

HIGH RESOLUTION NUCLEAR MAGNETIC
RESONANCE STUDIES OF ORGANIC COMPOUNDS:

^1H , ^{19}F AND ^{13}C SPECTRA

A Thesis Presented By

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To Jenny

Abstract

An extensive study of some derivatives of α fluoroacetic acid has been made by means of high resolution ^1H , ^{19}F and ^{13}C NMR spectroscopy.

The general theory of chemical shielding is reviewed briefly with particular attention to the recent theory describing the influence of the structural dependence of the inductive effect. It is found that this approach can be extended to explain successfully the variation in geminal H-F coupling constant with structure in the above series of compounds and permits an estimate of the group electronegativity of the amido function ($-\text{CONR}_2$) to be made. Use of this value in the application of the inductive effect theory to the chemical shifts of the series of α fluoroacetamides confirmed the overall validity of extending the theory to these molecules.

A general survey of isotope effects in NMR has been made with particular reference to ^{19}F spectroscopy. An unusually large, stereospecific, four bond deuterium isotope effect upon the ^{19}F shielding of the primary α fluoroacetamides has been discovered upon N- deuteration, and this has been examined in relation with the effect of successive N-methylation upon ^{19}F chemical shifts.

The series of α fluoroacids was extended to include all the commonly available α haloacetic acids for the purposes of a general ^{13}C NMR study. It is shown that the variation in ^{13}C chemical shifts of the carbons in the ester function can be explained in terms of the conformational preferences of the acetyl group substituents. An identical, although considerably smaller, effect could also be detected in ^1H spectra. This long range influence was also observed in certain ^{13}C NMR parameters of the α fluoroacetamides and their N-methyl derivatives.

Carbon -13 NMR has also been applied as a structural tool to some photolysis products of vitamin D₂. A data base derived from the successful assignment of 6 model compounds has enabled the elucidation of the structure of a further four photolysis products whose identity has remained unknown since work in this area commenced some 20 years ago.

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CHAPTER ONE

FLUORINE-19 N.M.R. STUDY OF
SOME DERIVATIVES OF
 α -FLUOROACETIC ACID

1.1 Introduction.

1.1.1 General Theory of Chemical Shielding and Inductive Effects.

1.1.1.1 Factors influencing chemical shifts.

The chemical shielding observed by the conventional high resolution NMR technique for a species in solution is not that of an isolated molecule, but is modified by the surrounding medium:

$$\sigma \text{ (observed)} = \sigma \text{ (molecule)} + \sigma \text{ (medium)} \quad \dots(1)$$

The term $\sigma \text{ (medium)}$ is generally known as the solvent effect, and thus before attempting to analyse the factors affecting the shielding constant of a nucleus in an isolated molecule ($\sigma \text{ molecule}$), initially, it is necessary to calculate or eliminate the solvent effect. It has been suggested that $\sigma \text{ (medium)}$ may have contributions from five sources:

$$\sigma \text{ (medium)} = \sigma_B + \sigma_A + \sigma_W + \sigma_E + \sigma_C \dots(2)$$

It is not proposed to give a full discussion of these terms here, as this has been covered in a recent review,² but to outline the origin of each term and its relevant importance, and indicate what precautions have been made to allow for it in the present work.

The term σ_B is due to the modification of the magnetic field experienced at the nucleus by the bulk magnetic susceptibility χ of the solvent. This can be calculated if χ is known, but is best eliminated by measuring the chemical shift relative to an internal reference compound.

The term σ_A occurs whenever the solvent molecules have an anisotropic magnetic susceptibility, and collisions between solute and solvent molecules are such as to lead to an averaged value of the magnetic susceptibility in the sphere immediately around the solute nucleus is different from the bulk value, χ . Thus the term will be of importance for disc-shaped molecules such

as benzene or rod-like solvents, e.g. carbon disulphide. Although the effect is calculable, it is best eliminated by using a magnetically isotropic solvent (e.g. carbon tetrachloride) and/or an internal reference of similar nature to the solute.

The term σ_W is a contribution arising from the Van der Waals interaction between the solute and solvent molecules. This interaction originates from the electrostatic forces between the electrons immediately surrounding the observed nucleus and those in neighbouring molecules, and decreases rapidly with the distance r between the groups. An approximate expression for σ_W has been derived³ in terms of the mean value of the square of the time-dependent electric field, $\langle F^2 \rangle$ and it has been suggested⁴

$$\sigma_W = -B \langle F^2 \rangle \quad \dots(3)$$

that $\langle F^2 \rangle$ will be proportional to r^{-6} . Considerable problems occur in the definition of B and $\langle F^2 \rangle$, since theoretical treatments of σ_W show both these parameters depend on the mutual orientation of the solute and solvent molecules, and will thus only be a constant for molecules of similar size and shape, whilst B depends on the nature of the nucleus and its electronic environment. In order to eliminate σ_W as far as possible, Emsley and Phillips proposed⁵ the use of an internal reference compound of similar chemical and physical shape to the molecule under investigation, and suggested CFCl_3 should be used as the reference for aliphatic compounds.

The term σ_E occurs only in the case of polar molecules. It arises from the reaction field set up by the polarization of the surrounding medium by the electric dipole of the solute. This electric field modifies³ the shielding by:

$$\sigma_E = -AE_z - BE^2 \quad \dots(4)$$

where E is the field at the nucleus and E_z is the component along the bond of the atom of interest. B is taken to be identical with that for the Van der Waals interaction. A is a measure of the

polarizability of the electrons around the nucleus in the bond direction, and as with B, will vary according to the nuclear species and electronic environment. Consequently, accurate determination of σ_E is difficult, with A, B and E being ill-defined, and thus its elimination requires the use of an internal reference with dipole moment and values of A and B equal to those of the sample. This is not achievable practically if a series of compounds of varying polarity are to be examined, and thus to reduce this effect to a minimum it is best to use a non-polar reference and a non-polar solvent, in order that the reaction field of the reference is eliminated and that of the sample is minimised.

The last term in the shielding expression, σ_C , is included to take into account any specific "chemical" interactions which occur between solute and solvent e.g. hydrogen bond, complexation. The definition is not a precise one, since the presence of specific interactions are generally not predictable and hence not calculable. Thus, it is usual to conclude that any variation in the observed shielding that is not attributable to any of the other effects is due to a specific interaction. However, this approach must be viewed with caution, since it is tantamount to defining σ_C as:

$$\sigma_C = \sigma(\text{medium}) - (\sigma_B + \sigma_A + \sigma_W + \sigma_E) \quad (5)$$

and thus σ_C will contain all the accumulated errors in the other terms. If internal referencing is in use (for which it is assumed σ_A and σ_B are zero) then errors in σ_E and σ_W may be the cause of the discrepancy in equation 5. Possible sources of error are that the medium is not isotropic, and any anisotropy could be misinterpreted as an indication of directional forces between solute and solvent which are called "chemical" as opposed to physical interactions. If, however, the value of σ_C obtained from equation (5) is considerably larger than any of the other terms, then this interpretation is less ambiguous. Because of the ill-defined nature of the "chemical" effects, no one approach can be used in their elimination, but it is reasonable to assume the possibility of such occurrence will be reduced if a non-polar solvent and reference are used.

An additional factor which should be taken into account when attempting to measure the chemical shift of a nucleus in an isolated molecule (σ_{mol}) is the effect of the concentration of the solution. The chemical shift of any nucleus varies to a greater or a lesser degree as the concentration is changed, due to changes in the bulk properties of the mixture and variations in the associative interactions of the solute molecules. Unfortunately, these changes are neither linear nor closely related for two different solutes, and thus shifts measured at a standard concentration need not necessarily reflect the shielding of the nucleus for an isolated molecule in the pure solvent. Such a value may only be obtained through recording the shift at a series of concentrations and extrapolating to infinite dilution.

It may be concluded from the foregoing comments that observation of the ^{19}F chemical shift in a non-polar solvent and using a non-polar aliphatic reference should eliminate σ_{A} and σ_{B} for the compounds of interest here, and minimise the contributions from the other terms, such that the shift recorded by extrapolation to infinite dilution is a good measure of $\sigma(\text{molecule})$.

It is now possible to consider the factors affecting the shielding constant within the molecule. Generally this is considered to be separable^{6,7} into two parts, called the diamagnetic and paramagnetic terms, but it has been pointed out⁸ that localised intramolecular contributions should be taken into account:

$$\sigma(\text{molecule}) = \sigma_{\text{d}} + \sigma_{\text{p}} + \sigma_{\text{l}} \quad \dots(6)$$

The diamagnetic term σ_{d} arises from the (diamagnetic) circulation of electrons (mainly s electrons) centred upon the nucleus in the applied magnetic field; the magnitude of this shielding is dependent upon the electron density at the nucleus. In the case of fluorine chemical shifts, this term has been shown to account⁸ for only one percent of the total shielding constant.

The contribution of σ_{l} may be separated⁹ into four terms:

$$\sigma_l = \sigma_a + \sigma_d + \sigma_e + \sigma_w \quad \dots(7)$$

The term σ_a arises from the diamagnetic circulation of electrons upon atoms or bonds remote from the nucleus under investigation. In solution, this effect is averaged over all molecular orientations with respect to the direction of the applied magnetic field and hence this term will be zero except in the case of groups with a marked anisotropy in their diamagnetic susceptibility, e.g. the carbonyl group, C=O. For an axially symmetric group the effect is given¹⁰ by

$$\sigma_a = \frac{\Delta\chi}{3r^3 N_o} (1 - 3\cos^2\theta) \quad \dots(8)$$

where r is the distance between the group concerned and the nucleus, $\Delta\chi$ is the difference in diamagnetic susceptibility of the group in the directions parallel and perpendicular to the group, N_o is Avogadro's number and θ is the angle between r and the group axis. Since the magnitude depends only on properties of the group and the molecular geometry, the effect is independent of the nucleus under study, and although the term is of importance in proton NMR, the much wider range of fluorine chemical shifts enable this effect to be safely ignored.

The term σ_d arises from the circulation of electrons in delocalised systems, and like the neighbouring atom anisotropy term, this contribution is independent of the nucleus under investigation, and therefore assumes a lesser importance in the case of fluorine chemical shifts.

The term σ_E is produced by the influence of electric fields on the shielding of the nucleus. The expression for σ_E is similar to that given for solvent reaction fields, except that the electric field E arises from permanent bond dipoles which are present with the molecule.

$$\sigma_E = -AE_z - BE^2 \quad \dots(9)$$

A and B are constants with similar significance to those defined for the solvent reaction fields.

The term σ_w expresses the effect of Van der Waals interactions, and arises because any group present in a molecule has associated with its electron distribution a fluctuating dipole moment, which produces a time-dependent electric field, F . The average square value $\langle F^2 \rangle$ is non-zero, and again the expression for σ_w is similar to that used for solvent interactions. An approximate expression⁴ for $\langle F^2 \rangle$ has been obtained as:

$$\langle F^2 \rangle = \sum_i 3P_i I_i / r_i^6 \quad \dots(10)$$

and although this was originally derived for solute-solvent interactions, it has been shown¹¹ that this can be applied to intramolecular situations. P_i is the polarizability of the electron group, I_i is the first ionization potential and R_i the distance separating the fluorine atom from the C-X electron group. Sutcliffe and co-workers¹²⁻¹⁵ have examined the importance of intramolecular Van der Waals electric fields in series of fluorinated compounds such as CF_3CXYZ ¹² and some partially halogenated perfluorocycloalkanes¹³ and cycloalkenes.¹³⁻¹⁵

Initial work was centred on the series of ethane derivatives, CF_3CXYZ , and it was considered that the CF_3 - group was sufficiently far removed from the remainder of the molecule to reduce inductive effects to a negligible amount. The comparable values of C-X bond dipole moments for X = halogen together with the variation in bond lengths enabled changes in the permanent electric fields within the molecules to be neglected across the series, and hence the observed chemical shift differences could be safely examined in terms of the Van der Waals field alone. For the purpose of calculating the latter electric field, the alkanes were assumed to be freely interconverting under the conditions of the investigation, and the value of $\langle F^2 \rangle$ obtained was therefore the weighted mean of the individual values for each rotamer with only staggered forms being considered. A plot of the ^{19}F chemical shift of the CF_3 - group against $\langle F^2 \rangle$ was linear for purely halogen-containing compounds (X = Y = Z = halogen); two further non-coincident lines were obtained for compounds containing one or two hydrogen substituents

(X and/or Y = H). Although the correlation depends on the degree of hydrogen substitution, it is very well defined within each sub-series. It is interesting to note that this dependence upon the degree of hydrogen substitution only occurs for fluorine resonance. Analogous studies of proton chemical shifts in $\text{CH}_3\text{.CXYZ}$ and for ^{13}C in $^{13}\text{CH}_3\text{.CXYZ}$ with $\langle F^2 \rangle$ yielded one linear plot for each nucleus. The apparently limited success with the ethanes prompted Sutcliffe et al. to continue their investigation into a series of fluorocyclobutanes¹³ and found they were able to estimate the observed chemical shifts of the ring fluorine atoms with an outer error limit of 3ppm. The calculation of $\langle F^2 \rangle$ involved assuming a planar geometry for the cyclobutane ring, which is actually slightly puckered, and further required the fractional population of conformers arising from unsymmetrical compounds to be determined. This further success encouraged these workers to apply the electric field theory to some cycloalkenes. The shifts produced by replacing F by Cl in some cyclopentenes¹⁴ were calculated and found to be in good agreement with experiment; similar results were found with the cyclohexenes.¹⁵

The most important factor contributing to the observed molecular shielding is σ_p , the paramagnetic term, and is responsible for the large variations in fluorine chemical shifts observed in practice. It arises from the restrictions imposed upon the circulation of electrons by chemical bonding, i.e. the electron distribution is not spherically symmetric. It is not proposed to go into the theoretical aspects of this term, but to examine how structural features within the molecule influence it in an empirical fashion.

1.1.1.2. The Structural Dependence of the Inductive Effect.

The fluorine chemical shifts of aliphatic compounds appear to exhibit several anomalous effects, and these have been discussed in some detail.¹⁶ A typical example is provided by the fluorine chemical shifts of the series of fluoromethanes: Successive replacement of fluorine by hydrogen in CF_4 causes an increase in

the shielding of the remaining fluorines, as would be expected from a classical inductive effect, but the change in shielding is not a linear function of the number of hydrogen atoms:

	CF_4	CF_3H	CF_2H_2	CFH_3
$\delta(\text{ppm})$	0	-18.2	-80.9	-210.0

In contrast to this, the effect of successive chlorination in the analogous series of chlorofluoromethanes is one of a progressive deshielding of the remaining fluorine nuclei, which is not predicted by a simple inductive approach. It was apparently conflicting data

	CF_4	CF_3Cl	CF_2Cl_2	CFCl_3
$\delta(\text{ppm})$	0	30	55	63

such as the above which led Phillips and Wray¹⁷ to develop a new method of calculating fluorine chemical shifts in a variety of fluoro-aliphatic compounds. This treatment is based on the assumption that the paramagnetic term (which is accepted as the dominant contribution to nuclear shielding) is dependent upon the degree of ionic character of the bond in which the fluorine is part.⁸

The simplest case which can be considered is a diatomic molecule, for which the ionic character of the bond is related to the difference in the electronegativities of the constituent atoms. Gutowsky and Hoffman¹⁸ found that for a variety of polyatomic binary fluorides, (MF_n) , the fluorine shielding was approximately proportional to the electronegativity of the central atom M. However, the data show a marked departure from linearity, and Phillips and Wray postulated¹⁷ that this was produced by mutual interactions between the several M-F bonds modifying the electronegativity of M and F. Hence it was proposed that the ionic character of the C-F bond in an alkyl fluoride was proportional to the difference in the effective electronegativities of carbon and fluorine, E_{C} , and E_{F} , and thus the observed shielding σ may be expressed as:

$$\sigma = \sigma_0 + k'(E_{\text{C}} - E_{\text{F}}) \quad \dots(11)$$

where σ_0 is the shielding in a purely covalent molecule.

It was then necessary to obtain estimates of these effective electronegativities in terms of interactions involving all the molecule C_{abdF} . It was convenient to adopt a perturbational approach, and consider the changes in electronegativity of carbon upon stepwise addition of the four substituents to an sp^3 hybridized carbon atom, and hence evaluate an expression for E_C . A similar treatment for the fluorine atom completed the analysis. All of the perturbations between any two parts of the molecule are mutual, and it was further proposed that the magnitude of such interactions should be proportional to the product of the Huggins electronegativities of the two centres.

It was possible to distinguish four different types of interaction within the typical alkyl halide, C_{abdF} . Thus, when two atoms bond together, each modifies the electronegativity of the other by a perturbation proportional to the product of their electronegativities. For example, direct bonding between a and C, C-a:

$$\begin{aligned} E_a' &= E_a + k_{D1}^{aC} E_a E_C \\ E_C' &= E_C + k_{D1}^{aC} E_a E_C \end{aligned} \quad \dots 12(a \text{ \& } b)$$

This was classified as a primary directly bonded interaction and the modification of E_C and E_a by the perturbation will also affect other groups bonded to the central carbon atom by a factor proportional to $E_C E_a$, e.g. $k_{D2}^{aC} E_a E_C$. This is identified as a secondary bonded interaction.

Interaction between pairs of geminal substituents were also taken into consideration. The first of these was that produced by the geminal delocalization of σ electrons,¹⁹ there being one such mutual perturbation for each pair of substituents. This was described as a primary geminal interaction and is typified by a term such as $k_{G1}^{bd} E_b E_d$. These interactions will also perturb the electronegativity of the substituents other than those involved in the geminal delocalization, in a manner analogous to the secondary geminal interactions, and could be sub-divided into those involving carbon, (e.g. $k_{G2} E_b E_d$) and those affecting other substituents, such as $k_{G2} E_a E_d$, which would be a perturbation to the electronegativity of b and F.

Using the above concepts, it was then possible to obtain estimates for E_C , and E_F , and hence derive an expression for the observed shielding σ in terms of the Huggins electronegativities of the substituents and a set of constants describing the nett effect of the above interactions. Hence equation (11) could be re-written as:

$$\begin{aligned} \sigma = \sigma_o + k' E_c (1 + k_1^{Ca} E_a + k_2^{Cb} E_b + k_3^{Cd} E_d) + E_F (-1 + \\ k_5^{aF} E_a + k_6^{bF} E_b + k_7^{dF} E_d) + E_d (k_8^{bd} E_b + k_9^{ad} E_a) \\ + E_b (k_{10}^{ba} E_a) \end{aligned} \quad \dots(13)$$

where k_1 , k_2 and k_3 represent the nett perturbation upon the electronegativity of both carbon and fluorine caused by directly bonded interactions between C and a,b, or d. The constants k_5 to k_{10} represent the perturbations caused by geminal delocalization between substituents; k_5 , k_6 and k_7 express the net effect of geminal interactions between the groups a, b or d and fluorine upon the electronegativity of fluorine (primary interaction) and carbon (secondary interaction), while k_8 , k_9 and k_{10} express the net effect of the geminal secondary interactions, which do not involve fluorine, upon the electronegativity of carbon and fluorine.

Equation 13 could in principle be used to evaluate the difference in chemical shift (i.e. substituent chemical shift, S.C.S.) between two molecules $CabdF$ and $CefgF$, whereby the σ_o term was eliminated. However, the resultant expression contained 18 of the above net interaction constants. Consequently, it was necessary to make several approximations before numerical values for all the constants could be obtained. Hence, it was assumed that those constants related to inter-halogen perturbations were independent of the nature of the halogen and had the same value, k^{xx} . Similarly, perturbation constants for interactions between non-halogen groups a or b were held to be dependent upon the nature of a or b but not of the halogen involved. It was then possible, by selecting suitable series of compounds, to obtain estimates for the various types of interaction constants.

Thus the S.C.S. for any compound $CabXF$ from $CabF_2$ (as an arbitrary reference) was given by the expression:

$$\Delta = (E_F - E_X) [154.12 - 26.63(E_a + E_b)] \quad \dots(14)$$

wherein X was a halogen, with an r.m.s. error of 3.3ppm. Equation (14) demonstrates that the effect of the difference between the inductive effects of groups X and F (which would be expected to produce a shielding on going from $\text{CabF}_2 \longrightarrow \text{CabXF}$) is modified by the electronegativities of the other substituents a and b. It is clear that if $(E_a + E_b)$ is less than 5.78 Huggins units then substitution of F by another halogen X produces a nuclear shielding, but if $(E_a + E_b)$ is greater than this value a deshielding is predicted, in apparent contradiction to the expected inductive effect.

Following up the success of this result, Phillips and Wray were encouraged to make further assumptions which enabled them to produce an expression for calculating chemical shifts in a more generally applicable form. Thus all the constants k_1 to k_3 (equation 13) relating to the primary directly bonded interactions (e.g. k_2^{bc}) were equated as a property of the carbon centre, and k_5 to k_7 (e.g. k_6^{bF}) concerned with the direct perturbation to the electronegativity of fluorine by geminal delocalisation were similarly treated as a property of F. However, the constants k_8 to k_{10} , which express the results of secondary (indirect) perturbations caused by geminal delocalization, could not be so treated. It was considered unreasonable to equate any of these without a prior knowledge of their nature.

It was now possible to produce the required expression for the chemical shift of the general alkyl fluoride CefgF from a reference CabdF , and CFCl_3 ($a = b = d = \text{Cl}$) was taken as this standard. The equation derived was:

$$\Delta_{\text{CefgF}}^{\text{CFCl}_3} = 154.12(9.45 - E_e - E_f - E_g) + 29.76k^{XX} - k^{ef}_{eF}E_f - k^{eg}_{eF}E_g - k^{fg}_{fF}E_g \quad \dots(15)$$

Since the value of the inter-halogen interaction constant was known ($k^{XX} = -25.91$ ppm) it was possible to use equation (15) to calculate the fluorine chemical shifts of several mixed fluoro-

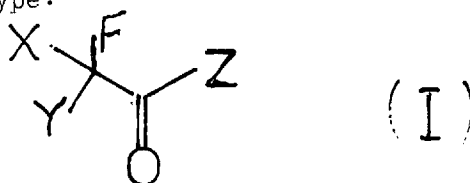
halo-methanes, with an r.m.s. error of 2.8 ppm. It will be recalled that the shifts of the series of chlorofluoro-methanes in particular showed great deviations from a linear dependence on chlorine content; the new treatment rationalized the data very well.

Further series of compounds could be treated upon derivation of the appropriate interaction constants. Thus for the series $\text{CF}_4 - \text{CF}_3\text{H} - \text{CF}_2\text{H}_2 - \text{CFH}_3$, the constants k^{HF} and k^{HH} were required, and could be estimated from CF_3H and CFH_3 respectively. Their validity was then checked by calculating the shielding of CF_2H_2 , which came to within 3 ppm of the observed value. Hence equation 15 was again capable of rationalizing the chemical shift variation in the series, and the large deviation from additivity upon successive replacement of F by H.

This treatment was not restricted to single atom substituents; CH_3 , CF_3 , NF_2 and OF groups could also be handled providing sufficient data was available for estimating any further geminal interaction constants.

Further work showed the theory was not confined to the fluoroalkanes. It was initially extended²⁰ to some series of partially fluorinated tin(IV) complex anions. In this case it was found that the secondary interactions, which were responsible for the deviations from additivity found for the fluorocarbons, were negligible. Subsequent studies showed that the concepts used above could be applied to geminal and directly bonded interactions influencing²¹ the shielding of a variety of nuclei such as ^1H , ^{13}C , ^{11}B , ^{31}P and ^{119}Sn , and the theory was capable of extension to include vicinal effects on ^{19}F shielding in both fixed²² and conformationally mobile systems.

It is of interest² to examine the applicability of the theory reviewed above to some other systems of a more general nature than those from which the equations were derived. The synthetic work undertaken in connection with the study of isotope effects (Chapter 2) yielded four series of compounds based on α fluoro-acetic acid, of the type:



where the acetyl group substituents X and Y were combinations of hydrogen or halogen (F, Cl or Br) and the derivitizing function Z was the methyl or ethyl ester ($-\text{OCH}_3$ or $-\text{OC}_2\text{H}_5$) or the primary, secondary or tertiary amide ($-\text{NH}_2$, $-\text{NHMe}$, $-\text{NMe}_2$). It was decided to study the fluorine chemical shifts of these compounds in the light of the previously established relationships.

However, before such an analysis can be attempted, it is necessary to derive a value for the group electronegativity of the alkoxy carbonyl ($-\text{CO.OR}$) or amido ($-\text{CO.NR}_1\text{R}_2$) moieties, and it would be attractive to acquire this independently of the chemical shift data. Examination of the geminal coupling $^2J_{\text{HF}}$ of the CFXY group (where X = H) revealed that this value appeared to be dependent upon X and Y, and hence the general validity of this observation was surveyed further. The data pertaining to this will be found in the relevant section of results presented later in this chapter.

Before examining the form of any such dependence of $^2J_{\text{HF}}$ upon the nature of geminal substituents, it is necessary to appreciate the origin of the coupling constant, and the relative importance of the various contributions to it.

1.1.2. Coupling Constants.

1.1.2.1 Mechanisms of Spin Coupling.

The simplest way to enter into a discussion of the mechanisms of spin-spin coupling is to consider the general expression of Ramsey²⁴ used to describe the interaction J_{AB} between two nuclei of spin $\frac{1}{2}$:

$$J_{\text{AB}} = J_{1\text{AB}} + J_{2\text{AB}} + J_{3\text{AB}} + J_{4\text{AB}} \quad \dots(10)$$

$J_{1\text{AB}}$ arises from the direct interaction of one nuclear dipole with the other, and is very large (typically 30KHz). However, in the fluid state, rapid tumbling of molecules averages this to zero, and so it does not enter into normal consideration. The remaining mechanisms all involve the molecular electrons and may thus be described as electron coupled interactions.

The second contribution, J_{2AB} , arises through the nuclear magnetic moment of A interacting with the orbital electron currents which in turn interact with the moment of B, and vice versa. This term is usually referred to as the orbital-orbital coupling, or spin-orbit coupling.

J_{3AB} is produced by a dipole interaction between the nuclear magnetic moment of A and the associated electron spin magnetic moments; the electron dipoles interact with the magnetic dipole of nucleus B and thus 'pass on' the "spin information" necessary for coupling. This term is known as the dipole-dipole coupling, or spin-dipole coupling.

The fourth term J_{4AB} is an interaction between the nuclear magnetic moments and electron spin in s orbitals which have non-zero value at the nucleus. Expressed alternatively, it arises from the fact that an electron associated primarily with one nucleus has a finite probability of being at the other nucleus, and hence transmitting spin information directly. Due to the nature of the term, this is known as the Fermi contact interaction.

In the case of interproton coupling, this term accounts for ca. 98% of the observed coupling, with the other two terms only making minor contributions. However, fluorine couplings are very much larger than those involving protons alone and it has been suggested²⁵ that the spin-orbit and spin-dipole couplings (J_{2AB} and J_{3AB}) become more effective when the atoms concerned possess p or d atomic orbitals. A theoretical treatment by Pople²⁵ has shown that, notwithstanding the large contribution to geminal H-F coupling by the spin-orbit mechanism (estimated value 13.3Hz) the predominant term is the Fermi contact for the observed range of couplings (44 to 81Hz).

1.2. Results and Discussion.

1.2.1. Geminal Proton - Fluorine Coupling $^2J_{\text{HF}}$.

1.2.1.1 Substituent effects in some model systems.

There are very few systematic studies of the variations of $^2J_{\text{HF}}$ with the nature of substituents, but Arison²⁶ has found that for a series of difluoromethyl compounds CHF_2X the geminal H-F coupling showed a marked increase with the electronegativity of X. (X = C, N, O, F). Thus in methylene fluoride (CH_2F_2 , X = H) $^2J_{\text{HF}}$ is 50.4 Hz. while in fluoroform (CHF_3 , X = F) $^2J_{\text{HF}}$ is 79.7 Hz.

A recent survey²⁷ of the published data on fluorine coupling constants enables a list of typical values of $^2J_{\text{HF}}$ in a wide variety of molecules of the type XYCHF to be drawn up (Table 1), and a plot of these against $(E_X + E_Y)$, the sum of the Huggins electronegativities of X and Y, is shown in figure 1. It is apparent that there is indeed a trend in which $^2J_{\text{HF}}$ increases with an increasing total substituent electronegativity, but this is not a simple relationship. Inspection of table 1 shows that if one of the substituents is carbon (e.g. an alkyl group) and the other is held constant, then the observed coupling constant may vary greatly as a result of structural variation within the carbon group, i.e. substituent effects β to the carbon to which the coupling nuclei are bound may be significant.

If a series of compounds is chosen with the intention of minimizing such β effects (i.e. the substituents are single atoms or simple groups such as CH_3 or OCH_3), the correlation of $^2J_{\text{HF}}$ with $(E_X + E_Y)$ is certainly not linear but shows marked curvature. Table 2 gives values for a series of such molecules, and the relevant graph is depicted in figure 2.

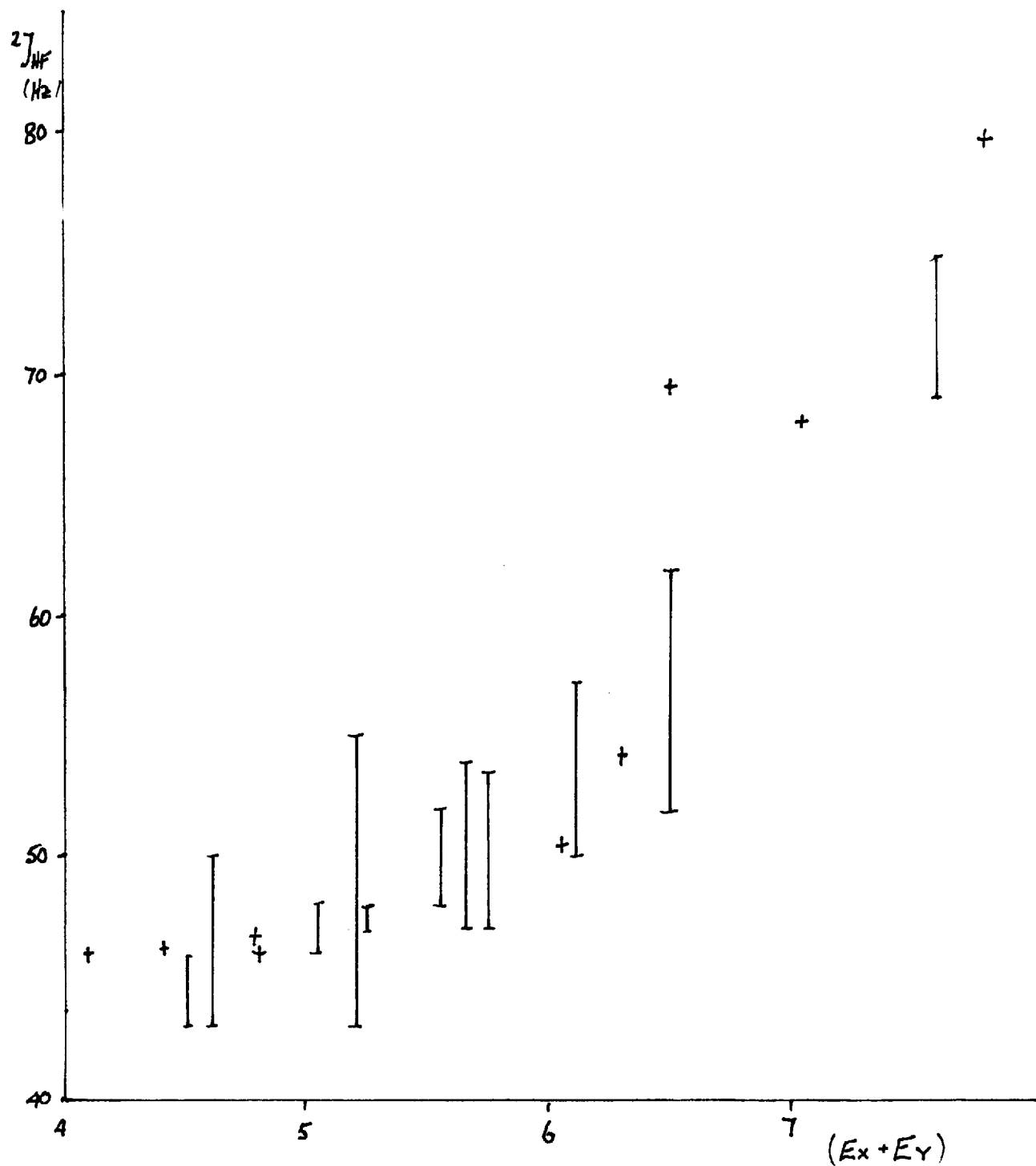
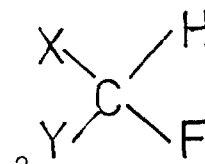


Figure 1

Plot of $^2J_{HF}$ vs. $(E_x + E_y)$ for general molecules XY.C.HF

Table 1. Typical values of ${}^2J_{\text{HF}}$ for the fragment



X	Y	$(E_X + E_Y)$	${}^2J_{\text{HF}}$
F	F	7.8	79.5
F	OR	7.6	69 - 75
F	Cl	7.05	63
F	SO_2CF_3	6.5	69.5
F	-P^{III}	6.05	50.4
F	R	6.5	52 - 62
Cl	Cl	6.3	53.5
R	OR	6.1	50 - 57
R	NR_2 or NO_2	5.65	42 - 54
R	Cl	5.75	47 - 53
R	$\text{SR}, \text{S}^{\text{VI}}$	5.2	43 - 49
R	Br	5.55	48 - 52
F	H	6.1	50.4
R	I	5.25	47 - 48
H	SF_5	4.8	46
Cl	Si	5.05	46 - 48
R	R	5.2	43 - 55
R	P^{V}	4.75	46.7
R	H	4.6	45 - 50
R	Si^{IV}	4.5	43 - 46
R	Ge^{IV}	4.5	45 - 46
H	H	4.4	46.3
H	SiMe_3	4.1	46.8

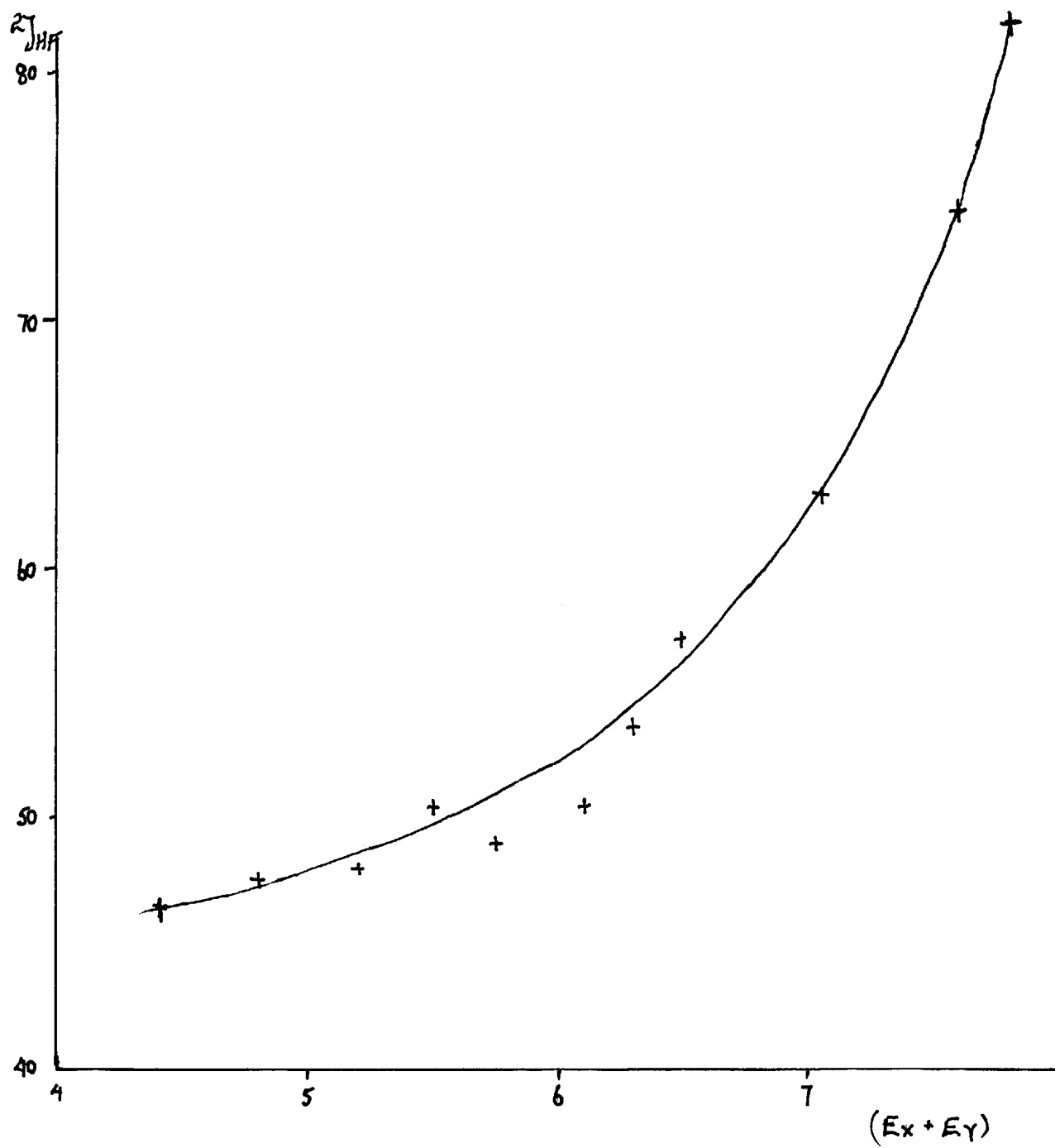


Figure 2

$2J_{HF}$ vs. $(E_x + E_y)$ for specific molecules of the type
XY.C.HF

Table 2. Values of ${}^2J_{\text{HF}}$ for specific molecules of the type

X	Y	$E_X + E_Y$	${}^2J_{\text{HF}}(\text{obs})$	${}^2J_{\text{HF}}(\text{calc})$
F	F	7.80	79.5	76.8
F	OCH_3	7.60	74.4	68.7
F	Cl	7.05	63.0	64.6
F	CH_3	6.50	57.2	55.7
Cl	Cl	6.30	53.6	57.2
F	H	6.10	50.4	49.2
Cl	CHCl_2	5.75	49.0	51.8
Br	CH_3	5.50	50.0	50.7
I	C_2F_5	5.20		
CH_3	CH_2I	5.20	48.0	48.9
CH_3	H	4.80	47.5	46.8
H	H	4.40	46.3	46.1

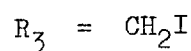
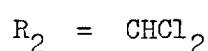
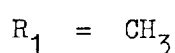
It is possible that substituent effects may be an additive property of the groups involved (even if apparently they are not simply related to electronegativity) and this may be examined by evaluating the effect of making the same substituent change in different molecules. The change in ${}^2J_{\text{HF}}$, $\Delta {}^2J_{\text{HF}}$, upon substitution of an alkyl group R by fluorine, has been calculated for four pairs of molecules and is given in table 3.

Table 3 shows that the magnitude of the change in ${}^2J_{\text{HF}}$ upon going from a molecule XYCHF to ZYCHF depends not only upon the electronegativity difference between X and Z but also upon the nature of the group Y. This conclusion is paralleled by the observations made about substituent effects upon nuclear shielding by Phillips and Wray¹⁷ and an approach similar to that used in their analysis of shielding data can be applied here.

In figure 3 the values of ${}^2J_{\text{HF}}$ quoted in table 2 are plotted in such a way as to demonstrate the structural dependence of the substituent effects upon ${}^2J_{\text{HF}}$. For four different series of molecules XYCHF , in which the group X is held constant and the group Y is varied, ${}^2J_{\text{HF}}$ is plotted against the Huggins electro-

Table 3. Substituent effects upon $^2J_{\text{HF}}$.

Compound	$^2J_{\text{HF}}$	Compound	$^2J_{\text{HF}}$	Δ^2J_{HF}
$R_1 \cdot \text{CF}_2\text{H}$	57.2	CF_3H	79.5	22.3
$R_2 \cdot \text{CClFH}$	49.0	$\text{CF}_2 \cdot \text{ClH}$	63.0	14.0
$R_3 \cdot \text{CMeFH}$	48.0	$\text{Me} \cdot \text{CF}_2\text{H}$	57.2	9.2
$R_1 \cdot \text{CH}_2\text{F}$	47.5	CH_2F_2	50.2	2.9



negativity of Y, E_Y . The results are satisfactorily linear and all lines appear to pass through a common point at $E_Y = 1.98$, $^2J_{\text{HF}} = 45.63\text{Hz}$. If the slope of the line for a given common substituent X is S_X , then each correlation may be expressed by the equation

$$^2J_{\text{HF}} = 45.63 + S_X(E_Y - 1.98) \quad \dots(16)$$

In turn, a plot of S_X vs. E_X (the electronegativity of X) is linear, and S_X may be expressed as:

$$S_X = 8.45(E_X - 1.98) \quad \dots(17)$$

Substitution of (17) into (16) provides a useful relationship for $^2J_{\text{HF}}$ in terms of the electronegativities of the groups X and Y:

$$^2J_{\text{HF}} = 78.76 + 8.45E_XE_Y - 16.73(E_X + E_Y) \quad \dots(18)$$

Equation (18) enables $^2J_{\text{HF}}$ for the molecules listed in table 2 to be calculated to a satisfactory degree of precision ($\pm 2.1\text{Hz}$ r.m.s.) and the calculated values are reproduced in table 2 for comparison.

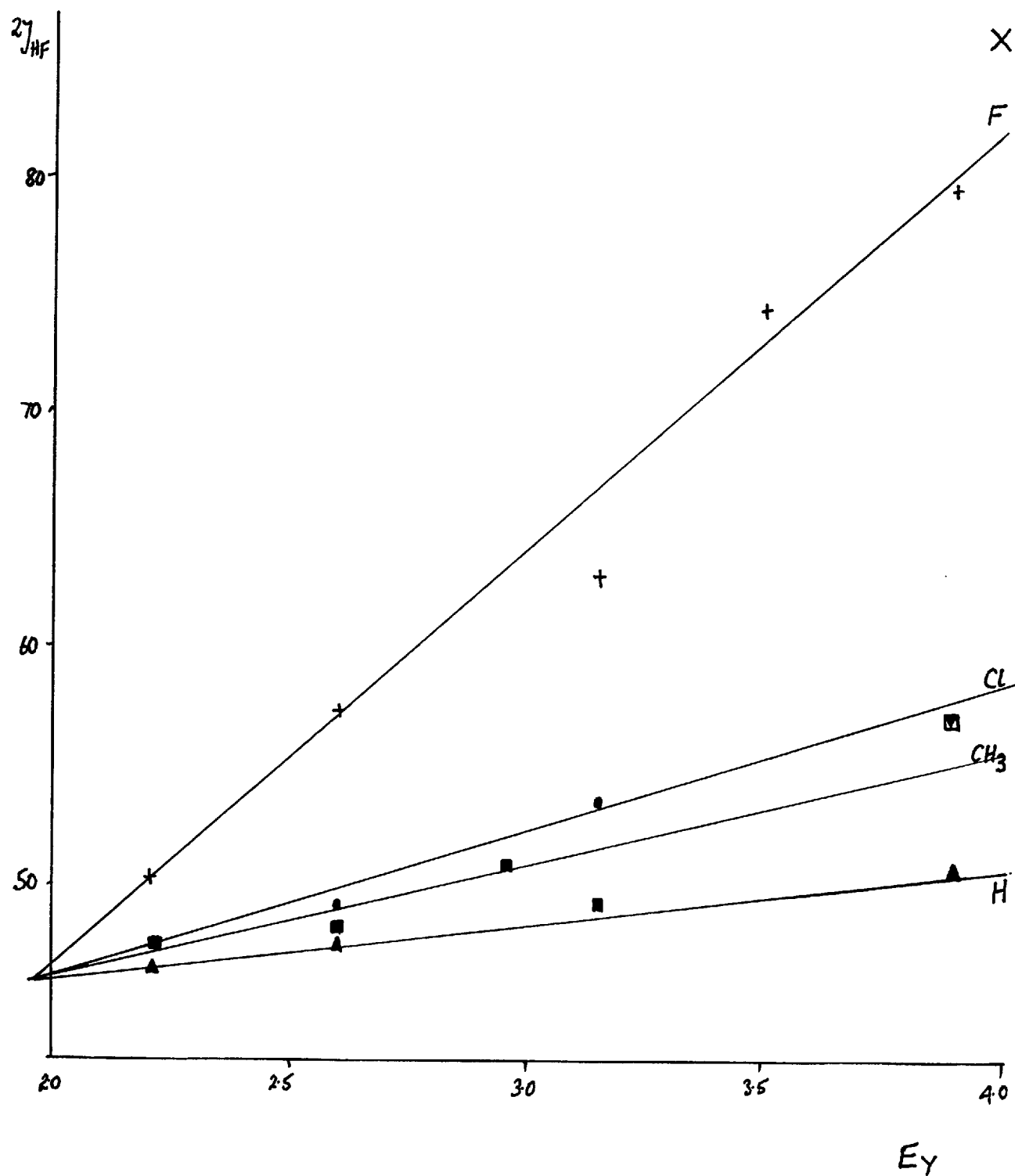


Figure 3

$2J_{HF}$ vs. E_Y for various series in which X is held constant

A further test of the general validity of equation (18) is provided by its mathematical form, which leads to two interesting conclusions. Firstly, for a series of compounds XYCHF in which the group X is held constant and has an electronegativity of 1.98, changing the nature of the group Y should have no observable effect upon $^2J_{\text{HF}}$, which should stay constant at ca 45.6Hz. Secondly, if E_X is less than 1.98, then a decrease in the electronegativity of group Y should lead to an increase in the value of $^2J_{\text{HF}}$. There is some evidence to support this conclusion in the case for when Y is Si^{IV} ($E = 1.90$) and this is provided in table 4.

Table 4. $^2J_{\text{HF}}$ in some methyl silyl fluorides $\text{Z}_3\text{Si.CHF.Y}$

Y	E_Y	Compound	$^2J_{\text{HF}}$	Ref.
Cl	3.15	$\text{Et}_3\text{Si.CHF.Cl}$	45.5	28
CH_3	2.6	$\text{Cl}_3\text{Si.CHF.Me}$	46.0	29
H	2.2	$\text{Me}_3\text{Si.CHF.H}$	46.8	30

Inspection of table 4 shows that there is indeed a small increase in $^2J_{\text{HF}}$ with the decreasing electronegativity order $\text{Y} = \text{Cl}, \text{CH}_3$ or H. It may be concluded that equation (18) provides a very good qualitative description of the manner in which relatively simple substituents affect $^2J_{\text{HF}}$ across carbon.

1.2.1.2 Coupling in some α fluoroacetic acid derivatives.

It was mentioned earlier that the values of $^2J_{\text{HF}}$ in the series of α -fluoroacetic acid derivatives ($\text{I}, \text{X.HCF.COZ}$) appeared to vary with the nature of the substituent Y. The data for these compounds are listed in table 5, and within each series, one group has been held constant ($\text{I} = \text{X.CHF.Y}, \text{Y} = \text{COZ}$) while the other is varied. A plot of $^2J_{\text{HF}}$ against the electronegativity of the substituent X for each series is linear (figure 4) with the respective correlation coefficients indicated in table 5.

Figure 4

$^2J_{\text{HF}}$ vs. E_X in molecules of the type:-

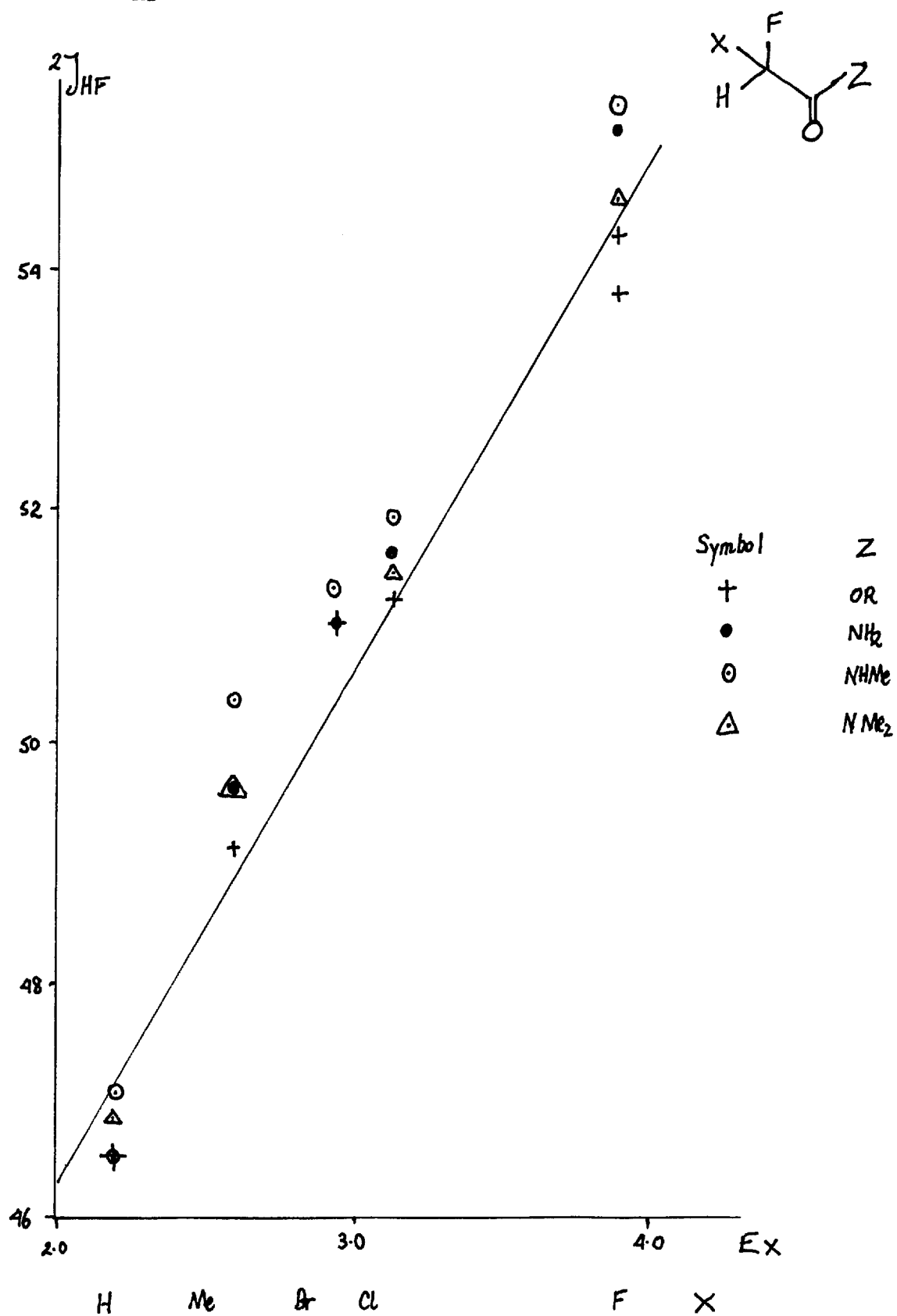
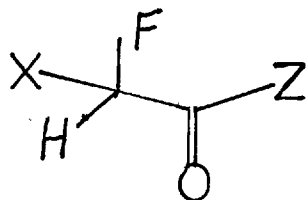


Table 5 Values of $^2J_{\text{HF}}$ for the substituted esters, amides, N-methylamides and N,N-dimethylamides (in Hertz, chloroform solution).



- (a) $-\text{OR} = -\text{OCH}_3$
 (b) $-\text{OR} = -\text{OCH}_2\text{CH}_3$

acetyl substituent X	Observed coupling for derivative -Z (Hz)				$^2J_{\text{HF}}$ Calc.
	Z = -OR	Z = -NH ₂	Z = -NHMe	Z = -NMe ₂	
H	46.5(a)	46.5	47.0	46.8	46.6
Me	49.1(b)	49.6	50.6	49.6	48.4
Br	51.0(b)	51.0	51.3	-	49.9
Cl	51.2(a)	51.6	51.8	51.4	50.8
F	54.3(a) 53.8(b)	55.2	55.4	54.6	54.1
corr. coeff	0.983	0.975	0.975	0.991	

Thus it may be concluded that the carboxyl derivative group (-Z) is behaving as a "simple" substituent, with negligible effects upon the coupling constant. Table 5 also shows that the observed coupling constant is virtually independent of the nature of Z, or expressed alternatively, the group electronegativities of $-\text{CO}_2\text{R}$, $-\text{CONH}_2$, $-\text{CONHMe}$ and $-\text{CONMe}_2$ are all very similar. Due to the linear plots observed, it is now possible to apply equation 18 to the case under consideration and obtain an estimate for the above group electronegativity; a value of 2.5 on the Huggins scale enables the coupling constants to be calculated to a satisfactory degree of precision, as shown in table 5. This is

a reasonable figure, because a value of 2.6 has been reported³¹ for $-\text{CH}_3$ and 2.8 for $-\text{CO}_2\text{H}$.

Attention may now be redirected towards the study of the fluorine chemical shifts of the compounds (I), and the value of the group electronegativity derived from equation (18) (using $^2J_{\text{HF}}$ data) may be used in equation (15) (relating to chemical shifts) to estimate shielding values for the same situations as were used to derive this electronegativity value. Such a test provides an excellent opportunity to study the overall usefulness of the Phillips - Wray approach to N.M.R. phenomena.

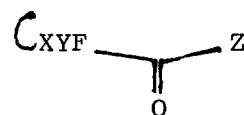
1.2.2. Fluorine chemical shifts.

The fluorine chemical shifts of the primary, secondary and tertiary acetamides ($-\text{CONH}_2$, $-\text{CONHMe}$ and $-\text{CONMe}_2$) have been obtained for infinitely dilute solutions in chloroform (CHCl_3), together with chemical shifts of the methyl or ethyl esters, as obtainable. Chloroform was chosen as solvent because this was the least polar medium capable of dissolving all the compounds (severe solubility problems were encountered with some of the primary amides), and since the data obtained from different series were to be compared with each other, it was desirable to employ a common solvent throughout.

All the spectra were recorded using hexafluorobenzene as the internal reference, since this compound contains a high proportion of fluorine and resonates as a single sharp line, and hence provides a good lock signal for the spectrometer. The fluorine spectrum of CFCl_3 was similarly recorded at infinite dilution in chloroform solution with hexafluorobenzene as reference, in order that all chemical shifts may be expressed in p.p.m. from the former.

A complete list of all the fluorine chemical shifts is given in table 6, and are negative if to high-field of the reference compound.

Table 6. Fluorine Chemical Shifts at Infinite Dilution in Chloroform for some α Fluoroacetic Acid Derivatives



δ = Shift from C_6F_6

ϕ = Shift from $\text{CFCl}_3(\text{a})$

CXYF	$\Sigma E^{(b)}$	Z = $-\text{NH}_2$		Z = $-\text{NHMe}$		Z = $-\text{NMe}_2$		Z = $-\text{OCH}_3$		Z = $-\text{OC}_2\text{H}_5$	
		δ	ϕ	δ	ϕ	δ	ϕ	δ	ϕ	δ	ϕ
CH_2F	8.30	-60.535	-222.81	-63.267	-225.54		-227.41	-68.369	-230.639	-68.033	-230.30
MeCHF	8.70	-18.001	-180.27	-20.470	-182.75	-16.266	-178.54	-	-	-22.551	-184.82
CHBrF	9.05	15.216	-147.05	13.777	-148.99	-	-	-	-	11.184	-151.08
PhCHF	9.10	-13.160	-175.43	-16.125	-178.40	-11.470	-173.74	-18.107	-180.38	-	-
CHClF	9.25	19.324	-142.95	17.871	-144.40	20.107	-142.16	15.859	-146.41	-	-
CHF_2	10.00	35.921	-126.35	35.564	-126.711	40.139	-122.13	35.160	-127.110	35.400	-126.87
CFCl_2	10.20	96.867	-65.40	96.288	-65.987	-	-57.21	-	-	97.373	-64.90
CF_2Cl	10.95	97.526	-64.74	97.855	-64.420	104.061	-58.21	-	-	97.913	-64.36
CF_3	11.70	85.706	-76.56	85.859	-76.416	92.294	-69.98	86.811	-75.459	86.542	-75.73

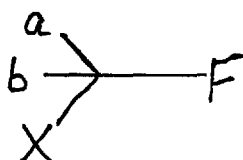
(a) $\delta = \phi + 162.270$ ppm.

(b) ΣE = sum of Huggins electronegativities of substituents.

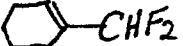
Inspection of Table 6 reveals that the fluorine chemical shifts tend to lower applied fields with increasing electronegativity of substituents, but it is apparent that the shift is not related linearly to the sum of the Huggins electronegativities, ΣE . Thus the lowest field shifts are observed for the CFCl_2Z compound in each series, and there is a downfield trend for the series CF_3Z , CF_2ClZ and CFCl_2Z where Z is as indicated in table 6. The variations of the chemical shifts are non-linear, and are contrary to that which would be predicted by a classical inductive theory, which would predict that successive replacement of fluorine by chlorine would lead to shielding, rather than deshielding, of the fluorine nuclei.

Such observations are similar to those made² for the chlorofluoromethanes, and the fluorine chemical shifts of these and many other "anomalous" fluorine compounds have been rationalized recently¹⁷ by Phillips and Wray using a new theory of the inductive effect. Therefore, it is reasonable to propose that the data presently under consideration should be analysable by a similar approach. A comprehensive study of geminal substituent effects upon ^{19}F chemical shifts enabled Phillips and Wray¹⁷ to derive an empirical expression for the fluorine chemical shift of the general alkyl fluoride Cefg.F , from CFCl_3 . Their approach was presented in the introduction (section 1.1.1.2) and led to the derivation of equation (15) for the calculation of the fluorine chemical shifts in a variety of alkyl fluorides. It was noted in that section that the various constants k within equation (15) were interaction constants which arose from geminal delocalization between the various pairs of substituents. Thus, if these parameters are known, it is possible to calculate the fluorine chemical shift of the alkyl fluoride from CFCl_3 .

The various series of acid derivatives may be considered as:



where X is the carbonyl function, $-\text{COZ}$, as defined in Table 6. It is seen that before equation 15 can be applied to these series, it will be necessary to determine values for the constants representing interaction between hydrogen and the sp^2 carbon of the carbonyl group, ($k_{\text{sp}^2\text{C-H}}$), and similarly for halogen interaction with the carbonyl group, ($k_{\text{sp}^2\text{C-X}}$). These values may be obtained from the fluorine chemical shifts of suitable model compounds by application of equation 15.

Thus $k_{\text{sp}^2\text{C-X}}$ may be evaluated from trifluoroacetic acid, $\text{CF}_3\cdot\text{CO}_2\text{H}$ (1, a=b=F, X = CO_2H), for which the fluorine chemical shift (ex CFCl_3) is known³² to be -77 ppm, and Wells has estimated³¹ the electronegativity of the $-\text{CO}_2\text{H}$ group as 2.8. This yields a value for the interaction constant $k_{\text{sp}^2\text{C-X}} = -28.90$ ppm. A suitable model for the other interaction constant is 1,1'-difluoro-methyl-cyclohex-1-ene. , which resonates³³ 110 ppm upfield of CFCl_3 and enables $k_{\text{sp}^2\text{C-H}}$ to be evaluated as -33.93 ppm. The value for the electronegativity of the $-\text{COZ}$ group in the acid derivatives has been obtained from the study of the geminal H-F coupling constants (section 1.2.1) as 2.5 Huggins units, thus values of all the parameters required for the application of equation (15) have been derived independently from the chemical shift data to be examined. Attention will be directed initially to the tertiary amides, ($-\text{CONMe}_2$), as a typical series of compounds, in order to test the general applicability of equation (15).

1.2.2.1. Fluorine chemical shifts of the tertiary amides.

The chemical shifts of the tertiary amides were calculated from CFCl_3 using the parameters discussed above, and the results are given in table 7. The substituent chemical shifts (S.C.S.'s) from the trifluoroamide have also been calculated, and the experimental values for both shifts are included for comparison.

Table 7. First Calculation of ^{19}F Chemical Shifts for tertiary amides.

Acetyl Group	Calculated shift ex. CFCl_3	(ppm) S.C.S	Experimental ex. CFCl_3	shift (ppm) S.C.S.
CF_3-	-55.56	0.0	-69.98	0.0
$\text{CF}_2\text{Cl}-$	-41.45	14.11	-58.21	11.77
CFCl_2-	-41.59	13.97	-57.21	12.77
CF_2H	-98.69	-43.13	-122.13	-52.15
$\text{CHBrF}-$	-110.74	-55.18	-	-
$\text{CHClF}-$	-108.19	-53.53	-142.16	-72.18
$\text{CH}_2\text{F}-$	-196.76	-141.20	-227.41	-157.43

It is seen from an internal comparison of the data within table 7 that the values of the chemical shift obtained with equation (18) are qualitatively very encouraging. Thus the theory is correctly predicting the downfield trend upon successive chlorination of trifluoroamide. It was noted above such a trend is contrary to a purely inductive effect upon shielding, and arises from the nature of the interaction terms within equation (18). However, the quantitative agreement between the calculated and experimentally observed shifts is poor, especially those amides where one or both of the acetyl group substituents (X/Y) is hydrogen, with the calculated shift of the difluoroamide being 16.6 ppm low, whilst that for the monofluoroamide is underestimated by 30.6 ppm.

The chief factor responsible for these errors must be the poor choice of models chosen for the interaction constants. The carbonyl carbon is a particular sort of sp^2 carbon, and a non-carbonyl compound was taken as a model for the $\text{sp}^2_{\text{C-H}}$ interaction,

which is probably why the errors associated with the partially hydrogenated acetyl groups are worse than for those containing only halogens. Better estimates of the interaction constants should be obtained if some of the experimental data is used for their estimation, and the electronegativity of the carboxyl group is taken to be 2.5 throughout. Hence $k_{sp^2 C-X}$ was estimated from the trifluoroamide as -29.63 ppm, and $k_{sp^2 C-H}$ was found to be -36.69 ppm by use of the monofluoroamide, $C-H$ (2, 1 = b = H) as a model. The chemical shifts of the amides were now recalculated using these parameters, with the results indicated in table 8.

It is seen from table 8 that the new calculation with the revised interaction constants provides a much better estimate of the fluorine chemical shifts for the series, and three of the observed shifts are within 4 ppm of their theoretical estimates. Probably the most important result is that the theory predicts that the difference between the chemical shift of the CF_3Cl_2- and CF_2Cl compounds is 1.22 ppm, which is in excellent agreement with the experimentally observed value of 1.35 ppm; and also that the latter compound should be to low field of the former, which again is in keeping with experiment.

It now becomes of interest to see if the method can be extended to the two amides containing non-halogen substituents, N,N-dimethyl fluorophenyl acetamide (3) (2, a = Ph, b = H), and N,N-dimethyl-2-fluoropropionamide (4), (2, a = Me, b = H). The former compound requires the derivation of two further interaction constants, that for interaction between the sp^2 carbon of the aromatic ring and the carbonyl group, $k_{sp^2 C - sp^2 C}$, and between the aromatic sp^2 carbon and hydrogen, $k_{sp^2 Car - H}$.

The first constant may be evaluated from the fluorine chemical shift of diphenyl difluoro methane (5) $Ph-CF_2-Ph$, which has³⁴ a chemical shift of 88.5 ppm and yields a value for $k_{sp^2 C-sp^2 C}$ of -26.17 ppm. The second constant was estimated from the fluorine chemical shift of benzyl fluoride³⁵ (-207 ppm) as $k_{sp^2 Car - H} = -26.17$ ppm.

Unfortunately, use of these constants, together with

Table 8. (a) Second Calculation of ^{19}F chemical shifts for the tertiary amides, using internally derived interaction constants.

Acetyl Group	ϕ_{calc}	ϕ_{obs}	$\phi_{\text{calc}} - \phi_{\text{obs}}$	$\phi_{\text{calc}} - 7\text{ppm}$ $\phi_{\text{calc}} - \phi_{\text{obs}}$	$\phi_{\text{calc}} - 3\text{ppm}$ $\phi_{\text{calc}} - \phi_{\text{obs}}$
CF_2Cl	-54.31	-58.21	3.9	-61.31 -3.10	-57.31 +0.9
CFCl_2	-53.09	-56.83	3.74	-60.09 -3.26	-56.09 +0.74
CHClF	-129.15	-142.16	13.01	-136.15 +6.01	- -
CHF_2	-120.97	-122.13	1.16	-127.97 +5.84	-123.97 -1.84
				RMS error = 4.75 ppm	RMS error = 1.26ppm

(a) all chemical shifts are in ppm to high field of CFCl_3

those derived above to calculate the chemical shift of 2 leads to a value of -139.11 ppm, some 34.63 ppm below the experimental value of -173.74 ppm. The reason for this apparent failure is the same as that for the initial shortcomings of the halogeno-amides, use of a poor model to derive the constant for the interaction between the sp^2 carbons of the aromatic ring and the carboxyl group. A better estimate of this parameter may be obtained from the fluorine chemical shift of amide (3), and may be checked by application in the other series of compounds. The value obtained is $k_{sp^2Car - sp^2COO} = -32.39$ ppm, which is considerably larger than the value of -26.17 ppm derived from (5) and reflects the differences between a carbonyl group and aromatic carbon.

Compound 3 requires the derivation of yet another constant for the interaction of the sp^3 carbon of the methyl group with the sp^2 carbon of the carbonyl group, $k_{sp^3C - sp^2C}$. It has not been possible to find a suitable model for this interaction, and if this were possible, by analogy with the other interaction constants derived from non-amide models, this procedure is expected to yield a poor estimate for the chemical shift. Thus, a value for this parameter was derived from the chemical shift of (3), $k_{sp^3C - sp^2C} = -32.98$ ppm, and its validity will be tested by application in the other series.

Further comment on the results presented in Table 8 will be deferred until a later section.

1.2.2.2 Fluorine chemical shifts of the primary amides.

Following the success of the calculations made for the tertiary amides through deriving the constants for interaction between the carbonyl moiety and halogen and hydrogen (k_{sp^2CO-X} and k_{sp^2CO-H} respectively), a similar approach was made for the primary amides, $-CONH_2$.

It is reasonable to allow for the differences between tertiary and primary amides in such a fashion, since the substituent

effects of N-methylation will be a through bond perturbation to the effective electronegativity of the carbonyl group, which will be allowed for in the slight modification of the interaction constants including this part of the molecule. The success of this approach will be reflected in the accuracy of the calculated chemical shifts. A detailed consideration of the individual substituent effects of N-methyl groups will be found in Chapter 2.

The values of the interaction constants obtained from the trifluoro- and monofluoroacetamides were $k_{sp^2CO-X} = -29.92$ ppm, and $k_{sp^2CO-H} = -36.29$ ppm, respectively. These together with those constants derived from the phenyl and methyl acetamides (3 & 4) in the previous section are now used to estimate the fluorine chemical shifts of the series of primary amides, and the results are given in table 9.

The increased number of compounds available (seven) in table 9 enables further checks to be made on the general applicability of calculations based on equation (15). It is seen that the method correctly predicts that the mixed chloro-fluoro amides (entries 1 & 2 of table 9) should resonate to low field of the trifluoro-compound ($\phi = -76.56$ ppm), and the calculated shifts of the methyl and phenyl derivatives (entries 6 & 7, table 9) are within 4 ppm of their observed values, which confirms the validity of the appropriate interaction constants derived from the tertiary amides.

Although the calculations indicate that the mixed chloro-fluoro amides should have comparable shifts, it is predicted that the CF_2Cl - compound should resonate 2.13 ppm to high field of the $CFCl_2$ analogue, whilst experimentally the converse relationship is found, with the former being 0.66 ppm to low field of the latter. The origin of this discrepancy could be in the assumption that all the halogen interaction constants are equal, and if the nature and hence value of those interactions involving chlorine were slightly different from those for fluorine, then the calculated shifts would be in error. It is interesting to note that such a discrepancy was not found for the NN-dimethylamides, which meant that these differences may be structurally dependent. However, since the

Table 9(a) Calculated fluorine chemical shifts of primary amides.

Acetyl group	ϕ_{calc}	ϕ_{obs}	$\phi_{\text{calc}} - \phi_{\text{obs}}$	$\phi_{\text{calc}} - 8\text{ppm}$ $\phi_{\text{calc}} - \phi_{\text{obs}}$	$\phi_{\text{calc}} - 6\text{ppm}$ $\phi_{\text{calc}} - \phi_{\text{obs}}$
CF ₂ Cl	-60.31	-64.74	4.74	-68.31 -3.57	-66.31 -1.57
CFC1 ₂	-58.18	-65.40	7.22	-66.18 -0.78	-64.18 1.22
CHF ₂	-122.09	-126.35	4.26	-130.09 -3.74	-128.09 -1.84
CHClF	-129.63	-142.95	13.62	-137.63 5.62	-(135.63 7.62)
CHBrF	-131.62	-147.05	15.43	-139.62 7.43	-(137.62 9.43)
MeCHF	-176.22	-180.27	4.05	-184.22 -3.95	-182.22 -1.95
PhCHF	-171.37	-175.43	4.06	-179.37 -3.94	-177.37 -1.94

(a) all chemical shifts to high
field of CFC1₃

RMS error = 4.55ppm
less HClF, HBrF,
RMS error = 3.41ppm

RMS error = 1.73ppm

calculations are only expected to predict the chemical shifts to ca. 3 ppm, it is felt that these differences are not very important.

Further discussion of the data in table 9 will be withheld until the method has been applied to the series of esters, when all the errors involved in this calculational approach will be considered.

