Nuclear Magnetic Resonance Studies
of
Fluorothiophenes

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Certified that the work presented in this thesis is the original work and has been carried out by me.

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M.K. Sharma
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CHAPTER I

INTRODUCTION
1.1 GENERAL INTRODUCTION

The Nuclear Magnetic resonance (NMR) spectroscopy is based on a method of detecting the magnetic properties of the nuclei of a sample material subjected to the forces of an external magnetic field oriented 90° from the polarizing field. The detected magnetic changes of the nuclei are then shown as NMR spectra on either an oscilloscope or a graphic recorder. Changes in the magnetic moment of the nucleus as it precesses around its magnetic axis establish the resonant frequency of the isotope and thereby provide the means of positive identification. Only nuclei possessing angular momenta and magnetic moments (i.e. non-zero spin) can be detected by NMR technique. The NMR technique depends upon the fact that certain isotopes possess an intrinsic nuclear spin which gives rise to angular momentum and magnetic moment. The finite magnetic moment of a nucleus of non-zero spin is detected and amplified to produce the NMR spectrum.

The Nuclear Magnetic Resonance signals of most liquids exhibit a fine structure arising primarily due to two important effects associated with the electronic
distribution in molecules, viz., the chemical shift and the indirect spin-spin interaction between nuclei. The chemical shifts represent variations in the electronic environment of the nuclei of interest at different nonequivalent sites in the molecule, and thus provide a sensitive method for observing slight and subtle changes in the electronic distribution. The chemical shift is directly proportional to the applied static field. The spin-spin interaction is due to coupling of the different nuclear spins in the molecule through the bonding electrons. The spin-spin splitting is independent of the applied static field. Some of the studies have already shown clearly that a good deal of information can be derived from the extensive study of these coupling constants and their sign. The analysis of high resolution NMR spectra for accurate determination of these parameters in molecules with varying degrees of bonding, forms an essential prerequisite for the more important aspect of deriving information from them.

When the chemical shifts between the different interacting nuclei are large compared to their mutual spin-spin splittings, (the condition being easily

* H, N, CI etc. type.*
satisfied by interacting nuclei belonging to different species e.g. proton and fluorine) the high resolution NMR spectrum shows several features of regularity and follows some simple rules (first order calculations)\textsuperscript{16-18} from which the parameters can be determined easily. But when the chemical shifts are of the same order of magnitude as the spin-spin splitting, the spectrum exhibits a complex pattern and irregular multiplets. The analysis then is not so simple and some detailed methods\textsuperscript{11,13,14} have to be followed to analyze the spectra and derive the parameters. Although in principle it looks that this complexity can be avoided or reduced considerably if one works at high magnetic fields, because the chemical shift, being proportional to the applied static field, can be increased considerably as compared to spin-spin coupling constant which is independent of it. But it is not so often realized in practice since an upper limit is set to the static magnetic field by the requirements of stability and resolution. Further it is always possible to have cases, even at the highest attainable fields, where the chemical shifts are still of the same order of magnitude as the coupling constants involved. The general method of

- $\text{AB, AB}_2, \text{A}_2\text{B}_2, \text{ABC}$ etc. type.
theoretical calculations of these types of spectra where no restriction is placed on the relative values of the chemical shifts and the coupling constants was given by McConnell, McLean and Reilly. The method is very much similar to the traditional methods used in other branches of spectroscopy, of repeated solution of the quantum mechanical eigen-value problem until the parameters chosen give a satisfactory agreement with the observed spectrum.

1.2 NUCLEAR MAGNETIC RESONANCE OF 19F

For the last two decades a lot of work has been reported on 1H NMR studies, but during the last few years there has been a rapid outflow of scientific publications dealing with every aspect of 19F NMR which indicates a widespread interest in this field. The reason for this can be ascribed to the large values of 19F chemical shifts and spin coupling constants and so it is often possible to obtain more information about molecular structures and molecular dynamic processes for fluorine-containing molecules than for the analogous hydrogen containing molecules. Theoretically, the understanding of the origin of 19F chemical shifts and
coupling constants is not as well developed as that for $^1$H nuclei due mainly to the greater complexity of the fluorine electronic configuration.

$^{19}$F is the only naturally occurring isotope of fluorine and it is an ideal nucleus for NMR investigations. Although it is both less sensitive to NMR detection and is usually easier to saturate than the hydrogen nucleus, fluorine NMR spectra can be obtained easily using the standard commercial NMR spectrometers. $^{19}$F has a spin-number of one half ($I = \frac{1}{2}$) and thus does not possess a quadrupole moment. Its univalency and reactivity are both responsible for a large number of fluorine-containing compounds which are available for examination and also that most of these compounds are liquids around 25°C. The ranges of observed chemical shifts and coupling constants in $^{19}$F NMR studies are large compared with those found in $^1$H spectra because each effect is controlled by a different factor for each nucleus. The sensitivity requirements of pure fluorine-containing liquid compounds are not stringent to interfere seriously with the resolution e.g. a splitting of 0.3 Hz between two lines can be readily resolved at 56.444 MHz in $^{19}$F NMR spectra. Compounds containing several differently
shielded fluorine nuclei coupled by indirect spin-spin interactions often show simple first order type spectra because the chemical shifts of different nuclei are quite large compared to the coupling constants involved.

1.3 **FARLIFR WORK ON THIOPHENES**

In earlier investigations a detailed study of the proton magnetic resonance spectra of thiophenes and a large number of substituted thiophenes was undertaken. The intervals for the different coupling constants and their relative signs have been determined. The relation between chemical shifts and substituent effects was studied and a qualitative relation between the properties of a substituent in the 2-position and the 5-hydrogen shifts was obtained. In subsequent works the relative signs of side chain couplings in substituted thiophenes were determined.

On account of much larger effects of substituents on the fluorine shifts and the good correlation obtained between such shifts and Hammet substituent constants ($\sigma$-values) makes a study of the fluorine resonance spectra of substituted fluorothiophenes attractive. The substituent shifts thus obtained could then be used to obtain $\sigma$-values for these substituents when attached to
the thiophene ring, and perhaps be useful for the prediction of chemical reactivity data. An increased knowledge of the magnitudes and signs of the H-F and F-F spin-spin coupling constants in aromatic systems such as thiophenes could contribute to a better understanding of the relative importance of the different mechanisms which contribute to these couplings. It is on this account that a detailed study of NMR of fluorothiophenes has been undertaken.

1.4 OUTLINE OF THE WORK PRESENTED IN THIS THESIS

After this chapter of general introduction, basic theory of analysis of an observed NMR spectrum is given in chapter II. In the same chapter experimental details of the apparatus along with its specifications are given.

In chapter III analysis of the two mono-fluorothiophenes is given. Both proton and fluorine magnetic resonance spectra are presented. For both the monofluorothiophenes the nature of the spectra are ABCX type and has been analysed by means of subspectral analysis 26. The results of the analysis (viz. the proton and fluorine chemical shifts, the
proton-proton, proton-fluorine and fluorine-fluorine spin coupling constants and also $^{13}$C - $^{19}$F coupling constants (and isotope shifts) are tabulated. The determination of relative signs of the various couplings (wherever possible) has also been made and given in the results.

In chapter IV, the study of four difluoro thiophenes (namely 2,3-, 2,4-, 2,5- and 3,4- difluoro thiophenes), 3-bromo-2, 5-difluoro thiophene, 5-bromo-2, 3-difluoro thiophene and 2,2,5- trifluoro thiophene has been undertaken. Proton and fluorine spectra for each one of them are presented and the results of the analysis tabulated. In the end of this chapter a general discussion has been made which indicates the ranges of various coupling constants found from the results of chapter III and IV.

In all the compounds the fluorine chemical shifts in cyclohexane solution at various concentrations were found and the shifts have been extrapolated to infinite dilution.

The work presented in chapter III has already been published in Acta Chemica Scandinavica 22 (1968) 907-920 (reprint attached) and the work of chapter IV is under publication in the same journal.
REFERENCES


CHAPTER II

THEORETICAL CONSIDERATIONS

AND

EXPERIMENTAL PROCEDURE
2.1 **BASIC THEORY OF ANALYSIS**

The quantum mechanical theory of the frequencies and intensities of the lines in NMR spectrum in terms of the chemical shifts and spin coupling constants will now be described briefly. In many cases the effects of chemical shift and spin-spin interaction give rise to a complex pattern of lines resulting from the merging of individual multiplets, which then have a few features of regularity. One is then faced with the problem of interpreting such a band system, assigning each line to a definite transition and finally extracting numerical values for the chemical shifts and spin coupling constants. The basic theoretical steps required for the detailed analysis of such spectra were developed by Gutowsky, McCall, and Stiecher\(^1\), Hahn and Maxwell\(^2\), McConnell, McLean, and Reilly\(^3\) and many others\(^4,5,6\). Accordingly, to calculate the energies and intensities of the transitions that may be observed in an NMR spectrum of a group of interacting nuclei, it is necessary to find the energies and stationary state wavefunctions for the system in the absence of the radio-frequency field. This oscillating field then causes transitions between the states and the corresponding transition probabilities can be found by perturbation
methods closely analogous to those used in the theory of optical transitions. Intensities calculated by using first order perturbation theory will of course only apply to intensities observed below the saturation power level.

The Hamiltonian operator \( \mathcal{H} \) for a system of \( p \) interacting nuclei, all of spin \( \frac{1}{2} \), (there will be \( 2^p \) possible states) is given by

\[
\mathcal{H} = \mathcal{H}(0) + \mathcal{H}(1) \quad \cdots (2.1)
\]

where \( \mathcal{H}(0) \) gives the sum of the interactions of the nuclei with the stationary applied field \( H_0 \) and \( \mathcal{H}(1) \) gives the sum of the spin-spin interactions of the pairs of nuclei. Thus for the \( i \)th nucleus,

\[
\mathcal{H}^{(0)} = \sum_{i=1} I_1 (1 - \sigma_1^i) H_0 I_2(1) \quad \cdots (2.2)
\]

or

\[
\mathcal{H}^{(0)} = \frac{1}{2} \sum_{i=1} \gamma_1 I_2(1) \quad \cdots (2.3)
\]

where \( \gamma_1 = \gamma_1 (1 - \sigma_1^i) H_0 \) and is in cycles per second if \( \gamma_1 \), the gyromagnetic ratio of the \( i \)th nucleus, is
in cycles per second, per gauss. And

$$\mathcal{H}^{(1)} = \sum_{i<j} J_{ij} \vec{I}_i \cdot \vec{I}_j$$

...(2.1)

where $J_{ij}$ is the spin coupling constant between the nuclei $i$ and $j$ and $\vec{I}_i$ and $\vec{I}_j$ are the spin angular momentum vectors of the $i$th and $j$th nucleus respectively. (The components of $\vec{I}_i$ are given by $I_x(1), I_y(1)$ and $I_z(1)$ and similarly for $I_j$.) In the absence of dynamic processes which modify the observed spectra, and when the molecular motions in the liquid are rapid enough for the direct dipole-dipole interactions to be neglected, the above form of the Hamiltonian is expected to represent faithfully all the observed features of high resolution N.M.R. spectra.

Let $\Psi_k^0$ and $\Psi_k$ represent the eigenfunctions of $\mathcal{H}^{(0)}$ and $\mathcal{H}$ respectively, and $\epsilon_k^0$ and $\epsilon_k$ the corresponding eigenenergies. The zero order eigenfunctions $\Psi_k^0$ then represent the stationary states in the absence of the term $\mathcal{H}^{(1)}$ in equation (2.1). The number of possible states is $\leq 2^p$, if all the interacting nuclei are of spin $\frac{1}{2}$, as is generally the case. The problem now is to determine a suitable linear combinations
of \(\psi_k^0\) which diagonalize the matrix of the complete Hamiltonian \(H\). The corresponding eigenvalues \(\lambda_k\) are given by the solution of the secular equation:

\[
|H_{mn} - \lambda \delta_{mn}| = 0 \quad \ldots \ldots \quad (2.5)
\]

where

\[
H_{mn} = \int \bar{\psi}_m^0 H \psi_n^0 \, d\tau \quad \ldots \ldots \quad (2.6)
\]

and

\[
\delta_{mn} = 0 \text{ if } m \neq n \text{ and } = 1 \text{ if } m = n \quad \ldots \ldots (2.7)
\]

The exact eigenfunctions \(\psi_k\) are then given by

\[
\psi_k = \sum_m a_{km} \bar{\psi}_m^0 \quad \ldots \ldots (2.8)
\]

where the coefficients \(a_{km}\) are given by a set of linear equations.

\[
\sum_m H_{mn} a_{km} = E_k a_{kn} \quad \ldots \ldots (2.9)
\]

The solution of which yields the ratios of these coefficients and the exact values are determined by the condition that the function \(\psi_k\) should be normalized i.e.,

\[
\sum_m a_{km}^* a_{km} = 1 \quad \ldots \ldots (2.10)
\]

where \(a_{km}^*\) is complex conjugate of \(a_{km}\).
The secular equation (2.5) is of \( 2^p \) order but with some proper choice of the zero order spin functions, this can be factorized into several equations of lower order. The method of choosing these functions is given in detail by several authors\(^8,2,9\). The secular equation first factors into \((p+1)\) equations corresponding to all possible values of \( F_z \), the total spin angular momentum component in the \( z \) direction, i.e.

\[
F_z = \sum_{i} I_z^i \tag{2.11}
\]

Further factorization of these equations results, if the molecule contains interacting nuclei of more than one species, as the off-diagonal matrix elements between states corresponding to different values of the \( z \)-component of the total spin of any of the different nuclear species can be taken as zero, to a high degree of approximation. The same argument can be applied, though to a lesser degree of approximation, to nuclei of the same species, where \( | \gamma_i - \gamma_j | \gg J_{ij} \). Even in these cases where this condition is not fully valid, this factorization can be carried out in order to obtain approximate solutions which can then be employed as a starting point for more valid and rigorous approximations\(^{10}\). The problem is further simplified if the molecule under study possesses
elements of symmetry. This has been realized by McConnell et. al\(^3\) themselves and is later treated more exhaustively by Wilson\(^5\). The zero order eigen-functions then fall into symmetric and antisymmetric classes and no mixing occurs between states belonging to different classes.

As soon as the secular equation (2.5) is solved completely, all the transition energies can be readily obtained by using the well known selection rule

\[
\Delta L_z = \pm 1
\]  

\(\text{(2.12)}\)

In the case of symmetric molecules, there is an additional selection rule by which transitions are allowed only between states of the same symmetry.

The intensity of transition between states corresponding to \(\psi_m\) and \(\psi_n\) is proportional to

\[
\left[ \langle \psi_m \mid : I_x (\mathbf{i}) \mid \psi_n \rangle \right]^2
\]  

\(\text{(2.13)}\)

which can be calculated for all transitions, if the exact eigenfunctions \(\psi_m\) are evaluated from equations(2-21C).

2.2 SPIN-STATISTICAL AND FOUR SPIN SYSTEMS

The method described in the previous section cannot be applied easily to all cases, as it is difficult (though,
in principle, not impossible) to derive explicit expressions for the transition energies in terms of the parameters, if the order of the subdeterminant is more than two. This condition is always satisfied if the number of interacting spins is only two (AB or AX type). But the spectra of molecules containing more than two spins are usually encountered.

The theoretical work \textsuperscript{11,12,13} has shown that a knowledge of the signs of the coupling constants is of considerable importance. In order to determine these signs it is necessary that the number of interacting nuclei are at least three \textsuperscript{6,14}. It is to be noted, however, that only relative signs of coupling constants can be determined in NMR experiments as the sign of the second term in equation (\textsuperscript{3.1}) is arbitrary (a positive sign of $J_{ij}$ in the form of $\mathcal{H}$ in equation (\textsuperscript{3.1}) corresponds to a preferred antiparallel correlation of the interacting spins $i$ and $j$).

The spectra of these systems (3 or more spins) are usually complex and one often encounters determinants of rank 3 or more to solve for the energy levels in terms
of the many parameters. The complexity of the spectrum is considerably reduced if the molecule possesses symmetry but the spectra of symmetrical molecules are usually insensitive to the signs of the spin coupling constants. On the other hand the spectra become rapidly complicated as the symmetry is reduced or when the number of nuclei is increased. Some useful simplification can, of course, be obtained in cases where the condition $|\mathcal{V}_1 - \mathcal{V}_j| >> j_{ij}$ is satisfied. However it will always be helpful if certain systematic features of the spectra could be found, though finally a good deal of trial and error, calculation is to be done to assign all the transitions to the lines observed in the experimental spectrum.

Spectra of a number of three and four spin systems have been studied and the methods of analysis are well given $^9,15-19$. It is therefore not desirable to give the theoretical considerations of all these here. Reference will be made to the methods when utilized. In the present work spectra which fall into $ABCX$ (chapter III), $ABX$, $ABRX$ $AX$, $AXRX$ $AQ$ (chapter IV) are analyzed and all

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If there are $n$ nuclei in the system, there will be $(n-1)$ chemical shifts and $n(n-1)/2$ spin coupling constants to be determined from the analysis.
the parameters (Chemical shifts and spin couplings with their relative signs, wherever possible) are determined.

2.3 EXPERIMENTAL PROCEDURE (GENERAL)

Nuclear Magnetic Resonance spectrometer systems are designed to provide means of determining the structure, spin and magnetic moment of the nuclei being tested. To accomplish this, a crossed coil probe, containing the sample to be tested, is placed in the polarizing field of an electromagnet. A fixed frequency RF transmitter generates an oscillating magnetic field in a coil of the probe which is at right angles to the polarizing field of the electromagnet. The polarizing field of the electromagnet is then adjusted to establish the Larmor angular frequency, causing transitions to be induced in the receiver coil surrounding the sample; this voltage in turn is amplified, detected and reproduced on the oscilloscope or a graphic recorder as NMR spectrum.

The polarizing field of the magnet is modulated at audiofrequencies by a sweep oscillator and amplifier that drives a pair of sweep coils in the probe then the output from the receiver is presented on the vertical axis of the oscilloscope and the horizontal axis is
driven by the sweep oscillator, any NMR signal that exists is presented on the oscilloscope as a function of the swept polarizing field (or frequency). In this type of display, the sweep amplitude can be greater than the signal linewidth in order to display the entire signal resonance curve or it can be reduced to view only a small portion of the signal resonance curve.

When the receiver output is to be displayed on a graphic recorder, additional circuits are used. The sweep amplitude is reduced to a fraction of the signal linewidth while the magnet polarizing field is swept across the resonance field, or the sweep frequency is swept across the resonance with the magnetic field held constant. The output of the receiver is fed to the recorder through the tuned audioamplifier and a phase sensitive detector which converts the sweep frequency component of the signal to direct current.

Because of the coherent nature of the NMR signal, it is possible to record signals whose strength is less than that of the system noise measured at the receiver coil. This is accomplished by filters installed after the phase detector which limit the bandpass to a very low level.
All that has been said above is accomplished in the commercially available spectrometers of Varian Associates. All the spectra presented in this work were obtained (except where specified otherwise) on a Varian HA 60 EMR spectrometer using a 12" electromagnet. Full details regarding the equipment and accessories are published by Varian Associates. However, a brief account of the parts and its specifications are given below.

