assignments of the proton spectra to individual protons are in most cases based on known substituent effects on the chemical shifts of the ring protons.[1,5-7]

Table 1. Proton[a] and fluorine[b] chemical shifts in 5-substituted 2-fluorothiophenes.

Substituent	$-\delta_F$ ppm	$-\delta_{H_3}$ ppm	$-\delta_{H_4}$ ppm	$-\delta_{H_5}$[c] ppm
OCH_3	23.62	5.89	5.61	3.67
CH_3	29.60	6.05	6.16	2.22
CH_2CH_3	29.21	6.06	6.20	2.61
$CH_2CH_2CH_3$	29.39	6.07	6.22	
$CH_2CH_2CH_2CH_3$	29.30	6.06	6.21	
$C(CH_3)_3$	28.57	6.05	6.27	
SCH_3	39.07	6.19	6.67	2.32
C_6H_5	31.83 ± 0.04	6.25	6.69	
Cl	34.51	6.09	6.38	
Br	36.17	6.10	6.56	
I	38.75	6.05	6.79	
CN	40.74 ± 0.04	6.52	7.28	
CHO	45.73 ± 0.15	6.59	7.48	9.69
$COCH_3$	43.14	6.50	7.40	2.39
COOH[d]	41.17	6.70	7.52	
$COOCH_3$	40.82 ± 0.03	6.40	7.34	
CHNOH *anti*[d,e]	33.98 ± 0.05	6.61	7.12	7.64
CHNOH *syn*[d,e]	34.14 ± 0.25	6.52	6.91	8.15
SO_2CH_3[a]	42.65	6.80	7.50	3.23
NO_2	46.31 ± 0.07	6.64	7.71	

[a] The proton shifts of the compounds dissolved in cyclohexane if not otherwise noted are given in ppm relative to TMS.
[b] The fluorine shift is given in ppm relative to hexafluorobenzene.
[c] The chemical shift of the side-chain proton closest to the thiophene ring.
[d] Dissolved in acetone.
[e] The shift of the hydroxyl proton is −10.3 ppm.

The proton chemical shifts are collected in Tables 1, 3 and 5, and they are given in ppm relative to TMS. Since they do not represent extrapolated values, but are given for most of the compounds at a concentration of about 30 % by weight, they are rounded off to the nearest 0.01 ppm even if the uncertainty in the values given is always smaller.

The fluorine chemical shifts at infinite dilution are given in ppm relative to hexafluorobenzene in Tables 1, 3 and 5. The fluorine shifts were in general measured at four different concentrations in cyclohexane and extrapolated

to infinite dilution, except for those compounds which are not soluble in this solvent, and were consequently run in acetone and for which the shifts given are extrapolated values in the latter solvent. The fluorine shifts are all towards lower field than the reference compound. The uncertainty in the fluorine shifts is not more than ± 0.02 ppm for most of the compounds, but if larger this is indicated in the tables.

The fluorine chemical shifts of the substituted thiophenes studied are generally not very concentration dependent. Except for three compounds, the difference between the shift at the highest concentration studied and the extrapolated shift to infinite dilution for the 5-substituted 2-fluorothiophenes is smaller than 0.3 ppm. The exceptions are the compounds containing the substituents NO_2, CN, and CHNOH, for which the differences in shift from 23 % solutions to infinite dilution are 0.8, 0.4, and 0.4 ppm, respectively. In the 4-substituted 2-fluorothiophenes and the 5-substituted 3-fluorothiophenes the difference is smaller than 0.2 ppm, except for 3-fluoro-5-acetylthiophene where the shift from a 34 % solution differs from the extrapolated value by 0.3 ppm.

The spin-spin coupling constants are given in Tables 2, 4, and 6. If possible the relative signs of the J_{AX} and J_{BX} couplings have been determined by double resonance (mainly tickling). In most cases, it has not been possible to obtain the sign of these couplings relative to those of proton-proton couplings, and they are thus given with the same absolute signs as those found in 2- and 3-fluorothiophene.[1]

In those compounds with a non-zero J_{MX} coupling, the sign of this coupling has been determined relative to a J_{AX} or J_{BX} coupling by double resonance, and in some cases with a sufficiently strongly coupled AB-part it has been determined relative to the J_{AM} and J_{BM} couplings from the asymmetry in the fluorine spectrum.