1.2.2.3 Fluorine chemical shifts of some esters.

In keeping with the general method used for both series of amides, the constants for the interaction of halogen or hydrogen with the carboxyl group were estimated from the trifluoro- and mono-fluoro-ethyl esters, and were found to be $k_{sp^2CO-X} = -29.93\text{ppm}$ and $k_{sp^2CO-H} = -36.98\text{ ppm}$. Unfortunately, a full series of methyl or ethyl esters was not obtainable, but the data (Table 6) available for compounds where it was possible to prepare both indicate that the difference in the fluorine chemical shift between a methyl or ethyl ester is very small (ca. 0.3 ppm) and consequently the effects of different ester groups will not have a significant influence upon the validity of the calculated chemical shifts. The calculated shifts are given in table 10.

The data in table 10 support the general observations made for the primary amides. Again the calculations predict the mixed chlorofluoro esters should resonate to low field of the trifluoro compound ($\phi = -75.73\text{ppm}$), and the interaction constants derived for the methyl and phenyl substituted esters provide very reasonable estimates of the observed chemical shifts.

1.2.2.4. Errors in the calculational approach.

A survey of the calculated chemical shifts for the amides and esters, presented as table 8 - 10, reveals that in every case, the calculated value is to low field of the observed shift, by typically 3 - 8 ppm. This may be expressed alternatively via the

Table 10. Calculated fluorine chemical shifts of some esters.

Acetyl group	ϕ calc.	ϕ obs.	ϕ calc. - ϕ obs.	ϕ - 8ppm ϕ calc.	ϕ calc. - ϕ obs.	ϕ - 6ppm ϕ calc.	ϕ calc. - ϕ obs.
CF ₂ Cl	-59.61	-64.36	4.75	-67.61	3.25	-66.61	-1.25
CFC1 ₂	-57.53	-64.90	7.37	-65.53	0.63	-63.53	1.37
CHBrF	-135.11	-151.08	15.97	-142.11	8.99	(-141.11	9.97)
CHClF	~~-133.11~~	-146.91	13.80	-141.11	5.80	(-139.11	13.80)
CHF ₂	-125.49	-126.87	1.38	-138.49	-6.62	-131.49	-4.64
MeCHF	-180.01	-184.82	4.81	-188.01	-6.62	-186.01	-1.19
PhCHF	-175.16	-180.38	5.22	-183.16	-2.78	-181.16	-0.78

RMS error = 5.16 ppm

RMS error = 1.21 ppm

(less HClF, HBrF)

conclusion that equation (15) is underestimating the fluorine chemical shifts from CFCl_3 . It is possible to re-write this equation as:

$$\begin{aligned} \Delta_{\text{CefgF}}^{\text{CFCl}_3} &= k^{\text{CFCl}_3} - 154.12(E_e + E_f + E_g) - k_{\text{ef}}E_eE_f \\ &\quad - k_{\text{eg}}E_eE_g - k_{\text{fg}}E_fE_g \quad \dots(19) \end{aligned}$$

where $k^{\text{CFCl}_3} = 154.12 \times 9.45 - 29.76k^{\text{XX}}$

k^{CFCl_3} is the correction term in equation (19) to enable the calculated shifts to be referenced from CFCl_3 , and it seems reasonable to propose that this is the cause of the errors in the calculated chemical shifts. Either of the terms contributing to k^{CFCl_3} may be responsible for the nett underestimation of this constant, and since these were derived empirically¹⁷ from a variety of chemical shifts probably recorded under different conditions, the most likely source of these errors would be in the different referencing procedures involved. If this error is allowed for by addition of a "correction term" of 7 ppm in table 8 and 8 ppm in tables 9 and 10, the resultant errors in the calculated chemical shifts reduce to an RMS deviation of ca. 5 ppm, which is very good over a range of chemical shifts exceeding 110 ppm, when the numerous approximations used in the calculations are taken into consideration.

It will be seen from tables 8 - 10 that two of the compounds persistently show greater deviation (12 - 15 ppm) from the calculated shift than the other, for which the range of error is 2 - 7 ppm. The compounds in question are the CHClF - and CHBrF -series, and the calculation of their chemical shifts involves the use of interaction constants for H with Cl and H with Br. One of the assumptions¹⁷ made in developing equations such as (15) was that all HX (hydrogen-halogen) interaction constants are equal. Since this feature is the major structural difference between these compounds and the others, it seems reasonable to presume this is the source of the increased error in the calculated shift, i.e. k_{HCl} and k_{HBr} are not equal to k_{HF} . Such differences were observed by Phillips and Wray in a later paper²¹ in their series, which was concerned (in part) with geminal effects upon proton

shielding, and it is logical to presume these differences will also have an influence in the realm of fluorine chemical shielding.

If these two compounds are now eliminated from the tables, it is seen that the magnitude of the "correction term" may be reduced to 6 ppm, whereupon the RMS error of the calculated shifts is less than 2 ppm (see cols. 7 & 8 of tables 8 - 10). This error is now in keeping with those found¹⁷ by Phillips and Wray in their original work with single atom substituents (or small groups such as CH_3 -) and indicates that the theory is correctly predicting the nature and magnitude of all the relevant interactions in the three series of carboxylic acid derivatives discussed above.

Therefore, it may be concluded that the equations derived for the aliphatic fluorides can be extended to the carboxylic acid derivatives providing that suitable compounds are chosen which model the interactions with the carbonyl group closely. Such a necessity is a limitation of the calculational approach, and is illustrated well by the initial failure with the tertiary amides (table 7) where the required parameters were derived from suitable model compounds independent of the data under examination. The need to derive separate specific values for the interaction of H or F with the sp^2 carbonyl carbon for each series indicates that equation (18) is sensitive to small changes in the magnitude of parameters used, and this again is a source of weakness.

1.2.3. Long Range F-H coupling.

1.2.3.1. Fluorine - NH coupling.

A fluorine NMR spectrum of monofluoroacetamide reveals besides the expected triplet from the geminal coupling in the CH_2F - group, a further doublet splitting, which is removed upon complete deuteration (Spectrum in D_2O), and hence must arise from one of the NH protons, the coupling from the other being too small to resolve (0.3 Hz). Consideration of this interaction indicates the fluorine nucleus is the X part of an ABM_2^X spectrum, with a major triplet splitting from the acetyl protons (M_2) and AB are assigned to the NH protons. If the sample temperature is increased, the rate of rotation about the C(=O)-N partial double bond increases

from the slow exchange condition of ambient probe temperature (31°C) such that the $-\text{NH}_2$ protons eventually become equivalent. The changes induced in the fluorine spectrum (X part) for this process of intramolecular exchange are as predicted by the work of Forsen,³⁶ and the nature of the line shape obtained for conditions of intermediate exchange may be used to estimate the thermodynamic parameters for activation of the rotation. Full details of this work have been published, and are included as an Appendix. It is to be concluded that this technique provides a convenient method of measuring the barriers to rotation in primary amides, $(-\text{CONH}_2)$, which would otherwise require either ^{14}N irradiation to remove quadrupolar broadening,³⁷ or ^{15}N enrichment^{38,39} ($I = \frac{1}{2}$), before data could be obtained from a high resolution proton spectrum.

The question that now arises is "to which $-\text{NH}$ proton is the fluorine nucleus stereospecifically coupled?" This problem may be resolved by a comparison of the splitting patterns produced by the long range fluorine-proton couplings in the primary and secondary amides, $-\text{CONH}_2$ and $-\text{CONHMe}$, and Table 2 lists these values, where measurable, for all the amides, taken from the fluorine spectra in chloroform. For two of the amides, (difluoro- and difluorochloroacetamide), the values of the fluorine-NH and fluorine- NCH_3 couplings were such that no fine structure could be measured from the spectrum due to the extensive overlap of the lines.

It will be seen from table 11 that, (with the exceptions noted), it was possible to measure a four-bond coupling from fluorine to an NH proton for both the $-\text{NH}_2$ and NHMe derivatives of each amide, and that the magnitude of this coupling was very similar for each pair of amides.

It is now well established⁴⁰ that the secondary amides exist entirely as the *Z* conformational isomer, with the N methyl group disposed syn to the carbonyl group:

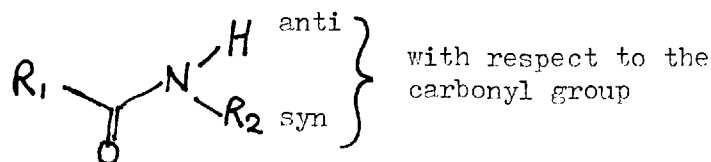


Table 11. Long Range Fluorine-Proton Coupling Constants in some
 α -Fluoroamides, $C_{XYF}.CO.NHR$ (Hz).

All data from ^{19}F spectra in $CHCl_3$ solution.

Acetyl group C_{XYF}	R = H	R = CH_3	
	$^4J_{F-NH}$	$^4J_{F-NH}$	$^5J_{F-NCH_3}$
CH_2F-	3.6	3.0	0.5
Me. $CHF-$	4.5	4.2	0.75
Ph. $CHF-$	3.0	3.5	-
$CHBrF-$	2.2	2.2	0.6
$CHClF-$	2.1	2.3	0.7
CHF_2-	1.0	$\frac{1}{2} = 4.1Hz$	
$CFCl_2-$	$\frac{1}{2} = 1.5Hz$	1.5	0.5
CF_2Cl-	0.9	$\frac{1}{2} = 3.0 Hz$	
CF_3-	1.1	1.2	0.6

The similarity of the four bond coupling constant for each pair of primary and secondary amides (Table 11) is strong circumstantial evidence that the same -NH proton is involved in the coupling mechanism in each case, and it may be concluded from the structural evidence that this must be the proton anti to the carbonyl group.

It is interesting to compare these results with previous studies of amides to be found in the literature. Akiyama et al. have studied⁴¹ the fluorine spectra of both trifluoroacetamide and its N methyl derivative in some polar solvents. The spectra of the former contained a four-bond fluorine-NH coupling constant of 1.8 Hz (in either tetrahydrofuran (THF) or $^2\text{H}_6$ -acetone solution), whilst the latter compound had a similar coupling constant of 1.1 Hz (dioxan solution). These workers also studied the proton spectrum of trifluoroacetamide in THF at -80° , under which conditions the intramolecular rotation was slow, and separate signals could be resolved for the two NH protons. Despite the poor quality of the reproduced spectra, they were able to conclude from line width measurements that the high field proton was coupled significantly to the fluorine nuclei, whilst that to low field was not. No actual splittings were detected. However, they were able to tentatively assign the upfield proton coupled to fluorine to that syn to the carbonyl group. This was based on an early study⁴² of the anisotropy of the carbonyl group, by Narasimhan and Rogers, which assumes that the shielding constants for N-substituents in dimethylformamide and formamide are comparable. Akiyama et al. seem to miss the significance of observing a fluorine-NH coupling in N-methyl trifluoroacetamide, and were unable to make a firm conclusion as to the stereospecificity of the four bond H-F coupling.

However, they were able to do this in a later study⁴³ by a proton NMR investigation of ^{15}N -trifluoroacetamide. The NH protons are now readily observable as a pair of doublets (due to ^{15}N spin-coupling, $I = \frac{1}{2}$). It was found that the components of the high field doublet exhibit a quartet splitting arising

from coupling with the trifluoromethyl group ($^4J_{\text{FH}} = 1.8 \text{ Hz}$ in methyl propyl ketone), whilst fluorine coupling to the low field signal was found to be negligible. It appears that the high field signal is assigned to that proton syn to the carbonyl group, i.e. the authors imply that the stereochemistry of the F-NH coupling is opposite to that found in the present work.

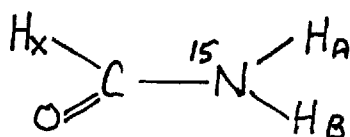
The cause of this discrepancy arises from a misunderstanding of the shielding properties of the amide group as a unit, as was hinted at above. This problem has been studied⁴⁴ in some detail by Paulsen and Todt, who have developed a model for the shielding influences of the amide group. Their results have been summarised in a recent review.⁴⁰ Qualitatively, the results obtained are similar to those for the carbonyl group, viz. protons in the plane of the carbonyl group are deshielded relative to those out of the plane, and the region of shielding/deshielding is strongest for positions syn to the carbonyl, i.e. nearest to the oxygen atom.

This model of the amide group's shielding characteristics may now be applied to the primary and tertiary amides under consideration here. The N-CH₃ group is out of the plane of the carbonyl function. Consequently, these protons are in a region of shielding; this effect will be stronger for the N-CH₃ group syn to the oxygen, and hence this group resonates to high field of the anti N-Me group. For the primary amides, (C(O)NH₂) the -NH₂ protons are in the plane of the amide group, arising from the rapid inversion of the nitrogen atom, and it is seen that the opposite conclusions now apply to those made for the N,N-dimethyl amides. Thus, the -NH proton syn to carbonyl is strongly deshielded relative to the anti proton and is expected to resonate to LOW field of the signal for the latter.

It is now apparent that the dichotomy between the assignments of Akiyama et al. and the conclusions reached over the identification of the -NH proton coupled to the CF₃- group above arise from a misunderstanding of the nature of the shielding properties of the amide group by the former worker. Reversal of his assignments to those in keeping with the Paulsen and Todt

model provides good confirmation that the long range fluorine-NH coupling is to the anti NH proton; as deduced from a consideration of the fluorine spectra of the primary and secondary amides ($-\text{CONH}_2$ and $-\text{CONHMe}$) in the present work.

This mis-assignment of the amido protons seems to have been initiated by Sunners and co-workers⁴⁵ from a consideration of the pattern of coupling constants observed for some isotopically substituted formamides:



They assumed that the partial double bond of the amide unit was directly comparable to the full double bond of an olefin, and based their assignments of the A and B protons on the assumption that trans coupling constants are always greater than cis couplings. Thus in the proton NMR of α - $^2\text{H}_1$ -formamide ($\text{H}_X = \text{D}$) they observed that the high field -NH proton was coupled to deuterium ($I = 1$, $J = 2.1$ Hz) whilst the low field signal was not, and hence assigned the high field signal to H_B , i.e. syn to carbonyl. It is seen that this is contrary to the Paulsen and Todt model, and that the proton coupled to deuterium should be assigned to that anti to the carbonyl group, H_A .

This erroneous pattern of assignments for amido protons has persisted in the literature until comparatively recently^{38,39,46} and there is only one report⁴⁷ where these protons have been identified correctly, in a multiple resonance study of $[\text{}^{14}\text{N}]$ -formamide.

It has now been demonstrated conclusively that the long range fluorine-NH coupling is to the anti NH proton, which is in a cisoid bond configuration, whilst that to the syn NH proton (transoid coupling) is unresolvable (i.e. less than 0.3 Hz). The coupling is over three single and one partial double bond (the $\text{C}(\text{O})-\text{N}$ bond) and may be considered to be of the allylic type. Allylic H-H

couplings⁴⁸ are usually greater for cisoid than transoid couplings in propenes, but this relationship may be reversed in other systems. However, the differences between the cisoid and transoid couplings observed here are much greater than those usually found for allylic couplings, and this marked discrepancy must reflect the difference in double bond order and the presence of a heteroatom in the coupling pathway.

Inspection of table 11 shows that the magnitude of the long range H-F coupling constant appears to depend on the nature of the acetyl group substituents, and table 12 lists further values of this coupling, which were obtained from the ¹⁹F spectra recorded in conjunction with the deuterium isotope study (Chapter 2). To investigate the dependence, the values of ⁴J_{HF} were plotted against the sum of the Huggins electronegativities of the acetyl group substituents, $\sum E$, with the results shown in figure 5.

Such a plot is shown in figure 5(a), but it is seen that ⁴J_{HF} does not appear to be linearly related to $\sum E$. Thus, the coupling constant decreases in a reasonably linear fashion with increasing electronegativity of substituents, for compounds where $\sum E$ is less than 10 (-CHF₂). In contrast, for the more electronegative compounds (-CFCl₂, -CF₂Cl and CF₃), the observed coupling constant appears to increase with increasing electronegativity at the acetyl carbon. However, if the sign of the coupling constant for these latter three compounds is assumed to be opposite to that of those for which $\sum E$ is less than or equal to 10, and the data replotted as figure 5(b), it is seen that the coupling constant now becomes a linear function of $\sum E$, the sum of the substituent electronegativities at the acetyl carbon, and this relationship is obeyed for all the compounds in each solvent.

It is seen (table 11 and 12) that there are variations of up to 1.2 Hz in the values of ⁴J_{HF} over the four solvents for any one compound, with the observations of smaller numerical values for the less polar CH₂Cl₂ and CHCl₃, and larger values for the polar CH₃OH and DMF solvents. This solvent dependent nature may arise from the solute-solvent interactions, probably via hydrogen bonding at either or both of the carbonyl oxygen and

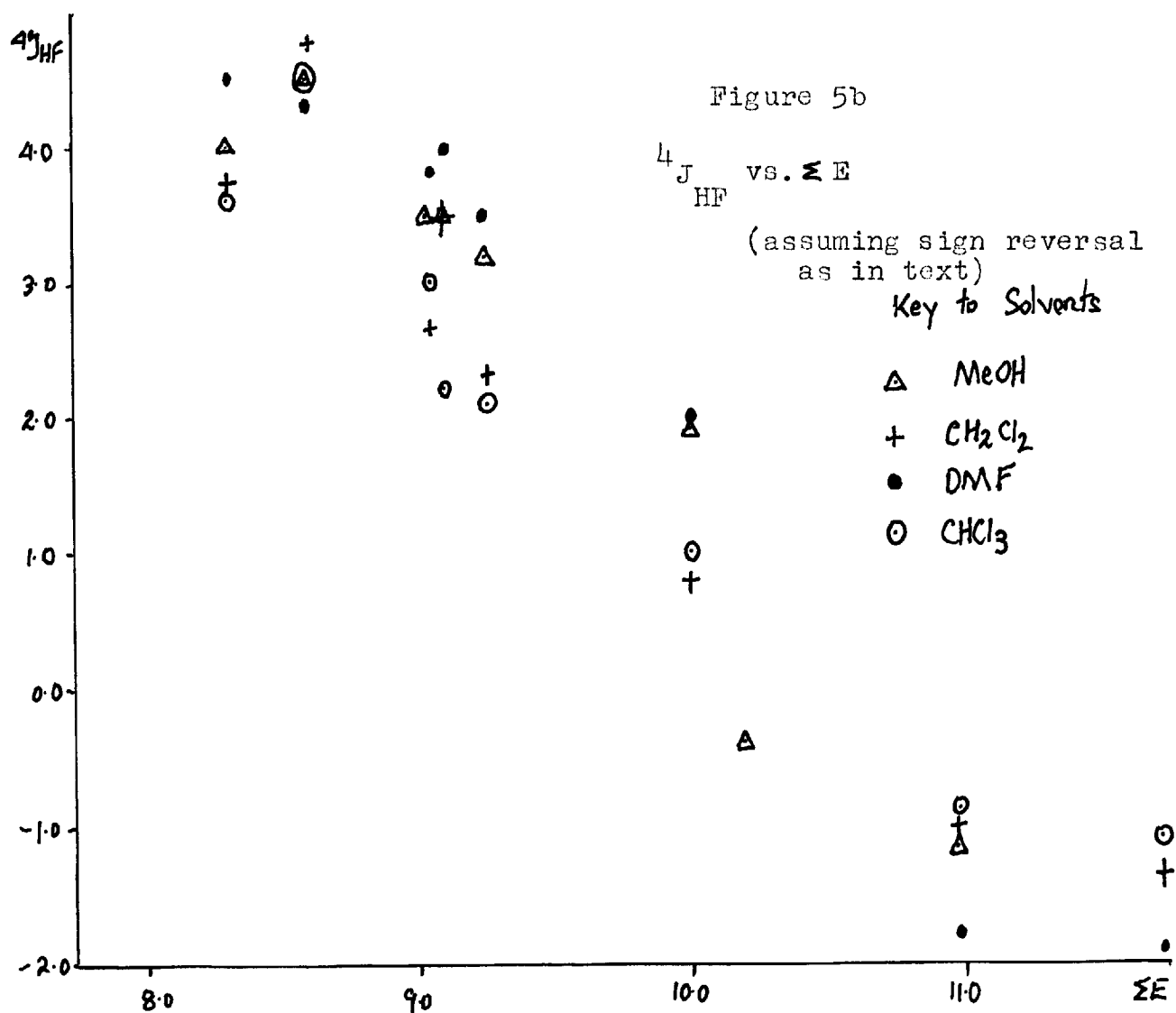
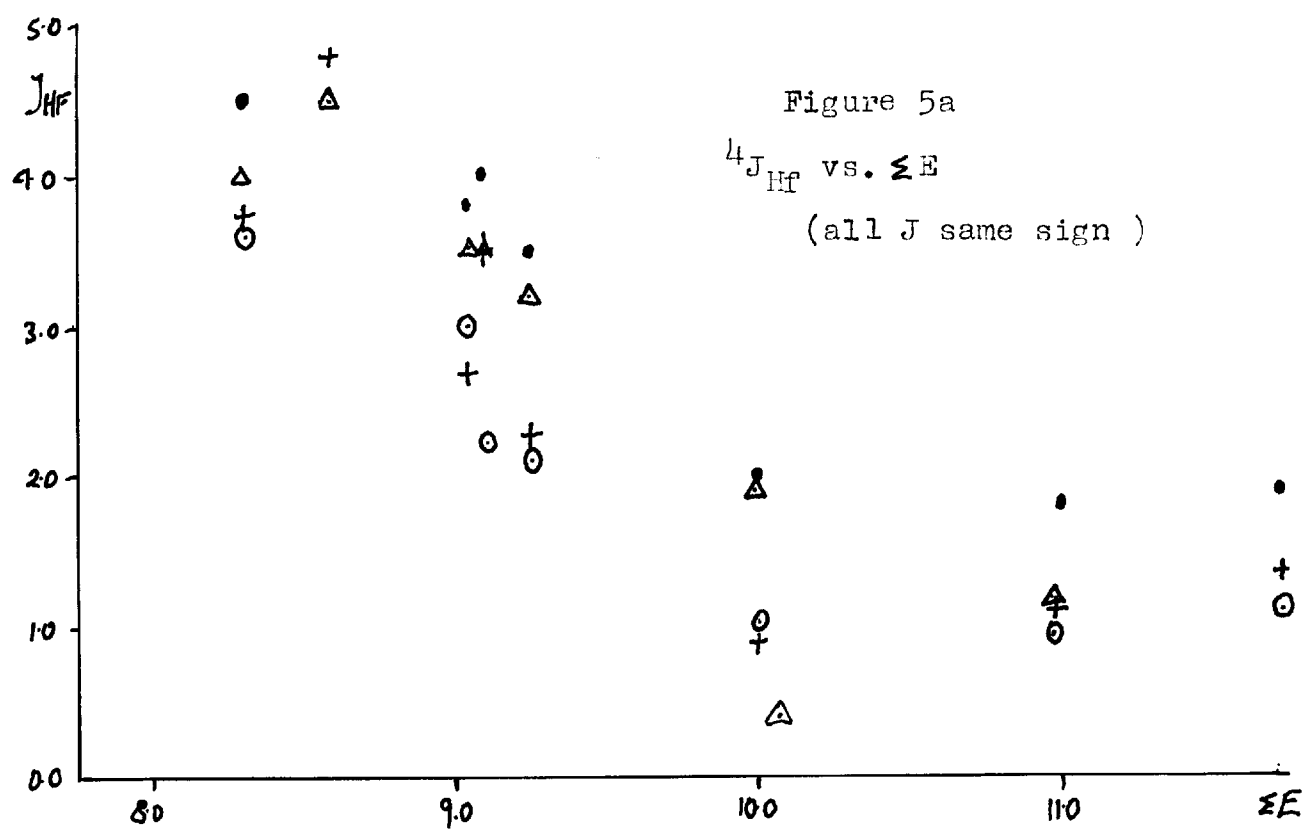


Table 12 Further values of the "allylic" coupling $^4J_{FH}$ in some α -fluoroacetamides. $C_{XYF}.CO.NH_2$.

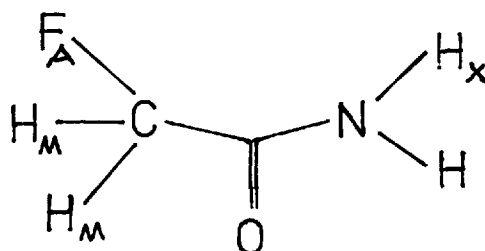
acetyl group	ΣE	observed coupling constant (Hz)		
		MeOH	CH_2Cl_2	DMF
H ₂ FC-	8.3	4.0	3.75	4.5
MeHFC-	8.7	4.5	4.8	4.3
BrHFC-	9.05	3.5	2.65	3.8
PhHFC	9.1	3.5	3.5	4.0
ClHFC-	9.25	3.2	2.3	3.5
F ₂ HC-	10.00	1.9	0.8	2.0
FC1 ₂ C-	10.20	0.4	(a)	(a)
F ₂ ClC-	10.95	1.2	1.1	1.8
F ₃ C-	11.7	s (b)	1.35	1.9

(a) not recorded

(b) singlet: fast exchange.

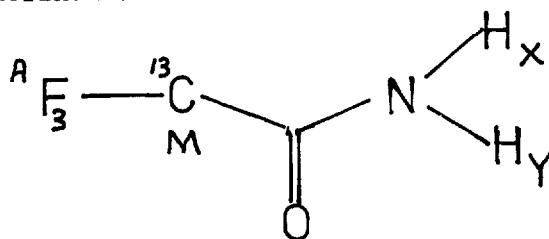
-NH₂ sites, which perturb the effective electron distribution in the C(O)-N bond and hence modify the coupling constant.

Although inter-proton allylic couplings are usually⁴⁸ negative in sign, and since the possibility of a change of sign of $^4J_{HF}$ has been proposed above, it would be very satisfying to determine this sign, and hence check the validity of such a proposal experimentally. It would be necessary to determine this sign for two compounds at either end of the range before this hypothesis could be confirmed. The first case to be considered would be monofluoroacetamide, which is an example of an AM₂X spectrum as indicated.



Theoretically,⁴⁹ the signs of J_{AM} and J_{AX} could be related by observing M whilst irradiating X, and since the geminal H-F coupling constant is known⁵⁰ to be positive, (J_{AM}) the sign of $^4J_{F-NH}$, J_{AX} would be determined. However, this requires the resolution of the small coupling J_{MX} (ca. 0.5 Hz, which has been measured as a line broadening of the M transitions), but would also require decoupling of the ¹⁴N quadrupole, before the proton irradiation could be performed. Such facilities are not possible with the available instrumentation, and hence the experiment could not be performed.

For trifluoroacetamide, there is no geminal H-F coupling to use as a reference sign, so an alternative approach must be found. Use could be made of the couplings to the acetyl carbon, C_M, if the amide were defined as:



Since the directly bonded C-F coupling is known⁵¹ to be negative, irradiation of X whilst observing M would relate J_{AM} (of known sign)

to J_{AX} (wanted). Unfortunately, this experiment fails on two points: initially the ^{14}N decoupling is again required, and secondly, H_X does not couple appreciably with C_M , but a vicinal coupling is observable between C_M and H_Y , as will be discussed in Chapter 3. Any relation of H_X and H_Y would also require ^{14}N decoupling facilities, and so once again it was not possible to undertake the required experiments.

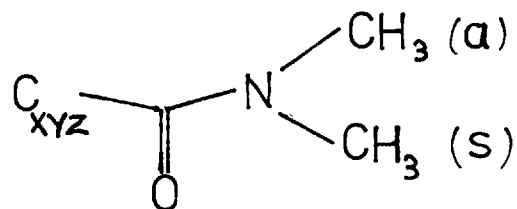
1.2.3.2. Fluorine-N Methyl Coupling.

The proton and fluorine spectra of the N-methyl and N,N dimethylamides show long range (5 bond) coupling between the fluorine and N-methyl groups. Table 13 gives the values of these couplings observed in the proton spectra of the tertiary amides in CFCl_3 solution under conditions of slow exchange.

The assignments of the methyl groups are made according to the Paulsen and Todt model⁴⁴ discussed above, i.e. the methyl group syn to the carbonyl oxygen will be more strongly shielded than its anti neighbour, and hence resonate to high field of it, and the data in table 13 have been listed accordingly. It is observed in all cases, that the anti methyl group has the stronger coupling to the fluorine, i.e. cisoid coupling pathway is more efficient than the transoid one. This conclusion is supported by the values of the fluorine-N methyl coupling observed for the secondary amides (-CONHMe), which are comparable to those of the syn methyl group. These couplings were generally observed in CCl_4 or CDCl_3 solution, and since it was not possible to record the tertiary amide data under similar conditions (due to the low temperature required), the data has been omitted for clarity.

The five bond coupling constant (across four single bonds and one partial double bond) may be classified as being of the homoallylic type, and if this is the case, then the sign of the coupling is expected^{48(a)} to be positive. Unfortunately, this information is not available here, but it has been shown⁵² that the couplings to the syn and anti methyl groups have the same relative sign. Thus, N,N-dimethyltrifluoroacetamide was found to exhibit

Table 13. Proton NMR data for N-CH₃ groups of some tertiary acetamides, CXYF.CO.NMe₂ in CFC1₃ solution.



-C _{XYF} group	Temp. of observation	-NMe chem. shift (δ)		Δν Hz	F-NMe coupling (Hz)	
		CH ₃ (a)	CH ₃ (s)		CH ₃ (a)	CH ₃ (s)
H ₂ FC-	0	2.996	2.890	9.6	2.0	1.0
MeHFC-	-10	3.079	2.904	17.5	2.4	1.6
HClFC-	-20	3.154	2.955	19.9	2.0	0.95
F ₂ HC-	-20	3.120	2.939	18.1	1.6	1.1
FC1 ₂ C-	-40	3.245	3.044	20.2	1.9	0.7
F ₂ C1C-	-50	3.186	3.026	16.0	1.65	0.7
F ₃ C-	-20	3.122	3.006	11.6	1.5	0.8

fluorine couplings of 1.6 and 0.8 Hz under conditions of slow exchange (35° , 1,1,2,2-tetrachloroethane), whilst the coupling recorded for fast exchange conditions (130°) was 1.2 Hz. Since the latter value of the coupling constant is the numerical average of the two former, then the couplings must be of like sign.

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Chapter Two.

Isotope effects in

Fluorine-19 NMR.

2.1 Introduction.

Substitution of an atom in a molecule by an isotope produces effects in the neighbouring molecular framework which can be examined by high resolution NMR spectroscopy.

The parameter most readily detected as a result of an isotopic substitution of another atom is a small change in the chemical shift of an observed nucleus, known as the isotopic shift. This was first reported by Wimett¹ in 1953 for a study on hydrogen gas:-

$$\sigma(\text{HD}) - \sigma(\text{H}_2) = 0.048 \pm 0.032 \text{ ppm.}$$

Shifts arising from heavy isotopic substitution have generally been observed as occurring to high field, i.e. the substituted derivative is more shielded, with a few exceptions which are discussed later.

The occurrence of isotope shifts is not restricted to observation of the hydrogen nucleus, but is a general one throughout the fields of organic chemistry and NMR. In 1958 Tiers reported² that mono deuteration of toluene produced an upfield isotopic shift for the methyl group of 0.015 ppm. At much the same time, the scope of isotope effects was extended into fluorine NMR with a report (also from Tiers³) of a large isotopic shift for the terminal CF_2 group in 1-H-perfluoropropane

$$\phi(\text{C}_2\text{F}_5 \cdot \text{CF}_2\text{D}) - \phi(\text{C}_2\text{F}_5 \cdot \text{CF}_2\text{H}) = 0.60 \pm 0.05 \text{ ppm.}$$

It is seen that the magnitude of the shift is much larger for fluorine resonance, possibly reflecting the importance of the paramagnetic contribution to nuclear shielding for nuclei other than hydrogen (where p electrons are absent and hence this factor is small).

Since this early work, isotope effects have been studied extensively, with both proton and fluorine magnetic resonance;⁴ more recently carbon-13,⁵ nitrogen-15,⁶ phosphorus-31⁷ and cobalt-59⁸ magnetic resonance have also been utilized as probes in the study of isotope effects.

Much of the reported data are concerned with the substitution of deuterium for hydrogen, but a considerable volume of information⁴ exists on the effects of substituting ^{13}C for ^{12}C in organo-fluorine compounds, in which the fluorine nucleus has proved a sensitive probe to such changes. The ^{13}C isotope shift on the ^{19}F resonance is typified by perfluoromethane (CF_4) at 0.118 ppm.⁹ Isotope shifts of fluorine resonances by Si, S and Se isotopes have been examined, and the effects of ^{13}C and ^{15}N substitution in the cyano ligand of $\text{K}_3\text{Co}(\text{CN})_6$ were found⁸ to induce isotopic shifts in the ^{59}Co magnetic resonance spectrum.

The vast majority of isotope shifts observed have been for one bond interactions (primary isotope effect) e.g. ^{13}C - ^{19}F or for "nearest neighbours" (secondary isotope effects) over two or more bonds, e.g. ^1H - C - D , ^{13}C - ^{12}C - ^{19}F , ^{15}N - ^{12}C - ^{59}Co and D_3 - C - $^{13}\text{C}(\text{D})\text{CD}_3$. A general conclusion from the reported data is that the magnitude of the isotope shift is dependent on how remote the isotope is from the nucleus under investigation. The largest effects are detected closest to the site of isotopic substitution, with rapid attenuation by an increasing number of intervening bonds, between the two nuclei. The ^{13}C isotope shifts for the fluorine absorption of the fluoromethyl groups in perfluoropropane provide a typical example:-¹⁰

$$\Delta\phi \text{ } ^{13}\text{C}-\text{F} = 0.135 \text{ ppm}; \Delta\phi \text{ } ^{13}\text{C}-^{12}\text{C}-\text{F} = 0.020 \text{ ppm}.$$

Lambert and Greifenstein recently found¹¹ that the geminal deuterium effect in equatorial 1-fluorocyclohexane was 0.81 ppm, whilst a 2-deutero substituent caused an isotopic shift of only 0.14 ppm.

The majority of carbon NMR data has appeared only recently,^{12,13} with studies on deuterated solvents, and that for monodeutero benzene serves as a typical illustration¹⁴ to the size of detectable effects:-

$$\begin{aligned} \Delta\delta_{\text{C}_1-\text{D}} &= 0.289 \text{ ppm}; \Delta\delta_{\text{C}_2-\text{C}-\text{D}} = 0.110 \text{ ppm} \\ \Delta\delta_{\text{C}_3-\text{C}-\text{CD}} &= 0.011 \text{ ppm}; J_{\text{C}_3-\text{D}} = 1.14 \text{ Hz}. \end{aligned}$$

This and other data will be discussed in more detail later (q.v.).

The magnitude of the observed isotope shift is also a function

of the observed nucleus. The geminal deuterium isotope effect for proton resonance is illustrated¹⁵ by CH_3D at 0.019 ppm, and for fluorine resonance a value of 0.60 ppm was noted³ for the geminal isotope effect in 1- $[\text{}^2\text{H}_1]$ -perfluoropropane. For comparison, the ^{13}C chemical shift for C_1 in 1- $[\text{}^2\text{H}_1]$ -heptane exhibits¹⁶ an upfield isotope effect of 0.28 ppm, and no isotope effects could be detected further down the carbon chain, in contrast to the monodeuterobenzene data.

Deuterium isotope effects in phosphorus NMR appear to depend on its oxidation state, with the trivalent (three coordinate) species having shifts ca. three times greater than the pentavalent (four coordinate) variety.⁷ Typical values would be:-

$$\begin{aligned}\Delta\delta_{31\text{P}}(\text{Pr}_2^{\text{I}}\text{PD}-\text{Pr}_2^{\text{I}}\text{PH}) &= 1.30 \text{ ppm (P}^{\text{III}}\text{)} \\ \Delta\delta_{31\text{P}}(\text{HDPOOH} - \text{H}_2\text{POOH}) &= 0.39 \text{ ppm (P}^{\text{V}}\text{)}\end{aligned}$$

Finally, the partially deuterated nitrogen-15 ammonia derivatives provide an interesting opportunity to study deuterium isotope effects on two nuclei within the same molecule. Mono-deuteration produces an isotopic shift of 0.029 ppm on a geminal proton,¹⁵ whilst the analogous ^{15}N shift was observed⁶ to be 0.68 ppm. The larger value of the latter shift compared with the former reflects the increased importance of a one bond over a two bond interaction.

Isotope shifts have been observed to be generally additive in nature, whether proton, fluorine or cobalt be the nucleus of interest. Such additivities are not restricted to one bond and geminal effects, and can be extended to vicinal effects and combinations of these parameters. The additivity of the deuterium isotope effects on fluorine resonance in fluoroethylenes provide¹⁷ a good example. The observed isotope shift of the fluorine nuclei in cis difluorodideuteroethylene at 0.920 ppm is in good agreement with that predicted as a combination of a geminal (0.502 ppm) and vicinal (0.418 ppm) contribution to the isotopic shielding of each nucleus. Lauterbur obtained⁸ an almost linear increase in the isotopic shielding of the ^{59}Co resonance with incremental addition of ^{13}C or ^{15}N containing ligands in the $\text{K}_3\text{Co}(\text{CN})_6$ complex. With carbon NMR, the isotopic

shift observed²⁰ with C_6D_6 (0.530 ± 0.005 ppm) is equal to the sum of the effects of nearest neighbour, ortho and meta interactions deduced¹⁴ from the monodeuterobenzene ($0.289 + 2 \times 0.0110 + 2 \times 0.011$) = 0.531 ppm. Additivity relationships have also been noted in phosphorus and nitrogen-15 nmr.

Another general conclusion which has been found is that the largest isotope effects can be expected where the fractional change in mass is highest. Thus the effects of deuterium substitution (D:H = 100% increase in mass) are always considerably larger than for other isotopic substitutions. The maximum value of ^{12}C - ^{13}C isotope shifts reported for fluorine resonance¹⁸ are 0.194 ppm for CFCl_3 , and for proton resonance⁹ is 0.007 ppm in $\text{CH}_2(\text{OMe})_2$; these values are to be compared with the much larger values obtained from deuterium substitution given above.

All of the data discussed above have been concerned with the isotope effects upon chemical shifts, which have been readily observable even at low field strengths. There are now an increasing number of reports of isotope effects upon coupling constants for a number of nuclei.

The possibility of a deuterium isotope effect on $^2J_{\text{HH}}$ was recognised during a study¹⁹ of magnetic non equivalence induced between the α protons of benzyl alcohol in the presence of a chiral shift reagent, (3-perfluoropropyl hydroxymethylene α -camphorato) $_3\text{Pr}^{\text{III}}$. Analysis of the AB spectrum yielded a value for the geminal coupling of 13.0 ± 0.2 Hz, whilst the value of $^2J_{\text{HD}}$ for the analogous deutero compound was 1.91 ± 0.01 Hz. Use of the relative gyromagnetic ratio ($\gamma_{\text{H}} : \gamma_{\text{D}} = 6.514$) to convert²⁰ the latter value to $^2J_{\text{HH}}$ leads to a "predicted" value of 12.45 Hz, the difference being outside the range of experimental error.

A possible origin for this effect could be that the geminal coupling derived from the "lanthanido-spread" spectrum could be modified by the coordination with the rare-earth complex. Such effects have been reported²¹ previously, and are considered to arise from differences in the conformational equilibria of the substrate between its free and complexed forms. This contribution was thought to be improbable in this case, since a constant value of $^2J_{\text{HH}}$ was obtained for relative concentrations of $[\text{Pr}]:[\text{alcohol}]$ up to 0.27M , but the coupling constant increased (i.e.

became less negative) with higher concentrations.

To investigate these findings more thoroughly, and to eliminate any of the above errors arising from the use of the lanthanide complex, a mixture of benzyl methyl sulphoxide and its mono-deutero derivative were studied in acetone. Identical values of the line width and H-D coupling at two temperature indicated the effects of quadrupole relaxation were nil. The observed geminal H-H coupling constant was 12.97 ± 0.02 Hz, whilst that derived from ${}^2J_{HD}$ (1.92 Hz) was 12.51 Hz; the difference of 0.46 Hz provided an accurate estimate of the primary deuterium isotope effect on geminal H-H coupling (3 - 5%). Since ${}^2J_{HH} < 0$, this discrepancy represents a positive contribution to coupling.

It is concluded that determination of geminal proton-proton coupling constants by isotopic substitution involves an inherent error, and it is hoped any future accurate measurements will utilise shift reagents wherever possible.

Several examples of heteronuclear couplings subject to isotope effects have been reported. Banwell and coworkers found²² a very small deuterium isotope effect on the geminal H-F coupling in CHF_3 , after a statistical treatment of over 40 spectra.

$$\text{for } \text{CHF}_3 : {}^2J_{HF} = 79.339 \pm 0.015 \text{ Hz}$$

$$\text{CDF}_3 : {}^2J_{HF} = 79.046 \pm 0.046 \text{ Hz (ex } {}^2J_{F-D})$$

$$\text{hence } J_{H-D} = 0.278 \pm 0.048 \text{ Hz}$$

Silyl fluoride was also studied and produced a similar very small decrease in the observed coupling constant:-

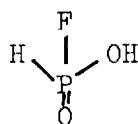
$$\text{SiH}_3\text{F} : {}^2J_{HF} = 45.764 \pm 0.015 \text{ Hz}$$

$$\text{SiD}_3\text{F} : {}^2J_{HF} = 45.611 \pm 0.050 \text{ Hz (ex } {}^2J_{F-D})$$

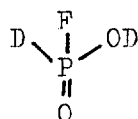
$$\text{hence } J_{H-D} = 0.153 \pm 0.052 \text{ Hz.}$$

These very small primary isotope effects do not seem very encouraging, particularly in view of the experimental difficulties, but a more recent report²³ by Murray offers more hope.

An equimolar mixture of trifluorosilane and its deuterated analogue ($\text{SiHF}_3/\text{SiDF}_3$) revealed $^2J_{\text{HF}} = 95.8 \text{ Hz}$ and $^2J_{\text{FD}} = 14.8 \text{ Hz}$. Conversion²⁰ of the latter value by the gyromagnetic ratio $\gamma_{\text{H}} : \gamma_{\text{D}}$ reveals a value for $^2J_{\text{HF}} = 96.41 \text{ Hz}$. Unfortunately the very large experimental errors ($\pm 2.0 \text{ Hz}$) preclude a comparison of these values, but more accurate data (to $\pm 0.2 \text{ Hz}$) obtained for fluorophosphorus acid do permit such an examination, where it was observed:



$$^2J_{\text{HF}} = 114.3 \pm 0.2 \text{ Hz}$$



$$^2J_{\text{DF}} = 17.3 \pm 0.2 \text{ Hz}; \quad ^2J_{\text{HF}} = 112.69 \pm 1.30 \text{ Hz}$$

revealing a possible decrease in the absolute value of the geminal coupling upon isotopic substitution of 1.6 Hz, but again this is comparable with the experimental error ($\pm 1.5 \text{ Hz}$).

However, this report²³ was centred on the numerically larger effects of the above deuterium substitution upon the one bond F-Si and F-P couplings, for which it was found:-

$$\delta. \quad ^1J_{\text{F-Si}} \quad (\text{HSiF}_3\text{-DSiF}_3) = 276.6 - 274.6 = 2.0 \text{ Hz}$$

$$\delta. \quad ^1J_{\text{F-P}} \quad (\text{H}_2\text{PO}_2\text{-D}_2\text{PO}_2\text{F}) = 1033.5 - 1030.0 = 3.5 \text{ Hz}$$

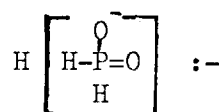
It is observed that the absolute value of the coupling constants are lowered by D substitution, although the two couplings $^1J_{\text{F-P}}$ & $^1J_{\text{F-Si}}$ are opposite in sign,²⁴ with the former negative and the latter positive.

However, these couplings may be compared better via their reduced coupling constants K , defined²⁵ by Pole and Santry as

$$K = \left(\frac{2\pi}{h\gamma_A \gamma_B} \right) J_{AB}$$

to eliminate nuclear effects, and since γ for ^{29}Si is negative ($I = -\frac{1}{2}$) the reduced coupling constants for both F-Si and P-F are negative, in keeping with theory.²⁵

During a general investigation on deuterium resonance spectroscopy, Diehl observed²⁶ a small decrease in $^1J_{\text{P-D}}$ for hypophosphorous acid,



$$^1J_{\text{P-D}} (\text{D}_2\text{PO}_2\text{H}) - ^1J_{\text{P-D}} (\text{HDPO}_2\text{H}) = -0.12 \pm 0.03 \text{ Hz}$$

Comparison of this reduction in coupling constant with that observed in the analogous proton study:-

$$^1J_{\text{P-H}} (\text{HDPO}_2\text{H}) - ^1J_{\text{P-H}} (\text{H}_2\text{PO}_2\text{H}) = -0.54 \pm 0.07 \text{ Hz}$$

indicates a similar effect, but the relative magnitudes of the changes are not in the ratio $\gamma_{\text{H}} : \gamma_{\text{D}}$.

Deuterium isotope effects on $^1J_{\text{PH}}$ have been the subject of a more extensive study,⁷ in some phosphorus compounds, where it was found that the sign of the effect depended on the coordination state of the central phosphorus atom. A primary isotope effect on $^1J_{\text{PH}}$ was determined by comparison of its value measured directly from ^1H spectra with that obtained by scaling $^1J_{\text{PD}}$ from ^2H spectra by the gyromagnetic ratio $\gamma_{\text{H}} : \gamma_{\text{D}}$. It was found that the isotope effect was a positive contribution to coupling for the three coordinate phosphorus, but negative for tetra coordinate species:-

$$^1J_{\text{PH}} (\text{C}_6\text{H}_5\text{PHD}) = 201.3 - 199.3 = +2.0 \pm 0.8 \text{ Hz}$$

$$^1J_{\text{PH}} (\text{HDPOOH} - \text{H}_2\text{POOH}) = 564.6 - 569.6 = -4.8 \pm 0.8 \text{ Hz}$$

The sign of the P-H coupling constant was proved to be positive in each system, and hence it would appear isotopic substitution must have different absolute effects in the two species.

A small secondary isotope effect on $^1J_{PH}$ was detected in these compounds by direct observation of $^1J_{PH}$ in the proton spectra. Again differences between the two coordination sites were noted:-

$$\begin{aligned} ^1J_{PH} (C_6H_5PHD - C_6H_5PH_2) &= 0.12 \text{ Hz} \\ ^1J_{PH} (HDPOOH - H_2POOH) &= -0.58 \text{ Hz} \end{aligned}$$

with the sign of the secondary isotope effect the same as that observed for the primary isotope effect. It is noted that the value of the secondary isotope effect recorded for hypophosphorous acid (-0.58 Hz) is comparable to that reported²⁶ by Diehl (-0.54 Hz).

Very few observations have been made on the effects of isotopic substitution on couplings to ^{13}C nuclei. In 1964 Diehl concluded²⁶ from a study of the directly bonded carbon-deuterium coupling constants in acetone, benzene and chloroform that there was no significant isotope effect on $^1J_{CH}$ for these compounds. The observed differences (< 1 Hz, after scaling by the gyromagnetic conversion factor γ_H/γ_D) were within the reported experimental errors. In support of these observations, a year later two groups of workers independently concluded^{27,28} from more accurate studies of α -deutero toluenes and analogous compounds that deuterium isotope effects on $^1J_{CH}$ were less than 1 Hz, and probably in the region 0.2 - 0.5 Hz, i.e. too small to measure by using ^{13}C satellite spectra and side-band calibration techniques. A recent study¹³ by Breitmaier *et al.* on deuterated solvents found an apparently significant deviation of $^1J_{CD}$ from that predicted by $^1J_{CH}$ of ca 1 Hz, but scrutiny of their results reveals that the major source of discrepancy probably arises from the relatively large error (± 0.6 Hz) in measuring $^1J_{CD}$. More accurate work^{12a} by Gold *et al.* supports the results of the early workers in that the deuterium isotope effects on $^1J_{CH}$ are of the order of 1 Hz or less, and within the range of experimental error.

It may be concluded that the majority of the above data relates to primary isotope effects on the coupling constant and geminal H-H coupling is noted to be the most sensitive (3.5%) to isotopic substitution. Proton couplings either directly to phosphorus or across it to fluorine are also relatively sensitive (1%) but $^2J_{HF}$ across silicon is approximately one-third as susceptible to deuterium substitution.

Secondary isotope effects have only been detected where the coupling constants are relatively large ($^1J_{\text{F-Si}} = 275 \text{ Hz}$, $^1J_{\text{F-P}} = 1030 \text{ Hz}$). The changes observed in these couplings were 2 and 3.5 Hz respectively, corresponding to 0.7 and 0.3 %.

Isotope effects on carbon couplings require more precise measurements before unambiguous conclusions may be drawn: present work indicates these effects will be very small. The very limited amount of data on the deuterated ^{15}N ammonia derivatives indicates⁶ there is no discernable isotope effect on the $^1J_{^{15}\text{N-H}}$ coupling constant.

2.1.1. Theoretical Considerations.

Several theoretical explanations of isotope effects have been put forward in an attempt to rationalize the experimental data. The hydrogen molecule and its isotopic variants have been the subject of several quantum mechanical treatments, based on modifications to the diamagnetic part of the screening constant as various functions of the changes in the vibrational energy levels and equilibrium bond distances. These have been summarized in a review⁴ and therefore it is not proposed to discuss these here, since all other molecules can only be treated approximately. Hence theoretical concepts that may be applied generally will be of prime interest here.

The first of these theories was put forward by Gutowsky²⁹ and based on an electrostatic deformation model, in which the contribution to the magnetic shielding of a proton by intramolecular electric fields is examined. These arise from the motion of bonding electrons within molecular orbitals, and it was proposed that the effect of the electrostatic field E produced by one atom would deform the electron distribution about a second (resonant) nucleus by a factor proportional to $\langle E^2 \rangle$, the mean

(time average) value. It was found that the decrease in magnetic shielding could be expressed approximately by

$$\frac{2\langle E^2 \rangle}{10^5} = 2 \frac{q^2}{b^4} \cdot \frac{1}{10^5}$$

where q is the electric charge on the first atom and b the inter-atomic separation. A deuterium atom has a larger mass than a hydrogen atom, and consequently is expected to have smaller vibrational amplitudes for the next molecular energy to remain constant. Therefore, a deuterium atom will not approach its neighbours as closely, nor, arising from the short-range b^{-4} term, polarise them as much. Thus deuterium (or similar heavy-isotope substitution) should result in an upfield shift of the observed nucleus, in accord with experimental observation.

For the geminal deuterium substitution of a $-\text{CH}_2-$ group, Gutowsky calculated the 1% change in proton shielding required a point charge of $0.65 q$ electrons on the deuterium atom. This extremely high value could be reduced to $0.3 - 0.5$ by allowing for a spatial distribution of charge, which still seems considerable. Gutowsky claimed better results were obtained in more complex calculations of the ^{19}F shieldings in CHF_2 and CDF_2 , but this work does not seem to have appeared in the literature and hence cannot be studied in detail.

The electrostatic deformation model has been invoked³⁰ to explain the deuterium isotope effects in water, where the large electric field from the OH group was discussed in terms of an exponential power series in $\langle E^2 \rangle$ and the resulting expression predicted the observed shift with reasonable accuracy (0.05ppm vs. 0.03ppm , experimentally).

In a general study¹⁸ of ^{13}C substituent effects on ^{19}F shielding, a large range of isotopic shifts ($^{12}\text{C}-^{13}\text{C}$) was observed (0.070 to 0.194 ppm), which led to doubts in the overall validity of the electrostatic deformation model. The marked non-linearity of this isotope shift with proton content for the series of fluoromethanes were also difficult to comprehend in terms of variation in the net atomic charge q since the isotope shift for CHF_3

was found to be greater than that for CF_4 .

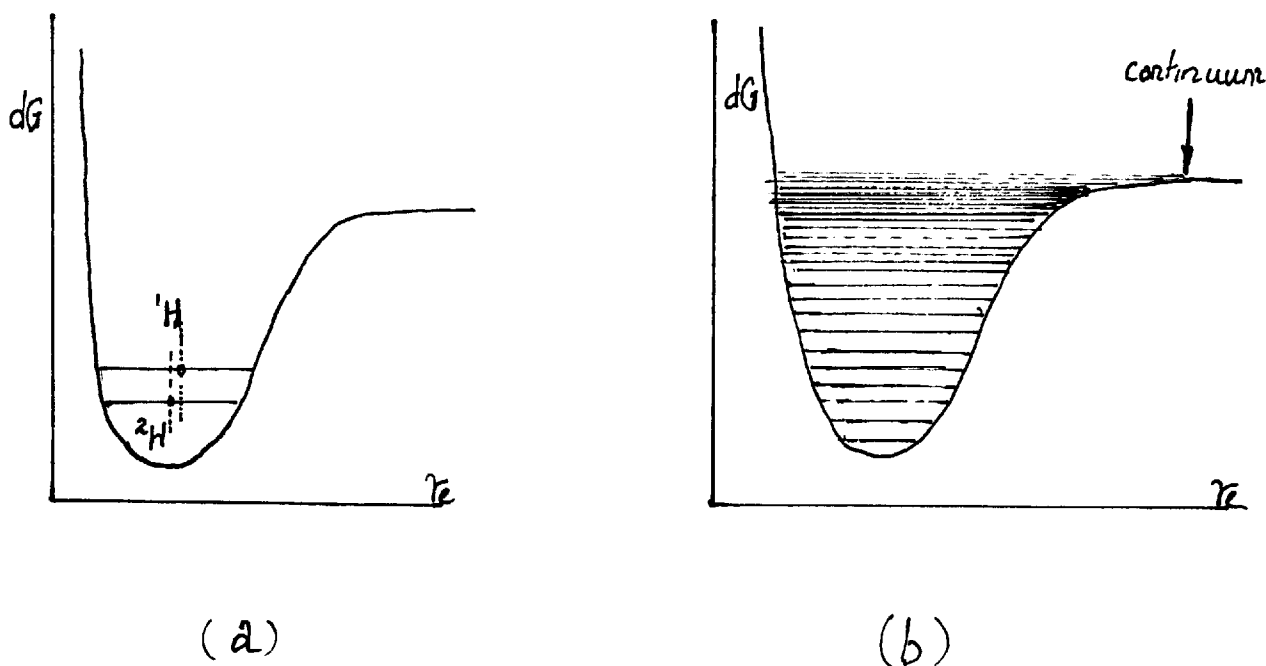
An alternative approach to understanding the isotope effect has come from evidence provided by microwave and electron diffraction studies, which lead to the important conclusion that isotopic substitution changes the dynamic state of a molecule. (This has already been mentioned in discussing the origin of the electrostatic deformation model above). The modified intramolecular motions (vibration, rotation, bending) will alter the electronic structure and hence magnetic shielding of the various nuclei. This theory may be used qualitatively to rationalize some general experimental observations on the isotope effect.

Firstly, it is anticipated that effects of any isotopic substitution will be attenuated with distance in the same way as these intramolecular forces, and therefore localised.

Secondly, a greater fractional change in mass will produce more profound modifications of intramolecular forces; in turn this should not only give rise to larger effects but also they should be observable at a greater distance from the site of isotopic substitution.

Consideration of vibrational and bending motions indicates that if heavy isotopic substitution takes place, the amplitudes of these motions must decrease to maintain the total molecular energy. This corresponds to a reduction in equilibrium bond distances, which may be represented pictorially in the concept of the anharmonic potential well (fig. 1a).

Using this concept it is now possible to explain primary isotope effects in terms of shortening of the bond holding the isotope, whilst secondary isotope effects would correspond to (lesser) shortenings of other bonds in the molecule.



- (a) Effect of isotopic substitution on bond length, using deuterium as an example.
- (b) Effect of increasing temperature on vibrational energy level population.

Good experimental support for the vibrational theory comes from a recent study³¹ of the temperature dependent isotopic shieldings of fluorine nuclei by chlorine and carbon isotopes. It was found that the fluorine isotope shifts uniformly increased as the temperature was lowered from 305°K to 193°K. The above theory predicts that at the limit of high temperature, where vibration is extensively excited, higher vibrational energy levels are populated and the "fine-grain" structure of the vibrational ladder (fig. 1b) tends to be lost as the continuum is approached. Hence the isotope effects will diminish, as was found experimentally.

In an attempt to put these considerations on a quantitative basis, the variation in chlorine isotope shielding for the fluorine resonances of $CFCl_3$ was recorded (Table 1) to determine if the results could be correlated with the corresponding changes in vibrational excitation.

Table 1 (ref. 23)

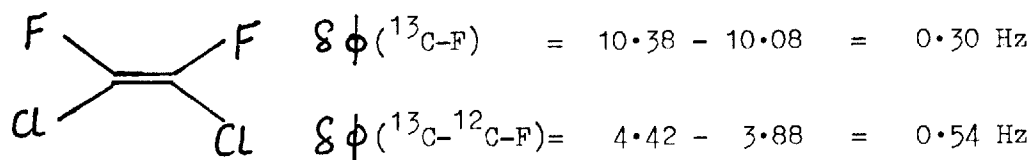
Effect^(a) of substitution of ^{37}Cl for ^{35}Cl on chemical shift of CFCl_3 .

Compound/temp. ($^{\circ}\text{K}$)	193	230	305
$\text{CF}^{35}\text{Cl}_2^{37}\text{Cl}$	0.8 ± 0.1	0.67 ± 0.01	0.53 ± 0.02
$\text{CF}^{35}\text{Cl}^{37}\text{Cl}_2$	-	1.35 ± 0.05	1.06 ± 0.05
$\text{CF}^{37}\text{Cl}_3$	-	2.00 ± 0.15	-

(a) shifts are given in Hertz at 94.1 Mhz.

The infra-red spectrum of CFCl_3 contains an absorption at 244 cm^{-1} which corresponds to a motion involving primarily bond bending, (relevant to the two bond chlorine isotope effect), and indicates a population of first and second excited states of 30% at ambient temperature. A second band at 349 cm^{-1} arises from primarily bond stretching, and is considered to include contributions from vibrations involving changes in C-F bond lengths. This latter frequency indicates that 12% of the molecules are excited at 233°K and 21% at 303°K , a difference of 9%. The observed temperature effect on the isotope effect is noted (table 1) to be ca. 21%. Unfortunately, quantitative relationships between vibrational energy level populations and isotope effects are unknown, and hence it cannot be concluded if these vibrations are stretching or bending modes, and possibly contributions from both will be the answer.

The importance of vibrational bending contributions was considered in an examination of ^{13}C isotope effects on fluorine shifts. The relative change with temperature for ^{19}F attached to sp^2 carbon was noted to be greater for a two bond than a one bond interaction, reflecting both the higher vibrational frequencies encountered and the increased contribution from lower energy bending modes. The data obtained (94.1 MHz) for cis dichlorodifluoroethene at 233 and 303°K serve to illustrate this point:-



The probable importance of bending mode contributions has been noted earlier in a study³² of ^{29}Si isotope effects on the proton NMR of trisilane, $n\text{-Si}_3\text{H}_8$. Isotopic substitution of a terminal silyl group $^{29}\text{SiH}_3$. $^{28}\text{Si}_2\text{H}_5$ produced a large isotope shift (0.01 ppm) on the bound protons; in contrast to central atom substitution, where no measurable effect was observed, in keeping with similar results from SiH_4 and Si_2H_6 . This marked discrepancy was held to arise from changes in the bending deformations of the Si-Si-Si backbone, through which substitution at a central atom would have much less effect on the proton spectrum than an end atom.

A complementary approach to the vibrational theory as an explanation of isotope effects is through the consideration that the small variations in average molecular geometry will cause a redistribution of the electrons within the molecular orbitals, and a consequent rehybridization of bonds, leading to a modification of the magnetic shielding of nuclei.

Irrefutable evidence exists pertaining to the shortening of bond lengths upon isotopic substitution.³³⁻³⁷ Electron diffraction studies indicate C-H bonds for methane^{34a} and ethane³⁵ are longer than the corresponding C-D bonds in the perdeutero- compounds by ca. 0.007 Å, but no variation in bond angles was detected.³⁵ These observations were supported^{34b} by Raman spectra of CH_3D . The vibrational amplitudes of C-D bonds in C_2D_6 were also concluded to be less than the C-H amplitudes in support of the vibrational theory above.

Evidence on changes of bond angles with isotopic substitution has been less conclusive. An early microwave study³⁷ of PH_3 and PHD_2 concluded that the H-P-H angle was decreased by 6.2' on deuteration, but

data on deuterated ammonias have been controversial.³⁸⁻⁴⁰ Early reports suggests either ~~small~~(10-20') decrease^{38a} or increase^{38b} in HNH angle for NH_2D and NHD_2 ; later infra-red work on the symmetrical NH_3 and ND_3 indicated³⁹ the angle decreased by 11.4' on deuteration, comparable with the microwave results³⁷ on phosphines. However, a recent study finds the H-N-H angle decreases by as much as 3° on total deuteration: if this is indeed the case, then the reduction in bond angle should have been detected more readily by earlier workers in this field. Inspection of their results indicates the error arises from an over-estimation of the H-N-H angle in NH_3 (109.1°) by ca. 2° , when compared with other data.^{38,39}

Bond rehybridization is not limited to a study of primary effects; the possibility of secondary effects has been detected in some cases. The C-C bond in C_2D_6 was estimated³⁵ to be 0.002 Å shorter in C_2H_6 , and a study⁴¹ of carbon-halogen bond distances in CH_3Cl and CH_3Br indicates perdeuteration reduced this bond by ca. 0.001 Å. Smaller variations were suspected for carbon, chlorine or bromine isotopic replacements.

The theory was invoked by Doddrell and Burfitt¹⁶ in an attempt to explain why for 1- $[\text{}^2\text{H}_1]$ -hept-1-yne the secondary isotope effect (0.50 ppm) was more than twice the primary effect (0.22 ppm) on ^{13}C shielding. Although the change in the $\text{C}\equiv\text{C}$ bond length on deuteration is unknown, the force constant for bond stretching is known⁴² to be 0.6% greater than for acetylene itself, suggesting bond rehybridization must be significant.

Similarly, Loewenstein and Shpoer^{8b} found that the large isotope shifts observed for ^{59}Co in $\text{K}_3\text{Co}(\text{CN})_6$ upon selective substitution of ^{13}C or ^{15}N could be interpreted as a regular decrease of Co-ligand distance by 1.2×10^{-3} per cent if the theory advanced to explain Co shielding were correct.

In an attempt to quantify the change of magnetic shielding with variations in bond lengths and angles, Bernheim and Batiz-Himandez studied⁴³ the geminal isotope shifts in some first row molecules (H_2O , NH_3 , CH_4). For CH_4 , calculation of the diamagnetic contribution to the magnetic shielding (σ_d) as a function of bond angle or bond length variations indicated the observed isotope effects (ca. 0.02 ppm) could be

explained either by a reduction in bond length of 0.0012 a.u. or a bond angle decrease of $10'$ ($\text{CH}_4 - \text{CH}_3\text{D}$); values which are comparable to experiment.³⁵ With NH_3 , where due allowance was made for the partially ionic N-H bonds, it was found a given bond angle change had a slightly greater effect on σ_d , but the final theoretical values of bond angle/bond length reductions were again of the same order of magnitude as experiment.³⁹

Borisenko *et al.* used⁷ the bond hybridization approach to predict the deuterium isotope shielding on the ^{31}P resonance of $\text{C}_6\text{H}_5\text{PH}_2$ as a function of the small variation in bond angles with isotopic substitution (cf. phosphine data, discussed³⁷ above). Unfortunately, they had to make several assumptions: (i) the published theory of ^{31}P shielding in symmetrical PZ_3 molecules was applicable, (ii) average valence angles and electronegativities could be employed, and (iii) the observed isotope shift could be explained purely as a function of a decrease in bond angle, for which the data³⁷ from the phosphines was used. Notwithstanding these limitations, the theoretical value of a 1.20 ppm isotope shift for $\text{C}_6\text{H}_5\text{PHD}$ is in remarkable agreement with the experimental value of 1.21 ppm.

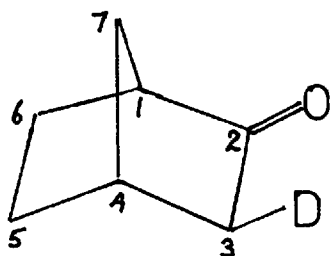
2.1.2 Applications of deuterium isotope effects in ^{13}C NMR.

Deuterium substitution was initially used by Roberts as a means of spectral simplification⁴⁴ and peak identification⁴⁵ in carbon NMR. During a study by ^{13}C NMR⁴⁴ of the proton couplings in benzene, (a 7 spin system) it was found that the spectral simplification observed for 1,2,3,5-tetradeuterobenzene enabled the long range coupling $^3J_{\text{CCCH}}$ to be determined as 7.4 Hz in the remaining 3 spin system. Extensive use of deuteration was made⁴⁵ in a comprehensive survey of the carbon spectra of steroidal ketones, as an aid to the spectral assignment of resonances. Isotopic exchange of protons to carbonyl groups resulted in the elimination of signals from the deuterated carbons. This arises because the deuterium nucleus has a magnetic moment ca. one-third that of the proton, and hence

the dipolar mechanism of relaxation of the carbon nuclei (characterized by T_1^{DD}) will be less efficient. Therefore the spin-lattice relaxation time will increase and hence the observed signal intensity decrease.

The advent of higher field (21 - 23.5 K.Gauss, 22.63 & 25.16MHz for ^{13}C) with Fourier transform facilities enables the ready detection of the small deuterium isotope effects, and their usage in the solution of problematical assignments. It will be appreciated that the small isotope shifts (typically¹⁴ 0.1ppm for geminal substitution and 0.3ppm for directly bonded) will only be detectable at higher field strengths when a natural line-width for ^{13}C of 1 Hz is taken into account.

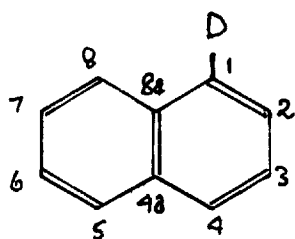
In a study⁴⁶ of some nor-camphors, Stothers recorded the ^{13}C spectrum of 3-exo- $[\text{}^2\text{H}_1]$ -norcamphor, (1), to obtain an unequivocal assignment



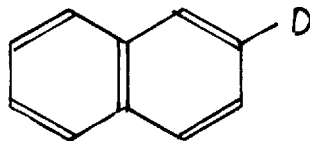
(1) 3-exo- $^2\text{H}_1$ norcamphor

of C_5 and C_6 . The C_3 resonance (directly-bonded) was seen to shift upfield by ca.0.5 ppm from the undeuterated signal, C_4 exhibited a typical geminal isotope shift (0.1 ppm) and one of the two unassigned methylene signals was considerably broadened (by either a long range deuterium coupling or a small isotope shift 0.1 ppm) whilst the other was unaffected by the C_3 substituent. These resonances were therefore designated as C_5 and C_6 . Similar isotope effects were employed to assign carbon spectra for the four possible 5,6 dimethyl norcamphors.

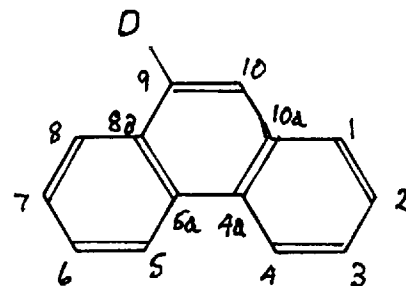
Isotope shifts have also found considerable use in assigning the carbon resonances of polycondensed hydrocarbons.⁴⁷ Results obtained on 1 and 2- $[\text{}^2\text{H}_1]$ -naphthalene (2,3) and 9- $[\text{}^2\text{H}_1]$ -phenanthrene (4) yielded values for the directly bonded, ortho and meta effects comparable to those reported by Bell¹⁴ for monodeuterobenzene.



2

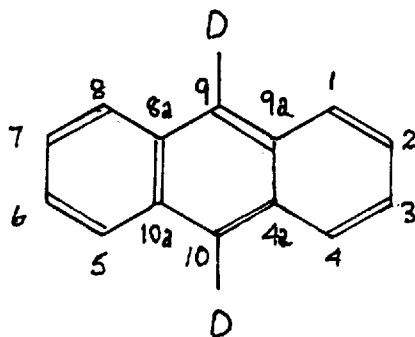


3



4

A small peri isotope effect of 0.04 ppm (e.g. C_8 in 4) was observed with a band broadening similar to that for meta broadening (ca. 2.3 Hz). Ortho high field isotope effects of quaternary carbons common to two rings (0.05 ppm) were also detected. This enlarged set of isotope effects was employed to make a new assignment of anthracene (as the 9,10- $[^2H_2]$ -derivative, 5).

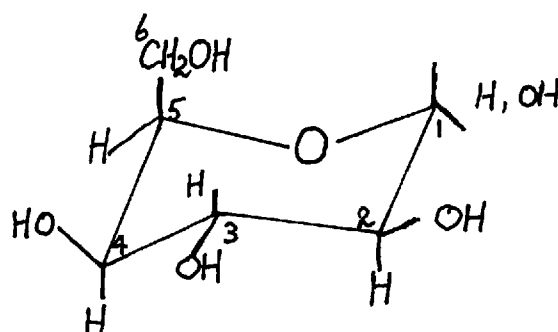


5

Apart from the triplet of the deuterated carbons (C_9 and C_{10}) characteristic ortho and peri isotope shifts were visible. Moreover, the signals of the ortho and peri carbons were broader than that from $C_{2,3,6,7}$ on account of meta and peri couplings:- $\nu_{\frac{1}{2}}(C_2) = 1 \text{ Hz}$;
 $\nu_{\frac{1}{2}}(C_1) = 2 \text{ Hz}$; $\nu_{\frac{1}{2}}(C_{4a}) = 2 \text{ Hz}$.

