ANNUAL REPORTS ON NMR SPECTROSCOPY

Volume 3

E. F. Mooney

ANNUAL REPORTS ON

NMR SPECTROSCOPY

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ANNUAL REPORTS ON NMR SPECTROSCOPY

Edited by

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PREFACE

Many readers will wonder why, when this series has become so well established, it has been found necessary to change the title. The title, *Annual Review of NMR Spectroscopy*, was chosen as being descriptive of the aims of this series and, although no copyright on the title of a book exists, I was certain that this title had not previously been used by any publishing house. I deem it important that no two books should have the same title because, although books may be distinguished by the Author's or Editor's name, in this particular series, when so many Authors are contributing articles year by year, the title should be the distinctive feature.

I did not, at the time the title was chosen in 1965, realize that a non-profit foundation known as Annual Reviews Incorporated existed in the United States of America, nor that all their publications start with the words "Annual Reviews". As a courtesy to the foundation, therefore, and to avoid confusion in the origin of the title we decided to change the name of our series to *Annual Reports on NMR Spectroscopy*. Before any Fellow of the Chemical Society becomes hot under the collar at the so very obvious use of a title of the Chemical Society permit me to express our gratitude to the Chemical Society for agreeing to the use of this title and for their expression of confidence in this series as augmenting the new series of Specialist Reports published by the Society.

Despite a new name the general aims and intention of this series have not changed, and it is obvious, from the manner in which these Volumes have been received, that this series had been accepted as the *vade-mecum* of all those using NMR spectroscopy. I am sure that readers will appreciate how gratifying this is to me, as Editor, for the series is well advanced before the reviews of the Volumes are received. As this Volume is being published manuscripts for Volume Four are already being completed and many articles for Volumes Five and Six already planned.

It is also intended to assist future readers in finding the information by producing cumulative Indexes after every five Volumes; the first will therefore be prepared at the end of 1971.

Again, as in previous Volumes, a General Review of Proton Magnetic Resonance is presented and the increased number of references cited is ample evidence of the ever increasing use of NMR spectroscopy. The work concerned with Conformational Analysis has been updated, from Volume One, by the same author, thus maintaining the style and standard of presentation. Fluorine-19 Magnetic Resonance has also been reconsidered from the period covered in Volume One but, from the extensive studies being made of this nucleus it is clear that, like proton NMR, this field must in future be covered every year. The field of Steroids is dealt with very amply by an author who has been long associated with the spectroscopy of steroids, even long before the days of NMR, and I am sure that this contribution will be welcomed by all those working in this sphere. Finally the aspects of the NMR spectra of paramagnetic species is considered and, with the growing interest in the field of co-ordination chemistry, this chapter is again most welcomed.

To all the contributors of this Volume I would like to express my sincere appreciation for the high standard achieved in preparing their manuscripts; this has made my task all the more enjoyable. My sincere appreciation must also be extended to all my friends and colleagues throughout the world for their continuing support and encouragement.

Finally, in a year of changes and at the commencement of a new decade, I must draw the attention of all readers to the section on NMR units which defines the chemical shift scales used in this and all future Volumes.

ERIC F. MOONEY

Birmingham,
December, 1969

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THE CHEMICAL SHIFT SCALES

The choice between the tau, τ, and delta, δ, chemical shift scales for proton magnetic resonance has, until recently, been left very much to the preference of individuals. With the increasing use of other nuclei, and more especially hetero-nuclei double resonance, there has been an increasing tendency to use the signs of the chemical shift scales in differing senses.

The ASTM Committee, in reviewing this subject, actually recommended that low field shifts should be positive for proton, but negative for other nuclei! This would additionally have excluded the tau scale as, by definition, low field shifts are more negative. The draft IUPAC recommendations were also based upon low field shifts of all nuclei being positive, which is more sensible. The basis of the choice of low field shifts being positive is that these shifts also correspond to an increase in frequency. The recommendations given below have been successfully employed in the *Journal of Organic Magnetic Resonance* for the past year and, from the point of view of the majority of chemists using proton magnetic resonance, it simply means that the delta and *not* the tau scale is now used. It is the shift data of nuclei other than hydrogen which are affected but, as indicated on page 262, other complications of shift data have used negative values for the high field (low frequency) shifts.

Convention adopted for Chemical Shift Scales

1. All shifts will be denoted by the delta scale, low field shifts being shown as positive and high field shifts as negative values. In all cases the standard will take the reference shift of δ 0.0.
2. No other symbols to denote shifts at infinite dilution will be used.

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General Review of Proton Magnetic Resonance

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Department of Chemistry, The University, Bailrigg,
Lancaster, England

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ANY ATTEMPT to summarize a year's work on proton magnetic resonance immediately poses several problems to a would-be author. Information could be gleaned from abstract journals, but a wealth of useful data may be lost in this way, for example, much information on proton–heteronuclear coupling constants appears to be buried in articles bearing non-spectroscopic titles. The writer of this present chapter feels that a general survey should make available and briefly discuss the type of information which is perhaps easily missed, and that analysis in depth of narrowly defined topics is better dealt with in the other chapters found in these Reviews.

Accordingly, most of the results here presented have been taken directly from the original papers. The topics of Conformational Analysis and Paramagnetic species are described at length in other chapters, therefore they are only given cursory attention here. Similarly only passing reference is made to systems containing fluorine, and to carbohydrate studies.

I. EXPERIMENTAL TECHNIQUES

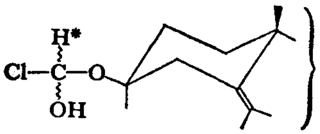
A. The sample

It is appropriate to commence by briefly discussing some aspects of sample preparation. Attention has again been drawn to problems associated with referencing. Tetramethylsilane (together with the analogous Ge, Pb and Sn derivatives) has been shown[1] to form weak complexes with such compounds as pyridine, nitrobenzene and aniline, with heats of formation of 1–2 kcal/mole. This corresponds to an additional shift of ca. 0·1 to 0·15 p.p.m., and emphasizes the problems associated with using internal reference standards. Neopentane or cyclohexane are suggested alternatives for such systems. The aqueous reference standard, DSS, is also prone to problems, for micelle formation has been found[2] in some systems containing paramagnetic ions. Concentrations should be kept below 2–3% and caution is advised in studies of electrolyte solutions. TMS has been found to decompose in trifluoroacetic acid solutions,[3] yielding a product with a signal at $\delta = 0{\cdot}48$ (presumably $CF_3CO_2SiMe_3$) and hence should only be added immediately prior to the spectral measurement.

A convenient method of obtaining PMR spectra from milligram samples (4 to 8 mg in 0·04 ml solvent) has been described,[4] in which the material, sealed in a short melting-point tube, is held annularly in the instrument probe by being immersed in a suitable solvent contained in a normal spinning sample tube. Improved resolution can be induced[5] by shaking the sample with a 10% solution of sodium dithionite in order to remove dissolved oxygen. The aqueous layer can remain while the spectrum is recorded. The addition of milligram amounts of basic alumina has been utilized[6] to suppress proton exchange and does not reduce ringing.

The solubility of some sparingly soluble compounds, including the steroids oestrone and prednisolone, has been enhanced[7] by the addition of ca. 5% antimony trichloride to the solvent (chloroform-*d* or carbon disulphide). Arsenic trichloride may be used with carbon tetrachloride, and chemical shifts are only slightly altered. The presence of *N*-methyl groups can be readily demonstrated[8] by the addition of two drops of trifluoroacetic acid to the spectral sample. A downfield shift of 0·5 to 0·7 p.p.m. is observed, corresponding to the change $\text{Me-N}< \rightarrow \text{Me-}\overset{\oplus}{\text{N}}\text{H}<$.

Reactions *in situ* have been described which are of use in the characterization of steroidal alcohols. In the first example[9] the normal spectrum is obtained, and is then re-run after the addition of excess freshly distilled chloral. For a series of chloralates thus prepared from some 3β-hydroxycholestenes and 3β- or 3β,17β-hydroxy-androstenes it has been found that two products, in varying ratios, are formed at each hydroxyl position, corresponding presumably to *R* and *S* chlorates (**1**). The shift and separation of these signals, which arise from H*, appear to be characteristic for the position of substitution—



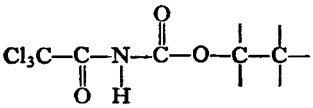
1

3β-H* Signals at $\delta = 5{\cdot}26, 4{\cdot}95$; $\Delta\delta\text{H}^* \simeq 0{\cdot}3$ p.p.m.

17β-H* Signals at $\delta = 4{\cdot}90, 4{\cdot}84$; $\Delta\delta\text{H}^* \simeq 0{\cdot}06$ p.p.m.

It is also observed that with Δ^5-sterols the vinylic proton is unshifted on complex formation, but that in Δ^4-sterols the vinylic C-4 proton shifts downfield by ca. 0·10 p.p.m. The combinations of changes observed in the proton shifts of H*, of the tertiary H(a) and also of angular methyl groups are reported to be characteristic for many steroid alcohols. A study of the mutarotation of *R* and *S* chloralates of optically active alicyclic alcohols has also been described.[10]

A further and similar *in situ* method for the classification of sterols[11] relies on the reaction of hydroxyl groups with trichloroacetylisocyanate (TAI). In the product (**2**) the NH signals appear at $\delta = 8$ to 9 as discrete singlets corresponding to each —OH group and the carbinol protons shift downfield



$$\text{Cl}_3\text{C}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{H}}{|}}{\text{N}}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\underset{|}{\overset{|}{\text{C}}}-\underset{|}{\overset{|}{\text{C}}}-$$

2

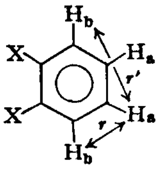
(0·5 to 0·9 p.p.m. for $-\text{CH}_2-\text{O}-$ and 1·0 to 1·5 p.p.m. for $-\overset{|}{\text{C}}\text{H}-\text{O}-$).

B. Specialized solvents

Considerable interest has been aroused in the use of liquid crystals in their nematic phase as solvents. The subject has recently been reviewed both with regard to the properties and uses of liquid crystals,[12] and to provide an introduction to the theory describing the spectra of solutes in oriented solvents.[13] The effect of variations in temperature, concentration and spinning speed on the spectra has been discussed.[14] The degree of orientation $|S|$ for a system should always be reported together with the above parameters and it is virtually linearly related to temperature. Addition of TMS can alter $|S|$ and should be avoided if possible. The variation of $|S|$ with temperature is potentially useful, in the analysis of complex spectra, for it allows the separation of direct and indirect coupling parameters. The critical spinning speed, above which orientation is destroyed, is a function of the magnet field strength [14,15] and can be as high as 200 Hz with superconducting magnet instruments, thus affording a considerable gain in resolution and also in sample temperature stability.

The use of the direct and the moment methods in the analysis of nematic phase spectra have been discussed with reference to 2,6-dibromopyridine and 1,2,4-trichlorobenzene.[16] There is an infinity of solutions for 2-spin systems if only line positions are used, but inclusion of intensity values reduced the total to two. Similarly with the 3-spin system, moment calculations allow solution unless a chemical shift is zero. In general[17] if a molecule has at least one more direct coupling than the number of independent orientation parameters, its geometry can be verified from the nematic phase spectrum. Thus if symmetry is absent, at least six direct couplings are needed.

Molecular and dipolar parameters have been determined for several symmetrically substituted benzenes. The internuclear ratios for a series of *ortho* disubstituted benzenes[18] (**3**)**a**–**c** are summarized in Table I. The direct and indirect couplings are of opposite sign. With the *meta*-disubstituted derivatives (**4a,b**)[19] the direct coupling is negative but it is not possible to



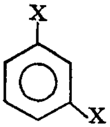
a. X = Br
b. X = Cl
c. X = CN

3

TABLE I

Interproton distance ratios for *ortho*-disubstituted benzenes (3a–c)

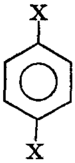
$x=$	Br	Cl	CN
r_B/r_A	1·985 ± 0·014	2·002 ± 0·014	1·994 ± 0·014
r/r_A	0·995 ± 0·010	1·017 ± 0·010	0·991 ± 0·010
r'/r_A	1·725 ± 0·007	1·742 ± 0·007	1·725 ± 0·007



a. X = Cl
b. X = Br

4

obtain accurate parameters for all the internuclear distances. When the two substituents are *para*-oriented (**5a–d**)[20] accurate determination is possible,

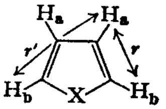


a. X = Cl
b. X = Br
c. X = I
d. X = F

5

and the ratios of H–H distances are in agreement with those from molecular models. For 1,3,5-trifluorobenzene[21] all direct couplings, except *J*(H–F, *para*), have been found to be positive in sign. Some heterocycles have also been investigated. In pyridine[22] the direct couplings are negative, and opposite in sign to the indirect interactions. The inter-proton distance ratios agree very closely with those obtained from microwave studies. The internuclear ratios have been calculated for furan[23] and thiophene[24] (**6a,b**), and are compared in Table II.

Studies on 3,3,3-trifluoropropyne[25] have shown that *J*(H–F) = – 3·3 ± 0·1 Hz and also suggest that the determination of proton shift anisotropies may involve large errors. (For this compound a value of $\Delta\sigma = \sigma_{\parallel} - \sigma_{\perp}$ of



a. X = O
b. X = S

6

$-1{\cdot}1 \pm 0{\cdot}9$ p.p.m. was obtained.) For dimethylacetylene[15] J(H–H) has been found to be $+2{\cdot}7 \pm 0{\cdot}2$ Hz. A study of the oriented hydrogen molecule[26] has afforded a value for $\Delta\sigma$ of between -29 ± 5 and -38 ± 6 p.p.m. Since theoretical values are +2 to +7 p.p.m. this further illustrates the limitations of the technique when the observed shifts are small and probably influenced by solvent.

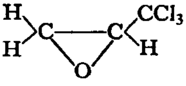
TABLE II

Interproton distance ratios for furan and thiophene (6a,b)

x=	O	S
r_B/r_A	$1{\cdot}47 \pm 0{\cdot}02$	$1{\cdot}745 \pm 0{\cdot}010$
r/r_A	$0{\cdot}98 \pm 0{\cdot}02$	$0{\cdot}995 \pm 0{\cdot}005$
r'/r_A	$1{\cdot}56 \pm 0{\cdot}02$	$1{\cdot}653 \pm 0{\cdot}006$

The magnetic orienting of poly-γ-benzyl-L-glutamate solutions has been observed in such solvents as dichloromethane and chloroform.[27,28] When *p*-xylene was added to such a solution its spectrum showed the expected dipolar splitting.

The logical step has recently been taken, of using an optically active (mixed) nematic solvent, which imposes the expected screw sense as well as orientation anisotropy.[29] Inactive solutes, such as benzene, produce a normal spectrum, but line doubling is observed with 3,3,3-trichloropropylene oxide (**7**). This is ascribed to the overlapped slightly different spectra of *d* and *l* molecules in the racemic solute. This leads to the discussion of optically active solvents in general. It is now well known that use of an



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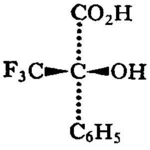
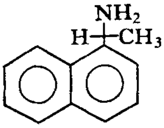
appropriate optically active solvent will cause the spectra of diastereomerically solvated enantiomers to differ. The "sense" of nonequivalence may be used[30] to assign configurations to both enantiomers. For example the



$F_3C-\overset{CO_2H}{\underset{C_6H_5}{C}}-OH$

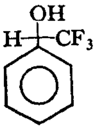
8

absolute configuration of *R*-(+)- (**8**) has been determined in (+)-α-(1-naphthyl)ethylamine (**9**). Most applications have involved the use of active



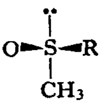
9

amines to induce nonequivalence in enantiomeric alcohols etc., but the converse also follows.[31] Using *S*-(+)-2,2,2-trifluorophenylethanol (**10**) a



10

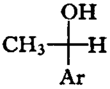
sample of partially resolved *R*-(+)-(1-naphthylethylamine) (**9**) shows methine signals as two unequally intense quartets and methyl groups as a pair of unequal doublets, with shift differences of 2·2 and 0·7 Hz respectively at 60 MHz. The same phenomenon is observed for a range of nine other amines. It is possible[32] to perform correlations of absolute configuration and determine optical purity in enantiomeric sulphoxides of type (**11**), and for the partly resolved derivative (**11**, R = *t*-Bu), dissolved in *R*-(−)- (**10**), two unequal *tert*-butyl signals are observed at $\delta = 1{\cdot}01$ and 1·02. The



$O-\overset{\cdot\cdot}{\underset{CH_3}{S}}-R$

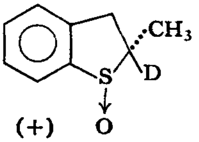
11

method even works for partially active trideuterodimethylsulphoxide (**11**, R = CD_3) with $\Delta\delta = 0{\cdot}017$ p.p.m. Similar effects have been observed[33] in chloroform-*d* or carbon tetrachloride solutions containing equimolar (0·3 M) amounts of racemic and active compounds. For example, in (±)-(**12**, where Ar = 9-anthryl), two temperature dependent signals for the methine proton are observed in the presence of diastereomeric (**13**) or (**14**).

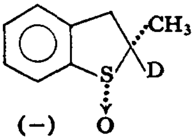


$$CH_3-\overset{OH}{\underset{Ar}{C}}-H$$

12



13



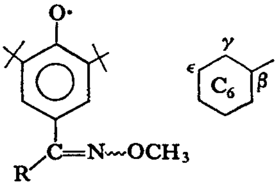
14

(7·2 Hz separation at −25° falling to 3·9 Hz at +25°.) The use of *l*-pinene as a solvent has demonstrated the diastereomeric nature of a four-coordinate nickel(II) complex.[34]

A novel solvent with exciting possibilities is the stable liquid free radical, di-*tert*-butyl nitroxide (DBNO).[35] Observation of NMR spectra from free radicals is possible when a mechanism exists for averaging electron spin states, and using DBNO it should be possible, in principle, to study most of the neutral radicals. The NMR spectra of organic radicals provide a measure of both the sign and magnitude of electron–nuclear coupling constants, from the magnitude and direction of line-shifts as given[36] by the equation—

$$a(i) = -\Delta H \Big/ \left(\frac{\gamma e}{\gamma H}\right)\left(\frac{gBH}{4kT}\right)$$

where $a(i)$ is the electron nuclear coupling constant and ΔH the shift. Line width increases with ΔH, consequently large couplings are hard to detect.



R = H, and cyclo-C_3 to C_7

15

TABLE III

Values of *a(i)* in gauss, for a series of phenoxy-radicals (15)

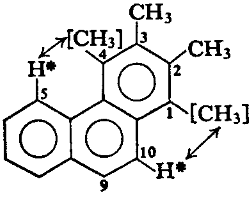
R	OCH_3		β-H		γ-H		ε-H		Bu^t
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*	*anti*
H	..	+0·935	..	+2·32	..	..	..	..	All are +0·068 except for R = H (+0·063)
Cyclo-C_3	+0·390	+0·82	−0·73	−2·02	..	..	..	..	
Cyclo-C_4	+0·372	+0·70	−0·19	−1·99	..	+0·104	..	−0·026	
Cyclo-C_5	+0·304	+0·715	−0·77	−0·338	+0·162	+0·115	..	−0·019	
Cyclo-C_6	+0·294	+0·675	−0·65	−0·290	..	+0·139	..	−0·048	
Cyclo-C_7	+0·306	+0·717	..	−0·348	+0·131	+0·103	..	−0·014	

The results[37] for a series of phenoxy-radicals (**15**) are summarized in Table III and show the observation both of long-range couplings and splittings too small for detection by ESR techniques. The ESR spectra calculated from these parameters agree well with those found experimentally.

C. Instrumental methods

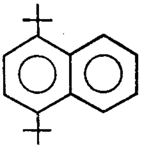
1. *The nuclear Overhauser effect*

This technique is now starting to prove a useful probe for the presence of steric overcrowding. For the first time, Nuclear Overhauser effects have been reported which involve aromatic protons. With 1,2,3,4-tetramethylphenanthrene (**16**) saturation of the overcrowded C(4)-methyl induces a



16

33·5% enhancement of the H(5) signal, while irradiation of CH$_3$(1) has a small (11%) effect on the intensity of H(10).[38]. The symmetrically substituted naphthalene (**17**) yields a 15% increase in the intensity of the *peri*-



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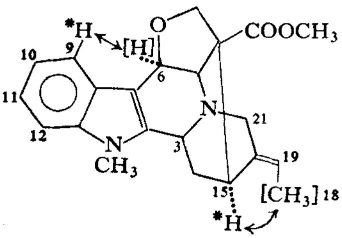
hydrogens when the *t*-butyl group is saturated.[39] The *t*-butyl group appears to be a useful tool for the detection of chemical and physical phenomena induced by steric crowding, and it is clear that these studies will be facilitated by further Nuclear Overhauser studies. Two studies are reported[40,41] where aromatic protons in alkaloids have afforded Overhauser effects and the results provide confirmations of molecular geometry. For dehydrovoachalotine (**18**) an Overhauser effect gives 25% enhancement of H(9) from interaction with H(6) and the 26% increase in signal area of H(15) when CH$_3$(18) is saturated; this establishes the *cis*-geometry of the ethylidene side-chain. The conformations of some terpene derivatives have also been clarified by this technique.[42–44] In one of these papers,[42] the authors comment that a



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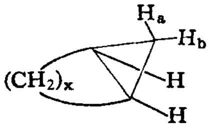
saturated field is not the same as a decoupling field, and often proves to be relatively weak. In a series of bicyclo[*x*.1.0] alkanes (**19**), the Overhauser



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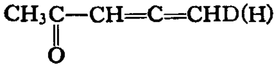
effect was used to show, by irradiation of proximal ring hydrogens, that H_a was the upfield proton;[45] with $x = 8$, this has the exceedingly high field shift of $\delta = -0{\cdot}48$. Overhauser enhancement parameters and spin-lattice relaxation times have also been obtained for methyl methacrylate.[46]

2. *Double quantum transitions* (*DQT*).

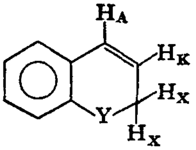
The transition lines which result from the use of high RF levels in the study of closely coupled systems can be used for relative sign determinations and the verification of spectral assignments. The latter use was applied to the analysis of the spectra from a series of Group IVb vinyl derivatives,[47] and DQT studies have shown the ^2J(H–H) allenic coupling in (**20**) to be negative



$$\mathrm{CH_3}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}CH{=}C{=}CHD(H)}$$

20

by analogy with the deutero derivative.[48] The technique has now been extended to molecules containing four coupled nuclei.[49] In (**21**) the DQT



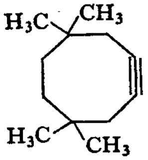
Y = S or O

21

lines from two of the three expected nuclei pairs were observed and it was possible to assign *J*(AX) opposite in sign to the other couplings. Spin-tickling has been performed in systems exhibiting both single and double quantum transitions and is useful as an independent check on energy diagram assignments.[50] It may also allow the assignment of DQT lines in complex systems, or where the lines are coincident.