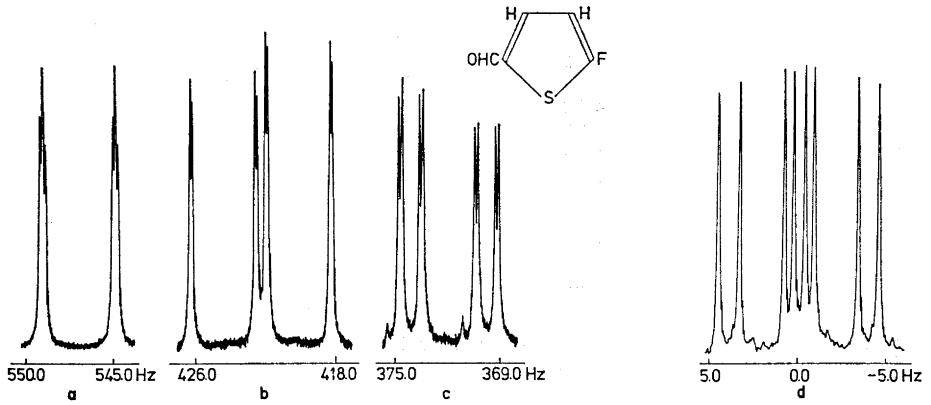


Fig. 1. The experimental proton and fluorine magnetic resonance spectra at 56.444 MHz of 2-fluoro-5-thiophenealdehyde. a, the aldehyde proton spectrum. b, the 4-proton spectrum. c, the 3-proton spectrum. d, the fluorine spectrum. The frequency scale for the proton spectra is given with respect to TMS as internal reference and for the fluorine spectrum it is given relative to the fluorine resonance frequency ν_F. The shifts in Hz of the protons are: $\nu_{CHO} = 546.90$, $\nu_4 = 422.30$, $\nu_3 = 371.87$.

The signs of the couplings J_{AM} and J_{BM} relative to J_{AB} have also been determined when possible by double resonance techniques.

The uncertainty of the couplings is in all cases at most ± 0.03 Hz except when they are obtained from line shape analysis.

Most of the spectra are analysed in a straightforward way and will not be further discussed. Some spectra of compounds with an interacting side-chain proton may, however, need further comments.

2.1. 5-Substituted 2-fluorothiophenes

2-Fluoro-5-thiophenealdehyde. In this compound the small J_{CHO-H} couplings could be resolved and their signs relative to J_{34} could be determined (Fig. 1). The sign of J_{CHO-4} is the same as the sign of J_{CHO-4} in 3-thiophenealdehydes [8] and 3-furanaldehydes,[9] and of the coupling between an aldehyde proton and a ring proton in the *ortho* position in benzaldehydes.[10-12]

Table 2. Spin-spin coupling constants in 5-substituted 2-fluorothiophenes.

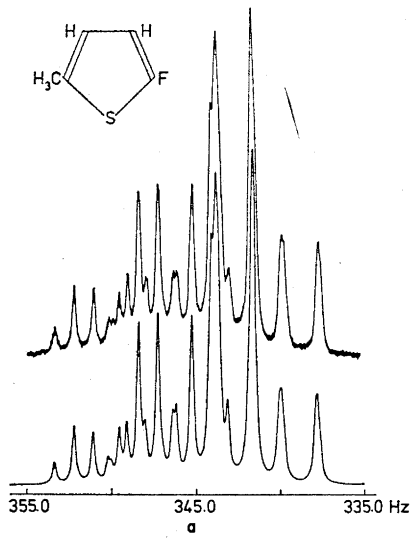
Substituent	J_{34} Hz	J_{F-3} Hz	J_{F-4} Hz	J_{F-4}[a] Hz
OCH_3	4.26	3.46	3.02	
CH_3 [b]	3.83	2.03	3.20	2.77
CH_2CH_3 [c]	3.86	1.95	3.20	2.66
$CH_2CH_2CH_3$ [d]	3.85	1.85	3.17	2.74
$CH_2CH_2CH_2CH_3$ [e]	3.83	1.90	3.14	2.75
$C(CH_3)_3$	3.94	1.75	3.19	
SCH_3 [f]	4.02	2.52	3.49	0.30
C_6H_5	4.09	1.92	3.48	
Cl	4.20	2.76	3.49	
Br	4.15	2.39	3.43	
I	4.06	2.22	3.22	
CN	4.30	1.82	3.74	
CHO [g]	4.25	1.17	3.66	4.20
$COCH_3$	4.29	1.45	3.52	0.44
COOH	4.28	1.76	3.89	
$COOCH_3$	4.23	1.50	3.85	
CHNOH *anti* [h]	4.27	2.23	4.01	3.76
CHNOH *syn* [i]	4.11	1.98	3.77	3.42
SO_2CH_3 [j]	4.30	1.47	3.75	0.32
NO_2	4.72	2.06	4.29	

[a] Spin-spin coupling between fluorine and the side-chain proton.
[b] $J_{CH_3-3} = 0.24$ Hz, and $J_{CH_3-4} = -1.24$ Hz.
[c] $J_{CH_3-3} = 0.23$ Hz, and $J_{CH_3-4} = -1.15$ Hz.
[d] $J_{CH_3-3} = 0.16$ Hz, and $J_{CH_3-4} = -1.05$ Hz.
[e] $J_{CH_3-3} \approx 0$ Hz, and $J_{CH_3-4} = -0.99$ Hz.
[f] $|J_{SCH_3-3}| = 0.06$ Hz.
[g] $J_{CHO-3} = 0.21$ Hz, and $J_{CHO-4} = -0.15$ Hz.
[h] $|J_{CHNOH-4}| = 0.48$ Hz.
[i] $|J_{CHNOH-4}| = 0.55$ Hz.
[j] $|J_{SO_2CH_3-4}| = 0.13$ Hz.

