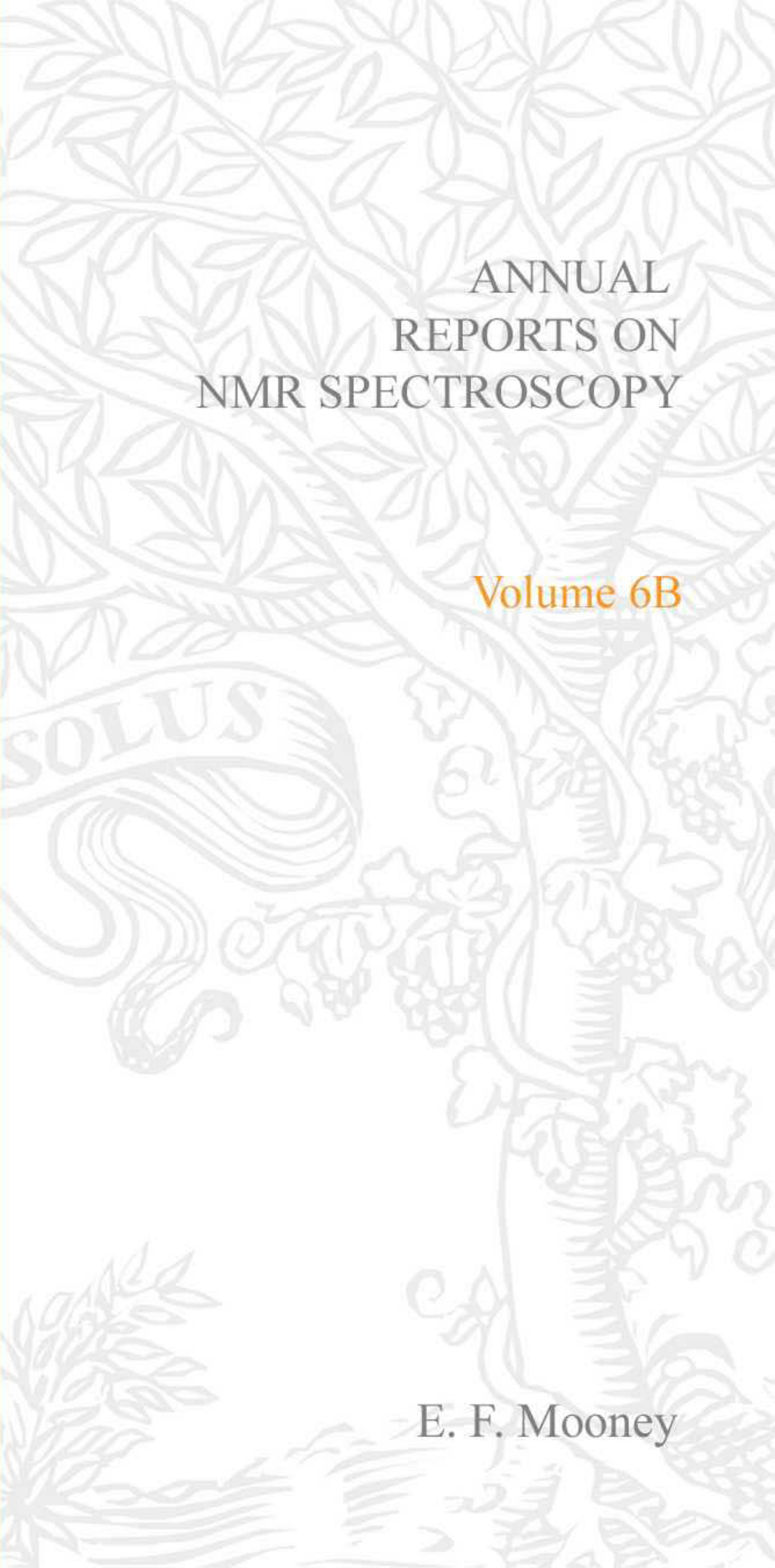

ANNUAL REPORTS ON NMR SPECTROSCOPY

Volume 6B

E. F. Mooney

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NMR SPECTROSCOPY

VOLUME 6B

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Edited by

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NMR and Conformations of Amino Acids, Peptides and Proteins[*]

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Singleton Park, Swansea, S. Wales[†]

I. INTRODUCTION

In the last fifteen years the determination of the solution conformations of organic molecules has been revolutionized by the continual improvements in NMR instrumental and theoretical and practical advances in the field. The recent breakthrough in the building of commercial spectrometers able to routinely examine ^{13}C or ^{15}N nuclei promises to inject even more interest in the topic of molecular conformation for a long time to come. The potential of the technique as applied to biological or biochemical problems has been realised particularly in the last two years (1970–71) and the

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[*] An appendix to this chapter can be found on p. 223.

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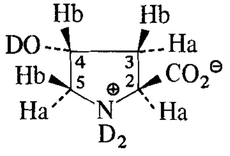
domain of the X-ray crystallographer has been infiltrated to a degree previously thought impossible.

In this review, the progress made in the conformational analysis of amino acids and peptides, using NMR as the major tool, is examined, to the end of December, 1971, with a few relevant references after this date also incorporated. The reviewer must apologise for not mentioning papers appearing in biological and biochemical journals which are not covered by Chemical Abstracts and with which he is not familiar.

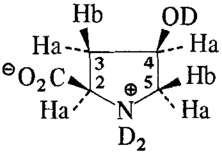
The time-lag in the development of the NMR technique in analysing the conformations of polypeptides and proteins was, in the main, because of the apparent lack of information available from complex spectra in aqueous solutions, insolubility in typical NMR solvents, severe line-broadening in the spectra of large peptides (proteins and enzymes) and a general disbelief that these problems could be overcome. Introduction of super-conducting magnets, computers and more recently, ^{13}C and ^{15}N facilities have overcome many of the early problems. In this review, the progress made in determining the conformations of amino acids and their derivatives, small peptides, cyclic peptides, polyamino acids and proteins will be dealt with in that order. For a more complete coverage of biological applications of NMR, several other reviews on various aspects of the subject have appeared, (1 to 13) which complement the material in this chapter.

II. AMINO ACID CONFORMATIONS

Most of the twenty or so common amino acids were examined using NMR as early as 1957–59. (14-16) Comprehensive and up-to-date coupling constants and chemical shifts have been tabulated. (1, 2) However, the conformations of these molecules were not thoroughly investigated by NMR techniques until the spate of papers following the valence-bond calculations of Karplus. (17, 18) Following the apparently successful treatment of simple cyclic organic compounds, Abraham and McLauchlan analysed completely the



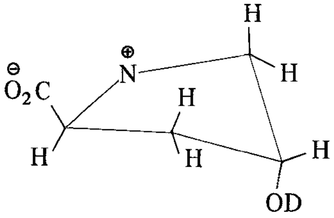
[1]



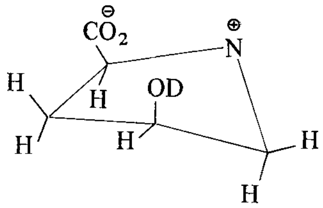
[2]

J_{2a3a}	7·66 Hz	J_{2a3a}	10·48 Hz
J_{2a3b}	10·44	J_{2a3b}	3·48
J_{3a3b}	−14·06	J_{3a3b}	−14·23
J_{3a4b}	1·41	J_{3a4a}	4·71
J_{3b4b}	4·31	J_{3b4a}	2·09
J_{4b5a}	1·22	J_{4a5a}	4·57
J_{4b5b}	4·09	J_{4a5b}	0·94
J_{5a5b}	−12·69	J_{5a5b}	−12·50
J_{3a5a}	1·6	J_{3b5b}	2·0

60 MHz spectra of aqueous solutions of 4-hydroxy-L-proline [1] and the corresponding *allo*-4-hydroxy-D-proline [2]. (19, 20)



[1a]



[2a]

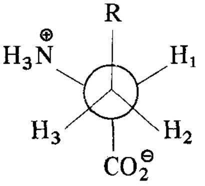
It was argued that the presence of large vicinal coupling constants in the spectra of both compounds implied that both molecules were relatively rigid in solution and not interconverting rapidly between two or more conformations (leading to time-averaging and hence decrease in the observed coupling constants). Using the accepted "Karplus" type equations:

$$J = K_1 \cos^2 \phi \qquad 0 \leqslant \phi \leqslant 90^\circ \tag{1}$$

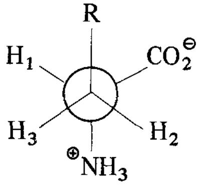
$$J = K_2 \cos^2 \phi \qquad 90^\circ \leqslant \phi \leqslant 180^\circ \tag{2}$$

where K_1 and K_2 were constants for each particular C–C fragment, and ϕ was the dihedral angle between the C–H bonds concerned, it was proposed that the conformations [1a] and [2a] were the most likely for these molecules in aqueous solution i.e. envelope conformations with four out of five ring atoms in a plane. The assignments for the protons fit these conformations, additional support coming from the presence in each molecule of 4-bond couplings between pseudo-equatorial protons. A similar investigation of these two compounds in acid and alkaline media suggested that in alkaline solution more than one conformation was present in each case, the increase in mobility perhaps arising in part due to the change $\overset{\oplus}{N}D_2 \rightarrow N\text{–}D$. (21) These papers were criticized by Robertson *et al.* in later work on a series of 4-substituted prolines. (22) In the light of present-day knowledge of stereochemical factors affecting NMR data, it seems that quantitative use of "Karplus equations" was unjustified at the time, though the qualitative features of the proposed conformations were probably correct. Five-membered rings have always proven difficult in conformation-determining exercises. In the paper published by Robertson and his co-workers (22) it was concluded that though the difference between *cis* and *trans* 4-substituted prolines could be rigorously defined by NMR, the individual conformations of these compounds were not easily defined. Similar problems have arisen with 3-methyl, (23, 24) 3-hydroxy, (25) 3,4-epoxy and 3,4-dihydroxy prolines, (26) where J_{2a3a} and J_{2a3b} often have similar magnitudes, making assignment difficult. Abraham and Gatti, however, claimed some success with the determination of the conformation of 3,4-cyclopropyl proline. (27)

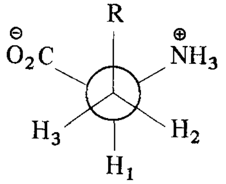
In acyclic amino acids of the type $RCH_2CH(\overset{\oplus}{N}H_3)CO_2^{\ominus}$ [3], assuming the classical staggered forms, there are three possible rotational isomers [3a, b and c]. In none of the isomers are H_2 and H_3 magnetically equivalent, the β-methylene protons thus being diastereotopic. Therefore no matter what the rate of rotation about the C_α–C_β bond and no matter what the mole fractions n_a, n_b and n_c may be, protons 1, 2 and 3 should show an ABC type of multiplet in the NMR spectrum. This is usually so except in cases of accidental equivalence, the extent of the non-equivalence depending on the state of ionization of the molecule and the nature of R. Pachler (28, 29) discovered that in amino acids of the type [3] the average vicinal coupling constant $\frac{1}{2}(J_{12} + J_{13})$ was largely independent of the group R and was always approximately 6.3 Hz in magnitude. This figure was arrived at by several independent routes. Making the assumption that $J_{gauche} = J_{12}$ in [a] $= J_{13}$ in [b] $= J_{12}$ or J_{13} in [c] and that $J_{trans} = J_{13}$ in [a] $= J_{12}$ in [b], it was found possible to derive the mole fractions n_a, n_b and n_c using the following equations:



[3a]



[3b]



[3c]

$$n_a + n_b + n_c = 1 \tag{1}$$

$$J_{12} = n_a J_g + n_b J_t + n_c J_g \tag{2}$$

$$J_{13} = n_a J_t + n_b J_g + n_c J_g \tag{3}$$

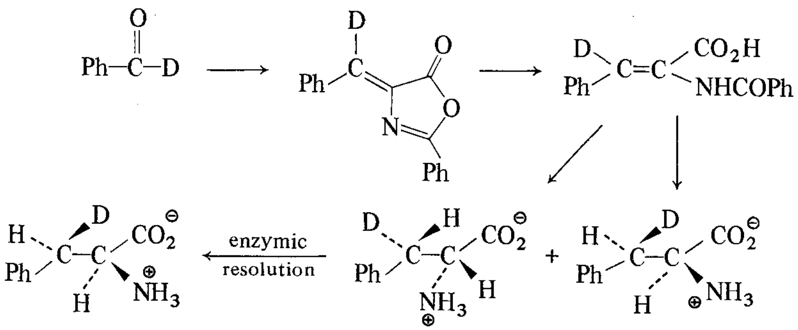
$$\therefore n_a = \frac{J_{13} - J_g}{J_t - J_g} \tag{4}$$

$$n_b = \frac{J_{12} - J_g}{J_t - J_g} \tag{5}$$

$$n_c = 1 - (n_a + n_b) \tag{6}$$

If suitable values for J_t and J_g can be inserted in the equations, the mole fractions n_a, n_b and n_c can be estimated. However, the errors implicit in the treatment may be considerable for the following reasons; (i) the initial assumption of one *gauche* and one *trans* coupling constant may be considered doubtful, since it is well-known that electronegativity effects are maximum when the electronegative group is *trans* to one of the coupling protons. It is therefore unlikely that all the *gauche* couplings are identical (for an example note the differences in the vicinal coupling constants in 4-phenyl-1,3-dioxan (30)). (ii) the initial values of J_t (13.6 Hz) and J_g (2.6 Hz), although suggested by perfectly rational argument, seem to be suspect in that J_t in particular has rarely been found to be greater than *ca.* 12 Hz even in systems where no electronegative substituents exist. Conversely the values J_t (6.27) and J_g (2.84) derived from a modified Karplus equation (1) seem to have J_t too small. An intermediate value of the order of 10.5 Hz for J_t and 2.7 Hz for J_g would seem to be more realistic. However, the errors made in the residence times by varying J_t and J_g are not > 25% over the range suggested, so that the treatment does apparently give a reasonable qualitative picture of the situation. Another assumption made, however, in order that the β-methylene protons be assigned is that the rotamer [a] is always the

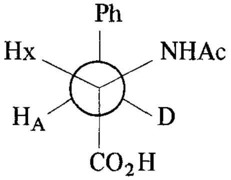
Scheme 1



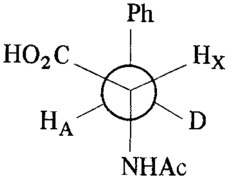
(2S, 3R)β-^{2}H phenylalanine

favoured form. If this is the case, then the larger coupling constant will always be J_{13} involving a *trans* coupling in rotamer [a]. The only unambiguous method of assigning H_2 and H_3 is to stereospecifically substitute one of the β-protons for deuterium. This experiment has been performed in the case of phenylalanine ([3], R = Ph) and tyrosine ([3], R = p-C_6H_4OH) by the following synthetic scheme. (31, 32, 33) (Scheme 1)

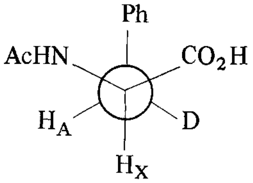
The vicinal coupling constants of the specifically deuterated phenylalanine derivatives [4] and [5] clearly indicate a marked preference for the rotamer ([4a] or [5a]) with the phenyl and carboxyl groups *trans*. These experiments confirm the previous assignments in phenylalanine, and also for tyrosine which appears to adopt a similar preferred rotational form.



[4a]

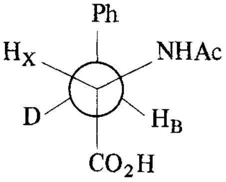


[4b]

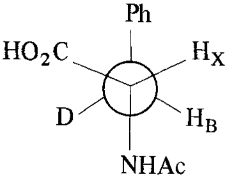


[4c]

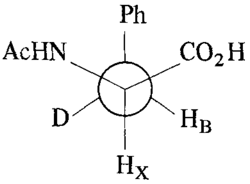
J_{AX}(ave.) = 4·9 Hz



[5a]



[5b]



[5c]

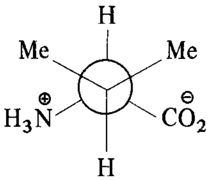
J_{BX}(ave.) = 8·7 Hz

The most detailed analyses of the spectra of acyclic amino acids have been performed on phenylalanine, tyrosine, tryptophan ([3], R = 3-indolyl), histidine ([3], R = 5-imidazoyl) and serine ([3], R = OH). In phenylalanine (34, 35) Cavanaugh found that the temperature variation of the vicinal coupling constants depended critically on the concentration: at low concentration the two vicinal coupling constants diverged with increasing temperature; at high concentration they converged. It was concluded that deviations from classical staggered conformations were small but that the anion rotamer energies varied with temperature and concentration, the two less favoured rotamers becoming more stable at lower temperatures and lower concentrations.

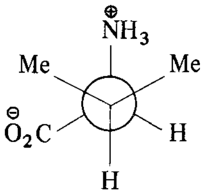
In the cation, however, the vicinal coupling constants varied very little with temperature and concentration, suggesting that rotamer energies do not vary to the same extent as in the anion. Similar results were found for the tryptophan anion, but for histidine and tyrosine slight differences in behaviour were noted. (36) However, in all cases the two less favourable rotamers became less stable with increase in temperature. These variations may arise from solvent-solute and solute-solute interaction, the precise nature of which were not defined. Although the concentration dependence of the NMR data for serine was not evaluated, changes in the vicinal coupling constants with temperature and pH were observed. (37) Throughout the pH range the rotamer ([3c], R = OH) with the –OH and $-CO_2^{\ominus}$ groups *gauche* was always the most stable in contrast to most amino acids, the dominance of this form increasing in the case of the cation. Again the Pachler treatment (28, 29) was used in all this work to derive the mole fractions of the rotational isomers.

The sulphur-containing amino-acids have received much attention, (38-41) the –SH group of cysteine ([3] R = SH), cystine, cysteic acid, lanthionine and djenkolic acid providing novel conformational features. The sulphur substituent is bulky, and in cysteine has an acidic proton which, in alkaline solution can be removed. Severe repulsion between the $-S^{\ominus}$ and $-COO^{\ominus}$ groups makes the conformation [3b or c] extremely unlikely. This feature is also true in aspartic acid and similar amino acids. Martin and Mathur (39) followed a different procedure from Pachler in examining cysteine, considering limiting cases in the three rotational isomers. However, the assumption of one J_g and one J_t was used once more, and the values adopted by Pachler did not fit the treatment for cysteine. In L-cystine $[-SCH_2CH(\overset{\oplus}{N}H_3)C\overset{\ominus}{O}O]_2$ in acid solution, it was suggested that there is a stabilizing interaction between the two moieties, which is absent in *meso*-cystine.

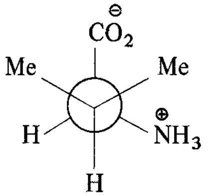
In valine [6] $[Me_2CH\ CH(\overset{\oplus}{N}H_3)C\overset{\ominus}{O}O]$ where the methyl groups



[6a]



[6b]

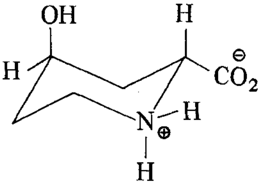


[6c]

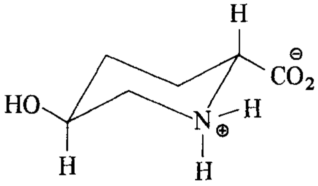
are diasterotopic the vicinal coupling constant varied from 5.1 Hz at pH 14.0 to 4.3 Hz at pH 1.0. (42, 43) Although the presence of a bulky group between the two methyl groups as in [6b] and [6c] would seem to be sterically unfavourable, the magnitude of the coupling does not indicate a marked preference for the rotamer [6a].

Several papers have appeared (44, 45, 46) in which it has been pointed out that the presence of an impurity in the racemic threonine [7] $[CH_3CH(OH)CH(N\overset{\oplus}{H}_3)C\overset{\ominus}{O}O]$ examined by Aruldhas (47) led to erroneous conclusions. By analogy with previous work, (47) it was clearly shown that separate rotameric forms are not seen in the NMR spectrum of threonine at room temperature and the impurity in the sample examined by Aruldhas arose from the presence of some of the *allo* isomer.

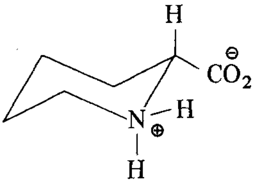
Further examples of successful conformational analysis with cyclic imino acids are found with the six-membered pipecolic acid derivatives [8] and [9]. Shoolery and Virtanen (48) from the 100 MHz spectrum of the aqueous solution of 4-hydroxy pipecolic acid [8] and 5-hydroxy pipecolic acid [9] established that the carboxyl and hydroxyl functions were *trans*. The α-proton splittings for [8] of *ca.* 11 and 5 Hz indicated an axial orientation for the α-proton, and the narrow septet for the –CH(OH) proton ($\Sigma J = 14$ Hz) clearly suggested an equatorial proton coupled to four neighbours with similar small couplings (axial-equatorial or equatorial-equatorial). The α-proton was similarly oriented in 5-hydroxy pipecolic acid [9] but the –CH(OH) proton was a considerably broader septet ($\Sigma J \simeq 28$ Hz). Thus the chair conformations shown were suggested for these two molecules. Pipecolic acid [10] itself adopts a similar chair conformation as expected, though acetylation (49) or nitrosation (50) of the nitrogen inverts the ring into the other chair form with the α-carboxyl function axial.



[8]



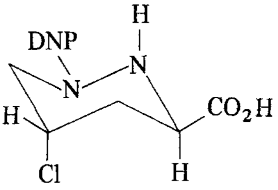
[9]



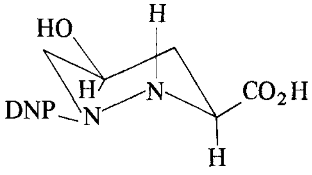
[10]

Similar arguments were put forward in assigning the configurations and conformations of the novel piperazic acids, products of hydrolysis of monamycin. (51, 52) The *N*-2,4-dinitro phenyl derivatives of the chlorine containing piperazic acid [11] and the hydroxyl containing compound [12] were shown to possess the configurations and conformations indicated using arguments similar to those put forward for the pipecolic acid derivatives. The large N*H* . C*H* coupling ($J \simeq 11$ Hz) in both cases (dimethyl sulphoxide-d_6 solvent) suggested that the N–H proton was axially-oriented, presumably to avoid steric interaction with the neighbouring bulky DNP group. Again incorporation of these amino acids into peptide functions reversed the chair conformations, forcing the α-carboxyl functions into the axial position on account of unfavourable steric interactions between the neighbouring amide groups for the equatorial conformation.

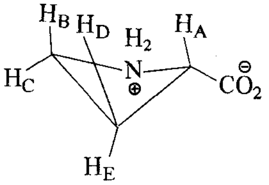
A complete analysis of the complex 5-spin spectrum of azetidine-2-carboxylic acid (53) [13] (previously published but not analysed



[11]



[12]



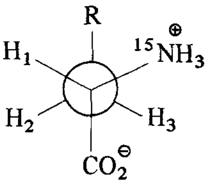
[13]

(54)) suggests that as in the crystal, (55) some buckling of the four-membered ring is present.

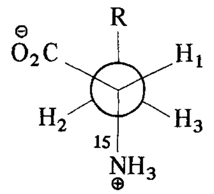
Although vicinal coupling constants in four-membered rings are often unpredictable, and affected by other factors than dihedral angle and electronegativity relationships, the vicinal couplings are consistent with buckling of the ring as shown [13]. Thus J_{CD} = 6.02 Hz, J_{BE} = 8.23 Hz, J_{CE} = 9.74 Hz and J_{BD} = 9.34 Hz in the C_β–C_γ fragment, the difference between J_{CD} and J_{BE} suggesting dihedral angle differences.

Future prospects for studying conformational analysis via the NMR spectra of ^{15}N (56) and ^{13}C (57, 58) enriched amino acids have been evaluated to some extent. Lichter and Roberts (56) examined the proton spectra of some ^{15}N enriched alanine, phenylalanine and aspartic acid in order to investigate the usefulness of ^{15}N–^{1}H coupling constants as conformational probes.

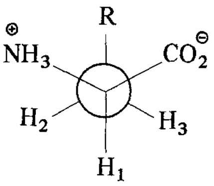
For ^{15}N-alanine (R = H), $J_{\mathrm{NH}_2} = J_{\mathrm{NH}_3}$ = 3.1 Hz; in ^{15}N-phenylalanine (R = Ph), J_{NH_2} = 3.4, J_{NH_3} = 2.9, and in ^{15}N-aspartic acid (R = COOH), J_{NH_2} = 3.4 and J_{NH_3} = 3.0 Hz. These couplings are time-averaged for the three rotamers [14a, b and c]. The results, taken with those from other ^{15}N enriched compounds show a trend



[14a]



[14b]



[14c]

for $^3J_{\mathrm{NH}}$ to follow a fairly shallow and somewhat skewed Karplus-type correlation with dihedral angle. However, before this can be taken as a useful technique, in conformation assignment in amino acids and peptides, a lot of "spade-work" is necessary. Fifteen of the naturally-occurring amino acids have been examined and their ^{13}C spectra assigned, using ^{13}C-enriched samples obtained from algae grown in an atmosphere of $^{13}CO_2$. (57) Although proton-decoupled ^{13}C spectra are desirable from the point of view of enhancing the S/N ratio and simplifying the spectra considerably, much conformational information such as one-, two-, three- and four-bond ^{13}C–H coupling constants is lost. Potentially, ^{13}C NMR is capable of providing much information about amino acids and peptides which is lacking in ^{1}H spectra. Tabulated data on amino acids and peptides as provided so far (57, 58) is invaluable in progressing towards this goal.

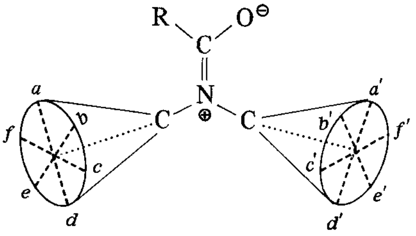
III. CONFORMATIONS OF *N*-ACYL AND RELATED AMINO ACID DERIVATIVES

Before discussing dipeptide and polypeptide conformations, it is worth examining the progress made in evaluating the conformational features of model compounds, i.e. *N*-acylated amino acids. The partial double-bond character of the amide bond presents a high barrier to rotation, giving rise to geometric isomers as shown [15a, b] normally detectable as an equilibrium mixture in NMR spectra.

[15a] [15b]

(59) Although the two forms are readily observed as separate species in the NMR spectrum, the assignment of the chemical shifts to one form or the other is by no means obvious. Theory in general proving inadequate, the experimental approach of Paulsen and Todt (60-64)

has enabled a model to be drawn demonstrating the anisotropic effect of the amide group [16]. In this model a proton *a* experiences greater shielding than in position *a*′. In the out of plane region, for



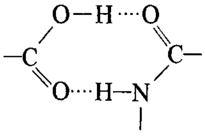
[16]

instance, a proton at *o*′ will be more shielded than one at *c*. In all positions, the experimental data obtained from rigid compounds of known stereochemistry supports this model. Thus in *N*,*N*′-dimethylformamide the methyl group *cis* to oxygen resonates at lower frequency than the *trans* methyl group, the assignments being proven by Nuclear Overhauser experiments. (65)

In *N*-acylated amino acids which are examples of monosubstituted amides, the tendency is for the amide bond to strongly prefer the *trans* form ([15a], R″ = H) with the N–H bond *trans* to the C=O. (59) *cis* Peptide bonds have rarely been reported in monosubstituted amides of this type in crystalline studies of peptides and proteins, though in small cyclic peptides, as we shall see later, *cis* peptide bonds are often a necessary requirement in the preferred conformation. One of the few examples quoted in the literature demonstrates *cis*/*trans* isomerism in *N*-carbobenzoxy derivatives of alanine [17]. (66) It is argued that the *cis* form is stabilized by dimerization through intermolecular hydrogen bonding as shown[18]. This isomerism was not observed at ambient temperatures, when the

$\mathrm{PhCH_2OCONH}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCOOH}$

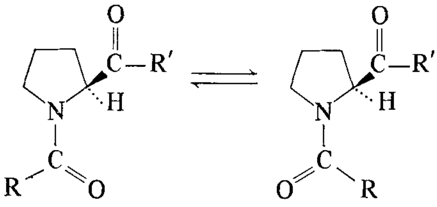
[17]



[18]

spectrum was that of the averaged species, but was clearly demonstrated at ~0°C.

In the cyclic imino acids, *cis*/*trans* isomerism about the amide bond is commonly found, since the energy difference between the two forms is governed primarily by the α-carboxy functions, and is generally small (< 10 KJ/mole). Proline derivatives [19] have naturally received most attention; it has been shown that in *N*-acetyl proline derivatives, (67) *N*-carbobenzoxy proline, (68, 69) 4-hydroxy proline derivatives, (70) and *N*-nitroso proline, (50, 71) *cis*/*trans* isomerism is a relatively slow process at room temperature, and the spectra of the two forms are clearly visible. The assignments of the two forms are by no means obvious. Benzene solvent shifts were successfully used in the case of the acetyl prolines to assign *cis* and *trans* isomers, (67) the *trans* form proving the more stable in most solvents.



trans [19] *cis*

Similar studies have been carried out on *N*-acetyl azetidine-2-carboxylic acid, (53) the four-membered ring homologue of *N*-acetylproline. Again the *trans* isomer was generally the more stable except for instance in pyridine solution. Acetylation was shown to flatten the four-membered ring considerably. ^{13}C NMR spectroscopy promises to be useful in studying conformational equilibria of this type. In Fig. 1, the proton decoupled ^{13}C spectrum of *N*-acetyl pipecolic acid clearly demonstrates the geometric isomerism the smaller peaks corresponding to the *cis* isomer. (49) It is an interesting fact that dissolution of crystalline *N*-acetyl pipecolic acid in d_4-methanol at −60°, and examination of the spectrum at this temperature unambiguously shows only the *cis* form in solution, in contrast to the acetyl derivatives of proline and azetidine-2-carboxylic acid where the crystal form is the *trans* conformation. (49) In all cases, the Paulsen model fits the observed spectra and assignments.

Newmark and Miller (72) have made a detailed study of the conformations of derivatives of valine and phenylalanine. The variation of vicinal couplings with solvent was used to deduce the populations of the usual rotational isomers using the Pachler approach. They suggest that intramolecular interactions are more important than the medium in determining rotamer energies. Finally, as expected, *cis*/*trans* isomerism about the sarcosine (*N*-methyl glycine) amide bond has been demonstrated. (73)

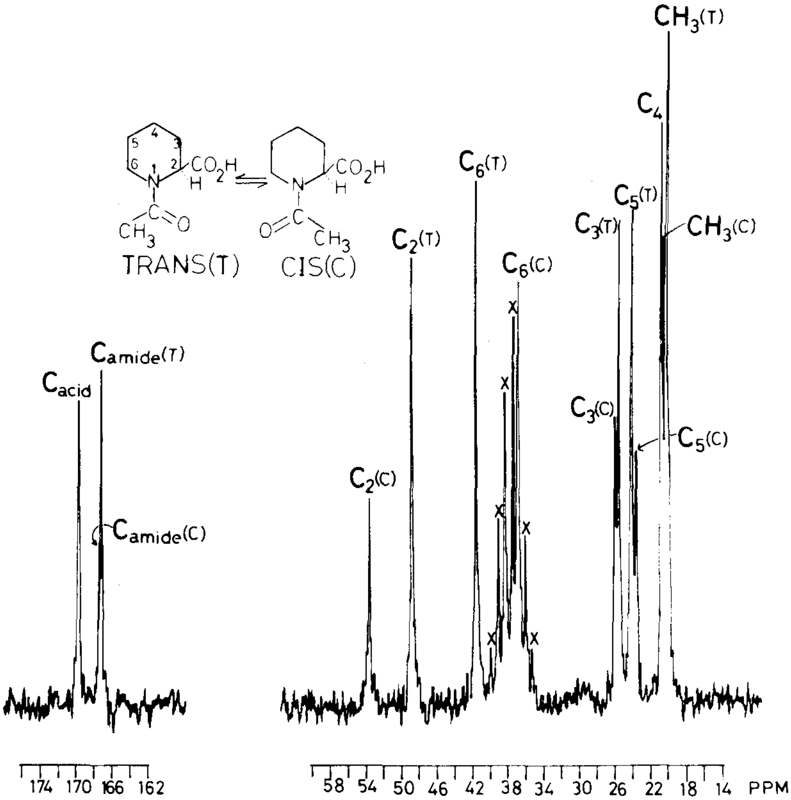
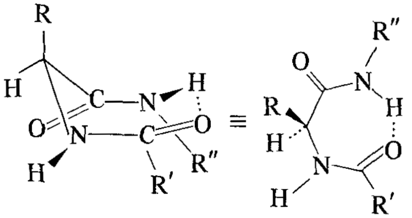


FIG. 1. The ^{13}C spectrum of *N*-acetyl pipecolic acid in dimethyl sulphoxide-d_6.

IV. DIPEPTIDE CONFORMATIONS

In recent years the study of dipeptide conformations by NMR spectroscopy has been a source of several papers. (66, 69, 74-92) The pioneering paper in the more recent series was undoubtedly the study of alanine dipeptides, (37) in which it was proposed that in non-polar solvents *ca.* 70% of the molecules existed in a folded form, stabilized by an intramolecular hydrogen bond enclosing a seven-membered ring [20]. Some criticism of the assignments made in this work have since been published. (66) This cyclic conformation of dipeptides had been previously suggested, (74) though in the context that the D,L forms of dipeptides preferred the folded form and the L,L forms a "stretched" conformation. A key factor in determining the conformation of the peptide backbone in dipeptides, and in fact



[20]

in almost all conformational work on peptides using NMR spectroscopy, has been the angular dependence of ^3J(CH–NH), a plot of this coupling against the dihedral angle θ following a similar proposed curve to that proposed for ^3J(CH–CH) (Fig. 2) with maxima at $\theta = 0$ or 180° and minima at $\theta \simeq 90°$.

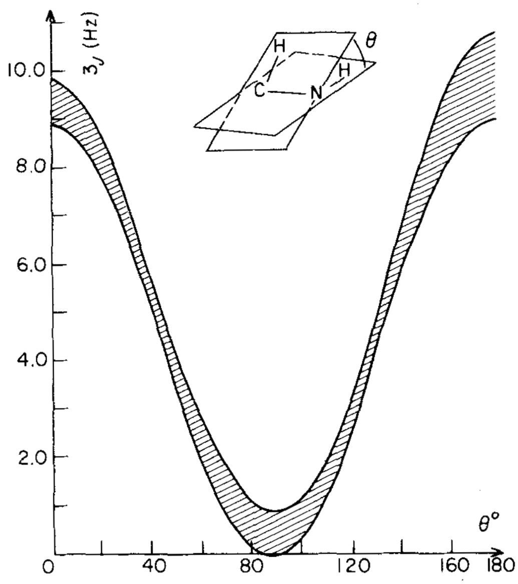


FIG. 2. The modified "Karplus" curve plotting J(NHCH) against dihedral angle θ. [From Bystrov *et al.* (82)].

Previous work on CH . NH fragments in a variety of compounds established the dihedral angle relationship, (93-103) but only in the last four years has it been put on a firm footing. Gibbons *et al.* have proposed that the use of ^3J(NH–CH) coupled with the use of conformational energy maps is the best way to determine the shape of peptide backbones. (104) This combination of experimental NMR data and the calculation of potential energy minima (105) appears to be becoming the most popular method of deriving conformational information. (12, 85, 88). Very recently, Ramachandran, Chandrasekaran and Kopple (106) have used PMR data and conformational energy calculations to establish a more quantitative coupling constant/dihedral angle relationship for the peptide unit. From eight examples in which the number of theoretical assumptions was least, best values were obtained for the coefficients A, B and C in the equation:

$$J = A \cos^2 \theta + B \cos \theta + C \sin^2 \theta \tag{7}$$

The values $A = 7.9$, $B = -1.55$ and $C = 1.35$ gave reasonable fits in cases where NMR and other data correlated well. In peptide fragments containing valine, isoleucine, phenylalanine and tyrosine, however, the agreement was not so good, probably on account of interactions not considered in the calculations.

In an exhaustive study of *N*-acetyl-alanyl-phenylalanines and related peptides, (90) it was concluded that in CCl_4 solutions, from 60–80% of the molecules were in a folded conformation, the preferred form having the CH . NH fragment *cis* in the D-D isomers, and *trans* in the D-L isomers. However, much of the evidence favouring the folded conformation of dipeptides is derived from IR data, outside the scope of this review. *Cis*/*trans* isomerism about the amide bond has been demonstrated in the case of *N*-methylated dipeptides, (87) and in dipeptides containing proline. (67, 69, 84) From the wealth of data obtained from the NMR spectra of dipeptides it is clear that even in these small molecules, the number of degrees of freedom allowed in the molecule complicates the issue enormously. Therefore the possibility of applying the technique to longer peptides is forbiddingly complex unless the number of possible conformations is restricted, as in cyclic peptides.

V. CONFORMATIONS OF LINEAR PEPTIDES WITH THREE OR MORE RESIDUES

The difficulties inherent in determining the conformations of tri-, tetra- and longer peptides are reflected in the fact that very little NMR work has been published on the investigation of such peptides, although in small biologically-active peptides, structure-activity relationships are most important. Some success (107) was achieved by examination of the *C*-terminal tetra peptide trp-met-asp-phe-NH_2 of gastrin which has the activity of the parent 17-residue hormone in stimulating acid secretion in the stomach. Rotamer populations of the side-chains were derived using the Pachler technique (28, 29) discussed earlier. It was concluded that the peptide backbone adopts an extended coil conformation, with no intramolecular hydrogen bonds and with the aromatic rings well-separated.

An ambitious study of antiotensin II analogues has been published by Weinkam and Jorgensen. (108, 109) The ^1H spectra of this biologically important octapeptide, (109) and in particular the heptapeptide analogue [21], showed evidence of conformational stability, manifested in low-frequency shifts of proline protons in close proximity to the imidazole ring, line broadening of the protons in the imadazole rings, and the presence of a single, intramolecular hydrogen bond. This result is in agreement with conclusions from previous studies involving the ESR spectra of free-radical containing antiotensin analogues. (108)

H-Gly . Val . Phe . Ileu . His . Pro . Phe-OH

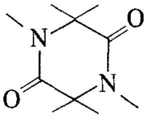
[21]

VI. CYCLIC PEPTIDES

Before discussing the information available from NMR studies of long chain polypeptides, proteins and enzymes, it is worthwhile reviewing the most fruitful area in the use of NMR in the conformational analysis of peptide molecules, i.e. cyclic peptides, where the restriction in mobility allows more definite conclusions to be made. Progress made in this field has been reviewed recently, (7, 8, 12) clearly showing the enormous expansion of interest in this area of chemistry.

1. Cyclic Dipeptides (Diketopiperazines)

Cyclic dipeptides (DKP's) with the general structure [22] have received much attention. Kopple and co-workers have been the most active in this area, (110-113) being the first research group to demonstrate the preferred folded conformation of DKP's having an aryl methyl side chain as shown [23]. Similar conclusions have been published elsewhere, (114) and the recent publication of the crystal structure of cyclo(gly-tyr) adds further weight to the argument. (115) The energy difference favouring the folded form is estimated to be 8 to 21 KJ/mole. (112) This attraction between the aromatic ring and the DKP ring appears to arise from interactions between the amide dipoles and dipoles induced in the π-electron cloud, and not from a component of π-π donor-acceptor interaction. (112) Hatton and Richards had proposed earlier that benzene-amide attractive interactions could account for the differential shielding of the *cis* and *trans* methyl groups in dimethylformamide. (116) Similar aromatic/ backbone interactions have been proposed in linear peptides with aromatic residues. (16, 117) It is interesting that when two aromatic side chains are *cis*. as in cyclo(L his–L his) [24], the aromatic rings



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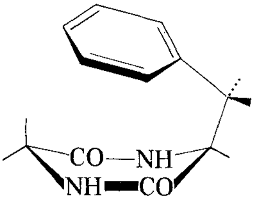

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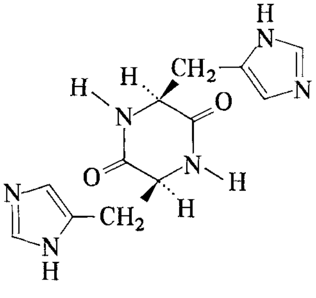
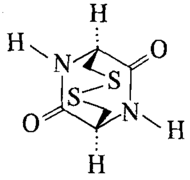


[24]

share the space over the DKP ring. (113) It should be noted that in diketopiperazines and similar structures, the DKP ring itself is not necessarily planar; (118, 119) various boat and skewed-boat conformations have been suggested, again as found in the crystal structures. (120-122) Quantum mechanical calculations have been used to predict the favoured conformations of DKP's, but this is outside the scope of this review. Finally, the NMR spectrum of the novel cyclo(L-cystine) [25] has been examined, and analysed to give

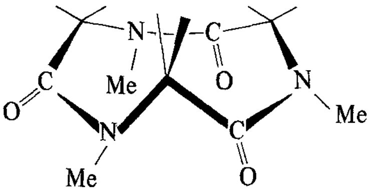


[25]

chemical shifts and coupling constants. (123) No conformational information was inferred from the result.

2. Cyclic Tripeptides

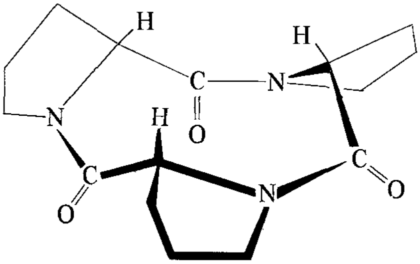
Dale and Titlestad in 1969 examined a series of cyclic oligopeptides of sarcosine $\lfloor N(Me){-}CH_2{-}CO \rfloor_n$. (124) In the NMR spectrum of the cyclic trimer ($CDCl_3$, 40°), the N–CH_3 groups appear as a singlet at 3.1 ppm, and the methylene protons as an AB quartet ($\delta_A \simeq 4{\cdot}9$, $\delta_B \simeq 3.5$, $J \simeq 16$ Hz). The only conformation fitting this data is a structure with all C=O bonds *cis* [26], in which



[26]

the inner/outer nature of the methylene protons clearly explains the large chemical shift difference observed. Coalescence of the methylene protons takes place at 145°C, giving a free energy of activation of 84.4 KJ/mole for the ring inversion process. (125)

The peptide backbone of cyclo tri-L-prolyl again must adopt the form with three *cis* peptide bonds, (126) and is probably even more rigid than the trisarcosyl derivative. Deber *et al.* (127) have analysed completely the 220 MHz NMR spectrum of this compound and related derivatives, determining all the vicinal coupling constants

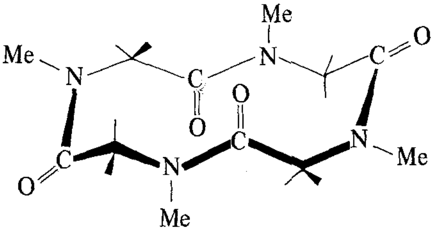


[27]

around the ring by computer-simulation. The three proline rings are symmetrically placed about the axis through the ring and there is therefore one multiplet for three equivalent α-protons, one multiplet for each of the two β-protons, etc. Using the Karplus-type relationship discussed previously, it was concluded that a rigid conformation was present [27] similar to [26], in which the four carbon atoms of each pyrrolidine ring were coplanar, with the nitrogen atoms out of the plane. A large low-frequency shift of H_α in cyclo(tri-L-prolyl) was observed on adding C_6D_6 to a solution in CD_2Cl_2. (128) This is interpreted as arising from the formation of stereospecific collision complexes, the preferred orientations resulting from attractive interactions between the electron-rich aromatic ring and the electropositive α-protons and/or nitrogen atoms in the peptide backbone, probably of a similar nature to these discussed previously. (112, 116, 117)

3. Cyclic Tetrapeptides

The conformation of the 12-membered ring of cyclic tetrapeptides in solution was the subject of much speculation, prior to the experimental work of Dale and colleagues, (124, 129, 130, 131) who showed clearly and unambiguously that cyclotetrasarcosyl adopts the conformation [28], similar to that in the crystal. (131, 132) The interesting features in this conformation are the presence of two *cis* amide bonds, and the close proximity of the two *trans* amide bonds (*ca.* 2.4 Å apart) suggesting that there is some transannular interaction tending towards the extreme case as shown in [29]. Apart from the evidence from the crystal structure, NMR evidence tends to



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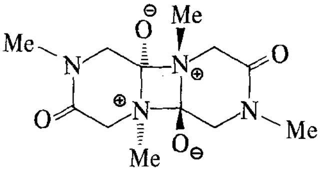
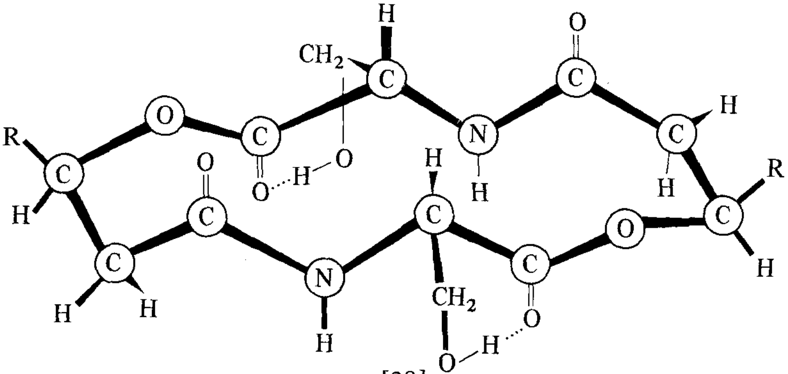


[29]

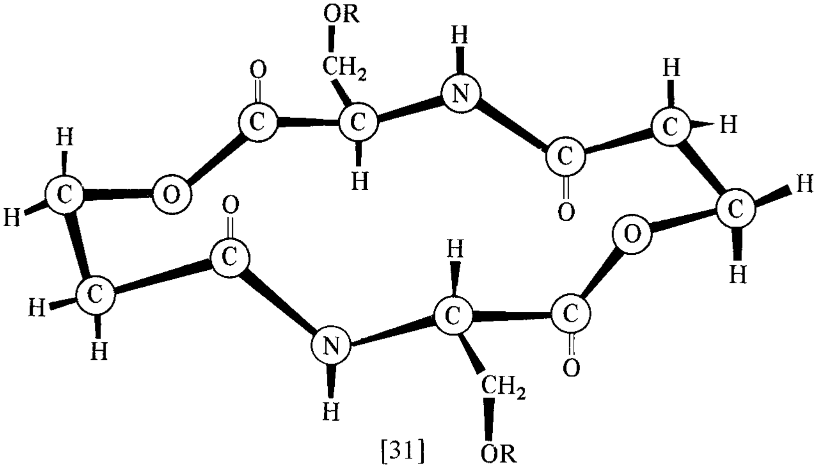
support such interactions since the coalescence temperature for cyclotetrasarcosyl (*ca.* 180°C) is very different from that in cyclo (sar-gly-sar-gly) (*ca.* 20°C), the difference being attributed to the lower basicities of NH than NMe, and consequently lesser trans-annular interaction. Very recently, results have appeared in which the conformations of protonated species of cyclotetrapeptides have been discussed. (130)

Turning to 14-membered rings, the conformation of the naturally occurring cyclodepsipeptide antibiotic serratamolide has been investigated using a combination of NMR and IR spectroscopy. (133) The presence of only five multiplets in the NMR spectrum of the peptide backbone protons, and the apparent absence of conformational mobility in the ring (between −85 and +150°C) suggested a two-fold axis of symmetry. In addition small vicinal couplings ($J \simeq 2,5$ Hz) for the $-CH_2CH-$ fragments in the ring, and a large coupling ($J \simeq 9$ Hz) for the CH . NH fragment suggested *gauche* and *trans* orientations respectively. Rapid exchange of the NH protons in methanol-d_4 and a high temperature dependence of the chemical shift of the NH protons confirmed the lack of intramolecular hydrogen bonding (NH . . . O=C). Again small vicinal couplings for the $-C_\alpha H\, C_\beta H_2-$



[30]

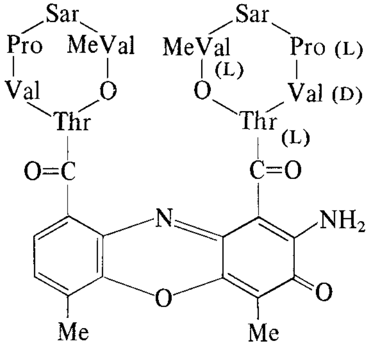
fragments of the seryl residues suggested predominant *gauche* relationships for these protons. This evidence, coupled with high dilution IR measurements suggested a conformation [30]. It is interesting to note that in the related compounds lacking the hydrocarbon side-chains, the di-*O*-*t*-butyl or di-*O*-acetyl derivatives apparently adopt similar conformations in solution, whereas the *meso*-compound [31] with one L and one D serine residue prefers the conformation shown. The NMR information from these compounds seems unambiguous, conformational rigidity being clearly present in the $-CH_2-CH_2-$ fragments, which appear as a readily analysable ABXY system in suitable solvents.



[31]

4. Cyclic Pentapeptides

Interest in the conformation of actinomycin D [32] lies in the desire to determine the mechanism of inhibition by this and related



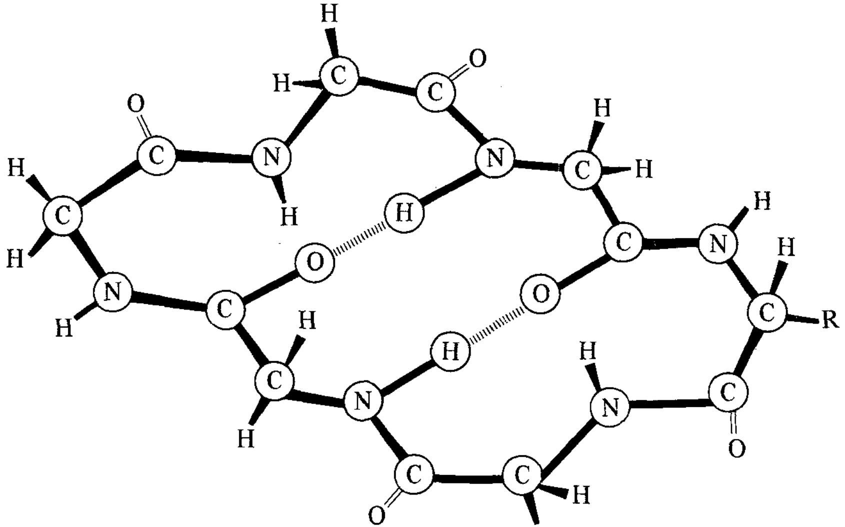
[32]

molecules of DNA dependent RNA synthesis. Some controversy has arisen over the interpretation of NMR data for actinomycin D. (134-141). It seems agreed that there are intramolecular hydrogen bonds in each peptide lactone ring in solution. The consensus of opinion at present indicates that the isolated pentapeptide lactones exist in solution with amide and ester bonds *trans*-oriented, except for the amide bond between sarcosine and proline which is *cis* (defined as in [19]). It is argued that Lackner's conformation (135, 136) with the sarcosine-proline amide bond *trans* has the *N*-methyl group too close to the proline ring. (141) It is agreed, however, that in the isolated peptide lactone rings there is a hydrogen bond between the D-valine NH proton and the sarcosine carboxyl group, demonstrated by slow exchange and a low temperature coefficient of the NH protons in the NMR spectrum. In the crystal structure, however, (142) there are two hydrogen bonds between D-valine residues in different rings, and *cis* sarcosine-proline amide bonds. Clearly, this topic is by no means exhausted.

5. Cyclic Hexapeptides

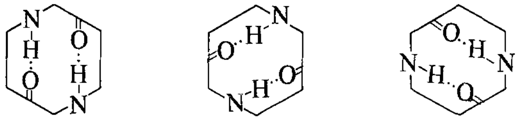
Cyclic hexapeptides and depsipeptides are probably the most-studied of the cyclic series, possibly because of their easy synthesis and ready availability. An interesting factor is the ability of some naturally-occurring and synthetic cyclohexapeptides or cyclohexadepsipeptides to complex with alkali metal cations. The ability of some cyclic peptides or more often, cyclodepsipeptides to act as selective ion transporters has been correlated with antibiotic activity, (143) but this has been disputed by various groups. It is generally agreed that the conformation of the peptide backbone is as shown [33] with two anti-parallel hydrogen bonds, in a β-pleated sheet structure as proposed by Schwyzer. (144-146)

The ^{1}H NMR spectra of a wide variety of cyclic hexapeptides has been studied, and the presence of two backbone NH protons shielded from solvent, and four exposed, is good evidence for the typical structure [33]. (147-151) Additional evidence concerning the peptide backbone conformation is afforded by measurements of ^3J(NHCH) for the six residues, where possible. An extensive examination of all possible combinations of L-alanine and glycine residues, and all possible combinations of diastereomeric cyclohexa-alanyls, showed that all the compounds examined revealed two groups of NH resonances in the ^{1}H NMR spectrum in the ratio 4:2, the 4 protons appearing to lower field. (149-151) It is suggested that, since the deuterium exchange rate does not differentiate between the two



[33]

groups, fast conformational isomerism of the type [34] is occurring. Further evidence of conformational isomerism in cyclic hexapeptides has appeared very recently. (152-154) From an examination of



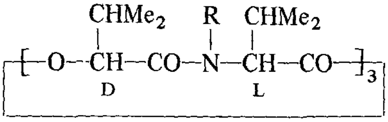
[A] [B] [C]

[34]

several cyclohexapeptides, Kopple *et al.* concluded that the trans-annular hydrogen bonds are not important conformational determinants and that the residues with side chains take up the most favourable positions energetically. (152)

A thorough 220 MHz NMR analysis of cyclo(pro-ser-gly-pro-ser-gly) provided convincing evidence that the molecule rapidly interconverts between two distorted β-structures, both with two gly–gly intramolecular hydrogen bonds, and both with *trans* gly-pro peptide bonds. (153) Further peaks in the spectra are consistent with a small population of an asymmetric conformation possessing one *cis* and one *trans* gly-pro amide bond, and separated from the more favoured symmetric conformations by a high energy barrier. A related examination of cyclo(ser-pro-gly-ser-pro-gly), (154) using evidence of ${}^3J$(NHCH), NH exchange rates and temperature dependence showed that this molecule adopts a major conformation in aqueous solution similar to [33], with two ser-ser intramolecular hydrogen bonds, but in DMSO solution, *cis* ser-pro amide bonds are preferred, with no hydrogen bonds. It is evident that the conformations of these cyclic hexapeptides are not limited to the β-structure, the actual conformation depending on the nature and order of the amino acids present and the solvent used.

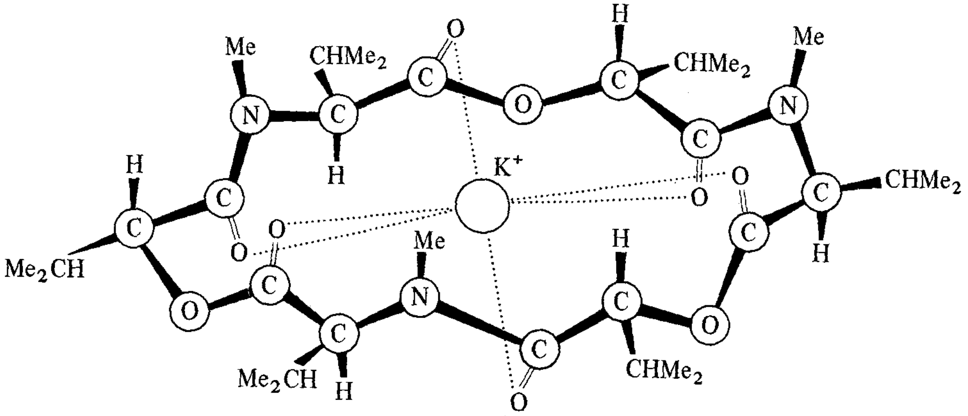
The naturally-occurring cyclodepsipeptide enniatin B ([35], $R = CH_3$) is one of the antibiotic molecules capable of increasing



$$\Big[\!-\text{O}-\underset{\text{D}}{\overset{\text{CHMe}_2}{\text{CH}}}-\text{CO}-\overset{\text{R}}{\text{N}}-\underset{\text{L}}{\overset{\text{CHMe}_2}{\text{CH}}}-\text{CO}-\Big]_3$$

[35]

specifically the ion permeability of artificial and biological membranes. (155) The NMR spectrum of [35] in CS_2-$CD_3C_6D_5$ (2:1) at different temperatures is shown in Fig. 3. At −127°C three equally intense *N*-methyl singlets are visible suggesting that a dissymmetric conformation has been frozen out or, less likely, that three different equally-populated conformations are present. Therefore it seems that in the preferred conformation at −127°C the three N-CH_3 groups are in different environments, and a conformation incorporating these features was proposed. This is in contrast to the structure of the complex with potassium iodide, in which the potassium resides in a compact symmetrical cavity equidistant from the oxygen atoms of the six carbonyl groups as shown [36]. In the corresponding $Li^{\oplus}$,



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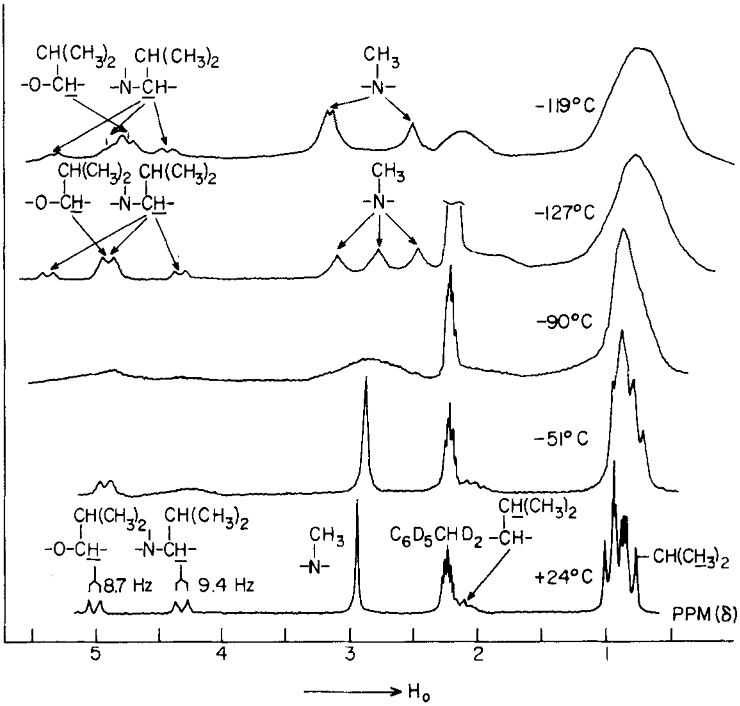
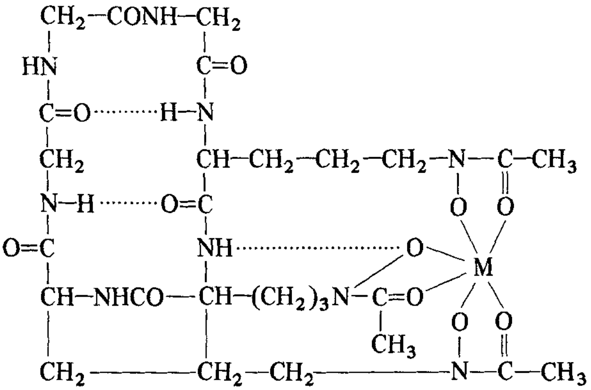


FIG. 3. The NMR spectrum of enniatin B in CS_2 at −119° (upper trace) and in $CS_2{:}CD_3C_6D_5$ (2:1) at different temperatures (lower spectrum) [From Ovchinnikov *et al.* (155).]

$Na^{\oplus}$, $K^{\oplus}$ and $Cs^{\oplus}$ complexes of tri-*N*-desmethyl enniatin B ([35], R = H) ^3J(NHCH) varied considerably (5.1, 6.5, 7.9 and 8.4 Hz respectively). This increase, it is suggested, reflects the "opening-out" of the carbonyl groups to accommodate the larger cation.

Ferrichrome [37], which can act as a growth factor for certain micro-organisms and is suspected to have a role in ion transport, is unsuitable for PMR studies owing to paramagnetic effects. A conformational study of deferrichrome and its $Al^{3\oplus}$ complex has been reported, using 220MHz NMR as the investigating tool. (156) It was concluded that the Schwyzer-type of structure was predominant, in solution, with two transannular hydrogen bonds.

The overwhelming evidence therefore suggests that the cyclohexapeptides, where possible, adopt the conformation [33] with the hydrogen bonds enclosing two 10-membered rings, termed β-turns (8) or β-loops. (7) It is encouraging that this structure has been found in the crystal of cyclo(gly-gly-D-ala-D-ala-gly-gly) (157) and in



[37]

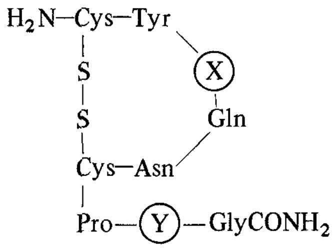
one of four conformations of cyclohexaglycyl. (158) The β-loop has been reported in many cyclic and linear peptides, (7, 8) and is now a common feature particularly in large cyclic peptides.

6. Cyclic Peptides with 7 to 9 Residues

Evolidine, isolated from the leaves of *evodia xanthoxyloides* has the structure cyclo(ser-phe-leu-pro-val-asn-leu) (all L). (159) The temperature dependence of the chemical shifts of the peptide NH protons indicated that those of the asparagine ([3], R = $CONH_2$) and phenylalanine residues were shielded from the solvent. Again problems arise with the proline residue, the best fit with the data having the leu-pro amide bond *cis* in the cycloheptapeptide.

A cyclononapeptide "Cyclolinopeptide A" was examined by Brewster and Bovey (160) and Tonelli. (161) Using the methods described above, they concluded that the 27-membered ring in dimethyl sulphoxide solution does not have intramolecular hydrogen bonds. Of the seven peptide NH protons in the structure, cyclo(phe-phe-leu-ile-ile-leu-val-pro-pro) (all L) five are apparently exposed to solvent and two not. Spin decoupling assignments clearly show that one of the proline α-protons appears as a sharp doublet ($J \simeq 8$ Hz) as is the case with several other cyclic peptides, (159, 162) suggesting dihedral angles of 30° and 90° with the β-C-H bonds, consistent with an envelope conformation with C_γ out of the plane of the other four ring atoms.

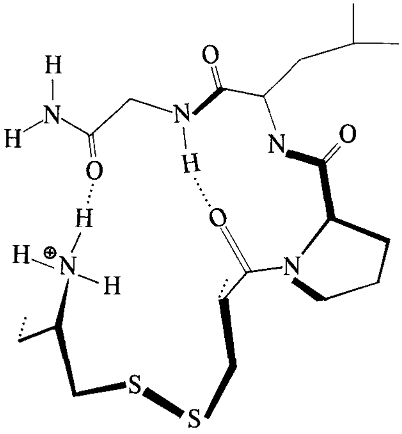
Oxytocin [38] and the related lysine vasopressin [39] have been the subjects of intense interest as far as conformational analysis is concerned. (163-170) Though these peptides are cyclic only in having disulphide bridges, the very presence of the latter produces



[38] X = Ileu, Y = Leu

[39] X = Phe, Y = Lys.

novel conformational features. The crystal structure of a derivative of the *C*-terminal tetrapeptide (*S*-benzyl-cys-pro-leu NH_2) includes a "β-loop", (171) though the crystal structure of the cyclic moiety has not, to the author's knowledge, been determined. In solution, NMR analysis shows the conformations of oxytocin and lysine vasopressin are different in dimethyl sulphoxide and aqueous solutions, the crucial issue, as in all studies of cyclic peptides, being the presence or absence of transannular hydrogen bonds. In dimethyl sulphoxide it is claimed that the 20-membered ring of oxytocin is stabilized by two Schwyzer-like hydrogen bonds (163, 165) one enclosing the familiar β-loop and that the *C*-terminal residue [40]

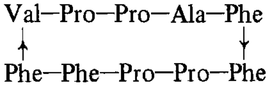


[40]

also includes a "β-loop" as in the crystal structure. (166) However, it has been shown that in dimethyl sulphoxide solution, derivatives of the side chain of oxytocin can adopt *cis* or *trans* conformations about the cys-pro bond, (167) although only the *trans* form was found in oxytocin itself. (166) Since aqueous solutions bear more relation to biological reality, it is interesting that Feeney *et al.* found no evidence for intramolecular hydrogen bonding in aqueous solutions of oxytocin and lysine-vasopressin, nor was the side-chain folded over the ring. (168) From these and related studies on lysine-vasopressin, (169, 170) it is clear that it is dangerous to extrapolate results in one solvent to predict conformations in another solvent, or to use crystal structures as a basis for arguing solution conformations.