3. 220 *MHz Spectra*

The advent of the superconducting magnet has encouraged the study of some previously intractable problems through the large relative shifts induced. Previously obscured shifts and couplings have been observed[51] in a study of the anisotropic effects of the cyclopropane ring in some steroids, and assignments have been made using this technique in some natural products including the macrocyclic dilactone colletodiol,[52] the alkaloid adifoline,[53] and in a series of amino acids.[54] The latter spectra were then utilized in a study of porcine and bovine insulin, and it proved possible to assign most of the signals arising from these biological molecules. A 220 MHz investigation of the barrier to conformational exchange in the tetramethylcyclooctyne (**22**) has been reported,[55] and the use of this high frequency has facilitated the complete analysis[56] of a series of difluorobenzenes (**23**). The ability to accurately determine chemical shifts has provided data[57] for the derivation of expressions describing the shielding effects of magnetically anisotropic disc-or rod-shaped solvent molecules on a spherical solute. The *in–out* isomerism of some macrobicyclic amines[58] has been observed, with some fascinating conclusions (see p. 63) and the observation of oriented systems is much simplified.[15,28] Low-temperature 220 MHz observations permit the determination of ligand exchange and isomerization in tris(triphenylphosphine)chlororhodium(I).[59]



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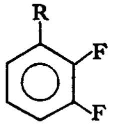
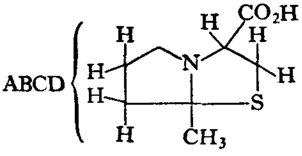


R = H, COOMe, CN, NH_2, OH, F

23

4. *Other techniques*

In a discussion of the AA′BB′ spectrum of propiolactone[60] it is clearly demonstrated that a search for the almost forbidden transitions in deceptively simple spectra can be well worthwhile. A technique long known, but only recently documented in detail, was used both in this study and in the analysis[61] of the ABCD system of (**24**), namely the application of an 8-to 10-fold increase in applied RF power which saturates the main transitions without affecting the weak lines.



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A technique has been described[62] which could perhaps be described as "virtual" double resonance, for it involves indirect spin saturation via spin–spin interaction. In an AB + C system system where A and C are exchanging and A and B are coupled, strong irradiation of C causes the spin states of A to saturate, while the splitting of B by A is not influenced. The theory is discussed and a new quantity T_3, the "spin-exchange relaxation time" introduced. The method has been applied to the slowly exchanging benzyl alcohol/*tert*-butanol and 2-phenoxyethanol/*tert*-butanol systems.

The principal relaxation mechanisms for double resonance in AB and ABX systems have been studied in experiments ranging from "tickling" to strongly decoupling in nature,[63] and are found to be of correlated, and uncorrelated random field type for AB and ABX cases respectively. A "partial saturation" study of temperature dependent species undergoing slow rotation has been described.[64] It was possible to obtain relative signs, individual line positions and even profiles of overlapped signals. The frequencies of hidden transitions, relaxation times, and exchange rates for individual transitions could also be determined by observing the recovery of a signal after the saturating field is removed from the related transition in the *other* rotamer. In high-resolution NMR it is possible[65] to impose a sufficiently weak second field on a given line such that saturation is restricted to a localized region of the sample volume; this is called "burning a hole" in the line. Observation of a regressively connected line shows that a similar hole appears, in an exactly corresponding region. This has been used as the basis of a technique for measuring frequency separations with a precision not primarily limited by the inhomogeneous linewidth, and extended to a 3-spin system (2-chlorothiophene) in which the experimental and calculated transition frequencies agreed within a mean deviation of 0·00008 Hz. The technique of "tickling" has been extended to a triple resonance experiment[66] and the observed behaviour correlated with theoretical predictions.

RASER action has previously been reported from chemically induced dynamic polarization, but only with the emitters having as a structural component one of the initial radicals. Now, RASER action has been observed[67] in a compound formed by radical transfer. Characteristic *emission* bands for but-1-ene and also for the postulated *N*,*N*-diethylvinylamine are present in spectra obtained immediately after mixing *n*-butyllithium, 1-bromobutane and triethylamine. Nuclear magnetic resonance emission has also been detected in triplet-state systems obtained by ultraviolet irradiation.[68,69] A dilute (0·005 M) solution of anthraquinone in C_6F_6 was irradiated to produce a low steady state triplet-state concentration and the effect of this on the ground state molecules observed. An emission spectrum resulted as the consequence of an Overhauser effect but was not simply an inversion of the absorption spectrum indicating that all of the hydrogens are not affected equally. A similar experiment, using pyrene in benzene-d_6, allowed a rate constant for the energy transfer process, of 4×10^7 litre mole^{-1} sec^{-1} to be calculated.

D. Calculations

Although computational methods are perhaps not strictly *experimental* they suitably end this section. Three review articles[70] describing the analysis of complex 2-, 3- and 4-spin systems in a manner suitable for the organic chemist have been published. Computer programs of the LAOCOON and NMRIT type are now in general use, but a new direct method of calculating high-resolution spectra has recently been documented.[71] This differs from conventional procedures in that no energy levels or wave functions are computed nor an explicit lineshape specified. The total information content can be expressed in two complex vectors, a ratio-frequency independent "shape vector" and a "spectral vector" which is a trivially simple function of the radio-frequency. The absorption spectrum is obtained as the negative real part of the scalar product of these vectors, and an AA′BB′ example is given.

II. CHEMICAL SHIFTS

A. Semi-empirical considerations

A useful semi-empirical method has been presented[72] for the calculation of some high-resolution NMR parameters, including chemical shifts, which involves the use of an equation of weighted averages. The method is much more widely applicable than just to proton resonance, but, as an example of

TABLE IV

Calculated Shifts

Molecule	—CH_2—		—CH_3	
	δ(calc)	δ(obs)†	δ(calc)	δ(obs)†
CH_3CH_2I	−4·33	−4·34	−5·73	−5·73
CH_3CH_2Br	−4·06	−4·08	−5·83	−5·83
CH_3CH_2Cl	−3·83	−3·80	−5·93	−5·93

† From C_6H_6 reference.

its power, calculated and observed shifts for the ethylhalides are given in Table IV. A correlation of chemical shift with "free electron model" (particle in a box) calculations is reported for the first time,[73] with a series of ions of type (**25**). Correlations of this type with electronic spectra are well known.

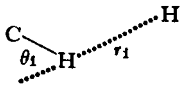
$$[(CH_3)_2C\overset{\cdots}{-}CH(CH\overset{\cdots}{-}CH)_{n-2}\overset{\cdots}{-}C(CH_3)_2]^{\oplus}$$

25

Both the ^{13}C and proton shifts have been calculated for pyridine[74] with fair accuracy using atom anisotropies together with a separate π-electron density term; SCF treatment provided the best results. A good linear relationship has been found between π-electron density and both ^{13}C and ^{1}H shifts for a series of diazoles and triazoles in trifluoroacetic acid[75] (with a ^{1}H correlation coefficient of 0·984). Hückel electron densities have been linearly related with shifts in aromatic amines and amides,[76] which also showed excellent correlation with Hammett substituent constants. A method for the prediction of ring proton shifts in heteroatomic molecules has been described which makes use of the known chemical shifts in model compounds.[77] Calculations have been performed to obtain screening effects from C–C and C–H bonds[78] and C–F and C–Cl bonds[79] which can be used to account for the proton shifts in a range of saturated molecules. Protons subjected to steric compression generally suffer a downfield shift. The degree of deshielding is dependent upon the geometrical relationship between the H–C bond and the interacting nucleus. An expression has been derived[80] for the steric shift

$$\delta_s^H = -105 \sum_i \exp(-2{\cdot}671\, r_i)$$

where the parameters are as shown in (**26**).



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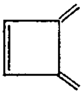
The proton shifts of a series of compounds $(CH_3)_nM$ and $(CH_3CH_2)_nM$ have been correlated with Pauling electronegativity (E) and the number of lone pairs on M (m) by the expressions[81]

$$\delta(CH_3M) = 1{\cdot}3E + 0{\cdot}4m - 2{\cdot}3$$

and

$$\delta(CH_3CH_2M) = 1{\cdot}0E + 0{\cdot}5m - 1{\cdot}0$$



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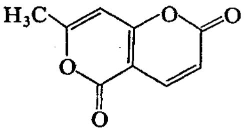
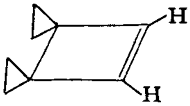
In 3,4-dimethylenecyclobutene (**27**) a local anisotropy model[82] was found best to account for the observed shifts. A ring current model failed and properties usually associated with $4n$ hydrocarbons were predicted. Molecular orbital calculations did however rationalize the experimental shifts for 2,3-dicarbahexaborane-8,[83] and in (**28**) the high resonance energy and observed shifts confirmed its aromatic character.[84] The novel compound (**29**) has recently been synthesized[85] and the chemical shifts should be of considerable theoretical interest, for the cyclopropyl rings are normal to the nodal plane of the double bond, allowing maximum delocalization between the π-system and the p-character bonds of the cyclopropane rings.



$\delta(CH_3) = 2.43$
(cf. toluene)

28



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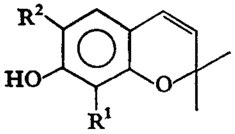
B. Shifts induced by aromatic solvents

A theoretical model for solvent effects induced by benzene in polar molecules has been proposed.[86] The geometry of the solute/solvent collision complexes formed between benzene (or C_6D_6) and thirty aromatic and thirty-eight non-aromatic compounds has been determined for dilute ($\leqslant 5\%$) solutions by Ledaal,[87] who suggests that solvent shifts should be referred to carbon tetrachloride solutions, since this solvent is more closely similar to benzene (by virtue of its dipole moment, dielectric constant, susceptibility, and molar volume) than is chloroform. The observed shifts could be rationalized by assuming that all arose from the same type of collision complex, in which the dipole axis of the solute was located along the 6-fold symmetry axis of the benzene nucleus with the positive end nearest.

Benzene induced shifts are proving valuable for determining the position, and relative orientation, of substituent groups in some natural products. Williams and co-workers[88] have tabulated values of $\Delta(=\delta(\mathrm{CDCl_3})-\delta(\mathrm{C_6H_6}))$ for the methoxyl resonances in sixteen flavones, finding good correlation with the substitution pattern, and a newly isolated chromene (Ripariochromene) has been identified as (**30a**) rather than (**30b**) by a similar technique.[89] The addition of trifluoroacetic acid to solvents can be used as an adjunct to the application of benzene-induced shifts.[90] This method has been investigated using methoxybenzenes, and applied[91] to flavones of type (**31**). The "TFA-addition" shifts [Δ(benzene/benzene + 3% TFA)] for methoxy-groups at C(5), C(7), C(2′) and C(4′) are very small in the absence of OMe or OH substituents *ortho* to these groups. In contrast, C(3) methoxy-groups, or those flanked by two *ortho*-OMe (or one *ortho*-OMe and one *ortho*-OH) functions, show appreciable positive addition shifts (+0·18 to +0·45 p.p.m.). A C(5) OMe suffers a marked increase in addition shift when a C(6) OMe group is introduced. (−0·36 to −0·44 becomes −0·48 to −0·62 p.p.m.) Protonation at the methoxyl and carbonyl



a. $\mathrm{R^1 = OMe}$; $\mathrm{R^2 = COCH_3}$
b. $\mathrm{R^1 = COCH_3}$; $\mathrm{R^2 = OMe}$

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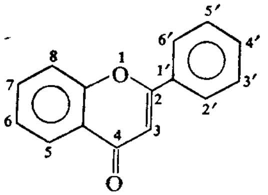

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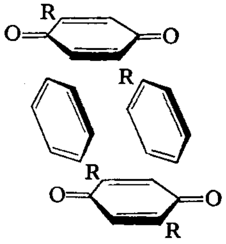
sites probably induces these shifts, which should prove valuable in structure elucidation.

The ring-proton shifts of 3,5-dichlorosalicylaldehyde, measured as a function of temperature in CCl_4 and benzene solutions,[92] indicate that if there is association with solvent molecules in benzene solutions then there is *also* association with carbon tetrachloride solvent molecules. A variable temperature study has been used to clarify the extent of steric factors in solvent–solute interaction.[93] In monosubstituted aromatic molecules with electron-withdrawing groups, the principal site of association is over the ring and the solvent shifts of the aromatic protons (relative to the solvent shift in absence of the polar group) decrease in magnitude with increasing steric factor. With electron-donating substituents however, the main association is in the region of the substituent, and it is diminished if there is actual steric inhibition of π-electron donation by the substituent group. Experimental results for solutions of maleic anhydride in benzene and carbon tetrachloride are best fitted[94] by a model in which the H-atoms of the *exo*-oriented solute are associated at a mean position 2.55 Å above the plane of the benzene ring. It appears[95] that, for a solute containing two electron-deficient sites, one molecule of benzene will if possible spread itself between two electron-deficient sites in *different* molecules, forming a cage complex possibly of type (**32**). This paper also emphasizes the need for measuring solvent shifts in dilute solutions where maximum complexing can occur. Aromatic solvent shifts have provided a facile micro-method for structural assignments in ubiquinone analogues[96] of general formula (**33**). The *s-cis* and *s-trans* conformations of α,β-unsaturated ketones can be readily differentiated using solvent shift data[97] and a study of $\Delta\,[=\delta(CCl_4) - \delta(C_6H_6)]$ has been reported for some α-diketones.[98] In the acyclic diketones the shift of the α-methylene protons is related to the length and bulk of the side chain, and the shifts for aromatic α-diketones are characteristic of the substitution positions. A series of free, and stannic chloride coordinated complexes of mono-, di- and cyanoethyl esters have been studied by the use of NMR



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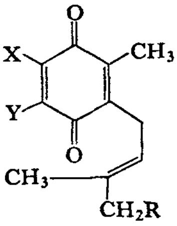

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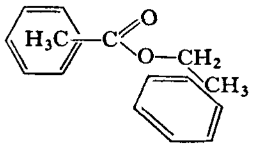
solvent effects.[99] An increase in polarity of the group adjacent to the ethoxy-group increases the interaction of benzene with the ethyl protons. This interaction is also increased on complexation with tin(IV). On the basis of the induced shift $\Delta[=\delta(C_6H_6) - \delta(C_6H_{12})]$ a structure for the benzene–



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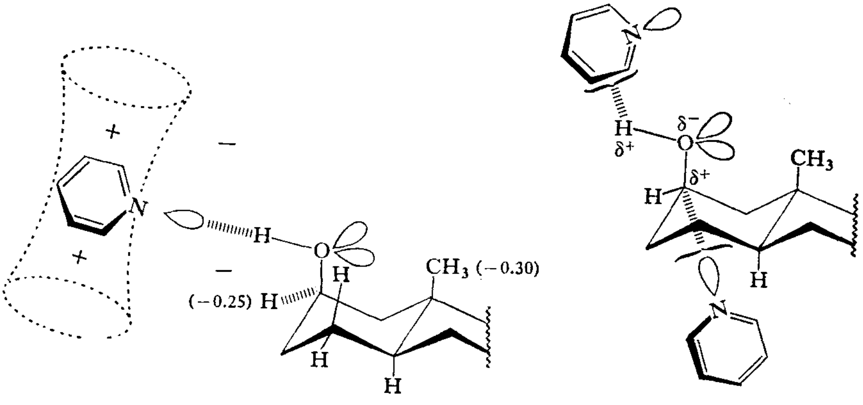
ethyl acetate collision complex is proposed which approximates to (**34**). Comparison of shifts measured in chloroform-*d* and pyridine-d_5 has shown

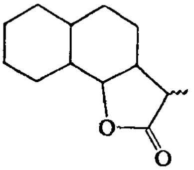


(a) (b)

FIG. 1. Stereochemical nature of solute-solvent association mechanisms: (a) hydrogen-bonding association and (b) collision complex association. (From Demarco *et al.*[100])

that, in saturated cyclic systems, the protons occupying positions 1,3-diaxial, vicinal or geminal to an —OH function are *deshielded,*[100] and that for phenolic compounds the protons *ortho* to the —OH group are much more strongly deshielded than the corresponding *meta-* and *para*-protons. These pyridine-induced shifts appear to be valuable for establishing the position and stereochemistry of protons neighbouring to hydroxyl groups. The proposed collision complex for a cyclohexyl type residue is shown in Fig. 1.

A simple method, using solvent shifts,[101] has been presented by which the stereochemistry of the C(11)-CH_3 group in the γ-lactone group of the eudesmane skeleton can be determined for derivatives of basic structures (**35**) and (**36**). For pseudo-axial geometry an upfield shift [$\delta(CDCl_3) - \delta(C_6H_6)$] of 0·46 ± 0.06 p.p.m. is found, which decreases to 0.23 ± 0.06 p.p.m. when the methyl group is in a pseudo-equatorial position. The conformation of α-methyl groups in cyclohexanone oximes (**37**) can be assigned from solvent shifts[102] and the results are summarized in Table V. In solutes



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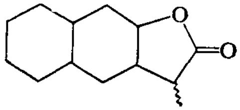

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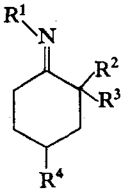

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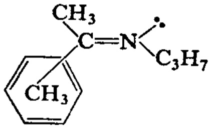
TABLE V

Solvent shifts in cyclohexanone oximes (38)

Group	$\Delta\nu$	$\Delta\nu^*$
2-CH_3 (eq)	−6·3 to −11·4	4·8 to 12·2
2-CH_3 (ax)	−7·0 to −11·0	−1·6 to 1·8

$\Delta\nu = \nu(CCl_4) - \nu(C_6H_6)$ Both in Hz
$\Delta\nu^* = \nu(CCl_4) - \nu(C_5H_5N)$ at 60 MHz

bearing a lone pair of electrons on nitrogen, the benzene–solute collision complex is likely to occur at a site as far as possible from the nitrogen.[103] Shifts have been summarized for aziridines, oximes and imines, and for the latter a complex of type (**38**) is proposed. Benzene induced shifts can distinguish between epoxides and 4-, 5- or 6-membered ethers, and also permits the assignment of α- and β-methyl substituents in tetrahydrofuran derivatives.[104] Values of $\Delta[=\gamma(CCl_4)-\gamma(C_6D_6)$; where $\gamma=$ the centre of resonance at infinite dilution and approaches δ as the system approximates to 1st-order character] for the α and β protons in five membered heterocycles (**39**) show that for the β-protons a linear relationship exists between $\Delta(\beta)$ and the dipole moment of the solute in benzene-d_6 solution.[105] This is to be expected if benzene solvates to the most electron-deficient site. A large diamagnetic shift (30 to 60 Hz), relative to carbon tetrachloride solutions, is observed for dilute solutions of aliphatic nitro-compounds in aromatic amines such as aniline and *N*,*N*-dimethylaniline.[106] A postulated collision complex for nitroethane is (**40**), with equal CH_2 and CH_3 shifts. On the basis of spectra measured in carbon tetrachloride and benzene,[107] the upfield aromatic induced shifts in a series of P^V compounds of type $P(X)R_{3-n}(NMe_2)_n$ ($X=O$ or S; $R=$ amino, alkylamino etc.) have been rationalized by means of a weak complex between benzene and the phosphorus compound. Aromatic solvent shifts are now being used[108] as probes in the configurational study of C(1) substituents in monosaccharides.



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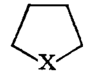
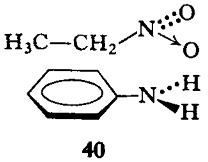


$X=CH_2, O, S, Se,$
$C{=}O, SO_2$

39



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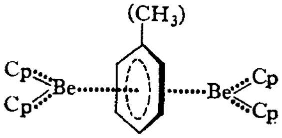
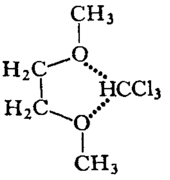
C. Other medium effects

Evidence has been presented for (**41**) as the probable structure of a complex formed between dicyclopentadienyl-beryllium and solvent toluene (or benzene).[109] Strong contact shifts were observed which were temperature dependent. It is suggested[110] that tetra-*n*-butylammonium salts may interact specifically, in ion pair form, with the aromatic ring of nitrobenzene, since such solutions show concentration dependent shifts for the *meta*- and *para*-protons which are of greater magnitude than for *ortho*-protons. In two ionic systems, shifts have been found to correlate with the dielectric constant of the non-polar solvents studied. For 1-methylpyridinium halides all the solvents investigated, except acetonitrile, showed a correlation,[111] and with the pair of compounds trioctylmethylammonium hexacyano-ferrate(III) and -cobaltate(III)[112] a linear correlation was found between $\Delta\nu$(Hz) [$=\nu(N\text{Me-Fe}) - \nu(N\text{Me-Co})$] and ϵ of the form: $\Delta\nu = 127{\cdot}4 - 2{\cdot}14\epsilon$ (at 60 MHz).



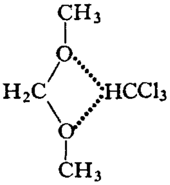
41

The binary collision model, used for interpreting the pressure dependence of gaseous chemical shifts, has been extended to liquids,[113] and the medium shifts of some non-polar solutes and their temperature variance, in magnetically isotropic solvents have been estimated almost quantitatively. A model based on steric and charge removal characteristics of ring substituents has been used to rationalize the low-field shifts induced by carbon tetrachloride, (with respect to cyclohexane) in the spectra of some polyhalobenzenes.[114] The shift of the chloroform proton resonance signal, when dissolved in some ethers and acid anhydrides, has been used to determine the relative basicities of these solvents.[115] The results are rationalized by steric and configurational effects in the resultant hydrogen-bonded complexes. For instance (**42**) is



$\Delta\delta = -0.84$ p.p.m.

42



$\Delta\delta = -0.56$ p.p.m.

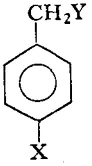
43

more stable than (**43**). The association shifts of chloroform, with a number of organic bases of type RX and R_2X (where X = Cl, Br, I, S, O, CO, NR, $NHNH_2$, SO and R = CH_3, Et or *iso*-Pr), can be quantitatively correlated to the basicity of X.[116] In weakly solvating media, the trihalomethanes associate specifically with the anions of tetraalkylammonium ion salts.[117] Values of ΔH suggest that differential solvation occurs, and the deshielding of CHX_3 (X = F, Cl, Br) by 1 to 3 p.p.m. indicates primarily hydrogen bonding. CHI_3, however, is more shielded, suggesting a polarization or charge transfer complex via the iodine atoms.

D. Substituent effects

A comparison has been made between the accurately determined shifts for a series of twenty-two monosubstituted benzenes[118] and those predicted by substituent constants obtained from polysubstituted benzene. Good correlation (0 to 3 Hz) was obtained for all except polar compounds. The *o*-, *m*- and *p*-substituent constants for eighteen benzene substituents have been measured and tabulated[119] for dilute carbon tetrachloride solutions, enabling the ring proton shifts of di- and tri-substituted benzenes to be calculated to within 0·05 p.p.m. of experimental values. When two substituents are adjacent, the *ortho*-substituents are often dependent on neighbouring groups and these have been tabulated separately. The *p*-constants were previously not readily accessible. An additivity scheme which takes account of *ortho*-substituent interactions[120] has been applied to thirty-nine proton shifts in a series of polysubstituted halobenzenes. In this method, the shift is written as the sum of two parameters, $D(X,Y)$ and one parameter d_p, where $D(X,Y)$ refers to a pair of substituents placed *ortho*(X) and *meta*(Y) and d_p to a group *para* to the proton involved. Mean deviations between observed and calculated shifts are 0·010 p.p.m. (cyclohexane); 0·012 p.p.m. (CCl_4), for 3 mole-% solutions, and the constants were tabulated.