2.4 **VARIAN ACCELERATOR MEGOC EQUIPMENT**

**V-4511 (Cu, Mo) FIELD FREQUENCY N.P. UNIT** containing:

(a) A transmitter section with a crystal controlled oscillator and two doubler stages.

(b) A crystal controlled receiver, driven from the low noise pre-amplifier of the probe, for amplification and detection of the EMR signal.

---

**Installed at the EMR division of the Institute of Physics, University of Uppsala, Uppsala, Sweden.**
V-4363  E. T. R. A. L. FREQUENCY NMR STABILIZING UNIT containing:
(a) A 60 Me r-f section in which the 60 Me radio-
frequency control signal control signal from the
probe is amplified and phase detected at r-f.
frequency.
(b) An audio amplifier section in which the control
signal is amplified and phase detected for
demodulation of the 2 KC component of the control
signal to produce the error signal which is used
to stabilize the magnetic field.
(c) A probe driver amplifier section which produces
the 2 KC probe sweep for the control sample.

V-4363B PROBE used with the V-4361 RF Unit containing:
(a) A control sample and coil to produce a control
signal.
(b) A transmitter coil which applies the H2 rotating
magnetic field to the sample.
(c) A receiver coil for detecting the NMR signal.
(d) Sweep coils for sweeping the H0 field.
(e) A means for spinning the sample for averaging
out inhomogeneities in the x and z axes of the
polarizing magnetic field.
V-4352 Linear Sweep Unit containing:

A linear sweep generator and power amplifier for driving the sweep coils in the V-4351 B probe.

V-4350 C Regulated Power Supply which supplies $E_p$ and filament power to spectrometer units ( $+300 \, V \, E_p$, $-105 \, V \, B_m$, $6.3 \, V \, a.e.$ filament and $12.6 \, V \, d.c.$ filament).

V-4362-1 Transistorized Power Supply which supplies $+20 \, V$ and $-7 \, V$ for operation of the V-4353 unit. This unit also provides $6.3 \, V \, a.e.$ for the recorder amplifier filaments and $32 \, V \, a.e.$ for the push-button lights of the recorder panel.

CSCILCSCOPI for visual display of the NMR signals.

V-4020 B Probe Holder for holding and positioning the probe in the magnetic field between the pole faces of the magnet.

V-3506 Flux Stabilizer which stabilizes the $H$ magnetic field to better than 1 part in $10^8$.

V-3507 Slow Sweep Unit which controls the V-3506 flux stabilizer to produce fast or very slow sweeps when not using proton stabilization.
V-4365 FIELD HOMOGENEITY CONTROL UNIT which allows the operator to establish small local fields in the magnet gap to correct any existing magnetic field inhomogeneities.

V-4018A MAGNET for generation of the (14002 gauss) $H_0$ magnetic field for NMR work at 60 MC. (for protons).

V-3520 MAGNET COOLANT CONTROL SYSTEM which provides temperature regulation of the magnetic cooling water to improve the temperature stability of the magnet.

V-21C0B MAGNET POWER SUPPLY which provides the magnet energizing current and the necessary means of control.

PLAT HD. READER with panel mounted operating controls.

WRAP-UP, which is internally mounted in the console.

V-3621A NMR INTEGRATOR DECOUPLER which supplies XIC sweep voltage, amplifies and phase detects the NMR signal and can be switched for integration of the NMR signal. This unit can also be switched to lower the modulation index and shift the modulation phase for spin decoupling operations.
V-4361 Power Supply which provides +225V and -225V for operation of the recorder sweep circuits.

V-4391 MULT-SELECTOR PANEL which provides, recorder, oscilloscope and sweep current switching. Also a recorder filtering control is provided.

2.5 SPECIFICATIONS OF VARIAN ASSOCIATES R60 SPECTROMETER

Resolution 1.5 Picos

It is one part in 2x10^8 corresponding to 0.3 cps. (76 microgauss, full linewidth at half maximum amplitude).

SENSITIVITY

Sufficient to detect the largest peak of the ethyl benzene quartet with 15:1 signal to average noise ratio using a standard Varian 1% solution test sample. This sensitivity is equivalent to detecting with 2:1 signal to average noise the resonance of a single proton species having less than 0.5 cps natural linewidth in a compound with molecular weight of 300, using 0.5 mg of sample in a 0.4 ml volume Varian precision sample tube.

TYPICAL SAMPLE VOLUME : 0.4 c.c.
CHART X- AXIS: CALIBRATION ACCURACY

± 0.2% of full scale or ± 0.2 cps whichever is greater on all ranges then sweeping at the same speed and in the same direction as the calibration run.

STABILITY A Ratio of field to frequency is maintained within 6 parts in 10^9 over a 10 minute period, with less than 1°C room temperature change from mean value and less than ± 10% line voltage fluctuation from nominal.

RANGE OF THE SCALE: 5.0 microgauss to 50 milligauss, variable in 1 db increments in proton stabilization or conventional mode and can be switched for approximately 70 milligauss maximum output.

SUPP. GAUSS: 50, 100, 250, 500, and 1000 cycles per second

SUPP. SPEEDS: 25, 50, 100, 250, 500, 1000, 2500 and 5000 seconds.

MAGNETIC FIELD INTENSITY: 14092 Gauss for protons

INTERNAL REPRODUCIBILITY: 1% full scale.

TYPICAL OPERATING FREQUENCY: 60 MC for protons.
2.6 OTHER ACCESSORIES USED

**HEVILIT-R F-300-ADJUST OSCILLATOR**: This was used to produce lock frequency for the internal stabilization in fluorine resonance experiments.

**HEVILIT-PAK 300 F-300 IF COUNTER MODEL 3724**: The resonance peaks in the experiments were measured by measuring inverse steep frequency on this electronic counter.

**PHILIPS OSCILLATOR DP/6050**: This was used for producing modulation frequency in the tickling experiments.

**CONTROL DATA 3600 COMPUTER**: The least squares fit calculations and the calculations of theoretical ABCX spectra in chapter III and other theoretical calculations of chapter IV, were performed on CD 3600 computer installed at 'Data Centre' UPPSALA, Sweden.

All the experiments reported in this thesis are done at temperature $\approx 27^\circ C$.

Further experimental details concerning specific cases are given at appropriate places.
REFERENCES

CHAPTER III

PROTON AND FluorINE NMR SPECTRA OF

(a) 3 - Fluorothiophene

(b) 2 - Fluorothiophene
ABSTRACT

High resolution $^1$H and $^{19}$F Nuclear Magnetic Resonance spectra of 2- and 3-fluorothiophenes are obtained and analyzed to determine all the parameters involved.

The H-F spin coupling constants are (in Hz or Cps):

\[ J_{2F-3} = 1.62, J_{2F-4} = 3.07, J_{2F-5} = 3.10, J_{3F-2} = 1.09, J_{3F-4} = 0.81 \text{ and } J_{3F-5} = 3.20. \]  

Except for $J_{3F-4}$, they are all of the same sign as the H-H spin coupling constants.

The proton-proton spin coupling constants are (in Hz):

\[ J_{45} = 5.38 \text{ and } 6.03, J_{24} = 1.52, J_{25} = 3.50, J_{34} = 3.59 \text{ and } J_{35} = 1.69. \]

The chemical shift of the fluorine resonance of 2-fluorothiophene when extrapolated to infinite dilution is 28.30 ± 0.02 ppm. and that of 3-fluorothiophene is 32.05 ± 0.02 ppm. downfield from hexafluorobenzene.

An isotope shift of the fluorine resonance of 2-fluorothiophene due to $^{34}$S was observed and is 0.014 ppm.

The $^{13}$C - $^{19}$F spin coupling constants are 286 and 286 Hz in 2- and 3-fluorothiophenes respectively.

3.1 INTRODUCTION

In earlier investigations a detailed study of the proton magnetic resonance spectra of thiophenes
and a large number of substituted thiophenes was studied\(^{1-5}\). The intervals for the different coupling constants and their relative signs have been determined. The relation between chemical shifts and substituent effect was studied and a qualitative relation between the properties of a substituent in the 2-position and 5-hydrogen shifts was obtained. The much larger effects of substituents on the fluorine shifts and the good correlation obtained between such shifts and Hammett substituent constants (\(\sigma\)-values) makes a study of the fluorine resonance spectra of substituted fluoro-thiophenes attractive. The substituent shifts thus obtained could then be used to obtain \(\sigma\)-values for these substituents when attached to the thiophene ring and perhaps be useful for the prediction of chemical reactivity data. An increased knowledge of the magnitudes and signs of the \(\hbar\)-F and \(\beta\)-F spin-spin coupling constants in aromatic systems such as thiophene could contribute to a better understanding of the relative importance of the different mechanisms which contribute to these couplings.

3.2 **EXPERIMENTAL DETAILS**

The samples of the compounds were prepared by Prof. S. Gronowitz and his associates at the Univ. of Lund, (Sweden) and a detailed method of preparation can be
found in Ref. 38.

The studies of 2- and 3-fluorothiophenes were
made in two solvents namely benzene and cyclohexane.
The internal reference used were TMS for protons and
hexafluorobenzene for fluorine. The two proton spectra
in 1(ω) and 6(ω) were recorded at 60.000 MHz whereas
all other spectra were obtained at 56.444 MHz using
HA60 spectrometer. The spectra were recorded in the frequency
sweep mode. The resonance peaks were measured
by counting the inverse sweep frequency (or the difference
between the sweep frequency and the lock frequency) on
HP 3734A frequency counter. In these measurements the
frequency was swept to exact resonance of the peak to be
counted, this was done for the two sweep directions
and a mean value was taken.

In the fluorine resonance experiments, the
resonance from hexafluorobenzene was used as internal
reference and as lock signal for internal stabilization
and the lock frequency was produced by a Muirhead D-890A
Decade oscillator.

For determining relative signs tickling experiments
were performed and in this the second weak rf field was
obtained by amplitude modulation of the magnetic field.
The modulation frequency was produced by a Philips
oscillator PP6050.
The least square fit calculations and the calculations of theoretical ABCX spectra were performed on a CDC 3600 electronic computer using Fortran programming.

The chemical shifts in cyclohexane were obtained at various concentrations (by weight) and then extrapolated to infinite dilution.

3.3 RESULTS AND INTERPRETATION

(a) 3-FLUOROTHIOPHENE

Proton and fluorine resonance spectra of the compound were obtained using Benzene and Cyclohexane as the solvents and TMS and Hexafluorobenzene as the internal references. The basic nature of the spectra in the two solvents is the same and the proton part of the resonance spectrum in a 46% (by wt.) benzene solution at 60,000 Hz is shown in Fig.1 and the fluorine part in the same solvent is shown in Fig. 2. The proton part of the spectrum is the ABC part of an ABCX spectrum, where the three protons (in 5, 4 and 2 positions of the ring) constitute the ABC part and the fluorine (in the 3 position of the ring) from the X-part. All the lines in the ABC part are clearly resolved and all the peaks have been measured. The upper part of the diagram shows
Fig. 1. Single resonance proton spectrum at 60 MHz of 3-fluorothiophene in a 46% benzene solution. The upper part shows the experimental spectrum and the calculated spectrum is given below.
Fig 2. The fluorine resonance spectrum at 56.444 MHz of 3-fluorothiophene.
the experimental spectrum and lower part is the calculated spectrum. In the experimental spectrum there are also some peaks from an impurity, probably from thiophene itself. The fluorine part of the spectrum at 6G.446 MHz depicts eight strong lines (X1 - X8) and four of the weaker lines (X9, X10, X11 and X12) are shown flanked on the outer side. The four weak lines are recorded with both higher rf field and higher amplification than the eight strong lines (X1 - X8). The lower part of the diagram shows the theoretical spectrum in which the four weaker lines are depicted with 20 times larger amplitude factor than the middle band.

To describe an ABCX spectrum completely four resonance frequencies and six spin coupling constants are required, namely,

\[ \gamma_A, \gamma_B, \gamma_C, \gamma_X, J_{AB}, J_{AC}, J_{AX}, J_{BX}, J_{CX} \]  \hspace{1cm} (III-1)

By the use of 'Effective Larmor Frequency' approach\(^10\) it is easily seen that this ABC part (Fig.1) is a superposition of two ABC (three-spin) subspectra each corresponding to one spin value of X (fluorine) nucleus with effective chemical shifts given by the equations:

\[ \gamma_A^\pm = \gamma_A \pm \frac{1}{2} J_{AX} \]  \hspace{1cm} (III-2)
\begin{align*}
\frac{\gamma_B}{2} &= \frac{\gamma_B}{2} \pm \frac{1}{2} J_{B_1} \\
\frac{\gamma_C}{2} &= \frac{\gamma_C}{2} \pm \frac{1}{2} J_{C_1} \\
\end{align*}

As is evident from fig. 1, the proton part is not strongly coupled and there is no overlapping of lines from different protons. With positive signs for the proton-proton spin coupling constants\(^1,2,11-14\) there are two sets of energy level diagrams for the two ABC spin systems that give theoretical spectra which agree with the experimental one. From the single resonance spectrum it is not possible to distinguish between the two cases where spin couplings between the fluorine and the protons in the 4- and 5- positions are of opposite signs i.e., it is not possible to get the sign of \(J_{3F-4}\) relative to those of \(J_{3F-2}\) and \(J_{3F-5}\). The reason for this is that the 2- proton is not coupled strongly enough to the other two protons. Therefore, using some tickling\(^{15}\) experiments (double resonance technique) in the ABC part of the spectrum were performed. One such result is shown in fig. 3. In this depiction the second rf. field \(H_2\) is at resonance on line \(A_1\) (of fig. 1) and the part B and C of ABC has been observed. It can be seen that the lines B2 and C1 appear to be regressesivly connected with A1 whereas B6 and C5 appear to be progressively connected with A1. Similar experiments were performed by having the
Fig 3. Double resonance (tickling) spectrum of the ABC - part of 3- fluorothiophene at 56.444 MHz with the second rf field $B_2$ at resonance on line A1.
second rf. field $H_2$ on other lines to confirm the predictions of fig. 3. From these experiments it is possible to choose the correct sign combination and construct appropriate energy level diagrams (see Fig. 4, where energy level diagram of the whole ABCX spin system is shown). The diagram (fig. 4) may be visualised as a combination of two cubes tilted so as to have three corners in the same plane. Each cube now belongs to one definite spin state ($\frac{1}{2}$ and $-\frac{1}{2}$) of the nucleus X and form the energy level diagram for one ABC subspin system. Each corner of the cube corresponds to one energy level and each cube edge corresponds to an A, B or C transition. The X-transitions are represented by lines joining the two cubes, the four visible combination lines of the X-part are indicated by dashed lines between the cubes. The lines have been numbered according to the figures 1 and 2.

From the tickling experiments it is evident that all the proton-proton couplings are of the same sign (as has been shown previously )$^{1,2,11}$ and that $J_{3F=4}$ is of opposite sign to $J_{3F=2}$ and $J_{3F=6}$.

With a least square fit programme the chemical shifts and the spin coupling constants which give the best fit to the experimental proton spectrum could be
Fig 4. Energy levels and transitions of the ABCX spin system of 3-fluoro-thiophene. The lines are numbered according to figs. 1 and 2. The four visible combination transitions of the X-part are indicated by dashed lines.
calculated. As seen from relations (III-2,3,4), the difference between the effective shifts of the two ABC spectra then gives the absolute values of the proton-fluorine couplings.

The fluorine spectrum of 3-fluorothiophene is shown in figure 2. The eight strong lines at first appear to be symmetrically situated around \( \nu_X \) but nevertheless with an accuracy better than \( \pm 0.03 \text{ Hz} \) in the measured frequencies of the experimental lines, a slight asymmetry around \( \nu_X \) is observed. This asymmetry is, however, more pronounced in the combination lines, in the outer flanks of the spectrum, four of which have intensities large enough to be detected (0.006 and 0.003 if the strongest of the eight lines has an intensity normalized to unity, all at the same rf. field and at negligible saturation). The sense of the asymmetry depends on the signs of the proton-fluorine couplings relative to those of the proton-proton couplings. With a change in the signs of all the proton-fluorine coupling constants, the spectrum will be reflected in \( \nu_X \) and therefore also the asymmetry. The asymmetry in the experimental 19F spectrum of 3-fluorothiophene is consistent with positive signs for \( J_{3F-2} \) and \( J_{3F-8} \) and negative sign for \( J_{3F-4} \).
The chemical shifts and spin coupling constants with their relative signs for 3-fluorothiophene are given in tables III-1, III-2 and III-3. (The results are given for the compound in both the solvents benzene and cyclohexane and also at various concentrations).

The assignment of the three proton bands to the protons in the 3-fluorothiophene is based on the known magnitudes of proton-proton spin couplings in thiophenes\(^3\) i.e.

\[ J_{45} > J_{25} > J_{24} \quad \ldots \ldots (III-6) \]

With an experimental uncertainty of at most \(\pm 0.03 \text{ Hz} \) in the observed resonance frequencies, the proton-proton and proton-fluorine coupling constants are given with an accuracy better than \(\pm 0.06 \text{ Hz} \). A complete ABCX spectrum calculated with these parameters gives an \(\lambda\)-part that agrees very well with the experimental fluorine spectrum.

During the measurements of the dependence of the fluorine resonance shift on concentration in cyclohexane it was discovered that the apparent asymmetry in the part of the fluorine spectrum with the strong lines is increased by dilution (here the weak lines on each side of
### Table III-1

**CHEMICAL SHIFTS\(^a\)\(^c\) (in Hz) IN 3-FLUOROTHIOPHENE**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>(\gamma_2)</th>
<th>(\gamma_3)</th>
<th>(\gamma_4)</th>
<th>(\gamma_5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>46</td>
<td>358.42(^b)</td>
<td>1813.34</td>
<td>369.54(^b)</td>
<td>330.71(^b)</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>77</td>
<td>366.30</td>
<td>1817.91</td>
<td>376.72</td>
<td>390.72</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>22</td>
<td>366.81</td>
<td>1810.99</td>
<td>376.85</td>
<td>393.91</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>6</td>
<td>367.41</td>
<td>1808.30</td>
<td>377.77</td>
<td>395.15</td>
</tr>
</tbody>
</table>

\(^a\) The proton shifts are given at 66.444 MHz relative to TMS as internal reference and the fluorine shifts are given relative to hexafluorobenzene as an internal reference.

\(^b\) Those shifts have been measured at 60.000 MHz and recalculated to 66.444 MHz.