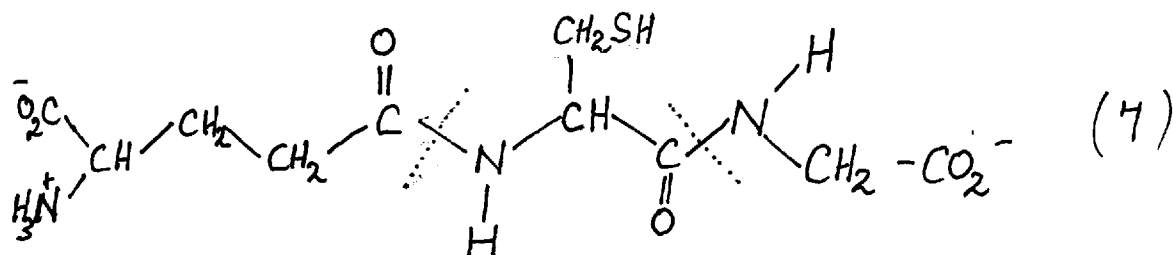
Application of deuterium isotope effects in the ^{13}C spectra of some sugars⁴⁸ provides another example where this technique has been used to distinguish between several resonances occurring close together. Thus

the C_5 resonance for 6- $[^2H_2]$ α,β -D-glucose (6) was shifted 0.12 ppm upfield by the secondary isotope effect, compared with its chemical shift in the parent compound. Monodeuteration at C_2 , C_3 or C_5 produced β effects on neighbouring carbons of ca. 0.06 ppm, reflecting the additivity of the



isotope shift. Similar results were obtained in galactose and mannose derivatives. In all cases, the directly deuterated carbon was eliminated from the spectrum, causing further spectral simplification and identification. C_6 was found to be the most useful deuteration site for all the hexoses, both for ease of substitution and the larger shift produced by the multiple replacement.

Deuterium isotope effects have found recent application in the biochemical field,⁴⁹ where it was possible to differentiate between the carbonyl resonances from amide and carboxylate groups in the tripeptide glutathione (7), γ glutamylcysteinylglycine). ^{13}C spectra in 50% H_2O/D_2O

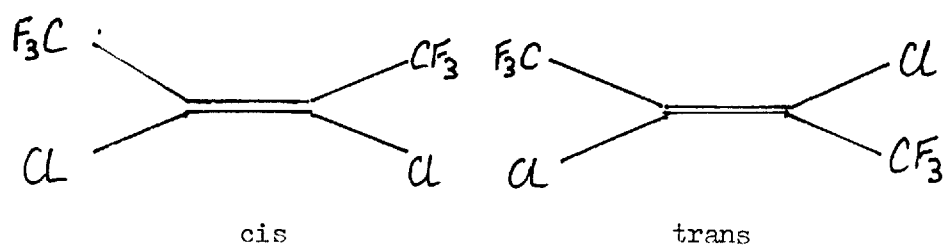


indicated two of the four carbonyl resonances to be doublets. The high field components were 0.1 ppm upfield, and originated from the isotopic

exchange at nitrogen to yield a mixture of -CONH- and -COND- peptide links. The pair of signals observed in each case was indicative of slow exchange of NH, in contrast to the carboxylate anions, where fast intermolecular exchange resulted in one line for each carbon.

2.1.3. Stereochemical dependence of isotope shifts.

Very few reports of stereochemical influences on isotope shifts exist, and none have been reported for ^1H NMR. The first observation was by Tiers,⁵⁰ from a study of the geometric dependence of the ^{13}C isotope shift on the ^{19}F resonance ($^{12}\text{C} \rightarrow ^{13}\text{C}$) for the perfluoromethyl groups in 2,3-dichloroperfluoro-but-2-enes.



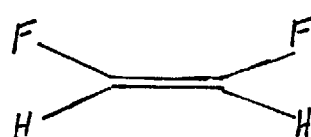
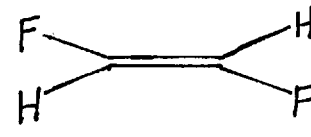
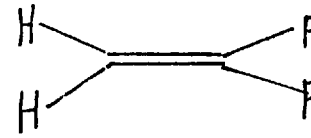
$(^{12}\text{C} \rightarrow ^{13}\text{C})^{19}\text{F} \quad 0.137 \pm 0.002\text{ppm} \quad 0.132 \pm 0.001 \text{ ppm}$

A cis arrangement of substituents is seen to produce a slightly larger value of the isotope shift than a trans relationship, but the difference (0.075%) is very slight.

Much larger stereochemical effects were observed¹⁷ in a series of fluoroethylenes, where substitution of D for H produced isotope shifts of upto 0.5 ppm on the fluorine resonances, and reflect the consequences of a much larger fractional change in mass. Data are reproduced in Table 2.

Table 2

Deuterium isotope shifts for the ^{19}F resonances of some fluoroethylenes.

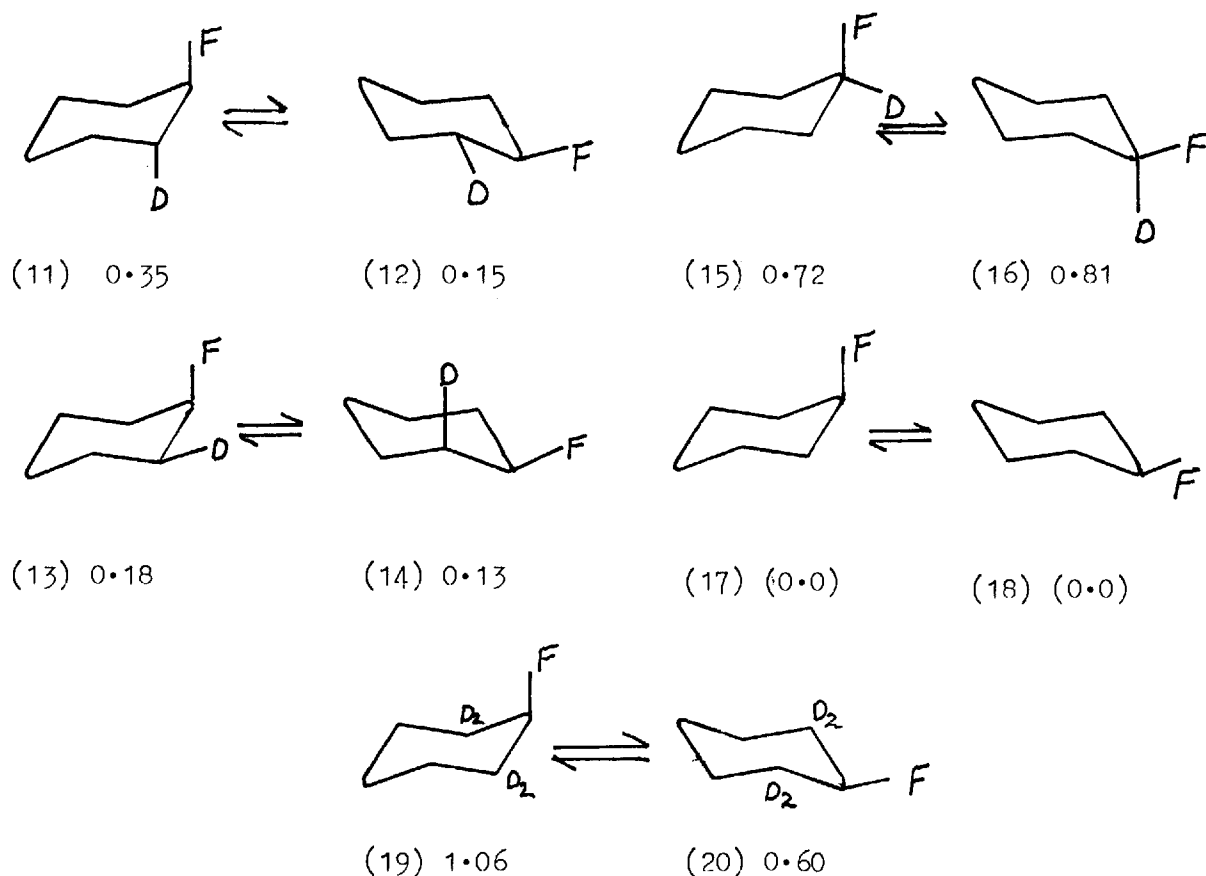
<u>Compound</u>	<u>site of deuterium incorporation</u>		
	geminal	trans	cis
 (8)	0.502	0.418	-
 (9)	0.498	-	0.293
 (10)	-	0.260	0.210

Inspection of the table for the cis and trans fluoroethylenes (8&9) reveals only a small geometric influence on the geminal isotope shift, but a strong dependence on cis/trans relationships. A trans disposition of fluorine and deuterium produces a much larger isotope shift, comparable to a geminal effect, than a cis relationship. Data for vinylidene fluoride (10) again reflect this cis/trans dependence, but the magnitude of the shifts are decreased considerably, indicating that the extent of fluorine substitution has an influence on the observed isotope shifts.

Large stereospecific isotope shifts have been observed in the fluorine spectra of saturated systems, with the recent results¹¹ obtained for some specifically deuterated cyclohexyl fluorides. The fluorine spectra were recorded under conditions of slow ring reversal at -85° in CFCl_3 , enabling both axial and equatorial substituent conformations to be examined,

and the isotope shifts were determined with respect to the corresponding cyclohexyl fluoride. Data are reproduced in table 3, and all values are in ppm.

Table 3



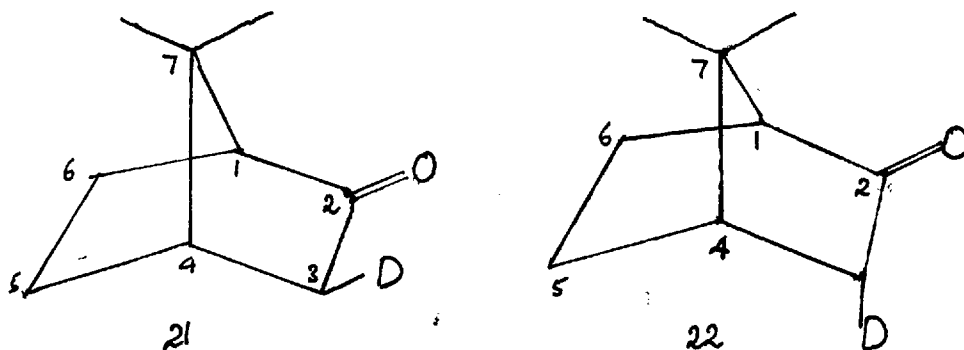
It is seen that there is an appreciable difference (0.09 ppm) between the geminal isotope effect for an axial and an equatorial fluorine substituent (15&16), with the latter being larger. Comparison of the four vicinally deuterated fluorides (11-14) reveals that the trans-diaxial derivative (11) has the largest isotope shift which is twice as large as the shifts for other conformers containing at least one equatorial substituent. For the latter three conformers, the axially fluorinated (13) exhibits a marked increase over the two equatorially fluorinated derivatives 12 & 14.

These observations indicate a marked angular dependence of the isotope shift, which is twice as large when the dihedral angle is 180° as when it is 60° .

The observed vicinal isotope effects were found to be additive by examination of the tetradeuterated 2,2,6,6- $[^2\text{H}_4]$ -cyclohexyl fluorides, 19 & 20. The shift of the axial fluorine in 19 (table 3) compared well with the sum of two axial-axial and two axial-equatorial shifts (calculated, 0.98 ppm, observed, 1.06 ppm). Similar calculations for 20 yield a predicted shift of 0.66 ppm which was in good agreement with the experimental value of 0.60 ppm.

The large geminal isotope shifts for 15 and 16 (0.72 and 0.80 ppm, respectively) are noted to be larger than that reported³ for $\text{C}_3\text{F}_7\text{D}$ (0.60 ppm). Because the spectra for the cyclohexyl fluorides were recorded at a reduced temperature (-85°), it is expected³¹ that there may be a significant positive contribution to the observed isotope shifts. Alternatively, this discrepancy may arise from the differing structural environments of the two systems.

Stereospecific isotope effects have also been observed for carbon NMR in a study⁵¹ of some deuterated camphors. The ^{13}C spectrum of 3 exo- $[^2\text{H}_1]$ camphor (21) exhibits a triplet for C_5 , by vicinal coupling between C_5 and the exo deuterium, as well as the expected isotope effects on C_3 ; whereas C_7 , also vicinal to C_3 is little affected. However, for the



stereoisomeric 3 endo- $[^2\text{H}_1]$ -camphor (22), these effects are reversed, and the C_7 carbon signal becomes a triplet. Hence these secondary vicinal isotope effects have a marked stereospecificity, being transmitted effectively by a trans-coplanar arrangement of bonds, but attenuated by a gauche disposition.

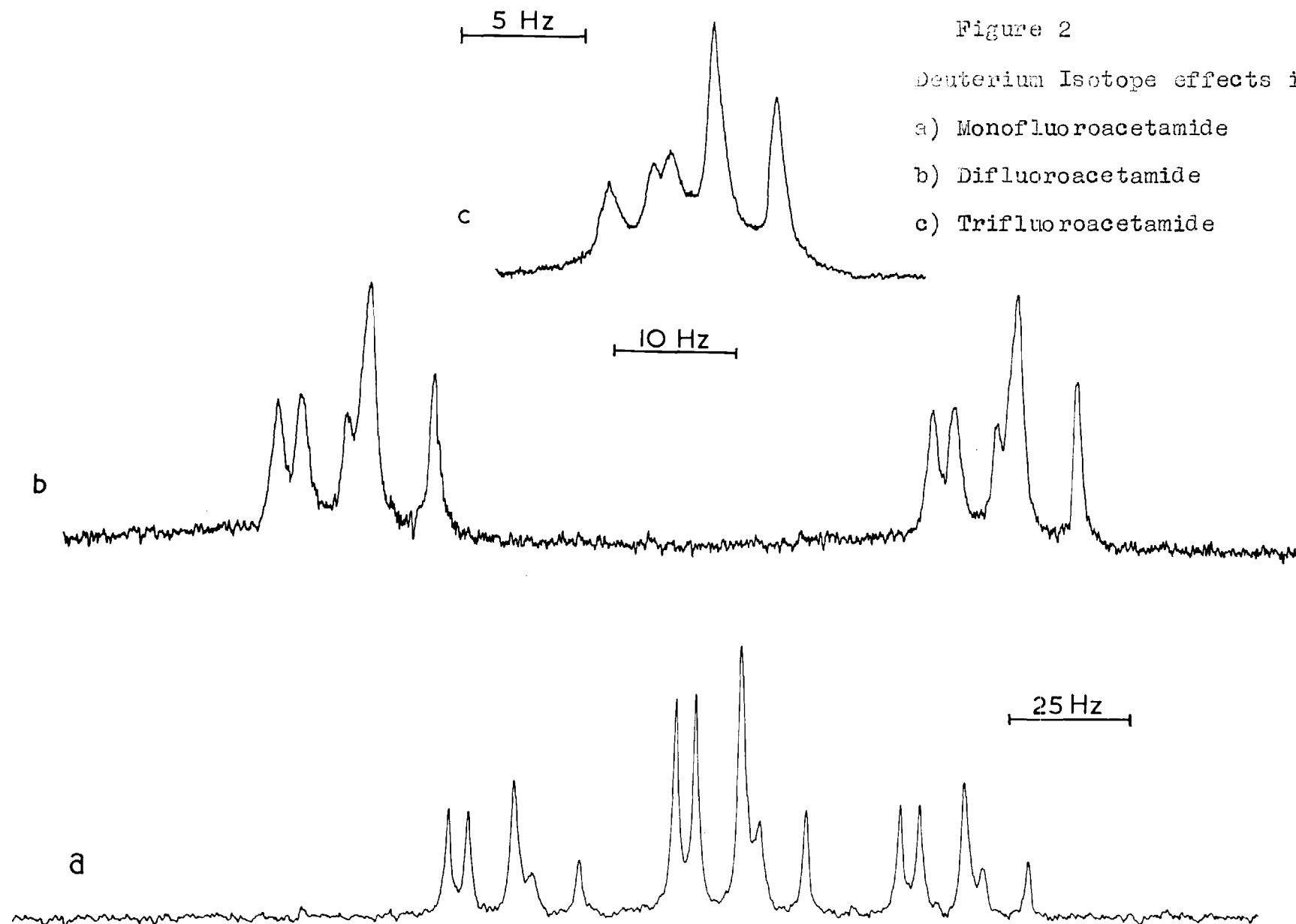


Figure 2

Deuterium Isotope effects in:-

a) Monofluoroacetamide

b) Difluoroacetamide

c) Trifluoroacetamide

2.2 Isotope effects in some α -fluoroacetamides.

In the course of examining the fluorine spectra of monofluoroacetamide, it was decided to remove the long-range H-F coupling by deuterium exchange of the -NH_2 protons. Addition of a few drops of deuterium oxide to a methanolic solution of the amide resulted in a spectrum which is reproduced in figure 2a. It is seen that the exchange is incomplete, and separate signals can be detected for the -NH_2 , -NHD and -ND_2 forms. Figure 2a also shows that the signals arising from the deuterated species are shifted upfield from that of the parent molecule, i.e. the fluorine nucleus experiences a considerable isotope shift.

Similar treatment of the di- and trifluoroacetamides produced comparable effects, the magnitude of which depend on the nature of the substituents at the acetyl carbon (figure 2b & 2c). Consequently, it was decided to examine this structural variation in full for the range of amides available.

The effects of successive methylation of the amido group, $\text{NH}_2\text{-NHCH}_3\text{-N(CH}_3)_2$, upon the ^{19}F chemical shift were also investigated to determine how a typical chemical substituent (-CH_3) compares with an isotopic substituent (-D).

Results

Deuterium isotope shifts.

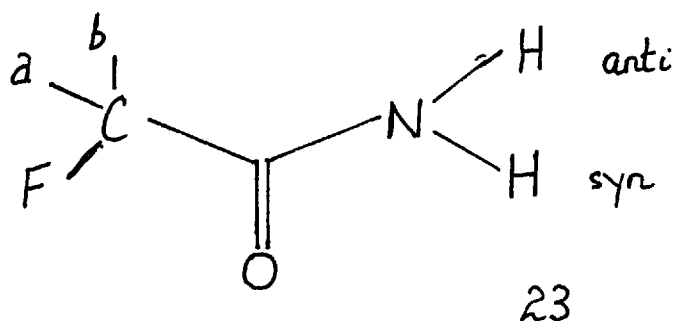
Table 4 lists the observed isotope shifts (relative to the parent undeuterated species) for the fluoro-amides in three solvents. The assignment for the mono deuterated species to syn and anti conformers is based on the conclusion reached in Chapter 1 that the 2-fluoro substituent is spin-coupled stereospecifically to the proton anti to the carbonyl group.

Table 4.

^{19}F Deuterium Isotope Shifts of the Fluoro-amides (syn and anti refers to the location of the deuterium isotope).

Compound		Methanol		Dichloro- methane		Dimethyl- formamide	
		NHD	ND ₂	NHD	ND ₂	NHD	ND ₂
FCH ₂ .CO.NHD	syn	12.75		14.1		13.75	
	anti	11.75		12.5		11.5	
FCH ₂ .CO.ND ₂			24.8		27.0		25.0
MeCHF.CO.NHD	syn	12.9		14.4		13.35	
	anti	11.2		12.8		11.2	
MeCHF.CO.ND ₂			24.2		26.25		24.9
Ph.CHF.CO.NHD	syn	12.5		10.5		11.0	
	anti	10.5		10.25		10.2	
Ph.CHF.CO.ND ₂			22.5		22.5		22.0
HFClC.CO.NHD	syn	10.5		11.1		10.4	
	anti	10.1		10.3		10.4	
HFClC.CO.ND ₂			20.5		21.4		20.3
HFBrC.CO.NHD	syn	11.3		11.2		11.2	
	anti	10.9		10.7			
HFBrC.CO.ND ₂			22.4		22.4		22.8
F ₂ HC.CO.NHD	syn	5.6		6.6		5.3	
	anti	6.4		6.6		6.0	
F ₂ HC.CO.ND ₂			11.8		12.6		11.2
F ₂ ClC.CO.NHD	syn	4.1		4.9		4.6	
	anti	4.7				5.2	
F ₂ ClC.CO.ND ₂			9.1		9.45		9.6
F ₃ C.CO.NHD	syn	singlet		3.0		2.6	
	anti			3.9		3.4	
F ₃ C.CO.ND ₂					6.9		6.1

All shifts are in Hz at 94.08 MHz and 31°C, and are to high field of the undeuterated material.



Inspection of table 4 reveals that the isotope effects for each compound are additive, a feature typical of isotopic substitution. For example, in dichloromethane the ^{19}F signal of mono-N-deuterofluoroacetamide occurs 13.3 Hz to high field of the non-deuterated material and that of the di-N-deutero compound is 27.0 Hz to high field.

The magnitude of the isotope shift is seen to vary with the nature of the substituents at the acetyl carbon, with the observation of the largest shift for the mono-fluoro compound (23, $a = b = \text{H}$) and lowest for the trifluoro compound (23, $a = b = \text{F}$). Clearly, the size of the isotope shift is influenced by the nature of the substituents a and b . This relationship may be studied by a plot of the total isotope shift ($-\text{ND}_2$ derivative) against the sum of the Huggins electronegativities⁵² of a and b , (figure 3). The electronegativity values used were :- $\text{H} = 2.2$, $\text{Br} = 2.95$, $\text{Cl} = 3.15$ and $\text{F} = 3.9$. The value for $-\text{CH}_3$ was taken⁵³ as 2.6 and a value for sp^2 carbon of 3.0 Huggins units has been suggested recently.⁵⁵

It is seen from figure 3 that the plot is linear for each solvent, and table 5 lists values of the slopes and correlation coefficients obtained for each plot by a least-squares computer analysis. The values of the latter are all in the range 0.96 - 0.97, which is satisfactory for the limited data available (8 points).

The magnitude and range of the total isotope shift ($-\text{ND}_2$ derivative) is seen to be almost independent of the nature of the solvent. Thus for the mono fluoroacetamide (23, $a = b = \text{H}$), changing the solvent

Total Isotope Shift
for $-ND_2$ deriv. (Hz)

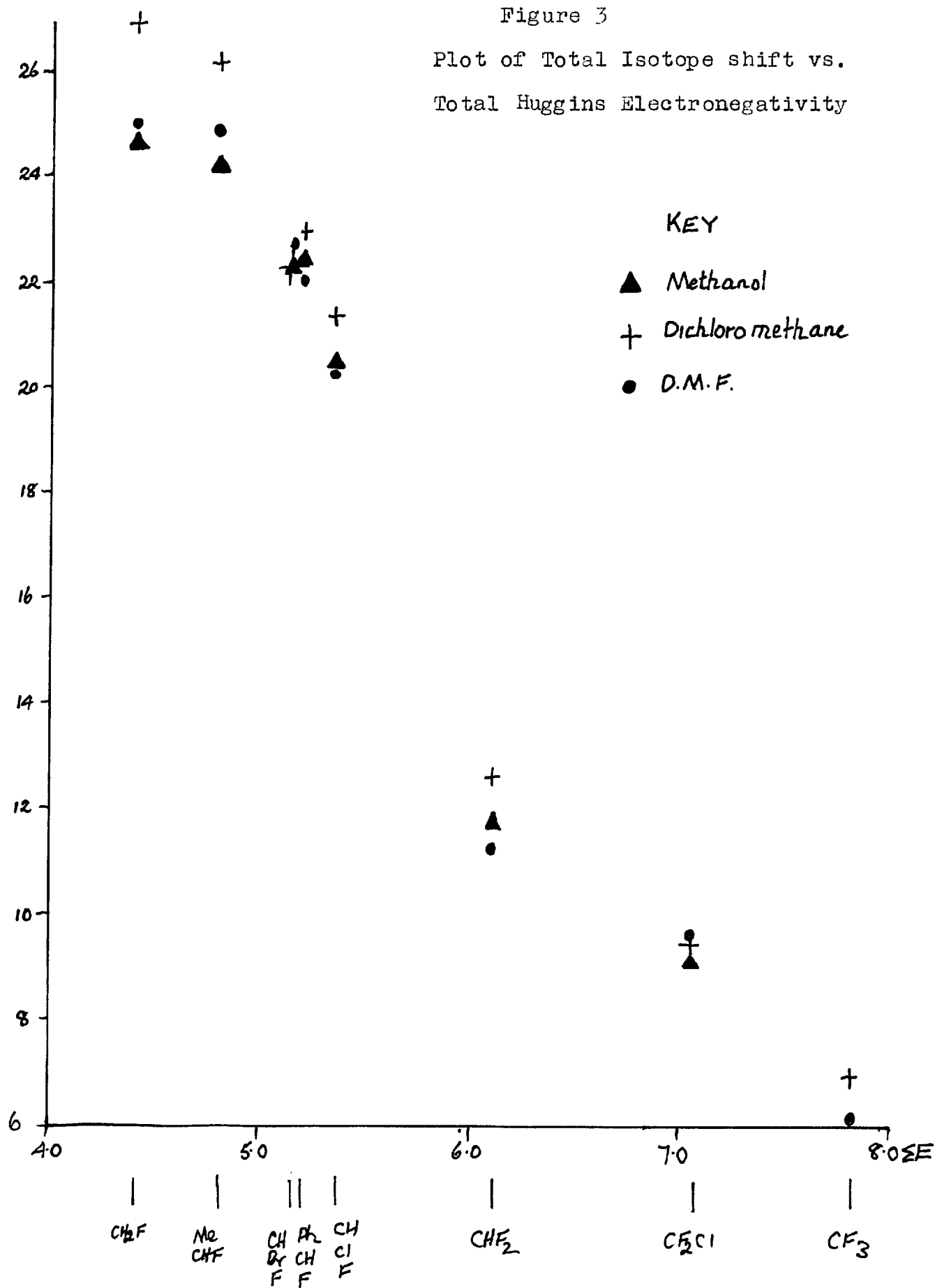


Table 5.

Least-Squares analysis of Isotope Shift data.

solvent	slope	correlation coefficient.
Methanol	-6.843	0.964
Dichloromethane	-6.500	0.977
Dimethylformamide	-6.250	0.968

from a dipolar protic (CH_3OH) to a dipolar aprotic medium (DMF) produces an addition to the isotope shift of 0.2 Hz, whilst with the relatively non-polar, aprotic solvent dichloromethane the isotope shift increases by only 2.0 Hz. Similar effects are noted for the other amides. It is apparent that hydrogen bonding ability and polarity of the solvent have little effect upon the size of the isotope effect.

The recent theory⁵⁵ of the structural dependence of inductive effects suggests that the factors influencing differences in shielding between nuclei in related structural environments may be considered to arise from through bond interactions of neighbouring groups amongst themselves and with the atom containing the resonant nucleus. The dependence of the isotope shift on the nature of the a and b substituents strongly suggests that this mechanism is responsible for the form of the relationship observed here. In terms of the theory,⁵⁵ the deuterium substitution at the amido nitrogen is causing a small but finite change to the effective electronegativity of the carbonyl centre.

A possible explanation for this phenomenon may be found in consideration of the nature of the N-H and N-D bonds. In the introduction it was noted that the balance of the available data³⁹ indicated that the N-D bond is probably shorter than the N-H bond, but the change in N-H bond length (ca. 0.002Å) on deuteration is considerably less than that

for a C-H bond. Consequently it is difficult to rationalise the observed isotope shifts as arising entirely from this very slight change in bond length and its associated bond rehybridisation. It seems unlikely that the isotope shift may arise from the differences in vibrational zero-point energies and amplitudes upon deuteration, since these are expected to be localised and not significant over the four bonds separating the fluorine nucleus from the site of isotopic substitution.

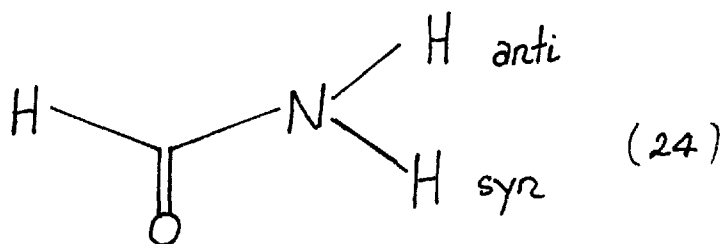
Halevi⁵⁶ has successfully interpreted the secondary isotope effects pKa of some α -[²H₁]-acetic acids in terms of an appreciably greater inductive electron donating ability of D or -C-D compared to H or -C-H, (i.e. D is less electronegative than -H). Consequently, N-deuteration of an amide can be expected to increase the electron density at the nitrogen atom and hence produce a redistribution of electrons in the C(O)-N amide bond. This bond rehybridization provides the required pathway for transmission of the effects of N-deuteration to the carbonyl carbon, and will modify its effective electronegativity.

Since Halevi has shown that D is less electronegative than H, it is anticipated that the total electronegativity of the amido group (-CONR₂) will decrease upon deuteration. However, trial calculations using the equation derived by Phillips and Wray⁵⁵ from their theory of inductive effects upon chemical shielding failed to provide a reasonable estimate for this anticipated change in electronegativity, and indeed, did not even predict the correct sign of such a difference. Such failure probably arises from the approximate nature of the empirical relationship and the assumptions made in its derivation.

Inspection of figure 2 indicates that the components of the ¹⁹F signal consist of a singlet and a doublet which are not centred at the same position; this is due to a chemical shift between the species in which the deuterium is syn to the carbonyl group and that in which it is anti. If it is assumed that the ⁴J_{F.NH} coupling constant is to the anti N-H proton (as discussed in chapter 1) then it may be concluded that for monofluoroacetamide in dichloromethane the D anti isomer resonates 1.6 Hz to low field of that with the D syn to the carbonyl group. For compounds

containing more than one fluorine substituent this pattern is reversed, with the D anti isomer being 0.9 Hz to high field of the D syn resonance for trifluoroacetamide in dichloromethane.

These differences may be understood with data obtained from microwave studies⁵⁷ on formamide (24). It was concluded from this study



that the two N-H bond lengths differ by some 1.2%, with the N-H syn to carbonyl being longer ($1.014\text{\AA}$) than that in an anti disposition ($1.002\text{\AA}$). The directly bonded ^{15}N -H coupling constants are also observed to be significantly different for the two amido protons: the values of these interactions have been recorded⁵⁸ as 92 Hz for the syn proton and 88 Hz for the anti proton in the neat liquid. Sunners *et al.* considered that the shorter anti -NH bond contained more s character than the longer syn NH bond, and by analogy with $^1J_{\text{NH}}$, if the Fermi contact term was the dominant contribution to $^1J_{\text{NH}}$, then the shorter bond length could contribute to making the NH coupling for the anti proton greater than that for the syn N-H proton.

It is to be concluded from these observations that the two NH bonds are physically non-identical, and consequently it is not surprising that deuterium substitution of the amido hydrogens produces different isotope effects.

An analogous situation to the stereospecificity of these isotope shifts is found for the substituent effects of the fluoro-olefins, for which Phillips and Wray⁵⁴ have suggested that the difference arises from the fact that in such systems there is a vicinal delocalisation of σ electrons.

This is characterised^{59,60} by a negative long range bond order for a cis arrangement of bonds and a positive long range bond order for a trans arrangement. Pople states⁶⁰ that qualitatively this corresponds to anti-bonding (or repulsion) between cis atoms and bonding (or attraction) between trans. This origin of this finite bond order lies in the non-zero value of a direct bond integral, β , between non-formally bonded substituents, the magnitude of which depends upon the proximity of the interacting species.⁶⁰

Corroborating evidence for the vicinal delocalization theory of stereospecific isotope effects is provided from a study of vicinal H(D)-C-C-F isotope effects in some cyclohexyl¹¹ and norbornyl fluorides, for which the relevant data were presented in the review section of this chapter (see structures 11-20, Table 3). Lambert and Greifenstein found that the magnitude of the isotope shift was at a maximum when the D and F atoms were in an anti periplanar arrangement (dihedral angle = 180°) in keeping with the results recorded for the α fluoroacetamides, and they concluded that vicinal delocalization provided the most viable explanation of their observations.

In an attempt to examine the possibility that a through bond transmission of the isotope effect may affect ^{13}C shielding, carbon-13 spectra of monofluoroacetamide were obtained for a partially deuterated sample in methanol solution. Unfortunately, neither the carbonyl nor acetyl carbon resonances could be resolved into separate signals assignable to each isotopically substituted species. However, it is interesting to compare the line widths ($\Delta\nu_{\frac{1}{2}}$) for the partially deuterated species with that obtained for the pure material (table 6). Values of $\Delta\nu_{\frac{1}{2}}$ for each carbon nucleus were measured individually and corrected against that of the methanol (solvent) resonance as standard; to allow for deviations produced by field homogeneity variations and digitization errors.

Table 6 shows that the carbonyl carbon resonance of the pure amide exhibits a line broadening of ca. twofold with respect to that of the standard, whilst no such effect is observed for the acetyl carbon: this must arise from the quadrupolar broadening of the former carbon.

Table 6. Line width measurements for partially deuterated Fluoroacetamide (Hz).

	Carbonyl resonance			Acetyl resonance		
	$\Delta\nu_{\frac{1}{2}}$ C=O	$\Delta\nu_{\frac{1}{2}}$ CH ₃ OH	Broadening factor	$\Delta\nu_{\frac{1}{2}}$ -CH ₂ F	$\Delta\nu_{\frac{1}{2}}$ CH ₃ OH	Broadening factor
Undeuterated	2.32	1.16	2.0	1.2	1.15	1.0
Partially deuterated	4.27	1.28	3.3	1.56	0.98	1.6

It is now apparent that partial deuteration of monofluoroacetamide causes additional broadening of the carbonyl carbon by ca. 50% (compared to the pure material) with a considerably less significant, but measurable effect on the acetyl carbon band-shape.

2.3. N-Methyl substituent chemical shifts for the amides.

Table 7 lists the ¹⁹F substituent chemical shifts (S.C.S.) in Hertz for successive introduction of N-methyl groups to the amides, data being for solutions in chloroform at infinite dilution. Column 5 of the table lists the corresponding total isotope shifts for the -ND₂ derivatives in dichloromethane solution for comparison. Positive shifts are taken to low field of the unsubstituted compound. The effects of successive N-methylation may be compared with the corresponding -ND₂ isotope shift by plotting the various S.C.S.'s listed in table 7 against the isotope shift, and this is shown in figures 4(a-c). In the determination of the S.C.S. arising from the introduction of one methyl group, (-NH₂ -NHMe)

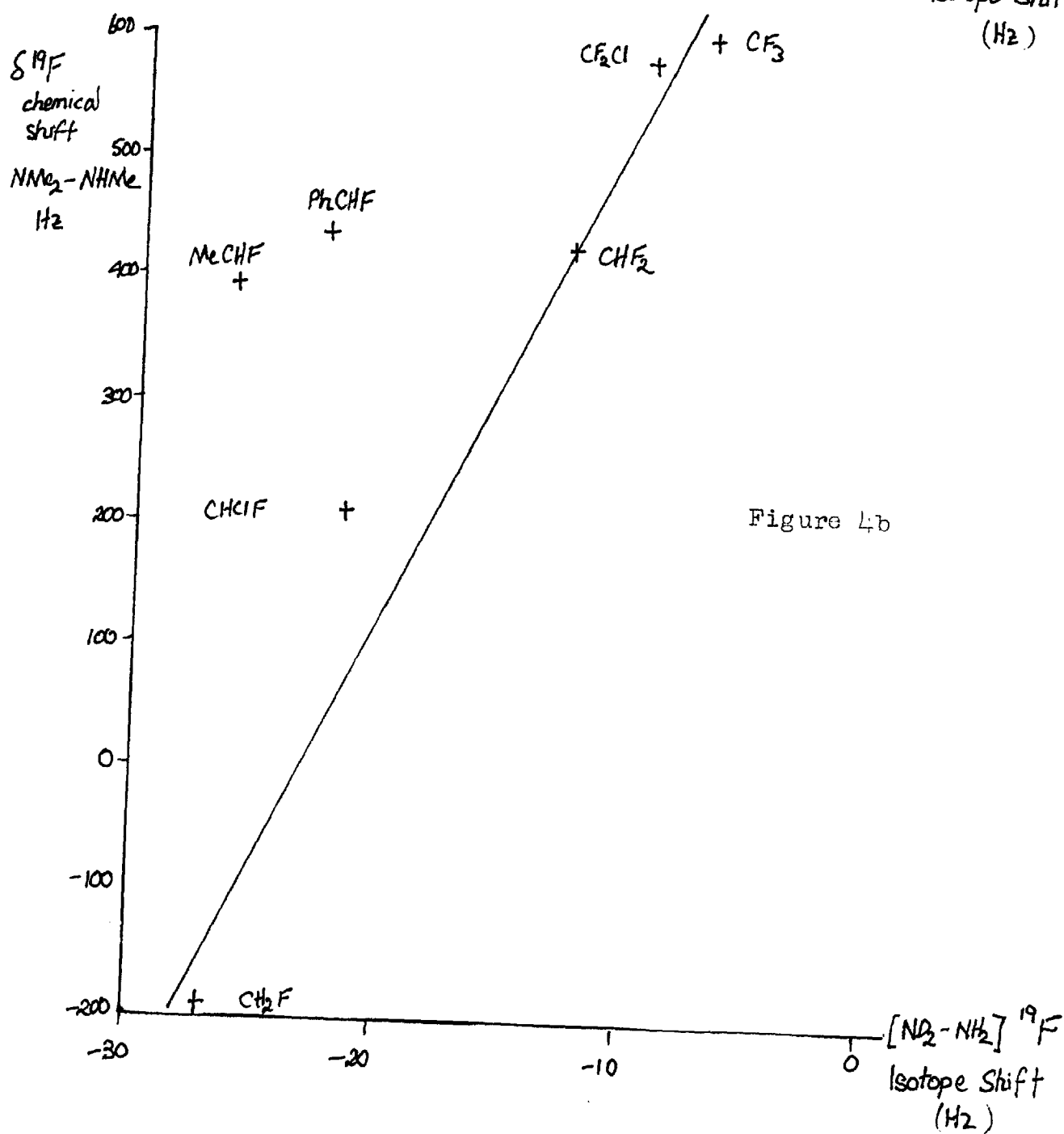
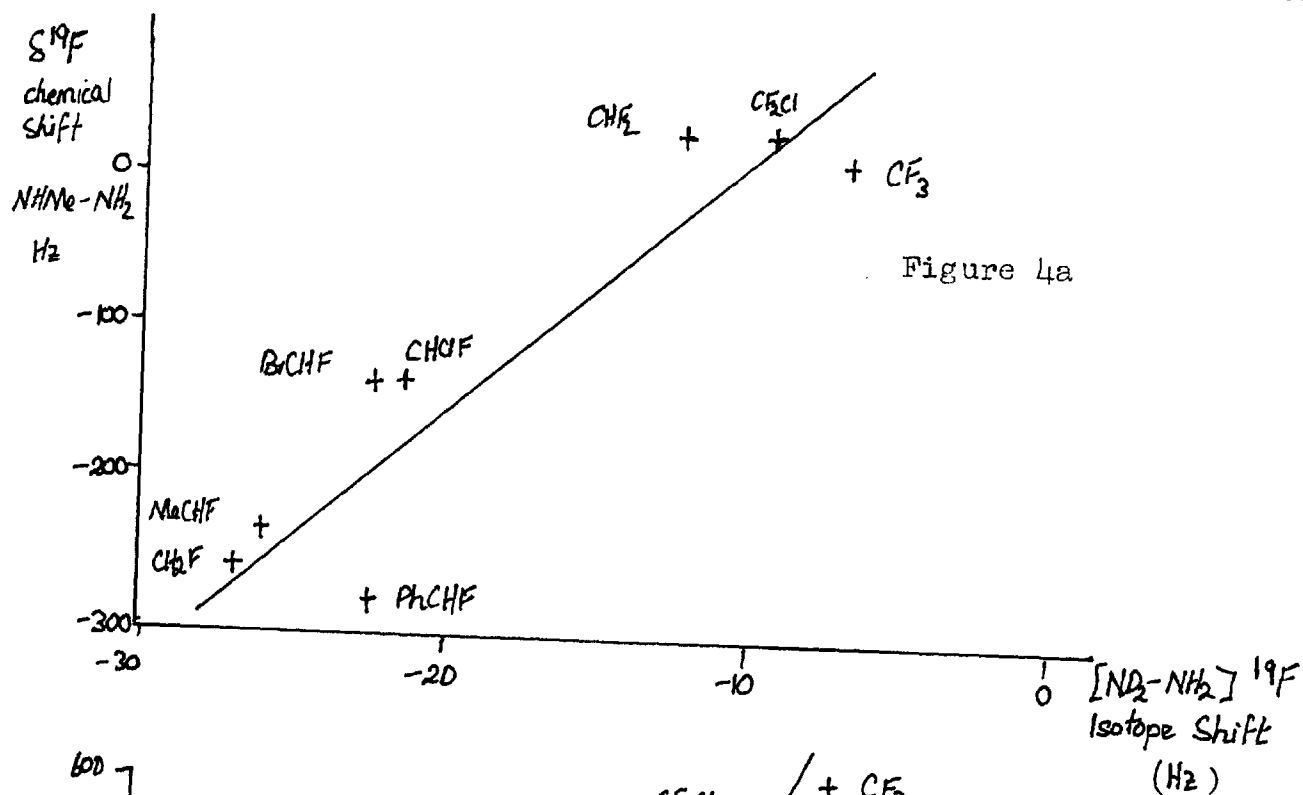
Table 7. Substituent chemical shifts for N-methylation of the fluoro-amides.

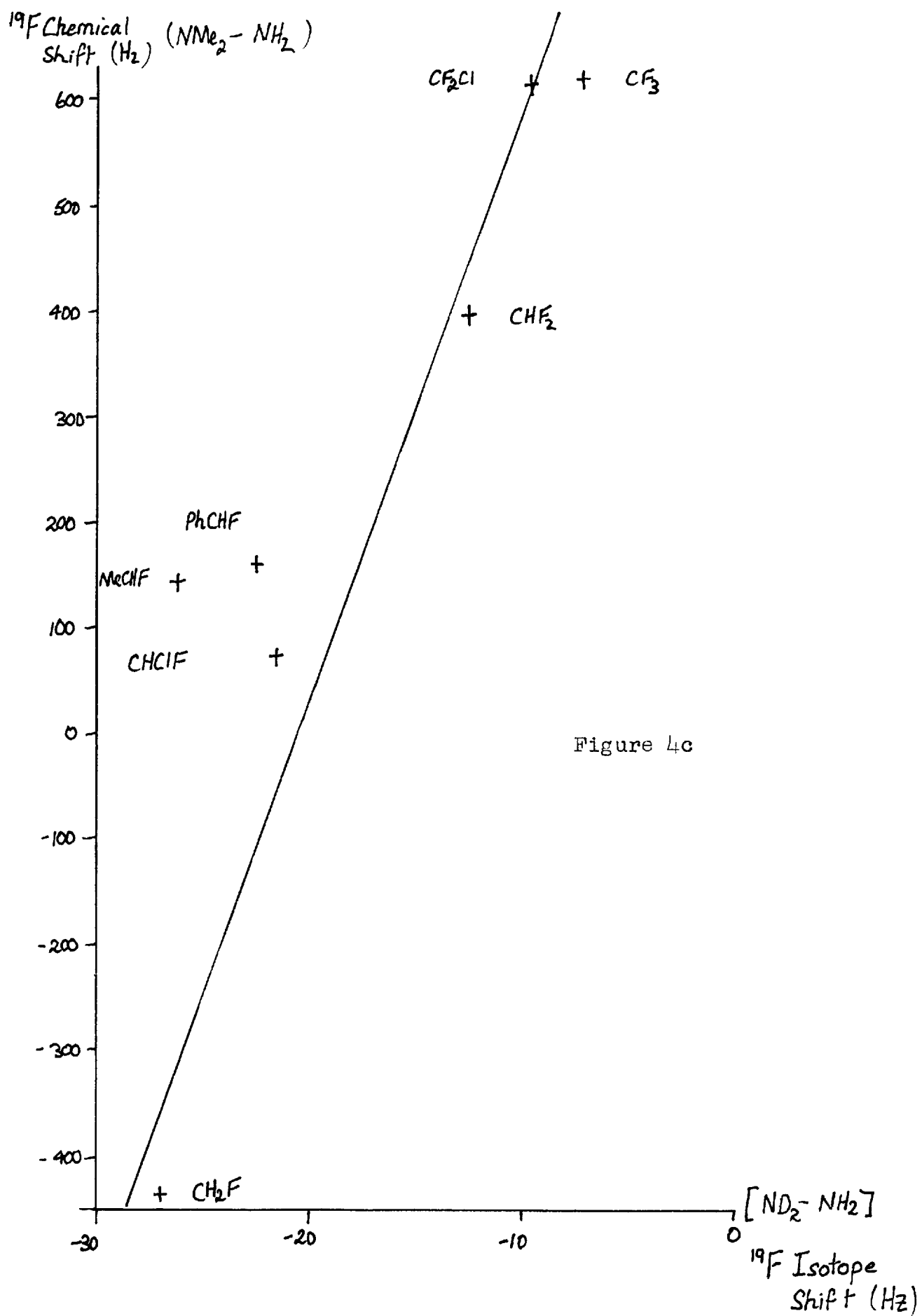
Acetyl Group	S.C.S. for N-Me substitution indicated (Hz)			ND ₂ isotope shift (Hz)
	NHMe-NH ₂	NMe ₂ -NHMe	NMe ₂ -NH ₂	
H ₂ FC-	-257.0	-196.4	-433.6	-27.0
MeHFC-	-232.3	395.5	143.2	-26.25
BrHFC-	-135.4	-	-	-22.4
PhHFC-	-279.8	437.9	158.1	-22.5
ClHFC-	-136.7	210.3	73.6	-21.4
F ₂ HC-	33.6	430.4	396.8	-12.6
FCF ₂ C-	54.5	825.5	771.0	-
F ₂ ClC-	31.0	583.6	614.8	- 9.45
F ₃ C-	14.2	605.4	619.6	- 6.90

it is assumed that the N methyl group is always syn to the carbonyl, i.e. trans to the acetyl group, in accord with the generally accepted views on the structure of secondary amides.⁶²

It is seen from table 7 that the effects of N-methylation are not additive, unlike isotopic substitution, for which only a small dependence on the site of substitution was observed. Thus for the mono-fluoro amides, addition of a syn methyl group produces a negative S.C.S. of 257Hz, whilst the second (anti) substituent induces a further upfield shift of 196.4 Hz. In contrast to this, mono (syn) methylation of trifluoroacetamide results in a very small downfield S.C.S. (14.2 Hz); while addition of the second methyl group produces a large downfield shift of 605 Hz.

Figure 4c shows that the effects of di-N-methylation and dideuteration on the ¹⁹F chemical shift are similar (with the exception of the PhHFC- and MeHFC compounds, which will be discussed in more





detail below). The plot of S.C.S. for -NMe_2 against the isotope shift for -ND_2 has a correlation coefficient of 0.979, and this may indicate that the effective mechanisms for transmission of the effects of chemical or isotopic substitution at the nitrogen atom could have a common origin.

Consider the effects of introducing the methyl groups at the amido nitrogen atoms. The methyl group may be considered as a weak electron donating (+I) species, and hence methylation of the nitrogen atom will modify the electron density at this centre. As discussed above for the case of the isotopic substitutions, consequent redistribution of this extra charge through the amido (-C(=O)-N) bond will modify the effective electronegativity of the carbonyl group, and hence induce chemical shifts in the fluorine nucleus. It is seen from the plot of the S.C.S. for mono-N methylation vs. isotope shift (figure 4a) that the effects of such a substitution are greatest for the least electronegative acetyl groups (23, $a = b = \text{H}$).

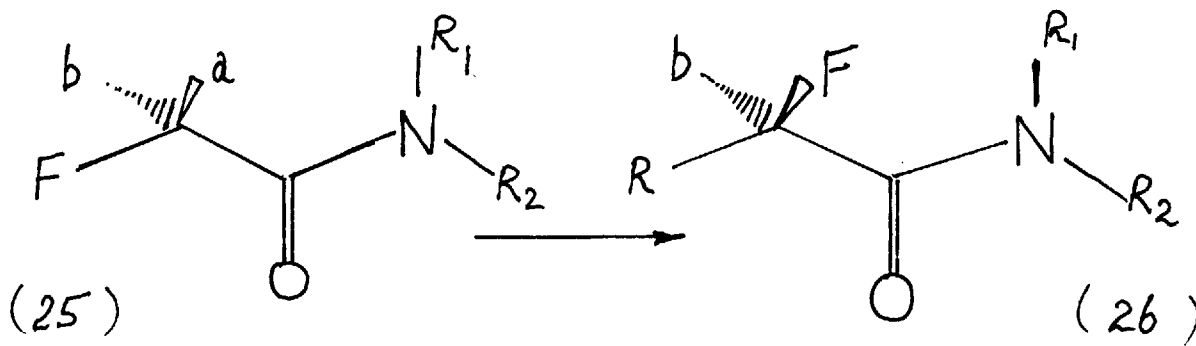
The effects of adding a second N-methyl group to the anti proton may now be considered. Similar electronic consideration to those made for syn methylation are applicable, so discussion can be centred on the nature of the variation of the S.C.S. with the acetyl group substituents. Figure 4b shows that the observed trend of the S.C.S. is in good accord with the corresponding isotope shift (correlation coefficient = 0.974). In contrast to the mono-methylation S.C.S., the relationship of the MeHFC- and PhHFC- cases, as noted for syn methylation.

It now remains to explain the differences between syn and anti N-methylation. It is possible to do so by consideration of the geometric relationships of the N methyl groups with the carbonyl and acetyl groups; these differ for the two substituents, and must be ultimately responsible for the pattern of the S.C.S.'s noted above. Together with these differences, it is possible to understand qualitatively the differences between sequential N-deuteration and N-methylation in terms of the considerably larger size of a methyl group over a deuterium atom.

Mono N-methylation introduces a methyl group syn to the carbonyl function, in which position it will not influence the conformational preferences of the acetyl group substituents. In such a situation, it

is possible that the S.C.S. observed for mono syn methylation could parallel that of deuteration, and this is illustrated in figure 4a.

A second methyl group at the anti position is considerably closer to the acetyl group, and capable of disturbing the conformational preferences of the latter. This would not arise for deuteration at the anti position, and hence it is not anticipated that the SCS observed for methylation ($\text{NHMe} - \text{NMe}_2$) will reflect the trend found for N deuteration. Indeed, it is seen from figure 4b that the shifts observed for compounds with methyl or phenyl as acetyl substituents (23, $a = \text{H}$, $b = \text{Me}$ or Ph) lie considerably off the general trend suggested by the simple halogenated acetamides. It is known⁶³ that for α -fluoro acetyl compounds, the fluorine atom has a conformational preference to eclipse the carbonyl oxygen, (this will be discussed further in Chapter 3). Thus introduction of a methyl or phenyl group at the acetyl carbon will probably disrupt this conformational preference, assuming a normal 'staggered' bond relationship, and hence the fluorine will be displaced into a gauche position with respect to the carbonyl group.



Therefore from the nature of the stereospecific interactions discussed above, it is not reasonable to expect these acetyl substituents to conform to the general trends for the halogens.

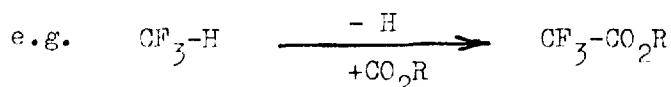
The remaining point of interest is the anomalously large S.C.S. observed for total methylation of the $\text{Cl}_2\text{FC}-$ compound. If it is assumed that the normal conformational preference is present (25, $a = b = \text{Cl}$) i.e. the fluorine is eclipsing the carbonyl oxygen, then molecular

models show that the chlorine atoms are spatially near the anti methyl group (25, R₁). This is sufficient to hinder completely free rotation of the acetyl and N-methyl groups, which can only take place by a "cogwheel effect". It would seem probable that the repulsive interaction between these groups must be the cause of the increased S.C.S. in this instance.

2.4 (¹³C-¹²C) ¹⁹F isotope shifts.

As a parallel study to the above, the directly bonded isotope effect of ¹²C-¹³C substitution at the acetyl carbon on the ¹⁹F chemical shift was also examined to see how this correlated with the published data^{4,9,18} on the fluoromethanes and determined if there were any correspondence between these effects and the observed long-range deuterium isotope effects. Because many of the primary amides are solids, the ¹²C-¹³C isotope effects were determined for the corresponding methyl or ethyl esters. Since both the esters and amides exhibit the same range of fluorine chemical shifts which can be analysed (chapter 1) in identical fashion, it is expected that the data obtained from the esters will be directly applicable to the amides.

Table 7 lists the isotope shifts observed for the ¹⁹F resonances on ¹³C isotopic substitution at the acetyl carbon, together with the ¹⁹F-¹³C directly bonded coupling constant (¹J_{CF}) determined from the ¹⁹F spectrum of the neat ester. The table also includes similar data (as available) taken from the literature⁴ for the corresponding fluoromethane; for this purpose the ester is considered to be derived from the methane by substitution of hydrogen by the alkoxy carbonyl (-CO₂R) group.



A plot of the isotope shift obtained for the fluoroester against the reported value for the corresponding fluoromethane is linear (figure 5a, correlation coefficient = 0.965) and an even better agreement

Table 7. $(^{13}\text{C}-^{12}\text{C})$ ^{19}F isotope shift for fluoromethanes and fluoroesters.

α fluoroester			fluoromethane		
acetyl group	$^1J_{\text{CF}}$ (Hz)	$(^{13}\text{C}-^{12}\text{C})^{19}\text{F}$ (ppm)	compound	$^1J_{\text{CF}}$ (Hz)	$(^{13}\text{C}-^{12}\text{C})^{19}\text{F}$ (ppm)
$\text{H}_2\text{FC}-$	178.6	0.0924	CH_3F (9)	158	0.072
$\text{MeHFC}-$	180.7	0.1019	-	-	-
$\text{PhHFC}-$	183.6	0.1072	PhCH_2F (60)	165	0.107
$\text{HFC}_2\text{C}-$	250.6	0.1359	-	-	-
$\text{HF}_2\text{C}-$	247.0	0.1189	CH_2F_2 (9)	235	0.115
$\text{FCl}_2\text{C}-$	303.8	0.1646	CFCl_2H (18)	294	0.156
$\text{F}_2\text{ClC}-$	299.7	0.1412	-	-	-
$\text{F}_3\text{C}-$	283.9	0.1274	CF_3H (9)	274	0.126

Figures in brackets refer to the original literature references.

is obtained for a graph of the corresponding C-F coupling constants (figure 5b, correlation coefficient 0.9997). These plots serve to indicate that the carbonyl group is behaving as a regular substituent in its influence on these properties, a similar conclusion with respect to the fluorine chemical shift was made in chapter 1.

A plot of the isotope shift for the fluoroesters against the total electronegativity of the acetyl group substituents, (figure 6) fails to reveal any correlation. In an earlier study of $(^{12}\text{C}-^{13}\text{C})$ ^{19}F isotope effects, Frankiss⁹ found that an approximately linear relationship existed between the magnitude of the isotope shift and the directly bonded ($^1J_{\text{CF}}$) coupling constant:-

$$\delta\phi(^{12}\text{C}-^{13}\text{C})^{19}\text{F} = 0.007 + 4.36 \times 10^{-4} J_{\text{CF}}$$

Figure 5b

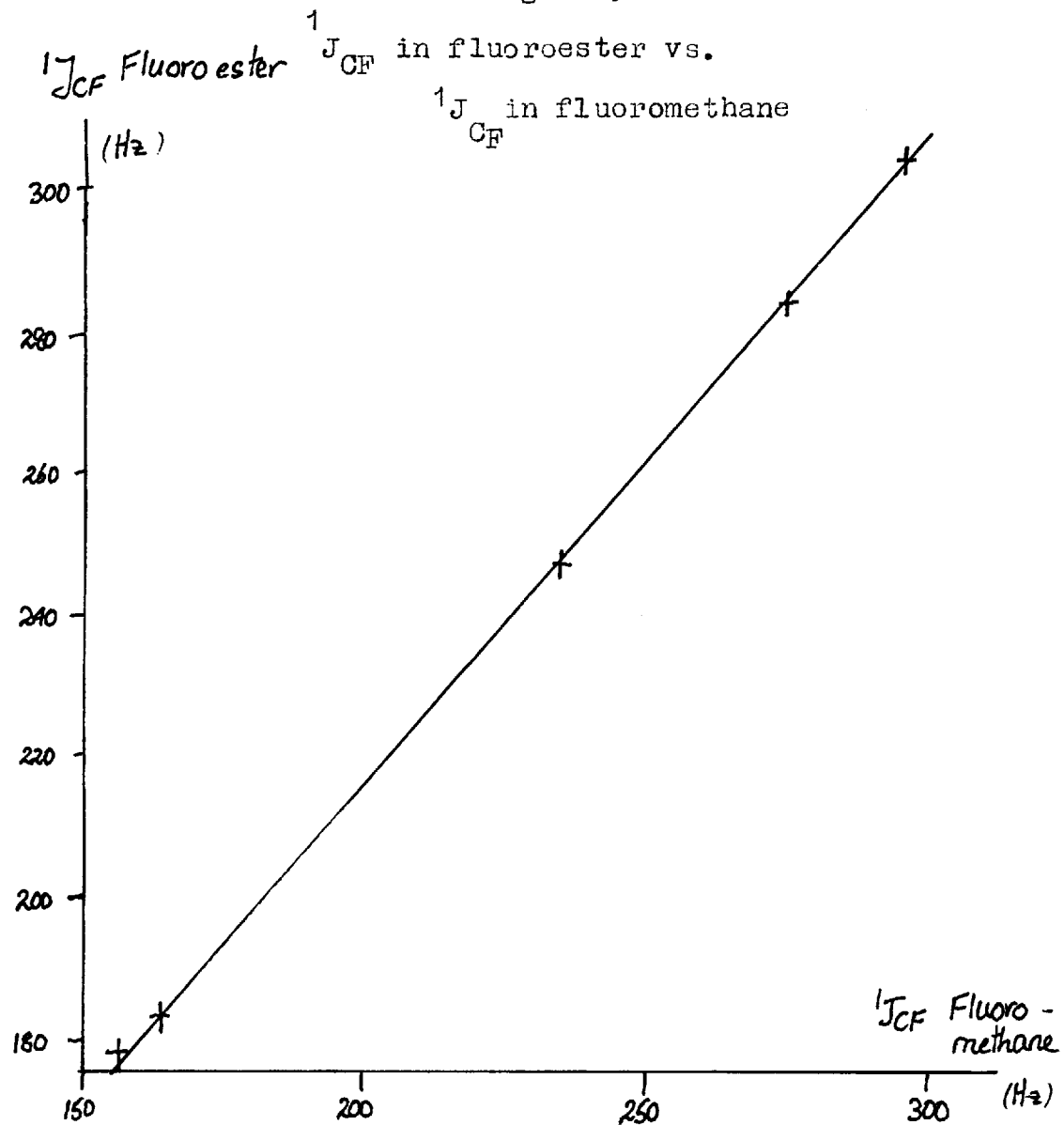
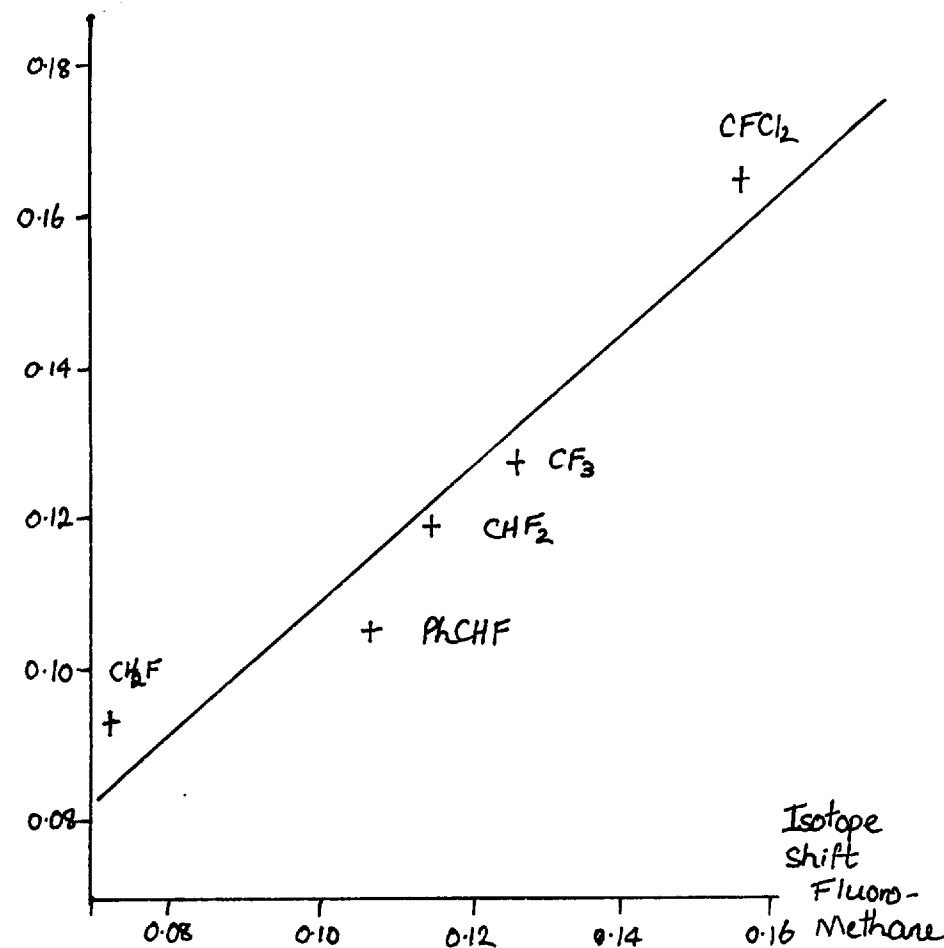


Figure 5a

(^{12}C - ^{13}C) ^{19}F isotope shift in fluoroester vs. (^{12}C - ^{13}C) ^{19}F isotope shift in fluoromethane

Isotope Shift Fluoroester



from a study of the these parameters obtained from fluoromethanes. Frankiss suggests that this relationship has the limitation that it only applies to sp^3 carbon substituted by elements from the first row of the Periodic Table and hydrogen, or less than three second row elements directly bound to the ^{13}C atom. Within these restrictions, it was possible to predict the observed isotope shift to within ± 0.012 ppm or better, an error of 8 - 10%. However, compounds such as CFBr_3 ($\delta\phi_{\text{obs}} = 0.191$ ppm) and CFCl_3 ($\delta\phi_{\text{obs.}} = 0.194$ ppm) showed large deviations (0.022 and 0.039 ppm, respectively) from their calculated isotope shifts, and no explanation has been put forward for these discrepancies.

Frankiss found that for the series $\text{CH}_{4-n}\text{F}_n$ ($n = 1-3$) the $(^{12}\text{C} \ ^{13}\text{C})^{19}\text{F}$ isotope shift increased in the order CH_3F , CH_2F_2 , CF_4 and CHF_3 . Harris has commented¹⁸ that it is difficult to rationalize these data in terms of the theory proposed by Gutowsky,²⁹ in which the isotope effect results from a deformation of the electrostatic field proportional to $\langle r^{-2} \rangle$. (This is discussed further in the introduction). Such a theory would require that the nett charge q on the carbon atom for CHF_3 to be greater than for CF_4 , and recent ab initio calculations by Pople⁶¹ show that this is probably not the case.

A plot of the $(^{12}\text{C}-^{13}\text{C})^{19}\text{F}$ isotope shift data obtained for the fluoroesters against $^1J_{\text{CF}}$ is shown in figure 7. Values of the isotope effect calculated by the Frankiss equation are listed in Table 8, and indicated as the solid line in the figure.

The average deviation of the line is $+0.0116$ ppm, which is comparable to that reported by Frankiss, but inspection of figure 7 shows that the equation is providing a particularly poor estimate of the isotope shift for the more highly halogenated compounds, with a discrepancy of $+0.025$ ppm (16%) being noted for that with two chlorine atoms (second row element).

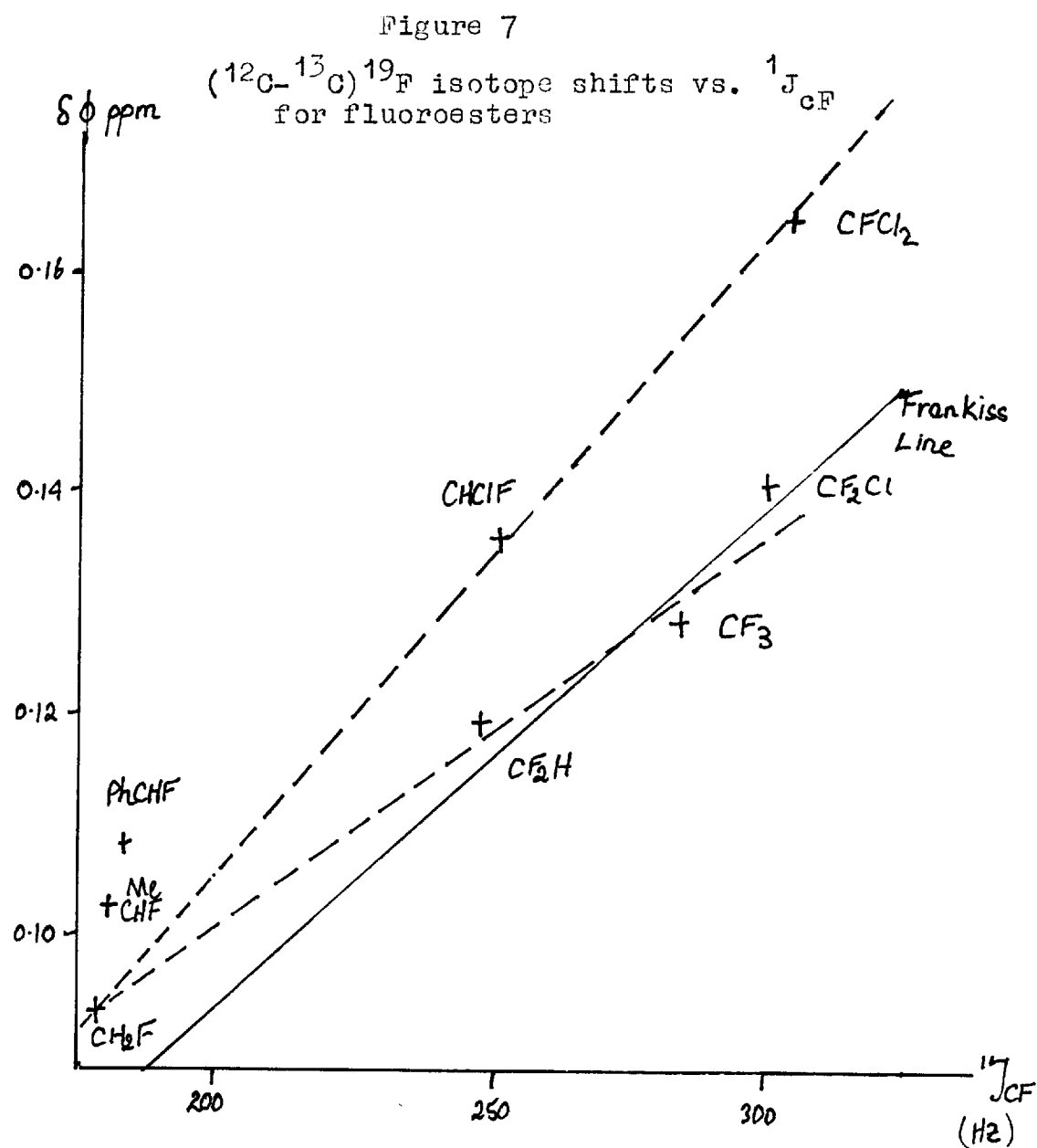
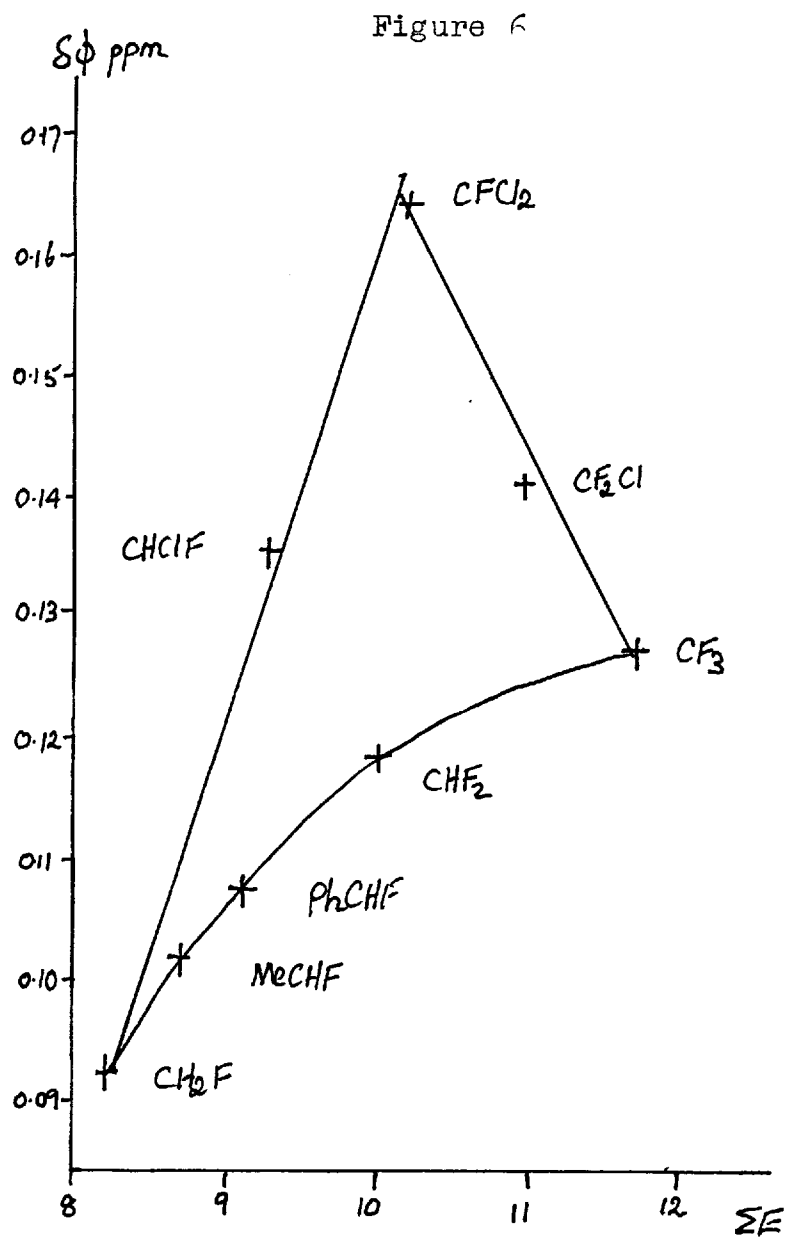


Table 8. Comparison of observed (^{12}C - ^{13}C) ^{19}F isotope shifts for fluoro-esters with those obtained from the Frankiss equation.