The sign of J_{CHO-3} agrees with earlier sign determinations of this coupling in 3-bromo-2-thiophenealdehyde,[13] 2-furanaldehydes,[9] and with the sign of the coupling between an aldehyde proton and a ring proton in the *meta* position in benzaldehydes.[10,11,14,15]

2-Fluoro-5-acetylthiophene. The lines in the 4-proton band (0.32 Hz) are slightly broader than the lines in the 3-proton spectrum (0.25 Hz) indicating a small unresolvable coupling between the $COCH_3$ group and the 4-hydrogen. This small coupling made it possible to determine the sign of J_{F-COCH_3} relative to J_{F-4} (*cf.* Table 2).

2-Fluoro-5-methylthiophene. This compound gives a strongly coupled ABM_3X spectrum (Fig. 2). The 3-proton spectrum as well as the spectrum



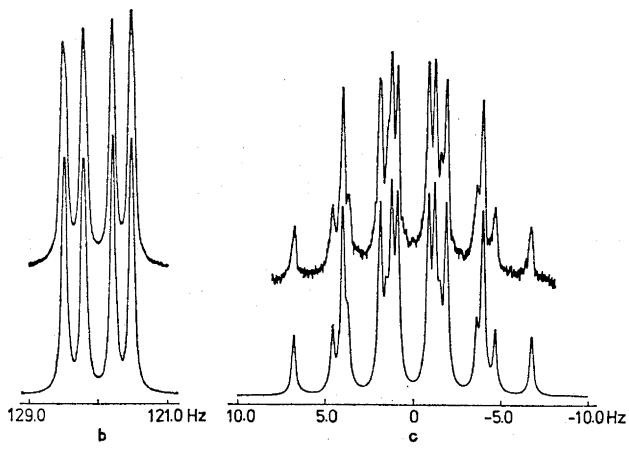


Fig. 2. The proton and fluorine magnetic resonance spectra at 56.444 MHz of 2-fluoro-5-methylthiophene. The upper parts show the experimental spectra and the computer simulated spectra are given below. The line-width of the Lorentzian lineshape used in the computer simulation is 0.26 Hz for all spectra. a, the ring proton spectrum. b, the spectrum of the methyl protons. c, the fluorine spectrum. The shifts in Hz of the protons are: $\nu_4 = 347.66$, $\nu_3 = 341.45$, $\nu_{CH_3} = 125.09$.

from the methyl protons consists of four relatively broad lines displaying no resolvable structure due to a non-zero coupling J_{CH_3-3}. The 3-proton lines (linewidth 0.4 – 0.5 Hz) and the methyl lines (linewidth 0.45 Hz) are, however, appreciably broader than the 4-proton lines (linewidth 0.25 Hz). In order to obtain a reasonable value for this coupling, the lineshapes of the signals due to both the ring protons and the methyl group were calculated, assuming a Lorentzian lineshape of a single NMR line. The theoretical ABM_3X spectra which formed the basis for lineshape analysis were calculated by the TWOSUM programme.[16] With a maximum uncertainty in the experimental linewidth equal to ± 0.02 Hz it was possible to obtain $J_{CH_3-3} = (0.24 \pm 0.03)$ Hz. The small differences in linewidth between the 3-proton lines belonging to different ABM_3 sub spin systems imply that $J_{CH_3-3} \times J_{CH_3-4} < 0$. A double resonance experiment * gave $J_{CH_3-4} \times J_{34} < 0$. These inequalities are in agreement with well known sign relations between these couplings.[17,18] For this compound it was also possible to obtain the relative signs of all couplings, as the asymmetry in the fluorine spectrum (*cf.* Fig. 2c) gave the sign of J_{F-CH_3} relative to $J_{CH_3-3} - J_{CH_3-4}$ (*cf.* Table 2).

2-Fluoro-5-ethylthiophene. No attempts were made to analyse the sidechain spectrum and therefore only the ABM_2X part of the total spetrum was considered. The subspectrum consists of a strongly coupled AB part with no resolvable structure in the four 3-proton lines due to a non-zero coupling J_{CH_3-3}. A lineshape analysis of this ring proton spectrum in the same manner as described above for the methyl compound gave, however, J_{CH_3-3} equal to (0.23 ± 0.03) Hz. The relative signs of the couplings are assumed to be the same as those of the methyl compound.[19]

2-Fluoro-5-propylthiophene. The ABM_2X subspectrum of this compound also consists of a strongly coupled AB part with no resolvable line-structure of the 3-proton lines. Lineshape analysis gave J_{CH_3-3} equal to (0.16 ± 0.04) Hz. In a benzene solution of this compound the protons are sufficiently strongly coupled to give an asymmetry in the fluorine spectrum, and thereby provide the inequality $J_{F-CH_3} \times (J_{CH_3-3} - J_{CH_3-4}) > 0$. The rest of the sign relations are assumed to be the same as those of the methyl and ethyl compounds above. The sidechain was not analysed.