7. Cyclic Decapeptides

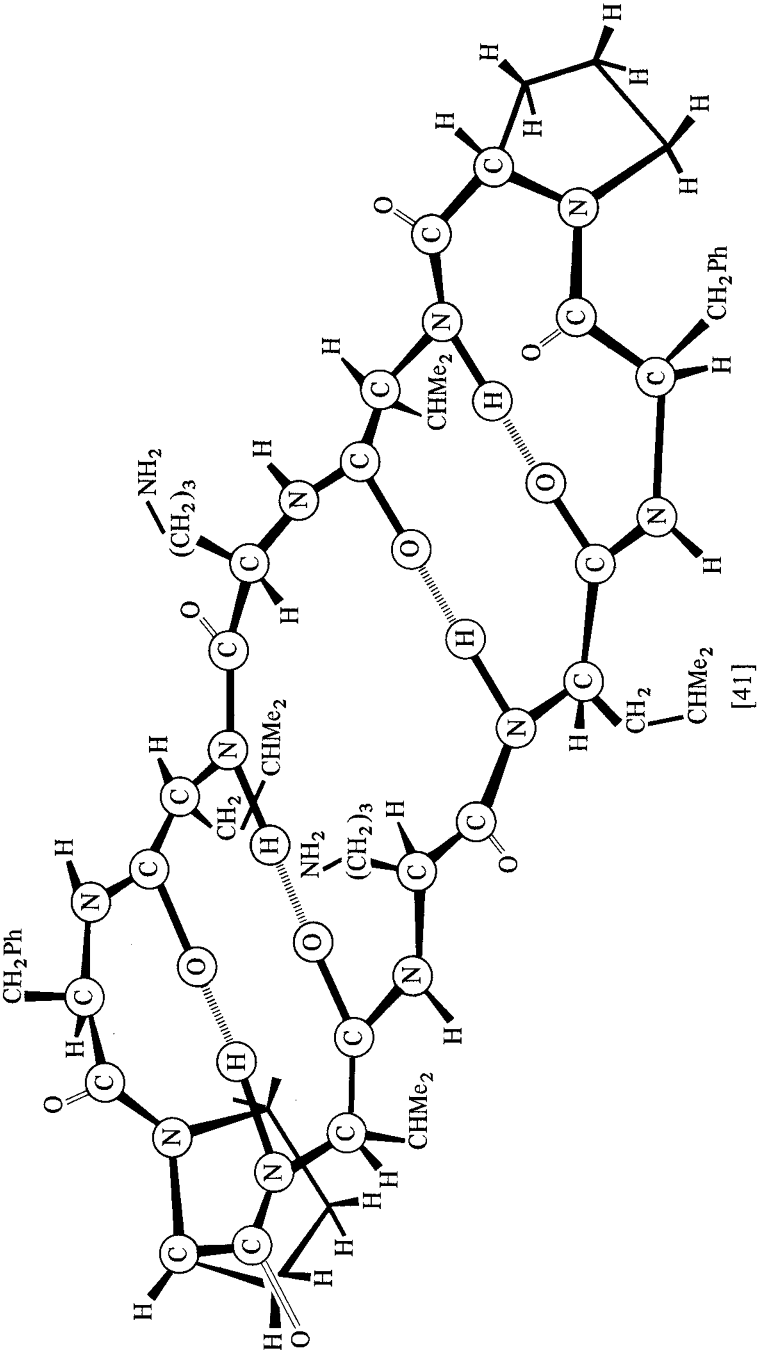
The conformation of Gramicidin S [41] has been sought after for about twenty years, but only in the last two years has the β-pleated sheet structure [41], first proposed by Hodgkin and Oughton, (712) been proved acceptable in solution by several research groups. (146, 173-177). NMR has again proved to be the most powerful available tool for unravelling the conformation. The C_2 symmetry of the conformation is evident from both ^{1}H (146, 173-177) and ^{13}C spectra, (178) and measurements of ^3J(NHCH), and the exchange-rates and temperature coefficients of the amide protons led to the assignment of [41] as the only form in solution, similar to that found in the crystal. (179) The anti-bacterial activity of this compound is certainly not related to ion-transport activity, since Gramicidin S, unlike the cyclodecapeptide antanamide [42], (180, 181) does not complex with alkali metal ions.



$$\begin{array}{ccccccccc} \text{Val} & — & \text{Pro} & — & \text{Pro} & — & \text{Ala} & — & \text{Phe} \\ \uparrow & & & & & & & & \downarrow \\ \text{Phe} & — & \text{Phe} & — & \text{Pro} & — & \text{Pro} & — & \text{Phe} \end{array}$$

[42]

At the present time the conformation of antanamide is a matter of some controversy, the American group (using NMR, C.D. and theoretical calculations) finding *no* intramolecular hydrogen bonding in their proposed model which has considerable symmetry, (180) and the Russian group (using NMR, ORD, IR and theoretical treatment) finding two conformations, one of which in non-polar solvents has no less than six hydrogen-bonded NH groups. (182) Both groups, however, agree that the amide bonds involving the proline nitrogen atoms are *trans* oriented. Further work on the sodium ion-dipole complex of antanamide (182) suggests that the cation residues in a cavity of a conformation similar to that adopted by nonactin, (183) the backbone resembling a tennis-ball seam, in wrapping itself around

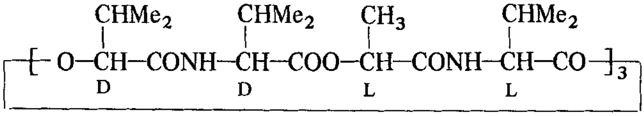

CH2Ph
CHMe2
(CH2)3
NH2
CH2
CHMe2
CH2Ph
CHMe2
(CH2)3
NH2
CH2
CHMe2

[41]

the cation, with six carbonyl groups involved in complexation. Finally, the novel conformational characteristics of a cyclic decapeptide analogue of Gramicidin S with a chiral cystine disulphide bridge have been reported, from NMR and CD investigations. (184)

8. Macrocyclic Peptides and Depsipeptides

From the previous discussion in this Review, the reader may naturally consider futile any investigations into the conformations of even larger rings, since the number of variables, and hence possible conformations, would seem to be unlimited. However, in the case of the 36-membered ring of the most famous of all cyclodepsipeptides, valinomycin [43], the high symmetry of the molecule means that

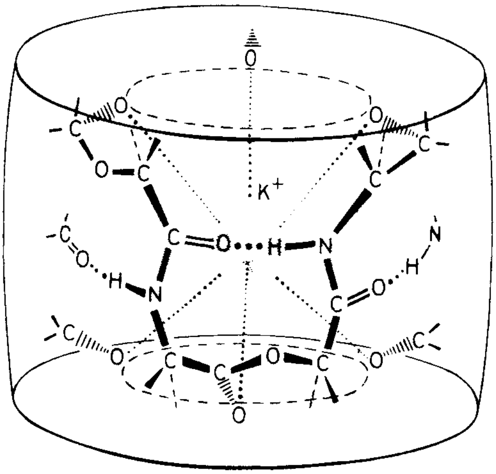


$$\left[\text{O}-\underset{\text{D}}{\overset{\text{CHMe}_2}{\text{CH}}}-\text{CONH}-\underset{\text{D}}{\overset{\text{CHMe}_2}{\text{CH}}}-\text{COO}-\underset{\text{L}}{\overset{\text{CH}_3}{\text{CH}}}-\text{CONH}-\underset{\text{L}}{\overset{\text{CHMe}_2}{\text{CH}}}-\text{CO}\right]_3$$

[43]

study of the conformation by NMR and other techniques is both practical and feasible, as noted by several groups. (8, 143, 175, 185-192) Although opinion is not unanimous on the conformation of the uncomplexed valinomycin, it appears that several conformations may exist depending on the solvent used. Ivanov *et al.* now consider that valinomycin adopts a conformation with three β-loops in non-polar solvents, and several conformations in polar solvents. Opinion is fairly unanimous that the potassium complex of valinomycin is as in the crystal, (193) with the potassium ion at the centre of a barrel-shaped peptide backbone, held together by 6 intramolecular hydrogen bonds each enclosing the usual ten-membered ring (β-loop) [44]. (8, 143, 175, 185-192) ^{13}C spectra of the free and complexed molecule indicate that the carbonyl resonances shift 4 ppm to high frequency on complexation, clearly a large effect readily monitored by ^{13}C NMR spectroscopy. (190, 191) It is thought that larger cations such as Rb$^{\oplus}$ and Cs$^{\oplus}$ cause the cavity in the complex to expand, thus lengthening and weakening the NH...OC hydrogen bonds. (188, 192)

Finally, the cyclic polypeptide alamethicin (with a 53-membered ring), which is yet another molecule with ion-transport properties, has been examined by NMR and other techniques and a conformation proposed, which must be highly speculative, judging by the difficulty of assigning conformations to even small cyclic peptides. (194-196)



Summarizing this section on cyclic peptides, it is clear that NMR alone is often insufficient to accurately predict the shapes adopted by the rings, but that is by far the most powerful technique available for determination of solution conformation. A combination of NMR with IR and ORD measurements, or better potential energy calculations seems to offer the best solution to the problem. Doubts still remain with regard to the presence or absence of transannular hydrogen bonds in these systems. Another technique for establishing the presence or absence of intramolecular hydrogen bonds or solvent shielded protons is to study the ^{1}H NMR spectrum in trifluoroethanol-solvent mixtures. (197) Examples clearly show a dramatic *low frequency* shift for the amide protons exposed to solvent, and a slight high-frequency shift for amide protons shielded from the solvent, without apparently changes in conformation occurring.

VII. POLY-AMINO ACIDS AND SEQUENTIAL CO-POLYMERS

The study of poly-amino acids by ^{1}H NMR spectroscopy is a review in itself and the reader is referred to several recent review articles on the subject. (3, 46) These molecules provide spectroscopic data for well-defined conformations in solution and transition to another conformation is effectively monitored. For example, the addition of trifluoroacetic acid (TFA) to chloroform-*d* solutions of poly-α-amino acids breaks down the α-helix to the random coil form in which different chemical shifts are observed. Sheard and Bradbury (4) summarize the situation up to early 1969 as follows:

(a) In chloroform solution, the α-proton chemical shift is apparently the same in helical and random coil conformations, though in aqueous solution small differences are apparent.
(b) Addition of TFA to chloroform solutions causes a large chemical shift to high frequency for the random coil α-CH peak. In the mixed solvent, the helix content may be estimated either from relative peak areas, or from the chemical shift of the time-averaged α-proton under conditions of rapid exchange.
(c) The α-proton chemical shift of an L-residue in a right-handed α-helix is similar to that in an L-residue of a left-handed helix.
(d) Side chains have a considerable effect on the α-proton chemical shifts in both helical and random-coil forms.

A selection of important papers appearing since 1969 are summarized as follows: the kinetics of the helix-coil transition in poly-L-ala, and poly-L-met have been followed by NMR/ORD, and the results suggest that the helix-coil interconversion of low molecular weight polypeptides has a longer relaxation time than high molecular weight polypeptides. (198) Helix-coil transitions and conformations have received further study in the case of poly(L-glutamic acid esters), (199-202) poly(L-aspartic acid esters), (203, 204) poly(L-lysines), (205) various polymers of residues containing aromatic groups, (206-209) poly(DL-alanine) and poly(L-alanine), (210, 211) poly(β-alanine), (212, 213) several alternating sequential polypeptides, (214, 215) poly(*N*-methyl-L-alanine), (216) poly(L-proline) I and II, (84, 89, 217, 218) poly(sarcosine) (219) and poly(L-thiazolidine-4-carboxylic acid) and poly(L-oxazolidine-4-carboxylic acid). (220) Polymers of L-proline and *N*-methylated amino acids are of immediate interest, the amide bonds in such compounds may be *cis* or *trans* oriented. Poly-L-proline I has a regular helical structure with all-*cis* peptide bonds and when dissolved in water isomerizes to the all-*trans* form II. This can effectively be monitored by NMR, since the α-protons have different chemical shifts in the two forms. (218) It is suggested with some experimental evidence that, in aqueous solution, the isomerization begins at the carboxyl end of the polymer and proceeds stepwise down the chain. (218)

Finally in this brief survey of the field of regular polypeptides, some important general papers have appeared. The assignment of α-CH peaks in the NMR spectra of polypeptides has been made with further experimental evidence. (221) The conformation about the N-C_α bond in random-coil polypeptides has been discussed. (222)

^{13}C NMR has been used to study the helix-coil transition of poly(γ-benzyl glutamate). (223)

VIII. IRREGULAR POLYPEPTIDES, PROTEINS AND ENZYMES

As stated previously, although the information present in the NMR spectrum should be sufficient to define the conformation of a polypeptide fairly rigorously, the ambiguitites associated with analysis of the spectrum, and with ^3J(CHNH) measurements of dihedral angle cause extreme difficulty. Urry and co-workers have bravely attempted to define conformational features of gramicidin A′, a mixture of penta-decapeptides differing only in the residue at position 11. (224-227) There is considerable evidence that this family of peptides form channels through liquid bilayer membranes, and also manifest many of the physical properties of proteins, e.g. aggregation and interaction with lipids and metal ions. It is proposed that gramicidin A′ adopts a lipophilic, left-handed helical structure termed the $\pi_{(\mathrm{L},\mathrm{D})}$ helix. Two such helices joined head to head form a channel through which cations may pass. NMR features, in particular ^3J(NHCH) values, are consistent with such a conformation in dimethyl sulphoxide solution.

Determination of the complete solution conformations of giant molecules such as proteins and enzymes is clearly impossible at the present state of development of NMR spectroscopy and theory. Most of the published work so far (228-240) has been concentrated on lysozyme, an enzyme with a single chain of 129 amino acids with four disulphide bridges. The proximity of the methyl groups of valine, leucine and isoleucine residues to the axes of aromatic rings in the enzyme in the folded form is demonstrated by the presence of a low-frequency shift at δ 0.7 to 1.0. These resonances are absent in the denatured enzyme. (229) In a more recent paper five out of the six indole NH protons have been resolved at 220 MHz and assigned to specific residues in the enzyme by means of chemical modification, deuterium exchange kinetics and inhibitor perturbation studies together with X-ray diffraction studies. (233) Summarizing briefly other lysozyme NMR research, the mechanism of the reversible denaturization of the enzyme has been studied, (232) partial deuterium substitution has been used to aid assignment, (234) ^{19}F NMR has been used to study the binding of fluorinated substances to the active site, (236, 238) and ^{13}C studies have been reported. (239, 240)

More dramatic chemical shift abnormalities have been found in protons containing paramagnetic metal species, e.g. the haem proteins, (242-245) ferredoxins, (246, 247) cytochrome C, (248) cyanoferrimyoglobin (249) and chromatium high potential iron protein. (250) Large pseudo-contact shifts in these molecules allow some conformational features to be recognized. A large number of papers have reported NMR studies of enzyme-substrate and enzyme-inhibitor complexes, and metal binding reactions of enzymes. This subject is outside the scope of this review, but a review of this work with 118 references has recently appeared. (251)

It is clear that at the present time the amount of conformational information gleaned from the NMR spectra of macromolecules of this type is very limited, owing in the main to the complexity of the spectra investigated. Use of nuclei other than hydrogen-^{13}C, ^{19}F appears to offer more scope, or examination of the ^{1}H spectra of massively deuterated proteins. The proteins. The problem of assignment of ^{13}C resonances has been simplified by a graphical technique using off-resonance decoupling at the proton frequency. (252) Use of lanthanide cations or complexes to simplify the spectra of peptides has scarcely been used up to the present time, but offers great potential as a conformational probe, and spectrum simplifier. (253)

IX. SUMMARY

It is clear that despite the problems and ambiguities associated with the determination of peptide conformations from NMR data, the technique offers more information than other physical methods in solution studies, particularly in the case of cyclic peptides, where the number of possible conformations is limited. However, a combination of NMR with other techniques used such as IR, ORD/CD and potential energy calculations appears to offer the best solution. Although it seems unlikely that all the information associated with the NMR spectra of proteins and enzymes will ever be extracted, valuable facts concerning active site interactions will probably be determined. A technique not discussed in this Review is the measurement of relaxation times of ^{13}C nuclei. Since these are sensitive to environment it is possible that yet another conformational probe will emerge in the near future.

I would like to thank those authors who kindly provided reprints and preprints of papers I have included in this Review.

REFERENCES

1. G. K. C. Roberts and O. Jardetsky, *Adv. Protein Chem.*, 1970, **24**, 447.
2. J. J. M. Rowe, J. Hinton and K. L. Rowe, *Chem. Rev.*, 1970, **70**, 1.
3. M. Goodman, A. S. Vardini, N. S. Choi and Y. Masuda, *Topics in Stereochemistry*, 1970, 5, 69.
4. B. Sheard and E. M. Bradbury, *Prog. Biophys. Mol. Biol.* 1970, **20**, 187.
5. A. Allerhand and E. A. Trull, *Ann. Rev. Phys. Chem.*, 1970, **21**, 317.
6. F. A. Bovey, "Polymer Conformation and Configuration", Polytechnic Press, New York, 1969.
7. C. H. Hassall and W. A. Thomas, *Chem. Britain*, 1971, **7**, 145.
8. D. W. Urry and M. Ohnishi, "Spectroscopic Approaches to Biomolecular Conformation", D. W. Urry (ed.), American Medical Association Press, 1970, p. 263.
9. M. Cohn, *Quart. Rev. Biophys.*, 1970, **3**, 61.
10. A. S. Mildvan and M. Cohn, *Adv. Enzymology*, 1970, **33**, 1.
11. W. A. Gibbons, G. Nemethy, A. Stern and L. C. Craig, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **67**, 239.
12. F. A. Bovey, A. I. Brewster, D. J. Patel, A. E. Tonelli and D. A. Torchia, *Accounts Chemical Res.*, 1972, **5**, 193.
13. G. N. Ramachandran, R. Chandrasekaran and K. D. Kopple, *Biopolymers*, 1971, **10**, 2113.
14. M. Takeda and O. Jardetsky, *J. Chem. Phys.*, 1957, **26**, 1346.
15. O. Jardetsky and C. D. Jardetsky, *J. Biol. Chem.*, 1958, **233**, 383.
16. F. A. Bovey and G. V. D. Tiers, *J. Amer. Chem. Soc.*, 1959, **81**, 2870.
17. M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
18. M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.
19. R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, 1962, **5**, 195.
20. R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, 1962, **5**, 513.
21. R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 1964, 3739.
22. R. H. Andreatta, V. Nair and A. V. Robertson, *Aust. J. Chem.*, 1967, **20**, 2701.
23. J. Collonitch, A. N. Scott and G. A. Doldouras, *J. Amer. Chem. Soc.*, 1966, **88**, 3624.
24. A. B. Mauger, F. Irreverre and B. Witcop, *J. Amer. Chem. Soc.*, 1966, **88**, 2019.
25. J. Blake, C. D. Willson and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 5293.
26. C. B. Hudson, A. V. Robertson and W. R. J. Simpson, *Aust. J. Chem.*, 1968, **21**, 769.
27. R. J. Abraham and G. Gatti, *Org. Magn. Resonance*, 1970, **2**, 173.
28. K. G. R. Pachler, *Spectrochim. Acta.*, 1963, **19**, 2085.
29. K. G. R. Pachler, *Spectrochim. Acta.*, 1964, **20**, 581.
30. K. C. Ramey and J. Messick, *Tetrahedron Lett.*, 1965, 4423.
31. G. W. Kirby and V. A. Moss, *J. Chem. Soc., C*, 1970, 2049.
32. G. W. Kirby and J. Michael, *Chem. Commun.*, 1971, 187.
33. K. R. Hanson, R. H. Wightman, J. Staunton and A. R. Battersby, *Chem. Commun.*, 1971, 185.
34. J. R. Cavanaugh, *J. Amer. Chem. Soc.*, 1967, **89**, 1558.
35. J. R. Cavanaugh, *J. Amer. Chem. Soc.*, 1968, *90*, 4553.
36. J. R. Cavanaugh, *J. Amer. Chem. Soc.*, 1970, **92**, 1488.
37. H. Ogura, Y. Arata and S. Fujiwara, *J. Mol. Spectroscopy*, 1967, **23**, 76.
38. K. D. Bartle, J. C. Fletcher, D. W. Jones and R. L'Amie, *Biochim. Biophys. Acta.*, 1968, **160**, 106.
39. R. B. Martin and R. Mathur, *J. Amer. Chem. Soc.*, 1965, **87**, 1065.

40. J. A. Glasel, *J. Amer. Chem. Soc.*, 1965, **87**, 5472.
41. S. Fujiwara and Y. Arata, *Bull. Chem. Soc. Japan,* 1964, **37**, 344.
42. S.Fujiwara and Y. Arata, *Bull. Chem. Soc. Japan,* 1693, **36**, 578.
43. F. Taddei and L. Pratt, *J. Chem. Soc.*, 1964, 1553.
44. K. G. R. Pachler and J. P. Tollenaere, *Spectrochim. Acta.*, 1968, **24A**, 1311.
45. B. Bak and F. Nicolaisen, *Acta Chem. Scand.*, 1967, **21**, 1980.
46. J. F. Newmark and R. A. Newmark, *Spectrochim. Acta.*, 1968, **24A**, 952.
47. G. Aruldhas, *Spectrochim. Acta.*, 1967, **23A**, 1345.
48. J. N. Shoolery and A. I. Virtanen, *Acta Chem. Scand.*, 1962, **16**, 2457.
49. W. A. Thomas and M. K. Williams, *Chem. Commun.*, 1972, 788, 994.
50. W. Lijinsky, L. Keefer and J. Lee, *Tetrahedron*, 1970, **26**, 5137.
51. C. H. Hassall, Y. Ogihara and W. A. Thomas, *J. Chem. Soc., C,* 1971, 522.
52. K. Bevan, J. S. Davies, M. J. Hall, C. H. Hassall, R. B. Morton, D. A. S. Phillips, Y. Ogihara and W. A. Thomas, *Experientia*, 1970, **26**, 122.
53. W. A. Thomas and M. K. Williams, *Org. Magn. Resonance*, 1972, **4**, 145.
54. M. Noma, M. Noguchi and E. Tamaki, *Tetrahedron Lett.*, 1971, 2017.
55. H. M. Berman, E. L. McGandy, J. W. Burgner II and R. L. Van Etten, *J. Amer. Chem. Soc.*, 1969, **91**, 6177.
56. R. L. Lichter and J. D. Roberts, *J. Org. Chem.*, **1970**, **35**, 2806.
57. W. Horsley, H. Sternlicht and J. S. Cohen, *J. Amer. Chem. Soc.*, 1970, **92**, 680.
58. W. Voelter, G. Jung, E. Breitmaier and E. Bayer, *Z. Naturforsch,* 1971, **26**, 213.
59. See for instance: W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 1970, **70**, 517.
60. H. Paulsen and K. Todt, *Angew. Chem. Int. Ed.*, 1966, **5**, 899.
61. H. Paulsen and K. Todt, *Chem. Ber.*, 1967, **100**, 3385.
62. H. Paulsen and K. Todt, *Chem. Ber.*, 1967, **100**, 3397.
63. H. Paulsen and K. Todt, *Z. Anal. Chem.*, 1968, **235**, 30.
64. H Paulsen and F. Leupold, *Carbohydrate Res.*, 1966, **3**, 47.
65. F. A. L. Anet and A. J. R. Bourne, *J. Amer. Chem. Soc.*, 1965, **87**, 5250.
66. J. L. Dimicoli and M. Ptak, *Tetrahedron Lett.*, 1970, 2013.
67. V. Madison and J. Schellman, *Biopolymers,* 1970, **9**, 511.
68. R. Garner and W. B. Watkins, *Chem. Commun.*, 1969, 386.
69. H. L. Maia, K. G. Orrell and H. N. Rydon, *Chem. Commun.*, 1971, 1209.
70. G. H. Cooper, *Chem. Ind.*, 1969, 1304.
71. F. H. C. Stewart, *Aust. J. Chem.*, 1971, **24**, 1949.
72. R. A. Newmark and M. A. Miller, *J. Phys. Chem.*, 1971, **75**, 505.
73. B. Liberek, K. Steporowska and E. Jereczek, *Chem. Ind.*, 1970, 1263.
74. V. F. Bystrov, S. L. Portnova, V. I. Tsetlin, V. T. Ivanov and Yu. A. Ovchinnikov, *Tetrahedron*, 1969, **25**, 493.
75. T. Wieland and H. Bende, *Chem. Ber.*, 1965, **98**, 504.
76. F. A. Bovey and G. V. D. Tiers, *J. Amer. Chem. Soc.*, 1959, **81**, 2870.
77. M. Takeda and O. Jardetsky, *J. Chem. Phys.*, 1959, **26**, 1346.
78. B. Halpern, D. E. Nitecki and B. Weinstein, *Tetrahedron Lett.*, 1959, 1967.
79. A. Nakamura and O. Jardetsky, *Proc. Nat. Acad. Sci., U.S.A.*, 1967, **58**, 2213.
80. V. J. Morlino and R. B. Martin, *J. Amer. Chem. Soc.*, 1967, **89**, 3107.
81. V. J. Morlino and R. B. Martin, *J. Phys. Chem.*, 1968, **72**, 2661.
82. V. F. Bystrov, S. L. Portnova, T. A. Balashova, V. I. Tsetlin, V. T. Ivanov, P. V. Kostetzky and Yu. A. Ovchinnikov, *Tetrahedron Lett.*, 1969, 5283.
83. F. Conti, C. Pietronero and P. Viglino, *Org. Magn. Resonance*, 1970, **2**, 131.
84. C. M. Deber, F. A. Bovey, J. P. Carver and E. R. Blout, *J. Amer. Chem. Soc.*, 1970, **92**, 6191.

85. A. E. Tonelli, A. I. Brewster and F. A. Bovey, *Macromolecules*, 1970, **3**, 412.
86. M. Nagai, A. Nishioka and J. Yoshimura, *Bull. Chem. Soc. Japan*, 1970, **43**, 1323.
87. S. L. Portnova, V. F. Bystrov, T. A. Balashova, V. T. Ivanov and Yu. A. Ovchinnikov, *Isv. Akad. Nauk. SSSR, Ser. Khim.*, 1970, 825.
88. G. Ramachandran and R. Chandrasekaran, *Biopolymers*, 1971, **10**, 935.
89. H. Okabayaski and T. Isamura, *Bull. Chem. Soc. Japan*, 1970, **43**, 359.
90. S. L. Portnova, V. F. Bystrov, T. A. Balashova, V. I. Tsetlin, P. V. Kostetskii, V. T. Ivanov and Yu. A. Ovchinnikov, *Zh. Obsch. Khim.*, 1971, **41**, 407.
91. S. V. Zenin, N. Y. Krasnobrizhii, V. E. Minaev, N. A. Poddubnaya and G. B. Sergeev, *Zh. Obsch. Khim.*, 1971, **41**, 665.
92. C. M. Thong, D. Canet, P. Granger, M. Marraud and J. Neel, *Compt. rendus*, 1969, **296C**, 580.
93. L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, 1964, **86**, 337.
94. M. Takeda and E. O. Stejskal, *J. Amer. Chem. Soc.*, 1960, **82**, 25.
95. C. Franconi, *Z. Electrochem.*, 1961, **65**, 645.
96. M. T. Rogers and L. A. LaPlanche, *J. Phys. Chem.*, 1965, **69**, 3648.
97. G. Müller and R. Marten, *Chem. Ber.*, 1965, **98**, 1097.
98. I. D. Rae, *Aust. J. Chem.*, 1966, **19**, 1983.
99. M. Chabre, D. Gagnaire and C. Nofre, *Bull. Soc. Chim. France*, 1966, 108.
100. P. Rouillier, J. Delmau, J. Duplan and C. Nofre, *Tetrahedron Lett.*, 1966, 4189.
101. P. Rouillier, J. Delmau and C. Nofre, *Bull. Soc. Chim. France*, 1966, 3515.
102. E. W. Randall and J. D. Baldeschwieler, *J. Mol. Spectroscopy*, 1962, **8**, 365.
103. A. T. R. Brown and E. W. Randall. *Mol. Phys.*, 1964, **8**, 567.
104. W. A. Gibbons, G. Nemethy, A. Stern and L. C. Craig, *Proc. Nat. Acad. Sci., U.S.A.*, 1970, **67**, 239.
105. H. A. Scheraga, *Chem. Rev.*, 1971, **71**, 195.
106. G. N. Ramachandran, R. Chandrasekaran and K. D. Kopple, *Biopolymers*, 1971, **10**, 2113.
107. J. Feeney, G. C. K. Roberts, J. P. Brown, A. S. V. Burgen and H. Gregory, *J. Chem. Soc., Perkin II*, 1972, 601.
108. R. J. Weinkam and E. C. Jorgensen, *J. Amer. Chem. Soc.*, 1971, **93**, 7028.
109. R. J. Weinkam, and E. C. Jorgensen, *J. Amer. Chem. Soc.*, 1971, **93**, 7038.
110. K. D. Kopple and D. H. Marr, *J. Amer. Chem. Soc.*, 1967, **89**, 6193.
111. K. D. Kopple and M. Ohnishi, *J. Amer. Chem. Soc.*, 1969, **91**, 962.
112. Ziauddin and K. D. Kopple, *J. Org. Chem.*, 1970, **35**, 253.
113. Ziauddin, K. D. Kopple and C. A. Bush, *Tetrahedron Lett.*, 1972, 483.
114. G. Gawne, G. W. Kenner, N. H. Rogers, R. C. Sheppard and K. Titlestad, "Peptides", E. Bricas (ed.), North-Holland, Amsterdam, 1968, p. 28.
115. L. E. Webb and C-F. Lin, *J. Amer. Chem. Soc.*, 1971, **93**, 3818.
116. J. V. Hatton and R. E. Richards, *Mol. Phys.*, 1962, **5**, 139.
117. B. Halpern, D. E. Nitcki and B. Weinstein, *Tetrahedron Lett.*, 1967, 3075.
118. E. M. Popov, V. Z. Pletnev, S. L. Portneva, V. T. Ivanov, P. V. Kostetskii and Yu. A. Ovchinnikov, *Zh. Obsch. Khim.*, 1971, **41**, 420.
119. I. Z. Siemion, *Ann.*, 1971, **748**, 88.
120. I. L. Karle, *J. Amer. Chem. Soc.*, 1972, **94**, 81.
121. E. Sletten, *J. Amer. Chem. Soc.*, 1970, **92**, 172.
122. C. Benedetti, P. Corradini and C. Pedone, *J. Phys. Chem.*, 1969, **73**, 2891.
123. B. Kamber, *Helv. Chim. Acta*, 1971, **54**, 927.
124. J. Dale and K. Titlestad, *Chem. Commun.*, 1969, 656.
125. J. Schaug, *Acta. Chem. Scand.*, 1971, **25**, 2771.

126. C. M. Venkatachalam, *Biochim. Biophys. Acta,* 1968, **168**, 397.
127. C. M. Deber, D. A. Torchia and E. R. Blout, *J. Amer. Chem. Soc.,* 1971, **93**, 4893.
128. D. A. Torchia and C. M. Deber, *Biopolymers,* to be published.
129. J. Dale and K. Titlestad, *Chem. Commun.,* 1970, 1403.
130. J. Dale and K. Titlestad, *J. Chem. Soc. Chem. Comm.,* 1972, 255.
131. J. Dale, *Pure Appl. Chem.,* 1971, **25**, 469.
132. P. Groth, *Acta Chem. Scand.,* 1970, **24**, 780.
133. C. H. Hassall, M. C. Moschidis and W. A. Thomas, *J. Chem. Soc. B,* 1971, 1757.
134. T. A. Victor, F. E. Hruska, C. L. Bell and S. S. Danyluk, *Tetrahedron Lett.,* 1969, 4721.
135. H. Lackner, *Tetrahedron Lett.,* 1970, 2807.
136. H. Lackner, *Tetrahedron Lett.,* 1970, 3189.
137. B. H. Arison and K. Hoogsteen, *Biochemistry,* 1970, **9**, 3976.
138. F. Conti and P. de Santis, *Nature,* 1970, **227**, 1239.
139. H. Lackner, *Tetrahedron Lett.,* 1971, 2221.
140. H. Lackner, *Chem. Ber.,* 1971, **104**, 3653.
141. P. de Santis, R. Rizzo and G. Ughetto, *Tetrahedron Lett.,* 1971, 4309.
142. H. M. Sobell, S. C. Jain and T. D. Sakore, *Nature New Biology,* 1971, **231**, 200.
143. M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, E. I. Vinogradova, A. M. Shkrob, G. G. Malenkov, A. V. Evstratov, I. A. Laine, E. I. Melnyk and I. D. Ryabova, *J. Membrane Biol.,* 1969, **1**, 402.
144. R. Schwyzer, *Record. Chem. Progr.* 1959, **20**, 147.
145. R. Schwyzer, J. P. Carrion, B. Gorup, H. Nolting and A. Tun-Kyi, *Helv. Chim. Acta,* 1964, **47**, 441.
146. R. Schwyzer and U. Ludescher, *Helv. Chim. Acta,* 1969, **52**, 2033.
147. K. D. Kopple, M. Ohnishi and A. Go., *J. Amer. Chem. Soc.,* 1969, **91**, 4264.
148. K. D. Kopple, M. Ohnishi and A. Go., *Biochemistry,* 1969, **8**, 4087.
149. S. L. Portnova, V. V. Shilin, T. A. Balashova, J. Biernat, V. F. Bystrov, V. T. Ivanov and Yu. A. Ovchinnikov, *Tetrahedron Lett.,* 1971, 3085.
150. S. L. Portnova, T. A. Balashova, V. F. Bystrov, V. V. Shilin, J. Biernat, V. T. Ivanov and Yu. A. Ovchinnikov, *Khim. Prir. Soedin,* 1971, **7**, 323.
151. V. T. Ivanov, S. L. Portnova, T. A. Balashova, V. V. Shilin, J. Biernat and Yu. A. Ovchinnikov, *Khim. Prir. Soedin,* 1971, **7**, 339.
152. K. D. Kopple, A. Go, R. H. Logan, Jr. and J. Savrda, *J. Amer. Chem. Soc.,* 1972, **94**, 973.
153. D. A. Torchia, A. di Corato, S. C. K. Wong, C. M. Deber and E. R. Blout, *J. Amer. Chem. Soc.,* 1972, **94**, 609.
154. D. A. Torchia, S. C. K. Wong, C. M. Deber and E. R. Blout, *J. Amer. Chem. Soc.,* 1972, **94**, 616.
155. Yu. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov, V. F. Bystrov, N. D. Abdullaev, E. M. Popov, G. M. Lipkind, S. F. Arkhipova, E. S. Efremov and M. M. Shemyakin, *Biochem. Biophys. Res. Comm.,* 1969, **37**, 668.
156. M. Llinas, M. P. Klein and J. B. Neilands, *J. Mol. Biol.,* 1970, **52**, 399.
157. I. L. Karle, J. W. Gibson and J. Karle, *J. Amer. Chem. Soc.,* 1970, **92**, 3755.
158. I. L. Karle and J. Karle, *Acta Crystallogr.,* 1963, **16**, 969.
159. K. D. Kopple, *Biopolymers,* 1971, **10**, 1139.
160. A. I. Brewster and F. A. Bovey, *Proc. Nat. Acad. Sci., U.S.A.,* 1971, **68**, 1199.
161. A. Tonelli, *Proc. Nat. Acad. Sci., U.S.A.,* 1971, **68**, 1203.
162. C. H. Hassall, M. C. Moschidis and W. A. Thomas, to be published.
163. L. F. Johnson, I. L. Schwartz and R. Walter, *Proc. Nat. Acad. Sci., U.S.A.,* 1969, **64**, 1269.

164. D. W. Urry, M. Ohnishi and R. Walter, *Proc. Nat. Acad. Sci., U.S.A.*, 1970, **66**, 111.
165. R. Walter, Structure-activity relationships of protein and polypeptide hormones, M. Margoulies and F. C. Greerwood (eds.), *Excerpta Medica*, 1971, 181.
166. D. W. Urry and R. Walter, *Proc. Nat. Acad. Sci., U.S.A.*, 1971, **68**, 956.
167. V. J. Hruby, A. I. Brewster and J. A. Glasel, *Proc. Nat. Acad. Sci., U.S.A., 1971,* **68**, 450.
168. J. Feeney, G. C. K. Roberts, J. H. Rockey and A. S. V. Burgen, *Nature New Biology*, 1971, **232**, 108.
169. P. H. Von Dreele, A. I. Brewster, H. A. Scheraga, M. F. Ferger and V. du Vigneaud, *Proc. Nat. Acad. Sci., U.S.A.*, 1971, **68**, 1028.
170. P. H. Von Dreele, A. I. Brewster, F. A. Bovey, H. A. Scheraga, M. F. Ferger and V. du Vigneaud, *Proc. Nat. Acad. Sci., U.S.A.*, 1971, **68**, 3088.
171. A. D. Rudko, F. M. Lovell and B. W. Low, *Nature New Biol.*, 1971, **232**, 18.
172. D. C. Hodgkin and B. M. Oughton, *Biochem. J.*, 1957, **65**, 752.
173. R. Schwyzer and U. Ludescher, *Biochemistry*, 1968, **7**, 2514.
174. A. Stern, W. A. Gibbons and L. C. Craig, *Proc. Nat. Acad. Sci., U.S.A.*, 1968, **61**, 735.
175. M. Ohnishi and D. W. Urry, *Biochem. Biophys. Res. Comm.*, 1969, **36**, 194.
176. F. Conti, *Nature*, 1969, **221**, 777.
177. Yu. A. Ovchinnikov, V. T. Ivanov, V. F. Bystrov, A. I. Miroshnikev, E. N. Shapel, N. D. Abdullaev, E. S. Efremov and L. B. Senyavina, *Biochem. Biophys. Res. Comm.*, 1970, **39**, 217.
178. W. A. Gibbons, J. A. Sogn, A. Stern, L. C. Craig and L. F. Johnston, *Nature*, 1970, **227**, 840.
179. G. Camilletti, P. de Santis and R. Rizzo, *Chem. Commun.*, 1970, 1073.
180. A. E. Tonelli, D. J. Patel, M. Goodman, F. Naider, H. Faulstich and Th. Wieland, *Biochemistry*, 1971, **10**, 3211.
181. Th. Wieland, H. Faulstich, W. Burgermeister, W. Otting, W. Möhle, M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov and G. G. Malenkov, *F.E.B.S. Lett.*, 1970, **9**, 89.
182. V. T. Ivanov, A. I. Miroshnikov, N. D. Abdullaev, L. B. Senyavina, S. F. Arkhipova, N. N. Uvarova, K. Kh. Khalilulina, V. F. Bystrov and Yu. A. Ovchinnikov, *Biochem. Biophys. Res. Comm.*, 1971, **42**, 654.
183. B. T. Kilburn, J. D. Dunitz, L. A. R. Pioda and W. Simon, *Helv. Chim. Acta,* 1967, **30**, 559.
184. U. Ludescher and R. Schwyzer, *Helv. Chim. Acta,* 1971, **54**, 1637.
185. D. H. Haynes, A. Kowalsky and B. C. Pressman, *J. Biol. Chem.*, 1969, **244**, 502.
186. V. T. Ivanov, I. A. Laine, N. D. Abdullaev, L. B. Senyavina, E. M. Popov, Yu. A. Ovchinnikov and M. M. Shemyakin, *Biochem. Biophys. Res. Comm.*, 1969, **34**, 803.
187. M. Ohnishi and D. W. Urry, *Science*, 1970, **168**, 1091.
188. V. T. Ivanov, I. A. Laine, N. D. Abdullaev, V. Z. Pletnev, G. M. Lipkind, S. F. Arkhipova, L. B. Senyavina, E. N. Mescheryakova, E. M. Popov, V. F. Bystrov and Yu. A. Ovchinnikov, *Khim. Prir. Soedin*, 1971, **7**, 221.
189. V. T. Ivanov, I. A. Laine, I. D. Ryabova and Yu. A. Ovchinnikov, *Khim. Prir. Soedin,* 1970, **6**, 744.
190. V. F. Bystrov, V. T. Ivanov, S. A. Kozmin, I. I. Mikhaleva, K. Kh. Khalilulina, Yu. A. Ovchinnikov, E. I. Fedin and P. V. Petrovskii, submitted to *F.E.B.S. Lett.*
191. M. Ohnishi, M. C. Fedarko, J. D. Baldschwieler and L. F. Johnson, *Biochem. Biophys. Res. Comm.*, 1972, **46**, 312.
192. D. F. Mayers and D. W. Urry, *J. Amer. Chem. Soc.*, 1972, **94**, 77.
193. M. Pinkerton, L. K. Steinrauf and P. Dawkins, *Biochem. Biophys. Res. Comm.*, 1969, **35**, 512.
194. H. Hauser, E. G. Finer and D. Chapman, *J. Mol. Biol.*, 1970, **53**, 419.

195. D. Chapman, R. J. Cherry, E. G. Finer, H. Hauser, M. C. Phillips, G. C. Shipley and A. I. McMullen, *Nature,* 1969, **224**, 692.
196. A. I. McMullen, D. I. Marlborough and P. M. Bayley, *F.E.B.S. Lett.,* 1971, **16**, 278.
197. T. P. Pitner and D. W. Urry, *J. Amer. Chem. Soc.,* 1972, **94**, 1399.
198. A. Warashina, T. Iio and T. Isemura, *Biopolymers,* 1970, **9**, 1445.
199. F. A. Bovey, J. J. Ryan, G. Spach and F. Heitz, *Macromolecules,* 1971, **4**, 424.
200. F. Heitz and G. Spach, *Macromolecules,* 1971, **4**, 429.
201. P. Temussi and M. Goodman, *Proc. Nat. Acad. Sci., U.S.A.,* 1971, **68**, 1767.
202. Y. Okamoto and R. Sakamoto, *J. Chem. Soc. Japan,* 1969, **90**, 669.
203. E. M. Bradbury, B. G. Carpenter, B. G. Crane-Robinson and H. Goldman, *Macromolecules,* 1971, **4**, 557.
204. D. N. Silverman, G. T. Taylor and H. A. Scheraga, *Arch. Biochem. Biophys.,* 1971, **146**, 587.
205. N. Anand, N. S. R. K. Murthy, F. Naider and M. Goodman, *Macromolecules,* 1971, **4**, 564.
206. E. Patrone, G. Conio and S. Brighetti, *Biopolymers,* **1970, 9**, 897.
207. V. N. Damle, *Biopolymers,* 1970, **9**, 937.
208. D. N. Silverman and H. A. Scheraga, *Biochemistry,* 1971, **10**, 1340.
209. J. S. Cohen, *Biochim. Biophys. Acta,* 1971, **229**, 603.
210. J. W. O. Tam and I. M. Klotz, *J. Amer. Chem. Soc.,* 1971, **93**, 1313.
211. J. A. Ferretti and L. Paolillo, *Biopolymers,* 1969, **7**, 155.
212. J. D. Glickson and J. Applequist, *J. Amer. Chem. Soc.,* 1971, **93**, 3276.
213. M. Guiata and L. F. Thomas, *Makromolek. Chem.,* 1968, **119**, 113.
214. T. Iio and S. Takahishi *Bull. Chem. Soc. Japan,* 1970, **43**, 515.
215. P. M. Hardy, J. C. Haylock, D. I. Marlborough, H. N. Rydon, H. T. Storey and R. C. Thompson, *Macromolecules,* 1971, **4**, 435.
216. F. Conti and P. de Santis, *Biopolymers,* 1971, **10**, 2581.
217. D. A. Torchia, *Macromolecules,* 1971, **4**, 440.
218. D. A. Torchia and F. A. Bovey, *Macromolecules,* 1971, **4**, 246.
219. F. A. Bovey, J. J. Ryan and F. P. Hood, *Macromolecules,* 1968, **1**, 305.
220. M. Goodman, G. C.-C. Niu and K.-C. Su, *J. Amer. Chem. Soc.,* 1970, **92**, 5219
221. E. M. Bradbury, P. Cary, C. Crane-Robinson, L. Paolillo, T. Tancredi and P. A. Temussi, *J. Amer. Chem. Soc.,* 1971, **93**, 5916.
222. A. E. Tonelli and F. A. Bovey, *Macromolecules,* 1970, **3**, 410.
223. L. Paolillo, T. Tancredi, P. A. Temussi, E. Trivellone, E. M. Bradbury and C. Crane-Robinson, *J. Chem. Soc. Chem. Comm.,* 1972, 335.
224. D. W. Urry, *Proc. Nat. Acad. Sci., U.S.A.,* 1971, **68**, 672.
225. D. W. Urry, M. C. Goodall, J. D. Glickson and D. F. Mayers, *Proc. Nat. Acad. Sci., U.S.A.,* 1971, **68**, 1907.
226. J. D. Glickson, D. F. Mayers, J. M. Settine and D. W. Urry, *Biochemistry,* 1972, **11**, 477.
227. D. W. Urry, J. D. Glickson, D. F. Mayers and J. Haider, *Biochemistry,* 1972, **11**, 487.
228. H. Sternlicht and D. Wilson, *Biochemistry,* 1967, **6**, 2881.
229. C. C. McDonald and W. D. Phillips, *J. Amer. Chem. Soc.,* 1967, **89**, 6332.
230. J. S. Cohen and O. Jardetsky, *Proc. Nat. Acad. Sci., U.S.A.,* 1968, **60**, 92.
231. J. H. Bradbury and N. L. R. King, *Nature,* 1969, **223**, 1154.
232. C. C. McDonald, W. D. Phillips and J. D. Glickson, *J. Amer. Chem. Soc.,* 1971, **93**, 235.
233. W. D. Phillips, J. D. Glickson and J. A. Rupley, *J. Amer. Chem. Soc.,* 1971, **93**, 4031.
234. H. L. Krespi and J. J. Katz, *Nature,* 1969, **224**, 560.
235. I. Putter, J. L. Markley and O. Jardetsky, *Proc. Nat. Acad. Sci., U.S.A.,* 1970, **65**, 395.

236. H. Ashton, B. Capon and R. L. Foster, *J. Chem. Soc., D*, 1971, 512.
237. J. H. Bradbury and N. L. R. King, *Aust. J. Chem.*, 1971, **24**, 1703.
238. R. A. Dwek, P. W. Kent and A. V. Xavier, *Eur. J. Biochem.*, 1971, **23**, 343.
239. P. C. Lauterbur, *Appl. Spectroscopy*, 1970, **24**, 450.
240. J. C. W. Chien and J. F. Brandts, *N. N. B. Y. A.*, 1971, **230**, 209.
241. C. C. McDonald and W. D. Phillips, "Biological Macromolecules", Vol. 4, S. N. Timasheff and G. D. Fasman (eds.), Marcel Dekker, New York, 1970.
242. K. Wüthrich, R. G. Shulman and J. Peisach, *Proc. Nat. Acad. Sci., U.S.A.*, 1968, **60**, 373.
243. R. G. Shulman, K. Wüthrich, T. Yamane, E. Antonini and M. Brunari, *Proc. Nat. Acad. Sci. U.S.A.*, 1969, **63**, 623.
244. R. G. Shulman, S. Ogawa, K. Wüthrich, T. Yamane, J. Peisach and W. E. Blumberg, *Science*, 1969, **165**, 251.
245. R. J. Kurland, D. G. Davis and C. Ho., *J. Amer. Chem. Soc.*, 1968, **90**, 2700.
246. M. Poe, W. D. Phillips, C. C. McDonald and W. Lovenberg, *Proc. Nat. Acad. Sci., U.S.A.*, 1970, **65**, 797.
247. M. Poe, W. D. Phillips and C. C. McDonald, *Biochem. Biophys. Res. Comm.*, 1971, **42**, 705.
248. R. K. Gupta and S. H. Koenig, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 1134.
249. D. Sheard, T. Yamane and R. G. Shulman, *J. Mol. Biol.*, 1970, **53**, 35.
250. W. D. Phillips, M. Poe, C. C. McDonald and R. G. Bartoch, *Proc. Nat. Acad. Sci., U.S.A.*, 1970, **67**, 682.
251. V. F. Bystrov and V. G. Sakharovskii, *Zh. Vses. Khim. Obschest.*, 1971, **16**, 380.
252. B. Birdsall, N. J. M. Birdsall and J. Feeney, *J. Chem. Soc., Chem. Comm.*, 1972, 316.
253. C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams and A. V. Xavier, *Nature*, 1971, **232**, 236.

Fluorine-19 NMR Spectroscopy

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INTRODUCTION

This review covers the 1971 year and is intended as an extension of the earlier reviews in Vols. 1, 3, 4 and 5 of this series. (1) The 1971

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year has seen a further increase in the number of papers on the topic of fluorine NMR in the literature. A large proportion of these were either purely descriptive of the NMR spectra or a structural elucidation of organic and inorganic molecules by NMR. A relevant number of papers were also concerned with a detailed treatment of the theoretical aspects of fluorine NMR Spectroscopy. The basic Sections of this chapter will be essentially the same as used in the other volumes of this Series. In Section III some aspects of the ^{19}F chemical shifts and coupling constants involving fluorine nuclei which come out in the 1971 year are discussed. All fluorine chemical shifts reported in this chapter are relative to $CFCl_3$ scale ($\delta_{CFCl_3} = 0$) are quoted as negative when the resonances are to lower frequency (higher field) of $CFCl_3$. When necessary, the chemical shifts were converted to $CFCl_3$ scale by taking the following shift values:

CF_3COOH	−78·5
CF_3COOCH_3	−74·2
C_6F_6	−162·9
$Ph \cdot CF_3$	−63·9
CF_3CCl_3	−82·2
$C_2F_2Cl_4$	−67·3
$(CF_2CCl_2)_2$	−114·1
WF_6	+162
F − anion	−201 (aqueous HF solution)
CHF_2Cl	−72·5 (J_g^{HF} = 63·1 Hz)
$CF_2Br \cdot CF_2Br$	−63·4

I. FLUOROHYDROCARBONS

A. Fluorinated Aliphatic Hydrocarbons

The complete analysis of two fluoroethanes, 1,2-difluoro- and 1,1,2-trifluoro- ethane, CH_2F CH_2F and CH_2F CHF_2, was presented. (2) The NMR spectrum of CFH_2 CFH_2 was also independently analysed by other workers. (3) The study of the solvent dependence of the coupling constants was performed following the procedure already outlined in other works of the same series. (4) The rotamer energies in vapour and liquid phase, $\Delta E = E_{gauche} - E_{trans}$, were found ΔE_v = −0·6 Kcal/mole, ΔE_1 = −2·6 Kcal/mole, for CH_2F CH_2F, and ΔE_v = 1·4 Kcal/mole, ΔE_1 = 0·0 Kcal/mole for CH_2F CHF_2. The ^{19}F NMR data are shown in [1] and [2].

A control study of the solvent dependence of the couplings was also carried out for a similar molecule, CF_3 CH_2F, for which no rotational isomerism exists. (2) Three nonsymmetrical 1,2-disubsti-

$-225{\cdot}2$

$CFH_2 \cdot CFH_2$

[1]

$^2J^{HF} = 48{\cdot}0$

	trans	*gauche*
$^3J^{HF}$	0	30·6
$^3J^{FF}$	−30	−10·9

$-128{\cdot}6$ $-241{\cdot}1$

$CF_2H \cdot CFH_2$

[2]

$^2J^{HF} = 54{\cdot}2$ $^2J^{HF} = 45{\cdot}4$

	trans	*gauche*
$^3J^{HF}(CH_2CF_2)$	12·4	15·5
$^3J^{HF}(CHCF)$	4·8	12·7
$^3J^{FF}$	−18·9	−13·7

$CF_2I \cdot CF_2Br$	$CF_2I \cdot CF_2Cl$	$CF_2Br \cdot CF_2Cl$
−60·95 −61·30	−62·88 −67·04	−67·01 −69·63
[3]	[4]	[5]

tuted tetrafluoroethanes, [3] to [5], were analysed. (5) Under certain conditions of solvent and temperature the deceptive simplicity of their AA′BB′ spectra could be lifted. Other fluoroethanes, [6] to [12], (5) and [13] (6) were considered. The results of [6] to [12] with those of [3] to [5], together with other data of

$J_{av} = -2{\cdot}6$	$J_{av} = -6{\cdot}02$	$J_{av} = -9{\cdot}9$
$CF_3 \cdot CF_2Br$	$CF_3 \cdot CFCl_2$	$CF_3 \cdot CFBr_2$
−84·8 −69·9	−85·7 −78·1	−82·9 −77·6
[6]	[7]	[8]

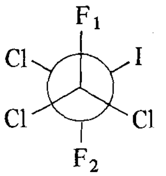
$J_{av} = -10{\cdot}6$	$J_{av} = -13{\cdot}0$	$J_{av} = -16{\cdot}4$
$CF_3 \cdot CFClI$	$CF_3 \cdot CFBrI$	CF_3CFI_2
−82·6 −78·3	−81·0 −85·9	−81·4 −87·5
[9]	[10]	[11]

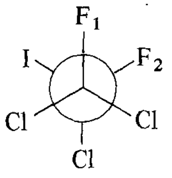
$J_{av} = -22{\cdot}3$

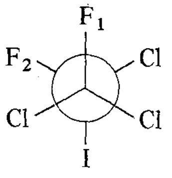
$CFCl_2 \cdot CFClI$

−65·21 −63·20

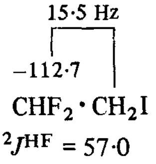
[12]







at −90°C				
	δ_{F_1}	64·4	68·8	75·4
	δ_{F_2}	59·6	63·5	67·6
	J_{12}	−19·5	−27·1	−22·0 (Hz)



$$\overset{\overset{15{\cdot}5\text{ Hz}}{-112{\cdot}7}}{CHF_2 \cdot CH_2I}\quad {}^2J^{HF} = 57{\cdot}0$$

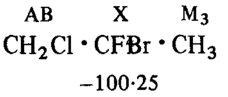
[13]

fluoroethanes reported in the literature, enable an attempt for some rotationalization and correlations from the trends to be made. (5)

Complete analysis of the $ABXR_3$ NMR spectra of two substituted propanes were performed for different temperature. The NMR parameters obtained at *ca.* 28° are shown in [14] and [15]. (7)

	δ	$^4J_{AR}$	$^4J_{BR}$	$^2J_{AB}$	$^3J_{RX}$	$^3J_{AX}$	$^3J_{BX}$
CF_3	−76·36						
$CFCl$	−133·24	9·68	11·75	174·7	−6·12	−6·69	−12·05
CF_2Cl	−63·78 −64·81						
[14]							
CF_3	−73·95						
$CFBr$	−132·19	9·02	12·58	176·8	−8·72	−14·70	−15·43
CF_2Br	−56·23 −58·22						
[15]							

From the temperature dependence of the F–F couplings the conformational energy difference between one of the *gauche* and the *trans* isomers was estimated to be 0.5 Kcal/mole, for the dichloro- and *ca.* 0 Kcal/mole for the dibromo-derivative. (5) For the dichloro-compound [14] values of $^3J_t = -2$ Hz and of $^3J_g = -16$ Hz in the $-CF_2Cl$. CFCl– fragment were derived, corresponding to the temperature-extrapolated coupling J_{AX} and J_{BX} respectively. ^4J_g can be taken as the average value of $J_{AR} = 9{\cdot}65$ Hz, from which the value of $^4J_t = ca.\ 12{\cdot}7$ Hz could be extracted. The complete analysis of the NMR spectrum of CH_2Cl CFBr CH_3, [16], in CCl_4 and acetone was



$$\overset{AB}{CH_2Cl} \cdot \underset{-100{\cdot}25}{\overset{X}{CFBr}} \cdot \overset{M_3}{CH_3}$$

$J_{AX} = 11{\cdot}04$ Hz
$J_{BX} = 23{\cdot}61$ Hz
$J_{MX} = 19{\cdot}56$ Hz

[16]

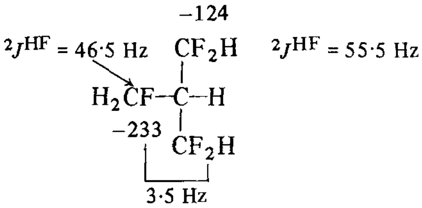
given. (8) From an analysis of the solvent dependence of the couplings the rotamer couplings and energies were obtained. The NMR spectra of $CH_3CF_2CH_2CF_3$, [17], in several solvents were analysed. (9) The ^{19}F NMR data, using $CFCl_3$ as solvent, are given below: ·

	δ	$^{3}J_{(CH_3-CF_2)}$	$^{3}J_{(CH_2-CF_3)}$	$^{4}J_{(CF_2-CF_3)}$	$^{5}J_{(CH_3-CF_3)}$	$^{3}J_{(CH_2-CF_2)}$
CH_3						
CF_2	−86·57					
CH_2		18·71	10·23	8·90	0·77	26·40
CF_3	−62·90					

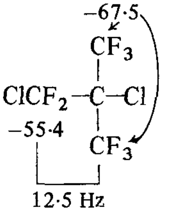
[17]

Decoupling experiments were performed showing that the pairs $^{3}J(CH_3\text{-}CF_2) \div {}^{3}J(CH_2\text{-}CF_2)$ and $^{5}J(CH_3\text{-}CF_3) \div {}^{3}J(CH_2\text{-}CF_3)$ must have equal signs. Calculations are consistent with a low energy difference between the *gauche* and the *trans* isomer, in agreement with the experimental observation that the spectrum is almost temperature invariant. It was found, in addition, that $^{5}J(CH_3\text{-}CF_3)$ is sensitive to the nature of solvent, i.e. to the conformational equilibrium. In particular it appears that this coupling, $^{5}J_{HF}$, is bigger in the *gauche* isomer than in the *trans* isomer, $^{5}J_g > {}^{5}J_t$. A quantitative evaluation was possible: $^{5}J_t^{HF} = 0{\cdot}16$ Hz, $^{5}J_g^{HF} = 0{\cdot}97$ Hz.

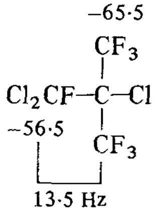
The reactions of polyhalotertiary alcohols with a variety of reagents, were described. Saturated and olefinic compounds, [18] to [24], were obtained. (10) During the investigation of the synthesis and decomposition of some diazoalkanes the NMR spectra of a number of compounds containing the $-CHF_2 \cdot CF_2-$ fragment were reported; (11) most of the ^{19}F NMR data are given in Table I. Chemical shift data were also reported for a diazofluoropentane



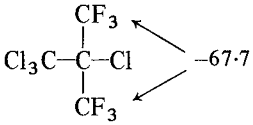
[18]



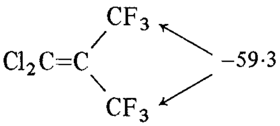
[19]



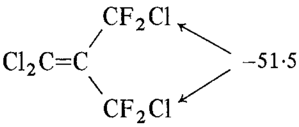
[20]



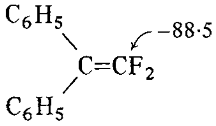
[21]



[22]



[23]



[24]

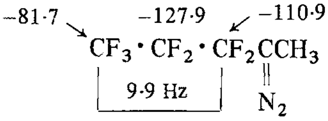
TABLE I

NMR data of $CHF_2 \cdot CF_2-X$ (11)
(1) (2)

-X	Chemical shift δ_{F_1}	Chemical shift δ_{F_2}		Coupling constant (H_2) H_1F_1	H_1F_2	H_3F_2	F_1F_2	H_3F_3
(3)								
$-CH_2Cl$	−140·3	−123·4		53·4	4	13·5	2·6	–
$-CH_2OH$	−141·2	−129·5		53·5	4·2	14·0	3·2	–
$-CH_2F$	−142·5	−131·9	247·9 (CH_2F)	53·0	4·5	12·0	3	45·5[a]
$-CH_2NH_3Cl$	−137·7	−121·3		52·5	–	16·0	4	–
$-CO_2H$	−143·1	−126·9		52·7	4·5	–	5·5	–
$-CO_2Et$	140·7	126·9		52·8	4·8	–	6·6	–

[a] $J(CF_2-CH_2F)$ = 14 Hz.

[25] and for two components of a reaction mixture which were tentatively assigned to the *cis*- and *trans*- isomer of [26]. Some other



$$CF_3 \cdot CF_2 \cdot CF_2\underset{\overset{\|}{N_2}}{C}CH_3$$

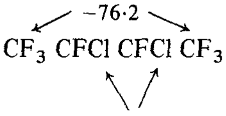
[25]

$CF_2H \cdot CF_2 \cdot CH=CH \cdot CF_2CF_2H$

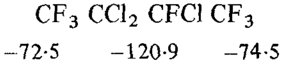
	cis	*trans*
$-CF_2H$	137·5	137·3
$-CF_2$	113·9	118·5

[26]

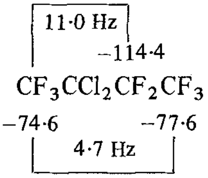
fluorohydrocarbons, shown in [27] to [29], (12) [30], (13) and [31] and [32], (14) were characterized by NMR. In the study of


$CF_3CFClCFClCF_3$

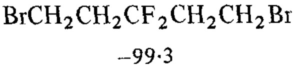
[27]


$CF_3CCl_2CFClCF_3$

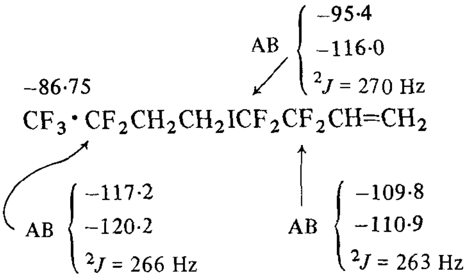
[28]


$CF_3CCl_2CF_2CF_3$

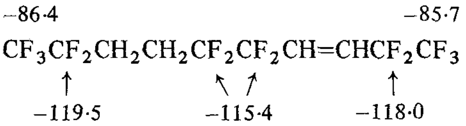
[29]


$BrCH_2CH_2CF_2CH_2CH_2Br$

[30]

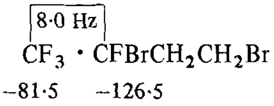

$CF_3\cdot CF_2CH_2CH_2ICF_2CF_2CH{=}CH_2$

[31]

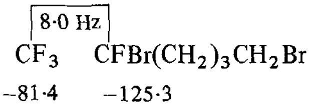

$CF_3CF_2CH_2CH_2CF_2CF_2CH{=}CHCF_2CF_3$

[32]

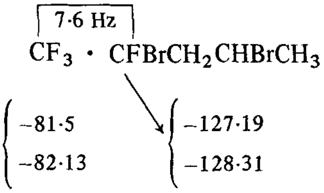
peroxide-initiated addition of 1,1-dibromotetrafluoroethane to ethylene, propylene and isobutene some new fluorohydrocarbons [33] to [45] were characterized in our laboratory by ^{19}F NMR. (15)


$CF_3\cdot CFBrCH_2CH_2Br$

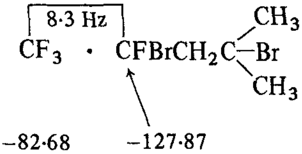
[33]


$CF_3CFBr(CH_2)_3CH_2Br$

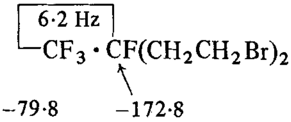
[34]


$CF_3 \cdot CFBrCH_2CHBrCH_3$

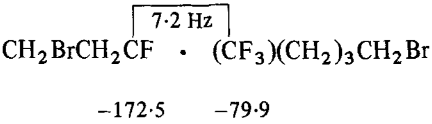
[35]


$CF_3 \cdot CFBrCH_2C(CH_3)_2Br$

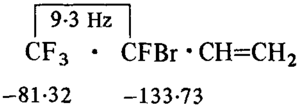
[36]


$CF_3 \cdot CF(CH_2CH_2Br)_2$

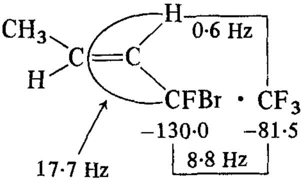
[37]


$CH_2BrCH_2CF \cdot (CF_3)(CH_2)_3CH_2Br$

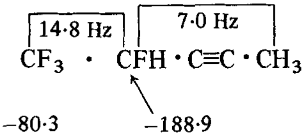
[38]


$CF_3 \cdot CFBr \cdot CH{=}CH_2$

[39]



[40]

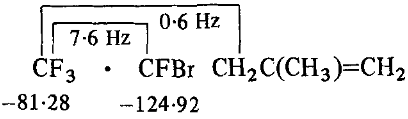

$CF_3 \cdot CFH \cdot C{\equiv}C \cdot CH_3$

$J(H \cdot CF_3) = 5{\cdot}25$ Hz.

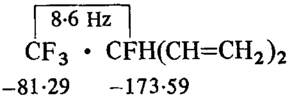
$J(CF_3 \cdot CH_3) = 0{\cdot}27$ Hz.

$^2J^{FH} = 46{\cdot}4$ Hz.

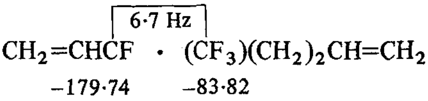
[41]


$CF_3 \cdot CFBr\ CH_2C(CH_3){=}CH_2$

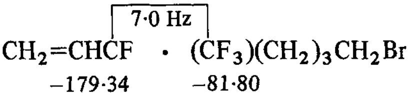
[42]


$CF_3 \cdot CFH(CH{=}CH_2)_2$

[43]


$CH_2{=}CHCF \cdot (CF_3)(CH_2)_2CH{=}CH_2$

[44]

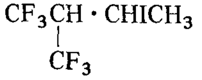

$CH_2{=}CHCF \cdot (CF_3)(CH_2)_3CH_2Br$

[45]

The photochemical reactions of trifluoroiodomethane or of HBr with $CF_3CH_2CH{=}CH_2$ were studied. (16) CF_3I gives in good yield [46] and [47]. Treating [46] with KOH, the *trans*-but-2-ene, [48],

$CF_3CH(CH_3)CHICF_3$

[46a]	*threo-*	$\delta_{CF_3} = -68{\cdot}5$	$^3J^{HF} = 8{\cdot}4$ Hz
		$\delta_{CF_3} = -73{\cdot}1$	$^3J^{HF} = 8{\cdot}4$ Hz
[46b]	*erythro-*	$\delta_{CF_3} = -64{\cdot}6$	$^3J^{HF} = 8{\cdot}2$ Hz
		$\delta_{CF_3} = -70{\cdot}7$	$^3J^{HF} = 8{\cdot}2$ Hz



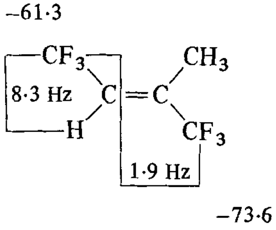
$CF_3\underset{\displaystyle CF_3}{\underset{|}{C}}H \cdot CHICH_3$

$\delta_{CF_3} = -53{\cdot}3$ $\quad ^3J^{HF} = 9{\cdot}0$ Hz

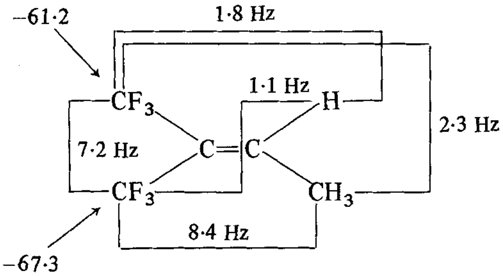
$\delta_{CF_3} = -66{\cdot}3$ $\quad ^3J^{HF} = 9{\cdot}0$ Hz

[47]

as well as some of the corresponding *cis*-isomer were prepared. [47] treated with KOH gave [49]. From the reaction of $CF_3CH_2CH{=}CH_2$ with HBr one obtains, on the contrary, [50] and [51] but also [52]. (16)



[48]



[49]

$CF_3CHBrCH_2CH_3$ $\quad ^3J^{HF} = 7{\cdot}2$ Hz

$^3J^{HF} = 0{\cdot}9$ Hz

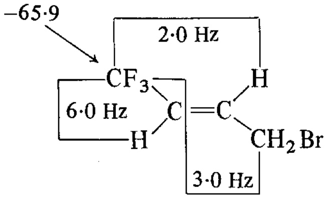
−74·0

[50]

$CF_3CH_2CHBrCH_3$ $\quad {}^3J^{HF} = 10{\cdot}4$

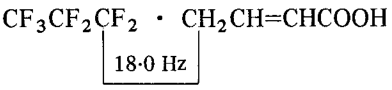
$-65{\cdot}9$

[51]



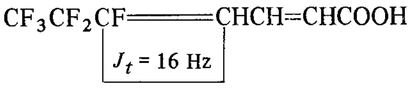
[52]

In the preparation of fluorinated sorbic acid analogues some fluorinated compounds, such as $R_fCH_2CHICH_2COOH$ and $R_fCH_2CHICH_2CN$ [$R_f = CF_3(CF_2)_n$- with n = 2 and higher], were synthetized and characterized by proton NMR. (17) Vicinal HF couplings near to 20 Hz were extracted. Vicinal HF coupling constants for [53] and [54] were also obtained. (17) The methyl nonafluoro-5,5-dimethoxyhexanoate, [55], was characterized by ^{19}F NMR. (18) The use of specific ^{19}F substitution in lipids was demonstrated using three monofluorostearic acid derivatives $CH_3(CH_2)_mCHF(CH_2)_{n-2}CO_2H$ where n = 4, 7 and 12. (19) The ^{19}F chemical shift of the three acids were $-178{\cdot}9$ (n = 4), $-176{\cdot}25$ (n = 7) and $-175{\cdot}9$ (n = 12). The linewidths of the ^{19}F resonance, when the acids are incorporated in lecithin vehicles, were measured as a function of temperature



$CF_3CF_2CF_2 \cdot CH_2CH{=}CHCOOH$ (18·0 Hz)

[53]



$CF_3CF_2CF{=}CHCH{=}CHCOOH$ ($J_t = 16$ Hz)

[54]

$CF_3C(OMe)_2CF_2CF_2CF_2CO_2Me$

$-73{\cdot}0 \quad -115{\cdot}3 \quad -122{\cdot}2 \quad -118{\cdot}3$

[55]

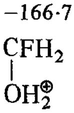
B. Derivatives of Fluorinated Hydrocarbons

1. Alcohols, ethers, peroxy-compounds

Monomeric formaldehyde, generated by thermal depolymerisation of paraformaldehyde, dissolved in 3 : 1 (v./v.) HF–SbF_5 solution, at

−78° gave a white precipitate (probably a polymeric formaldehyde). This precipitate, when the temperature is increased to −40°, is partly dissolved. The clear supernatant consists of a saturated solution of fluoromethylalcohol, [56], in its stable protonated form. (20a) The

$$\mathrm{CH_2O + HF \longrightarrow FCH_2OH \xrightarrow[SbF_6^{\ominus}]{H^{\oplus}} FCH_2OH_2^{\oplus} + SbF_6^{\ominus}}$$



$$\overset{-166\cdot7}{\mathrm{CFH_2}}-\mathrm{OH_2^{\oplus}}$$

$^2J^{\mathrm{HF}} = 47{\cdot}9$ Hz

$^3J(\mathrm{F}\div\mathrm{OH_2^{\oplus}}) = 1{\cdot}7$ Hz

[56]

^{19}F NMR spectrum of [56] is a triplet of triplets. The value of $\delta = -166{\cdot}7$ compares well with that obtained for FCH_2OCH_3 ($\delta = -163{\cdot}7$). (20a) The proton spectrum, AA′BB′X, of $FCH_2 . CH_2OH$ was analysed in various solvents with the aim of obtaining reliable couplings for the *gauche* isomer. (20b) This compound, however, does not exist as *gauche* isomer only, but contains up to 20% of the *trans* isomer in solvents of low dielectric constants. The relevant fluorine parameters given for $FCH_2 \cdot CH_2OH$ are the $^2J_{\mathrm{HF}}$ and $^3J_{\mathrm{HF}}$ couplings, as shown below:

	Solvent	$^3J_{\mathrm{HF}}$	$^2J_{\mathrm{HF}}$
	$CHCl_3$	29·7	47·7
FCH_2CH_2OH	Neat	30·8	47·9
	D_2O	31·8	47·7

Some polyesters have been prepared from 3-oxa-2,2,5,5-tetrafluoropentane and aromatic diacid chlorides. The preparation of [57] is described. (21) Difluoromethyl-1,1,2-trifluoroethyl ether,

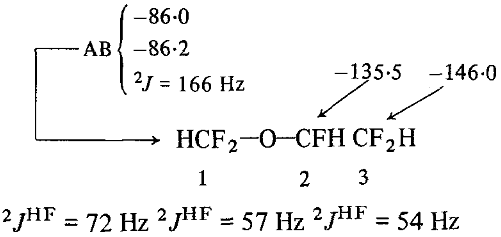
−80·9

$O(CF_2CH_2OH)_2$

[57]

[58], was characterized by NMR. (22) In the same paper the sulfide [59] was obtained and it is included here for comparison.