Acetyl group	Isotope shift (ppm)		δ (observed - calculated)
	calculated	observed	
$\text{FH}_2\text{C}-$	0.0849	0.0924	0.0075
$\text{MeHFC}-$	0.0858	0.1019	0.0161
$\text{PhHFC}-$	0.0870	0.1072	0.0202
$\text{HClFC}-$	0.1163	0.1359	0.0196
$\text{F}_2\text{HC}-$	0.1147	0.1189	0.0042
$\text{FCl}_2\text{C}-$	0.1395	0.1646	0.0251
$\text{F}_2\text{ClC}-$	0.1377	0.1412	0.0035
$\text{F}_3\text{C}-$	0.1308	0.1274	-0.0034

2.5 Experimental.

^{19}F NMR spectra were recorded on a modified Varian HA-100 NMR spectrometer operating at 94.08 MHz in extended-lock mode with automatic phase correction.⁶³ The deuterium isotope effect spectra were obtained by addition of 1-2 drops of D_2O to a dilute solution of the amide in 'Analar' methanol, sufficient to enable detection of all the isotopically substituted species. The solvent was removed after recording the spectrum by a stream of nitrogen gas, and the spectrum re-recorded in dichloromethane (G.P.R.). This process was repeated and the sample re-dissolved in dry re-distilled dimethylformamide. Spectra of the N-methylated amides were obtained for solutions at infinite dilution in chloroform, as described in chapter 1. It was necessary to use this as solvent due to the polar nature of the primary amides, as it was desirable to employ a common solvent for all three series of compounds.

Hexafluorobenzene was used a lock and reference for all the spectra and frequencies were measured on 100 or 50 Hz sweep widths, using a frequency counter.

The ($^{12}\text{C} \rightarrow ^{13}\text{C}$) ^{19}F isotope shift data were recorded with a Varian XL 100-12WG spectrometer at a centreband frequency (for CFCl_3) of 94.151 MHz. Spectra were obtained for neat samples of the ester in 5mm tubes contained in a 10mm tube filled with D_2O , which served as the lock signal. Full proton decoupling was employed where necessary, with a band width of 1000Hz, centred at 4 δ in the proton spectrum. Spectra were recorded using the Fourier transform technique, with a pulse angle of ca. 80° (18 μsec pulse) and an effective "sweep width" of 512 Hz. It was found that approx. 100 transients were sufficient to enable unambiguous identification of the ^{13}C satellites.

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Chapter 3.

Carbon-13 NMR Study of Some Derivatives of

α Fluoroacetic Acid.

3.1 Introduction.

The advent of proton noise decoupling and Fourier transform (FT) technology has enabled carbon-13 NMR to become a relatively accessible spectroscopic technique with currently available instrumentation. Observation of ^{13}C provides a useful probe with which to examine the chemical environment of all the carbons at the various sites within a molecule, whether or not they bear more readily detectable nuclei such as proton or fluorine. The carbon-13 isotope has a spin of $+\frac{1}{2}$, and hence yields sharp absorption signals, and the low natural abundance (1.1%) implies that the probability of spin-spin interaction with a second carbon nucleus is very low (10^{-4}); consequently the only coupling observed will be with other nuclei of high natural abundance (e.g. ^1H , ^{19}F , ^{31}P).

Although the factors influencing ^{13}C shielding have not been investigated as fully as for fluorine or proton nuclei, the general outline presented in chapter 1 will be applicable. Since the carbon nucleus has a p electron valency shell, it is considered^{1,2} that the paramagnetic term will provide the dominant contribution to the magnetic shielding.

Therefore a general carbon-13 investigation of the series of α fluoroacetamides, which were studied by fluorine NMR in Chapters 1 and 2, was undertaken, in order to examine the nature of the substituent effects produced by N-methylation on the carbon skeleton. The series of methyl and ethyl esters was extended to include the esters of all the available haloacetic acids: the spectroscopic data from these compounds should reflect the effects of substituents upon the acetyl group alone.

3.2 Results and Discussion.

3.2.1. Methyl and Ethyl Esters of some α Haloacetic acids.

3.2.1.1. Chemical shifts of the Acetyl and Carbonyl carbons.

Table 1 gives the ^{13}C chemical shifts (ex TMS) for the acetyl and carbonyl carbons of the esters, at infinite dilution in carbon tetrachloride solution. (Positive shifts are to low field of reference).

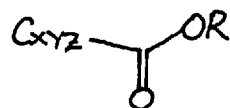
Inspection of table 1 reveals that the change of ester group from $-\text{CH}_3$ to $-\text{C}_2\text{H}_5$ has a small but measurable influence on the chemical shift of the acetyl methyl carbon, and the effect is such as to deshield it by 0.2 to 1 ppm. The change of a $-\text{CH}_3$ to $-\text{C}_2\text{H}_5$ ester may be classified³ as a δ effect, and such a substitution is typically in the range +0.3 ppm for paraffins. Thus, the downfield shifts observed here are of the expected magnitude and in the correct direction.

This change of ester group is a χ effect when related to the carbonyl carbon, for which the typical shift observed with the paraffins is -2.5 ppm (i.e. to high field). Table 1 shows that the effect of the change $-\text{OCH}_3 \rightarrow -\text{OCH}_2\text{CH}_3$ is to shield the carbonyl but only by 0.4 - 0.6 ppm, and hence it is apparent that the effects of this substitution are attenuated by the ester oxygen atom.

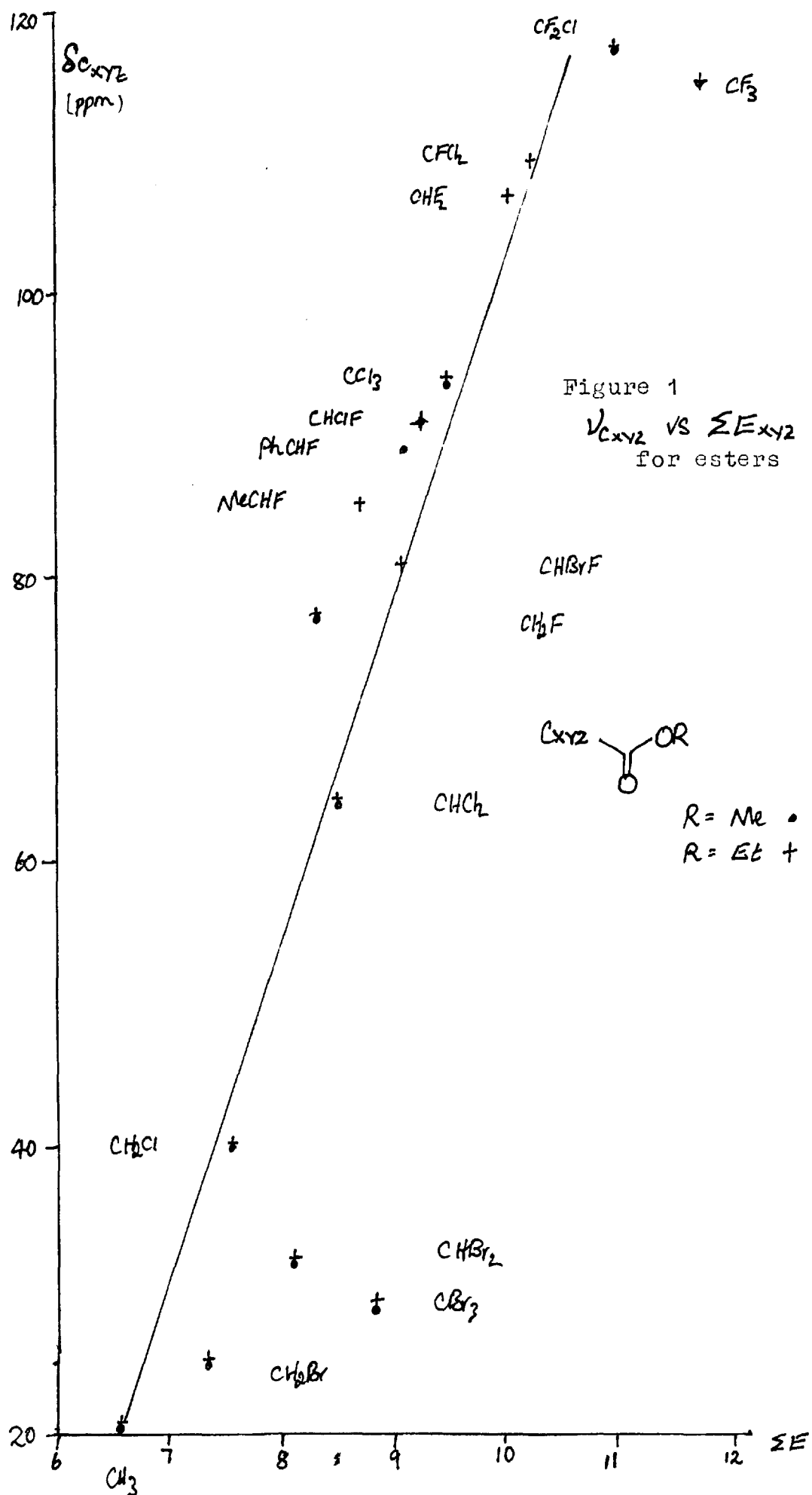
To summarize, it may be concluded that for the series $\text{C}_{\text{XYZ}}\cdot\text{CO}\cdot\text{OR}$, the nature of R has little effect (for the two types of R studied) on the chemical shift of these carbons, and thus the magnitude of the observed shielding is dominated by the acetyl carbon substituents X, Y and Z.

The nature of this dependence may be examined via plots of the chemical shifts of the acetyl and carbonyl carbons against the sum of the Huggins electronegativities⁴ of the substituents (ΣE), and these are shown in figures 1 and 2 respectively.

Table 1. Carbon chemical shifts of the acetyl and carbonyl carbons for some α haloacetic acid esters.



Acetyl group	Δ E	^{13}C (acetyl)		^{13}C (carbonyl)	
		R = Me	R = Et	R = Me	R = Et
CH_3	6.6	20.08	20.44	168.95	168.58
CH_2Br	7.35	24.26	25.03	168.98	165.50
CH_2Cl	7.55	39.81	39.96	166.07	165.52
CHBr_2	8.10	31.20	31.84	163.79	163.33
CH_2F	8.30	76.62	76.74	166.63	166.09
CHCl_2	8.50	63.54	63.78	163.69	163.09
MeCHF	8.70	—	84.70	—	168.81
CBr_3	8.85	28.00	29.18	161.52	160.92
CHBrF	9.05	—	80.49	—	163.20
PhCHF	9.10	88.62	—	167.46	—
CHClF	9.25	90.62	—	163.22	—
CCl_3	9.45	93.30	93.68	161.56	160.97
CHF_2	10.00	106.20	106.31	161.69	161.32
CCl_2	10.20	—	108.66	—	159.96
CF_2Cl	10.95	118.48	116.56	158.80	158.26
CF_3	11.70	114.24	114.20	157.13	156.59



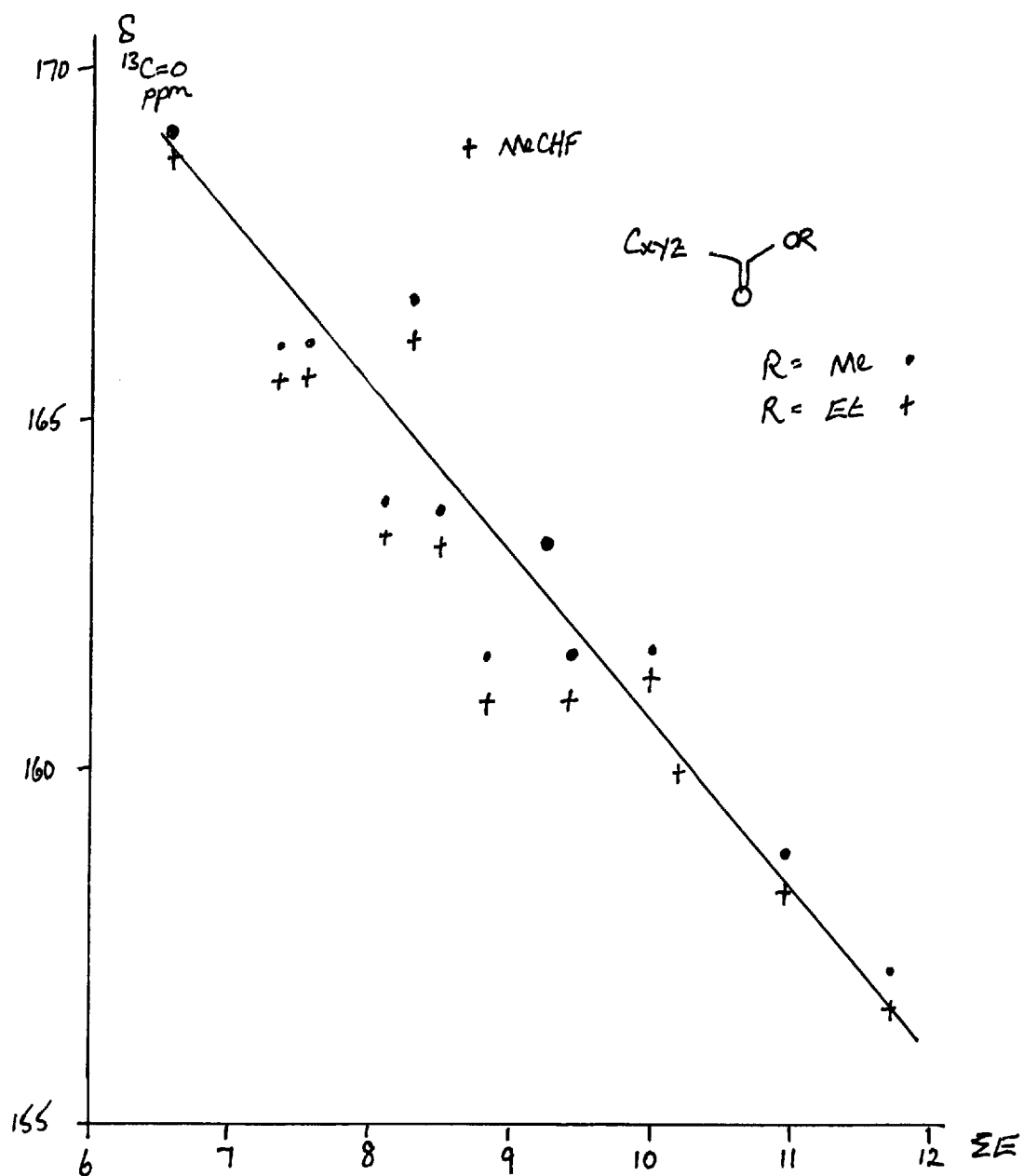


Figure 2

Chemical shift of carbonyl carbon vs. ΣE

Attention may initially be directed to the chemical shift of the acetyl carbon. Figure 1 reveals that the shielding is an approximate linear function of the substituent electronegativities, with some important exceptions. Thus for the series of α bromoesters, $\text{CH}_2\text{Br} - \text{CHBr}_2 - \text{CBr}_3$, the dibromo-compound appears to lowest field of the three, with the tribromo-derivative absorbing midway between the other two members of the series. All of the shifts lie well away from the indicated line. The other important exception is for the series of chloro-fluoro esters, $\text{CFCl}_2 - \text{CF}_2\text{Cl} - \text{CF}_3$, where the $-\text{CF}_2\text{Cl}$ compound ($\Sigma E = 10.95$) lies to low field of the $-\text{CF}_3$ group ($\Sigma E = 11.70$), which is well 'off' the indicated line in figure 1.

These observations are reminiscent of those made with the fluorine resonances (of the appropriate compounds) in chapter 1, whereby these departures from a purely additive inductive effect were analysed in terms of the new theory⁵ by Phillips and Wray. These workers showed that the observed effects (on fluorine shielding) arose from interaction of the substituents with each other and the carbon to which they were directly bonded, such as to modify the effective electronegativity of all the interacting groups by these perturbations. The original paper was concerned purely with geminal effects upon fluorine shielding, but in a later report⁶ this concept was extended to both geminal and directly bonded substituent effects for several other nuclei, including a successful analysis of the carbon-13 chemical shifts of a variety of halogenated methanes.

It will be interesting to determine if this theory can be used here. Application of this theory to the acetyl carbon requires use of the general expression for ^{13}C shielding in the molecule C_{abde} (see equation 7 of ref. 6) and this in turn necessitates that estimates of the interaction constants for hydrogen, halogen and the central carbon atom with the carbonyl group be obtained. Trial calculations with the trihalo- compounds (CF_3- , CCl_3- , CBr_3-) to determine the halogen-carbonyl interaction indicated this was significantly different for the three halogens, and hence it was not possible to assume this was equal for all the halogens. It is to be noted that in their calculations

on the ^{13}C halomethanes,⁶ Phillips and Wray had assumed all interhalogen and halogen-carbon interaction constants were independent of the nature of the halogen, whilst small differences were found in the hydrogen-halogen interaction constants.

Attention was thus confined to one of the halogens and the range of chloro compounds was chosen as a typical series ($\text{CH}_3 - \text{CH}_2\text{Cl} - \text{CHCl}_2 - \text{CCl}_3$), to determine all three of the interaction constants. Expressions were obtained for the hydrogen-carbonyl ($k_{\text{H.CO}}$) and halogen-carbonyl ($k_{\text{Cl.CO}}$) interactions in terms of the carbon-carbonyl ($k_{\text{C.CO}}$) interaction from the shift of the CH_3 and CCl_3 compounds (referred to $^{13}\text{CH}_4$) respectively, but substitution of these into the expression for the mono-chloro derivative led to a grossly unrealistic estimate of the carbon-carbonyl ($k_{\text{C.CO}}$) interaction constant, and hence the others.

Consequently, a quantitative analysis of this data has not been possible, but the results available from the calculations on the partially halogenated methanes do enable a qualitative explanation of the above-noted discrepancies to be made. The changes in shielding noted for the series of bromo-compounds are paralleled by the corresponding methanes (replacing $-\text{CO}_2\text{R}$ by H), and it was shown⁶ by Phillips and Wray that the marked non-linearity in the plot of carbon shielding against halogen content could be satisfactorily accounted for in terms of the appropriate interaction constants used in the general expression for carbon shielding. Although fluoro- and mixed chlorofluoro-methanes were not investigated, it was found in Chapter 1 that in the sets of acid derivatives, the progressive deshielding of the fluorine nuclei in the series $\text{CF}_3 - \text{CF}_2\text{Cl} - \text{CFCl}_2$ could be understood in terms of the theory, and since the carbon atom is at the opposite end of the C-F bond, it seems reasonable to expect the carbon shielding to respond similarly. It may be concluded, therefore, that it is possible to understand the observed shieldings of the acetyl group in a qualitative fashion.

Figure 2 shows that the carbonyl carbon chemical shift is directly proportional to the sum of the electronegativities of the substituents at the acetyl carbon, and hence it may be concluded that the effects of the various indirect geminal interactions have a negligible influence at the carbonyl centre. Least squares analysis of the data indicates that the chemical shifts of the carbonyl groups may be estimated according to the expressions:-

$$\Delta_{C=O} = 182.08 - 2.175 \Sigma E_{\text{ppm}}(\text{Ethyl ester}) \quad (1)$$

$$\Delta_{C=O} = 184.39 - 2.313 \Sigma E_{\text{ppm}}(\text{Methyl ester}) \quad (2)$$

If these are referred to the ester of the unsubstituted acid, the equations reduce to:-

$$\Delta_{C=O} = 13.50 - 2.175 \Sigma E_{\text{ppm}}(\text{Ethyl ester})$$

$$\Delta_{C=O} = 15.44 - 2.313 \Sigma E_{\text{ppm}}(\text{Methyl ester})$$

The r.m.s. deviation of the chemical shifts may thus be estimated to 0.98 and 1.62 ppm respectively (to eqn 1 & 2).

3.2.1.2. Chemical Shifts for Carbons of the Ester Groups.

Attention may now be directed to examining the effects of the acetyl group substituents upon the carbon resonances of the ester groups. Table 2 lists the chemical shifts of the ester group carbon resonances taken from the same spectra as used to compile table 1 (i.e. for infinitely dilute solutions in carbon tetrachloride). The chemical shifts of the methoxyl ($-\text{OCH}_3$) and methylene ($-\text{OCH}_2$) carbons have been plotted against the sum of the Huggins electronegativities of the acetyl carbon substituents as figures 3 and 4 respectively.

Plots of ^{13}C chemical shifts for ester oxycarbon vs. ΣE

Figure 3 - $-\text{O}^{13}\text{CH}_2\text{CH}_3$

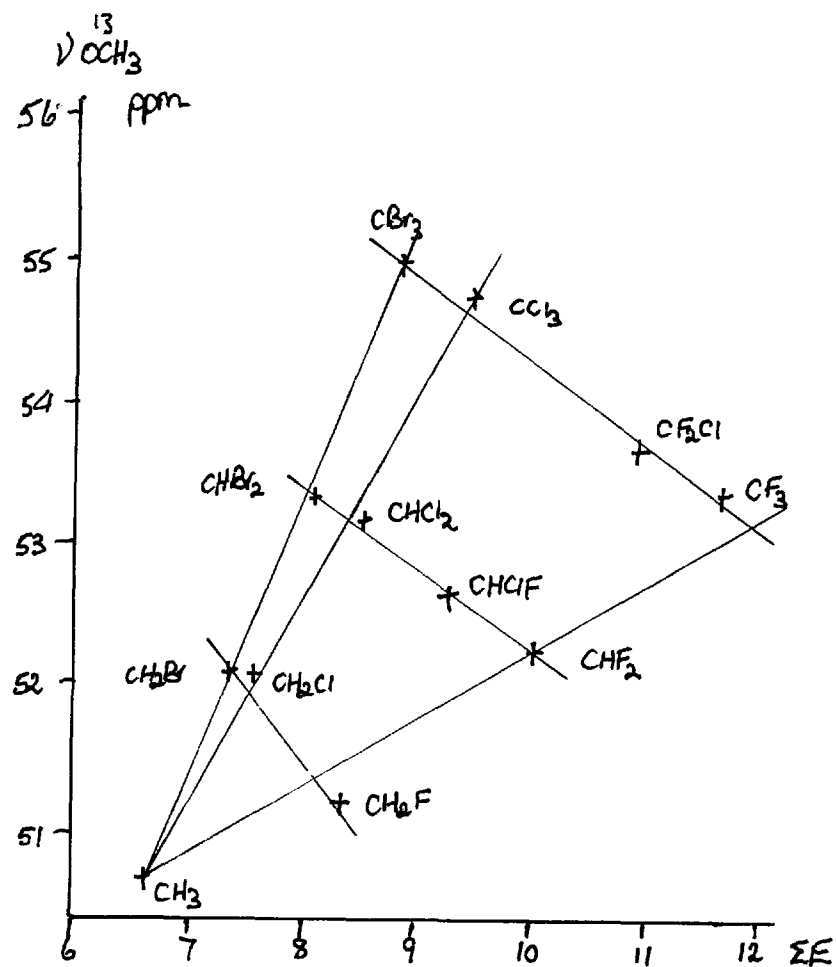
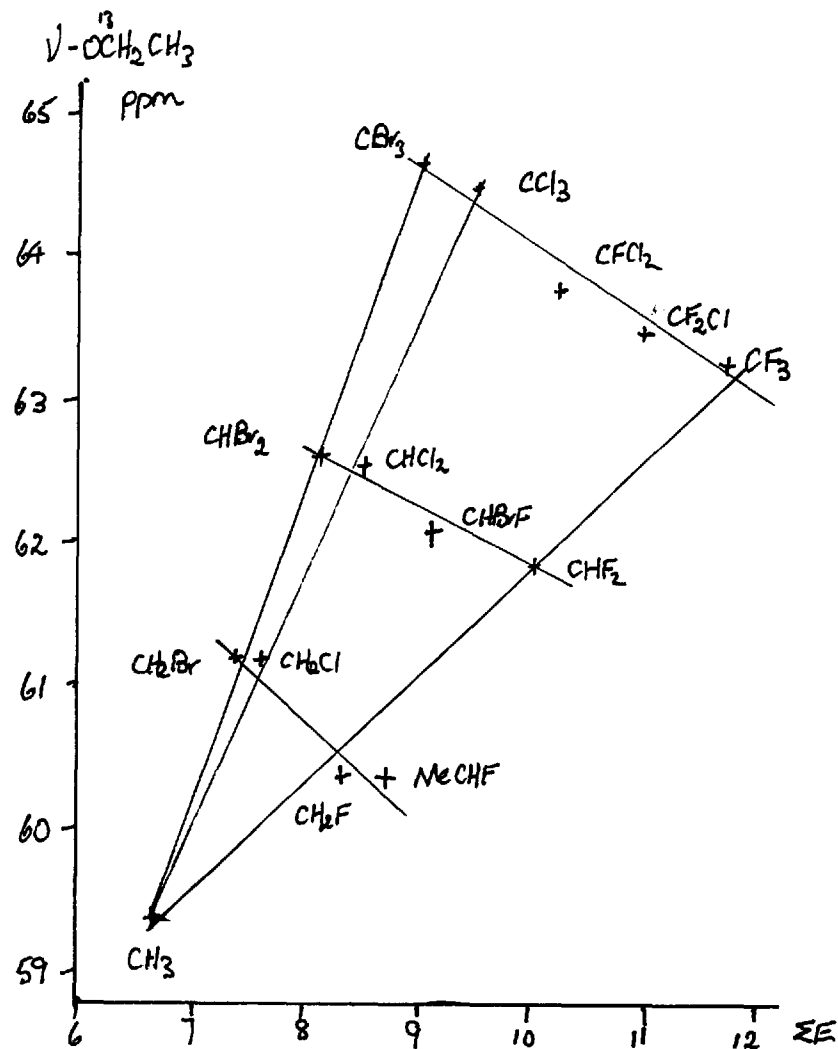
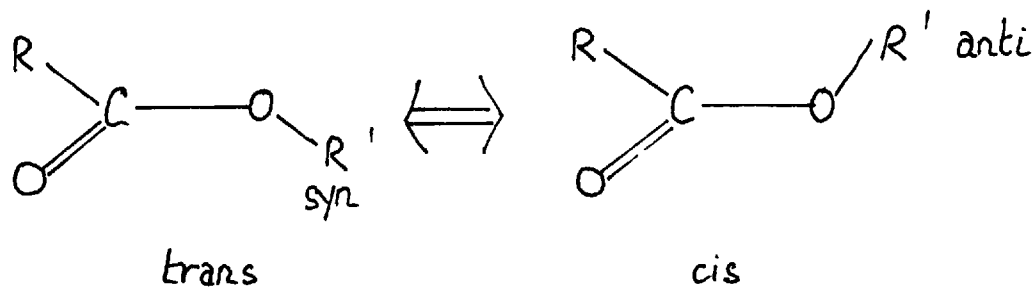


Figure 4 - $-\text{O}^{13}\text{CH}_3$



It is seen that each plot consists of several 'families of lines'. Thus for a particular halogen, the resonances corresponding monohalo- dihalo and trihalo compounds all fall on one line, and successive introduction of a halogen (at the acetyl group) produces a deshielding of the ester α carbon resonance in every case. Each halogen produces its own line, and all three lines intersect at the point corresponding to the position of the unsubstituted acid, i.e. this is a common point. It is also observed that there are lines reflecting the number of hydrogens (or halogen substituents) on the acetyl group. Although the range of the effects are slightly different for the $-\text{OCH}_3$ and $-\text{OCH}_2-$ carbons (4.31 and 5.18 ppm respectively), the nature of the phenomenon is exactly comparable for both series, which indicates that it must arise from a property of the acetyl group.

Several experimental techniques⁸ have been used to establish that esters of carboxylic acids, which are in principle capable of existing in either of the two planar conformations exhibit a preference for the trans rotamer with the ester group syn to the carbonyl oxygen:



The energy barrier to interconversion of the planar forms has been determined^{8c} from infra-red spectra to be 15.9 kcal/mole for methyl acetate and 13.1 kcal/mole for methyl formate, and these high activation energies arise from the partial double-bond character of the C-O single bond, which has been estimated^{8d} to be approximately 20% for the latter compound.

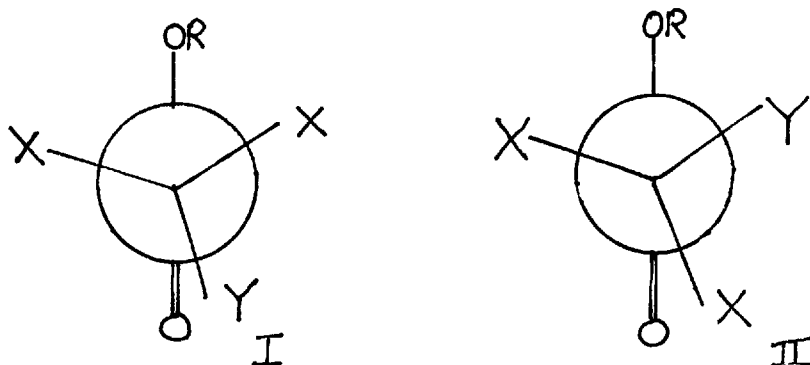
Shapiro and Sardella⁷ have studied the solvent dependence of the ^1H and ^{19}F spectra of methyl mono-, di- and tri-fluoroacetate

Table 2. Chemical shifts of the ester groups of the haloacetic acids

Acetyl Group		$\delta^{13}\text{C}-\text{O}^{13}\text{CH}_2\text{CH}_3$		$\delta^{13}\text{C}-\text{OCH}_2-^{13}\text{CH}_3$		$\delta^{13}\text{C}-\text{O}^{13}\text{CH}_3$	
C_{XYZ}	ΣF	Hz	ppm	Hz	ppm	Hz	ppm
CH_3	6.6	1495.8	59.45	357.0	14.18	1277.0	50.75
CH_2Br	7.35	1540.5	61.22	351.0	13.95	1313.2	52.19
CH_2Cl	7.55	1539.7	61.19	353.7	14.05	1312.2	52.15
CHBr_2	8.10	1575.3	62.61	342.6	13.61	1343.6	53.40
CH_2F	8.30	1519.5	60.39	354.5	14.08	1289.8	51.26
CHCl_2	8.50	1574.2	62.56	345.7	13.74	1340.8	53.29
MeCHF	8.70	1519.4	60.38	352.7	14.01	-	-
CBr_3	8.85	1626.2	64.63	342.3	13.60	1385.4	55.06
CHBrF	9.05	1559.3	61.97	346.1	13.75	-	-
PhCHF	9.10	-	-	-	-	1300.2	51.67
CHClF	9.25	-	-	-	-	1327.5	52.76
CCl_3	9.45	1622.9	64.50	344.6	13.69	1378.5	54.78
CHF_2	10.00	1556.4	61.86	347.6	13.81	1317.0	52.34
CFCl_2	10.20	1604.8	63.78	342.5	13.61	-	-
CF_2Cl	10.95	1597.0	63.47	344.4	13.68	1352.4	53.75
CF_3	11.70	1591.6	63.25	343.4	13.64	1344.5	53.43

and established that the magnitude of the geminal H-F coupling depends upon the orientation of the -CHF grouping relative to the adjacent carbonyl group. The long-range H-F couplings (between the fluorine and methyl ester protons) were found to be largest when the fluorine eclipsed the carbonyl group. It is apparent that the conformational preference of the acetyl group influences nmr parameters throughout the entire molecule, and it is probable that this property is responsible for the nature of the variation in ^{13}C chemical shielding of the ester groups observed above.

The above proposal may be examined by a method analogous to that used by Shapiro⁷ which assumed that a disubstituted methyl group -CXY- can adopt either of two conformations relative to the adjacent carbonyl group.



The chemical shift of the ester group -OR may now be expressed in terms of S.C.S.'s which reflect both the nature of X and Y and their orientation (trans or gauche) to the ester group. Thus the chemical shifts are given by expressions of the type:-

$$\text{for I, } \nu_R = 2\delta X_g + \delta Y_t \quad (3)$$

$$\text{for II, } \nu_R = \delta X_g + \delta X_t + \delta Y_g \quad (4)$$

In such a manner it is possible to write equations representing all combinations of hydrogen and halogen with type I or II conformational preference, and the whole was analysed by a least squares computation. Initial estimates of the various S.C.S.'s were obtained manually, but even gross errors in these were allowed for in the program. The final results of the computer analysis are given in Tables 3 and 4.

Table 3. Acetyl Chemical Shifts for Methyl esters (Hz).

Acetyl Substituents	Observed S.C.S.	Calculated S.C.S.	Error Obs.-Calc.
-CH ₂ Cl	35.2	33.05	2.15
-CHCl ₂	63.8	66.10	-2.30
-CCl ₃	101.5	101.54	-0.04
-CHClF	50.5	48.65	1.85
-CF ₂ Cl	75.1	74.43	0.68
-CH ₂ Br	36.2	33.88	2.32
-CHBr ₂	66.6	67.76	-1.16
-CBr ₃	108.4	108.40	0.00
-CH ₂ F	12.8	15.61	-2.81
-CHF ₂	40.0	41.38	-1.38
-CF ₃	67.5	67.15	0.36

derived A.S.C.S.'s:-

F _g 25.77	Cl _g 33.05	Br _g 33.88
F _t 15.61	Cl _t 33.44	Br _t 40.64

Standard deviation of error = 1.66 Hz.

The calculations on both sets of data produced the same conclusions with respect to the conformational preferences of the acetyl group substituents. These were that for compounds containing one or two fluorine atoms, one fluorine atom always preferred to *eclipse* the carbonyl oxygen, whilst in contrast to this, compounds with one or

two chlorine or bromine (but not fluorine) atoms always preferred to have both the halogens oriented gauche to the ester groups, with no eclipsing of the carbonyl function. Those compounds with a mixture of fluorine and other halogens always produced the most accurate result

Table 4. Acetyl Substituent Chemical Shifts for $-O^{13}CH_2$ of Ethyl Esters (Hz)

Acetyl Substituents	Observed S.C.S.	Calculated S.C.S.	Error: S.C.S. (obs)- S.C.S. (calc).
$-CH_2Cl$	43.9	40.89	3.01
$-CHCl_2$	78.4	81.78	-3.38
$-CCl_3$	127.1	127.47	-0.37
$-CHFBr$	63.5	65.29	-1.79
$-CFCl_2$	109.0	106.72	2.29
$-CF_2Cl$	101.2	101.29	-0.09
$-CH_2Br$	44.7	40.36	4.34
$-CHBr_2$	79.5	80.71	-1.21
$-CBr_3$	130.4	130.46	-0.06
$-CH_2F$	23.7	24.94	-1.24
$-CHF_2$	60.6	60.40	0.20
$-CF_3$	95.8	95.86	-0.06

derived A.S.C.S.:—

F_g	35.46	Cl_g	40.89	Br_g	40.36
F_t	24.94	Cl_t	45.69	Br_t	49.75

standard deviation of error = 2.06 Hz.

when the fluorine atom eclipsed the carbonyl group. Expressed alternatively, these conformations enabled all the ^{13}C chemical shifts of the oxymethyl and oxymethylene groups to be calculated with a r.m.s. error of 2 Hz (0.08 ppm) or better whilst use of other combinations of rotamers produced significantly greater discrepancies in the calculations of total S.C.S. with standard deviations of 3 - 4 Hz (0.16 ppm).

It now becomes clear why the attempts to calculate the ^{13}C chemical shifts of the acetyl carbon using the Phillips-Wray equations (section 3.2.1.1) failed - the theory does not allow for unequal population of conformers. Indeed, it would predict that the gauche and trans acetyl substituent chemical shifts (ASCS) for the ester carbons would be identical, which is certainly not the case for the ester molecules.

Following the success of the above analysis, it is of interest to examine the variation of chemical shift of the terminal methyl carbon of the ethyl ester, and a plot of $\delta^{13}\text{C}$ against $\sum \sigma_{\text{XYZ}}$ (acetyl) is shown in figure 5. It is seen that addition of electronegative substituents to the acetyl group induce shieldings of the terminal methyl carbon in contrast to the deshieldings observed for the oxymethylene and oxymethyl groups. The magnitude of the effect is also considerably smaller and covers a total range of only 15 Hz (0.6 ppm) compared with 140 Hz (5.6 ppm) for the oxymethylene group. However, it is possible to discern some pattern of substituent effects similar to that of the oxycarbons analysed above (see figs. 3 and 4) but the point corresponding to any one 'family' exhibit a significantly greater scatter, and all the chemical shifts for the di and trisubstituted species lie within a very narrow band of 5 Hz (0.2 ppm). This latter point taken together with the small total range prevent an analysis of the chemical shieldings in terms of trans and gauche effects from acetyl substituents because the error would be comparable with the total range of shifts to be examined and hence a meaningful result is not anticipated.

3.1.2.3. Carbon-Hydrogen Coupling Constants.

In parallel with the above study the directly bonded carbon-hydrogen coupling constants have been recorded and these are presented in table 5.

It is seen from table 5 that the C-H coupling constants for the ester group carbons are essentially constant for all the compounds and that introduction of electronegative atoms at the acetyl carbon produce a total range of only 2 Hz for the oxycarbons and 1 Hz for the

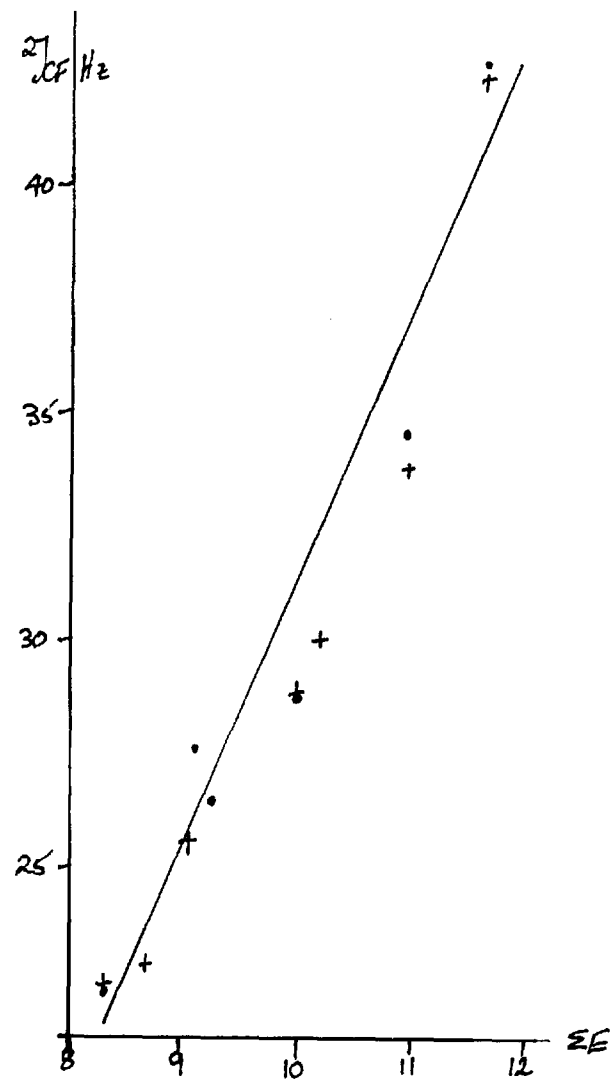
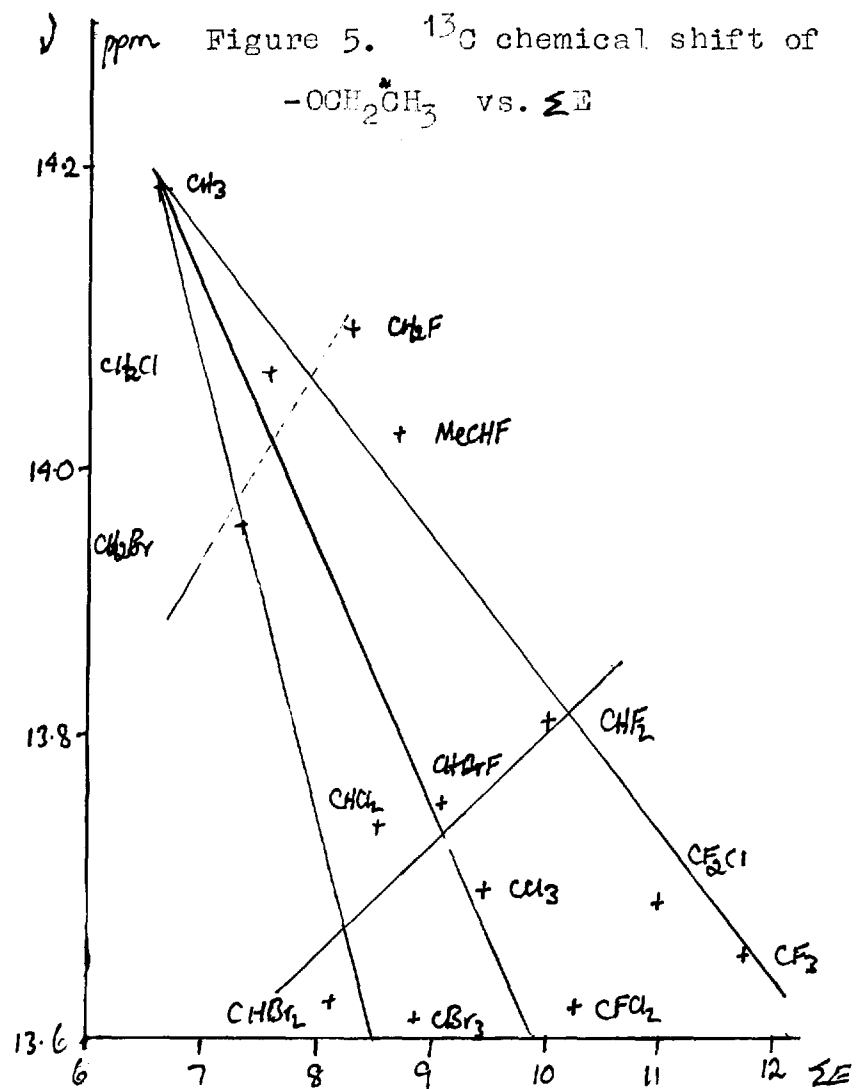


Figure 6

Table 5. Directly bonded C-H coupling constants for esters (Hz).

Acetyl Group	Ethyl $^1J_{CH}$	Ester $^1J_{OCH_2}$	$^1J_{CH_3}$	Methyl $^1J_{CH}$	Ester $^1J_{OCH_3}$
-CH ₃	129.1	145.7	126.2	129.1	146.2
-CH ₂ Br	153.3	148.0	127.0	153.0	147.4
-CH ₂ Cl	151.3	147.8	128.2	151.5	147.6
-CHBr ₂	181.2	148.9	127.5	180.7	148.6
-CHF ₂	153.6	148.0	127.2	153.6	147.6
-CHCl ₂	180.3	148.8	127.5	180.4	148.5
MeCHF ₂	155.0	147.8	127.0	-	-
-CBr ₃	-	149.3	127.5	-	149.1
-CHBrF	188.3	149.0	127.5	-	-
PhCHF-	-	-	-	157.0	-
-CHClF	-	-	-	187.0	148.0
-CCl ₃	-	149.5	127.8	-	148.9
-CHF ₃	190.5	149.0	127.5	190.7	148.6
-CFCl ₂	-	149.7	127.9	-	-
-CF ₂ Cl	-	-	-	-	149.3
-CF ₃	-	149.9	127.8	-	149.3

Data are for 20 mole % solutions in CCl₄.

terminal carbon of the ethyl group. Consequently, it is not proposed to examine these long range effects in further detail.

The directly bonded coupling constant for the acetyl carbon shows considerable variation with the nature of its substituents, and this may be analysed in a manner analogous to that used by Malinowski⁹ for $^1J_{CH}$ in polysubstituted methanes CHXYZ. Malinowski found that this could be expressed as a linear additive function of quantities ζX , ζY and ζZ , which describe the separate contributions of the substituents X, Y and Z respectively:-

$$^1J_{CH} (CHXYZ) = \zeta X + \zeta Y + \zeta Z \quad (5)$$

Thus the coupling component for the hydrogen atom ζ H was evaluated from the data for methane, $^1J_{\text{CH}} = 125$ Hz. Malinowski's equation states:-

$$^1J_{\text{CH}}(\text{CH}_4) = 3\zeta \text{ H} = 125 \text{ Hz} \quad (6)$$

and hence $\zeta \text{ H} = 41.7$ Hz. Zeta values for various substituents were then derived from CH_3X type compounds.

$$\zeta \text{ X} = J_{\text{CH}}(\text{CH}_3\text{X}) - 2\zeta \text{ H} \quad (7)$$

Table 6 lists coupling components for some of the common substituents derived by Malinowski.

Table 6. Malinowski parameters⁹ for common substituents X (Hz).

X	$\zeta \text{ X}$	X	$\zeta \text{ X}$	X	$\zeta \text{ X}$
-H	41.7	-I	67.6	-CN	52.6
-F	65.6	-OH	59.6	-COOH	47.1
-Cl	68.6	-S(O)CH ₃	54.6	-CHO	43.6
-Br	68.6	-NH ₂	49.6	-CH ₃	42.6

Before the data in table 5 can be analysed in terms of Malinowski parameters, a value for the coupling component of the alkoxycarbonyl group $-\text{CO}_2\text{R}$ must be obtained and this is derived readily by use of equation (7) with $^1J_{\text{CH}}(\text{CH}_3-\text{CO}_2\text{R})$, which yields a value of 45.6 Hz. It is seen from table 6 that this is close to the value for $-\text{CO}_2\text{H}$ and may therefore be considered a reasonable estimate. Table 5 shows that the directly bonded coupling constant of the acetyl carbon is independent of the nature of the ester group (methyl or ethyl) within observational error (± 1 Hz) and hence the average values are compared (table 7) with those derived from equation (5).

Table 7. Calculated & observed coupling constants for Acetyl Carbon using Malinowski parameters.

C_{XYZ}	$^1J_{CH}$ Coupling Constant		Error = Calc. - obs.
	observed	calculated	
$-CH_2Br$	153.15	155.9	+4.75
$-CH_2Cl$	151.4	155.9	+2.5
$-CH_2F$	153.6	152.9	-0.7
$-CHClF$	187.0	179.8	-7.2
$-CHBrF$	188.3	179.8	-8.5
$-CHF_2$	190.6	176.8	-13.8
$-CHCl_2$	180.3	182.8	+1.6
$-CHBr_2$	180.9	182.8	+1.9

It may be concluded from table 7 that the Malinowski parameters provide a reasonable estimate (within 4.7 Hz) for 5 of the 8 esters, but yields a considerably greater error (up to 14 Hz) for dihalo carbons bearing at least one fluorine atom. This failure is not confined to the esters: several other cases have been reported¹⁰⁻¹². Muller and Rose found¹⁰ some very large deviations from additivity in multiply substituted methanes containing $-F$ or $-OCH_3$ as high as +41, 31 and -16 Hz for CHF_3 , CHF_2Cl and $CH(OCH_3)_3$ respectively. Deviations of +6.7 and +21.7 Hz have been reported¹¹ for CH_2FCN and CHF_2CN but not for the corresponding chlorine analogues.

Douglas¹³ has examined these consistent deviations from additivity of substituent effects. He assumed that the 'direct' substituent effect parameters from the monosubstituted methanes to be constant regardless of the degree of substitution and found that the introduction of pairwise interaction constants (empirically derived) for highly electronegative elements or groups enabled him to calculate directly bonded C-H coupling constants for multiply substituted methanes to within 3 Hz by use of a modified form of Malinowski's equation:-

$$^1J_{C-H} = N_X f(X) + N_{X-Y} g(X,Y) + J_{C-H}(CH_4) \quad (8)$$

N_X is the number of X atoms or groups; $f(X)$ is the 'direct' substituent effect (difference in $^1J_{CH}$ of CH_3X from CH_4); N_{X-Y} is the number of distinct X-Y pairs substituted on the carbon atom and $g(X,Y)$ is the empirical 'interaction' constant. These parameters are used in Table 8, and any pair not listed is considered to possess a negligible interaction effect.

Table 8. Empirical substituent parameters for polysubstituted methanes.

'Direct' effect		'Interaction effect'		
X	f(X)	X	Y	g(X,Y)
-F	24	-F	-F	13
-Cl	25	-F	-Cl	9
-OCH ₃	15	-F	-CN	4
-CN	13	-OCH ₃	-OCH ₃	6
-CH ₃	1	-Cl	-Cl	3

Using equation 8 and the values in table 8, Douglas reduced the discrepancies for CHF_3 and $CHClF_2$ from +41 to +2 and +33 to +2 Hz respectively. It is of interest to test this modified substituent effect approach for those polyhalogenated esters which yielded a poor result with the Malinowski equation. This requires the derivation of the 'direct' effect of $-CO_2R$ on $^1J_{CH}$ and is readily obtained in the manner used above for the Malinowski parameter $-CO_2R$, which yields a value of 4.1 Hz. It will be assumed initially that because $-CO_2R$ is not highly electronegative ($F_{CO_2R} = 2.5$, Chapter 1) that the 'interaction effects' associated with it are small and can be neglected. It will be assumed further that the parameters associated with -Cl will be directly applicable to -Br, as none are given by Douglas. The results of these calculations are shown in Table 9.

Table 9. Directly bonded $^1J_{\text{CH}}$ for acetyl carbon using the Douglas equation.

C_{XYZ}	$^1J_{\text{CH}}$ coupling constant (Hz)		Error calcd - obs.
	observed	calculated	
$-\text{CH}_2\text{Br}$	153.15	154.1	1.1
$-\text{CH}_2\text{Cl}$	151.4	154.1	2.7
$-\text{CH}_2\text{F}$	153.6	153.1	-0.5
$-\text{CHClF}$	187.0	185.1	-1.9
$-\text{CHBrF}$	188.3	185.1	-3.2
$-\text{CHF}_2$	190.5	190.1	-0.4
$-\text{CHCl}_2$	180.3	182.1	1.8
$-\text{CHBr}_2$	189.9	182.1	-1.2

It is readily apparent from table 9 and a comparison of the errors noted there with those of table 7 that the pairwise interaction between fluorine and itself or the other halogens have very successfully accounted for the discrepancies noted from the simple Malinowski approach. It is also clear that little correction is needed for pairwise interactions between halogens (including fluorine) and the $-\text{CO}_2\text{R}$ group and it was valid to assume that these terms could be neglected. The compound with the largest residual error (3.2 Hz) is $-\text{CHBr}$ and to obtain a more accurate estimate of the directly bonded coupling precise measurements of $^1J_{\text{CH}}$ for the model compounds CH_3Br and CH_2BrF are needed. Similarly, trial calculations to obtain the Br-Br pairwise interaction constant indicate this to be in the range of 0 - 3 Hz and again necessitates accurate data.

3.2.1.4. Carbon-Fluorine Coupling Constants.

In parallel with the above study of the carbon-hydrogen spin-interactions, the coupling of fluorine with both the directly bonded acetyl carbon and the geminal carbonyl carbon were recorded for the fluoroacetate esters and are presented in Table 10.

Table 10. C-F Coupling Constants of fluoroacetates (Hz).

Acetyl Group	Methyl Ester		Ethyl Ester	
	$^1J_{CF}$	$^2J_{CF}$	$^1J_{CF}$	$^2J_{CF}$
-CH ₂ F	182.6	22.1	182.6	22.4
-MeCHF	-	-	183.5	22.8
-PhCHF	188.0	27.5	-	-
-CHBrF	-	-	264.1	25.5
-CHClF	253.4	26.4	-	-
-CHF ₂	248.8	28.7	249.5	28.9
-CFCl ₂	-	-	305.7	30.0
-CF ₂ Cl	300.5	34.5	300.6	33.7
-CF ₃	284.8	42.2	285.1	42.4

It is apparent from table 10 that the alkyl ester group has no effect upon the observed coupling constants within the range of experimental error (± 0.5 Hz) and hence analysis of the data from the nine fluoroacetates will be conducted upon the average values. Table 10 also reveals an interesting difference between the two types of coupling constant: the geminal coupling to the carbonyl carbon increases steadily from the least to the most electronegative member (top to bottom of table); whilst the directly bonded coupling with the acetyl carbon exhibits a maximum for -CFCl₂ (306 Hz) which is considerably greater than that for -CF₃ at 285 Hz.

It would be valuable if the directly bonded coupling constants could be analysed in a manner similar to that employed for the C-H couplings. Early attempts at such a method were undertaken independently by Harris¹⁴ and van der Kelen¹¹ for some fluoromethanes and fluoronitriles, using an approach analogous to that described above for a simple additive substituent analysis of $^1J_{CH}$ by Malinowski.⁹ (Equation 5). Harris found that values of ζ obtained from CF_3X compounds and used to predict $^1J_{CF}$ for CF_2X_2 and CF_3 yielded theoretical values considerably in excess of the observed coupling constants. It was concluded that the apparent ζ values dropped in the series $CF_3X - CF_2X_2 - CF_3$ with deviations from additivity which were negative in sign with respect to $^1J_{CF}$. This was particularly marked for $X = H$ and was also true for $X = Cl$ or Br , and was also true for compounds of the type $CFXY$. The data in table 11 indicate the apparent fluctuations in ζ_X found by Harris.

Table 11. Apparent ζ_X values for $^1J_{CF}$ (Harris)¹⁴

ζ_X	CF_4	CF_3X	CF_2X_2	CFX_3
$X = F, \zeta_F$	86.4			
$X = H, \zeta_H$	-	101.5	74.2	157.4
$X = Cl, \zeta_{Cl}$	-	-	119	112.2
$X = Br, \zeta_{Br}$	-	-	135	123.9

Van der Kelen reported¹¹ a similar non-additivity of ζ_H for the series $CF_3CN - CHF_2CN$ and CH_2FCN . It was assumed that ζ_{CN} , calculated from CF_3CN was constant at 85.2 Hz, which yielded values of ζ_H of 71.9 and 43.4 Hz respectively.

It is clear that the simple additive relationship was not providing a realistic estimate for J_{CF} , particularly molecules containing several highly electropositive elements. Malinowski¹⁵ was quick to note this failure paralleled that of J_{CH} , and extended the Douglas treatment¹³ of J_{CH} using parameters which reflected pairwise interaction of substituents to cover $^1J_{\text{CF}}$ and $^1J_{\text{SiF}}$. Malinowski considered that the Douglas equation (8) could be re-expressed as:-

$$J_{\text{CH}} = \mathfrak{S}_X + \mathfrak{S}_Y + \mathfrak{S}_Z + \mathfrak{S}_{XY} + \mathfrak{S}_{XZ} + \mathfrak{S}_{YZ} \quad (9)$$

where $\mathfrak{S}_{XY}$ was the interaction parameter associated with substituents X and Y and independent of substituent Z. He now redefined the interaction parameter by:-

$$\gamma_{XY} = \mathfrak{S}_{XY} + 0.5(\mathfrak{S}_X + \mathfrak{S}_Y) \quad (10)$$

such that equation 9 reduced to

$$J_{\text{CF}}(\text{XYZ}) = \gamma_{XY} + \gamma_{YZ} + \gamma_{XZ} \quad (11)$$

Table 12 lists the parameters calculated from equation 11.

Table 12. Interaction parameters for $^1J_{\text{CF}}$ calculation (Hz).

X-Y	γ_{XY}	X-Y	γ_{XY}
H,H	52.6	F,H	93.6
F,F	86.0	F,Br	119.0
Cl,Cl	112.2	F,Cl	106.5
Br,Br	124.0	F,CN	89.0
Cl,H	90.8	H,CN	59.7

The C-F coupling constants calculated for CF_2X_2 and CF_2XY using γ_{XY} (table 13) are now in very good agreement with the observed values, with a maximum error of 6 Hz for CH_2F_2 . The errors in $^1\text{J}_{\text{CF}}$ which would occur if the simple additive approach were used are also recorded in table 13 to illustrate the considerable success of the pairwise interaction approach (e.g. error for $\text{CH}_2\text{F}_2 = 63 \text{ Hz}$).

Table 13. Application of γ_{XY} to $^1\text{J}_{\text{CF}}$ (Hz).

Compound	$\text{J}_{\text{obsd.}}$	Using γ_{XY}		Using $\sum \gamma_{\text{XY}}$	
		J_{calc}	$\text{J}_{\text{calc}} - \text{J}_{\text{obs}}$	J_{calc}	$\text{J}_{\text{calc}} - \text{J}_{\text{obs}}$
CH_2F_2	233.4	239.7	+6.3	289.4	+63.0
CF_2Br_2	357.8	362.0	+4.2	386.8	+29.0
CF_2Cl_2	324.7	325.2	+0.5	344.8	+20.0
CF_2HCN	243.5	242.3	-1.2	* 273.1	+29.6

† - Values calculated using $\sum_{\text{Cl}} = 127.2 \text{ Hz}$ (ex $^1\text{J}_{\text{CF}} \text{CF}_3\text{Cl} = 299 \text{ Hz}$)
 $\sum_{\text{Br}} = 151.2 \text{ Hz}$ (ex $^1\text{J}_{\text{CF}} \text{CF}_3\text{Br} = 324 \text{ Hz}$): data from ref. 16
 * - Using $\sum_{\text{CN}} = 85.2 \text{ Hz}$ ref. 11.

The success of these calculations suggests that equation 11 will accurately predict the coupling constants observed for the highly electronegative ester molecules under investigation. This requires estimates of the γ parameters representing interaction between the alkoxy carbonyl $-\text{CO}_2\text{R}$ group and H, F and Cl, which can be obtained from $\text{CF}_3\text{CO}_2\text{R}$, $\text{CHF}_2\text{CO}_2\text{R}$ and $\text{CFCl}_2\text{CO}_2\text{R}$. The derived values can be checked on the esters CHClF- , $\text{CHF}_2\text{-}$ and $\text{CF}_2\text{-CO}_2\text{R}$. Calculation of $^1\text{J}_{\text{CF}}$ for the other esters necessitates the derivation of other interaction parameters (e.g. $\gamma_{\text{Br-CO}_2\text{R}}$; $\gamma_{\text{Me-CO}_2\text{R}}$) which are not accessible with the limited data available. However, the 'permitted' calculations should provide a check on the application of the interaction parameter approach to the ester molecules.

The data in table 10 enables the required interaction parameters to be estimated as $\gamma_{\text{H,CO}_2\text{R}} = 65.0 \text{ Hz}$, $\gamma_{\text{F,CO}_2\text{R}} = 99.4 \text{ Hz}$

and $\gamma_{\text{Cl}, \text{CO}_2\text{R}} = 96.8 \text{ Hz}$. These values, together with those in table 12, were used to calculate $^1J_{\text{CF}}$ for the test esters with the results shown in table 14.

Table 14. Calculation of $^1J_{\text{CF}}$ for fluoroacetates (Hz).

Compound	$^1J_{\text{CF}}$	Calculated	J_{obs}	$J_{\text{calc}} - J_{\text{obs}}$
$\text{CHF}_2\text{CO}_2\text{R}$	$\gamma_{\text{HF}} + \gamma_{\text{H.CO}_2\text{R}} + \gamma_{\text{F.CO}_2\text{R}} =$	258.0	249.1	-8.9
$\text{CHFCl.CO}_2\text{R}$	$\gamma_{\text{HCl}} + \gamma_{\text{H.CO}_2\text{R}} + \gamma_{\text{Cl.CO}_2\text{R}} =$	252.6	253.4	-0.8
$\text{CF}_2\text{Cl.CO}_2\text{R}$	$\gamma_{\text{FCl}} + \gamma_{\text{H.CO}_2\text{R}} + \gamma_{\text{Cl.CO}_2\text{R}} =$	302.7	300.6	-2.1

It is seen from table 14 that equation 11 provides a very good estimate of the F-C directly bonded coupling constants. The only compound to display a significant error is the difluoro ester, (-8.9 Hz) and this discrepancy is similar to that for difluoromethane ($+6.3 \text{ Hz}$) which also displayed the greatest error for the series of fluoromethanes (table 13). Within the limited data available, it may be concluded that the method is capable of extension to the compounds of interest.

The remaining point of interest in this section is the variation of the geminal fluorine-carbonyl carbon coupling with the nature of the acetyl group substituents. It was noted earlier from the data in table 10 that $^2J_{\text{CF}}$ appeared to increase steadily with the total acetyl group electronegativity, and figure 6 reveals that this is indeed the case. A least-squares analysis yields a correlation coefficient of 0.986.

3.2.1.5. Proton chemical shifts of the ester groups.

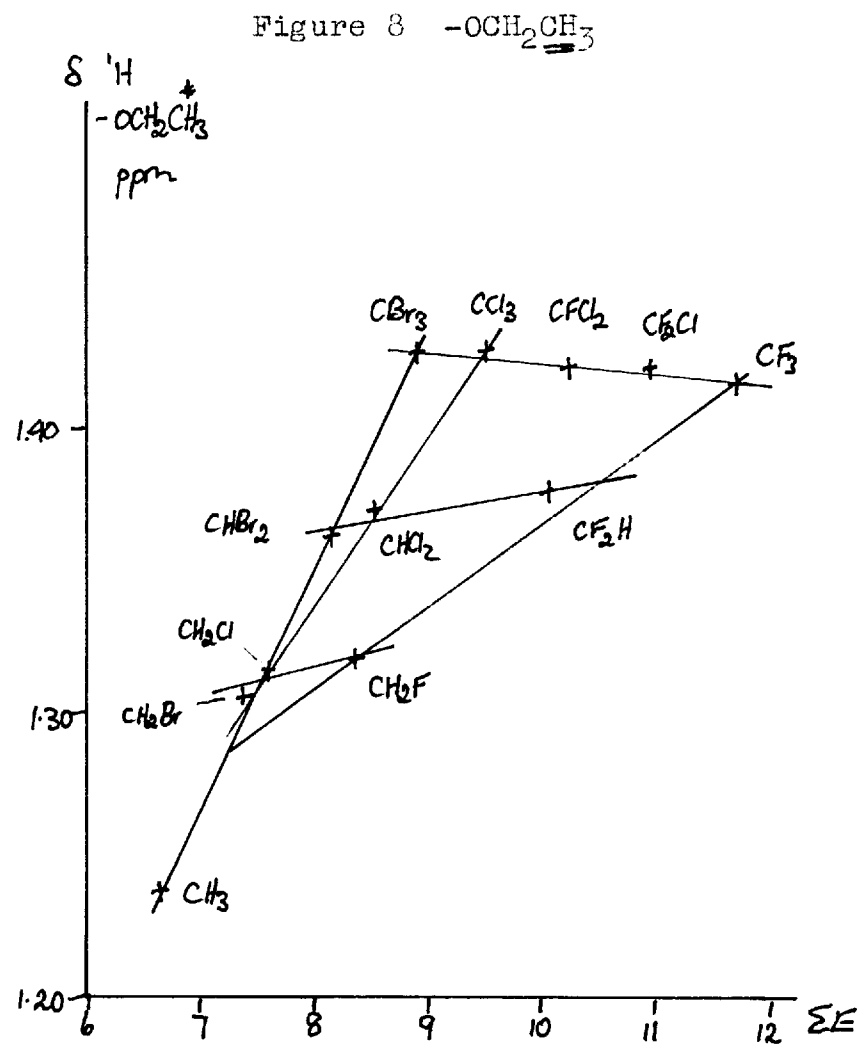
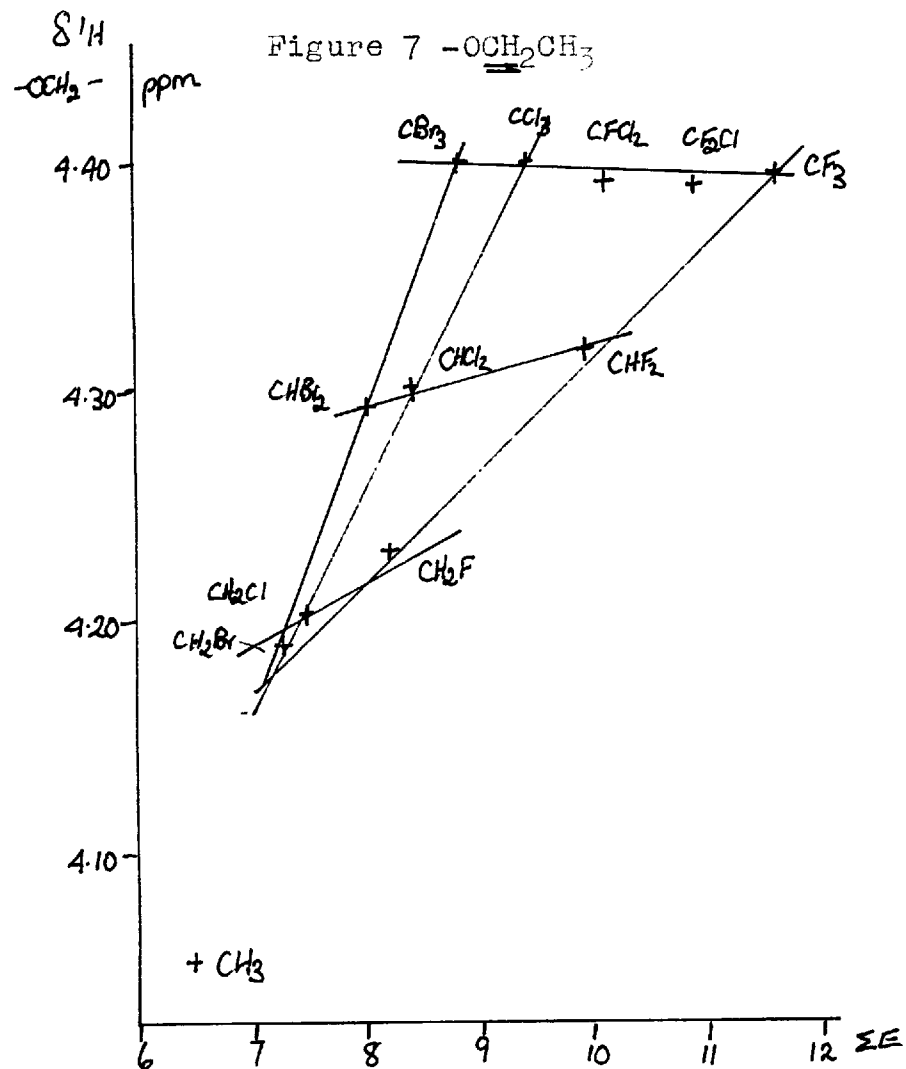
To complete this NMR study of the haloacetic esters it will be interesting to examine the variation (if any) of the ^1H chemical shifts of the hydrogens in the ester groups, as a function of the acetyl group substituents. Although ^1H is a less sensitive nucleus than ^{13}C and the protons are located one bond further away from the acetyl group carbon, it is possible that the protons may show such variations.

Since the range of substituent chemical shifts anticipated is small, it is important to observe at conditions of infinite dilution, or a concentration at which solvent effects are negligible. Therefore, CCl_4 was chosen as a suitably inert solvent and trial dilutions made using $\text{CHCl}_2\text{CO}_2\text{R}$, which had been found to exhibit the largest dilution shifts in ^{19}F and ^{13}C spectra. It was found that the observed chemical shifts were constant over the range 1 mole % to 0.0625 mole %, and hence it was concluded that dilution effects on proton spectra would be negligible. Table 15 records the chemical shifts of all 25 esters for 1 mole % solutions in CCl_4 at 31°C (ambient probe temperature).

It is seen from table 15 that the chemical shifts of the ester group protons experience a marked dependence on the nature of the acetyl group substituents: the $-\text{OCH}_2-$ and $-\text{OCH}_3$ protons exhibit a range of 0.35 and 0.40 ppm respectively and even the terminal methyl group of the ethyl radical has a total variation of 20 Hz. The corresponding values observed in the ^{13}C spectra are 5.2 ppm, 4.6 ppm and 0.6 ppm, and these reflect the greater sensitivity of the latter nucleus to the substituents. The nature of these variations may be suitably examined via plots of the chemical shifts against the sum of the Huggins electronegativities of the acetyl group substituents, and these are shown in figures 7 - 9 respectively.