2-Fluoro-5-butylthiophene. The lines of the ring proton spectrum of this compound have all about the same linewidth, and are broader than the lines of the 4-proton spectrum of the above three compounds. Consequently no lineshape analysis was performed. For this reason, the J_{CH_3-3} coupling is set equal to zero in the table, although it is probably non-zero. The signs of the couplings are assumed to be the same as those in the other 2-fluoro-5-alkylthiophenes.

2-Fluoro-5-t-butylthiophene. This compound gives a moderately strong coupled ABX spectrum. The lines of the 3-proton band are slightly broader (0.40 Hz) than those of the 4-proton band (0.32 Hz), indicating at least a small $J_{(CH_3)_3-3}$ coupling. The lines of the fluorine spectrum are unusually

* In order to avoid any ambiguity in the interpretation of the experiment the double resonance spectrum was compared with theoretical spectra obtained from complete numerical diagonalisation of the double resonance Hamiltonian matrix.

broad (≈0.7 Hz), probably due to an unresolvable coupling between the fluorine and the *t*-butyl group.

2-Fluoro-5-methylthiothiophene. There is a small coupling between the fluorine nucleus and the methylthio protons, equal to 0.30 Hz (Fig. 3). The

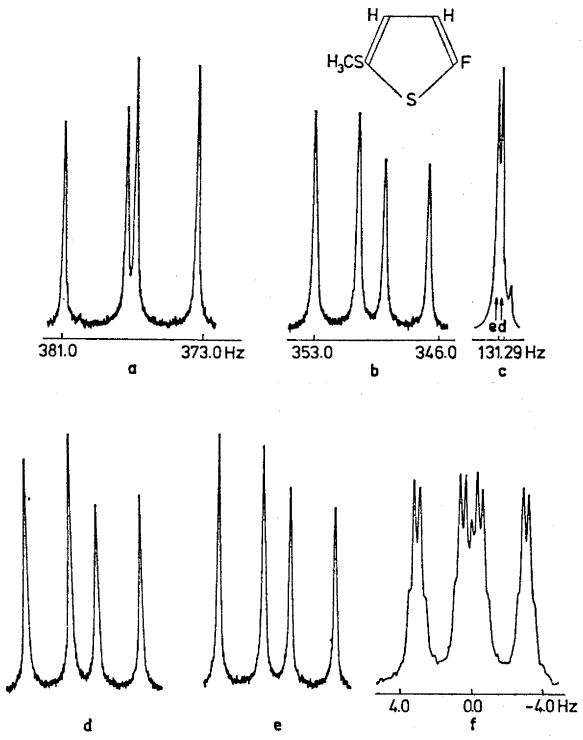


Fig. 3. The experimental proton and fluorine resonance spectra of 2-fluoro-5-methylthiothiophene at 56.444 MHz. a, the 4-proton spectrum. b, the 3-proton spectrum. c, the spectrum of the methylthio protons. The arrows give the positions of the decoupling r.f. field in a double resonance experiment with "selective" decoupling of J_{SCH_3-3}. The resulting 3-proton spectra are shown in Fig. 3, d and e. f, the fluorine spectrum. The proton shifts in Hz are: $\nu_4 = 377.04$, $\nu_3 = 349.86$, $\nu_{SCH_3} = 131.29$.

lines in the 3-proton band (0.26 Hz) are slightly broader than those in the 4-proton band (0.20 Hz) indicating a small J_{SCH_3-3} coupling. Comparison of experimentally determined ratios between the line intensities of the two proton spectra and those calculated for different values of J_{SCH_3-3} provided a value of (0.06 ± 0.02) Hz for this coupling. Decoupling with γH_2 in the SCH_3 band while observing the 3-proton spectrum showed $J_{F-3} \times J_{F-SCH_3} > 0$ (*cf.* Fig. 3).

2-Fluoro-5-methylsulphonylthiophene. The lines of the 4-proton band are rather broad (0.43 Hz) compared to those of the 3-proton spectrum (0.20 Hz), thereby revealing a small unresolvable $J_{SO_2CH_3-4}$ coupling. Lineshape analysis

on ring proton spectra recorded with an expanded sweep scale of 0.20 Hz/cm and with a sweep speed of 0.01 Hz/s was performed. This analysis gave a value of (0.13 ± 0.02) Hz for $J_{SO_2CH_3-4}$. A double resonance experiment showed $J_{F-4} \times J_{F-SO_2CH_3} > 0$.

2-Fluoro-5-methoxythiophene. Assignment of the proton spectra to the 3- and 4-proton is based on substituent effects on the proton chemical shifts (*cf.* Ref. 4). It should be noted that this is the only case hitherto observed, where J_{2F-3} is larger than J_{2F-4}. The lines of the 4-proton band are slightly broader than those of the 3-proton band.