\(^c\) In order to compare the substituent shifts of the protons with other monosubstituted thiophenes, the \(\delta\)-values at infinite dilution relative to cyclohexane (measured to -1.44 ppm) are calculated to be (in ppm):

<table>
<thead>
<tr>
<th></th>
<th>(\gamma_2)</th>
<th>(\gamma_3)</th>
<th>(\gamma_5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-5.07</td>
<td>-5.25</td>
<td>-5.57</td>
</tr>
</tbody>
</table>
### TABLE III - 2

PROTON-PROTON SPIN COUPLING CONSTANTS (IN Hz) IN 3-FLUOROTHIOPHENE

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>J_{45}</th>
<th>J_{24}</th>
<th>J_{25}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>46</td>
<td>5.38</td>
<td>1.52</td>
<td>3.50</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>77</td>
<td>5.26</td>
<td>1.54</td>
<td>3.48</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>22</td>
<td>5.33</td>
<td>1.54</td>
<td>3.47</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>6</td>
<td>5.36</td>
<td>1.50</td>
<td>3.46</td>
</tr>
</tbody>
</table>

### TABLE III - 3

FLUORONE-PROTON SPIN COUPLING CONSTANTS (IN Hz) IN 3-FLUOROTHIOPHENE

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>J_{3F-2}</th>
<th>J_{3F-4}</th>
<th>J_{3F-5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>46</td>
<td>1.08</td>
<td>-0.81</td>
<td>3.30</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>77</td>
<td>1.06</td>
<td>-0.84</td>
<td>3.23</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>22</td>
<td>0.94</td>
<td>-0.88</td>
<td>3.17</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>6</td>
<td>0.92</td>
<td>-0.88</td>
<td>3.16</td>
</tr>
</tbody>
</table>
the central band have too low intensity to be detected.

A complete analysis of the whole ABCX spectrum at three different concentrations in cyclohexane was performed. The fluorine spectra at the concentrations 77\% and 22\% are shown in Fig. 5. At first it was thought that the asymmetry arose because of a decrease in the shift differences between the protons. Recordings of the proton spectrum, however, showed that the shifts had actually increased on dilution, especially that between proton in the 8-position and other protons. A comparison of the proton-fluorine coupling constants in the three solutions shows that the more pronounced asymmetry obtained at the lower concentrations is due to the fact that $J_{3P-4}$ and $J_{3P-2}$ are nearly equal in magnitude. The coupling constant $J_{3P-2}$ has decreased by 0.14 Hz due to dilution whereas $J_{3P-4}$ has increased slightly in magnitude (0.04 Hz) as given in Table III-3. The near equality makes some of the splittings smaller in the fluorine spectrum and a small asymmetry becomes therefore more evident (see Fig. 5).

The chemical shift of the fluorine resonance in cyclohexane extrapolated to infinite dilution is

\[
(\delta)_{\text{infinite dilution}} = 32.05 \pm 0.02 \text{ ppm (III-6)}
\]

Extrapolation to infinite dilution on the low-field side of hexafluorobenzene.
Fig 5. The fluorine resonance spectrum of 3-fluorothiophene in (a) a 22 % solution and (b) a 77 % cyclohexane solution.
The $\text{^{13}C} - \text{^{19}F}$ coupling was also measured from the $\text{^{13}C}$ satellite spectrum of the fluorine resonance in the benzene solution and is

$$J_{\text{^{13}C}-\text{^{19}F}} = 256 \pm 1 \text{ Hz} \quad \text{..... (III-7)}$$

The isotope shift is 5.0 Hz = 0.089 ppm. The $\text{^{19}F} - \text{^{13}C} (\text{^{12}C})$ isotope shift calculated from the linear relationship between $\text{^{13}C} - \text{^{19}F}$ couplings and isotope shifts$^{16}$ for $\text{sp}^2$ hybridized carbon is 0.090 ppm.

(b) 2-FLUOROTHIOPHENE

For this compound also the proton and fluorine resonance spectra were obtained both in benzene and cyclohexane with $\text{^1H}$ and hexafluorobenzene as the internal references. The proton part of the spectrum in 50% (by wt.) benzene solution at 60,000 MHz is shown in fig. 6 and the fluorine resonance spectrum is shown in fig. 7. As in 3-fluorothiophene the proton part of 2-fluorothiophene spectrum is an $\text{ABC}$ part of an $\text{ABXY}$ spectrum where the three protons constitute the $\text{ABC}$ system and fluorine part is the $\text{X}$ system. All the lines in the $\text{ABC}$ part (Fig. 6) are clearly resolved and the peaks have been measured. The upper part of the diagram shows the experimental spectrum and the lower part is the calculated one. The fluorine resonance spectrum at 56,444 MHz (Fig. 7) shows eight strong lines and four
Fig 6. The proton resonance spectrum at 60.000 MHz of 2-fluorothiophene in a 50% benzene solution. The upper part shows the experimental spectrum and the calculated spectrum is given below.
Fig 7. The fluorine resonance spectrum of 2-fluorothiophene. The calculated spectrum is shown with eight strong lines and four combination lines of finite intensity.
combination lines of finite intensity. In the experimental spectrum it is also possible to see (in four cases) some of the $^{34}S-2$ fluoro thiophene satellite lines on the high field side of the ordinary $^{32}S-2$ fluoro thiophene lines.

As in the 3-fluoro thiophene case it is preferred to interpret the ABC part by the use of subspectral analysis. As the ABC part is strongly coupled, it was not immediately possible to construct the appropriate energy level diagram for the two ABC sub-spin systems. By performing a series of tickling experiments\(^{15}\) it was, however, possible (as in the case of 3-fluoro thiophene) to pick out transitions with an energy level in common and together with the rule of repeated spacings\(^{17}\) and the intensities of the lines it was then not too difficult to construct the correct energy level diagrams (in the same form for the ABCX system as in fig. 4). From the energy level diagrams it is inferred that all the proton-fluorine coupling constants carry the same sign and, as found earlier\(^{1,2}\), that the proton-proton coupling constants are all of the same sign. Using the same procedure as in 3-fluoro thiophene case the parameters given in tables III-4, III-5 and III-6 below were obtained.
### TABLE III - 4

**CHIMICAL SHIFTS**<sup>a,b,c</sup> **(IN Hz) IN 2-FLUOROTHIOPHENE**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by vol. %</th>
<th>ν&lt;sub&gt;2&lt;/sub&gt;</th>
<th>ν&lt;sub&gt;3&lt;/sub&gt;</th>
<th>ν&lt;sub&gt;4&lt;/sub&gt;</th>
<th>ν&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>60</td>
<td>1583.28</td>
<td>348.19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>358.31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>360.07&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>41</td>
<td>1587.93</td>
<td>554.83</td>
<td>367.78</td>
<td>361.78</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>5</td>
<td>1595.97</td>
<td>356.14</td>
<td>369.65</td>
<td>364.01</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> The proton shifts are given at 56.444 MHz relative to TMS as internal reference and the fluorine shifts are given relative to hexafluorobenzene as internal reference.

<sup>b</sup> These shifts have been measured at 60.000 MHz and recalculated to 56.444 MHz.

<sup>c</sup> In order to compare the substituent shifts of the protons with other unsubstituted thiophenes, the δ - values at infinite dilution relative to cyclohexane (measured to -1.44 ppm) are calculated to be (in ppm):

<table>
<thead>
<tr>
<th>ν&lt;sub&gt;2&lt;/sub&gt;</th>
<th>ν&lt;sub&gt;4&lt;/sub&gt;</th>
<th>ν&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4.88</td>
<td>-5.12</td>
<td>-5.02</td>
</tr>
</tbody>
</table>
### TABLE III - 5

**PROTON-PROTON SPIN COUPLING CONSTANTS (IN Hz) IN 2-FLUOROTHIOPHENE**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>$J_{34}$</th>
<th>$J_{45}$</th>
<th>$J_{35}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>50</td>
<td>3.89</td>
<td>6.02</td>
<td>1.69</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>41</td>
<td>3.88</td>
<td>6.01</td>
<td>1.68</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>5</td>
<td>3.85</td>
<td>5.93</td>
<td>1.68</td>
</tr>
</tbody>
</table>

### TABLE III - 6

**FLUORINE - PROTON SPIN COUPLING CONSTANTS (IN Hz) IN 2 - FLUOROTHIOPHENE**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>$J_{2F-3}$</th>
<th>$J_{2F-4}$</th>
<th>$J_{2F-5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>50</td>
<td>1.63</td>
<td>3.07</td>
<td>3.10</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>41</td>
<td>1.54</td>
<td>3.07</td>
<td>3.08</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>5</td>
<td>1.43</td>
<td>2.95</td>
<td>2.27</td>
</tr>
</tbody>
</table>
The assignment of the resonance frequencies $\nu_A$, $\nu_B$, and $\nu_C$ to the three protons is also done here by means of the known magnitudes of the proton-proton couplings in thiophenes.

With the parameters obtained, a theoretical $X$-part spectrum was calculated and its result (Fig.7, lower diagram) were compared with experimental fluorine spectrum. As can be seen from Fig. 7, the spectrum is not symmetrical about the centre $\nu_X$. The asymmetry shown indicates that the proton-fluorine coupling constants are of the same sign as the proton-proton couplings and therefore probably positive in absolute sign. The calculated $X$-part agrees well with the experimental fluorine spectrum. The deviations in the eight strong lines are about 0.02 Hz. The deviation in the combination lines is in one case as large as 0.03 Hz, probably due to the fact that these lines have not been measured very accurately. The average deviation between the 36 calculated and measured transitions of the total ABCX spin system is 0.024 Hz, which is within experimental uncertainty ($\pm 0.03$ Hz except for a few lines). The proton-proton and proton-fluorine couplings are given with an accuracy of $\pm 0.03$ Hz and $\pm 0.05$ Hz respectively.

* The spectra of 3- and 2-fluorothiophenes have also been analyzed by a least square fit of all the 36 measured lines. In each case shifts and coupling constants were obtained that agree very well within the experimental uncertainty with our ABCX subspectral analysis. The proton part of 2-fluorothiophene has also been recorded at 160 MHz. The coupling constants obtained agree well with the 60 MHz analysis.
The spectrum of this compound has also been studied at different concentrations in cyclohexane. The results of the analysis of the ABCX spectrum at two concentrations are given in tables III-4, III-5 and III-6. The proton-proton couplings agree well with those of the benzene solution except $J_{45}$ which has decreased by 0.03 Hz. As seen from table III-6 the proton-fluorine couplings vary with the concentration outside the experimental uncertainty. There is also some evidence that the proton-fluorine couplings (cf. $J_{2F,3}$) vary with solvent, but no extensive study of these couplings in different solvents was performed during these measurements.

The fluorine spectrum in the cyclohexane solutions is simple and consists of six strong lines (vide : fig. 8 where the fluorine resonance spectrum in 41% (by wt.) cyclohexane solution is shown ). It was not possible from this spectrum to obtain the sign of the proton-fluorine couplings relative to that of the proton-proton couplings. The chemical shift of the fluorine resonance in cyclohexane extrapolated to infinite dilution is

\[
(\gamma_2)_{\text{infinite dilution}} = 23.30 \pm 0.02 \text{ ppm} \quad \text{(III-8)}
\]
Fig 8. The fluorine resonance spectrum of 2-fluorothiophene in a 40% cyclohexane solution. As this spectrum is simpler than that in Fig 7 all the eight $3g_8$ satellite lines are clearly visible on the high field side of the stronger lines.
In addition to the ordinary fluorine spectrum in the cyclohexane solutions, small peaks appear on the high field side of each of the strong lines (see fig. 8). These peaks have an intensity about 4% of the strong lines and form another fluorine spectrum, a satellite spectrum, shifted 0.31 Hz upfield from the ordinary spectrum. The possibility that these lines may be spinning sidebands can be ruled out as they do not move when the spinning speed is changed and that they are not symmetrical around the stronger lines.

It has been concluded that this is an isotope effect on the chemical shift and that the satellite spectrum is that of the naturally present (4%) $^{34}$S-2-fluorothiophene. The absence of such a satellite spectrum in the spectrum of 3-fluorothiophene, the intensity of the satellite spectrum, and the magnitude of the isotope shift exclude the possibility that the satellite spectrum is that of $^{13}$C-2-fluorothiophene. This isotope shift $^{19}$F-C - $^{34}$S ($^{32}$S) is therefore (0.014 ± 0.001) ppm. In the fluorine spectrum of 2-fluorothiophene in the benzene solution the effect of the isotope shift is not very evident, owing to the complexity of the spectrum but is nevertheless visible here also.
The $^{13}\text{C} - ^{19}\text{F}$ coupling constant as measured from the $^{13}\text{C}$ satellite spectrum of the fluorine resonance in the benzene solution is

$$J_{^{13}\text{C} - ^{19}\text{F}} = 236 \pm 1 \text{ Hz} \quad \ldots \ldots \quad (\text{III} - 9)$$

and the isotope shift $^{19}\text{F} - ^{13}\text{C}$ ($^{12}\text{C}$) is $5.8 \text{ Hz} = 0.103 \text{ ppm}$. The isotope shift calculated from the linear relation$^{16}$ between $^{13}\text{C} - ^{19}\text{F}$ coupling and the isotope shift is $0.105 \text{ ppm}$.

3.4 DISCUSSION

The chemical shifts of the hydrogens of 2-fluorothiophene in dilute cyclohexane solution relative to those of $\alpha$ - protons ($-5.72 \text{ ppm}$) and $\beta$ - proton ($-5.53 \text{ ppm}$)$^3$ of thiophene are thus

$$\omega_2 = 0.65 \text{ ppm},$$
$$\omega_4 = 0.41 \text{ ppm},$$
and $$\omega_5 = 0.70 \text{ ppm} \quad \ldots \ldots \quad (\text{III} - 10)$$

The corresponding values for the hydrogens of 3-fluorothiophene are

$$\omega_2 = 0.65 \text{ ppm},$$
$$\omega_4 = 0.28 \text{ ppm},$$
and $$\omega_5 = 0.15 \text{ ppm} \quad \ldots \ldots \quad (\text{III} - 11)$$
The upfield shifts of the hydrogens of 2-fluorothiophene show the characteristic alternating pattern observed for \(-I + M = 2\) substituted thiophenes. The shift of the 5-hydrogen is of the same magnitude as that observed in 2-methoxythiophene (0.82 ppm). Normally in \(-I + M = \) substituted thiophenes such as 2-methoxy- and 2-aminothiophene, the upfield shift of the 3-hydrogen resonance is larger than that of the 5-hydrogen, but in 2-fluorothiophene these shifts are reversed, most probably due to the much stronger \(-I =\) effect of the fluorine than of the other substituents.

The shifts of the hydrogen resonances of 2-fluorothiophene also show the expected pattern for \(-I + M = 3\) substituted thiophene. Possible reasons for the larger upfield shift of the 2-hydrogen resonance as compared to that of the 4-hydrogen resonance have been discussed earlier.

An estimate of the shift of the protons caused by the magnetic anisotropy of the fluorine atom was made in a manner similar to that described in Ref. 4. A magnetic anisotropy of \(\Delta \chi = 8 \times 10^{-30} \text{ cm}^3 / \text{ atom}\) gave diamagnetic contributions to the shifts of the protons in 2- and 3-fluorothiophenes, which are at most 0.05 ppm and will therefore not change the discussion above.
It is interesting to note that while in the proton magnetic resonance spectra of thiophene, the 2-hydrogen resonance occurs at lower field than that of the 3-hydrogen, the 2-fluorine is more shielded than the 3-fluorine in 2- and 3-fluorothiophenones, respectively.

Similar inversion between proton and fluorine shifts was also observed when napthalene was compared with α- and β-fluoronapthalene\(^\text{19,20}\). Prosser and Goodman\(^\text{21}\) have, using an idea of Karplus and Das\(^\text{22}\) given the following equation which relates chemical shifts in conjugated compounds with \(\pi\)-electron densities on the fluorine atom and the bonded carbon atom and with C-F bond order.

\[
\delta = 488 \Delta F^{-1} \left[11.9 \Delta q(F) + 3.9 \Delta p(C,F) + 0.1 \Delta q(C)\right]
\]

\(\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldOTS

This equation gave good agreement with para substituted fluorobenzences\(^\text{23}\) and it has also been used by Boden et al. in substituted perfluorobenzences\(^\text{24}\). In addition they also introduced a term for the chemical shift from intramolecular electric field contributions.
TABLE III - 7

BOND ORDERS AND \( \omega \) - ELECTRON DENSITIES

1. Calculated with parameters according to Refs. 25 and 26.
2. Calculated with parameters according to Refs. 25 and 24 adjusted to the \( \omega \) method.

<table>
<thead>
<tr>
<th>2-Fluorothiophene</th>
<th>3 - Fluorothiophene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>q(Cz)</td>
<td>1.0101</td>
</tr>
<tr>
<td>q(Fz)</td>
<td>1.9836</td>
</tr>
<tr>
<td>p(CzFz)</td>
<td>0.1269</td>
</tr>
</tbody>
</table>

A modified method\(^{25}\) was used to calculate the \( \pi \)-electron densities and bond orders of 2- and 3-fluorothiophenes.

Using \( \alpha_c = \alpha \), \( \alpha_s = \alpha + \beta \), \( \beta_{cc} = 0.75 \beta \), and \( \beta_{cs} = 0.45 \) (parameter set 3, Ref. 25) together with \( \alpha_F = \alpha + 3 \beta \) and \( \beta_{CF} = 0.5 \beta \) (derived from those of Streitwieser \(^{26}\)) the charge densities and bond orders given in table 7 were obtained. Formula III-12 then gave a larger screening of the 2-fluorine: \( \delta = 7.12 / \Delta E \) ppm (\( \Delta E > 0 \), in eV).
However, in order to obtain the correct order for the para-fluorine shift of perfluorochlorobenzene, Boden et al.\textsuperscript{24} found it necessary to change the fluorine parameters of Streitwieser\textsuperscript{26} to $\alpha_F = \alpha + 2\beta$ and $\beta_{CF} = \beta$. With these parameters, adjusted to the $\omega$-method by changing $\beta_{CF}$ to 0.75$\beta$, a reverse order of shift $\omega = -23.3/\Delta E$ ppm. (see also table 7) was obtained, i.e. a smaller screening of the 2-fluorine as compared to that of the 3-fluorine. It is obvious that the calculated shifts are very sensitive to the parameters used. It can in addition not be excluded that the different molecular environments of 2- and 3-fluorothiophenes (field effects from the hydrogens and the sulphur) also make contributions to the chemical shift. It is hoped that an application of the formula of Presser and Goodman to $\omega$-substituted 2-fluorothiophene will be helpful in finding a consistent set of parameters.

Muller and Carr\textsuperscript{27}, who have studied the spin-spin coupling constants between $^{19}$F and directly bonded $^{13}$C nuclei, found that these coupling constants increased with decreased shielding. They suggested that the degree of C-F double bond character is the most important single parameter influencing both the chemical shift and the C-F coupling constants, while the C$^+$-F$^-$ ionic
character is quantitatively less important. They also suggested that when the s-character of the carbon orbital of the C-F bond is increased the C-F coupling is reduced. It is interesting to note that the C-F coupling for 3-fluorothiophene (256 Hz) is smaller than that of 2-fluorothiophene (286 Hz), although the fluorine resonance of the former compound occurs at lower field. Whereas the chemical shifts do not follow the order of C-F double bond character in the two fluorothiophenes, the magnitude of the C-F coupling does.

Isotope shifts due to sulphur isotopes have earlier been observed by Gillespie and Quail in compounds where fluorine is directly bonded to sulphur in compounds such as SF₆ and SOF₂. The isotope shift varied between 0.022 and 0.453 ppm. For SF₆ the isotope shift due to the presence of ²³S (natural occurrence 0.74 %) was also observed. As this isotope has spin 3/2 these authors could also obtain J₃³S-F from the satellite spectrum. No attempt was made to observe the satellite spectrum from ³²S in this work. To the best of the knowledge the ²⁴S isotope shift in 2-fluorothiophene of 0.014 ppm is the first isotope shift observed for a fluorine not directly bonded to sulphur. is there is no detectable ²⁴S isotope shift of the fluorine resonance of 3 - fluoro thiophene, the ³⁴S shift of the 2-fluorine resonance is of great
help in identifying fluorine resonances in difluoro-thiophenes such as 2,3- and 2,4- difluoro-thiophenes as described in next chapter.