Fluorine-labeled nonionic detergents as 8,8,8-trifluorooctylhexaoxyethyleneglycol monoether, $CF_3(CH_2)_2O(C_2H_4O)_6H$, and 8,8,8-trifluorooctylmethylsulfoxide, $CF_3(CH_2)_7S(O)CH_3$, have been

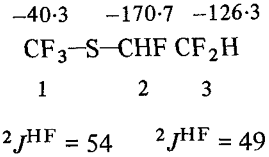


$$\overset{\text{AB}\,\{-86{\cdot}0,\ -86{\cdot}2,\ {}^2J = 166\ \text{Hz}\}}{\underset{1}{\mathrm{HCF_2}}}\!-\!O\!-\!\overset{-135{\cdot}5}{\underset{2}{\mathrm{CFH}}}\ \overset{-146{\cdot}0}{\underset{3}{\mathrm{CF_2H}}}$$

$^2J^{HF} = 72$ Hz $^2J^{HF} = 57$ Hz $^2J^{HF} = 54$ Hz

$J(F^1_A-F^2) = 7{\cdot}0$ Hz
$J(F^1_B-F^2) = 5{\cdot}5$ Hz
$J(F^2-F^3) = 7{\cdot}5$ Hz
$J(F^2-H^3) = 3{\cdot}0$ Hz
$J(F^3-H^2) = 4{\cdot}5$ Hz

[58]



$$\overset{-40{\cdot}3}{\underset{1}{\mathrm{CF_3}}}\!-\!S\!-\!\overset{-170{\cdot}7}{\underset{2}{\mathrm{CHF}}}\ \overset{-126{\cdot}3}{\underset{3}{\mathrm{CF_2H}}}$$

$^2J^{HF} = 54$ $^2J^{HF} = 49$

$J(F^1-F^2) = 4$ Hz
$J(F^2-F^3) = 21$ Hz

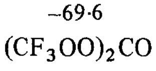
[59]

investigated. (23) Fluorine chemical shifts were measured and compared with those of anionic trifluoroalkyl detergents. (24) In solution (in H_2O, in 2 M and 4 M urea solution, in 2 M dioxane and 2 M tetrahydrofurane solution) each detergent produces a triplet fluorine signal ($^3J^{HF} = 10.5$ Hz) indicating that exchange of monomeric and micellar material is rapid on the NMR time scale. Micelle shifts $\delta_{(Sm)}$ were obtained by extrapolating the high concentration data. Monomer shifts, $\delta_{(S)}$, are the limiting values obtained in the most dilute solutions. C.m.c. (critical micelle concentrations) were found by extrapolating the two linear portions of chemical shifts, one in concentrated solutions and the other in diluted solutions, until they intersect. Typical value for $CF_3(CH_2)_2O(C_2H_4O)_6H$ in H_2O at 27° are:

$$\delta_{(S)} = -67{\cdot}71; \quad \delta_{(S_m)} = -68{\cdot}75 \qquad \text{c.m.c.} = 1{\cdot}8 \times 10^2\ \text{M}$$

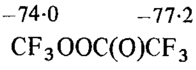
The values found (23) are nearly the same as corresponding values of anionic trifluoroalkyl detergents.

An improved method for the preparation of trifluoromethylhydroperoxide, $CF_3OOH(\delta = -72{\cdot}3)$, is described, which permitted an investigation of its properties, and in particular of its reactions, to be undertaken. (25) Five new compounds, [60] to [64], were



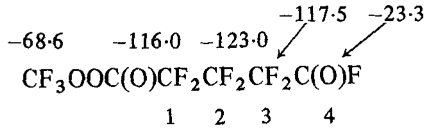
$$\overset{-69{\cdot}6}{\mathrm{(CF_3OO)_2CO}}$$

[60]



$$\overset{-74{\cdot}0}{\mathrm{CF_3OOC(O)}}\overset{-77{\cdot}2}{\mathrm{CF_3}}$$

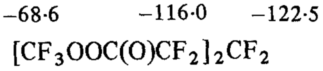
[61]



$CF_3OOC(O)CF_2CF_2CF_2C(O)F$

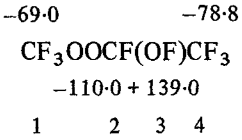
$J_{13} = 10{\cdot}0$ Hz
$J_{14} = 2{\cdot}0$ Hz
$J_{24} = 7$ Hz
$J_{34} = 7$ Hz

[62]



$[CF_3OOC(O)CF_2]_2CF_2$

[63]



$CF_3OOCF(OF)CF_3$

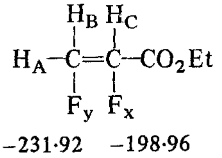
$J_{12} = 5{\cdot}3$ Hz
$J_{13} = 1{\cdot}7$ Hz
$J_{23} = 37{\cdot}0$ Hz
$J_{34} = 12{\cdot}5$ Hz

[64]

prepared and characterized by ^{19}F NMR. (25) The compound CF_3OOCl, which is the first stable compound containing an $-OOCl$ linkage, was prepared and a single resonance was observed at −69·9. (26) Ether-trifluoroacetic anhydride (TFAA) adducts, $CF_3\overset{O}{\overset{\|}{C}}[(OCH_2)_m]_nO\overset{O}{\overset{\|}{C}}CF_3$, were prepared; the ^{19}F NMR for the CF_3 group was a sharp singlet in the range −75·8 to −75·9.

2. Ketones, esters, amides, nitroalkanes

1-Bromo-1-chloro-1-fluoroacetone, $BrClFCC(O)CH_3$, and some other halogeno-acetones were prepared. (28) Proton NMR spectra were recorded; so only the H–F coupling parameters are available. Some $^4J^{HF}$ are of interest; it was found that these vary in the range 1·5 to 4 Hz. A reinvestigation of the proton and fluorine NMR spectra of $CFH_2 \cdot CHFCOOEt$ [65], has been described. (29). The

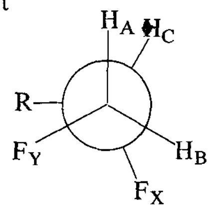


$J_{AX} = 30{\cdot}25$
$J_{BX} = 21{\cdot}30$
$J_{CY} = 28{\cdot}42$
$J_{XY} = -11{\cdot}16$
$J_{AY} = 46{\cdot}59$
$J_{BY} = 47{\cdot}94$
$J_{CX} = 47{\cdot}31$

[65]

CH_2FCHF- fragment was analysed as an ABCXY spin system. The NMR parameters obtained were critically compared with those already known in the literature. It was concluded that the molecule examined must exist principally as isomer [66]. In addition this

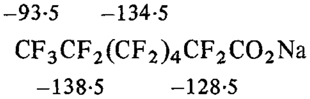
$R = -CO_2Et$



[66]

dominant rotamer is likely to be considerably distorted from a perfectly staggered orientation. Consideration of the coupling constants obtained suggests a distortion as depicted in [66], resulting from a repulsion between the electric dipoles of the fluorine atoms. (29)

Trifluoroacetamide, CF_3CONH_2, and *N*-methyltrifluoroacetamide, $CF_3CONHCH_3$, was studied by NMR. (30) The fluorine spectrum of CF_3CONH_2 shows a triplet (0·7 Hz) at high temperature and a doublet (1·8 Hz) at low temperature. The experimental observation of this doublet indicates that the fluorine nuclei are coupled weakly with only one of the two protons at low temperature. (30) The fluorine spectrum of $CF_3CONHCH_3$ in acetone-d_6 consists of six peaks: a doublet by coupling with NH (1·1 Hz) which is further split into a quadruplet by coupling with CH_3 (0·7 Hz). (30) The perfluoroalkyl detergent, [67], was studied by NMR. (31)



$$\overset{-93\cdot5}{CF_3}\underset{-138\cdot5}{CF_2}(CF_2)_4\overset{-134\cdot5}{}\underset{-128\cdot5}{CF_2}CO_2Na$$

[67]

The concentration dependence of the chemical shifts yielded a critical micelle concentration (c.m.c.) of 0·030 M at 35°. Some *para*-substituted hexafluoroacetone *N*-phenylimine were studied by ^{19}F NMR at variable temperature in pyridine or acetone as solvent. (32) The kinetic parameters were obtained by line-shape analysis of the NMR spectra. The free-energies of activation at 25° are collected in Table II together with the spectral parameters; Δ is the chemical shift difference in Hz at 0° between the two CF_3 resonances. Each CF_3 resonance, below the coalescence temperature, is a quartet arising from the $^4J^{FF}$ coupling. (32) In the study of the Mannich

TABLE II

Kinetic and ^{19}F NMR parameters of *para*-substituted *N*-phenylimines (32)

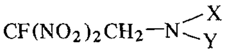
$(CF_3)_2C = NC_6H_4{-}X$

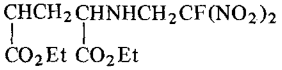
-X	Δ(Hz)	$^4J_{FF}$(Hz)	$G^\ddagger$(kcal/m)
H	434	7·1	15·45
Cl	429	6·9	15·53
F	419	6·9	15·35
OCH_3	367	7·2	14·35
CH_3	416	6·9	15·14
MO_2	430	6·6	14·90

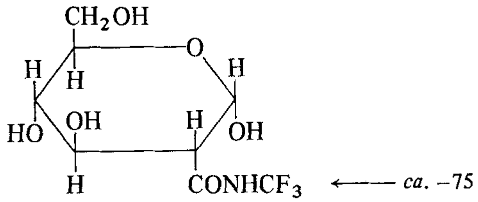
reaction of 2-fluoro-2,2-dinitroethanol with primary and secondary amines, 2-fluoro-2,2-dinitroethylamines were obtained. (33) 2-Fluoro-2,2-dinitroethylamine reacts with chloroformates giving *N*-fluorodinitroethylcarbamates. (33) The fluorine NMR data of the compounds obtained are collected in Table III. 2-Deoxy-2-trifluoroacetamido-α-D-glucose, [68], shows a CF_3 low-frequency shift in presence of lymozyne. (34) An aqueous solution of [68] has two ^{19}F signals, at 339·6 and 312·0 Hz to high-frequency of ext. CF_3COOH ($\delta = -78{\cdot}5$), arising from the α- and β- anomers respectively. (18) In presence of lymozyne the signal of the α-anomer moves to low-frequency to an extent depending on the concentration of lymozyne.

TABLE III

^{19}F NMR parameters of 2-fluoro-2,2-dinitroethylamines (33)


$CF(NO_2)_2CH_2{-}N\begin{matrix}X\\Y\end{matrix}$

X	Y	$^\delta$CF	$^3J_{HF}$
CH_3	H	−109·8	18·7
CH_2CO_2H	H	−109·7	18·0
CH_2CO_2Et	H	−110·2	18·3
$CH_2CH(OEt)_2$	H	−109·5	18·0
$CH(CO_2H)CH_2COOH$	H	−109·8	15·0
$CH_2CH{=}CH_2$	H	−109·3	19·7
$CH_2CH{=}CH_2$	$CH_2CF(NO_2)_2$	−108·2	18·0
 $\underset{CO_2Et}{CH}CH_2\underset{CO_2Et}{CH}NHCH_2CF(NO_2)_2$	H	−110·0	17·0
$NHCH_2CF(NO_2)_2$	H	−109·0	17·5
CO_2Et	H	−109·5	14·9
$H_3SO^\ominus$	$H^\oplus$	−101·0	10·4



[68]

The signal of the β-anomer moves to high-frequency (*ca.* 4 Hz) and the shift is concentration independent. (34)

The ^{19}F NMR spectrum of a protein modified by covalent attachment of a small fluorinated probe moiety was described. (34b) The fluorine probes used were trifluoroacetyl groups introduced specifically at lysine residues 1 and 7 of bovine pancreatic ribonuclease S (R Nase S). It was possible, by comparison with model compounds, to assign all the observed ^{19}F resonances in the spectrum of trifluoroacetylated *S*-peptide and to further monitor all such resonances caused by binding of inhibitors to the *S*-protein. (34b)

3. Olefins

When substituted 1-chloroperfluoroolefins were treated with methoxide ion to obtain β-substituted 1-methoxyperfluoro olefins (35) (Table IV) retention of the original *cis* or *trans* configuration was observed in all cases. The absolute configuration of the methoxy products

TABLE IV

^{19}F NMR data of β-substituted 1-methoxyperfluoro olefins (35)

$$\underset{[1]}{Y(CF_2X)}C{=}\underset{[2]}{C(F)}OCH_3$$

Y	X	isomer[a]	δ_1	δ_2	J_{12}(Hz)
C_6H_5	F	*cis*	−81·7	−57·2	24
C_6H_5	F	*trans*	−80·0	−57·2	13
C_6H_5	CF_3	*cis*	−79·8	−108·3	26
C_6H_5	CF_3	*trans*	−75·3	−108·0	10
p-ClC_6H_4	F	*cis*	−81·4	−57·1	24
p-ClC_6H_4	F	*trans*	−80·8	−57·7	13
p-$MeOC_5H_4$	F	*cis*	−80·7	−56·8	24
p-$MeOC_5H_4$	F	*trans*	−79·4	−57·3	13
c-C_5H_{11}	F	*cis*	−82·8	−57·4	27
c-C_5H_{11}	F	*trans*	−81·9	−58·0	13

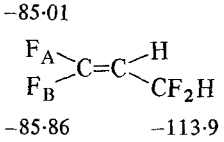
[a] The configuration is that of $CF_2X(1)$ vs. F(2).

was determined by ^{19}F NMR spectroscopy. The assignment derives from previous observations; *cis*-vinylfluorine to CF_2X coupling constants are in the range 24 to 27 Hz and the corresponding *trans* couplings are in the range 10 to 13 Hz. From the irradiation of 3-diazo-1,1,2,2-tetrafluoropropane there was isolated, as a by-product, a high boiling material in which two components were tentatively assigned to the *cis*- and *trans*- isomer of [69] (11). The couplings of 1,1,3,3-tetrafluoropropene, [70], are of interest. (11) The

$CF_2HCF_2CH{=}CHCF_2CF_2H$

[69]

cis		*trans*
−137·5	$-CF_2H$	−137·3
−113·9	$-CCF_2-$	−118·5

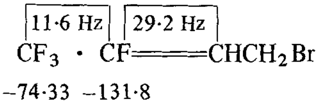


[70]

$^2J^{FF} = 26{\cdot}6$ Hz
$^2J^{HF} = 54{\cdot}8$ Hz
$J_g(H{-}CF_2H) = 7{\cdot}0$ Hz

$J_t(CF_2H \cdot F_A) = 14$ Hz
$J_c(CF_2H \cdot F_B) = 4$ Hz
$J_c(F_A \cdot H) = 1{\cdot}5$ Hz
$J_t(F_B \cdot H) = 22{\cdot}5$ Hz

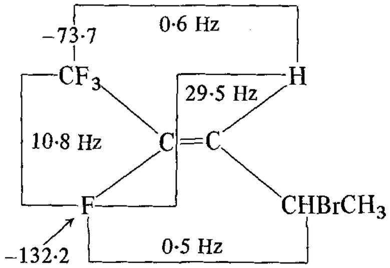
vinylic fluorines were assigned on the basis that J^{HF} (*trans*) $> J^{HF}$ (*cis*). On this basis $J(CF_2H\text{-}H)$ (*trans*) is greater than $J(CF_2H\text{-}H)$ (*cis*), whereas from similar olefins containing the CF_3 group just the opposite is expected. (11) Some olefin products were characterized by NMR in our laboratory. (15) These are shown in [71] to [76].



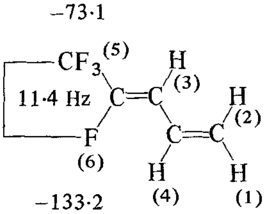
$CF_3 \cdot CF{=}CHCH_2Br$

$J(F \cdot CH_2) = 2{\cdot}0$ Hz
$J(CF_3 \cdot CH_2) = 1{\cdot}4$ Hz
$J(CF_3 \cdot H) = 0{\cdot}7$ Hz

[71]

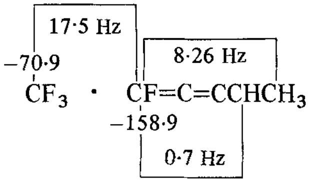


[72]

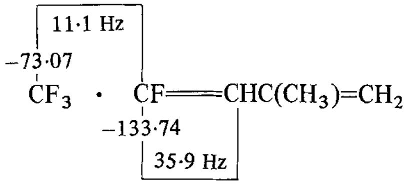


[73]

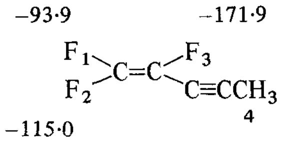
$J_{56} = 11{\cdot}4$ Hz
$J_{45} = 0{\cdot}7$ Hz
$J_{35} = 0{\cdot}6$ Hz
$J_{46} = 0{\cdot}7$ Hz
$J_{36} = 31{\cdot}0$ Hz



[74]



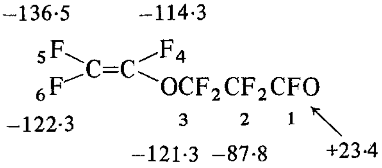
[76]



[75]

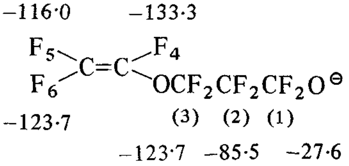
J_{12} = 53·8 Hz
J_{14} = 1·9 Hz
J_{24} = 1·9 Hz
J_{13} = 28·9 Hz
J_{23} = 115·8 Hz
J_{34} = 5·2 Hz

In the preparation of some novel perfluoroheterocyclic compounds the compounds [77] and [78] were isolated and characterized by NMR. (36) A spectroscopic study of the rotational equilibria in fumaryl fluoride, [79], and maleoyl fluoride, [80], was performed. (37) The relative energies of the three possible isomers, for each compound, may be arranged in six ways. The NMR data are consistent with only two of these arrangements. The variable temperature NMR data of [79] ($^3J^{\mathrm{H\,F}}$ = 6·5 to 7·5 between −13° and +47°C) and of [80] ($^3J^{\mathrm{H\,F}}$ and $^4J^{\mathrm{H\,F}}$ in the range 4·2 to 5·2 between −53° and +27°C) may in fact be explained on the basis of the



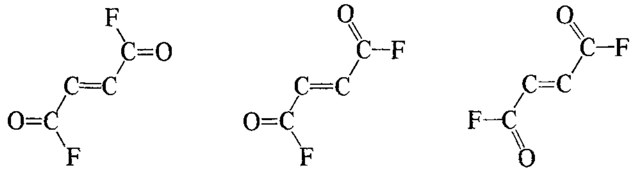
[77]

J_{13} = 8·0 Hz
J_{45} = 64·5 Hz
J_{46} = 83·6 Hz
J_{56} = 109·9 Hz



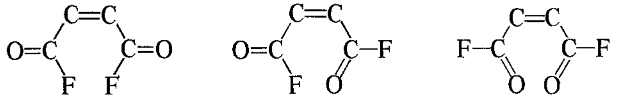
[78]

J_{45} = 60·0 Hz
J_{46} = 103 Hz
J_{56} = 83 Hz



trans-trans *cis-trans* *cis-cis*

[79]



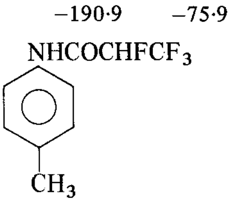
trans-trans *cis-trans* *cis-cis*

[80]

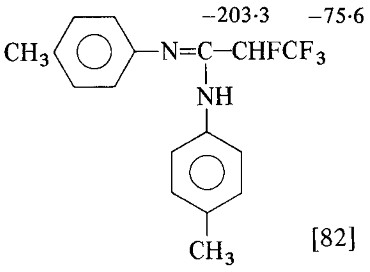
following ordering of energies: *cis-trans, trans-trans, cis-cis* or *cis-cis, trans-trans, cis-trans,* where *cis* and *trans* refer to the conformation of the double bonds about the single bonds. The preparation and reactions of some carbinols containing the pentafluoropropenyl group were described. (38) The type of reaction described gave exclusively (Z)-pentafluoropropenyl carbinols. The *cis*-structure was elucidated by the small F-F coupling (^3J = *ca.* 10 Hz) through a double bond. Treating (Z)-$CF_3CF{=}CFC(CF_3)_2OH$ with SF_4, the (E)-isomer was obtained; this was confirmed by the large value of $^3J(CF{=}CF)$ = *ca.* 137 Hz. (38)

4. *Aromatic alkyl substituent groups*

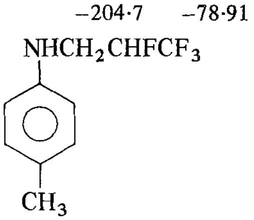
The reaction of hexafluoropropylene with arylamines to prepare tetrafluoropropionarylides and tetrafluoropropylarylamides was described. (39) The products [81] to [83], were also characterized by ^{19}F NMR.



[81]

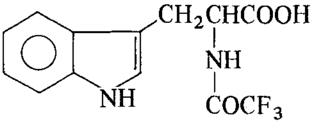


[82]

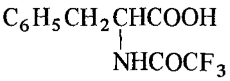


[83]

The binding of *N*-trifluoroacetylated amino-acids by chymotrypsin was investigated by ^{19}F NMR spectroscopy. (40) The fluorine signal of *N*-trifluoroacetyl-*D*-tryptophan, [84], goes to higher frequency in the presence of chymotrypsin in the pH range 6·33 to 8·12. The fluorine signal of *N*-trifluoroacetyl-D-phenylalanine, [85], and of *N*-trifluoroacetyl-L-tryptophan is shifted to higher frequency at pH = 6·34. (40)



[84]



$$C_6H_5CH_2\underset{\displaystyle NHCOCF_3}{\underset{|}{C}}HCOOH$$

[85]

5. *Polymers*

The results of a study at 94·1 Mc/Hz, using the techniques of noise decoupling and of time averaging to improve the spectral quality, is reported for poly(vinyl fluoride). (41) Whereas the undecoupled spectrum is completely useless, because of the large H–F couplings, the noise-decoupled spectrum reveals several resonances which may be ascribed to individual groupings within the polymer. Eleven resonances were observed, as can be expected if a five-atom fragment centred on fluorine is considered (Table V). The assignments, as given in Table V, were made on an empirical, but reasonable, basis. The fraction of head-to-head imperfections depends on the polymerization conditions. Only diads effects are important in determining the polymer structure. The various tacticities deviate little from a statistical distribution and there is little difference between the fraction of *meso*- and *dl*- head-to-head units. Additional fine structure was evidentiated on the resonances of heterotactic and syndiotactic triads of the head-to-tail sequences, which were associated with the existence of pentad structures of monomer units. Pentad effects were not visible on the isotactic triad (head-to-tail

TABLE V

The eleven triad sequences of poly(vinyl fluoride) (41)

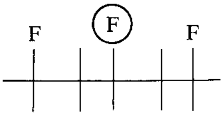
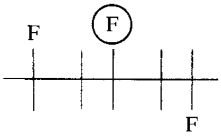
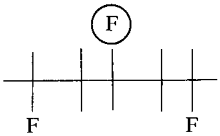
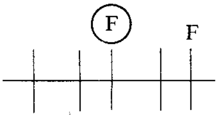
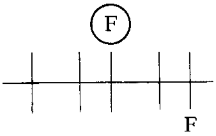
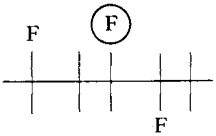
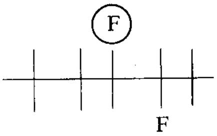
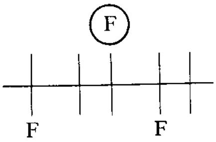
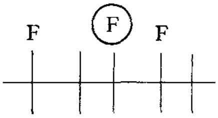
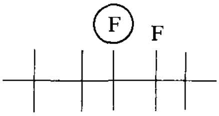
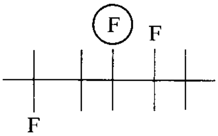
	Sequence CHF—CH$_2$CHF—CH$_2$CHF—	Chemical shift of Ⓕ	Assignment
(1)		−178·5	Head-to-tail
(2)		−180·65	Head-to-tail
(3)		−182·0	Head-to-tail
(4)		−179·2	Tail-to-tail
(5)		−181·1	Tail-to-tail
(6)		−189·2	Head-to-head (*meso*)
(7)		−191·1	Head-to-head (*meso*)
(8)		−191·6	Head-to-head (*meso*)

TABLE V—*cont.*

	Sequence CHF—CH$_2$CHF—CH$_2$CHF—	Chemical shift of Ⓕ	Assignment
(9)		−195·3	Head-to-head (*dl*)
(10)		−196·1	Head-to-head (*dl*)
(11)		−196·7	Head-to-head (*dl*)

sequence); neither the head-to-head nor the tail-to-tail triads revealed fine structures. Copolymer isobutylene-chlorotrifluoroethylene, I–F, was investigated by proton and fluorine NMR. (42–44) A study was carried out at various temperatures for copolymers deviating from the alternating structure. (42) Apart from the considerations obtained from the proton spectra, in the fluorine spectra, in addition to an AB-type quartet ($-CF_2-$) centred at −114·0 and a triplet ($-CFCl-$) at −118·5 characteristic of the alternate structure, (45) there appear an additional quartet centred at −113·2 and two extra peaks at −117·5 and −117·8. These new peaks are explained in terms of tetrads of monomer units. The assignment found is reported in Table VI. I and F are isobutylene and trifluorochloroethylene units respectively. The $-CFCl-$ resonances are explained as X-parts of ABX spectra with the following coupling parameters:

IFII $|J_{AX} + J_{BX}| = 28$ to 29 Hz

IFIF $|J_{AX} + J_{BX}| = 54$ to 56 Hz

The two quite different values of $|J_{AX} + J_{BX}|$ suggest that the spectra must be quite sensitive to the conformational structure of the polymer segment. The temperature dependence of the spectra was

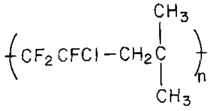
TABLE VI

Assignment of fluorine resonances of isobutylene-trifluorochloroethylene copolymer (42)

	Assignment	Pattern	Chemical shift (central position)
$-CF_2-$	I I F I^a	AB quartet	−113·2
$-CF_2-$	F I F I	AB quartet	−113·0
$-CFCl-$	I F I I	Two lines	−117·8; −117·5
$-CFCl-$	I F I F	Triplet	−118·5

^{a} I and F are isobutylene and trifluorochloroethylene units respectively.

also investigated: $|J_{AX} + J_{BX}|$ increases with decreasing temperature; only the values for the IFIF arrangement are, however, reported. (42) The difference of chemical shift between the geminal fluorine atoms in CF_2 groups also increases with decreasing temperature. The alternate copolymer, isobutylenetrifluorochloroethylene, with composition 50 : 50, already considered in a previous paper, (45) was reinvestigated (43, 44) by both proton



$$\left(CF_2CFCl-CH_2\overset{CH_3}{\underset{CH_3}{C}} \right)_n$$

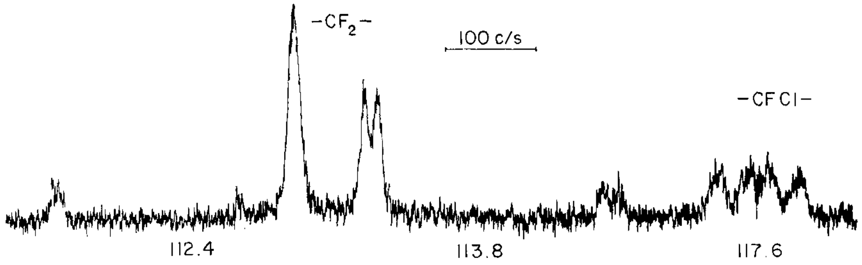


FIG. 1. The ^{19}F NMR spectrum at 94·1 Mc/H_2 in C_2Cl_4 of isobutylene-dichlorotrifluoroethylene copolymer (1:1 molar ratio). (From Cavalli. (43))

and fluorine NMR. The fluorine spectrum of the $-CF_2CFCl-$ fragment was interpreted as constituted by two partially overlapped ABX patterns, where the AB part is the CF_2 group and the X part is $-CFCl-$. The NMR parameters of the two ABX parts are given in [86]. This interpretation is consistent with variable temperature

		F_A–C–F_B	CFCl		$^2J_{FF}$	$^3J_{HF}$	$^3J'_{HF}$
(1)	ABX	−112·4	−113·7	−117·3	265	33	<10
(2)	ABX	−112·4	−113·9	−117·6	265	33	<10

[86]

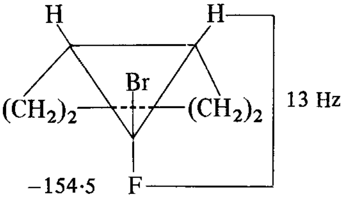
measurements, which showed that the two broad doublets at low-frequency (CFCl absorption) can move apart by varying the temperature. The fluorine resonance, as well as the proton absorption, was explained by the existence of a random configuration or stereo-block configuration of the copolymer: the former hypothesis is most likely. (43, 44) These conclusions are, however, contrary to those of previous workers (45) who suggested for the 1:1 copolymer a stereospecific structure, which is probably the isotactic one.

Wide line NMR and the spin-echo methods were used to study the structure of graft polymers of polytetrafluoroethylene and styrene. (46)

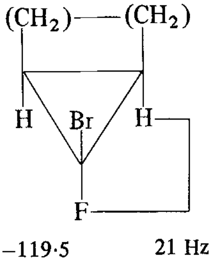
C. Fluorinated Cyclo Hydrocarbons

1. *Saturated systems*

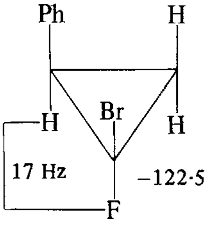
Some *gem*-bromofluorocyclopropanes were prepared and characterized in order to study their reduction with lithium aluminium hydride. (47) The structure assignments given in [87] to [90] were



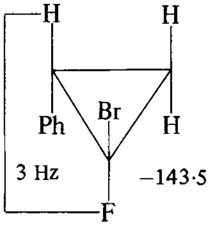
[87]



[88]

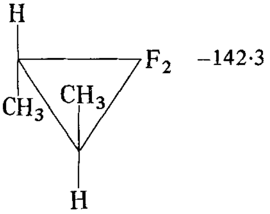


[89]

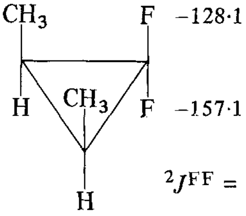


[90]

made on the basis of some generalizations known for fluorocyclopropanes: $^3J^{HF}$ and $^3J^{HH}$ are larger for nuclei in *cis*-arrangement than for nuclei in *trans*-arrangement, and the ring proton and fluorine are shielded by *cis*- and deshielded by *trans*-substituents. The two isomers, [91] and [92], of 1,1-difluoro-2,3-dimethylcyclopropane were also reported. (48) The ^{19}F NMR spectrum of *the cis* isomer was described in detail and the NMR parameters obtained are shown in [92]. (48)



[91]



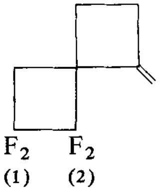
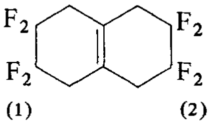
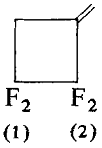
[92]

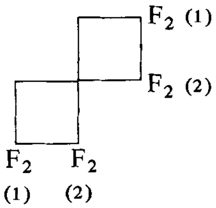
$^3J^{HF}_{cis} = 14{\cdot}1$ $J(F{-}CH_3)cis = 0{\cdot}13$

$^3J^{HF}_{trans} = $ ca.O $J(F{-}CH_3)trans = 0{\cdot}3$

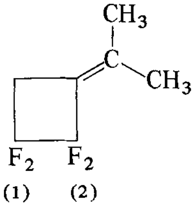
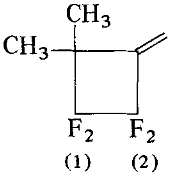
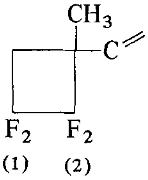
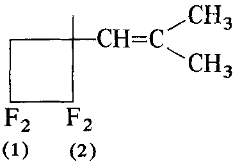
$^2J^{FF} = 157{\cdot}6$

Thermal cycloaddition of tetrafluoroethylene to propadiene gives [93] and [94] in addition to [95] and [96]. (49) The tetrafluoro-

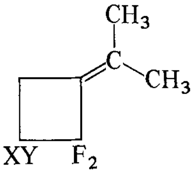
	δCF$_2$(1)	δCF$_2$(2)	$^2J^{FF}$(Hz)	$^3J^{HF}$(Hz)
 F2 F2 (1) (2) [93]	−116·4	−124·1	*ca.* 210	13
 F2 F2 F2 F2 (1) (2) [94]	−124·1	−124·1	–	8 *ca.*
 F2 F2 (1) (2) [95]	−118·8	−117·3	–	12

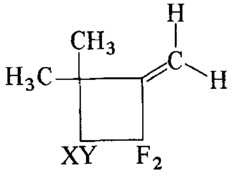
 [96]	−116·9	−123·3	211 217	13

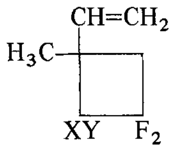
ethylene reacts with 3-methylbuta-1,2-diene to give a mixture of isomeric 1:1 adducts [97], [98], and [99]. (49) To assign the

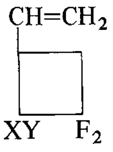
	$\delta CF_2(1)$	$\delta CF_2(2)$	$^3J^{HF}$
 [97]	−117·0	−113·8	12 Hz
 [98]	−128·4	−115·0	
 [99]	AB (1) −111·4 −112·4 $^2J^{FF}$ = 216 Hz	AB (2) −122·0 −124·0 $^2J^{FF}$ = 206 Hz	13 Hz
 [100]	AB (1) −111·0 −113·5 $^2J^{FF}$ = 226 Hz	AB (2) −121·5 −126·0 $^2J^{FF}$ = 226 Hz	14 Hz

structure of [98] the absence of any C*H*–C*F* coupling is particularly decisive. The reaction of tetrafluoroethylene with 2,4-dimethylpenta-2,3-diene gives a product which was identified as having the structure [100]. (49) Thermal cycloaddition of chlorotrifluoroethylene and 1,1-dichlorodifluoroethylene to $Me_2C{=}C{=}CH_2$ gives mixtures of four 1:1 adducts, [101] to [104]. (50) The analysis of


[101]


[102]


[103]


[104]

the products were performed in order to obtain useful mechanistic information of the reactions. It was also desirable to test the orientation specificity in the addition of unsymmetrical fluoro-olefins, to show whether σ-bond formation occurs concertedly or in a step-wise manner. The identification of the products and the definition of their structures was done by spectroscopy, including ^{19}F NMR technique. ^{19}F NMR data for a few 1:1 adducts are given in Table VII. Proof that the CF_2 group of the olefin is attached to

TABLE VII

^{19}F NMR parameters of the 3-methylbuta-1,2-diene cycloadducts (50)

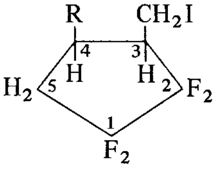
Adduct			Chemical shift			Coupling constant (Hz)	
	X	Y	δ_{CF_2}		δ_{CFCl}	$^2J_{FF}$	$^3J_{HF}$
[101]	Cl	F	−100·3;	−109·9	−120·6	215	13
[101]	Cl	Cl	−96				
[102]	Cl	F	−102·7;	−112·3	−128·6	219	–
[102]	Cl	Cl	−99·5				
[103]	Cl	F(*cis* or *trans*)	−100·5;	−109·7	−125·3	202	10
[103]	Cl	F(*trans* or *cis*)	−103·3;	−110·9	−128·1	203	14
[104]	Cl	F(*cis* or *trans*)	−100·7;	−121·2	−140·6	199	14
[104]	Cl	F(*trans* or *cis*)	−107·5;	−112·5	−109·5	200	–

the *sp*-hybridized carbon of the allene in the adducts [101] to [102] follows from a detailed study of their proton and fluorine NMR spectrum. (50)

The peroxide-initiated cyclodimerization of $CH_2{=}CHCF_2CF_2I$ gives a mixture of the geometrical isomers of the cyclopentane,

[105], where R = $-CF_2CF_2I$. (51) The assignments were given on the empirical basis of the electric substituent rule. (51) Reactions of

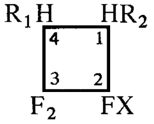
R = $-CF_2CF_2I$



[105]

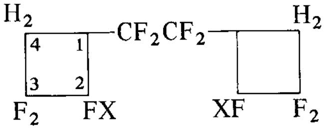
	δCF_2I	δCF_2(*exoc.*)	δCF_2–1	δCF_2–2
cis	–59·7	–106·6	–117·2	–113·3
		–115·5	–119·8	–132·2
		$^2J^{FF}$ = 266	$^2J^{FF}$ = 242	$^2J^{FF}$ = 241
trans	–59·1	–100·0		–119·7
		–111·7	–115·4	–126·6
		$^2J^{FF}$ = 261		$^2J^{FF}$ = 243

3,3,4,4-tetrafluorohexa-1,5-diene, $CH_2=CH-CF_2CF_2CF_2CF_2-CH=CH_2$, were studied. (14, 52) Thermal addition of this olefin to tetrafluoroethylene, to chloro-trifluoroethylene and to pentafluoro-iodoethane gives cyclic mono- and di- adducts, [106] and [107], the



[106]

X = F, Cl
R_1 = H, $-CH_2CF_2CF_3$
R_2 = $-CF_2CF_2CH=CH_2$, $-CF_2CF_2Et$, $CF_2CF_2CHBrCH_2Br$, CH_2I, CH_3



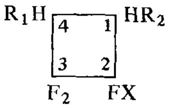
X = F, Cl

[107]

structures of which were established by spectroscopic methods. (14, 52) The NMR parameters are collected in Table VIII and Table IX. The assignment of the *cis*- and *trans*- cyclobutane structure was made following the criteria derived from chemical shift calculations, (53) which show that relative fluorine chemical shifts are mainly determined by the electric field effect of neighbouring groups. According to these calculations a fluorine paramagnetic shift is expected to be more pronounced the more polarizable and nearer to the resonant

TABLE VIII

^{19}F NMR parameter of cyclobutanes [106] (14, 52)



[106]

	X	R_1	R_2	$\delta[\mathrm{CFX}(-2)]$	$\delta[\mathrm{CF_2}(-3)]$	$\delta[\mathrm{CF_2CH}<]$	
	F	H	$-CF_2CF_2CH{=}CH_2$	−105·33 −131·06 $^2J_{FF}$ = 218	−110·49 −120·15 $^2J_{FF}$ = 210	*ca.* −118	−115·85 ($CF_2CH{=}$)
trans	Cl	H	$-CF_2CF_2CH{=}CH_2$	−107·20	−98·66 −119·43 $^2J_{FF}$ = 196	−118·34 −120·70 $^2J_{FF}$ = 276	−114·66 ($CF_2CH{=}$)
cis	Cl	H	$-CF_2CF_2CH{=}CH_2$	−139·23	−107·36 −108·14 $^2J_{FF}$ = 195	*ca.* −119	−114·52 ($CF_2CH{=}$)
	F	H	$-CF_2CF_2Et$	−105·46 −131·18 $^2J_{FF}$ = 215	−110·63 −120·18 $^2J_{FF}$ = 212	*ca.* −118	−116·73 ($-CF_2Et$)
trans	Cl	H	$-CF_2CF_2Et$	−107·23	−98·67 −119·44 $^2J_{FF}$ = 196	−118·23 −120·67 $^2J_{FF}$ = 276	−116·68 ($-CF_2Et$)
cis	Cl	H	$-CF_2CF_2Et$	−139·42	−107·38 −108·15 $^2J_{FF}$ = 195	*ca.* −119	−116·52 ($-CF_2Et$)

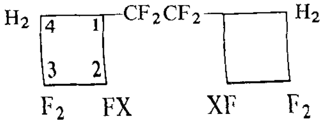
TABLE VIII—*cont.*

	X	R_1	R_2	δ[CFX(−2)]	δ[CF_2(−3)]	δ[$CF_2CH<$]	
	F	H	$-CF_2CF_2CHBrCH_2Br$	−105·19 −130·65 $^2J_{FF} = 214$	−110·43 −119·73 $^2J_{FF} = 210$	*ca.* −115	−106·86 −107·27 −114·11 −114·94 $^2J_{FF} = 277$ $^2J_{FF} = 277$ (—CF_2CHBr—)
cis	F	$CH_2CF_2CF_2$	CH_2I	−109·8 −135·3 $^2J_{FF} = 213$	−111·0 −132·7 $^2J_{FF} = 212$	—	−117·6 −118·1 $J_{FF} = ?$ (—CF_2CH_2—) −86·3 (CF_3)
trans	F	$CH_2CF_2CF_3$	CH_2I	−113·3 −127·7 $^2J_{FF} = 212$	−113·3 −125·8 $^2J_{FF} = 216$	—	−117·8 −113·4 $J_{FF} = 260$ (—CF_2CH_2—) −86·3 (CF_3)
cis	F	$CH_2CF_2CF_3$	CH_3	−111·0 $^2J_{FF} = 216$	−36·5 −111·6 $^2J_{FF} = 210$	—	*ca.* −119 (—CF_2CH_2—) −86·5 (CF_3)
trans	F	$CH_2CF_2CF_3$	CH_3	−118·1 −125·0 $^2J_{FF} = 211$	−109·6 −127·8 $^2J_{FF} = 211$	—	*ca.* −118 (—CF_2CH_2—) −86·5 (CF_3)

TABLE IX

^{19}F NMR parameters of di-adducts [107] (52)

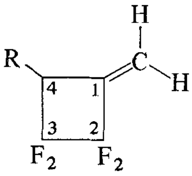
[107]



X	δ[CFX(−2)]	δ[CF$_2$(−3)]	δ[>CH(CF$_2$)$_2$CH<]
F	−105·41 −129·84 $^2J_{FF}$ = 215	−110·40 −119·45 $^2J_{FF}$ = 210	*ca.* − 117
trans. Cl	−107·02	−98·48 −119·16 $^2J_{FF}$ = 195	−118·1 −120·3 $^2J_{FF}$ = 276
cis. Cl	−138·6	*ca.* −107·6	*ca.* −117

fluorine nuclei the neighbouring group is. The internal chemical shift between the two fluorine of CF$_2$ groups in [106] and [107] is expected to be greater for the CF$_2$ at C-2 (observed δ_{AB} = *ca.* 25 ppm) than for that at C-3 (observed δ_{AB} = *ca.* 9 ppm). Analogously the chemical shift difference of the −CFCl− fluorine in the *cis-* and *trans-* structure of [106] and [107] should be quite large (observed *ca.* 32 ppm), with the lower field resonance assignable to the *trans*-structure. (52, 53)

Dehydroiodination of 3,3,4,4-tetrafluoro-1-iodo-methyl-2-(2,2,3,-3,3-pentafluoropropyl)-cyclobutane gave one methylenecyclobutane derivative, [108]. (14) An isomeric saturated monoadduct containing a five-membered ring, [109], and series of acyclic monoadducts were also isolated. (14) The latter compounds have been already discussed in Section IB. In the study of the gas phase chlorination of fluorohexane there was the problem to identify the



R = CH$_2$CF$_2$CF$_3$

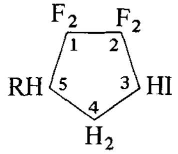
[108]

δCF$_2$(−2) $\left\{\begin{array}{l} -114{\cdot}5 \\ -116{\cdot}3 \\ ^2J^{FF} = 226\ \text{Hz} \end{array}\right.$

δCF$_2$(−*exo*) $\left\{\begin{array}{l} -117{\cdot}0 \\ -118{\cdot}1 \\ ^2J^{FF} = 266\ \text{Hz} \end{array}\right.$

δCF$_2$(−3) $\left\{\begin{array}{l} -113{\cdot}8 \\ -130{\cdot}6 \\ ^2J^{FF} = 211\ \text{Hz} \end{array}\right.$

δCF$_3$ = −86·43



$R = CH_2CF_2CF_3$

[109]

$$\delta CF_2(-1)\begin{cases} -112{\cdot}3 \\ -118{\cdot}3 \\ ^2J^{FF} = 232\text{ Hz} \end{cases} \qquad \delta CF_2(exo)\begin{cases} -115{\cdot}7 \\ -119{\cdot}9 \\ ^2J^{FF} = 266\text{ Hz} \end{cases}$$

$$\delta CF_2(-2)\begin{cases} -109{\cdot}5 \\ -126{\cdot}3 \\ ^2J^{FF} = 239\text{ Hz} \end{cases} \qquad \delta CF_3 = -85{\cdot}5$$

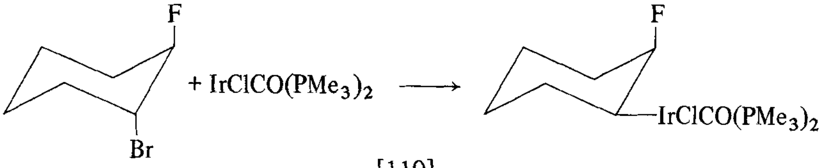
products of the reaction constituted by isomeric chlorofluorocyclohexanes. (54) ^{19}F NMR as well as ^1H NMR spectroscopy were employed in the identification of the compounds reported in Table X.

TABLE X

^{19}F NMR spectral data of the isomeric chlorofluorocyclohexanes (54)

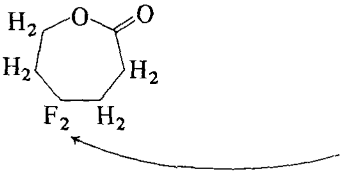
Compound	δ_F	$^2J_{HF}$ (Hz)
trans-1,2-chlorofluorocyclohexane	−200·7	45
trans-1,3-chlorofluorocyclohexane	−192·0	–
cis-1,3-chlorofluorocyclohexane	−188·7	48
trans-1,4-chlorofluorocyclohexane	−182·7	45
cis-1,4-chlorofluorocyclohexane	−181·2	46

The addition of *trans* 1-bromo-2-fluorocyclohexane to *trans*-$IrClCO-(PMe_3)_2$ was said to occur with inversion of configuration (55) according to the equation below, [110]:



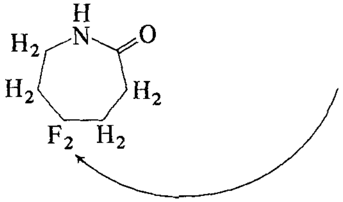
[110]

The work was reinvestigated (56) and it was found that no reaction occurs under the reported or more severe reaction conditions. Only one fluorine resonance at −166·3, characteristic of 1-bromo-2-fluorocyclohexane, was observed and the appearance of a new signal at −142·7, claimed in previous work, was not observed. (56) Ring inversion in γ,γ-difluoro-ε-caprolactone, [111], and γ,γ-difluoro-ε-caprolactam, [112], was studied. (57) [111] displays a quintet



−22·4*
−35·8 at −85°
$^2J^{FF} = 240$ Hz

[111]



−18·2*
−18·9 at −81°
$^2J^{FF} = 241$ Hz

[112]

($^3J^{HF}$ = 14·5 Hz), −30·8,* at room temperature; at −85° an AB pattern is observed. Also [112] shows a quintet (−29·4* with $^3J^{HF}$ = 14.1 Hz) at room temperature, which becomes an AB pattern at low temperature (−81°). The rates of ring inversion of [111] and [112] were measured to give free energies of activation of 10·0 and 10·4 Kcal/mole respectively (at −53°). The NMR spectra of both compounds were best interpreted in terms of the existence of the only chair conformations. (57)

A detailed study was made of the ^{19}F NMR spectra of the anomeric pairs of all five deoxyfluoro-D-glucopyranoses and of 2-deoxy-2-fluoro-D-mannopyranose in D_2O. (58) Each carbohydrate studied contains only one fluorine atom and the behaviour of equatorially disposed fluorine atoms in the various positions of the D-glucopyranose ring system and of axial fluorine atoms in the 2-positions of the D-mannopyranose ring was examined. (58) Samples of each carbohydrate dissolved in D_2O were set aside until the anomeric equilibrium was established. The NMR spectra of [113] to [118] were analysed on first-order basis; the ^{19}F NMR parameters obtained are collected in Table XI. Configurations and conformational properties of these molecules were established by the values of $^2J^{HF}$ and $^3J^{HF}_{vic}$, together with the ^{1}H NMR parameters and observed equilibrium anomer concentrations. The same types of interactions which control the variation of HF coupling constants (see Section II) also control variations in the shielding of the fluorine

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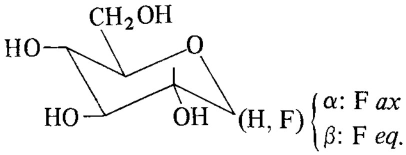
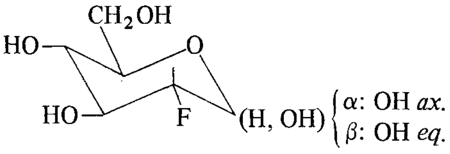
* ^{19}F chemical shifts to low frequency with respect to ethyl chlorodifluoroacetate.



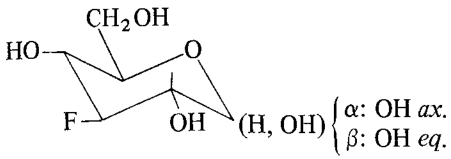
1 deoxy-1-fluoro-D-glucose

[113]



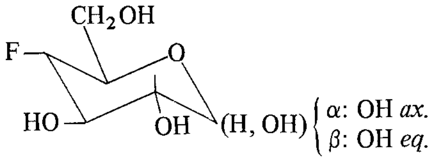
2-deoxy-2-fluoro-D-glucose

[114]



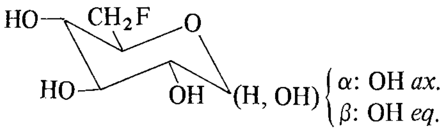
3-deoxy-3-fluoro-D-glucose

[115]



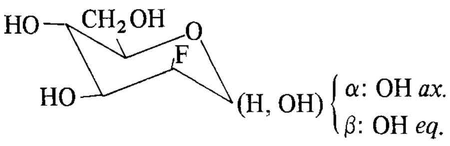
4-deoxy-4-fluoro-D-glucose

[116]



6-deoxy-6-fluoro-D-glucose

[117]

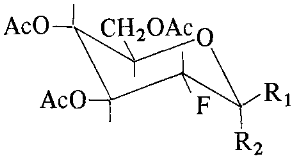


2-deoxy-2-fluoro-D-mannose

[118]

nuclei. (58) In Table XI is shown the consequences of changing the OH at C-1, from the axial to the equatorial orientation, upon the shielding of a 2-, 3- and 4- equatorial fluorine atom and of a 6-fluorine atom. (58)

Four isomers of the 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluorohexopyranosyl fluoride, [119] to [122], were studied by ^1H and ^{19}F

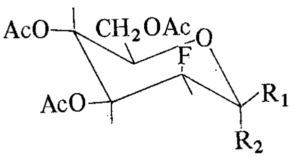


$R_1 = H; R_2 = F$

[119]

$R_1 = F; R_2 = H$

[120]



$R_1 = H; R_2 = F$

[121]

$R_1 = F; R_2 = H$

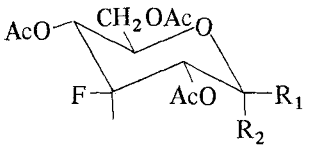
[122]

TABLE XI

NMR parameters of the deoxyfluoro-D-glucoses and 2-oxy-2-fluoro-D-mannose in D_2O (58)

Compound		Chemical shift δ_F	H–F Coupling constant (Hz) $J(F \cdot H_1)$	$J(F \cdot H_2)$	$J(F \cdot H_3)$	$J(F \cdot H_4)$	$J(F \cdot H_5)$	$J(F \cdot H_6)$
[113]	α	−146·08	52·2	27·2	–	–	–	
	β	−139·04	52·9	12·0	–	–	–	
[114]	α	−195·41	<0·5	49·0	14·5	–	–	
	β	−195·23	2·5	50·0	14·5	–	–	
[115]	α	−195·95	3·9	12·0	53·0	12·0		
	β	−191·04	<0·5	13·5	52·0	13·5		
[116]	α	−194·15	3·5	–	15·0	49·0	*ca.* 4·5	*ca.* 3·0
	β	−196·16	0	–	16·0	49·5	*ca.* 4·5	*ca.* 2·0
[117]	α	−231·27	–	–	–	–	28·0	47·3
	β	−230·54	–	–	–	–	27·0	47·5
[118]	α	−200·74	7·5	49·0	30·0	–		
	β	−219·22	20·0	52·0	32·0	–		

NMR spectroscopy. (59) The configurations and conformations of these molecules were based on conventional analytical data and on NMR data, in particular on the H–H coupling constants. The values of J_{34}^{HH} and J_{45}^{HH}, for example, enable the approximate ${}^4C_1(D)$ conformations to be stated for all four compounds. The angular and configurational dependences of the other couplings (HF and FF) could be consequently studied. The magnitude of the F–F couplings were estimated from both the normal ^{19}F spectrum and the proton-decoupled spectrum F {H}. The signs of many coupling constants were determined using heteronuclear double resonance experiments. (59) Two isomers, the α- and β- anomers, of 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-D-glucopyranosyl fluoride, [123], [124], and one



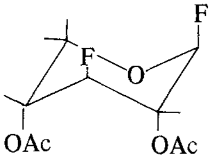
α: $R_1 = H; R_2 = F$

[123]

β: $R_1 = F; R_2 = H$

[124]

isomer, the β-anomer, of 2,4-di-*O*-acetyl-3-deoxy-3-fluoro-D-xylopyranosyl fluoride, [125], were studied by ^{1}H and ^{19}F NMR spectroscopy. (60) The H-H and H-F couplings are consistent with the $^4C_1$(D) conformation as shown in [123], [124] and [125]. Chemical shifts, H-F and F-F couplings of [119] to [125] are collected in Table XII. (59, 60)



[125]

TABLE XII

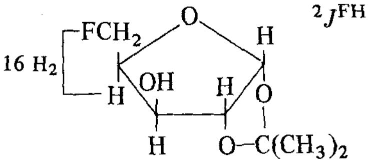
Chemical shift and coupling constant of fluorinated carbohydrates (59, 60)

	[119]	[120]	[121]	[122]	[123]	[124]	[125]
δF_1	−151·5	−140·3	−143·4	−146·4	−149·8	−138·8	−137·7
δF_2	−204·5	−200·9	−207·2	(−207·0)	–	–	–
δF_3	–	–	–	–	−201·1	−196·0	−195·7
JH_1F_1	+53·3	+51·7	+48·0	+48·5	+52·2	+51·5	+49·8
JH_2F_2	+48·3	+49·0	+48·5	+49·0			
JH_2F_1	+23·8	+11·2	0	+8·0	+22·6	+10·8	7·7
JH_1F_2	0	+4·0	+4·0	+13·5			
JH_3F_2	+12·3	+15·0	+27·0	+22·4			
JH_3F_1	0·5	−1·0	+2·5	0·5	1·0	0	0·1 to 0·2
JH_5F_1	0	0	0	0·8	0·5[a]	0[a]	0[a]
JH_4F_2	0	0	0	+2·0			
JH_5F_2	0	0	0	0·5			
$J(H_6F_1) + (H_6F_1)$	0	1·5	0	2·0			
JH_3F_3					+51·5	+51·3	+45·5
JH_2F_3					+14·5	+15·0	+12
JH_4F_3					+13·5	+13·5	+12
JH_1F_3					+4·0	0	0
JH_5F_3					1·0[a]	−1·0[a]	+2·5[a]
					–	–	0·3[b]
JFF *cis.*	−18·8	−15·8	−20·0	−13·5			
^4JFF					+1·0	−3·0	+10·4

[a] HF vicinal coupling involving axial proton.

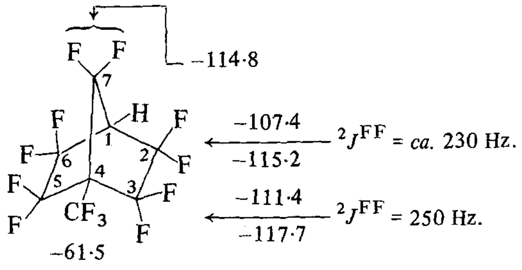
[b] HF vicinal coupling involving equatorial proton.

Configurational dependences of the ^{19}F-shifts in fluoromonosaccharides were reported. (61) Preliminary communications were made of the ^{19}F chemical shifts for F(1) and F(2) for a number of fluorocarbohydrates. (62) Some of the earlier values were revised and the investigation was extended to F(3) in the pyranose series. (61) Potentially the use of ^{19}F-shifts offers a powerful means of specific stereochemical determination. Values were found at –125 to –156 for F(1), at –211 to –215 for F(2), at –229 to –230 for F(6) and at –60 to –61 for $-OCF_3$. F(3) in pyranoses show two sets of resonances, at –194 and –200 to –202, attributed to the β- and α- anomers respectively. Several HF couplings were also reported; (61) it is noticeable that in the pyranose series the *gem* couplings $^2J(F_a\ H_e)$ are greater ($J = 53$ Hz) than the values $^2J(F_e\ H_a)$ ($J = 46$ Hz) when the fluorine nucleus is equatorially disposed. The H–F vicinal couplings are in the expected order: *trans* diaxial > axial-equatorial > equatorial – equatorial. The fluorine spectrum of 5-deoxy-5-fluoro-1,2-*O*-isopropylidene-α-D-xylopentose, [126], was reported and discussed. (63) 1*H*,4-trifluoromethyl-decafluorobicyclo-[2,2,1]heptane, [127], was prepared and its fluorine NMR spectrum described. (64)



$^2J^{FH} = 47$ Hz

[126]



[127]

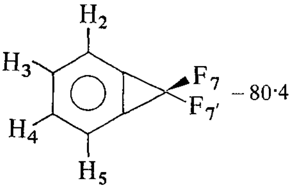
$J(CF_3 \cdot F\ \text{bridge}) = 4{\cdot}7$ Hz

$J(CF_3 \cdot F_3\ \textit{endo}) = 4{\cdot}7$ Hz

$J(CF_3 \cdot F_3\ \textit{exo}) = 17{\cdot}6$ Hz

2. *Unsaturated systems*

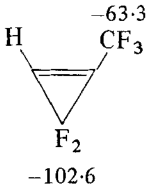
The proton and fluorine NMR spectrum of 7,7′-difluoro-benzocyclopropane, [128], was analysed to obtain all the chemical shifts



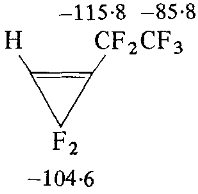
[128]

and coupling constants. (65) The ${}^{19}F$ NMR spectrum shows a triplet at −80·4 with splitting value of 3·4 Hz. The H–F couplings were derived from the proton analysis of the spectrum and were ${}^{4}J^{HF}$ = +3·64 Hz and ${}^{5}J^{HF}$ = −0·33 Hz respectively. The signs, in such a case, were established from heteronuclear double resonance experiments, [128] was also observed in *N*-(*p*-ethoxybenzylidene)-*p*-*n*-butylaniline as nematic solvent at 30°. (66) The dipole coupling constants were: D_{27} = −48·6 Hz, D_{37} = −48·2 Hz and D_{77} = 455·1 Hz.

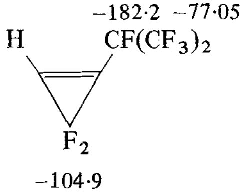
The ${}^{19}F$ NMR data of three cyclopropenes, [129] to [131], were



[129]

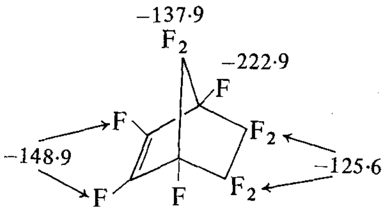


[130]



[131]

reported in relation to a study of some fluorocyclopropenyl derivatives. (48) On the extension of a work on highly-fluorinated norbornanes the ${}^{19}F$ NMR spectrum of decafluorobicyclo[2.2.1]-hept-2-ene (decafluoronorbornene), [132], was described. (67) An effective method for the synthesis of 7,7′-difluoronorbornene and of

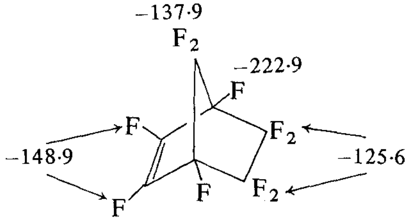


[132]

its *endo*-5-phenyl derivative was described; (68) a chemical shift difference of Δδ = 8·6 ppm was found for the 7-CF_2 group with

TABLE XIII

^{19}F chemical shifts and geminal coupling constants for some derivatives of decafluorobicyclo[2.2.1] heptene [132] (69)



[132]

	CF$_2$—7			CF$_2$—5			CF$_2$—6			=CF		
	δ_{anti}	δ_{syn}	$^2J_{FF}$(Hz)	δ_{exo}	δ_{endo}	$^2J_{FF}$(Hz)	δ_{exo}	δ_{endo}	J_{FF}(Hz)	δ_2	δ_3	δ_4
1H, 4H—	−103·7	−131·0	207	−112·6	−124·6	233	−112·6	−124·7	233	−141·7	−141·7	
1I, 4I—	−109·4	−127·2	193	−104·6	−116·0	218	−104·6	−116·0	218	−132·9	−132·9	
1I, 4F—	−115·6	−136·5	195	−122·1	−122·1	–	−105·8	−118·1	220	−131·1	−148·3	−214·4
1H, 4I—	−104·9	−129·4	196	−108·2	−113·5	218	−109·3	−117·9	226	−140·4	−134·4	
1H, 4F—	−115·7	−139·3	205	−124·4	−124·4	–	−111·9	−115·8	229	−138·7	−149·4	−216·8
1Br, 4F—	−120·0	−139·9	188	−122·6	−122·6	–	−112·6	−120·3	218	−138·3	−148·6	−216·8
1H, 4Me—	−112·0	−137·6	205	−120·2	−120·2	–	−111·9	−115·6	231	−143·5	−147·8	
1Me, 3Me—	−123·3	−145·9	209	−122·1	−122·1	–	−123·1	−127·0	225	−129·0	–	−217·5

$^2J^{\mathrm{FF}}$ = 186 Hz. The ^{19}F NMR spectra of a series of derivatives of decafluoro[2.2.1]heptene were examined. (69) The assignments of the chemical shifts were made utilizing the previously reported electric field method. (70) The compounds examined are collected in Table XIII. Relative intensities, trends in chemical shifts and coupling constant details were used to perform the assignments as reported in Table XIII. Chemical shift calculations for the 7-CF_2 suggest that the fluorine *syn*- to the double bond gives rise to the low-frequency lines and that the fluorine *anti*- to the double bond resonates at high frequency in the appropriate AB band in each of the spectra. (69) For the fluorine at C-5 and C-6 it was calculated that the *endo*-nuclei are *ca.* 10·4 ppm more shielded than the *exo*-nuclei. Experimentally a 2·0 ppm shift was observed. This assignment is in agreement with the coupling which is exhibited at the bridge fluorine

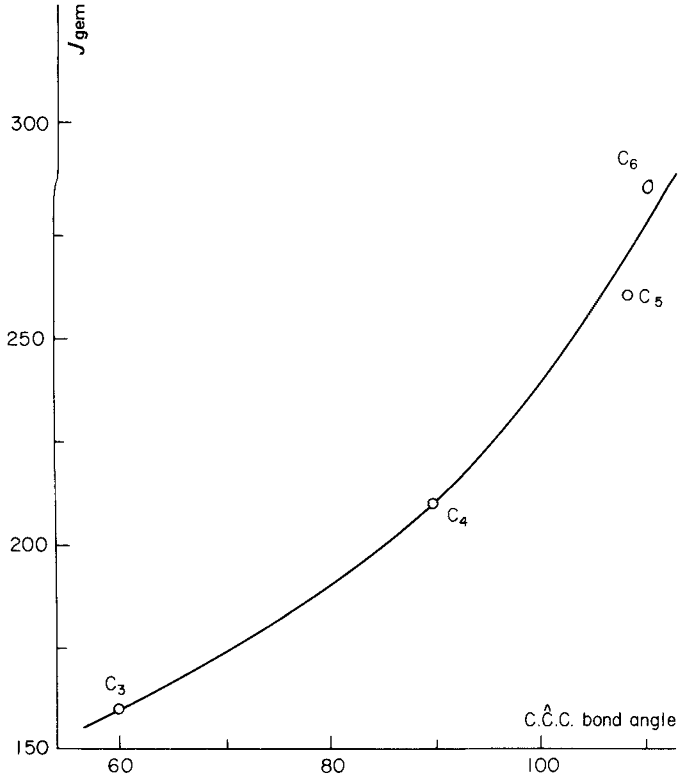
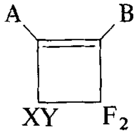


FIG. 2. The dependence of geminal F · F coupling on C–C–C internal ring angles in saturated cyclic fluorocarbons. (From Homer and Callaghan. (69))

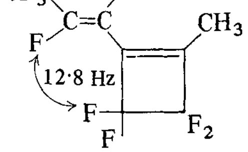
at C-7, *anti* to the double bond (a triplet of *ca.* 20 Hz). This coupling is evident as a doublet on the low-field pair of lines of the AB band of the CF_2 groups at C-5 and C-6. These triplet-doublet splittings are likely to arise from couplings between F_7-anti and $F_{5,6}$-*exo*. The geminal coupling constants of the compound [132] (69) were compared with analogous couplings in other fluorinated cyclic compounds. Despite some approximations arising from the uncertainty of the right geometry of the molecules there is indication that the $^2J^{FF}$ coupling becomes larger with an increase of the internal ring angle, C–C–C, of the carbon skeleton (Fig. 2). The same $^2J^{FF}$ trend was elucidated by other workers. (14) The value of $^2J^{FF} = ca.$ 256 Hz, found for the 5-CF_2 and 6-CF_2, corresponds approximately to an internal angle of *ca.* 104° in agreement with the same calculations relative to bicyclo[2.2.1]heptane skeleton. (71) The value of $^2J^{FF}$ = *ca.* 206 for the CF_2 at C-7 indicates that the angle in the bicyclo-[2.2.1]heptene molecule is *ca.* 88°, which is an angle smaller than that proposed for the bicyclo[2.2.1]heptane (71) (95°).

A series of fluorinated cyclobutenes, [133], have been reported.

