ACTA CHEMICA SCANDINAVICA 25 (1971) 3841–3854

Nuclear Magnetic Resonance of Aromatic Heterocyclics

V. The ^1H and ^{19}F Spectra of Substituted Fluorothiophenes. NMR Parameters and Substituent Effects

SÖREN RODMAR,[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 chemical shifts and spin-spin coupling constants of 5- and 4-substituted 2-fluorothiophenes and of 5-substituted 3-fluorothiophenes have been correlated with the reactivity constants $\mathscr{F}$ and $\mathscr{R}$ of Swain and Lupton by means of linear two parameter equations $z = i + f\mathscr{F} + r\mathscr{R}$. Good correlations are obtained for most of the NMR parameters, except for J_{2F-3} and J_{2F-5} in 4-substituted 2-fluorothiophenes, and J_{3F-4} in 5-substituted 3-fluorothiophenes. The atoms Br and I have been excluded in the regression analyses of the fluorine shifts and coupling constants, and for the fluorine shift in 5-substituted 2-fluorothiophenes, the SCH_3 group has also been excluded, as these groups deviate significantly more from the correlations than other groups. A possible reason for this behaviour is indicated. For the proton shifts, I and SCH_3 have not been included on the same grounds. The relative inductive and mesomeric contributions to the shifts and coupling constants, as expressed by the constants f and r, are discussed. The substituent effects on the ^{19}F and ^1H chemical shifts of the fluorothiophenes are compared with those on the ^{19}F chemical shifts of fluorobenzenes and on the ^1H chemical shifts of monosubstituted thiophenes. One linear relation between the spin coupling constants J_{2F-3} and J_{3F-2} in the 5-substituted fluorothiophenes, and one between the fluorine shifts in the "meta" substituted fluorothiophenes are given.

1. INTRODUCTION

In the preceding paper [1] the ^1H and ^{19}F spectra of a number of 5- and 4-substituted 2-fluorothiophenes and 5-substituted 3-fluorothiophenes were analysed and the NMR parameters were tabulated. The three series of *ortho* substituted fluorothiophenes were not studied due to possible complicating influence of steric effects on the NMR parameters.

2. DISCUSSION

In order to interpret substituent effects on spin-spin couplings and chemical shifts it has been very common to relate the couplings to the electronegativity of the substituents and the chemical shifts either to the electronegativity or to different sets of substituent parameters (for a review see Ref. 2). During recent years correlations between spin couplings and substituent parameters have also been found (*cf.* below).

Thus good correlations have in this way been established for H – H couplings in monosubstituted ethylenes,[3,4] mono- and disubstituted benzenes,[5–9] *N*-substituted pyridines,[10] and 2-substituted thiophenes.[11] The dependence on electronegativity and the short-range character of the substituent effects on H – H couplings have been taken as evidence for an inductive mechanism of these couplings where the substituent effect is primarily transmitted through the σ electrons. In halosubstituted fluorobenzenes, the H – F couplings have also been shown to correlate well with the electronegativity of the substituents.[12,13]

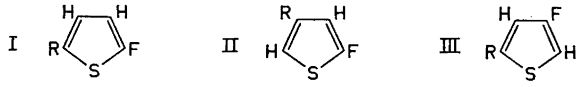
Correlations have also been found between F – F spin coupling constants in pentafluorophenyl derivatives and substituent parameters σ_I, σ_R[14], between F – F spin couplings in pentafluorophenyl and fluorophenyl derivatives and σ_m, σ_p,[14,15] and between ring proton-aldehyde proton couplings in benzaldehyde derivatives and $\mathscr{F}$, $\mathscr{R}$.[16] Methyl $^{13}C-H$ couplings in benzene derivatives[17] and $^{15}N-H$ couplings in aniline derivatives[18] have also been correlated with Hammett substituent constants.

Chemical shifts have been more extensively related to reactivity parameters than spin couplings, and good correlations between ^1H, ^{13}C and ^{19}F chemical shifts in aromatic molecules and Hammett constants σ_m, σ_p and Taft constants σ_I, σ_R have been found.[2,14,17,19,20]

In the present work we have attempted to make empirical correlations for these NMR parameters of substituted fluorothiophenes in order to obtain a better understanding of substituent effects on this class of compounds.

2.1. Electronegativity correlations

H – H couplings. At first it is reasonable to attempt to correlate the H – H couplings with substituent electronegativities in the three different series of molecules studied.



If the correlations are restricted to the halogen substituents linear relations (not shown) are obtained. The H – H couplings increase with increasing electronegativity (according to Pauling) with a maximum deviation of 0.03 Hz from the line. However, the points for the unsubstituted fluorothiophenes lie 0.07 Hz below these lines. Plots with inclusion of a few substituents contain-

ing more than one atom using Dailey and Shoolery electronegativities[21] show greater scatter. This is probably due to difficulties in defining electronegativities for groups.

H−F couplings. The three *ortho* H−F couplings show a linear increase with increasing electronegativity of the halogens, with a maximum deviation of 0.11 Hz. The points for the unsubstituted compounds lie considerably away from these lines and the differences are as much as 1.1 Hz and 0.5 Hz for J_{2F-3} in II and J_{3F-4} in III, respectively. A plot of the two remaining H−F couplings J_{2F-4} in I and J_{2F-5} in II, shows an almost linear increase with electronegativity from I to Cl, with the point for H near this line, but with F as substituent some kind of a saturation effect on these couplings seems to enter, and they are of the same size as the couplings for Cl, or slightly smaller. The increase with electronegativity of J_{2F-3} in I and of J_{3F-2} in III is opposite to that found for the *ortho* H−F couplings in monohalosubstituted fluorobenzenes, where there is an increase in the couplings only when the substituent is *ortho* to either the fluorine or the proton involved. Otherwise there is a slight decrease with increasing electronegativity.[13] Attempts to include substituents containing more than one atom were not at all successful. It is very likely that the H−F couplings are not only influenced by inductive factors, but that they are also sensitive to mesomeric variations.[13] The good correlations obtained for the halogens may be due to the fact that the +M character of the halogens decreases with decreasing electronegativity.