A linear relationship exists between Hammett σ values for *para*-substituents and the benzylic proton shifts in eleven series of *para*-substituted toluenes (**44**) bearing different α-substituents.[121] The slope varies between 0·0 and 0·2 p.p.m./σ and the variation is conformationally dependent—a fact not explicable by current theory. Certain *ortho*-substituted acetanilides



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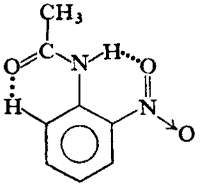
show signals for both the amido-proton and the proton adjacent to the amido-group which are strongly deshielded.[122] This has been ascribed to intramolecular hydrogen bonding of the type shown in (**45**). The effect of



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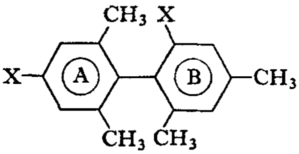
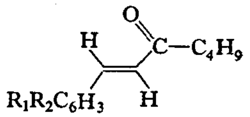
group X(B) on the CH_3(A) shifts, in a series of biphenyls (**46**), is negligible[123]



X = Cl, Br, I and H

46

and it is concluded that halogen diamagnetic anisotropy effects on aromatic proton shifts are not important. For a series of 1-phenylhept-1-en-3-ones



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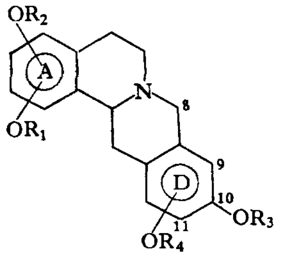
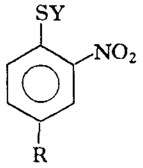
(**47**) the shifts of the two olefinic protons correlate with the Taft and Hammett values of the nuclear substituents, the α-H being deshielded by the ring-



48

current.[124] The effect of the D ring substituents, in some tetrahydroprotoberberine alkaloids (**48**), on the shift of the C(8) benzylic hydrogens is such that the structural isomers with C(9),C(10) and C(10),C(11) substituents can be readily distinguished.[125] In the former case an AB quartet is observed [$\delta(A) = 4{\cdot}35$, $\delta(B) = 3.65$; $J(AB) = 16$ Hz] whereas in the 10,11-substituted derivatives a broad singlet results, at $\delta = 4{\cdot}05$. As a result of an investigation into the correlation between Hammett σ-values and the methyl or methylene shifts in some nitrophenyl derivatives (**49**), transmission factors (ϵ) have been determined as shown below[126]—



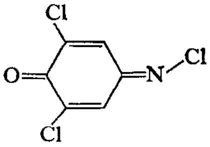
Y = CH_2COCH_3, Et, SEt, CH_2Ph or OEt

49

	ϵ
—CH_2—	0·67 ± 0·07
—S—	0·60 ± 0·09
—O—	0·69 ± 0·16

The spectral properties of the compounds C_6H_5Li and C_6H_5MgBr have been determined, and show parameters similar to those of pyridine.[127] The protons *ortho* to the C–M bond are considerably deshielded with respect to benzene. Since the phenyl anion and pyridine are isoelectronic, to the degree that the C–M bond is ionic, the same effects should account for all the shifts. Similarly, some aromatic derivatives of Li, Mg and Ca, including *meta*-dilithiobenzene[128] were found to be similar in character to the corresponding heterocycles. In particular, the protons *ortho* to the metal were strongly deshielded, and their shifts correlated with the metal electronegativity. *Ortho* deshielding has also been noted in the isomeric thienyllithiums[129] and in the two α-lithiated thienothiophenes.[130]

The anisotropic effect of the chlorimino group in (**50**) was found[131] to be similar to the analogous oxime group. In basic media downfield shifts



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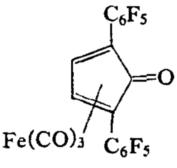
occurred which were greater for the more shielded *anti*-proton due to hydrogen bonding. The observation of a signal in (**51**) at $\delta = 6{\cdot}62$ confirmed,



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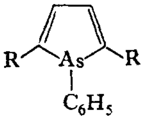
on anisotropic grounds, that the aromatic substituents were α-oriented.[132] In monosubstituted ferrocenes[133] the substituents of an olefinic side chain barely perturb the shift of the unsubstituted ring resonance, at $\delta \sim 4{\cdot}0$. Data[134] for a series of trisubstituted arsoles (**52**) show that the π-electron



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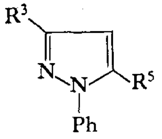
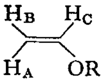
character of the heterocyclic ring is similar to the analogous phospholes. Proton shifts afford a useful guide to 5-substitution in the 1-arylpyrazole skeleton.[135] When the two rings are planar as in (**53a**) the phenyl resonance



a. $R^3 = R^5 = H$
b. $R^3 = CH_3$; $R^5 = Ph$

53

is a multiplet with the *o*-protons ca. 0·2 p.p.m. to low field of the other signals. In (**53b**), however, when coplanarity is absent, both ring current and electric field deshielding mechanisms are minimized and the phenyl signal collapses to a characteristic singlet. Variable temperatures studies performed on a number of compounds (**54**) ,with R in the series methyl to *t*-butyl, have



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indicated[136] that the value of $\delta_A - \delta_B$ acts as an indication of the degree of resonance, as well as the already documented variation of $J(AB)$. Linear slopes were obtained for plots of $\Delta\delta/T°$ indicating increased populations of less stable isomers at elevated temperatures. Phenomena other than the expected anisotropic shielding effects have been observed[137] for some substituted acetylenes, $XC{\equiv}CH$. If X can withdraw electrons from the π-system, a relatively stronger deshielding should result. This has been discussed in terms of back-bonding of the $Si \leftarrow C_\pi$ type, and inductive polarization. The predicted series for shielding of $SiR_3 < CH_3 < CR_3 < CH_2SiR_3$ is upheld by the observed shifts ($\delta = 2{\cdot}24$, $2{\cdot}02$, $1{\cdot}92$ and $1{\cdot}55$ respectively with $R = CH_3$).

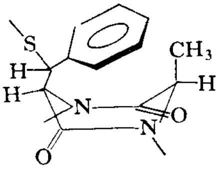
The Dailey–Schoolery Equation, relating the electronegativity of the central metal atom in CH_3CH_2M-groups with the internal $\Delta(CH_2{-}CH_3)$ shift for aluminium derivatives, has been extended[138] to *iso*-butylaluminium compounds and their complexes. The derived equation—

$$\chi(i\text{-}Bu_nAlCl_{3-n}) = 0{\cdot}73\delta + 2{\cdot}08$$

fits the experimental data with a correlation coefficient of 0·976. Studies involving trimethyl- and triethyl-aluminium have demonstrated that the apparent electronegativity of the metal decreases on coordination with donors, proportionate to the donating power of the coordinating molecule.[139] Shifts are summarized for a number of donors (mostly ethers). The electronegativity of the oxygen in diethyl ether generally increased with coordination to triethylaluminium in contrast to previous reports.

E. Shielding effects

The 6-methyl groups in (**55**) and similar compounds, derivatives of methylthio-bis-hydroxamic acid, are observed at the unusually high position



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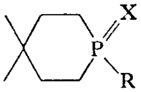
of $\delta = 0{\cdot}57$ to $0{\cdot}73$ p.p.m.[140] This is probably due to shielding by the aromatic ring which, according to models, has a significant influence even if the



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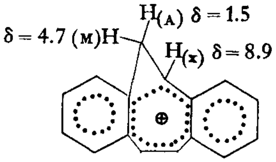
hetero-ring is almost planar. The two substituents must therefore be *cis*-oriented. The preferential shielding of the axial methyl group in (**56**) suggests that the aralkyl group (R) and the phosphoryl bond lie in the equatorial and axial positions respectively.[141] The NMR spectrum of (**57**) provides evidence for its homoaromatic character.[142] H(A) is above the ring while H(M) is in the deshielding zone. The observation that in styrenes the β-*cis*-H is shielded relative to the β-*trans*-H has also been shown to be valid for the methyl groups in the isomeric 1-phenyl propene derivatives[143] and has been used to assign geometric structures. The results from NMR studies on some unsymmetrically substituted Si- and Ge-phthalocyanines have shown that the shielding furnished by the ring drops off without major reversals in the region above its surface and near its fourfold axis.[144] Comparison with two analogous germanium phthalocyanines demonstrated that the latter ring offers a weaker shielding influence. The interpretation of the NMR spectrum of (**58**) suggests that the $Cr(CO)_3$ residue adopts a preferred conformation through non-bonded interactions with the *cis*-methyl group, by assuming that protons lying under superimposed M–CO bonds are deshielded relative to those in the alternant exposed positions.[145]



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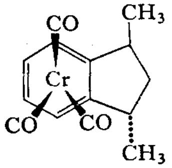
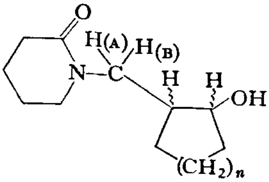


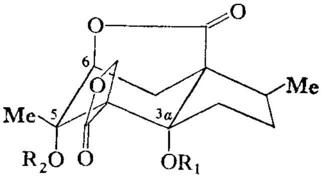
58

In a number of *N*-substituted piperidones (**59**) an unusually large



59

difference in the chemical shifts of the —CH_2— protons attached to the ring nitrogen has been observed, which were correlated with the stereochemistry of the attached group.[146] The difference is believed to result from the anisotropy of the keto-group of the piperidone residue. The chemical shifts of protons α-, β- and γ- to the halogen atoms in 9α-halo-11β-hydroxy progesterones, 2β-halo-3α-hydroxy-5α-cholestanes and model halocyclohexanols[147] can be correlated with electronegativity if allowance is made for a calculated "C–C bond shift". Studies have been reported on steroids containing groups of the type $CXNO_2(X=H, NO_2, Cl, Br)$, CClNO and $C{=}N.NO_2$ at positions 3, 4, 6, 7 and 17 of the skeleton.[148] Equatorial NO_2 groups deshielded the 19-protons, while axial groups were more variable in their effect; for each equatorial/axial pair, however, the low-field shift was larger with the former. With related pairs of $CCl.NO_2$ and CCl.NO groups, the latter were observed to induce larger low-field shifts, suggesting a general deshielding effect of the nitroso-group. The conformations of the NO_2 groups could most readily be ascertained from the ½-height widths of the $CHNO_2$ signals, being greater (~22 Hz) for axial than for equatorial (~10 Hz) groups. In the bicyclo[3.1.0]alkanes (**19**), discussed earlier,[45] the high field H(a) shifts were consistent with other medium ring effects, but these must be combined with a continuous change in C–C bond anisotropy effects. The anisotropic effect of a vicinal tertiary acetoxyl group is responsible for the 1·1 p.p.m. downfield shift observed for the C(6)-H in (**60**) and



a. $R_1=R_2=H$
b. $R_1=H; R_2=Ac$

60

similar compounds upon C(5)-acetylation[149]—an effect normally only observed for the methine proton of the carbon actually bearing the OH(OAc) group. The common structural feature of compounds exhibiting this phenomenon is that the H(eq) deshielded by acetylation is vicinal to an axial *tert*-OH to which a further *tert*-OH group is disposed in a 1,3-diaxial relationship.

F. Hydride shifts

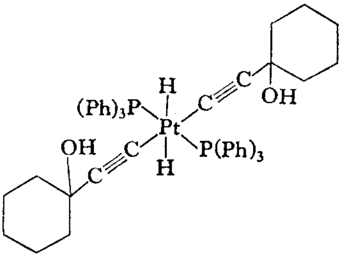
Several papers have quoted values for the shifts of protons bound to nuclei other than those commonly encountered. The parameters observed for some silanes[150] and germanes[151] are summarized in Table VI. The former values should offer interesting correlations with the analogous ethanes. The latter are quoted to be similar to the sila-propanes and -butanes but at ca. 0·2 p.p.m. upfield. Shifts have also been summarized[152] for a series of siloxane and methoxysilane derivatives, from which it was concluded that Si–H protons are less shielded in the siloxanes.

TABLE VI

Chemical shifts for some silanes and germanes

Compound	δMH_3	δMH_2	δMH
SiH_3SiH_2Cl	3·37	4·82	. .
SiH_2ClSiH_2Cl	. .	4·80	. .
SiH_3SiHCl_2	3·48	. .	5·7
$SiH_2ClSiHCl_2$	. .	4·79	5·75
$SiHCl_2SiHCl_2$	. .	. .	5·85
$CH_3GeH_2GeH_3$	3·21	3·58	. .
$C_2H_5GeH_2GeH_3$	3·16	3·65	. .

The novel structure (**61**) has recently been assigned by NMR spectroscopy;[153] the Pt–H resonance signal was observed at $\delta = -22 \cdot 88$.[†] Good linear intercorrelations between δ(Pt–H), *J*(Pt–H) and the infrared ν(Pt–H) have been found for a series of *trans*-PtHL(PEt$_3$)$_2$ complexes (L = subst. benzoato or subst. acetato ligand).[154] The shifts are solvent dependent, but individual changes in a given medium are ascribed to changes in the Pt–H distance. [δ(Pt*H*) = −22 to −23 p.p.m., $CDCl_3$; −21·5 to −22·2 p.p.m., C_6H_6; −21·6 to −22·1 p.p.m., cyclohexane]. For a series of ionic platinum complexes the reported parameters[155] show that the *trans* ligand in *trans*-PtHL(PEt$_3$)$_2^{\oplus}$ClO$_4^{\ominus}$ appears to strongly affect both δ(Pt–H) and *J*(Pt–H). For example, with L = pyridine, $\delta = -19 \cdot 32$, but for L = CO and PEt$_3$,



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[†] Readers are reminded that −ve δ values refer to high field (lower frequency) shifts.

TABLE VII

Hydride shifts

Compound	δ(MH)	Ref.	
$HFe(C_6H_4PPh.CH_2CH_2.PPh_2)(EDP)$	–14·2	156	
trans-$(HFeCl(EDP)_2)$	–29·2	156	
$CoHN_2(PPh_3)_3$	–19·0	157	Trigonal bipyramid; H and H_2 trans
$(C_5H_5)_2WH_2 \rightarrow W(CO)_5$	–15·18	158	
$HRu_3(CO)_{10}SR$ (R = Et, Bu)	–15·4	159	
$H_2Ru(Ph_2PCH_3)_4$	–9·54	160	
$H_2Ru(CO)(Ph_2PCH_3)_3$	–8·02 and –6·80	160	
$HRh(Ph_3P)_4$	–10·6	160	Tetrahedral ?
$HRh(Ph_3P)_3$	–8·9	160	
$HRh(Ph_2PCH_3)_4$	–12·1	160	Square pyramidal
$Et_4N^{\oplus}[ReH_8(Ph_3P)]^{\ominus}$	–7·3	161	It is of interest to note that substitution of a *tert*-phosphine or -arsine group for one H atom has little effect on the hydride shift.
$Et_4N^{\oplus}[ReH_8(Et_3P)]^{\ominus}$	–8·2	161	
$Et_4N^{\oplus}[ReH_8(^nBu_3P)]^{\ominus}$	–8·1	161	
$Et_4N^{\oplus}[ReH_8(Ph_3As)]^{\ominus}$	–8·4	161	
$(Et_4N)_2^{2\oplus}(ReH_9)^{2\ominus}$	–8·5	161	

$\delta = -4{\cdot}76$ and $-6{\cdot}24$ respectively. The hydride shifts for some complexes of Fe,[156] Co,[157] W,[158] Ru,[159,160] Rh[160] and Re[161] are summarized in Table VII.

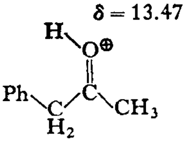
G. Solvation

A study has been documented[162] of the solvation of $Li^{\oplus}$, $NH_4^{\oplus}$ and $Na^{\oplus}$ salts by dimethyl sulphoxide. A plot of shift against the ratio DMSO/MX (in pentanol solvent) showed a clear change at 2:1 for both LiI and NH_4CNS, but while a solid solvate could be isolated from NaI/DMSO its stoichiometry was less defined, the results being in accord with the usual behaviour of $Li^{\oplus}$ and $Na^{\oplus}$ in solution. In both ethylenediamine/water and ammonia/water systems, there is an indication of 1:1 complexation, and of a liquid structure in which hydrogen bonding is stronger than a simple average between pure water or amine.[163] Low temperature measurements with magnesium(II) solutions[164] show that the primary solvation sphere in methanolic acetone is $Mg(CH_3OH)_6^{2\oplus}$, while for aqueous acetone or water it is $Mg(H_2O)_6^{2\oplus}$. The relative coalescence temperatures for the peaks from bulk and coordinated solvents suggest that the order of increasing lability for the complexes is $Mg(CH_3OH)_6^{2\oplus} < Mg(H_2O)_6^{2\oplus}$ (aq. acetone) $<$ $Mg(H_2O)_6^{2\oplus}$ (aq.). This has been confirmed by Fratiello and co-workers[165] for the acetone/water and water systems, and these authors have also shown that Al^{III} and Ga^{III} ions are hexahydrated in the primary coordination sphere, together with In^{III}, while Be^{II} is solvated by four water molecules. Except for the latter ion there was no evidence for ion-pairing. Variable temperature determinations of the proton shifts in aqueous $Al(NO_3)_3$ solutions, followed by analysis using a two-state model applicable to dilute solutions,[166] indicated that the *total* hydration was 13·4. This could be rationalized either by assuming that each of the six water molecules in the primary layer was bound to two molecules in the second layer with $NO_3^{\ominus}$ ions replacing some secondary water, or by postulating that Al^{III} hydrates with six water molecules while each $NO_3^{\ominus}$ can hydrate to two or three water molecules. The coordination number of six for Al^{III} in acetonitrile[167] has also been observed.

Studies of the complexes, formed between pyridine and similar bases with BF_3 or BCl_3, have suggested[168] that within the temperature range +35° to −40° only one ligand molecule is bound to each BX_3. Mixed coordination studies indicated a decreasing Lewis Base strength in the order pyridine > 1-methylimidazole > imidazole and pyrimidine. Linewidth studies at −30° afforded a value of $6{\cdot}0 \pm 0{\cdot}2$ for the coordination number of nickel(II) in aqueous solution,[169] and a method has been presented[170] for the determination of the relative concentrations of water and dioxane, dimethylformamide, or dimethyl sulphoxide in the inner coordination spheres of the binary solvent mixtures. DMSO and DMF are good competitors for coordination sites, but dioxane is excluded by water.

H. Hydrogen bonding

The low temperature spectra of β-phenyl ketones in SO_2—FSO_3H—SbF_5 medium show typically two $C{=}\overset{\oplus}{O}{-}H$ signals, one at unusually high field and the other at a much lower position.[171] For instance, with phenylacetone these two signals, assigned to *syn*- and *anti*-configurations (**62**) and (**63**)



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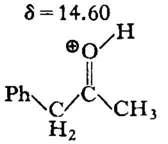

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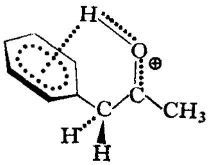
$\Delta\delta = 1{\cdot}13$ p.p.m. The high value for the *syn*-isomer is postulated to arise through π-hydrogen bonding with the phenyl ring as in (**64**).



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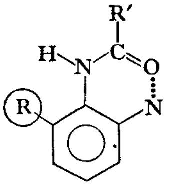
Several papers have discussed intramolecular hydrogen bonding. The position of the enolic proton in some β-diketones, *o*-hydroxyaldehydes and *o*-hydroxyketones has been interpreted in terms of steric and electronic effects which affect the strength of the hydrogen-bond.[172] Benzylic shifts in some 4,5-polymethylene salicylates and related compounds have been measured in order that the sites of hydrogen bonding in some similar isophthalates and carboxylic acids could be established.[173] The spectra of *N*-acylanilines have merited mention in a number of papers. If the molecule is *ortho*-substituted then strong deshielding of the other *ortho*-H is found. Part of the effect must be steric,[174] as in (**65**), but a further *ortho*-"locking" device exists when $R = NO_2$[122,174–176] or a similar group, e.g. COR, sulphonyl or sulphamoyl.[122,176] An investigation of diacylbenzoyl- and



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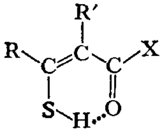
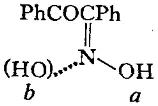
acyldibenzoyl- methanes,[177] in which only two of the three acyl groups are involved in the chelate ring, has suggested that the benzyl group (for steric, not electronic reasons) is not involved in the enolic system. The equilibrium in some β-thioketo-derivatives[178,179] has been found to lie consistently towards the enethiol, as in (**66**). The effect of solvents on this chelated system has been discussed. Spectroscopic investigations[180] have shown that no intramolecular H-bonding exists in either *syn*- or *anti*-benzil α-monoxime (**67**) but is found in the *syn*-isomer of (**68**). A simple method of detecting such intramolecular bonds was discovered, by the comparison of shifts measured in different solvents, as illustrated for (**67**) and (**68**) in Table VIII.



X = OR″, SR″ or R″

66



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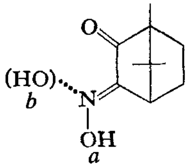

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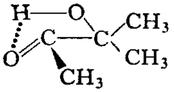
TABLE VIII

Solvent shifts in oximes as an indication of intramolecular hydrogen bonding

Compound	Group	δ(CDCl$_3$)	δ(acetone)	Δδ
67	*a*	7·68	11·35	3·67
67	*b*	7·20	10·82	3·62
68	*a*	7·40	10·93	3·52
68	*b*	11·98	11·30	−0·68

The variation of the hydroxyl proton shift of hydroquinone in the presence of varying excesses of tetrahydrofuran provided[181] an equilibrium constant for $H_2Q.THF + THF \leftrightarrows H_2Q.(THF)_2$ and gave a value of −3·6 kcal/mole for the enthalpy change on hydrogen bond formation. The interaction between pyrrole and dimethyl sulphoxide, as indicated by the concentration and temperature dependence of the NH shift,[182] is probably of the *n*-donor type, with a ΔH for complex formation of $-3{\cdot}0 \pm 0{\cdot}5$ kcal/mole. Two studies have been reported[183,184] on the association of nucleosides. Guanosine produced hydrogen bonded dimers in DMSO solution; when both guanosine and cytidine were present in DMSO a Watson–Crick type hydrogen bonded dimer resulted. The shifts of the amine hydrogens in several aliphatic secondary amines can be interpreted[185] in terms of a monomer–dimer association model, if allowances are made for steric hindrance and other factors. Internal hydrogen bonding appears[186] to be important in stabilizing the preferred conformations of the diastereomeric *meso*- and *rac*-2,4-disubstituted pentanes, which serve as model compounds for vinyl polymers. The spectra of several alcohols capable of exhibiting both inter- and intramolecular hydrogen bonding have been investigated over wide ranges of concentration,[187] and in each case the equilibrium which best fitted the data required parameters to be included for free monomer, intramolecularly bonded monomer (e.g. **69**) and a cyclic dimer.