The proton-proton couplings in 3-fluoro-thiophene are close to the couplings found in 3-nitro-thiophene\(^2\). The value of \(J_{25}\) is the largest found in 3-substituted thiophenes. The proton-proton couplings in 2-fluoro-thiophene are all among the largest found in 2-mono-substituted thiophenes.

The magnitude of the ortho H-F couplings in the two thiophenes studied here is surprisingly small and it is also a little unexpected that \(J_{3F-4}\) and \(J_{3F-2}\) are of opposite signs. Vicinal H-F couplings of similar magnitude have been observed for the cis H-F coupling in some fluoroethylenes\(^29,30\). The magnitude of these ortho couplings is, however, considerably smaller than the ortho H-F coupling in fluorobenzenes (6.2 to 10.4 Hz)\(^31-36\). The meta couplings \(J_{2F-4}\) and \(J_{2F-5}\) are larger than the ortho couplings, but they are only about half the magnitude of the meta H-F couplings in fluorobenzenes (4.3 to 8.3 Hz)\(^31-36\). The coupling \(J_{2F-5}\) is also larger than the ortho coupling and is larger in magnitude than the para coupling in fluorobenzenes (-1.3 to -2.7 Hz)\(^31,35\).

* The para H-F coupling has been found to be of opposite sign to the ortho and meta H-F couplings in fluorobenzenes.
All the proton-fluorine couplings except $J_{\text{F-4}}$ in these two fluorothiophenes are of the same sign as the proton-proton couplings and therefore assumed to be positive in absolute sign.$^1,2,11-14$.
REFERENCES

18. Reference 16, p. 75.


CHAPTER IV

PROTON AND FLUORINE NMR SPECTRA OF

(a) 2,3 - Difluorothiophene
(b) 2,4 - Difluorothiophene
(c) 2 - Bromo - 2,5 - Difluorothiophene
(d) 2,5 - Difluorothiophene
(e) 3,4 - Difluorothiophene
(f) 5 - Bromo - 2,3 - Difluorothiophene
(g) 2,3,5 - Trifluorothiophene.
The $^{1}$H and $^{19}$F nuclear magnetic resonance spectra of 2,3-difluorothiophene, 2,4-difluorothiophene, 3-bromo-2,6-difluorothiophene, 2,5-difluorothiophene, 3,4-difluorothiophene, 5-bromo-2,3-difluorothiophene and 2,3,5-trifluorothiophene have been analyzed. The ranges for the $^{1}$H-$^{19}$F spin couplings in these compounds are 

(in Hz): $J_{2F-3} = 1.29$ to $3.40$; $J_{3F-2} = 1.23$ to $2.92$; $J_{3F-4} = -0.33$ to $+0.38$; $J_{2F-4} = 3.08$ to $3.66$; $J_{3F-5} = 3.17$ to $4.61$; $J_{2F-5} = 3.40$ to $4.47$. The magnitudes of the different F-F spin couplings are 

(in Hz): $J_{2F-3F} = 0.22$ to $4.35$; $J_{2F-4F} = 9.23$ to $15.26$; $J_{3F-4F} = 12.88$ and $J_{2F-5F} = 22.91$ to $27.76$. The coupling $J_{3F-4F}$ was found to be of opposite sign to the proton-proton spin coupling $J_{2F}$. In the polyfluorothiophenes with a fluorine atom both in the 2- and 3- position a considerable increase of the fluorine chemical shifts compared to the fluorine shifts in 2- and 3- fluorothiophene was observed. In 2,3-difluorothiophene this upfield shift is 21.87 ppm for the 2-fluorine and 18.68 ppm for the 2-fluorine. In 3,4-difluorothiophene there is also an increased shielding of the fluorine nuclei with 8.08 ppm compared to that of 3-fluorothiophene. In 2,5-difluorothiophene,
the fluorine chemical shift is 1.80 ppm upfield from that of 2-fluorothiophene whereas in 2,4-difluorothio-
phone the 2-fluorine resonance is shifted 8.97 ppm and the 4-fluorine resonance is shifted 7.73 ppm downfield from the fluorine resonance in 2- and 3-fluorothiophenes respectively.

4.1 INTRODUCTION

In the preceding chapter\textsuperscript{1}, the NMR spectra of 2- and 3-fluorothiophenes were analyzed. In the present chapter the results from an investigation of the four difluorothiophenes and one trifluorothiophene as well as from two bromosubstituted fluorothiophenes are reported.

The "ortho" spin couplings \( J_{2\text{F}-3\text{F}} \), \( J_{3\text{F}-2\text{F}} \), and \( J_{3\text{F}-4\text{F}} \) are the smallest \( H-F \) spin couplings in 2- and 3-fluorothiophenes\textsuperscript{1} and are surprisingly small compared to the ortho \( H-F \) coupling in fluorobenzene\textsuperscript{2-11}, fluoro dibenzofuran\textsuperscript{12} and fluoro pyridines\textsuperscript{13}, and it is therefore of interest to see if the magnitude of these couplings is changed with one or two more fluorine atoms attached to the thiophene ring and also to obtain intervals for all the \( H-F \) couplings. It is also desirable to determine the magnitude of the \( F-F \) coupling constants in general and the ortho \( F-F \) coupling constants in particular as it is possible that these latter couplings
are the smallest of them and like the H-F couplings considerably smaller than the corresponding ortho couplings in fluorobenzenes 2,5,6,11,14-17, fluorodibenzofurans 12 and fluoropyridines 13 and thereby may give some indication that a similar mechanism is responsible for the small ortho H-F and F-F couplings in fluorothiophenes.

Further, it was noticed in chapter III that in 2-fluorothiophene all the H-H couplings are among the largest found in 2-monosubstituted thiophenes 18 and in 3-fluorothiophene the value of H-H coupling $J_{25}$ is the largest observed in 3-substituted thiophenes 18. Thus it might be assumed that still larger H-H coupling would be observed in the polyfluorothiophenes compared to those in the disubstituted thiophenes investigated in the previous comprehensive work of Hoffman and Gronovitz 19.

The strong-$I$ and $+$M character of the fluorine atom makes it important to determine the substituent shifts of the protons in these fluorothiophenes and see how well they fit into the scheme of proton chemical shifts in disubstituted thiophenes previously obtained 19.

4.2 SOME EXPERIMENTAL DETAILS

The samples of all the seven compounds mentioned in this chapter were prepared and supplied by Prof. S. Gronovitz and his associates.
The studies of these fluorothiophenes were made in benzene and or cyclohexane solutions except in the case of 2,3,5-trifluorothiophene where a neat compound with TMS and C₈ F₆ and also carbon tetra-chloride has been used. All the spectra were recorded by HA60 spectrometer. For the proton spectra the TMS (present in 5% by wt.) served as the lock signal and for the fluorine resonance spectra the hexafluorobenzene (present in 10% by wt.) signal was used as lock signal for the internal stabilization. The lock frequency was produced by a Muirhead D-890A Decade Oscillator. The spectra were recorded in the frequency sweep mode and the resonance peaks were measured by counting the inverse sweep frequency on HP 3734A electronic frequency counter. In these measurements the frequency was swept to exact resonance of the peak to be counted and this was done for the two sweep directions and a mean value was taken. In the tickling experiments the second weak rf field E₂ was obtained by amplitude modulation of the magnetic field. The modulation frequency was produced by a Philips Oscillator PP 6050. The ¹³C satellite spectra of 2,5-difluorothiophene were obtained by using Varian C-1024 time averaging computer.

The chemical shifts in cyclohexane were obtained at various concentrations and thence extrapolated to infinite dilution.
4.3 RESULTS AND INTERPRETATION

(a) 2,3-DIFLUOROTHIOFENE

The spectrum of the compound in 11% cyclohexane solution is shown in figs. 1 and 2. The spectrum is of the ABX type where the two protons are regarded as AB part and the two fluorines as H and X. Fig. 1 shows the AB part of the spectrum where all the sixteen lines are more or less clearly resolved and the peaks measured. The upper part (Fig. 1) shows the experimental part and the computer-simulated spectrum is given in the lower part. Fig. 2 shows the fluorine part of the spectrum; the left part of the spectrum is from 3-fluorine and that to the right from the 2-fluorine and the computer-simulated spectrum is given in the lower part. The combination lines are missing in the experimental fluorine spectrum and even in the computer-simulated spectrum as these lines of the 2-fluorine spectrum are not given as they here have 10 and 20 times weaker intensity as compared to those of the 3-fluorine spectrum.

The whole spectrum is conveniently analyzed by means of the subspectral analysis. The proton band is regarded as four overlapping ordinary
Fig 1. The proton resonance spectrum of 2,3-difluorothiophene at 56.444 MHz in a 11% cyclohexane solution. The upper part shows the experimental spectrum and the computer-simulated spectrum is given below.
Fig 2. The fluorine resonance spectrum of 2,3-difluorothiophene at 56.444 MHz.
AB spectra with four different effective chemical shifts of the A and B nuclei owing to the four combinations of the two spin states of the fluorine nuclei. The AB part is strongly enough coupled to make the intensity distribution of the lines of one AB subspectrum different from that of the others. It is therefore possible to pick out the four lines that form each AB subspectrum in an unambiguous way. From these four AB subspectra the proton-proton coupling and the four effective chemical shifts are easily obtained.

From these shifts the real proton shift $\gamma_A - \gamma_B$ ($\gamma_A > \gamma_B$) and two differences of H-F spin couplings, $J_{AM} - J_{BM}$ and $J_{AX} - J_{BX}$ are obtained and from the midpoints of the AB subspectra the sums $1/2(J_{AM} + J_{BM})$ and $1/2(J_{AX} + J_{BX})$ are also obtained. The magnitudes of the couplings $J_{AM}$, $J_{BM}$, $J_{AX}$ and $J_{BX}$ are then easily calculated together with the relative signs of $J_{AM}$ and $J_{BM}$ and of $J_{AX}$ and $J_{BX}$. It is found that $J_{AM}$ and $J_{BM}$ are of opposite sign whereas $J_{AX}$ and $J_{BX}$ carry the same sign.

As $\gamma_A$ is put arbitrarily larger than $\gamma_B$ the low field lines of the proton spectrum are denoted A and the high field lines B (see fig.1). The experimental spectrum is then only consistent with the following
assignment of the H-F spin couplings: $J_{AM} = -0.09$ Hz, $J_{AX} = 3.08$ Hz, $J_{BX} = 4.41$ Hz and $J_{BX} = 4.29$ Hz. This assignment can also immediately be made from inspection of the proton spectrum without calculation, as the smallest H-F coupling (−0.09 Hz) must give the smallest H-F splittings $A1 - A2$, $A5 - A6$, $A3 - A4$ and $A7 - A8$ and therefore it must be denoted $J_{AM}$ and consequently $J_{BM}$ is equal to 4.41 Hz. The splittings $B1 - B2$, $B4 - B6$, $B3 - B5$ and $B7 - B8$ due to $J_{BM}$ are then easily identified, as well as the splittings $B1 - B3$, $B4 - B7$, $B2 - B5$ and $B6 - B8$ due to $J_{BX}$ and the splittings $A1 - A3$, $A5 - A7$, $A2 - A4$ and $A6 - A8$ due to $J_{AX}$. As the splittings due to $J_{AX}$ are smaller than the splittings due to $J_{BX}$, the H-F coupling equal to 3.08 Hz is assigned to $J_{AX}$ and the H-F coupling equal to 4.29 Hz is assigned to $J_{BX}$.

In sum, from the proton spectrum of 2,3-difluorothiophene it is possible to obtain the chemical shifts $\gamma_A$ and $\gamma_B$ of the protons, the proton-proton spin coupling $J_{AB}$ and the H-F spin couplings, two of which to one fluorine nucleus, are of opposite signs and differ by 4.3 Hz in absolute value whereas the remaining two, to the other fluorine nucleus, are of the same sign and differ only by 1.20 Hz.

The fluorine spectrum at −6.43 ppm from C$_6$F$_6$ is assigned to the α-fluorine owing to the presence of
$^{34}$S satellite lines$^1$ and therefore the fluorine band at -12.37 ppm is assigned to the $\beta$-fluorine$^*$. From the fluorine spectra (shown in fig. 2) it is seen that the H-F couplings to the 2-fluorine nucleus must be the two couplings denoted by $J_{AX}$ and $J_{BX}$ and the H-F couplings to the 3-fluorine nucleus must be the two couplings denoted by $J_{AM}$ and $J_{BM}$. The X-fluorine is therefore identified with the 3-fluorine and the X-fluorine with the 2-fluorine. As in 2-fluorothiophene$^1$ the coupling $J_{3F-4}$ (-0.30 Hz) is of opposite sign to that of $J_{3F-6}$ (3.20 Hz) and smaller in magnitude, it is most reasonable to assign the proton denoted by $A$ to the 4-proton and the proton denoted by $B$ to the 5-proton (fig. 1). This assignment of the protons also gives an order of the chemical shifts of the protons which agrees with that calculated from the shifts in 2- and 3-fluorothiophenes assuming additivity of the shifts (see discussion below).

The H-F coupling $J_{BX}$ is equal to the splitting between the lines in the doublets $(M_1,M_2)$, $(M_7,M_8)$, $(X_1,X_2)$ and $(X_7,X_8)$. This coupling can also be calculated from the doublets $(M_5,M_6)$ and $(X_5,X_6)$ but in this case the effective chemical shifts calculated from the proton spectrum must be used. The fluorine spectra are asymmetrical around their resonance frequencies $\nu_M$ and $\nu_X$. From this asymmetry it is possible to obtain the relative

* In the fluorine spectra of the rather dilute solution shown in fig.2 the $^{34}$S satellite lines are not clearly visible but spectra of a more concentrated solution (24 % by wt.) were also recorded and in these spectra the satellite lines were easily recognized.
sings of all the H-F couplings and also the sign of $J_{MX}$ relative to these couplings. The couplings $J_{AX}$, $J_{BM}$ and $J_{EX}$ are determined to be of the same relative sign and to be of opposite sign to that of $J_{AM}$ and $J_{MX}$. How these relative signs are obtained is described below.

The proton shifts and the fluorine-fluorine coupling are given in Table IV-1(a) and the proton-fluorine couplings together with the proton-proton coupling are given in Table IV-2(a). The H-F couplings are given with the same signs as they have in 2- and 3- fluorothiophenes and therefore the F-F coupling is given with a negative sign. The uncertainty in the H-H coupling is ± 0.03 Hz and that of the other couplings is ± 0.06 Hz. In Table IV-3(a) the chemical shifts of the fluorine nuclei extrapolated to infinite dilution in cyclohexane are given and they show that in 2,3-difluorothiophene the fluorine nuclei are more shielded than in 2- and 3- fluorothiophenes.

The appearance of the M-fluorine spectrum is now to be discussed in detail. The large separation between the doublets (M1, M2) and (M7, M8) is equal to the sum of the couplings* $J_{AM}$ and $J_{BM}$ and therefore mainly

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* The sums $J_{AM} + J_{BM}$ and $J_{AX} + J_{EX}$ are also obtained from the M- and X-fluorine spectra respectively and can together with these sums obtained from the proton spectrum be used for the calculation of $J_{AM}$, $J_{BM}$, $J_{AX}$ and $J_{EX}$. 
### Table IV - 1(a)

Proton and fluorine chemical shifts* and fluorine-fluorine spin coupling in 2,3 - Difluorothiophene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling J_{2F - 3F} (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>≈ 20</td>
<td>355.95  773.64  344.13  326.16</td>
<td>0.77</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>24</td>
<td>346.33  752.19  368.06  363.02</td>
<td>0.22</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>11</td>
<td>356.36  753.22  367.30  360.68</td>
<td>0.22</td>
</tr>
</tbody>
</table>

The proton shifts (γ₄ and γ₅) are given in Hz relative to TMS as internal reference and the fluorine shifts (γ₂, γ₃) are given in Hz downfield relative to C₆F₆ as internal reference at 56.444 MHz.
Table IV - 2(a)

Fluorine-proton spin couplings and proton-proton spin coupling (in Hz) in 2,3 - Difluorothiophene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>Fluorine-Proton spin couplings (in Hz)</th>
<th>Proton-Proton spin coupling J_45 (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>J_3F_4</td>
<td>J_2F_4</td>
</tr>
<tr>
<td>Benzene ≈ 20</td>
<td></td>
<td>-0.12</td>
<td>3.12</td>
</tr>
<tr>
<td>Cyclohexane 24</td>
<td></td>
<td>-0.13</td>
<td>3.09</td>
</tr>
<tr>
<td>Cyclohexane 11</td>
<td></td>
<td>-0.09</td>
<td>3.08</td>
</tr>
</tbody>
</table>

Table IV - 3(a)

Fluorine chemical shifts in 2,3-difluorothiophene in ppm relative to C_6 F_6 (Δ - values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2-and 3-fluorothiophenes (δ - values).*

<table>
<thead>
<tr>
<th>Δ_2</th>
<th>Δ_3</th>
<th>δ_2</th>
<th>δ_3</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6.43</td>
<td>-13.37</td>
<td>21.87</td>
<td>18.68</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low-field side of the reference signal.
due to $J_{BM}$. If the F-F coupling is for a moment set equal to zero, the M-fluorine spectrum will contain six lines, the collapsed doublets $(M_1, M_2 \uparrow)$ and $(M_7, M_8)$ and the doublets $(M_3, M_4)$ and $(M_5, M_6)$, now all symmetrically situated about $\nu_M$. The splitting between the collapsed doublet $(M_1, M_2)$ and the lines $M_3$ and $M_4$ and the splitting between the collapsed doublet $(M_7, M_8)$ and the lines $M_5$ and $M_6$ is 0.47 and 0.61 Hz respectively. The major part of these splittings (0.55 and 0.69 Hz) arises from "virtual spin coupling" between the M-fluorine and the $A$-proton which is then decreased slightly (0.08 Hz) by almost the whole $J_{AB}$ coupling (0.08 Hz) to the splittings observed. The doublet splitting 0.14 Hz of $(M_3, M_4)$ and of $(M_5, M_6)$ so obtained may be denoted "Partial virtual spin coupling" between the fluorine nuclei. It is called "partial virtual spin coupling" as it only appears in $K$-transitions between states with spin zero of the AB sub spin system ('mixed transitions') and not in the transitions $(M_1, M_2)$ and $(M_7, M_8)$ between states with spin ± 1 of the AB sub spin system ('unmixed transitions'). This 'partial virtual spin coupling' is due to the fact that the effective chemical shifts of the AB nuclei for the $K$-transitions are influenced by the spin state of the $X$-nucleus.

* For full details of 'Partial virtual spin coupling' see ref. 22.
To this "partial virtual spin coupling" the real \( J_{MX} \) coupling -0.22 Hz is then added or subtracted owing to the spin state of the X-nucleus, which gives the doublet splittings \((M3, M4)\) and \((M5, M6)\) equal to 0.36 Hz and 0.08 Hz respectively, and in this way the asymmetry of the spectrum is explained.