It is observed that all three proton species yield plots that are very similar in nature to those of the ^{13}C nuclei, with several 'families of lines' being apparent. Thus all members of a series $\text{CH}_2\text{X}-$

Plots of ^1H chemical shifts for ester protons vs. ΣE



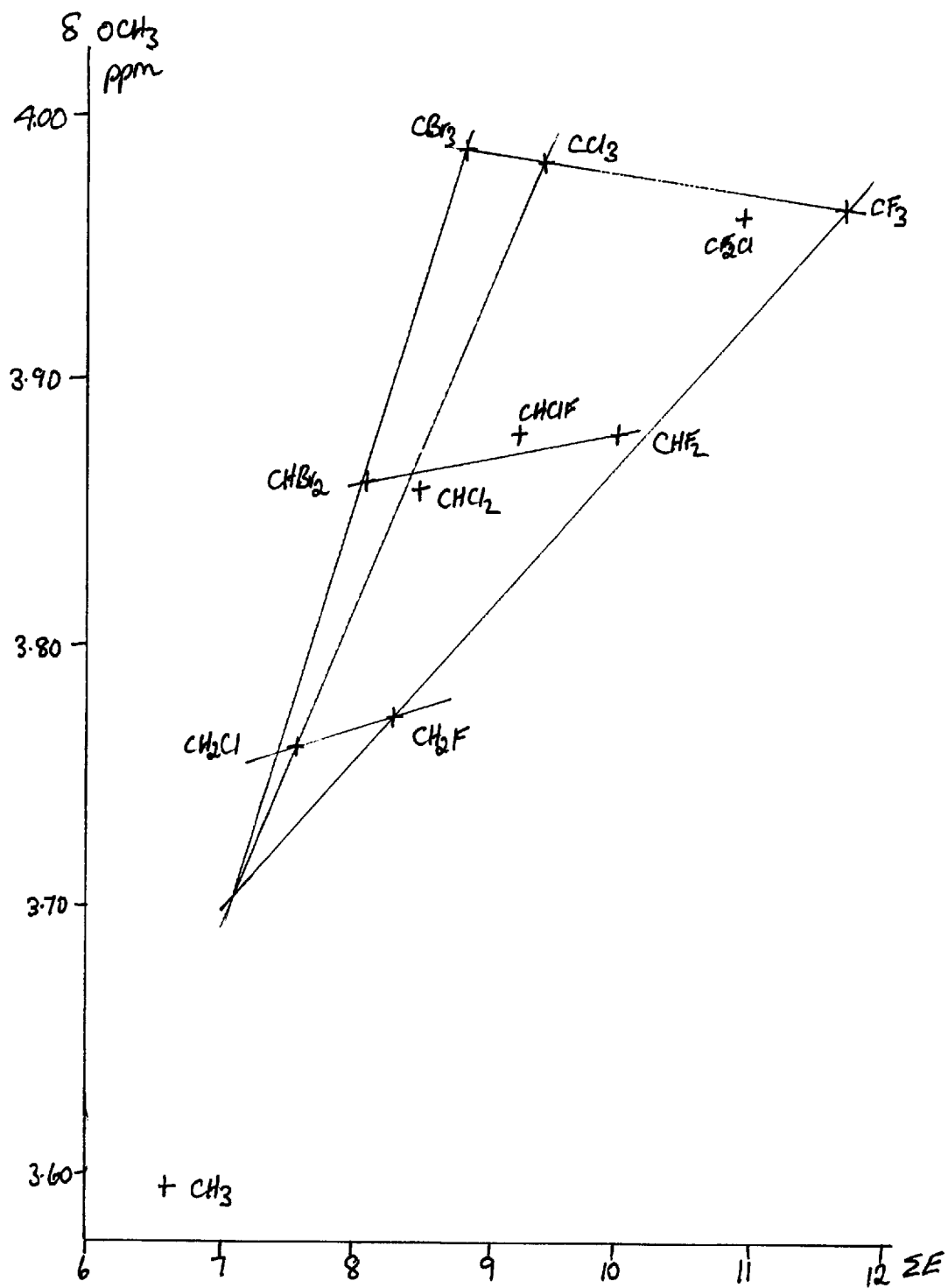


Figure 9

^1H chemical shifts of $-OCH_3$ protons vs. ΣE

Table 15. ^1H chemical shifts † of haloacetic acid esters $\text{C}_{\text{XYZ}}\text{CO}_2\text{R}$.

C_{XYZ}	ΣF	$\text{R} = \text{C}_2\text{H}_5$			$\text{R} = \text{CH}_3$	
		ν_{CHXY}	ν_{OCH_2}	$\nu_{\text{OCH}_2\text{CH}_3}$	ν_{CHXY}	ν_{OCH_3}
$-\text{CH}_3$	6.6	195.8	404.8	123.6	197.5	359.5
$-\text{CH}_2\text{Br}$	7.35	370.7	418.9	130.5		
$-\text{CH}_2\text{Cl}$	7.55	393.9	420.2	131.3	395.3	376.2
$-\text{CHBr}_2$	8.10	571.0	428.9	136.1	573.3	386.3
$-\text{CH}_2\text{F}$	8.30	531.7	422.7	131.8	474.4	377.3
$-\text{CHCl}_2$	8.50	583.0	429.9	137.0	585.8	387.6
$-\text{CBr}_3$	8.85	-	440.2	142.4	-	398.9
$-\text{PhCHF}$	9.10	-	-	-	564.6	373.2
$-\text{CHClF}$	9.25	-	-	-	622.8	388.0
$-\text{CCl}_3$	9.45	-	439.8	142.7	-	398.3
$-\text{CHF}_2$	10.00	579.7	431.7	137.7	582.5	388.0
$-\text{CFCl}_2$	10.20	-	439.0	142.1	-	-
$-\text{CF}_2\text{Cl}$	10.95	-	438.7	142.0	-	396.3
$-\text{CF}_3$	11.70	-	439.4	141.7	-	396.6

† data in Hz to low field of TMS: $\delta = \text{CS} \times 10^{-2}$ ppm

CHX_2- , CX_3- lie on one line (for each X) and all compounds with a common number of H or X substituents lie on a separate line.

Introduction of any halogen substituent at the acetyl carbon deshields the protons, even of the terminal methyl group of the ethyl moiety, in contrast to its ^{13}C shift, which experiences increased shielding. Further comparison of the ^1H and ^{13}C data reveals that in the family $\text{CH}_n\text{X}_{3-n}$, n constant, the effect of increasing the atomic weight of X, F - Cl - Br is always deshielding for ^{13}C chemical shifts, but for ^1H the opposite is found to be the case, with shielding for n = 1 or 2, and only very slight deshielding (total range 0.02 ppm) for CX_3 . Figures

7 - 9 also show that the resonances corresponding to the unsubstituted acetates are not (apparently) the common points for the lines, but are offset ca. 0.1 ppm to high field of the point of intersection.

It must be concluded from the extensively similar nature of figures 7 - 9 with figures 1 - 4, that the protons of the ester group are experiencing the same influences upon their chemical shift as the ^{13}C of the $-\text{OCH}_2-$ and OCH_3 moieties. It will be recalled (section 3.2.1.2.) that the latter data were successfully analysed in terms of additive acetyl substituent chemical shifts, when due allowance was made for the conformational preferences of the halogens. Hence it was decided to test this proposal via analysis of this data in the manner described for the ^{13}C chemical shifts of the oxycarbons (section 3.2.1.2) to determine if the ^1H chemical shifts were able to support the conclusions reached in that section from ^{13}C data. The initial least-squares computer analysis for all three types of proton failed to confirm the prediction found with the ^{13}C data. The probable reason for this apparent failure has been noted in part above: the families of lines for compounds of the type $\text{CH}_n\text{X}_{3-n}.\text{OC}_2\text{R}$, X constant, intersect very close to the point corresponding to the parent acetic acid for the ^{13}C data but there is a considerable error for the ^1H nuclei. This fact taken in connection with the considerably smaller range of chemical shifts experienced for ^1H must yield a greater statistical error in any analysis, based on substituent chemical shifts. Thus, although σ for ^{13}C and ^1H data are 1 - 2 Hz in both cases, in the former this is 1% of the total range but is an order of magnitude greater for the proton data.

In an attempt to test this hypothesis, the S.C.S. ^1H data for $-\text{OCH}_3$ were corrected by the approximate amount of the apparent 'zero error' in S.C.S. (10.5 Hz, see fig. 8) and the least squares analysis repeated. The standard deviations were markedly reduced (to 0.8 - 0.9 Hz for all possibilities of conformational preference) but again a well defined conformational preference failed to appear.

It is clear from the nature of figures 7 - 9 that the protons of the ester groups are indeed experiencing the same stereochemical effects as the ^{13}C nuclei (figures 1 - 4) but the method of analysis is not sufficiently accurate to confirm this with the data obtained from a

less sensitive nucleus and hence subject to considerably greater error. It is concluded that the pattern of ^1H S.C.S. can be understood on a qualitative basis from the knowledge obtained from the ^{13}C spectra.

3.2.2. Amido Derivatives of some α -Fluorohaloacetic Acids.

The ^{13}C NMR spectra of the three series of α -fluoroacetamides are now examined to complement the ^{19}F investigation, described in chapter 1. The choice of solvent(s) presented problems similar to those given in that chapter, viz. the low solubility of these polar compounds, (especially the primary amides), in CCl_4 , and it was not possible to record ^{13}C spectra in this solvent. Two further complications arose in this area. Firstly arising from the low natural abundance and detectability of ^{13}C and the reduction in the signal-to-noise ratio caused by the complex spin-coupled multiplets in undecoupled spectra, it was desirable to obtain 10 - 20 mole % solutions for this purpose to yield well-defined absorption bands from which to measure coupling constants accurately. Secondly, it was necessary to record spectra of the N,N-dimethyl amides at temperatures sufficiently low that all internal rotation about the (C)C-N amide bond had ceased.

Although no one solvent was able to fulfill all these considerations, deuteriochloroform was found to be suitable for all the spectra of the N-methyl amides and the majority of those for the primary amides. The coupling constants of the latter series were also recorded in methanol for the above noted reasons. Severe problems with phase separation were encountered when attempting to use CDCl_3 as solvent for the tertiary amides and the low temperatures required (-20° to -80°C), but this was overcome through employing CFCl_3 , with CD_3OD (ext) as lock signal.

Spectra of some of the primary amides in CDCl_3 were of necessity recorded at elevated temperatures ($45 - 55^\circ$) to obtain dissolution. In these instances, the solution concentrations were 5 mole % or less and hence the measured chemical shifts were considered to represent closely

the values at infinite dilution. The chemical shifts of the other primary amides and all the secondary amides were extrapolated to infinite dilution in CDCl_3 : such a procedure was not feasible for the N,N-dimethyl amides, whose spectra required 12 hours accumulation for 5 or 10 mole % solutions, and hence a small quantity of TMS was included in the solutions. Full details of the experimental conditions used for the acquisition ^{13}C spectra of the amides will be found in sections 3.2.2.3 to 3.2.2.5.

3.2.2.1 Chemical shifts of the acetyl and carbonyl carbons.

The chemical shifts of the acetyl and carbonyl carbons of all three types of amide will be considered initially: it is anticipated that these will exhibit the same general trends with acetyl substituents found for the series of esters but may display some minor variations which are a function of the amido nitrogen substituents.

Values of the chemical shifts of the acetyl and carbons in the series of amides are given in tables 16 and 17.

Table 16 indicates the results of successive N-methylation upon the acetyl chemical shift are not additive or of equal effect, as was found for the effect of successive N-methylation upon ^{19}F chemical shifts in Chapter 2. Mono-N-methylation generally induces a downfield (positive) shift of ca. 0.5 ppm, with the exception of the MeCHF- and $\text{CF}_3\text{-}$ amides, for which a considerably greater degree of shielding and deshielding is noted respectively. Introduction of a second N-methyl group generally yields a shielding influence of under 1 ppm, but this is considerably greater for the propionamide derivative (MeCHF- , - 2.58 ppm); whilst the di- and trifluoroacetamides experience a deshielding of upto 2 ppm. There is again no significant correlation with the nature of the acetyl group substituents. Although the overall effect of di- N methylation produces a change in shielding of under 1 ppm, there exists a range from -6.05ppm for MeCHF- to +3.61 ppm for CF_3 and it is apparent that these effects are not directly related to the nature of the acetyl group or the

Table 16. ^{13}C chemical shifts of acetyl carbon in $^{13}\text{C}_{\text{XYZ}}\cdot\text{CO}_2$ (ppm).

C_{XYZ}	ΣE_{XYZ}	$\text{Q} = \text{NH}_2$	$\text{Q} = \text{NHMe}$	$\text{Q} = \text{NMe}_2$	$\delta\nu(\text{NHMe}-\text{NH}_2)$	$\delta\nu(\text{NMe}_2-\text{NHMe})$	$\delta\nu(\text{NMe}_2-\text{NH}_2)$
CH_3-	6.6	22.34	23.10	21.44	0.76	-1.66	-0.90
$\text{CH}_2\text{F}-$	8.3	80.01	80.39	80.18	0.38	-0.21	0.17
$\text{MeCHF}-$	8.7	92.50	80.03	86.45	-3.47	-2.58	-6.05
$\text{CHBrF}-$	9.05	84.06	84.66	-	0.60	-	-
$\text{PhCHF}-$	9.10	91.69	91.99	-	0.30	-	-
$\text{CHClF}-$	9.25	93.71	94.08	93.07	0.37	-1.01	-0.64
CHF_2-	10.00	108.17	108.55	110.59	0.38	2.04	2.47
CFCl_2-	10.2	111.79	112.36	111.99	0.57	-0.37	0.20
$\text{CF}_2\text{Cl}-$	10.95	118.60	119.13	118.55	0.53	-0.58	-0.05
CF_3-	11.7	113.19	115.95	116.80	2.76	0.85	3.61

Table 17. ^{13}C chemical shifts of carbonyl carbon in $\text{C}_{\text{XYZ}}\cdot^{13}\text{CO}_2$ (ppm).

C_{XYZ}	ΣE_{XYZ}	$\text{Q} = \text{NH}_2$	$\text{Q} = \text{NHMe}$	$\text{Q} = \text{NMe}_2$	$\delta\nu(\text{NHMe}-\text{NH}_2)$	$\delta\nu(\text{NMe}_2-\text{NHMe})$	$\delta\nu(\text{NMe}_2-\text{NH}_2)$
CH_3-	6.6	173.59	170.91	169.05	-2.68	-1.86	-4.54
$\text{CH}_2\text{F}-$	8.3	170.41	168.18	-	-2.23	-	-
$\text{MeCHF}-$	8.7	177.72	171.11	167.93	-6.11	-3.18	-9.79
$\text{CHBrF}-$	9.05	167.42	165.42	-	-2.00	-	-
$\text{PhCHF}-$	9.10	-	169.03	-	-	-	-
$\text{CHClF}-$	9.25	166.59	164.65	163.10	-1.94	-1.55	-3.49
CHF_2-	10.0	164.82	163.18	161.81	-1.64	-1.37	-3.01
CFCl_2-	10.2	163.48	162.02	159.36	-1.46	-2.66	-4.12
$\text{CF}_2\text{Cl}-$	10.95	161.53	160.06	158.11	-1.47	-1.85	-3.42
CF_3-	11.7	158.91	157.95	156.26	-0.96	-1.69	-2.65

¹³C N-Methylation shifts of carbonyl carbon vs. ΣE

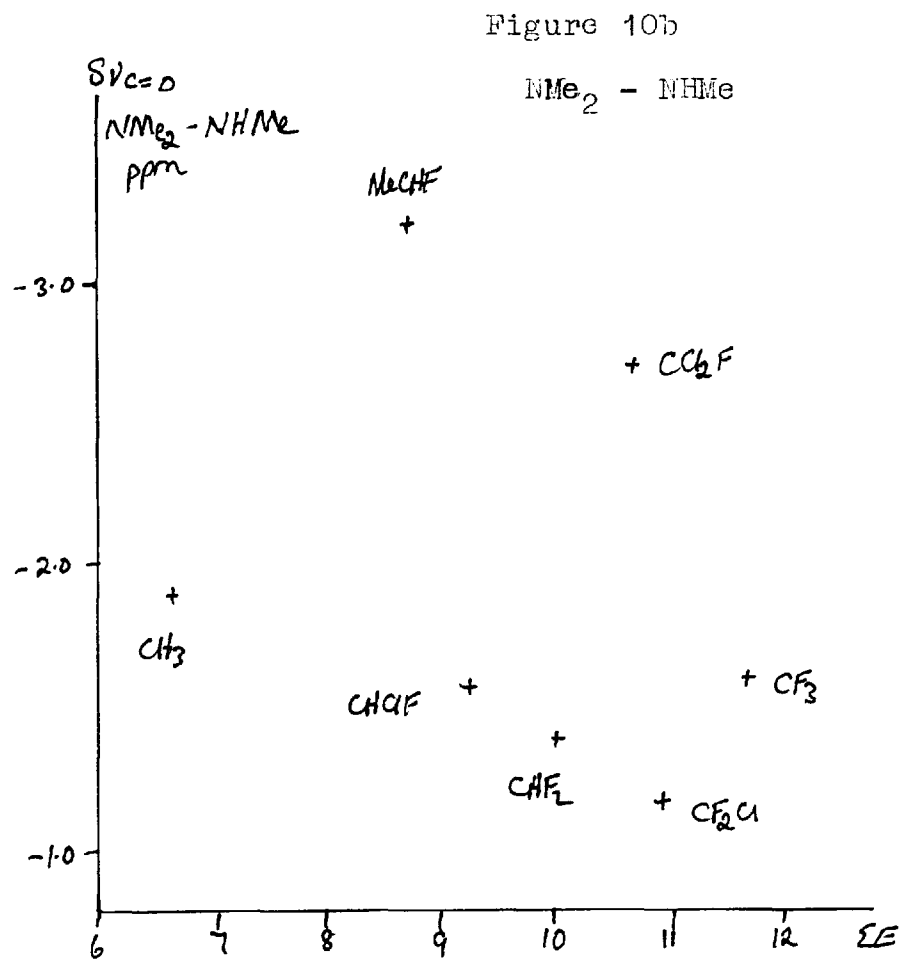
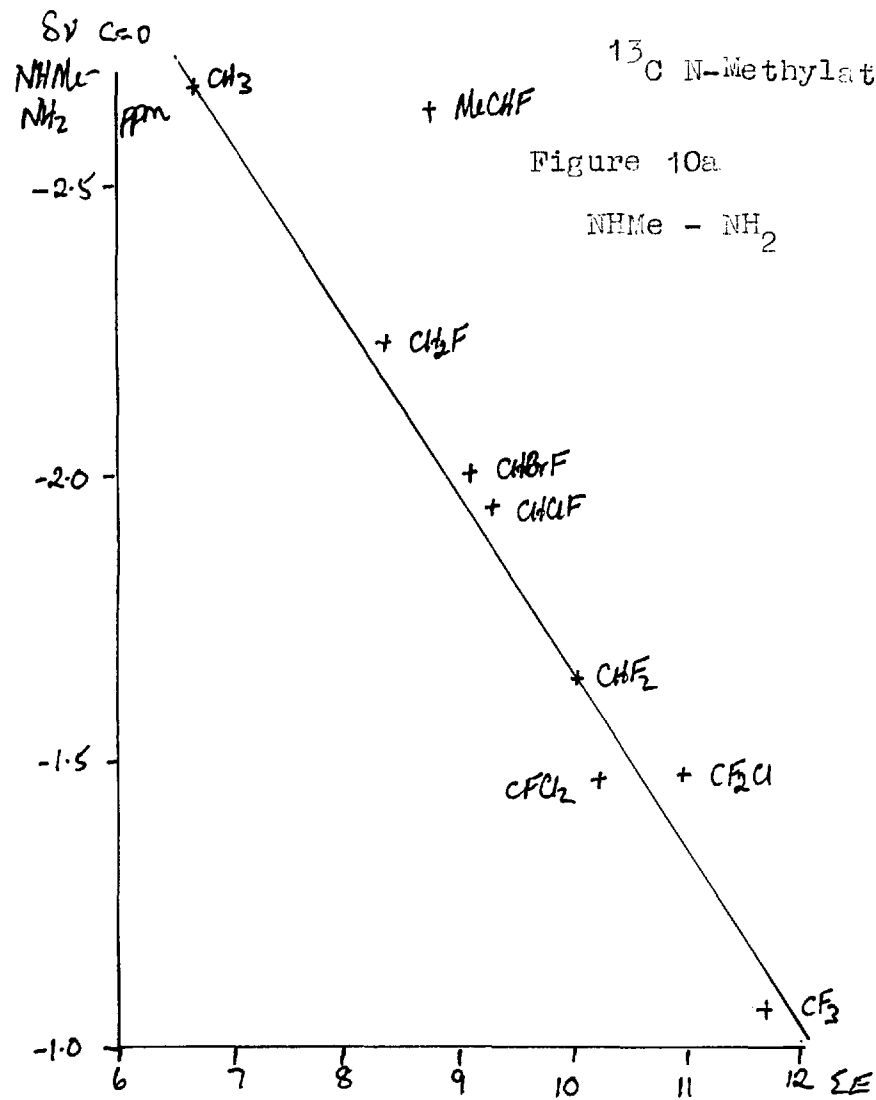
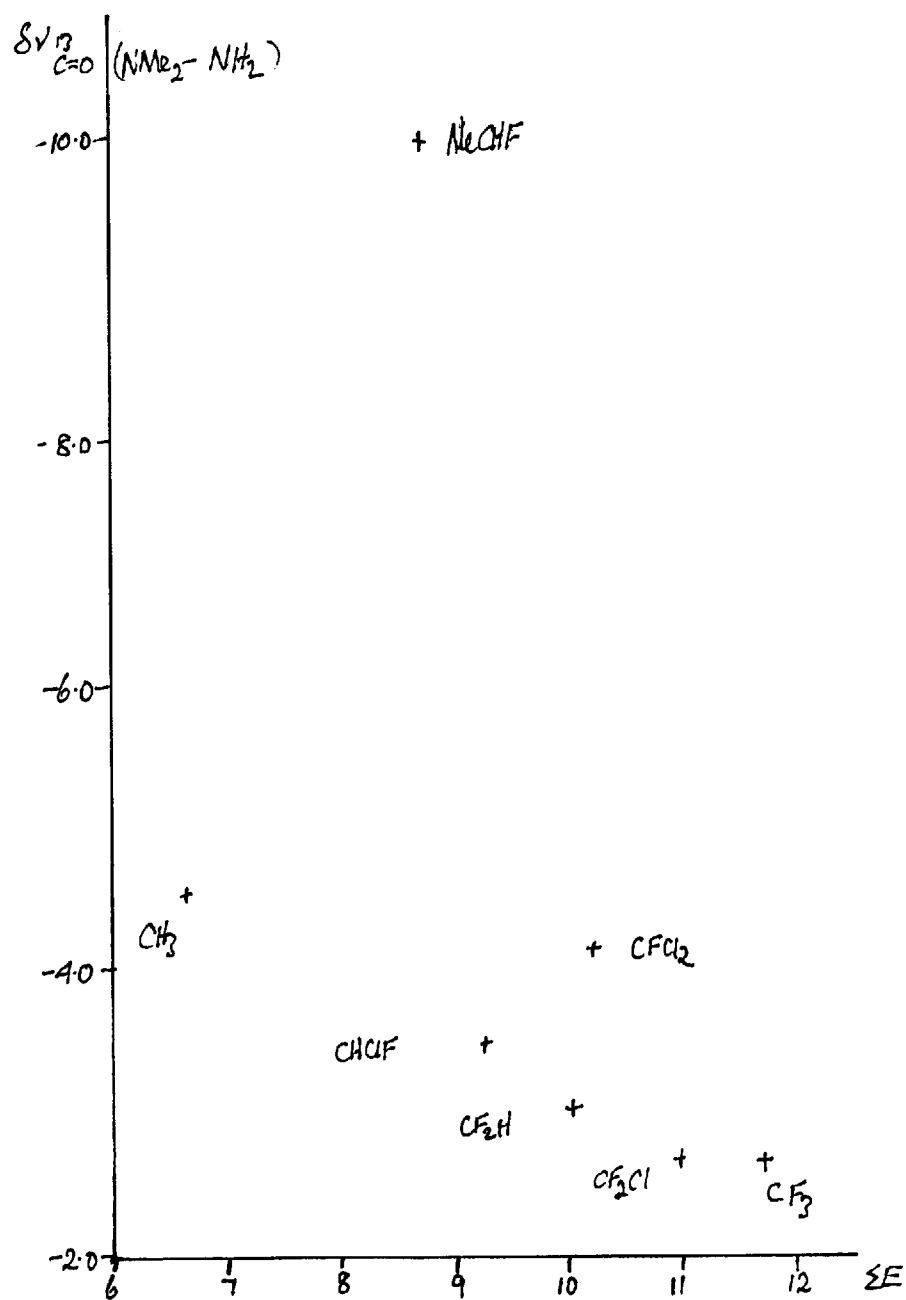
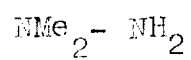


Figure 10c



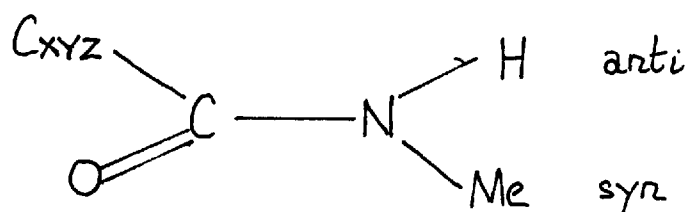
^{13}C N-Methylation shift of carbonyl
carbon for total methylation



site of N-methylation in a simple fashion.

The effects of successive N-methylation upon the carbonyl carbon chemical shifts are listed in table 17, and depicted graphically in figure 10 (a - c). It is seen from table 17 that mono-N-methylation produces a shielding of the carbonyl carbon of 0.96 to 2.7 ppm, and figure 9a reveals that this correlates well with the total electronegativity (ΣE) of the acetyl group substituents. Addition of a second methyl group yields further general shielding of 1.5 to 3 ppm and figure 10b shows there is little dependence upon ΣE . The overall effect of N-methylation ($NH_2 \rightarrow NMe_2$) is illustrated by figure 10c which shows that nett shielding of 2.65 to 4.54 ppm is to be expected, with the exception of the 2-fluoropropionamide derivative, which experiences a considerably greater upfield shift of 9.49 ppm.

The above behavioural pattern of non-additivity and increasingly poor correlation with successive methylation parallels that observed for the effects of N-methylation upon ^{19}F chemical shifts (Chapter 2) and these are probably founded in a common origin. It is known¹⁷ that mono-N-methylation of an amide introduces the methyl group in the syn position with respect to the carbonyl group:-



and it was proposed in chapter 2 (section 2.3) that because the N-methyl group is remote from the acetyl carbon it will not disturb the conformational preferences of the latter centre. Introduction of the second methyl group to the anti position places the hydrogen atoms spatially closer to the acetyl substituents such that they could influence and hence modify these conformation preferences.

An example of this hypothesis is probably provided by the series of 2-fluoropropionamides. The conformational preferences of

the Me.CHF- moiety could not be studied in the previous section (3.2.1), because it was not possible to synthesise Me₂.CF-CO.OR. Consequently it is not known if the preferred conformation is that with F or Me eclipsing the carbonyl group. If the latter were found to be true, it would not be reasonable to expect data relating to this compound (MeCHF.CO.NR₁R₂) to show much correspondence with the series of α -fluoro-haloacetamides, which have been shown to exist with one fluorine atom preferentially eclipsing the carbonyl oxygen atom. This point is however one of speculation and cannot be discussed further.

It will be recalled that the series of esters examined in section 3.2.1. were taken as models of the parent acid fragment C_{XYZ}.CO- which could be studied without any influence of the amido- moiety. It is instructive to examine any differences which do occur between the ester and primary amide for each compound, and these are set out in table 18.

Table 18. Differences in acetyl and carbonyl chemical shifts for esters and amides of the type C_{XYZ}.CO.Q. (ppm).

C _{XYZ}	Σ^F_{XYZ}	¹³ C _{XYZ}			¹³ C=O		
		$\nu_Q = \text{OMe}$	$\nu_Q = \text{NH}_2$	$\delta\nu_{\text{NH}_2-\text{OMe}}$	$\nu_Q = \text{OMe}$	$\nu_Q = \text{NH}_2$	$\delta\nu_{\text{NH}_2-\text{OMe}}$
CH ₃ -	6.6	20.08	22.34	2.26	168.95	173.59	4.64
CH ₂ F-	8.3	76.62	80.01	3.39	166.63	170.41	3.78
MeCHF-*	8.7	84.70	92.50	7.80	168.81	177.72	8.91
CHBrF-*	9.05	80.49	84.06	3.57	163.20	167.42	4.22
CHClF-	9.25	90.62	93.71	3.09	163.22	166.59	3.37
CHF ₂ -	10.00	106.20	108.17	1.97	161.69	164.82	3.13
CFCl ₂ -	10.20	108.66	111.79	3.13	159.96	163.48	3.52
CF ₂ Cl-	10.95	118.48	118.60	0.12	158.80	161.53	2.73
CF ₃ -	11.70	114.24	113.19	-1.05	157.13	158.91	1.78

Change in carbon chemical shifts upon conversion of ester to amide

$\Delta \nu_{C_{xyz}}$

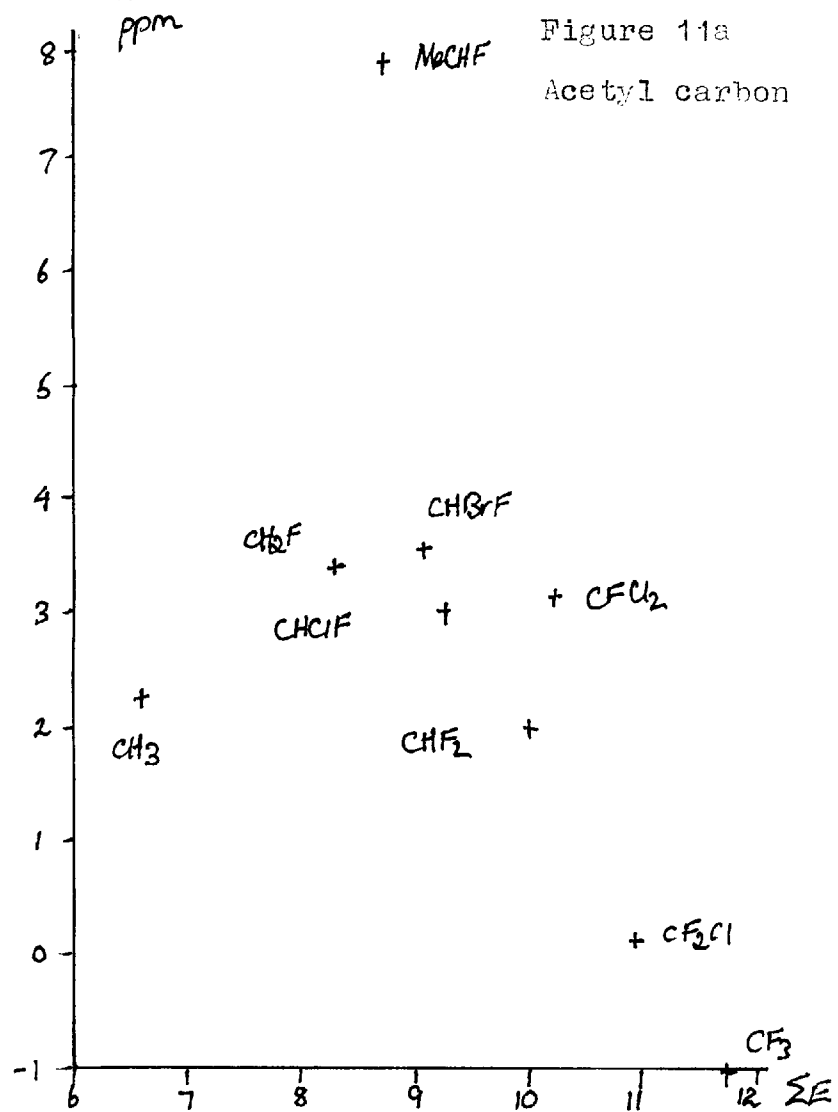


Figure 11b

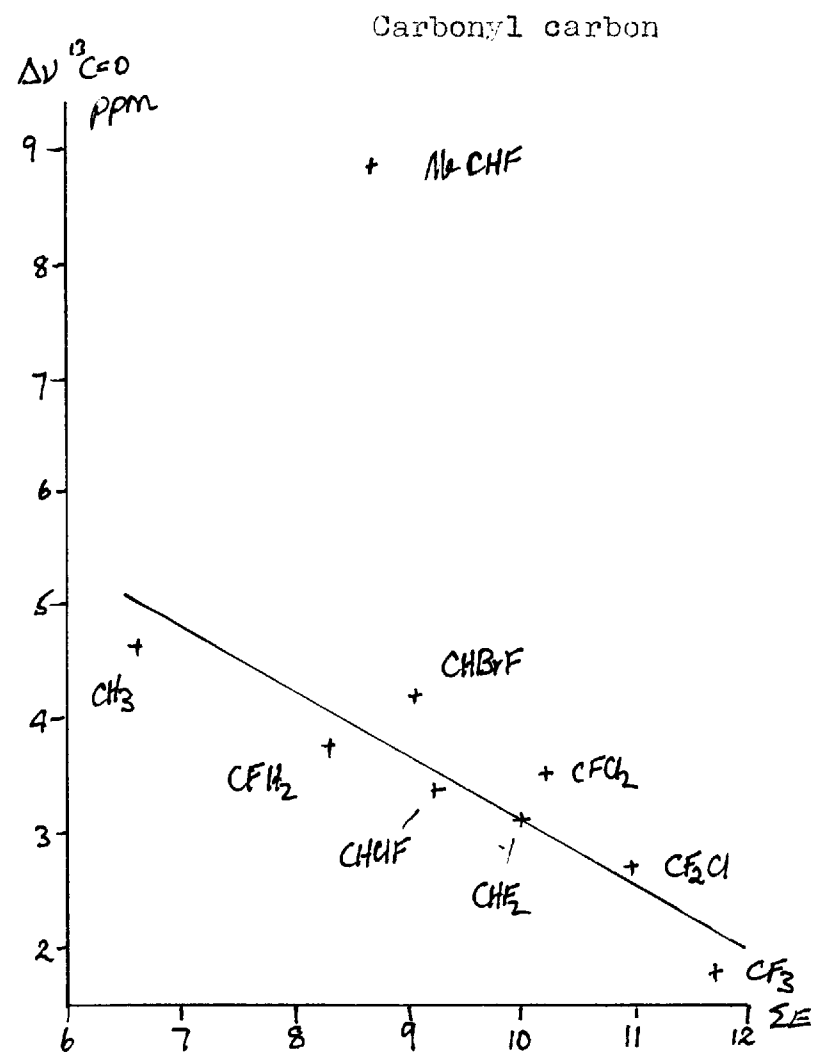


Table 18 indicates that the acetyl carbon undergoes an average deshielding of ca. 2.9 ppm upon ammonolysis of the ester. The propionic acid derivative exhibits a much larger difference whilst the two most electronegative compounds experience little change and slight shielding respectively. Figure 11a indicates there is little correlation with total acetyl substituent electronegativity (ΣE).

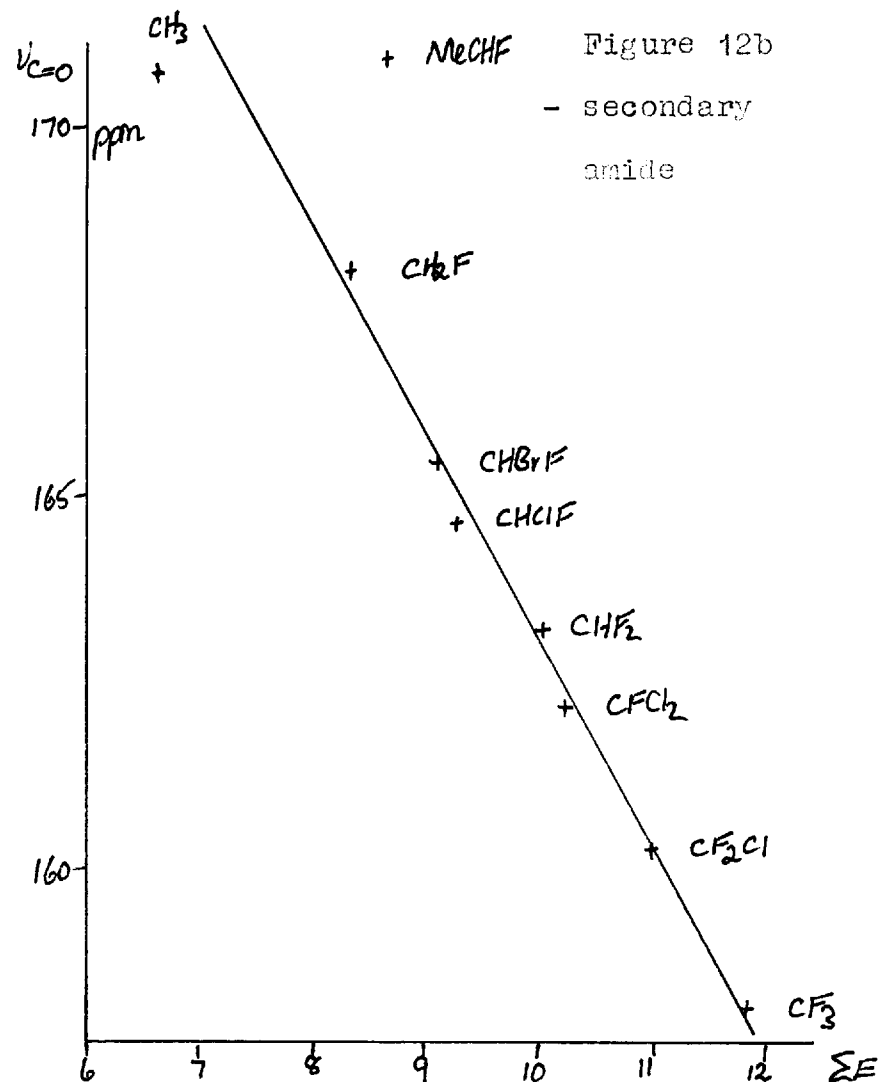
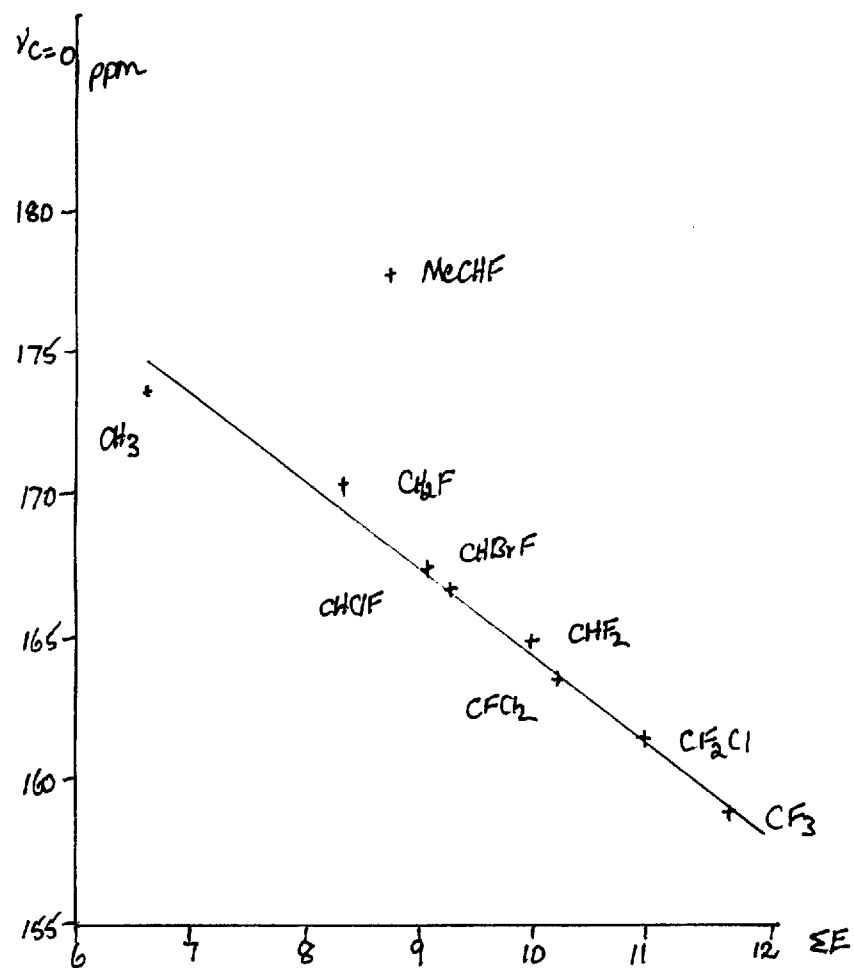
The carbonyl carbon also experiences a deshielding upon conversion of ester to amide ranging from 4.6 ppm to 1.8 ppm, and figure 11b indicates that this difference is proportional to ΣE . Again the propionic acid derivatives yield anomalous data.

It is noteworthy that the change in shielding recorded for both the acetyl and carbonyl carbons of 2-fluoropropionate upon ammonolysis are considerably larger than the range of values found for the series of α -fluorohaloacetic acid derivatives. These observations lend support to the proposal discussed above that the MeCHF- moiety exists in a conformation in which the fluorine atoms does not eclipse the carbonyl oxygen.

It is recalled from the study on esters (section 3.2.1.1) that a plot of the chemical shift of the carbonyl carbon against the sum of the Huggins electronegativities of the acetyl group substituents (ΣE) was linear (figure 2). Since it has been found that the difference in chemical shift of this carbon between ester and corresponding amide is also proportional to ΣE (figure 11b) it is anticipated that a direct plot of chemical shift vs. ΣE will produce a linear relationship, with the results shown in figure 12 (a - c) for the three amide types. It is observed that the point corresponding to the propionamide depart considerably from the relationship indicated by the remaining compounds, and the values derived from a least-squares analysis for the latter are presented in table 19, along with that obtained for the methyl esters for comparison. It is concluded that the factors influencing the chemical shifts of the carbonyl group for the amides are similar to those discussed for the esters.

^{13}C carbonyl chemical shifts of amides vs. ΣE

Figure 12a - primary amide



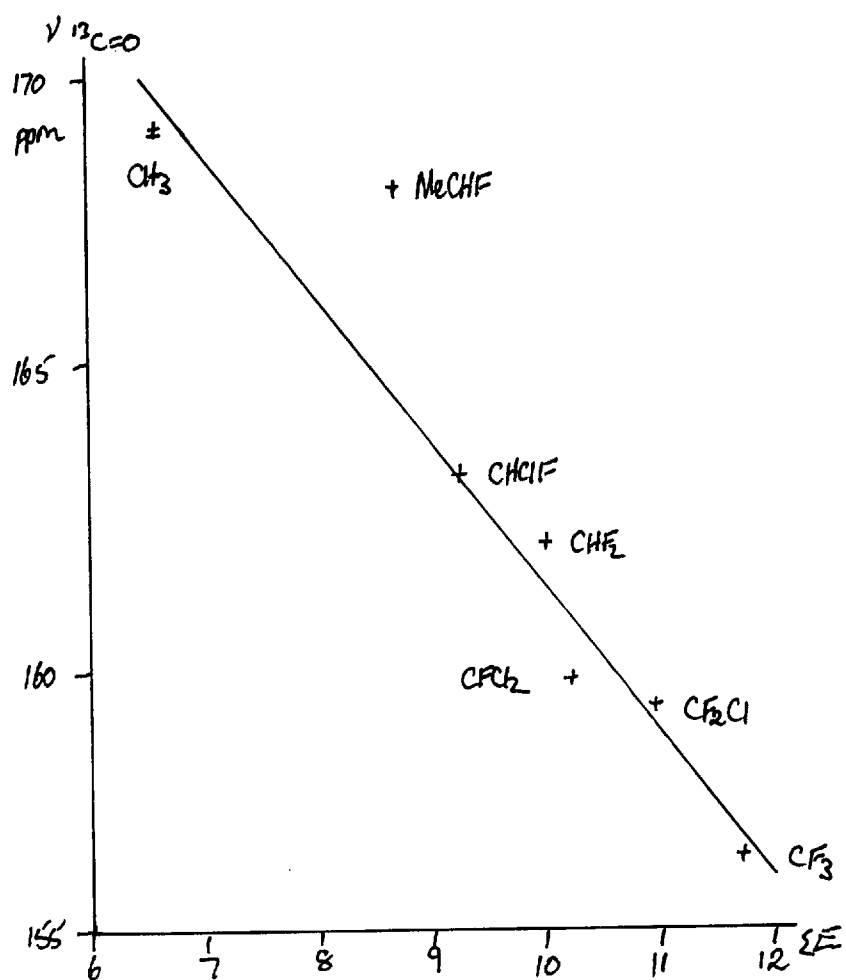


Figure 12c

^{13}C carbonyl chemical shift of tertiary amide vs. ΣE

Table 19. Least squares analysis of carbonyl chemical shifts.

$$\sigma_{XYZ} \cdot {}^{13}\text{CO}_2 - \text{figure 11.}$$

σ	slope ppm. E^{-1}	intercept (ppm)	correlation coefficient	std. devn. (ppm)
-OMe	-2.313	184.08		
-NH ₂	-2.95	193.89	0.9927	0.532
-NMe	-2.70	190.16	0.9457	1.311
-NMe ₂	-2.53	186.07	0.9888	0.618

3.2.2.2 Coupling constants of the acetyl and carbonyl carbons.

Attention in this section will be confined to the directly bonded and geminal coupling constants of the acetyl ($\sigma_{XYZ}\text{CO-}$) moiety; other couplings associated with the amide part of the molecule will be considered in following sections dealing with features specific to each amide series. Values of the directly bonded coupling constants (${}^1J_{\text{CH}}$ and ${}^1J_{\text{CF}}$) recorded in CDCl_3 solution (CFCl_3 for the N,N dimethyl amides) are listed in table 20, with those of the corresponding ester for comparison (data from tables 5 and 10). It is seen from table 20 that values of the observed coupling constants are essentially independent of the nature of the acid derivative (ester, amide - dimethyl amide) and consequently the analyses of these coupling constants discussed in section 3.2.1.3 and 3.2.1.4 are valid here.

The general coupling constants of the fluorine to the carbonyl carbon were also recorded and are presented in table 21 in a manner analogous to that for the directly bonded couplings. It is seen from this table that the three values of the geminal coupling for the amides

Table 20. Directly bonded coupling constants in amides $C_{XYZ} \cdot CO \cdot Q$

C_{XYZ}	$^1J_{C-H}$ (Hz)			$^1J_{C-F}$ (Hz)			
	$Q = NH_2$	$Q = NHMe$	$Q = OR$ (b)	$Q = NH_2$	$Q = NHMe$	$Q = NMe_2$	$Q = OR$ (b)
CH_3-	127.9	127.8	129.1	-	-	-	-
CH_2F-	154.5(a)	155.1	153.6	186.3	185.2	178.5	182.6
$MeCHF-$	156.0(a)	155.8	155.0	183.0	182.5	176.1	183.5
$CHBrF-$	188.3	188.1	188.3	266.0	265.7	-	264.1
$PhCHF-$	158.3(a)	156.4	157.0	188.0	187.4	-	188.0
$CHClF-$	187.0	186.7	187.0	255.2	254.4	252.7	253.4
CHF_2-	192.4	190.4	190.6	251.8	249.9	252.2	249.1
$CFCl_2-$	-	-	-	307.5	307.0	303.7	305.7
CF_2Cl-	-	-	-	301.6	302.0	300.5	300.5
CF_3-	-	-	-	287.3(a)	286.7	287.4	285.0

(a) MeOH solvent (b) CCl_4 solvent.Table 21. Geminal $^2J_{C-F}$ coupling in amides $C_{XYZ} \cdot CO \cdot Q$ (Hz)

C_{XYZ}	$Q = -NH_2$ (a)	$Q = NHMe$ (a)	$Q = NMe_2$ (b)	$Q = OR$ (c)	Av. $^2J_{CF}$ (amide)	$J(OR) - J(NRR')$ Av.
CH_2F	15.1	17.1	18.4 (d)	22.2	16.1	6.1
$MeCHF$	21.0	19.0	18.9	22.8	19.6	3.2
$CHBrF$	22.0	21.1	-	25.5	21.5	4.0
$PhCHF$	19.0	21.6	-	27.5	20.3	7.2
$CHClF$	23.3	22.5	22.6	26.4	22.8	3.6
CHF_2	24.5	24.7	25.1	28.3	24.7	4.1
$CFCl_2$	27.2	25.2	25.7	30.0	26.1	3.9
CF_2Cl	31.5	29.8	29.1	34.1	30.1	4.0
CF_3	-	37.4	35.9	42.3	36.7	5.6

(a) $CDCl_3$ (b) $CFCl_3$ (c) CCl_4 (d) CCl_4 @ ambient

$^2J_{CF}$ - geminal coupling constant for the amides vs. ΣE

Figure 13a - primary amide

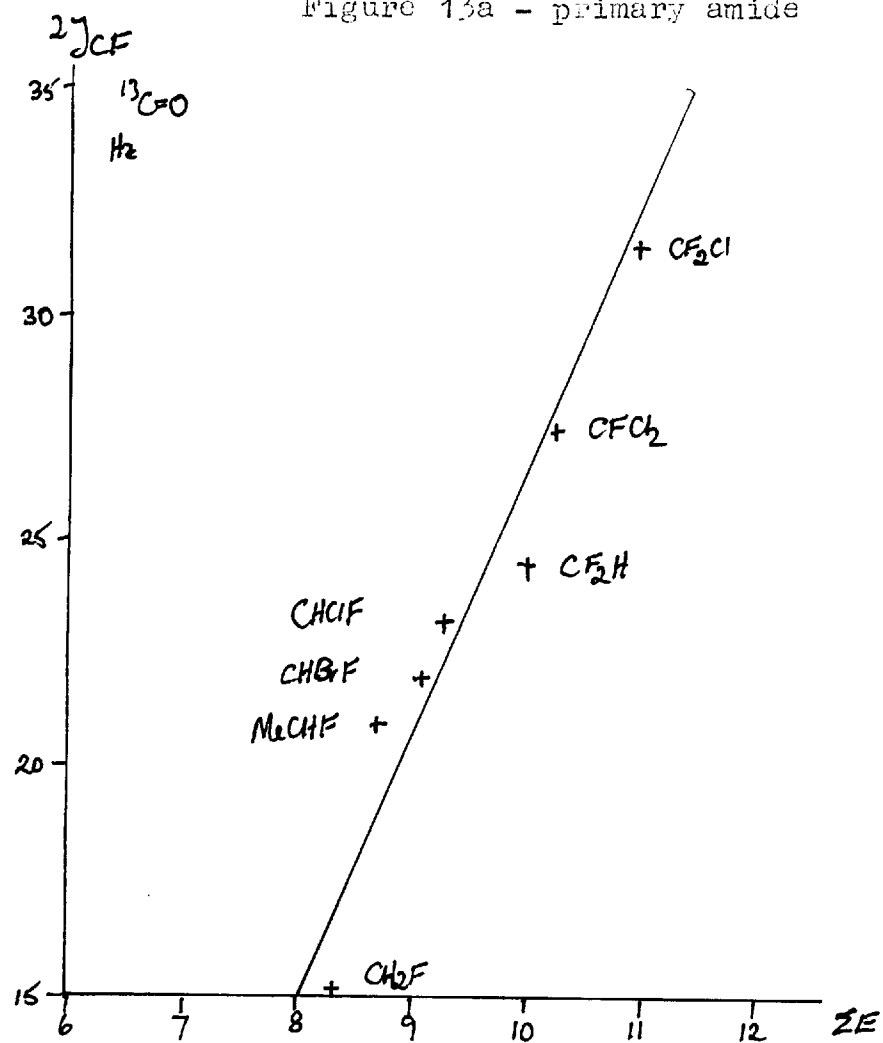
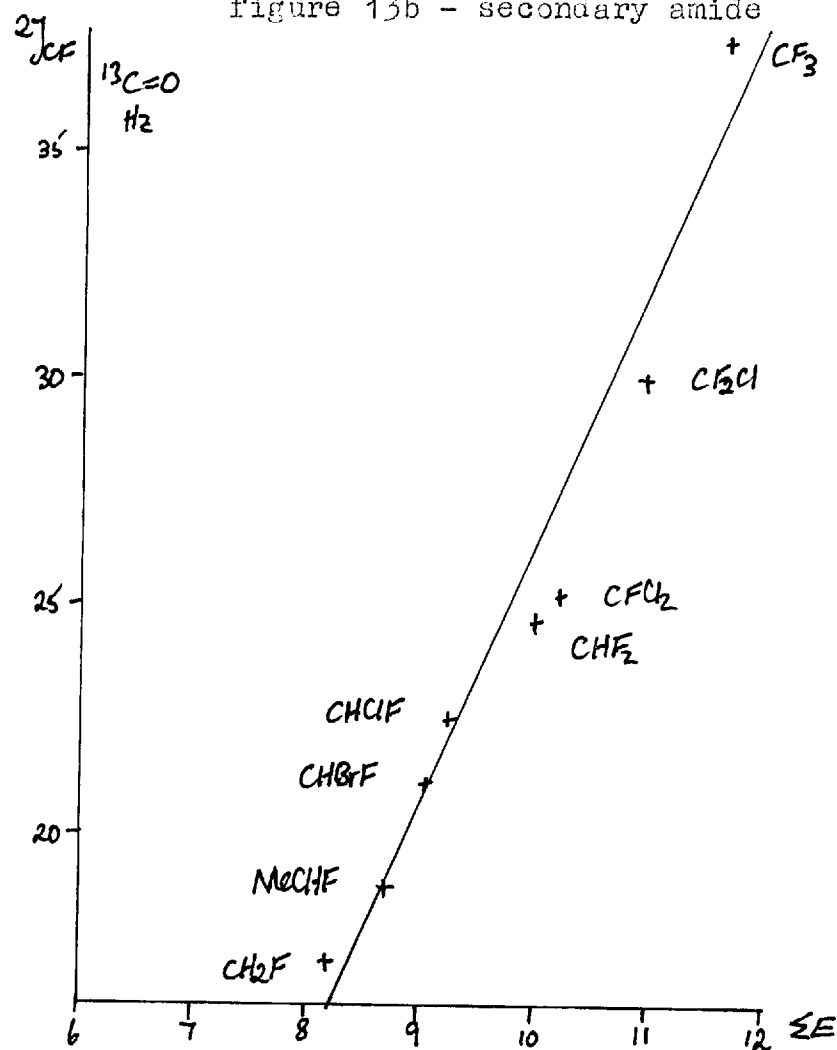


figure 13b - secondary amide



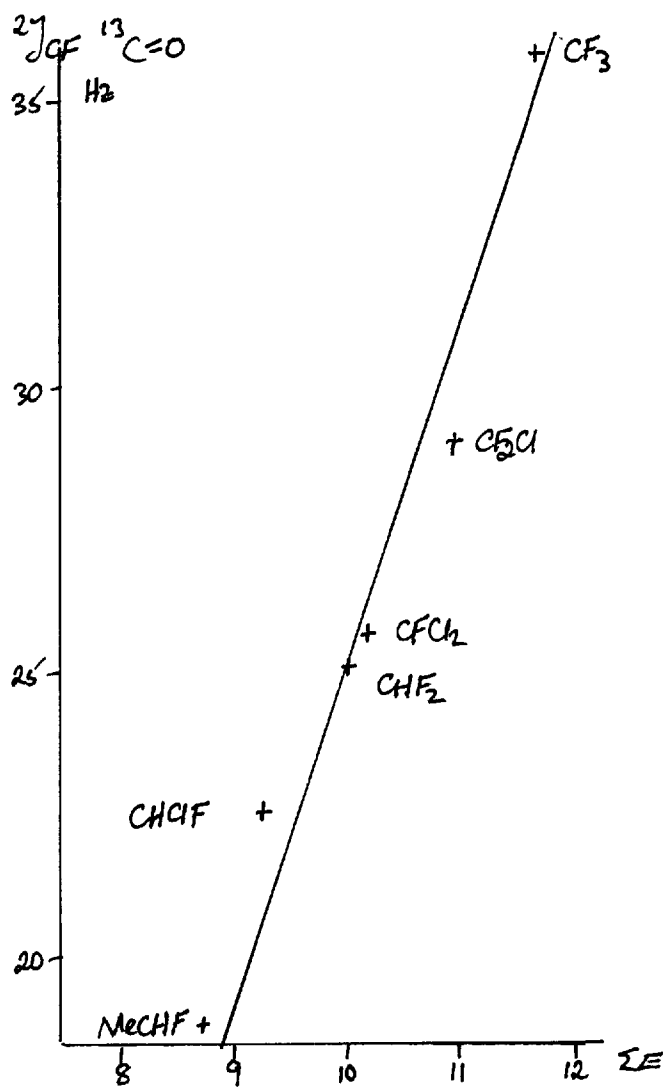


Figure 13c

$2J_{CF}$ - geminal coupling constant
vs. ΣE for tertiary amide

derived from any one parent acid all lie within a range of 2 Hz, which is the order of error expected in their measurement (400 Hz spectral width implies digitization in the frequency domain of 1 Hz/point). Comparison of the averaged coupling for the three amides with that of the corresponding ester indicates that the former is always less than the latter, and this difference amounts to an average of 4.6 Hz.

It is concluded that N-methylation is without effect upon the geminal fluorine-carbonyl coupling constant, but that this is reduced upon substitution of the highly electronegative alkoxy group ($-\text{OR}$) by the less electronegative amido ($-\text{NH}_2$), which represents a change of $3.5 - 3.05 = 0.45$ Huggins electronegativity units. Plots of ${}^2J_{\text{CF}}$ vs. ΣE are linear (figure 13 a - c) as found for the esters (fig. 6) and data derived from the least-squares analyses indicate that the above change in coupling constant is consistent with a reduction in the total directly bonded electronegativity of 0.83 Huggins units.

3.2.2.3. Features specific to the primary amides.

Herein interest centres upon a long-range coupling ${}^3J_{\text{CH}}$ observed between the acetyl carbon and one of the amido protons. These vary with the nature of the acetyl groups substituents and are listed in table 22. The nature of this variation may be examined in a manner analogous to that employed for the long range (${}^4J_{\text{F.NH}}$) fluorine-NH coupling (chapter 1) by a plot of ${}^3J_{\text{C.NH}}$ against E . Figure 14 depicts such a plot for the coupling recorded in methanol. It is seen that the values are not directly proportional to ΣE (as was found for ${}^4J_{\text{F.NH}}$) but appear to exhibit 'families of lines' similar to those observed for the chemical shifts of the ester carbons.

The observation of this long range coupling is specific to the primary amides, and it is not detected for the $-\text{NHMe}$ series. It is known¹⁷ that the latter always exists with the N-methyl group syn to the carbonyl and hence this implies that the ${}^3J_{\text{C.NH}}$ coupling must

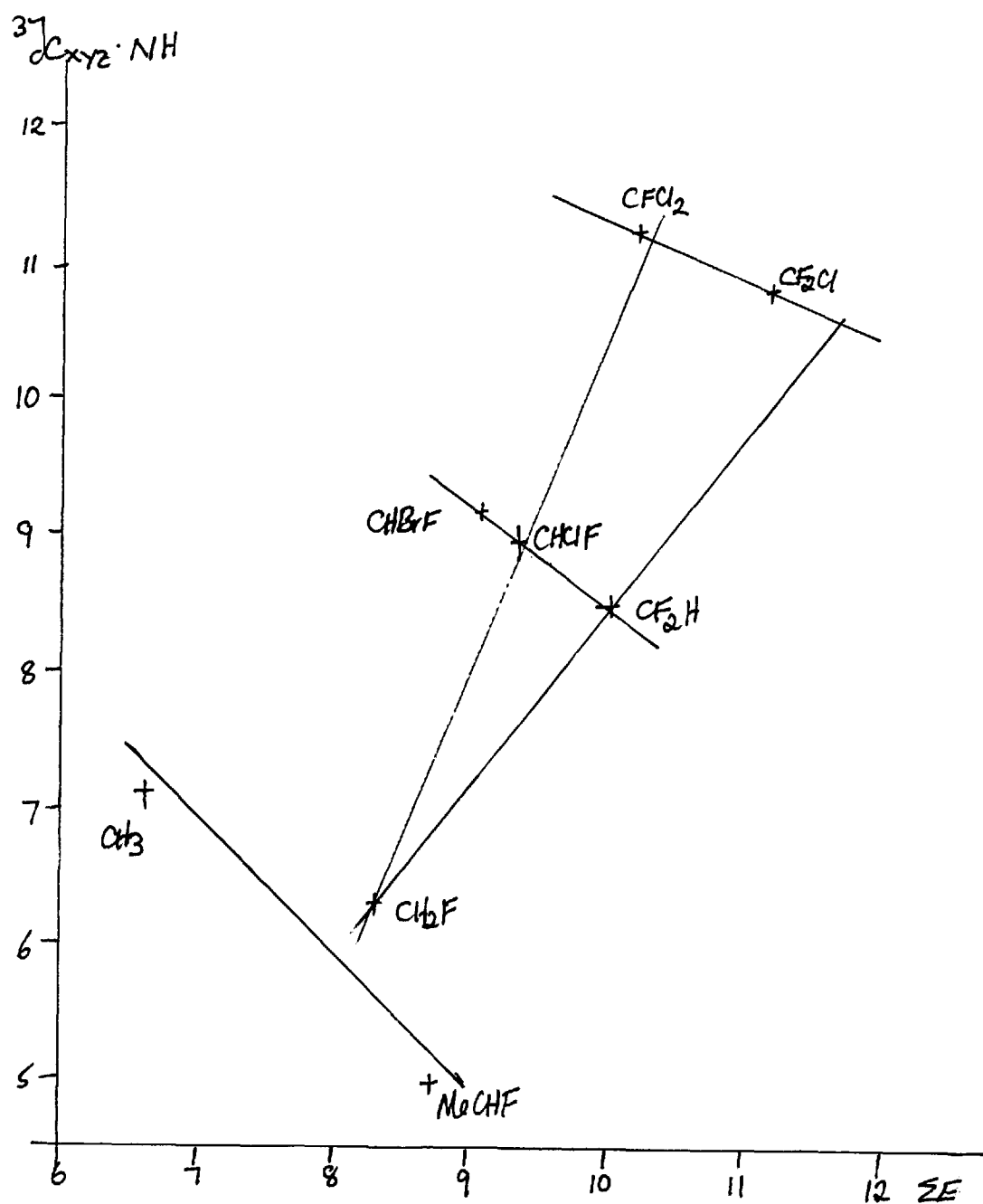


Figure 14

$^3J_{C-NH}$ coupling vs. ΣE in $CXYZ.CO.NH_2$

Table 22. Long range C-H coupling in primary amides $^{13}\text{C}_{\text{XYZ}}\cdot\text{CO}\cdot\text{NH}_2$ (Hz)

C_{XYZ}	$\Sigma \rho_{\text{XYZ}}$	$^3\text{J}_{\text{CH}}$ in [†] MeOH	$^3\text{J}_{\text{CH}}$ CDCl_3	temp ($^{\circ}\text{C}$) (a)
CH_3	6.6	7.1	7.15	50
CH_2F	8.3	6.3	-	-
MeCHF	8.7	5.0	-	-
CHBrF	9.05	9.2	7.77	-
PhCHF	9.10	$\nu_{\text{H}}^{12.0}$	-	-
CHClF	9.25	9.05	7.75	-
CHF_2	10.0	8.5	7.3	45 (b)
CFCl_2	10.2	11.25	-	55
CF_2Cl	10.95	10.9	10.0	43
CF_3	11.7	<1.0	0	50

Notes: [†] all data in MeOH at ambient probe temperature (25 $^{\circ}\text{C}$)

(a) when not given, data at probe temperature

(b) chemical shift data recorded at ambient on diluted solutions.

be to the -NH which is syn to the carbonyl oxygen. This is the opposite to that found for $^4\text{J}_{\text{F}\cdot\text{NH}}$ where it was shown (Chapter 1) similarly that the acetyl fluorine atom couples to the anti -NH proton.

Data for trifluoroacetamide is unfortunately absent because the compound undergoes intramolecular exchange in methanol (Chapters 1 and 2) and also apparently in CDCl_3 solution. This prevents a more detailed examination of the variation in coupling constants in a manner utilized with the ester chemical shifts.

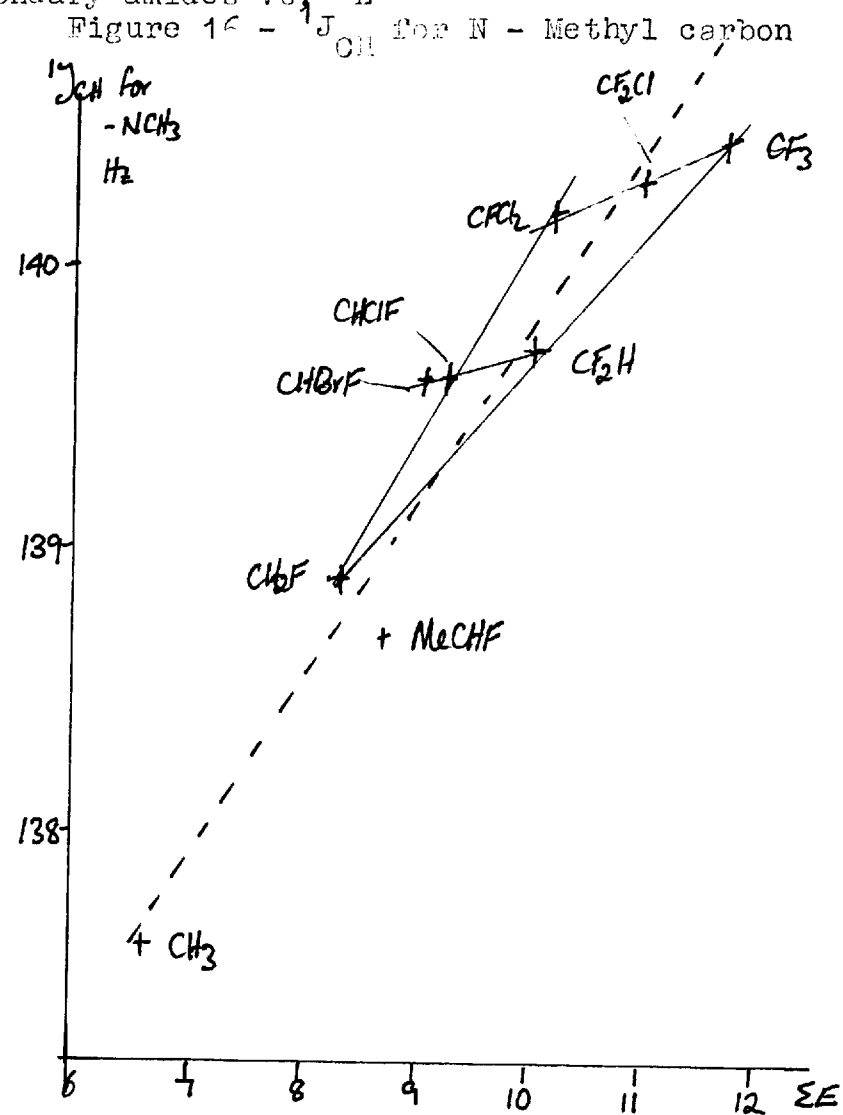
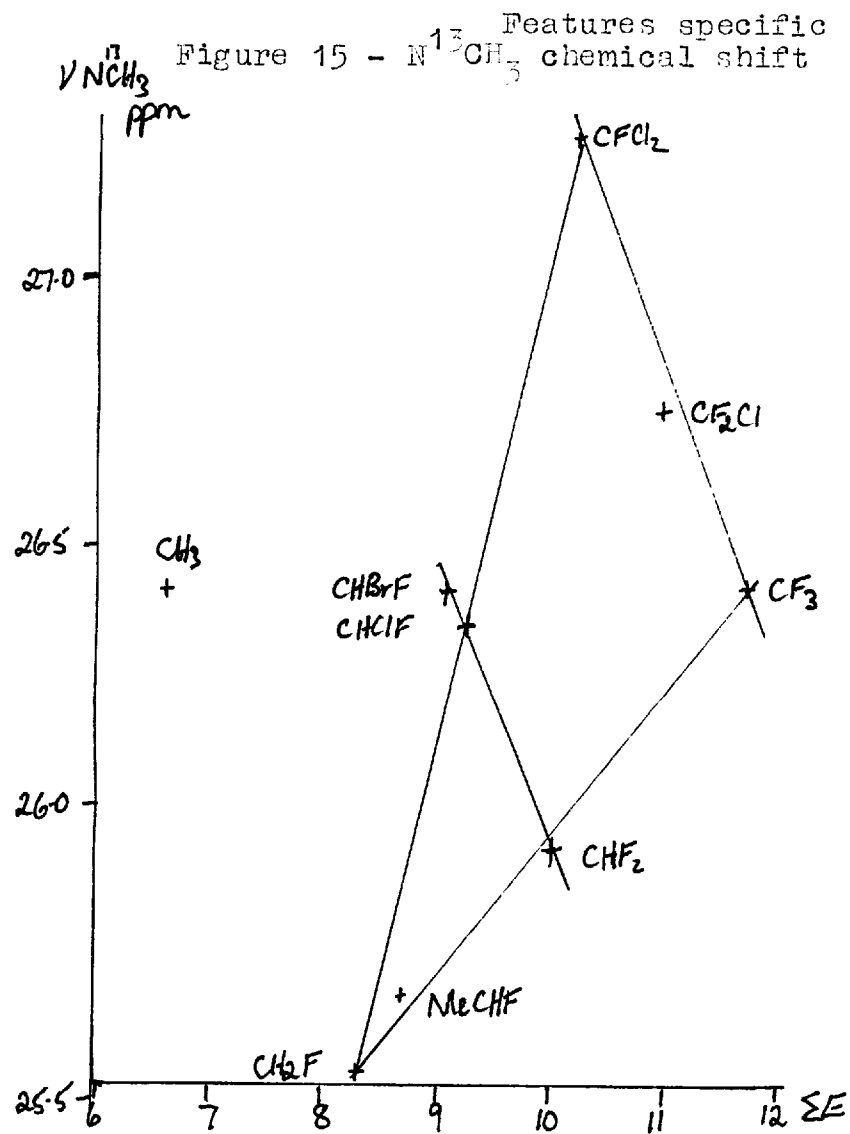
3.2.1.4. Features specific to the secondary amides.