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The HCl/dimethyl ether system has been used[188] to show that NMR can be employed for the study of vapour phase hydrogen bonding, by using signal enhancement techniques. An analysis of the pressure and temperature dependence of the proton signal in HCl allowed the calculation of the medium-independent values for ΔH, of $-7{\cdot}01 \pm 0{\cdot}8$ kcal/mole, and for ΔS, of $-25{\cdot}7 \pm 1{\cdot}3$ e.u.

The signal positions for the sulphanes (H_2S_x) depend upon the sulphur chain length, concentration and temperature.[189] It has been concluded that they participate in hydrogen bonding interactions, and that there may be a special type of intramolecular bonding operative in H_2S_3.

I. Miscellaneous

A graphic representation has been published[190] showing the shift values for ca. 250 methine protons. The correlation charts provide definitive ranges of the shifts and are presented according to the nature of the neighbouring substituents. Results have also been presented, in tabular form,[191] for the ^{1}H-shifts observed in a series of unsaturated aliphatic acids and esters, alcohols and ethers, enabling correlations to be made. The ring proton chemical shifts have been reported[192] for a set of 109 substituted anilines, *N*-methylanilines, heterocyclic amines, and the derived acetamides and 4′-bromobenzamides. The magnitude of the downfield shift accompanying acylation has been correlated with the preferred configuration of the amide.

III. COUPLING CONSTANTS

A. Proton–Proton coupling

1. *Theoretical and general considerations*

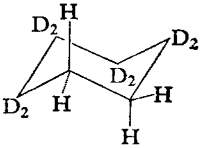
The nuclear spin–spin couplings in the series CH_4, C_2H_6, ethylene and acetylene have been calculated using the Ramsey perturbation formalism.[193] SCF molecular orbitals determined by the CNDO method were used, and the results showed considerable improvement over those obtained by independent electron methods, being in reasonable agreement with experimental values. A simple molecular orbital model has been proposed[194] for calculating the charge or spin delocalization at the start of an abstraction reaction, which shows that there should be a direct proportionality between the distribution of charge or spin induced in the molecule RH* and the hyperfine coupling (NMR or ESR) of the proton H* being abstracted, with other magnetic nuclei in RH*. By this model, some empirical correlations between coupling constants and reactivities can be explained.

Several papers have proposed additivity schemes for predicting ring proton coupling constants in variously substituted benzenes. The spectra of twenty types of monosubstituted benzenes have been accurately analysed,[195] and empirical relationships obtained between *J* and substituent electronegativities. The equations below were derived for the monosubstituted derivatives and a method given, by which *o*-, *m*- and *p*-couplings in disubstituted benzenes could be estimated.

$$J(2,3) = 6{\cdot}55 + 0{\cdot}49E(x)$$
$$J(2,6) = -0{\cdot}35 + 0{\cdot}85E(x)$$
$$J(2,4) = 1{\cdot}79 - 0{\cdot}20E(x)$$

Precise parameters have been measured[196] for some *o*-, *m*- and *p*-halofluorobenzenes, from which correlations between the various H–F couplings and substituent electronegativity have been calculated, which vary in direction and magnitude according to the position of substitution. Analyses have been performed[197] on the four monosubstituted benzenes substituted by —OH, —SH, $—NH_2$ and —COOH, together with thirteen disubstituted compounds containing these same groups. Substituent effects on the coupling constants were determined for all positions and found to be additive in the disubstituted benzenes, with an average deviation (for sixty-two couplings) of 0·085 Hz. The tabulated results correlate well with electronegativity and should prove useful in NMR assignments. Data were recorded[198] for twenty-two disubstituted benzenes, and substituent effects determined for both J(H–H) and J(C–H). The additivity of the effects was established and Cl, Br, I, NO_2 and OCH_3 substituent constants were tabulated (with respect to the benzene values) for coupling constants. The spectra of thirty-two disubstituted benzenes, analysed by iterative methods,[199] gave J values which could be compared with those calculated from substituent constants derived from the C_6H_5X series. From the results, it would appear that, with appropriate caution, the substituent effects can be usefully applied in the interpretation and analysis of NMR spectra, by the assumption of additivity. A similar treatment,[200] applied to some trisubstituted benzenes, showed that *ortho*-couplings were well reproduced (RMS deviation of 0·05 Hz) but for *meta*- and *para*-couplings saturation effects were indicated. A warning was given that polar solvents are to be avoided in obtaining data by which additivity schemes are to be tested.

A deuterium substitution technique[201] has allowed the calculation of the previously unrecorded values for the vicinal and geminal couplings in cyclohexane. By deuterium decoupling of (**70**) at −103° the resultant AA′BB′



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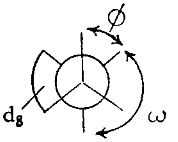
spectrum afforded $J(gem) = -13{\cdot}05$ Hz, $J(trans;\ a,a) = 13{\cdot}12$, $J(trans;\ e,e) = 2{\cdot}96$ and $J(cis;\ a,e) = 3{\cdot}65$). Assuming that ω in (**71**) is 120°, a value for



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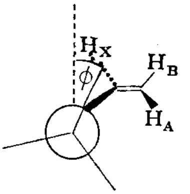
ϕ of approximately 57° was obtained, using the theoretical relationship between vicinal couplings and the dihedral angle. Results have been obtained[202] which illustrate the close dependence of spin–spin coupling on geometry in some six-membered rings.

Two analyses are reported for the *cis*- and *trans*-isomers of but-2-ene. The barrier restricting rotation about the C–C single bonds is intermediate between pure 3-fold and pure 6-fold[203] and the favoured conformation is skewed from that in which a CH_3 proton eclipses the C=C bond. The vicinal coupling, $^3J(S)$ is 0·2 Hz greater in *cis*-butene[204] and it is probable that effects other than skewing, for instance actual repulsion, are operative. Some recent observations[205] have indicated that a reinterpretation of the theoretical basis of allylic coupling is required. It has been found that with 4-, 5-, rigid 6-, and probably with 3-membered rings, with exocyclic methylene or alkylidene groups, $|J\ transoid| > |J\ cisoid|$, contrary to the commonly observed relative magnitudes. It was concluded that as ϕ in (**72**) approaches 0° or 180°, $J(t)$ becomes consistently larger than $J(c)$.

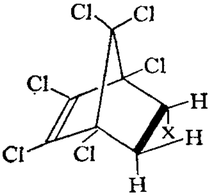


72

Structures have been assigned to the diastereomeric *cis*,*cis*- and *trans*,*trans*-diacetoxybuta-1,3-dienes[206] on the basis of the observed values of N in the AA′XX′ patterns. The results suggest *trans*-coplanar conformations, with $N(cc) = 5{\cdot}4$ Hz; $N(tt) = 11{\cdot}8$ Hz.

2. *Medium effects*

The spectra of acetal and some haloacetals, measured for a series of solvents and concentrations,[207] reveal a small but observable dependence of $J(CH_2, gem)$ on the medium. The solvent study demonstrated a monotonic variation of $J(gem)$ with the reaction field parameter $Z(\epsilon)$, where $Z(\epsilon) = (\epsilon - 1)/(2\epsilon + 2{\cdot}5)$, and ϵ = dielectric constant. $J(gem)$ decreases (i.e. becomes more negative) as the value of the dielectric constant increases.[208] The solvent dependence of ^2J(H–H) and *cis*- and *trans*-^3J(H–H) has been investigated in some 5-substituted hexachlorobicyclo[2.2.1]heptenes (**73**)



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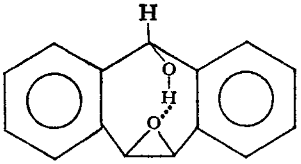
and a similar behaviour to that of the acetal series was observed[209] for ^2J(H–H), while changes in the ^3J values were less than 0·25 Hz. The general solvent effect was attributed to the solvent electric field which in turn is controlled by the net electric dipole of the solute molecule. These solvent-dependent couplings would appear to offer a useful probe for the investigation of both weak solute–solvent interactions and electron redistributions in dissolved molecules.

The variations in coupling for *meso*-2,3-dichlorobutane with change in solvent are to some extent correlated with conformer populations as a function of dielectric constant, using an Onsager model.[210] In the racemic isomer no such dependence was observed. Results showing a variation of $J(3,4)$ between 8·22 and 7·44 Hz depending on solvent and concentration[211] for *meta* substituted nitro- and chloro-benzenes indicate that the recent report[212] that H–H couplings in these compounds are insensitive to variations in inductive effect and independent of resonance effects, is unwarranted.

3. *Specific hydroxyl coupling*

Normally, coupling to hydroxyl protons has been observed in DMSO solution and, since C–O bond rotation is not readily restricted, *cis*- and *trans*-J(HCOH) values have not hitherto been obtained, allowing only a qualitative analogy to be made between the steric requirements of ^3J(HCCH) and ^3J(HCOH). Two molecules have now, however, been studied in which the molecular environment of the hydroxyl proton can be well defined, due to internal hydrogen bonding. In (**74**) a value for the *trans*-locked J(HOCH) of 12·5 Hz was found,[213] ($\phi = 180°$) while in (**75**) where models show that $\phi = 167°$,[214] J(HOCH) was 11.4 Hz, allowing $J(\phi = 180°)$ to be estimated at 12·0 Hz. Since aromatic substituents would be expected to induce a slight increase in the coupling, both these results suggest that a quantitative relationship exists between J(HCCH)(ϕ) and J(HCOH)(ϕ). The first case of strongly nonequivalent hydroxyl coupling in a primary alcohol has been recorded[215]—an observation which further supports the angle dependence of J(HOCH) proposed above. Intramolecular interactions combine, in (**76**), to yield J(HCOH) = 11·0 and J'(HCOH) = 2·8 Hz while models suggest a 20° deviation from coplanarity, compared with the 18° calculated assuming that $J(180°) = 12·0$ Hz. The steric requirements of ^4J(H—C—C—X—H) (X = O,S) have also been documented[216] and couplings for a series of alcohols, in which the values are rotationally averaged are given in Table IX.



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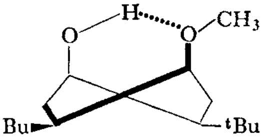

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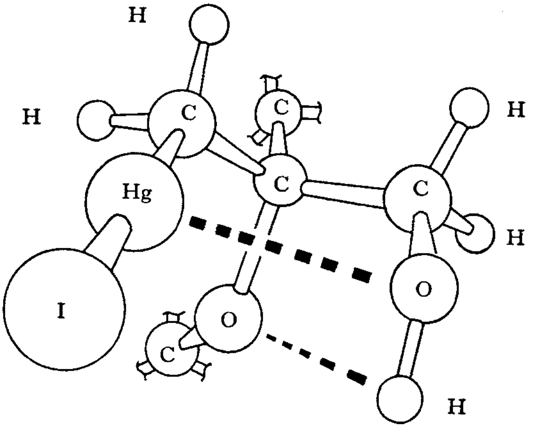

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The much larger dependence on substitution in the thiol compounds suggests direct interaction between methyl protons and the sulphur orbitals.

TABLE IX

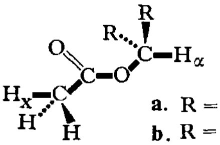
^{4}J(HCCXH) couplings (in Hz) for $CH_3\cdot\overset{|}{\underset{|}{C}}—X—H$ systems

RXH	X = O	X = S
R = ^{t}Bu	0·09 ± 0·01	+0·57 ± 0·02
R = ^{i}Pr	0·10 ± 0·01	+0·37 ± 0·01
R = Et	~0·10	~0·03†

† Observed by selective decoupling.

4. *Long-range coupling*

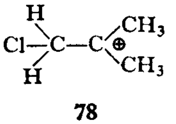
Although ^{5}J couplings have previously been observed in some simple alkyl formates these were thought to be absent in non-formate esters. Resolvable coupling has now been reported in such compounds as methyl acetate[217] presumably via an extended W system, such as (**77a**). With



a. R = H $^{5}J(\alpha X) = 0.25$ Hz
b. R = Me $^{5}J(\alpha X) = 0$

77

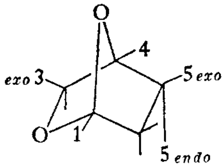
methyl substituents, as in (**77b**), the ^{5}J splitting is absent, presumably because the residence time in the conformation shown is small. It has been suggested[218] that in molecules of the type $(CH_3)_2C{=}X$, the relative sign of ^{4}J(H–H) is dependent upon the electronegativity of X, rather than being always negative.[219] In support of this it was predicted that the crossover point should occur with X = N (cf. $^{4}J = +0{\cdot}53$ Hz in acetone, and $-0{\cdot}49$ Hz in isopropenyl acetate) and indeed no long-range coupling could be observed between the methyl groups in acetone anil. A long-range ^{4}J coupling of 5 Hz has been observed[220] in the cation (**78**). The *exo-exo*-^{4}J couplings are



$ClCH_2{-}\overset{\oplus}{C}(CH_3)_2$

78

characteristically large ($3{\cdot}0$ Hz) in the dioxabicyclo[2.2.1]heptanes (**79**) relative to the value of $1{\cdot}5$ Hz found for the bornanes.[221]



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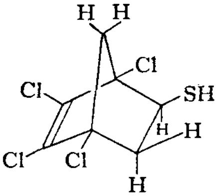
The absolute signs of the vicinal (^{3}J) and long-range (^{4}J) couplings of the S–H proton have been determined[222] for (**80**) by double resonance experiments [$^{3}J(\text{HSCH}) = +4{\cdot}03$; $^{4}J(exo) = +1{\cdot}17$; $^{4}J(endo) = +0{\cdot}49$]. It seems probable that for both C and S there are similar mechanisms for transmission of coupling, and also similar stereochemical correlations for vicinal and long-range coupling. The magnitudes of $^{3,4}J$(H–H) and $^{3,4}J$(H–F) in some cyclic dienones have been discussed, and their usefulness in conformational studies evaluated.[223] From this data, a modified Karplus expression was derived, applicable to unstrained systems. A complete analysis has been performed[224] on cyclobutanone in which the long-range couplings were large [$^{4}J(cis) = +4{\cdot}17$, $^{4}J(trans) = -2{\cdot}99$ Hz]. For eighteen cyclobutenes of type (**81**) no coupling was observed[225] between a methyl group at A and a proton at X,



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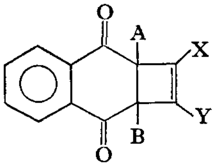
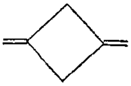


81

through a $^4J(\mathrm{H{-}C{-}C{-}\underset{\Vert}{C}{-}H})$ skeleton, but in the reverse situation, $^4J(\mathrm{H{-}C{-}\underset{\Vert}{C}{-}C{-}H})$ was 1·3 to 1·6 Hz. This was rationalized by assuming overlap between the *p*-lobe of the sp^2 carbon and the two C–H bonds. In (**82**)



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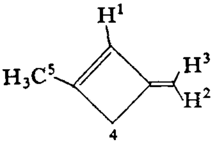
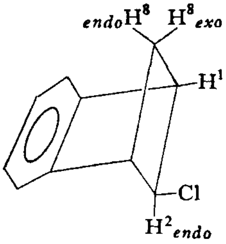
a value of $^4J(\mathrm{H{-}C{=}C{-}C{-}H}) = 2{\cdot}55$ Hz was found, while in the isomeric (**83**) two ^6J couplings were observed, as shown.[226]



$^6J(2,5) = 0.60$ Hz
$^6J(3,5) = 0.65$ Hz

83

In a number of papers the unusually large ^4J(H–H) couplings observed in bridged cyclobutanes have been discussed. It has been suggested that all such couplings are positive, as in (**84**) where ^4J(2-*endo*,8-*endo*) = +7·4 Hz.[227]



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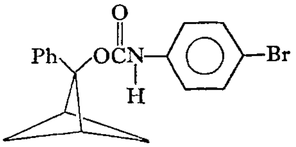
Crystallographic studies, which show non-bonded contact (1.89 Å separation) between the bridgehead carbon atoms in (**85**) have been used to



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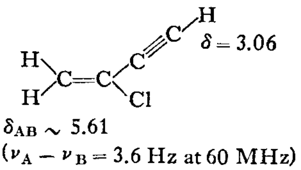
rationalize the very large (18 Hz) ^4J coupling observed between the bridgehead protons.[228] Strong overlap between the small lobes "behind" the C–H bonds must exist in this molecule. The ^4J bridgehead couplings in the related molecules myrtenal[229,230] verbenone[230] and α-pinene[230] all lie within the range +5·8 to +6·4 Hz. The analogous ^4J bridgehead couplings in norbornene and norbornadiene[231] have also been found to be of considerable magnitude (+2·89 and +2·85 Hz respectively).

The spectrum of chlorobutatriene[232] has been reported and is of ABX type. A complete analysis has not yet been performed but it is certain that one ^5J value must be >6·4 Hz, which is close to the value predicted (7·8 Hz) for butatriene itself. The same authors report parameters[233] for the chlorobutenyne (**86**) in which the two long-range ^5J couplings are both ±0·5 Hz. A



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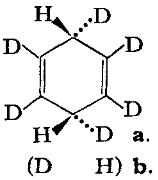
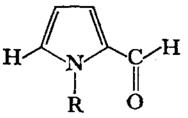
deuterated 1,4-cyclohexadiene, consisting of the mixed isomers (**87a,b**) has



87

been prepared in order to investigate the conformation of this skeleton.[234] The two ^5J allylic-allylic couplings, assigned 8·04 (*trans*) and 9·63 Hz (*cis*) respectively, show it to be almost planar (D_{2h}) with an angle between the C=C bonds calculated as 172°.

It has been shown[235] that the long-range proton–methyl couplings in propene, mesitylene, 9-methylphenanthrene and acenaphthene are linearly related to the square of the mobile bond order between the carbon atoms bound to the methyl and the proton. Substituents, however, may affect the coupling and should be taken into account in the application of such a relationship. An exact analysis[236] of the spectrum of *trans*-2,4-pentadienoic acid has afforded values for $^5J(cc)$ (0·662 ± 0·014 Hz) and $^5J(tc)$ (0·657 ± 0·014 Hz) in agreement with the value of ca. 0·7 Hz earlier predicted.[237] Studies on *N*-substituted 2-formylpyrroles (**88**) have shown that the conformation approximates to the W pattern even with the *tert*-butyl derivative,[238] the steric strain being accommodated by a slight twisting of the formyl group. Deviations from symmetry in inherently symmetrical spectra[239] have been utilized to study small long-range couplings between benzylic groups and ring protons. For both sp^2 and sp^3 hybridized benzylic carbon atoms, maximum coupling to *ortho*-ring protons seems to be associated with out-of-plane conformations, while *meta*-couplings are strongest for in-plane conformations. A stereospecific ^5J hydroxylic coupling of 0·6 Hz to H(B) has been observed[240] in the dichlorosalicylaldehyde (**89**) and stereospecific ^5J coupling has also been found[241] in α,α,2,6-tetrachloro-



With R = Bu^t, ^5J = 1.2 Hz

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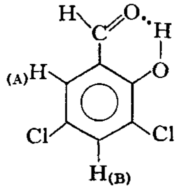

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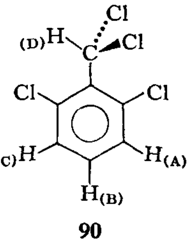
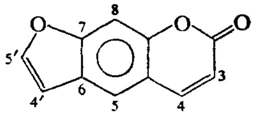


90

toluene (**90**). At –40°, ^5J(AD) = 0·5 Hz, with a zero *para*-coupling, as is expected if a hyperconjugative mechanism is present. Long range (^4J and ^6J) interactions have also been documented[242] for 2,6-dimethyl-3,4-dibromophenol [$^6J(CH_3–CH_3)$ = 0·21 Hz] and 3,5-dimethyl-4-hydroxybenzaldehyde. High resolution spectra of some substituted coumarins and furanocoumarins[243] have shown transannular ^{4-7}J couplings; for instance in (**91**),



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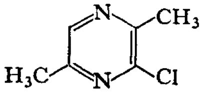
$^5J(3,5)$ = 0·3, $^4J(4,5)$ = 0·35, and via a W configuration, $^5J(4,8)$ = 0·65 Hz. Couplings over 5 and 7 bonds have also been reported[244] in a series of substituted pyrazines. The methyl signals in (**92**), with $^7J(CH_3–CH_3)$ 0·7 Hz, are reproduced in Figure 2.



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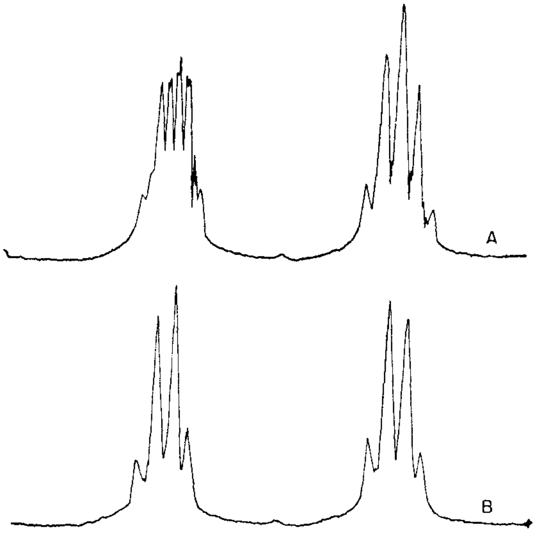
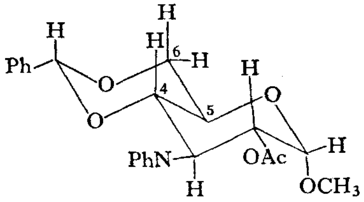


FIG. 2. Proton NMR spectrum of the methyl protons of 2-chloro-3,6-dimethylpyrazine in chloroform-*d* solution at 100 MHz: (A) normal spectrum and (B) proton 5 irradiated spectrum. (From Cox and Bothner-By.[244])

A revised expression for the π-electron contribution to proton–proton coupling has been presented[245] in which, even for ^5J couplings, it is predicted that a significant proportion arises from a σ-electron mechanism. Values of ^4J have been discussed for compounds in which the stereochemistry is thought to be the dominant factor determining their magnitude.[246] A simple σ-molecular orbital treatment[247] has given calculated coupling constants in agreement with experiment. The approach is generalized to include distorted cyclohexane fragments and the results are presented in graphical form.

5. *Virtual coupling*

This phenomenon has been encountered in several situations, and a selection of references are outlined below. Partial virtual coupling has been observed[248] between the axial 6-proton and the 4-proton in the benzylidene glucoside derivative (**93**). The algebraic significance of partial virtual coupling in this ABMX system was discussed, with reference to calculated and observed spectra. A novel example of virtual long-range coupling including a hydroxyl proton has been described,[249] in which solvent shifts induce strong coupling between the C(2)H and OH protons in (**94**) causing virtual coupling to be apparent on the C(1) and C(3) proton signals. Long-range virtual coupling has also been discovered[250] between protons 1(2) and 5(6) in the bicycloheptan-2,5-dione (**95**), the conclusion being confirmed by comparison of the experimental spectrum with a computed model, which also contained the observed weak transitions. The phenomenon has also been reported[221] in 2,7-dioxabicyclo[2.2.1.]heptanes.