2-Fluoro-5-thiophenealdoxime. The NMR spectrum of a freshly prepared sample of the oxime consisted of only one isomer with the expected ^1H and ^{19}F resonances. However, when the NMR spectrum of the same sample was reinvestigated two years later, the spectrum revealed the presence of another isomeric aldoxime, constituting 23 % of the mixture. Each 3-proton spectrum of the two isomers consists of four sharp lines (0.20 Hz) whereas each 4-proton spectrum appears with a coupling to the proton in the aldoxime group. The aldoxime proton spectrum of the predominant isomer consists of two broad lines (1.5 Hz) which are separated by the coupling to the fluorine. The large linewidth is probably due to spin-spin coupling to the ^{14}N nucleus, which is strongly relaxed by quadrupole interaction with electric field gradients in the liquid. On the other hand, the spectrum of the same proton of the minor isomer consists of four sharp lines (0.20 Hz). The smaller linewidth of the signals from this isomer are more likely to be due to smaller $^{14}N-C-H$ coupling than to a faster quadrupole relaxation relative to that in the other isomer. Indeed, it has been found that in ^{15}N-aldoximes the geminal $^{15}N-C-H$ coupling of the *anti* forms is about five times larger than that of the *syn* forms.[20,21] Consequently, the dominant isomer is assumed to be the *anti* form, and the other the *syn* form of 2-fluoro-5-thiophenealdoxime.

There is some overlap between the fluorine spectra of the two isomers. In the fluorine spectrum the lines (0.30 Hz) of the *anti* isomer are somewhat broader than the lines (0.20 Hz) of the *syn* isomer. The larger linewidth indicates the existence of a non-zero coupling between ^{19}F and ^{14}N which, combined with rapid quadrupole relaxation, gives the linewidth observed.

Only one signal from the hydroxyl proton is observed from the two isomers, with a large linewidth of about 45 Hz. The sign of J_{45} could not be determined in these compounds, but it is probably negative. This is the sign of J_{45} in 3-fluoro-5-thiophenealdoxime (*cf.* Table 6).

2-Fluoro-5-phenylthiophene. The lines of the fluorine spectrum are rather broad (≈ 0.6 Hz), which indicates unresolvable couplings between fluorine and the phenyl protons.

2.2. 4-Substituted 2-fluorothiophenes

2-Fluoro-4-chlorothiophene. The spectrum of this compound is an extremely strongly coupled ABX spectrum (Fig. 4). The intensities of the lines in the fluorine spectrum had to be considered in order to obtain the proper parameter set. From the analysis the same relative sign of the H–F couplings was

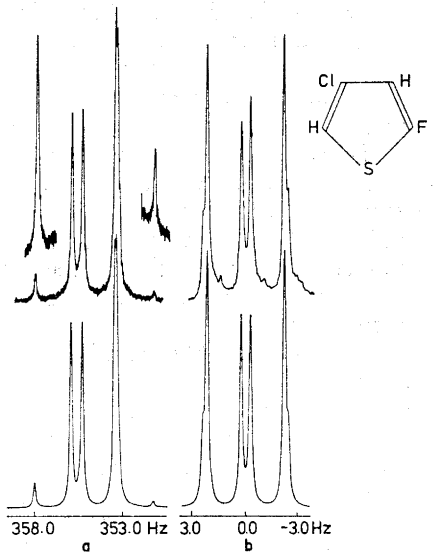


Fig. 4. The proton and fluorine resonance spectra of 2-fluoro-4-chlorothiophene at 56.444 MHz. The upper parts show the experimental spectra and the computer simulated spectra are given below. a, the proton spectrum. The two weakest lines in the spectrum shown are also recorded with about 4.5 times larger r.f. field and two times larger amplification than the total spectrum below. The proton shifts in Hz are: $\nu_5 = 354.81$, $\nu_3 = 354.32$. *b*, the fluorine spectrum, which is recorded with lower low pass filter than the proton spectrum.

obtained. The assignment of the H – F couplings is based on known magnitudes of these couplings from other 4-substituted 2-fluorothiophenes, where an assignment of the protons can unambiguously be done from chemical shift considerations. From the assignment done it follows that the 5-proton resonance frequency is to lower field than that of the 3-proton.

Table 3. Proton and fluorine chemical shifts in 4-substituted 2-fluorothiophenes.

Substituent	$-\delta_F$ ppm	$-\delta_{H_3}$ ppm	$-\delta_{H_5}$ ppm	$-\delta_{H_4}$ ppm
CH_3	30.61 ± 0.04	6.12	6.02	2.05
SCH_3	33.24 ± 0.03	6.28	6.13	
C_6H_5	31.99	6.61	6.53	
Cl	35.36	6.28	6.29	
Br	34.60	6.33	6.46	
I	33.25	6.37	6.63	
CN	34.49	6.65	7.34	
CHO	35.38	6.79	7.52	9.62
$COCH_3$	33.40	6.79	7.42	2.33
COOH [a]	33.00	6.92	7.70	
$COOCH_3$	32.98	6.78	7.38	
CHNOH *anti* [a,b]	29.56	7.11	7.51	7.25
CHNOH *syn* [a,b]	32.39	6.82	7.02	7.99
SO_2CH_3 [a]	36.72	7.02	7.72	3.14

[a] Dissolved in acetone.
[b] The shift of the hydroxyl proton is – 10.8 ppm for the *anti* isomer, and – 10.2 ppm for the *syn* isomer.