These are associated with the properties of the N-methyl group, viz. its chemical shift, directly bonded coupling constant and geminal C-NH coupling with the amido proton, which are given in table 23 for infinitely dilute or 10 - 20 mole % solutions in CDCl_3 respectively.

Table 23. NMR parameters of NMe group in $\text{C}_{\text{XYZ}}\cdot\text{CO}\cdot\text{NMe}$.

C_{XYZ}	δ^{E}	$\nu_{\text{N-CH}_3}$ (ppm)	$^1\text{J}_{\text{C-H}}$ (Hz)	$^3\text{J}_{\text{C-NH}}$ (Hz)
CH_3	6.6	26.40	137.6	2.7
CH_2F	8.3	25.55	138.9	2.47
MeCHF	8.7	25.69	138.7	2.5
CHBrF	9.05	26.40	139.6	2.35
PhCHF	9.10	25.85	139.0	2.8
CHClF	9.25	26.34	139.6	2.25
CHF_2	10.0	25.94	139.7	2.1
CFCl_2	10.20	27.19	140.2	2.1
CF_2Cl	10.95	26.71	140.3	2.05
CF_3	11.7	26.41	140.45	1.9

The variation in chemical shift with the nature of the acetyl group is examined in figure 15, from which it is seen that 'families of lines' exist with $-\text{CH}_2\text{F}-$ as the common point. Although the parent CH_3- acid is not the point of origin, this form of relationship is to be expected because the N-methyl group is in the same geometrical relationship to the acetyl group as the alkoxyl ester groups, and hence the nature of the effect observed here must arise from the same origin. Similarly, it is not surprising that this influence should also be permeated into a variation of the directly bonded C-H spin coupling



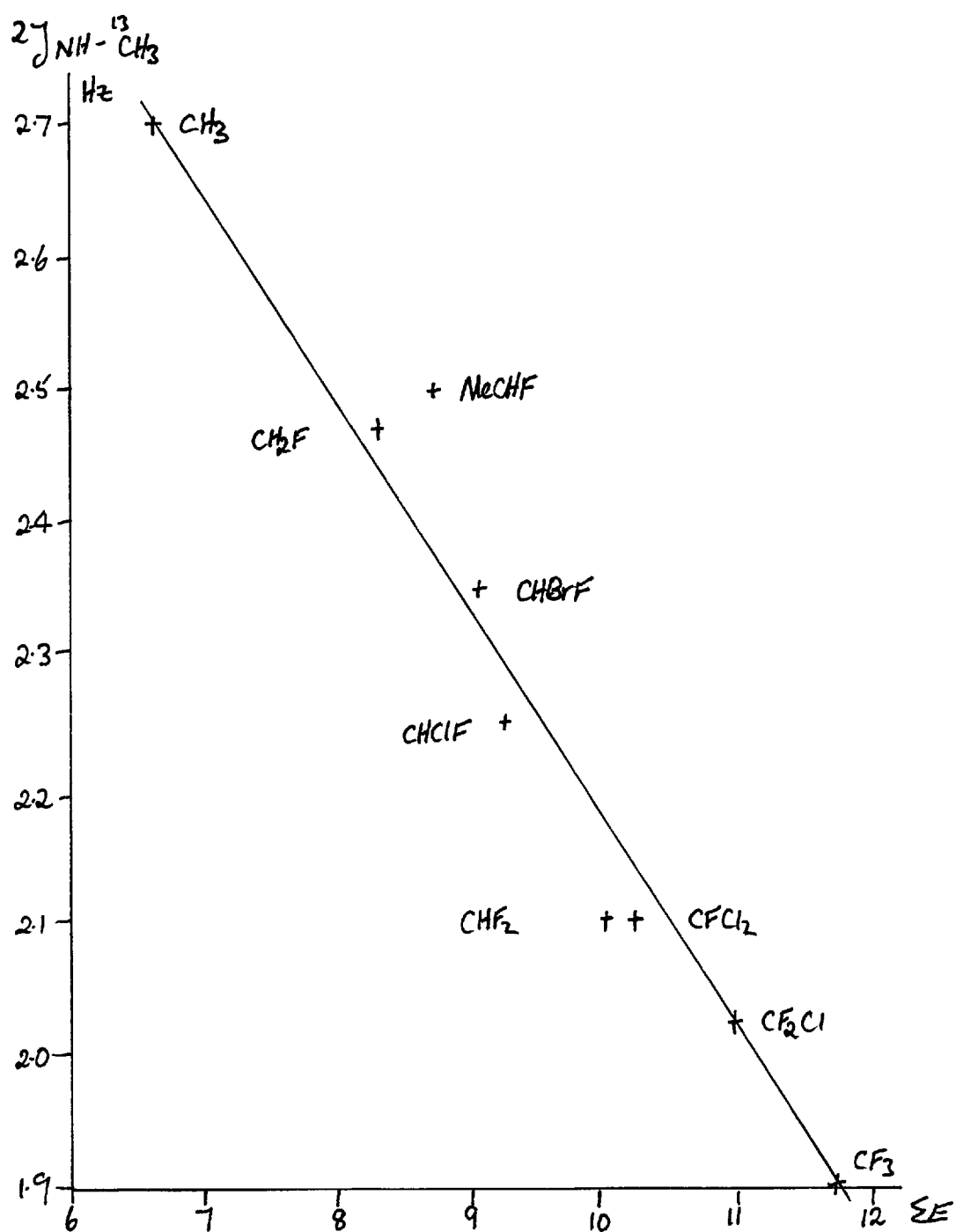


Figure 17

$^2J_{\text{NH-CH}_3}$ geminal coupling in the
secondary amides vs. ΣE

(figure 16), from 137.6 Hz to 140.5 Hz. Although this is only a range of 3 Hz it is real because all the coupling constants reported in this section were recorded under conditions of relatively high resolution (1000Hz spectral width implying a digitization of 0.25 Hz/point).

The observed range of the chemical shift variation, 1.65 ppm, is considerably less than that for the alkoxyl groups ($-\text{OCH}_2-$, 5.18 ppm, and $-\text{OCH}_3$ 4.31 ppm) but analysis of the data in a manner analogous to that of section 3.2.1.2 is prevented because the data from the acetamides do not represent the point of origin. Consequently it is not possible to utilize this data to confirm the conformational preferences deduced from the ester chemical shifts.

It was possible to resolve a small geminal coupling across the nitrogen atom between the N-methyl carbon and the amido proton. Table 23 shows that this amounts to 2.7 Hz for N-methyl acetamide and decreases (sign unknown, assumed positive) with introduction of electronegative substituents at the acetyl carbon, yielding a range of 0.8 Hz. Figure 17 reveals that this trend correlated well with ΣP , and both these observations exactly parallel those for the long range coupling between acetyl fluorine and the same (i.e. anti NH) proton.

3.2.2.5 Features specific to the tertiary amides.

The points of interest are the chemical shifts and long range couplings of the N-methyl groups and the relevant data are listed in table 24. All the spectra were recorded in CFCl_3 at temperatures sufficiently low that internal rotation about the $\text{C}(\text{O})-\text{N}$ bond had ceased, this point will be discussed in further detail later. It is seen that the effects of temperature and concentration differences are minimal from the data for dimethylacetamide at -30° and -80°C , and consequently the chemical shift values obtained for the other amides are considered to represent very closely that at infinite dilution.

^{13}C chemical shifts of the N methyl groups vs. ΣE - tertiary amides

Figure 18a-low field carbon

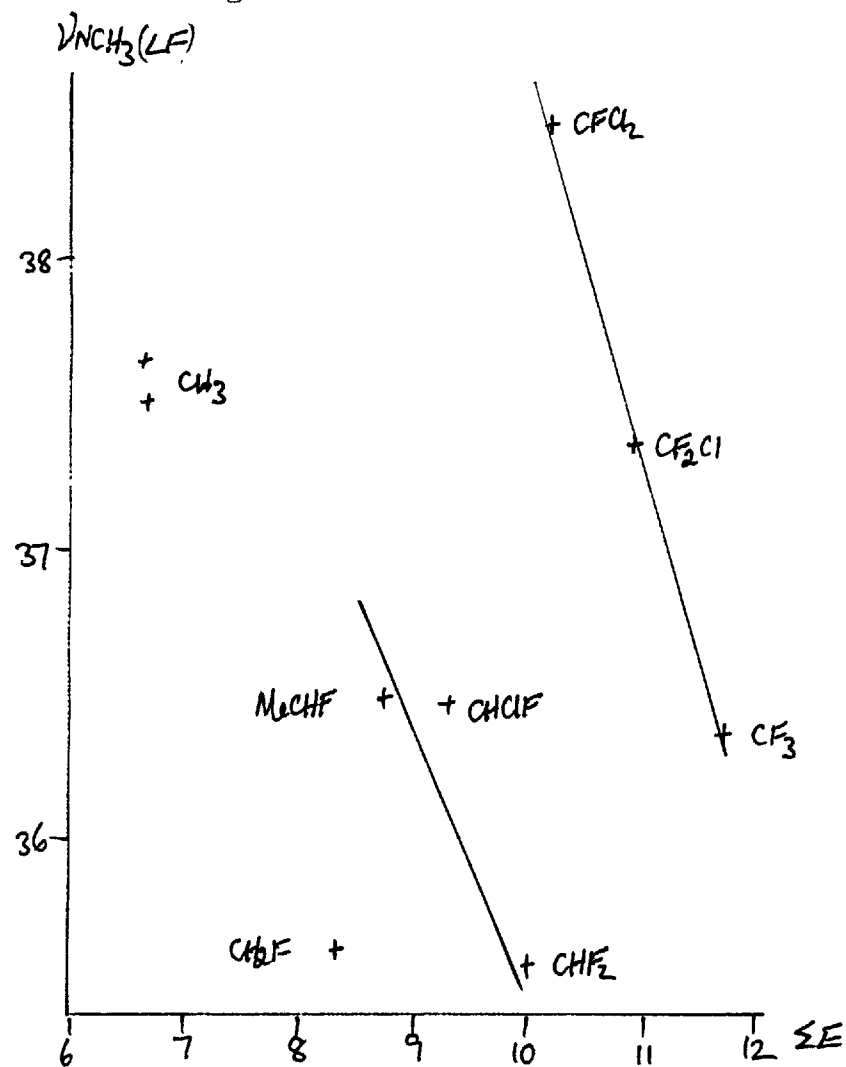


figure 18b-high field carbon

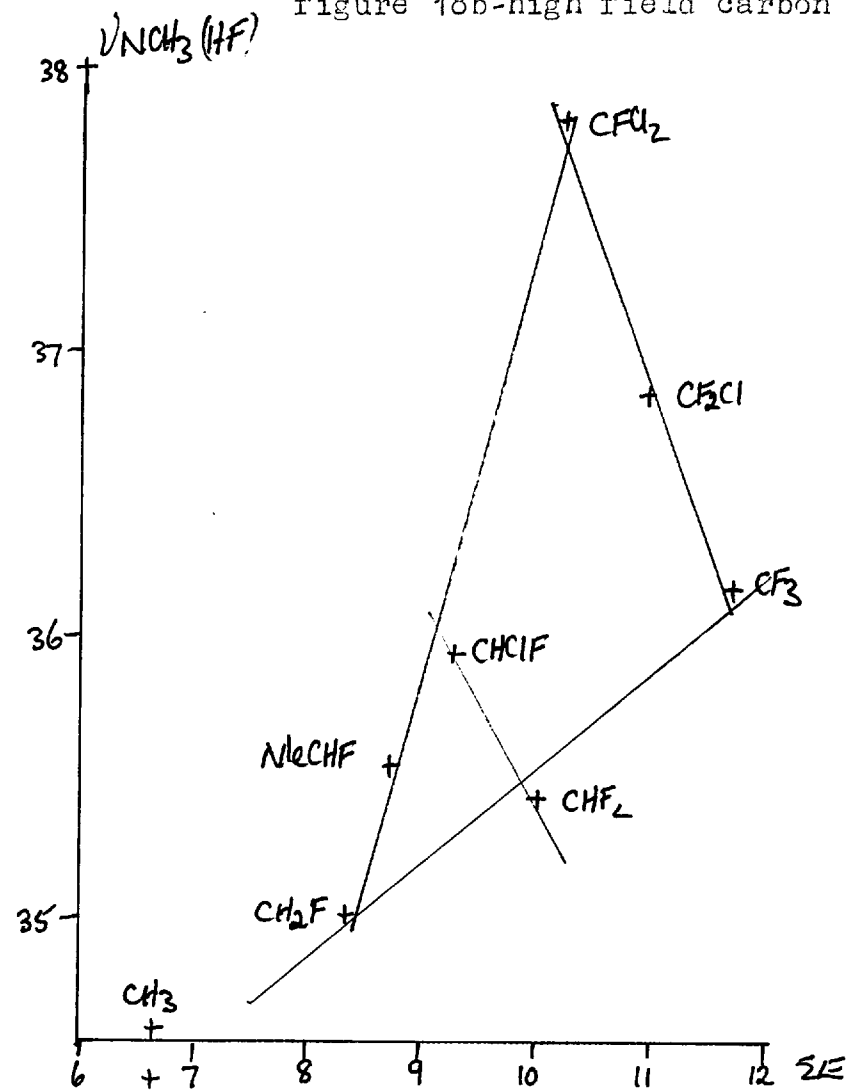


Table 24. ^{13}C NMR data for N-methyl groups in $\text{C}_{\text{XYZ}}\cdot\text{CO}\cdot\text{NMe}_2$.

C_{XYZ}	ΣB	ν_{NCH_3} (LF)		ν_{NCH_3} (HF)		$\Delta\nu_{\text{NMe}_2}$		$^4J_{\text{FNMe}}$	Concn	Temp.
		Hz	ppm	Hz	ppm	Hz	ppm			
CH_3	6.6	946.7	37.63	871.2	34.63	75.5	3.00	-	10	-30
		943.9	37.52	866.5	34.44	77.4	3.08	-	5	-80
CH_2F	8.3	894.9	35.57	880.8	35.01	14.1	0.56	5.4	5	-5
MeCHF	8.7	917.1	36.45	893.8	35.53	23.2	0.93	6.6	7	-30
CHClF	9.25	916.8	36.45	903.9	35.93	12.9	0.51	3.0	9	-20
CHF_2	10.0	894.1	35.54	891.0	35.41	3.1	0.12	4.1	10	-20
CFCl_2	10.2	967.7	38.46	950.8	37.79	16.9	0.67	4.8	10	-50
CF_2Cl	10.95	939.7	37.35	926.6	36.83	13.1	0.52	4.1	10	-50
CF_3	11.7	914.5	36.50	909.4	36.15	5.1	0.20	3.6	10	-40

The variation in chemical shift of the two N-methyl groups with the nature of acetyl groups is depicted in figure 18 (a & b) from which it is seen that the high field methyl exhibits a pattern of shifts similar to that observed for the secondary amide (figure 18b). Introduction of electronegative acetyl substituents deshields this high field methyl, with that of the unsubstituted amide (CH_3 -) now being to highest field in contrast to that for the secondary amide carbon. The low field N-methyl carbon shows a pattern of shifts similar to that of the high field but with significantly less correlation to the families of lines detected previously for regular changes e.g. the series CF_3 - CF_2Cl - CFCl_2 produces a straight line for both the methyl groups, but CH_2F - CHF_2 - CF_3 is only linear for the high field carbon and introduction of electronegative acetyl substituents shields the N methyl with the one exception of the CFCl_2 - derivative (figure 18a).

The key to the relative assignments of the two methyl groups is provided by the observation of a selective long-range coupling between the acetyl fluorine substituent(s) and the low field N-methyl carbon. Such a coupling is not found to the secondary amides ($-\text{NMe}$), which is known to exist with the N-methyl group syn to the carbonyl oxygen and hence this coupling must be to the N-methyl carbon in the

Features specific to the tertiary amides vs. ΣE

Figure 19 - $^4J_{F.NMe}$ (LF)

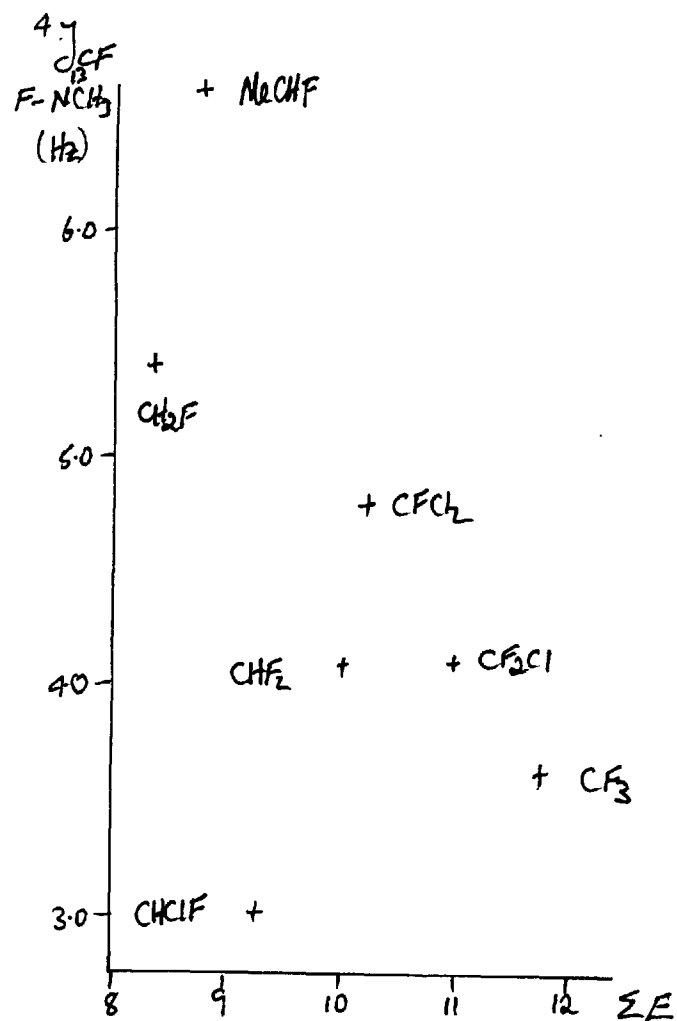
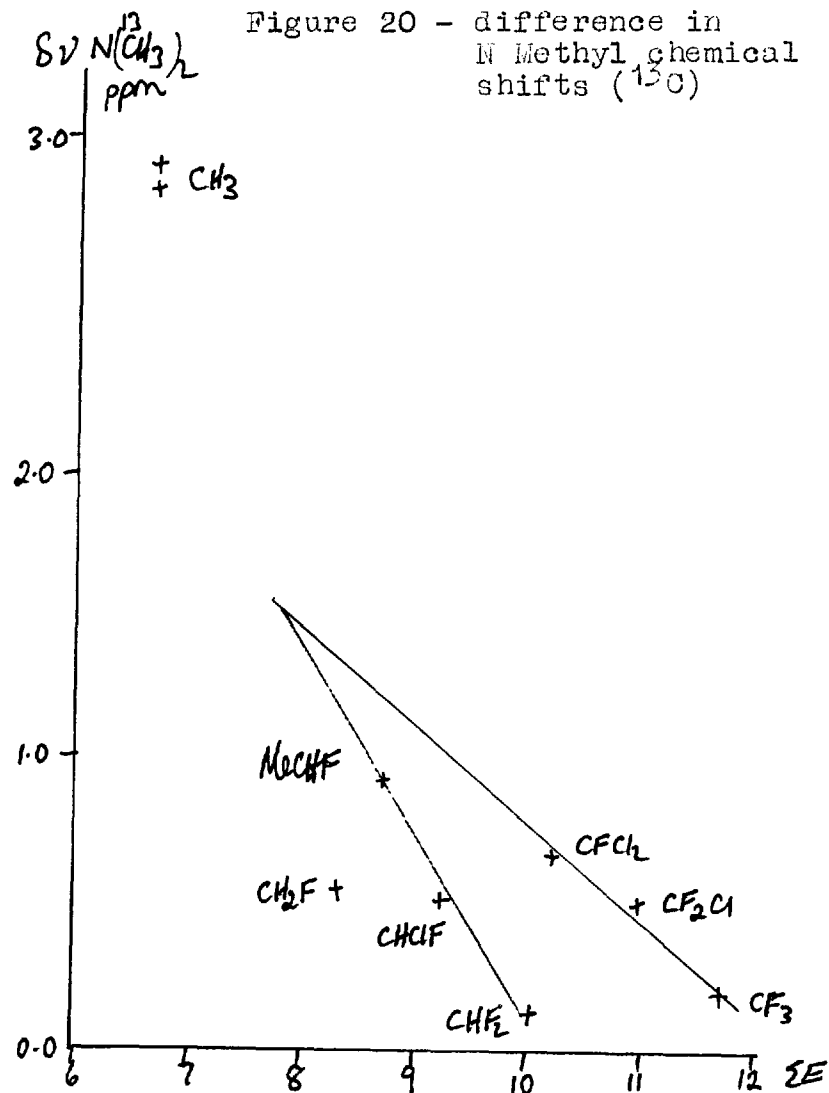


Figure 20 - difference in N Methyl chemical shifts (^{15}O)



anti position, which enables unambiguous assignments to be made. This result is the same as that found for ^1H resonances viz. the methyl group syn to the carbonyl is in a region of increased shielding with respect to that in the anti position.

Table 24 indicates that this long-range coupling varies between 3.0 and 6.6 Hz but figure 19 shows that it does not possess a simple relationship to the nature of the acetyl substituents, although a general reduction in value with increasing substituent electronegativity is noted.

The chemical shift difference between the carbons of the N-methyl groups is 3.0 ppm for dimethylacetamide (table 24) but this is reduced considerably to under 1 ppm upon introduction of electronegative substituents and is as little as 3.0 Hz (0.12 ppm) for the difluoro (CHF_2 -) analogue (figure 20). It is noteworthy that this is the smallest difference observed and that for trifluoro (CF_3 -) is approximately twice this value, (5.1 Hz, 0.20 ppm). It would appear that introduction of these highly electronegative substituents considerably reduces the difference between the environments of the two N-methyl carbons.

This very small difference in chemical shift is surprising because it is not observed in proton spectra of the dimethyl amides under the same conditions. Table 25 lists the chemical shifts and differences recorded at various temperatures in CFCl_3 : these data indicated the conditions for observation of the ^{13}C spectra under 'frozen-rotation'. It is seen from this table that the smallest difference is shown by the two N-methyl groups of $\text{CH}_2\text{F.CO.NMe}_2$ with a separation of 9.6 Hz, and that for the difluoro derivative is comparable with that of the 2-fluoropropionamide. These observations contrast with the ^{13}C data and suggest that the two nuclear species (^1H and ^{13}C) are responding to the acetyl substituents differently.

Table 25. ^1H NMR data for $\text{C}_{\text{XYZ}}\cdot\text{CO}\cdot\text{NMe}_2$ in CFCl_3 .

C_{XYZ}	temp set $^{\circ}\text{C}$	Hz	NMe_2		$^5\text{J}_{\text{F}\cdot\text{NMe}}$ (Hz)	
			Low field	High field	LF	HF
CH_2F	0	9.6	2.996	2.890	2.0	1.0
	-20	8.5	2.973	2.888	1.8	1.2
MeCHF	-10	17.5	3.079	2.904	2.4	1.6
	-30	17.5	3.082	2.907	2.4	1.6
CHClF	0	20.0	3.149	2.949	2.0	0.95
	-20	19.9	3.154	2.955	2.0	0.95
	-30	19.5	3.155	2.961	1.9	0.90
CHF_2	0	17.8	3.116	2.938	1.6	1.1
	-20	18.1	3.120	2.939	1.6	1.1
	-40	18.15	3.122	2.940	1.65	1.15
CFCl_2	-20	19.65	3.285	3.062	2.0	0.8
	-40	20.2	3.245	3.044	1.9	0.7
	-50	20.3	3.248	3.045	1.95	0.8
CF_2Cl	-20	15.8	3.175	3.017	1.65	0.7
	-40	15.9	3.181	3.022	1.6	0.7
	-50	16.0	3.186	3.026	1.65	0.7
CF_3	0	11.5	3.116	3.002	1.5	0.7
	-20	11.6	3.122	3.006	1.5	0.8
	-40	11.6	3.128	3.012	1.5	0.8
CH_3^*						

* Data supplied by S.J.Roberts.

3.3 Experimental.

All the ^{13}C spectra were recorded on a Varian XL100-12 WG at 25.16 MHz in the Fourier Transform mode using the Varian 620L computer with 16K of 16 bit storage. Complete proton heteronuclear decoupling was achieved with the Gyrocode decoupler unit using an irradiating frequency centred 4 ppm downfield from the ^1H resonance of TMS and modulated with a noise bandwidth of 1000 Hz at 4w transmitted power. Fluorine decoupling (where required) was achieved by use of the same unit so adjusted to generate the required frequency in the 94 MHz region with a noise bandwidth of 500-1000Hz to ensure complete decoupling. Spin coupled spectra were obtained by use of the gated-decoupling technique. Ambient pulse temperature was 25°C and temperatures other than this were controlled to $\pm 2^\circ\text{C}$ of the indicated value by the standard variable temperature unit.

Samples were examined as solutions as described above, in 10 mm o.d. tubes spun at 20 rps with an internal, concentrically mounted, 5 mm tube containing D_2O or CD_3OD as necessary for locking if CDCl_3 was not used as solvent. The ^{13}C observation frequency of TMS was always determined under conditions similar to those used for recording the samples. Typical parameters used for data acquisition would be:-

Spectral width	4000 Hz
Acquisition time	1 sec.
Pulse width	15 - 20 μsec (tip angle 30 - 40°)
Pulse delay	0
No. transients	3K - 30K dependent on solution conc.
Sensitivity enhancement (Time constant)	0.8 sec.

Conditions were always so adjusted for recording small coupling constants to obtain the maximum possible rate of digitization in the transformed spectrum.

3.4 References.

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Chapter FourExperimental

4.0 Introduction.

All chemicals and solvents were of C.P.R. quality and used as received unless required pure or anhydrous, for which purposes standard procedures were employed. Ether and dichloromethane extracts were dried with MgSO_4 and all distillations were conducted under a pure dry H_2 atmosphere.

Materials used for fluorination reactions were rendered anhydrous as follows:- KF by heating the solid in the reaction vessel to 200° at 1mm pressure for 72 hours, the substrate by dessication under vacuum over P_2O_5 and digol by storage over freshly heated anhydrous CaSO_4 for 72 hours followed by vacuum distillation; a middle fraction was used for reaction solvent.

Infra-red spectra were obtained on nujol mulls (solids) or liquid films between NaCl plates in a Perkin Elmer 257 spectrometer, and Ultra Violet spectra on solutions in A.R. ethanol with a Unicam SP800 spectrometer. Microanalyses were performed by the Imperial College Microanalytical Service.

The α fluoroacetamides were synthesised by ammonolysis of the corresponding methyl or ethyl ester; these were either obtained commercially or prepared according to the procedures described in section 4.1.

4.1 α -Fluoroacetic ester syntheses.

Ethyl monofluoroacetate (38)

Chloroacetic acid was converted to the ethyl ester by acid catalysed treatment according to the method of Vogel¹ in 69% yield. The anhydrous chloro-ester (300g, 2.46m) was fluorinated using potassium fluoride anhyd. (200g, 2.90m) in molten acetamide (100g) according to the procedure described by Bergmann. Redistillation in a heated Hepna41 column yielded the pure fluoroacetate (147g, 61%) bp $120-121^\circ/756$ mm, $n_D^{15.5}$ 1.3800

(lit.³ 1.3767), $\nu_{\max}$ 1755, 1730, 1300, 1225, 1090 cm^{-1}

Ethyl difluoroacetate.

This was prepared from the acid by the method of Gilman and Jones, and the crude product used directly for preparation of amides.

Ethyl trifluoroacetate (54).

This was prepared similarly to the difluoroacetate; distillation of the crude product afforded the pure ester in 55% yield, bp 60-61°/758, n_D^{20} 1.3075.

Ethyl 2-chloro-2,2-difluoroacetate (196).

Chlorodifluoroacetic acid (10.0 g, 0.0766m) was converted to the ester following the procedure of Gilman and Jones⁴ for ethyl trifluoroacetate. The anhydrous ether extract was distilled at atmospheric pressure to yield the ester 9.05 g, 74%, bp 75°/760 mm, n_D^{25} 1.3551, $\nu_{\max}$ 1795, 1785, 1775, 1220, 1180-1120, 1020, 980, 840, 740 cm^{-1} .

Methyl 2-chloro-2-fluoroacetate (235).

2-Chloro-1,2,2-trifluoroethyl methyl ether (ex Fluorochem) was hydrolysed to the corresponding methyl ester by ice-cold, concd. H_2SO_4 according to the procedure described by England for the ethyl analogue.

Thus the ether (10.0g, 0.0673m) afforded the ester (4.9g, 65%) bp 115-6°/756mm, $\nu_{\max}$ 1775, 1220, 1100, 1015, 820 cm^{-1} , n_D^{25} 1.3903.

2-bromo-1,2,2-trifluoroethyl ethyl ether (237).

The α,α -difluoroether was obtained in 84% yield by base catalysed addition of ethanol to bromotrifluoro-ethylene, according to the procedure

described by England⁶ for the chloro analogue. Thus (110g, 0.6175m) gas yielded (107.3g, 0.516m) ether, bp $92^{\circ}/760\text{mm}$, ν_{max} 1380, 1360, 1310, 1280, 1220, 1150, 1090, 1060, 900, 830, 760, 740 cm^{-1} .

$\text{C}_4\text{H}_6\text{BrF}_3$ requires C 23.21%, H 2.92%, Br 38.61%, F 27.53%
 found C 23.46% H 2.96% Br 38.99% F 27.04%

ethyl 2-bromo-2-fluoroacetate (238).

The above prepared ~~α~~ difluoroether was hydrolysed to the ester according to the procedure employed for the chloro analogue above. Thus the ether (15.58g, 0.0749m) was treated with ice-cold conc. H_2SO_4 over 6 hours, to yield the ester, (9.66g, 0.0522m) 70%, bp $73-5^{\circ}/44-45\text{ mm}$, ν_{max} 1680-1660, 1300, 1255, 1185, 1100, 1025 cm^{-1} .

N-benzyl 2-bromo-propionamide (167)

Propionic acid (100g, 1.35m) was converted to the acyl chloride by treatment with thionyl chloride (167g, 1.423m) at reflux in benzene for 2½ hrs. The product was α -brominated by treatment with purified bromine (234g, 75ml, 1.46m) with red P as catalyst, according to the procedure described by Vogel¹ for acetyl chloride. The solution was fractionally distilled to yield 220g of liquid with bp $130-150^{\circ}/1\text{ atm}$, which corresponds to a mixture of α -Br acyl chloride and bromide (bp 133° and 152° respectively). The mixed acyl halides were converted to the N-benzamide according to the method of Bischoff.⁷ Anhydrous benzylamine (200g, 1.869m) was added to a stirred solution of the acyl halide (220g) in benzene (1l) over 30' at $5-10^{\circ}$. After a further period of stirring 10min, the crude product was poured into water, (400ml) to remove benzylamine hydrochloride. The organic layer was washed and dried. The crude product was recrystallized from MeOH:benzene (1:5) to yield the N-benzamide 174.1g, 0.719m, 53% based on acid, mp $87-88.5^{\circ}$ (lit⁸ 85°) ν_{max} 3250, 1660, 1570, 1470, 770, 720 cm^{-1} .

N-benzyl-2-fluoropropionamide (168).

The reaction details are modelled on those given by Bergman⁹ for N-phenyl 2 fluoro-2 phenyl acetamide.

Anhydrous N-benzyl 2-bromopropionamide (48.43g, 0.200m) was added to a stirred solution of anhydrous KF (34.9g, 0.6m) in digol (160ml, bp 100°/mm) at 120°. After 25 min, precipitation of KBr commenced, and reaction stirred further 3 hrs at 125°. Cooled to ambient, poured into water (200ml) and extracted with CHCl₃ (1 x 300 ml) and CH₂Cl₂ (2 x 150ml), washed and dried. Evaporation gave an orange oil 45.2g, which partially solidified to an orange yellow sticky semi-solid, and was shown to consist of 1 major and 3 minor components. The material was chromatographed over alumina (350g, Grade III) with 25% CH₂Cl₂: Pet Ether (40 - 60) as eluent to yield a pale yellow solid, recrystallized from Et₂O:Pet ether (40-60) (1:1) to yield white leaflets, mp 43-4° (22.3g, 85.5%) $\nu_{\max}$ 3300, 1650, 1550, 1470, 1110, 1020, 760, 720 cm.⁻¹ C₁₀H₁₂FO requires:- C 66.27% H 6.67% N 7.73% F 10.48; found C 66.37% H 6.87% N 7.68% F 10.23%.

N-ethyl 2-fluoropropionate (212).

N-benzyl 2-fluoropropionamide (5.0g, 0.0275m) was refluxed at 110° in 20% ethanolic sulphuric acid (c H₂SO₄, 8.1 g, 0.0825m, 4.4ml, in ethanol 22ml) for 20 hrs, when tlc (SiO₂, CHCl₃) indicated the reaction to be essentially complete. The cooled solution was poured into brine (75ml) and extracted with ether (1 x 100, 2 x 50 ml). The dried (NaHCO₃) solution was used for preparation of amides.

N-benzyl 2-bromo-2-phenylacetamide (155).

Phenylacetic acid (100g, 0.753m) was converted to the bromo-phenacyl chloride according to the procedure described by Vogel¹ for acetic acid to yield pure product (150g, 0.6425m, 85.3% bp 127°/15mm). The acyl chloride (79g, 0.337m) was treated with benzylamine as described above to yield the desired benzamide, which was recrystallized from ethanol: i propanol (1:1) with 10% H₂O, 79.6g, 0.2617m, 77.6%, mp 116°, $\nu_{\max}$

3300, 1655, 1550, 1500, 1240, 1170, 1070, 1030, 750, 700, 625 cm^{-1}
 λ_{max} 233nm ($\epsilon = 6480$, $\log \epsilon = 3.812$).

N-Benzyl 2-fluoro-2-phenylacetamide (161).

All reagents were rendered anhydrous according to the methods described in the introduction. The α bromobenzamide (30.4g, 0.1m) was stirred into KF (18g, 0.3m) and digol (80ml) at 120° . Within 2 min a precipitate of KBr was observed, and the reactions was allowed to continue for 3 hrs at $120-125^\circ$. The mixture was cooled, poured into water (400ml). The crude product obtained after chloroform and dichloromethane extraction was recrystallized from ethanol:isopropanol (1:1) with addition of 10% H_2O and the crystals washed with ice cold solvent to yield product 12g. The mother liquors were evaporated and the residue chromatographed over alumina with 50% CH_2Cl_2 : Pet ether (40-60) as eluent yielded a further 3.2g product. Total yield 15.2g, 62.3%. mp $98-99^\circ$. ν_{max} 3350, 1675, 1560, 1460, 1050, 760, 730, 700 cm^{-1} . λ_{max} 214nm ($\epsilon = 10825$, $\log \epsilon = 4.034$)
 $\text{C}_{15}\text{H}_{14}\text{FNO}$ requires: C 74.05% H 5.80% N 5.75% F 7.8%
 found C 73.58% H 6.13% N 5.45% F 7.5%

Methyl 2-fluorophenyl acetate (190)

N-benzyl-2-fluorophenylacetamide (9.5g, 0.039m) was refluxed in 20% methanolic sulphuric acid (acid, 11.5g, in MeOH, 50 ml) for 30 hrs, at which time the reaction was judged complete by tlc. The cooled mixture was poured into brine (200ml) and extracted with ether (1 x 100, 2 x 50ml), dried (NaHCO_3) and residual oil after solvent evaporation was distilled to yield the ester, bp $77^\circ/1.75\text{mm}$, 4.05g, 61.5%. ν_{max} 1760, 1285, 1225, 1195, 1060, 740, 705 cm^{-1} . Structure was confirmed by ^1H NMR and mass spectrometry.

4.2 Synthesis of α fluoroacetamides.

All the amides were prepared from the corresponding esters by treatment with ammonia or a solution of the appropriate amine. The procedures will be described in detail for one amide of each type in the relevant sections below.

4.2.1. Primary amides.

Fluoroacetamide (45)

A solution of ethyl fluoroacetate (5.3g, 0.05ml) in ether (15ml) was cooled in ice and treated with concd. aq. ammonia (2ml) for 1 hr. Removal of solvent yielded a pasty mass which was dried azeotropically with ethanol and benzene. The anhydrous mass was recrystallized from AR methanol to yield plates 2.83g, 75%, mp 105° (lit¹⁰ 108°) $\nu_{\max}$ 3400, 3200, 1665, 1630, 1125, 1050 cm.⁻¹

2-fluoropropionamide (213)

A solution of the ethyl ester in methanol was treated with ammonia gas at ice temperature. The crude product was recrystallized from CHCl₃:benzene 1:4 to afford fine needles, 0.640g, (25% based on N-benzamide) mp 71-72°, $\nu_{\max}$ 3400, 3200, 1660, 1120, 1100, 1040, 910 cm.⁻¹
 C_3H_6FNO requires C 39.55% H 6.64% N 15.38% F 20.85%
 found C 39.08% H 6.44% N 14.60% F 21.21%

2-fluorophenylacetamide (164)

The crude product obtained from the methyl ester (0.35g, 2.08mM) was recrystallized twice from CH₂Cl₂:MeOH to yield fine needles (150 mg, 0.972 mM, 47%) mp 131-132.5°, $\nu_{\max}$ 3450, 3250, 1685, 1470, 1050, 1035, 760, 710 cm.⁻¹ $\lambda_{\max}$ 215 nm (log ϵ = 3.333)
 C_8H_8FNO requires C 62.77% H 5.26% N 9.15% F 12.41%
 found C 62.75% H 5.47% N 8.93% F 12.83%

2 bromo-2-fluoroacetamide (238a)

The ethyl ester 2.0g (0.0128M) in ice cold methanol (15ml) was treated with a satd. solution of NH₃ in methanol (5 ml). After 10 min, the indicated reaction was complete and the solvents were evaporated. The crude produce was recrystallized from EtO₂:Pet ether (40-60) ca 2:1 to give colourless needles, 1.3g, 83%, mp 40.5° (lit. mp 44°) $\nu_{\max}$ 3400, 3200, 1690, 1630, 1100, 1065, 770 cm.⁻¹

2-chloro-2-fluoroacetamide (210)

Methyl chlorofluoroacetate (2.0g, 0.0158M) was treated with NH_3 -methanol as described for the bromo analogue. The crude product was obtained as a colourless oil, which was distilled to yield the pure amide, bp $65^\circ/1.2\text{mm}$, 1.27g, 65% which substantially solidified on standing to a colourless solid mp $30.5\text{--}31.5^\circ\text{C}$ (lit.¹² bp $72^\circ/1\text{mm}$) ν_{max} 3350, 3200, 1710, 1620, 1070, 920, 830 cm^{-1}

Difluoroacetamide (55)

The crude product obtained from methyl difluoroacetate was recrystallized from ether:pet. ether (1:1) to yield the pure amide (0.158g, 51%) mp $47.5\text{--}49^\circ$ (lit.¹³ mp 51°) ν_{max} 3400, 3200, 1675, 1620, 1120, 1070, 880 cm^{-1}

2,2-dichloro-2-fluoroacetamide (222)

The crude product obtained from the ester (1.5 g, 0.0085 m, ex Fluorochem) was recrystallized from chloroform into prisms, 0.99g, 79%, mp $123\text{--}125^\circ$ lit.¹⁴ 126.5° ν_{max} 3350, 3200, 1700, 1630, 1125, 1095, 980, 880, 630 cm^{-1}

2-chloro-2,2-difluoroacetamide (196)

The impure amide was recrystallized from CCl_4 : cyclohexane 5:1 to yield fine colourless needles, 60% mp $80\text{--}81^\circ$ (lit.¹⁵ mp 78.5°) ν_{max} 3380, 3200, 1710, 1150, 980 cm^{-1}

Trifluoroacetamide (54)

The crude amide was recrystallized from ether:pet. ether (40-60) 1:4 to yield the pure product as long colourless needles, 67% mp $70\text{--}71^\circ$, lit.¹⁶ mp 75° ν_{max} 3250, 3175, 1690, 1635, 1195, 1150, 1130 cm^{-1}

4.2.2. N-Methyl amides.

N-Methyl fluoroacetamide (50)

Ethyl fluoroacetate (2.5g, 0.025m) was treated with a satd. aqueous solution of methylamine (10ml) for 48 hrs. The colourless solution was evaporated to dryness azeotropically and recrystallized from methanol-ether to yield colourless needles 0.72g, 61%, or from CHCl_3 :pet. ether 1:1. mp $59-61^\circ$ (lit.¹⁷ 64° ex CHCl_3).

N-methyl 2-fluoro-propionamide (243)

The ethyl ester (1.0g, 0.0083m) in ether (5ml) was cooled to ice temperature and treated with ethanolic methylamine (ca. 33% 1.5 ml) and stored at 0° for 24 hrs. The oil obtained upon evaporation of solvent was fractionally distilled to afford pure N-methyl amide, 0.65g, bp $90^\circ/43\text{mm}$, 74%. ν_{max} 3300, 1670, 1555, 1420, 1160, 1130, 1095, 1015 cm^{-1}

$\text{C}_4\text{H}_8\text{FNO}$ requires C 45.70% H 7.66% F 18.07%
found C 45.53% H 7.78% F 17.88%

All the remaining N-methyl amides were prepared according to this method.

N-methyl 2-fluorophenylacetamide (247)

The crude product obtained upon solvent evaporation was a light yellow oil, which solidified upon *maturation* with pet. ether. This was recrystallized from benzene: pet ether (40-60), 2:1, to afford needles, 79%, mp $63-4^\circ$, ν_{max} 3300, 1660, 1555, 1210, 1160, 1020, 800, 770, 720 cm^{-1}

$\text{C}_9\text{H}_{10}\text{FNO}$ requires C 64.65% H 6.02% N 8.38% F 11.36%
found C 65.00% H 6.01% N 8.15% F 10.84%

N-methyl 2-bromo-2-fluoroacetamide (238a)

The crude product obtained from the ethyl ester (2.0g, 0.0108m) as a viscous oil was fractionally distilled to yield the pure amide, 1.65g,

68%, bp 85°/3mm. $\nu_{\max}$ 3300, 1680, 1555, 1090, 1065, 1035, 800, 610 cm^{-1}
 $\text{C}_3\text{H}_5\text{BrFNO}$ requires C 21.19% H 2.96% N 8.24% Br 47.01% F 11.17%
 found C 21.39% H 3.40% N 7.95% Br 46.70% F 11.05%

N-methyl 2-chloro-2-fluoroacetamide (235a)

The methyl ester (2.5g, 0.0197m) was treated in the standard manner to yield the crude N-methyl amide as a viscous liquid, which could be induced to solidify with liquid N_2 but remained a liquid at lab. temp. Fractional distillation yielded the pure product, 1.49g, 61%, bp 112-113/21mm, which solidified on standing to a colourless mass, mp ca. 23-25° (warm water bath). $\nu_{\max}$ 3350, 3140, 1720, 1700, 1685, 1570, 1560, 1420, 1110, 1070, 1030, 825 cm^{-1}
 $\text{C}_3\text{H}_5\text{ClFNO}$ requires C 28.70% H 4.01% Cl 28.24 F 15.13%
 found C 28.98% H 4.14% Cl 28.16% F 15.14%

N-methyl difluoroacetamide (234)

The impure amide was recrystallized from Et_2O :pet ether (40-60) to yield plates 40%, mp 32-3° $\nu_{\max}$ 3350, 3150, 1730-1550, 1180-1060 cm^{-1}
 $\text{C}_3\text{H}_5\text{F}_2\text{NO}$ requires C 33.03% H 4.62% N 12.84% F 34.83%
 found C 33.39% H 4.88% N 12.85% F 34.78%

N-methyl 2,2-dichloro-2-fluoroacetamide (234)

The impure amide was obtained as a yellow viscous oil, which was induced to crystallize (exothermically) by cooling with liquid N_2 for 10-15 sec. Recrystallization from Et_2O :pet ether (40-60) yielded the pure N-methyl amide as rhombic prisms, 0.925g, 80%, mp 44.5-45°. $\nu_{\max}$ 3350, 1700, 1560, 1100, 1060, 930, 880, 780 cm^{-1}

$\text{C}_3\text{H}_4\text{Cl}_2\text{FNO}$ requires C 22.52% H 2.51% N 8.75% Cl 44.32% F 11.87%
 found C 22.69% H 2.71% N 9.02% Cl 41.91% F 11.18%

The structure was proved by mass spectrometry.

N-methyl 2-chloro-2,2-difluoroacetamide (236b)

The residual viscous oil from solvent evaporation of the reaction mixture was distilled to yield the desired compound, 90% bp $112^{\circ}/61$ mm
 n_D^{25} 1.3998 $\nu_{\max}$ 3350, 3100, 1735, 1715, 1565, 1420, 1135, 1040, 980, 820 cm^{-1}

$\text{C}_3\text{H}_4\text{ClF}_2\text{NO}$ requires C 25.10% H 2.80% Cl 24.70% F 26.47%
 found C 26.70% H 3.28% Cl 24.31% F 26.98%

The structure was confirmed by mass spectrometry.

N-methyl trifluoroacetamide (238)

The amide was recrystallized from Et O to yield pure product 49%
 mp $47-8^{\circ}$ $\nu_{\max}$ 3330, 1700, 1575, 1230, 1160, 1120 cm^{-1}

4.2.3. N,N-dimethylamides.N,N-dimethyl 2-fluoroacetamide (51)

Ethyl fluoroacetate (5.3g, 0.05m) was treated with a satd. solution (aqueous) of dimethylamine (40%, 10ml) at 0° . After 2 days water was removed azeotropically (ethanol, benzene) to leave a colourless oil which was fractionally distilled at reduced pressure to yield the pure amide bp $39-41^{\circ}/1.4-1.6$ mm, 2.35g, 47%, n_D^{24} 1.4339, $\nu_{\max}$ 1670, 1070 cm^{-1}
 $\text{C}_4\text{H}_9\text{FNO}$ requires C 45.71% H 7.62% N 13.33% F 18.10%
 found C 45.21% H 7.62% N 13.21% F 16.11%

N,N dimethyl 2-fluoropropionamide (243)

This procedure was used as standard for the other amides. The ethyl ester (1.0g, 0.0083m) in ether was treated with dimethylamine in ether (ca 30%, 2ml). After 18 hrs. the solvent was removed and the residual oil distilled to yield the product, 0.483g, 48% bp $95-6^{\circ}/44$ mm
 $\nu_{\max}$ 1660, 1120, 1100, 1050 cm^{-1}
 $\text{C}_5\text{H}_{10}\text{FNO}$ requires C 50.40% H 8.46% N 11.75% F 15.94%
 found C 50.12% H 8.34% N 11.51% F 16.20%

NN-dimethyl 2-fluorophenylacetamide (191)

Crude fluoro ester (ex hydrolysis of benzamide) 2.0g, was treated in the standard manner with dimethylamine. Tlc indicated 4 products on evaporation of solvent, and the material was purified by column chromatography over SiO_2 with CHCl_3 as eluent. This yielded a mixture of product and unhydrolysed benzamide, which were separated by further chromatography over alumina(100g, Grade III) with CH_2Cl_2 :P.E. (1:1) as eluent. The desired NN dimethylamide eluted as the second compound as a light yellow oil and was recrystallized from Et_2O :pet ether (40-60) (1:1), 630mg, mp $58-9^\circ$ ν_{max} 1650, 1450, 1040, 760, 720, 700 cm^{-1}
 $\text{C}_{10}\text{H}_{12}\text{FNO}$ requires C 66.27% H 6.67% N 7.73% F 10.48%
 found C 66.59% H 6.74% N 7.80% F 10.51%

NN dimethyl 2-chloro-2-fluoroacetamide (211)

This was obtained as a colourless oil, bp $70^\circ/16\text{mm}$, 48% yield, n_D^{18} 1.4575, ν_{max} 1680, 1090, 840, 810, 670 cm^{-1}
 $\text{C}_4\text{H}_7\text{ClFNO}$ requires C 34.42% H 5.05% N 10.03% Cl 25.40% F 13.61%
 found C 34.59% H 5.09% N 10.40% Cl 25.14% F 13.87%

NN-dimethyl difluoroacetamide (233)

Distillation of the crude product yielded a colourless oil bp $61^\circ/29\text{ mm}$, 52%, n_D^{22} 1.4030. ν_{max} 1680 1100 cm^{-1} No satisfactory micro-analysis could be obtained and the structure was confirmed by mass-spectrometry.

NN-dimethyl 2,2-dichloro-2-fluoroacetamide (234a)

The crude product was isolated as a light yellow oil which was fractionally distilled at reduced pressure to yield the pure amide as a colourless liquid, bp $107-8^\circ/19\text{mm}$, 83%, n_D^{25} 1.4558, ν_{max} 1690, 1400, 1255, 1100, 1080, 990, 880, 840, 720, 690, 660 cm^{-1} Arising from the hygroscopic nature of this compound, the molecular formula was confirmed by mass spectrometry and not micro-analysis.

NN dimethyl-2-chloro-2,2-difluoroacetamide (236)

Fractional distillation yielded the tertiary amide as a colourless liquid, bp $83-5^{\circ}/35\text{mm}$, 96% n_D^{25} 1.4098, ν_{max} 1690, 1150, 1110, 985, 905 cm^{-1}

$\text{C}_4\text{H}_6\text{ClF}_2\text{NO}$ requires C 30.49% H 3.84% N 8.89% Cl 22.50% F 24.11%
found C 30.68% H 4.02% N 9.38% Cl 21.90% F -

NN dimethyltrifluoroacetamide (235a)

The amide was obtained as a colourless liquid bp $62-3^{\circ}/50\text{ mm}$, 45% ν_{max} 1700, 1150, 1100 cm^{-1}

$\text{C}_4\text{H}_6\text{F}_3\text{NO}$ requires C 34.03% H 4.25% N 9.93% F 11.34%
C 34.21% H 4.16% N 9.81% F 11.56%

4.2.4. Mass Spectrometry of Amides.

Mass spectra of some of the amides were obtained in instances where accurate micro-analyses could not be obtained due to their hydroscopic nature. These were recorded using either the AFI MS902 or Perkin-Elmer spectrometers.

Compound	m/e	Intensity (% base peak)	Interpretation
$\text{CH}_3\cdot\text{CHF}\cdot\text{CONH}_2$	44	100	$-\text{CONH}_2$
	45	6	CONH_3^+
	47	6	$\text{CH}_3\cdot\text{CHF} = \text{N}-\text{CONH}_2$
	55	14	$\text{CH}_2=\text{C}=\text{O} \text{ M}-\text{HC}-\text{NH}_2$
	71	3	$\text{M}-\text{HF}$
	91	27	M^+
$\text{CH}_3\cdot\text{CHF}\cdot\text{CO}\cdot\text{NHCH}_3$	47	37	$\text{M}-\text{CONHCH}_3$
	58	100	CONHCH_3
	105	45	M^+
$\text{CH}_3\cdot\text{CHF}\cdot\text{CO}\cdot\text{N}(\text{CH}_3)_2$	72	100	$\text{CO}\cdot\text{NMe}_2$
	119	17	M^+

$\text{CHBrF} \cdot \text{CF}_2 \cdot \text{OC}_2\text{H}_5$	95	100	$\text{CF}_2 \cdot \text{O} \cdot \text{C}_2\text{H}_5$
	105	22	
	111	25	CHBrF
	113	23	
	161	44	$\text{M} \cdot \text{OC}_2\text{H}_5$
	163	41	
	206		M^+
	208		
$\text{CHBrF} \cdot \text{CO} \cdot \text{NHCH}_3$	58	100	$\text{O}=\text{C}=\text{NHCH}_3^+$
	90	2	$\text{M}-\text{Br}$
	111	2	CHBrF
	113	2	
	169	8	M^+
	171	8	
$\text{CHClF} \cdot \text{CO} \cdot \text{NHCH}_3$	44	19	$\text{O}=\text{C}=\text{NH}$
	58	100	$\text{O}=\text{C}=\text{NHCH}_3^+$
	67	11	CHClF
	69	4	
	90	6	$\text{CHF} \cdot \text{CO} \cdot \text{NHCH}_3$
	125	13	M^+
	127	8	
$\text{CHF}_2 \cdot \text{CO} \cdot \text{NHCH}_3$	51	16	$\text{M}-\text{CONHCH}_3$
	58	100	$\text{CO} \cdot \text{NHCH}_3$
	109	35	M^+
$\text{CHF}_2 \cdot \text{CO} \cdot \text{N}(\text{CH}_3)_2$	51	29	CHF_2
	72	100	CONMe_2
	123	71	M^+

4.3 Synthesis of haloacetates.

The methyl and ethyl esters of non-fluorine containing acids were obtained directly from the acid, either via the acyl halide, or conversion to the sodium salt followed by treatment with alcohol/ CH_2SO_4 according to the method of Gilman and Jones.⁴ Excess alcohol and acid was removed by addition of CaCl_2 and NaHCO_3 to the crude product, which was purified by distillation. All the compounds are well known in the literature and hence details of physical constants are not presented.

4.4. References

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CHAPTER FIVE

CARBON-13 N.M.R. SPECTRA OF SOME

PHOTOLYSIS PRODUCTS OF VITAMIN D₂.

5.0 Introduction.

In the course of other work in this department, it became desirable to study the carbon-13 spectra of photolysis products of ergosterol and ergocalciferol (vitamin D₂) with a view to identifying compounds with unknown structures.

Initial studies were centred on the two starting materials ergosterol (1) and ergocalciferol (2), together with its 3,5, dinitrobenzoate ester (35DNBz)(2a)

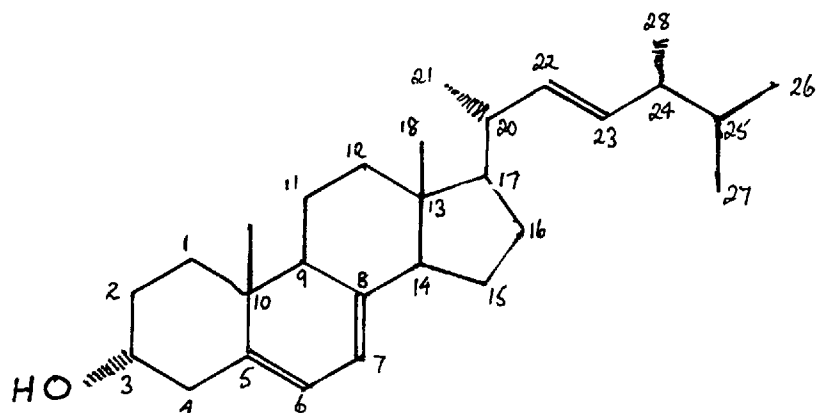
Homogeneous hydrogenation of (2) using Wilkinson's catalyst gave two products, dihydrovitamin D₂ IV (3, with its 3,5-DNBz, 3a) and the isomeric dihydrovitamin D₂ II, which was isolated as the 35DNBz (4).

Stigmasterol (5) was utilised as a further model to assist in the unambiguous assignment of the ergosterol chain resonances. This is very important since photolytic reactions centred on the butadiene/hexatriene system in 1 and 2 are usually held to leave the side chain unaffected, and it is very desirable to check this assumption.

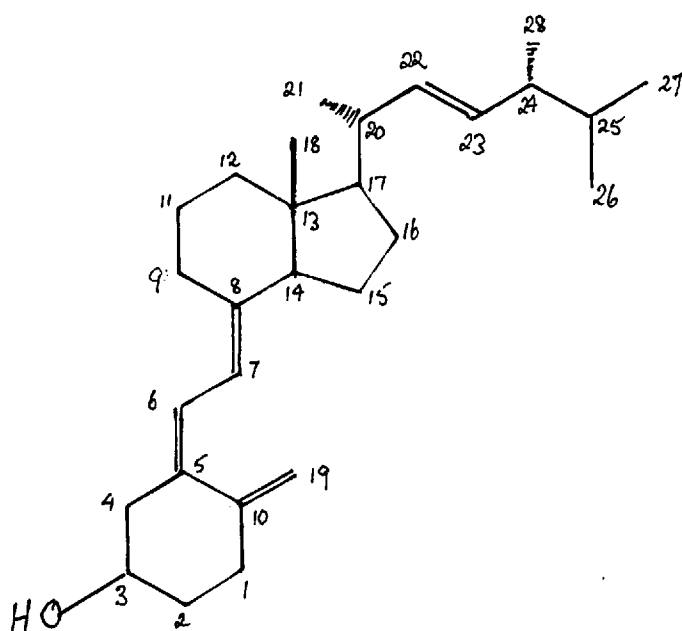
Suprasterol II has been identified as a photolysis product of ergocalciferol, and its structure has been determined both chemically^{1a} and by X-ray^{1b} techniques: this was examined as both the free alcohol (6) and its 35DNBz ester (6a). Catalytic hydrogenation of 6 removed the cyclopropane ring, by cleaving the C₆-C₇ bond, and saturated the side chain at C₂₂-C₂₃ to yield tetrahydrosuprasterol II, which was again studied as the free alcohol (7) and 35DNBz ester (7a).

It has been possible to make unambiguous assignments for all the resonances in the above compounds, and the results are presented in table 1. In order to facilitate this, lanthanide shift data were obtained for some of the free alcohols by addition of Eu(fod)₃ in 0.05-0.10M increments. The approximately linear paramagnetic shifts obtained (up to a maximum sterol:lanthanide ratio of 0.30M) were

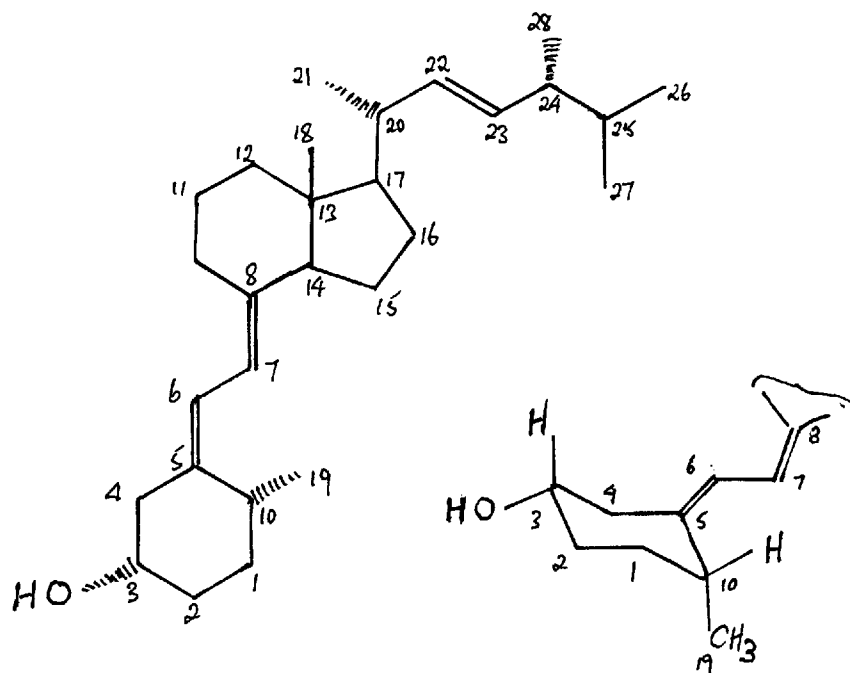
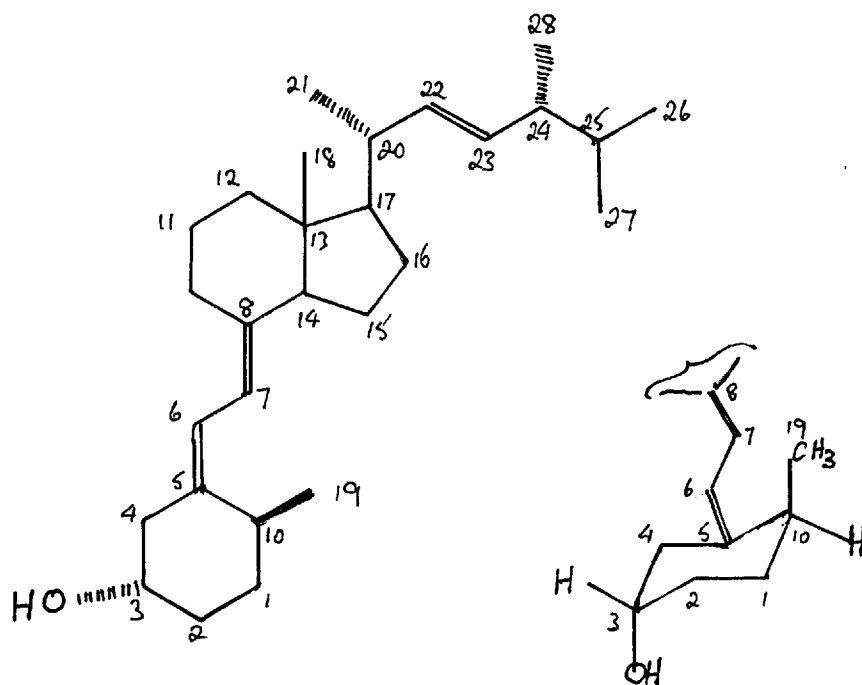
Figure 1. Structures of Model Compounds

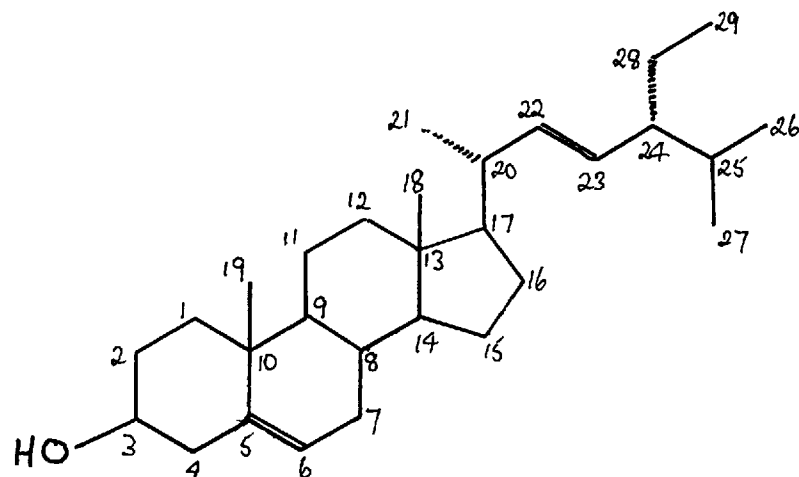


1. Ergosterol

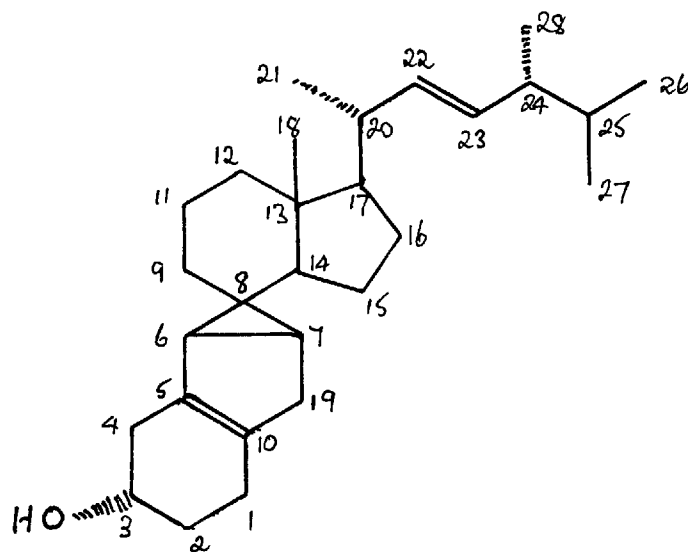


2. Ergocalciferol

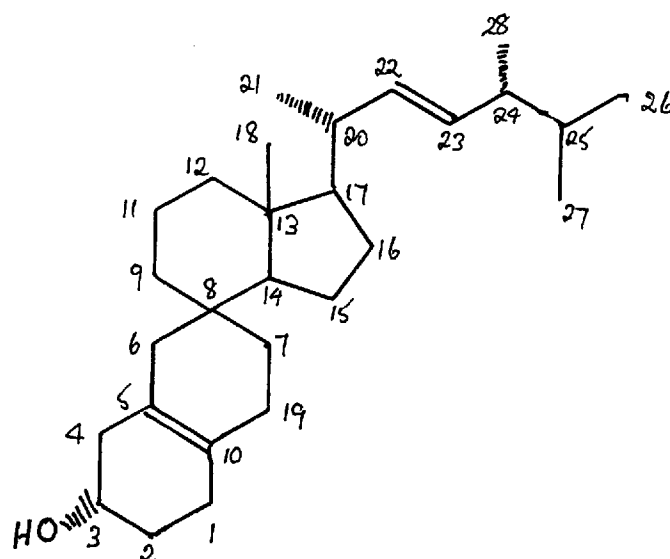
3. Dihydrovitamin D₂ IV4. Dihydrovitamin D₂ II



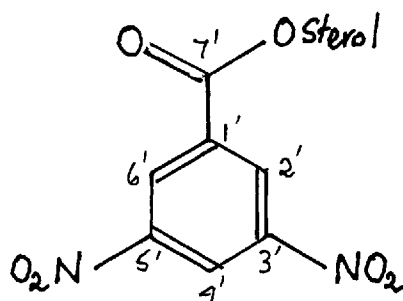
5. Stigmasterol



6. Suprasterol II



7. Tetrahydrosuprasterol II



3,5 dinitrobenzoate ester function

Table 1. ^{13}C chemical shifts of model compounds.

	1	2	2a	3	3a	4	5
1	31.80	31.93	31.84	30.04	29.81	27.41	37.27
2	38.68	35.20	32.11	30.42	26.55	24.92	31.60
3	70.31	69.20	74.97	69.47	77.04	74.66	71.79
4	39.68	45.94	42.02	42.57	38.32	38.62	42.25
5	141.46	145.11	143.92	140.14	137.76	136.71	140.77
6	119.76	122.49	123.18	119.59	121.16	121.11	121.72
7	116.59	117.54	117.31	115.45	115.15	114.94	31.91
8	140.27	142.22	143.13	141.65	142.89	142.42	31.91
9	46.56	29.05	29.05	28.77	28.89	28.76	50.18
10	37.29	135.12	133.27	29.05	29.02	29.82	36.54
11	21.33	22.25	22.22	22.31	22.30	22.24	21.11
12	40.66	40.41	40.48	40.38	40.39	40.38	39.71
13	43.12	45.79	45.87	45.62	45.76	45.69	42.25
14	54.80	56.49	56.47	56.39	56.44	56.37	56.89
15	23.23	23.59	23.59	23.44	23.49	23.46	24.39
16	28.13	27.81	27.79	27.77	27.78	27.80	28.95
17	56.04	56.49	56.47	56.47	56.52	56.46	55.98
18	12.20	12.30	12.28	12.40	12.39	12.26	12.07
19	16.67	112.42	113.34	18.07	17.92	17.62	19.43
20	40.57	40.41	40.36	40.38	40.39	40.38	40.54
21	21.27	21.14	21.14	21.14	21.15	21.14	21.24
22	135.76	135.65	135.62	135.65	135.63	135.67	138.36
23	132.24	131.99	132.00	131.97	132.04	131.99	129.31
24	43.12	42.86	42.85	42.85	42.89	42.86	52.26
25	33.35	33.12	33.11	33.13	33.14	33.12	31.91
26	19.96	19.66	19.67	19.67	19.67	19.66	21.11
27	20.07	19.96	19.96	19.97	19.99	19.96	19.02
28	17.77	17.61	17.61	17.63	17.65	17.62	25.44
29							12.29
1'			134.42		134.55	134.73	
2'			129.43		129.45	129.45	
3'			148.69		148.69	148.64	
4'			122.26		122.26	122.16	
5'			148.69		148.69	148.64	
6'			129.43		129.45	129.45	
7'			161.89		161.85	162.00	

Table 1. (cont.)