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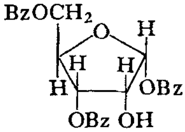

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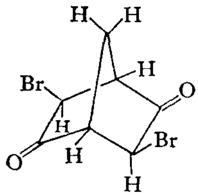
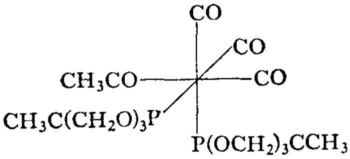
The observation of virtual coupling between P(Me$_2$Ph) ligands is often



95

used as evidence for a *trans* arrangement, because of its apparent mutual exclusiveness. Since this phenomenon arises through strong ^{31}P–^{31}P coupling, which also exists between *cis*-oriented ligands, it is possible that the appearance of virtual coupling could possibly lead to incorrect structural assignments. Strong evidence[251] has now been presented that (**96**) has in-



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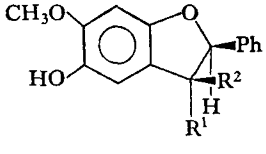
deed the *cis*-structure shown, while also exhibiting virtual coupling. This may perhaps arise through the strong π-acceptor capacity of the ligand involved, but nevertheless should be taken as a *caveat.*

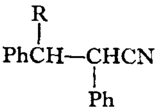
6. Erythro-threo *correlations*

Caution should be exercised in the use of the magnitudes of coupling constant as a guide to configuration. For example, it has been noted[252] that for both (**97a**) and (**97b**) $J(2,3) = 8$ Hz. In some derivatives of type (**98**) it has been found[253] that an increase in the steric requirements of the alkyl group



a. $R^1 = CH_3$; $R^2 = H$
b. $R^1 = H$; $R^2 = CH_3$

97



$$\begin{array}{c} R \\ | \\ PhCH\text{—}CHCN \\ | \\ Ph \end{array}$$

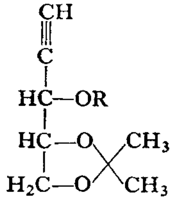
98

TABLE X

***Erythro* and *threo* couplings (Hz) in PhCHR—CHPhCN**

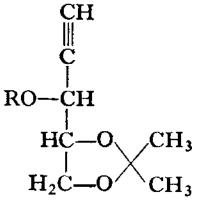
R	*J*(*erythro*)	*J*(*threo*)
CH_3	7·2	6·8
Et	6·4	7·1
^{i}Pr	4·8	8·4
^{t}Bu	3·7	10·2
—SPh	5·5	7·1
C_6H_{11}—	5·3	8·3

causes a decrease in the vicinal coupling constant of the *erythro*-isomer while conversely the *threo*-isomer shows increasing values. This presumably arises from a change in conformational preference, and the results for a series of alkyl groups are listed in Table X. The measurement of vicinal couplings in the diastereomeric acetylenic sugar derivatives (**99**) and (**100**) shows[254] that



J(*threo*) = 3.8 Hz

99



J(*erythro*) = 8 Hz

100

the stereoelectronic requirements of the —OR group (R = 3,5-dinitrobenzoyl) are greater than those of the ethynyl chain.

In a series of ten racemic *erythro*- and *threo*-isomers of 1,2-disubstituted 1-arylpropanes[255] the methyl signals of the *erythro* isomers were consistently at lower field than in the *threo* isomers, but for six of the compounds the vicinal coupling constant was smaller for the *erythro*-isomer, again indicating that the magnitude of $J(AB)$ is a poor criterion of configuration.

Several other papers have discussed *erythro*/*threo* configurations in aliphatic compounds[256,257] and the side chains of aromatic molecules[258,259] in relation to the magnitudes of vicinal coupling constants.

B. Proton–heteroatom coupling

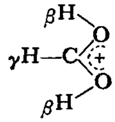
1. *Carbon-13*

An empirical correlation[260] has been discovered between $J(^{13}\text{C–H})$ for the methyl group and the product $E(X).\gamma(X\text{–}C)$ where $E(X)$ is the electronegativity of the methyl substituent X and γ(X–C) is the X–C bond length, from which it is possible to predict unknown values of $J(^{13}C–H)$. The results were obtained for a series of alkyls which included $(CH_3)_2Cd$, $(CH_3)_3Ga$ and $(CH_3)_2O$. The values of J(CXCH) and J(C–H) for some $X(CH_3)_4$ derivatives have been discussed[261] in terms of the Fermi contact coupling mechanism, and are summarized in Table XI. The effect of protonation on the $J(^{13}C–H)$ coupling in HCN has been recorded[262] and reflects the hybridization [J(C–H) = 269 Hz in HCN; 320 Hz in $HC\equiv\overset{\oplus}{N}—H$]. It was already known that two protonated forms of formic acid (**101** and **102**), exist at low temperatures, but the values and signs of the proton–carbon coupling constants have now been determined,[263] as indicated, and only show qualitative agreement with values calculated by the method of Pople and Santry.

TABLE XI

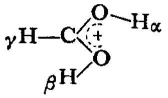
^{13}C–H couplings (Hz) in $X(CH_3)_4$ derivatives

X	^3J(CXCH)	^1J(CH)
C	4·8	124·3
Si	2·1	118·2
Ge	1·9	124·4
Sn	1·3	127·7
Pb	1·05	134·4



$J(CH\gamma) = +226$ Hz
$J(CH\beta) \simeq -0.6$ Hz

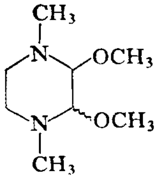
101



$J(CH\gamma) = +238$ Hz
$J(CH\alpha) = -7.8$ Hz
$J(CH\beta) = -1.8$ Hz

102

A technique of weak double irradiation has been described[264] by which hidden ^{13}C–H satellite bands can be precisely located, thus allowing the



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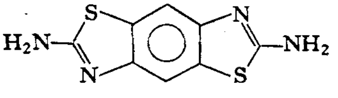
determination of C–C–H coupling constants. The detection of direct C–H satellites can be of use in the assignment of structure when further splitting is also present. For instance, the evaluation of the *J*(HCCH) coupling from satellite spectra has shown that the product of reaction between glyoxal and $CH_3NHCH_2CH_2NHCH_3$ in methanol is a mixture of *trans*- (**103**) (88%, 3 to 4 Hz coupling) and the corresponding *cis*-isomer in which no further coupling was observed.[265] Similarly, structures (**104** and **105**) have been assigned unambiguously by the observation of *p*- and *o*-couplings, of <1 and ~8 Hz respectively, in the ^{13}C satellite peaks to the aromatic signals.[266]



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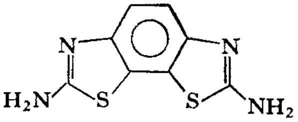

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The analysis of ^{13}C–H satellites in some 1-substituted aziridines has been reported,[267] in which considerably different C–H couplings are observed for protons *cis*- and *trans*- to the nitrogen lone pair (171 ± 1 and 161 ± 1 Hz respectively), and the results are discussed in terms of the orientation of the electron pair. A fairly good linear correlation has been observed[268] between experimental $J(^{13}C\text{–}H)$ values and "*s*" bond order, calculated by an SCF method, for some simple hydrocarbons. This result, applied to the cyclopropenyl ion, shows that the large observed value for $J(^{13}C\text{–}H)$ arises from the molecular charge, which increases the orbital exponents of the *s* orbitals for the C and H atoms [$J(\text{obs.}) = 265$, $J(\text{calc.}) = 269$ Hz]. The satellite spectra for some molten dihalobenzenes have been observed and analysed.[198,269] For the three symmetrical *p*-dihalobenzenes (Cl, Br,I) the explanation of some detailed features requires the assumption of small, but apparently real long-range[13] C isotope effects (ca. 0·3 Hz) on the chemical shifts.

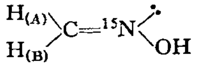
2. *Nitrogen-14 and -15*

The relative signs of all the couplings in $^{14}NH_3D^{\oplus}$ and $^{15}NH_3D^{\oplus}$ have been determined[270] as follows—

$$J(HD)\mp;\ J(^{14}NH)\pm;\ J(^{15}NH)\mp;\ J(^{14}ND)\pm;\ J(^{15}ND)\mp.$$

In protonated hydrogen cyanide,[262] $^1J(^{15}NH) = 134$ Hz, while the indirect coupling $^3J(^{15}NCH) = 19{\cdot}0$ Hz. A configurational dependence of $^3J(^{15}NNCH)$ has been reported in some *N*-nitrosamines.[271] The tabulated results indicate a marked difference in magnitude depending on whether the α-H is *cis*- or *trans*- to the nitroso-oxygen atom. For example, in [nitroso-^{15}N]dibenzylnitrosamine, and related compounds, $J(cis) = 0{\cdot}0$ to $0{\cdot}8$ Hz (often 0·0) while $J(trans) = 2{\cdot}1$ to 3·1 Hz. In dimethylnitramine, $(CH_3)_2N—NO_2$, the methyl signal is a 1:1:1 triplet[272] due to a 1·5 Hz coupling with nitrogen. This coupling is, as expected, temperature dependent being clearly resolved at 120°, while the signal is a sharp singlet at –20°. The interaction is probably from the nitro-group and only extends to the α-carbon atoms in ethyl methylnitramine.

The relative signs of the two $^2J(^{15}NCH)$ couplings in ^{15}N-formaldoxime have been determined. These are of opposite sign, as shown in (**106**), and the

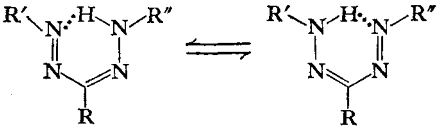


$^2J(^{15}NCH(A)) = \pm 14.0$ Hz
$^2J(^{15}NCH(B)) = \mp 2.4$ Hz

106

results are discussed with respect to structural and electronic effects.[273] Further use has been made[274] of a suggestion that the increase in linewidth, due to proton–nitrogen coupling, can be a good indication of orientation with respect to nitrogen in aziridine derivatives. Long-range coupling has been observed as a broadening of the *cis*-proton signals in substituted styrenamines. A study has been made of some ^{15}N-labelled imides at low temperature in strong acid media.[275] The N–H coupling constant was related to the *s*-character using the formula of Roberts *et al.*,[276] and in diprotonated phthalimide, with $J(^{15}NH) = 105$ Hz, the *s*-character was calculated to be 39%.

Some evidence for an angular dependence of ^{14}N–H coupling has been obtained[277] with some rigid quaternary bicyclic derivatives, in which it was possible to observe interactions between the nitrogen and a vicinal hydrogen. During investigations of chelation, using ^{15}N labelling, rapid tautomerism was ruled out for sugar osazones, since a typical doublet ($J = 93$ Hz) was observed[278] (cf. the anilino-proton in labelled 3-(^{15}N)anilino-1-phenyl-2-pyrazolin-5-one, with $J(NH) = 91$ to 92 Hz).[279] For a series of labelled formazans,[280] however, rapid intramolecular exchange between two equivalent sites was indicated, as in (**107**), since $J(^{15}NH)$ had dropped to 46·5 Hz. The attenuation in $J(^{15}NH)$ through tautomeric exchange has also been used to estimate the position of azo-hydrazo equilibrium in some *ortho*-hydroxy



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aromatic azo-derivatives.[281] Similarly, the low temperature spectrum of 2-(1H)-pyridone-^{15}N provides evidence of a >50:1 excess of the pyridone over the hydroxy-pyridine tautomer, with $J(^{15}NH) = 90$ Hz.[282] The ^{14}N–H couplings in pyrrole and pyrrole-d_4 are 69·5 ± 1 and 68·6 ± 1 Hz respectively.[283] Multiplication by $\gamma(^{15}N)/\gamma(^{14}N)$ yields a value of 97·5 ± 1·4 Hz for the corresponding ^{15}N–H coupling.

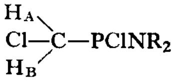
The origin of line-broadening in the signals of protons α- to the *N*-atom in some heterocycles has been examined,[284] and it is concluded that the observed effect arises from incomplete washing out of $^{14}N–H_{\alpha}$ coupling by quadrupolar relaxation. In the same paper, several ^{15}NH couplings to α- and β-hydrogens in some heterocycles have been summarized, and it was noted that protonation, or quaternization, produced a marked decrease in the magnitude of $J(^{15}N–H_{\alpha})$. Some ^{14}N–H couplings have been observed in quaternized pyrazines[285] and the phenomena discussed in terms of substituent electronegativity. Studies on substituted 5-aryltetrazoles labelled with ^{15}N have yielded the following parameters;[286] $J(^{15}NCH_3) = 1·85$ Hz, and $J(^{15}NNCH_3) = 1·7$ Hz, again indicating larger two-bond coupling with a nitrogen atom as separator.

Some ^{15}NH couplings have been measured for NH groups bound to Group IV nuclei, both in natural abundance using a CAT and in enriched samples, as a test for $(p \rightarrow d)$-π interactions in such bonds.[287] Values of 74 to 76 Hz for $(CH_3)_3M^{15}NHPh$ (M = Si, Ge, Sn) were interpreted in terms of the pyramidal structure at nitrogen.

3. *Phosphorus-31*

The observation of ^1J(P–H) in some hypophosphite complexes has shown[288] that in certain cases more than one mode of coordination is possible. For example, a low temperature study of solutions containing aluminium shows two or three distinct doublets, depending on the relative ion concentrations. The smallest of these (J(P–H) = 518 Hz) is due to uncoordinated $H_2PO_2^{\ominus}$, while the doublets of J(P–H) = 522 Hz and 591 Hz have been assigned to $Al(H_2PO_2)_n$ complexes and to the bridged dinuclear hypophosphite $Al_2(H_2PO_2)$ respectively. The PH couplings in H_2PPF_2 have been measured[289] and compare with the analogous values for P_2H_4 as follows: ^1J(P–H) = 189 (cf. 186·5 Hz) and ^2J(PPH) = 17 (cf. 11.9 Hz).

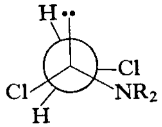
The values of ^2J(PCH) have been determined,[290] together with their relative signs for a series of 3-coordinate phosphorus compounds. The results have been plotted as ^2J against α, the dihedral angle between P and H. The curve shows two maxima, at $\alpha = 0°$ ($J = +26$ Hz) and $\alpha = 180°$ ($J \approx 0$ Hz), and a minimum at ca. 110° ($J = -6$ Hz). These results are of potential use in stereochemical assignments and can immediately be applied to some organophosphorus derivatives described by Goldwhite and Rowsell,[291] where opposite signs of $^2J(\mathrm{PCH})$ are found for the two non-equivalent protons in a —CH_2P group. The proton spectrum of (**108a**) at –20° shows $J(\mathrm{H_ACP})$ = ±26 Hz and $J(\mathrm{H_BCP}) = \mp 3$ Hz, while (**108b**) at –40° affords $J(\mathrm{H_ACP}) = \pm 24$ Hz and $J(\mathrm{H_BCP}) = \mp 1$ Hz. The authors concluded that the difference in magnitude between the couplings of H_A and H_B was due to a strong conformational preference, probably arising from dipolar interactions which cause the C–Cl and P–Cl bonds to be mutually *trans*. Since calculations by the method of ref. 290 suggest that in (**108a**) $\alpha(\mathrm{H_ACP}) \approx 0°$ and $\alpha(\mathrm{H_BCP}) \approx 140°$ while in (**108b**) $\alpha(\mathrm{H_ACP}) \approx 30°$ and $\alpha(\mathrm{H_BCP}) \approx 165°$, the resultant conformation (**109**) correlates well with this suggestion. Similarly, since $^2J(\mathrm{PCH})$ is ±7·6 Hz in $CH_2Cl—PH_2$,[292] it can be suggested that the probable conformation of this compound is that shown in (**110**).



$Cl—CH_AH_B—PClNR_2$

a. $R = CH_3$
b. $R = Et$

108



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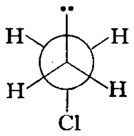

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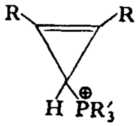
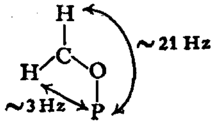
The $^2J(\mathrm{PCH})$ values for seventy-eight acyclic compounds have been tabulated[3] and the effect of substitution at C and P was discussed. No simple theory accounted for the observed variations, but the compounds were in various valency states. The $^2J(\mathrm{PCH})$ coupling in (**111**)—probably the first *J*(*gem*) reported for a cyclopropene—is sensitive to substituents but also unusually large (52·0 Hz when $R = n\mathrm{Bu}$, $R' = \mathrm{Ph}$, and 42·8 Hz when $R = \mathrm{Ph}$, $R' = n\mathrm{Bu}$).[293] It has been predicted that in complexed phosphines $^2J(\mathrm{PCH})$, for such molecules as PPh_2CH_3, should vary linearly with the *s*-character of the P–CH_3 bond. This has been observed[294] for some manganese polycarbonyl derivatives and the results were presented graphically.



$ClO_4^{\ominus}$

111

Some ^2J couplings have been recorded in which the intervening atom is not carbon. For instance, in the rhenium derivatives[161] described earlier (Table VII) ^2J(PReH) is typically ca. 18 Hz, and in the trigonal cobalt complex[157] also mentioned (Table VII) ^2J(HCoP) = 50 Hz. In the mixed "hydride" GeH_3PD_2,[295] the ^2J(PGeH) value is 15·0 Hz. Three-bond couplings to phosphorus have been documented in which various intermediate elements were present. In the PCCH system it appears that this coupling is also angle dependent. For Pr^i_2PhP, the first reported compound[296] in which phosphorus is a centre of asymmetry (see later), two values for $^3J(PCCH_3)$ were observed, of 14·7 and 11·0 Hz. Stereospecific dependencies for J(POCH) couplings are also recorded,[297] as shown in (**112**) for some phosphate esters,



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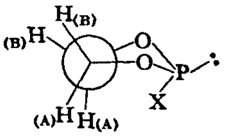
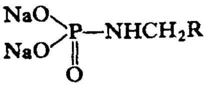
and in (**113**) for cyclic ethylene phosphites and sulphites.[298] The magnitudes



$J(PH_A) \simeq 2$ Hz
$J(PH_B) \simeq 9$ Hz

113

of ^3J(PNCH) couplings appear to be a little larger than the analogous POCH values. In a series of derivatives with general structure (**114**), ^3J(PNCH) = 7

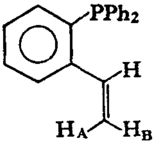


$(NaO)_2P(=O){-}NHCH_2R$

114

to 10·5 Hz,[299] while for some aliphatic phosphonium salts[300] in which d_π–p_π bonding is involved, ^3J(PNCH) is typically 11·5 Hz.

An analysis of the $POCH_2CH_3$ groups in seventeen esters of 3- and 4-coordinate phosphorus[301] has shown that $^3J(POCH) = 7{\cdot}20$ to 12·55 Hz, while $^4J(POCCH) = 0{\cdot}28$ to 1·24 Hz. In the *cis*-isomers of type $(Et_3P)_2Pt(X)Ge(CH_3)_3$ the four bond coupling $J(HCGePtP) \approx 2$ Hz, while some similar complexes, with Si or Ge *trans* to P, values for ^4J(HCSiPtP) and ^4J(HCGePtP) of 2·5 and 1·9 Hz respectively were observed.[302] Long-range 4- and 5-bond couplings have been observed in the P—CO—N—CH—CH framework,[303] and the mechanisms involved were discussed; since no 3-bond P—CO—N—H coupling could be found in the carbamylphosphonate skeleton, in this at least, two mechanisms with opposite signs must operate simultaneously. The ^5J long-range coupling found in *ortho*-styryldiphenylphosphine (**115**), which is stereospecific to H_A, involving an unfavourable path, suggests some kind of direct interaction.[304] The tentative explanation is that the 1·10 Hz coupling arises by direct overlap of the phosphorus lone pair with the σ-electrons of H_A in a type of hydrogen bonding, but the H_A shift is unexceptional.



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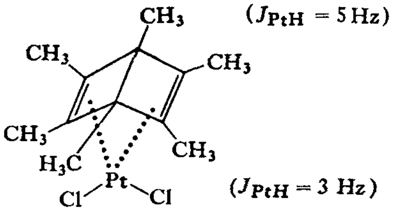
4. *Platinum-195*

Spectra have been measured[305] for Pt^{II} complexes of six types of amino acids, and the presence or absence of ^{195}Pt satellites used to determine the coordination sites in multidentate ligands. The data suggest a strong conformational dependence for ^{195}Pt–H coupling constants, which vary between 10 and 60 Hz in PtNCH fragments, being a minimum for dihedral angles near 0° and a maximum at 180°. In the complex (**116**) derived from hexamethyldewarbenzene it is noteworthy that even the bridgehead groups



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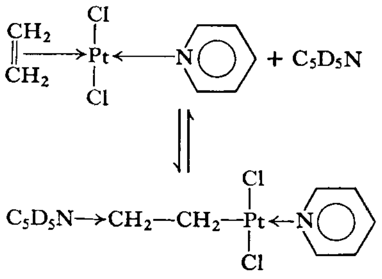
couple ($J = 5$ Hz) with platinum.[306] Satellite resonances and other spectral features provide evidence[307] for $\pi \rightarrow \sigma$ ligand conversion as shown in (**117**).



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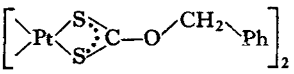
An alkyl CH_2 group, at higher field, and with larger J(Pt–H) is observed in spectra obtained at –50° after addition of deuterated pyridine. Satellite spectra also provide direct evidence for the formation of a 5-coordinate Pt^{II} complex as a reaction intermediate, prior to ligand substitution.[308] When CH_3Ph_2P is added to a solution of (**118**), the methyl signal has ^{192}Pt satellites, with J(Pt–H) = 40 Hz, indicating direct Pt–phosphine bonding. The platinum hydride complexes discussed earlier, of type *trans*-$PtHL(PEt_3)_2$[154] show a good correlation, for a given solvent, between ^1J(Pt–H), δ(Pt*H*) and ν(PtH). The couplings are also slightly solvent dependent, but a typical range is 1192 to 1245 Hz (in $CDCl_3$). In the spectra of the cationic complexes *trans* $PtHL(PEt_3)_2^{\oplus}ClO_4^{\ominus}$, the J(Pt–H) value is strongly dependent on the nature of L.[155] When L = pyridine, the Pt–H coupling constant is 1106 Hz, but this diminishes through 967 Hz (L = CO) to 790 Hz with L = PEt_3. Some long-range (^3J) couplings have been reported, through Si and Ge and ^3J(HCSiPt) and ^3J(HCGePt) were 17·8 and 12·8 Hz respectively in analogous complexes.[302]



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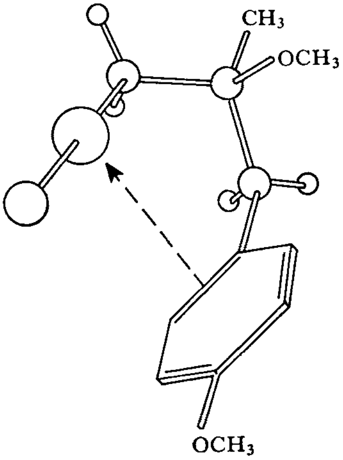
5. *Mercury-199*

In some mercuri-esters (RCO_2HgMe; R = CH_3, Ph, *p*-$NO_2C_6H_4$, CH_2Cl, $CHCl_2$ or CF_3) a good correlation has been found between J(^{199}Hg–H) and the pK value of the corresponding acid, RCO_2H.[309] Since this indicates that the coupling is dependent upon the electronegativity of the mercury substituent it is further evidence for coupling via a Fermi contact interaction. The relationship is $J(^{199}\text{Hg–H}) = 227{\cdot}4 - 3{\cdot}1\ \text{pK}$, and the J value in aryl derivatives also closely parallels the analogous ^{207}Tl coupling constants. The $^4J(\text{HgCCCH}_3)$ coupling in (**119**) shows solvent dependence, and falls in the range 34 to 48 Hz,[310] but more important, however, is the conformational dependence, for the $^4J(\text{HgCCCH}_2)$ coupling in the same molecule is only ca. 5 Hz. Both these effects are probably due to the intramolecular mercury–arene coordination shown.