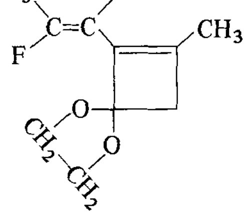


[133]

(14, 72, 73) Table XIV collects the ^{19}F chemical shifts. Some of the structures for the cyclobutenes [133] were defined by NMR. [133], for example, displayed (14) a coupling J^{HF}_{vic} = 34 Hz, consistent with H and F in *trans* neutral position. Irradiation of the CF_3 group of [133f] revealed that the CF resonance has an FF coupling J^{FF} = 12·8 Hz, which must come from the nearest ring-CF_2 group. The lack of this coupling in [133g] demonstrates that the ethylene acetal group



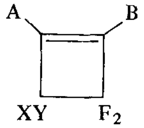
[133 f]



[133 g]

TABLE XIV

^{19}F chemical shifts of fluorinated cyclobutenes [133]



[133]

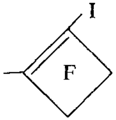
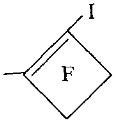
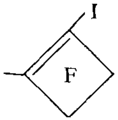
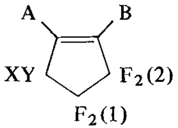
	X	Y	A	B	δ_{CXY}	δ_{CF_2}		δ_B	δ_A	Ref.
(a)	F	F	I	I	−113·1	−113·1		–	–	Unpubl.
(b)	F	F	F	I	−116·4	−118·4		–	−104·9	(73)
(c)	F	F	F	H	−114·0	−118·7		–	−105·3	Unpubl.
(d)	F	F	Cl	I	−114·6	−117·0		–	–	(73)
(e)	F	F	I	H	−111·9	−113·3		–	–	(73)
(f)	F	F	CF$_3$CF=CH—	CH$_3$	−113·9	−117·4		–	−73·4 (CF$_3$) −116·3 (—CF=)	(14)
(g)	—O(CH$_2$)$_2$O—		CF$_3$CF=CH—	CH$_3$	–	−116·1		–	−73·1 (CF$_3$) −119·0 (—CF=)	(14)
(h)	H	OCH$_3$	H	F	–	*ca.* −110·1 *ca.* −123·2	$^2J_{FF}$ = 215 Hz.	110·4	–	(72)
(i)	H	OCH$_3$	H	OCH$_3$	–	*ca.* −109·4 *ca.* −122·7	$^2J_{FF}$ = 197·5 Hz.	–	–	(72)
(l)	H	OEt	H	F	–	*ca.* −109·5 *ca.* −122·6	$^2J_{FF}$ = 214 Hz.	109·3	–	(72)
(m)	I	F	F	H	−109·9	−99·1 −113·0	$^2J_{FF}$ = 182 Hz.	–	−100·7	(73)
(n)	F	F	I		−109·9	−113·1				(73)
(o)	F	F			−108·9	−108·9		(−112, −113·0)		(73)

TABLE XV

^{19}F chemical shifts of fluorinated cyclopentenes [134]



[134]

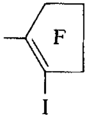
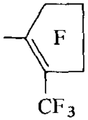
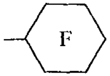
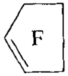
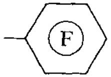
X	Y	A	B	δ_{CXY}	$\delta_{CF_2(1)}$	$\delta_{CF_2(2)}$	δ_B	δ_A	Ref.
F	F	I	I	−106·8	−130·0	−106·8	–	–	(73)
F	F	I	Cl	−106·9	−129·9	−114·0	–	–	(73)
F	F	I	F	−107·2	−129·0	−115·1	−115·1	–	(73)
F	F	I		−108·8	−131·4	−109·6	–	–	(73)
H	OMe	H	F	–	−116·2 −130·8 $^2J_{FF}$ = 246 Hz.	−116·1 −123·9 $^2J_{FF}$ = 260	−135·2	–	(72)
H	OMe	H	OMe	–	−116·7 −131·4 $^2J_{FF}$ = 255 Hz.	−115·0 −123·0 $^2J_{FF}$ = 269 Hz.		–	(72)
OMe	OMe	H	H	–	−129·63	−111·06	–	–	(72)
H	H	CF_3	H	–	−116·9	−113·3	–	−70·4	(18)
H	H	CHF_2	F	–	−115·2	−121·9	−137·0	−122·0	(18)
H	H	CH_2F	F	–	−115·1	−120·9	−142·2	−230·0	(18)
H	H	CHF_2	H	–	−117·0	−113·0	–	−122·0	(18)
F	F	CF_3	F	−111·0	−131·3	−121·3	−115·6	−68·1	(18)
F	F	CH_3	F	−114·1	−131·0	−120·1	−137·2	–	(18)

TABLE XV—*cont.*

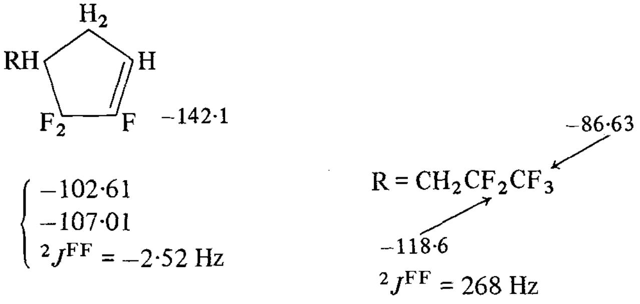
X	Y	A	B	δ_{CXY}	$\delta_{CF_2(1)}$		$\delta_{CF_2(2)}$	δ_B	δ_A	Ref.
F	F	CF_3	H	−112·1	−132·4		−113·0	–	−65·5	(18)
F	F	CH_3	H	−116·9	−132·0		−109·7	–	–	(18)
F	F	CF_3	I	−111·9	−131·0		−108·9	–	−62·5	(18)
F	F	I	COH	−109·0	−131·0		−111·2	–	–	(18)
F	F	F	CF_2Cl	−121·1	−131·9		−110·1	−50·9	−116·9	(18)
F	F	F	CF_2I	−121·1	−127·2		−114·0	−44·5	−117·9	(18)
F	Cl	F	CF_2Cl	−111·9	−120·8 −129·7	$^2J_{FF}$ = 233 Hz. *ca.*	−109·4	−50·5	−124·9	(18)
F	F	CF_3		−108·9 −115·9	−131·9 −134·5		−110·6 −117·0	−62·0	–	(18)
[a]F	F	CF_3		$>$CF = 176·0	–		–	−57	–	(18)
[b]F	F	F	—$(CF_2)_2$ 	−121·8	−131·9		−111·6	–	−111·0	(18)
[c]F	F	CF_3		−112·1	−132·8		−113·1	–	−62·8	(18)
=NH		F	NH_2	–	−119·97		−119·97	–	−159·97	(76)
H	NH_2	F	NH_2	–	(two AB^+ at −104 to −130)			–	−147 to −150	(76)

[a] The fluorine resonances give a too complex spectrum to be interpreted.

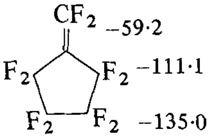
[b] $=CCF_2CF_2C=$ resonates at −108·0.

[c] *o*-F = −137·9; *m*-F = −161·0; *p*-F = −148·8.

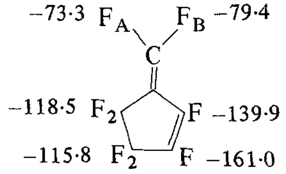
is in the position adjacent to $CF_3CF{=}CH-$. (14) The electric field method (53) was utilized to assign the chemical shifts of these fluorinated cyclobutenes. The same method, in conjunction with intensity criteria and coupling constant values, was used to assign the chemical shifts of several fluorinated cyclopentenes, [134], prepared from the photochemical isomerization of decafluorocyclohexene. (18) A group of these compounds together with some others (72, 73, 76) are reported in Table XV. A further cyclopentene, which could not be included in Table XV, is shown in [135]. Perfluoromethylenecyclopentane, [136], and perfluoro-(3-methylenecyclopentene), [137], have been described. (18)



[135]

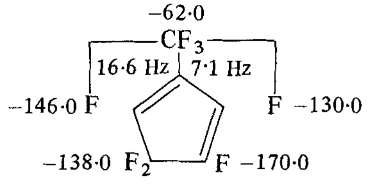


[136]

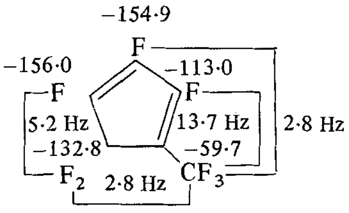


[137]

Two perfluoro-cyclopentadienes, [138] and [139], were also characterized by ^{19}F NMR. (18) The diene [139] was heated to

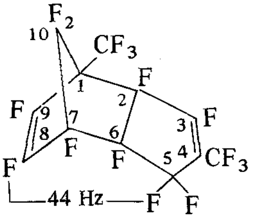


[138]



[139]

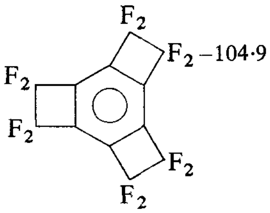
ascertain its thermal stability; perfluoro-1,4-dimethyltricyclo-[5.2.1.0] deca-3,8-diene, [140], was obtained and its structure was assigned on the basis of spectroscopic measurements. The dimer [140] is likely to have an *endo*-configuration in agreement with some literature results (74) and the existence of a long-range F–F coupling (J = 44 Hz) between 8-F and one of CF_2-5 fluorine nuclei. (18)



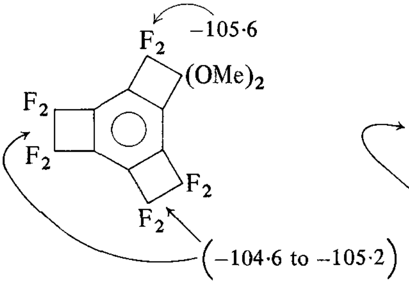
[140]

1: CF_3 −61·4
4: CF_3 −61·0
5: CF_2 AB $\begin{cases} -94{\cdot}5 \\ -109{\cdot}4 \\ {}^2J^{FF} = 269\ \text{Hz} \end{cases}$
10: CF_2 AB $\begin{cases} -116{\cdot}1 \\ -131 \\ {}^2J^{FF} = 184\ \text{Hz} \end{cases}$
3: =CF −102·8
8: =CF −140·9
9: =CF −146·1
2: >CF −175·8
6: >CF −189·9
7: >CF −213·0

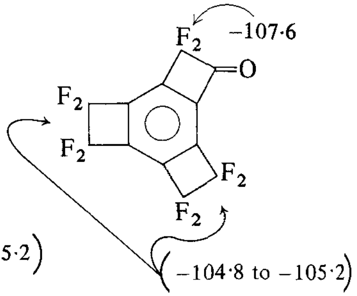
In the study of the synthesis of 1-iodo- and 1,2-diiodo- perfluoro-cyclo-olefins a few polycyclo-olefins were also obtained and characterized by NMR (73) [141] to [147]. In the AB spectrum of the



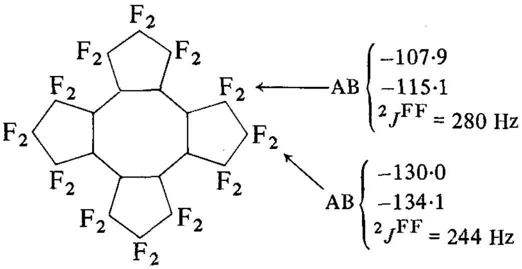
[141]



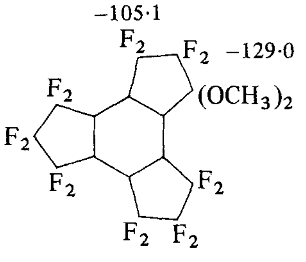
[142]



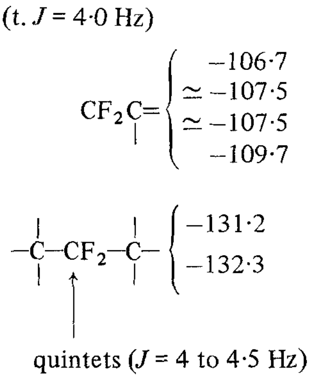
[143]

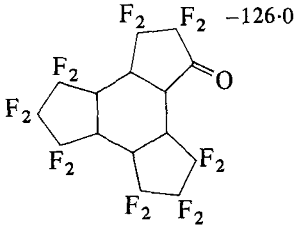


[144]

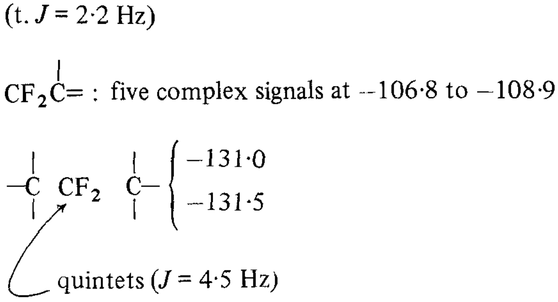


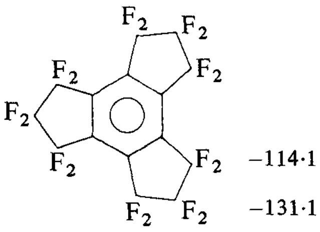
[145]





[146]



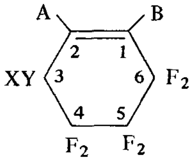


[147]

$-\overset{|}{\underset{|}{C}}CF_2\overset{|}{\underset{|}{C}}-$ group of [144] at room temperature, the A part is made up of two triplets ($^3J^{FF}$ = 5·0 Hz) arising from the coupling with the two vicinal fluorines which resonate at −115·1 and B consists of two broad bands (half width = *ca.* 10 Hz). A variable temperature study of the NMR spectrum of [144] indicates that the cyclo-octatetraene ring must have a very low rate of inversion because, even at +180°, the rate of inversion increases only to average the vicinal

TABLE XVI

^{19}F chemical shifts of fluorinated cyclohexenes

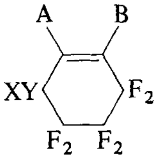


[148]

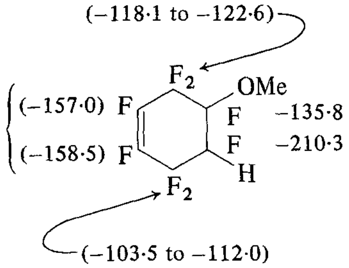
X	Y	A	B	δ_3	δ_4	δ_5	δ_6	δ_B	δ_A	Ref.
H	OMe	H	F	–	–117·0 –127·5 $^2J_{FF}$ = 293	–125·4 –133·0 $^2J_{FF}$ = 268	–131·9 –139·7 $^2J_{FF}$ = 276	–132·4	–	(72)
F	OMe	H	H	–119·4	–105·8 –113·6 $^2J_{FF}$ = 300 Hz.	–130·9 –139·9 $^2J_{FF}$ = 269	–130·8	–	–	(72)
H	F	H	OMe	–187·5	–126·2 –133·3 $^2J_{FF}$ = 295 Hz.	–134·4 –136·8 $^2J_{FF}$ = 286 Hz.	–119·9	–	–	(72)
OMe	OMe	H	H	–	–128·3	–138·1	–108·6	–	–	(72)
H	F	OMe	F	–199·7	–127·4 –130·4 –140·5 –143·5	–125·3 –133·4 –136·4	–111·4 –114·4 –122·3	–167·8		(75)
=NH		CF_3	NH_2	–	–117·3	–136·8	–122·4	–56·9		(76)
$=NCH_3$		F	$-NHCH_3$	–	–116	–134·3	–116	–154·0		(76)
=O		F	$-NHCH_3$	–	–114·3	–133·3	–123·4	–165·1		(76)

coupling constants but not the geminal couplings or the difference in the chemical shifts. (73)

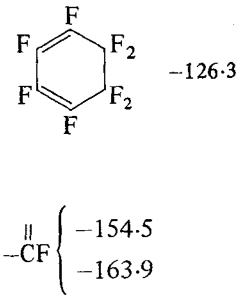
A few fluorinated cyclohexenes were obtained, Table XVI, by treating 1*H*,2*H*-octafluorocyclohexene with CH_3OH in the presence of base. (72) In Table XVI other cyclohexenes are also included. (75, 76) A further fluorinated cyclohexene, which could not be included in Table XVI, is shown in [149]. (75) The assignments of the ^{19}F chemical shifts of these cyclohexenes were not always given. The assignments reported in Table XVI are only tentative being mainly made by comparison with other cyclo-olefins. Some cyclohexa-1,3- and 1,4- dienes, [150] to [157], were prepared in the study of nucleophilic substitution reactions of octafluorocyclohexa 1,3- and 1,4- diene. (75) Two heptafluorobicyclo[2.2.2]oct-2-enes, [160], were also obtained. (75) Some other cyclohexadienes, [158] and [159], (76) and [161] and [162], (77) were obtained and characterized by ^{19}F NMR.



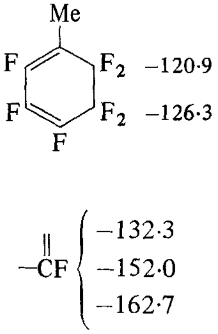
[148]



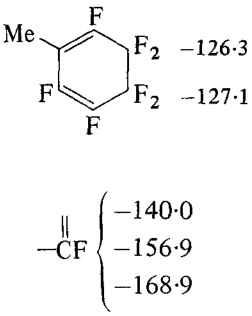
[149]



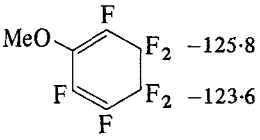
[150]



[151]

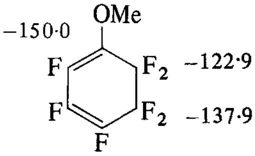


[152]



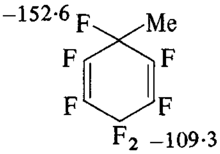
$-\overset{\|}{C}F\begin{cases}-149\cdot1\\-167\cdot3\\-171\cdot5\end{cases}$

[153]



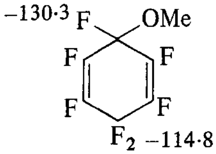
$-\overset{\|}{C}F\begin{cases}-156\cdot8\\-164\cdot6\end{cases}$

[154]



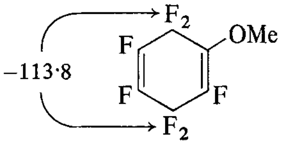
$-\overset{\|}{C}F\begin{cases}-148\cdot7\\-161\cdot8\end{cases}$

[155]



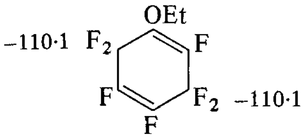
$-\overset{\|}{C}F\begin{cases}-157\cdot0\\-168\cdot8\end{cases}$

[156]



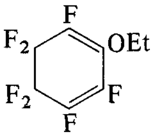
$-\overset{\|}{C}F\begin{cases}-162\cdot9\\-170\cdot0 \leftarrow \text{intensity} = 1\end{cases}$

[157]



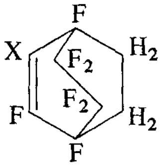
$-\overset{\|}{C}F\begin{cases}-157\cdot1\\-158\cdot9\\-163\cdot3\end{cases}$

[158]



$CF_2\begin{cases}-122\cdot3\\-124\cdot4\end{cases}$ $-\overset{\|}{C}F\begin{cases}-147\cdot0\\-166\cdot0\\-168\cdot5\end{cases}$

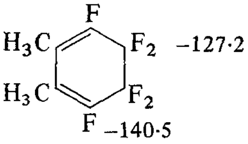
[159]



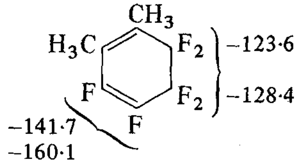
[160]

X = Me
CF_2 centred at −128·0, −129·7
=CF −133·6
—CF −191·8, −201·3

X = OMe
CF_2 centred at −127·8, −128·8
=CF −161·0
—CF −195·6, −198·6

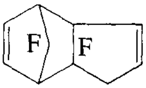


[161]

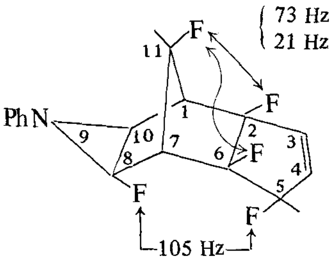


[162]

Studying the cyclo-addition of benzyl azide with olefins it was of interest to examine the action of phenyl azide on the thermal dimer of perfluorocyclopentadiene [163]. (78) At 70° a slow reaction occurs to afford [164]. (78) Several important comparisons may be



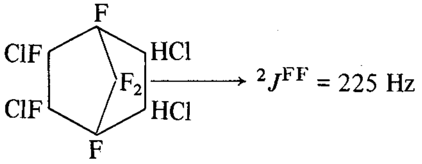
[163]



[164]

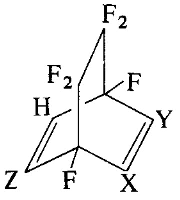
$CF_2(5)$ centered at −107·0, $^2J^{FF}$ = 260 Hz
$CF_2(11)$ centered at −125·5, $^2J^{FF}$ = 220 Hz
CF(3 or 4) −137·0
CF(4 or 3) −146·5
CF(8) −164·8
CF(10) −169·9
CF(2 or 6) −181·7
CF(6 or 2) −189·6
CF(1 or 7) −209·4
CF(7 or 1) −210·9

drawn between the spectra of the aziridine [164], (78) of [163] (74) and [140]. (18) A coupling, with a large through-space component, between one fluorine at C–5 and the fluorine at C–8 (J = 105 Hz) was in fact observed. This suggests an *exo*-fusion of the aziridine ring which forces F–8 and F–10 into *endo*-positions. Another large coupling (73 Hz) was assigned to the interaction through space between one F–11 and one of the tertiary fluorine (F–2 or F–6). Coupling of the same F–11 with the other nucleus of the F–2/F–6 pair is appreciably weaker (J = 21 Hz), which suggests that the aziridine molecule is twisted. It is noteworthy that the value of $^2J^{FF} = 220$ Hz, for the bridging CF_2 group, falls between those observed for the corresponding group of some bicyclo[2.2.1]-hept-2-enes ($^2J^{FF}$ = 172 to 185 Hz), and those for CF_2 groups in nearly planar polyfluorocyclopentanes ($^2J^{FF}$ = 265 to 275 Hz). This suggests that the $\underline{C(1) \cdot C(10) \cdot C(8) \cdot C(7) \cdot C(11)}$ ring in the aziridine ring is closer to planarity than the corresponding rings in the bicycloheptenes; a similar effect was also noticed for [165]. (78)

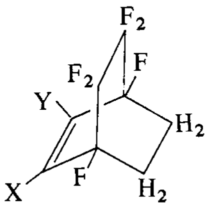


[165]

The study of the Diels-Alder reactions between perfluoro-cyclohexa-1,3-diene and substituted alkenes and alkynes has been extended. (77) Reactions employing 2*H*,3*H*-hexafluorocyclohexa-1,3-diene and its adducts were investigated. (77) Several adducts, bicyclo-[2.2.2]octa-2,5-dienes, [166], bicyclo[2.2.2]oct-2-enes, [167], and

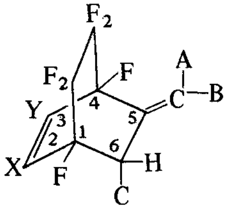


[166]

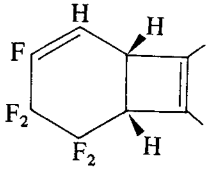


[167]

5-methylenebicyclo[2.2.2]oct-2-enes, [168], were prepared and characterized by elemental analysis and spectroscopy. ^{19}F NMR spectra were the major factors used to assign structures. The ^{19}F NMR parameters obtained for the three series of adducts [166], [167] and [168] are reported in Tables XVII, XVIII and XIX. For [166] compounds the presence of two fluorine resonances in the region associated with bridgehead fluorines, as well as some other characteristics of the proton resonances, exclude the alternative bicyclo-[4.2.0] structures, [169]. For compounds of the type [168] the NMR spectra could establish the structures and the stereochemistry at the 5-fluoromethylene groups. For one of the [168] compounds (Table XIX), in the region appropriate for bridgehead fluorines, it was observed that the lower-frequency resonance of one of the two fluorine resonances is split into a doublet (J^{FF} = 44 Hz) through a coupling with vinylic fluorine. (77) This coupling was interpreted as arising from the close proximity of the vinylic fluorine and of a bridgehead fluorine. The single symmetrical resonance for the 6–CF$_3$ group of two of the [168] compounds is evidence that only one isomer must be present for these compounds; on the basis of models the *endo*-configuration is suggested. (77)

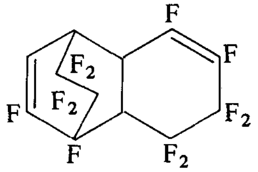


[168]

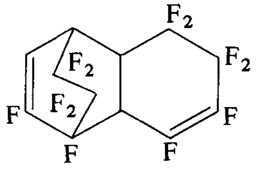


[169]

The Diels–Alder addition of two of the alkynes, perfluorobut-2-yne and 3,3,3-trifluoropropyne to 1*H*,2*H*-hexafluorocyclohexa-1,3-diene, was also investigated. (79) 1*H*,2*H*-hexafluorocyclohexa-1,3-diene was found to slowly dimerize at room temperature to give a product the structure of which may be either of those shown in [170]. The ^{19}F NMR spectrum of [170] shows a bridgehead fluorine $-\overset{|}{\underset{|}{C}}F$ at −203·4,



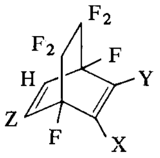
[170a]



[170b]

TABLE XVII

^{19}F NMR parameters for polyfluorobicyclo[2.2.2]octa-2,5-dienes (77)



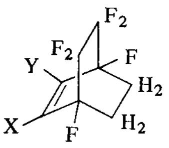
[166]

X	Y	Z	Chemical shift (δ)			
			$-\overset{|}{\underset{|}{C}}F$	$-CF_2-CF_2-$	$=CF$	CF_3
CF_3	CH_3	H	−195·9, −199·7	−117·3	–	−55·3
CH_3	CH_3	H	−196·7	−118·1	–	–
CH_3	CH_3	F	−199·1, −211·0	−121·1, −125·8	−124·3	–
CF_3	CF_3	H	−196·7	−118·7	–	−54·3
H	CF_3	H	−194·5, −201·5	−115·8, −120·4	–	−60·9
H	CH_3	H	−193·5, −197·9	−117·4	–	–
H	CH_3	F[a]	−198·4, −214·2 (2·5 I.)	−121·4 to −126·2	–	–
CH_3	H	F	−201·7, −210·3 (1 I.)			

[a] The two isomers were observed in mixture (ratio 2·5 : 1) and were not assigned.

TABLE XVIII

^{19}F NMR parameters for polyfluorobicyclo[2.2.2]oct-2-enes [167] (77)

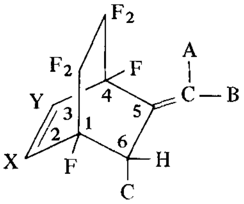


[167]

X	Y	Chemical shift, δ		
		$-\overset{|}{\underset{|}{C}}F$	$-CF_2-CF_2-$	$=CF$
H	H	−187·1	−127·1	–
F	H	−184·9, −100·9	−126·4, AB $\begin{cases}-126·7\\-130·4\\{}^2J_{FF} = 220\text{ Hz}\end{cases}$	−119·5
F	F	−200·7	−129·2	−152·4
CH_3	CH_3	−195·0	−132·2	–

TABLE XIX

^{19}F NMR parameters for polyfluoro-5-methylenebicyclo[2.2.2]oct-2-enes [168] (77)

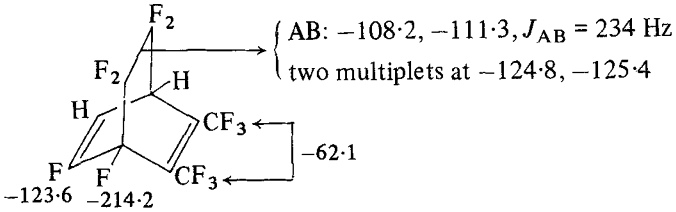


[168]

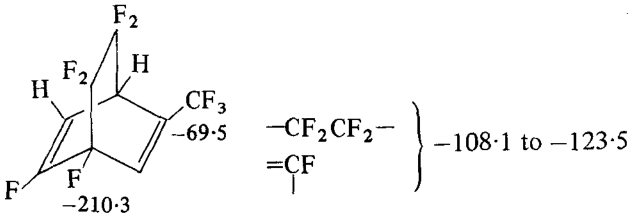
X	Y	A	B	C	Chemical shifts, δ			
					$-\overset{|}{\underset{|}{C}}F$	$-CF_2CF_2-$	$=CF$	CF_3
H	H	H	H	H	−190·9, −198·2	−127·0; AB {−125·0 −129·7	–	–
F	F	H	H	H	−204·4, −209·0	−127·8	−152·0, −154·0	–
H	H	F	H	H[a]	−190·8, −198·8	−126·9; AB {−128·8 −124·6 $^2J_{FF}$ = 234 Hz	−127·9	–
H	H	H	F	H[b]	−191·7, −200·7	−127·8, AB {−125·6 −129·2 $^2J_{FF}$ = 234 Hz	−131·3	–
H	H	H	F	CF_3[c]	−191·1, −199·1	−120·0, −126·8	*ca.* −126	−59·9
H	H	H	H	CF_3	−192·5, −197·6	−128·0, {−120·7 −123·1 $^2J_{FF}$ = 240 Hz	–	−61·3

[a] $^2J_{HF}$ = 79–80 Hz; J_{FF}(A –F-4) = 44 Hz.
[b] $^2J_{HF}$ = 79–80 Hz; J_{FF}(B–F-4) = *ca.* 0 Hz.
[c] $^2J_{HF}$ = 83 Hz; J_{FF}(B–F-4) = *ca.* 0 Hz.

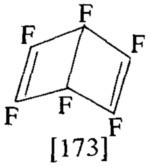
one distinct vinylic fluorine at −146·1 and a complex set of resonances between −89 and −131·7, from which one may distinguish one AB quartet: $\delta_A = -113{\cdot}0$, $\delta_B = -118{\cdot}4$, $J_{AB} = 230$ Hz. Besides this structure, the addition of the alkynes to the diene gives [171] and [172]. (79) It was found that hexafluorobicyclo-[2.2.0]hexa-2,5-diene, [173] is an active dienophile, forming with a variety of electron-rich cyclic and acyclic dienes, both 1:1 adducts and, more slowly, 1:2 adducts at ambient temperature and in good yield (22 to 100%), [174] to [180]. (80) The reaction of [173]



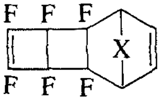
[171]



[172]

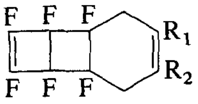


[173]



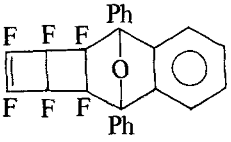
$X = CH_2, NH, O, -CCH_3{=}CCH_3-, -(CH_2)_2-$

[174]

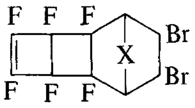


$R_1 = R_2 = CH_3$
$R_1 = R_2 = H$
$R_1 = H; R_2 = CH_3$

[175]

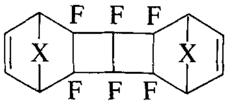


[176]



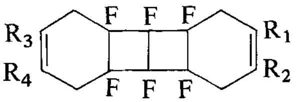
X = CH_2, NH, O

[177]



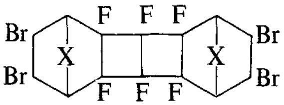
X = CH_2, NH, O, $>C{=}C(CH_3)_2$

[178]



$R_1 = R_2 = R_3 = R_4 = CH_3$
$R_1 = CH_3$, $R_2 = H$, $R_3 = H$ (or CH_3)
$R_4 = CH_3$(or H)

[179]



X = CH_2, O

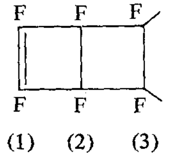
[180]

with pyrrole to give 1:1 and 1:2 adduct is noteworthy: it is in fact the first example of Diels–Alder adducts of this diene. (80) NMR investigation showed that reaction occurs by 1,4-addition to the diene and 1,2-addition to the dienophile and that 1 : 2 adduct formation occurs by addition of the second molecule of diene in the same stereochemical sense as that of the first molecule of diene. The ^{19}F NMR chemical shifts of several adducts are shown in Tables XX and XXI.

All 1:1 adducts show an absorption band in the ^{19}F NMR spectra which is shifted slightly from that of the olefinic fluorines in the parent bicyclohexadiene [173] ($\delta = -125{\cdot}1$). Chemical shift assignments for 1:1 adducts follow from the shifts of the olefinic fluorines well removed from the other fluorines, from the substantial coupling of F-3 with protons, from the weak coupling between F-1 and F-3, and from the trends of chemical shifts, which are fairly regular for similar fluorines in corresponding adducts. (80) Chemical shift assignments for the 1:2 adducts follow from the relative intensities 2:1 of the absorption bands. Considerations of the ^{19}F NMR results obtained are in agreement with *exo*-attack upon the bicyclohexa-2,5-diene, [173], and also with *exo*-attack upon

TABLE XX

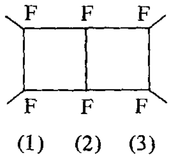
^{19}F NMR chemical shifts of the 1:1 adducts (80)



	Compound	$\delta_{(1)}$	$\delta_{(2)}$	$\delta_{(3)}$
[174]	X = CH_2	-121·7	-191·7	-176·7
[174]	X = NH	-122·7	-193·1	-181·1
[174]	X = O	-122·8	-194·3	-182·7
[174]	X = $C(CH_3)=C(CH_3)-$	-118·2	-187·9	-172·7
[174]	X = $-(CH_2)_2-$	-122·0	-189·3	-174·1
[175]	$R_1 = R_2 = CH_3$	-122·1	-195·7	-167·0
[175]	$R_1 = R_2 = H$	-120·8	-191·9	-162·8
[175]	$R_1 = H, R_2 = CH_3$	-122·7	-189·3	-165·8 -166·8
[176]		-121·9	-188·9	-170·5
[177]	X = CH_2	-121·5	-191·7	-185·9
[177]	X = NH	-121·7	-192·9	-189·4
[177]	X = O	-120·3	-192·1	-187·1

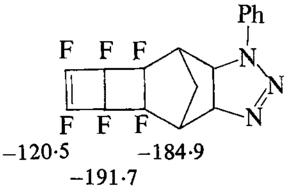
TABLE XXI

^{19}F NMR chemical shifts of the 1:2 adducts (80)



	Compound	Chemical shift	
		$\delta_{(1)}$	$\delta_{(2)}$
[178]	X = CH_2	-182·9	-184·1
[178]	X = NH	-183·7	-185·5
[178]	X = O	-188·1	-190·1
[178]	X = $-C(CH_3)=C(CH_3)-$	-181·9	-182·7
[179]	$R_{1,2,23,4} = CH_3$	-172·4	-189·6
[179]	$R_1 = CH_3$, $R_2 = H$ $R_3 = H(CH_3)$, $R_4 = CH_3(H)$	-169·0 -170·3 -170·8	-186·4
[180]	X = CH_2	-193·3	-193·7
[180]	X = O	-193·3	-187·9

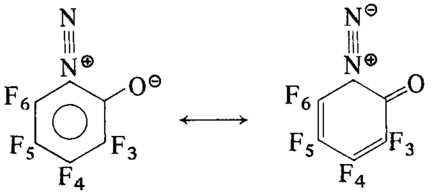
cyclic dienes. Further support is provided by the ^{19}F NMR spectrum of the phenyl azide adduct, [181], in which pairs of non-equivalent fluorines have very similar chemical shifts, implying that the heterocyclic portion is well removed from their environment. (80)



[181]

D. Fluoroaromatics

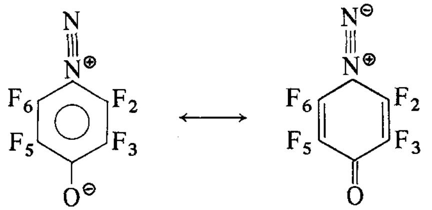
The synthesis of 1-diazotetrafluorobenzene 2-oxide, [182], and of the isomeric 1,4-compound, [183], together with some reactions of the former, are described. (81) Pentafluorobenzonitrile was



[182]

F_3	F_4	F_5	F_6
−163·2	−145·3	−176·6	−145·3

J_{34} = 14·7 Hz
J_{35} = 7·1 Hz
J_{36} = 11·4 Hz
J_{45} = 18·2 Hz
J_{46} = 3·2 Hz
J_{56} = 16·9 Hz



[183]

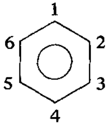
$F_{2,6}$	$F_{3,5}$
−144·0	−157·9

J_{23} = 14·4 Hz
J_{25} = 2·2 Hz
J_{26} = 7·8 Hz
J_{35} = 4·3 Hz

prepared (82) and some reactions of it also reported. (83) In these studies several fluorinated aromatics were identified and characterized by NMR. Their fluorine chemical shifts are collected in Table XXII.

TABLE XXII

Fluorine chemical shifts of fluorinated aromatic derivatives[a]



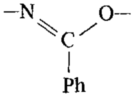
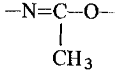
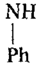
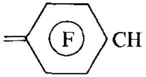
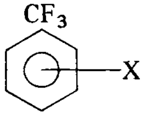
1	2	3	4	5	6	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	Ref.
OH	NO_2	F	F	F	F	–	–	–151·4	–171·1	–152·4	–162·0	(81)
OH	F	F	NO_2	F	F	–	–163·0	–151·0	–	–151·0	–163·0	(81)
OH	F	OH	NO_2	F	F	–	–162·7	–	–	–150·8	–169·6	(81)
OCO	F	OH	NO_2	F	F	–	–151·8	–	–	–150·8	–159·2	(81)
OH	NH_2	F	F	F	F	–	–	–167·3	–176·3	–181·1	–170·5	(81)
OH	F	F	NH_2	F	F	–	–166·4	–165·4	–	–165·4	–166·4	(81)
Ph	F	F	F	F	OH	–	–146·6	–173·9	–162·1	–164·3	–	(81)
F	 $-N=\underset{Ph}{C}-O-$		F	F	F	–154·8	–	–	–162·0	–163·3	–165·5	(81)
F	 $-N=\underset{CH_3}{C}-O-$		F	F	F	–156·2	–	–	–163·4	–165·3	–167·1	(81)
CN	F	Cl	F	F	F	–	–112·1	–	–124·0	–161·7	–129·5	(82)
CN	F	Cl	F	Cl	F	–	–106·3	–	–101·3	–	–106·3	(82)
F	Cl	F	F	F	H	–117·5	–	–133·1	–163·5	–134·6	–	(82)
F	Cl	F	Cl	F	H	–112·8	–	–111·7	–	–112·8	–	(82)
CN	F	F	NH_2	F	F	–	–140·8	–163·7	–	–163·7	–140·8	(83)
CN	NH_2	F	F	F	F	–	–	–162·8	–152·5	–177·1	–139·4	(83)
CN	F	F	 $\underset{Ph}{NH}$	F	F	–	–138·0	–151·6	–	–151·6	–138·0	(83)

TABLE XXII—*cont.*

1	2	3	4	5	6	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	Ref.
CN	F	F	Cl	F	F	–	−132·3	−137·7	–	−137·7	−132·3	(83)
CN	F	F	Br	F	F	–	−131·7	−129·4	–	−129·4	−131·7	(83)
CN	F	F	I	F	F	–	−132·0	−116·7	–	−116·7	−132·0	(83)
CN	F	F		F	F	–	(−134·6)	(−137·4)	–	(−137·4)	(−134·6)	(83)
F	CH_3	CH_3	F	H	H	−123·3	–	–	−123·3	–	–	(77)
F	H	CH_3	F	H	H	(−120·1)	–	–	(−126·2)	–	–	(77)
CF_3	H	F	F	H	H	−64·5	–	−134·1	−137·4	–	–	(79)
CF_3	H	F	Cl	H	H	−63·8	–	−112·5	–	–	–	(79)
OH	F	NH_2	F	F	F	–	(−160·9)	–	(−168·9)	(−169·8)	(−174·6)	(76)
OH	F	$NHPr^i$	F	F	F	–	(−156·8)	–	(−165·6)	(−168·5)	(−171·6)	(76)
NH_2	CF_3	NH_2	F	F	F	–	−55·1	–	−172·5	−158·0	−172·5	(76)
$NHCH_3$	F	$NHCH_3$	H	F	F	–	(−140·0)	–	–	(−158)	(−167)	(76)
OEt	F	F	F	F	F	–	−157·9	−165·2	−165·2	−165·2	−157·9	(76)
OMe	F	F	H	F	F	–	(−158·5)	(−140·8)	–	(−140·8)	(−158·5)	(92)
OMe	F	F	SH	F	F	–	(−158·0)	(−139·4)	–	(−139·4)	(−158·0)	(92)
CO_2Br	Br	F	OMe	F	F	–	–	(−123·3)	–	(−140·0)	(−150·8)	(94)

[a] Values in parentheses were not assigned.

A number of *m*- and *p*- substituted benzotrifluorides, [184], was examined to evaluate the solvent effects of the fluorine chemical shift and to determine the ^{13}C–F coupling constants of some



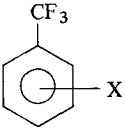
[184]

	$X = p\text{–}NH_2$	$X = p\text{–}H$	$X = p\text{–}NO_2$
	$J(^{13}C\text{–}F) = -270$ Hz	−272 Hz	−275 Hz

representative cases. (84) In Table XXIII there are collected the ^{19}F chemical shifts of some new benzotrifluoride derivatives together with some others already reported. Whereas there is little change in the chemical shift with *m*-substitution there is significant spread in the ^{19}F chemical shift for the *p*-substituted cases. It is also interesting to note that the value $\Delta(p - m)$, the chemical shift difference between *m*-substituted compounds and *p*-substituted compounds, gradually increases, becoming more negative as the electron donating ability of the substituent group increases. In addition it was noted that the ^{19}F chemical shifts at infinite dilution in general decrease as the dielectric constants of the solvents used increase. A possible explanation of these data may be found either on the basis

TABLE XXIII

^{19}F chemical shifts for benzotrifluoride derivatives at infinite dilution in $CFCl_3$ (84)

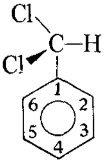


[184]

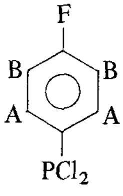
X		*p*-Substituted	*m*-Substituted	$\Delta(p - m)$
CN	−64 at	−64·19	–	–
NO_2		−64·10	−63·87	+0·23
$COCH_3$		−64·05	–	–
I		−64·04	−63·87	+0·17
Br		−63·76	−63·79	−0·03
Cl		−63·48	–	–
F		−62·97	−63·82	−0·85
OH		−62·37	−63·69	−1·32
NH_2		−62·29	−63·82	−1·53
$H(CH_3)_2$		−61·98	−63·73	−1·75

of negative hyperconjugation or p-π interactions which should operate in the paramagnetic term $1\text{-}\sigma_{p1}$ of the ^{19}F shielding constant and thereby produce a net high-frequency shift. The ^{13}C–F couplings of three benzotrifluorides X = p-NH$_2$, p-H, p-NO$_2$, were also reported, (84) observing that the trend of the values is analogous to that observed for halomethanes.

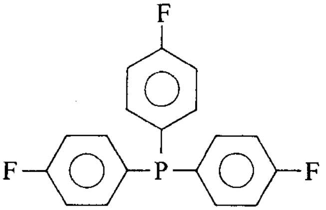
^{19}F NMR spectroscopy was extensively used to study the reactions of pentafluorophenyl-lithium with halogeno-olefins (85) and the synthesis of polyfluoro aralkyl amines. (86) The three monofluorobenzaldehydes as well as 2-chloro-6-fluorobenzaldehyde and 4-fluoro-2-nitrobenzaldehyde were studied by proton NMR. The ring proton-fluorine couplings and the couplings over four and five bonds, ^4J(F, CHO) and ^5J(F, CHO), were reported. (87) The proton NMR spectrum of *para*-fluorotoluene was analysed to derive the σ- and π-contribution to J_p^{HF} ($J_p^{\mathrm{HF}} = 1{\cdot}14$ Hz). 2-Fluoro-5-chloro-, 2-fluoro-6-chloro-3-nitro- and 2-fluoro-6-chloro-5-nitro-benzalchlorides, [185] were studied by proton NMR. (89) The long range H–H and H–F couplings were shown to be stereospecific. In particular, the coupling over four bonds between side-chain proton and the ring fluorine is $-0{\cdot}3$ Hz when the C–H and C–F bonds are arranged *cis* to each other but is $-2{\cdot}5$ Hz when these bonds have a *transoid* planar arrangement. These molecules prefer conformations in which the C–H bond of the side-chain lies in the plane of the aromatic ring. (89) The AA′BB′MX spin system was considered with application to the analysis of two molecules: *para*-fluorophenyl dichlorophosphine [186] and tris-*para*-fluorophenylphosphine, [187]. (90)



[185]



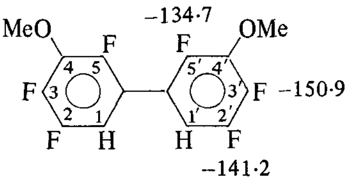
[186]



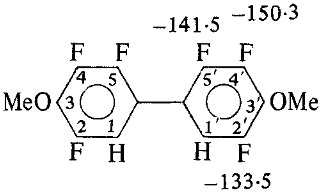
[187]

	δ_F	$J_{AM}(^4J_{HF})$	$J_{BM}(^3J_{HF})$	$J_{MX}(^5J_{PF})$
[186]	–	5·40	8·53	−5·35
[187]	−118·2	5·60	8·72	−4·54

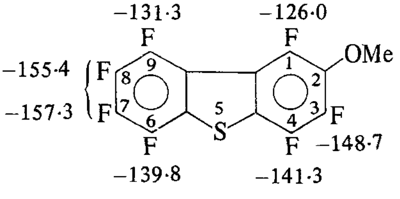
Unambiguous synthesis of 2,2′,3,3′,5,5′-hexafluoro-4,4′-dimethoxybiphenyl, [188], (91) 2,2′,4,4′,5,5′-hexafluoro-3,3′-dimethoxybiphenyl, [189], (91) and heptafluoro-2-methoxydibenzothiophen, [190], (92) were reported. On the basis of chemical shift results of [188], [189] and [190], several fluorine assignments had to be



[188]



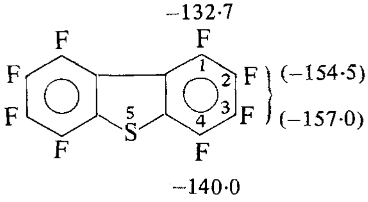
[189]



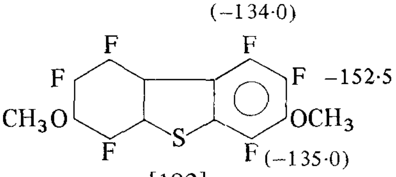
[190]

J_{13} = 7·5 Hz
J_{14} = 13·5 Hz
J_{34} = 19·4 Hz
J_{67} = 18·9 Hz
J_{69} = 13·0 Hz
J_{89} = 18·0 Hz

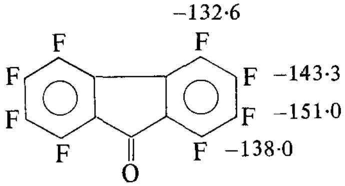
reconsidered in some perfluoroaromatic derivatives of the dibenzo-series. The compounds, the chemical shifts of which were amended, are shown in [191] to [199]. 2,2′-Dibromo-octafluorobiphenyl, [200], was also prepared (92) as intermediate in the synthesis of [190]. These results permitted it to be demonstrated that 2*H*,2*H*′-octafluorobiphenyl is attacked by sodium methoxide at the 4,4′-



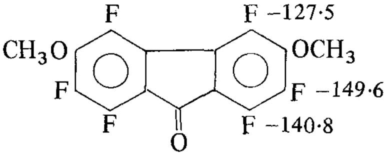
[191]



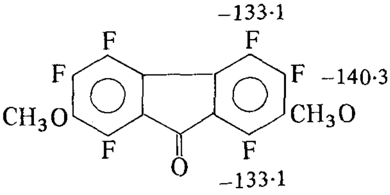
[192]



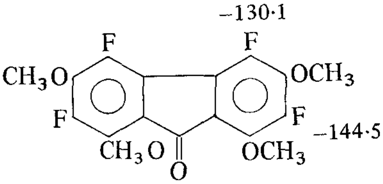
[193]



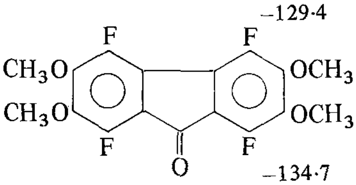
[194]



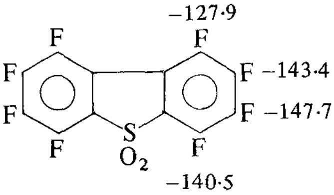
[195]



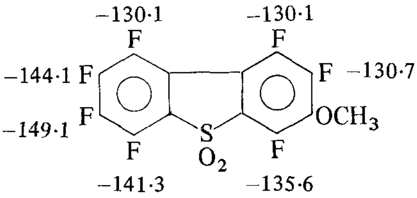
[196]



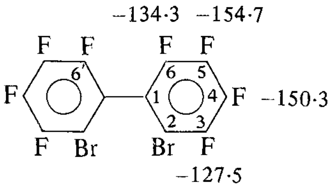
[197]



[198]



[199]

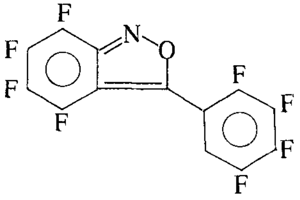


[200]

J_{34} = 20·6 Hz
J_{35} = 3·7 Hz
J_{36} = 9·6 Hz
J_{45} = 19·2 Hz
J_{46} = 4·4 Hz
J_{56} = 21·2 Hz
$J_{66'}$ = 1·6 Hz

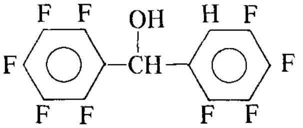
positions and not at 5,5′ as claimed in earlier literature. (91) Analogously octafluororen-9-one is attacked by methoxide at the 3- and not at the 2- position and octafluorodibenzothiophen and its dioxide are attacked at the 2- and not at the 3- position.

In the study of the electrochemical oxidation of polyfluoroaromatic amines, anthranil, [201], benzhydrol, [202], and benzophenone, [203] to [205], derivatives were obtained and characterized by ^{19}F NMR. (93)



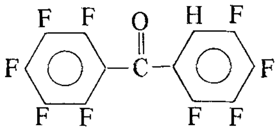
[201]

−137·9	2	intensity
−147·2	2	intensity
−148·6	1	intensity
−153·7	1	intensity
−156·1	1	intensity
−158·5	2	intensity



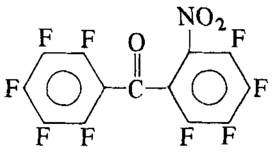
[202]

−139·3	1	intensity
−143·1	2	intensity
−143·9	1	intensity
−155·4	1	intensity
−157·5	2	intensity
−162·7	2	intensity



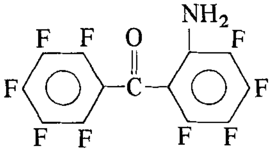
[203]

−136·0
−137·7
−141·9
−144·1



[204]

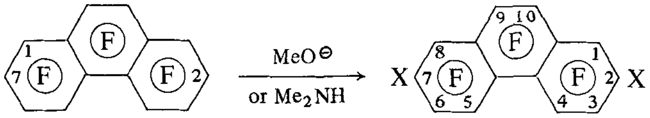
−138·7 1 intensity
−140·5 2 intensity
−141·8 1 intensity
−145·3 2 intensity
−146·8 1 intensity
−160·6 2 intensity



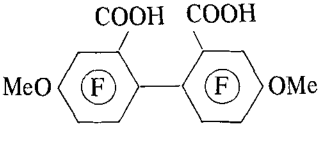
[205]

−140·2 1 intensity
−143·6 2 intensity
−146·6 1 intensity
−153·6 1 intensity
−161·0 2 intensity
−162·8 1 intensity
−175·8 1 intensity

Nucleophilic replacements in decafluorophenanthrene were described; this compound in fact reacts with sodium methoxide and with dimethylamine with replacement of the fluorine atoms at positions 2 and 7. (94) The 2,7-replacement was proved by NMR spectroscopy and chemical analysis. The ^{19}F NMR spectrum of [206] shows an AB pattern (−140·4, −147·4, J_{AB} = 85 Hz), assignable to 1-, 8-, 9- and 10-fluorine, and two bands at −129·4 and −149·4, assignable to 4-, 5- and 3-, 6- fluorine respectively. The ^{19}F NMR spectrum of [207] shows signals of equal intensity at −131·4 (F-4, F-5), at −142·9 (F-3, F-6) and an AB pattern (F-1, F-8: −138·2, F-9, F-10: −147·8, J_{AB} = 88 Hz). Oxidation of [206] with potassium permanganate gave the hexafluoro-4,4′-dimethoxy biphenyl-2,2′-dicarboxylic acid, [208]. NMR parameters were also reported for the hexafluoro-5,5′-dimethoxybiphenyl-2,2′- dicarboxylate and dicarboxylic acid, [209]. (94)

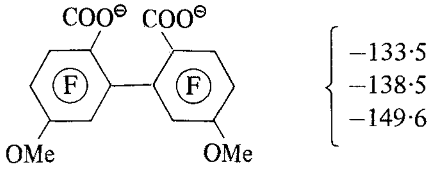


[206] X = OMe
[207] X = NMe

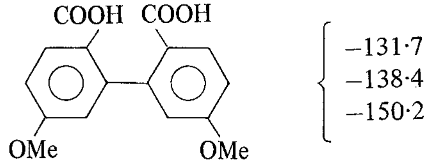


−131·9
−139·2
−149·0

[208]



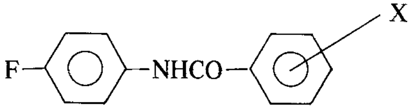
[209a]



[209b]

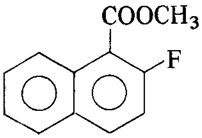
A study of a series of substituted Me-aromatic derivatives has been reported, which are pertinent to the question of interaction between the unshared *p*-electrons of substituents on a Me group and the π-system of an aromatic ring to which the Me group is bonded. (95) A series of *meta-* and *para-* α-substituted fluorotoluenes, FC_6H_5X, where X is a mono-, di- and tri- substituted Me group, CH_2Y, CHY_2 and CY_3 (Y = F, Cl, Br, OMe, SCF_3 and CN), a total of 24 new products, were investigated. (95) The ^{19}F chemical shifts at infinite dilution were measured relative to C_6H_5F. The data obtained were compared with results of other related substituted fluorotoluenes. From comparison of all the ^{19}F NMR data it appears that the electron withdrawing character of the methyl groups increases with substitution. However, for the trihalomethyl groups, particularly in the chloro- and bromo- series, the effect definitely drops off so that trisubstitution is not significantly better than disubstitution. There is some sort of saturation effect for halomethyl groups, particularly with bromine and chlorine, where two substituents do as well as three. This is not the case for the cyano-substituent, for which an additive linear effect of substitution was found. The observed substituent effects strongly suggest that unshared *p*-electrons on substituents Y of CY_3 groups interact with the π-system of the adjacent aromatic ring and may be of some importance in transmission of electronic effects. A through space *p*-π donation is an attractive way, even if not the only one, to interpret this interaction. (95) If was shown by ^{19}F NMR studies that the amide linkage does transmit electronic effects in the ground state. The transmission of electronic effects through the amide linkage for a series of 3- and

4-substituted -4′-fluorobenzanilides, [210] was in fact reported. (96) Plotting the shielding parameters against Taft's σ^0 constants, a quantitative measurement of transmission was obtained. It was found that the amide is *ca.* 40% as effective as a double bond in transmitting conjugation. Some reactions of 1,2,3,4-tetrafluoronaphthalene (97) and the thermal decomposition of 1,2,3,4-tetrafluoro-5,8-dihydro-5,8-(*N*-methylimino)-naphthalene (98) were studied making extended use of ^{19}F NMR spectroscopy.

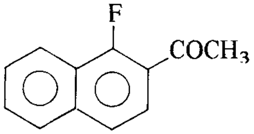


[210]

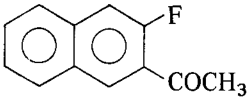
As a part of a general study of substituent effects in the naphthalene ring system, some substituted fluoronaphthalenes, namely [211a] to [211d] were prepared and studied by proton and fluorine NMR. (98b) The relevant NMR parameters of these compounds together with those of *ortho-*, *meta-* and *para-* fluoroacetophenones were reported.



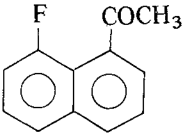
[211a]



[211b]



[211c]



[211d]

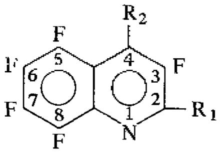
II. HETEROCYCLIC COMPOUNDS

A. Nitrogen heterocyclics

As an extension of previous work, where it was found that acid-induced processes are particularly useful for fluorinated heterocyclics, reactions of pentafluoropyridine, heptafluoro- quinoline and isoquinoline with hydrogen halides in tetrahydrothiophene were described. (99) Replacement of fluorine *ortho-* and *para-* to the ring nitrogen by another halogen occurs. The mechanism of the reactions was discussed in terms of nucleophilic displacement of fluoride ion from the protonated species. All products of reaction were characterized by NMR, in particular by ^{19}F NMR spectroscopy; structure determinations were mainly given on NMR basis. (99) The fluorine NMR parameters are collected in Tables XXIV, XXV and XXVI. Assignments, when possible, are given in parentheses. In the case of polyfluoroquinolines, 2-, 4- and 5- fluorine resonances were assigned on the basis of their chemical shifts and the large *peri*-coupling (J^{FF} = *ca.* 44 to 50 Hz) between the 4- and 5- fluorine atoms. It is known, in addition, that resonances *ortho-* to a halogen or hydrogen are shifted to higher frequency; on this basis, the highest-frequency resonances for the dihalogeno-derivatives may be assigned to the 3-fluorine. The assignment of the methoxy-group to the 2- or 4- position was deduced from the proton NMR spectra. For the polyfluoroisoquinoline the 1- and 3- fluorine atom could be distinguished by their high-frequency position and the large *peri*-coupling (J^{FF} = *ca.* 60 to 65 Hz) between 1- and 8- fluorine atoms. The assignments of polyfluoropyridines were made on the basis of the large chemical shift difference between the α-, β- and γ- fluorine atoms and the known effect of halogen on fluorine chemical shifts. The proton NMR spectra of the methyl derivatives of 2-fluoropyridine were analysed. (100) Dramatic changes were observed in the ring proton-fluorine couplings, while the couplings involving CH_3 vary little from those in the corresponding toluene derivatives. Coupling over six bonds, $^6J(F, CH_3)$, was found to be 1·25 Hz in 2-fluoro-5-methylpyridine. (100) Using 'super acids', i.e. mixtures of HF with antimony pentafluoride or boron trifluoride, hexafluoroantimonate salts of perfluoro- pyridine, quinoline, isoquinoline, pyrazine and 3,5-dichloropyridine were isolated. (101) The ^{19}F NMR spectra are consistent with *N*-protonation. The ^{19}F NMR data for the salts, dissolved in SO_2, are given in Table XXVII; comparison is also made with the free bases in the same solvent. As shown, fluorine atoms in positions *para* to ring nitrogen have substantial high-frequency shifts; smaller high-frequency shifts are observed for corresponding *meta* positions, but, in contrast, positions *ortho* to nitrogen are shielded. ^{19}F shifts, therefore, may be used, at least qualitatively, to reflect electron distribution in charged systems in comparison with neutral molecules. It was also possible to give a relative order of base strength by making measurements on mixtures of bases with acids. (101) It appeared that the most important factor which changes the relative order of base

TABLE XXIV

^{19}F Chemical shifts for polyfluoroquinolines [212] (99)



[212]

R_1	R_2	Chemical shift[a]						
F	F	−77·2 (F-2)	−126·0 (F-4)	−145·7 (F-5)	−148·3	−150·7	−154·4	−160·6
Cl	F		−128·0 (F-4)					
Cl	Cl			−144·7	−146·6	−152·2		−116·8 (F-3)
Br	F		−128·7 (F-4)					
Br	Br			−143·9	−146·1	−151·9		−100·7 (F-3)
I	I			−143·0	−146·4	−152·5		−73·9 (F-3)
H	H			−149·2	−150·9	−155·5		−125·3 (F-3)
Cl	OMe			−144·5	−149·7	−153·5	−156·6	−140·9 (F-3)
OMe	Cl			−146·1	−150·0	−153·4	−158·9	−133·9 (F-3)
Br	OMe			−144·5	−148·9	−153·7	−156·3	−133·8 (F-3)
b	*b*			−140·8	−148·5	−151·2	−161·7	−120·0 (F-3)

[a] Assignments are in parentheses.

b ⟶

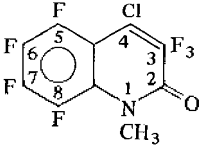
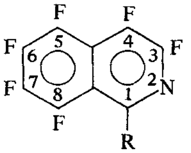


TABLE XXV

^{19}F Chemical shifts of polyfluoroisoquinolines [213] (99)

[213]



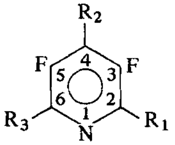
R	Chemical shift^a						
F	−61·0 (F-1)	−96·5 (F-3)	−138·9	−144·5	−145·2	−152·4	−154·6
Cl		−94·5 (F-3)	−136·8	−144·3 (F-5)	−145·9	−151·9	
Br		−93·7	−136·5	−144·3 (F-5)	−146·3	−151·6	

[a] Assignments are in parentheses.

TABLE XXVI

^{19}F Chemical shifts of polyfluoropyridines [214] (99)

[214]



R_1	R_2	R_3	Chemical shift^a				
F	F	F	−86·3 (F-2,6)		−132·7 (F-4)		−160·5 (F-3,5)
Cl	Cl	Cl			−117·2		
Br	Br	Br			−103·7		
OH	Br	Br		−117·1 (F-5)		−130·9 (F-3)	
Br	I	Br			−91·6		
F	Cl	F	−88·6 (F-2,6)				−141·3 (F-3,5)

[a] Assignments are in parentheses.

strength from hydrocarbon to fluorocarbon series is the number of fluorine atoms which flanks the ring nitrogen in each system. Preparation and nucleophilic substitution of hexafluoroquinoxaline were reported (102) (Table XXVIII).

Thermal rearrangement of perfluoropyridazine and perfluoroalkylpyridazines to pyrimidines was studied. (103) ^{19}F NMR spectroscopy was used as an analytical tool and some new pyrimidine and pyrazine derivatives [216] and [217] have been characterized. The

TABLE XXVII[a]

^{19}F NMR chemical shifts of the hexafluoroantimonate salts of some perfluoroheterocyclic compounds and of the bases dissolved in strong acids (101)

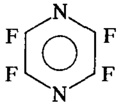
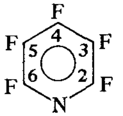
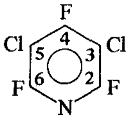
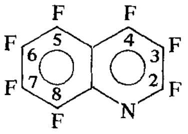
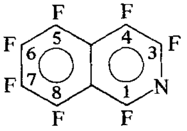
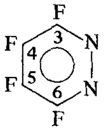
		Base in SO_2	Salt in SO_2	Base in H_2SO_4	Base in FSO_3H	Base in FSO_3H/SbF_5
		−95·9	−90·9 (5·0)	−93·7 (2·2)	−92·6 (3·3)	–
	F-2,6	−89·5	−97·8 (8·3)	−91·8 (2·3)	−97·4 (7·9)	−96·4 (6·9)
	F-4	−135·0	−107·1 (−28·9)	−126·0 (−9·0)	−109·4 (−25·6)	−102·8 (−32·2)
	F-3,5	−163·5	−156·4 (−7·1)	−160·0 (−3·5)	−156·7 (−6·8)	−154·5 (−9·0)
	F-2,6	−71·1	−79·1 (8·0)			
	F-4	−96·8	−68·1 (−28·7)			

TABLE XXVII—*cont.*

		Base in SO_2	Salt in SO_2	Base in H_2SO_4	Base in FSO_3H	Base in FSO_3H/SbF_5
	F-2	−75	−78·1 (3·1)	−86·1 (11·1)	−85·3 (10·3)	−77·3 (2·3)
	F-4	−126·5	−95·2 (−313)	−92·1 (−34·4)	−91·5 (−35·0)	−40·5 (−36·0)
			−138·1	−134·1	−134·1	−135·0
	F-5	−148·5	−140·0 (−5·5)	−136·3 (−12·2)	−136·0 (−12·5)	−137·7 (−10·8)
		−151·0	−147·0	−144·9	−143·8	−145·5
		−154·2	−150·7	−146·5	−146·2	−151·2
		−157·5	−159·4	−156·2	−156·0	−158·2
		−163·7				
	F-1	−63·5	−69·1 (5·6)			
	F-3	−99·3	−113·9 (14·6)			
		−141·6	−133·2			
		−147·3	−134·8			
		−148·0	−142·7			
		−155·3	−147·1			
		−157·5	−150·3			
	F-3,6	−90·7		−80·2 (−10·5)	−81·0 (−9·7)	−80·3 (−10·4)
	F-4,5	−144·7		−121·4 (−23·2)	−123·0 (−21·6)	−122·0 (−22·6)

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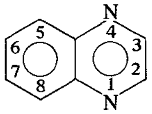
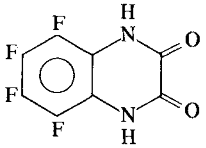
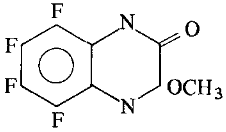
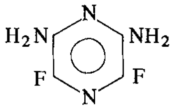
[a] In parentheses chemical shift difference with the free base.

TABLE XXVIII

^{19}F Chemical shifts for polyfluoroquinoxalines [215] (102)



[215]

2	3	5	6	7	8	Chemical shift				
F	F	F	F	F	F	−152·6		−149·5	−78 ($F_{2,3}$)	
F	F	Cl	F	F	F^a	−152·3	−144·4	−126·6 (F-6)	−79·6 (F_2 or F_3)	−77·4 (F_3 or F_2)
F	F	H	H	H	H	−82·4				
Cl	Cl	F	F	F	F	−151·0	−150·0			
H	H	F	F	F	F	−149·2	−147·5			
F	OCH_3	F	F	F	F	−153·9	−156·0	−152·3	−76·3 (F-2)	
OCH_3	OCH_3	F	F	F	F	−161·6 ($F_{6,7}$)	−154·5 ($F_{5,8}$)			
OCH_3	OCH_3	F	F	OCH_3	F	−155·7	−155·1	−148·1 (F-8)		
(a) 						−159·4	−170·0			
(b) 						−152·1	−160·0	−164·3	−165·8	
(c) 						−118·8				

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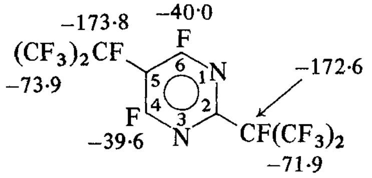
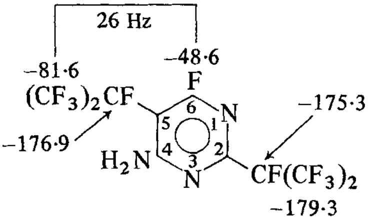
[a] J_{23} = 30 Hz.

isolation of the first valence isomer of an aromatic diazine is reported. (104) Photolysis of perfluoro-(4,5-bisisopropylpyridazine), in fact, yielded a *para*-bonded valence isomer, the structure of which

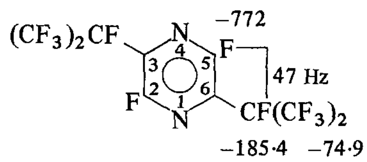


[216a]

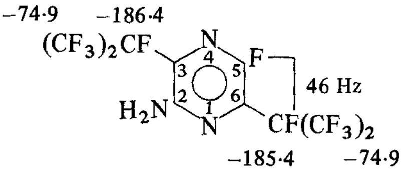


[216b]

(Structures [216c] to [216l] are shown in Table XXIX)

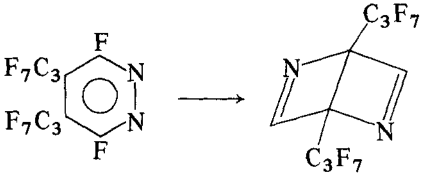


[217a]



[217b]

was demonstrated to be [218]. The ^{19}F NMR spectrum gives a resonance at −37·0, characteristic of a $-CF{=}N-$ group, a resonance at −181·1 for $-\overset{|}{\underset{|}{C}}F$ and two resonances at −74·2 and −75·7 for the



[218]

CF_3 groups. The existence of two CF_3 resonances is likely to arise from restricted rotation of the perfluoroisopropyl group. (104) Reaction of hexafluoropropene with tetrafluoropyrimidine in a dipolar aprotic solvent, in the presence of caesium fluoride, was shown to give [216d, e, f] and [216h], in amounts determined by reactant ratio and reaction conditions. (105) Treatment of [216e] with sodium cyanide gave [216h]. One of the cyano-groups so introduced may be displaced by a heptafluoroisopropyl carbanion giving [216i]. ^{19}F NMR data of these compounds are presented in Table XXIX. (105)

TABLE XXIX

^{19}F NMR parameters of polyfluoropyrimidines [216] (105)

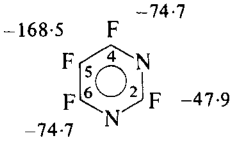
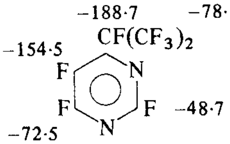
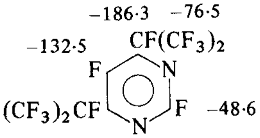
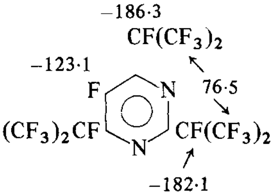
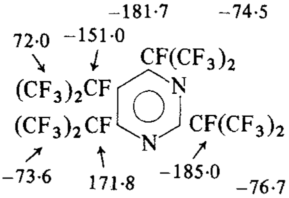
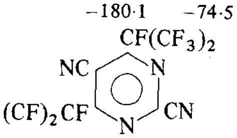
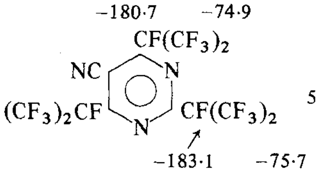
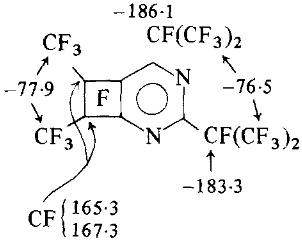
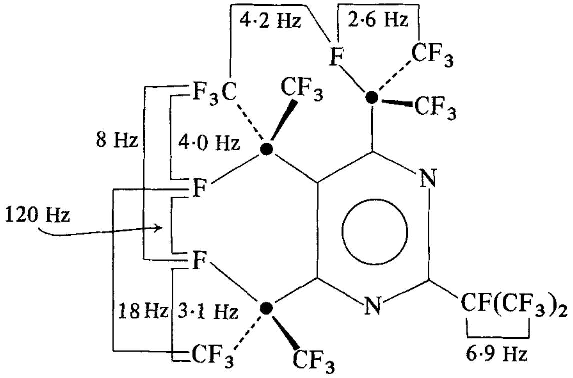
	$J(CF-CF_3)$ at C-4	$J(CF-CF_3)$ at C-2	$J(CF-F_5)$	$J(CF_3-F_5)$	$J(CF-F_2)$	J_{25}	J_{56}
[216]							
(c) 	–	–	–	–	–	26	17·5
(d) 		5·9	50·0	5·1	2·3	29·0	20·0
(e) 	5·9	–	56·0	5·6	1·7	32·0	–
(f) 	5·9	6·8	56·0	5·1	–	–	–
(g) 	2·6 3·1	6·9	–	–	–	–	–

TABLE XXIX–*cont.*

		$J(CF-CF_3)$						
		at C-4	at C-2	$J(CF-F_5)$	$J(CF_3-F_5)$	$J(CF-F_2)$	J_{25}	J_{56}
(h)		6·2	–	–	–	–	–	–
(i)		5·6	6·8	–	–	–	–	–
(l)								

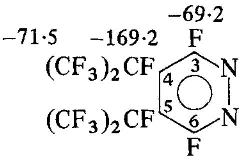
It was observed that the average effect on ring-fluorine chemical shifts by the introduction of a -$CF(CF_3)$ group into the pyrimidine nucleus was: *ortho* +22·5, *meta* +1·0, *para* +9·4. The $-CF(CF_3)_2$ groups at C-4 and C-6 are not equivalent, [216g]. This compound at room temperature is in a fixed conformation, in which rotation of the 2-substituent is free, but the rotation of the 4-, 5- and 6-substituents is highly hindered. The assignments of the coupling constants as given in [216g] were mainly made on the assumption that very large couplings are associated with nuclei in close proximity and upon the spectral changes on raising the temperature. (105) From the coalescence of the CF_3 resonances of the groups at C-4 and C-6 (111 to 127°C) was calculated a free energy of activation of 19·6

Kcal/mole for [216g]. (105) Reactions starting from tetrafluoropyridazine and involving fluoride ion were described. (106) Prepara-

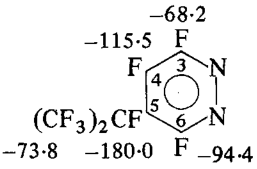


[216g]

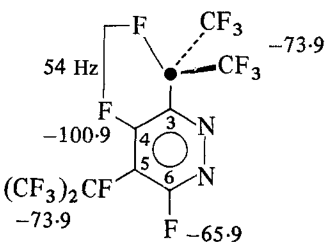
tion, rearrangement and hydrolysis of some perfluoroisopropylpyridazines were reported and the compounds [219] to [223] were characterized. (106) A heptafluoroisopropyl group either in 3- or in



[219a]



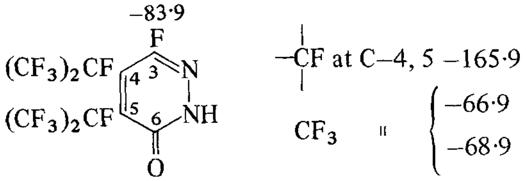
[219b]



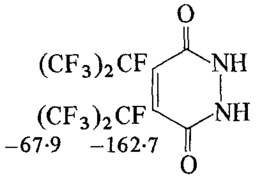
[219c]

$-\overset{|}{\underset{|}{C}}F$ at C—3 −185·9; doublet ($J = 54$ Hz) of heptets

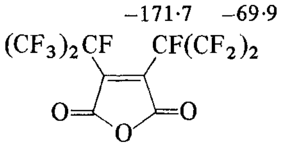
$-\overset{|}{\underset{|}{C}}F$ at C—5 −180·9; doublet of doublets ($J \simeq J \simeq 40$ Hz) of heptets



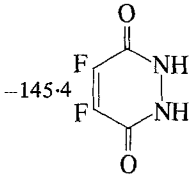
[220]



[221]

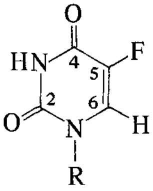


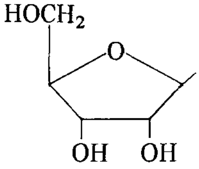
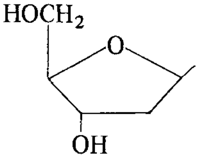
[222]



[223]

6- position of the pyradizine system adopts a fixed conformation as shown in [219c]. This is demonstrated by the large coupling, $J = 54$ Hz, between –CF group and F-4 fluorine, close to the value observed in the pyridine series. (107) The ^{19}F NMR of the heptafluoroisopropyl groups in the 4- and 5- positions of the pyridazine system, indicates a fixed conformation only at low temperature, (106) as already observed for the same group in the 4-position of the pyridine system. (107) At room temperature the resonance of the $-\overset{|}{\underset{|}{C}}F$ group at C-5 in [219c] consists of an overlapping doublet of doublets (of heptets), arising from coupling with F-4 and F-6. At –40° this resonance reduces to a doublet (of heptets), from coupling with only one ring fluorine atom. The direct synthesis of 5-fluorouracil bases and nucleosides by direct fluorination was reported. This is the first direct synthesis of the biochemically and therapeutically important fluoropyrimidines and nucleosides. (108) The compounds [224] were characterized by ^{19}F NMR.