	6	6a	7	7a
1	22.80	21.87	29.06	28.22
2	31.60	27.31	31.99	28.65
3	67.98	73.20	68.18	74.41
4	35.77	31.69	40.36	36.33
5	134.57	134.94	124.25	123.69
6	34.26	34.15	33.72	33.67
7	20.99	21.01	34.18	34.17
8	27.18	27.31	34.79	34.82
9	34.31	34.37	36.63	36.52
10	131.99	130.77	126.13	126.52
11	20.84	20.83	19.33	19.32
12	40.92	40.74	40.94	40.93
13	44.43	44.40	42.82	42.85
14	53.13	52.99	59.39	59.33
15	22.33	22.41	26.21	26.19
16	27.66	27.60	27.30	27.31
17	56.64	56.60	57.44	57.47
18	12.57	12.64	13.37	13.36
19	24.62	24.52	26.47	26.48
20	40.09	40.06	35.87	35.90
21	21.09	21.01	18.69	18.69
22	135.86	135.77	30.53	30.57
23	131.78	131.84	33.51	33.52
24	42.84	42.88	39.08	39.11
25	33.12	33.11	31.45	31.48
26	19.67	19.65	17.60	17.63
27	19.98	19.97	20.47	20.54
28	17.65	17.63	15.44	15.46
29				
1'		134.54		134.63
2'		129.22		129.40
3'		148.65		148.69
4'		122.25		122.19
5'		148.65		148.69
6'		129.22		129.40
7'		162.04		162.09

Table 2. Lanthanide Induced Shifts (extrapolated to equimolar lanthanide:sterol concentration); values in Hz from original line positions. " $\delta_{\text{H}\alpha}$ ".

Carbon No.	Compounds			
	<u>2</u>	<u>5</u>	<u>6</u>	<u>7</u>
1	265	103	188	192
2	376	264	314	348
3	1441	1018	1419	1575
4	258	254	327	387
5	235	69	232	49
6	258	88	113	130
7	90	40	105	73
8	75	32	101	70
9	25	49	99	74
10	215	119	212	43
11	25	38	40	38
12	8	22	44	27
13	22	18	44	25
14	26	26	56	39
15	13	14	85	21
16	16	9	23	20
17	21	12	26	17
18	13	17	39	11
19	139	90	125	103
20	8	8	14	9
21	3	8	8	4
22	6	6	9	8
23	7	6	7	6
24	5	5	8	3
25	0	2	0	4
26	0	0	0	2
27	0	0	0	9
28	0	0	0	3
29		0		

extrapolated to a relative concentration of 1.0M, to obtain δ_{Eu} , the shift that would be induced by a 1M concentration of lanthanide. No corrections were made for contact shifts or lanthanum complexation shifts, since the data as obtained were sufficiently accurate to enable distinction between nuclei close to, or remote from the site of complexation. The final values of the lanthanide induced shifts are given in table 2.

It is to be expected² that the observed paramagnetic shifts will be predominantly pseudocontact in origin and if the lanthanide-substrate complex can be assumed to have axial symmetry, the magnitude of the observed shifts on complexation ($\nu_{Eu} - \nu_0$) will be given by

$$\nu_{Eu} - \nu_0 = \frac{K(3\cos^2\theta - 1)}{r^3}$$

where r is the distance of the perturbed nucleus from the lanthanide and θ the angle this vector subtends to the principal magnetic axis. Recent work³ by Apsimon et al. on ^{13}C spectra of keto- and hydroxy-steroids has shown that $Eu(fod)_3$ induces additional contact shifts at both α and β positions to the site of complexation. Thus data obtained for these carbons will not obey the above relationship, and consequently calculation of their relative shifts is not possible.

Besides the conventional proton noise-decoupled carbon spectra, extensive use was made of coherent (single frequency) off-resonance spectra, with the decoupler power (10-12 watts) centred 1-2 ppm above TMS. The resulting ^{13}C spectrum retains most of the NOE found in noise decoupling, but shows splittings from the large one-bond coupling constants which are used to assign a carbon resonance to a methyl, methylene or quaternary carbon. These splittings, termed reduced coupling constants, are smaller than the actual coupling constants and greatly reduce the problem of overlapping peaks. It has been shown that the reduced coupling constant is given approximately by:

$$J_R = \frac{\Delta\nu}{\gamma_{H_2}} \cdot J_{CH}$$

where $\Delta\nu$ is the decoupler offset from resonance and γ_{H_2} is the intensity of the decoupling field.

Naively, it would generally be assumed that a methylene group would yield a triplet in off-resonance spectra, and a methine a doublet, on a first-order basis. Unfortunately, this is not always the case, and complex band shapes are often observed⁵⁻⁷ in off-resonance spectra, particularly for groups in a vicinal relationship. A good example is provided⁵ by 1,2-dichloroethane (CH_2Cl-CH_2Cl), where the off-resonance spectrum consists of a complex multiplet resembling a triplet, but the maximum intensity of the outer lines is only 20% that of the centre peak.

The physical explanation of this behaviour is identical with that of virtual coupling in proton spectra. The off-resonance decoupling reduces the effective J_{CH} coupling constant to a point where it is comparable with the vicinal $^3J_{HH}$ inter-proton coupling. Hence, although the $^2J_{CCH}$ (4Hz) has been reduced to, say 0.5Hz by the off-resonance decoupling, the carbon nucleus appears to be coupled to the vicinal- CH_2Cl group by virtual coupling via the strongly coupled proton system.

Such second order off-resonance spectra are not confined to vicinal methylene groups, and an even more deceptive example is provided by the trans double bond of fumaric acid, $HO_2C.CH=CH.CO_2H$. Instead of the expected doublet for the olefinic carbons, off-resonance spectra consisted of complex multiplets of 5 to 7 lines, for which the centre line could be the strongest. The band shapes would be readily explained as arising from virtual coupling of the ^{13}C with the geminal proton (on the other sp^2 carbon) via the strong trans $^3J_{HH}$ coupling (16Hz) and reduced $^1J_{CH}$ of 20 to 50 Hz. Analytically, the ^{13}C is the X part of an ABX spin system, where there is strong coupling between AB and AX, but not BX.

The second order nature of methylene and methine groups is usually not so dramatic as the above examples, and is generally confined to various degrees of line broadenings on the basic triplet or doublet structure. In a general study of these phenomena, Grutzner⁷ concluded that second order effects are to be expected in a $A_m B_n X$ spin system ($^{13}C = X$) when J_{AX} and J_{BX} are appreciably different, and typically this will be the case if A and B are on adjacent carbons.

Many of the above 'types' of second-order line shapes have been observed in the course of this work, and have proved very useful in identifying carbon resonances in several situations.

5.1. Model Compounds.

5.1.1. Ergosterol (1) and Stigmasterol (5).

The chemical shift data obtained for the ergosterol nucleus were in substantial agreement with that reported by Roberts,⁹ but with the reversal of his assignments for C_{12} and C_6 , as is now well established.¹⁰ Several differences were noted in the side chain resonances with the reversal of C_{22} and C_{23} (as suggested by Stothers¹⁰), and the reassignment of the side chain methyl groups C_{21} , C_{26} and C_{27} , for which Roberts stated that he was unable to make unambiguous indentifications. These new values, and an overall check on the side chain resonances, including C_{22} and C_{23} , have been made possible by a comparison of predicted line positions with experimental, and by examination of the effects of methyl substitution at C_{28} . Stigmasterol (5) was selected as a suitable compound for the latter investigation, and its structure maybe regarded as a molecular composite of a cholesterol ring framework ("backbone") with a C_{28} methylated ergosterol side chain. The resonances arising from the cholesterol part are readily distinguished on the basis of Roberts work,⁹ and IIS data served to distinguish between ring and side chain resonances in

cases of doubtful assignments. Table 3 indicates the anticipated effects of such a methyl substitution, and lists the predicted (on the basis of the ergosterol s.c.) and the observed shifts for the side-chain resonances in 5.

C_{21} in the ergosterol side-chain is assigned to the methyl resonance at 21.27 ppm. Comparison of the ergosterol and stigmasterol side-chain structures (fig.1) indicates that C_{21} is removed from the C_{28} methylation site and should hence exhibit a minimal chemical shift difference between 1 and 5. The absorption at 21.27 ppm (1) and 21.24 ppm (5) is the only one to satisfy this criterion.

Line positions of the side chain groups at C_{25} are now estimated using the additivity relationships of Lindeman and Adams,¹¹ based on the work¹² of Grant and Paul; the side chain is treated as a saturated paraffin, no allowance being made for the double bond. Using the notation and tables given in Levy & Nelson's book^{13a}, these results are recorded as Table 4.

C_{28} in the ergosterol side chain is expected to occur at highest field (after C_{18}) and the closest experimental line is 17.6 ppm. Stothers¹⁰, using oct-3-ene as his model, calculated C_{28} to be at 17.8 ppm. Correction for the β effect of the double bond by +1.45 ppm seems reasonable, when compared with a deshielding of ca. 2-5 ppm for an sp^3 carbon α to an olefin. Table 3 indicates this assignment is correct, because the line position allocated to C_{28} in (5) reflects the expected chemical shift changes very accurately.

Table 4 predicts C_{25} in (1) to occur at 32.53 ppm, in good agreement with the observed position of 33.35 ppm, and table 3 indicates this resonance undergoes the expected γ shift to its position in the side chain of (5), in confirmation of the original assignment and indicating a term for the effect of the double bond of 0.78 ppm.

Use of the original Grant and Paul substituent parameters with trans oct-4-ene as a model predicts C_{20} and C_{24} to appear at

Table 3. Estimated side chain resonances in Stigmasterol.

C _n	Position in 1	effect of C ₂₈ methylation	total change	predicted ppm	observed
21	21.27	$> \epsilon$	0	21.27	21.24
20	40.57	$\epsilon = 0.1$	0.1	40.67	40.54
22	135.76	γ' olefinic	1.5	137.26	138.36
23	132.24	γ olefinic	-1.5	130.74	129.33
24	43.12	$\beta = -1.5$ $\beta = +9.4$	6.8	49.92	51.26
change in substitution 3y (1y) to 3y(2ndy) = -2.6					
25	33.35	$\gamma = -2.5$	-2.5	30.85	31.91
26	19.96	$\delta = 0.3$	0.3	20.26	19.02
27	20.07			20.37	21.11
28	17.77	$\alpha = +9.1$	7.7	25.47	25.44
change in substitution 1y(3y) to 2ndy (3y) = -1.4					

Table 4. Calculation of ergosterol side chain resonances based on Lindeman and Adams parameters.

Carbon	Param.	S	D ₂	D ₃	D ₄	N _{K3}	N _{K4}	C _n
28		1	0	1	0	3	1	16.15
21		1	1	0	0	3	5	18.11
26,27		1	0	1	0	2	1	19.14
25		3	0	1	0	3	1	32.53

39.7 & 44.7 ppm. in reasonable agreement with the observed values. The two carbons may be distinguished by the effects of C₂₈ methylation as illustrated in table 3. C₂₀, in an ϵ relationship to C₂₈, will be affected by ca. 0.1 ppm, whilst C₂₄ will be associated with a much larger β effect. The observed changes are in accord with the above assignments for 1.

Calculations,¹⁰ by Stothers, of the shifts expected for the olefinic centres C₂₂ and C₂₃ fail to provide reasonable estimates for these line positions. In the off-resonance spectra, the resonances at 132.24 & 135.76 ppm indicate the virtual coupling pattern expected from the trans geometry of the protons and carbons in this fragment as discussed above (ABX, ¹³C = X). The two absorptions may be distinguished by reference to the methylation effects expected in the stigmasterol side chain (table 3). The carbons would be expected to both undergo shifts of ca. 1.5 ppm, but in opposite directions, providing an unambiguous aid to the assignments indicated in table 1, which are contrary to those originally reported by Roberts.⁹

The asymmetric centre C₂₄, adjacent to the side chain carbons C₂₆ and C₂₇ could induce chemical non-equivalence between these nuclei. Using the data in table 4, these carbons are assigned to the methyl resonances at 19.96 and 20.07 ppm for 1. Table 3 indicates that the consequences of C₂₈ methylation (to yield stigmasterol) should be a downfield shift of 0.3 ppm, but inspection of table 1 reveals that each carbon has been further separated by a shift ca. three times as large and in opposite directions, to produce a chemical shift difference between C₂₆ and C₂₇ of 2.1 ppm. These observations are consistent with those made by Roberts' group,¹⁴ during a study of the chemical non-equivalence of isopropyl methyl groups with variation in the bulk of neighbouring substituents, for compounds of the type (CH₃)₂CH.(CH₂)_n.CHRR'. 2,3-Dimethyl pentane (n = 0, R = Me, R' = Et) (figure 2) provides a good model for the free end of the stigmasterol side chain, and the isopropyl methyl groups were found to resonate at 18.1 and 20.3 ppm,

i.e. a chemical non-equivalence of 2.2 ppm. These values are in excellent agreement with those observed for stigmasterol (table 1), and Roberts explained the origin of the chemical shift difference in

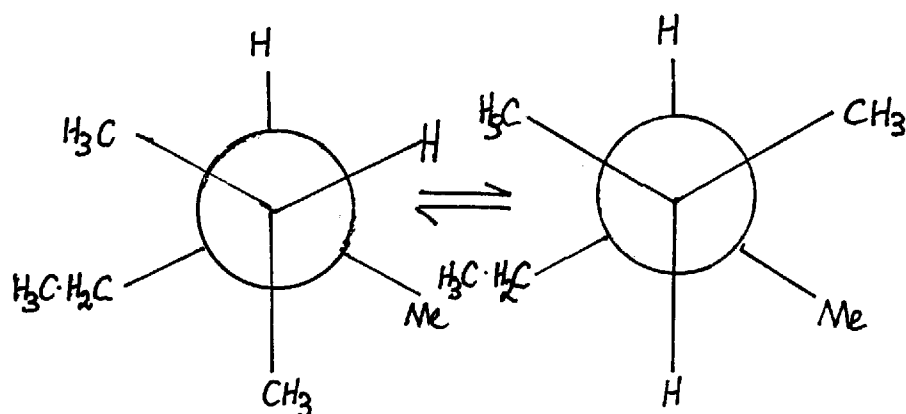


Figure 2

terms of a steric deshielding of one of the isopropyl methyl groups by its close proximity to the bulkier ($R = Et$) vicinal substituent. Larger effects were noted for $R' = iPr$ and tBu and in the latter case the non-equivalence amounted to 7.2 ppm.

5.1.2 Ergocalciferol (2).

All the side chain resonances were readily identified by reference to the parent compound, ergosterol (1). In cases of doubt, resorting to the LIS data (table 2) served to differentiate these from the ring skeleton. Carbons 12, 13, 15 and 16 were assigned in a similar manner, with the off-resonance spectrum providing confirmation of C_{13} .

The ring B opening which has taken place (1-2) causes C_{14} to move downfield 1.69 ppm such that it and carbon 17 become coincidental at 56.49 ppm. It is noted C_{17} undergoes a very small (0.31 ppm) shift difference with respect to 1, which reflects its position remote from C_9 and is in keeping with its earlier assignment above.

The LIS data serve to identify those carbons in the A ring, and these can then be differentiated by the esterification shifts (2-2a) and off-resonance spectra. Carbon 3 bearing the ester group is readily identified to low field in both compounds, with an esterification shift of 5.77 ppm. The three aliphatic carbons with large values of δ_{Fu} (table 2) must be carbons 1, 2, and 4. Of these three carbons, C_4 is substituted β by both an oxygen function (C_3) and the triene system (C_5), and will hence have the lowest field chemical shift. Further, C_4 is the X part of an $AB(C_4H_2)M(CHOH)X(C_4)$ spin system, and is thus expected to show the least second order structure in an off-resonance spectrum, as discussed previously. The latter also serves to locate C_4 in the 3,5DNBz ester (2a), from which an upfield esterification shift of 3.92 ppm is obtained, comparable to that reported¹⁵ for cyclohexanol (-3.8 ppm). Thus C_4 is assigned as in table 1. Carbons 1 and 2 may be differentiated both on chemical shift grounds and esterification shifts. Carbon 2 is β to the oxygen function, whilst C_1 is in a γ relationship, and by analogy with cyclohexanol, C_2 is expected to possess a larger esterification shift than C_1 . Therefore the chemical shift of C_1 should be comparable in 2 and 2a, and the assignments fulfil these requirements.

In the hexatriene system the exocyclic methylene carbon C_{19} is readily identified as the highest field olefinic absorption, yielding the expected triplet in off-resonance spectra. Carbon 8 at the end of the conjugated chain is remote from the C_3 lanthanide complexation site, and hence should have the smallest LIS value for the quaternary carbons, distinguishing it from C_{10} and C_5 . C_8 should also be least influenced by C_3 esterification.

It remains to differentiate the pairs of absorptions for the centre chain C_6 and C_7 and the $C_5 - C_{10}$ quaternary carbons. The observed LIS data for these carbons will be predominantly pseudocontact in nature, and calculation of the $(3\cos^2\theta - 1)/r^3$ term enables a relative ordering of resonances to be obtained. The geometry of the lanthanide complex coordination with the hydroxyl function is unknown, and therefore

approximate data² obtained for adamantan-1-ol were employed. Thus the Eu atom was assumed to be $2.1\text{\AA}$ distant from the oxygen atom and the Eu-O-C bond was defined as colinear and taken to be the principal magnetic axis. The r vector was obtained from measurements on Preiding models and the angle this subtended to the Eu-O bond was calculated by trigonometry. The results are presented in table 5.

Table 5. Pseudocontact term calculations for hexatriene system.

Carbon No.	$r(\text{\AA})$	θ	$\cos \theta$	$(3\cos^2\theta - 1)/r^3 \times 10^3$
6	6.30	$21^\circ 7'$	0.9329	6.4436
7	7.65	$19^\circ 31'$	0.9426	3.7201
5	5.45	$15^\circ 20'$	0.9644	11.064
10	5.90	$12^\circ 28'$	0.9765	9.060

Inspection of tables 5 and 2 shows that although both C_6 and C_7 subtend comparable angles to the lanthanide the increased distance of the latter is such as to produce large differences in the pseudocontact term in keeping with the observed LIS data (table 2) and confirming the assignments of table 1.

The pair of quaternary resonances C_5 and C_{10} may be similarly distinguished using table 5, which predicts C_5 to have a slightly greater LIS than C_{10} , which is reflected by the experimental values. These nuclei may now be assigned with reasonable confidence as indicated (table 1).

The calculated values of $(3\cos^2\theta - 1)/r^3$ must be considered approximate, because no allowance was made for the Eu-O geometry. Data obtained² from 'metal-search' computer programs, which fit the observed shifts (with the elimination of contact contributions) to

the pseudocontact equation suggest the Pu atom more normally subtends an angle to the O-C bond of $120-150^\circ$ rather than being colinear with it.

The hexatriene resonances for 2a are now readily assigned by comparison with the free alcohol. It is interesting to note that C_{10} has a larger diamagnetic shift than C_5 (-1.85 vs. -1.19 ppm), also that C_9 exhibits a small upfield shift in contrast to those downfield for C_6 (0.68) and C_8 (0.91 ppm). These variations probably reflect the polarisation of the conjugated system by C_3 esterification. The effects are illustrated in figure 3.

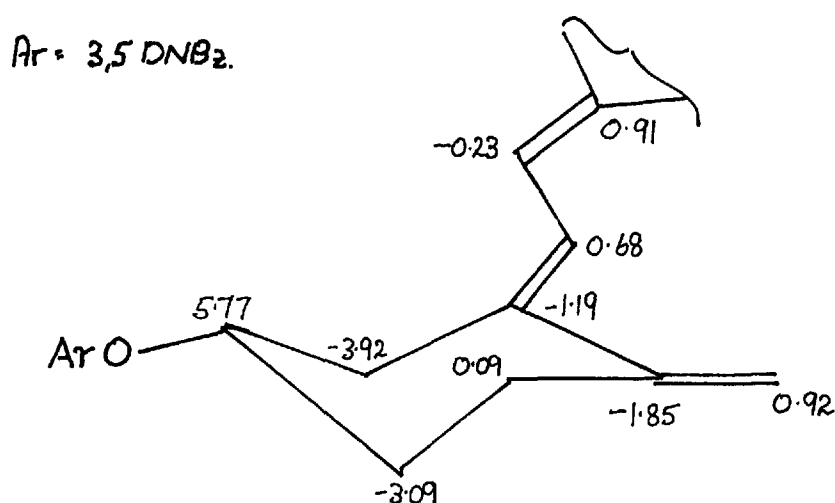


Figure 3, Esterification shifts - ergocalciferol

Such long range bond polarisations are not without precedent. The source of non-equivalence in ^{13}C chemical shifts of unsaturated carbons in some long chain fatty acids has been shown¹⁶ to have its origin in a linear electric field effect arising from the substituent ($-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}$, $-\text{OH}$) at one end of the paraffin chain, and to be detectable upto eight C-C bonds away from the head group dipole.

The two remaining resonances are C_{11} and C_9 , which may be readily distinguished by chemical shift. C_{11} has no α substituents and is γ to the sp^2 centre C_8 , and hence is expected to be the

highest field methylene group; whilst C_9 is α to the triene system and is therefore deshielded. Neither resonance should show an esterification shift, in keeping with the assignments proposed in table 1.

5.1.3. Dihydrovitamin D₂II and D₂IV.

Carbons 11-17 in the C and D rings and all the side chain were readily identified by comparison with ergocalciferol (2). It is observed that carbons 14 and 17 are now resolved by 0.08ppm, and it seems reasonable to assign C_{14} to the higher field absorption, since C_{17} is less likely to be affected by hydrogenation of the C_{10} - C_{19} double bond in 2.

The homogeneous hydrogenation of 2 to 3 and 4 converts C_{19} to a methyl group, which is readily identified from off resonance spectra and assigned as indicated (table 1).

The chemical shift of C_8 in the butadiene chain is expected to vary little upon either esterification (3-3a) or reorientation of the C_{10} methyl group (3a-4). These structural modifications serve to distinguish this quaternary olefinic carbon resonance from the other arising from C_5 and enable unambiguous assignments as tabulated.

The two mid-chain butadiene resonances are initially differentiated via esterification shifts. Comparison with 2-2a (see fig 2) suggests C_6 will show a downfield esterification shift, whilst C_7 will probably undergo a small upfield shift and assignments as tabulated fulfil these predictions. Inspection of molecular models of 3a and 4 suggests that the reorientation of the C_{19} methyl group about C_{10} from a trans diaxial arrangement in D₂II to the axial-equatorial conformation of D₂IV will relieve steric interaction with C_7 -H but leave C_6 unaffected. The observed effect in the chemical shift of C_7 for this change is -0.21ppm, which must be considered a real effect in the light of a negligible (0.05 ppm) change in the chemical shift of C_6 .

Within the A ring, carbon 3 is easily identified by its characteristic low-field shift, and it is noted that the ester shift $\underline{3}$ - $\underline{3a}$ is 7.57ppm, ca. 2ppm larger than that recorded for ergocalciferol.

Carbon 4 is distinguished by its chemical shift and off-resonance spectrum, as discussed above. An esterification shift of -4.25ppm is observed for the D_2IV isomer ($\underline{3}$ - $\underline{3a}$), comparison of $\underline{3a}$ and $\underline{4}$ indicates the conformational changes affect C_4 by only 0.3ppm.

By analogy with the 4-methyl cyclohexanols,¹⁷ carbon 10 is identified as the methine resonance at ca. 30ppm with a negligible esterification shift $\underline{3}$ - $\underline{3a}$, but an appreciable downfield shift (0.8ppm) $\underline{3a}$ - $\underline{4}$ upon reorientation of this centre, reflecting the differences between the two A ring conformations in $\underline{3}$ and $\underline{4}$.

By analogy with ergocalciferol ($\underline{2}$) and cyclohexanol derivatives, C_2 in the D_2IV isomer ($\underline{3}$) is expected to exhibit an ester shift comparable to carbon 4, whilst C_1 will probably have a very small ester shift. Arising from the substituent pattern within the ring, carbon 2 is expected to resonate to low field of carbon 1, as discussed above.

Inspection of Table 1 reveals that carbons 1 and 2 in dihydrovitamin D_2IV ($\underline{3}$) occur within 0.4ppm of each other, and hence it is possible that these two assignments might be interchangeable: however, those given provide the most compatible pattern of esterification shifts in the light of figure 2. It is difficult to calculate shifts for 3 in terms of an axial methyl substituent upon cyclohexanol, as ring geometry and hence electronic distributions, are distorted by the C_5 sp^2 olefinic centre.

The overall effects of esterification in dihydrovitamin D_2IV are illustrated in figure 4.

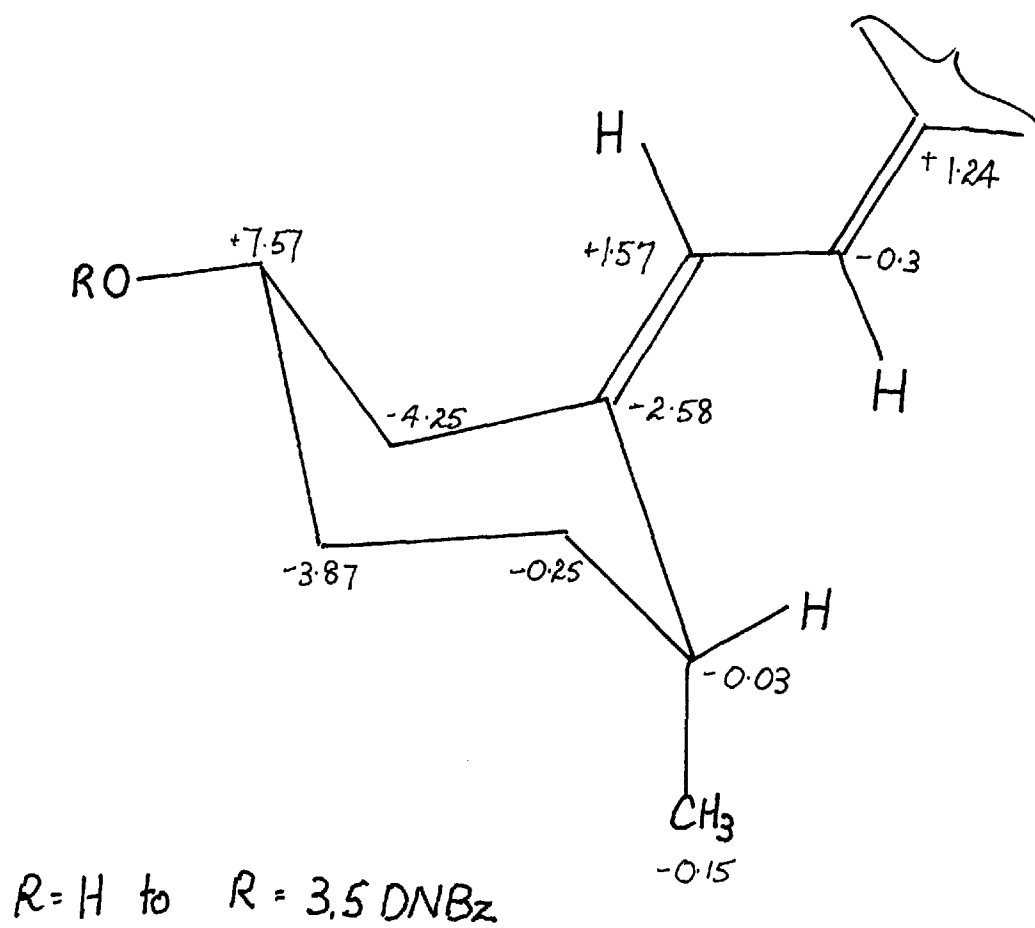


Figure 4. Esterification shifts in
Dihydrovitamin D₂ IV

5.1.4 Suprasterol II.

The introduction of the C₈ spiro centre and cyclopropane ring into the skeletal structure cause quite significant changes in the chemical shifts of the C and D rings. However, comparison of the chemical shift data with assignments made for ergocalciferol (2) identifies all the side chain resonances together with the C₁₈ angular methyl group, the C₃ oxygen-bearing carbon and carbons 12 and 13 in the C ring. Carbon 17 is remote from the C₈ spiro centre, and hence is expected to differ little from that in 2, whilst C₁₄ is α to the spiro centre and thus its chemical shift will be modified from that in 2. It is observed that C₈ induces an upfield shift in C₁₄ of 3.51 ppm, causing the usually coincidental absorptions of C₁₄ and C₁₇ to become well resolved when compared to ergocalciferol.

The second quaternary carbon C₈ is identified from off-resonance spectra, the extreme high-field position being ascribed to the stress associated with the spiro centre within the cyclopropane ring.

The A/B ring junction consists of the C₅-C₁₀ double bond. C₅ is both α to the tertiary centre C₆ and β to the oxygen function C₃; in contrast C₁₀ has the C₁₉ methylene carbon as its corresponding α substituent in the B ring and is γ to the hydroxyl function. Hence C₅ is expected to occur to low field of C₁₀ and the assignments are made accordingly.

The remaining carbon atoms were identified unambiguously with the aid of esterification shifts and LIS data. An off-resonance spectrum of the "Th^{III} shifted-solution" enabled all methylene and methine centres to be differentiated, which was not possible in the Eu-free solution.

The three carbons with the largest values of δ_{Eu} (table 2) (excluding C₃, C₅ and C₁₀) must lie in ring A. Carbon 4, with both the oxygen function and the double bond as α substituents will be to

the lowest field of carbon 1,2 and 4, and is analogous to its counterpart in ergocalciferol (2). Hence the comments made of 2 (above) concerning the minimal second order nature of the off-resonance spectra of C_4 are applicable here and serve to confirm its assignment in 3 and identification in 3a, from which an esterification shift of -4.08ppm is deduced, comparable to that found in 2-2a. Carbons 1 and 2 are now readily differentiated, both with the aid of LIS data (table 2) and on chemical shift grounds, from which C_2 is expected to absorb to low field of C_1 . Further comparison of 6 and 6a permits the identification of C_1 as that having a comparable esterification shift to C_4 , with C_2 exhibiting a much smaller effect.

The only methylene carbon in the B ring is C_{19} , which is now readily identified from the LIS data as that methylene resonance with the most significant value of δ_{Fu} .

The off-resonance spectrum of the " Eu^{III} shifted solution" indicates two methine resonances with a considerable LIS, which must be C_6 and C_7 . Although both carbons have the spiro centre C_8 as a common α substituent, C_7 is also α to the C_{19} methylene group whilst C_6 has the increased substitution of the C_5-C_{10} double bond as its other α substituent. Consequently, C_6 is assigned as the lower field of the two absorptions. This assignment is supported by the off-resonance spectrum, which shows a more clearly defined doublet for the low field over the upfield resonance. These differences arise from the different spin systems of the two carbons; C_6 bears one isolated proton (which is clearly resolved in a 220 MHz proton spectrum as a sharp singlet at 8.35τ), whilst C_7 can couple to the protons on C_{19} in an ABCX spin system. It is noted that the larger directly bonded coupling constants¹⁸ characteristic of cyclopropanes ($^1J_{\text{CH}} = 161\text{ Hz}$) compared with a value of ca. 125 Hz for paraffins are reflected in the size of the residual splittings observed in the off-resonance spectra, when measured against these from other methine resonances.

Carbon 9 in ring C is α to the quaternary centre C_8 , and is thus similar to C_{12} , which is α to the other quaternary centre C_{13} .

On chemical shift grounds this carbon is hence assigned to the low field absorption overlapping C_6 .

It remains to distinguish the absorptions arising from carbons 11, 15 and 16. As discussed for ergocalciferol, C_{11} is expected to be the highest field methylene resonance and it is observed that the assigned line is shifted upfield 1.38 ppm, in keeping with the change at C_8 (the χ position) from an sp^2 to a strained sp^3 centre. Carbon 16 is δ to C_8 and hence less susceptible to these variations: the assigned resonance corresponds very closely with that recorded for 2.

Carbon 15 also bears a χ relationship to C_8 and it is seen that this centre once again reflects the hybridisation changes discussed above, with an upfield shift of 1.23 ppm.

Comparison of the full assignments for suprasterol and its 35DNBz reveals the effects of esterification are more short-range in nature than for compounds 2 - 4, and despite quite large shifts upto the AB ring junction, minimal changes permeate throughout the B rings, as illustrated in figure 5.

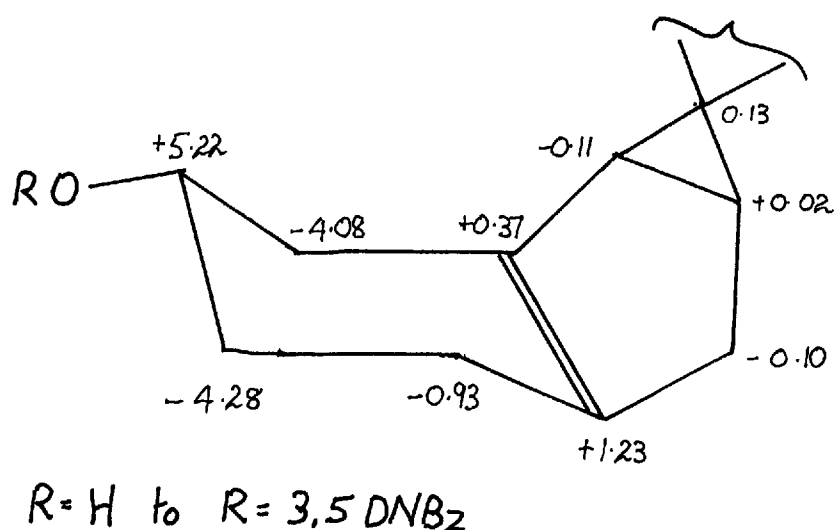


Figure 5. Esterification shifts - Suprasterol II

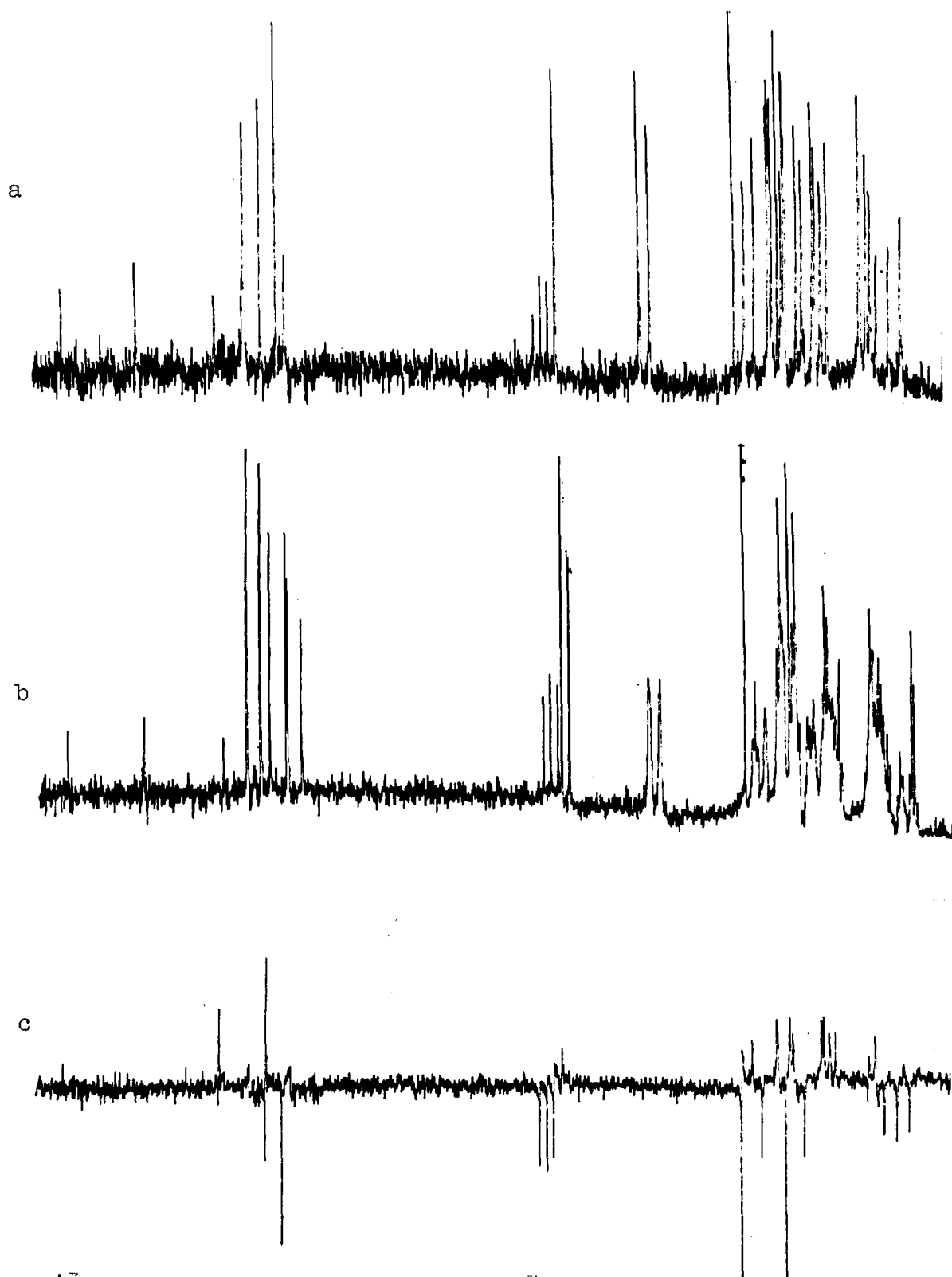
5.1.5 Tetrahydrosuprasterol II.

Catalytic hydrogenation of suprasterol II initially saturates the side chain double bond ($\Delta^{22,23}$) and secondly opens the cyclopropane ring by cleaving the C_6-C_7 bond. Consequently, the molecule contains only one double bond ($\Delta^{5,10}$) and the ^{13}C spectrum of the aliphatic region contains 26 lines crowded together (figure 6). This produces extensive overlap of absorption bands in the off-resonance spectrum, and it was not possible to make unambiguous identification of methylene and methine signals in some instances. This problem was overcome by obtaining a proton decoupled partially relaxed Fourier transform (PRFT) spectrum of the 3,5DNBz ester (7a), using an inversion-recovery $(180-\tau-90-T)_n$ pulse sequence, and the resulting spectrum is shown in figure 6. Allerhand¹⁹ has found that $-CH_2-$ and $-CH-$ groups in cholesteryl chloride had relaxation times T_1 of ca. 0.25 ± 0.02 and 0.5 sec. respectively. Thus a time interval τ of 0.26 seconds between the 180° and 90° pulse should effectively "null" methylene resonances (or in some instances produce a small positive absorption), whilst the more slowly relaxing methine resonances should appear as negative signals. Assignments were aided further through the use of LIS data obtained for the alcohol in the manner described previously for the model compounds, and the relevant data are recorded in table 2.

Saturation of the side chain will modify the chemical shifts of all the side chain carbons, but it is possible to estimate these new values through the consideration that the 'new' side chain could arise from a cholesterol side chain (for which the chemical shifts are well documented^{9,10,13}) via the introduction of a methyl group at C_{24} . Table 6 indicates the results of such a calculation, together with the observed shifts for comparison.

The angular methyl group C_{18} is readily identified as that resonance at highest field. C_{28} in the side chain is assigned by comparison with the C_3 methyl group of 2,3-dimethylhexane, which occurs¹¹ at 15.1 ppm. The signals corresponding to those indicated

Figure 6 ^{13}C spectra - Tetrahydrosuprasterol



a) ^{13}C - $[^1\text{H}]$ noise decoupled b) ^{13}C - $[^1\text{H}]$ off resonance

c) Inversion - recovery PRFT spectrum

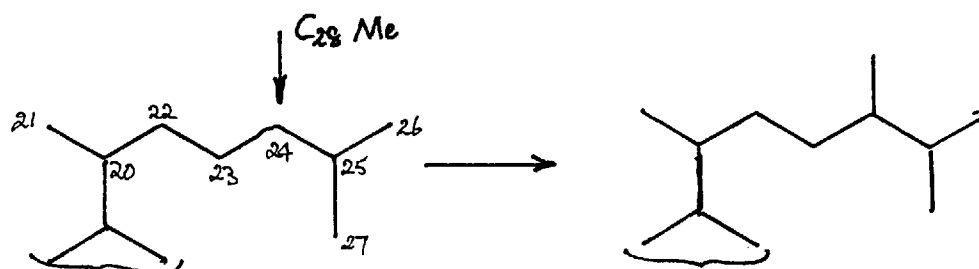
by table 6 for C_{22} and C_{23} were difficult to identify as methylene resonances from the off-resonance spectra, but the LIS data provided a facile means of distinguishing these (and other side-chain resonances) from neighbouring signals of carbon nuclei in the B and C rings of the molecule. Thus Table 6 provided a good indication to the region of the C_{20} resonance; and use of LIS data (table 2) together with a comparison of the chemical shifts of free alcohol and 35DNBz ester and off-resonance spectra enabled the final assignment.

A striking example of this procedure is provided by the assignment of C_{22} . Table 6 suggests a value of 34.2ppm, but LIS data indicates the resonance at this position to be C_9 (see later) and that C_{22} is actually that absorption at 30.53 ppm. Neither off-resonance or PRFT spectra were able to provide clear evidence in this case, and the discrepancy of 3.7ppm indicates the need for caution when using only one piece of data.

Clear evidence that the assignments indicated for C_{24} and C_{25} from table 6 and off-resonance spectra were correct was provided by the PRFT spectrum. Both methine resonances appeared as negative responses, i.e. with longer relaxation times compared to the C_3 methine resonance. This discrepancy arises¹⁹ from the internal motion at the end of the side chain, which reduces the efficiency of the dipole-dipole relaxation process²⁰ and therefore increase the relaxation time T_1 . Hence the negative responses observed are consistent with the location of C_{24} and C_{25} near the end of the side chain.

The terminal methyl groups C_{26} , C_{27} and C_{21} should¹⁹ all show evidence of the internal motion (i.e. fast spinning), and this was used to distinguish between absorptions arising from CH_3 - and $-CH_2$ - groups in the 17-21 ppm region. This was especially relevant for the C_{29} absorption, since table 6 indicates this carbon could be the resonance at 19.32 ppm, but a positive response in the PRFT spectrum precludes this possibility. C_{21} was finally assigned to the 18.69 ppm resonance, (negative PRFT response), whilst C_{26} and C_{27} were identified as indicated in table 1, and it is observed these assignments are in

Table 6. Estimated side chain resonances in tetrahydrosuprasterol.



C_n	position in cholesterol	effect of C_{24} methylation	total change	predicted (ppm)	observed (ppm)
21	19.1	$\epsilon = 0.1$	0.1	19.2	18.69
20	36.3	$\delta = 0.3$	0.3	36.6	35.87
22	36.7	$\gamma = -2.5$	-2.5	34.2	30.53
23	24.4	$\beta = 9.4$	9.4	33.8	33.52
25	28.3	$\alpha = 9.4$	3.6	31.9	31.49
change in substitution					
3ry (2ndy) 3ry(3ry)					
$= -5.8$					
26,27	22.8, 23.0	$\gamma = -2.5$ (but also intro. of assymmetry at C_{24})	-2.5	20.3 20.5	17.63 20.54
24	40.0. This resonance is best calculated as a derivative ¹¹ of 2,3-dimethylhexane (C_{24} = carbon 3) with correction factors (δ effects) for addition of C_{21} and the steroid nucleus. Thus $C_{24} = 38.5 + 2 \times 0.3 = 39.1$ ppm.				

excellent agreement with the absorptions recorded¹¹ for the C₁ resonances of 2,3 dimethylhexane (17.8 and 20.0 ppm). As discussed previously for the stigmasterol side chain, these differences in shielding of the terminal methyl groups probably arise¹⁴ from deshielding of one of the methyl groups by the steric interactions with the main part of the side chain.

Hydrogenation of the C₆-C₇ bond in 6 to 7 relieves the bond angle strain at C₈ considerably, and this is reflected by the chemical shift changes in the immediate neighbourhood. Thus a comparison of 7 with its parent 6 shows that the quaternary carbon C₁₃ has been shifted upfield 1.6ppm, and enables the resonances for C₁₄ and C₁₇ to be assigned as indicated in table 1. C₁₇ is remote from the spiro centre C₈, and thus should exhibit only a small shift 6-7 (0.9 ppm); whilst C₁₄ is in an α relationship to C₈ and undergoes a considerable downfield shift (6.3ppm) to its position in 7.

The spiro carbon C₈ is identified from its off-resonance spectra and it is observed that the steric relief 6 to 7 produces a downfield shift of 7.6 ppm. The PRFT spectrum indicates C₈ has a long relaxation time comparable to C₁₃, as is to be expected¹⁹ for non-protonated carbons.

As discussed previously, C₁₁ must be the highest field methylene absorption and the PRFT spectrum enables its assignment to the resonance at 19.3 ppm. Comparison with its position in 6 at 21.00 ppm indicates that C₁₁ is influenced by the relief of steric strain at C₈ to the extent of 1.7 ppm.

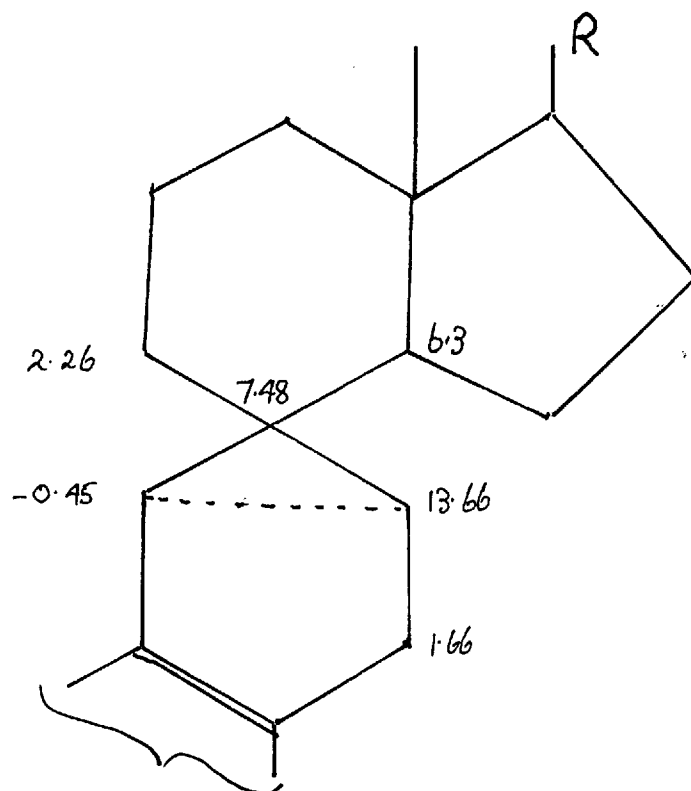
The A/B ring junction consists of the 5,10 double bond, and it is seen that the relevant signals are separated by only 2-3 ppm. Thus it is difficult to make unambiguous assignments either on the basis of the relative positions of the carbons with respect to the spiro centre and the oxygen function or ester shifts, which are comparable (-0.59 and -0.39 ppm) for the two signals. However, C₅ is α to C₆, whilst C₁₀ is β to C₇, and thus removal of the

$C_6 - C_7$ cyclopropane bond in 6 - 7 will probably induce greater shifts in C_5 over C_{10} . Assignment of C_5 to the high field resonance and C_{10} to the low field resonance is in accordance with this hypothesis, and yields values of an upfield shift for C_5 of 10.3 ppm, and 6.9 ppm for C_{10} . The alternative assignments are thought to be less probable, as this would yield comparable values of the "steric-strain" shifts for 6 - 7.

The magnitude of the lanthanide shifts serve to distinguish these resonances in the A and B rings from those in C and D, which are remote from the C-3 coordination centre. Use of this information in conjunction with ester shifts and the other model compounds permits a full assignment. Thus carbon 3, as the functionalised centre is readily identified as the lowest field sp^3 resonance and has the greatest induced shift, whilst the remaining A ring resonances are those with the next greatest LIS values. Individual identification of carbons 1, 2 and 4 is made on the grounds of ester shifts, as discussed previously, and these are recorded in table 1.

The remaining carbons with relatively large LIS values are those in ring B and C_9 from ring C. The major structural difference between suprasterol II (6) and its tetrahydro derivative (7) is that the hydrogenation cleaves the cyclopropane ring in ring B and this relieves the considerable internal strain. This is reflected in the differences of the chemical shifts found for this ring, and provides a useful aid to assignments - for example, it was noted above that hydrogenation produced a downfield shift for the C_8 spiro centre of 7.5 ppm. Carbons 6 and 19 are distinguished from C_7 and C_9 by larger LIS values, and have chemical shifts close to those for 6; C_6 is anticipated to absorb to low field of C_{19} because it is α to the C_8 spiro centre. Carbon 9 in ring C is expected to possess a chemical shift close to that found in suprasterol, whilst C_7 in the B ring will experience considerable relief of bonding compression upon hydrogenation 6-7, and hence exhibit a considerable downfield shift. The assignments recorded in table 1 support this conclusion, and the general pattern of "steric strain" shifts is illustrated in figure 7.

Figure 7. "Steric strain" shifts upon hydrogenation of C_6-C_7 bond in Suprasterol II (dotted line).



There remain but three carbons to identify and carbon 12 is assigned to the usual position at ca 40ppm. Carbon 15 and 16 in ring D must be the remaining absorptions, and it is expected that the chemical shift of C_{16} should be very comparable to its position in suprasterol because it is remote from the C_8 spiro centre, which has undergone relief of steric strain. Carbon 15, although in a γ relationship, will be more susceptible to the effects of such a change, and the shifts recorded in table 1 are in keeping with this assumption.

5.2 Compounds of Unknown Structure.

5.2.1. Lumicalciferol.

This compound is isolated as the major biproduct of the photolysis of ergocalciferol to suprasterol II, but is of unknown structure. This problem was investigated by recording the ^{13}C spectra of lumicalciferol (8) and its 3,5DNBz ester (8a) in CDCl_3 solution, together with the single frequency (off-resonance) decoupled spectra. Chemical shifts are listed in table 9, and because the compound under investigation is a by-product of suprasterol II (6) formation, a comparative table of chemical shifts against those observed for 6 was drawn up as table 7.

From these tables, the standard set of ergosterol side chain resonances was identified readily. Similarly, the highest field resonance in the methyl region, normally assigned to the C_{18} angular methyl group, was detected but with a downfield shift of 0.23ppm, compared to that in suprasterol II. The other absorption with an unambiguous chemical shift was the C_3 hydroxyl function, with an esterification shift (+6.17 ppm) which was very comparable with that of 6.

In the olefinic region, two quaternary absorptions are observed at 131.02 and 134.33 ppm, indicating lumicalciferol possesses one totally substituted double bond (excluding side-chain unsaturation). Inspection of the cross-correlation table 7 between suprasterol II and lumicalciferol reveals a very marked similarity - both of these resonances agree to within 0.5 ppm with those of the $\text{C}_5\text{-C}_{10}$ double bond in 6, and further the small esterification shifts for 8 8a exhibit the same trends as for 6 6a; viz. the higher field resonance shows an upfield shift of 0.73 ppm for 8 (cf. 6 -1.23 ppm) and the lower field absorption a downfield shift ca. one-third as large (+0.23 ppm for 8 cf. 6 +0.37 ppm).

The aliphatic region of the off-resonance spectra reveals

Table 7.^a Comparison of chemical shifts for Lumicalciferol with
Suprasterol II.

SUPRASTEROL II		SUPRASTEROL II 3,5 DNBz		LUMICALCIFEROL 3,5 DNBz		LUMICALCIFEROL	
12.57	18	12.64	18	12.83	18	12.84	18
17.65	28	17.73	28	17.64	28	17.65	28
19.67	26	19.65	26	19.64	26	19.66	26
19.98	27	19.97	27	19.96	27	19.98	27
20.84	11	20.83	11	20.79	11	20.79	11
20.99	7						
21.08	21	21.01	7 & 21	21.07	21	21.09	21
		21.86	1	21.84	15	21.86	15
22.33	15	22.41	15	22.46	1	22.38	1
22.80	1			22.89	7	22.74	7
24.62	19	24.52	19				
				24.93	9	24.91	9
27.18	8	27.31	2 & 8	27.43	8	27.32	8
27.66	16	27.60	16	27.68	2 & 16	27.69	16
						30.92	2
31.60	2	31.69	4	31.71	4		
				32.67	6	32.79	6
33.12	25	33.11	25	33.11	25	33.13	25
34.26	6	34.15	6				
34.31	9	34.38	9				
				34.87	19	34.83	19
35.77	4					35.32	4
40.09	20	40.06	20	40.07	20	40.11	20
40.92	12	40.74	12	40.81	12	40.85	12
42.84	24	42.89	24	42.85	24	42.84	24
44.43	13	44.40	13	44.79	13	44.78	13
53.13	14	52.99	14	53.54	14	53.59	14
56.64	17	56.60	17	56.56	17	56.55	17
67.98	3					67.64	3
		73.20	3	73.81	3		
		130.77	10	130.29	10	131.02	10
131.78	23	131.84	23	131.84	23	131.79	23
131.99	10						
134.57	5	134.94	5	134.56	5	134.33	5
135.86	22	135.77	22	135.82	22	135.86	22

a) Figures to right hand side of columns denote assignments.

the presence of two quaternary carbons. The low field resonance at 44.78ppm is in the range expected for C₁₃ at the C/D ring junction, but is shifted downfield 0.4 ppm from its position in 6. The higher field quaternary at 27.32 ppm(8) is within 0.14 ppm of the resonance for the spiro centre C₈ of the cyclopropane ring in 6 (27.18 ppm). This quaternary resonance in lumicalciferol shows a small esterification shift (+0.11 ppm) very comparable to that observed for suprasterol II (+0.13 ppm); these two observations taken together provide strong evidence to suggest the B/C ring junction in lumicalciferol is a spiro centre in a very similar structural environment to that in suprasterol II.

Two doublet resonances are seen at the low field end of the aliphatic region, that corresponding to C₁₇ in 6 has an identical chemical shift (56.56 ppm) whilst the C₁₄ absorption is displaced downfield by 0.5 ppm from the analogous position in 6.

An additional peak in the low field aliphatic region can be distinguished using the cross-correlation table 7, which indicates the triplet resonance at 40.85 ppm (8) possessing a negligible esterification shift, should be assigned to C₁₂ in ring C. Notwithstanding the methine resonances associated with the side chain, two further such absorptions are detected, comparable to those recorded for the cyclopropyl carbons C₆ and C₇ in suprasterol II, but exhibiting appreciable chemical shift differences from these, viz:

carbon	suprasterol II	difference	lumicalciferol
C ₇	20.83	+1.91	22.74
C ₆	34.15	-1.36	32.79

It may be concluded from all the above information that the high field quaternary centre must be in a cyclopropane ring (to provide the necessary strain and hence chemical shift) and this spiro centre is α to C₁₄ to maintain the chemical shift of the latter comparable to that observed in

suprasterol II, i.e. the spiro centre must be C₈. Both of these conditions must be satisfied for the observed chemical shift to be within 0.1 ppm of that recorded for C₈ in suprasterol II.

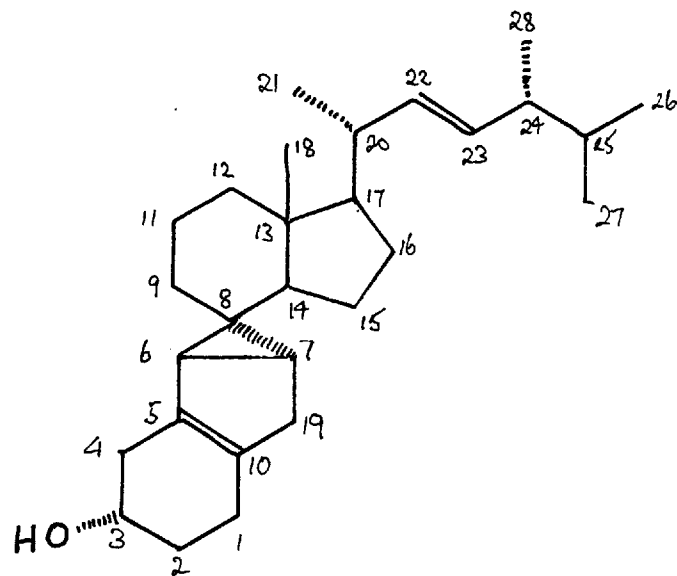
The almost identical chemical shifts recorded for the tetra-substituted double bond in lumicalciferol compared with that in suprasterol II indicates these two carbons are in the same chemical environments in both compounds, with reference to both the hydroxyl function and the cyclopropane ring. Hence it is concluded that lumicalciferol is structurally very similar to suprasterol II and possessing identical structural fragments in the same relationships, and the only possible structure is a geometrical isomer of 6, as illustrated in figure 8.

The lanthanide shift data (see table 8) enabled a complete and unambiguous assignment to be made for lumicalciferol and permitted a full comparison with suprasterol II. As was discussed in an earlier section of this chapter, the actual LIS value recorded for each nucleus is a function of not only the distance from the metal but also the angle this vector subtends to the principle magnetic axis. Therefore it is apparent that even for the corresponding carbon atoms in the isomeric pair under consideration, at least one of these parameters will be modified, notwithstanding any difference in the binding constant of the Eu-sterol complex. Thus comparison of the LIS data between suprasterol II and lumicalciferol can only be on a semi quantitative basis.

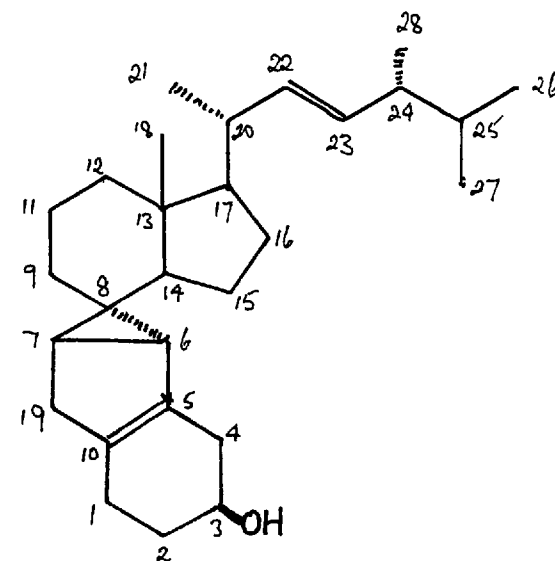
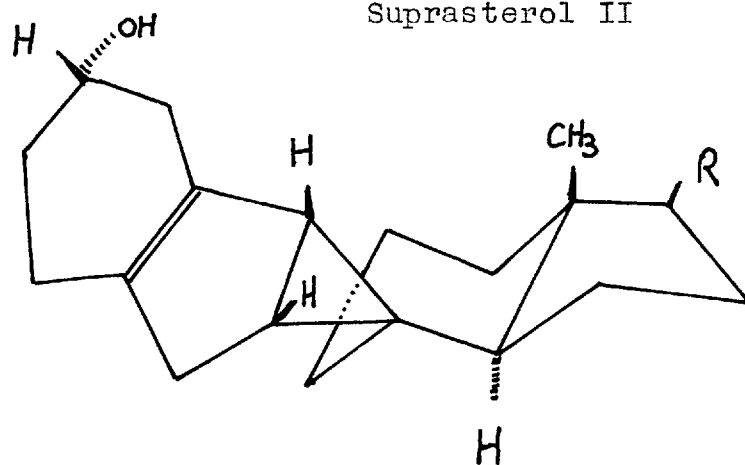
The LIS data serve to locate the A ring carbons C₁, C₂ and C₄ which are finally assigned on grounds of relative chemical shifts and esterification shifts, as has been utilized for the model compounds, and by reference to table 7. It is interesting to note that although C₂ and C₄ have esterification shifts similar to those found for suprasterol II, carbon 1 exhibits a small downfield shift (+0.086 ppm) in contrast to that found for 6 (-0.93 ppm). Figure 9 depicts the full range of esterification shifts found for this compound.

In ring B, the assignments for the cyclopropyl carbons C₆ and C₇ are confirmed by the relatively large values of δ_{Eu} , whilst C₁₉, as the remaining carbon in ring B, is distinguished similarly as

Figure 8



Suprasterol II



Lumicalciferol

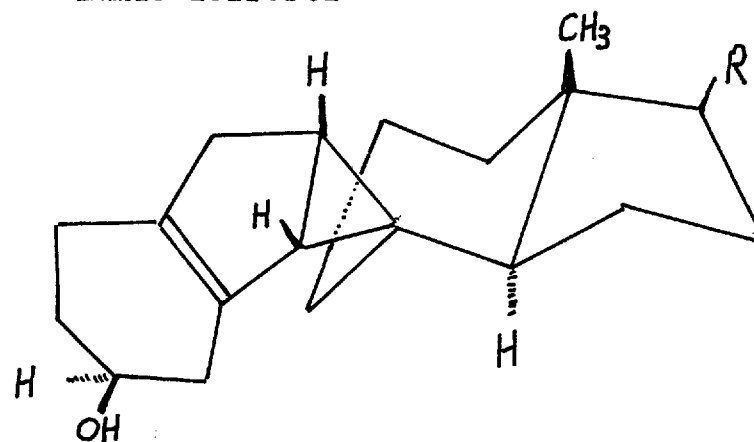


Table 8. " δ_{Fu} " - Lanthanide Induced Shifts in Lumicalciferol and some
Toxisterols: (extrapolated to equimolar lanthanide:toxisterol
concentration).

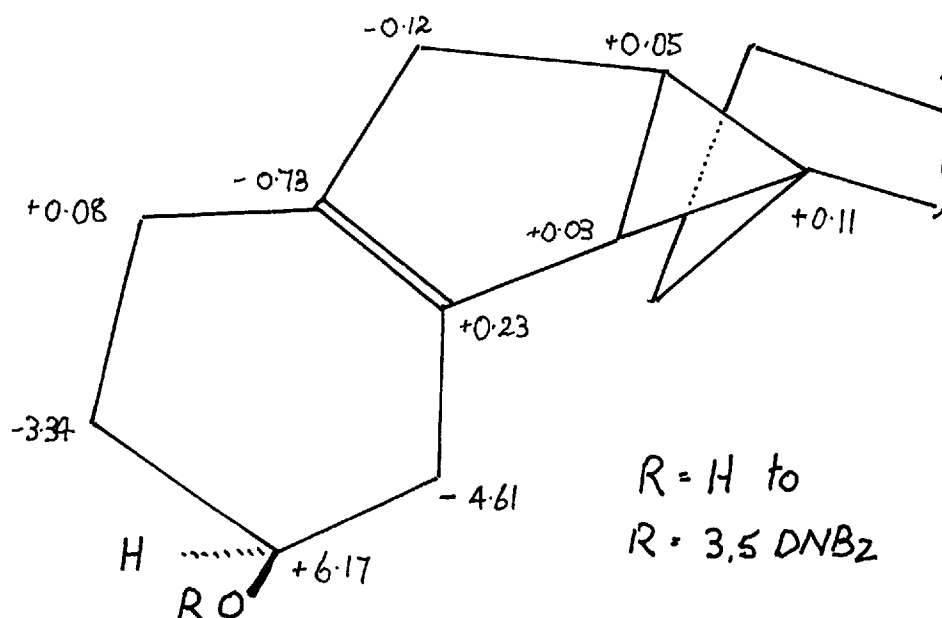
Carbon No.	Compounds		
	<u>8</u>	<u>9</u> (B21)	<u>10</u> (B22)
1	233	583	233
2	278	202	409
3	1351	1250	934
4	303	61	9
5	274	179	260
6	142	91	161
7	93	84	150
8	82	276	250
9	71	185	264
10	264	44	225
11	35	70	133
12	31	49	60
13	34	92	80
14	48	234	112
15	43	134	83
16	22	53	48
17	23	30	42
18	30	54	73
19	133	52	79
20	15	16	21
21	10	6	12
22	13	-18	16
23	10	-4	17
24	7	-17	11
25	5	-14	9
26	3	-17	4
27	3	-17	6
28	5	-24	9

that resonance at 32.67 ppm.

Three carbons are to be identified in ring C, viz. C₉, C₁₁ and C₁₂. Carbon 12 is remote from the stereoisomeric differences between suprasterol II and lumicalciferol, and hence is expected to absorb close to its position in the former compound. Similar remarks apply to C₁₁, which is additionally anticipated to be the highest field methylene absorption. However, carbon 9 is α to the C₈ spiro centre, i.e. close to the site at which the geometric isomerism is sited, and thus it is not surprising that the LIS data indicate this carbon to be that resonance at 24.91 ppm, some 9.4 ppm from its position in suprasterol II.

It remains to differentiate carbons 15 and 16 in ring D as the two residual signals: neither carbon should have a chemical shift very different from that found for 6, and hence assignments were made using table 7. It is interesting to note that C₁₅ absorbs ca. 0.5 ppm to high field of the analogous carbon in 6, whilst this discrepancy is not seen for C₁₆, and it is felt that this variation is a reflection of the differences in intramolecular interaction in the two molecules produced by the geometrical isomerism.

Figure 9. Esterification shifts in lumicalciferol (ppm).



5.2.2. Toxisterol B21.

A preliminary comparison of the ^{13}C spectra (table 9) obtained from the free alcohol (2) and its 3,5DNBz ester (2a) enables the identification of several structural features. Thus the resonances of the ergosterol side chain were readily distinguished by comparison with those found in the model compounds (table 1), and it was evident that the double bond $\Delta^{22,23}$ had not participated in the photochemical rearrangement from ergosterol (1).

Secondly, the C_{18} angular methyl group and the quaternary carbon C_{13} in the C/D ring junction were identified from off-resonance spectra and use of table 1. Further comparison of these chemical shifts with those observed for the model compounds showed that C_{18} had undergone a downfield shift of ca. 1.8 ppm, whilst C_{13} had moved upfield ca. 2.0 ppm with respect to the corresponding absorptions found for ergocalciferol (2) and the dihydrovitamin derivatives (3,4).

The low field methine absorptions arising from C_{14} at the C/D ring junction and C_{17} , the point of attachment of the side chain, were similarly identified from table 1. Their close proximity to the corresponding positions in 1 - 5, together with the assignments for C_{18} and C_{13} , provide good evidence to suggest that the C and D rings are intact, but that there is a structural modification, possibly in ring C, which causes a perturbation to the chemical shifts of C_{13} , C_{14} and C_{18} .

The sp^2 region of the spectrum contained four resonances additional to the two already associated with the side chain. This indicated the compound must be a four ring structure, and consequently was unlike the ring B opened structures of the model compounds 2 - 4. The off-resonance spectra revealed that two of the olefinic carbons had one directly bonded hydrogen, whilst the other two were quaternary in nature, i.e. there had been no redistribution of protons between the saturated and unsaturated parts of the molecule. Examination of a 100 MHz proton NMR revealed the resonances of these olefinic protons

Table 9. ^{13}C chemical shifts in some photolysis products of ergosterol, and derivatives therefrom.

	8	8a	9	9a	10	11	11a
1	22.38	22.46	35.22	35.81	26.31	31.44	29.66
2	30.92	27.68	33.86	29.17	31.28	34.00	31.08
3	67.64	73.81	69.83	76.51	66.92	69.90	73.89
4	35.32	31.71	54.05	50.76	44.57	59.73	56.25
5	134.33	134.56	122.75	123.53	122.30	120.72	121.27
6	32.79	32.67	129.29	129.23	125.88	128.71	128.70
7	22.74	22.89	140.69	140.37	147.82	140.72	140.79
8	27.32	27.43	54.11	53.94	52.74	53.21	53.18
9	24.91	24.93	31.52	31.04	32.88	35.62	35.61
10	131.02	130.29	135.76	134.34	138.52	137.97	137.68
11	20.79	20.79	20.12	19.86	21.31	19.58	19.39
12	40.85	40.81	32.92	40.30	40.67	40.10	39.67
13	44.78	44.79	43.85	43.72	42.21	44.86	44.64
14	53.59	53.54	55.78	56.12	57.27	48.31	48.56
15	21.86	21.84	22.30	22.45	21.71	24.00	23.94
16	27.69	27.68	27.64	27.43	27.16	29.51	29.53
17	56.55	56.56	57.04	57.80	57.27	54.20	54.29
18	12.84	12.83	14.20	14.07	12.47	18.35	18.37
19	34.83	34.86	18.38	18.36	19.08	26.03	26.10
20	40.11	40.07	40.01	40.10	40.03	40.17	39.99
21	21.09	21.07	20.62	20.63	20.87	21.98	21.94
22	135.86	135.82	135.76	135.32	135.70	136.18	136.08
23	131.79	131.84	131.76	132.05	131.88	131.85	131.88
24	42.84	42.85	42.84	42.62	42.89	42.98	42.97
25	33.13	33.11	33.10	33.08	33.12	33.18	33.15
26	19.66	19.64	19.67	19.68	19.67	19.67	19.68
27	19.97	19.96	19.98	19.89	19.99	20.03	20.03
28	17.65	17.64	17.64	17.33	17.70	17.70	17.68
1'		135.56		134.82			130.81
2'		129.42		129.54			129.53
3'		148.68		148.82			128.42
4'		122.22		122.39			132.79
5'		148.68		148.82			128.42
6'		129.42		129.54			129.53
7'		162.17		161.97			166.18

occurred as a broad singlet at 3.65τ , whilst at 220 MHz the absorption could be analysed as a strongly coupled AB sub-spectrum, and indicated that the two protons were in a cis relationship.