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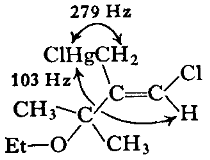
The spectra of some oxymercurials, derived from ethylene and propylene,[311] have shown that there is no evidence for the formation of the postulated mercurinium ion. The coupling constants to α- and β-protons were listed, as are those[312] for a series of mercuri-esters derived from the vinyl interchange reaction. A strong ^4J coupling has been observed in a mercuri-olefin, as shown in (**120**).[313] Parameters have been reported[314] for *para*- and *meta*-fluorophenyl- and -benzyl mercurials of types R_2Hg and RHgX (X = halide). There was no evidence for direct aryl–mercury conjugation, and the fluoro-substituents had little effect on the coupling



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constants. The change RHgX → R_2Hg was accompanied, as has been previously noted, by a reduction in J by a factor of a half, e.g. for R = $PhCH_2$ the J values were 260 and 134 Hz respectively. In a magnetic double resonance study[315] of some aryl mercury compounds, both $^3J(HgH_{ortho})$ and $^4J(HgH_{meta})$ have been found to be positive in sign. The Fermi contact interaction dominates, with for instance, $^3J = +204$ and $^4J = +54$ Hz respectively, in PhHgOAc.

6. *Other nuclei*

The spectra of ^{11}B-enriched diborane have been measured[316] over a temperature range of −7° to −60°. The terminal protons were non-equivalent and the parameters can be summarised as follows (all in Hz)—

$$J(B\text{–}H_{(b)}) = +46{\cdot}2;\ J(B\text{–}H_{(t)}) = 133;\ J'(B\text{–}H_{(t)}) = +4$$

Some heteronuclear couplings have been recorded[317] for the complex $(CH_3)_3N \rightarrow Al(BH_4)_3$. The values of $^2J(^{11}B\text{–}H) = 90$ Hz and $^3J(^{27}Al\text{–}H) = 46$ Hz may be compared with the corresponding couplings in $Al(BH_4)_3$, of 89 and 44 Hz respectively. A consistent trend has been observed[152] in the magnitudes of $^1J(^{29}Si\text{–}H)$ for a series of siloxanes and methoxysilanes which is probably related to Lewis basicity.

The very broad phenyl peak ($\delta = 7{\cdot}0$ to $7{\cdot}2$) observed for triphenylscandium has been explained[318] by a possible coupling to $^{45}Sc(I = 7/2)$. This seems unlikely, and the effect may well be due to phenyl exchange. Two $^1J(^{103}Rh\text{–}H)$ couplings have been reported,[160] and may act as indicators of symmetry, since in the possibly tetrahedral $HRh(Ph_3P)_4$ $J(Rh\text{–}H) = 13{\cdot}0$ Hz, while in the square-pyramidal $HRh(Ph_2PCH_3)_4$ the J value is 7·0 Hz. Exchange reactions have been studied and ^{111}Cd, ^{113}Cd couplings recorded for some methylcadmium alkoxides.[319] In CH_3CdOR, the average $^2J(CdCH)$ values, in Hz, are as follows—

R = CH_3, 9; R = Et, 7; R = *iso*-Pr, 6.

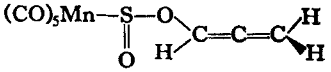
A heteronuclear double resonance study[320] of hexamethylditin has shown that the two hetero-couplings, $^2J(^{119}Sn\text{–}H)$ and $^3J(^{119}Sn\text{–}H)$ are opposite in sign, being +49·5 and −17·3 Hz respectively. One and two-bond couplings have been reported[158] for tungsten, where ^{183}W, with $I = \frac{1}{2}$ and 14·3% abundance, affords $^1J(W\text{–}H) = 63{\cdot}0$ and $^2J(WW\text{–}H) = 19{\cdot}2$ Hz in the complex $(C_5H_5)_2WH_2 \rightarrow W(CO)_5$. Couplings to ^{205}Tl and ^{203}Tl have been measured[321] in the insertion compound $CH_3SO_2Tl(CH_3)_2$. The average coupling (both nuclei have $I = \frac{1}{2}$) for $^2J(Tl\text{–}Ch)$ is 426 Hz. The signals, already 10 Hz wide at 39°, broaden further on cooling suggesting the possibility of monomer–dimer exchange, which is retarded at lower temperatures.

IV. SPECTRA-STRUCTURE CORRELATIONS

A. Magnetic non-equivalence

This subject, fascinating perhaps because it is not always easy, at first sight, to understand the geometrical niceties involved, has received much attention recently, and has provided material for a timely review[322] which should do much to promote interest and general understanding of the topic.

Several papers have described asymmetry induced by the presence of sulphur. In the compound (**121**), formed by insertion of sulphur dioxide into a metal–carbon bond,[323] the two terminal protons are rendered non-equivalent ($\delta = 5{\cdot}16$ and $5{\cdot}53$ p.p.m., with $J_{AB} = 15$ Hz) by the asymmetry at sulphur. Application of the principles involved in non-equivalence has allowed the allocation of structures to the two 2,4-dithiapentane-2,4-dioxides (**122**) since only the *meso*-form can show non-equivalent diastereotopic methylene protons.[324] Substituent and solvent effects made it possible[325] to give an absolute assignment of the individual methylene protons of benzyl *p*-chlorophenyl sulphoxide (**123**). Non-equivalence in some



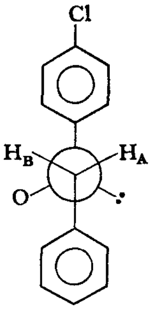
$$(CO)_5Mn{-}\underset{\underset{O}{\|}}{S}{-}O{-}\overset{}{\underset{H}{C}}{=}C{=}CH_2$$

121

meso—

(+) — or (−) —

122



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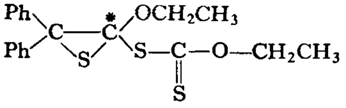
sulphoxy acids[326] has also been discussed. In the episulphide (**124**) two distinct non-equivalent methylene groups are observed, arising from the



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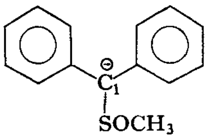
asymmetric centre indicated.[327] In the temperature dependent spectra of sulphinyl carbanions of type (**125**) the most salient feature[328] is the appearance, at low temperatures, of non-equivalent *para*-protons. Known cases of non-equivalence arising from the pyramidal sulphinyl group are of the "ethane-type",[322] which can be excluded in this case. A probable origin is indicated in (**126**) where the two phenyl groups are rendered distinct by restricted rotation about the C(1)-S bond. The differing δ-values observed are suggested to arise because of unequal negative charge densities close to the two rings, but it could also simply be due to different shieldings from a lone pair and an oxygen in (**126**).



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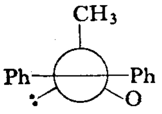

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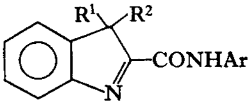
Methylene proton non-equivalence is well known in sulphites, but the presence of differential shifts for analogous methyl groups has now been demonstrated for the first time, with di-*iso*-propyl sulphite.[329] Two papers[330,331] have described the shift phenomena arising from the introduction of a second asymmetric centre into a sulphite. For instance, with the sulphite derived from natural menthol,[331] the two methine protons are distinct, at $\delta = 4{\cdot}24$ and 4·34 p.p.m.

The first example has been reported of a system in which tervalent phosphorus is the centre of asymmetry.[296] In di-*iso*-propylphenylphosphine, δ(AB) between the two distinct *iso*-propyl methyl groups is 0·17 p.p.m., and since the spectrum is virtually temperature-invariant this implies that inherent asymmetry, rather than an unequal distribution of rotamer populations, is the main cause.

Non-equivalence has been recorded also for geminal methyl groups in some substituted *iso*-butyric acids[332] and in the *iso*-propyl and *iso*-butyl side-chains of acyl 1,2-dihydro-*iso*-quinaldonitriles[333] together with the geminal substituents R of some ethyl-, benzyl- and *iso*-propyl-3*H*-indoles (**127**).[334]



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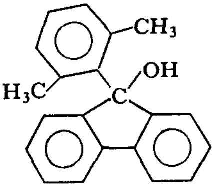
A novel source of anisochronism is the 2-substituted ferrocenyl group.[335]

Methylene and bis-methyl shift differences can be used to monitor optical resolutions, as with some tolylcyclohexanols,[336] and for the evaluation of stereochemical purity, as has been achieved for chiral *sec*-carbinols (with ±1% accuracy)[337] and aryl alcohols and amines,[338] by the use of a dissymetric tag-molecule.

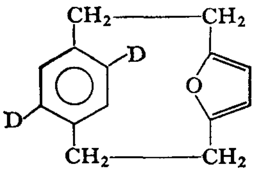
Anisochronism is a useful indicator of slow internal motion, and examples have been described in a wide range of compounds. For instance, with the triarylcarbinol (**128**) the barrier to internal rotation has been measured by a



$E_a = 17$ Kcal/mole

128

lineshape analysis of the methyl groups shown,[339] and similar studies made[340] on tetra-arylmethanes. Low temperature studies[341] on biphenyl



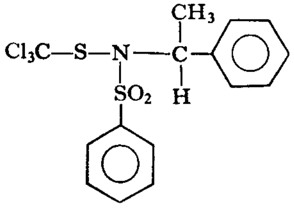
$E_a = 11.1 \pm 0.3$ Kcal/mole

129

derivatives, such as the inherently asymmetric podototarins, have demonstrated that lineshape analyses can afford activation energies for rotation which are lower than can be determined by the racemization method. Data for the interconversion of enantiomeric paracyclophanes such as (**129**) and derivatives have been presented.[342]

B. Inversion at Nitrogen

The ambient temperature spectrum of (**130**) shows the presence of a 1·05:1·00 mixture of two diastereomers, with methyl doublets at $\delta = 1{\cdot}27$ and 1·78 p.p.m.[343] The coalescence temperature of 68° indicates a $\Delta G^{\ddagger}$ of 17·2 kcal/mole. Some attention has been given to rates of inversion in small-ring heterocycles, such as aziridines[344–346] and azetidines.[345,346] In the former, $\Delta G^{\ddagger}$ can be very high, for instance >23·5 kcal/mole in (**131**), but in some 3 to 6 membered cyclic derivatives, containing sulphur bound to the ring N, it has been suggested that hindered N–S rotation may be the rate process operating.[346] With oxazolidines and tetrahydro-1,2-oxazines[347,348] nitrogen inversion is the observed process. The energy barrier is raised by ca. 1·3 kcal/mole in strongly hydrogen-bonding solvents, which correlates well with the fact that in *N*-inversion, but not with ring inversion, a hydrogen bond must be broken. An unequivocal inversion rate has been determined for piperazinium monochloride.[349] A 0·4 molar solution in HCl at pH 2 gives $k_A = 1{\cdot}51 \times 10^{-4}$ sec^{-1}, and analysis also indicates the relative basicities of the unsymmetrical diamine obtained (the α,α'-disubstituted nitrogen N_1 is least basic; $\Delta pK = +0{\cdot}17$). In the tetramethyltetrazine (**132**) the low-temperature spectrum indicates a preference for axial positioning of the *N*-methyl groups, with an energy barrier to *N*-inversion of 11·7 kcal/mole.[350] The temperature-dependent spectra of some *N*-aryl piperidine



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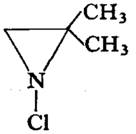

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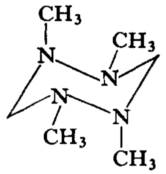

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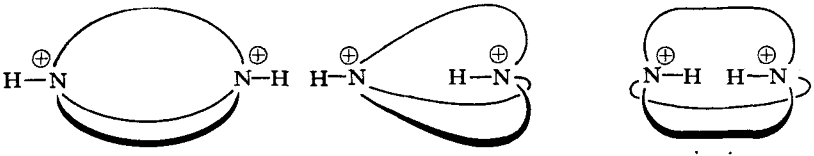
derivatives show that rates of inversion for different substituents decrease in the order shown[351]—

$$\mathrm{Ph{-}SO_2{-}N}\!\!< \; > \; \mathrm{Ph{-}SO{-}N}\!\!< \; > \; \mathrm{Ph{-}S{-}N}\!\!<$$

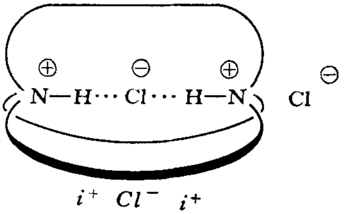
A 220 MHz study[58] has shown that protonated macrobicyclic amines exist in *out* and *in* isomeric forms of the type shown in (**133**). Interconversion



out–out *out–in* *in–in*

133

between these structures in aqueous solvents involves a sequence of prototropic reactions and nitrogen inversions rather than a homeomorphic isomerization (in which one chain passes through the ring defined by the other chains). The *in–in* form has been found to encapsulate halide ions as in (**134**) to yield a discrete species which has been given the name katapinate.



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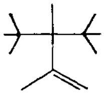
(Katapinosis—Greek καταπινω, to swallow up—is defined as the diffusion of molecules into a larger molecule with a sensible cavity to give a discrete molecular species.)

C. Mobility about C–C bonds

This subject has received a great deal of attention and a variety of systems have been studied. Restricted rotation has been observed in *tert*-butylcycloalkanes.[352] At very low temperatures (–130 to –160°) the *tert*-Bu protons appear as 2:1 doublets, the rotational barrier varying from 6·0 to 7·8 kcal/mole for 5- to 10-membered rings in a qualitatively understandable fashion. The di-*tert*-Bu-derivative (**135**) has a temperature-dependent



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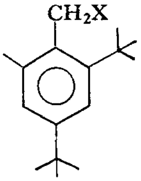
spectrum which can be interpreted[353] in terms of a 15 kcal/mole barrier to rotation about the C(2)–C(3) bond. A series of substituted benzyl halides (**136**), showing hindered motion around the benzylic bond, provide evidence[354] that the preferred conformation is that in which a benzylic hydrogen is eclipsed with the larger *ortho* substituent. The energy barriers for different halide substituents are 11·3 (Cl), 12·5 (Br) and 15·9 (I) kcal/mole respectively.



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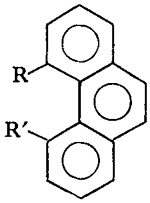
The activation parameters for inversion of non-planar phenanthrenes of general type (**137**) have been determined from line-shape studies.[355] For example, with R = COOH and R′ = COOEt, $\Delta G^{\ddagger}$ (290°K) = 15·2 ± 0·2 kcal/mole. Line-shape studies[356] have yielded the barriers to ring inversion in some dihydroanthracenes, as shown in (**138**).



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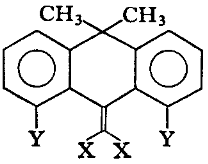
The conformational mobilities of humulene and zerumbone (**139**) have been investigated, and the free energies of activation for inversion are calculated to be 15·8 and 10·6 kcal/mole respectively.[357] The nature of the mobility in this ring system is uncertain. The unsaturated macrocyclic



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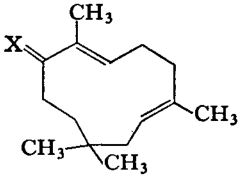
a. $X=H, Y=Cl\ \Delta F^{+}=15.9$
b. $X=Cl, Y=H\ \Delta F^{+}=17.4$
c. $X=Br, Y=H\ \Delta F^{+}=19.0$
(kcal/mole)



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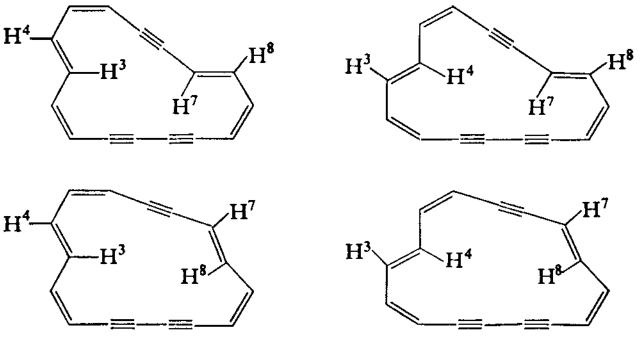
a. $X=H_2$; humulene
b. $X=O$; zerumbone

compounds 1,3,5-tridehydro[16]annulene and 1,3-bisdehydro[16]annulene are the first dehydroannulenes in which interconversion between non-equivalent conformers is observed, and the former is the first example of a dehydroannulene in which the protons on a *trans* double bond adjacent to an acetylene are being transferred between internal and external positions.[358] The observed shifts, at much lower field for inner protons, provide evidence



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for a magnetically induced paramagnetic ring current, as has been predicted for [4*n*] annulenes. The configurations involved for the tridehydro-derivative are shown in (**140**).

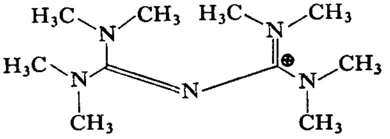
D. Mobility about C–N bonds

As with studies concerning C–C bonds, there has been great interest, resulting in a wealth of papers which can only be briefly described here. In formamide, one of the simplest structures possible for this type of investigation, heteronuclear double resonance has been used to remove quadrupolar effects, and from activation energies determined in various solvents the effect of hydrogen bonding to the carbonyl group on the rotational exchange barrier and the magnitude of vicinal couplings has been established.[359] Values of E_a for intermolecular proton exchange are also tabulated. The pure *cis*- and *trans*-isomers of *o*-methylformanilide have been isolated, and NMR was used to study the kinetics of equilibrium between them at low temperatures.[360] Variously substituted *p*-formanilides have also been investigated[361] in work which has outlined some of the difficulties involved in attempting to determine rotational barriers reliably for systems in which temperature-dependent solute–solute or solute–solvent interactions are likely to be important.

Much has previously been said about slow rotation around *N*-aryl bonds in *o*-substituted anilides and similar compounds, but in ureas the phenomenon has only been observed at low temperatures. A paper has now appeared[362] which reports slow rotation in some ureas at temperatures up to 180°. For example, *N*-ethyl-*N*-(1-naphthyl)urea shows a coalescence temperature of 119°. Substitution at the second nitrogen, contrary to steric expectations, reduces the rotational barrier around the *N*-aryl bond.

Quantitative evidence has been presented to support the assumption that dimethylformamide molecules associate as dimers in dilute CCl_4 solutions,[363] via bonding between *N* and *O* moieties in the substantially dipolar structure. A reappraisal of the activation energy for rotation in this molecule has been presented[364] which takes account of formyl–methyl coupling and the temperature dependence of the limiting $N–CH_3$ chemical shift. The value obtained, 20·5 ± 0·2 kcal/mole, is similar to that in other amides.

In a study of guanidines and biguanide cations[365] the former are shown to be freely rotating, the charge being delocalized over the five nitrogen atoms in (**141**) resulting in complete methyl equivalence. The latter, however, possess temperature-dependent spectra. Hindered motion about the *N*-aryl bond in anilinium ions has been reported for the first time.[366] For



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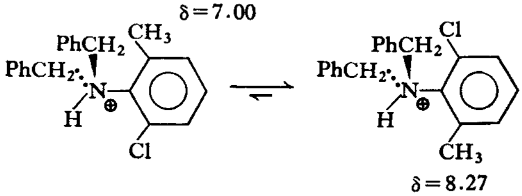
example, with the *N*,*N*-dibenzyl anilinium salt (**142**) the equilibrium lies on the right-hand side (82%).



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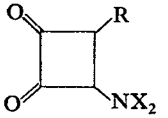
An investigation of the low temperature spectra of some *N*,*N*-di-*sec*-alkyl amides[367] has brought to light a potentially serious complication in the determination of rotational rates by signal shape analysis for rotors to which 2-propyl and related groups are attached. In such compounds selective broadening of the methine signals was observed, and is attributed to slow rotation about the 2-propyl-to-*N* bonds. In the spectra of some squaramides and related compounds containing *N*-substituents (**143**) the free energies of activation about the N–C bond were similar (for the ethoxy-derivatives) to those for acyclic vinylogous amides and urethanes.[368] Substitution of a phenyl group in place of the ethoxy group slightly lowers the barrier, as is expected for steric destabilization of the ground state (e.g. for $N(CH_3)_2$, $\Delta G^{\ddagger} = 16{\cdot}9$ (OEt) and 15·4 (Ph) kcal/mole respectively). Few reports have appeared for high rotational barriers of an $N(CH_3)_2$ group attached to a heterocyclic ring. One such example has been given[369] for 5-(*N*,*N*-dimethylamino)-1,3,4-oxathiazole-3,3-dioxide, in which $E_a = 17{\cdot}9 \pm 0{\cdot}7$ kcal/mole, i.e. of the same order as amides and thioamides.

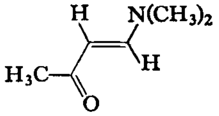


$X = CH_3$, Et or CH_2Ph
R = Ph or OEt

143

Results have been recorded for barrier heights in 6-dialkylaminofulvenes,[370] which show that a quantitative approach can be made to the estimation of π-electron delocalisation energies from this type of measurement. A study of the dimethyl group in a purine of diazafulvene-like structure has also been reported.[371]

Restricted motion about both C–C and C–N bonds has been observed[372] in the vinylogous amide 4-dimethylaminobut-3-en-2-one (**144**), while with



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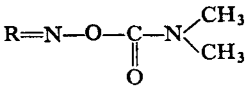
the analogous vinylogue of an aryl chloride, lifetimes in the *s-cis-* and *s-trans*-rotamers are too short to be observed by NMR techniques even at –60°. This has been attributed to a highly increased bond order in the amide vinylogues.

Few reports have appeared to date of barriers to internal rotation about the CO–N bond in carbamates, and only one[373] has been documented for *O*-(*N*,*N*-dimethylcarbamoyl)-oximes, where a substantial reduction was observed with respect to the barriers in simple amides. For instance in (**145**),



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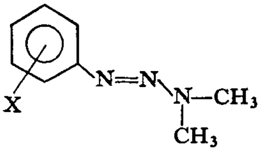
with $R = Me_2C{=}$, $\Delta F^{\ddagger} = 14{\cdot}4 \pm 0{\cdot}2$ kcal/mole. It is assumed that canonicals involving partial double bond character of the CO–O bond attain importance at the expense of the CO–N linkage. Studies of a trialkyl formamidine,[374] in which the non-equivalence of methyl shifts was accentuated by use of aromatic solvents, have also shown a diminution in the free energy of activation compared to those found for other molecules of the general type $RC(=X)—NMe_2$.