2.2. Correlation with reactivity parameters

Since the introduction by Hammett of substituent constants to relate structure to reactivity, attempts have been made to modify these constants in various ways. Significant progress was made by the introduction of two-parameter equations.[22] This, however, has led to over twenty sets of substituent constants. Recently, Swain and Lupton constructed a new set of substituent constants, the field (inductive) parameter $\mathcal{F}$ and the resonance parameter $\mathcal{R}$, which they claim to be more physically significant independent variables than earlier sets.[23] However, it should be noted that substituent constants have mainly been obtained from reactivity measurements on benzene derivatives. Attempts to apply the Hammett treatment to thiophene derivatives have hitherto been only moderately successful due to the limited number of reactions and substituents studied (For reviews see Refs. 24, 25). Some authors have tried to construct a special set of σ-constants for substituents connected with a thiophene ring, using the same reaction constants ϱ as for benzenes.[25,26] Attempts have also been made to ascribe special σ-values to the 2- and 3-thienyl groups.[27,28] However, we find it basically more sound to keep the substituent constants for each group fixed and allow the reaction or regression (*cf.* below) constants to vary with the nature of the aromatic ring and the relative position between substituent and reaction center or atoms involved in the physical property under investigation. Some recent reactivity data indicate that similar σ- and ϱ-values may be used for thiophenes and benzenes.[26,29]

Table 1. $\mathcal{F}$ and $\mathcal{R}$ constants from Ref. 23 for the substituents used in the regression analyses in this paper.

Substituent	$\mathcal{F}$	$\mathcal{R}$	Substituent	$\mathcal{F}$	$\mathcal{R}$
OCH_3	0.413	−0.500	I	0.672	−0.197
CH_3	−0.052	−0.141	CN	0.847	0.184
$C(CH_3)_3$	−0.104	−0.138	$COCH_3$	0.534	0.202
SCH_3	0.332	−0.186	COOH	0.552	0.140
Phenyl	0.139	−0.088	SO_2CH_3	0.900	0.215
F	0.708	−0.336	NO_2	1.109	0.155
Cl	0.690	−0.161	H	0.000	0.000
Br	0.727	−0.176	SH	0.464	−0.111

We have therefore mainly used the reactivity parameters of Swain and Lupton [23] in order to correlate NMR data, although some attempts have also been made to use the ordinary Hammett σ_p and σ_m values.

The various NMR parameters were assumed to be correlated with a linear combination of the substituent parameters $\mathcal{F}$ and $\mathcal{R}$. For convenience these parameters for the substituents included in the regression analyses in this paper are listed in Table 1. The regression equations,

$$z_k = i_k + f_k\mathcal{F} + {}_kr\mathcal{R} \qquad (1)$$

where z_k is the NMR parameter, i_k is the intercept and f_k, r_k are the regression constants, were calculated by a linear least-squares multiple correlation computer program.

Since the H − F couplings were found to be solvent dependent,[30] the compounds dissolved in acetone were excluded in the regression analyses of these couplings. The fluorine chemical shifts are estimated not to differ more than

Table 2. Regression equations relating the ^{19}F chemical shifts [a] of monosubstituted fluorothiophenes and fluorobenzenes [b] to the substituent constant $\mathcal{F}$ and $\mathcal{R}$.

Equation	σ [c]	C [d]	N [e]
$\delta_F^{I} = -3.8 \pm 1.1 - (7.5 \pm 1.8)\mathcal{F} - (25.0 \pm 3.1)\mathcal{R}$	2.2	0.96	12
$\delta_F^{II} = -1.3 \pm 0.5 - (8.0 \pm 0.9)\mathcal{F} + (5.3 \pm 1.6)\mathcal{R}$	0.9	0.94	10
$\delta_F^{III} = -1.6 \pm 0.6 - (6.4 \pm 1.0)\mathcal{F} + (4.9 \pm 1.6)\mathcal{R}$	1.1	0.89	11
$\delta_F^{p} = 1.0 \pm 0.8 - (5.0 \pm 1.2)\mathcal{F} - (22.5 \pm 1.5)\mathcal{R}$	1.5	0.98	16
$\delta_F^{m} = 0.9 \pm 0.3 - (4.2 \pm 0.4)\mathcal{F} - (0.6 \pm 0.5)\mathcal{R}$	0.5	0.95	14

[a] In the regression analyses the shifts are given in ppm relative to that of the unsubstituted compound, and a minus sign of a shift means a downfield shift.

[b] The experimental shifts of the *para* and *meta* substituted fluorobenzenes are taken from Ref. 39.

[c] Standard deviation in ppm.

[d] Correlation coefficient.

[e] Number of substituents in the regression analysis.

0.5 ppm between the cyclohexane and acetone solutions,[30] and the H–H couplings are solvent independent. Therefore all of the substituents regardless of solvent are included in the analyses of these two parameters.

Table 3. Regression equations relating the spin-spin coupling constants (in Hz) of monosubstituted fluorothiophenes to the substituent constants $\mathcal{F}$ and $\mathcal{R}$.