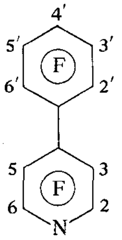
	=C–F	$^3J_{HF}$
(a) R = H	−171	6·0 Hz
(b) R = CH_3	−170	7·0 Hz
(c) R = 	−165·8	6·5 Hz
(d) R = 	−165·8	6·6 Hz

[224]

Nucleophilic substitution in perfluoro-(4-phenylpyridine), [225], was studied. (109) It was found that initial anionic attack by sodium methoxide in methanol and concentrated aqueous ammonia, or by

TABLE XXX

^{19}F chemical shifts of polyfluoro(4-phenylpyridines) [225] (109)

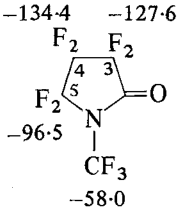


[225]

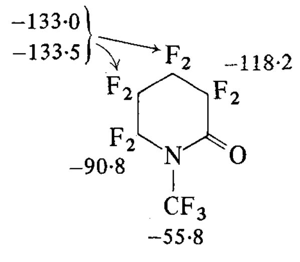
	2,6	3	5	2′,6′	3′,5′	4′
[225]	−92·3	−141·9	−141·9	−140·1	−164·0	−152·3
(a) 2-OCH_3	−95·2	−141·8	−152·9	−140·4	−164·2	−153·2
(b) 2-OH	−95·0	−142·2	−153·1	−140·5	−164·2	−153·4
(c) 2-NH_2	−95·2	−143·1	−159·8	−140·7	−164·7	−154·1
(d) 2,4′-$(OCH_3)_2$	−95·5	−141·8	−153·0	−142·5	−160·1	–
(e) 2,4′-$(OH)_2$	−94·9	−141·7	−152·3	−142·9	−163·5	–
(f) 2,4′-$(NH_2)_2$	−95·8	−142·6	−158·7	−144·2	−164·1	–
(g) 2,6,4′-$(OCH_3)_3$	–	−151·9	−151·9	−142·5	−159·9	–
(h) 2,6,4′-$(NH_2)_3$	–	−157·0	−157·0	−145·1	−165·3	–

potassium hydroxide in *t*-butyl alcohol occurs predominantly or exclusively at the 2-position in the tetrafluoropyridyl ring. Further attack on the mono-substituted compounds, thus formed, occurs first at the 4-position in the pentafluorophenyl ring and then, in the case of the first two reagents, at the 6-position of the pyridyl ring. The ^{19}F NMR data are presented in Tables XXX and XXXI. The chemical shifts were assigned by comparison with previous studies of polyfluoro- pyridines and benzenes. the two rings were shown to be highly non-coplanar. In the 2-substituted derivatives the 2′,6′-fluorine nuclei were chemically equivalent and approximately equally coupled to the non-equivalent 3,5-fluorines. These results suggest that, on a time-averaged basis, the two rings are mutually perpendicular. (109) The couplings (Table XXXI) were assigned on the basis of previously known results, for example $|^{3}J^{FF}| > |^{5}J^{FF}|$ in polyfluorobenzenes and $|^{3}J^{FF}| < |^{5}J^{FF}|$ in polyfluoropyridines. (109)

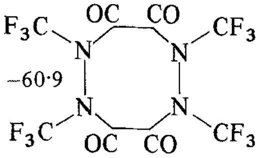
Some novel perfluoroheterocyclic compounds were produced by cyclizations via fluoride ion-induced isomerization. (36) The compounds examined by ^{19}F NMR are shown in [226] to [236]. *N*-Phenyl-4,5,6,7-tetrafluoro-2-phenylindole, [237], was synthesized by a new cyclization reaction. (110) The reaction of aziridine with chlorotrifluoroethylene, perfluorobenzene, cyclic perfluoroolefins and tetracyanoethylene was investigated. (110b) Some products, resulting from substitution of fluoroatoms or cyano groups by aziridine, were characterized by ^{19}F NMR.



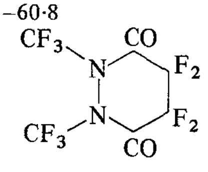
[226]



[227]



[228]



AB −118·2

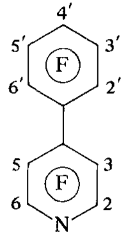
AB −135·4

$^{2}J^{FF} = 282$ Hz

[229]

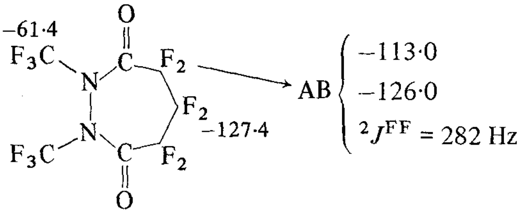
TABLE XXXI

Coupling constant of polyfluoro-(4-phenylpyridines) [225] (109)

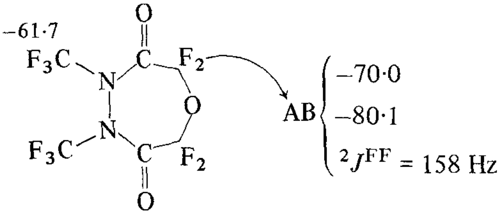


[225]

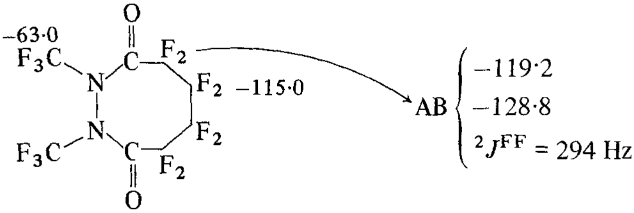
	Moduli of coupling constant (Hz)													
	23	25	26	35	36	56	32' 36'	52' 56'	2'3' 5'6'	2'4' 4'6'	2'6' 3'6'	2'6'	3'5'	3'4'
[225]	20·4	29·0	14·4	1·3	29·0	20·4	9·9	9·9	21·2	3·9	8·0	6·1	0·4	19·9
(a)	–	–	–	4·9	30·2	21·7	8·9	8·6	21·4	3·3	7·8	5·5	0·3	20·1
(b)	–	–	–	5·8	30·2	22·7	9·1	8·8	21·2	3·2	7·7	5·4	<0·5	20·4
(c)	–	–	–	8·4	30·9	24·3	8·5	8·3	22·0	3·1	8·2	5·3	0·8	20·1
(d)	–	–	–	4·4	30·0	21·9	9·2	8·8	20·6	–	8·2	4·7	2·1	–
(e)	–	–	–	4·7	29·5	22·9	9·7	9·4	21·6	–	8·9	5·7	4·9	–
(f)	–	–	–	6·4	30·4	24·6	9·7	9·3	20·7	–	8·2	4·1	8·6	–
(g)	–	–	–	–	–	–	8·2	8·2	20·7	–	8·5	4·8	2·1	–
(h)	–	–	–	–	–	–	7·8	7·8	–	–	–	–	–	–



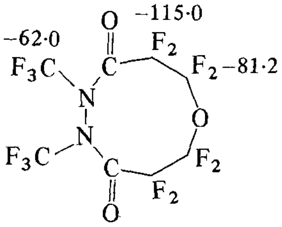
[230]



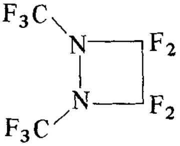
[231]



[232]

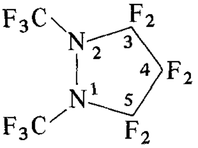


[233]



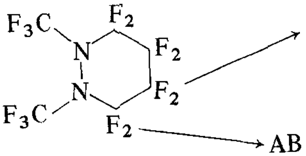
[234]

T°C	+65°	–86°
CF$_3$	–67·4;	–66·5 doublet (J = 16·0 Hz)
CF$_2$	–97·0;	AB –87·9 –103·9 $^2J^{FF}$ = 135·9 Hz



[235]

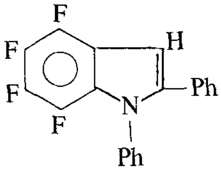
T°C	+64°	−58°
CF_3	−63·6	−63·7 doublet (J = 20 Hz)
CF_2 at C–3, 5	−99·8	−90·2
CF_2 at C–4	−126·5	AB −109·2 −126·0 $^2J^{FF}$ = 189 Hz



[236]

AB −128·0
−138·3
$^2J^{FF}$ = 270 Hz

AB −91·1
−117·2
$^2J^{FF}$ = 220 Hz

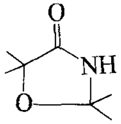


[237]

−151·9
−159·6
−166·1
−169·7

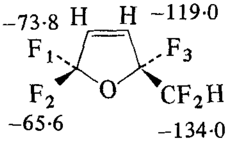
B. Oxygen and Sulphur Heterocyclics

Several new fluorinated 4-oxazolidinones, [238] were prepared by the reaction of cyanide ion with fluoroketones. (111) In these compounds the CF_3 groups adjacent to the carbonyl function (−71 to −75)



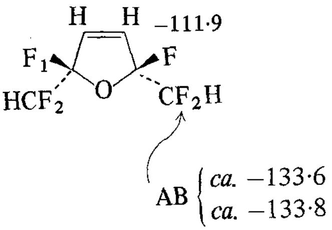
[238]

were at higher frequency than those adjacent to the nitrogen function (−75 to −81). The $-CF_2-$ and $-CF_2H$ resonances appeared in the region −121 to −144, and CF_2Cl in the −55 to −66 region. (111) 2-Methyltetrahydrofuran and 2,5-dimethyltetrahydrofuran were fluorinated with potassium tetrafluorocobaltate(III). (112) The major product in the former case was [239] and in the latter a mixture of the *cis* and *trans* isomers of [240]. (112) The stereochemistry of the isomers [240] were tentatively assigned on the assumption that the $-CF_2H$ group, which is a prochiral centre and α

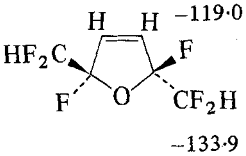


J_{12} = 158 Hz
J_{13} = 12 Hz
J_{23} = 12 Hz

[239]

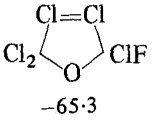


[240a]

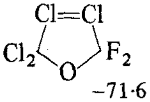


[240b]

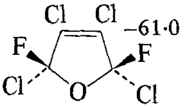
to a chiral centre, will show greater chemical shift difference (AB character) between the ^{19}F nuclei in the *cis*-isomer. A few 2,5-dihydrofuran derivatives, [241] to [245], were prepared by fluori-



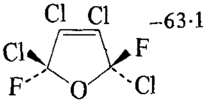
[241]



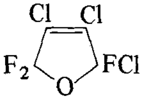
[242]



[243a]



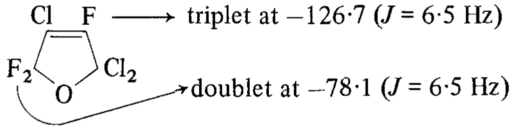
[243b]



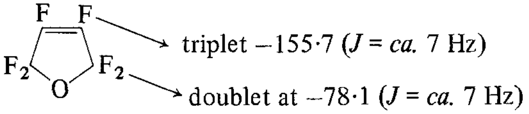
[244a]

AB) CF_2 { −67·2
−72·6
$^2J^{FF}$ = 151·0 Hz

X) CFCl −53·6 { J_{AX} = 4·6 Hz
J_{BX} = 7·5 Hz

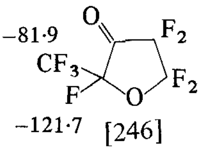


[244b]



[245]

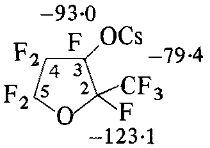
nation of perchloro-2,5-dihydrofuran. (113) In the study of cyclizations *via* fluoride ion-induced isomerizations some novel oxygen perfluoroheterocyclic compounds were obtained (36) [246] to [248] in addition to compounds [226] to [236] already reported.



[246]

AB {−121·1, −132·1}

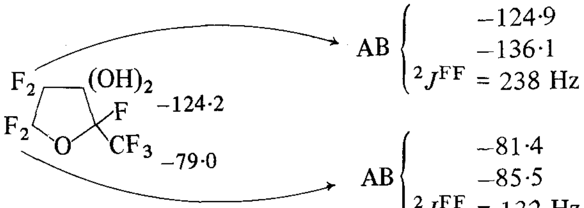
AB {−79·5, −93·4}



[247]

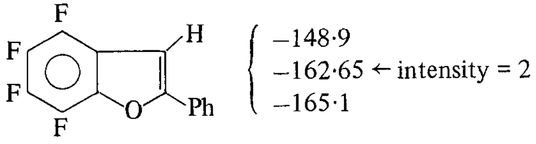
CF_2 at C–4 {−124·2, −137·6, $^2J^{FF}$ = 248 Hz}

CF_2 at C–5 {−82·0, −85·8, $^2J^{FF}$ = 128 Hz}



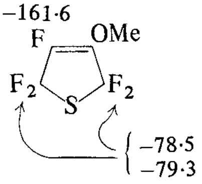
[248]

The synthesis of 4,5,6,7-tetrafluorobenzofuran and of 4,5,6,7-tetrafluoro-2-phenylbenzofuran, [249], by a new cyclization reaction was described. (114) Only the ^{19}F NMR data of [249] were reported.

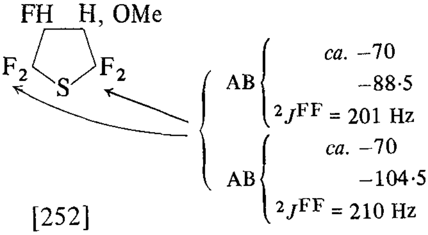


[249]

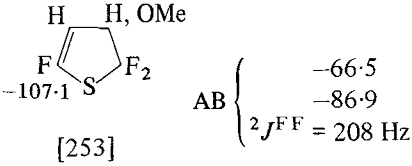
A second fully fluorinated five-membered heterocycle, tetrafluorothiophen, [250], (the first one was tetrafluorofuran) has been described together with some other polyfluorothiophenes. (115) The ^{19}F NMR spectra of these thiophenes could be rationalized if the chemical shift of the α-fluorines were taken at low frequency with respect to those of the β-fluorines and if the J_{25}^{FF} coupling is large (26 to 31 Hz). The fluorine NMR data are collected in Table XXXII. Some reaction products were also characterized; these are shown in [251] to [253]. (115) Tetrachlorothiophen, thiophen and tetrahydrothiophen were fluorinated over cobaltic and manganic trifluorides and over potassium tetrafluorocobaltate(III). (12) Polychloropolyfluorobutanes (see page 49) and cyclic sulphur compounds were obtained [254] to [263] depending on the reaction conditions. (12)



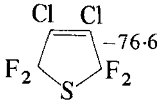
[251]



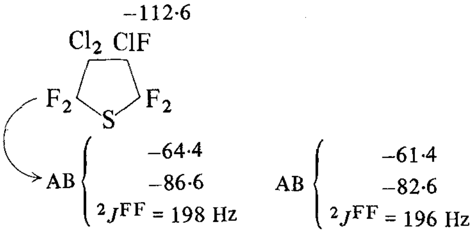
[252]



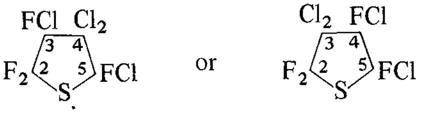
[253]



[254]



[255]

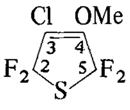


[256]

F–5 −60·9

F–3 (or F–4) −110·3

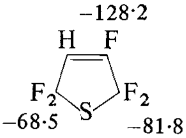
CF_2–2 AB $\left\{\begin{array}{l} -66{\cdot}3 \\ -87{\cdot}5 \\ {}^{2}J^{FF} = 196\ \text{Hz} \end{array}\right.$



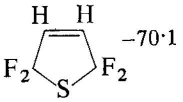
F–2 (or F–5) −73·5

F–5 (or F–2) −75·3

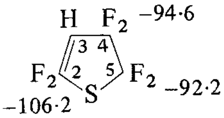
[257]



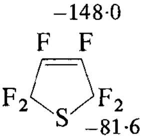
[258]



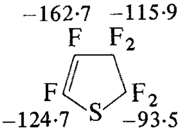
[259]



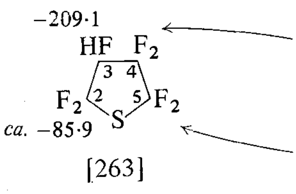
[260]



[261]



[262]



[263]

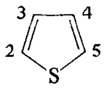
AB $\left\{\begin{array}{l} -123{\cdot}5 \\ -130{\cdot}1 \\ {}^{2}J^{FF} = 256\ \text{Hz} \end{array}\right.$

AB $\left\{\begin{array}{l} -74{\cdot}5 \\ -84{\cdot}8 \\ {}^{2}J^{FF} = 212 \end{array}\right.$

Some 2-substituted-5-fluorothiophenes were synthesized and investigated by NMR. (116) The assignment of the position of substitution was based upon comparisons with known coupling constant for 2-fluorothiophenes. (117) In all cases typical $J(F{-}H_3)$ = 1·4 to 2·1 Hz values were observed (Table XXXII). The H-F coupling increases in going from H_4 to H_3 in 5-fluorothiophenes. This effect is further exemplified in the quite large $^{5}J(F{-}CHO)$ = 4·2 Hz of 5-fluoro-2-thenaldehyde, [250/xi]. The conformation as

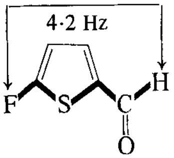
TABLE XXXII

^{19}F NMR data of polyfluorothiophenes [250]



	2	3	4	5	Chemical shift				Coupling constant (Hz)						Ref.
					F_2	F_3	F_4	F_5	23	24	25	34	35	45	
(i)	F	F	F	F	−164·9	−155·9	−155·9	−164·9	7	17	31	7	17	7	(115)
(ii)	F	H	H	F	−136·9	–	–	−136·9	3·5	3·5	–	–	3·5	3·5	(115)
(iii)	F	OMe	H	F	−165·2	–	–	−137·7	2·0	3·8	26·5	–	–	3·8	(115)
(iv)	F	F	OMe	F	−166·8	−153·1	–	−164·9	5·4	–	30·6	–	15·4	2·1	(115)
(v)	F	F	F	OMe	−164·0	−156·1	−154·6	–	5·4	17·8	–	10·0	–	0·6	(115)
(vi)	H	H	H	F				–					3·1	1·6	(116)
(vii)	$COCH_3$	H	H	F				−119·5					3·6	1·4	(116)
(viii)	COOH	H	H	F				–					4·0	1·8	(116)
(ix)	I	H	H	F				–					3·6	2·1	(116)
(x)	NO_2	H	H	F				–					4·6	2·0	(116)
(xi)	CHO	H	H	F				−116·7					3·8	1·4	(116)
(xii)	F	H	H	OCH_3	−139·28				3·46	3·02					(119)
(xiii)	F	H	H	CH_3	−133·30				2·03	3·20	2·77				(119)
(xiv)	F	H	H	Et	−133·69				1·95	3·20	2·66				(119)
(xv)	F	H	H	*n*-Pr	−133·51				1·85	3·17	2·74				(119)
(xvi)	F	H	H	*n*-Bu	−133·60				1·90	3·14	2·75				(119)
(xvii)	F	H	H	$C(CH_3)_3$	−134·40				1·75	3·19	–				(119)
(xviii)	F	H	H	SCH_3	−123·83				2·52	3·49	0·30				(119)
(xix)	F	H	H	C_6H_5	−131·07				1·92	3·48					(119)
(xx)	F	H	H	Cl	−128·39				2·76	3·49					(119)
(xxi)	F	H	H	Br	−126·73				2·39	3·43					(119)
(xxii)	F	H	H	I	−124·15				2·22	3·22					(119)
(xxiii)	F	H	H	CH	−122·16				1·82	3·74					(119)
(xxiv)	F	H	H	CHO	−117·17				1·17	3·66	4·20				(119)
(xxv)	F	H	H	$COCH_3$	−119·76				1·45	3·52	0·44				(119)
(xxvi)	F	H	H	COOH	−121·73				1·76	3·89	–				(119)

(xxvii)	F	H	H	$\mathrm{COOCH_3}$	−122·08	1·50	3·85	–			(119)
(xxviii)	F	H	H	CHNOH(*anti*)	−128·96	2·23	4·01	3·76			(119)
(xxix)	F	H	H	CHNOH(*sym*)	−128·76	1·98	3·77	3·42			(119)
(xxx)	F	H	H	$\mathrm{SO_2CH_3}$	−120·25	1·47	3·75	0·32			(119)
(xxxi)	F	H	H	$\mathrm{NO_2}$	−116·59	2·06	4·29	–			(119)
(xxxii)	F	H	$\mathrm{CH_3}$	H	−132·29	1·55	0·11	3·55			(119)
(xxxiii)	F	H	$\mathrm{SCH_3}$	H	−129·66	1·34		3·44			(119)
(xxxiv)	F	H	$\mathrm{C_6H_5}$	H	−130·91	1·74		3·54			(119)
(xxxv)	F	H	Cl	H	−127·54	0·95		3·40			(119)
(xxxvi)	F	H	Br	H	−128·30	0·78		3·32			(119)
(xxxvii)	F	H	I	H	−129·65	0·61		3·13			(119)
(xxxviii)	F	H	CN	H	−128·41	1·18		3·55			(119)
(xxxix)	F	H	CHO	H	−127·52	1·37	3·29	3·63			(119)
(xl)	F	H	$\mathrm{COCH_3}$	H	−129·50	1·53		3·55			(119)
(xli)	F	H	COOH	H	−129·90	1·56		3·92			(119)
(xlii)	F	H	$\mathrm{COOCH_3}$	H	−129·92	1·36		3·86			(119)
(xliii)	F	H	CHNOH(*anti*)	H	−133·34	2·04	1·07	3·97			(119)
(xliv)	F	H	CHNOH(*sym*)	H	−130·51	1·98	2·27	3·78			(119)
(xlv)	F	H	$\mathrm{SO_2CH_3}$	H	−126·18	1·12		3·82			(119)
(xlvi)	H	F	H	$\mathrm{CH_3}$	−128·25	1·45		–	−0·69	−0·22	(119)
(xlvii)	H	F	H	$\mathrm{SCH_3}$	−126·31	1·75			−0·90	0·11	(119)
(xlviii)	H	F	H	$\mathrm{C_6H_5}$	−126·85	1·21			−0·54		(119)
(xlix)	H	F	H	Cl	−124·50	2·00			−0·80		(119)
(l)	H	F	H	Br	−125·14	1·88			−0·96		(119)
(li)	H	F	H	I	−126·32	1·54			−1·16		(119)
(lii)	H	F	H	CN	−126·55	1·08			−0·86		(119)
(liii)	H	F	H	CHO	−125·93	0·58			−0·99	0·57	(119)
(liv)	H	F	H	$\mathrm{COCH_3}$	−125·68	0·78			−0·96		(119)
(lv)	H	F	H	COOH	−126·02	1·15			−0·80		(119)
(lvi)	H	F	H	$\mathrm{COOCH_3}$	−126·42	0·87			−0·87		(119)
(lvii)	H	F	H	CHNOH(*anti*)	−131·18	1·61			−0·55		(119)
(lviii)	H	F	H	$\mathrm{SO_2CH_3}$	−124·69	0·87			−1·09		(119)
(lix)	H	F	H	$\mathrm{NO_2}$	−121·88	1·55			−0·89		(119)



[250 xi]

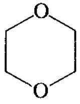
shown in [250/xi] was suggested in analogy with results on substituted benzaldehydes, because it allows the transmission of the interaction by a **W** effect. (116)

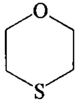
Other substituted fluorothiophenes were extensively investigated by NMR. Nineteen 5-substituted-2-fluorothiophenes, thirteen 4-substituted-2-fluorothiophenes and fourteen 5-substituted-3-fluorothiophenes were prepared. (118) Their NMR spectra were analysed and the NMR parameters are tabulated in Table XXXII. (119) The relative signs of the couplings between fluorine and ring protons were determined by double resonance. In 5-substituted-3-fluorothiophenes J(F-4) is of opposite sign to J(F-2), which is assumed to be positive as are the other pairs of H–F couplings. In order to obtain a better understanding of substituent effects on this class of compounds, empirical correlations for the NMR parameters were also attempted. (120) Good correlations for most of the NMR parameters were found with the reactivity constants. The three *ortho* H–F couplings were found to increase linearly with increasing electronegativity of the halogen. The substituent effects on the ^{19}F chemical shifts of fluorothiophenes compare well with those on the ^{19}F chemical shifts of fluorobenzenes. One linear relation between the couplings J(2F-3) and J(3F-2) (J(3F-3) = 0·61 + 1·02 J(3F-2)) in the 5-substituted fluorothiophenes and one between the fluorine shifts in the *meta* substituted fluorothiophenes: [δF(5-substituted-3-fluorothiophenes) = −0·2 + 0·81 δF(4-substituted-2-fluorothiophenes] was given. (120)

Fluorination of 1,4-dioxan, (22) 1,4-oxathian (22) and of 1,4-dithian (121) were reported. The structures of a large number of fluorinated dioxans and oxathians were deduced from their ^{19}F NMR spectra by means of a chemical shift parameter scheme. (122) The parameter scheme is given in Table XXXIII for CF_2 and CFH type fluorine groups. Some eighty-one chemical shifts of fluorine atoms in some twenty-six molecules were correlated well in such a way. The axial fluorine was assumed to resonate to high frequency of the equatorial, in line with the polyfluorocyclohexane results. It was, in addition, assumed that the molecules adopt a certain conformation, which is the one having the most -C*F*H- fluorine atoms axial; in other words it was assumed that a strong anomeric effect, or its

TABLE XXXIII

^{19}F chemical shift parameters (in ppm) for polyfluoro-1,4-dioxans [264] and -1,4-oxathians [265] (119)


[264]


[265]

	F axial					F equatorial				
	α H_{ax}	α H_{eq}	β H_{ax}	β H_{eq}	Base volume	α H_{ax}	α H_{eq}	β H_{ax}	β H_{eq}	Base volume
CH*F* fluorines										
α to oxygen in [252]	–11	6	–5	0	–140	16	2	0	–2	–158
α to oxygen in [253]	–5	6	–5	0	–139	9	10	–	–3	–153
α to sulphur in [253]	–3	4	0	0	–166	–	11	–	–3	–178
in polyfluoro-cyclohexane	–4·5	–	–	–	–212·2	11	7·6	–	–	–233·2
C*F*$_2$ fluorines										
α to oxygen in [252]	–5	7	–5	0	–82	9	4	0	–4	–90
α to oxygen in [253]	–4	5	–	0	–78	17	12	0	–5	–88
α to sulphur in [253]	–12	9	–9	0	–82	6	5	0	–7	–97
in polyfluoro-cyclohexane	–2·3	4·3	–	–	–124·2	15	10·5	–4	–	–142·7

equivalent, prevails over any other effects in deciding the conformation of these rings. There are a few compounds which do not fit the parameter scheme; these compounds, however, must adopt flexible conformations for relatively large percentages of the time. The *geminal* coupling constants are also useful structurally: (122) CF_2 vicinal to oxygen has a $^2J^{FF}$ value equal to 140 to 170 Hz, while CF_2 α to sulphur gives $^2J^{FF} = 220$ to 260 Hz. As far as the fluorination of 1,4 dithian is concerned, (122) the main products were polyfluoro-2-methyl-1,3-dithiolans, [266]. Evidence for these compounds was that peaks characteristic of CF_3-C groups and peaks in positions reasonable for $-\mathrm{S}-\overset{|}{\mathrm{C}}F-\mathrm{S}-$ fluorine groups were observed in the spectra. The fluorine data of five compounds are reported in Table XXXIV. Other major fluorination products, polyfluoro-1,4-dithians, were obtained. (122) These all showed similar NMR spectra: bands at -157 to -173 due to $-\mathrm{CFH}-\mathrm{S}-$ ($^2J^{HF} =$ *ca.* 45 Hz) and AB patterns ($^2J^{FF} =$ *ca.* 250 Hz) at -70 to -101.

III. THEORETICAL CONSIDERATIONS

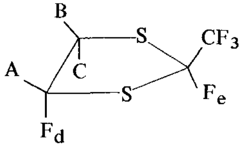
A. Chemical Shifts

One volume (Vol. 7) of the Progress in Nuclear Magnetic Resonance Spectroscopy was completely devoted to a discussion of fluorine chemical shifts. (123) The book consists of a comprehensive review on the fluorine literature on attempts to use ^{19}F shifts to give information on the electronic structure of molecules and on the nature of intermolecular interactions. The importance of medium effects on ^{19}F shifts was stressed; a discussion on the theoretical calculations of ^{19}F chemical shifts and on the correlations between ^{19}F chemical shifts and semi-empirical parameters, such as Hammet and Taft σ-values, was given in detail. The bulk of the book, however, consists of an extensive compilation of ^{19}F chemical shifts, which are believed to cover the fluorine literature up to January 1968.

A simple method was given to calculate the effects of geminal substituents upon the differences in shielding between ^{19}F nuclei bonded to sp^3 carbon in a variety of compounds. (124) Only the Huggins electronegativity of α-substituents was used. The method permits the calculation of the chemical shifts (referred to $CFCl_3$) of ^{19}F nuclei in a variety of molecules containing the elements C, H, N, O, F, Cl, Br, and I. The method was applied with success to the calculation of the chemical shift of fluorine nuclei bonded to tin(IV).

TABLE XXXIV

^{19}F NMR data of polyfluoro-2-methyl-1,3-dithiolans [266] (122)



[266]

			Chemical shift						Coupling constant (Hz)		
A	B	C	A	B	C	F_d	F_e	CF_3	$J(A \cdot F_d)$	J_{BC}	$J(CF_3 \cdot F_e)$
F	F	F	−92·4	−92·4	−89·0	−89·0	−113·4	−79·9	210	210	10·3
F	F	F	−92·4	−92·4	−87·9	−87·9	−116·6	−132·7[a]	202	202	18·8
F	F	H	−70·3	−152·6	–	−92·7	−113·9	−78·6	220	53	10·8
F	H	F	−88·6	–	−151·9	−72·8	−108·1	−78·4	221	52	10·0
H	F	H	–	−146·0	–	−146·0	−111·0	−76·9	50	50	11·8

[a] Fluorine shift of CF_2H group.

(125) The fluorine chemical shift parameter scheme deduced to elucidate the structures of polyfluoro- 1,4-dioxans, [264], and 1,4-oxathian, [265], has already been mentioned in Section IIB, p. 134. Molecular orbital calculations of ^{19}F chemical shifts in fluorothiophenes were performed showing that it is possible to account satisfactorily for the substituent effects on chemical shifts. (126)

Accurate ^{19}F NMR chemical shift in pure CF_4, SiF_4 and SF_6 gases and their mixtures with other gases were obtained in an attempt to explain the pressure and temperature effect on their shifts. (127a and b) A gas-tight sample tube was designed to keep a pressure up to *ca.* 60 atm. The chemical shift of CF_4 was in the range –430 to –480 Hz (from CF_3CO_2Et at 56·44 MHz) and that of SiF_4 in the range +5400 to 5450 Hz (again from CF_3CO_2Et at 56·44 MHz). A distinct non-linear temperature dependence was found. (127b) The changes in chemical shift may be adequately described in terms of the London dispersion field and a field due to repulsion. (127a and b) The proton and fluorine chemical shifts of fluoroform, CHF_3, in a variety of solvents was determined; (128) this is one of the few solvent studies involving nuclei other than proton. With the exceptions of benzene and anisole (aromatic solvents) it was observed that all proton chemical shifts were downfield from the value observed in least polar solvents, i.e. cyclohexane. The fluorine chemical shifts, on the contrary, were upfield in all solvents compared to cyclohexane. This behaviour suggests the proposal that the operation of the solvent "reaction field" is the dominant effect. Specific complexation of CHF_3 to benzene was also suggested by the marked low frequency shifts of both proton and fluorine chemical shifts. The fluorine shift varies from –35·96 in cyclohexane to –34·39 in acetonitrile. The H–F coupling, on the contrary, may be considered solvent independent, J^{HF} = 79·2 to 79·4 Hz. (128)

Another solvent study is that relative to pentafluorophenol (PFP). (129) The NMR parameters of PFP were shown to be sensitive to solvent conditions. The most pronounced variation for the chemical shift was observed for the *para* fluorine nucleus. The coupling constants change by as much as 3 Hz, the effect being greatest for nuclei situated *meta* to each other. The fluorine magnetic resonance solvent shifts $\Delta\sigma(F)$ relative to the gas phase of a number of simple, non-polar compounds (CF_4, SiF_4, SF_4, $C_{66}F_6$, *p*-fluorotoluene and *p*-difluorobenzene), each at infinite dilution in a series of non-polar solvents, $C(NO_2)_4$, $Si(OMe)_4$, $Si(OEt)_4$, $SiEt_4$ $SnEt_4$, $SnMe_4$, $SiCl_4$, CCl_4, CS_2 were also presented. The gas phase fluorine chemical shifts of the molecules studied are shown below: (129b)

	δ_F
SF_6	−49·47
CF_4	70·03
p-fluorotoluene	126·68
p-difluorobenzene	128·27
C_6F_6	171·69
SiF_4	174·22

The same molecules observed in solution show high frequency ^{19}F chemical shifts, a reduction in shielding which is in the range of 3 to 16 p.p.m. These shifts are about twenty times larger than those found in proton resonance. Comparisons with proton solvent shifts reveal a parallel behaviour of proton and fluorine solvent shifts, $\Delta\sigma(H)$ and $\Delta\sigma(F)$. The London dispersion forces are likely to be the main factor responsible for the solvent effects upon fluorine chemical shifts. However, unlike proton resonance, where the local diamagnetic shielding is mostly affected, it is probably through the local paramagnetic shielding that solvents alter fluorine chemical shifts. (129b)

A series of *p*-fluorophenyl derivatives were studied by ^{19}F NMR. (130) In particular, it drew attention to the secondary hydrogen-deuterium isotope effect upon the fluorine chemical shift of some methyl *p*-fluorophenyl carbonium ions, (Table XXXV). Evidence was

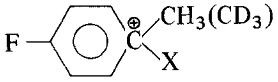
TABLE XXXV

Fluorine chemical shifts and isotope effects for *p*-fluorophenyl derivatives (130)

R	Solvent	°C	Chemical shift	$\Delta^{CH_3}_{CD_3}$[a]
$C(CH_3)_2OH$	CCl_4	25	−116·4	0·5
$C(CH_3)_2OH$	CH_3OH	25	−120·6	0·0
$C(CH_3)O$	CCl_4	25	−106·3	0·5
$C(CH_3)O$	CH_3OH	25	−108·8	0·0
$N(CH_3)_3^{\oplus}\ I^{\ominus}$	H_2O	25	−111·5	−0·5
$N(CH_3)_3^{\oplus}\ I^{\ominus}$	CH_3CH	25	−113·2	0·0
$N(CH_3)_3^{\oplus}\ I^{\ominus}$	HMPA	25	−113·8	0·5
$C(CH_3)NH_2^{\oplus}$	MA	−40	−97·4	2·0
$C(CH_3)OH^{\oplus}$	MA	−40	−32·8	6·0
$C{\equiv}C{-}C(CH_3)_2^{\oplus}$	MA	−40	−77·6	8·0
$C(CH_3)_2^{\oplus}$	MA	−40	−61·5	12·5
$C(CH_3)H^{\oplus}$	MA	−40	−47·4	18·5
$C(CH_3)CF_3^{\oplus}$	MA	−40	−27·7	22·5

[a] Isotope effects on the fluorine shifts; positive signs denote resonance for CH_3 at higher field than CD_3.

obtained which indicates that there are little or no steric interaction effects on the observed β-deuterium ^{19}F shifts. The shifts follow the electronic sequence X = NH_2 < OH < Me < H < CF_3 in the series [267]. There is, in addition, an excellent correlation of the β-deuterium ^{19}F shifts for the series [267] with the corresponding observed effects of the substituent, X, on the ^{19}F shifts of the carbonium ions. (130)



[267]

B. Spin Coupling Constants

Several one-, two-, three- and four- bond ^{13}C–F couplings were determined for a series of substituted monofluorobenzenes by direct observation of ^{13}C NMR spectra. (131) The carbon fluorine couplings in fluorobenzenes are ^{1}J(C–F) = −245·3 Hz, J(CCF) = +21·0 Hz, J(CCCF) = +7·7 and J(CCCCF) = +3·3 Hz. Carbon-fluorine couplings were also extracted for three difluorobenzenes, benzotrifluoride, three tetrafluorobenzenes, pentafluorobenzene, a few pentafluoro derivatives, hexafluorobenzene and 1- and 2-fluoronaphthalene. A linear correlation between the one-bond C–F couplings in *para*-substituted fluorobenzenes and the fluorine chemical shifts was found. (131) The determination of carbon-fluorine couplings was also extended to some aliphatic compounds. (131) It appears that the one-bond C–F coupling in cyclic geminal difluorides is sensitive to the hybridization of the carbon orbital. This coupling in fact becomes more negative as the *S* character in the carbon orbital increases: ^{1}J(C–F) = −240 Hz in C_6, −280 Hz in C_4 and −330 Hz in C_3 cyclic hydrocarbons. A new method to measure ^{13}C resonance positions in fluorinated organic compounds was described; (132) ^{19}F{^{13}C} double resonance experiments, for example, allowed the value J(^{13}C–F) = 283 Hz to be determined for $^{13}CF_3COOH$. The density dependence of the coupling constant, J(^{29}Si–F) in SiF_4 (gas phase) was studied. (133) The measurements were made for the pure SiF_4 and in various gaseous solvents. The hypothetical liquid phase values fall nicely into the range (170·5 to 178·5 Hz) of the extrapolated gas-phase values. (133)

An investigation of the anisotropy of the indirect fluorine-fluorine coupling in $CF_2{=}CH_2$ and the determination of its tensor elements was reported. (134) The NMR spectra of $CF_2{=}CH_2$, partially oriented in nematic solvents were measured at different concentrations and temperatures. (134) The indirect couplings involving fluorine were found to be: J_t^{HF} = +34·7 Hz; J_c^{HF} = +0·9 Hz; J^{FF} = +32·5 Hz. The signs were relative to those of the anisotropic couplings and the magnitudes were determined in the isotropic phase of 4-ethoxy-4′-*n*-butylbenzylideneaniline (EBBA). J^{FF} could also be determined from spectra in nematic phase. In EBBA it was found that J^{FF} = +330·5 Hz. The separate components of the J^{FF} tensor were calculated with the relation:

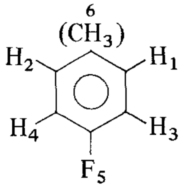
$$J^{FF} = \frac{1}{3}(J_{XX} + J_{YY} + J_{ZZ}) = 32{\cdot}5 \text{ Hz}$$

Assuming some geometrical parameters, the tensor elements resulting from the calculations are: J_{XX} = −720 ± 39 Hz, J_{YY} = +339 ± 39 Hz, J_{ZZ} = +478 ± 26 Hz.

The interpretation of the NMR spectra of 1,2-difluorobenzene in nematic solvents leads to a very small anisotropy in the indirect coupling between the fluorine nuclei. (135) The geometrical data obtained from the dipolar couplings are compared with those obtained from microwave work and a molecular geometry is proposed which is consistent with the results of these two methods. NMR measurements of CH_3F in a liquid crystalline solvent gave evidence of large anisotropic indirect spin-spin couplings. (136) It was found that direct dipole-dipole interactions show a large discrepancy with respect to the total anisotropic couplings observed. It is concluded that solvent effects on isotropic couplings seem to be the most obvious cause of the observed discrepancy. (136) CH_3F was also studied in order to investigate the influence of vibrations on molecular structure determinations from NMR spectra in liquid crystals. (137)

1. HF coupling constants

An attempt has been made (88) to establish the π contribution to ^5J*para*(H–F) in fluorobenzene and thus to determine the σ-contribution to the same coupling, already known for a series of fluorobenzene derivatives. The proton magnetic resonance of *p*-fluorotoluene, [268], was carefully analysed using LAOCN 3 and LAME programs. (88) The coupling over six bonds, between the fluorine nucleus and the methyl protons, ^6J*para*(CH_3–F) = 1·15 Hz, was taken as a measure of the π-electron contribution to the coupling



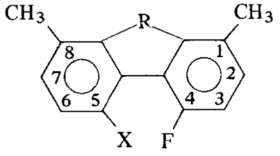
$J_{15} = J_{25} = 5{\cdot}43$ Hz
$J_{35} = J_{45} = 8{\cdot}96$ Hz
$J_{56} = +1{\cdot}15$ Hz

[268]

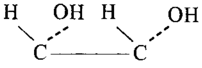
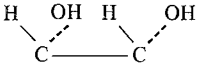
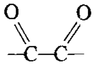
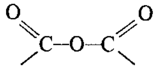
over five bonds between the fluorine nucleus and the *para*-proton in fluorobenzene, ^{5}*Jpara*(H–F). In other words the value $-1{\cdot}15$ Hz represents the π-electron contribution to ^{5}*Jpara*(H–F). The ^{5}*Jpara*(H–F) in fluorobenzene lies between 0·2 to 0·4 Hz, depending on solvent and analytical conditions. Writing ${}^5J(\text{H–F})_{\text{obs}} = {}^{\pi}J + {}^{\sigma}\text{J}$, it follows that ${}^{\pi}$*Jpara*(H–F) = *ca.* 1·4 Hz in fluorobenzene. *Jpara*(H–F) of a few 2-X- and 3-X- fluorobenzene derivatives were also considered to demonstrate that the observed dependence of *Jpara*(H–F) on the electronegativity of X, E_X, is exactly as expected from previous observations on the E_X dependence of *o*, *m* and *p* J^{HH} and of *o* and *m* J^{HF} in benzene and pyridine derivatives. (88) Consequently H–F couplings in aromatic compounds show the same qualitative dependence on E_X as do H–H couplings. The magnitude of the changes is, however, larger for H–F than for H–H couplings. In contrast, the analogous F–F couplings behave quite differently. (138) The importance of through-space contributions to H–F coupling was sought by determining whether long-range H–F and F–F couplings show comparable stereochemical dependence in related compounds. (139) A series of derivatives of 4,5-difluoro- and 4-fluoro-5-methyl- phenanthrenes were considered (Table XXXVI). (139) Compounds [269a] and [269c] may be considered planar molecules. The other molecules, on the contrary, must exist in nonplanar enantiomeric forms. This is clearly demonstrated by ^{19}F spectrum of [269b]; the proton decoupled spectrum of this compound, ^{19}F{H}, exhibits a single ^{19}F resonance at room temperature. Upon cooling, however, this resonance progressively broadens and eventually resolves into a typical AB pattern. This behaviour is clearly indicative of the slowing of the interconversion of the non-planar enantiomeric forms of [269b]. Going from [269a] to [269b] there is an increase of the fluorine-fluorine distance. This, as expected for a through-space coupling mechanism, produces a dramatic decrease in F–F coupling: ${}^5J^{\text{FF}} = 170$ Hz [269a] ${}^5J^{\text{FF}} = 98$ Hz [269b]. Consequently there must be changes in the distance between the 4 and 5 position along the series of compounds considered, which are also reflected by changes in the coupling

TABLE XXXVI

Coupling constants and chemical shifts for derivatives of 4,5-difluoro- and 4-fluoro-5-methylphenanthrenes [269] (139)



[269]

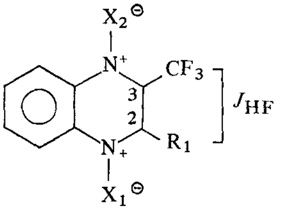
	R	X	$J(X-F_4)$(Hz)	F-4
(a)	–CH=CH–	F	170	−103·9
(b)		F	98	−111·2
(c)	CH=CH	CH_3	11·9	–
(d)		CH_3	7·7	–
(e)		CH_3	8·2	–
(f)		CH_3	3·7	–

constants between these two positions. The decrease in $^{5}J^{\mathrm{F\,F}}$ from [269a] to [269b] can be taken as a standard fractional decrease in through-space coupling as a consequence of this structural variation: ($^{5}J^{\mathrm{F\,F}}$ in [269b]): ($^{5}J^{\mathrm{F\,F}}$ in [269a]) = 0·57. The observation that H–F coupling decreases by a comparative amount, $^{6}J(CH_3-F)$ in [269d]/$^{6}J(CH_3-F)$ in [269c] = 0·64, implies that a through-space interaction contributes substantially to the $^{6}J^{\mathrm{H\,F}}$. The H–F coupling of 11·9 Hz in [269c] appears to be the largest $^{6}J^{\mathrm{H\,F}}$ coupling reported to date. (139)

Further support for through-space H–F long-range coupling was obtained when studying a novel class of 2-substituted-3-trifluoromethylquinoxalines, their 1-oxides and 1,4-dioxides (Table XXXVII).

TABLE XXXVII

H–F couplings in 2-substituted-3-trifluoromethylquinoxalines, their 1-oxides and 1,4-dioxides [270] (140)

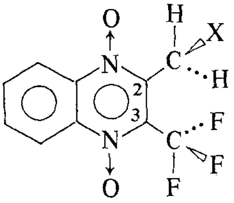


[270]

	R_1	X_1	X_2	J(HF)(Hz)
(a)	H	O[a]	O	*ca.* 0
(b)	CH_3	O	O	3·0
(c)	CH_2CH_3	O	O	2·1
(d)	CH_2Br	O	O	1·3
(e)	CH_2OH	O	O	*ca.* 0
(f)	CH_2OCH_3	O	O	2·0
(g)	CH_2OMO_2	O	O	2·0
(h)	CH_2Br	O	–	*ca.* 0
(i)	CH_3	O	–	1·2
(l)	CH_3	–	–	1·6

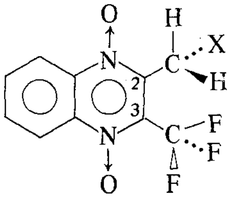
[a] O = oxygen.

(140) The through-space mechanism provides a good explanation for the variations of the J^{HF} observed in Table XXXVII. In quinoxaline 1,4-dioxides, [270a to g), there are two possible important con-

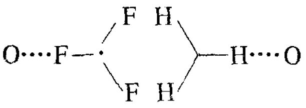


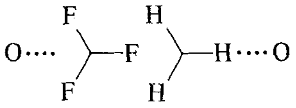
A

[270 a to g]

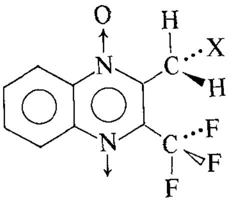


B

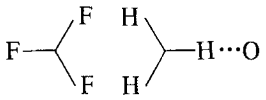




formational isomers of the CF_3 group, A and B. One fluorine of the CF_3 group can be either coplanar (A) or skew (B) with the 4-oxide oxygen. Isomer B was supposed to be strongly favoured. If only across-space interaction is operative, there are only two out of a possible nine which contribute to the observed coupling constant: $J(\text{obs}) = \frac{2}{9}J'$, where J' is the coupling for the closest fluorine and hydrogen nuclei. For compound [270b] it is found that: $3 = \frac{2}{9}J'$ and hence $J' = 13{\cdot}5$ Hz. When X is not a proton: $J(\text{obs}) = \frac{1}{6}J'$, from which one may calculate J (calc.) $= 13{\cdot}5/6 = 2{\cdot}2$ Hz. In the case of quinoxalines and their 1-oxides [270h to l) only one conformer for the CF_3 group can be postulated, where no fluorine-oxygen repulsion exists. When X = H, compound [270i], one finds: $J(\text{obs}) = \frac{2}{9}J' = 1{\cdot}22$ Hz, $J' = 5{\cdot}49$ Hz. For X = Br, $J(\text{calc.}) = \frac{1}{6}J' = 0{\cdot}91$; this explains the broad singlet of [270h]. (140)



[270 h to l]



The results of three fluoroethanes (2, 4), $CH_2F\cdot CH_2F$, $CH_2F\cdot CHF_2$, $CHF_2\cdot CHF_2$ were considered together in detail to give the couplings of every fluoroethane. Vicinal H–F couplings, $^3J^{HF}$, appear to behave as the corresponding H–H couplings both as regards their orientation and substituent dependence. The effect of successive fluorination on $^3J_t^{HF}$ is a general decrease (Fig. 3); the change is greater, however, if the fluorine atom is attached to the $-\overset{|}{\underset{|}{C}}H$ group of the $>CH\cdot CF<$ fragment. The values of $^3J_g^{HF}$ demonstrate the large orientation effect of electronegative substituents. (2) Calculations were performed on CH_3CH_2F in order to derive a stereochemical dependence of vicinal H–F coupling; $^3J^{HF}$ was found to go through a minimum at 90° and maxima around 0° and 180°. (141) The dihedral angle dependence of vicinal H–F coupling was studied employing finite perturbation molecular orbital

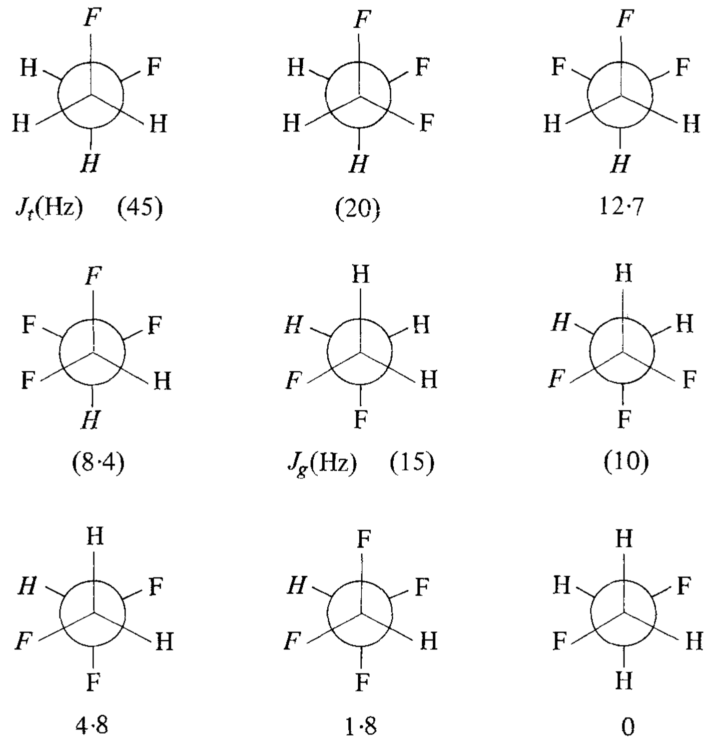


FIG. 3. $^3J^{HF}$ couplings in fluoroethanes. (From Abraham and Kemp. (2))

method. (142) Several H–F couplings were obtained in the carbohydrate series (see compounds [113] to [118] and Table XI). (58) It was found that geminal H–F couplings all lie in the range normally associated with sp^3-hybridized carbon in a six membered ring (J_g^{HF} = 47 to 57 Hz). The vicinal H–F coupling ranges from 0·5 Hz to 32 Hz. The *trans* vicinal H–F coupling (20·0 to 32·0 Hz) decreases as the number of directly bonded oxygen atoms increases. The *gauche* coupling situation (0·5 to 16 Hz) is more complex.

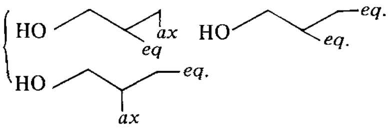
A detailed examination (58) shows that the changes in observed couplings parallel the changes in three important factors in the environment of the coupling fragment, namely:

(1) The number of substituent oxygen atoms on the carbon atoms of the coupling fragment.

(2) The presence of an oxygen atom which is *trans* to the fluorine atom via the coupling pathway.

(3) The presence of a hydroxy-group which is *trans* to the C–C bond of the coupling pathway; this contribution depends upon whether the coupled nucleus (H or F) on the central C atom is axial or equatorial.

Effects (1) and (2) are already known, but (3) is novel. It was possible to calculate empirical contributions to ${}^3J_g^{\mathrm{H\,F}}$ for each of the three previous factors, which are as follows:

Contribution to ${}^3J_g^{\mathrm{HF}}$	Factor
−2·5	1
−7·0	2
−2·0 +2·0	3 

From the values quoted previously the *gauche* ${}^3J_g^{\mathrm{H\,F}}$ coupling may be calculated for all situations of the carbohydrate investigated [113] to [118]. It was shown that it is also applicable to a variety of different carbohydrate classes already reported in the literature. The large value of the H–F coupling between H_5 and F in compound [117] ($J^{\mathrm{H\,F}}$ = 27 to 29 Hz) was indicated as evidence of the existence of a favoured conformer, in which F-6 is antiparallel to H_5. (58) As far as long-range H–F couplings in these carbohydrates are concerned it was shown that five-bond coupling has a stereospecific dependence showing maximum values when it can be regarded as a linear extension of the **W** characterizing the four-bond coupling. (58)

2. *F–F couplings*

In the case of the vicinal F–F coupling of fluoroethanes it was found (2) that the *trans* oriented coupling, ${}^3J_t^{\mathrm{F\,F}}$, varies enormously, from −30 to *ca.* 0 Hz. (Fig. 4), with successive fluorine substitution and the decrease is most marked for the first fluorine atom introduced. ${}^3J_g^{\mathrm{F\,F}}$, on the contrary, is relatively unaffected (−13·7 to −5·4 Hz) and shows no consistent change with substitution. These results for ${}^3J^{\mathrm{F\,F}}$ are in agreement with those obtained in the $-CF_2-CF_2-$ fragment of the 1,2-dihalotetrafluoroethane. (5) It was found that for these compounds ${}^3J_t^{\mathrm{F\,F}}$ varies considerably (from −18·5 to +6·6 Hz) becoming absolutely more positive as the electronegativity of the substituents increases. ${}^3J_g^{\mathrm{F\,F}}$, on the contrary, is almost unaffected and the direction of the small change observed (from −6·6 to *ca* −11 Hz) is opposite to that of ${}^3J_t^{\mathrm{F\,F}}$. (5) The geminal and vicinal couplings of these halofluoroethanes are

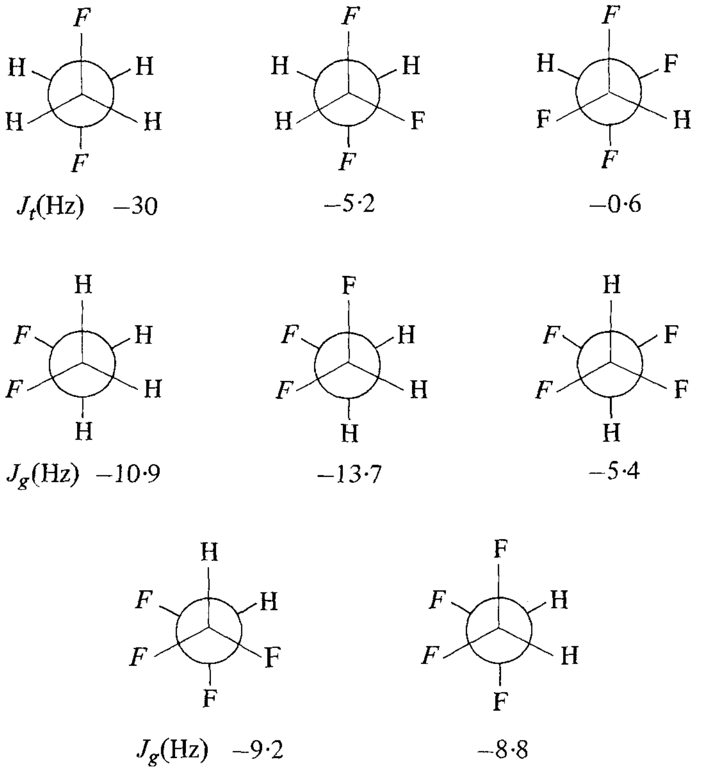


FIG. 4. ${}^3J^{\mathrm{FF}}$ couplings in fluoroethanes. (From Abraham and Kemp. (2))

shown in Table XXXVIII, together with the couplings of the single isomers derived using energy differences $\Delta E(E_g - E_t)$ between *gauche* and *trans* isomers determined by IR. A correlation between rotationally averaged couplings, $J_{\mathrm{av}}^{\mathrm{FF}} = [\frac{1}{3}(J_t + 2J_g)]$, and the sum of the Huggins electronegativities, ΣE, of the four remaining substituent atoms in the $>$CF–CF$<$ fragment of fluoroethanes was also reported (Fig. 5).

TABLE XXXVIII

Coupling constants (Hz) of 1,2-disubstituted tetrafluoroethanes -CF$_2$·CF$_2$- (5)

AA′	BB′	${}^2J_{\mathrm{A}}$	${}^2J_{\mathrm{B}}$	${}^3J$	${}^3J'$	J_t	J_g	$\Delta E(E_g - E_t)$ kcal./m.
CF$_2$I	·CF$_2$Br	203·2	170·5	−9·60	−8·67	−9·9	−8·5	1150
CF$_2$I	·CF$_2$Cl	213·0	171·0	−6·12	−8·47	−4·7	−9·2	870
CF$_2$Br	·CF$_2$Cl	177·1	170·2	−2·79	−7·76	+5·5	−11·9	600

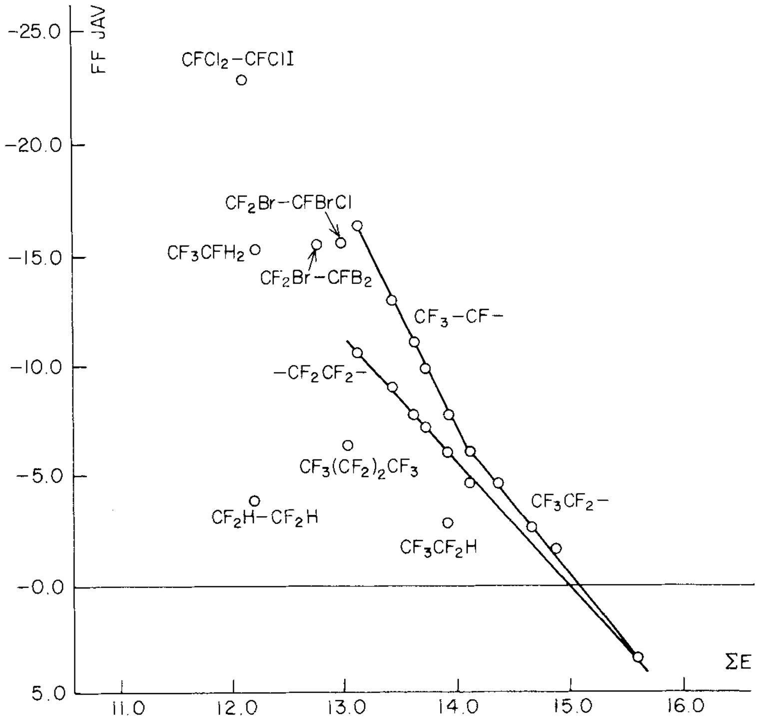
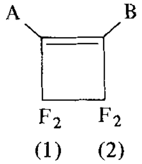


FIG. 5. Rotationally averaged couplings, ${}^3J_{av}^{FF}$, against the sum of the Huggins electronegativity, ΣE, of the four remaining substituent atoms in the $>$CF–CF$<$ fragment. (From Cavalli (5))

A new series of F-F coupling constants have recently become available for cyclic compounds such as cyclobutenes (Table XXXIX) and cyclopentenes (Table XL). (143) The assignments of the couplings in the fluorocyclobutenes follow those already known, which indicated a large positive value for ${}^3J_t^{FF}$ and a negative value for ${}^3J_g^{FF}$. The assignments of the couplings and their signs in the fluorocyclopentenes are only tentative: these were mainly made on the basis of electronegativity considerations and of the detailed analysis of the NMR spectra. Evidence that the ${}^4J^{FF}$ coupling is extremely dependent upon the relative orientation of the fluorine substituents and on the nature of the nearby substituents is demonstrated by the results obtained for some carbohydrate molecules (60) (see [123], [124] and [125] and Table XII), ideal molecules for this purpose. The magnitudes of the ${}^4J^{FF}$ couplings of these molecules

TABLE XXXIX

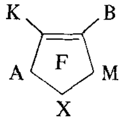
Coupling constants in fluorocyclobutenes (143)



A	B	^3J *trans* (F–F)	^3J *cis* (F–F)			
I	I	24·47	−15·35			
I	Cl	24·7	−13·8			
I	F	25·7	−14·13	$J_{1\mathrm{B}} = 17{\cdot}8$	$J_{2\mathrm{B}} = 5{\cdot}2$	
H	I	27·5	−14·0	$J_{1\mathrm{A}} = 1{\cdot}4$	$J_{2\mathrm{A}} = 9{\cdot}7$	
H	F	27·7	−12·5	$J_{1\mathrm{B}} = 19{\cdot}8$ $J_{1\mathrm{A}} = 1{\cdot}6$	$J_{2\mathrm{B}} = 5{\cdot}1$ $J_{2\mathrm{A}} = 9{\cdot}8$	$J_{\mathrm{AB}} = 7{\cdot}1$

TABLE XL

Coupling constants (Hz) of fluorocyclopentenes (143)

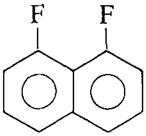


		MX coupling		AX coupling		AM coupling	
K	B	^3J_t	^3J_c	^3J_t	^3J_c	^4J_t	^4J_c
I	I	−8·44	−1·37	−8·44	−1·37	+1·24	+4·12
Cl	Cl	−5·75	−1·03	−5·75	−1·03	+1·32	+3·01
Cl	I	−6·89	−0·91	−6·42	−1·44	+1·28	+3·56
F	I^a	−5·55	+0·66	−4·45	−1·85	+1·68	+3·07

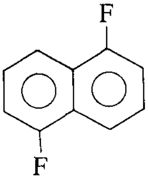
^{a} $J_{\mathrm{AK}} = -15{\cdot}71$; $J_{\mathrm{XK}} = +4{\cdot}91$; $J_{\mathrm{MK}} = +10{\cdot}64$.

were obtained from ^{19}F{H} spectra. The signs of the corresponding couplings were derived with the help of double resonance experiments. For [123] and [125] it was found unequivocally that $^4J^{\mathrm{FF}}$ must be positive. For [124], even if it cannot be stated with certainty, the spectra may most readily be interpreted on the basis of the negative sign of $^4J^{\mathrm{FF}}$. The stereospecific dependences of the long-range $^4J^{\mathrm{FF}}$ coupling in these carbohydrates are found to be: (60) $^4J_{aa} = +10{\cdot}4$ Hz, $^4J_{ae} = +1{\cdot}0$ Hz and $^4J_{ee} = -3{\cdot}0$ Hz. In the carbohydrate series (59) it is also worthwhile to mention some vicinal F–F couplings (see [119] to [122], Table XII). It was found that these vicinal F–F couplings are all negative. Furthermore, the value of the *trans* coupling ([121], $J = -20{\cdot}0$ Hz) is approximately the same as that of the *gauche* couplings ([119], $J = -18{\cdot}8$ Hz; [120], $J = -15{\cdot}8$ Hz; [122], $J = 13{\cdot}5$ Hz). (59) Attention was concentrated on ^{19}F NMR studies with complete proton decoupling, which permits, in many instances, the analysis of the spectrum by simple inspection. (144)

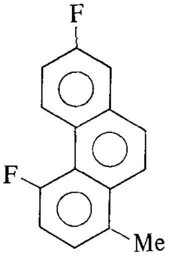
Several fluoroaromatic hydrocarbons were studied under similar conditions. Besides confirmation of numerous ^{19}F NMR parameters already known, a number of examples of long-range F–F coupling were also obtained for the first time; these are shown in [271] to [276].