E. Mobility about other bonds

The rates of rotation around the N–N bond in triazines of type (**146**) are



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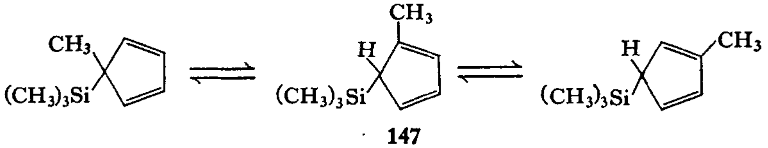
measurable by standard NMR methods,[375] and the exchange averaging process obeys a linear free energy relationship. A plot of *k* against Hammett σ constants yields a linear plot, with ρ values of $-2{\cdot}01$ and $-2{\cdot}03$ at 0° and 25° respectively. This is of interest, since some previous attempts at systematic correlation of electronic effects of substituents in a variety of NMR exchange processes have been unfruitful. A sizeable substituent effect ($\rho = -2{\cdot}01$) has also been reported in this class of compound by Akhtar *et al.*,[376] who suggest that a stereospecific association of benzene with the triazenes studied results in the benzene ring being closer to the *trans* N–CH_3 group in the 1,3-dipolar resonance hybrid.

A proton resonance study of the unstable molecule, CH_3SNO, shows that two conformations exist at –60°.[377] Unlike the analogous CH_3ONO, where the populations are roughly equal, the *cis*-form (97%) is predominant, indicating a large energy difference between the conformations.

Studies on $PhClP—N(CH_3)_2$ have resulted in the first report[378] of the barrier height to rotation about a P–N bond. The coalescence temperature is –60°, yielding a barrier of ca. 12 kcal/mole, with a low and high field doublet, at $\delta = 2{\cdot}78$ and $2{\cdot}25$, corresponding to the two methyl groups which show ^3J(PNCH) couplings of 19·2 and 6·7 Hz respectively.

F. Valence tautomerism

Contrary to earlier reports, concerning the temperature dependent spectra of methylcyclopentadienyl-silicon and -tin compounds, it has now been demonstrated that the assumption that substitution in the ring causes the compound to assume a static configuration is unjustified.[379] The complex low temperature spectrum of the silicon derivative is ascribed to the three isomers (**147**) interconverting in the NMR timescale.



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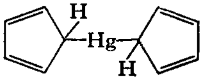
Cotton[380] has introduced a simplified nomenclature for naming organometallic systems, and has described a tris-cyclopentadienyl compound $(C_5H_5)_3MoNO$ in which there are three interconverting non-equivalent cyclopentadienyl rings at room temperature. The behaviour on cooling is complex and shows first the appearance of a slowly interconverting monohapto ring [h^1-C_5H_5, indicating σ-bonding of the type seen in (**147**)] and later the possible presence of non-equivalent h^3- and h^5-rings.

There has been a certain amount of disagreement concerning the structure of non-transition metal cyclopentadienyl derivatives of Groups V and VI. In sulphur dioxide solution at –70° dicyclopentadienylmercury affords three signals, in the ratio 2:2:1. This was taken[381] as evidence that this compound belonged to the series in which mercury migrates round the ring by a series of 1,2-shifts (**148**). This has been disputed, however, by Russian workers[382]



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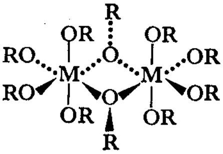
who provide data, from ^{13}C and ^{199}Hg satellite studies, which suggest π-coordination. In acetone solution at 34°, $J(\text{Hg–CH}) = 68{\cdot}9$ and $J(\text{C–H}) = 159 \pm 1$ Hz were observed, the latter being similar to that for benzene.

G. General correlations

1. *Inorganic systems*

Recent publications[150,151] make it possible to record values of the "ethanic" coupling constants in H—Si—Si—H and H—Ge—Ge—H fragments of ca. 2·5 and 3·9 Hz respectively (cf. 6 to 7 Hz in similar carbon fragments).

Two studies have been reported of niobium and tantalum penta-alkoxides.[383,384]. The structures are as shown in (**149**) with rapid intra-



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molecular exchange at differing rates for *t-t* and *t-b* pairs. (Ta; $\Delta G^{\ddagger}tt = 12{\cdot}0 \pm 0{\cdot}5$, $\Delta G^{\ddagger}tb = 14{\cdot}4 \pm 0{\cdot}7$ kcal/mole; Nb; $\Delta G^{\ddagger}tt = 13{\cdot}4 \pm 0{\cdot}5$, $\Delta G^{\ddagger}tb = 15{\cdot}8 \pm 0{\cdot}7$ kcal/mole; for $R = CH_3$ in toluene solution.)

The spectra of titanium ethoxide, *n*-propoxide and *n*-butoxide prove them to be trimeric in solution, in contrast to the *iso*-butoxide and neopentoxide which exist as a mixture of monomers, dimers and trimers.[385] Zirconium and hafnium *iso*-propoxides have also been found to exist as mixtures of oligomers in solution.

The tricyclopropylaluminium dimer has been prepared[386] and appears to possess the most stable hydrocarbon bridges so far reported in Group III derivatives. Rapid exchange on the NMR time scale does not occur until ca. 70°.

In a series of papers on aluminium alkyl and aryl dimers[387–391] Australian workers have described the first direct evidence for mixed bridges.[387] The mechanism of exchange between Lewis-base complexed alkyls and aryls, using excess anisole[388] or pyridine,[389] has been elucidated, and solutions of dimethylaluminium phenoxide have been found to slowly equilibrate, forming a mixture of dimer and trimer.[390] Kinetic studies of methyl group exchange between trimethylaluminium and dimethyl(phenylethynyl)-aluminium indicate that, in the rate determining step, a monomer of the former attacks a dimer of the latter.[391]

The mixed systems $AlMe_3$–$AlEt_3$, $AlMe_3$–$Al(n\text{-}Pr)_3$ and $AlMe_3$–$Al(Bu^i)_3$ have provided data for bridge-bonding factors, which are defined as a measure of the tendency of the alkyl group to occupy the bridge position in the mixed dimer.[393] The factor depends upon the bulkiness of the group, being $\frac{1}{6}$, $\frac{1}{7}$ and $\frac{1}{17}$ for Et, Pr^n and Pr^i substituents respectively.

Proton resonance data[393] have helped to confirm that in compounds of the chlorides and bromides of Sn^{IV}, Ti^{IV}, Nb^{IV} and Ta^{IV}, bonding from coordinated thioxan and selenoxan ligands is through S or Se, and not through O; the behaviour has been equated with the current theory of hard and soft acids and bases. A scale of relative Lewis acidities has been set up, from PMR data, for a series of inorganic halides, based on the ratios of changes in shifts of the α-protons in ethers on complex formation.[394] For the chlorides of Group IIIb elements, acidities increase with the electronegativity of the element; with Group IVb halides, steric rather than electronic factors appear to be dominant.

2. *Saturated molecules*

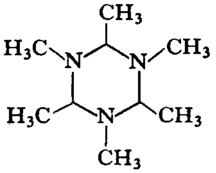
One of the papers in a growing series of publications concerning stable carbonium ions (too numerous to discuss in detail here) has provided evidence for the protonation of methane.[395] Using the "magic acid" solvent FSO_3H/SbF_5 the $CH_5^{\oplus}$ species has been observed, which undergoes proton scrambling at room temperature if FSO_3D is used.

The spectra of acetylacetaldehyde and malondialdehyde[396] indicate that the enol forms exist in the *s-cis*-conformation in carbon tetrachloride, chloroform and dichloromethane solution, while assuming the *s-trans*-conformation in water. It is possible that in $CHCl_3$ and H_2O solutions respectively, acetylacetaldehyde exists in keto- and hydrated keto-forms.

An interesting example of amide tautomerism has been recorded for an isomer of dichlorobis(trimethylacetamide)platinum(II) which shows sharp signals at $\delta = 10{\cdot}44$ and $1{\cdot}23$, and a broad band at $6{\cdot}75$ p.p.m., with relative intensities 1:9:1. This indicates that the molecule must exist in the iminol form.[397] The NMR spectra of 2-chlorocyclobutanone and its 2,4,4-trideutero-derivative have been interpreted in terms of an essentially planar structure,[398] in marked contrast to the previously reported conformation.

By a combination of NMR and mass spectrometry the structural isomer distribution in ring polymers of propylene oxide has been determined.[399] All four dimers and twenty-two of the twenty-three geometrical isomers of the tetramer have been observed, and the majority isolated and assigned to a structural configuration.

Infrared and NMR spectra have shown that the product from condensation of acetaldehyde with methylamine is more complex than the expected $CH_3CH{=}NCH_3$.[400] The neat liquid product appears to be largely two isomers of the cyclic trimer (**150**). Measurements at 56·4 and 100 MHz



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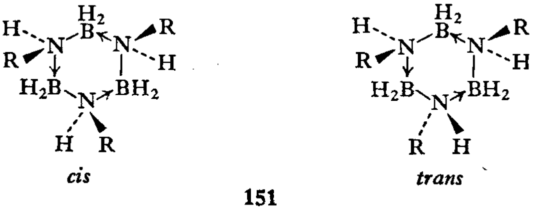
have allowed the assignment of shifts and identification of isomers for some *cis* and *trans* aminoboranes (**151**).[401]



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3. *Bridged systems*

A group of papers have appeared which discuss the assignments of shifts in molecules containing the norbornyl and similar skeletons. Decoupling experiments using *exo,exo*-5,6-dideuteronorbornene have clearly shown that the 7-*syn*-proton absorbs at lower fields than the 7-*anti*-proton.[402] Previously, there have been some incorrect assignments in this type of compound, but this assignment of the 7-*syn*-shift has been confirmed[403] by a stereospecific synthesis of 7-*anti*-deuteronorbornene.

The spectra of a number of *anti*-7-benzo-norbornadienyl and -norbornenyl derivatives have been presented and discussed in terms of an unequivocal assignment of configuration.[404] With the former compounds the key factor is the small long-range coupling (0·5–1·0 Hz) found between the olefinic and the C(7) bridge proton, no such coupling being found to the *exo* or *endo* protons in the benzonorbornenes.

In the 2,7-dioxabicyclo[2.2.1]heptanes[221] the relative chemical shifts of the *endo* and *exo* protons (**79**) have been found to be the reverse of those in the analogous carbocyclic systems.

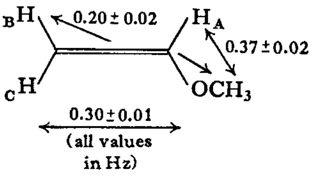
4. *Unsaturated molecules*

The enol–keto tautomerism in some diethyl acylmalonates (**152**) has been investigated by NMR.[405] The percentage of enol is dependent on the nature

152

of the substituent R, being 60% for R = CH_3 (at 38°) and falling to 0% when R = Bu^t.

The anomalously high-field chemical shifts ($\delta = 3{\cdot}8$ to $4{\cdot}2$) of the terminal olefinic protons in vinyl ethers have previously been explained by considering possible delocalization from the C=C bond into the C–O bond. Further evidence for this has now been obtained[406] by the observation of a long-range coupling between the alkoxy protons and the three vinyl protons in such compounds. Since the protons in methoxy groups rarely couple, the observation of the couplings shown in (**155**) support the C–O delocalization theory.



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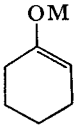
A series of metallic derivatives (**154**) of cyclohexenol have been investigated,[407] and the vinyl proton shift serves to give a rough indication of the



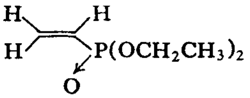
M = Li, MgBr or K

154

O–M bond looseness, which should be related to the ability of the enolate to function as a base toward the protons α to a carbonyl group.

In the newly synthesized vinyl isocyanide the vinyl protons show considerably more diamagnetic shielding than those in acrylonitrile, in accord with predicted conjugative effects and in opposition to inductive effects.[408] The ^{14}N–^{1}H couplings observed were characteristic of isonitriles.

The PMR spectrum of diethylvinylphosphonate (**155**) has been reported[409] and is of particular interest for it is an example of an ABCX type



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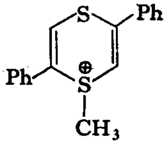
whose analysis is made possible solely by virtue of the couplings of the protons to the heteronucleus.

Variable temperature studies[410] have indicated that haloprenes exist largely in the *s-trans*-conformation, whereas the 1,1,3-trihalobutadienes are largely in a skew conformation.

It has been postulated that when singly bonded sulphur bears a positive charge it can expand its valency shell. Thus it might be possible to achieve aromaticity in dithiin salts of type (**156**). The NMR evidence has shown,



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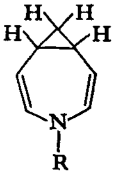
however, that this diphenyl derivative is essentially olefinic in character.[411] One proton is shifted down to $\delta = 8{\cdot}75$, by proximity to the sulphonium centre, but the other ($\delta = 6{\cdot}90$) remains at a very similar position to the parent dithiin ($\delta = 6{\cdot}98$).

Spectral parameters have been recorded for some substituted azepines[412] and homoazepines (**157**) and (**158**) where substituent $R = H$[413] or



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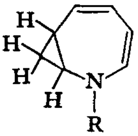

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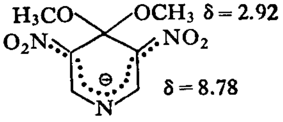
$CO_2CH_2CH_3$.[414] The homoazepines showed temperature invariant signals, indicating that the internal cyclopropyl bond is not prone to delocalization or valence bond isomerization; thus they fail to exhibit antiaromaticity.

5. *Aromatic systems*

A complete analysis of the 100 MHz spectrum of toluene has been performed.[415] All protons are shifted upfield from the position of benzene, by 0·186 (*o*), 0·074 (*m*) and 0·155 (*p*) p.p.m. respectively. This is in qualitative agreement with the allegedly increased π-electron densities at the corresponding C atoms caused by hyperconjugative interaction of the methyl group with π-electrons from the aromatic ring. The *meta*-shift cannot however be completely rationalized by current theories. The AA′BB′ spectra of a series of 4-substituted anilines, 4,4′-disubstituted diphenylamines and 4,4′,4″-trisubstituted triphenylamines have been analysed[416] and show the regularities expected for increasing arylation. They suggest that anisotropic ring field effects are exerted on the *ortho*-protons by adjacent rings.

There have been several reports concerning Meisenheimer-type salts. For example, NMR spectroscopy has shown[417] that these compounds could be formed by the addition of alkali metal methoxides to 4-cyano-2,6-dinitroanisole, 4-methoxy-3,5-dinitropyridine and 2,6-dinitroanisole, but not with 2-methoxypyrimidine. The stabilities of these salts were found to be dependent on the ability of ring substituents to accept negative charge. Their formation disrupted the ring current of the parent anisoles such that the methoxy signal moved upfield by about 1 p.p.m. The 3,5-dinitropyridine derivative (**159**) has also been described.[418] In some naphthalene complexes, upfield shifts of 1·33 to 1·42 p.p.m. have been observed for methoxy substituents, while the OCH_2— and —CH_3 signals in ethoxy groups are shielded by 1·36 to 1·50 and 0·53 to 0·35 p.p.m. respectively.[419] It has been suggested[420] that the highly coloured compounds produced by the interaction



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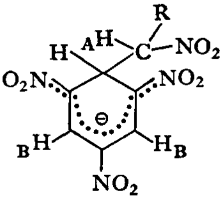

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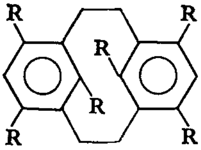
of aromatic and aliphatic nitro-compounds are sigma-complexes, as typified by the trinitrobenzene derivatives (**160**). If R ≠ H a small non-equivalence between the two H(B) protons is observed, arising from the resultant asymmetry of the substituent group.

The medium ring metacyclophane (**161**) (R = H) and its derivatives have received some spectroscopic attention. The parent compound displays an NMR spectrum which remains unchanged between –80° and +90°, indicating that the 10-membered ring is frozen in a chair conformation.[421] The stereospecific syntheses of 4,14-dimethyl- and 4,14-dimethoxy[2.2]metacyclophanes have been achieved and, together with other similarly substituted derivatives, provide correlations for substituent effects on aryl and methylene shifts.[422] For protons *meta-* to the substituent, the shifts correlated with Hammett σ_m constants, and are summarized by linear equations. Polymethylated derivatives have also been prepared, which exhibit anomalous NMR spectra.[423] For example, in (**161**) with R = CH_3, the methyl groups at C(8) and C(16) are unusually shielded (δ = 0·48 p.p.m.) by the ring current effect of the opposite ring. In the axial-equatorial isomer of 1,2-dimethyl[2.2]metacyclophane the shifts of H(8) and H(16) are different (δ = 4·22 and 4·50), again due to the chair form of the locked ring.[424]

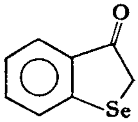


a. R = H
b. R = CH_3

161

Two complimentary papers have appeared which describe substituent effects in the benzo[*b*]thiophen series.[425,426] Seventy different compounds are documented, and the changes in shifts and couplings following oxidation to the 1,1-dioxides recorded and discussed. The vicinal coupling *J*(6,7) in 5-substituted derivatives varied directly and linearly with the electronegativity of that substituent.[426] Both with these, and some nitrobenzo[*b*]-thiophenes,[427] long-range couplings of <1·0 Hz are frequently observed, between protons at 2 and 6, or 3 and 7 positions. It is known that 3-hydroxythiophene exists in the enol form both in neutral and acidic media. It has now been shown,[428] however, that the selenium analogue (**162**) exists exclusively in the *keto* form in both trifluoroacetic acid and chloroform solutions.

The spectra of eighty compounds in several flavan classes have been studied, and the shifts and couplings for the aromatic and hetero protons tabulated and discussed.[429] The geometric configuration of substituents in



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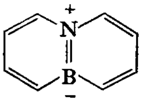
the heterocyclic ring follow unequivocally from the magnitudes of the vicinal coupling constants.

The 100 MHz spectrum of 10,9-borazanaphthalene (**163**) has been completely analysed,[430] and indicates a similar geometry and π-system to that of naphthalene. The coupling $J(3,4)$ was unusually large (11.2 Hz), and qualitative agreements were found between spectral parameters and SCFMO calculations, but simple HMO theory predicted positive charge at positions 1 and 3 whereas only 3 bears a formal positive charge. Complete analyses have been performed for the benzodiazoles (**164**) and some derivatives.[431]



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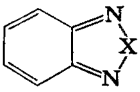

X = O, S, Se

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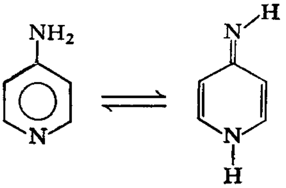
The *ortho* couplings (and the benzylic coupling in methyl derivatives) are apparently related to the π-bond order of the intervening C–C bond, and this evidence, in connection with molecular orbital calculations, confirms that the carbocyclic ring is essentially quinonoid in nature. These authors have also demonstrated a high degree of bond fixation in 1,2,5-selenadiazolo-[3.4-*c*]pyridine while with the -[3.4-*b*] isomer the parameters are similar to those reported for substituted pyridines.[432]

The proton spectrum of pyridine has been analysed using subspectral, direct and perturbation techniques, and the results showed close agreement with those obtained by the iterative method.[433] A semi-empirical SCFMO calculation of proton shifts has been performed for pyridine and pyridinium ion which included all valence electrons, and the results thus obtained suggested that neglect of σ polarization in such CNDO/2 calculations is not warranted.[434]

NMR spectroscopy has been used to provide proof that the equilibrium (**165**) does not exist in 4-amino-quinolines and pyridines.[435] The coupling observed between the amino proton and α-ring protons would not be observed if the proton were on a heterocyclic nitrogen. With 2-hydroxypyrazine, evidence for the dominance of the keto-tautomer has been presented.[436] Earlier publications, concerning the spectrum of 1,2,4-triazole, have either ignored tautomerism or have considered systems contaminated with water. A careful study[437] has now shown that in the melt, and in dry dimethyl sulphoxide, two signals in 2:1 ratio are present at $\delta = 7{\cdot}85$ (8·25 in DMSO) and 13·9 p.p.m., corresponding to (**166**). In pure hexamethylphosphoramide, however, two CH signals were found, and at −34° the structure was that shown in (**167**).



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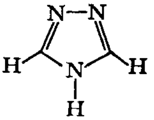

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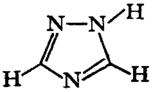

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Nuclear Magnetic Resonance Spectroscopy as an Aid in Conformational Analysis

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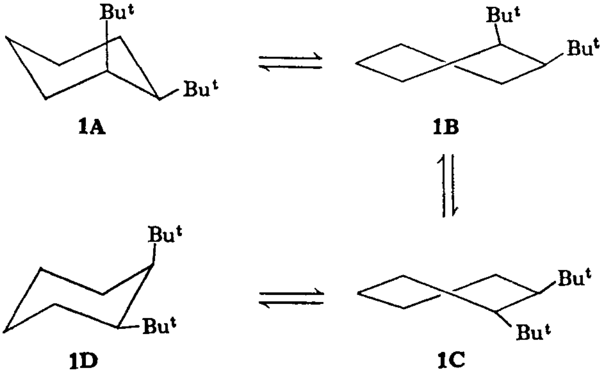
THIS REVIEW, covering the literature in the period from January 1967 to December 1968 with some more recent papers briefly mentioned, attempts to convey the progress made in the use of NMR spectroscopy in the determination of the conformations of cyclic and acyclic compounds. In structural analysis, of both organic and inorganic compounds, NMR is used to such a wide extent that to discuss every paper in which the technique has aided configurational and conformational assignments would be an impossible task. Therefore, in the main, the papers reviewed here are those in which NMR is used as the chief probe into the nature of the conformational effects under investigation. It is hoped that this chapter will be read in conjunction with other specialized reviews on similar lines, notably those written on heterocyclic compounds,[1] carbohydrates[2,3] and their fluorinated analogues,[4] and the general review in Volume 1 of this series,[5] dealing with the previous literature on this subject. It is notable that the last two years have seen a remarkable increase in the number of papers dealing with the conformation of heterocyclic compounds, nitrogen heterocyclics in particular. Such compounds are very amenable to NMR spectroscopic determinations and constitute a large section of this review article.