Equation	σ	C	N
$J_{34}^{I} = 3.91 \pm 0.05 + (0.59 \pm 0.09)\mathcal{F} - (0.11 \pm 0.16)\mathcal{R}$	0.11	0.90	13
$J_{2F-3}^{I} = 1.54 \pm 0.04 + (0.99 \pm 0.06)\mathcal{F} - (3.17 \pm 0.12)\mathcal{R}$	0.08	0.99	11
$J_{2F-4}^{I} = 3.26 \pm 0.09 + (0.58 \pm 0.15)\mathcal{F} + (0.72 \pm 0.28)\mathcal{R}$	0.19	0.85	11
$J_{35}^{II} = 1.83 \pm 0.06 + (0.27 \pm 0.10)\mathcal{F} - (0.69 \pm 0.17)\mathcal{R}$	0.10	0.80	10
$J_{2F-3}^{II} = 1.64 \pm 0.11 - (0.57 \pm 0.20)\mathcal{F} + (0.35 \pm 0.37)\mathcal{R}$	0.18	0.69	8
$J_{34}^{III} = 1.52 \pm 0.07 + (0.62 \pm 0.11)\mathcal{F} - (0.78 \pm 0.22)\mathcal{R}$	0.12	0.87	11
$J_{3F-2}^{III} = 0.90 \pm 0.06 + (0.98 \pm 0.10)\mathcal{F} - (3.30 \pm 0.22)\mathcal{R}$	0.11	0.98	9
$J_{3F-4}^{III} = -0.83 \pm 0.10 + (0.07 \pm 0.15)\mathcal{F} - (0.82 \pm 0.33)\mathcal{R}$	0.17	0.60	9

The regression equations for the fluorine chemical shifts and the spin couplings are given in Tables 2 and 3, respectively, together with standard deviations and correlation coefficients.* The substituents Br and I, and for the fluorine chemical shift δ_F in I also the SCH_3 group, were excluded from the least-squares fit calculations as the values calculated from the regression equations deviate considerably more from the experimental ones for these substituents than for the others.

5-Substituted 2-fluorothiophenes (I). For compounds of the general structure I there are good correlations for all of the parameters, especially for J_{2F-3}. According to the regression equation for δ_F in I, the substituent contributions to the chemical shift from the $\mathcal{F}$ and $\mathcal{R}$ terms for –I–M substituents are both negative, giving large downfield shifts, whereas for the –I+M substituents the two contributions are of opposite signs and thereby in some cases with strong +M substituents (OCH_3, F) upfield shifts are observed. For the J_{2F-3} coupling the constants f and r are of opposite signs and therefore large values of J_{2F-3} are obtained for the +M substituents, while for the –M substituents the two terms partially cancel each other and small substituent contributions are obtained. Plots of the experimental fluorine chemical shifts and J_{2F-3} couplings *vs.* the values calculated from the equations in Tables 2 and 3 are shown in Figs. 1 and 2, respectively. The correlation for J_{2F-4} is not as good as for the two former parameters. The regression constants are again of the same sign and the largest coupling is observed for the NO_2 substituted compound. Compared to J_{2F-3} the inductive contribution as expressed by the ($f\mathcal{F}$) term is relatively more important and gives the largest contribution, except for the methoxy and the alkyl groups. J_{34} shows no significant dependence on $\mathcal{R}$, which is consistent with the assumption that the substituent effects

* In the regression analyses of the parameters given in the tables, the unsubstituted fluorothiophenes[31] and the difluorothiophenes are also included.[32]

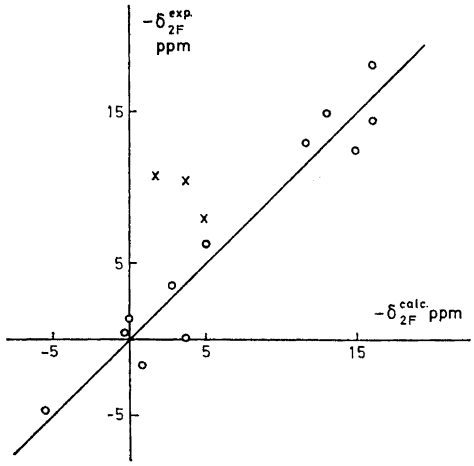


Fig. 1. Plot of the experimental fluorine shift in 5-substituted 2-fluorothiophenes *vs.* the quantity $\delta_{2F}^{calc} = -3.8 - 7.5\mathscr{F} - 25.0\mathscr{R}$. The shift is given in ppm relative to that of 2-fluorothiophene. The line represents perfect agreement between experimental and calculated shifts. The positions of the groups Br, I, and SCH_3 are marked with × (see the text).

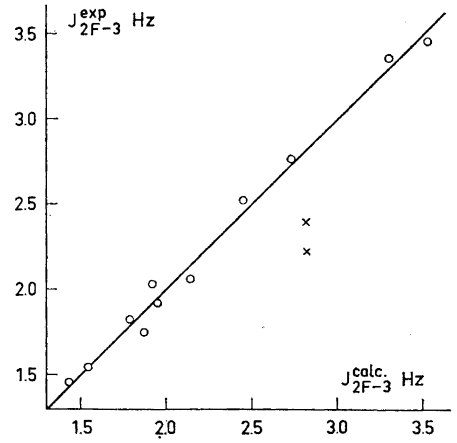


Fig. 2. Plot of the experimental H–F spin-spin coupling constant J_{2F-3}^{exp} in Hz in 5-substituted 2-fluorothiophenes *vs.* the best combination of the substituent constants $\mathscr{F}$ and $\mathscr{R}$, $J_{2F-3}^{calc} = 1.54 + 0.99\mathscr{F} - 3.17\mathscr{R}$. The positions of the substituents Br and I are marked with × (*cf.* text) and the lines is of unit slope.

on vicinal H–H couplings primarly operate *via* the σ-electron framework.[10,13]

5-Substituted 3-fluorothiophenes (III). The major contribution to δ_F comes from the $\mathscr{F}$ term, and ($f\mathscr{F}$) is 2 to 9 times larger than ($r\mathscr{R}$). As seen from Table 3 the regression constants r, f for J_{3F-2} in III and for J_{2F-3} in I are almost