2-Fluoro-4-thiophenealdehyde. The lines of the 5-proton spectrum and the aldehyde band are as sharp as those of the 3-proton spectrum (0.12 Hz), providing no evidence for a non-zero J_{CHO-5} coupling. The sign of J_{CHO-3} could not be determined in this compound, but on the basis to earlier findings in thiophene- and furanaldehydes [8,9] it is probably negative.

2-Fluoro-4-acetylthiophene. There is no resolvable coupling between the $COCH_3$ group and the fluorine nucleus, but the lines in the fluorine spectrum are somewhat broader (≈ 0.5 Hz) than those of the proton spectra (0.35 Hz).

2-Fluoro-4-methylthiophene. The splittings due to J_{F-CHO} (0.11 Hz) could only be resolved in the fluorine spectrum, where they give rise to a significant asymmetry, which is consistent with J_{F-CH_3} and $J_{CH_3-3} - J_{CH_3-5}$ having the same sign.

2-Fluoro-4-methylthiothiophene. The lines of the 5-proton band are somewhat broader than those in the 3-proton spectrum (linewidths 0.45 Hz and 0.33 Hz, respectively), and the lines of the fluorine spectrum are rather broad (≈ 0.70 Hz), indicating unresolvable J_{SCH_3-5} and J_{F-SCH_3} couplings.

2-Fluoro-4-methylsulphonylthiophene. No resolvable couplings to the SO_2CH_3 group are observed. The lines (0.45 Hz) of the 5-proton spectrum and those of the fluorine spectrum (0.40 Hz) are broader than the 3-proton lines (0.30 Hz), which provides evidence for unresolvable couplings $J_{SO_2CH_3-5}$ and $J_{F-SO_2CH_3}$.

2-Fluoro-4-thiophenealdoxime. The synthesis of 2-fluoro-4-thiophenealdoxime [3] led to two fractions, one crystalline, and one liquid. The NMR spectrum of the crystalline fraction indicated it to consist of one isomer, most probably the *anti* isomer judging from the broad aldoxime doublet (Fig. 5). The liquid fraction consisted predominantly of the *syn* form. On standing, the *anti* form isomerised to a mixture of *syn* and *anti* forms, containing more than 50 % of the *syn* form. As the substituent shift of the aldoxime

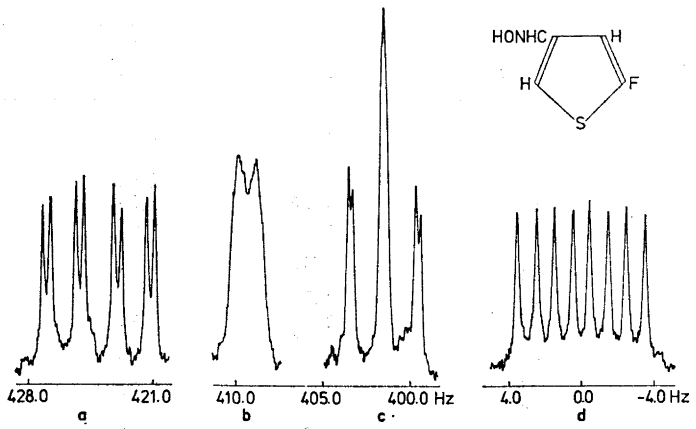


Fig. 5. The proton and fluorine spectra of the *anti* isomer of 2-fluoro-4-thiophenealdoxime at 56.444 MHz. a, the 5-proton spectrum. b, the aldoxime proton spectrum. c, the 3-proton spectrum. d, the fluorine spectrum. The proton shifts in Hz are: $\nu_5 = 424.03$, $\nu_{CHNOH} = 409.27$, and $\nu_3 = 401.46$.

Table 4. Spin-spin coupling constants in 4-substituted 2-fluorothiophenes.

Substituent	$J_{3,5}$ Hz	J_{F-3} Hz	J_{F-5} Hz	J_{F-4} Hz
CH_3 [a]	1.98	1.55	3.55	0.11
SCH_3	2.02	1.34	3.44	
C_6H_5	2.03	1.74	3.54	
Cl	2.03	0.95	3.40	
Br	1.98	0.78	3.32	
I	1.85	0.61	3.13	
CN	1.85	1.18	3.55	
CHO [b]	1.81	1.37	3.63	3.29
$COCH_3$	1.88	1.53	3.55	
COOH	1.88	1.56	3.92	
$COOCH_3$	1.85	1.36	3.86	
CHNOH *anti* [c]	1.88	2.04	3.97	1.07
CHNOH *syn* [d]	1.88	1.98	3.78	2.27
SO_2CH_3	2.00	1.12	3.82	

[a] $J_{CH_3-3} = -0.34$ Hz, and $J_{CH_3-5} = -1.19$ Hz.
[b] $|J_{CHO-3}| = 0.38$ Hz.
[c] $J_{CHNOH-3} = -0.27$ Hz, and $J_{CHNOH-5} = -0.46$ Hz.
[d] $J_{CHNOH-3} = -0.47$ Hz, and $J_{CHNOH-5} = -0.43$ Hz.

group of 3-thiophenealdoxime is not available, the assignment of the protons is based on the magnitudes of the H – F couplings. This can be safely done, since J_{F-5} lies between 3 and 4 Hz and J_{F-3} is smaller than 2 Hz for the remainder of the 4-substituted 2-fluorothiophenes (*cf.* Table 4).