In the same way the asymmetry of the X-fluorine spectrum is obtained with the same doublet splittings as the rule of repeated spacings is always valid\(^{23}\) but the sense of symmetry need not necessarily be the same.

The sense of the asymmetry in the M-fluorine spectrum depends on the sign of \( J_{MX} \) relative to the sign of the difference \( J_{AX} - J_{BX} \) and the sense of the asymmetry in the X-fluorine spectrum depends on the sign of \( J_{MX} \) relative to the difference \( J_{AM} - J_{BM} \). The asymmetries present in the spectra shown are consistent with the same sign of \( J_{MX} \) and these differences. As these differences carry the same sign and as

\[
|J_{BM}| > |J_{AM}| \quad \text{and} \quad |J_{BX}| > |J_{AX}|
\]

it can be concluded that \( J_{BM} \), \( J_{AX} \) and \( J_{BX} \) are of the same relative sign and of opposite sign to that of \( J_{AM} \) and \( J_{MX} \).
A complete analysis of the spectrum in a 24\% cyclohexane solution was also performed. The resolution of this spectrum is not as good as that of 11\% solution and it was not possible to resolve the J_{2F-3F} coupling in the "unmixed" transitions of the fluorine spectra. The fluorine spectra here are also asymmetric about their centres with a well resolved low field doublet of the "mixed" transitions and a collapsed high field doublet, which is considerably narrower than the "unmixed" doublets. The J_{2F-3F} coupling could, therefore, only be obtained from the well resolved doublet together with the effective shifts evaluated from the proton spectrum. Thus the phenomenon of "partial virtual spin coupling", the magnitude of which is mainly dependent on the shift between the protons, causes an enlargement of the real coupling and thus makes it possible to obtain an accurate measurement of a coupling even if the splitting equal to that coupling cannot be resolved in the experimental spectrum.

The spectrum of the same compound in a benzene solution was also recorded. The peaks here are broader and the uncertainty of the parameters therefore a little

* The results are given in table IV-1(a) and table IV-2(a).
+ The results given in table IV-1(a) and table IV-2(a).
greater than that in the cyclohexane solutions. In the analysis the larger proton-fluorine couplings were all assumed to be positive, because the protons are not strongly coupled enough so as to make an unambiguous assignment of lines to the four AB subspectra. Here it turns out that $J_{3F-4}$, the corresponding splitting of which is not resolved in the spectrum, carries the opposite sign to $J_{3F-5}$. Nothing can be said about the sign of the fluorine-fluorine coupling, which in this solution is larger in magnitude than that in cyclohexane solutions (0.77 Hz instead of 0.22 Hz).

(b) 2,4-DIFLUOROTHIOPHENE

The NMR spectra of this compound in a 45 $\%$ (by wt.) cyclohexane solution is shown in figs 3, 4 and 5. The spectrum is a loosely coupled AMX-type where AM is assigned to the two proton nuclei (in 3 and 5 positions) and RX is assigned to the two fluorine nuclei. The fluorine spectrum at the highest field is assigned to the $\alpha$-fluorine due to the presence of 348 satellite lines in the spectrum (chapter III). The smallest H-F splitting is found in the $\beta$-fluorine spectrum and is assumed to be due to $J_{4F-3}$ and as the same splitting appears in the proton spectrum at lowest field this band is assigned to the $\beta$-proton. The analysis of the spectrum is straightforward and the results are given in tables IV-1(b) and IV-2(b). It is, however, not possible from the single
Fig 3. The proton resonance spectrum of 2,4-difluorothiophene in a 45 % cyclohexane solution. The left part being assigned to 3-proton and the right hand side to 5 - proton.
Fig 4. The fluorine resonance (in the 4- position) spectrum of 2,4- difluorothiophene in a 45% cyclohexane solution.
Fig 5. The fluorine resonance (in the 2-position) spectrum of 2,4-difluorothiophene in a 45% cyclohexane solution.
### Table IV - 1(b)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt%</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling JF-F (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>γ_2</td>
<td>γ_3</td>
</tr>
<tr>
<td>Benzeze</td>
<td>58.9</td>
<td>2198.30</td>
<td>&lt;40.07</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>45.9</td>
<td>2193.44</td>
<td>&lt;48.05</td>
</tr>
</tbody>
</table>

* The proton shifts (γ_3 and γ_5) are given in Hz given in Hz relative to TMS as internal reference and the fluorine shifts (γ_2, γ_4) are given in Hz downfield relative to C_F_6 as internal reference at 56.444 MHz.
**Table IV - 2(b)**

Fluorine-proton spin couplings and proton-proton spin coupling (in Hz) in 2,4 - Difluorothiophene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Cons. by wt %</th>
<th>Fluorine-Proton Spin couplings (in Hz)</th>
<th>Proton-Proton Spin coupling J_{35} (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>55.0</td>
<td>J_{2F-3} 1.35 J_{4F-3} 2.92 J_{4F-5} -0.27 J_{2F-5} 3.45</td>
<td>2.32</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>45.0</td>
<td>1.29 2.81 -0.33 3.40</td>
<td>2.29</td>
</tr>
</tbody>
</table>

**Table IV - 3(b)**

Fluorine chemical shifts of 2,4 - difluorothiophene in ppm relative to C_{6}F_{6} (Δ - values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophene (δ - values):

<table>
<thead>
<tr>
<th>Δ₂</th>
<th>Δ₄</th>
<th>δ₂</th>
<th>δ₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>-37.27</td>
<td>-39.78</td>
<td>-3.97</td>
<td>-7.73</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low-field side of the reference signal.
resonance spectrum alone to determine the relative signs of the spin couplings. Tickling experiments in the proton and fluorine parts were performed by applying the second rf. field $H_2$ on one line and observing its effect in the other part. It was found that $J_{3F-3}$ is of opposite sign compared to the other three proton-fluorine couplings. Nothing can be said about the sign of the fluorine-fluorine coupling $J_{3F-4F}$. The fluorine resonances at infinite dilution in cyclohexane were extrapolated and given in Table IV-3(b). In this compound the two fluorine resonances are shifted towards lower field than those of the two monofluorothiophenes.

(c) 3-BROMO-2,5-DIFLUOROTHIOPHENE

The NMR spectra of this compound in a 43% (by wt.) cyclohexane solution is shown in Figs. 6, 7 and 8. The spectrum is a simple ABX spectra where AB has been assigned to the two fluorine resonance spectra and the proton in the 4th position is assigned X. The analysis of the spectrum is quite simple by using the fact that this AB system can be thought of two AB subspectra, one for each fluorine nuclei. The results of the analysis have been summarized in Tables IV-1(C) and IV-2(C). The spectrum of the same compound was also
Fig. 6. The proton resonance spectrum (X-part of an AJK system) of 3-bromo-2,6-difluorothiophene in a 43% cyclohexane solution.
Figs. 7 and 8. The fluorine resonance spectrum of 3-bromo-2,5-difluorothiophene in a 43% cyclohexane solution.
### Table IV - 1(c)

**Proton and fluorine chemical shifts** and fluorine - fluorine spin coupling in 3-Bromo- 2,5 - Difluorothiophene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling J&lt;sub&gt;2F-5F&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \gamma_2 )</td>
<td>( \gamma_4 )</td>
</tr>
<tr>
<td>Benzene</td>
<td>18</td>
<td>1413.26</td>
<td>315.11</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>43</td>
<td>1602.94</td>
<td>540.43</td>
</tr>
</tbody>
</table>

*The proton shift (\( \gamma_4 \)) is given in Hz, relative to TMS as internal reference and the fluorine shifts \( \gamma_2, \gamma_5 \) are given in Hz downfield relative to \( \text{C}_6 \text{F}_6 \) as internal reference at 56.44 MHz.*
### Table IV - 2 (c)

**Fluorine-proton spin couplings (in Hz) in 3 - Bromo - 2,5 - Difluorothiophene**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt. %</th>
<th>$J_{2F-4}$</th>
<th>$J_{5F-4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>18</td>
<td>3.52</td>
<td>2.89</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>43</td>
<td>3.43</td>
<td>2.81</td>
</tr>
</tbody>
</table>

### Table IV - 3(c)

**Fluorine chemical shifts of 3 - Bromo - 2,5 - Difluorothiophene in ppm relative to C₆F₆ * (Δ - values) at infinite dilution in Cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophenes (δ - values)**.

<table>
<thead>
<tr>
<th></th>
<th>Δ₂</th>
<th>Δ₅</th>
<th>δ₂</th>
<th>δ₅</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-28.39</td>
<td>-28.21</td>
<td>2.91</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low-field side of the reference signal.
obtained in benzene solution and the results are also summarized in the above mentioned tables.

The chemical shifts of fluorine nuclei extrapolated to infinite dilution is given in table IV-3(C). The investigations\textsuperscript{26} of 3-bromo-2-fluorothiophene and of 4-bromo-2-fluorothiophene has given the shifts of 29.62 and 36.63 ppm, respectively relative to C\textsubscript{6}F\textsubscript{6} in cyclohexane solutions, for the fluorine resonances. Therefore the fluorine band at the lowest field is assigned to the 5-fluorine and the band at the highest field to the 2-fluorine. This assignment gives a relative size of the H-F spin couplings consistent with values of these couplings in other substituted 2-fluorothiophenes\textsuperscript{1,26}. By a tickling experiment\textsuperscript{24} in the fluorine spectrum these H-F couplings were found to carry the same sign.

In this tickling experiment as well as in the tickling experiments performed in 2,4 - difluorothiophene and in the fluorine spectra of 2,3,5 - trifluorothiophene (given below), generalized Overhauser effects\textsuperscript{25} of the unsplit lines not belonging to the tickled state of the proton or protons appeared. As similar Overhauser effects have also been observed in tickling experiments performed in the proton spectra of 2,4 - difluorothiophene in
this work and of 5-substituted 2-fluorothiophenes, it can be concluded that the spin lattice relaxation times for the fluorine nuclei and the protons are of same magnitude in fluorothiophenes.

(d) 2,5-DIFLUOROTHIOPHENE

The NMR spectrum of this compound in 26% (by wt.) cyclohexane solution is shown in figs. 9 (proton part) and 10 (fluorine part). This compound gives a deceptively simple $A_{XX}'$ spectrum in which the proton and fluorine spectra give rise to a 1:2:1 triplet. This simple spectrum need not necessarily imply equal H-F spin couplings as the F-F coupling can be fairly large in this compound causing the four lines that build up the middle peak to coalesce. An estimate of the magnitude of the F-F coupling can be obtained from 3-bromo-2,5-difluorothiophene (discussed above) and 2,3,5-trifluorothiophene (see below, where it is 26.1 and 27.7 Hz, respectively.

With the use of a time averaging computer (Varian model C-1024) it was, however, possible to record the $^{13}C - ^{19}F$ satellites as well as one $^{13}C - ^{19}F$ satellite of 2,5-difluorothiophene. In the $^{13}C - ^{19}F$ satellite spectrum the two fluorine nuclei are no
Fig 9. The proton resonance spectrum of 2,5-difluorothiophene in a 25% cyclohexane solution.

Fig 10. The fluorine resonance spectrum of 2,5-difluorothiophene in a 25% cyclohexane solution.
longer equivalent and this non-equivalence makes it possible to measure the $J_{2F-5F}$ coupling, and the $J_{34}$ coupling is similarly obtained from the $^{13}C-H$ satellite spectrum. The $J_{2F-5F}$ coupling is $22.91 \pm 0.08$ Hz and the proton-proton coupling $J_{34}$ is $4.42 \pm 0.07$ Hz. The sum of the $H-F$ couplings obtained from the satellite spectra is $6.89$ Hz which can be compared with $6.92$ Hz obtained from the $^{12}C-19F$ and $^{12}C-H$ spectra.

Every observed satellite spectrum represents the A lines of a rather weakly coupled AB part of an ABXY spectrum and consists of a pair of approximately 1:2:1 triplets, with a separation between the triplets equal to $J_{2F-5F}$ and $J_{34}$ respectively. In order to obtain the difference, $L$, between the $H-F$ couplings, it would have been necessary to know the spin couplings between $^{13}C$ and not directly bonded $H$ and $^{19}F$ nuclei, as these couplings give different effective shifts to the two protons and the two $^{19}F$ nuclei in the ABXY sub spin system of the 5-spin systems. It would also have been necessary to resolve the splitting between the two lines of the middle peak of the satellite triplets. No attempt was made to determine the long-range $^{13}C$ to $H$ and $^{12}C$ to $H$ and $^{13}C$ to $^{19}F$ couplings as the $^{13}C$ satellite spectra were of weak intensity due to the fact that they were recorded on a rather dilute
solution of 2,5-difluoro thiophene in benzene (18\%).
As it therefore is not even possible to get an estimate of \( L \) from the \(^{13}C\) satellite spectra the ordinary fluorine spectrum was used for this purpose. The linewidth in this spectrum is small, 0.10 Hz, and a lower intensity of the middle peak as compared to that of the non-degenerate lines ought to be visible if the splittings between the lines in the middle peak are not too small (\(< 0.01 \text{ Hz.}\)).

In order to compare the peak heights of the 1:2:1 triplets a number of spectra were recorded at the lowest possible sweep speed (0.01 Hz/sec.) all at the same constant amplification to get good statistical values of the intensities, which is possible with the high reproducibility of the HA-60 spectrometer. Spectra were also recorded at the same sweep speed at another gain and at the sweep speed of 0.05 Hz/sec. to get an estimate of the non-linearity of the spectrometer. The middle peak of the triplets consists of four lines, all depending on \( L \) (cf Ref. 27), and the intensity in the middle of this peak is calculated assuming a Lorentzian shape of a single NMR line. If the whole experimental difference (1.42\%) between twice the height of the non-degenerate lines and the height of the middle peak of the triplet is due to this multiplet
structure it can be accounted for by an 'L' value safely smaller than 0.8 Hz at the linewidth 0.10 Hz of the single lines. If the non-linearity of the spectrometer is taken into account, consistent intensity ratios of the spectra taken at the sweep speeds 0.01 Hz/sec and 0.05 Hz/sec are obtained with 'L' equal to 0.6 Hz. The combined uncertainty of the measurements of the intensity ratios and the linewidths leads, however, to an upper limit of 'L' that is equal to 0.8 Hz whereas it is impossible to give a definite lower limit as it is possible that 'L' can be zero within this uncertainty. In sum, it is suggested that 'L' is most probably 0.6 Hz but with the uncertainties mentioned above it is preferred that 'L' be put equal to (0.4 ± 0.4) Hz. The H-F spin couplings are then 3.66 ± 0.20 Hz and 3.26 ± 0.20 Hz and are of course of the same sign as the sum of the couplings is larger than the difference between them. Even if the smaller of these couplings is the ortho H-F coupling it is still larger than this coupling in all of the substituted 2-fluorothiophenes studied so far except 2,3,5-trifluorothiophene where it is of the same magnitude or slightly larger (3.35 Hz). The results are tabulated in tables IV-1(d) and IV-2(d).

The \(^{13}\text{C}\) satellite spectra also give the couplings

\[ J_{13\text{C}}^{19\text{F}} \quad \text{and} \quad J_{13\text{C}}^{1\text{H}} \]
Table IV - 1(d)

Proton and fluorine chemical shifts* and fluorine-fluorine spin coupling in 2,5-Difluorothiophenes

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Conc. by wt %</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\gamma_2$</td>
<td>$\gamma_3$</td>
</tr>
<tr>
<td>Benzene</td>
<td>18</td>
<td>1497.63</td>
<td>314.98</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>26</td>
<td>1495.85</td>
<td>333.63</td>
</tr>
</tbody>
</table>

The proton shifts ($\gamma_3$ and $\gamma_4$) are given in Hz relative to TMS as internal reference and the fluorine shifts ($\gamma_2$ and $\gamma_5$) are given in Hz downfield relative to C$_6$F$_6$ as internal reference at 56.414 MHz.
### Table IV - 2(d)

Fluorine - proton spin couplings and proton-proton spin coupling (in Hz) in 2,5 - Difluorothiophene

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Fluorine-proton spin couplings (in Hz)</th>
<th>Proton-proton spin coupling (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>18</td>
<td>3.26, 3.66</td>
<td>4.42</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>26</td>
<td>0.5, ( J_{2F-3} + J_{2F-4} )</td>
<td>( J_{34} )</td>
</tr>
</tbody>
</table>

\[ J_{34} = 3.36 \]

### Table IV - 3(d)

Fluorine chemical shifts of 2,5-Difluorothiophene in ppm relative to C6 F6* (Δ- values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophenes (Δ - values)*.

<table>
<thead>
<tr>
<th>Δ2</th>
<th>Δ3</th>
<th>δ2</th>
<th>δ5</th>
</tr>
</thead>
<tbody>
<tr>
<td>-26.50</td>
<td>-26.50</td>
<td>1.80</td>
<td>1.80</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low field side of the reference signal.
\[ J_{13C - 19F} = 288.8 \pm 0.4 \text{ Hz} \]

and the isotope shift $^{35}F - 19F = 13C \ (12C) \text{ is 5.1 Hz}$ (0.09 ppm).

If the isotope shift (if any) of the proton resonance is neglected $J_{13C - H}$ is found to be

\[ J_{13C - H} = 171.8 \pm 0.4 \text{ Hz} \]

In table IV-3(d) the chemical shifts of the fluorine resonances extrapolated to infinite dilution in cyclohexane are given.

(e) 3,4'-DIFLUOROTHIOPHENE

The NMR spectrum of this compound is of $AAX'$ type\(^{27}\). As both the proton and fluorine nuclei give the same type of the spectrum only the fluorine spectrum of the compound in a 4\% cyclohexane solution is shown in Fig 11. The total spectrum is given at the sweep speed 0.05 Hz/sec, to the right and to the left only the strong intensity part c d e f g h is given at the sweep speed 0.01 Hz/sec. The frequency scale is given with respect to $\gamma p$. The larger tail of the lines c d e f g h on the high field side as compared to the low field side is due to the improper phase of
Fig 11. The fluorine resonance spectrum of 3,4-difluorothiophene at 56.444 MHz in a 41% cyclohexane solution. The larger tail of the lines c d e f g h on the high field side as compared to the low field side due to an improper phase of the spectrum.
the spectrum. The spectrum is symmetric around $\gamma_A$.

Only seven lines are well resolved in the spectrum shown here. The middle peak is broader than the other ones and consists of four lines. At the lowest sweep speed possible this part could be resolved into a doublet (see the side diagram in Fig. 11).