[271]



[272]



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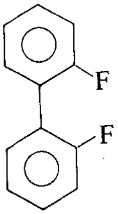
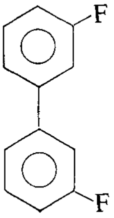


[274]



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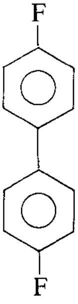


[276]

The value of 0·8 Hz for [273] is a seven-bond coupling and no other example of $^{7}J^{FF}$ in an unsaturated molecule is known. A solvent dependence study was also carried out. (144) The behaviour of J^{FF} in these aromatic systems shows no correlation with solvent dielectric constant, which is interpreted to imply that reaction field mechanisms are not important here. However, the smaller variations in $^4J^{FF}$ and $^5J^{FF}$ reasonably correlate with the dielectric constant of the solvent, which suggests that the reaction field mechanism is more significant here.

IV. ORGANO-METALLIC AND METALLOID COMPOUNDS

One volume on characterization of organometallic compounds considers shortly some aspects of ^{19}F NMR spectroscopy which pertains directly to organometallic compounds. (145) Some literature results relative to fluoroalkyl-, fluoroalkenyl- and pentafluorophenyl- derivatives were reported. In all cases fluorine atoms located near to the metal show a paramagnetic shift, which is quite large when the metal is a transition metal. A short discussion on the dominant contribution to the ^{19}F chemical shift of these compounds is also reported.

Group II

^{19}F NMR data were presented for *o*-, *m*- and *p*- $(CF_3C_6H_4)_2Hg$ and $CF_3C_6H_4HgBr$. (146) The CF_3 fluorine shift varies in the range −63·2 to −64·8. Evidence that a "through-space" mechanism is the main contributor to $^4J(^{199}Hg\text{-}F)$ (26 to 29 Hz) in the *ortho*-compounds was given. (146) Magnetic non-equivalence in a bis(perfluorovinyl)mercury compound was demonstrated. (147). The NMR data are collected in Table XLI. (147)

Group III

In the study with perfluoroalkylhypochlorites, a novel reaction with boron trichloride was discovered in which displacement of chlorine from BCl_3 yields perfluoroalkylborate esters, $[(Rf\,0)_3B]$. (149) The ^{19}F NMR spectrum of $[(CF_3)_3CO]_3B$ showed a single sharp resonance at −68·1. Indium(I) halides react with 1,2-bis(trifluoromethyl)dithieten, L = $\overline{S(CF_3)C{=}C(CF_3)S}$, to give the compounds InLX (X = Cl, Br, and I), which are believed to be polymeric indium(III)-dithiolato-complexes. (150) Reaction of these latter compounds with DMSO gave $[InL(DMSO)_4]X$. A brief investigation by ^{19}F NMR spectroscopy was performed on the free ligand and on $[InL(DMSO)_4]X$. The free ligand gave a single resonance at +64.1, whereas for the DMSO complexes the resonance signal was found at +51·5 (X = Cl), +51·6 (X = Br) and +51·55 (X = I). (150) Covalent fluoro-substituted isopropoxides of aluminium and of some Group IV elements were synthesized, $(HFIP)_{3\,\mathrm{or}\,4}$ X, where HFIP =

TABLE XLI

^{19}F NMR data of (perfluorovinyl) mercury compounds (147)

	F_A	F_B	F_C	^2J	^3J_c	^3J_t	^4J_s	$^5J_{HF}$	^5J_c	^5J_t	$^6J_{cc}$	$^6J_{ct}$	$^6J_{tt}$	^2J(Hg–F)
$(CF_2{=}CF)_2Hg$	−184·79	−123·73	−89·24	74·71	36·72	−108·8	−3·35		0·094	2·47	0·45	−0·09	0·47	820·5
$(CF_2{=}CF)HgCH_3$	−183·83	−126·96	−91·69	81·2	36·5	−107·1		0·28						584·6
$(CF_2{=}CF)_2$	−179·95	−108·22	−94·12		See Ref. 148									

$(CF_3)_2CHOH$ and X = Al, Si, Ge, Ti, Zr and HF. (151) The ^{19}F shift or the parent alcohol of HFIP is −76·8 and those of the complexes vary in the range −73·6 to −76·4. The progressive higher-frequency shift observed from Si to Hf may arise from the degree of covalency of the metal ions and/or to an increase in the mass of the central metal atoms. (151)

Group IV

In the liquid-phase photochemical chlorination of $(CF_3CH_2CH_2)_3SiCl$, silicon-containing compounds were formed with the chlorine atom in a trifluoropropyl group, in α-position to the Si atom. (152) In this way the orienting effect of the CF_3 group could be established. ^{19}F shifts of the CF_3 groups are in the range −110·1 to −114·2. As a part of an investigation of the chemistry of $Hg(SiMe_3)_2$, its reactions, under uv irradiation, with some fluoroolefins and acetylenes were reported. (153) The reaction with $CF_2{=}CF_2$ gave Me_3SiF (−156·5) and $Me_3SiCF{=}CF_2$ (−88·5, −117·5, −198·5) and a high boiling liquid residue in which was identified $Me_3SiCF_2CF_2HgSiMe_3$ (−105·5). The reaction with hexafluorocyclobutene, hexafluoropropene, perfluorobut-2-yne and perfluoropropyne affords products resulting from the replacement of one or more vinylic fluorine atoms by trimethylsilyl groups. The NMR data of these compounds are collected in Table XLII. (153) In the synthesis of α,ω-bis(silyl)polyfluoroalkane the ^{19}F chemical shift parameters of $[Cl(CF_3CH_2CH_2)(CH_3)SiCH_2CH_2]_2CF_2$ were reported (CF_3: −69·0, CF_2: −103·4). (13) The preparation of group IV derivatives of the alkynes $HC{\equiv}CRf$, [$Rf = CF_2CF_3$ and $-CF(CF_3)_2$] were reported (Table XLIII), $(CH_3)_nM(C{\equiv}CRf)_{4-n}$. (154) The ^{19}F shifts of the fluorine atoms go to higher frequency as the metal changes from Si to Ge, to Sn. In addition, in those compounds where M and Rf are constant the fluorine shift values go to low frequency as *n* decreases (3 → 0). (154)

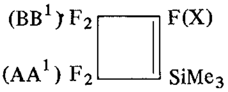
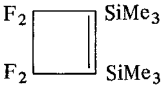
A novel class of organometallic compounds in which a Group IV element (Ge and Sn), other than carbon, is σ-bonded to a cyclopropene ring at vinylic position were prepared. (48) Analytical and spectroscopic data leave no doubt concerning the proposed structures, $(CH_3)_nM(\overline{C{=}CRfC}F_2)_{4-n}$; ^{19}F chemical shift of the CF_2 bridge groups ranges in −102 to −105. (48)

Groups V and VI

In the X-ray study of the structure of a complex containing a decafluoro-arsenobenzene, $F_2(CO)_4(AsC_6F_5)_2$, a spectroscopic investigation was also carried out. (155) The ^{19}F NMR spectrum

TABLE XLII

^{19}F NMR data of trimethylsilylperfluoro-olefins (153)

	A	B	X	J_{AB}	J_{AX}	J_{BX}
	−113·28	−119·16	−102·70	−15·05 +27·85	22·9	4·5
	−107·3					
$CF_3CF{=}CFSiMe_3$(*trans*) X A B	−159·3	−168·5	−69·7	138·0	22·0	10·5
$CF_3CF{=}CFSiMe_3$(*cis*)	−138·7	−142·7	−59·3	10·7	13·5	7·3
$CF_3C(SiMe_3){=}CFSiMe_3$[a] X A	−72·5	–	−53·5	–	8·4	–
$CF_3C(SiMe_3){=}CFSiMe_3$[a]	−68·0	–	−66·0	–	7·9	–
$CF_3C(SiMe_3){=}C(SiMe_3)CF_3$ (*trans*)	–	–	−53·5	(J_{HF} = *ca.* 1 Hz)		
$CF_3CF(HgSiMe_3)CF_2SiMe_3$	—CF_3	X	−67·4;	J_{AX} = 7·0;		J_{BX} = 11·3
or	—CF_2—	AB	−100·2;	−112·8		J_{AB} = 355
$CF_3CF(SiMe_3)CF_2HgSiMe_3$	—CF	K	−197·8;			J_{KX} = 11·3

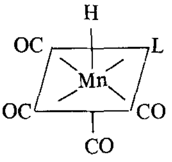
[a] The *cis* and *trans* isomer cannot be assigned unambiguously.

TABLE XLIII

^{19}F NMR parameters of the parent fluoroalkynes and Group IV perfluoroalkynyl derivatives, $(CH_3)_nM(C{\equiv}C\ Rf)_{4-n}$ (154)

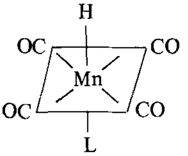
	CF_3	CF_2	CF	J_{FF}
$HC{\equiv}CCF_3$	−55·55			
$(CH_3)_3SiC{\equiv}CCF_3$	−49·95			
$(CH_3)_2Si(C{\equiv}CCF_3)_2$	−53·41			
$(CH_3)_3GeC{\equiv}CCF_3$	−51·35			
$(CH_3)_2Ge(C{\equiv}CCF_3)_2$	−52·6			
$CH_3Ge(C{\equiv}CCF_3)_3$	−52·85			
$Ge(C{\equiv}CCF_3)_4$	−53·35			
$(CH_3)_3SnC{\equiv}CCF_3$	−50·25			
$(CH_3)_2Sn(C{\equiv}CCF_3)_2$	−51·54			
$HC{\equiv}CCF_2 \cdot CF_3$	−88·7	−105·9		3·6
$(CH_3)_3GeC{\equiv}CCF_2CF_3$	−86·65	−101·9		4·1
$(CH_3)_2Ge(C{\equiv}CCF_2CF_3)_2$	−86·9	−103·7		3·8
$(CH_3)_3Sn(C{\equiv}CCF_2CF_3)$	−86·43	−101·1		4·1
$HC{\equiv}CCF(CF_3)_2$	−90·7		−171·8	9·9
$(CH_3)_3GeC{\equiv}CCF(CF_3)_2$	−73·0		−166·0	10·6

shows *ortho*-, *meta*- and *para*- resonances centred at −117·9, −159·2 and −150·7 respectively. The reaction of pentacarbonyl manganese hydride, $HMn(CO)_5$, with bis-trifluoromethylphosphino- derivatives $(CF_3)_2PX$ where X = I, Br, Cl, F, CH_3 or CF_3 was described. (156) The main reaction is an exchange of halogen for hydrogen to give $XMn(CO)_5$. Some bridged complexes, which are also hydrides, have been produced (156) as minor products in a mixture of *cis* and *trans* isomers, [277a and b] $HMn(CO)_4[P(CF_3)_2X]$ (Table XLIV). Proton



(*cis*)

[277a]



(*trans*)

[277b]

TABLE XLIV

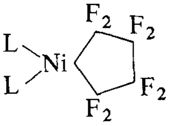
NMR data for fluorocarbon phosphines and their complexes with $HMn(CO)_5$ (156)

	CF_3	PF	$^1J_{FP}$	$^3J_{FF}$	$^3J_{FH}$
$P(CF_3)_2F$	−66·5	−219·0	1013	3·46	–
cis-$HMn(CO)_4[P(CF_3)_2F]$	−69·9	−139·6	988	3·8	0·7
trans-$HMn(CO)_4[P(CF_3)_2F]$[a]	−69·1	−134·0	1002	2·2	31·0
$P(CF_3)_3$	−50·8				
cis-$HMn(CO)_4[P(CF_3)_3]$	−57·1				
trans-$HMn(CO)_4[P(CF_3)_3]$	−56·5				
$P(CF_3)_2CH_3$	−66·9				
cis-$HMn(CO)_4[P(CF_3)_2CH_3]$	−63·4				
trans-$HMn(CO)_4[P(CF_3)_2CH_3]$	−62·8				

[a] $^4J_{FH}$ = 1·8 Hz.

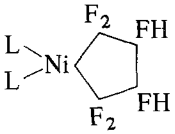
and fluorine NMR spectroscopy were useful to demonstrate that each of the new hydrides was a mixture of *cis*- and *trans*- isomers and to establish their relative proportions. In the ^{19}F NMR spectra the resonance of the CF_3 group is consistently at slightly lower frequency, with a larger J(F–C–P) in the *cis*- than in the *trans*- isomer. In the *trans* isomer of $HMn(CO)_4[P(CF_3)_2F]$ $^3J_{FH}$ and $^4J_{FH}$ had values of 31·0 and 1·8 Hz respectively; in the corresponding *cis*-isomer $^3J_{FH}$ was drastically reduced to 0·7 Hz and $^4J_{FH}$ was undetectable. In both isomers, in addition, the P*F* resonance was shifted 80 ppm to high frequency from that of the free ligand. (156)

The reaction of arsine substituted Ni complexes and of bis(π-2-methylallyl)Ni were investigated. (157) Treatment of L_4Ni, where $L = PhAsMe_2$ or *o*-$C_6H_4(AsMe_2)_2$, with C_2F_4 or C_2F_3H gave [278a and b] respectively. (157)



[278a]

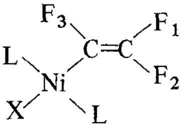
	$\alpha \cdot CF_2$	$\beta \cdot CF_2$	$J(F_\alpha\text{-}F_\beta)$
(i) $L = PhMe_2As$	−99·0	−139·1	< 1 Hz
(ii) $L = o\text{-}C_6H_4(AsMe_2)_2$	−99·0	−137·5	< 1 Hz



[278b]

(i) $L = PhMe_2As$	αCF_2 AB −85·6 −94·4 $^2J^{FF}$ 259 Hz	CFH: −2102
(ii) $L = o\text{-}C_6H_4(AsMe_2)_2$	multiplet −85, −95,	−210

The compounds C_2F_3Cl, C_2F_3Br, $CCl_2{=}CF_2$ and $CFCl{=}CFCl$ react with $(PhMe_2As)_4Ni$ to give respectively the stable crystalline σ-bonded vinylnickel complexes [279], [280] and [281]. (157) Hexafluorobuta-1,3-diene reacts with $(PhMe_2As)_4Ni$ to give [282].

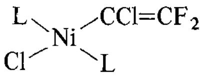


[279]

	F_1	F_2	F_3	J_{12}	J_{13}	J_{23}
(a)	−87·5	−130·8	−163·8	109·0	36·0	109·0
(b)	−86·1	−130·8	−162·9	106·0	36·0	106·0

(a) $L = PhMe_2As$ $X = Cl$

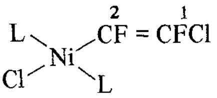
(b) $L = PhMe_2As$ $X = Br$



[280]

AB −70·7, −98·0, $^2J^{FF} = 73·0$ Hz

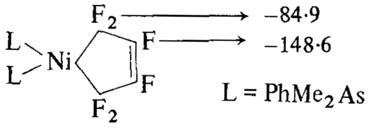
$L = PhMe_2As$



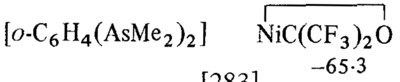
[281]

F_1	F_2	J_{12}	
−88·4	−106·3	14	*cis* isomer
−123·5	−131·0	122	*trans* isomer

$L = PhMe_2As$



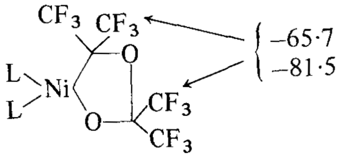
[282]



$[o\text{-}C_6H_4(AsMe_2)_2]\ \overline{NiC(CF_3)_2O}$ −65·3

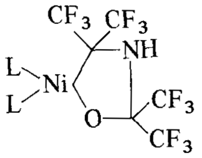
[283]

The stable crystalline complex [283], prepared by displacement of cyclo-octa-1,5-diene from $(1,5\text{-}C_8H_{12})\underline{NiC(CF_3)_2O}$, reacts with $(CF_3)_2CO$ and with $(CF_3)_2CNH$ to form five-membered ring compounds, which are likely to be [284] in one case and one of the two isomeric structures [285]. (157) Double irradiation of one CF_3 multiplet of [285] collapsed the other CF_3 to a singlet. Bis-(π-2-methylallyl)nickel and C_2F_4 gives a complex to which is tentatively assigned the structure [286]. (157) Two resonances were observed for [286] at −100·7 and −107·9 (J^{HF} = 180 Hz); the two



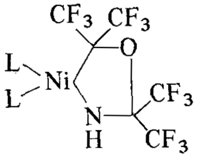
$L = o\text{-}C_6H_4(AsMe_2)_2$

[284]



$L = o\text{-}C_6H_4(AsMe_2)_2$

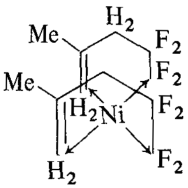
[285a]



$L = o\text{-}C_6H_4(AsMe_2)_2$

[285b]

[285a] or [285b] } multiplets at −64·4 and −82·0

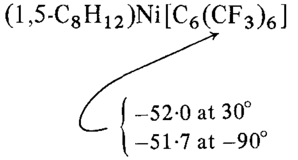


[286]

resonances were assigned to the two C_2F_4 groups inserted between the Ni atom and the two 2-methylallyl groups. ^{19}F NMR studies were performed on the following systems: (1) fluorochromate(VI) chloride, (2) fluorochromate(VI) fluoride, and (3) chromylfluoride-chromyl chloride. (158) For system (1) the exchange in DMSO was shown to be slow. No substitution was detected in acetonitrile for system (2) and rapid fluorine exchange was observed in system (3).

Groups VII and VIII

The reactions of low-valent metal complexes with fluorocarbons continue to be extensively studied. The effect of hexafluorobut-2-yne, $CF_3C{\equiv}CCF_3$, on various zero-valent nickel complexes was investigated. (14) In C_6H_6 bis-(cyclo-octa-1,5-diene)Ni reacts with $CF_3C{\equiv}CCF_3$ at room temperature to give two purple-red crystalline complexes, [287] and [288]. (159) The ^{19}F NMR spectrum of [288] shows resonances at −49·4, −52·4 and −53 with relative intensities 1 : 3 : 2 respectively. The resonance at high frequency (−49·4) is extremely broad and the relative intensities of the three peaks are temperature dependent. Cyclo-octa-1,5-diene may be displaced from the mononuclear complex [287] by I = Ph_2PMe, $PhMe_2As$, Ph_3P, $(MeO)_3P_4$ and $MeC(CH_2O)_3P$ to give the complexes $L_2Ni[C_6(CF_3)_6]$. (159) The ^{19}F NMR spectra of these complexes show only one single resonance (−50·2 to 52·1); however, in some cases the single resonance appears as a well-resolved triplet owing to the coupling with ^{31}P nuclei. This triplet structure is evidence of the symmetry of the bonded $C_6(CF_3)_6$ unit with respect to the two ^{31}P nuclei of the co-ordinated phosphorus ligands. At −90° the ^{19}F NMR spectrum of these complexes shows a general line broadening and a collapsing to a broad singlet for those showing a triplet pattern. It is suggested that these Ni-complexes are extremely fast 18-electron fluxional systems. Treatment of [288] with $(MeO)_3P$ or $MeC(CH_2O)_3P$ gave [289] and [290]. (159)



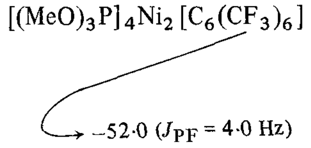
$(1,5\text{-}C_8H_{12})Ni[C_6(CF_3)_6]$

$\begin{cases} -52{\cdot}0 \text{ at } 30° \\ -51{\cdot}7 \text{ at } -90° \end{cases}$

[287]

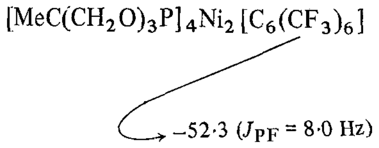
$(1,5\text{-}C_8N_{12})_2Ni_2[C_6(CF_3)_6]$

[288]



$[(MeO)_3P]_4Ni_2[C_6(CF_3)_6]$

[289]

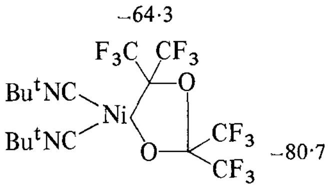


$[MeC(CH_2O)_3P]_4Ni_2[C_6(CF_3)_6]$

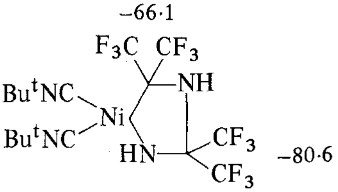
[290]

A plausible structure of [288], [289] and [290] is a fluxional system where the $L_2Ni–NiL_2$ system is free to rotate about an axis perpendicular to the plane of the ring and the Ni–Ni bond.

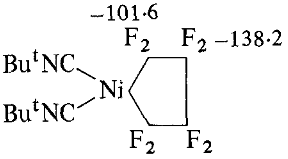
Reaction of $Ni(Bu^tNC)_4$ with $(CF_3)_2CO$ and $(CF_3)_2$ CNH affords [291] and [292]. (160) the reaction with C_2F_4 and $CF_2{=}CFCF{=}CF_2$ gave [293] and [294]. Using an excess of $(CN)_2C{=}C(CF_3)_2$ the reaction affords [295]. $(PhNC)_4Ni$ reacts with $(CF_3)_2CO$ to give [296]. (160) The corresponding 3-membered ring complexes with ligand L = Bu^tNC was also prepared, [297] and [298]. (15) Treatment of [297] with $(CF_3)_2CNH$ or treatment of [298] with $(CF_3)_2CO$ leads to a 3- to 5-membered ring expansion reaction and to the formation of a complex which is likely to have structure [299]. (160) Treatment of [296] with $(CF_3)_2CNH$ affords, on the contrary, the complex [300]. $(CF_3)_2CO$ reacts with $(Bu^tNC)_2N(O_2)$ (1:1 molar equivalent) to form [301]; with an excess of $(CF_3)_2CO$ one has yellow crystals of [302]. (160) [301] is unstable in diethyl ether and gives [303]. An investigation of the



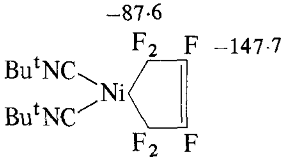
[291]



[292]



[293]



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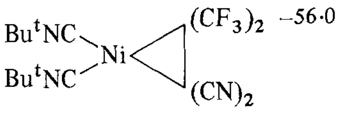

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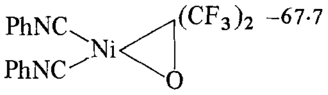
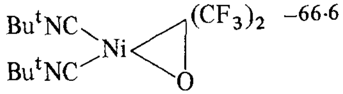
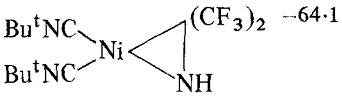


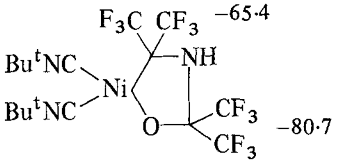
[296]



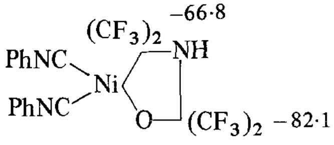
[297]



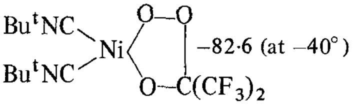
[298]



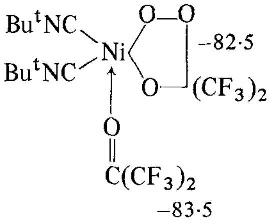
[299]



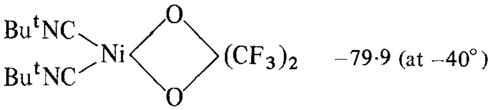
[300]



[301]



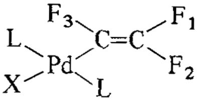
[302]



[303]

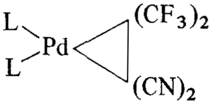
reactions of Pd(Bu^{t}NC)$_2$, Pd(AsMe$_2$Ph)$_4$, and Pd(PPh$_3$)$_4$ with CF$_2$=CFX (X = Cl, Br or CF$_3$) and (CF$_3$)$_2$C=X [X = O, NH or C(CN)$_2$] was performed. (161)

A series of new compounds [304] to [308] were characterized by ^{19}F NMR. (161) For [306] only one line (−61·7) was observed. As already discussed for related Pt and Ni complexes, this indicated either a change in the hybridization of the N atom on co-ordination to metal or the existence of a dynamic system (rapid inversion of the nitrogen atom). The CF$_3$ chemical shift values for [307] and [308]



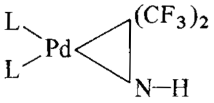
[304]

	L	X	F_1	F_2	F_3	J_{12}	J_{13}	J_{23}
(a)	Bu^tNC	Cl	−97·5	−126·1	−149·4	95·0	45·0	108·0
(b)	Bu^tNC	Br	−97·5	−115·9	−127·5	97·5	48·0	107·0
(c)	$AsMe_2Ph$	Cl	−94·2	−129·2	−151·9	105·0	43·0	108·0



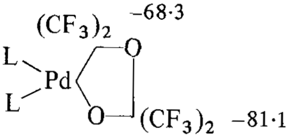
[305]

	L	CF_3	J^{PF}_{cis}	J^{PF}_{trans}
(a)	Bu^tNC	−54·1	–	–
(b)	$AsMe_2Ph$	−55·0	–	–
(c)	$P(OMe)_3$	−55·06	–	–
(d)	$PMePh_2$	−54·4	4·0	10·0
(e)	$P(Et)_3$	−54·2	2·0	11·0
(f)	$(Ph_2PCH_2)_2$	−54·5	5·0	11·0



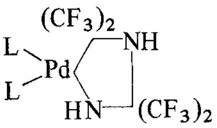
[306]

L	CF_3	J^{PF}_{cis}	J^{PF}_{trans}
PPh_3	−61·7	3·0	12·0



L = Bu^tN

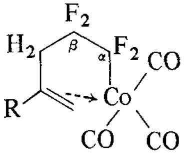
[307]



[308]

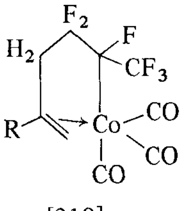
(a)	L = Bu^{t}NC	−65·7 (α · CF_3)	−80·5 (β · CF_3)	
(b)	L = AsMe$_2$Ph	−64·4 (α · CF_3)	−81·1 (β · CF_3)	$^4J^{FF}$ = 3·0 Hz.

suggest the illustrated head to tail linkage of the $(CF_3)_2C{=}X$ units in agreement with results of some related Ni-complexes. (157) The reactions of tricarbonyl (π-allyl) · Co complexes with fluoro-olefins and with hexafluorobut-2-yne were studied. (162) The fluoro-olefins insert themselves into the carbon-Co-σ-bonds of the allyl systems to give stable σ,π-fluoroalkyl cobalt tricarbonyl complexes ([309] to [312]). These compounds react with PPh_3 to form σ-bonded derivatives such as [313] and [314]. (162) UV irradiation of



[309]

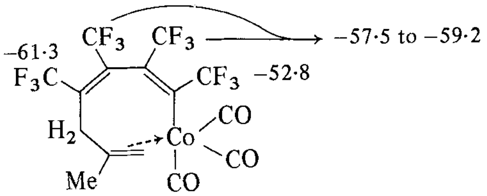
R = H	−73·2 (αCF_2)	−108·5 (βCF_2)
R = Me	−73·4 (αCF_2)	−107·4 (βCF_2)



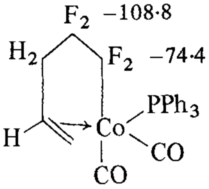
[310]

R = H −67·5 (CF_3) −161·7 ($-\overset{|}{\underset{|}{C}}F$) AB (β · CF_2) −96·7, −105·3, $^2J^{FF}$ = 240 Hz

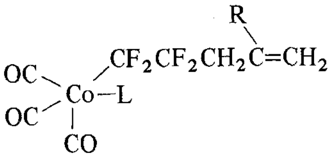
R = Me −67·6 (CF_3) −162·4 ($-\overset{|}{\underset{|}{C}}F$) AB (β · CF_2) −94·0, −106·7, $^2J^{FF}$ = 230 Hz



[311]

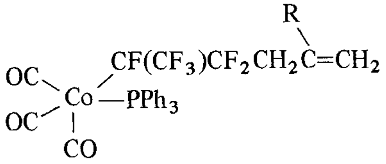


[312] J^{PF} = 33 Hz



[313]

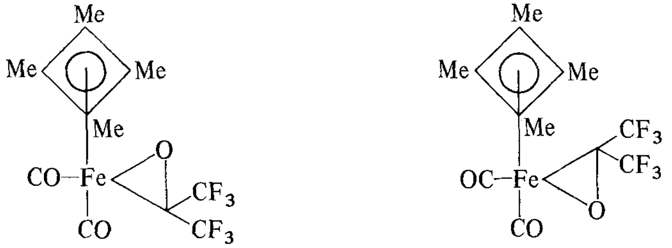
		$\alpha\cdot CF_2$	$\beta\cdot CF_2$	J^{PF}	J^{HF}
R = H	L = PPh_3	−51·1	−101·2	34	19
R = Me	L = PPh_3	−50·9	−100·7	29	19
R = Me	L = $AsPh_3$	−49·0	−100·5	—	19



[314]

	CF_3	$-\overset{\vert}{\underset{\vert}{C}}F$	$CF_2(AB)$
R = H	−65·7	−145·9	−76·0; −98·0; $^2J^{FF}$ = 270 Hz
R = Me	−66·4	−145·0	−76·5; −98·0; $^2J^{FF}$ = 260 Hz

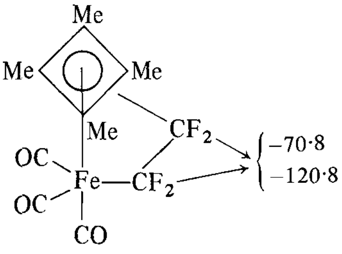
[Fe(CO$_3$$\pi$−C$_4Me_4$] with CF$_3$COCF$_3$ afforded $[\overline{\text{FeC(CF}_3)_2\text{O}}(\text{CO})_2$-$\pi$−C$_4Me_4$]; (163) ^{19}F NMR spectrum displays two singlets at −80·0 and −82·8 which are assigned to the two possible isomers [315]. The



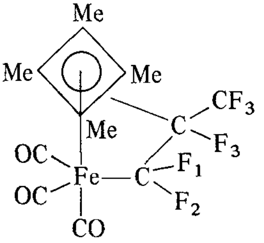
a b

[315]

corresponding reaction with fluoroolefins affords novel π-allylic complexes; (136) the reaction with CF$_2$=CF$_2$ gave [316]; the reaction with CF$_3$CF=CF$_2$ gave [317]. The reaction on irradiation



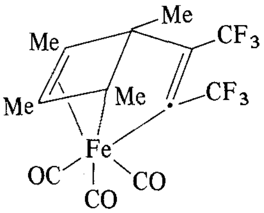
[316]



[317]

CF_3	−69·3	J_{12} = 240·0 Hz	$J(F_1{-}CF_3)$ = 3·0 Hz
F_1	−107·6	J_{13} = 12·0 Hz	$J(F_2{-}CF_3)$ = 17·0 Hz
F_2	−112·3		
F_3	−155·0	J_{23} = 6·0 Hz	$J(F_3{-}CF_3)$ = 12·0 Hz

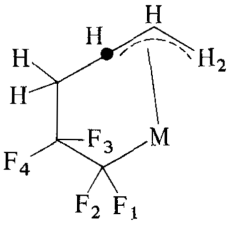
of $[Fe(CO)_3\pi{-}C_4Me_4]$ with $CF_3C{\equiv}CCF_3$ was also investigated; the compound obtained, on the basis of spectroscopic evidence, is likely to have structure [318]. (163)



−55·2 (quartet: J^{FF} = 18)
−55·4 (J^{FF} = 18; J^{FH} = 3·0)

[318]

Some reactions of fluoro-olefins with tricarbonyl (buta-1,3-diene, trimethylenemethane, or cinnanaldehyde) iron were reported. (164) UV irradiation of a hexane solution of C_2F_4 and buta-1,3-diene tricarbonyliron afforded high yields of a crystalline 1:1 adduct, [319]. The related reaction using $CF_3 \cdot CF{=}CF_2$ gave a similar 1:1 adduct. Reaction under UV irradiation of tricarbonyl (trimethylenemethane)iron with C_2F_4 gave the adduct [320] (164) In an attempt to obtain an insight into the mechanism of these reactions the



[319]

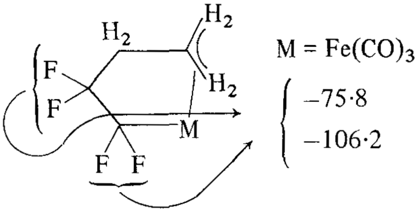
$M = Fe(CO)_3$

$F_1 - 108{\cdot}5$ $J_{12} = 222$ $J_{34} = 236$

$F_2 - 104{\cdot}5$ $J_{13} = 2{\cdot}0$ $J_{14} = J_{16} = 14{\cdot}0$

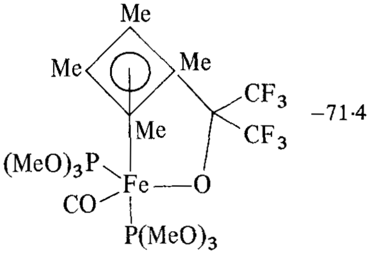
$F_3 - 87{\cdot}3$ $J_{23} = 8{\cdot}0$ $J_{24} = 1{\cdot}0$

$F_4 - 76{\cdot}8$ $J_{25} = 38{\cdot}0$



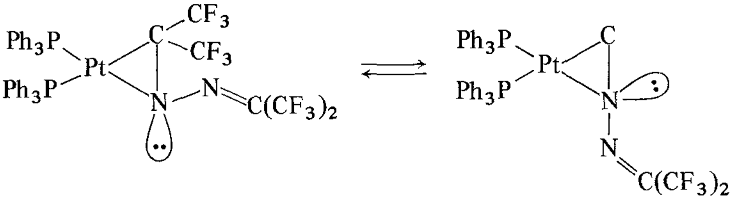
[320]

complex, $[\overline{\text{Fe C(CF}_3)_2\text{O}}\ (\text{CO})_2\pi\text{–C}_4\text{Me}_4]$, (163) was treated with trimethyl phosphite, leading to a similar linking reaction; (164) the adduct obtained was assigned the structure [321].



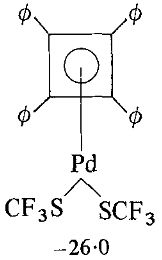
[321]

Bis(trifluoromethyl) diazomethane, $(CF_3)_2CN_2$, was shown to react with zerovalent Ni, Pd and Pt complex to give compounds having the general formula $L_2\overline{\text{MC(CF}_3)_2\text{N}}\text{–N : C(CF}_3)_2$. (165) NMR investigation indicated that these are all isostructural. A typical ^{19}F NMR spectrum is reported for $P(Ph_3)_2PtC(CF_3)_2NN : C(CF_3)_2$:– three resonances were observed at −59·5 ($2CF_3 : J_{P\text{-}F} = 10$ Hz, $J(\text{Pt–F}) = 79$ Hz), −63·5 ($1CF_3 : J(\text{F–F}) = 6{\cdot}0$ Hz, $J_{P\text{-}F} = 2{\cdot}5$ Hz, −65·8 ($1CF_3 : J(\text{F–F}) = 6{\cdot}0$ Hz, $J(\text{P–F}) = 6{\cdot}0$ Hz). NMR observations and chemical behaviour support the structure [322]. The ^{19}F

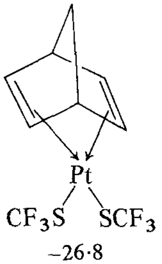


[322]

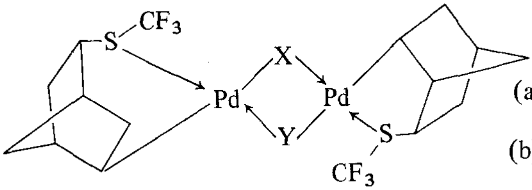
NMR spectrum of the above compound requires that, on the NMR time scale (even at −80°C), the CF_3 groups attached to the carbon adjacent to the platinum are in identical environments. (165) It is therefore necessary to postulate that in solution rapid inversion occurs at the nitrogen bonded to the platinum. The reactions of CF_3SAg with metal halides having olefinic ligands were described. (166) The work resulted in the preparation of the first compounds with two terminal CF_3S-groups attached to a single metal atom [323] and [324] as well as novel nortricyclic derivatives of the type $[(C_7H_8SCF_3)Pd]_2XY$ ([325]: X = Y = Cl and X = Cl, Y = CF_3S–).



[323]



[324]



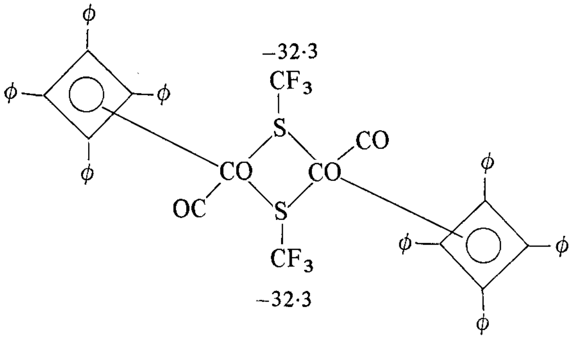
(a) X = Y = Cl(CF_3) −40 to −43

(b) X = Cl; Y = CF_3S $\begin{cases} 1 & -26 \\ 2 & -40 \text{ to } -43 \end{cases}$

[325]

(166) The resonance at *ca.* −26 is in the range associated with terminal CF_3S groups bonded to transition metals. Structure [325], on the contrary, has an unusual type of CF_3S group, which bridges between carbon and palladium atoms. This can justify the high

chemical shift observed (−40 to −43). A cobalt derivative, [326], was also prepared, $[(C_6H_5)_4C_4Co\text{-}(CO)SCF_3]_2$. (166)



[326]

The action of a number of ligands on $Pt(C_2F_4)(AsPh_3)_2$ was investigated. (167) It was found that phosphines displace triphenylarsine, to give air stable, white crystalline complex, $Pt(C_2F_4)(PR_3)_2$· α,α′-Bipyridyl, *o*-phenanthroline, and 5-methyl-*o*-phenanthroline similarly displace triphenylarsine to give complexes $Pt(C_2F_4)(N\text{-}N)_2$. All ^{19}F NMR spectra show satellites due to coupling with ^{195}Pt (I = 1/2, abundance 33%). The spectra of the phosphine derivatives give patterns typical of an $X_2AA'X_2'$ system. The results are in agreement with an essentially square planar arrangement of atoms around platinum. It is suggested that the high value of J(Pt–F) indicates a strong platinum-ethylene bond in the tetrafluoroethylene complex. ^{19}F NMR data obtained for the $Pt(C_2F_4)L_2$ complexes are collected in Table XLV. The zero valent

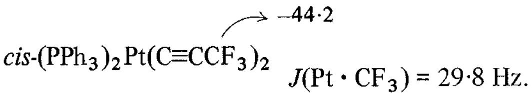
TABLE XLV

^{19}F NMR data for the complexes $Pt(C_2F_4)L_2$ (167)

L	δ_F	J(Pt–F) (Hz)
$H_2HCH_2CH_2NH_2$	−124·0	501
$\alpha_1\alpha^1$-bipy.	−124·9	494
o-phen.	−124·4	491
s-Me-*o*-phen.	−124·4	485
$AsPh_3$	−125·0	343
$Ph_2PCH_2CH_2PPh_2$	−129·2	316
PEt_2Ph	−130·1	290
PMe_2Ph	−131·3	286
$PMePh_2$	−130·7	284
PBu^n_3	−130·8	281
PPh_3	−130·5	278

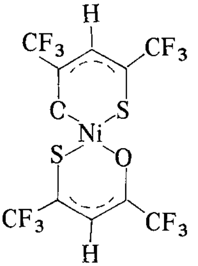
complex $Pt(AsPh_3)_2(PF_3)_2$ [$\delta_F = -10{\cdot}5, J^{PF} = 1337$ Hz] was also produced by action of PF_3 on the complex $Pt(C_2F_4)(AsPh_3)_2$. (167)

Reactions of some fluorinated acetylenes with tetrakis(triphenylphosphine) platinum(0) were investigated. The compound [327] was characterized by NMR. (168) The syntheses of

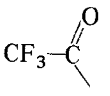

$$cis\text{-}(PPh_3)_2Pt(C{\equiv}C\overset{-44{\cdot}2}{CF_3})_2 \quad J(Pt \cdot CF_3) = 29{\cdot}8\ \text{Hz.}$$

[327]

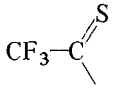
hexafluroro-monothioacetylacetone was described and the possibility of this compound giving stable chelate-complexes with metal ion was elucidated. (169). The ^{19}F NMR parameters of a Ni-complex, [328], were reported. (169)



[328]



$\delta = -73{\cdot}63$



$\delta = -63{\cdot}61$

V. FLUORINATED DERIVATIVES OF ELEMENTS

Boron

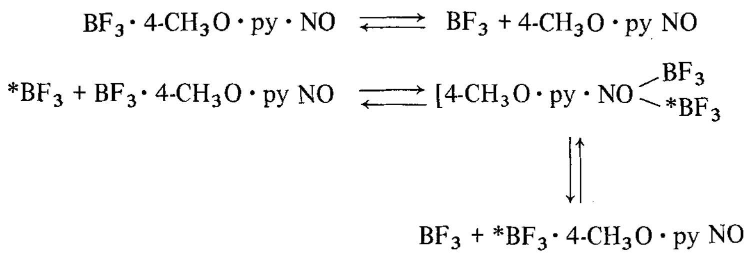
Choosing aromatic amine-oxides as ligands (where Z-pyNO, Z-QNO and Z-ANO represent the substituted pyridine-1-oxides, quinoline *N*-oxides, and acridine *N*-oxides respectively), some adducts of BF_3 were investigated especially the study of solvent and concentration effects on the chemical shifts and the variations in ^{11}B–^{19}F coupling due to differing donor basicity of ligands. (170) The ^{19}F NMR parameters of these adducts are collected in Table XLVI. The opinion is that the negative contribution to $J(^{11}B$–$^{19}F)$ decreases as the bond polarity increases. The examination of the trend of the absolute magnitude of $J(^{11}B$–$^{19}F)$ relative to the

TABLE XLVI

^{19}F NMR parameters for some substituted aromatic amine oxide adducts of BF_3 (170)

Z	$BF_3\cdot$ Z-py NO		$BF_3\cdot$ Z-Q NO		$BF_3\cdot$ Z-A NO	
	δ_F	$J(^{11}B-^{19}F)$	δ_F	$J(^{11}B-^{19}F)$	δ_F	$J(^{11}B-^{19}F)$
4-CH_3O	−154·3	5·0	−153·1	5·3		
4-CH_3	−153·7	4·5	−152·6	4·8		
4-H	−153·6	4·3	−152·7	4·6	−149·8	5·5
4-Cl	−153·8	4·3	−152·9	4·1		
4-$CH_3OC(O)$	−153·6	3·8	–	–		
4-CN	−153·5	3·5	−152·6	3·4		
4-NO_2	−153·5	3·3	−152·6	3·3		
2-CH_3	−152·5	4·7				
2-Et	−152·1	4·5				
2,4-$(CH_3)_2$	−152·5	5·2				
2,6-$(CH_3)_2$	−149·1	4·9				
3,6-$(CH_3)_2$	−153·7	4·6				

basicity of the donor molecule suggests that this coupling should be negative. The same conclusion may be reached considering the hybridization of the boron when complexed. It also appears that the chemical shifts reflect the bulky nature of the ligand, and its interaction with the fluorine NMR spectra, in addition, appeared to be temperature dependent. (170) Rapid fluorine exchange among the boron atoms is occurring since there is a collapse of the quartet at high temperature (^{11}B, $I = 3/2$). A possible mechanism, [329], involving a 1-oxide bridge is proposed. (170)



$$BF_3\cdot 4\text{-}CH_3O\cdot py\cdot NO \rightleftharpoons BF_3 + 4\text{-}CH_3O\cdot py\ NO$$

$$\begin{aligned} {}^*BF_3 + BF_3\cdot 4\text{-}CH_3O\cdot py\ NO &\rightleftharpoons \left[4\text{-}CH_3O\cdot py\cdot NO\begin{smallmatrix}\nearrow BF_3\\ \searrow {}^*BF_3\end{smallmatrix}\right. \\ &\qquad\qquad \updownarrow \\ &\qquad BF_3 + {}^*BF_3\cdot 4\text{-}CH_3O\cdot py\ NO \end{aligned}$$

[329]

The formation and the stereochemistry of Borane adducts of a series of methylhydrazines and of trifluoromethylphosphinehydrazines were studied using mainly NMR techniques. (171) The fluorine NMR data are collected in Tables XLVII and XLVIII respectively.

TABLE XLVII

^{19}F NMR data for the BF_3 adducts with hydrazines (171)

	BF_3	J_{BF}
$MeNH\cdot NH_2\cdot BF_3$	−151·6	17
$BF_3\cdot NH(Me)\cdot NH_2$	−159·2	15·1
BF_4^-	−149·3	–
$Me_2N\cdot NH_2\cdot BF_3$	−166·9	13·5
$Me_2N\cdot NHMe\cdot BF_3$	−162·7	14·2
$Me_2N\cdot NMe_2\cdot BF_3$	−151·1	–

TABLE XLVIII

^{19}F NMR data for trifluoromethylphosphinohydrazines and their BX_3 adducts (171)

		CF_3	BF_3	$J_{P,F}$
$(CF_3)_2PNMe\cdot NM_2$		−63	–	82
$(CF_3)_2PNMe\cdot NM_2$	$\cdot BMe_3$	−61·5	–	85·5
$(CF_3)_2PNMe\cdot NM_2$	$\cdot BF_3$	−59·6	−153·4	88·5
$(CF_3)_2PNMe\cdot NM_2$	$\cdot BCl_3$	−58·1	–	93·3
$(CF_3)_2PNH\cdot NMe_2$		−63·5	–	84·0
$(CF_3)_2PNH\cdot NMe_2$	$\cdot BMe_3$	−65·0	–	83·0
$(CF_3)_2PNH\cdot NMe_2$	$\cdot BF_3$	−63·7	−163·4	–
$(CF_3)_2PNH\cdot NMe_2$	$\cdot BCl_3$	−62·7	–	89·0
$(CF_3)_2PNMe\cdot NH_2$		−60·6	–	84·3
$(CF_3)_2PNMe\cdot NH_2$	$\cdot BMe_3$	−60·6	–	83·7
$(CF_3)_2PNMe\cdot NH_2$	$\cdot BF_3$	−59·8	–	89·5
$(CF_3)_2PNH\cdot NHMe$		−63·8	–	80·0
$(CF_3)_2PNH\cdot NHMe$	$\cdot BMe_3$	−63·5	–	82·7
$(CF_3)_2PNH\cdot NHMe$	$\cdot BF_3$	−62·9	−159·0	86·5

Nonoctahedral clathro-chelate complexes, $[M(P_{cc}BF)]BF_4$ with M = Fe, Co, Ni, Zn and $P_{cc} = C_{18}H_{12}N_6O_3$, were synthesized from tris(2-aldoximo-6-pyridyl)phosphine and boron trifluoride or tetrafluoroborate. (172) The ^{19}F NMR data are reported in Table XLIX. A study of the ^{19}F NMR spectra of complexes formed by BF_3 with several aliphatic and aromatic ethers was performed showing that the ^{19}F chemical shifts may serve as a measure of the complexing power of the ethers and that information on the nature of the donor-acceptor bond may be gained. (173)

Addition of fluoride ion to aqueous solutions containing Al salts and phosphoric acid resulted in the formation of eight new fluorophosphato-aluminium complexes containing direct Al–F bonds,

TABLE XLIX

^{19}F NMR data of [M(P$_{cc}$BF)]BF$_4$ (172)

	Chemical shift	
M	B–F	BF_4^-
Fe	−166·7 (13)^a	−150·6
Co	−133·8	−148·2
Ni	−240·4	−144·4
Zn	−167·1 (12)^a	−150·9

^{a} In parentheses: $J(^{11}B \cdot F)$ values.
$P_{cc} = C_{18}H_{12}N_6O_3$.

(174) in addition to the known binary complexes $AlF^{(3-n)\oplus}$. ^{19}F NMR at room temperature showed a sharp peak due to $AlF_2^{\oplus}$ and $AlF^{2\oplus}$ and a very broad high-frequency peak. At −130° the spectrum was resolved into eleven peaks, three of which were assigned to $AlF^{2\oplus}$, $AlF_2^{\oplus}$ and to exchanging $AlF_n^{(3-n)\oplus}$ (n = 3 to 6), $F^{\ominus}$, HF and HF_2. The remaining eight peaks were assigned to complexes containing both fluorine and phosphorus. The ^{19}F shifts were given respect to $BF_3 \cdot OEt_2$ (−153·0). $AlF_2^{\oplus}$ and $AlF^{2\oplus}$ resonate at −154·6 and 155·65 respectively. The eight new peaks resonate in the range −141·8 to −153·0. (174)

In the study of system $(CH_3)_3P/BF_3$ the fluorine spectrum of a mixture of the two components in the ratio 1:1 was recorded. A broad signal (*ca.* 500 Hz half width) was observed at −138 ppm. (174b)

Silicon

Several halogenodisilanes (Table L) were identified as products coming out from the action of an ozoniser-type silent-electric discharge on fluoro-, chloro- and bromo- monosilanes. (175) Two new fluorodisilanes, $SiH_2F \,.\, SiH_2F$ and $SiHF_2 \cdot SiHF_2$ were prepared. (175) Their NMR spectra are of interest because, in contrast to the corresponding chloro- and bromo- derivatives, these are not first order, but of type $X_2AA'X_2'$; their spectra were analysed by trial and error calculations assuming $J_{XX} = 0$ (this assumption is, however, not valid for $SiHF_2 \cdot SiHF_2$). Some fluorochloro-, and fluorobromo- trisilanes were also described. (176) The ^{19}F NMR spectra were useful to define the structure of $SiH_3 \cdot SiH_2 \cdot SiH_2F$, $SiH_3 \cdot SiH_2 \cdot SiHF_2$ and $SiH_3 \cdot SiH_2 \cdot SiF_3$. (176) No ^{19}F chemical shifts were given. The $SiHF_2$-resonance is a doublet ($^2J^{HF}$ = 53·2

TABLE L

^{19}F NMR parameters of some fluorinated disilanes (175)

	δ_{SiF}	J_g^{HF}	$J_{vic.}^{HF}$	$J_{vic.}^{FF}$	$J(Si \cdot F)$
$SiH_3 \cdot SiHF_2$	−142·0	53·0	6·0	–	–
$SiH_3 \cdot SiF_3$	−120·3	–	6·0	–	356
$SiH_2F \cdot SiH_2F$	?	45·0	7·0	5·0	–
$SiHF_2 \cdot SiHF_2$	−152	52·0	9·0	8·0	–
$SiH_3 \cdot SiHClF$	−159	51·5	5·8	–	–

Hz) of triplets ($^3J^{HF}_{vic}$ = 6·2 Hz). The triplets are further split into quartets from long-range coupling, ^4J(HSiSiSiF) = *ca.* 1 Hz. The $-SiF_3$ resonance is a triplet (J^{HF}_{vic} = 4·9 Hz) of quartets (^3J(HSi · Si · Si · F) = 0·9 Hz). The analyses of the difluoro- and trifluoro- trisilane derivatives were done by trial and error calculations using the first part of LAOCOO NII. (176) CF_3SiCF_3, [330], was obtained in high yield and its salient properties determined. (177) Some monofluoro halosilanes, [331] to [335], were also prepared and characterized by ^{19}F NMR. (178) The fluorine spectra consist of singlets with ^{29}Si satellites. Increasing the electronegativity of substituents the signals are shifted to lower frequency and the $J(^{29}Si–F)$ value decreases. (178) By reaction of xenon difluoride with organosilicon compounds some new compounds, [336] to [340], were identified by their characteristic ^{19}F NMR spectra. (179)

$$\overset{-66\cdot3}{CF_3}\overset{-150\cdot7}{SiF_3}\quad\left\{\begin{array}{l} J(F–F) = 10\cdot9\ \text{Hz}\\ J(Si–F) = 273\cdot2\ \text{Hz}\\ J(Si–CF) = 72\cdot2\ \text{Hz}\end{array}\right.\qquad [330]$$

	δ_F	$J(^{29}Si–F)$ (Hz)
[335] $SiFClI_2$	−70·0	401
[331] $SiFClBr$	−74·5	380
[332] $SiFBr_3$	−76·5	365
[333] $SiFClBr_2$	−81·5	351
[334] $SiFCl_2Br$	−87·0	332

The NMR spectra of some fluorosilyl amines, of the type $F_3Si–$ and $-SiF_2-$, were also reported. (180) The chemical shifts, δ_F, are all in the range −148 to −157 and the $J(^{29}Si–F)$ values near to 202 to 219

$\overset{-159}{(CH_3)_2C_6H_5SiF}$ $J(F \cdot CH_3) = 7{\cdot}5$ Hz

[336]

$\overset{-139}{CH_3(CH_2Cl)SiF_2}$

[337]

$\overset{-164}{C_6H_5(CH_3)(CH_2Cl)SiF}$

[338]

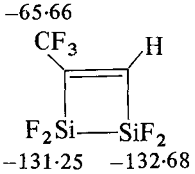
$\overset{-136}{CH_3(C_6H_5)SiF_2}$

[339]

$\overset{-170{\cdot}8}{CH_3(C_6H_5)SiHF}$ $\begin{cases} {}^2J(FSiH) = 58 \text{ Hz} \\ J(F \cdot CH_3) = 8 \text{ Hz} \end{cases}$

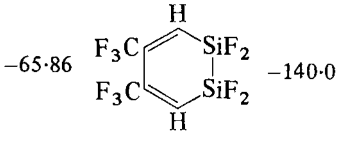
[340]

Hz. (180) The results of the reaction between SiF_2 and trifluoropropyne were reported. (181) Two products were isolated with formulae $C_3HSi_2F_7$ and $C_6H_2Si_2F_{10}$. Spectroscopic investigations are in agreement with the structure [341] and [342]



[341]

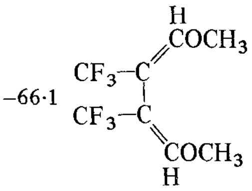
$J(CF_3 \cdot H) = 1{\cdot}6$ Hz
$J(CF_3SiF_2) = 2{\cdot}4$ Hz
$J(HSiF_2) = 16{\cdot}5$ Hz
$J(CF_3 \cdot Si \cdot SiF_2) = 0{\cdot}8$ Hz
$J(H \cdot Si \cdot SiF_2) = 1{\cdot}6$ Hz



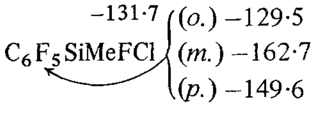
[342]

$J(CF_3 \cdot H) = 0{\cdot}5$ Hz
$J(CF_3 \cdot SiF_2) = 0{\cdot}6$ Hz

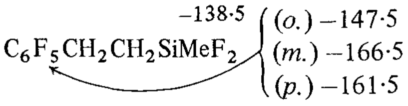
respectively. (181) When [342] was treated with CH_3OH/KOH solutions, compound [343] was obtained. (181) The preparation of some pentafluorophenyl- and 2-(pentafluorophenyl) ethyl- derivatives of silicon and of the corresponding polymers were described. (182) Only the compounds shown in [344] to [346] were characterized by ^{19}F NMR spectroscopy.



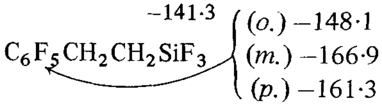
[343]



[344]



[345]



[346]

Nitrogen

The reactions of $(CF_3)_2$ NBr with *cis* and *trans* but-2-ene and of $(CF_3)_2NCl$ with *trans*-but-2-ene in the dark at low temperature were investigated in order to determine whether reaction under such conditions proceeds via ionic intermediates (expected *trans*-addition), by a four-centre mechanism (expected *cis*-addition), or by a mixed mechanism. (183) After 3 days in the dark at −78°C, *trans*-addition products, [347] and [348], were obtained, showing that the reaction proceeds via ionic intermediates. The determination of the configurations of [347] and [348] is based

$$(CF_3)_2N\cdot CHMe\cdot CHMeBr\begin{cases}\textit{threo}\cdot\text{isomer} & -55{\cdot}0\\ \textit{erythro}\cdot\text{isomer} & -55{\cdot}5\end{cases}$$

[347]

$$(CF_3)_2N\cdot CHMe\cdot CHMeCl\begin{cases}\textit{threo}\text{-isomer} & -54{\cdot}7\\ \textit{erythro}\text{-isomer} & -55{\cdot}0\end{cases}$$

[348]

on proton NMR evidence. Dehydrobromination of [347] gave *cis*- and *trans*- olefin, [349]. (183) These olefins, together with other *N,N'*-bistrifluoromethylvinylamine derivatives, are shown in [349] to [351]. The reactions of $(CF_3)_2NCl$ with propene and vinyl fluoride

$$(CF_3)_2NC(CH_3){=}C(H)CH_3 \begin{cases} cis & -56{\cdot}9 \\ trans & -57{\cdot}4 \end{cases}$$

[349]

$$(CF_3)_2NC(H){=}C(H)CH_3 \begin{cases} cis & -60{\cdot}4 \\ trans & -59{\cdot}8 \end{cases}$$

[350]

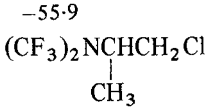
$$(CF_3)_2NC(CH_3){=}CH_2 \qquad -58{\cdot}1$$

[351]

and of $(CF_3)_2NI$ with vinylfluoride, carried out under ionic conditions, were also investigated. (184) The series of compounds shown in [352] to [357] was prepared and characterized. (184) *N*-

$$\overset{-55{\cdot}4}{(CF_3)_2}NCH_2CHClMe$$

[352]



$$\overset{-55{\cdot}9}{(CF_3)_2}N\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Cl$$

[353]

$$\overset{-59{\cdot}8}{(CF_3)_2}NCH_2\overset{-145{\cdot}6}{CHFCl} \begin{cases} {}^4J(CF_3\cdot H) = 1{\cdot}2\ Hz \\ {}^4J'(CF_3\cdot H) = 1{\cdot}6\ Hz \\ {}^5J(CF_3\cdot H) = 0{\cdot}5\ Hz \end{cases} \qquad \begin{matrix} {}^3J_{HF} = 10{\cdot}1\ Hz \\ {}^3J'_{HF} = 25{\cdot}7\ Hz \end{matrix}$$

[354]

$$\overset{-56{\cdot}9}{(CF_3)_2N}\cdot\overset{-148{\cdot}8}{CHF}\cdot CH_2Cl$$

[355]

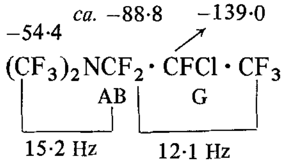
$$\overset{-562}{(CF_3)_2N}\cdot\overset{-138{\cdot}3}{CHF}\cdot CH_2I$$

[356]

$$\overset{-59{\cdot}9}{(CF_3)_2N}\overset{-83{\cdot}5}{CF}{=}CH_2 \begin{cases} {}^3J\ trans\ (H{-}F) = 30{\cdot}5\ Hz \\ {}^3J\ cis\ (H{-}F) = 4{\cdot}9\ Hz \\ J(CF_3{-}F) = 2{\cdot}5\ Hz \end{cases}$$

[357]

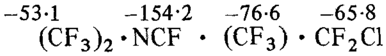
Halogenoamines, in particular $(CF_3)_2NCl$ and $(CF_3)_2NI$, were also made to react, under free-radical conditions, with olefins such as hexafluoropropene, trifluoroethylene and vinylfluoride. (185) The reaction with hexafluoropropene gave [358], [359] and [360]. The reaction with trifluoroethylene gave a series of adducts, the ^{19}F



$(CF_3)_2NCF_2 \cdot CFCl \cdot CF_3$

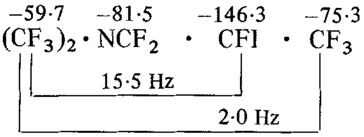
$J_{AG} = 10{\cdot}0$ Hz
$J_{BG} = 2{\cdot}4$ Hz

[358]



$(CF_3)_2 \cdot NCF \cdot (CF_3) \cdot CF_2Cl$

[359]



$(CF_3)_2 \cdot NCF_2 \cdot CFI \cdot CF_3$

[360]

NMR parameters of which are collected in Table LI. The reaction with vinyl fluoride gave, on the contrary, another series of adducts, which are shown in Table LII. ClF was found to add to $>C{=}NF$

TABLE LI

^{19}F NMR parameters of the trifluoroethylene adducts, Y-CF_2CFH–Z [361] (185)

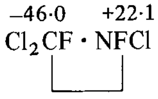
Y	Z	δ_{CF_2}	δ_{CHF}	δ_Y	δ_Z	$^2J_{FF}$	$^2J_{HF}$
Cl	$(CF_3)_2N$	−68·2	−167·0	–	−57·3	172	42·4
Br	$(CF_3)_2N$	−62·8	−165·5	–	−56·7	–	–
I	$(CF_3)_2N$	−54·7	−163·1	–	−56·6	*ca.* 200	42·1
$(CF_3)_2N$	Cl	−97·1	−156·2	−54·3	–	*ca.* 240	47·8
$(CF_3)_2N$	Br	−94·0	−157·3	−56·5	–	229	47·7
$(CF_3)_2N$	I	−90·1	−167·1	−56·6	–	*ca.* 240	47·5

TABLE LII

^{19}F NMR parameters of the vinyl fluoride adducts, Y-CF_2CHF–Z [362] (185)

Y	Z	δ_{CHF}	$\delta_{(CF_3)_2N}$	$^2J_{HF}$
Cl	Cl	−139·0	–	50·4
$(CF_3)_2N$	Cl	−145·6	−59·8	52·0
$(CF_3)_2N$	Br	−147·9	−59·4	51·8
$(CF_3)_2N$	I	−155·4	−58·3	51·6
Cl	$N(CF_3)_2$	−148·8	−56·9	46·3
Br	$N(CF_3)_2$	−144·5	−56·9	46·6
I	$N(CF_3)_2$	−138·3	−56·2	46·8

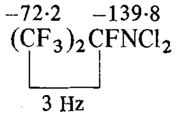
imines when the carbon substituents are chlorine or fluorine. (186) In some cases, when CF_3 is bonded to the imine carbon, caesium fluoride is required to catalyse the reaction. The compounds shown in [363] to [368] were obtained and then characterized by ^{19}F



$$\overset{-46\cdot0}{\mathrm{Cl_2CF}}\cdot\overset{+22\cdot1}{\mathrm{NFCl}}$$

28 Hz

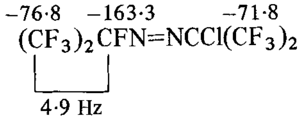
[363]



$$\overset{-72\cdot2}{\mathrm{(CF_3)_2}}\overset{-139\cdot8}{\mathrm{CFNCl_2}}$$

3 Hz

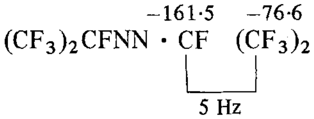
[364]



$$\overset{-76\cdot8}{\mathrm{(CF_3)_2}}\overset{-163\cdot3}{\mathrm{CFN{=}NCCl}}\overset{-71\cdot8}{\mathrm{(CF_3)_2}}$$

4·9 Hz

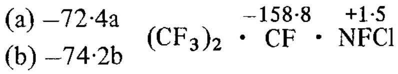
[365]



$$\mathrm{(CF_3)_2CFNN}\cdot\overset{-161\cdot5}{\mathrm{CF}}\ \overset{-76\cdot6}{\mathrm{(CF_3)_2}}$$

5 Hz

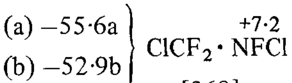
[366]



$$\begin{matrix}(a)\ -72\cdot4a\\(b)\ -74\cdot2b\end{matrix}\ \mathrm{(CF_3)_2}\cdot\overset{-158\cdot8}{\mathrm{CF}}\cdot\overset{+1\cdot5}{\mathrm{NFCl}}$$

[367]

at −40°
$J(CF_3{}^a\cdot NF) = 24\cdot1$ Hz
$J(CF_3{}^b\cdot NF) = 9\cdot7$ Hz
$J(CF_3{}^a\cdot CF) = 2\cdot8$ Hz
$J(CF_3{}^b\cdot CF) = 3\cdot8$ Hz
$J(CF_3{}^a\cdot CF_3{}^b) = 9\cdot4$ Hz

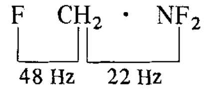


$$\left.\begin{matrix}(a)\ -55\cdot6a\\(b)\ -52\cdot9b\end{matrix}\right\}\ \mathrm{ClCF_2}\cdot\overset{+7\cdot2}{\mathrm{NFCl}}$$

[368]

$J(CF^a\cdot NF) = 24$ Hz
$J(CF^b\cdot NF) = 13$ Hz
$J(CF^a\cdot CF^b) = 128$ Hz

NMR. The imine $NF{=}CCl_2$ gave a single broad peak at +57·3. (186) The coalescence temperature for the two CF_3 resonances of [367] is at *ca.* +60°C. The two $\rangle$CF-resonances of [368] still do not coalesce at +100°C. From photodifluoroamination of fluoromethane, which contrasts dramatically with that of methane, one of the products was $FCH_2\cdot NF_2$, [369]. (187) An improved synthesis of perfluorourea, $F_2NC(O)NF_2$, was reported. (188)

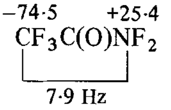


$$\overset{-202\cdot8}{\mathrm{F}}\ \mathrm{CH_2}\cdot\overset{+27\cdot6}{\mathrm{NF_2}}$$

48 Hz 22 Hz

[369]

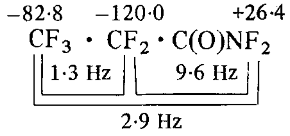
A 20% solution in $CFCl_3$ yields a broad resonance at +33·4, with no indication of splitting arising from nitrogen. (188) The reaction of $HNF_2 \cdot KF$ molecular complex with various fluorinated acyl fluorides gave a new class of compounds, $RfC(O)NF_2$. (189) These fluorinated amides, as well as the ester $CF_3CO_2C(NF_2)CF_3$, were characterized by ^{19}F NMR; the compounds reported are shown in [370] to [374]. The NMR spectra are all typically first order except that of [374], which is rather complex. The reaction of bis-trifluoromethyl nitroxide radical, $(CF_3)_2NO\cdot$, with N_4S_4 and with some of its derivatives was studied. (190) For example: sulphamuric bis-trifluoromethyl nitroxide, $N_3S_3O_3[ON(CF_3)_2]_3$, was obtained from $(CF_3)_2NO\cdot$ and $S_3N_2O_2$; a singlet (−69·3) is observed corresponding to the *cis*-form, which slowly isomerizes to the *trans* form (−68·1); thiazyl bis-trifluoromethyl nitroxide, $NSON(CF_3)_2$, obtained from reaction of $Hg[ON(CF_3)_2]_2$ with NSF, displays a singlet at −69·4. (190) Reactions of $(CF_3)_2NO$ with acetylene, 3,3,3-trifluoropropyne, perfluoropropyne, perfluorobut-2-yne, perfluorodiphenylacetylene and glyoxal (191) were also investigated as well as reactions of $(CF_3)_2NO\cdot$ with some alkanes and alkenes. (192) Several compounds obtained by these reactions were characterized by ^{19}F NMR. The NMR spectral data of some previously unreported compounds are shown in [375] to [397]. (191, 192)



$\overset{-74\cdot5}{CF_3}C(O)\overset{+25\cdot4}{NF_2}$

7·9 Hz

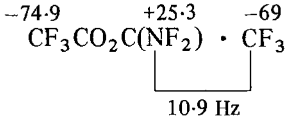
[370]



$\overset{-82\cdot8}{CF_3}\cdot\overset{-120\cdot0}{CF_2}\cdot C(O)\overset{+26\cdot4}{NF_2}$

1·3 Hz, 9·6 Hz, 2·9 Hz

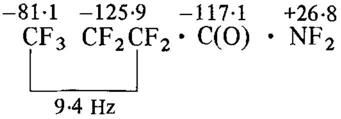
[371]



$\overset{-74\cdot9}{CF_3}CO_2C(\overset{+25\cdot3}{NF_2})\cdot\overset{-69}{CF_3}$

10·9 Hz

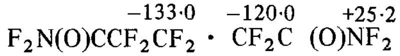
[372]



$\overset{-81\cdot1}{CF_3}\ \overset{-125\cdot9}{CF_2}\overset{-117\cdot1}{CF_2}\cdot C(O)\cdot\overset{+26\cdot8}{NF_2}$

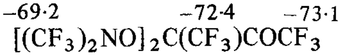
9·4 Hz

[373]



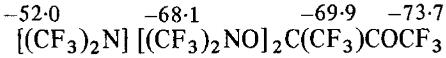
$F_2N(O)CCF_2\overset{-133\cdot0}{CF_2}\cdot\overset{-120\cdot0}{CF_2}C\ (O)\overset{+25\cdot2}{NF_2}$

[374]



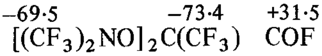
$\overset{-69{\cdot}2}{[(CF_3)_2NO]_2}C\overset{-72{\cdot}4}{(CF_3)}CO\overset{-73{\cdot}1}{CF_3}$

[375]



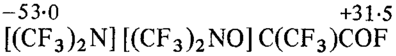
$\overset{-52{\cdot}0}{[(CF_3)_2N]}\ \overset{-68{\cdot}1}{[(CF_3)_2NO]_2}C\overset{-69{\cdot}9}{(CF_3)}CO\overset{-73{\cdot}7}{CF_3}$

[376]



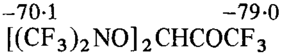
$\overset{-69{\cdot}5}{[(CF_3)_2NO]_2}C\overset{-73{\cdot}4}{(CF_3)}\ \overset{+31{\cdot}5}{COF}$

[377]



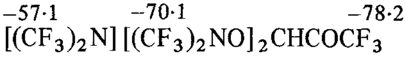
$\overset{-53{\cdot}0}{[(CF_3)_2N]}\ [(CF_3)_2NO]\,C(CF_3)\overset{+31{\cdot}5}{COF}$

[378]



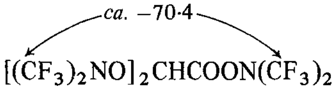
$\overset{-70{\cdot}1}{[(CF_3)_2NO]_2}CHCO\overset{-79{\cdot}0}{CF_3}$

[379]



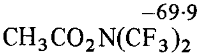
$\overset{-57{\cdot}1}{[(CF_3)_2N]}\ \overset{-70{\cdot}1}{[(CF_3)_2NO]_2}CHCO\overset{-78{\cdot}2}{CF_3}$

[380]



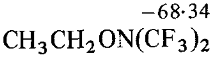
$\overset{ca.\ -70{\cdot}4}{[(CF_3)_2NO]_2CHCOON(CF_3)_2}$

[381]



$CH_3CO_2N\overset{-69{\cdot}9}{(CF_3)_2}$

[382]



$CH_3CH_2ON\overset{-68{\cdot}34}{(CF_3)_2}$

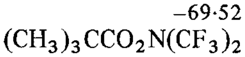
[383]

$(CH_3)_2CHON\overset{-69{\cdot}72}{(CF_3)_2}$

[384]

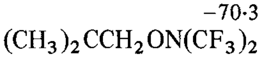
$(CH_3)_3CON\overset{-67{\cdot}84}{(CF_3)_2}$

[385]



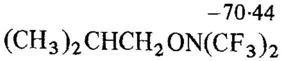
$(CH_3)_3CCO_2N\overset{-69{\cdot}52}{(CF_3)_2}$

[386]



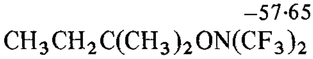
$(CH_3)_2CCH_2ON\overset{-70{\cdot}3}{(CF_3)_2}$

[387]



$(CH_3)_2CHCH_2ON\overset{-70{\cdot}44}{(CF_3)_2}$

[388]

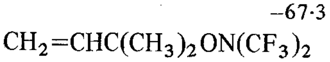


$CH_3CH_2C(CH_3)_2ON\overset{-57{\cdot}65}{(CF_3)_2}$

[389]

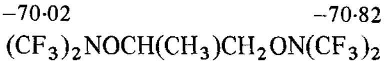
$(CH_3)_2C{=}CHCH_2ON\overset{-70{\cdot}12}{(CF_3)_2}$

[390]



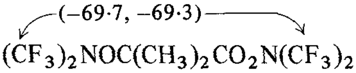
$CH_2{=}CHC(CH_3)_2ON\overset{-67{\cdot}3}{(CF_3)_2}$

[391]



$\overset{-70{\cdot}02}{(CF_3)_2}NOCH(CH_3)CH_2ON\overset{-70{\cdot}82}{(CF_3)_2}$

[392]



$\overset{(-69{\cdot}7,\ -69{\cdot}3)}{(CF_3)_2NOC(CH_3)_2CO_2N(CF_3)_2}$

[393]

−58·4 −70·4
$(CF_3)_2NOC(CH_3)_2CH_2ON(CF_3)_2$
[394]

−70·5 −68·5
$(CF_3)_2NOCH_2CH_2C(Et)(CH_3)ON(CF_3)_2$
[395]

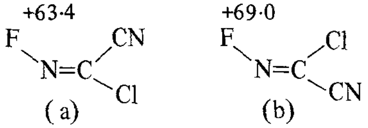
−58·1 −58·9
$(CF_3)_2NOC(CH_3)_2CH(CH_3)ON(CF_3)_2$
[396]

−67·5
$(CF_3)_2NOC(CH_3)_2C(CH_3)_2ON(CF_3)_2$
[397]

Difluoroamidosulphurylchloride, [398], dichlorocyano difluoroaminomethane, [399], and two imine isomers, [400], were prepared.