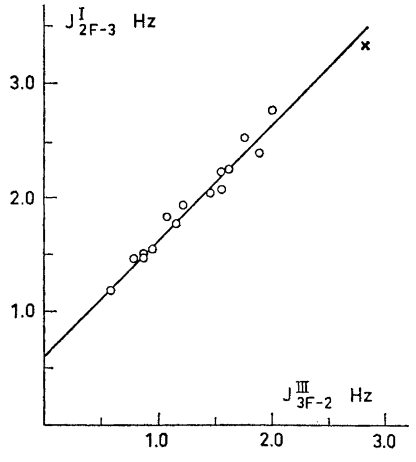


Fig. 3. The spin coupling constant J_{2F-3}^{I} in Hz in 5-substituted 2-fluorothiophenes plotted against the spin coupling constant J_{3F-2}^{III} in 5-substituted 3-fluorothiophenes. The line is given by the equation $J_{2F-3}^{I} = 0.61 + 1.02J_{3F-2}^{III}$. The point for the two couplings with F as substituent is marked with × since these couplings were not included in the regression analysis (*cf.* text).

equal, and the intercept differs by 0.63 Hz, which shows the existence of a linear relationship between these two couplings with a slope close to unity. A least-squares fit gives

$$J_{2F-3}^{I} = 0.61 \pm 0.07 + (1.02 \pm 0.05) J_{3F-2}^{III} \quad (2)$$

with a correlation coefficient equal to 0.98 and a standard deviation of 0.08 Hz. A plot of this correlation is shown in Fig. 3. In the calculation of regression equation (2) more compounds were included than in the equations of Table 3 as the solvent effects seem to be the same for the two couplings involved, and some substituents have also been included for which no $\mathscr{F}$ and $\mathscr{R}$ parameters are available. Fluorine is excluded since there is no J_{2F-3}^{I} value exactly determined in this case. The J_{3F-2} coupling of 3,5-difluorothiophene equal to 2.81 Hz in eqn. (2) gives J_{2F-3}^{I} in 2,5-difluorothiophene equal to 3.48 Hz which is a little larger than the mean value 3.36 Hz of J_{2F-3}^{I} and J_{2F-4}^{I} used in the regression analyses of Table 3. The equations for J_{2F-3}^{I} and J_{2F-4}^{I} in this table on the other hand put J_{2F-3}^{I} equal to 3.30 Hz and J_{2F-4} equal to 3.43 Hz, but it is not possible on statistical grounds to draw any definite conclusion about the relative size of these two couplings.

For J_{24} the inductive contribution is a few times larger than the resonance contribution for all substituents except the CH_3 group. It is interesting to note that the regression constant f in the equation for J_{24}^{III} is equal to that in the equation for J_{2F-4}^{I}, while the regression constants r have the same absolute value but opposite signs. The poor correlation for J_{3F-4} may be due in part to a small concentration dependence. Owing to the small range of this coupling (0.62 Hz for the compounds included in the regression analysis), the concentration dependence is relatively more important for J_{3F-4} than for J_{3F-2}, but it is also possible that the simple dependence on the $\mathscr{F}$ and $\mathscr{R}$ parameters assumed breaks down for this coupling.

4-Substituted 2-fluorothiophenes (II). There is a good correlation for δ_F and an acceptable correlation for J_{35}, but the correlation for J_{2F-3} is poor, and there is no significant correlation between J_{2F-5} couplings and the $\mathscr{F}$ and $\mathscr{R}$ parameters of the type described by eqn. (1). The dependence of δ_F^{II} on the $\mathscr{F}$ and $\mathscr{R}$ parameters is similar to that of δ_F^{III}, indicating a linear relation between the two fluorine chemical shifts. Least-squares fit analysis gives

$$\delta_F^{III} = -0.2 \pm 0.5 + (0.81 \pm 0.08)\ \delta_F^{II} \quad (3)$$

with a standard deviation of 0.8 ppm and a correlation constant of 0.93. A plot of this correlation is shown in Fig. 4. The ($f\mathscr{F}$) and ($r\mathscr{R}$) contributions to J_{35} are of the same magnitude and cancel each other to some extent for $-I-M$ substituents. J_{2F-5} has the smallest substituent dependence of all the $H-F$ couplings studied in this work. The variation of this coupling in the regression analysis is 0.47 Hz, and it is 0.78 Hz for all of the compounds in cyclohexane solutions. The poor correlation for J_{2F-3} is more difficult to understand. The small and insignificant dependence on $\mathscr{R}$, in contrast to J_{2F-3} in I and J_{3F-2} in III, reflects the small mesomeric effect on the 2 position in this type of compounds as compared to compounds such as I and III.

In the regression analyses giving the equations of Tables 2 and 3 the heavier atoms Br and I, and for δ_F in I also the SCH_3 group, were excluded because

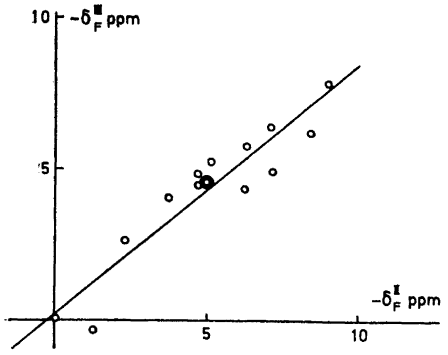


Fig. 4. The fluorine shift in 5-substituted 3-fluorothiophenes plotted against the fluorine shift in 4-substituted 2-fluorothiophenes. The shifts are given in ppm relative to those of 2- and 3-fluorothiophene. The line represents the equation $\delta_F^{III} = -0.2 + 0.81\ \delta_F^{II}$.

they deviated significantly more than the other substituents from the correlation lines for some of the NMR parameters (*cf.* Figs. 1 and 2).