The weak lines 'a', 'j' and 'b', 'i' on each side of the strong part of the spectrum with intensities proportional to $\sin^2 \theta_a$ and $\sin^2 \theta_b$ depend mainly on the parameters $M$ and $K$ respectively (cf. Ref. 27). In order to determine the relative magnitudes of $K$ and $M$ a generalized Overhauser type experiment was performed. The two sharp lines c and h on each side of the middle peak are transitions between energy levels having symmetric wave functions and as seen from the energy level diagram (Fig. 12), these lines have no energy levels in common with other fluorine lines. The energy level diagram for this $AAXX$ spin system is split as seen from Fig. 12 into two different sets according to the symmetric and antisymmetric representation of the system. The problem was to determine whether the lines 'b' and 'i' belong to the symmetric representation (as suggested in Fig. 12) and are given by the parameters $K$ and $L$ or belong to the antisymmetric representation, and therefore also whether the lines 'a' and 'j' belong to the antisymmetric
Fig 12. The energy level diagram for an $AA'XX'$ spin system. It is split into two different sets according to the symmetry representation. To the left the energy level diagram of the symmetry representation is given and to the right that of antisymmetric representation. The fluorine transitions are indicated with full lines and the proton transitions with dashed lines.
representation and are given by the parameters M and L or belong to the symmetric representation. A continuous saturation of the 'h' or the 'c' line will, if the spin-lattice relaxation of the protons is not much slower than that of the fluorine nuclei, give intensity reductions of the lines 'b', 'd', 'g' and 'i' and leave the lines 'a', 'e', 'f' and 'j' unchanged (cf. Fig. 12).

In the experiment performed, line 'h' was irradiated with a weak second rf. field while the two weak lines on the low field side of the spectrum were recorded.

Intensity reduction was observed in the line 'b' whereas line 'a' remained unchanged. This shows that \( M > K \) i.e. the fluorine-fluorine spin coupling \( J_{2F} \) and the proton-proton spin coupling \( J_{2P} \) have opposite signs.

In order to get the values of the spin couplings either the splitting \( (M^2 + L^2)^{1/2} - M \) between lines 'e' and 'f' or the splitting \( (K^2 + L^2)^{1/2} - K \) between lines 'd' and 'g' in the middle peak must be used. The structure in this peak could, however, not be completely resolved as in the experimental spectrum only a poorly resolved doublet was observed.

If this doublet splitting is set equal to the mean value of \( (M^2 + L^2)^{1/2} - M \) and \( (K^2 + L^2)^{1/2} - K \) it is possible to get good values of \( K, M \) and a value of \( L \)
The uncertainty in measuring the splitting as the difference between the resonance frequencies of the two components of the doublet is estimated to be not less than ± 0.03 Hz if the standard deviation of the single lines is as small as ± 0.02 Hz, which gives an uncertainty in L equal to ± 0.18 Hz, and hence in the H-F couplings ± 0.09 Hz, whereas the error in K and N due to that of L is negligible (less than 0.01 Hz). It is, however, believed that a more accurate value of L is obtained when the whole lineshape of the strong lines in the spectrum is calculated and compared with the experimental one.

With different values of L and with different linewidths the whole lineshape of the central part of the spectrum was calculated as a superposition of Lorentzian curves of the lines 'c', 'd', 'e', 'f', 'g' and 'h'. The spectra were compared with the experimental spectrum obtained at the lowest sweep speed 0.01 Hz/sec. At this sweep speed both the dip of the doublet and the slightly lower intensity of the doublet (owing to the non-zero splitting of the lines 'd', 'e' and 'f', 'g' respectively) as compared to the lines 'c' and 'h' were observed. Best agreement is obtained with L equal to 1.94 Hz and the linewidth 0.11 Hz. The linewidth seems for this
spectrum a little too small when compared to the linewidth of the single lines 'c' and 'h', but it is the largest linewidth that together with the corresponding L reproduce both the dip and the lower intensity of the doublet well. The computer-simulated spectrum at the sweep speed 0.05 Hz/sec. is given with the same L and with the linewidth 0.17 Hz, which gives the best fit of the lines 'c', 'd', 'e', 'f', 'g' and 'h' as far as the intensity ratios between them are concerned, even if this linewidth also seems a little too small.
The experimental middle peak (d e f g) has a shoulder on its high field side and the calculated spectrum is depicted with a small splitting.

The experimental spectra were recorded on the smallest sweep width possible on a conventional RÅ-60 spectrometer (1 Hz/cm). It was, therefore, not possible to spread out the spectrum more and take the experimental curveform of a single line to use in a complete lineform calculation. From the experimental point of view this demands higher stability of especially the sweep oscillator but also of the field frequency lock system.

The uncertainty in L determined in the way described is estimated to be ± 0.06 Hz. In this uncertainty the error due to the approximation of a single NMR line with a Lorentzian curve-form is not taken into account but for the spectra shown here and
for spectra of an unpublished work, this approximation has proved to be very good.

With this L value it is possible to obtain the spin couplings as the other parameters, N, M and K for an AXX spin system are all well determined. The results are listed in table IV-1(e) and IV-2(e). As N is larger than L, the couplings $J_{3F-2}$ and $J_{3F-5}$ must be of the same sign, which is assumed to be positive as in 3-fluorothiophene (chapter VII) and $J_{3F-2}$ is taken as the smaller of them. The proton-proton coupling must be the smaller of the couplings given by K and M and is positive in sign; thus the fluorine-fluorine coupling must carry a negative sign.

With a standard deviation of the lines 'c' and 'h' equal to 0.02 Hz and of the lines 'a', 'b', 'i' and 'j' equal to 0.04 Hz the standard deviation of the couplings $J_{3F-2}$ and $J_{3F-5}$ is 0.04 Hz and that of the couplings $J_{3F-4F}$ and $J_{25}$ is 0.02 Hz. The spectrum of 3,4-difluorothiophene has also been investigated in a benzene solution and the results are given in tables IV-1(e) and IV-2(e).

The chemical shifts of the fluorine nuclei extrapolated to infinite dilution are given in table IV - 3(e).
Table IV - 1(e)
Proton and fluorine chemical shifts* and fluorine-fluorine spin coupling in 3,4-Difluorothiophenes

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling J_{3F-4F} (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Benzene</td>
<td>32</td>
<td>--</td>
<td>1336.70</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>41</td>
<td>367.27</td>
<td>1343.22</td>
</tr>
</tbody>
</table>

* The proton shifts (2 and 3) are given in Hz relative to TMS as internal reference and the fluorine shifts (3 and 4) are given in Hz downfield relative to C6 F6 as internal reference at 56.444 MHz.
Table IV-2(a)

Fluorine-proton spin couplings and proton-proton spin coupling (in Hz) in 3,4-Difluorothiophene.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Fluorine-Proton Spin coupling (in Hz)</th>
<th>Proton-Proton spin coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$J_{3F-2}$</td>
<td>$J_{3F-5}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{4F-5}$</td>
<td>$J_{4F-2}$</td>
</tr>
<tr>
<td>Benzene</td>
<td>32</td>
<td>1.35</td>
<td>3.26</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>41</td>
<td>1.23</td>
<td>3.17</td>
</tr>
</tbody>
</table>

Table IV - 3(a)

Fluorine Chemical shifts in 3,4-Difluorothiophene in ppm relative to C$_6$F$_6$ (Δ-values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophenes (δ-values)*.

<table>
<thead>
<tr>
<th>Δ$_3$</th>
<th>Δ$_4$</th>
<th>δ$_3$</th>
<th>δ$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-23.97</td>
<td>-23.97</td>
<td>8.08</td>
<td>8.08</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low field side of the reference signal.
(f) 5-BROMO-2,3 - DIFLUOROTHIOPHENE

The NMR spectrum of 5-bromo-2,3-difluorothiophene in a 55%* cyclohexane solution is shown in figs. 13, 14 and 15. The spectrum is of the simple AMX type. The proton part of the spectrum (fig. 13) consists of only two lines (the sharp high peaks) as the coupling \( J_{3F-4} \) is vanishingly small, that is to say that this coupling is at least too small to give any additional broadening of the lines in the 3-fluorine spectrum as compared to the single lines in the 2-fluorine spectrum, both having a line width of 0.12 Hz. The fluorine part of the spectrum consists of two parts: one corresponding to the fluorine in the 3-position, a doublet \( (J_{3F-4} \approx 0, \text{fig. 14}) \), and the other corresponding to the fluorine in the 2-position giving rise to a triplet (fig. 15) owing to the fact that both \( J_{2F-3F} \) and \( J_{2F-4} \) are more or less of the same magnitude. The fluorine resonance at highest field is assigned to the \( \alpha \)-fluorine owing to the presence of 34S satellite lines (chapter III),

* In 5-bromo - 2,3 - difluorothiophene solution there were also present three other substituted fluorothiophenes as impurities. From the proton spectrum it was estimated that only around 51% of the total number of thiophene molecules are 5-bromo-2,3-difluorothiophene molecules and therefore the concentration given here must be taken bearing this in mind.
Fig. 14. The fluorine resonance spectrum (in 3-position) of 5-bromo-2,3-difluorothiophene in a 55% cyclohexane solution.

Fig. 15. The fluorine resonance spectrum (in 2-position) of 5-bromo-2,3-difluorothiophene in a 55% cyclohexane solution.
Table IV - 1(f)

Proton and fluorine chemical shifts* and fluorine-fluorine spin coupling in 5-bromo-2,3-difluoro-thiophene [in Cyclohexane as the solvent (55 % by wt.)]

<table>
<thead>
<tr>
<th>Chemical Shifts (in Hz)</th>
<th>Fluorine-Fluorine spin coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_2$</td>
<td>$\gamma_3$</td>
</tr>
<tr>
<td>678.10</td>
<td>945.78</td>
</tr>
</tbody>
</table>

* The proton shift ($\gamma_4$) is given in Hz relative to TMS as internal reference and the fluorine shifts ($\gamma_2$ and $\gamma_3$) are given in Hz downfield relative to $C_6F_6$ as internal reference at 56.444 MHz.
Table IV - 2(f)

Fluorine - proton spin couplings (in Hz) in 5-bromo-2,3-difluorothiophene [in Cyclohexane as the solvent (55 % by wt.)].

<table>
<thead>
<tr>
<th>$J_{3F-4}$</th>
<th>$J_{2F-4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\approx 0.00$</td>
<td>3.56</td>
</tr>
</tbody>
</table>

Table IV - 3(f)

Fluorine chemical shifts in 5-bromo-2,3-difluorothiophene in ppm relative to $C_{6}F_{6}$+ (Δ - values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophenes (δ - values) *.

<table>
<thead>
<tr>
<th>$\Delta_2$</th>
<th>$\Delta_3$</th>
<th>$\delta_2$</th>
<th>$\delta_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-11.98</td>
<td>-16.59</td>
<td>16.32</td>
<td>15.46</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low field side of the resonance signal.
and consequently the fluorine band at lowest field is assigned to the $\beta$-fluorine. The compound was recorded at four different concentrations in cyclohexane and it was thereby noticed that the magnitude of the fluorine-fluorine coupling decreased slightly upon dilution. It decreased from its highest value, 3.46 Hz at the highest concentration (55 % by wt.) to 3.26 Hz at the lowest concentration (8 %), whereas the H-F coupling $J_{2F-4}$ is constant at 3.56 Hz within experimental error. The results are tabulated in tables IV-1(f) and IV-2(f).

The $^{13}C - ^{19}F$ couplings were determined and that of the $\alpha$-fluorine is $(283 \pm 1)$ Hz and that of the $\beta$-fluorine $(257 \pm 1)$Hz. The corresponding isotope shifts $^{36} 19F - ^{13}C (^{12}C)$ are 0.127 and 0.071 ppm, respectively.

The chemical shifts of the fluorine resonances in cyclohexane solution extrapolated to infinite dilution are given in table IV-3(f).

(g) 2,3,5-TRIFLUOROTHIOPHENE

The NMR spectrum of this compound ( neat compound + TMS + HFB ) is shown in figs. 16, 17, 18 and 19*.

* The compound contained ether, 2,5-difluorothiophene and 2-fluorothiophene as impurities.
Fig. 16. The proton resonance spectrum of 2,3,5-trifluorothiophene (neat compound + TMS + HFB)
Fig 17. The fluorine resonance spectrum (in 2-position) of 2,3,5-trifluorothiophene (neat compound + TMS + HFB).
Fig 18. The fluorine resonance spectrum (in 3-position) of 2,3,5-trifluorothiophene (neat compound + TMS + HFB).

Fig 19. The fluorine resonance spectrum (in 5-position) of 2,3,5-trifluorothiophene (neat compound + TMS + HFB).
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Chemical shifts (in Hz)</th>
<th>Fluorine-Fluorine spin couplings (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\gamma_2$</td>
<td>$\gamma_3$</td>
</tr>
<tr>
<td>Neat Compound</td>
<td>--</td>
<td>-152.56</td>
<td>6325.34</td>
</tr>
<tr>
<td>Carbon Tetrachloride</td>
<td>unknown</td>
<td>-152.07</td>
<td>611.03</td>
</tr>
</tbody>
</table>

The proton shift ($\gamma_4$) is given in Hz relative to TMS as internal reference and the fluorine shifts ($\gamma_2$, $\gamma_3$ and $\gamma_5$) are given in Hz downfield relative to C$_6$F$_6$ as internal reference at 56.444 Hz.
Table IV - 2(a)

**Fluorine - proton spin couplings in 2,3,5-Trifluorothiophene (in Hz)**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conc. by wt %</th>
<th>Fluorine - Proton Spin Couplings (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neat compound</td>
<td>--</td>
<td>3.40 0.38 3.62</td>
</tr>
<tr>
<td>Carbon Tetrachloro-</td>
<td>unknown</td>
<td>3.30 0.80 3.60</td>
</tr>
</tbody>
</table>

Table IV - 3(g)

**Fluorine chemical shifts of 2,3,5 - trifluorothiophene in ppm relative to C6 F6* (Δ - values) at infinite dilution in cyclohexane and the substituent shifts in ppm relative to fluorine chemical shifts in 2- and 3-fluorothiophene (δ - values)**.

<table>
<thead>
<tr>
<th>Δ2</th>
<th>Δ3</th>
<th>Δ5</th>
<th>δ2</th>
<th>δ3</th>
<th>δ5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.57</td>
<td>-14.45</td>
<td>-26.46</td>
<td>30.87</td>
<td>17.60</td>
<td>1.84</td>
</tr>
</tbody>
</table>

* A minus sign means that the fluorine resonance is on the low field side of the reference signal.
The spectrum is simple AMX type. The proton part of
the spectrum (fig. 16) consists of 8 sharp lines and
so is true about the three fluorines (fig. 17, 18 and 19).
The analysis is straightforward. The fluorine bands with
satellites are assigned to the \( \alpha \)-fluorines and the
band that displays the smallest F-F coupling to the
3-fluorine is assigned to the 2-fluorine. This assignment
seems to be in line with known fluorine shift relations
(cf. 2,3- and 2,4-difluorothiophenes) By a series of
homonuclear tickling experiments the F-F couplings
were found to be of the same relative sign and so were
the H-F couplings. The analysis of the compound was
also made in carbon tetrachloride solution. All the
results are tabulated in tables IV-1(g) and IV-2(g).

The chemical shifts of the fluorine nuclei
extrapolated to infinite dilution are given in table
IV - 3(g).

4.4 DISCUSSION

(a) PROTON CHEMICAL SHIFTS

The protons in all the difluorothiophenes are
shifted upfield when compared to their shifts in the two
monofluorothiophenes (cf. table IV-4). This is most
probably due to the strongly \( \pi \) character of the fluorine
### Table IV - 4

Proton chemical shifts* of fluorothiophenes in ppm relative to the shifts of the \( \text{\( \alpha \) - and } \text{\( \beta \) -protons in thiophene}

<table>
<thead>
<tr>
<th></th>
<th>( \delta_2 )</th>
<th>( \delta_3 )</th>
<th>( \delta_4 )</th>
<th>( \delta_5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-fluorothiophene</td>
<td>0.65</td>
<td>0.41</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>3-fluorothiophene</td>
<td>0.65</td>
<td>0.28</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>2,3-difluorothiophene</td>
<td>0.46</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-difluorothiophene</td>
<td>0.79</td>
<td>1.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,4-difluorothiophene</td>
<td>0.75</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,5-difluorothiophene</td>
<td>1.06</td>
<td>1.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3,5-trifluorothiophene</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-bromo-2,3-difluorothiophene</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-bromo-2,5-difluorothiophene</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The proton shifts for these fluorothiophenes are obtained from cyclohexane solutions but except for the first two are not extrapolated to infinite dilution. This error probably gives somewhat too low shifts in the Table. The chemical shift of the \( \text{\( \alpha \) - proton is } -7.16 \text{ ppm and that of the } \text{\( \beta \) - proton is } -8.97 \text{ ppm relative to TMS}^{19}.\)
atom. The shift of the 5-hydrogen in three of them is well given (within 0.08 ppm.) by addition of the substituent proton shifts in 2- and 3-fluorothiophenes. The 5-hydrogen shifts calculated in this way are all somewhat higher than the observed ones. The substituent shift of the 3-hydrogen in 2,4-difluorothiophene and of the 4-hydrogen in 2,5-difluorothiophene calculated assuming additive shifts are 0.14 and 0.23 ppm respectively larger than those observed. The observed shift of the hydrogens in 2,5-difluorothiophene happens to coincide with the sum of the 3- and 4-hydrogen shifts in 2-fluorothiophene.

The upfield shifts of the 4- and 5-protons in 2,3-difluorothiophene (0.46 and 0.77 ppm, respectively) are much larger than those observed in any other disubstituted thiophenes\(^{30}\) (0.3 and 0.4 ppm) and in 2,4-difluorothiophene the upfield shifts of the 3- and 5-hydrogens (0.79 and 1.30 ppm respectively) are considerably larger than those found in other thiophenes\(^{30}\) (0.1 and 0.2 ppm). The large upfield shifts in these two difluorothiophenes must reflect the higher +M character of the fluorine atom compared to the +H substituents investigated in the work of Hoffman and Gronowitz\(^{30}\), \(\text{SH}_2\), \(\text{SCH}_3\) and \(\text{CH}_3\). The upfield shift of
the hydrogens in 2,5-difluorothiophene (1.06 ppm) is of the same size as the upfield shift of the 3-hydrogen in 2-methoxy - 5-methylthiophene (1.1 ppm) and in 3,4-difluorothiophene the upfield shift of the protons (0.75 ppm) is somewhat higher than the largest upfield shift previously found for a proton in 3,4-disubstituted thiophenes (0.6 ppm). For the trisubstituted thiophenes there are large differences between the observed shifts and those calculated by addition of the substituent shifts. In 2,3,5-trifluorothiophene and 5-bromo - 2,3 - difluorothiophene the deviations are about 0.5 ppm and in 3-bromo - 2,5-difluorothiophene the deviation is 0.20 ppm.

(b) FLUORINE CHEMICAL SHIFTS

The fluorine shifts are given in ppm, relative to hexafluorobenzene together with the substituent chemical shifts relative to 2- and 3-fluorothiophene in tables IV - 3(a to g). In the three compounds with fluorines in the 2- and 3-positions a considerable upfield shift of these fluorine resonances is observed. The upfield shift is 21.87 ppm for the 2-fluorine nucleus in 2,3-difluorothiophene and as much as 30.87 ppm for the same nucleus in 2,3,5-trifluorothiophene. The upfield shift of the 3-fluorine is smaller and varies
between 15.46 ppm in 5-bromo-2,3-difluorothiophene and 18.68 ppm in 2,3-difluorothiophene. The upfield shift of the fluorine resonance in the other ortho position is smaller and is 8.08 ppm in 3,4-difluorothiophene. In fluorobenzenes a similar large upfield shift of the fluorine shifts of two fluorine nuclei ortho to each other has been observed and is 25.9 ppm in ortho difluorobenzene\textsuperscript{37,38}. There is up to now no complete explanation of this large upfield shift\textsuperscript{39} even if a part of it seems to be attributable to intramolecular electric fields arising mainly from Van der Waals interactions\textsuperscript{37,38,40}.