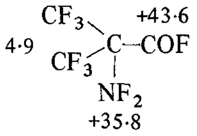
+55·2
NF_2SO_2Cl
[398]

+48·3
NF_2CCl_2CN
[399]



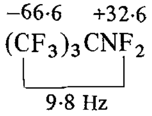
[400]

(193) The assignment of the configurations of the two imine isomers, [400], was made by comparison with other similar compounds. Some perfluorinated *N*-fluoroimines of the type: RfRf′C=NF, RfCF=NF and RfC(CN)=NF were studied. (194) These compounds were prepared and their reactions with some nucleophiles (amines, alcohols, water, diazomethane) leading to fluorinated diaziridines, *N*-fluoro imino-acids and their derivatives, *gem*-alkoxy-*N*-fluoroamines and *N*-fluoroethyleneimines, were investigated. (194) Many of these compounds are shown in [401] to [421]. The ^{19}F NMR data of



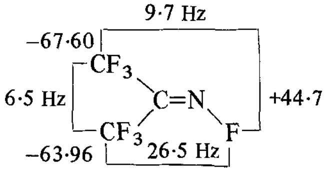
$J(CF_3 \cdot NF_2) = 12{\cdot}9$ Hz
$J(CF_3 \cdot COF) = 8{\cdot}9$ Hz

[401]



$(CF_3)_3CNF_2$

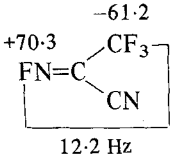
[402]



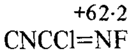
[403]

(a) (b)

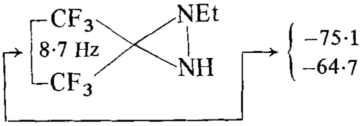
[404]



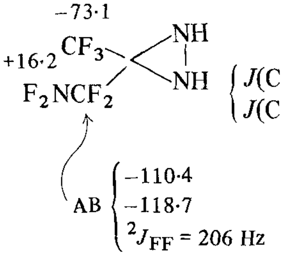
[405]


$\overset{+62\cdot2}{\mathrm{CNCCl{=}NF}}$

[406]

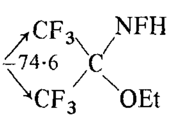


[407]



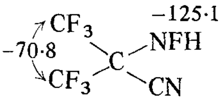
$J(CF_3 \cdot F_A = 5\cdot6$ Hz
$J(CF_3 \cdot F_B = 4\cdot8$ Hz

[408]



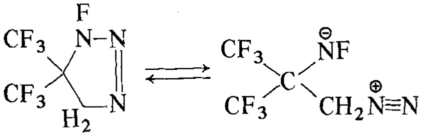
$J_{FA} = 50\cdot7$ Hz
$J(CF_3 \cdot NF) = 11\cdot6$ Hz

[409]

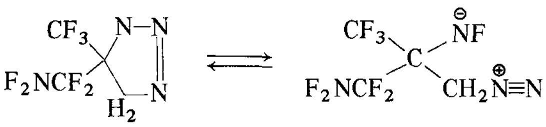


$^2J_{HF} = 45\cdot6$ Hz
$^4J(NF \cdot CF_3) = 10\cdot5$

[410]

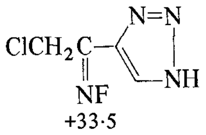


[411]
CF_3: −70·7
NF: −37·2

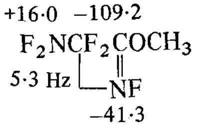


[412]

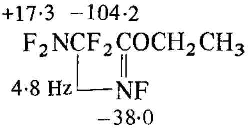
CF_3: −71·3
CF_2: −111·1
NF: −37·7
NF_2: +14·3



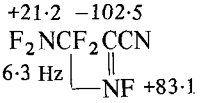
[413]



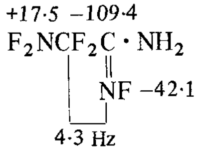
[414]



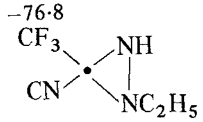
[415]



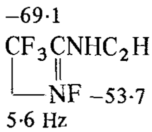
[416]



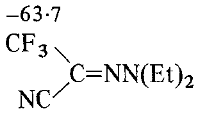
[417]



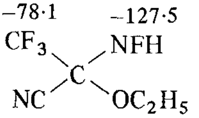
[418]



[419]



[420]

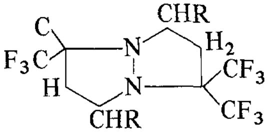


[421]

$^2J_{FH} = 49{\cdot}3$
$^4J(CF_3 \cdot F) = 12{\cdot}0$

$F_2NCF_2CF{=}NF$ and $CF_3CF{=}NF$ and of their hydrolysis products, on the contrary, are collected in Table LIII. (194)

The thermal and photochemical reaction of hexafluoroacetone-azine, $(CF_3)_2C{=}NN{=}C(CF_3)_2$, with three olefins, ethylene, propene and but-1-ene, gave in each case 2 : 1 olefin: azine adducts as the major products, (195) which were found to have the structure of 1,5-diazabicyclo[3.3.0)octanes, [422]. Acetylene reacted only



R = H, $-CH_3$, $-CH_2CH_3$
(a) (b) (c)

[422]

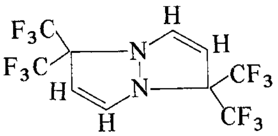
TABLE LIII

^{19}F NMR parameters of $F_2NCF_2CF{=}NF$ and $CF_3CF{=}NF$ and their hydrolysis products (194)

	CF_3	CF_2	CF	NF	NF_2
$F_2NCF_2CF{=}NF$	–	−108·0	−76·4	−12·6	+20·7
$F_2NCF_2C(OH){=}NF$	–	−111·4	–	−45·8[a]	+15·5
$F_2NCF_2C(OCH_3){=}NF$	–	−109·8	–	−41·3	+15·9
$F_2NCF_2CO_2H$	–	−110·9	–	–	+18·7
$F_2NCF_2CO_2CH_3$	–	−109·9	–	–	+17·7
$CF_3CF{=}NF$	−74·9	–	−85·6	−23·9	–
$CF_3C(OH){=}NF$	−79·0	–	–	−52·0	–
$CF_3C(OCH_3){=}NF$	−72·3	–	–	−40·8	–

[a] The NF chemical shift varies (−45·3 to −58·6) depending on the concentration.

thermally to give the corresponding 1,5-diazabicyclo-[3.3.0]octa-2,6-diene, [423]. (195) The ^{19}F NMR data of these



[423]

adducts are presented in Table LIV. The singlet observed for the CF_3 group of [422a] suggests that rapid nitrogen inversion, on the NMR time scale, is taking place at both nitrogen atoms. For [422b and c] there are two isomers depending on the *cis* and *trans* orientation of the R groups. In each configuration the geminal CF_3 groups are

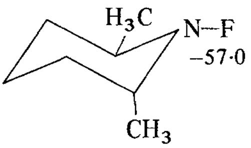
TABLE LIV

^{19}F NMR data of 2:1 olefin: azine and acetylene: azine adducts (195)

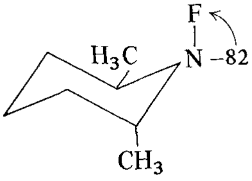
			δ_{CF_3}		$^4J(CF_3 \cdot CF_3)$ (Hz)
[422a]	R = H		−72·9		–
[422b]	R = CH_3	isomer 1	−73·0	−68·5	10
		isomer 2	−73·6	−68·3	10
[422c]	R = Et	isomer 1	−73·4	−68·4	10
		isomer 2	−73·0	−68·0	10
[423]			−66·9	−59·5	6·2

non-equivalent and rapid nitrogen inversion must again take place. In the case of [423], because of the presence of two signals for CF_3, it is suggested, on the contrary, that inversion at both nitrogens is slow on the NMR time scale, which would render the geminal CF_3 groups non-equivalent. (195)

Problems such as six-membered ring reversal *vs.* nitrogen inversion were *tackled using N-fluoro compounds. (196) The two N-fluoro derivatives of cis- and trans- 2,6-dimethylpiperidine, [424]* and [425], were prepared separately. The ^{19}F NMR of the *trans-N*-fluoroderivative, [424], for which ring reversal is allowed, shows at room temperature one signal at −64. (196) At low temperature

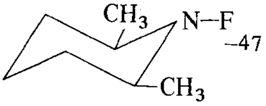


[424a]

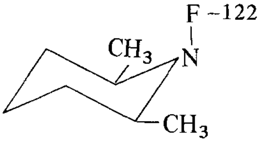


[424b]

(−65°) this signal splits into a doublet (J = 20·5 Hz), δ_F at −57 and a doublet of doublets (J = 11·8 Hz, J = 58 Hz), δ_F at −82, with relative intensities 85 : 15 respectively. On the basis also of the proton NMR spectra it was concluded that the molecule has a nitrogen rigidity (compared to the NMR time scale) even at room temperature. A fluorine atom is always *trans* to one of the methyl groups and always *cis* to the other. At low temperature the ring reversal is slowed down and the two conformations, [424a and b], appear clearly. (196) The spectral behaviour of the *cis-N*-fluoro derivative, [425], confirms this interpretation. For this isomer ring reversal is not allowed; the methyl groups are always equatorial. At room temperature two signals were observed:



[425a]



[425b]

a triplet (J = 22·8 Hz), δ_F at −47, and a triplet (J = 48·3 Hz), δ_F at −122, of relative intensities 95 : 5 respectively. In this case it was shown that nitrogen does not invert fast (compared to NMR time scale) even at +60°C. (196) An unambiguous assignment of the conformers of [424] and [425] cannot be made, however, on the hypothesis that the *H*CN*F* coupling constant follows a Karplus type law (as in the case of *H*CC*F* coupling) one can predict that $^3J_{aa} > 3J_{ea}$. On this basis the (a) conformers correspond to the equatorial N–F bond and the (b) conformers to the axial N–F bond. Consequently the nitrogen-halogen bond seems to be more stable in the equatorial position. (196)

The proton spectrum of $(CH_3)_2NCOCF_3$ was recorded in several solvents of varying dielectric constants at room temperature as well as the high temperature rotationally averaged spectrum. (197) The two $^5J^{HF}$ were accurately measured ($^5J^{HF} = 0{\cdot}6$ to $0{\cdot}8$ Hz and $^5J^{HF'} = 1{\cdot}5$ to $1{\cdot}7$ Hz); it was shown that it is likely they have the same relative sign. By decoupling the HF spin-spin interaction, the proton spectrum simplifies to a doublet. Line-shape analysis of the temperature-dependent doublet peaks, in $CHCl_2 \cdot CHCl_2$ as solvent, gave the activation parameters for the hindered internal rotation around the central C–N bond ($\Delta H^\ddagger = 19{\cdot}2$ Kcal/mole, $\Delta S^\ddagger = 1{\cdot}1$ e.u., $\Delta G^\ddagger = 18{\cdot}8$ Kcal/mole). (197) Similar values of the activation parameters were obtained for the same molecule using complete ^{1}H NMR line-shape analysis. (198)

Complete ^{1}H NMR line-shape analysis was used to study the internal hindered rotation around C–N bond of $(CH_3)_2NC(O)F$ ($\Delta H^\ddagger = 17{\cdot}7$ Kcal/mole, $\Delta S^\ddagger = 1{\cdot}4$ e.u., $\Delta G^\ddagger = 18{\cdot}1$ Kcal/mole). (199) The two H–F couplings were also measured ($^4J^{HF} = 0{\cdot}30$ Hz, $^4J^{HF'} = 0{\cdot}80$ Hz) and were shown to be temperature independent. (199a)

Phosphorus

From the Proton NMR spectrum at variable temperature the values of the coupling constants and their relative signs for $(CH_3)_2PF_4$ were derived (199b) ($J(F\,.\,H) = +3{\cdot}0$ Hz and $J(F_a \cdot H) = +12{\cdot}6$ Hz). The activation energy of the intramolecular exchange was estimated to be 15 ± 2 Kcal/mole in TMS as solvent. From a new synthesis of unsymmetrical diphosphines and arsenophosphines the two products shown in [426] were characterized by ^{19}F NMR. (199c)

$$\overset{-52{\cdot}5}{(CF_3)_2P_{II}P_IH_2} \qquad \left\{\begin{array}{l} ^2J_{PF} = 70{\cdot}0\ \text{Hz} \\ ^3J_{PF} = 5{\cdot}5\ \text{Hz} \end{array}\right. \qquad J_{FH} = 0{\cdot}35\ \text{Hz}$$

[426a]

$$(\overset{-47\cdot7}{CF_3})_2AsPH_2 \qquad \begin{cases} {}^3J_{PF} = 5\cdot25\ \text{Hz} \\ {}^4J_{FH} = 0\cdot46\ \text{Hz} \end{cases}$$

[426b]

Commercial difluorophosphoric acid, $HOPOF_2$, [427], could be purified by treating it with excess of P_4O_{10} at 0°. (200) μ-oxobis(phosphoryl difluoride), [428] was obtained pure in high yield

$$HOPOF_2 \quad \begin{matrix} \delta_F = -86\cdot2 \\ J_{PF} = 992\ \text{Hz} \end{matrix}$$

[427]

$$P_2O_3F_4 \quad \begin{matrix} \delta_F = -81\cdot0 \\ J_{PF} = 1048\ \text{Hz} \end{matrix}$$

[428]

from photolysis of POF_2Br with excess of oxygen. (200) Two mixed dihaloacids, $H[PO_2ClF]$ and $H[PO_2BrF]$, [429] were obtained by reaction of $H[PHO_2F]$ with chlorine or bromine. (201)

$$H[PO_2ClF] \quad \begin{matrix} \delta_F = -45\cdot2 \\ J_{PF} = 1055\ \text{Hz} \end{matrix}$$

[429a]

$$H[PO_2BrF] \quad \begin{matrix} \delta_F = -322 \\ J_{PF} = 1106\ \text{Hz} \end{matrix}$$

[429b]

The formation of diphosphinoethanes from a number of olefins by reaction with P_2Me_4 or $P_2(CF_3)_4$ was described. (202) The NMR spectra of these compounds are complex and not susceptible to a complete analysis. The ^{19}F shifts of some of them are shown in [430] to [438]. (202)

$$Me_2PCH_2\overset{-196\cdot5}{CHF}PMe_2$$

[430]

$$Me_2PCH_2\overset{-96}{CF_2}PMe_2$$

[431]

$$(\overset{-49\cdot5}{CF_3})_2P\overset{-104\cdot5}{CF_2CF_2}P(CF_3)_2$$

[432]

$$(\overset{-55\cdot5}{CF_3})_2PCH_2CH_2P(CF_3)_2$$

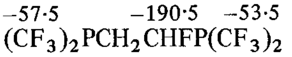
[433]

$$(\overset{-53\cdot5}{CF_3})_2PCHMe\cdot CHMeP(CF_3)_2$$

[434]

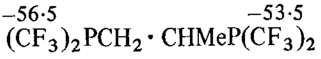
$$(\overset{-58\cdot5}{CF_3})_2P\cdot \overset{-85\cdot5}{CF_2}CH_2\cdot P(\overset{-52\cdot5}{CF_3})_2$$

[435]



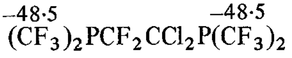
$$\overset{-57\cdot5}{(CF_3)_2}PCH_2\overset{-190\cdot5}{CHF}\overset{-53\cdot5}{P(CF_3)_2}$$

[436]



$$\overset{-56\cdot5}{(CF_3)_2}PCH_2\cdot CHMe\overset{-53\cdot5}{P(CF_3)_2}$$

[437]



$$\overset{-48\cdot5}{(CF_3)_2}PCF_2CCl_2\overset{-48\cdot5}{P(CF_3)_2}$$

[438]

Spectroscopic investigations of the uncoordinated phosphines and of some of their transition-metal carbonyl derivatives were undertaken. (203) In order to determine the significance of steric effect in the fluorophosphines, Bu^t_2PF and Bu^tPF_2, a comparison of NMR parameters within the series R_3P, R_2PF, RPF_2 and PF_3 was made for R = Me, Bu^t, Ph, and CF_3. (203) The fluorine shifts for these phosphines are reported in Table LV. The ^{19}F shielding increases vary substantially in the order $PF_3 < Bu^tPF_2 < Bu^t_2PF$. It is suggested that the inductive effect of the Bu^t-group causes an increasing polarization in the sense $P^{\oplus}-F^{\ominus}$, and this gives rise to an increase of electron density at fluorine. A series of transition-metal carbonyl derivatives were also prepared. (203) In Table LVI are collected the ^{19}F NMR parameters of monosubstituted $M(CO)_5L$ and $Ni(CO)_3L$, complexes (M = Cr, Mo, W; L = Bu^tPF_2 and Bu^t_2PF). As shown, the δ_F values change only slightly in going from chromium via molybdenum to tungsten and nickel. Some multiple substituted derivatives of Group VI carbonyl, *cis*-$Mo(CO)_4L_2$ and *cis*-$Mo(CO)_3L_3$ were also characterized (Table LVII). (203) The ^{19}F NMR spectra have been reported for the diphosphine $(CH_3CF_3P)_2$ and the thio-bisphosphine $(CH_3CF_3P)_2S$, together with the corresponding deuterated analog $(CD_3CF_3P)_2S$, the spectrum of which is an $M_3XX'M'_3$ spin system. (204) The ^{19}F NMR spectra of these compounds show two

TABLE LV

^{19}F NMR parameters of some fluorophosphines (203)

	δ_F			J_{PF}(Hz)		
R	PF_3	PF_2R	PFR_2	PF_3	PF_2R	PFR_2
Bu^t	−35	−111·5	−215·4	1411	1219	−873·6
CH_3	–	−92	−195·5	–	1167	823
Ph	–	−92·3	−202·0	–	1173	905
CF_3	–	−106·9	−219·0	–	1250	996

TABLE LVI

^{19}F NMR parameters for monosubstituted transition-metal complexes, $M(CO)_5L$ and $Ni(CO)_3L$ (203)

	δ_F	J_{PF}(Hz)
$PF_3 \cdot Cr(CO)_5$	-2·06	1315
$PF_3 \cdot Mo(CO)_5$	-4·70	1310
$PF_3 \cdot W(CO)_5$	-7·89	1245
$PF_2Bu^t \cdot Cr(CO)_5$	-67·3	1184
$PF_2Bu^t \cdot Me(CO)_5$	-66·4	1114
$PF_2Bu^t \cdot W(CO)_5$	-66	1104
$PFBu^t_2 \cdot Cr(CO)_5$	-164·2	865
$PFBu^t_2 \cdot Me(CO)_5$	-169·2	853
$PFBu^t_2 \cdot W(CO)_5$	-182·3	848
$PF_2Bu^t \cdot Me(CO)_3$	-71·2	1135
$PFBu^t_2 \cdot Me(CO)_3$	-179·8	870

TABLE LVII

NMR parameters of multiple substituted derivatives of Group VI carbonyls, *cis*-$Mo(CO)_4L_2$ and *cis*-$Mo(CO)_3L_3$ (203)

	δ_F	$\lvert J_{PF} + {}^3J_{PF} \rvert$	$^4J_{FH}$
$(PF_3)_2Mo(CO)_4$	-2·9	1305	–
$(PF_2Bu^t)_2Mo(CO)_4$	-65·4	1104	1·2
$(PFBu^t_2)_2Mo(CO)_4$	-172·1	855	1·3
$(PF_3)_3Mo(CO)_3$	-2·1	1306	–
$(PF_2Bu^t)_3Mo(CO)_3$	-63·4	1087	0·8
$(PFBu^t_2)_3Mo(CO)_3$	-170·0	–	0·7

chemically shifted absorption bands. Although no evidence conclusively establishes the nature of the two isomers, all the results strongly support their assignment as the *meso*- and *d,l*-diastereoisomers. Complete analysis of the ^{19}F NMR spectra was only possible for $(CD_3CF_3P)_2S$. Coupling constants are shown in [439] and [440]. The temperature dependence of the ^{19}F NMR spectra of the above compounds with those of $(CF_3)_2PP(CF_3)_2$, $(CF_3)_2POP(CF_3)_2$ and $(CF_3)_2PSP(CF_3)_2$ were examined over a

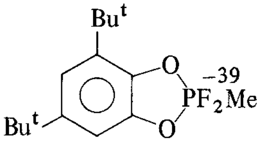
		J_{PF}	J_{PPF}	J_{FF}
$(CD_3CF_3P)_2S$ [439]	high field isomer	66·1	4·3	0·3
	low field isomer	66·1	4·3	2·0

$$(CH_3CF_3P)_2S \begin{cases} \text{high field isomer} & 79{\cdot}1^* \\ \text{low field isomer} & 73{\cdot}1^* \end{cases}$$

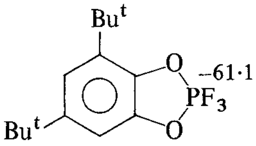
[440] $^* J^{PF} + J^{PPF}$

wide range of temperature. (204) No significant variations in spectral patterns could be observed even at temperatures down to −100°. This means that the rotational barrier about the P–P bond must be less than *ca.* 7 Kcal/mole. It was suggested that the high-frequency isomer of $(CH_3CF_3P)_2S$ may be the *meso*-diastereoisomer because of the larger five bond F–F coupling justified by conformation considerations. (204)

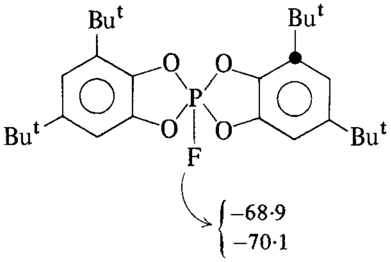
The reaction of NO with some uncoordinated trifluoromethylphosphino-derivatives [CF_3PX_2, X = F, Cl, H and CF_3; $(CF_3)_2PX$, X = F, Cl, H and $P(CF_3)_2$] was explored. (205) The oxidation of $(CF_3)_2PF$ and $(CF_3)_2PP(CF_3)_2$ by NO gave two new compounds, $(CF_3)_2P(O)F$ and $(CF_3)_2P(O)OP(O)(CF_3)_2$ respectively. (205) The ^{19}F NMR spectra of the products obtained show two distinct areas of absorption: (1) a high-frequency (CF_3: −68 to −72) doublet of doublets caused by coupling of the equivalent fluorine atoms of the trifluoromethyl groups with phosphorus and with the distant fluorine atom and (2) a low-frequency (PF: −106 to −137) doublet of septets, assigned to the single fluorine atom. (205) The preparation and the NMR characterization of some di-and tri-fluorophosphines, containing the 2,4-di-*t*-butylcatechol ring system linked to five-coordinate phosphorus, were described ([441] and [442]). (206) The NMR parameters observed for [441a and b] are intermediate between normal



[441a]

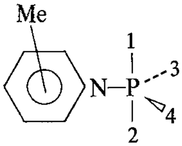


[441b]

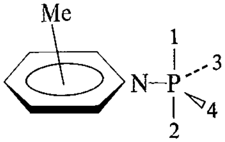


[442]

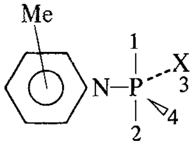
axial and equatorial values. At −88° the fluorine spectrum of [441a] for example, becomes the AB part of an ABX spin system, where X is the P atom. Because of the unsymmetrical substitution of the catechol rings, two isomers are expected for [442], as observed. (206) 2-Methyl-, 3-methyl- and 4-methyl- piperidylfluorophosphoranes, [443], were prepared and characterized by ^{19}F NMR.



[443]



[443I]



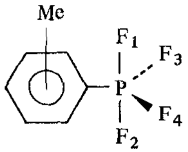
[433II]

(207) The results are all consistent with a trigonal-bipyramidal structure in which the amine and hydrocarbon groups occupy the equatorial positions. Di-, tri- and tetra- fluorophosphoranes were considered (Table LVIII). The ^{19}F NMR spectra of [443a, b and c] at room temperature, are constituted by an average resonance which can be explained by the exchange of the fluorine atoms in the axial and equatorial positions. Only at low temperature (*ca.* < −60°) this exchange is slowed down to permit observation of distinct axial and equatorial fluorines. For compounds [433a and b] the two axial fluorines, F_1 and F_2, are equivalent, whereas the equatorial ones, F_3 and F_4, are non-equivalent. For [433c] all fluorines are equivalent even at low temperature. For difluoro-compound [443g] an AB spectrum is observed for the two fluorines at low temperature; for [443h] no substantial spectral change was observed when cooling down. This is consistent with an axial position for the two fluorines (F_1 and F_2). For the trifluoro-compounds, [443d and e] all three fluorines are already non-equivalent at room temperature. For [443f] two fluorines remain always equivalent at −90°. All these observations may be explained by the rate of positional exchange of fluorines and the rate of P–N bond rotation being within the time scale of the NMR measurements. It is suggested that the piperidyl ring will take the position of least stereochemical hindrance, which is the equatorial plane for the tetrafluoro-compounds, [443 I], and the axial plane for the trifluoro- and difluoro-compounds, [443 II]. (207) For the 4-methylpiperidylfluorophosphoranes no conformational preference can be inferred for the piperidyl ring because the axial and equatorial fluorines were always noted to be equivalent. (207) The reaction of aryl- and alkyl- fluorophosphoranes, R_nPF_{5-n}, with silyl ethers was reported. (208)

Benzodioxaphospholes, containing at least one fluorine atom on

TABLE LVIII

^{19}F NMR data for methylpiperidylfluorophosphoranes [443] (207)

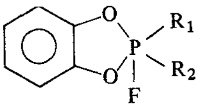


[443]

	F_1	F_2	F_3	F_4	J_{12}	J_{13}	J_{14}	J_{23}	J_{34}	$J_{P\text{-}1}$	$J_{P\text{-}2}$	$J_{P\text{-}3}$	$J_{P\text{-}4}$	T °C
Tetrafluorophosphoranes														
(a) $2\text{-}CH_3$		⟨−66·9⟩								⟨846⟩				30
	−60·3	−60·3	−72·2	−74·2	–	74	67	–	51	781	781	921	905	−100
(b) $3\text{-}CH_3$		⟨−67·8⟩								⟨849⟩				30
	−60·2	−60·2	−72·1	−74·0	–	77	63	–	50	763	763	940	940	−100
(c) $4\text{-}CH_3$		⟨−67·6⟩								⟨865⟩				30
Trifluorophosphoranes														
(d) $2\text{-}CH_3$	−42·6	−44·3	−67·8	–	14	55	–	55	–	828	814	965	–	30
(e) $3\text{-}CH_3$	−43·4	−43·7	−69·1	–	14	55	–	55	–	823	820	1006	–	30
(f) $4\text{-}CH_3$	−43·5	−43·5	−68·1	–	0	56	–	56	–	820	820	965	–	30
Difluorophosphoranes														
		⟨−37·9⟩								⟨712⟩				30
(g) $2\text{-}CH_3$	−34·6	−36·8	–	–	14					689	689			−70
		⟨−38·1⟩								⟨715⟩				30
(h) $4\text{-}CH_3$		⟨−38·1⟩								⟨715⟩				−70

TABLE LIX

NMR data for 1,3,2-dioxo-4,5-benzophosphole derivatives [444] (208)



[444]

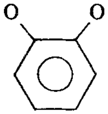
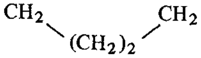
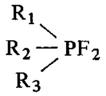
	R_1	R_2	δ_F	J_{FP}(Hz)
(a)	F	Et	−46·6	987
(b)			−70·4	1011
(c)	Me	Me	−8·0	741
(d)	Ph	Ph	−30·3	772
(e)	Me	Ph	−18·3	766
(f)	Me	CH_2Ph	−15·0	764
(g)	 $CH_2(CH_2)_2CH_2$		−21·8	799

TABLE LX

^{19}F NMR data of some alkoxyfluorophosphoranes [445] (209)



$R_1R_2R_3PF_2$

[445]

R_1	R_2	R_3	δ_F	J_{PF}
C_6H_5O	C_6H_5O	C_6H_5O	−44·8	768
C_6H_5O	C_6H_5O	CH_3	−18·1	825
C_6H_5O	C_6H_5O	C_6H_5	−35·0	829
C_6H_5O	CH_3	CH_3	−4·2	736
C_6H_5O	C_6H_5	C_6H_5	−33·3	797
C_6F_5O	C_6F_5O	C_6F_5O	−50·3	809
C_6F_5O	C_6F_5O	CH_3	−21·9	870
C_6F_5O	C_6F_5O	C_6H_5	−38·2	817
C_6F_5O	CH_3	CH_3	−5·3	747
C_6F_5O	C_6H_5	C_6H_5	−35·1	812

phosphorus, [444], were obtained (Table LIX). (208) The fluorine spectrum of [444a] consists of only one resonance, a doublet because of J^{PF}. Fast positional exchange must occur in this compound because it is likely that there would be one equatorial and one axial fluorine atom. The single fluorine of [444b] and of [444g] is suggested to occupy an equatorial- and axial- position respectively. (208) The first known examples of aryloxyfluorophosphoranes, [445], were reported. (209) Unlike the alkoxyfluorophosphoranes, these new compounds are thermally stable and they may be prepared in high yields by reaction of fluorophosphoranes with aryl trimethylsilyl ethers. The ^{19}F NMR (Table LX) together with those of ^{31}P suggest that the molecules are trigonal bipyramidal in every case, with two axial fluorine atoms. The ^{19}F data for the ionic compounds $[(C_6H_5O)_4P]^{\oplus}[PF_6]^{\ominus}$ and $[(C_6H_5O)_2[(CH_3)_2N]_2P]^{\oplus}[PF_6]^{\ominus}$, [446] and [447], and for the trifluorophosphorane $C_6H_5OPF_3C_6H_5$, [448], which can be considered as an intermediate species, were also given. (209)

$[(C_6H_5O)_4P]^{\oplus}[PF_6]^{\ominus}$

$\begin{cases} -72{\cdot}8 \\ J_{PF} = 720 \text{ Hz} \end{cases}$

[446]

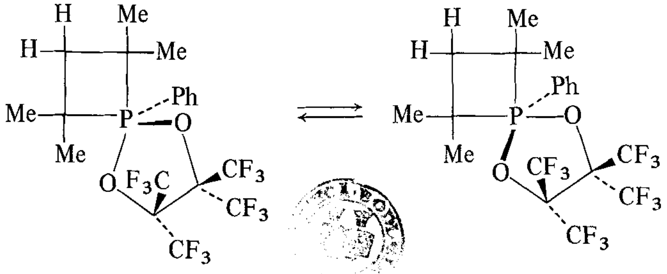
$[(C_6H_5O)_2((CH_3)_2N)_2P]^{\oplus}[PF_6]^{\ominus}$

$\begin{cases} -73{\cdot}0 \\ J_{PF} = 715 \text{ Hz} \end{cases}$

[447]

	axial region	equational region
$C_6H_5OPF_3C_6H_5$	$\delta_{F_a} = -38{\cdot}3$	$\delta_{F_e} = -65{\cdot}4$
[448]	$J(\text{P–F}) = 864$ Hz	$J(\text{P–F}) = 986$ Hz
	$J(F_a\text{–}F_e) = 72$ Hz	$J(F_a\text{–}F_e) = 72$ Hz

The 1 : 2 adduct formed by 2,2,4,4-tetramethyl-1-phenylphosphetan and hexafluoroacetone was studied by ^{19}F NMR spectroscopy at variable temperature. (210) The ^{19}F spectrum at room temperature and below in *o*-dichlorobenzene consists of two signals at −67·07 and −69·91. Above 120° these signals broaden and finally coalesce at 155°. The behaviour was interpreted as arising from pseudorotation between two equivalent structures, [449]. The free energy of activation for this process at 155° was calculated to be 20·1 Kcal/mole. (210) A series of four-membered ring compounds containing only one five-coordinate phosphorus atom, were in-

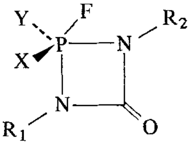


[449a] [449b]

vestigated. (211) The NMR data obtained for these compounds (Table LXI) could best be understood by assuming the configuration [450]. For compounds [450a to f] the values of J^{PF} are in the range 828 to 959 Hz and the value of δ_F within the range −66·9 to −79·3. These data suggest that the fluorine atoms are in axial and equatorial environments around a trigonal-bi-pyramidal phosphorus and that rapid positional exchange is taking place. For [450l and m], on the contrary, axial and equatorial fluorines were distinctly observed at −40°; δ_F values (−33·7 to −40·6) and J_{PF} in the range 733 to 759

TABLE LXI

^{19}F NMR data for some N,N′-disubstituted-1,2,4-phosphadiazetidin-3-ones [450] (211)

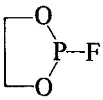


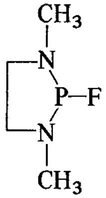
[450]

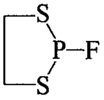
	X	Y	R_1	R_2	δ_F	J_{PF}	J_{FH}
(a)	F	F	Me	Me	−79·3	959	
(b)	F	Me	Me	Me	−62·8	930	7
(c)	F	Et	Me	Me	−69·3	949	6
(d)	F	Ph	Me	Me	−66·9	937	
(e)	F	NMe_2	Me	Me	−75·8	887	2
(f)	F	NEt_2	Me	Me	−72·0	828	
(g)	Me	Me	Me	Me	−34·7	733	
(h)	Me	Ph	Me	Me	−33·7	746	
(i)	Ph	Ph	Me	Me	−40·6	759	
(l)	F	Me	Me	Ph	−60·4	945	
(m)	F	Et	Me	Ph	−68·3	885	

Hz for compounds [450g, h and i] are consistent with only axial fluorine environment. (211)

The proton NMR spectra of the trivalent fluorophospholanes, [451] to [453], were analysed. (212) Double resonance experiments, irradiating in the ^{31}P and in the ^{19}F region, permitted the extraction of the relative signs of some coupling constants (referred to the known negative sign of $^1J_{PF}$). The $^4J_{FH}$ couplings, which transmit through the F · PXC · H fragment, are all positive and do not show any stereospecificity, contrary to analogous $^4J_{FH}$ couplings through F–CCC–H fragment. Details of the synthesis and properties of the mixed-valence compound, the diphosphorus compound, [454], in which the phosphorus atoms are bridged by a sulfur atom and the related tetrasulfur-diphosphorus compound, [455] were reported. The best evidence for the mixed-valence







$^4J_{FH}$	2·1	5·7	4·0
$^4J'_{FH}$	1·6	5·8	2·3
$^1J_{PF}$	−1226	−1055	−1120
$^4J(FPNCH_3)$	–	3·1	–
[451]		[452]	[453]

$$\overset{-68\cdot7}{(CF_3)_2}P(S)S\overset{-53\cdot8}{P(CF_3)_2} \quad \begin{cases} ^2J(CF_3P^V) = 111\cdot7 \\ ^4J(FP^V) = ca.\ 0\cdot6 \\ ^6J(FF) = 0\cdot5 \\ ^2J(CF_3P^{III}) = 81\cdot3 \\ ^4J(FP^{III}) = 4\cdot9 \end{cases}$$

[454]

$$\overset{-66\cdot5}{(CF_3)_2}P(S)\text{—}S\cdot S\text{—}\overset{-66\cdot5}{P(S)(CF_3)_2} \qquad |^2J(P\cdot CF_3) + {}^5J(PF)| = 105\cdot5$$

[455]

structure of [454] is provided by the ^{19}F NMR data. ^{31}P NMR spectra of [454] and [455] were also described. (213) Trifluorophosphazodifluorophosphine, [456], was prepared from PF_3Cl_2 and PF_2NH_2; (214) no coupling was observed between P^{III} and ^{19}F through three bonds.

$$\overset{-82\cdot 8}{F_3P^V} = \overset{-45\cdot 7}{NP^{III}F_2} \qquad \left\{ \begin{array}{ll} ^1J(P^{III}F) = 1279 & J(P^VF) = 1031 \\ ^3J(P^VF) = 24\cdot 1 & ^4J(FF) = 7 \end{array} \right.$$

[456]

Four new compounds, methylamino-derivatives of some difluoro- and bis(trifluoromethyl)- phosphorus compounds, [457] and [458], were prepared and proton and fluorine NMR observed. (215) The

$(CF_3)_2P(X)NHCH_3$

(a) X = O −72·2, $J^{PF} = 112$ Hz

(b) X = S −72·3, $J^{PF} = 106$ Hz

[457]

$F_2P(X)NHCH_3$

(a) X = O −80·5, $J^{PF} = 991$ Hz

(b) X = S −52·4, $J^{PF} = 1083$ Hz

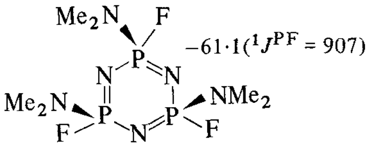
[458]

N-deuterated analogs were also prepared and investigated. The spectra were observed down to −90°, but, with the exception of [458b] no change with temperature was observed. The variable temperature investigation (down to −90°) did not provide evidence of distinct rotational isomers in any of these compounds. (215) Aminodifluorophosphine, [459], was prepared in high yield by the

$$\overset{-59\cdot 0}{PF_2 \cdot NH_2} \left\{ \begin{array}{l} J^{PF} = 1180 \text{ Hz} \\ J(^{15}N\text{—}F) = 6\cdot 4 \text{ Hz} \\ J^{HF} = 13\cdot 3 \text{ Hz} \end{array} \right.$$

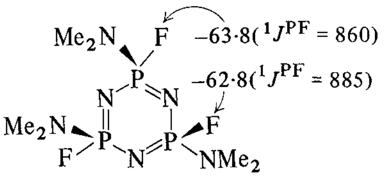
[459]

gas-phase reaction of NH_3 and PF_2Br. (216) The ^{19}F NMR spectrum was obtained for solutions of [^{15}N]-amino-difluorophosphine in $CFCl_3$/cyclohexane as solvent. The reactions of fluorination of tris- and tetra-kis- dimethylaminochlorotriphosphonitriles were described. (217) Assignments of the structure of the compounds obtained, [460] to [464], follows mainly from ^1H and ^{19}F NMR data. (217) Methylaminotetrafluorophosphorane, [465], was prepared by reaction between $(CH_3)_3SiNHCH_3$ and PF_5. (218) The ^{19}F NMR spectrum of [465] at 70° shows that all fluorines are equivalent ($\delta_F = -74\cdot 0$; $J^{PF} = 847$ Hz). At 30° no resonances were observed but


−61·1($^1J^{PF}$ = 907)

[460]

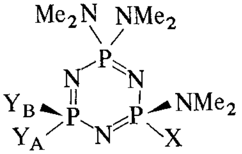
cis-tris-


−63·8($^1J^{PF}$ = 860)

−62·8($^1J^{PF}$ = 885)

[461]

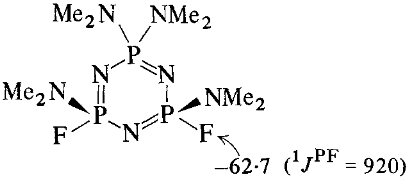
trans-tris-


[462]

gem-tris-

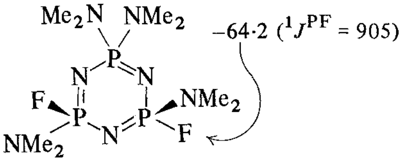
(a) X = F; Y = Cl −62·7 ($^1J^{PF}$ = 910 Hz)

(b) X = Y = F
- F_A −69·6 ($^1J^{PF}$ = 900 Hz)
- F_B −68·8 ($^1J^{PF}$ = 900 Hz)
- F −62·6 ($^1J^{PF}$ = 905 Hz)


−62·7 ($^1J^{PF}$ = 920)

[463]

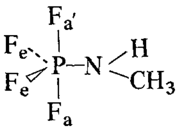
cis-tetrakis-


−64·2 ($^1J^{PF}$ = 905)

[464]

trans-tetrakis-

at −80° three fluorine environments were present. These results are in agreement with a trigonal-bipyramidal structure with non-equivalent axial fluorine atoms. Two effects must contribute to the behaviour of the fluorine spectrum of [465] at variable temperature: (1) pseudorotation exchange process and (2) hindered rotation around the P–N bond. (218) There are few examples of nitrogen bridged phosphorus compounds. Two of these ([466] and [467]) have now been prepared from the action of $Me_3Si \cdot NMe \cdot PF_2$ on PF_5 and


[465]

$\delta_a = -60$
$\delta_{a'} = -70$
$\delta_e = -83$

$J^2_{P_a}$	$J_{P_{a'}}$	J_{P_e}	J_{ae}	J^1_{ae}
755	770	920	68	69
J_{aa}	$J_{CH_3 \cdot a'}$	$J_{CH_3 \cdot e}$	$J_{NH \cdot a'}$	
2·8	2·8	2·1	27·6	

		δ_A	δ_B	$J(P_AF_A)$	$J(P_BF_B)$	$J(P_BF_A)$
[466]	$PF_2 \cdot NMe \cdot POF_2$	−70	−61	1280	896	3·7

$J(P_AF_B)$	$J(F_AF_B)$	$J(F_AH)$	$J(F_BH)$
87·0	9·8	2·7	2·0

	A B	δ_A	δ_B	$J(P_AF_A)$	$J(P_BF_B)$	$J(P_BF_A)$	$J(P_AF_B)$
[467]	$PF_2 \cdot NMe \cdot PF_4$	−71	−68	1272	1039	8·2	–

$J(F_AF_B)$	$J(F_AH)$	$J(F_BH)$
4·5	1·7	0·5

PF_2Cl respectively. (219) The NMR spectra were interpreted on the basis of first-order analysis. NMR data of $MeNHPXF_2$ (X = lone pair, 0 and F_2), [468] to [470] were also given. (219)

$$\overset{-72\ (J_{PF} = 1193)}{MeNHPF_2} \qquad \overset{-79\ (J_{PF} = 1000)}{MeNHPOF_2} \qquad \overset{-74\ (J_{PF} = 847)}{MeNHPF_4}$$

[468] [469] [470]

Three new substances, [471] to [473], were prepared combining $(CH_3)_2NPF_2$ and F_2PH as bases in adducts with triborane and diborane. (220) Spectroscopic data were also presented for $(CH_3)_2NPF_2 \cdot B_3H_7$, [474]. (220) The synthetic procedures for the

$$(F_2PH)_2B_2H_4 \begin{cases} -53{\cdot}8 \\ J_{PF} = 1147\ \text{Hz} \\ J(\text{HPF}) = 50{\cdot}3\ \text{Hz} \end{cases} \qquad F_2PH \cdot B_3H_7 \begin{cases} -59{\cdot}5 \\ J_{PF} = 1100\ \text{Hz} \\ J(\text{HPF}) = 56\ \text{Hz} \end{cases}$$

[471] [472]

$$[(CH_3)_2NPF_2]_2B_2H_4 \begin{cases} -76{\cdot}3 \\ J_{PF} = 1140\ \text{Hz} \end{cases} \qquad (CH_3)_2NPF_2 \cdot B_3H_7 \begin{cases} -76{\cdot}5 \\ J_{PF} = 1100\ \text{Hz} \end{cases}$$

[473] [474]

preparation of H_2PPF_2 and $(CF_3)_2PPF_2$ and their interactions with B_2H_6 were reported. (221) The ^{19}F NMR spectra of these compounds showed the expected first-order splitting patterns. Their NMR data and those of the adducts, $H_2PPF_2 \cdot BH_3$ and $(CF_3)_2PPF_2 \cdot BH_3$ are shown in Table LXII. These data were compared with those already known of $HPF_2 \cdot BH_3$, F_3PBH_3 and H_3PBH_3. It was possible to establish that BH_3 coordinate only to the PF_2 site: neither H_2PPF_2 nor $(CF_3)_2PPF_2$ were found to coordinate two BH_3 groups. (221)

The preparation of some chlororhodium complexes with

TABLE LXII

NMR data for H_2PPF_2 and $(CF_3)_2PPF_2$ and of their adducts with BH_3 (221)

	$(CF_3)_2PPF_2$	H_2PPF_2	$(CF_3)_2PPF_2 \cdot BH_3$	$H_2PPF_2 \cdot BH_3$
$\delta(CF_3)$	$-45{\cdot}9^a$		$-43{\cdot}6^c$	–
$\delta(PF_2)$	$-94{\cdot}6^a$	$-89{\cdot}8^b$	$-77{\cdot}8^c$	-74^a
J(P–F)	1249	1190	1267	1204
J(P–PF)	87·4	83	32	29·5
J(FCPPF)	3·7	–	–	–
J(FCP)	60·0	–	76·3	–
J(FCPP)	14·0	–	5·2	–
J(HPPF)	–	22·0	–	14·4
J(FPBH)	–		27·0	23·2

[a] At −40°.
[b] At −20°.
[c] At 0°.

$PF_2 \cdot NEt_2$ were described. (222) The ^{19}F NMR data are shown in [475] to [477]. The complex [477], showing two resonances,

$$PF_2 \cdot NEt_2 \begin{cases} -63{\cdot}9 \\ ^1J(PF) = 1206\ \text{Hz} \end{cases}$$

[475]

$$[RhCl(PF_2NEt_2)_2]_2 \begin{cases} -47{\cdot}4 \\ ^1J_{PF} + {}^3J_{PF} = 1100\ \text{Hz} \end{cases}$$

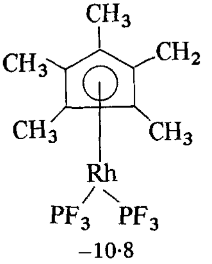
[476]

$$cis\text{-}[RhCl(PF_2NEt_2)_2(PPh_3)] \begin{cases} -34{\cdot}9 \quad (^1J_{PF} + {}^3J_{PF} = 1106) \\ -48{\cdot}4 \ (^1J_{PF} + {}^3J_{PF} = 1148) \end{cases}$$

[477]

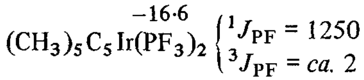
indicates the non-equivalence of the two $PF_2 \cdot NEt_2$ groups. Metal-trifluorophosphine complexes are prepared by a new general method consisting of the thermal reaction of various transition metal derivatives with an excess of the commercially available $Ni(PF_3)_4$, as source of the trifluorophosphine ligands. (223) The compounds shown in [478] to [480] were characterized by ^{19}F NMR. (223) The single fluorine resonance attached to Ir in [480] failed to be observed. The reaction of di-iron enneacarbonyl with aminofluorophosphines resulted in the formation of compounds of the type $R_2NPF2 \cdot Fe(CO)_4$ or $(R_2N_2)PF \cdot Fe(CO)_4$. (224) These compounds can then react with anhydrous HCl and HBr to form mixed halogenophosphine adducts containing the $Fe(CO)_4$ moiety. The ^{19}F chemical shifts range between +5·2 and +8·0 for the mixed halogenofluorophosphine compounds and between −28·0 and

$(CH_3)_5C_5Rh(PF_3)_2$



$\left\{\begin{array}{l}{}^1J_{PF} = 1334\ \text{Hz}\\ {}^2J_{RhF} = ca.\ 30\ \text{Hz}\\ {}^3J_{PF} = ca.\ 6\ \text{Hz}\end{array}\right.$

[478]

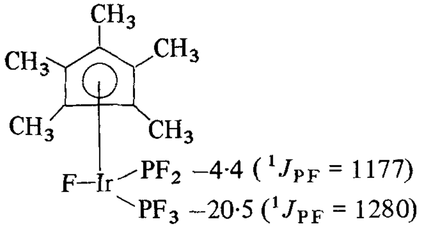


$\overset{-16\cdot6}{(CH_3)_5C_5Ir(PF_3)_2}\left\{\begin{array}{l}{}^1J_{PF} = 1250\\ {}^3J_{PF} = ca.\ 2\end{array}\right.$

[479]

$(CH_3)_5C_5IrF(PF_2)PF_3$

[480]



−45·5 for the others. Low-temperature NMR studies failed to demonstrate the presence of the two possible types of isomers. (224) For the first time the limiting, slow exchange, NMR spectra of a class of transition metal hydrides, HML_4, [481], (M = Os, Rh, Ru, Co, Ir; L = PF_3) was observed. (225) The ^{19}F NMR spectra are rather complex and a complete analysis was not possible in any case. The NMR data which could be extracted are collected in Table LXIII; $^1J_{PF}$ couplings were all *ca.* 1250 Hz. In the low temperature limit the ^{19}F NMR spectra are consistent with a coordination sphere having three coplanar P nuclei, and the hydrogen atom and the remaining P nucleus, *trans* to each other, on the threefold axis of the P_3 plane. The ^{19}F resonances assigned to the axial and equatorial groups were well separated and integration gave intensities close to the expected 1 : 3 ratio. A preliminary line-shape analysis gave the free-energy values reported in Table LXIII. (225) Some related molecules of the form $M(PF_3)_5$ [M = Fe, Ru and Os] were also observed at low temperature, down to −160° ($CHClF_2$ solutions). (225) There were no indications that these

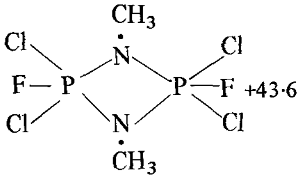
TABLE LXIII

^{19}F NMR data for complexes HML$_4$ [481] (223)

	$HCo(PF_3)_4$	$HRh(PF_3)_4$	$HIr(PF_3)_4$	$HRu(PF_3)_4$	$HOs(PF_3)_4$
High temp. limit					
J_{HF}	9·75	16·5	14·75	16·5	15·0
δ_F	−7·3	−4·4	−14·4	+5·9	+3·5
Low temp. limit					
$\delta_{F\,axial}$	−6·4	−8·3	−20·2	+0·4	−2·5
$\delta_{F\,equat.}$	−8·3	−4·2	−14·5	+6·5	+4·1
ΔG^*(kcal/m)	5·5	9·0	10·0	7·0	8·0

complexes are fluxional on the NMR time scale. Anionic species formed in hydrolysis of some trivalent and pentavalent trifluoromethylphosphorus compounds were characterized. (226) In the course of the study complete ^{19}F NMR data of some new oxythiophosphorus compounds were obtained. The ^{19}F NMR chemical shifts for the ions $CF_3PS_2O^{2\ominus}$, $CF_3PSO_2^{2\ominus}$, $CF_3PS_2OH^{\ominus}$ and $CF_3PSO_2H^{\ominus}$ in aqueous solution were found in the range −74·6 to −77·1. (226)

The compound $(CH_3NPFCl_2)_2$, [482], was obtained by reaction



[482]

of BF_3 with $(CH_3NPCl_3)_2$ in benzene solution. (227) The two fluorine atoms are located at the axial positions of the two trigonal bipyramidal phosphorus atom environments. The reaction between $C_6H_4O_2PCl_3$ and BF_3 in C_6H_6 resulted in the formation of two new compounds, [483] and [484]. (227) Diethylaminotetrafluorophosphorane, [485], was prepared by fluorolytic cleavage of the P=N bond. (228)

$C_6H_4O_2PF_2Cl$ −18·6

[483]

$C_6H_4O_2PF_3$ −60·5

[484]

$(C_2H_5)NPF_4\begin{cases}-65{\cdot}1\\ J_{PF}\ 859\ \text{Hz}\end{cases}$

[485]

The theory for the X spectrum of an $[AX_n]_3$ spin system, in the limits $|J_{AX}| \gg |J_{AA}| \gg |J_{AX'}| > |J_{XX}| = 0$, was extended (228b)

TABLE LXIV

^{19}F NMR data for *fac*-$[L_3Mo(CO)_3]$ complexes (228b)

	δ_F(free ligand)	δ_F(complex)	$^1J_{PF}$(free ligand)	$^1J_{PF}$(complex)	$^3J_{PF}$
fac-$[(PhPF_2)_3Mo(CO)_3]$	−92·3	−43·2	−1174	−1096	6·7
fac-$[(PhO_2PF)_3Mo(CO)_3]$[a]	−37·0	+1·08	−1307	−1269	1·2
fac-$[(PhOPF_2)_3Mo(CO)_3]$	−44·5	−12·12	−1326	−1243	2·5
fac-$[(PF_3)_3Mo(CO)_3]$	−33·7	−1·17	−1441	−1296	2·4

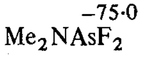
[a] $^4J_{FF}$ = 0·5 Hz.

to give details of the intensities. The theory was applied to the ^{19}F spectra of complexes of the type *fac*-$L_3Mo(CO)_3$ for the ligands L = $C_6H_4O_2PF$ (n = 1), $PhOPF_2$ (n = 2), PF_3 (n = 3) and $PhPF_2$ (n = 2). The general ^{19}F pattern in the region of the X spectrum, is two groups of eleven lines each. If the magnitudes of J_{AX}, J_{AA}, $J_{AX'}$ and J_{XX} are in the limits already given, the lines fall into a "doublet of quintets" pattern from which it is possible to measure J_{AA}, J_{AX} and $J_{AX'}$ directly. (228b) The relative intensities were calculated for the individual lines of the "quintet" in an $[AX_n]_3$ spin system. For n = 1 the relative intensities are in the ratio: 7 : 20 : 42 : 20 : 7; for n = 2, 1 : 5 : 12 : 5 : 1 and for n = 3, 23 : 148 : 426 : 148 : 23. The ^{19}F NMR parameters found for the complexes investigated are collected in Table LXIV. From the data reported in Table LXIV it is evident that $|^1J_{PF}|$ decreases and δ_F is reduced (high frequency shift) on complex formation. This probably arises from changes in hybridization of the P orbitals involved in forming bond with F and changes in bond angles. The absolute signs of the couplings given in Table LXIV are based on the assumption that $^1J_{PF}$ is negative; hence $^3J_{PF}$ was found to be positive as well as the $^4J_{FF}$ coupling of one compound (see Table LXIV). The results for the long range P–F coupling, $^3J_{PF}$, are of the same order of magnitude as found for *cis*-fluorophosphine molybdenum complexes. However, comparison of *cis*- and *trans*-isomers indicates that this coupling, $^3J_{PF}$, increases by an order of magnitude on going from a *cis*- to a *trans*- isomer (for example the value for *trans*- $(PF_3)_2Mo(CO)_4$ is +37 Hz). (228b)

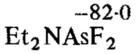
Arsenic and Antimony

The kinetics of the fluoride exchange of $(C_6H_5CH_2)_3AsF_2$ in CH_2Cl_2 were reported. (228c) One could ascertain that the fluoride exchange is intermolecular; the calculated enthalpy and entropy of activation are 11·5 Kcal/mole and −11 e.u. respectively. (228c)

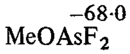
Cleavage reactions of AsF_3 with element-trimethylsilyl compounds were performed. (229) Mono-trimethylsilyl-substituted compounds gave rise to the corresponding -AsF_2 derivatives, while some unusual products were obtained from bis- or tris- trimethylsilyl precursors. NMR spectroscopy was used to characterise the products obtained, which are shown in [486] to [491]. In the study of the reactions between AsF_5 and trimethylsilyl compounds, compounds


$\overset{-75\cdot0}{Me_2NAsF_2}$

[486]


$\overset{-82\cdot0}{Et_2NAsF_2}$

[487]


$\overset{-68\cdot0}{MeOAsF_2}$

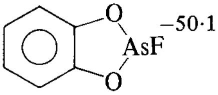
[488]

$\overset{-65\cdot5}{\mathrm{EtOAsF_2}}$

[489]

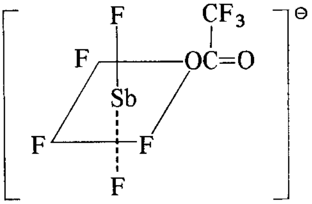
$\overset{-67\cdot0}{\mathrm{(EtO)_2AsF}}$

[490]



[491]

such as $MeSiF_3$ (−135·5), Me_2SiF_2 (−130·0), Me_3SiF (−156), AsF_3 (−43·5) and MeF (−268·0) were identified. (229) ^{19}F NMR studies showed that SbF_5 forms $HSbF_5(OOCCF_3)$ in CF_3COOH. (230) The ^{19}F resonance of the fluorine attached to antimony of $HSbF_5(OOCCF_3)$ is broadened by exchange process at +25°. At −15° these processes are slowed sufficiently and the spectrum of F nuclei on Sb consists of an AX_4 type. (230) The chemical shifts and areas of the resonances observed are those expected for the complex anion, [492].



[492]

Using fluorine resonance, the interactions of SbF_3 with $SbCl_5$, SO_2Cl_2, and COF_2, generally in sulphuryl chlorofluoride as solvent were studied. (231) Low temperature ^{19}F NMR spectra of systems NbF_5-SbF_5-SO_2ClF and of TaF_5-SbF_5-SO_2ClF were studied. (232) The spectra, as well as the conductivities of the liquid systems, are consistent with the formation of neutral fluorine-bridged polymers with mixed transition metal and antimony units. These polymers may be fluxional on the NMR time scale. The results are shown below. (232)

Molar ratio	Chemical shift	Half width (Hz)
NbF_5/SbF_3	F on Nb	
0·063 to ∞	−274·5 to −180·7	200 to 900
TaF_5/SbF_5	F on Ta	
0·067 to ∞	−165 to −95·5	–

Adding XeF_2 it was possible to enhance the solubility of XeF_4 in SbF_5 so that the ^{19}F NMR spectrum of the solution could be interpreted. (232b) The high-frequency Xe–F region is dominated by an

AB_2 spectrum with ^{129}Xe satellites. The AB_2 spectrum was assigned to the $XeF_3^\oplus$ ion, where B, at higher frequency, are the axial fluorines, and A is an equatorial fluorine. The NMR parameters extracted are listed below:

		δ_F	J_{FF}	$J_{(Xe\text{-}F)}$
$XeF_3^\oplus$	A	−23·0	174	2440
	B_2	−38·7		2620
$XeF^\oplus$		+291·5		7260
$SbF_5/SbF_{11}^\ominus$		+112·5		

This enhancement of the solubility of XeF_4 is apparently due to the increased ionizing power of the solvent resulting from the presence of the $XeF^\oplus$ and $Sb_nF_{5n+1}^\ominus$ ions. (232b)

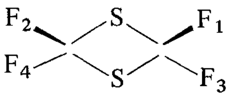
Sulphur

In the study of the low temperature reactions of H_2S with FSSF, SSF_2, SF_4 and SOF_2 it was found that mixtures of sulfanes, HS_nH, were formed; (233) ^{19}F NMR spectroscopy was employed to analyze the products. The mixture of FSSF, SSF_2 and SF_4, obtained by reaction of AgF with sulfur were condensed directly into a NMR tube and then analysed at −100°. Two triplets were observed at −91·5 and −35·3, both assigned to SF_4, together with two considerably more intense peaks: one at −78·3 and the other at −122·7. These peaks were assigned to SSF_2 and FSSF respectively. Allowing the NMR tube to warm to room temperature the ^{19}F NMR spectrum showed that the two SF_4 triplets have collapsed to a single broad resonance at −63·4, the SSF_2 has increased in intensity and the FSSF peak has diminished to a very low intensity. Fluorosulfanes, S_nF_2 with $n > 3$ were unable to be observed by ^{19}F NMR. (233) The nature of the adduct of chlorine with bis-(*p*-fluorophenyl)sulfide in CH_2Cl_2 was investigated. (234) It was found that a rapid equilibrium exists between adduct and starting material. The equilibrium, [493], is likely to be the best description of the process in

$$(F\phi)_2S + Cl_2 \rightleftharpoons (F\phi)_2S{-}Cl_2$$

[493]

solution. At low temperature (−39°) only one multiplet is observed for the fluorine nuclei, which moves to high frequency with an increasing ratio chlorine/sulfide (from 268·3 Hz to 3202 Hz high frequency with respect to C_6F_6; 94·1 MHz?). Tetrafluoro-1,3-dithietane, [494],



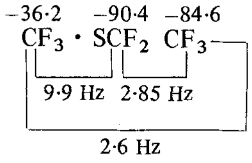
[494]

$J_{12} = 5{\cdot}19$ Hz
$J_{13} = 137{\cdot}06$ Hz
$J_{14} = 31{\cdot}91$ Hz
$J(^{13}C{-}F) = -315{\cdot}31$ Hz
$J(^{13}CSCF) = 13{\cdot}49$ Hz

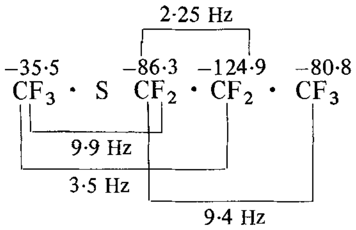
$D_{12} = 53{\cdot}61$ Hz
$D_{13} = -450{\cdot}08$ Hz
$D_{14} = 16{\cdot}08$ Hz

was observed in isotropic (70% in CF_3CCl_3) and lyotropic crystalline medium ($D_2O{-}C_{10}H_{21}SO_4Na_2{-}C_{10}H_{21}OD{-}Na_2SO_4$) by ^{19}F and ^{13}C NMR. (235) The signs were chosen such that the geminal F-F coupling was positive. Interchange of *cis* and *trans* coupling, J_{12} and J_{14}, gave an equally good NMR analysis. In the lyotropic mesophase the indirect and direct couplings and the chemical shifts were extracted. (235) Only the experimental direct couplings, D_{ij}, with signs relative to positive J_{13}, are reported for [494]. The values of D_{ij} for [494] are for a temperature of 26°C and concentration of 3·02% w/w. These parameters, in fact, vary in general with both temperature and concentration. The nematic phase results permitted the unambiguous assignment of the smaller coupling ($^4J_{FF} = 5{\cdot}19$ Hz) to the *cis*-arrangement. It was also possible to conclude that the anisotropic indirect contribution to the spin-spin coupling is negligible in this molecule. From the spectra, in addition, it was not possible to determine all bond distances. However, assuming the values of the C-F and C-C distance, an $\widehat{FCF}$ angle value of 109·2° could be calculated. (235)

Photolysis of $CF_3SOC(O)CF_2CF_3$ and $CF_3SOC(O)CF_2CF_2CF_3$ gave some previously unreported sulfides, $CF_3SCF_2CF_3$, [495], and $CF_3SCF_2CF_2CF_3$, [496]. (236) The fluorine resonance for CF_3S– occurs at *ca.* –36, which is typical of trifluoromethyl groups bonded to sulphur. Fluorination of bis(perfluoroalkyl) sulfides with ClF led to some new derivatives, [497] to [500], such as $CF_3SF_2CF_3$, $CF_3SF_2CF_2CF_3$ and $CF_3SF_2CF_2CF_3$. (236) The spectrum of [497] is first order. The higher members of the series have much

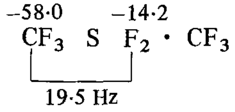


[495]

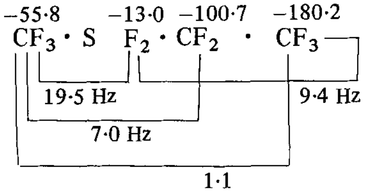


[496]

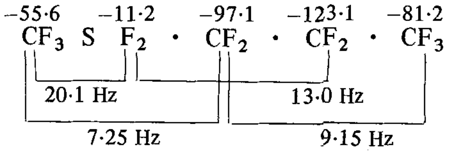
more complex spectra owing to the magnetic non-equivalence (AA'XX') of the fluorines bonded to the sulfur atom and of those of the α-methylene carbon atom. The analysis of these compounds is, however, incomplete and it will be the subject of further investigation. Some bis(perfluoroalkyl) sulphoxides, ([501] to [504]), were



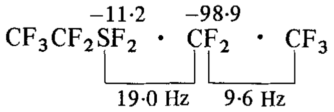
[497]



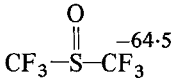
[498]



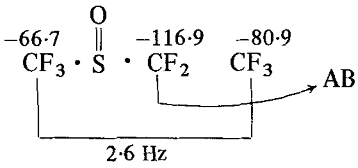
[499]



[500]



[501]

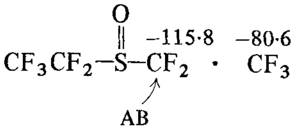


$J(F_A \cdot F_B) = 242$ Hz

$J(CF_3S \cdot F_A) = 14{\cdot}0$ Hz

$J(CF_3S \cdot F_B) = 10{\cdot}0$ Hz

[502]

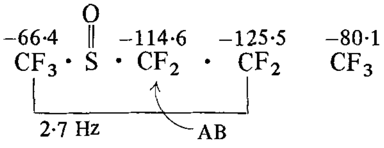


$J(F_A \cdot F_B) = 228$ Hz

$J(F_A \cdot CF_3) = 3{\cdot}8$ Hz

$J(F_B \cdot CF_3) = 2{\cdot}2$ Hz

[503]



$J(F_A \cdot F_B)$ 242 Hz

$J(F_A \cdot CF_3S) = 15{\cdot}0$ Hz

$J(F_B \cdot CF_3S) = 8{\cdot}8$ Hz

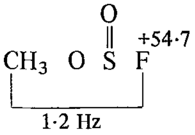
$J(F_A \cdot CF_3) = 9{\cdot}1$ Hz

$J(F_B \cdot CF_3) = 9{\cdot}1$ Hz

[504]

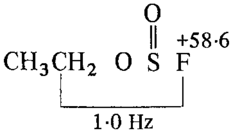
also described. (236) The resonances assigned to fluorines of the trifluoromethyl groups bonded directly to >S=O appear at −64·5 to −66·7, which is considerably lower than values observed for compounds $CF_3S(O)X$ where $X = OCH_2CF_3$, NH_2, OCH_2CH_3, Cl, F, O_2CCF_3. (237) For these molecules the α-methylene fluorines are magnetically non-equivalent.