The points for these substituents may be moved closer to the lines if they are given more positive $\mathscr{R}$ values than those of Ref. 23, which then indicates a decrease of the π-electron donor property when they are connected to the fluorothienyl ring compared to the situation in disubstituted benzenes. For these substituents it is assumed to be a donation of π electrons from the thienyl ring to vacant *d* orbitals in the valence shells on Br, I, and S which counterbalance the π $(p-p)$ donation of these substituents to the ring (*cf.* Refs. 33 – 35). The relative importance of these two possible routes for π-electron transfer then determines the π-electron acceptor-donor property of the substituent. CNDO – MO calculations [36] with and without 3*d* orbitals on S shows that the $3p\pi$-electron density on S of SCH_3 is the same in both cases, whereas there is a decrease of the $p\pi$-electron density of the fluorothienyl ring at the expense of a small nonzero $3d\pi$-electron density of S in the former calculation compared to the latter. For the SO_2CH_3 group, on the other hand, the presence of the *d* orbitals does not change the electron withdrawing property of this group as the electron density in the 3*d* orbitals on S equals the difference in populations of the *p* orbitals (mainly on sulphur and the two oxygens) between the two calculations, and this may explain the good correlations obtained for this group with the substituent parameters of Ref. 23. It should be mentioned that from the CNDO results cited above only qualitive conclusions should be drawn and therefore it is more the effect of *d*-orbital participation that should be considered than the actual degree to which the electrons are transferred, since the parameters used for the *d* orbitals are less well defined than those used for *s* and *p* orbitals in CNDO calculations.[37,38]

Two-parameter correlation analyses of the NMR parameters with the Hammett constants σ_m and σ_p were also performed, in the same manner as described for $\mathscr{F}$ and $\mathscr{R}$. The correlations obtained were of the same quality as those given in Tables 2 and 3. We preferred to use the $\mathscr{F}$ and $\mathscr{R}$ constants as they are assumed to be more accurately defined and more physically significant independent variables for correlating substituent effects than σ_m and

σ_p,[23] which allows qualitative conclusions to be more easily drawn from the regression equations.

Regression analyses of the fluorine chemical shifts in *para* and *meta* substituted fluorobenzenes determined by Taft *et al.*[39] were performed for comparison with the results on the fluorothiophenes. These regression equations are also given in Table 2. Comparison of the regression equations for 5-substituted 2-fluorothiophenes and *para*-substituted fluorobenzenes shows that the fluorine shifts are very similarly affected by the resonance parameter. The fluorothiophene shift is, however, 50 % more sensitive to the inductive effect. Furthermore, for the "*meta*"-substituted thiophenes the field effect is of greater importance in the determination of the chemical shifts than for *meta*-substituted fluorobenzenes. However, while the mesomeric contribution to the shifts is of importance in the cases of the two thiophenes, it is insignificant in the benzene case in agreement with earlier findings.[39] It should be noted that in contrast to the thiophene system, the substituents Br, I, and SCH_3 could be included in the regression analysis. This is not surprising since the calculation of $\mathscr{F}$ and $\mathscr{R}$ is in part based on data obtained from benzoic acids.[23]

For comparison between proton chemical shifts in monosubstituted thiophenes [40] and monosubstituted fluorothiophenes,[1] regression analyses of the shifts in these two series of compounds were undertaken. In these analyses only thiophenes dissolved in cyclohexane were included as the proton shifts are solvent sensitive. In order to make the comparison as unambiguous as possible only the same substituents in the two classes of thiophenes were included. There is, however, one exception. As there were no data available for Cl in 3-substituted thiophenes the SH-group was included instead. The results of the analysis of the monosubstituted thiophenes are collected in Table 4. The values of the regression constant r in the table reproduce the

Table 4. Regression equations relating proton chemical shifts [a] of monosubstituted thiophenes to substituent constants $\mathscr{F}$ and $\mathscr{R}$.

Equation	σ	C	N
$\delta_3^2 = 0.04 \pm 0.08 - (0.34 \pm 0.12)\mathscr{F} - (2.15 \pm 0.18)\mathscr{R}$	0.12	0.98	9
$\delta_4^2 = 0.07 \pm 0.03 + (0.08 \pm 0.05)\mathscr{F} - (0.73 \pm 0.07)\mathscr{R}$	0.05	0.96	9
$\delta_5^2 = 0.03 \pm 0.07 - (0.05 \pm 0.09)\mathscr{F} - (1.65 \pm 0.15)\mathscr{R}$	0.10	0.97	9
$\delta_2^3 = 0.04 \pm 0.05 - (0.34 \pm 0.09)\mathscr{F} - (2.42 \pm 0.15)\mathscr{R}$	0.08	0.99	8
$\delta_4^3 = 0.00 \pm 0.08 - (0.12 \pm 0.13)\mathscr{F} - (1.19 \pm 0.24)\mathscr{R}$	0.12	0.88	8
$\delta_5^3 = 0.05 \pm 0.04 - (0.06 \pm 0.08)\mathscr{F} - (0.40 \pm 0.14)\mathscr{R}$	0.07	0.72	8

[a] The shifts are given in ppm relative to those of thiophene. The notations δ_i^2, δ_j^3 denote the shifts of the i- and j-proton of 2- and 3-substituted thiophenes, respectively.

proposed order of the mesomeric effect on proton chemical shifts in Ref. 40. Thus the resonance effect on the 2-proton shift in 3-substituted thiophenes is larger than that on the 4-proton shift. It is also larger than that on the

3-proton shift in 2-substituted thiophenes, which in turn is larger than the resonance effect on the 5-proton in the same compounds. The smaller resonance effect on the "*meta*" protons are also reproduced by the r-values, the smallest effect being that of the 5-proton in 3-substituted thiophenes. The ratios between the mesomeric contributions to the proton shifts are as follows

$$\delta_5^3 : \delta_4^2 : \delta_4^3 : \delta_5^2 : \delta_3^2 : \delta_2^3 = 0.17 : 0.32 : 0.49 : 0.68 : 0.89 : 1.$$

In Ref. 40 questions were put forward about the relative magnitudes of the inductive effect on proton shifts in different positions without being satisfactorily answered. From the regression equations now obtained it seems that there are significant inductive contributions only on the *ortho* proton shifts. For the 4-proton shift in 2-substituted thiophenes the inductive contribution becomes important for substituents with large $\mathscr{F}$-values, *e.g.* CN, NO_2. The small positive value of f, leading to upfield shift contributions for $-I$ substituents, can, however, not be readily explained.