The aldoxime proton spectrum of the *syn* form (Fig. 6) gives a doublet of triplets with lines as sharp as those of the 3- and 5-proton spectra. The hydroxyl proton line of the *anti* isomer (linewidth ≈45 Hz) is also much broader than that of the *syn* isomer (linewidth 3 Hz). The smaller linewidth of the

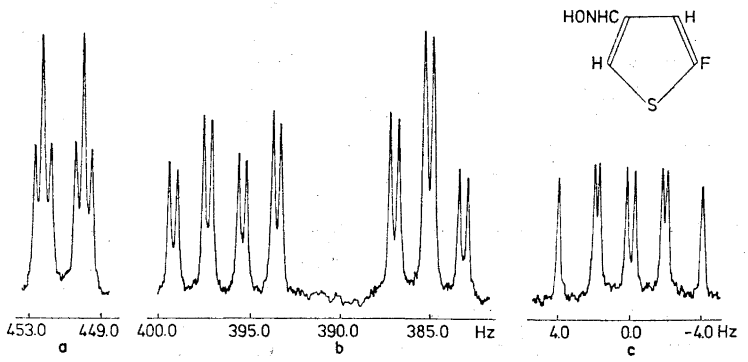


Fig. 6. The proton and fluorine spectra of the *syn* isomer of 2-fluoro-4-thiophenealdoxime at 56.444 MHz. a, the aldoxime proton spectrum. b, the ring proton spectrum. c, the fluorine spectrum. The proton shifts in Hz are: $\nu_{CHNOH} = 451.14$, $\nu_5 = 396.37$, and $\nu_3 = 385.20$.

side-chain proton spectrum of the *syn* isomer is probably due to a smaller $^{14}N-C-H$ coupling of the *syn* isomer compared to that of the *anti* isomer, as suggested above for 2-fluoro-5-thiophenealdoxime.

2.3. 5-Substituted 3-fluorothiophenes

3-Fluoro-5-thiophenealdehyde. The 4-proton couples with an almost unresolvable coupling to the aldehyde proton (Fig. 7). Lineshape analysis was performed on ring proton spectra recorded with an expanded sweep scale of 0.20 Hz/cm and for the 4-proton spectrum also 0.10 Hz/cm and with a sweep

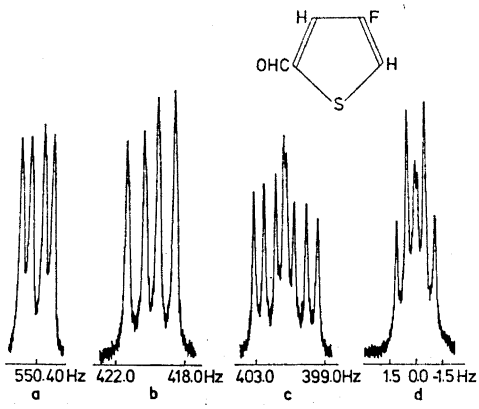


Fig. 7. The proton and fluorine resonance spectra of 3-fluoro-5-thiophenealdehyde at 56.444 MHz. a, the aldehyde proton spectrum. b, the 4-proton spectrum. c, the 2-proton spectrum. d, the fluorine spectrum. The proton shifts in Hz are: $\nu_{CHO}=550.40$, $\nu_4=419.89$, $\nu_2=401.30$.

speed of 0.01 Hz/s. This analysis provided a value of (0.14 ± 0.02) Hz for J_{CHO-4}. The signs of J_{CHO-2} and J_{CHO-4} were determined by double resonance. J_{CHO-4} is of opposite sign to J_{24} and J_{CHO-2} carries the same sign as J_{24} in agreement with earlier experiments.[9,13,22,23]

3-Fluoro-5-methylthiothiophene. The SCH_3 protons couple with the fluorine ($J_{F-SCH_3}=0.11$ Hz). This is most easily resolved in the fluorine spectrum, but the sign of this coupling could not be determined. The 2-hydrogen lines (0.22 Hz) are slightly broader than those of the 4-hydrogen (0.18 Hz).

3-Fluoro-5-acetylthiophene. The lines of the fluorine spectrum are very sharp (0.16 Hz), indicating a zero coupling to the $COCH_3$ group. All of the lines in the proton spectrum apparently have the same linewidth (≈0.30 Hz), which is probably due to small couplings with the $COCH_3$ group.