Partially fluorinated sulphinyl esters, $CF_3S(O)OR$, were prepared by the alcoholysis of trifluoromethylsulfinyl fluoride, $CF_3S(O)F$. (237) Analogous reactions with the mercaptans, ethanethiol and methanethiol, do not give the thiolsulfinates but rather disulfides, $RSSCF_3$. Primary and secondary amines also react with $CF_3S(O)F$ to give mono- and bis- (trifluoromethylsulfin)amides. (237) The new compounds characterized by NMR, together with two alkyl fluorosulfites already known and included for comparison, (238) are shown in [505] to [513]. The presence of CF_3S– or $CF_3S(O)$– group may



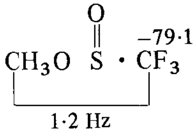
$CH_3\ O\ \overset{\overset{O}{\|}}{S}\ F$

[505]



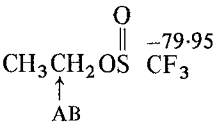
$CH_3CH_2\ O\ \overset{\overset{O}{\|}}{S}\ F$

[506]



$CH_3O\ \overset{\overset{O}{\|}}{S} \cdot CF_3$

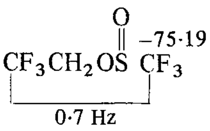
[507]



$CH_3CH_2O\overset{\overset{O}{\|}}{S}\ CF_3$

$J(H_A \cdot CF_3) = 0·6$ Hz
$J(H_B \cdot CF_3) = 1·1$ Hz

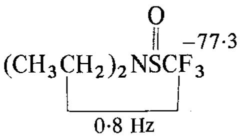
[508]



$CF_3CH_2O\overset{\overset{O}{\|}}{S}\ CF_3$

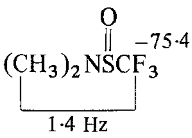
$J(F_A \cdot SCF_3) = 0·6$
$J(F_B \cdot SCF_3) = 1·0$

[509]



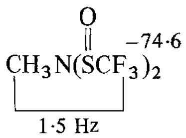
$(CH_3CH_2)_2N\overset{\overset{O}{\|}}{S}CF_3$

[510]



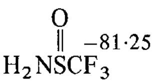
$(CH_3)_2N\overset{\overset{O}{\|}}{S}CF_3$

[511]



$CH_3N(\overset{\overset{O}{\|}}{S}CF_3)_2$

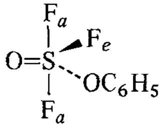
[512]



$H_2N\overset{\overset{O}{\|}}{S}CF_3$

[513]

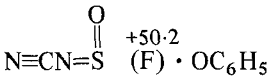
be easily determined from NMR spectra since the fluorine resonance in the former occurs over the range −35 to −55 and in the latter over the range −74 to −85. (237) The resonance observed at −46·3 may be assigned as CF_3S- rather than $CF_3S(O)$ and consequently must arise from the presence of $CF_3SSCH_2CH_3$. (237) The reaction of $(CH_3)_3SiOC_6H_5$ with OSF_4 gave $C_6H_5O\underset{\underset{O}{\|}}{S}F_3$, [514]. (239) The



$F_a = +88{\cdot}15$
$F_e = +67{\cdot}40$
$J(F_a \cdot F_e) = 202{\cdot}87$ Hz

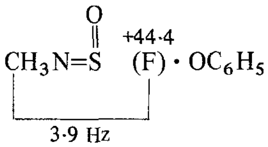
[514]

NMR data shown in [514] suggest a trigonal-bipyramidal structure, where one F_e, the phenoxy group and the oxygen atom lie in the plane; the other fluorines, F_a, are in axial orientation. Reaction of [514] with $(CH_3)_3SiN{=}C{=}N{-}Si(CH_3)_3$ gave [515]. (239) [514] treated with $[(CH_3)_3Si]_2NCH$ gave, on the contrary, [516]. (236) The treatment of [514] with $CF_3C[OSi(CH_3)_3]{=}NSi(CH_3)_3$ gave [517]. (239)



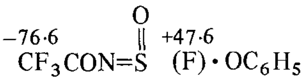
$N{\equiv}CN{=}\overset{\overset{O}{\|}}{S}\overset{+50{\cdot}2}{(F)} \cdot OC_6H_5$

[515]



$CH_3N{=}\overset{\overset{O}{\|}}{S}\overset{+44{\cdot}4}{(F)} \cdot OC_6H_5$

[516]



$\overset{-76{\cdot}6}{CF_3}CON{=}\overset{\overset{O}{\|}}{S}\overset{+47{\cdot}6}{(F)} \cdot OC_6H_5$

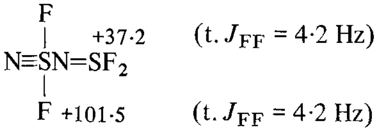
[517]

The reaction of fluorosulphuryl isocyanate, FSO_2NCO, with various alkali metal fluorides were examined to determine whether addition products would form. (240) Solid adducts having a molar ratio, $FSO_2NCO : MF$, close to 1:1 and with M = Cs, K, and Na were obtained. Physical and chemical data supported formulation of these adducts as $M^+[N(SO_2F)C(O)F]$. Two fluorine resonances, split into doublets ($^4J_{FF}$ = 15 to 16 Hz), were displayed by these adducts: one at −46 to −47·7 (SO_2F) and the other at −3·9 to −4·7 [C(O)F]. The hitherto unreported chlorodifluorosulphur(VI) oxide hexafluoroarsenate(V), $OSClF_2^+[AsF_6]^-$, was prepared by the reaction of ClF, AsF_5 and OSF_2. (241) The ^{19}F NMR spectrum of this compound in a large excess of anhydrous HF ($\delta = -201$) at room temperature showed a single peak at +70. The lack of a fluorine signal attributable to $AsF_6^{\ominus}$ could arise from solvent exchange. The ^{19}F chemical shift

$OSF_3^{4\oplus}$	+32	OPF_3	−94·8
$OSClF_2^{\oplus}$	+70	$OPClF_2$	−48·6

[518]

of $OSClF_2^+$ shown in [518] is compared with OSF_3^{4+}, OPF_3 and $OPClF_2$. (241) The first sulphur-nitrogen compound, [519], containing SN single, double and triple bonds was described. (242) Perfluoroalkanesulfinic acids, [520] and RS(O)OH, were isolated for the first time. (243)



$N{\equiv}S(F)_2N{=}SF_2$

+37·2 (t. J_{FF} = 4·2 Hz)

+101·5 (t. J_{FF} = 4·2 Hz)

[519]

$\overset{-78}{CF_3}S(O)OH$

[520]

Selenium, tellurium and tungsten

The results concerning the temperature dependence of the proton NMR spectra of dimethyl-, diethyl- and diisopropyl- selenium difluoride and the ^{19}F NMR spectrum of diisopropylselenium difluoride, $[(CH_3)_2CH]_2SeF_2$ were reported. (244) Such a fluorine spectrum exhibits a single peak at room temperature which broadens on cooling. At −60° one has the expected triplet, (J_{HF} = *ca.* 7 Hz) along with satellites due to ^{77}Se–^{19}F coupling (J = 642·1 Hz). The results of such a study which was mainly considered via ^1HNMR spectroscopy, suggest that the rate-determination step for the fluorine exchange process in R_2SeF_2 molecules is mainly heterolytic Se–F bond breaking, i.e. a first order dissociative process as the following: (244) $R_2SeF_2 \rightarrow R_2SeF^{\oplus} + F^{\ominus}$. The reactions of tellurium hexafluoride with silylamines, $R_2N \cdot SiMe_3$ were described in detail. (245) Dialkylaminotellurium pentafluorides, $TeF_5 \cdot X$, and some tellurium tetrafluorides, $TeF_4 \cdot X_2$, were prepared (Table LXV). ^{125}Te–^{19}F couplings (*ca.* 3000 to 4000 Hz) and ^{123}Te–^{19}F couplings (*ca.* 3000 to 3150 Hz) were also observed. The ^{19}F NMR spectra of the tellurium tetrafluorides consist of two triplets in agreement with the *cis*-orientation of the two amino groups. (245) Tungsten hexafluorides and tungsten oxotetrafluorides were studied

TABLE LXV

^{19}F NMR data of tellurium(VI) pentafluoride[a], TeF_5X, and tellurium(VI) tetrafluorides[a], TeF_4X_2 (245)

X	δ_A	δ_B	J_{AB}(Hz)
$TeF_5 \cdot NMe_2$	−37·4	−59·6	168
$TeF_5 \cdot NEt_2$	−33·9	−55·9	165
$TeF_5 \cdot NC_4H_8$	−35·8	−55·7	172
$TeF_5 \cdot NMeSiMe_3$	−37·9	−53·0	170
$TeF_5 \cdot N(Me)C_2H_4N(Me)SiMe_2F$	−35·0	−59·5	173
$TeF_4 \cdot (NMe_2)_2$	−47·5	−78·4	135
$TeF_4 \cdot (NMe_2)(NEt_2)$	(δ_{AB} = 32·6)		142

[a] The fluorine spectra exhibit second-order AB_4 and A_2B_2 pattern.

by both ^{19}F and ^{183}W NMR spectroscopy with the help of ^{19}F {^{183}W} double-resonance experiments. (246) These are the first reported measurements of tungsten chemical shifts. The relative signs of various spin-spin couplings were also obtained, making possible certain unequivocal structural assignments. The compounds studied are shown in Table LXVI together with the ^{19}F NMR data. The

TABLE LXVI

^{19}F NMR parameters of WF_6 and WOF_4 derivatives (246)

			$J(^{183}W–^{19}F)^b$		
	$\delta(F_c)^a$	$\delta(F_t)^a$	F_c	F_t	$J(F_c \cdot F_t)^b$
WF_6	+162		44		
WF_5OMe	+116	+87	±43	±33	±66
cis-$WF_4(OMe)_2$	+61	+41	±45	±25	±67
cis-$WF_3(OMe)_3$		+16			
trans-$WF_3(OMe)_3$	+34	+10	45		62
cis-$WF_2(OMe)_4$		−20		12	
$WF(OMe)_5$		−42			
$WF_5(OPh)$	+129	+115	±42	±38	±63
cis-$WF_4(OPh)_2$	+85	+78	35	38	62
WOF_4, OMe_2	+61		67		
$WOF_4, OP(OMe)_2Me$	+62		67		
$WOF_4, OS(OMe)_2$	+66		67·5		
WOF_5^-	+51	−81	±71	∓58	±53
$(F_4OWFWOF_4)^\ominus$	+63	−142	±70	∓49	±58

[a] F_t refers to a fluorine atom *trans* to a substituent (0), while F_c indicates a fluorine atom *trans* to another fluorine.

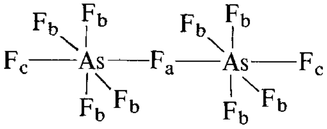
[b] For the relative signs obtained it should not be assumed that there is necessarily any relation between the signs quoted for different compounds.

compounds studied contain octahedrally co-ordinated tungsten. The spectroscopic properties of the WOF_4,L complexes are consistent with a monomeric structure having oxygen and L in *trans*-positions. The ^{19}F chemical shifts of $WF_{6-n}(OMe)_n$, $n = 1$ to 3, may be represented by the equation $\delta_F = 45c + 68t$, where δ_F is chemical shift relative to WF_6 ($\delta = +162$) and c and t are the number of methoxy-groups respectively *cis* and *trans* to the fluorine atom. δ_F is dominated by the variation of the effective nuclear charge; the ^{19}F shift moves to lower frequency as the number of less electronegative methoxy-groups increases. (246)

VI. COMPLEX FLUORIDE ANIONS

The ^{19}F NMR spectrum at low temperature of bifluoride ion, as tetraalkylammonium salts, dissolved in aprotic solvents, shows a doublet (J = 120·5 Hz). (247) The two fluorines in $FHF^{\ominus}$ are symmetric with respect to the hydrogen, on the NMR time scale. The shielding of $FHF^{\ominus}$ is temperature dependent: (247) from −145·5 to −149·5 going from −20° to +70°C. In the investigation of the methods for the preparation of high purity $LiAsF_6$, the commercial $HAsF_6$ was studied by IR and NMR. (248) Such a study suggests that in addition to $AsF_6^{\ominus}$ ions (−64·3 with $J(^{75}As^{19}F)$ = 933 Hz) the commercial $HAsF_6$ contains several percent of fluoroarsenate species (probably $AsF_5OH^{\ominus}$ and $AsF_4(OH)_2^{\ominus}$) and smaller amounts of other fluoroarsenate species (possibly the dimeric or polymeric anions). Solutions of the acids SbF_5, AsF_5 and PF_5 were investigated in HF as solvent. (249) Cryoscopic and conductimetric measurements showed that AsF_5 dissolves to form the strong electrolyte $H_2F^{\oplus}As_2F_{11}^{\ominus}$. In such conditions no ^{19}F NMR evidence was found for the As_2F_{11} ion. Solutions of AsF_5 in HF showed only one average absorption at all temperatures, which is likely the result of rapid exchange between $As_2F_{11}^{\ominus}$ and the solvent and presumably also with any small concentrations of AsF_5 and $AsF_6^{\ominus}$ ions, which may be present. The dimeric anion was isolated as the tetraethylammonium and tetrabutylammonium salts. (249) These salts are soluble in SO_2 and the ^{19}F NMR spectra of these solutions consisted of a single broad line in the fluorine-on-arsenic region. $Bu^nN^{\oplus}AsF_6^{\ominus}$ in $SO_2ClF + SO_2$ as solvent displays a ^{19}F NMR spectrum constituted by a 1:1:1:1 quartet [$I(^{75}As) = 3/2$; J(As–F) = 900 Hz). This coupling persists down to *ca.* −90°, then the absorption broadens and collapses to a single line which is relatively sharp at −105°. This behaviour is associated with rapid relaxation of the quadrupolar ^{75}As nucleus at low temperature. At room temperature an SO_2ClF solution of Bu_4N

product gave a broad signal in the fluorine-on-arsenic region. (249) At $-140°$ a more complicated spectrum appears: a single line at $-61{\cdot}6$, which can be assigned to $AsF_6^\ominus$ ions; then three other resonances at $-21{\cdot}1$, $-48{\cdot}6$ and -85, with intensity ratio 1 : 8 : 2, which can be attributed to F_a, F_b and F_c respectively of the $As_2F_{11}^\ominus$ (shown in [521]). The coupling constants could also be



[521]

extracted and had the following values: $J_{ab} = 51$ Hz, $J_{bc} = 127$ Hz and $J_{ac} < 10$ Hz. The reaction of Me_2PF_3 with several *N*-trimethylphosphine imines, $Me_3SiN{=}PR_3$, was investigated. (250) Salts of the hitherto unknown dimethyltetrafluorophosphate anion, $[Me_2P(N{=}PR_3)_2]^\oplus[Me_2PF_4]^\ominus$ were obtained. The formation of such salts was established by NMR spectroscopy. The fluorine resonance consisted of a doublet of septets at $-20{\cdot}9$ ($^1J_{PF} = 856$ Hz, $^3J_{HF} = 10$ Hz). The NMR data are consistent with an octahedral structure of the anion; the possibility, however, of rapid positional exchange processes within the fluoroanion cannot be excluded. (250)

The reactions of V_2O_5 and vanadates with anhydrous HF, in an attempt to isolate a solid $VOF_4^\ominus$ salt, were studied. (251) When vanadium pentoxide and caesium fluoride reacted in anhydrous HF at $-30°$, a green solution was obtained, from which crystals of $CsVOF_4$(C_{4v} symmetry) were obtained. The ^{19}F NMR spectra in anhydrous HF or 49% acqueous HF solution gave a broad doublet at $+57{\cdot}7$ (measured relative to solvent HF, $\delta_F = -201$). The V–F coupling was 120 Hz at $-20°$ in 49% HF and 140 Hz at $-80°$ in anhydrous HF. The shape of the observed ^{19}F spectra are consistent with a partially collapsed spectrum of fluorines coupled to a nucleus (^{51}V) with $I = 7/2$. It is suggested that the $VOF_4^\ominus$ ion in solution may be in rapid interconversion between C_{4v} and C_{2v} symmetries (square pyramidal and trigonal bipyramidal arrangement) or rapid exchange amongst the fluorines in both these symmetries. In such situations the fluorines will appear to be magnetically equivalent and also the electric field gradient at the ^{51}V nucleus will be averaged to a small value by the rapid intermolecular motion such as to allow the observation of the V–F coupling. (251)

The isolation and spectroscopic properties of the species SbF_3,

$SbF_4^{\ominus}$ and $SbF_5^{2\ominus}$ were described. (252) Dichloromethane or acetonitrile solutions containing $SbF_4^{\ominus}$ failed to reveal a ^{19}F NMR signal. Only when the F : Sb ratio was in excess of 4 : 1, a relative sharp signal was observed at room temperature, −69·1 in CH_2Cl_2 and −66·7 in CH_3CN, which may be compared with the value of *ca.* −55 for SbF_3 and *ca.* −150 for $F^{\ominus}$ in CH_3CN. For the pure $SbF_4^{\ominus}$ ion, as well for the parent SbF_3, ^{121}Sb–^{19}F (I = 5/2) and ^{123}Sb–^{19}F (I = 7/2) couplings produce resonances so diffuse as to escape detection (J(Sb–F) = *ca.* 1800 Hz). Only in presence of an excess of fluoride ions, ligand exchange become sufficiently rapid to produce a detectable resonance. (252)

The ^{19}F NMR spectra of a number of Nb^V complexes in aqueous and non-aqueous HF solution were investigated to confirm the presence of $NbOF_5^{2\ominus}$ and $NbF_6^{\ominus}$ ions and to establish whether or not the $NbF_7^{2\ominus}$ ion exists in solution. (253) $NbOF_5^{2\ominus}$ is present in solutions of Nb^V complexes containing up to 30% HF, and gives a signal at *ca.* −41. $NbF_6^{\ominus}$ ion is present when the HF concentration is more than 30% and resonates at *ca.* +44. Solutions of Nb^V complexes in anhydrous HF showed the existence of two overlapping signals: a doublet centred at *ca.* +92 with $W_{1/2}$ = *ca.* 3000 Hz, and a singlet at +94. The doublet arises from a partially collapsed $NbF_6^{\ominus}$ decet (^{93}Nb : I = 9/2) and the singlet must arise from another Nb–F ion, probably the $NbF_7^{2\ominus}$ ion. This is the first spectroscopic evidence for an ion, other than $NbF_6^{\ominus}$, which contains only Nb and F. An unusual feature of the ^{19}F NMR spectrum of solutions in anhydrous HF was that the HF peak splits into a sharp doublet at −75° ($^2J_{HF}$ = 490 Hz). (253)

Some 1:1 and 2 : 1 complexes of TaF_5 with organic ligands were investigated to determine whether or not they possess the same chemical and spectral properties of the analogous Nb complexes and to study the NMR behaviour of the $TaF_6^{\ominus}$ ion. (254) $AgTaF_6$ in several solvents shows a broad signal (*ca.* +41·5) in the region characteristic of $TaF_6^{\ominus}$ ion. The 1:1 complexes display a quite sharp signal, the chemical shift of which is too high (+61·5 to 81·5) to be due to $TaF_6^{\ominus}$ ions. The 2 : 1 complexes are not very soluble. The only complex sufficiently soluble to give a useful spectrum is $TaF_5 \cdot 2$ DMSO. Four peaks were observed, at +35·5, +42·8, +58·9 and +70·4. The peak at +42·8 was assigned to the $TaF_6^{\ominus}$ ion. The other peaks can only arise from other Ta–F species in solution. The NMR spectra of the (TaF_5, 2L) complexes are in marked contrast to those of the Nb complexes. (255) To a significant extent the differences in the NMR spectra may be attributed to the contrasting magnetic properties of the Nb and Ta nucleus. The completely collapsed octet for the $TaF_6^{\ominus}$ ion ($I = 7/2$ for ^{181}Ta) is due almost entirely to the very large quadrupole moment of Ta and the consequent fast rate of quadrupole relaxation. The analogous spectra of the $NbF_6^{\ominus}$ ions are extremely broad or show the Nb–F coupling (a decet because of $I = 9/2$ for ^{93}Nb); this is caused by the slower rate of quadrupole relaxation of Nb. (254)

REFERENCES

1. R. Fields, Ann. Reports on NMR Spectroscopy, 1972, **5A**, 99.
2. R. J. Abraham and R. H. Kemp, *J. Chem. Soc.*, B, 1971, 1240.
3. B. Pedersen, P. Klaeboe and T. Torgrimsen, *Acta Chem. Scand*, 1971, **25**, 2367.
4. L. Cavalli and R. J. Abraham, *Mol. Phys.*, 1970, **19**, 265.
5. L. Cavalli, "Fourth International Symposium on Magnetic Resonance", August 25–31, 1971, Israel. *J. Magn. Res.*, 1972, **6**, 298.
6. G. L. Flemming, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.*, C, 1971, 3829.
7. A. De Marco and G. Gatti, II Congresso Chimica Fisica, Pisa, Settembre 1971. *J. Magn. Res.*, 1972, **6**, 200.
8. R. J. Abraham and W. L. Oliver, *Org. Magn. Resonance*, 1971, **3**, 725.
9. A. De Marco and G. Gatti, *Org. Magn. Resonance*, 1971, **3**, 599.
10. R. E. A. Dear, E. E. Gilbert and J. J. Murray, *Tetrahedron*, 1971, **27**, 3345.
11. J. H. Atherton, R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, C, 1971, 336.
12. J. Burdon, I. W. Parsons and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 346.
13. Y. K. Kim, O. R. Pierce, W. X. Bajzer and A. G. Smith, *J. Fluorine Chem.*, 1971, **1**, 203.
14. P. Piccardi, M. Modena and L. Cavalli, *J. Chem. Soc.*, C, 1971, 3959.
15. P. Piccardi, *J. Chem. Soc., Perkin*, 1972, **1**, 2017.
16. R. Gregory, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.*, C, 1971, 1216.
17. N. O. Brace, *J. Org. Chem.*, 1971, **36**, 1904.
18. G. Camaggi and F. Gozzo, *J. Chem. Soc.*, C, 1971, 925.
19. N. J. M. Birdsall, A. G. Lee, Y. K. Levine and J. C. Metcalfe, *Biochim. Biophys. Acta*, 1971, **241**, 693.
20. (a) G. A. Olah and G. D. Mateescu, *J. Amer. Chem. Soc.*, 1971, **93**, 781.
20. (b) K. G. R. Pachler and P. L. Wessels, *J. Mol. Structure*, 1970, **6**, 471.
21. W. J. Feast, W. K. R. Musgrave and N. Reaves, *J. Pol. Sci.*, A-1, 1971, **9**, 2733.
22. J. Burdon and I. W. Parsons, *Tetrahedron*, 1971, **27**, 4533.
23. N. Muller, and F. E. Platko, *J. Phys. Chem.*, 1971, **75**, 547.
24. N. Muller, and T. W. Johnson, *J. Phys. Chem.*, 1969, **73**, 2042.
25. P. A. Bernstein, F. A. Hohorst and D. D. Des Morteau, *J. Am. Chem. Soc.*, 1971, **93**, 3882.
26. C. T. Ratcliffe, C. V. Hordin, L. R. Anderson and W. B. Box, *J. Am. Chem. Soc.*, 1971, **93**, 3886.
27. M. A. Wuonola and W. A. Sheppard, *J. Org. Chem.*, 1971, **36**, 3640.
28. G. C. Barret, D. M. Hall, M. G. Hargreaves and B. Modarai, *J. Chem. Soc.*, C, 1971, 279.
29. G. Hägele, R. K. Harris and P. Sartori, *Org. Magn. Resonance*, 1971, **3**, 463.
30. H. Akiyama, F. Yamauchi and K. Ouchi, *J. Chem. Soc.*, B, 1971, 1014.

31. N. Muller and H. Simsohn, *J. Phys. Chem.*, 1971, **75**, 942.
32. G. H. Hall, W. J. Middleton and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 4778.
33. V. Grakanskas and K. Baum, *J. Org. Chem.*, 1971, **36** 2599.
34. (a) H. Ashton, B. Capon and R. L. Foster, *Chem. Commun.*, 1971, 512.
34. (b) W. H. Huestis and M. A. Raftery, *Biochemistry*, 1971, **10**, 1181.
35. D. J. Burton and H. C. Krutrsch, *J. Org. Chem.*, 1971, **36**, 2351.
36. P. H. Ogden, *J. Chem. Soc.*, C 1971, 2920.
37. F. Koster, T. P. Vasileff and G. L. Carlson, *Spectrochim. Acta*, 1971, **27**, 1633.
38. P. Tarrant, R. W. Whitfield and R. H. Summerville, *J. Fluorine Chem.*, 1971, **1**, 31.
39. E. Ishikawa and T. Muramatsu, *Bull. Chem. Soc., Japan*, 1971, **44**, 1699.
40. H. Ashton and B. Capon, *Chem. Commun.*, 1971, 513.
41. F. J. Weigert, *Org. Magn. Resonance*, 1971, **3**, 373.
42. K. Ishigure, Y. Tabata and K. Oshima, *Polymer J.*, 1971, **2**, 321.
43. L. Cavalli, 2nd European Symp. Polymer Spectroscopy, Milan, June 1971, 17.
44. D. Carcano, M. Modena, M. Ragazzini and O. Pilati, *Chim. Ind. (Milan)*, 1971, **53**, 547.
45. K. Ishigure, Y. Tabata and K. Oshima, *Macromolecules*, 1970, **3**, 27.
46. Z. Veksli, J. N. Herak, P. Hedvig and J. Dobo', *European Pol. J.*, 1971, **7**, 231.
47. H. Yamanaka, T. Yagi and K. Teramura, *Chem. Commun.*, 1971, 380.
48. W. R. Cullen and M. C. Waldam, *J. Fluorine Chem.*, 1971, **1**, 151.
49. D. R. Taylor, M. R. Warburton and D. B. Wright, *J. Chem. Soc.*, C, 1971, 385.
50. D. R. Taylor and D. B. Wright, *J. Chem. Soc.*, C, 1971, 391.
51. P. Piccardi and M. Modena, *Chem. Commun.*, 1971, 1041.
52. P. Piccardi, M. Modena and E. Santoro, *J. Chem. Soc.*, C, 1971, 3894.
53. J. Feeney, L. H. Sutcliffe and S. M. Walker, *Mol. Phys.*, 1966, **11**, 117.
54. D. S. Ashton and J. M. Tedder, *J. Chem. Soc.*, B, 1971, 1723.
55. J. A. Labinger, R. J. Braus, D. Dolphin and J. A. Osborn, *Chem. Commun.*, 1970, 612.
56. F. R. Jensen and B. Knickel, *J. Amer. Chem. Soc.*, 1971, **93**, 6339.
57. E. A. Nuoe and J. D. Roberts, *J. Amer. Chem. soc.*, 1971, **93**, 7261.
58. L. Phillips and V. Wray, *J. Chem. Soc.*, B, 1971, 1618.
59. L. D. Hall, R. N. Johnson, J. Adamson and A. B. Foster, *Can. J. Chem.*, 1971, **49**, 118.
60. L. D. Hall, R. H. Johnson, A. B. Foster and J. H. Westwood, *Can. J. Chem.*, 1971, **49**, 236.
61. P. W. Kent, R. A. Dwek and N. F. Taylor, *Tetrahedron*, 1971, **27**, 3887.
62. P. W. Kent and R. A. Dwek, *Biochem. J.*, 1971, **121**, 11.
63. P. W. Kent and R. C. Young, *Tetrahedron*, 1971, **27**, 4057.
64. R. Stephens, J. C. Tatlow and K. N. Wood, *J. Fluorine Chem.*, 1971, **1**, 165.
65. H. Günther and J. B. Pawlicrek, *Org. Magn. Resonance*, 1971, **3**, 267.
66. J. B. Pawlicrek and H. Günther, *J. Amer. Chem. Soc.*, 1971, **93**, 2050.
67. S. F. Campbell, J. M. Leach, R. Stephens and J. C. Tatlow, *J. Fluorine Chem.*, 1971, **1**, 85.
68. C. W. Jefford and W. Broeckx, *Helv. Chim. Acta*, 1971, **54**, 1479.
69. J. Homer and D. Callaghan, *J. Chem. Soc.*, B, 1971, 2430.
70. J. Homer and D. Callaghan, *J. Chem. Soc.*, B, 1969, 247.
71. C. F. Wilcox, *J. Amer. Chem. Soc.*, 1960, **82**, 414.
72. A. B. Clayton, D. Collins, R. Stephens and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 1177.
73. G. Camaggi, *J. Chem. Soc.*, C 1971, 2382.
74. R. fields, M. Green and A. Jones, *J. Chem. Soc.*, B, 1967, 270.
75. A. B. Clayton, W. J. Feast, D. R. Sayers, R. Stephens and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 1183.

76. A. M. Doyle and A. E. Padler, *J. Chem. Soc.*, C, 1971, 282.
77. W. J. Feast, W. K. R. Musgrave and R. G. Weston, *J. Chem. Soc.*, C, 1971, 937.
78. R. E. Banks, M. Bridge, R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, C, 1971, 1282.
79. W. J. Feast, W. K. R. Musgrave and R. G. Weston, *J. Chem. Soc.*, C, 1971, 1547.
80. M. G. Barlow, R. N. Haszeldine and R. Hubbard, *J. Chem. Soc.*, C, 1971, 90.
81. J. M. Birchall, R. N. Haszeldine, J. Nikokavouras and E. S. Wilks, *J. Chem. Soc.*, C, 1971, 562.
82. J. M. Birchall, R. N. Haszeldine and M. E. Jones, *J. Chem. Soc.*, C, 1971, 1341.
83. J. M. Birchall, R. N. Haszeldine and M. R. Jones, *J. Chem. Soc.*, C, 1971, 1343.
84. C. G. Moreland and C. L. Bumgardner, *J. Magn. Res.*, 1971, **4**, 20.
85. D. D. Callander, P. L. Coe, J. C. Tatlow and R. C. Terrel, *J. Chem. Soc.*, C, 1971, 1542.
86. W. L. White and R. Filler, *J. Chem. Soc.*, C, 1971, 2062.
87. R. Wasylishen and T. Schaefer, *Can. J. Chem.*, 1971, **49**, 3216.
88. R. Wasylishen and T. Schaefer, *Can. J. Chem.*, 1971, **49**, 94.
89. H. M. Hutton, J. B. Rowbotham, B. H. Barber and T. Schaefer, *Can. J. Chem.*, 1971, **49**, 2033.
90. T. J. Batterham and R. Bramley, *Org. Magn. Resonance*, 1971, **3**, 83.
91. J. Burdon, B. L. Kane and J. C. Tatlow, *J. Fluor. Chem.*, 1971, **1**, 185.
92. R. D. Chambers and D. J. Spring, *Tetrahedron*, 1971, **27**, 669.
93. C. M. Jenkins, A. E. Pedler and J. C. Tatlow, *Tetrahedron*, 1971, **27**, 2557.
94. J. Burdon, B. L. Kane and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 1601.
95. W. A. Sheppard, *Tetrahedron*, 1971, **27**, 945.
96. R. G. Pews, *Chem. Commun.*, 1971, 458.
97. P. L. Coe, G. M. Pearl and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 604.
98. (a) P. L. Coe and A. J. Uff, *Tetrahedron*, 1971, **27**, 4065.
98. (b) W. Adcock, D. G. Matthews and S. Q. A. Rizvi, *Austr. J. Chem.*, 1971, **24**, 1829.
99. R. D. Chambers, M. Hole, W. K. R. Musgrave and J. G. Thorpe, *J. Chem. Soc.*, C, 1971, 61.
100. J. B. Rowbotham, R. Wasylishen and T. Schaefer, *Can J. Chem.*, 1971, **49**, 1799.
101. S. L. Bell, R. D. Chambers, W. K. R. Musgrave and J. G. Thorpe, *J. Fluor. Chem.*, 1971, **1**, 51.
102. C. G. Allison, R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Fluor. Chem.*, 1971, **1**, 59.
103. R. D. Chambers, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc.*, C, 1971, 3384.
104. R. D. Chambers, W. K. R. Musgrave and K. C. Srivastava, *Chem. Commun.*, 1971, 264.
105. C. J. Drayton, W. T. Flowers and R. N. Haszeldine, *J. Chem. Soc.*, C, 1971, 2750.
106. R. D. Chambers, Y. A. Cheburkov, J. A. H. MacBride and W. K. R. Musgrave, *J. Chem. Soc.*, C 1971, 532.
107. R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, L. H. Sutcliffe and G. J. T. Tiddy, *Tetrahedron*, 1970, **26**, 71.
108. M. J. Robins and S. R. Naik, *J. Amer. Chem. Soc.*, 1971, **93**, 5277.
109. R. E. Banks, M. G. Barlow, R. N. Haszeldine and E. Phillips, *J. Chem. Soc.*, C, 1971, 1957.
110. (a) G. M. Brooke, W. K. R. Musgrave, R. J. D. Rutherford and T. W. Smith, *Tetrahedron*, 1971, **27**, 5653.
110. (b) F. Lautenschlaeger, M. Myre, F. Hopton and J. Wilson, *J. Heterocyclic Chem.*, 1971, **8**, 241.
111. W. J. Middleton, D. Metzger and K. B. Cunningham, *J. Fluor. Chem.* 1971, **1**, 69.

112. I. W. Parsons, P. M. Smith and J. C. Tatlow, *J. Fluor. Chem.*, 1971, **1**, 141.
113. W. J. Feast, W. K. R. Musgrave and N. Reeves, *J. Chem. Soc.*, C, 1971, 769.
114. G. M. Brooke, W. K. R. Musgrave and T. R. Thomas, *J. Chem. Soc.*, C, 1971, 3596.
115. J. Burdon, J. G. Campbell, I. W. Parsons and J. C. Tatlow, *J. Chem. Soc.*, C, 1971, 352.
116. R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, 1971, **36**, 2188.
117. S. Rodmar, B. Rodmar, M. K. Sharma, S. Gronowitz, H. Christiansen and U. Rosen, *Acta Chem. Scand.*, 1968, **22**, 907.
118. S. Gronowitz and U. Rosen, *Chemica Scripta*, 1971, **1**, 33.
119. S. Rodmar, L. Moraga, S. Gronowitz and U. Rosen, *Acta Chem. Scand*, 1971, **25**, 3309.
120. S. Rodmar, S. Gronowitz and U. Rosen, *Acta Chem. Scand.*, 1971, **25**, 3841.
121. J. Burdon and I. W. Parsons, *J. Chem. Soc.*, C, 1971, 355.
122. J. Burdon and I. W. Parsons, *Tetrahedron*, 1971, **27**, 4553.
123. J. W. Finsley, J. Feeney and L. H. Sutcliffe, "Progress in NMR Spectroscopy", Vol. 7, Pergamon Press, 1971.
124. L. Phillips and V. Wray, *J. Chem. Soc.*, B, 1971, 2068.
125. L. Phillips and V. Wray, *J. Chem. Soc.*, B, 1971, 2074.
126. S. Rodmar, *Mol. Phys.*, 1971, **22**, 123.
127. (a) S. Mohanty and H. J. Bernstein, *J. Chem. Phys.*, 1971, **54**, 2254.
127. (b) S. Mohanty, *Phys. Review*, A, 1971, **4**, 136.
128. W. B. Smith and A. M. Ihrig, *J. Phys. Chem.*, 1971, **75**, 497.
129. (a) A. J. Dale, *Spectrochim. Acta*, 1971, **27**, 81.
129. (b) W. T. Raynes and M. A. Raza, *Mol. Phys.*, 1971, **20**, 555.
130. J. W. Timberlake, J. A. Thompson and R. W. Taft, *J. Amer. Chem. Soc.*, 1971, **93**, 274.
131. F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 2361.
132. D. Ziessow, *Chem. Commun.*, 1971, 463.
133. K. Jameson and J. P. Reger, *J. Phys. Chem.* 1971, **75**, 437.
134. J. Gerritsen and C. MacLean, *J. Magn. Resonance*, 1971, **5**, 44.
135. J. Gerritsen and C. MacLean, *Spectrochim. Acta*, 1971, **27**, 1495.
136. J. Bulthuis and C. MacLean, *J. Magn. Resonance*, 1971, **4**, 148.
137. N. J. D. Lucas, *Mol. Phys.*, 1971, **22**, 147.
138. R. J. Abraham, D. B. MacDonald and E. S. Pepper, *J. Amer. Chem. Soc.*, 1968, **90**, 147.
139. K. L. Servis and F. R. Jerome, *J. Amer. Chem. Soc.*, 1971, **93**, 1535.
140. E. Abushanab, *J. Amer. Chem. Soc.*, 1971, **93**, 6532.
141. G. Govil, *Mol. Phys.*, 1971, **21**, 953.
142. M. S. Gopinathan and P. T. Narasimhan, *Mol. Phys.*, 1971, **21**, 1141.
143. L. Cavalli and R. K. Harris, unpublished results, *J. Magn. Res.*, 1973.
144. M. A. Cooper, H. E. Weber and S. L. Manatt, *J. Amer. Chem. Soc.*, 1971, **93**, 2369.
145. M. Tsutsui, "Characterization of Organometallic Compounds", Part II, R. G. Kidd, p. 398, Wiley-Int. 1971.
146. W. McFarlane, *Chem. Commun.*, 1971, 609.
147. R. B. Johannesen and R. W. Duerst, *J. Magn. Res.*, 1971, **5**, 355.
148. M. T. Bowers, T. I. Chapman and S. L. Manatt, *J. Chem. Phys.*, 1969, **50**, 5412.
149. K. Tanaka and G. Blyholder, *Chem. Commun.*, 1971, 736.
150. A. F. Berniaz, G. Hunter and D. G. Tuck, *J. Chem. Soc.*, A, 1971, 3254.
151. K. S. Mazdiyasni, B. J. Schaper and L. M. Brown, *Inorg. Chem.*, 1971, **10**, 889.
152. M. A. Kadina and V. A. Ponomarenko, *Zhurnal. Obshchei. Khimii.* (English translation), 1971, **41**, 169.

153. P. Fields, R. N. Haszeldine and A. F. Hubbard, *J. Chem. Soc.,* C, 1971, 3838.
154. W. R. Cullen and M. C. Waldman, *J. Fluor. Chem.,* 1971, **1**, 41.
155. P. S. Elmes, P. Leverett and B. O. West, *Chem. Commun.,* 1971, 747.
156. R. C. Dobbie, *J. Chem. Soc.,* A, 1971, 230.
157. J. Browning, M. Green and F. G. A. Stone, *J. Chem. Soc.,* A, 1971, 453.
158. A. M. Akena, D. S. Brown and D. G. Tuck, *Can. J. Chem.,* 1971, **49**, 1505.
159. J. Browning, C. S. Cundy, M. Green and F. G. A. Stone, *J. Chem. Soc.,* A, 1971, 448.
160. M. Green, S. K. Shakshooki and F. G. A. Stone, *J. Chem. Soc.,* A, 1971, 2828.
161. H. D. Empsall, M. Green, S. K. Shakshooki and F. G. A. Stone, *J. Chem. Soc.,* A, 1971, 3472.
162. A. Greco, M. Green and F. G. A. Stone, *J. Chem. Soc.,* A, 1971, 3476.
163. A. Bond and M. Green, *Chem. Commun.,* 1971, 12.
164. A. Bond, M. Green, B. Lewis and S. F. W. Lowie, *Chem. Commun.,* 1971, 1230.
165. J. Clemens, R. E. Davis, M. Green, J. D. Oliver and F. G. A. Stone, *Chem. Commun.,* 1971, 1095.
166. R. B. King and A. Efraty, *Inorg. Chem.,* 1971, **10**, 1376.
167. R. D. W. Kemmit and R. D. Moore, *J. Chem. Soc.,* A, 1971, 2472.
168. W. P. Cullen and F. L. Hou, *Can. J. Chem.,* 1971, **49**, 3404.
169. E. Bayer and H. P. Müller, *Tetrahedron Lett.,* 1971, 533.
170. R. S. Stephens, S. D. Lessley and R. O. Ragsdale, *Inorg. Chem.,* 1971, **10**, 1610.
171. L. K. Peterson and G. L. Wilson, *Can. J. Chem.,* 1971, **49**, 3170.
172. J. E. Parks, B. E. Wagner and R. H. Holm, *Inorg. Chem.,* 1971, **10**, 2472.
173. S. G. Katal'nikov, A. M. Voloshehnk, M. A. Sokal'skü and T. A. Kozik, *Russian J. Phys. Chem.,* 1971, **45**, 1028.
174. (a) J. W. Akitt, N. N. Greenwood and G. D. Lester, *J. Chem. Soc.,* A, 1971, 2450.
174. (b) J. Grobe and U. Möller, *Z. Naturforsch.,* 1971, **26**, 639.
175. J. E. Drake and N. P. C. Westwood, *J. Chem. Soc.,* A, 1971, 3300.
176. J. E. Drake, N. Goddard and N. P. C. Westwood, *J. Chem. Soc.,* A, 1971, 3305.
177. K. G. Sharp and T. D. Coyle, *J. Fluor. Chem.,* 1971, **1**, 249.
178. F. Höfler and W. Veigl, *Ang. Chem. Int. Ed.,* 1971, **10**, 919.
179. J. A. Gibson and A. F. Janzen, *Can. J. Chem.,* 1971, **49**, 2168.
180. W. Airey, G. M. Sheldrick, B. J. Aylett and I. A. Ellis, *Spectrochim. Acta,* 1971, **27**, 1505.
181. C. S. Liu and J. C. Thompson, *Inorg. Chem.,* 1971, **10**, 1100.
182. J. M. Birchall, R. N. Haszeldine, M. J. Newlands, P. H. Rolfe, D. L. Scott, A. E. Tipping and D. Ward, *J. Chem. Soc.,* A, 1971, 3760.
183. M. G. Barlow, G. L. Fleming, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.,* C, 1971, 2744.
184. G. L. Fleming, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.,* C, 1971, 3829.
185. G. L. Fleming, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.,* C, 1971, 3833.
186. R. F. Swindell, L. M. Zaborowski and J. M. Shreeve, *Inorg. Chem.,* 1971, **10**, 1635.
187. C. L. Bumgardner, E. L. Lawton and H. Carmichael, *J. Org. Chem.,* 1971, **36**, 3819.
188. I. Kapovits and A. Kalman, *Chem. Commun.,* 1971, 649.
189. R. A. De Marco and J. M. Shreeve, *Inorg. Chem.,* 1971, **10**, 911.
190. H. J. Emeleus and R. J. Poulet, *J. Fluor. Chem.,* 1971, **1**, 13.
191. R. E. Banks, R. N. Haszeldine and T. Myerscough, *J. Chem. Soc.,* C, 1971, 1951.
192. R. E. Banks, R. N. Haszeldine and B. Justin, *J. Chem. Soc.,* C, 1971, 2777.
193. L. M. Zaborowski and J. M. Shreeve, *Inorg. Chem.,* 1971, **10**, 407.
194. B. L. Dyatkin, K. N. Makarov and I. L. Knunyants, *Tetrahedron,* 1971, **27**, 51.

195. T. P. Forshaw and A. E. Tipping, *J. Chem. Soc.*, C, 1971, 2404.
196. J. Cantacuzene and J. Leroy, *J. Amer. Chem. Soc.*, 1971, **93**, 5263.
197. S. Ng, *J. Chem. Soc.*, A, 1971, 1586.
198. L. W. Reeves, R. C. Shaddick and K. N. Shaw, *Can. J. Chem.*, 1971, **49**, 3683.
199. (a) L. W. Reeves and K. N. Shaw, *Can. J. Chem.*, 1971, **49**, 3671.
199 (b) H. Dreeskamp and K. Hildenbrand, *Z. Naturforsch.*, 1971, **26**, 269.
199. (c) R. Demuth, J. Grobe and L. Steiner, *Z. Naturforsch.*, 1971, **26**, 731.
200. P. A. Bernstein, F. A. Hohorst, M. Eisenberg and D. D. DesMarteau, *Inorg. Chem.*, 1971, **10**, 1549.
201. H. Falius and K. P. Giesen, *Ang. Chem. Int. Ed.*, 1971, **10**, 555.
202. P. Cooper, R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, C, 1971, 3031.
203. O. Stelzer and R. Schmutzler, *J. Chem. Soc.*, A, 1971, 2867.
204. D. K. Kang, K. L. Servis and A. B. Burg *Org. Magn. Resonance*, 1971, **3**, 101.
205. R. C. Dobbie, *J. Chem. Soc.*, A, 1971, 2894.
206. M. Eisenhut and R. Schmutzler, *Chem. Commun.*, 1971, 1452.
207. M. J. C. Hewson, S. C. Peake and R. Schmutzler, *Chem. Commun.*, 1971, 1454.
208. G. O. Doak and R. Schmutzler, *J. Chem. Soc.*, A, 1971, 1295.
209. S. C. Peake, M. Field, M. J. C. Hewson and R. Schmutzler, *Inorg. Chem.*, 1971, **10**, 2723.
210. R. E. Duff, R. K. Oram and S. Trippett, *Chem. Commun.*, 1971, 1011.
211. R. E. Dunmor and R. Schmutzler, *J. Chem. Soc.*, A, 1971, 1289.
212. J. P. Albrand, A. Cogne, D. Gagnaire, J. Martin, J. B. Robert and J. Verrier, *Org. Magn. Resonance*, 1971, **3**, 75.
213. A. A. Pinkerton and R. G. Cavel, *J. Amer. Chem. Soc.*, 1971, **93**, 2384.
214. G. E. Graves, D. W. McKennon and M. Lustig, *Inorg. Chem.*, 1971, **10**, 2083.
215. R. G. Cavell, T. L. Charlton and W. Sim, *J. Amer. Chem. Soc.*, 1971, **93**, 1130.
216. D. W. H. Rankin, *J. Chem. Soc.*, A, 1971, 783.
217. B. Green, D. B. Sowerby and P. Clare, *J. Chem. Soc.*, A 1971, 3487.
218. J. S. Harman and D. W. A. Sharp, *Inorg. Chem.*, 1971, **10**, 1538.
219. J. S. Harman, M. E. McCartney and D. W. A. Sharp, *J. Chem. Soc.*, A, 1971, 1547.
220. E. R. Lory and D. M. Ritter, *Inorg. Chem.*, 1971, **10**, 939.
221. H. W. Schiller and R. W. Rudolph, *Inorg. Chem.*, 1971, **10**, 2500.
222. M. A. Bennett, G. B. Robertson, T. W. Turney and P. O. Whimp, *Chem. Commun.*, 1971, 762.
223. R. B. King and A. Efraty, *J. Amer. Chem. Soc.*, 1971, **93**, 5260.
224. W. M. Douglas and J. K. Ruff, *J. Chem. Soc.*, A, 1971, 3558.
225. P. Meakin, J. P. Jesson, F. N. Tebbe and E. L. Muetterties, *J. Amer. Chem. Soc.*, 1971, **93**, 1797.
226. A. A. Pinkerton and R. G. Cavell, *Inorg. Chem.*, 1971, **10**, 2720.
227. V. H. Binde, *Z. Anorg. Allg. Chem.*, 1971, **384**, 193.
228. (a) M. Bermann and J. R. VanWazer, *Ang. Chemie Int. Ed.*, 1971, **10**, 733.
228. (b) R. K. Harris, J. R. Woplin and R. Schmutzler, *Ber. Bunsenges. physik. Chem.*, 1971, **75**, 134.
228. (c) C. G. Moreland, R. J. Beam, C. W. Wooten and S. M. Horner, *Inorg. Nucl. Chem. Lett.*, 1971, **7**, 243.
229. R. J. Singer, M. Eisenhut and R. Schmutzler, *J. Fluor. Chem.*, 1971, **1**, 193.
230. M. G. Harris and J. B. Milne, *Can. J. Chem.*, 1971, **49**, 2937.
231. J. Bacon, P. A. W. Dean and R. J. Gillespie, *Can. J. Chem.*, 1971, **49**, 1276.
232. (a) P. A. W. Dean and R. J. Gillespie, *Can. J. Chem.*, 1971, **49**, 1736.
232. (b) R. J. Gillespie, B. Landa and G. J. Schrobilgen, *Chem. Commun.*, 1971, 1543.

233. B. Meyer, T. V. Oommen, B. Gotthardt and T. R. Hooper, *Inorg. Chem.*, 1971, **10**, 1632.
234. G. E. Wilson and M. M. Y. Chang, *Tetrahedron Lett.*, 1971, 875.
235. R. C. Long and J. H. Goldstein, *J. Chem. Phys.*, 1971, **54**, 1563.
236. D. T. Sauer and J. M. Shreeve, *J. Fluor. Chem.*, 1971, **1**, 1.
237. D. T. Sauer and J. M. Shreeve, *Inorg. Chem.*, 1971, **10**, 358.
238. F. Seel, J. Boudier and W. Gomblez, *Chem. Ber.*, 1969, **102**, 443.
239. S. P. von Halasz, O. Glemser and M. F. Feser, *Chem. Ber.*, 1971, **104**, 1242.
240. J. A. Roderiguez and R. E. Noftle, *Inorg. Chem.*, 1971, **10**, 1874.
241. C. Lau and J. Passmore, *Chem. Commun.* 1971, 930.
242. O. Glemser and R. Höfer, *Ang. Chem. Int. Ed.*, 1971, **10**, 815.
243. H. W. Roesky, *Ang. Chem., Int. Ed.*, 1971, **10**, 810.
244. K. J. Wynne, *Inorg. Chem.*, 1971, **10**, 1868.
245. G. W. Fraser, R. D. Peacock and P. M. Watkins, *J. Chem. Soc.*, A, 1971, 1125.
246. W. McFarlane, A. M. Noble and J. M. Winfield, *J. Chem. Soc.*, A, 1971, 948.
247. J. S. Martin and F. Y. Fujiwara, *Can. J. Chem.*, 1971, **49**, 3071.
248. E. W. Lawless, C. J. W. Wiegand, Y. Mizumoto and C. Weis, *Inorg. Chem.*, 1971, **10**, 1084.
249. P. A. W. Dean, R. J. Gillespie, R. Hulme and D. A. Humphreys, *J. Chem. Soc.*, A, 1971, 341.
250. W. Stadelmann, O. Stelzer and R. Schmutzler, *Chem. Commun.*, 1971, 1456.
251. J. A. S. Howell and K. C. Moss, *J. Chem. Soc.*, A, 1971, 270.
252. C. J. Adams and A. J. Downs, *J. Chem. Soc.*, A, 1971, 1534.
253. J. A. S. Howell and K. C. Moss, *J. Chem. Soc.*, A, 1971, 2481.
254. J. A. S. Howell and K. C. Moss, *J. Chem. Soc.*, A, 1971, 2483.
255. K. C. Moss, *J. Chem. Soc.*, A, 1970, 1224.

NMR and Conformations of Amino Acids, Peptides and Proteins–Appendix

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Due to the very long delay in publication of this review, it is felt that some attempt should be made to cover the intervening period, at least by highlighting some key references summarizing the recent advances made in the field. In general, advances have been made in areas where improved instrumentation has helped to overcome previous experimental difficulties.

The availability of very high magnetic fields (up to *ca.* 8 Tesla), probes for larger sample tubes (up to 20 mm O.D.), better software for Fourier Transform techniques allowing measurements of NOE effects and spin-lattice relaxation times (T_1), plus the ready availability of ^{13}C and ^{15}N labelled materials, and shift reagents, has led to a general acceptance by chemists and biologists of the potential of the NMR technique in the examination of biological systems.

Amino Acids and Derivatives

Detailed examination of a variety of amino acids has continued without pause. Proline and its derivatives have again been the most popular target, with further detailed conformational studies at different pH and in various solvents (254-261). Histidine is another popular amino acid (262) primarily due to the fact that in the ^1H and ^{13}C spectra of proteins, the histidine nuclei are often clearly resolved. A method for overcoming the uncertainty in assignment of the diastereotopic protons in amino acids, makes use of $^3J_{CH}$ to determine the preferred side chain conformation of some amino acids (263, 264). The library of ^{13}C (265, 266) and ^{15}N (267, 268) chemical shifts has continued to grow. Lanthanide ion shifts have been used to reinvestigate the conformation of L-azetidine-2-carboxylic acid (269) the results being similar to those found previously, La^{+++} binds only to the carboxylate group and not to the amino group nor to hydroxyl groups in the side-chain (270).

^{13}C spin-relaxation times have been measured to a high degree of accuracy in aqueous solution (271, 272). Convincing argument has suggested that it is vital to remove all paramagnetic impurities present in commercially available D_2O (272); e.g. in glycine $T_1(C{=}O) = 86$ seconds, far longer than measured previously.

Small Linear Peptides

The Karplus relationship between J_{NHCH} and torsion angle has been further refined (273-278). Bystrov in particular has been active in the theory and practical measurement of three-bond $^{15}N{-}H$ and $^{13}C{-}H$ coupling constants, as reported in a recent review (274). The coupling between the ^{15}N of the amide bond and the α-protons has been shown to follow a normal $\cos^2 \phi$ relationship, though the curve obtained is too shallow to be a reliable and sensitive measure of conformation (279).

The use of ^{13}C in defining the cis/trans nature of amide bonds preceding proline has been the subject of several groups (49, 280-283). Since proline is also found in the neurohypophyseal hormones, oxytocin and lysine-vasopressin angiotensin II, and in the releasing hormones thyrotropin-releasing hormone (TRH), luteinizing hormone releasing hormone (LRH) and others, the subject of the conformations of these small peptides has mushroomed considerably. It is not possible to provide all the references here, but useful reviews have been published (281, 284, 285). The general consensus seems to be that small linear peptides are not, as was originally suggested, in single conformations in solution, particularly in water, where there is no evidence for intramolecular hydrogen bonding (see, for instance, 286, 287). Both *cis* and *trans* proline are found in these compounds, the *trans* form being normally favoured (except when the preceding residue is phenylalanine (288)) and the ratio depends on the solvent used.

An examination of fully ^{13}C enriched TRH has recently been reported (289). ^{13}C spin-lattice relaxation times have also been reported, confirming the flexibility of these small linear peptides (e.g. 285, 290).

Several papers (291-294) have reported the possibility of using NMR to sequence small peptides, by high field analysis, NOE effects between the CH_α of one residue and the NH of another, and by complexation at the carboxylate end by Gd^{+++}. Finally in this section, the presence of cis/trans isomerism in peptides due to the presence of cyclic imino acids, or *N*-methylated amino acids, leads to differences in the pK_a of the acidic or basic functions present for each conformer. These can be measured by ^{13}C or ^{1}H NMR plotting chemical shift versus pH in the usual way (258, 288, 295, 296).

Cyclic Peptides

The literature has been very comprehensively covered in a recent review by Ovchinnikov and Ivanov (297). The last three years have been used to re-examine cyclic peptides examined previously, in the light of the newer techniques, higher fields, ^{13}C, T_1 measurements and shift reagents. Valinomycin, enniatin B and antanamide have all been shown to complex with metal ions in solution in "sandwiches", with ratios of 2 : 1 or 3 : 1 (peptide : metal ion) 285 p. 195, 297).

This adds further weight to the proposed mechanism of action of the cyclic antibiotics in which the peptide molecules are thought to stack up in the biomembrane in cylindrical formation, passing the ions from one to the other in a tunnelling effect.

The elucidation of those NH protons involved in intramolecular H-bonding has continued to be a source of high activity. The difficulty of differentiating between NH protons shielded from the solvent, and those which are involved in intramolecular H-bonding is still apparent. In addition to the combination of chemical shift temperature gradients, exchange with ^{2}H, and solvent delineation, nitroxyl radicals (285 p. 139) and solvent saturation methods (285, p. 159) have been used to good effect. Peptide ionophores have been shown to complex not only with metal ions, but also with NH_4^+ (298) and amino acid esters ($H_3N^+CH(R)COOR_1$) (285, p. 203). The novel technique of ^{23}Na NMR has been used to study the kinetics of complexation of valinomycin/sodium), by measurement of the T_1 of the sodium ions (299).

The assignment of NH protons in peptides is often a slow and difficult process requiring extensive homonuclear spin-decoupling experiments, and not generally applicable in FT mode. The triple resonance method of Campbell *et al.* (300) as applied to bacitracin in H_2O solution is a particularly attractive method which should be applicable to aqueous solutions of many complex peptides, in FT mode.

The other attractive technique is that of Gibbons *et al.*, i.e. the homonuclear INDOR approach, which not only provides the scalar decoupling experiment, but also significant NOE effects and time-resolved difference spectra as described earlier (294).

Work on the solution conformation of actinomycin D has been reviewed (301) the nature of the bonding of this molecule to DNA being one of the prime targets. Complex formation of this type has been the subject of several papers by Patel (302) and Krugh (303). ^1H studies of the aggregation of Actinomycin D in aqueous solution (304) and ^{13}C assignments (305) have been reported.

It is not possible to cover in this brief survey the continuing work on other cyclic peptides such as valinomycin, enniatin, beauvericin, antanamide, phalloidin, telomycin, stendomycin and other natural products, not to mention the large number of synthetic peptides whose conformation is of interest. The reviews mentioned above provide detailed information on these compounds.

Proteins and Enzymes

Although three or four years ago the spectra of proteins in the folded state seemed uninterpretable, high magnetic fields and/or 20 mm tubes, together with difference spectroscopy and lanthanide probes have meant that considerable progress is possible. Individual carbon sites of proteins in solution have been reported by Allerhand *et al.* (306). The Oxford group has shown considerable resolution enhancement of the ^1H spectrum of lysosyme (307). The same group has reported a probe method for simplification of protein spectra, making use of the fact that T_2 for NH's (~7 msec), aromatic CH's (~30 msec) and the C_2 histidyl protons (~150 msec) are very different from each other (308).

Benz and Roberts have reported some elegant studies of the unfolding of ribonuclease by guanidine hydrochloride, using the four histidine and residues as a probe for conformational changes (309).

There have been innumerable studies of the binding of small molecules and metal ions to enzymes, reviewed by Jardetsky *et al.* (310). One interesting application has been the ^{19}F study of the binding of racemic N-trifluoroacetyl phenylalanines to chymotrypsin, showing preferential binding of the L isomer (311). Binding of ^{13}CN, $^{13}CO_2$ and $H^{13}CO_3$ to carbonic anhydrase has been studied (312, 313).

Basic pancreatic trypsin inhibitor, a "small" peptide of 58 residues (molec. wt. 6,500) has been thoroughly examined by H^1 (314) and ^{13}C (315) NMR spectra. The stability of this peptide up to 85°C helps considerably in the analysis of the spectrum. In this compound there is clear evidence of slow rotation of the aryl rings of phenylalanine and tyrosine, leading to non-equivalence of the 2 and 6 protons or carbons.

In conjunction with this Review, a number of other reports should be consulted regularly. These include the Chemical Society Specialist Periodical Reports Vol. 1-7 and the proceedings of the 4 American peptide symposia already referred to.

Finally, the author apologizes for the brevity of this Appendix and for not mentioning all the aspects of NMR and conformation of amino acids and peptides which are undoubtedly worth their place. In order to do this properly, the Appendix would have to be twice as large as the initial Review.

REFERENCES

254. M. Ellenberger and L. Pogliani, *Biochem. Biophys. Res. Comm.*, 1974, **58**, 613.
255. M. Ellenberger, L. Pogliani, K. Haeuser and J. Valat, *Chem. Phys. Letters*, 1974, **27**, 419.
256. L. Pogliani and M. Ellenberger, *J. Amer. Chem. Soc.*, 1974, **96**, 1621.
257. M. Ellenberger and J. Valat, *Org. Mag. Res.*, 1975, **7**, 61.
258. G. R. Bedford and P. G. Sadler, *Biochim. Biophys. Acta.*, 1974, **343**, 656.
259. J. T. Gerig and R. S. McLeod, *J. Amer. Chem. Soc.*, 1973, **95**, 5725.
260. T. Prange, C. Garbey-Jaureguiberry, B. Roques and M. Anteunis, *Biochem. Biophys. Res. Comm.*, 1974, **61**, 104.
261. E. W. B. de Leer and J. M. van der Toorn, *Rec. Trav. Chem. Pays. Bas.*, 1975, **94**, 119.
262. R. J. Weinkam and E. C. Jorgensen, *J. Amer. Chem. Soc.*, 1973, **95**, 6084.
263. J. Feeney, P. E. Hansen and G. C. K. Roberts, *Chem. Commun.*, 1974, 465.
264. P. Hansen, J. Feeney and G. C. K. Roberts, *J. Mag. Res.*, 1975, **17**, 249.
265. W. Voelter, St. Fuchs, R. H. Seuffer and K. Zech, *Monatsh. Chem.*, 1974, **105**, 1110.
266. S. Tran-Dinh, S. Fermandjian, E. Sala, R. Mermet-Bouvier, M. Cohen and P. Fromageot, *J. Amer. Chem. Soc.*, 1974, **96**, 1484.
267. J. A. Sogn, W. A. Gibbons and E. W. Randall, *Biochem.*, 1973, **12**, 2100.
268. R. A. Cooper, R. L. Lichter and J. D. Roberts, *J. Amer. Chem. Soc.*, 1973, **95**, 3724.
269. F. Inagaki, S. Takahashi, M. Tasumi and T. Miyazawa, *Bull. Chem. Soc. Japan*, 1975, **48**, 853, 1590.
270. E. W. Robb, P. Choma and E. K. Onsager, *ACS Abstr.*, 1975, *ORGN*, 145.
271. I. M. Armitage, H. Huber, H. Pearson and J. D. Roberts, *Proc. Nat. Acad. Sci., U.S.A.*, 1974, **71**, 2096.
272. H. Pearson, D. Gust, I. M. Armitage, J. D. Roberts, R. E. Stark, R. R. Vold and R. L. Vold, *Proc. Nat. Acad. Sci., U.S.A.*, 1975, **72**, 1599.
273. V. N. Solkan and V. F. Bystrov, *Isvest. Akad. Nauk. U.S.S.R. Ser. Khim.*, 1974, **102**, 1308.
274. V. F. Bystrov, S. L. Portnova, T. A. Balashova, S. A. Kozmin, Y. D. Gavrilov and V. A. Afanasev, *Pure Appl. Chem.*, 1973, **36**, 19.
275. D. B. Davies and M. A. Khaled, *J. Chem. Soc., Perkin II*, 1973, 1651.
276. K. D. Kopple, G. R. Wiley and R. Tauki, *Biopolymers*, 1973, **12**, 627.
277. M. T. Cung, M. Marraud and J. Neel, *Macromolecules*, 1974, **7**, 606.
278. N. S. Ostlung and M. J. Prunish, *J. Mag. Res.*, 1974, **15**, 549.
279. J. A. Sogn, W. A. Gibbons, L. C. Craig and E. W. Randall, *ACS* Abs., *BIOL*, 1975, 238.
280. D. G. Gorman and F. A. Bovey, *J. Org. Chem.*, 1973, **38**, 2379.
281. I. C. P. Smith, R. Deslauriers and R. Walter, Chemistry and Biology of Peptides. (Proc. 3rd American Peptide Symp.) Ed. J. Meinhofer, Ann Arbor Science, Ann Arbor, Mich. 1972, p. 29.
282. K. Wüthrich, A. Tun-Kyi and R. Schwyzer, *FEBS Letters* 1972, **25**, 104.
283. W. Voelter and O. Oster, *Chem. Zeitung*, 1972, **96**, 586.

284. V. R. Hruby, Chapter I in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," Ed. B. Weinstein, Marcel Dekker Inc. N.Y. 1974.
285. Several papers in "Peptides, Chemistry, Structure and Biology" (Proc. 4th American Peptides Symposium) Ed. R. Walter and J. Meinhofer, Ann Arbor Science, Ann Arbor, Mich. 1975.
286. J. Feeney, G. R. Bedford and P. Wessels, *FEBS Letters*, 1974, **42**, 347.
287. A. F. Bradbury, A. S. V. Burgen, J. Feeney, G. C. K. Roberts and D. G. Smyth, *FEBS Letters*, 1974, **42**, 179.
288. K. Wüthrich and C. Grathwohl, *FEBS Letters*, 1974, **43**, 337.
289. S. Fermandjian, S. Fran-Dink, J. Savrda, E. Sala, R. Mermet-Bouvier, E. Bricas and P. Fromageot, *Biochem. Biophys. Acta*, 1975, **399**, 313.
290. R. Deslauriers, A. C. M. Paiva, K. Schaumburg and I. C. P. Smith, *Biochemistry*, 1975, **14**, 878.
291. T. Kasei and S. Sakamura, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 2155.
292. M. Anteunis and J. Gelon, *J. Amer. Chem. Soc.*, 1973, **95**, 6502.
293. J. H. Bradbury, M. W. Crompton and B. Warren, *Analyt. Biochem.*, **1974**, 62, 310.
294. W. A. Gibbons, D. Crepaux, J. Delayre, J. J. Dunand, G. Hajdukovic and H. R. Wyssbrod, ref. 285, p. 127.
295. R. A. Morton and S. S. Danyluk, *Canad. J. Chem.*, 1974, **52**, 2348.
296. C. A. Evans and D. L. Rabenstein, *J. Amer. Chem. Soc.*, 1974, **96**, 7312.
297. Yu. A. Ovchinnikov and V. T. Ivanov, *Tetrahedron*, 1975, **31**, 2177.
298. D. G. Davis, *Biochem. Biophys. Res. Comm.*, 1975, **63**, 786.
299. M. Shporer, H. Zemel and Z. Lux, *FEBS Letters*, 1974, **40**, 357.
300. I. D. Campbell, C. M. Dobson, G. Jeminet and R. J. P. Williams, *FEBS Letters*, 1974, **49**, 115.
301. H. Lackner, *Angew. Chem. Internat. Ed.*, 1975, **14**, 375.
302. D. J. Patel, *Biochemistry*, 1974, **13**, 1476, 2388 (and references therein).
303. T. R. Krugh and Yu C. Chen., *Biochemistry*, 1975, **14**, 4912 (and references therein).
304. N. S. Angerman, T. A. Victor, C. L. Bell and S. S. Danyluk, *Biochemistry*, 1972, **11**, 2402.
305. U. Hollstein, E. Breitmaier and G. Jung, *J. Amer. Chem. Soc.*, 1974, **96**, 8036.
306. E. Oldfield, R. S. Norton and A. Allerhand, *J. Biol. Chem.*, 1975, **250**, 6368, 6381, 6403.
307. I. D. Campbell, C. M. Dobson, R. J. P. Williams and A. V. Xavier, *J. Mag. Res.*, 1973, **12**, 30.
308. I. D. Campbell, C. M. Dobson, R. J. P. Williams and P. E. Wright, *FEBS Letters*, 1975, **57**, 96.
309. F. W. Benz and G. C. K. Roberts, *FEBS Letters*, 1973, **29**, 263.
310. O. Jardetsky and N. G. Wade-Jardetsky, *Ann. Rev. Biochem.*, 1971, **40**, 605.
311. B. C. Nicholson and T. M. Spotswood, *Aust. J. Chem.*, 1973, **26**, 135.
312. J. Feeney, A. S. V. Burgen and E. Grell, *Eur. J. Biochem.*, 1973, **34**, 107.
313. S. Koenig, R. Brown, T. Needham and N. Matwiyoff, *Biochem. Biophys. Res. Comm.*, 1973, **53**, 624.
314. K. Wüthrich and G. Wagner, *FEBS Letters*, 1975, **50**, 265.
315. W. Maurer, W. Haar and H. Rüterjans, *Z. Phys. Chem.*, 1974, **93**, 119.

SUBJECT INDEX

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