In the regression analyses no corrections of the proton shifts due to contributions from the magnetic anisotropy of the substituents were made as it is difficult to obtain reliable estimates of such contributions. The good correlations obtained did not seem to be significantly deteriorated by not taking the magnetic anisotropy effect into account.

The assignments of the proton resonances in the NMR spectra of the substituted fluorothiophenes in the preceding paper [1] could in almost all cases be made in an unambiguous way from additivity considerations of the proton chemical shifts. For the compounds of series I, rather good but not linear relations between calculated and experimental shifts of the 3- and 4-hydrogens were obtained. The experimental proton shifts are more to low field than the calculated ones for $-I-M$ substituents, while for $-I+M$ substituents the experimental shifts are well reproduced by the calculated ones. The experimental differences between these two shifts are, however, well given by the calculated differences (see Fig. 5). This must be due to a factor (possibly through-conjugation), which causes deviation from additivity for both shifts to the same extent. The same trend as found for the individual proton shifts

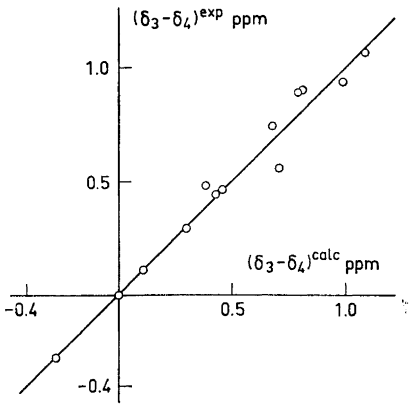


Fig. 5. The experimental difference $(\delta_3 - \delta_4)^{exp}$ in ppm between the proton shifts in 5-substituted 2-fluorothiophenes is plotted *vs.* the additivity – calculated difference $(\delta_3 - \delta_4)^{calc}$.

in series I was observed for the 2- and 4-proton shifts in the 5-substituted 3-fluorothiophenes. There is an approximate linear relation between the small experimental and calculated differences of the two shifts, but it is not of unit slope since the range of the experimental differences is smaller than that of the calculated ones. In the 4-substituted 2-fluorothiophenes the same trend as for the proton shifts in the two series above was observed for the 5-proton shifts, whereas the 3-proton shifts are well reproduced by the calculated shifts. The range of the experimental differences $\delta_3 - \delta_5$ is in this case larger than the range of the calculated ones, but the experimental and calculated values of $\delta_3 - \delta_5$ are also in this case approximately linearly correlated.

The results of the regression analyses of the proton shifts in the substituted fluorothiophenes are given in Table 5, together with linear relations between some of the shifts. A comparison of the regression constants r and f in Tables 4 and 5 shows that in the fluorothiophenes the proton shifts in all positions

Table 5. Regression equations relating proton chemical shifts [a] of fluorothiophenes to substituent constants $\mathcal{F}$ and $\mathcal{R}$, and linear relations between some of the shifts.

Equation	σ	C	N
$\delta_3^{I} = 0.07 \pm 0.06 - (0.11 \pm 0.08)\mathcal{F} - (1.05 \pm 0.13)\mathcal{R}$	0.09	0.95	9
$\delta_4^{I} = 0.01 \pm 0.10 - (0.52 \pm 0.14)\mathcal{F} - (2.56 \pm 0.22)\mathcal{R}$	0.15	0.98	9
$\delta_3^{II} = -0.02 \pm 0.05 - (0.24 \pm 0.09)\mathcal{F} - (1.06 \pm 0.15)\mathcal{R}$	0.08	0.94	8
$\delta_5^{II} = -0.02 \pm 0.06 - (0.51 \pm 0.10)\mathcal{F} - (2.86 \pm 0.18)\mathcal{R}$	0.09	0.99	8
$\delta_2^{III} = 0.06 \pm 0.13 - (0.35 \pm 0.18)\mathcal{F} - (2.11 \pm 0.37)\mathcal{R}$	0.19	0.92	8
$\delta_4^{III} = 0.05 \pm 0.12 - (0.52 \pm 0.18)\mathcal{F} - (2.21 \pm 0.36)\mathcal{R}$	0.18	0.94	8
$\delta_4^{I} = 0.01 \pm 0.02 + (0.89 \pm 0.03)\delta_5^{II}$	0.06	0.99	11
$\delta_4^{III} = -0.01 \pm 0.02 + (0.87 \pm 0.03)\delta_4^{I}$	0.07	0.99	16
$\delta_2^{III} = 0.10 \pm 0.03 + (0.88 \pm 0.05)\delta_4^{III}$	0.08	0.98	13
$\delta_3^{II} = -0.22 \pm 0.03 + (0.99 \pm 0.12)\delta_3^{I}$	0.11	0.92	13

[a] The shifts in the regression analyses are given in ppm relative to those of the unsubstituted fluorothiophenes. The notation δ_i^{I} denotes the shift of the i-proton in compounds of type I.

except the 3-proton shift in II, are more influenced by resonance effects than in monosubstituted thiophenes and that the f constants of the fluorothiophenes are significantly more negative than those of the monosubstituted thiophenes. However, the reasons for these differences are not clear. As seen from Table 5 the proton shifts are better correlated to each other than to ($\mathcal{F}$,$\mathcal{R}$) but the ratios of the regression constants are in the same order as the ratios of the constants r, once more providing evidence that the proton shifts are mainly affected by the resonance properties of the substituents.