(c) PROTON–PROTON SPIN COUPLINGS

The proton-proton spin couplings of the compounds of this work (present chapter) are all larger than or among the largest proton-proton couplings found earlier in substituted thiophenes\textsuperscript{18,30}. The largest values of the couplings \(J_{45}\), \(J_{35}\) and \(J_{25}\) are about 0.6, 0.4 and 0.25 Hz greater than the values of the same couplings found earlier\textsuperscript{18,30}. \(J_{34}\) in 2,5-difluorothiophene is about the same size as the largest \(J_{34}\) couplings in 2,5-disubstituted thiophenes in the earlier investigation\textsuperscript{30}. For \(J_{34}\) and \(J_{35}\) this seems to be due to the strong electronegativity of the fluorine atom, as in the
earlier work the largest $J_{34}$ and $J_{35}$ couplings are found in disubstituted thiophenes with two strongly electron-attracting groups. No such regularity was found for the proton-proton couplings $J_{25}$ and $J_{45}$ in that work but it seems likely that the high electronegativity of the fluorine atom could also here account for the high values of these couplings in the difluorinated thiophenes.

(d) **FLUORINE–PROTON SPIN COUPLINGS**

The H-F spin couplings are given in tables IV-2(a to g) and as in no case could their sign relative to a H-H coupling be determined, they are all given with the same sign as they gave in 2- and 3-fluorothiophenes in chapter III, except $J_{3F-4}$ which is given a positive sign in 2,3,5-trifluorothiophene.

The ortho $J_{3F-4}$ coupling is found to be small and of opposite sign to the other H-F couplings in 2,3- and 2,4-difluorothiophene; and of the same sign as the other H-F couplings in 2,3,5-trifluorothiophene. As this coupling is the smallest of the H-F couplings and equal to - 0.86 Hz in 3-fluorothiophene whereas the others are positive it is most probable that $J_{3F-4}$ gets more positive the greater the number of fluorine
atoms directly bonded to the thiophene ring, and in 2,3,5-trifluorothiophene it has changed its sign and is equal to 0.84 Hz.

The ortho $J_{3F-4}$ or $J_{5F-4}$ coupling in the polyfluorothiophenes is found to be larger in the compounds with two fluorine atoms in the $\alpha$-positions (2.8 - 3.4 Hz) than in 2,4-difluorothiophene and 2-fluorothiophene (chapter III) with only one fluorine in the $\alpha$-position (1.3 and 1.5 Hz respectively). The ortho coupling $J_{4F-5}$ (2.8 Hz) in 2,4-difluorothiophene with one fluorine atom in the $\alpha$-position is more than twice the corresponding $J_{3F-5}$ coupling in 3,4-difluorothiophene and 3-fluorothiophene (chapter III) (1.2 and 1.0 Hz respectively) with no fluorine atom in the $\alpha$-position. These ortho H-F couplings are, however, still smaller than the ortho H-F couplings in fluorobenzenes$^{2-11}$, fluorodibenzofurans$^{12}$ and fluropyridines$^{13}$ (6.2-11.4 Hz).

The variation of the meta H-F coupling $J_{3F-4}$ in the fluorothiophenes investigated here is not very large. The smallest magnitude is 3.1 Hz in 2,3-difluorothiophene and the largest magnitude is estimated to have a value between 3.6 and 5.8 Hz. The other meta H-F coupling $J_{3F-5}$, on the other hand, varies
of a H-H coupling. In 3,4- difluorothiophene the 
J_{3F-4F} coupling was found to be of opposite sign to the 
H-H coupling J_{26}. The magnitude of J_{3F-4F} is somewhat 
lower than the smallest ortho F-F couplings in fluoro-
benzenes^2,6,6,11,14-17, fluorodibenzofurans^12 (13-23 Hz) 
and fluoropyridines^13 (16-23 Hz). The sign of the small 
J_{2F-3F} coupling in 2,3-difluorothiophene in cyclohexane 
solution could be obtained relative to those of the 
H-F couplings and is therefore given with negative sign. 
In the other difluorothiophenes only the magnitude of 
the F-F couplings could be determined and in 2,3,5-
trifluorothiophene the relative signs of the F-F 
couplings were determined. Therefore only some features 
about the magnitudes of these couplings can be noted.

The J_{2F-3F} coupling increases from 22.9 Hz in 
3,5-difluorothiophene to 25.1 Hz in 3-bromo-2,5-
difluorothiophene and further to 27.7 Hz in 2,3,5-
trifluorothiophene. It is larger than the para F-F 
coupling in fluorobenzenes (0-15 Hz)^2,5,6,11,14-17 and 
in fluorodibenzofurans (15-19 Hz)^12 and it is also 
larger than the meta J_{2F-3F} coupling over the nitrogen 
in fluoropyridines (13-16 Hz)^13, but it falls within 
the range of the para F-F couplings of 
pyridines (22-32 Hz)^13.
The F-F couplings $J_{2F-3F}$ and $J_{2F-4F}$ also increase with an additional fluorine or bromine atom connected to the ring (cf. tables IV-1(a-g)). The ortho coupling $J_{2F-3F}$ in the three thiophenes in this work is unexpectedly small ($0.2 - 4.9$ Hz) and it is very much smaller than the other ortho coupling $J_{2F-4F}$ (cf. above). The meta coupling $J_{2F-4F}$ ($9.2$ Hz and $15.3$ Hz) falls somewhat outside the range of the meta F-F couplings in fluorene derivatives (-10 to +12 Hz) but it is smaller than the largest meta $J_{2F-4F}$ coupling in fluoropyridines, which can be rather large ($8-25$ Hz)$^{13}$.

(f) $^{13}C - ^{19}F$ AND $^{13}C-H$ COUPLINGS.

The $^{13}C - ^{19}F$ couplings for the $\alpha$-fluorine in 5-bromo-2,3-difluoro thiophene (238 Hz) and 2,5-difluoro thiophene (288.8 Hz) are both close to the $^{13}C - ^{19}F$ coupling in 2-fluoro thiophene (chapter III) and the $^{13}C - ^{19}F$ coupling for the $\beta$-fluorine in 5-bromo-2,3-difluoro thiophene is close to this coupling in 2-fluoro thiophene (chapter III), whereas the corresponding isotope shifts of the fluorine resonances due to $^{13}C$ (cf. under 4.3 (c) and 4.3 (d)) are not the same as in monofluoro thiophenes (chapter III). The $^{13}C-H$ coupling in 2,5-difluoro thiophene (171.8 Hz) is a few Hz larger than previously reported values of this coupling in thiophenes$^{43}$. 
REFERENCES


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29. Kuhlman, K. and Balderachieler, J.D., J. Am. Chem. Soc. 80 (1958), 1010, and ref. 25, pp. 82 and 158.
37. Ref. 2, pp. 898 ff.
38. Ref. 23, pp. 155 ff.
Fig 13. The proton resonance spectrum of 5-bromo-2,3-difluorothiophene in a 55% cyclohexane solution.
Nuclear Magnetic Resonance of Aromatic Heterocyclics

I. The Proton and $^{19}$F Spectra of 2- and 3-Fluorothiophene

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The $^1$H and $^{19}$F magnetic resonance spectra of 2- and 3-fluorothiophene have been analyzed. The $\text{H} - \text{F}$ spin coupling constants are (in Hz): $J_{2\text{H}-2\text{F}} = 1.62$, $J_{3\text{H}-3\text{F}} = 3.07$, $J_{3\text{H}-4\text{F}} = 3.10$, $J_{3\text{H}-4\text{F}} = 1.08$, $J_{2\text{H}-4\text{F}} = -0.81$, $J_{2\text{H}-4\text{F}} = 3.30$. Except for $J_{2\text{H}-4\text{F}}$, they are all of the same sign as the $\text{H} - \text{H}$ spin coupling constants. The shift of the fluorine resonance of 2-fluorothiophene is 28.30 ppm and that of 3-fluorothiophene 32.05 ppm downfield from hexafluorobenzene. An isotope shift of the fluorine resonance of 2-fluorothiophene due to $^{19}$F was observed, and is 0.014 ppm. The $\text{C} - \text{F}$ spin coupling constants are 285 and 256 Hz in 2- and 3-fluorothiophene, respectively.

In earlier investigations a detailed study of the proton magnetic resonance spectra of thiophene and a large number of substituted thiophenes was undertaken. The intervals for the different coupling constants and their signs have been determined. The relation between chemical shifts and substituent effects was studied and a qualitative relation between the properties of a substituent in the 2-position and the 5-hydrogen shifts was obtained. The much larger effects of substituents on the fluorine shifts and the good correlation obtained between such shifts and Hammett substituent constants ($\sigma$-values) makes a study of the fluorine resonance spectra of substituted fluorothiophenes attractive. The substituent shifts thus obtained could then be used to obtain $\sigma$-values for these substituents when attached to the thiophene ring, and perhaps be useful for the prediction of chemical reactivity data. An increased knowledge of the magnitudes and signs of the $\text{H} - \text{F}$ and $\text{F} - \text{F}$ spin-spin coupling constants in aromatic systems such as thiophene makes such a study particularly attractive.

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could contribute to a better understanding of the relative importance of the different mechanisms which contribute to these couplings.

In the present paper the analysis of the proton and fluorine magnetic resonance spectra of 2- and 3-fluorothiophene is given. In a following paper the spectra of the four difluorothiophenes, one trifluorothiophene and some other derivatives will be discussed.

MATERIALS

2-Fluorothiophene was first prepared in low yield by the reaction of 2-bromothiophene with SbF₅. The route to fluorothiophenes was, however, opened by Schuetz et al., who found that 2-thienyllithium and 5-methyl-2-thienyllithium, which are obtained by metatation of thiophene and 2-methylthiophene with butyllithium, reacted with perchloryl fluoride to yield 2-fluorothiophene and 2-fluoro-5-methylthiophene. It has earlier been demonstrated that substituted thienyllithium derivatives are easily available from the metatation reaction or by halogen-metal interconversion with substituted bromothiophenes. The reaction of these lithium derivatives with various reagents is a convenient method for the preparation of different disubstituted thiophenes.

3-Fluorothiophene was obtained by halogen-metal interconversion between 3-bromothiophene and ethyllithium at −50°C followed by the reaction with perchloryl fluoride. Both 2- and 3-fluorothiophene could be separated from thiophene by means of preparative gas-chromatography. The fluorothiophenes were difficult to analyze for carbon and hydrogen. However, analytical gas-chromatography and mass spectrometry as well as proton and ¹⁹F magnetic resonance spectra indicated that sufficiently pure compounds had been obtained.

It has also been found that the reaction of thienyllithium derivatives and perchloryl fluoride is of general preparative usefulness for the preparation of fluorothiophenes and a large number of these compounds, which will be described in the following papers, have been synthesized.

RESULTS

3-Fluorothiophene. The proton part of the magnetic resonance spectrum of 3-fluorothiophene in a 45 % benzene solution is shown in Fig. 1a. It is the ABC-part of an ABCX spectrum, where the fluorine resonance is denoted the X part. By use of the “effective Larmor frequency” approach it is easily seen that this ABC part is a superposition of two ABC (three-spin) subspectra with effective chemical shifts:

\[
v_A^\pm = v_A \pm \frac{1}{2} J_{AX} \quad v_B^\pm = v_B \pm \frac{1}{2} J_{BX} \quad v_C^\pm = v_C \pm \frac{1}{2} J_{CX}
\]  

(1)

As seen from Fig. 1a the proton part is not strongly coupled and there is no overlapping of lines from different protons. With positive signs for

* In order to avoid separation problems ethyllithium was used instead of butyllithium.
Fig. 1a. The single resonance proton spectrum at 60.000 MHz of 3-fluorothiophene in a 46 % benzene solution. The upper part shows the experimental spectrum and the calculated spectrum is given below. The frequency scale is given with respect to TMS as internal reference. In the experimental spectrum there are also some peaks from an impurity, probably thiophene itself.

Fig. 1b. The fluorine resonance spectrum at 56.444 MHz of the same compound as in Fig. 1a. The four weak lines (X9,X10,X11,X12) are recorded with both higher rf. field and higher amplification than the eight strong lines (X1~X8). In the theoretical spectrum these four lines are depicted with thirty times larger amplitude factor than the middle band.

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the proton-proton couplings\textsuperscript{1,5,11-14} there are two sets of energy level diagrams for the two ABC spin systems that give theoretical spectra that agree with the experimental one. From the single resonance spectrum it is not possible to distinguish between the two cases where the spin couplings between the fluorine and the protons in the 4- and 5-positions are of opposite signs, \textit{i.e.} it is not possible to get the sign of $J_{4F-2}$ relative to those of $J_{3F-4}$ and $J_{3F-5}$. The reason for this is that the 2 proton is not coupled strongly enough to the other two protons. By some tickling\textsuperscript{15} experiments (one is shown in Fig. 2) in the ABC part it was, however, possible to choose the correct sign combina-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Double resonance (tickling) spectrum of the ABC-part of 3-fluorothiophene at 50.444 MHz with the second rf field $H_2$ at resonance on line A1. The A-lines are not shown. The lines B2 and C1 appear to be regressively connected with A1 whereas B6 and C5 appear to be progressively connected with A1 (cf. the energy level diagram in Fig. 3). This experiment alone shows that all the proton-proton couplings carry the same sign and that $J_{3F-4}$ is of opposite sign to $J_{3F-2}$ and $J_{3F-3}$.
}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Energy levels and transitions of the ABCX spin system of 3-fluorothiophene. The diagram may be visualized as a combination of two cubes tilted so as to have three corners in the same plane. Each cube belongs to one definite spin state of nucleus X and form the energy level diagram for one ABC sub spin system. (In the text the two cubes are called one set of energy level diagrams for the two ABC sub spin systems). Each corner of the cube corresponds to one energy level and each cube edge corresponds to an A, B, or C transition. The X transitions are represented by lines joining the two cubes. The lines are numbered according to Figs. 1a and 1b. The four visible combination transitions of the X part are indicated by dashed lines between the two cubes.
}
\end{figure}
Table 1 Chemical shifts $^a$,$^c$ and proton proton spin couplings in 2 fluorotriphenylene and 3 fluorotriphenylene

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Conc. Wt %</th>
<th>$\delta_2$</th>
<th>$\delta_3$</th>
<th>$\delta_4$</th>
<th>$\delta_5$</th>
<th>$J_{34}$</th>
<th>$J_{35}$</th>
<th>$J_{24}$</th>
<th>$J_{25}$</th>
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<tr>
<td>2 Fluorotriphenylene</td>
<td>benzene</td>
<td>50</td>
<td>1583 23</td>
<td>348 19</td>
<td>358 31</td>
<td>350 07</td>
<td>3.89</td>
<td>6.02</td>
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<td>cyclohexane</td>
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<td>1587 93</td>
<td>354 83</td>
<td>367 78</td>
<td>361 78</td>
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<td>6.01</td>
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<td>5</td>
<td>1595 97</td>
<td>356 14</td>
<td>369 65</td>
<td>364 01</td>
<td>3.85</td>
<td>5.93</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>3 Fluorotriphenylene</td>
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<td>46</td>
<td>358 42</td>
<td>1813 34</td>
<td>369 54</td>
<td>380 71</td>
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<td>1817 91</td>
<td>375 72</td>
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<td>366 81</td>
<td>1810 39</td>
<td>376 85</td>
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<td>367 41</td>
<td>1808 30</td>
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<td>5.36</td>
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<td>3.46</td>
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</table>

$^a$The proton shifts are given at 56 444 MHz relative to TMS as internal reference and the fluorine shifts are given relative to hexafluorobenzene as internal reference.

$b$These shifts have been measured at 60 000 MHz and recalculated to 56 444 MHz.

$c$In order to compare the substituent shifts of the protons with other monosubstituted thiophenes, the $\delta$ values at infinite dilution relative to cyclohexane (measured to $-1.44$ ppm) are calculated to be (in ppm).

2 fluorotriphenylene $\delta_2 = -4.88$ $\delta_3 = -5.12$ $\delta_4 = -5.02$

3 fluorotriphenylene $\delta_2 = -5.07$ $\delta_3 = -5.25$ $\delta_4 = -5.37$
tion and construct appropriate energy level diagrams (see Fig. 3, where the energy level diagram for the whole ABCX spin system is shown). From the tickling experiments it is evident that \( J^p_2 \) is of opposite sign to \( J^p_3 \) and, as previously shown, all the proton-proton couplings carry the same sign.\(^{1,11}\)

With a least squares fit program the shifts and spin coupling constants which give the best fit to the experimental proton spectrum could be calculated. As seen from relation (1), the difference between the effective shifts of the two ABC spectra then gives the absolute values of the proton-fluorine couplings.

The fluorine spectrum of 3-fluorothiophene is shown in Fig. 1b. The eight strong lines at first appear to be symmetrically situated around \( \nu_X \) but nevertheless with an accuracy better than \( \pm 0.03 \) Hz in the measured frequencies of the experimental lines, a slight asymmetry around \( \nu_X \) is observed. This asymmetry is, however, more pronounced in the combination lines, in the outer flanks of the spectrum, four of which have intensities large enough to be detected. (0.006 and 0.003 if the strongest of the eight lines has an intensity normalized to 1, all at the same rf. field and at negligible saturation). The sense of the asymmetry depends on the signs of the proton-fluorine couplings relative to that of the proton-proton couplings. With a change in the signs of all the proton-fluorine couplings the spectrum will be reflected in \( \nu_X \) and therefore also the asymmetry. The asymmetry in the experimental \(^19\)F spectrum of 3-fluorothiophene is consistent with positive signs for \( J^p_2 \) and \( J^p_3 \) and negative sign for \( J^p_4 \).

The shifts and coupling constants with their relative signs are given in Tables 1 and 2. The assignment of the three proton bands to the protons in 3-fluorothiophene is based on the known magnitudes of proton-proton spin couplings in thiophenes:\(^3\) \( J^p_5 > J^p_5 > J^p_4 \).

Table 2. Fluorine-proton spin couplings in 2-fluorothiophene and 3-fluorothiophene (in Hz).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Conc. Wt. %</th>
<th>( J^p_{2F-4} )</th>
<th>( J^p_{2F-4} )</th>
<th>( J^p_{2F-4} )</th>
<th>( J^p_{2F-4} )</th>
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<td>2-Fluorothiophene</td>
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<td>1.62</td>
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<td>cyclohexane</td>
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<td>1.54</td>
<td>3.07</td>
<td>3.08</td>
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<tr>
<td></td>
<td></td>
<td>5</td>
<td>1.43</td>
<td>2.95</td>
<td>2.87</td>
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<tr>
<td>3-Fluorothiophene</td>
<td>benzene</td>
<td>46</td>
<td>1.08</td>
<td>-0.81</td>
<td>3.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cyclohexane</td>
<td>77</td>
<td>1.06</td>
<td>-0.84</td>
<td>3.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>0.94</td>
<td>-0.88</td>
<td>3.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>0.92</td>
<td>-0.88</td>
<td>3.16</td>
<td></td>
</tr>
</tbody>
</table>

With an experimental uncertainty of at most \( \pm 0.03 \) Hz in the observed resonance frequencies, the proton-proton and proton-fluorine couplings are given with an accuracy better than \( \pm 0.06 \) Hz. A complete ABCX spectrum calculated with these parameters gives an X part that agrees very well with the experimental fluorine spectrum.