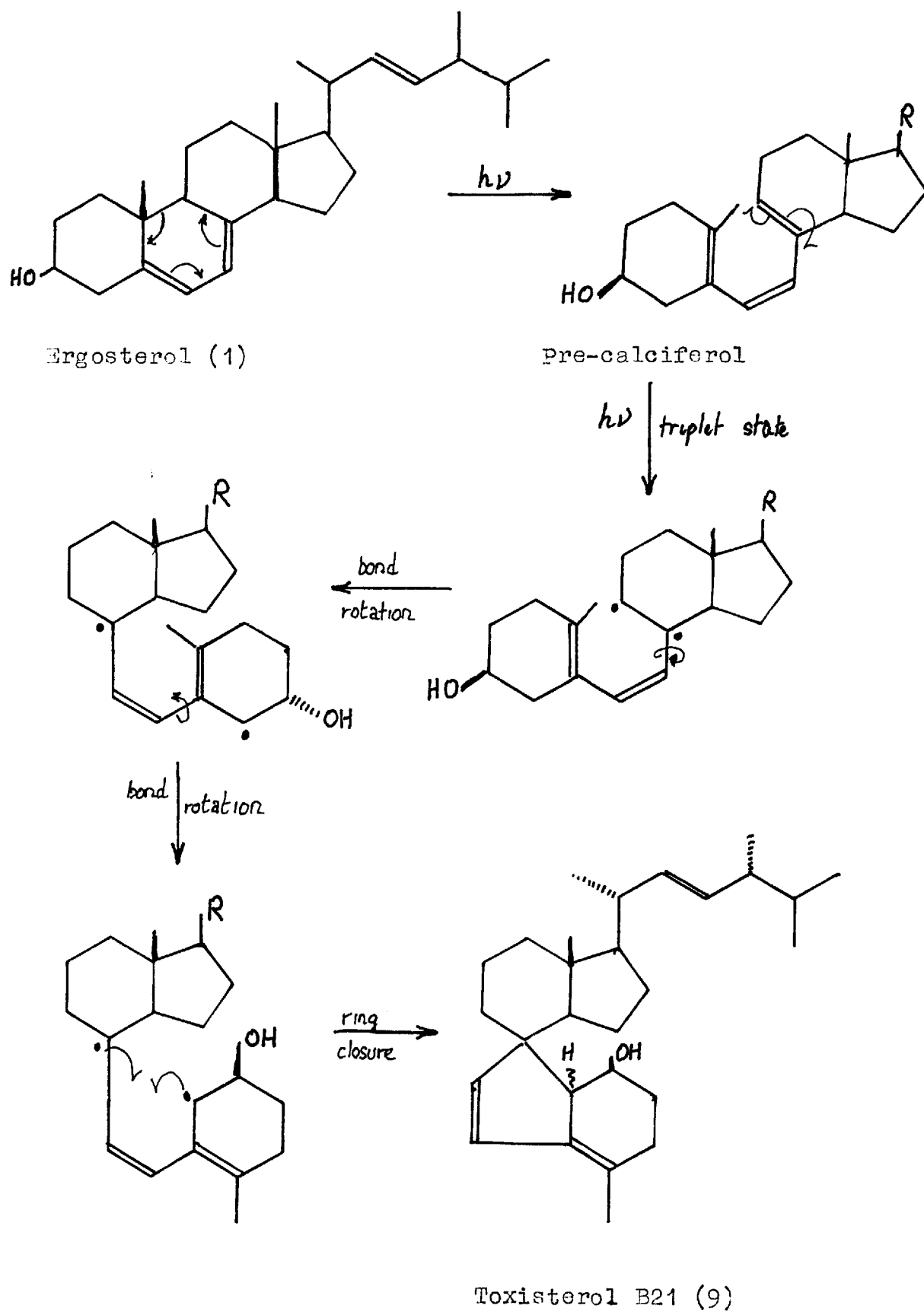
Detailed analysis of the off-resonance ^{13}C spectra enabled all the carbon resonances to be classified into methyl, methylene, methine and quaternary centres, and indicated the molecule contained a total of $6(\text{CH}_3-)$, $7(-\text{CH}_2-)$, $7(>\text{CH})$, $4(\text{CH}=\text{C})$, $2(>\text{C}-)$ and $2(>\text{C}=\text{C})$ units.

The second quaternary aliphatic resonance identified from the off-resonance spectra occurred at 54 ppm. Since the C_{10} carbon at the A/B ring junction of ergosterol (bearing the C_{19} angular methyl group) resonates at considerably higher field (37.4 ppm, table 1), it seems unlikely that the junction between the new A and B rings bears much resemblance to a normal steroid.

The 220 MHz proton NMR spectrum contains four doublet methyl resonances arising from the side chain methyl groups, together with the singlet absorption for the C_{18} methyl group at 9.15τ , which is somewhat to lower field than that observed for C_{18} in ergosterol (9.4τ) and is in keeping with the suggested structural disturbance in this region. A further strong singlet methyl absorption occurred at 8.25τ and could possibly arise from an olefinic methyl group.

One of the initial products²¹ obtained upon photolysis of ergosterol (1) is precalciferol, via ring B opening, and on the basis of the above observations, it was possible to propose²² a structure for toxisterol B_{21} , based on this intermediate. The proposed reaction and structure are depicted in scheme 1, and the number system for the toxisterol is taken from its ergosterol parent and given in figure 10.

It will be seen from scheme 1 that the stereochemistry about C_8 and C_4 , involved in the final step of ring closure, cannot be defined mechanistically. Inspection of Dreiding models reveals that for the two diastereomeric possibilities at the spiro centre C_8 , that with the $\text{C}_6\text{-C}_7$ double bond above the C-D ring surface (β face) will force

Scheme 1. Formation of toxisterol B₂₁

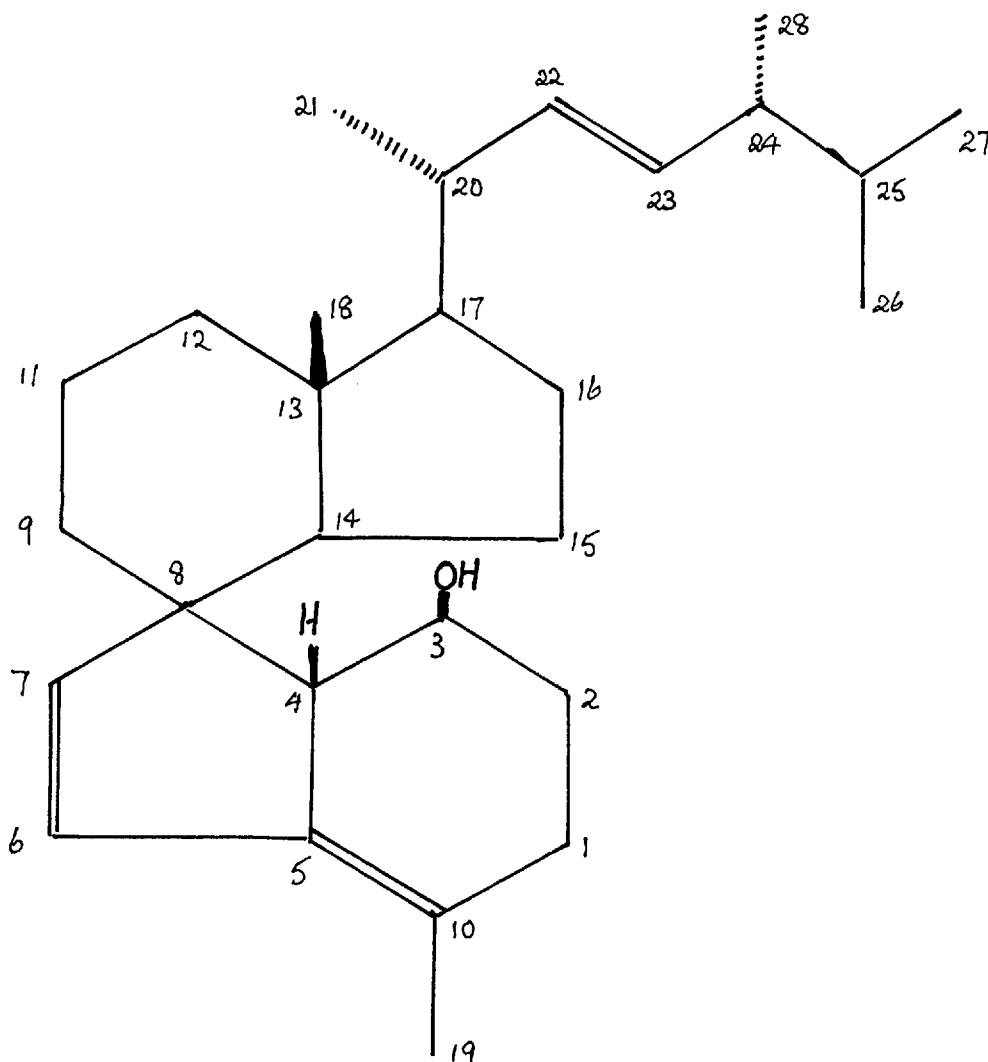


Figure 10. Nomenclature of toxisterol B₂₁.

the C₇ proton into close proximity with the C₁₈ angular methyl group. such an interaction could account for the perturbations of the ¹³C chemical shifts of C₁₃ and C₁₈ discussed above, and would be expected to produce a homonuclear proton Nuclear Overhauser Effect (NOE) between the two groups.

Such an effect was readily detected in the 100 MHz proton spectrum. Strong irradiation of the C₁₈ methyl group at 9.15 τ produced an enhancement in the olefinic proton signal at 3.70 τ of 17.5%, measured against that arising from the residual CHCl₃ in the CDCl₃ solvent. Because this olefinic absorption is produced by two protons and only one can be providing the NOE, the observed effect corresponds to a true NOE of 35%, and confirms that the geometry at C₈ is as described above, with strong interaction between the C₇ proton and the C₁₈ angular methyl group.

It is now possible to confirm the structure proposed for toxisterol B₂₁ from ¹³C NMR data. Values of "ester shifts" obtained from a comparison of 2 and 2a served to identify those carbons near the hydroxyl functionality, and were complemented by lanthanide induced shift (LIS) data obtained from incremental addition of Eu(fod)₃ to the alcohol (2), in a manner analogous to that described for the model compounds. Table 8 gives the values of δ_{Eu} , the value of the LIS extrapolated to a relative concentration of toxisterol:Eu(fod)₃ of 1.0 M.

As discussed above, all the side chain resonances, together with carbons 18 and 13 could be identified by direct comparison with model compounds via table 1. The spiro centre C₈ must be the second quaternary resonance observed to low field of C₁₃. A good estimate of its position can be obtained through consideration of C₈ as a derivative of a 3,3-disubstituted cyclopentene, which yields a value of 50.8 ppm, in good agreement with the observed chemical shift of 54 ppm, especially when no allowance has been made for the conjugated system and other substituents.

The olefinic methyl group C₁₉ must be the unassigned CH₃-absorption at 18.37 ppm, and in keeping with the corresponding proton resonance at 8.25 τ .

Preliminary identification of carbons 14 and 17 has been made above. C₁₇ is remote from C₈, the point of attachment of ring B, whilst C₁₄ is α to the spiro centre and hence closer to the C₃ hydroxyl function. Consequently, it is expected that C₁₄ will exhibit a greater LIS value than C₁₇ (table 8) and the assignments recorded in table 9 are made accordingly.

The structural environment of C₁₂ differs little from that in the model compounds, and hence this absorption could be identified by suitable comparisons from table 1. Similar remarks apply to C₁₁, which is assigned to the highest field methylene resonance, as is to be expected from the steric interactions of the C₁₁ hydrogen with the C₁₈ angular methyl group and the C₇ hydrogen.

Suprasterol II (6) and its tetrahydro-derivative (7), both with C_8 spiro centres, provided good models for the structural environment of carbons 15 and 16 in ring D, and enabled these resonances to be distinguished readily as indicated in table 9, where the assigned lines correspond to those for (6) to ± 0.1 ppm.

This completes the assignments of resonances for ring C (with the exception of C_9), ring D and the side chain, and attention may now be directed to the new A and B rings. Carbon 3 bears the electronegative hydroxyl function and must be the lowest field sp^3 resonance, with an esterification shift of 6.68 ppm.

Carbons 1, 2 and 4 can be differentiated from C_9 via the combined use of esterification shifts and LIS data. Carbon 2 is expected to undergo an upfield shift on esterification of 3-4 ppm (see Figs 3 - 6), and additionally to possess the largest value of δ_{Eu} for the three methylene resonances to be distinguished. Carbon 1 should also experience an esterification shift, which is expected to be ca. 1 ppm, but the observed value (table 8) of -0.59 ppm for the resonance at 33.85 ppm (9) is comparable to that recorded for the other unassigned methylene resonance at 31.52 ppm (-0.48 ppm). The problem was resolved by resorting to the LIS data (table 8) where the considerably larger value of δ_{Eu} obtained for the former resonance enabled its assignment to C_1 , and the latter to C_9 .

Carbon 4 must be the unassigned methine resonance at 54.05 ppm and possesses an upfield esterification shift of 3.3 ppm, comparable to that for C_2 , as expected from the above work (figures 3-6). However, examination of the LIS data (table 8) reveals that C_4 has a value of δ_{Eu} less than one third that for C_2 which indicates that the bulky shift reagent is not symmetrically disposed about the plane of the H_4-C_4-OH bond.

Although the geometry of the lanthanide-toxisterol complex is unknown, and the stereochemistry about C_4 is as yet undefined, it is possible to suggest (through the inspection of molecular models) that if the C_4 hydrogen were on the β face (C_3 has β OH) i.e. H_3 and H_4

this assignment, with the value of δ_{Eu} obtained for C_5 being about four times as large for C_5 than C_{10} . The high field position of C_5 (122.8 ppm in 10) is ascribed to the structural strain produced at the A-B ring junction by the fusion of the cyclopentane and cyclohexane rings.

Carbons 6 and 7 exhibit comparable ester shifts and LIS data, and hence it is difficult to distinguish between the two centres on this basis. However, it is possible to obtain an approximation to the chemical shift of C_7 if the $\text{C}_6\text{-C}_7$ double bond is treated as an isolated unit. Data obtained²⁵ from 4,4-dimethyl pent-2-ene ($\text{CH}_3\text{.CH=CH-Bu}^t$, where C_4 is compared to C_8 in the toxisterol), suggest C_7 should resonate at ca. 142 ppm. The assignments indicated in table 9 complete the identification of carbon resonances for toxisterol B21.

5.2.3. Toxisterol B22.

The ^{13}C spectrum of Toxisterol B22 (10) is generally very similar to that recorded for B21 (9, see Table 9) and off-resonance spectra indicate the former compound is composed of the same combination of $\text{CH}_3\text{-}$, $\text{-CH}_2\text{-}$, >CH , >C- and sp^2 carbons as the latter. The 220 MHz ^1H spectrum has similar features to that of 9, with an allylic methyl group at δ 8.25 τ and a pattern of methyl group absorption at δ 8.9-9.4 τ comparable to those of ergosterol. Two olefinic protons resonate at δ 3.84 τ and 4.63 τ : this system is first order with $J_{\text{AX}} = 5.5$ Hz, indicating the protons are in a cis geometry. Irradiation of the allylic methyl group failed to produce any detectable NOE of the olefinic protons.

Arising from these observations, it may be concluded that B22 has the same structural framework as B21 and is a stereoisomer of it, possessing different stereochemistry at C_8 and possibly C_4 .

Assignment of the carbon resonances is again aided by resort to LIS data, obtained in a manner analogous to that for 9, and the values of the induced shifts extrapolated to equimolar Eu^{III} :sterol concentration are presented in table 8.

Comparison of the ^{13}C spectrum with that of B₂₁ and the model compounds (tables 9 and 1, respectively), enabled ready identification of the ergosterol side chain, together with C₁₁ as the highest field methylene resonance, C₁₂, C₁₄-C₁₇ and the C₁₃ quaternary absorption. Carbon 8 is identified as the second quaternary to low field of C₁₃ and the olefinic methyl group C₁₉ to be the additional -CH₃ absorption at 19.08 ppm: both signals are at comparable positions to those recorded for toxisterol B21. The C₁₈ angular methyl group is the highest field methyl at a position typified for that carbon by the model compounds ergosterol and ergocalciferol, and not to lower field (+1.7ppm) as found for B21. This difference in chemical shift for C₁₈ between the two compounds provides strong circumstantial evidence that there is no intramolecular interaction similar to that found in B21 in B22.

It is now possible to identify the A ring sp^3 carbons. The C₃ hydroxyl function is of course the lowest field aliphatic resonance, and LIS data permits the distinction of C₁ and C₂. The latter (C₂) is expected to absorb to low field of the former (C₁) carbon, for reasons discussed with B21 and the model compounds and the assignments are made accordingly (Table 9).

The remaining aliphatic carbons must be C₉ (methylene) and C₄ (methine) and C₄ (methine) and are confirmed by off-resonance spectra and comparison with B21. It is seen that the chemical shift of C₉ (32.88 ppm) is close to that recorded for B21 (31.52 ppm), whilst C₄ at the AB ring junction has been displaced upfield 9.48 ppm with respect to the analogous carbon in B21. These differences most probably arise from the variations in stereochemistry between the two toxisterols. it is interesting to note that although C₄ is in a β position to the C₃ hydroxyl function, it has an anomalously low LIS value (Table 9), a

situation similar to that found with B21, for which it was concluded that the Eu^{III} atom was situated in a markedly ~~asymmetric~~^{asymmetric} position with respect to carbons 2 and 4.

The four carbons of the skipped diene system in the A and B rings are initially separated into the individual double bonds by the off-resonance spectra. The $\Delta^{5,10}$ bond must be the two singlet sp^2 resonances and are finally identified by the close agreement found with the chemical shifts for this unit in B21. Carbons 7 and 10 are the two remaining absorptions and comparison of these chemical shifts with those of B21 (9) indicate that the lower-field resonance at 147.82 ppm is 7.12 further downfield than its counterpart in 2, whilst that to high field is seen to be 3.41 ppm to higher field than its counterpart. The low field resonance is ascribed to C_7 and the high field to C_{10} for B21, and the observed changes in chemical shifts are consistent with similar assignments for B22. The chemical shift of C_7 in B21 must be influenced by the strong interaction of its proton with those of the C_{18} methyl group. Relief of this intramolecular force in B22 by inversion of the stereochemistry at C_8 will produce a larger effect at C_7 than C_6 , and the differences found here substantiate such a proposal.

5.2.4. Toxisterol B31 and benzoate ester (11 & 11a).

This compound is chemically similar to the other toxisterols, and the nmr data confirm this to be true. Thus in the 220 MHz ^1H spectrum, specific items of interest are the presence of an allylic methyl group at 8.31 τ , and a two proton olefinic system as a pair of doublets at 3.62 and 3.91 τ , with $J_{\text{AX}} = 6$ Hz, comparable to that found for B22. The ^{13}C spectrum is also very similar, both with respect to the pattern of chemical shifts observed and the composition of the molecule in terms of carbon types (CH_3 -, $-\text{CH}_2$ -, $\rightarrow\text{CH}$ -, $\rightarrow\text{C}$ - and sp^2) as revealed by off-resonance spectra.

Consequently this toxisterol was deduced to be structurally identical with B21 and B22, and must hence be a stereoisomer of these compounds. Although LIS data are not available it is possible to make a full assignment of the carbon resonances, with ester shifts providing a indication of the 'A' ring.

The ergosterol side chain carbons C_{20} - C_{28} are identified readily by comparison with the model compounds and the other toxisterols (tables 1 and 9). The C_{18} angular methyl group must be the higher field of the two remaining methyl signals at 18.3 ppm, which is 4.2 ppm downfield from its position typified by the model compounds and toxisterol B21. The allylic methyl group C_{19} is also found considerably to low field (7.6 ppm) of the shift recorded for both of the other toxisterols; it is concluded that these changes must result from the changes in stereochemistry at C_4 and C_8 for this compound with the other toxisterols, which accordingly modify the spatial interactions experienced by these methyl groups.

Further comparison with the model compounds and other toxisterols enables identification of C_{11} as the highest field methylene resonance, C_{12} , the two quaternary carbons C_{13} and C_8 , and the C_3 hydroxyl bearing carbon. Carbons 15 and 16 in the D ring can also be distinguished as the remaining signals in the 20 - 30 ppm region, although absorbing upto 2 ppm to lower field than observed for B21 and B22. Carbon 17, at the junction of the side chain with ring D, is remote from the C_8 spiro centre, and is thus expected to have a chemical shift similar to that found for the model compounds and other toxisterols and possess a negligible ester shift: hence this carbon is assigned to the methine resonance at 54.2 ppm. In contrast to this, carbon 14, at the C/D ring junction is α to C_8 and hence its chemical shift may differ markedly from the value exemplified by the other toxisterols: the methine resonance at 48.3 ppm has a negligible ester shift (which serves to separate it from neighbouring signals) and is accordingly assigned to C_{14} . This latter position for C_{14} is 7.5 ppm to high field of that found in toxisterols B21 and B22 and demonstrates the marked dependence of this carbon chemical shift on the neighbouring structural

environment.

The sp^3 carbons in the A ring (C_1, C_2 and C_4) are now identified from comparison of the spectra of the free alcohol and benzoate as those signals with large ester shifts (greater than 1 ppm). As discussed for other compounds, C_2 is expected to absorb to lower field than C_1 , and the larger ester shift (-2.23 ppm) observed for the resonance at 34.00 ppm (10) confirms this assignment. Hence C_1 must be the higher field methylene carbon as listed in table 9, with a smaller ester shift (-1.79 ppm). These large ester shifts separate these methylene carbons from the C_9 absorption, and hence distinguish this carbon as the remaining methylene signal. Carbon 4 is β to the C_3 hydroxyl function and thus is expected to exhibit an ester shift comparable to that of C_2 , i.e. 2 - 3 ppm. Comparison of the chemical shifts for (11) and (11a) indicates C_4 must be the methine absorption at 59.73 ppm (11) with an esterification shift of -2.47 ppm. This is some 5 ppm to lower field than the analogous absorption for B21, and 9 ppm lower than in B22, and must be a consequence of the difference stereochemistry at C_4 and/or C_8 compared with the other toxisterols. These changes are of such magnitude as to bring this signal downfield into the region (56 - 59 ppm) normally associated with C_{14} and C_{17} , and underlines the need for caution in the assignment of carbon chemical shifts, which can only be made unambiguously with the aid or corroborating information such as esterification shifts.

The four olefinic carbons of the butadiene system in rings A and B cannot be assigned other than by comparison with the other toxisterols, and since all four shifts are within one ppm of those for B21, the signals are identified accordingly. The only absorption to show an appreciable esterification shift is that to highest field (0.54 ppm for the 120.72 ppm signal), which is reasonable for a carbon in a γ relationship to the -OH function and confirms this to be carbon 5.

5.3. Experimental.

Carbon-13 spectra were obtained at 25.16 MHz using a Varian Associates XL-100-12WG spectrometer in Fourier Transform mode. Deuterio-chloroform, purified by standing over potassium carbonate (anhyd.) and degassed with oxygen free nitrogen, was used as solvent, and solution concentrations were typically in the range 50 - 150 mg sterol/2.0 ml CDCl₃. Full proton decoupling was obtained by use of the Gyrocode decoupler with a noise bandwidth of 1 KHz centred 4 ppm downfield from TMS, and a power of 4w, whilst off-resonance spectra were recorded with full proton decoupler power (12 w) centred 1 - 2 ppm to high field of TMS. All spectra were recorded at 25°C.

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BARRIERS TO ROTATION ABOUT C—N BONDS—I: ROTATION ABOUT THE C—N BOND IN MONO-, DI- AND TRIFLUOROACETAMIDE, AND DEUTERIUM ISOTOPE EFFECTS UPON ^{19}F SHIELDING

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Abstract—The ^{19}F NMR spectra of mono- and difluoroacetamide are used to derive the activation parameters for rotation about the C—N bond; it is not possible to obtain useful results for trifluoroacetamide. A total line shape analysis is used.

Unusually large deuterium isotope effects upon the shielding of the ^{19}F nucleus are observed for *N*-deuterated derivatives. The magnitude of the isotope effect is different for mono-, di- and trifluoroacetamides, and in the mono-deuterated species the isotope effect is different for *cis* and *trans* rotational isomers.

INTRODUCTION

RECENT work in this laboratory¹ has indicated the existence of long-range substituent effects upon the barrier to rotation about the C—N bond in ring-substituted *N,N*-dimethylphenylacetamides. In common with many previous studies of such energy barriers² the temperature variation of the ^1H NMR spectrum of the N—CH₃ groups was studied, and the thermodynamic parameters obtained by line shape analysis in the region between slow and fast exchange.³ It has become desirable to study the long-range effects in the more interesting series of ring-substituted phenylacetamides, XC₆H₄CH₂C(O)NH₂, but the rapid relaxation of the hydrogen spins due to the quadrupolar ^{14}N nucleus causes such a degree of broadening of the N—H lines in the spectrum that it is not possible to study the effects of temperature variation without recourse to heteronuclear (N—H) spin decoupling or ^{15}N enrichment.⁴

Work to date has always concentrated upon the NMR spectrum of the N-substituents, but the protons of the αCH_2 group would be of use in such studies if they were involved in long-range coupling with the N—H protons, since such coupling may be stereospecific and reflect the *cis* or *trans* relationship between the coupled species. Unfortunately such long-range couplings between protons are not usually resolvable; however, if there is a fluorine atom substituted on the α -carbon the variation of the much larger F—H coupling, FCH₂.C(O)NH₂, with temperature may yield the necessary information. In a preliminary study, it was decided to examine the ^{19}F spectra of the title compounds in order to measure the barriers to rotation about the C—N bonds in these compounds. It was also decided to study *N*-deuterated derivatives in an attempt to consider isotope effects upon the magnitude of the barrier and the ^{19}F NMR spectrum.

EXPERIMENTAL

NMR measurements were carried out with a modified Varian HA-100 NMR spectrometer operating at 94.1 MHz in extended-lock mode with automatic phase correction.⁵ Materials were dissolved in dimethylformamide, together with hexafluorobenzene as an internal standard for locking purposes. Chemical shifts were measured by the frequency difference technique using a Beckmann frequency

counter. Temperature was varied using a standard Varian Associates variable temperature probe and controller; measurements are believed to be accurate to within $\pm 1^\circ\text{C}$, the range being calibrated using the normal techniques employing ethylene glycol and methanol. The fluorinated amides were prepared from the corresponding ethyl fluoroacetate and ammonia by standard procedures;⁶ their identity and purity was established by comparison with the literature, by spectroscopic studies and by microanalysis.

RESULTS AND DISCUSSION

Monofluoroacetamide:

Figure 1 shows the ^{19}F NMR spectrum of this compound, dissolved in dimethylformamide, at several temperatures; (a) is in the region where rotation about the C—N bond is slow, (b) where rotation is of intermediate rate and (c) where rotation is fast. The changes were observed to occur in a variety of solvents (e.g. methanol, chloroform, methylene dichloride and dimethylsulphoxide) at similar temperatures, but no attempt was made to evaluate the thermodynamic parameters in these situations.

Figure 1a shows the expected triplet ($J = 47$ Hz) due to *geminal* spin-spin coupling between H and F in the CH_2F group. The component lines of the triplet are further split into doublets ($J = 4.5$ Hz) due to coupling to just one of the N—H protons, the

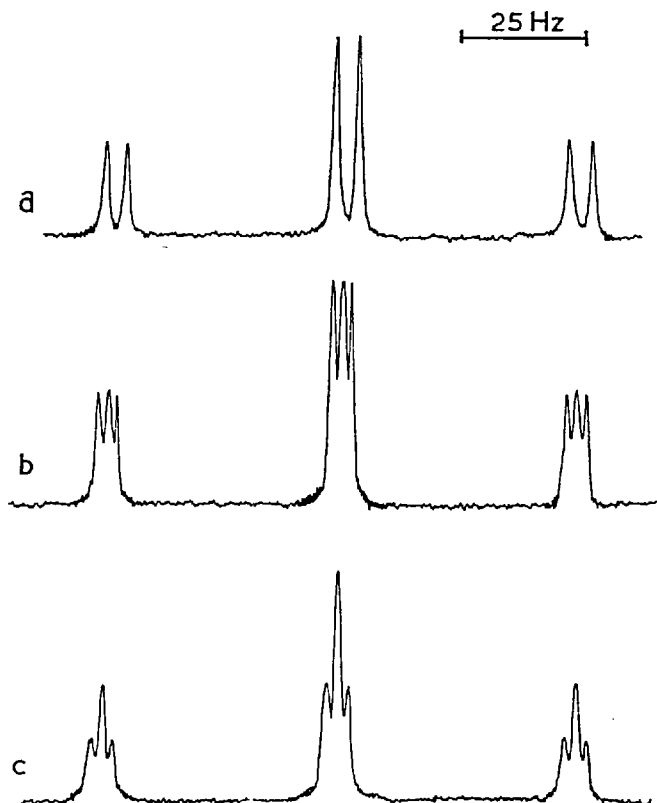
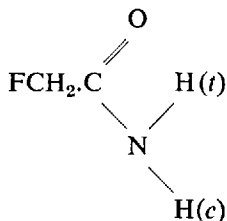


FIG. 1. The ^{19}F NMR Spectrum of Fluoroacetamide under conditions of (a) slow, (b) intermediate and (c) rapid exchange.

coupling to the other being too small to resolve (<0.3 Hz). It is impossible to say unequivocally which of the two N—H protons (*cis* or *trans* to the CH_2F group,



is involved in the coupling; Akiyama *et al.*⁷ assume that in

trifluoroacetamide the *trans* coupling is the larger, but if the double-bond order of the C—N bond is large (as indicated by the high barriers to rotation usually observed in such situations²) the four-bond F—H coupling may be of the 'allylic' type, in which case the assignment could well be reversed.⁸ Under rapid rotation conditions (Fig. 1c), the doublet structure ($J = 4.5$ Hz) changes to a triplet ($J = 2.25$ Hz); this is due to averaging of the long-range couplings and hence the spectral variations in the region of intermediate rotation (e.g. Fig. 1b) should be analysable to yield the thermodynamic activation parameters for the rotation process. If these lines are considered to arise from the X components of the ABX sub-spectra of the total spin system, the changes under these intermediate conditions are as predicted by the work of Forsen *et al.*;⁹ the outer lines (of separation 4.5 Hz) diminish in size without changing their position, and in their centre a third line develops and increases in intensity to form the triplet ($J = 2.25$ Hz) due to equal (averaged) coupling between the fluorine and the N—H protons. At high temperatures, the fine structure disappears, although the width of the lines does not diminish; this may be due to the onset of intermolecular exchange of the N—H hydrogen atoms, or may arise from the increased efficiency of the ^{14}N quadrupolar relaxation process at high temperatures.¹⁰

The density matrix method, using the DENSMAT program of Forsen *et al.*⁹ was used to simulate the spectra at a variety of temperatures in the intermediate exchange situation (33 to 71.5°) and to evaluate the thermodynamic parameters for activation of the rotation process, quoted in Table 1.

Diffuoroacetamide

At low temperatures the doublet ($J = 54.5$ Hz) due to *geminal* H—F coupling showed a doublet fine structure ($J = 2.0$ Hz), which changed to a broadened triplet ($J = 0.75$ Hz) at higher temperatures. The spectrum in the intermediate-exchange situation was analysed by DENSMAT and the thermodynamic parameters derived are quoted in Table 1.

Trifluoroacetamide

Although at low temperatures the ^{19}F spectrum showed a doublet splitting ($J = 1.65$ Hz) due to stereospecific long-range coupling to one of the N—H protons,

TABLE 1. ACTIVATION PARAMETERS FOR ROTATION ABOUT THE C—N BOND IN FLUORO-AMIDES

Compound	$\Delta E_a(\text{kJ mole}^{-1})$	$\Delta H(\text{kJ mole}^{-1})$	$\Delta S(\text{J deg}^{-1} \text{ mole}^{-1})$
Monofluoroacetamide	66.1	64.0	-17.2
Diffuoroacetamide	81.2	78.3	+6.3

the change to a triplet structure on increasing the temperature was not well behaved and could not be analysed by the procedures used for the other amides. The separation of the outer lines does not remain constant and this probably reflects significant inter-molecular exchange, as indicated by the work of Akiyama *et al.*⁷

To summarise, analysis of the fluorine signal gives a satisfactory method of establishing rotation barriers in fluorinated amides and some data are shown in Table 1. The presence of two fluorines on the α sp^3 carbon atom (in difluoroacetamide) causes a significant increase in the rotation barrier for the C—N bond, compared with the monofluorinated molecule; it seems probable, then, that such studies in α -X-fluoroacetamides may give information about the effects of α -substitution upon the C—NH₂ rotation barrier. The change is large enough to indicate that long range substituent effects in ring-substituted phenylfluoroacetamides may also be studied using this technique.

Deuterium isotope effects

Attempts were made to study the effect upon the barrier of replacing the NH protons by deuterium; unfortunately the coupling between the fluorine and the D nuclei is too small to be of use, and even in the absence of rotation (i.e. at very low temperatures) the ¹⁹F spectra of the *N,N*-dideutero-fluorinated amides appear with only slightly broadened lines. It was, however, observed that a significant deuterium isotope effect occurs upon the shielding of the fluorine and it was decided to study the mono-deuterated analogues for comparable effects; by adding one drop of D₂O to a dilute solution of fluoroacetamide in a suitable solvent, the spectra of mono-, di- and undeuterated materials may be studied simultaneously. Figure 2 shows the ¹⁹F NMR spectra for mono-, di- and trifluoroacetamide recorded in this way, and Table 2 lists the chemical shifts of the ¹⁹F nuclei (relative to the undeuterated species) of the various compounds in a variety of solvents.

The deuterium isotope effects are additive and large. For example, in dichloromethane at 94.1 MHz the ¹⁹F signal of mono-*N*-deutero-fluoroacetamide occurs at 13.3 Hz to high field of the non-deuterated material and that of the di-*N*-deutero compound occurs at 27.0 Hz to high field. The magnitude of the 'isotope shift' only depends to a small extent upon the solvent in which the observation is made; for monofluoroacetamide, the shift is 12.4 Hz per D in methanol, 13.5 Hz per D in dichloromethane and 12.5 Hz per D in dimethylformamide. Apparently, hydrogen bonding ability and polarity of the solvent have little effect upon the size of the isotope effect.

The magnitude of the isotope shift does depend significantly upon the number of fluorines in the molecule, however. On average it is 12.8 Hz per D in monofluoroacetamide, 5.9 Hz per D in difluoroacetamide and 3.3 Hz per D in the trifluoro

derivative. Apparently, in a molecule of general formula
$$\begin{array}{c} \text{a} \\ | \\ \text{F}-\text{C}-\text{C}(\text{O})\text{NH}_2(\text{D}_2) \\ | \\ \text{b} \end{array}$$

the deuterium isotope effect upon the shielding of F depends upon the nature of a and b; further studies will be necessary in order to evaluate the form of this dependence, but the implication may be that it arises from the dependence of a through-bond

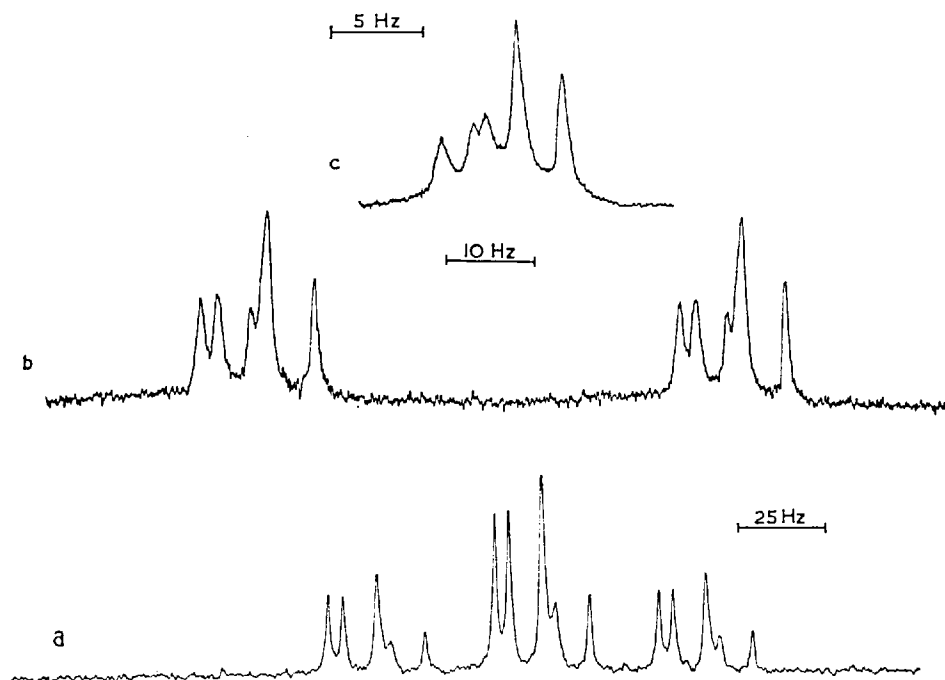


FIG. 2. The ^{19}F NMR spectra of mixtures of un-, mono- and di-deuterated amides: (a) monofluoroacetamide, (b) difluoroacetamide and (c) trifluoroacetamide.

TABLE 2. ^{19}F DEUTERIUM ISOTOPE SHIFTS OF THE FLUORO-AMIDES

Compound	Methanol		Dichloromethane		Dimethylformamide	
	NHD	ND ₂	NHD	ND ₂	NHD	ND ₂
FCH ₂ ·CO·NHD <i>cis</i>	12.75		14.1		13.75	
<i>trans</i>	11.75		12.5		11.5	
FCH ₂ ·CO·ND ₂		24.75		27.0		25.0
F ₂ CH·CO·NHD <i>cis</i>	5.6		6.6		5.3	
<i>trans</i>	6.4				6.0	
F ₂ CH·CO·ND ₂		11.8		12.6		11.2
F ₃ C·CO·NHD <i>cis</i>	singlet		3.0		2.6	
<i>trans</i>			3.9		3.4	
F ₃ C·CO·ND ₂				6.9		6.1

All shifts are in Hz at 94.1 MHz and 33°C, and are to high field of the undeuterated material.

perturbation to the environment of the fluorine as has recently been discussed for other substituents.¹¹ It is also significant that in the mono-deuterated species the *cis* and *trans* isomers about the C—N bond show different isotope effects. Thus, in the mono-*N*-deutero fluorinated acetamides the components of the ^{19}F signal consist of a singlet and a doublet which are not centred at the same position; this is due to a chemical shift between the species in which the deuterium is *cis* with respect to the alkyl group and that in which it is *trans*. This phenomenon has been observed previously in the case of trifluoroacetamide⁷ and if the assignment of that work is accepted, then it may be deduced that in the case of monofluoroacetamide the D *trans* isomer occurs 1.6 Hz

to low field of the D *cis*; in the case of di- and trifluoroacetamide the D *trans* isomer absorbs to high field of the D *cis* isomer, by 0.7 Hz and 0.9 Hz respectively.

A possible origin for the effects observed in the present work could lie in the different hydrogen-bonding abilities of N—H and N—D bonds, which would cause different solvation in hydrogen-bonding solvents. The experimental results are so similar in a variety of solvents, however, (CH_2Cl_2 , CH_3OH , $\text{HC(O)N(CH}_3)_2$ and $(\text{CH}_3)_2\text{C=O}$), that this suggestion seems to be untenable. A further possibility might lie in different averaging about the zero-point in the potential-energy surface for rotation about the C—N bond, even in a fixed (non-rotating) conformation.* It is felt, however, that the dependence upon the nature of the C-substituents and the stereo-specificity of the effect in the mono-*N*-deuterated molecules demand some other explanation.

There are similarities between these observations and the much larger *vicinal* deuterium isotope effects reported for fluoro-olefins.¹² In *cis* 1,2-difluoroethylene for example, replacement of H by D causes a shift to high field of the *vic trans* ^{19}F signal by 0.418 ppm; in *trans* 1,2-difluoroethylene replacement of H by D causes a high field isotope shift of 0.293 ppm of the *vic cis* ^{19}F signal. In 1,1-difluoroethylene the *trans* isotope effect is 0.260 ppm, while the *cis* isotope shift in the same molecule is 0.210 ppm. Thus, the magnitude of the isotope effect decreases with the number of fluorine atoms in the group ($\text{CFH} > \text{CF}_2$) and *trans* effects are bigger than *cis*. These trends are paralleled by the longer-range (four-bond) isotope shifts in the fluorinated amides, although the extra bond (or distance) involved causes marked attenuation. A common origin is indicated, but theories of such isotope shifts are not well-developed.¹³

Phillips and Wray¹⁴ have recently offered an explanation for the difference between *cis* and *trans* substituent effects upon ^{19}F shielding in fluoroolefins. This work suggests that the difference arises from the fact that in such systems there is *vicinal* delocalisation of sigma electrons, characterised by a negative long-range double-bond order for a *cis* arrangement of bonds and a positive long-range bond order for a *trans* arrangement.^{15,16} Pople and Segal¹⁶ point out that qualitatively this corresponds to anti-bonding (or repulsion) between *cis* atoms and bonding (or attraction) between *trans*. The origin of the finite bond order lies in the non-zero value of a direct bond integral, β , between non-formally bonded substituents, the magnitude of which depends upon the proximity of the interacting species;¹⁶ since C—D bonds are considerably shorter than C—H bonds¹⁷ the long-range bond orders will diminish upon deuteration and this may be sufficient to cause the observed increase in the shielding of *vicinal* fluorines observed in the deuterio-fluoroethylenes. Presumably in the case of the four-bond effects observed in the *N*-deuterio-fluoroacetamides, the perturbation is directly to the environment of the carbon atom, but is relayed to the fluorine and hence attenuated; it will be interesting to observe the magnitude of the isotope effects upon the shielding of the carbon nucleus, but such data are not presently available.

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The Structural Dependence of the Inductive Effect. Part VII.¹ Effects of 1-Substituents upon Geminal Proton-Fluorine Spin-Spin Coupling Constants ($^2J_{\text{FH}}$)

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The Structural Dependence of the Inductive Effect. Part VII.¹ Effects of 1-Substituents upon Geminal Proton-Fluorine Spin-Spin Coupling Constants ($^2J_{\text{FH}}$)

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A detailed empirical analysis has been made of the nature of 1-substituent effects upon $^2J_{\text{FH}}$ in situations where the nuclei are bonded to carbon and to silicon. The non-additivity of such effects is explained in terms utilised previously by us in connection with nuclear shielding and a useful, simple, expression is given which enables $^2J_{\text{HF}}$ to be calculated in terms of the Huggins electronegativities of the substituents.

CONSIDERABLE attention has been given recently to theoretical and empirical descriptions of $^2J_{\text{HH}}$ in a variety of systems. Sternhell has reviewed the subject comprehensively,² and a successful theoretical rationalisation has been given by Pople and Bothner-By.³ More

recently, Maciel and his co-workers have made use of Finite Perturbation Theory⁴ to calculate $^2J_{\text{HH}}$ in a wide variety of systems,⁵⁻⁸ and several empirical analyses have also appeared.⁹⁻¹³

In contrast, relatively little attention has been paid

¹ Part VI, L. Phillips and V. Wray, *J.C.S. Perkin II*, 1972, 536.

² S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.

³ J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339.

⁴ J. A. Pople, J. W. McIver, and N. S. Ostlund, *J. Chem. Phys.*, 1968, **49**, 2965.

⁵ G. E. Maciel, J. W. McIver, N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 4151, 4497.

⁶ P. D. Ellis and G. E. Maciel, *J. Amer. Chem. Soc.*, 1970, **92**, 5829.

⁷ P. D. Ellis and G. E. Maciel, *Mol. Phys.*, 1971, **20**, 433.

⁸ G. E. Maciel and K. D. Summerhays, *J. Amer. Chem. Soc.*, 1971, **93**, 520.

⁹ M. J. Lacey, C. G. Macdonald, A. Fross, J. S. Shannon, and S. Sternhell, *Austral. J. Chem.*, 1970, **23**, 1421.

¹⁰ P. J. Chivers and T. A. Crabb, *Tetrahedron*, 1970, **26**, 3389.

¹¹ P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc. (B)*, 1971, 1320.

¹² G. Swaelens, M. Anteunis, and T. Travernier, *Bull. Soc. chim. belges*, 1970, **79**, 441.

¹³ M. Anteunis, G. Swaelens, and J. Gelan, *Tetrahedron*, 1971, **27**, 1917.

to $^2J_{\text{HF}}$ although there have been several attempts^{10,14-16} to calculate this parameter for simple situations using both Finite Perturbation Theory⁴ and the 'Sum Over States' method.¹⁷ The various methods give widely varying results for even the simplest of molecules, CH_3F , depending upon the form of the wavefunctions utilised, and only the results of Ditchfield and Snyder¹⁴ are in reasonable agreement with experimental data. All calculations are in accord with the earlier suggestion by Pople¹⁸ that the Fermi-contact mechanism dominates the coupling, and the calculated contribution of 17% of the observed total arising from the spin-orbital mechanism has been verified by later work.¹⁴ There has as yet been no theoretical study of the influence of substituents upon $^2J_{\text{HF}}$, and the empirical descriptions of the observed trends are rather imprecise.

Arison *et al.*¹⁹ have studied the effect upon $^2J_{\text{HF}}$ of varying the substituent X in compounds of the type CHF_2X , and have shown that the magnitude of this parameter increases markedly with increase in electronegativity of X. Substituent effects are non-additive however, as may be seen from the fact that successive replacement of hydrogen in CFH_3 by fluorine causes a non-linear increase in $^2J_{\text{HF}}$:

	CH_3F ²⁰	CH_2F_2 ²¹	CHF_3 ²²
$^2J_{\text{HF}}$	46.3	50.4	79.7

Frankiss²³ observed that in compounds of the type SiHFX_2 , $^2J_{\text{HF}}$ also increases with increase in the electronegativity of the substituents X and Y and thereby deduced that the sign of the coupling must be the same as in the analogous carbon compounds. He commented, however, that the situation is by no means simple since substituent effects are not additive.

We have observed interesting variations in $^2J_{\text{HF}}$ as a result of substituent changes in several related series of molecules (see later), and decided to examine the possibility of obtaining a generally applicable qualitative picture of substituent effects upon this parameter.

EXPERIMENTAL AND RESULTS

Monofluoro-, difluoro-, bromofluoro-, chlorofluoro-, and 1-fluoro-1-methyl-acetamides, -N-methylacetamides, and -NN-dimethylacetamides were prepared by the standard procedure from the appropriate methyl or ethyl ester and amine. Many of the compounds are new, and the details of synthesis will be described elsewhere.¹⁹ ^{19}F and ^1H N.m.r. spectra were recorded with a Varian HA-100 spectrometer operating in field-frequency locked mode. Dilute solutions (ca. 5% w/v) of each compound in deuteriochloroform were studied at normal probe temperature (31 °C) and line positions were measured, in spectra recorded using 100 Hz sweep width, with a frequency counter. The

¹⁴ R. Ditchfield and L. C. Snyder, *J. Chem. Phys.*, 1972, **56**, 5823.

¹⁵ H. Nakatsuji, I. Morishima, H. Kato, and T. Yonezawa, *Bull. Chem. Soc. Japan*, 1971, **44**, 2010.

¹⁶ A. D. C. Towl and K. Schaumburg, *Mol. Phys.*, 1971, **22**, 49.

¹⁷ Y. Kato and A. Saika, *J. Chem. Phys.*, 1967, **46**, 1975.

¹⁸ J. A. Pople, *Mol. Phys.*, 1958, **1**, 216.

¹⁹ B. H. Arison, T. Y. Shen, and N. R. Trenner, *J. Chem. Soc.*, 1962, 3828.

values of $^2J_{\text{HF}}$ were taken directly from the spectra, which are first-order in nature, and are reported in Table 1.

TABLE 1

Values of $^2J_{\text{HF}}$ for the substituted acetamides, N-methylacetamides, and NN-dimethylacetamides

X	$^2J_{\text{HF}}$ (calc.)/ Hz	XCHF· CONH ₂ J/Hz	XCHF· CONHMe J/Hz	XCHF· CONMe ₂ J/Hz
H	46.6	46.5	47.0	47.0
Me	48.4	49.6	50.6	49.6
Br	49.0	51.0	51.3	
Cl	50.8	51.6	51.8	51.4
F	54.1	55.2	53.4	54.6

DISCUSSION

We have made a compilation of coupling constants involving fluorine which will be published elsewhere,²⁴ and in order that our data may be discussed in context we list in Table 2 values taken from this work for typical

TABLE 2

Typical values of $^2J_{\text{HF}}$ in molecules XYCHF

X	Y	$^2J_{\text{HF}}$ /Hz	Ref.
F	F	79.5	22
F	OR	69—75	24
F	Cl	63	a
F	SO_2CF_3	69.5	b
F	$\text{P}(\text{OMe})\text{CF}_3$	50.4	c
F	R	52—62	24
Cl	Cl	53.5	a
R	OR	50—57	24
R	NR_2 , NO_2	42—54	24
R	Cl	47—53	24
R	SR, S^{VI}	43—49	24
R	Br	48—52	24
F	H	50.4	21
R	I	47—48	24
H	SF_6	46	d
Cl	Si^{IV}	46—48	24
R	R	43—55	24
R	PCl_2	46.7	e
R	H	45—50	24
R	Si^{IV}	43—46	24
R	Ge^{IV}	45—46	24
H	H	46.3	20
H	SiMe_3	46.8	f

R = alkyl or substituted alkyl.

^a G. Levi and M. Chalaya, *Compt. rend.*, 1967, **264(B)**, 857.
^b R. A. Mitsch and J. E. Robertson, *J. Heterocyclic Chem.*, 1965, **2**, 152. ^c H. Goldwhite, R. N. Haszeldine, and D. G. Rowsell, *Chem. Comm.*, 1965, 83. ^d H. J. Emeleus and B. W. Tattershall, *J. Inorg. Nuclear Chem.*, 1966, **28**, 1823. ^e J. Dyer and J. Lce, *J. Chem. Soc. (B)*, 1970, 409. ^f G. A. Olah and G. D. Mateescu, *J. Amer. Chem. Soc.*, 1971, **93**, 781.

ranges of $^2J_{\text{HF}}$ observed in a wide variety of molecules of the type XYCHF. It is apparent that, qualitatively at least, $^2J_{\text{HF}}$ does increase with increase in the electronegativity of the groups X and Y; the Figure illustrates this in a plot of the data of Table 2 against the sum of the Huggins electronegativities of the groups X and Y (for composite groups, the electronegativity of the atom bonded to the coupling fragment is used). The data

²⁰ T. R. Krugh and R. A. Bernheim, *J. Chem. Phys.*, 1970, **52**, 4942.

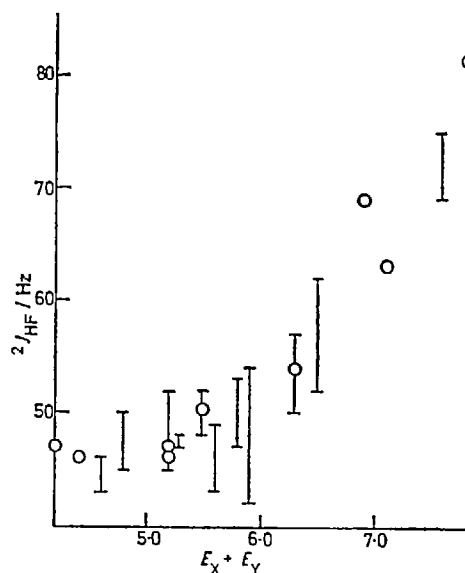
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²⁴ J. W. Emsley, L. Phillips, and V. Wray, *Progr. N.M.R. Spectroscopy*, in the press.

suggest that β -substituent effects (*i.e.* from groups vicinal to the coupling H and F nuclei) must be significant for if one of the substituents is an alkyl group (and the other remains constant) the observed value of $^2J_{\text{HF}}$ may vary considerably as a result of structural variation within that group.

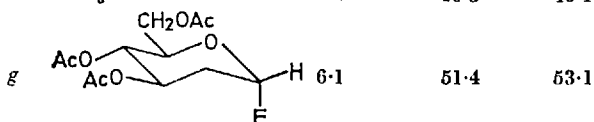


If a range of compounds is chosen with the object of minimising such β -effects (*i.e.* the substituents are single atoms or simple groups such as CH_3 or OCH_3), the correlation is still non-linear and curves markedly with apparent discontinuities. Table 3 lists data for such a series of molecules.

TABLE 3

Values of $^2J_{\text{HF}}$ (Hz) in specific molecules; experimental results and values calculated by using equation (3)

Ref.	Structure	$E_X + E_Y^*$	$^2J_{\text{HF}}$ obs.	$^2J_{\text{HF}}$ calc.
22	CHF_3	7.8	79.5	76.8
a	CHF_2OMe	7.4	74.4	68.7
b	CHF_2Cl	7.05	63.0	64.6
c	CHF_2Me	6.5	57.2	55.7
b	CHFCl_2	6.3	53.6	57.2
21	CH_2F_2	6.1	50.4	49.2
d	$\text{CHFCl}\cdot\text{CHCl}_2$	5.75	49.0	51.8
e	CHFBBrMe	5.55	50.5	50.7
f	$\text{MeCHF}\cdot\text{CH}_2\text{I}$	5.2	48.0	48.9
c	MeCH_2F	4.8	47.5	46.8
20	CFH_3	4.4	46.3	46.1



* The values for the electronegativities were taken as follows: F 3.90, OR 3.40, Cl 3.15, Br 2.95, C 2.60, H 2.20 (M. L. Huggins, *J. Amer. Chem. Soc.*, 1953, **75**, 4123).

^a Footnote b, Table 2. ^b Footnote a, Table 2. ^c D. D. Elleman, L. C. Brown, and D. Williams, *J. Mol. Spectroscopy*, 1961, **7**, 303. ^d R. R. Dean and J. Lee, *Trans. Faraday Soc.*, 1968, **64**, 1409. ^e J. W. Coomber and E. Whittle, *J. Chem. Soc.*, 1965, 6661. ^f G. Olah, J. M. Bollinger, and J. Brinich, *J. Amer. Chem. Soc.*, 1968, **90**, 2587. ^g L. D. Hall and J. F. Manville, *Chem. and Ind.*, 1967, 468.

If our data on fluorinated amides XCHFC(O)NR_2 are examined in a similar way by plotting $^2J_{\text{HF}}$ (listed in Table 1) vs. E_X , a linear graph results. In this situation, one group has been held constant [$X = \text{CHF}_2$, $Y = \text{C(O)NR}_2$] while the other is varied and we shall show later that this is a general observation for analogous situations.

It is interesting to note the effect of making the same substituent change in different molecules; in Table 4 the change in the value of $^2J_{\text{HF}}$ (Δ^2J_{HF}) which occurs when an alkyl group is replaced by fluorine, is shown for four pairs of molecules. It is apparent that the magnitude of the change in $^2J_{\text{HF}}$ on going from XYCHF to ZYCHF depends not only upon the electronegativity difference between X and Z but also upon the nature of the group Y.

TABLE 4

Change in $^2J_{\text{HF}}$ (Δ^2J_{HF}) on replacing an alkyl group by fluorine

Structure (1)	$^2J_{\text{HF}}$ /Hz	Structure (2)	$^2J_{\text{HF}}$ /Hz	$\Delta^2J_{\text{HF}}[(1)-(2)]$ /Hz
$\text{R}^*\text{CF}_2\text{H}$	57.2	CF_3H	79.5	22.3
$\text{R}^\dagger\text{CClFH}$	49.0	CF_2ClH	63.0	14.0
$\text{R}^\ddagger\text{CMeFH}$	48.0	MeCF_2H	57.2	9.2
$\text{R}^*\text{CH}_2\text{F}$	47.5	CH_3F_2	50.4	2.9

$\text{R}^* = \text{Me}$; $\text{R}^\dagger = \text{CHCl}_2$; $\text{R}^\ddagger = \text{CH}_2\text{I}$.

These observations are reminiscent of those made previously concerning substituent effects upon nuclear shielding,²⁵ and the approach used in our analysis of shielding data may easily be applied to the present problem even though the number of analysable data is relatively small.

It is unnecessary to give the method of analysis in detail, since its basis is fully documented elsewhere.^{2,26} Four different series of molecules of the type XYCHF were chosen, with $X = \text{F}$, Cl , CH_3 , or H , respectively, while the group Y is variable; for each series $^2J_{\text{HF}}$ was plotted against the Huggins electronegativity of Y (E_Y) to give satisfactorily linear graphs. Each graph has its own characteristic slope which depends on the group X, and may be defined by equation (1).

$$^2J_{\text{HF}} = 45.63 + S_X(E_Y - 1.98) \quad (1)$$

In turn, a plot of S_X vs. E_X is linear, and may be expressed by equation (2).

$$S_X = 8.45(E_X - 1.98) \quad (2)$$

Substitution of (2) into (1) gives a useful expression (3) for $^2J_{\text{HF}}$ in terms of E_X and E_Y . This expression

$$^2J_{\text{HF}} = 78.76 + 8.45(E_X E_Y) - 16.73(E_X + E_Y) \quad (3)$$

enables $^2J_{\text{HF}}$ for the molecules listed in Table 3 to be calculated to a satisfactory degree of precision (± 2.1 Hz r.m.s.); the calculated values are compared with experimental data in Table 3.

We may now examine the relevance of this treatment to our data on fluorinated amides listed in Table 1, by using it to estimate a group electronegativity for

²⁵ L. Phillips and V. Wray, *J. Chem. Soc. (B)*, 1971, 2068.

²⁶ L. Phillips and V. Wray, *J.C.S. Perkin II*, 1972, 214.

C(O)NRR'; a value of 2.5 on the Huggins scale enables the coupling constants, $^2J_{\text{HF}}$, in Table 1 to be calculated to a satisfactory degree of precision, as shown in the relevant column of this Table. This is a reasonable figure, since Wells²⁷ gives values of 2.6 for CH₃ and 2.8 for CO₂H.

TABLE 5

Observed and calculated values [equation (4)] of $^2J_{\text{HF}}$ in compounds of the type XYSiHF

Compound *	$^2J_{\text{HF}}^{\text{SI}}$ obs./Hz	Ref.	$^2J_{\text{HF}}^{\text{SI}}$ calc./Hz
SiF ₃ H	96.2	a	98.1
SiF ₂ HSiH	75.2	b	70.0
SiF ₂ HMe	67.5	23	70.0
(MeSiFH) ₂ O	68.2	23	65.4
GeH ₃ ·SiF ₃ H	54.5	c	57.0
SiH ₃ ·SiF ₃ H	53.0	d	54.9
SiH ₃ ·SiH ₂ ·SiF ₂ H	53.2	e	54.9
SiF ₂ H·SiF ₂ H	52.0	d	54.9
SiF ₂ SH·SiF ₂ H	54.9	b	54.9
Me ₂ SiFH	52.1	23	55.2
SiH ₃ ·SiFHCi	51.5	d	50.5
SiH ₃ ·SiFH ₂	43.2	f	44.9
SiFH ₂ ·SiFH ₂	45.0	d	44.9

* The values for the electronegativities of Si, S, and Ge were taken as 1.90, 2.60, and 2.00, respectively (F. A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry,' 2nd edn., Interscience, New York, 1966, p. 103).

* R. B. Johanneson, *J. Chem. Phys.*, 1967, **47**, 3088. ^b K. G. Sharp and J. L. Margrave, *Inorg. Chem.*, 1969, **8**, 2655. ^c D. Solan and P. L. Timms, *Inorg. Chem.*, 1968, **7**, 2157. ^d J. E. Drake and N. P. C. Westwood, *J. Chem. Soc. (A)*, 1971, 3300. ^e J. E. Drake, N. Goddard, and N. P. C. Westwood, *J. Chem. Soc. (A)*, 1971, 3305. ^f J. E. Drake and N. Goddard, *J. Chem. Soc. (A)*, 1970, 2587.

The form of equation (3) leads to some interesting conclusions; for a series of compounds XYCHF in which the group X is held constant and has an electro-

negativity of 1.98, changing the nature of group Y should have no observable effect upon $^2J_{\text{HF}}$, which should stay constant at ca. 45.6 Hz. Moreover, if $E_X < 1.98$ then $^2J_{\text{HF}}$ should increase with a decrease in the electronegativity of Y. There is, in fact, some evidence to support this suggestion for when the group X is Si^{IV} ($E_X = 1.90$) the value of $^2J_{\text{HF}}$ for molecules in which Y = Cl, CH₃, or H actually does increase slightly in this order rather than decrease. (For Et₃SiCH₂Cl, $^2J_{\text{HF}} = 45.5$; ²⁸ for Cl₃SiCFHMe, $^2J_{\text{HF}} = 46.0$; ²⁹ and for Me₃SiCH₂F, $^2J_{\text{HF}} = 46.8$ Hz.³⁰)

It was mentioned earlier that Frankiss²³ has observed a similarity in the effects of substituents upon $^2J_{\text{HF}}$ when both nuclei are bonded to carbon or silicon. Table 5 lists values of $^2J_{\text{HF}}$ in compounds of the type XYSiHF, and by using the same procedure as outlined above for XYCHF it is possible to derive equation (4), which may be used to calculate $^2J_{\text{HF}}$ for the compounds in Table 5 to a satisfactory degree of precision (r.m.s. ± 2.4 Hz).

$$^2J_{\text{HF}}^{\text{Si}} = 49.08 + 7.85(E_X E_Y) - 9.03(E_X + E_Y) \quad (4)$$

In summary, we now understand (qualitatively at least) the effects upon $^2J_{\text{HF}}$ of substituents directly bonded to the same atom as the H and F nuclei. It is inevitable however that there are anomalies and these probably arise from the influence of substituents which are upon adjacent atoms in the molecule, i.e. β or γ effects; this question will be examined elsewhere.

We are indebted to Wilkinson Sword (Research) Ltd. for a maintenance grant (to M. H. P.).

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²⁷ P. R. Wells, *Progr. Phys. Org. Chem.*, 1968, 111.

²⁸ D. Seyferth and K. V. Darragh, *J. Org. Chem.*, 1970, **35**, 1297.

²⁹ J. Dyer and J. Lee, *Spectrochim. Acta*, 1970, **26A**, 1045.

³⁰ E. S. Alexander, R. N. Haszeldine, M. J. Newlands, and A. E. Tipping, *J. Chem. Soc. (A)*, 1970, 2285.

**Structures of the Toxisterols,[†] X-Ray Crystal Structure of Toxisterol,-A
3,5-Dinitrobenzoate**

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Structures of the Toxisterols₂.† X-Ray Crystal Structure of Toxisterol₂-A 3,5-Dinitrobenzoate

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Summary The structures of toxisterol₂-A, -B, and -C have been determined by spectroscopic and chemical evidence supplemented by an X-ray crystallographic study of toxisterol₂-A 3,5-dinitrobenzoate.

TOXISTEROLS are substances of undetermined structure and of reputed biological activity originally described about 50 years ago.¹ Only one toxisterol (toxisterol₂-A) has been properly characterised before.¹ All toxisterols have a u.v. maximum near 250 nm. We report the isolation, characterisation (Table) and structure determination of three such compounds, toxisterols₂-A, -B, and -C.

0.4% citric acid at room temperature for 22–25 h gave a resin. Repeated chromatography over alumina (Grade II) gave (from 40 g of resin) toxisterol₂-A as 3,5-dinitrobenzoate (190 mg), -B (50 mg) and -C as benzoate (410 mg)]. We have not yet located the fourth possible stereoisomer.

¹H N.m.r., u.v., and i.r. data, which need not be detailed here, showed that all three toxisterols₂ had the 22(23)-*trans*-double bond intact and contained a cyclic heteroannular diene system of the type -CH=CH-C=C-(Me)-. Since the C₁₈ methyl group was also present in all compounds the vinylic methyl was presumed to be the original C₁₉ methyl.

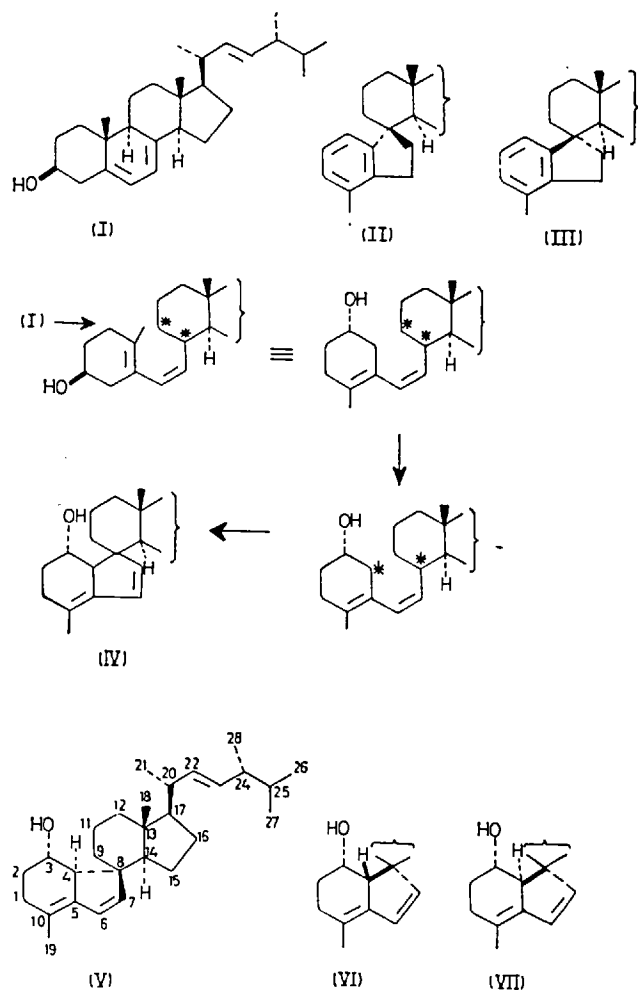
TABLE

Toxisterols ₂	M.p.	[α] _D (CHCl ₃)	λ _{max} /nm (ε)	Other derivatives
A(V)	Oil	-157°	250(21,000) ^a	<i>p</i> -Phenylazobenzoate ^b m.p. 124–126°
Acetate	103–105°		250(20,000) ^c	Benzoate m.p. 106–108°
3,5-Dinitrobenzoate ^d ..	173–174°	-1	232(28,000) ^a	<i>p</i> -Nitrobenzoate m.p. 102–104°
B (VI)	107–109°	+169	253(22,000) ^c	
C (VII)	Oil	+17	250(17,000) ^a	
Benzoate	Oil	+133	228(25,000) ^a 235(22,000) 250(17,000)	

^a In cyclohexane. ^b Lit.,¹ m.p. 125–126°. ^c EtOH. ^d Lit.,¹ m.p. 171–172°.

Irradiation (Phillips HPK 125 W type 57203 B/00) of ergosterol (I) in degassed ethanol containing 5% water and The ¹³C n.m.r. spectra were especially helpful and showed that an 'extra' quaternary carbon was present.

† The subscript 2 indicates that the compounds are derived from ergosterol rather than cholesterol (subscript 3).



that these compounds were 1,2,3-trisubstituted benzenes with one of the substituents being methyl.

Accepting the data at their simplest level of interpretation and using the plausible hydrogen atom transfer depicted in the Scheme, then structure (IV) seems reasonable for the toxisterols₂. This permits four stereoisomers about C-4 and C-8. The relationship of the configuration at C-3 (unchanged) and that at C-4 was established by ¹H n.m.r. spectroscopy. The configuration at the C-8 spiro centre was determined by the Nuclear Overhauser effect in the proton n.m.r. spectrum between the C-18 methyl group and the C-7 vinyl hydrogen (observed for the A isomer, but not for the B and C isomers).

Toxisterols₂-A, -B and -C can therefore be represented by formulae (V), (VI), and (VII) respectively. The complete structure of toxisterol₂-A was also determined independently by an X-ray crystallographic study of the derived 3,5-dinitrobenzoate.

Crystal data: C₃₅H₄₆O₆N₂, monoclinic, $a = 6.358(1)$, $b = 21.808(3)$, $c = 12.259(2)$ Å, $\beta = 102.81(1)^\circ$, space group $P2_1$ (C_2 , No. 4), $D_c = 1.18$ cm⁻³, $Z = 2$. $\mu(\text{Cu} - K_\alpha) = 6.6$ cm⁻¹.

X-Ray intensity data were collected using Ni-filtered Cu radiation on a Hilger-Watts Y290 automated four-circle diffractometer. 1856 Independent reflections for which $I \geq 3\sigma(I)$ were measured over the range $0 \leq \theta \leq 70^\circ$, and were corrected for Lorentz and polarisation effects; no correction was made for absorption. Several attempts to determine the structure using direct methods of phase determination were unsuccessful. The structure was eventually solved with extreme difficulty using a vector verification technique² to locate the 3,5-dinitrobenzoate unit, followed by iterative Fourier syntheses to find the remaining atoms. The structure has been refined using a partial full-matrix method to give a conventional R value of 0.056 with all non-hydrogen atoms treated anisotropically.

The figure is a stereo-drawing of the sterol portion of the molecule viewed along the crystallographic y axis, and

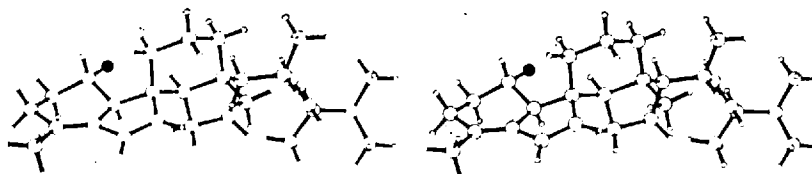


FIGURE. A stereo-drawing of toxisterol₂-A, showing the configuration at the spiro carbon atom C-8. The shaded atom at C-3 is the oxygen atom of the 3,5-dinitrobenzoate group which has been omitted for clarity.

Treatment of toxisterol₂-A with CHCl₃-HCl afforded smoothly a benzene derivative (II), m.p. 88–89.5°, $[\alpha]_D -55^\circ$ (all $[\alpha]_D$ in CHCl₃). Treatment of toxisterol₂-B and -C in the same way gave a different benzene (III), m.p. 69–71°, $[\alpha]_D + 6.0^\circ$. The n.m.r. and i.r. data showed

clearly shows the spiro-configuration at C-8. The methyl hydrogen atoms have been placed in calculated positions but the remainder were located from a difference Fourier synthesis.

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¹ P. Westerhof and J. A. Keverling Buisman, *Rec. Trav. chim.*, 1956, **75**, 1245; and references there cited.

² P. B. Braun, J. Hornstra, and J. I. Leenhouts, *Philips Res. Repts.*, 1969, **24**, 85.