The differences that exist between the regression constants of the shifts in Tables 4 and 5 indicate that the proton shifts in the substituted fluorothiophenes cannot in general be exactly reproduced by calculations assuming additivity of the substituent effects on the shifts.

It is evident that the $\mathcal{F}$ and $\mathcal{R}$ values of Swain and Lupton used to characterize a substituent have been very useful for correlations of ^{19}F shifts

in various aromatic systems and also for correlations of proton chemical shifts in thiophenes and fluorothiophenes. It is therefore probable that this treatment can be used for the correlations of chemical shifts in other heterocyclic systems, providing information about the relative importance of inductive and mesomeric effects. It seems reasonable to us that our treatment also should be applicable to chemical reactivity data.

2.3. Correlations with bond orders

From the strong dependence of the ortho H–F couplings J_{2F-3}^{I} and J_{3F-2}^{III} on the $\mathscr{R}$ parameter it is reasonable to assume that the (r$\mathscr{R}$) contributions are dominated by a $\sigma-\pi$ exchange mechanism. Bearing in mind the severe "average energy approximation", which is embodied in eqn. (4), we nevertheless anticipate ΔE to be rather constant for the similar compounds involved here, and therefore the (r$\mathscr{R}$) contributions should be roughly proportional to the square of the C_2-C_3 π bond order according to the simple McConnell relation,[41]

$$J_{H-F}^{\pi} = \frac{\beta^2 Q_{CH} Q_{CF}}{h\Delta E} (p^{\pi}_{C_2-C_3})^2 \qquad (4)$$

where Q_{CH} and Q_{CF} are the effective hyperfine interaction constants in gauss for the C–H and C–F bond, respectively, β is the Bohr magneton and ΔE is average excitation energy.

The π bond orders were calculated with the CNDO SCF method used in a semiempirical calculation of fluorine chemical shifts.[36] For J_{2F-3}^{I} a roughly linear correlation is obtained, with the highest π bond order and (r$\mathscr{R}$) value for the OCH_3 group, and the lowest C_2-C_3 π bond order and (r$\mathscr{R}$) value for the $COCH_3$ group. Increasing (r$\mathscr{R}$) values with increasing π bond orders would imply a negative value of Q_{CF} since Q_{CH} is equal to about -25 gauss, which is in contrast to the positive value empirically found for fluorobenzene derivatives,[42–45] but Q_{CF} is a composite term and may vary considerably in magnitude.[43] The sensitivity of $p^{\pi}_{C_2-C_3}$ to substituent variations is too small to account for the observed difference between the (r$\mathscr{R}$) values for different substituents. The difference between the OCH_3 and $COCH_3$ (r$\mathscr{R}$) values is 2 Hz and would, with ΔE equal to 3 eV, require Q_{CF} equal to -1000 gauss, which is unreasonably low in value, and which would also give large π-electron contributions to J_{2F-3}^{I} equal to $\sim$45Hz. The J_{2F-3}^{I} and J_{3F-2}^{III} couplings themselves show the same trend as the (r$\mathscr{R}$) contributions but more scatter in a plot *vs.* $(p^{\pi}_{C_2-C_3})^2$.

In an approximate MO treatment of the Fermi contact term for spin-spin couplings, where the average excitation energy is also invoked, the H–F couplings are given by [46]

$$J_{H-F} = h\gamma_H\gamma_F \frac{16\beta^2}{9\Delta E} s_H^2(0) s_F^2(0) p_{s_H s_F}^2 \qquad (5)$$

where γ_H, γ_F are the magnetogyric ratios, $s_H^2(0)$, $s_F^2(0)$ are the 1*s* and 2*s* orbital densities at the proton and the fluorine nuclei, respectively, and $p_{s_H s_F}$

is the hydrogen 1*s*-fluorine 2*s* bond order. The correlations of the J_{2F-3}^{I} and J_{3F-2}^{III} couplings with $p^2 s_H s_F$ are better than the correlations with π bond orders, but the sensitivity to substituent variation is also small in this case. The difference of 2 Hz between the J_{2F-3}^{I} couplings with the OCH_3 and $COCH_3$ groups as substituents has to be accounted for by a ΔE equal to 1.6 eV, which seems too low, and the calculated J_{2F-3}^{I} couplings from eqn. (5) would then be too large (about 53 Hz). The bond orders $p_{s_H s_F}$ and $p^{\pi}_{C_2-C_3}$ are roughly linearly correlated with each other with increasing C_2-C_3 π bond order with increasing $1s_H-2s_F$ bond order. This means that a correlation between the experimental spin-spin couplings and the π bond orders need not necessarily imply a dominant π interaction mechanism for these couplings, as such a mechanism is not implicit in eqn. (5) with $p_{s_H s_F}$ calculated with the CNDO method.

In order to calculate H – F couplings from eqns. (4) and (5) with empirical $Q_{CF}/\Delta E_{\pi}$ and ΔE values, respectively, of the same magnitude as the small experimentally determined couplings, the two contributions must be of almost the same magnitude and of opposite signs. The sensitivity to substituent variation is, however, almost the same for the two terms and it is therefore not possible to simultaneously reproduce the variation with substituent and the size of the experimental couplings. The failure of reproducing these couplings is not unexpected in view of the severe approximations made in deriving eqns. (4) and (5), which were mainly used to form a basis for the correlations discussed above. There is evidently a need for a more accurate method such as the finite perturbation method used by Pople *et al.*,[47] together with an SCF MO method which includes one-center exchange integrals to account for the H – F couplings, even if this method in calculations of spin-spin couplings involving fluorine [47,48] has not been as successful as in calculations of H – H and C – H couplings.

Acknowledgements. The authors wish to thank Professor K. Siegbahn for the facilities placed at their disposal. Grants from the *Swedish Natural Science Research Council* to S. G., and from the *Faculty of Science of the University of Lund* and the *Royal Physiographic Society* to U. R. are gratefully acknowledged.