3-Fluoro-5-methylsulphonylthiophene. The assignments of the protons are based on additivity considerations of proton chemical shifts, but is not as unambiguous as for the other compounds. The lines of both the proton and fluorine spectra are broad (0.4 Hz).

3-Fluoro-5-thiophenealdoxime. The NMR spectrum of only one isomer, most probably the *anti* form, could be observed for this aldoxime, although

Table 5. Proton and fluorine chemical shifts in 5-substituted 3-fluorothiophenes.

Substituent	$-\delta_F$ ppm	$-\delta_{H_2}$ ppm	$-\delta_{H_4}$ ppm	$-\delta_{H_5}$ ppm
CH_3	34.65	6.21	6.36	2.28
SCH_3	36.59	6.48	6.70	2.36
C_6H_5	36.05	6.38	6.83	
Cl	38.40	6.31	6.59	
Br	37.76	6.46	6.71	
I	36.58	6.56	6.86	
CN [b]	36.35	6.90	7.22	
CHO	36.97	7.11	7.44	9.75
$COCH_3$	37.22	6.97	7.33	2.41
COOH [a]	36.88	7.31	7.54	
$COOCH_3$	36.48 ± 0.03	6.87	7.36	
CHNOH *anti* [a,c]	31.72	7.10	7.23	7.69
SO_2CH_3 [a]	38.21	7.50	7.61	3.26
NO_2	41.02	7.44	7.83	

[a] Dissolved in acetone.
[b] The parameters of this compound in acetone solution are: $\delta_F = -36.10$, $\delta_{H_2} = -7.47$, $\delta_{H_4} = -7.66$ ppm.
[c] The shift of the hydroxyl proton is -11.2 ppm.

Table 6. Spin-spin coupling constants in 5-substituted 3-fluorothiophenes.

Substituent	J_{24} Hz	J_{F-2} Hz	J_{F-4} Hz	J_{F-5} Hz
CH_3 [a]	1.70	1.45	−0.69	−0.22
SCH_3 [b]	1.75	1.75	−0.90	0.11
C_6H_5	1.65	1.21	−0.54	
Cl	1.99	2.00	−0.80	
Br	1.90	1.88	−0.96	
I	1.73	1.54	−1.16	
CN [e]	1.72	1.08	−0.86	
CHO [c]	1.73	0.58	−0.99	0.57
$COCH_3$	1.69	0.78	−0.96	
COOH	1.84	1.15	−0.80	
$COOCH_3$	1.83	0.87	−0.87	
CHNOH *anti* [d]	1.80	1.61	−0.55	
SO_2CH_3	1.87	0.87	−1.09	
NO_2	2.28	1.55	−0.89	

[a] $J_{CH_3-2} = -0.23$ Hz, and $J_{CH_3-4} = -1.08$ Hz.
[b] The sign of J_{F-SCH_3} could not be determined.
[c] $J_{CHO-2} = 1.29$ Hz, and $J_{CHO-4} = -0.14$ Hz.
[d] $J_{CHNOH-2} = 0.83$ Hz, and $J_{CHNOH-4} = -0.41$ Hz.
[e] The coupling constants of this compound in acetone solution are: $J_{24} = 1.78$ Hz, $J_{F-2} = 1.45$ Hz, and $J_{F-4} = -0.67$ Hz.

the spectrum indicated the presence of trace amounts of the other isomer. The assignment of the ring protons can be based on proton chemical shift data [6] as well as on the couplings between the ring protons and the aldoxime proton.[6] There is no observable coupling between fluorine and the aldoxime proton, and the linewidth of the fluorine lines is equal to that of the ring proton lines. The aldoxime proton consists of one broad line (2.0 Hz), and the hydroxyl proton line is also very broad ($\approx$40 Hz).

Through our studies the NMR parameters for a large number of substituted fluorothiophenes have become available. To our knowledge, the only other investigation of such compounds is a study of tetrafluorothiophene and two methoxytrifluorothiophenes.[24]

3. EXPERIMENTAL

The NMR spectra were obtained using a Varian Associates HA-60 spectrometer operating at 56.444 MHz. All spectra were recorded in the frequency sweep mode. The lock signal for internal stabilization was from TMS (present in *ca.* 5 % by wt.) for the proton spectra, and from hexafluorobenzene (present in *ca.* 10 % by wt.) for the fluorine spectra. The lock frequency was in both cases produced by a Muirhead D-890-A decade oscillator. The frequencies of the lines in the spectrum were measured by taking the period average of the sweep frequencies and the lock frequency on a Hewlett-Packard frequency counter model 3734A. In these measurements, the sweep frequency was swept to exact resonance of the peak to be counted for both sweep directions, and a mean value was taken. The uncertainty in the frequency of well-resolved lines is at most $\pm$0.03 Hz. The fluorine spectra were for most of the compounds recorded at four different concentrations in cyclohexane (or, if not soluble, in acetone) in order to obtain values extrapolated to infinite dilution for the fluorine chemical shifts. In the double resonance experiments the third r.f. field was obtained by amplitude modulation of the magnetic field. The modulation frequency was produced by a Philips oscillator PP 6050.

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