During the measurements of the dependence of the fluorine resonance shift on concentration in cyclohexane it was discovered that the apparent

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asymmetry in the part of the fluorine spectrum with the strong lines is increased by dilution (here the weak lines on each side of the central band have too low intensity to be detected). A complete analysis of the whole ABCX spectrum at three different concentrations in cyclohexane was therefore performed.

The fluorine spectra at the concentrations 77 % and 22 % are shown in Fig. 4. At first it was thought that the asymmetry arose because of a decrease in the shift differences between the protons. Recordings of the proton spectrum, however, showed that the shifts had actually increased on dilution, especially that between H5 and the other protons. A comparison of the proton-fluorine couplings in the three solutions shows that the more pronounced asymmetry obtained at the lower concentrations is due to the fact that $J_{\text{sp}-4}$ and $J_{\text{sp}-2}$ here are nearly equal in magnitude. The coupling $J_{\text{sp}-2}$ has decreased 0.14 Hz due to dilution whereas $J_{\text{sp}-4}$ has increased slightly in magnitude (0.04 Hz) as given in Table 2. The near equality makes some of the splittings smaller in the fluorine spectrum and a small asymmetry becomes therefore more evident (see Fig. 4).

The shift of the fluorine resonance in cyclohexane extrapolated to infinite dilution is 32.05 ± 0.02 ppm on the low field side of hexafluorobenzene.

The $^{13}$C-$^{19}$F coupling was measured from the $^{13}$C satellite spectrum of the fluorine resonance in the benzene solution and is 256 ± 1 Hz. The isotope shift is 5.0 Hz = 0.089 ppm. The $^{19}$F-$^{13}$C(12C) isotope shift calculated from the linear relationship between $^{13}$C-$^{19}$F couplings and isotope shifts$^{18}$ for $sp^2$ hybridized carbon is 0.090 ppm.

2-Fluorothiophene. The proton resonance spectrum of 2-fluorothiophene in 50 % benzene solution is shown in Fig. 5a. As in the 3-fluorothiophene case we preferred to interpret the ABC part by use of subspectral analysis. As the ABC part is strongly coupled, it was not immediately possible to con-

---

Fig. 4. The fluorine resonance of 3-fluoro-
thiophene in a) a 22 % cyclohexane and b) a 77 % cyclohexane solution.
Fig. 5. a. The proton resonance spectrum at 60,000 MHz of 2-fluorothiophene in a 50 % benzene solution. The upper part shows the experimental spectrum and the spectrum calculated with the parameters in Tables 1 and 2 is given below. b. The fluorine resonance spectrum of the same sample as in Fig. 5a. The calculated spectrum is shown with eight strong lines and four combination lines of finite intensity. In the experimental spectrum is it possible to see (in four cases) some of the $^8$S-2-fluorothiophene satellite lines on the high field side of the ordinary $^8$S-2-fluorothiophene lines.

struct the appropriate energy level diagrams for the two ABC sub spin systems. By performing a series of tickling experiments it was, however, possible to pick out transitions with an energy level in common and together with the rule of repeated spacings and the intensities of the lines it was then not too difficult to construct the correct energy level diagrams. From the energy level diagrams it is inferred that all the proton-fluorine couplings carry the same sign and, as found earlier, the proton-proton couplings are all of the same sign. Using the same procedure as in the 3-fluorothiophene case the parameters given in Tables 1 and 2 were obtained. The assignment of the resonance frequencies $v_A$, $v_B$, and $v_C$ to the three protons is also here done by means of the known magnitudes of the proton-proton couplings.

With the parameters obtained, a theoretical X part spectrum could be calculated and compared with the experimental fluorine spectrum. As seen from Fig. 5b, the spectrum is not symmetrical about the center $v_X$. The asymmetry shown indicates that the proton-fluorine couplings are of the same sign as the proton-proton couplings and therefore probably positive in absolute sign. The calculated X part agrees well with the experimental spectrum. The deviations in the eight strong lines are at most 0.02 Hz. The deviation in the combination lines is in one case as large as 0.08 Hz, probably due to the

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Fig. 6. The fluorine resonance spectrum of 2-fluorothiophene in a 40 % cyclohexane solution. As this spectrum is simpler than that in Fig. 5b all the eight 34S satellite lines are clearly visible on the high field side of the stronger lines.

fact that these lines have not been measured very accurately. The average deviation between the 36 calculated and measured transitions of the total ABCX spin system is 0.024 Hz, which is within the experimental uncertainty (± 0.03 Hz except for a few lines). The proton-proton and proton-fluorine couplings are given with an accuracy of ± 0.03 Hz and ± 0.05 Hz, respectively.*

The spectrum of this compound has also been studied at different concentrations in cyclohexane. The result of the analysis of the ABCX spectrum at two concentrations is given in Tables 1 and 2. The proton-proton couplings agree well with those of the benzene solution except J45 which has decreased by 0.09 Hz. As seen from Table 2 the proton-fluorine couplings vary with concentration outside the experimental uncertainty. There is also some evidence that the proton-fluorine couplings (cf. J2F-3) vary with solvent, but no extensive study of these couplings in different solvents was performed at this point.

The fluorine spectrum in the cyclohexane solutions is simple and consist of six strong lines (cf. Fig. 6). It was not possible from this spectrum to obtain the sign of the proton-fluorine couplings relative to that of the proton-proton couplings. The shift of the fluorine resonance in cyclohexane extrapolated to infinite dilution is 28.30 ± 0.02 ppm.

In addition to the ordinary fluorine spectrum in the cyclohexane solutions small peaks appear on the high field side of each of the strong lines (see Fig. 6). These peaks have an intensity about 4 % of the strong lines and form another fluorine spectrum, a satellite spectrum, shifted 0.81 Hz upfield from the ordinary spectrum. The possibility that these lines may be spinning sidebands can be ruled out as they do not move when the spinning speed is changed and they are not symmetrical around the stronger lines. It has been concluded that this is an isotope effect on the chemical shift and that the satellite spectrum is that of the naturally present (4 %) 34S-2-fluorothiophene. The absence of such a satellite spectrum in the spectrum of 3-fluorothiophene the intensity of the satellite spectrum, and the magnitude of the isotope

* The spectra of 3- and 2-fluorothiophene have also been analyzed by a least squares fit of all the 36 measured lines. In each case shifts and coupling constants were obtained that agree very well within the experimental uncertainty with our ABCX subspectral analysis. The proton part of 2-fluorothiophene has also been recorded at 100 MHz. The coupling constants obtained agree well with the 60 MHz analysis.

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shift exclude the possibility that the satellite spectrum is that of $^{13}$C-2-fluorothiophene. The isotope shift $^{19}$F-$^{13}$C-$^{34}$S($^{35}$S) is therefore ($0.014 \pm 0.001$) ppm. In the fluorine spectrum of 2-fluorothiophene in the benzene solution the effect of the isotope shift is not very evident owing to the complexity of the spectrum but is nevertheless visible here also.

The $^{13}$C-$^{19}$F coupling as measured from the $^{13}$C satellite spectrum of the fluorine resonance in the benzene solution is 285 ± 1 Hz and the isotope shift $^{19}$F-$^{13}$C($^{13}$C) is 5.8 Hz = 0.103 ppm. The isotope shift calculated from the linear relation between the $^{13}$C-$^{19}$F coupling and the isotope shift is 0.105 ppm.

**DISCUSSION**

The chemical shifts of the hydrogens of 2-fluorothiophene in dilute cyclohexane solution relative to those of the $\alpha$-proton ($-5.72$ ppm) and $\beta$-proton ($-5.53$ ppm) of thiophene are thus $\delta_3 = 0.65$ ppm, $\delta_4 = 0.41$ ppm, and $\delta_5 = 0.70$ ppm. The corresponding values for the hydrogens of 3-fluorothiophene are $\delta_3 = 0.65$ ppm, $\delta_4 = 0.28$ ppm, and $\delta_5 = 0.15$ ppm.

The upfield shifts of the hydrogens of 2-fluorothiophene show the characteristic alternating pattern observed for $-\text{I} + \text{M}$-2-substituted thiophenes. The shift of the 5-hydrogen is of the same magnitude as that observed in 2-methoxythiophene (0.82 ppm). Normally in $-\text{I} + \text{M}$-substituted thiophenes such as 2-methoxy- and 2-aminothiophene, the upfield shift of the 3-hydrogen resonance is larger than that of the 5-hydrogen, but in 2-fluorothiophene these shifts are reversed, most probably due to the much stronger $-\text{I}$-effect of the fluorine than of the other substituents.

The shifts of the hydrogen resonances of 3-fluorothiophene also show the expected pattern for a $-\text{I} + \text{M}$-3-substituted thiophene. Possible reasons for the larger upfield shift of the 2-hydrogen resonance as compared to that of the 4-hydrogen resonance have been discussed earlier. An estimate of the shift of the protons caused by the magnetic anisotropy of the fluorine atom was made in a manner similar to that described in Ref. 4. A magnetic anisotropy of $\Delta \chi = -8 \times 10^{-26}$ cm$^3$/atom gave diamagnetic contributions to the shifts of the protons in 2- and 3-fluorothiophene, which are at most 0.05 ppm and will therefore not change the discussion above.

It is interesting to note that while in the proton magnetic resonance spectra of thiophene the 2-hydrogen resonance occurs at lower field than that of the 3-hydrogen, the 2-fluorine is more shielded than the 3-fluorine in 2- and 3-fluorothiophene, respectively.

Similar inversion between proton and fluorine shifts was also observed when naphthalene was compared with $\alpha$- and $\beta$-fluoronaphthalene. Prosser and Goodman have, using an idea by Karplus and Das, given the following equation which relates chemical shifts in conjugated compounds with $\pi$-electron densities on the fluorine atom and the bonded carbon atom and with C–F bond order

$$\delta = 488 \Delta E^{-1}[11.9 \Delta q (F) + 3.9 \Delta p (C)] + 0.1 \Delta q (C)$$  

(2)
This equation gave good agreement for para substituted fluorobenzenes and it has also been used by Boden et al. in substituted perfluorobenzenes. In addition they also introduced a term for the chemical shift from intra-molecular electric field contributions.

Table 3. Bond orders and π-electron densities:

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<tr>
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<th>2-Fluorothiophene</th>
<th>3-Fluorothiophene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>q(C)</td>
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</tbody>
</table>

A modified ω-method was used to calculate the π-electron densities and bond orders of 2- and 3-fluorothiophene.

Using \( \alpha_C = \alpha, \alpha_S = \alpha + \beta, \beta_C = 0.75 \beta, \) and \( \beta_S = 0.4 \beta \) (parameter set 3 Ref. 25) together with \( \alpha_F = \alpha + 3\beta \) and \( \beta_F = 0.5\beta \) (derived from those of Streitwieser) the charge densities and bond orders given in Table 3 were obtained. Formula (2) then gave a larger screening of the 2-fluorine: \( \delta = 7.12/\Delta E \) ppm \( (\Delta E > 0, \text{ in eV}) \).

However, in order to obtain the correct order for the para fluorine shift of perfluorochlorobenzene, Boden et al. found it necessary to change the fluorine parameters of Streitwieser to \( \alpha_F = \alpha + 2\beta \) and \( \beta_F = \beta \). With these parameters, adjusted to the ω-method by changing \( \beta_{CF} \) to 0.75μ, we obtained the reverse order of shift \( \delta = -23.8/\Delta E \) ppm (see also Table 3), i.e. a smaller screening of the 2-fluorine as compared to that of the 3-fluorine. It is obvious that the calculated shifts are very sensitive to the parameters used. It can in addition not be excluded that the different molecular environments of 2- and 3-fluorothiophene (field effects from the hydrogens and the sulphur) also make contributions to the chemical shift. We hope that an application of the formula of Prosser and Goodman to 5-substituted 2-fluorothiophenes will help us to find a consistent set of parameters.

Muller and Carr, who have studied the spin-spin coupling constants between \(^{19}\text{F}\) and directly bonded \(^{19}\text{C}\) nuclei, found that these coupling constants increased with decreased shielding. They suggested that the degree of C—F double bond character is the most important single parameter influencing both the chemical shift and the C—F coupling constants, while the C—F ionic character is quantitatively less important. They also suggested that when the s-character of the carbon orbital of the C—F bond is increased the C—F coupling is reduced. It is interesting to note that the C—F coupling for 3-fluorothiophene (256 Hz) is smaller than that of 2-fluorothiophene (285 Hz) although the fluorine resonance of the former compound occurs at lowest field. Whereas the chemical shifts do not follow the order of C—F double bonds.
bond character in the two fluorothiophenes, the magnitude of the C—F
coupling does.

Isotope shifts due to sulphur isotopes have earlier been observed by Gillespie
and Quail in compounds where fluorine is directly bonded to sulphur in
compounds such as SF₆ and SOF₆. The isotope shift varied between 0.033
and 0.053 ppm. For SF₆ the isotope shift due to the presence of $^{33}$S (natural
occurrence 0.74 %) was also observed. As this isotope has spin $\frac{3}{2}$ these
authors could also obtain $J_{\beta\gamma}$ from the satellite spectrum. We have made
no attempt to observe the satellite spectrum from $^{33}$S. To our knowledge the
$^{33}$S isotope shift in 2-fluorothiophene of 0.014 ppm is the first isotope shift
observed for a fluorine not directly bonded to sulphur. As there is no detectable
$^{33}$S isotope shift of the fluorine resonance of 3-fluorothiophene, the $^{33}$S shift
of the 2-fluorine resonance is of great help in identifying fluorine resonances
in difluorothiophenes such as 2,3- and 2,4-difluorothiophenes and will be dis-
cussed in a following paper.

The proton-proton couplings in 3-fluorothiophene are close to the couplings
found in 3-nitrothiophene. The value of $J_{2\gamma}$ is the largest found in 3-substi-
tuted thiophenes. The proton-proton couplings in 2-fluorothiophene are all
among the largest found in 2-monosubstituted thiophenes.

The magnitude of the "ortho" H—F couplings in the two thiophenes
studied here is surprisingly small and it is also a little unexpected that $J_{3\gamma-4}$
and $J_{3\gamma-5}$ are of opposite signs. Vicinal H—F couplings of similar magnitude
have been observed for the cis H—F coupling in some fluoroethylenes. The
magnitude of these "ortho" couplings is, however, considerably smaller
than the ortho H—F coupling in fluorobenzenes (6.2—10.4 Hz). The meta
couplings $J_{2\gamma-4}$ and $J_{3\gamma-5}$ are larger than the "ortho" couplings, but they are
only about half the magnitude of the meta H—F couplings in fluorobenzenes
(4.3—8.5 Hz). The coupling $J_{2\gamma-5}$ is also larger than the "ortho" couplings
and is larger in magnitude than the para coupling in fluorobenzenes (—1.3 to
—2.7 Hz). All the proton-fluorine couplings except $J_{3\gamma-4}$ in these two fluoro-
phosphines are of the same sign as the proton-proton couplings and therefore assumed
to be positive in absolute sign. A more detailed discussion of the H—F
coupling constants will be given in subsequent papers.

EXPERIMENTAL

The NMR spectra were obtained using a Varian Associates HA-60 spectrometer.
The two proton resonance spectra shown in Figs. 1a and 5a were recorded at 60.000 MHz
whereas all other spectra were obtained at 56.444 MHz. The spectra were recorded in
the frequency sweep mode.

In the fluorine resonance experiments, the resonance from hexafluorobenzene was
used as internal reference and as lock signal for the internal stabilization, and the lock
frequency was produced by a Muirhead D-890-A decade oscillator.

The resonance peaks were measured by counting the inverse sweep frequency (or the
difference between the sweep frequency and the lock frequency) on a Hewlett-
Packard frequency counter model 3734 A. In these measurements the frequency was

* The para H—F coupling has been found to be of opposite sign to the ortho and meta H—F
couplings in fluorobenzenes.

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swept to exact resonance of the peak to be counted; this was done for the two sweep directions and a mean value was taken.

In the tacking experiments the second weak rf. field was obtained by amplitude modulation of the magnetic field. The modulation frequency was produced by a Philips oscillator PP6050.

The least squares fit calculations and the calculations of theoretical ABCX spectra were performed on a C2 3500 computer.

2. Fluorothiophene. In a nitrogen swept wide neck reaction vessel with a five socket flat flange lid, fitted with a stirrer, a thermometer, nitrogen inlet, perchloryl fluoride inlet, and a reflux condenser protected with a calcium chloride tube was placed 100 ml of 1.1 N ethereal ethylithium solution. 70 g (0.85 mole) of thiophene in 100 ml of anhydrous ether was added at such a rate that gentle reflux was maintained. The mixture was then refluxed for 20 min, cooled to —15°C and perchloryl fluoride bubbled into the reaction mixture at a moderate rate, while the temperature was kept at —15°C. When 20% excess of perchloryl fluoride had been bubbled into the solution, the cooling bath was removed and nitrogen was bubbled through for 60 min. The reaction mixture was poured into saturated sodium carbonate solution, the organic layer separated and washed once with soda solution. Most of the ether was distilled off and the residue steam-distilled. The distillate was extracted with ether, dried and fractionated through an efficient column. 37 g of a fraction, b.p. 65—80°C was obtained. GLC analyses on a 2 m x 1/8" column packed with apiezon L (20 %) on Chromosorb P (60—80 mesh) using a Perkin-Elmer F 11 Gas Chromatograph indicated this fraction to consist of 86 % of 2-fluorothiophene and 14 % of thiophene. Preparative gas-chromatography on a 2.7 m x 3/8" column packed with apiezon M grease (20%) on Chromosorb A (45—60 mesh) using a Perkin-Elmer F 21 preparative Gas Chromatograph yielded pure 2-fluorothiophene, b.p 76°C/760 mm Hg. For mass spectrum see Ref. 9.

3. Fluorothiophene. In the same apparatus as described above 750 ml of 1.21 N ethylithium was cooled to —50°C and 127 g (0.78 mole) of 3-bromothiophene in 100 ml of anhydrous ether was added in a slow stream. The temperature was allowed to rise to —30°C, perchloryl fluoride was bubbled in, and the mixture worked up as described. 30 g of a fraction, b.p. 80—83°C, was obtained. VPC analyses as described above for the 2-isomer gave only one peak. However, on a 2.7 m x 3/8" column packed with polyethylene glycol on Chromosorb A (45—60 mesh) using a Perkin-Elmer F 21 preparative Gas Chromatograph thiophene and 3-fluorothiophene separated clearly and indicated the mixture to consist of 77 % of 3-fluorothiophene and 23 % of thiophene. The retention times for thiophene and 3-fluorothiophene were 23 mm and 31 mm, respectively, at a column temperature of 70°C. Pure 3-fluorothiophene, b.p. 87°C/760 mm Hg was thus obtained. For mass spectrum see Ref. 9.

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