REFERENCES

1. Rodmar, S., Moraga, L. Gronowitz, S. and Rosén, U. *Acta Chem. Scand.* **25** (1971) 3309.
2. Emsley, J. W., Feeney, J. and Sutcliffe, L. H. *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon, Oxford 1966, Vol. 2, Chapters 10 – 12.
3. Waugh, J. S. and Castellano, S. *J. Chem. Phys.* **35** (1961) 1900.
4. Schaefer, T. *Can. J. Chem.* **40** (1962) 1.
5. Castellano, S. and Sun, C. *J. Am. Chem. Soc.* **88** (1966) 4741.
6. Evans, Jr., H. B., Tarpley, A. R. and Goldstein, J. H. *J. Phys. Chem.* **72** (1968) 2551.
7. Tarpley, A. R., Evans, Jr., H. B. and Goldstein, J. H. *J. Anal Chem.* **41** (1969) 402.
8. Cox, P. F. *J. Am. Chem. Soc.* **85** (1963) 380.
9. Hayamizu, K. and Yamamoto, O. *J. Mol. Spectry.* **25** (1968) 422.
10. Castellano, S. and Kostelnik, R. *J. Am. Chem. Soc.* **90** (1968) 141.
11. Bulman, M. J. *Tetrahedron* **25** (1969) 1433.
12. Hutton, H. M., Richardson, B. and Schaefer, T. *Can. J. Chem.* **45** (1967) 1795.
13. Loemker, J. E., Read, Jr., J. M. and Goldstein, J. H. *J. Phys. Chem.* **72** (1968) 991.
14. Hogben, M. G. and Graham, W. A. G. *J. Am. Chem. Soc.* **91** (1969) 283.

15. Abraham, R. J., Macdonald, D. B. and Pepper, E. S. *J. Am. Chem. Soc.* **90** (1968) 147.
16. Danyluk, S. S., Bell, C. L. and Schaefer, T. *Can. J. Chem.* **47** (1969) 4005.
17. Yoder, C. H., Tuck, R. H. and Hess, R. E. *J. Am. Chem. Soc.* **91** (1969) 539.
18. Axenrod, T., Pregosin, P. S., Wieder, M. J. and Milne, G. W. A. *J. Am. Chem. Soc.* **91** (1969) 3681.
19. Hayamizu, K. and Yamamoto, O. *J. Mol. Spectry.* **29** (1969) 183.
20. Maciel, G. E. and Natterstad, J. J. *J. Chem. Phys.* **42** (1965) 2427.
21. Dailey, B. P. and Shoolery, J. N. *J. Am. Chem. Soc.* **77** (1955) 3977.
22. Yukawa, Y. and Tsuno, Y. *Bull. Chem. Soc. Japan* **32** (1959) 971.
23. Swain, C. G. and Lupton, Jr., E. C. *J. Am. Chem. Soc.* **90** (1968) 4328.
24. Gronowitz, S. *Advan. Heterocyclic Chem.* **1** (1963) 1.
25. Jaffe, H. H. and Jones, H. L. *Advan. Heterocyclic Chem.* **3** (1964) 209.
26. Butler, A. R. *J. Chem. Soc.* **B 1970** 867.
27. Clementi, S., Linda, P. and Marino, G. *J. Chem. Soc.* **B 1970** 1153.
28. Taylor, R. *J. Chem. Soc.* **B 1970** 1364.
29. Butler, A. R. and Hendry, J. B. *J. Chem. Soc.* **B 1970** 848.
30. *Unpublished results.*
31. Rodmar, S., Rodmar, B., Sharma, M. K., Gronowitz, S., Christiansen, H. and Rosén, U. *Acta Chem. Scand.* **22** (1968) 907.
32. Christiansen, H., Gronowitz, S., Rodmar, B., Rodmar, S., Rosèn, U. and Sharma, M. K. *Arkiv Kemi* **30** (1969) 561.
33. Hogben, M. G., Gay, R. S., Oliver, A. J., Thompson, J. A. J. and Graham, W. A. G. *J. Am. Chem. Soc.* **91** (1969) 291.
34. Goodman, L. and Taft, R. W. *J. Am. Chem. Soc.* **87** (1965) 4385.
35. Taft, R. W. and Raksys, Jr., J. W. *J. Am. Chem. Soc.* **87** (1965) 4388.
36. Rodmar, S. *Mol. Phys.* **22** (1971) 123.
37. Santry, D. P. and Segal, G. A. *J. Chem. Phys.* **47** (1967) 158.
38. Santry, D. P. *J. Am. Chem. Soc.* **90** (1968) 3309.
39. Taft, R. W., Price, E., Fox, I. R., Lewis, I. C., Andersen, K. K. and Davies, G. T. *J. Am. Chem. Soc.* **85** (1963) 709, 3146.
40. Gronowitz, S. and Hoffman, R. A. *Arkiv Kemi* **16** (1960) 539.
41. McConnell, H. M. *Mol. Phys.* **1** (1957) 11.
42. Blears, D. J., Danyluk, S. S. and Schaefer, T. *J. Chem. Phys.* **47** (1967) 5037.
43. Brown, J. K. and Williams, W. G. *Trans. Faraday Soc.* **64** (1968) 298, and references therein.
44. Ray, N. K. *Chem. Phys. Letters* **3** (1969) 261.
45. Hudson, A. and Lewis, J. W. E. *Mol. Phys.* **19** (1970) 241.
46. McConnell, H. M. *J. Chem. Phys.* **24** (1956) 460.
47. Pople, J. A., McIver, Jr., J. W. and Ostlund, N. S. *J. Chem. Phys.* **49** (1968) 2965.
48. Maciel, G. E., McIver, Jr., J. W., Ostlund, N. S. and Pople, J. A. *J. Am. Chem. Soc.* **92** (1970) 1, 11, 4151, 4497, 4506.

Received January 30, 1971.