I. THE STUDY OF RING INVERSION PROCESSES, AND HINDERED ROTATION IN ACYCLIC COMPOUNDS

A. Cyclohexane and its derivatives

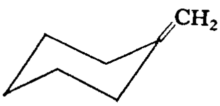
The activation parameters, associated with the ring inversion of cyclohexane, appear to be still in doubt as far as the enthalpy and entropy of activation are concerned, whereas both high resolution NMR variable temperature studies, and the spin echo technique give values for the free energy of activation ($\Delta G^{\ddagger}_{cb}$) for the chair–boat inversion process in excellent agreement.[5] It has been pointed out by Harris and Shepherd[6] that earlier attempts to measure $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were overambitious, in that too small a temperature range was used leading to large errors. They suggest that instead of plotting the logarithm of the inversion rate constant K_{cb} against T^{-1} (1/Absolute Temperature), it is more accurate to plot $\log(K_{cb}/T)$ against T^{-1}, obtaining $\Delta H^{\ddagger}$ from the slope $(\Delta H^{\ddagger}/R)$ and $\Delta S^{\ddagger}$ from the intercept $(\ln(K/h) + \Delta S^{\ddagger}/R)$. This treatment assumes that the two activation parameters are independent of temperature. The parameter $\Delta S^{\ddagger}$ is concluded to be too unreliable for any information concerning the conformation of the transition state to be obtained, although *relative* values, in a series of compounds measured under similar conditions, may be useful. In this review, therefore, normally just $\Delta G^{\ddagger}$ values will be quoted, determined either from the coalescence temperature of the exchanging sites ($\Delta G^{\ddagger}_{c}$) or by a full line-shape treatment over a temperature range above and below coalescence. Wolfe and Campbell,[7] in an examination of the inversion of symmetrically substituted cyclohexanes, implied that the ring inverts *via* the half-chair transition state of minimum energy, i.e. that with the maximum possible number of methylene groups eclipsed in one plane. Until it can be demonstrated that these half-chair forms do differ considerably in energy, such statements must be regarded with caution.

Conformations of the cyclohexane ring other than the chair form are still rare occurrences. An interesting temperature dependence of the NMR spectrum of *cis*-1,2-di-*t*-butyl cyclohexane has been demonstrated.[8] In theory, at least, the ring can adopt the four conformations (**1A**, (**1B**), (**1C**) and (**1D**). Two coalescences occur in the NMR spectra of the *t*-butyl



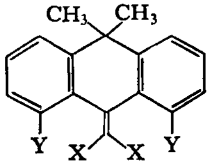
protons, one at 35° in chloroform-*d* ($\Delta G^{\ddagger}_{35} = 16{\cdot}3 \pm 0{\cdot}3$ kcal/mole), and another at –81° in carbon disulphide ($\Delta G^{\ddagger}_{-81} = 10{\cdot}1$ kcal/mole). The former process involves coalescence of the two *t*-butyl peaks into one at 35°C. The latter coalescence involves the "freezing out" of the high field signal into two further bands. The authors attribute this to the chair-twist boat inversion process, which is found to favour the twist boat by 0·2 kcal/mole. The coalescence at 35°C is clearly due to interconversion between the two twist boat forms (**1C**) and (**1B**). Slow rotation about the C–C bond joining the *t*-butyl groups to the ring, however, does not appear to have been considered, a process which could possibly account for the low temperature phenomenon.

1,1,4,4-Tetramethyl cyclohexane has been reinvestigated,[9] using a more accurate full line shape treatment for coalescence of the methyl groups, the $\Delta G^{\ddagger}$ value at –62° being 11·4 kcal/mole, in good agreement with previous results. The presence of an sp^2 carbon in the six-membered ring appreciably lowers the energy barrier to inversion, to such an extent that 4,4-difluorocyclohexanone is still inverting rapidly at –180°C, the present low limit for NMR spectrometers.[10] This means that the free energy of activation must be $\leqslant 2{\cdot}3$ kcal/mole. On the other hand, in exomethylene cyclohexane (**2**)



2

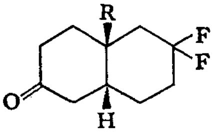
$\Delta G^{\ddagger}_c$ is reported to be 7·7 kcal/mole by two groups of workers,[11,12] whereas the methyl ether of cyclohexanone oxime gives a value of 5·6 ± 0·5 kcal/mole.[12] Cyclohexanone itself is reported to have a barrier not greater than 5·2 kcal/mole,[12] significantly higher than in the 4,4-difluoro derivative. If the cyclohexane ring with an exocyclic methylene group is constrained between two aromatic rings, as in the series (**3A**), (**3B**) and (**3C**), the inversion rate is considerably slowed, $\Delta G^{\ddagger}$ values ranging from 15·9 to 19·0 kcal/mole depending on the nature of X and Y.[13] Clearly inversion is hindered by the X and Y groups having to pass each other during inversion.



3

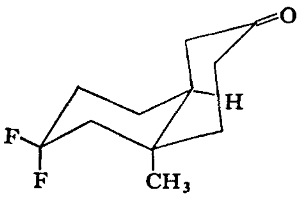
(A) X = H, Y = Cl
(B) X = Cl, Y = H
(C) X = Br, Y = H

Although the cyclohexanone ring is such a mobile system, it is possible to "freeze out" inversion when the ring is attached to another cyclohexane ring, with a *cis* ring junction (**4**) and (**5**).[10]

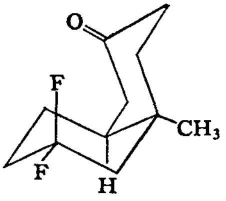


4 R = H; **5** R = CH$_3$

The ^{19}F spectra of the two compounds were run at low temperatures, and $\Delta G^{\ddagger}$ values measured as 9·5 and 9·1 kcal/mole for (**4**) and 9·8 and 10·4 kcal/mole for (**5**) respectively. The two values in each case correspond to the fact that the two conformers in each case are of different stability due to their different non-bonded interactions as shown in (**5A**) and (**5B**). In *cis*-decalin itself the barrier to inversion has been previously measured to be ~12·8 kcal/mole,[14] the difference probably reflecting the increase in mobility caused by replacing the CH$_2$ by C=O in the 2 position. Low temperature spectral studies of the coalescence of the methoxyl resonances of 2,2,7,7-tetramethoxy-*cis*-decalin indicated a similar free energy of activation



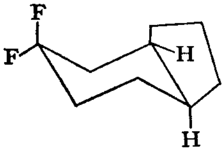
5A



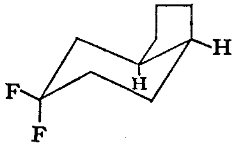
5B

(12.4 kcal/mole at ~-47°C) to that of *cis*-decalin itself.[15] In 9,10-disubstituted-*cis*-decalins (substituents —CH_2R, where $R = CO_2CH_3$, Br or CN) the activation energy, however, is raised to 14.7 → 15·9 kcal/mole depending on the substituents present.[16]

Five-membered rings are normally thought to be conformationally very mobile rings in which a low energy pseudorotation process is occurring. Again, however, constraining the ring with a *cis* ring junction, as in *cis* hydrindan, slows the ring inversion down to a measurable rate. Lack and Roberts followed the conformational equilibrium of 5,5-difluoro-*cis*-hydrindan (**6A**) and (**6B**) and its 9-methyl derivative.[17]



6A



6B

The results ($\Delta G^{\ddagger} \sim 7{\cdot}3$ for (**6**) and $\sim$7·6 for its 9-methyl derivative) were in fair agreement with those for hydrindan itself measured back in 1961.[18] Again the two conformers (**6A**) and (**6B**) have different preferences and slightly different activation parameters, due to the asymmetry caused by the *gem* difluoro group.

B. Heterocyclic six-membered rings

Harris and Spragg have recently reported the parameters for ring inversion in a number of substituted piperazine and morpholine derivatives.[19] The inversion of the nitrogen centres in these molecules constitutes a separate process and will be considered later in this Chapter. The $\Delta G_c^{\ddagger}$ values were obtained for coalescence of the axial and equatorial protons, which are complicated by strong coupling effects in the AA′BB′ spectra which can cause considerable errors. The results obtained in this and other work are reported in Tables I and II. Inspection of the Tables leads to the conclusion that oxygen, sulphur and silicon tend to lower the free energy of activation for ring inversion, whereas nitrogen and especially methylated nitrogen, tend to raise the barrier. The values of $\Delta G^{\ddagger}$ obtained tend to correlate with the barriers to internal rotation in the analogous acyclic compounds. For instance the small energy barrier for bond deformation of silicon in CH_3SiCH_3 of 1·70 kcal/mole is in agreement with the low activation energy for the cyclic silicon derivative[29] (**24**) in Table II.

Carbohydrate rings were previously thought to be unsuitable for low temperature NMR studies for a variety of reasons, the chief one being lack of

TABLE I

Axial-equatorial chemical shift differences, coalescence temperatures, and free energies of activation for ring inversion obtained at 100 MHz[19]

	Solvent	Conc., %	Signal	δ_{ae}, Hz	T_c, °K	$\Delta G^{\ddagger}$, kcal/mole
(7) Piperazine	CH_2Cl_2	5 w/v	N–CH_2	16	208	10·3
(8) Morpholine	CH_2Cl_2	5 v/v	O–CH_2	23	203	9·9
(9) *N*,*N′*-Dimethylpiperazine	CH_2Cl_2	20 v/v	N–CH_2	62	265	12·5
	MeOH	20 v/v	N–CH_2	68	270	12·7
(10) *N*-Methylpiperazine	CH_2Cl_2	20 v/v	$MeNCH_2$	80	247	11·5
	MeOH	20 v/v	$MeNCH_2$	80	252	11·7
(11) *N*-Methylmorpholine	CH_2Cl_2	20 v/v	N–CH_2	55	242	11·5
			O–CH_2	22	233	11·5
	MeOH	20 v/v	N–CH_2	56	243	11·5
	$C_6H_{11}Me$	10 v/v	N–CH_2	50	236	11·2
(12) *trans*-2,6-Dimethylmorpholine	CH_2Cl_2	5 v/v	C–Me	30	187	9·0
(13) *cis*-2,5-Dimethylpiperazine	CH_2Cl_2	5 w/v	C–Me	26	199	9·6
(14) *N*,*N*-Dimethylpiperazinium chloride hydrochloride	SO_2		NH_2	34	214	10·3

TABLE II

Free energies of activation[a] for ring inversion, calculated from literature values of axial-equatorial shift differences[b] and coalescence temperatures

	Solvent	Signal	δ_{ae}, Hz	T_c, °K	$\Delta G_c^{\ddagger}$, kcal/mole	Ref.
(15) Cyclohexane	CS_2	$C\mathit{H}D$	28·7	212	10·3	20
(16) Pentamethylene sulphide	CH_2Cl_2	$S–CH_2$	30[c]	180	8·7	21
(17) Thian-1-oxide	CH_2Cl_2	$S–CH_2$	52·2	203	9·8	21
(18) Tetrahydropyran	CD_3OD	$O–CH_2$	33[d]	193	9·3	21
	CS_2	$O–CH_2$	55	208	9·9	22
(19) Piperidine	CD_3OD	$N–CH_2$	26·1	210	10·4	23
(20) *N*-Methylpiperidine[e]	CD_3OD	$N–CH_2$	56·5	252	11·9	23
(21) 1,3-Dioxan	Me_2CO	$2-CH_2$	19·3	188	9·3	24
(22) 1,3-Dimethylhexahydropyrimidine	$CDCl_3$	$2-CH_2$	73·8	244	11·3	25
(23) 1,3,5-Trimethylhexahydrotriazine	$CDCl_3$	$N–CH_2$	54·7	268	12·7	26
	$CDCl_3$	$N–CH_2$	52·8	269·5	12·8	27
	$CHFCl_2$	$N–CH_2$	53·8	268·1	12·8	28
(24) Cyclopentamethylenedimethylsilane	CF_3Br	$Si–CH_2$	. .	115·9	5·5	29

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[a] ΔG Calculated from the coalescence of AB spectra in all cases except (**15**) and (**24**).

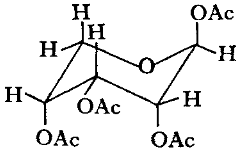
[b] Spectrometer frequency 60 MHz in some cases and 100 MHz in others.

[c] Values estimated from comparison with other compounds.

[d] The value is assumed to be the same (in p.p.m.) as in solution [20] in CS_2.

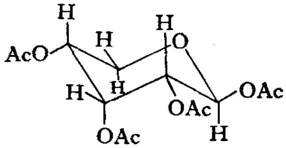
[e] A $\Delta G^{\ddagger}$ value of ca. 11·4 kcal/mole was obtained for an undeuteriated sample of this compound in CH_2Cl_2 solution.[19]

solubility in suitable solvents. Bhacca and Horton have slowed down the inversion rate of β-D-ribopyranose tetraacetate (**25A**) and (**25B**) in acetone-d_6 solution, coalescence of the anomeric proton resonances occurring at −60°C[30] ($\delta_{ae} = 58{\cdot}5$ Hz at −84°C), suggesting a free energy of activation of ~10·3 kcal/mole. The ratio of conformers is 2:1 in favour of the 1C conformation, as expected, the free energy difference $-\Delta G_0$ being 0·3 kcal/mole at −84°C.



1C

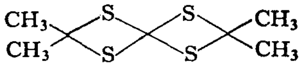
25A



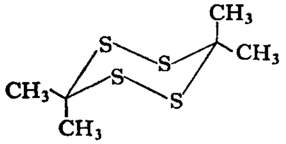
C1

25B

Isolation of a conformationally pure twist-boat form of a six-membered ring is a rare occurrence. Low temperature studies of the NMR spectra of duplothioacetone unequivocally show that a symmetrical twist-boat form (**26A**) is present in addition to the chair conformation (**26B**).[31,32]

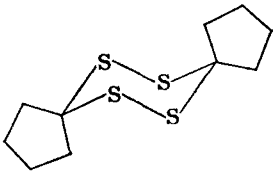


26A



26B

In the spectra of the chair forms interconverting slowly at low temperature, two singlet peaks of equal area are expected for the axial and equatorial methyl groups respectively. A third peak ($\delta = 1{\cdot}68$), between the other pair of singlets, was assigned to the twist-boat conformer (**26A**) in which the methyl groups are equivalent. The ratio of chair to boat conformations is 1·0:2·2 respectively, leading to $-\Delta G_0$ at 0°C = 0·8 kcal/mole. The barrier to inversion, measured at coalescence was $\Delta G^{\ddagger}_{50} = 16 \pm 1$ kcal/mole. X-ray crystallography studies confirm that a boat conformation is present in the crystal lattice.[32] On cooling a crystalline sample down to −80°C and dissolving it in CS_2 at this temperature, the NMR spectrum obtained shows only a sharp singlet at δ1·8, indicative of the boat form. Allowing the solution to warm up, the normal equilibrium is reached once more. This interesting experiment has also been tried successfully with crystalline tri-*o*-thymotide, which is discussed later in the text.[33,34] Further work by Bushweller with the analogous spiro molecule (**27**) has shown that this compound exists mostly in the chair form in solution, and entirely in the chair form in the crystal.[35]



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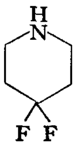
Slow ring inversion has also been observed in 4,4-difluoro-piperidine (**28**),[36] *N*-chloro-piperidine (**29**),[37] hexahydropyrimidines (**30**),[23,38] hexahydro-*S*-triazines (**31**),[24,26,38] tetrahydro-1,2- and 1,3-oxazines (**32**)[41] and (**33**) respectively, and 1,2,4,5-tetramethyl-1,2,4,5-tetrazine (**34**).[42] In many of these cases, however, the rate of nitrogen inversion is also slow on the NMR time scale, and it is often difficult to differentiate between the two processes. In the compounds with two hetero atoms adjacent, an inversion process can also be "frozen out" in the corresponding five-membered rings,[39,40] suggesting that nitrogen inversion is the dominant process. Similarly *N*-chloropyrrolidine (**35**)[37] also appears to undergo slow nitrogen inversion. The activation energies for ring inversion and/or nitrogen inversion in these compounds generally lie in the range 9–15 kcal/mole. Solvent dependence of the $\Delta G^{\ddagger}$ value in these compounds generally indicates that the process is nitrogen inversion, which is markedly affected by hydroxylic solvents.[39] Nitrogen inversion is also discussed in the next section.



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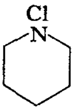

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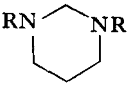

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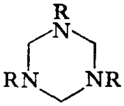

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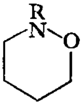

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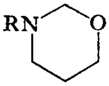

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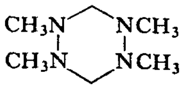

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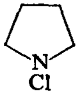

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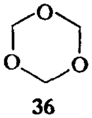
Finally in six-membered ring heterocyclic compounds, *S*-trioxan (**36**) and *S*-trithian (**37**) appear to be inverting very rapidly at low temperatures,



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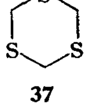


37

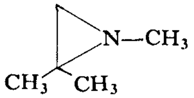
unless of course the chemical shift difference between the axial and equatorial protons is too small or zero, in which no coalescence process is observable.[28] Some support for this is indicated by an approximate spin echo study of (**37**) which gave a value for $\Delta G^{\neq}$ of ~8 kcal/mole.

C. Slow Nitrogen inversion in cyclic and acyclic compounds

Slow nitrogen inversion in the three-membered aziridine ring has been known for some years. Similarly, it is now a well-known fact that, in cyclic compounds containing two adjacent substituted nitrogen atoms, slow synchronous nitrogen inversion takes place.[5]

The nitrogen inversion in 1,2,2-trimethyl aziridine (**38**) has been reinvestigated by the NMR method, with an improved line shape treatment of the spectrum of the *gem* dimethyl protons over a temperature range.[43] The free energy of activation is found to vary from 17·9 kcal/mole in the neat-liquid to 18·9 kcal/mole in deuterochloroform solution, a much higher value than reported previously.

Brois has investigated the influence of steric factors on nitrogen inversion rates in 1-substituted aziridines, without reporting kinetic parameters for the compounds.[44] He noted that, as the size of the *N*-substituent increased, the chemical shift between the ring protons decreased markedly. Rather higher rates of nitrogen inversion were found in some 1-fluoroalkyl aziridines with E_A (the activation energy) varying from 5·8 to 9·1 kcal/mole.[45] The authors attribute the higher rate of *N*-inversion to double bond–no bond resonance. *N*-acyl aziridines have also been examined, which apparently undergo nitrogen inversion, rather than having the more planar amide type of bond. The rate of nitrogen inversion was found to be much higher than in *N*-alkyl aziridines.[46] *N*-haloaziridines have been studied by three groups,[47–49] all of whom found very slow nitrogen inversion occurring. Felix and Eschenmoser[47] actually isolated the two geometric isomers of 7-chloro-7-aza-bicyclo[4,1,0]heptane (**39A**) and (**39B**), the less stable conformer being slowly converted to the other form on heating. Lehn and Wagner[48] found



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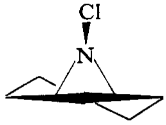
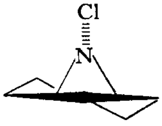
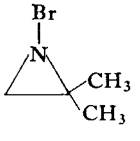


39A



39B

$\Delta G_c^{\ddagger}$ values in excess of 21 and 23·5 kcal/mole for (**40**) and (**41**) respectively, whereas Brois[49] actually isolated the two forms of (**42**). Presumably, therefore, such stable nitrogen pyramids should be capable of resolution into optical antipodes at room temperature, which was not thought possible a few years ago. In a similar way the NMR spectra of 1-amino-aziridines are unchanged up to $\sim$150°C in xylene solution, indicating a minimum value for $\Delta G^{\ddagger}$ of 22 kcal/mole.[50] Similarly the *N*-substituted derivatives (**43**) and (**44**)



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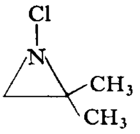

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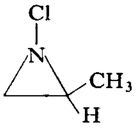

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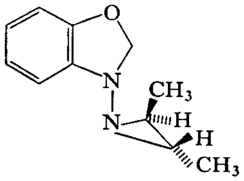

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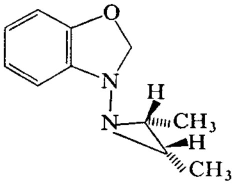

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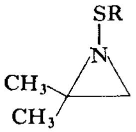
show temperature invariant spectra.[51] Even larger barriers to inversion are probably present in oxaziridines,[48] which have been isolated as separate isomers, and diaziridines,[52] where the adjacent heteroatoms severely hinder inversion. In the sulphenamides of general type (**45** to **47**) both slow nitrogen inversion and hindered rotation about the N–S bond are found.[53] In the aziridines (**45**), hindered nitrogen inversion is the temperature-variable



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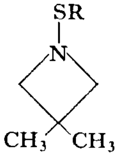

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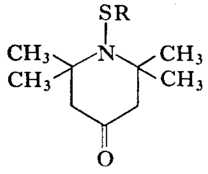

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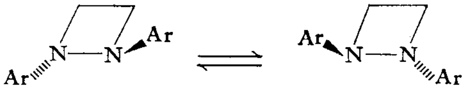
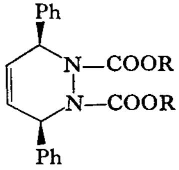
property, whereas in the larger rings, the dominant feature is hindered N–S bond rotation. Similarly, 1-chloro-, 1-bromo- and 1-methyl-3,3-dimethylazetidine have been shown to undergo slow *N*-inversion, with $\Delta G_c^{\ddagger}$ values of 11·5, 11·5 and 8·85 kcal/mole respectively.[48] Diazetidines of the type



48A **48B**

(**48A**) and (**48B**), as expected with adjacent nitrogen atoms present, have rather high $\Delta G_c^{\ddagger}$ values of 12·8 to 16 kcal/mole.[54]

The slow nitrogen inversion in rings containing two adjacent nitrogens is well established.[55] In the last two years more complex systems have been examined, notably those which contain adjacent N—COOR groups.[56–59] The presence of the carbonyl group apparently makes the N–CO bond a planar amide type, so preventing nitrogen inversion taking place,[56] in contrast to the *N*-alkyl derivatives. Hindered N–CO bond rotation is observed, however, in addition to ring inversion in the monocyclic derivatives (**49** to **52**), whereas in the bridged molecules (**53** to **57**), though ring inversion is prevented, a "bridge flipping" process involving non-planarity of the hydrazine system is in operation. Bridge flipping occurs only in the bicyclo[2,2,2]octane types and not in the more strained bicyclo[2,2,1]rings.[56,59]



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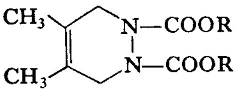

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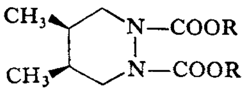

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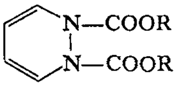

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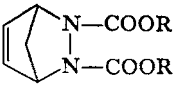

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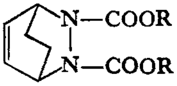

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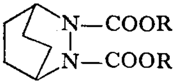

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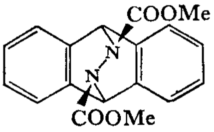

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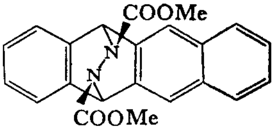

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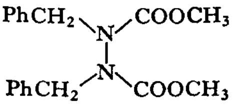
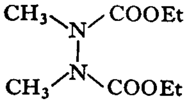
In these papers attempts are made to work out the different kinetic parameters involved in the various rate processes, in which large free energies of activation are involved, requiring high temperature NMR studies. In the analogous acyclic compounds (**58** and **59**) the situation is even more complex, in that eighteen possible conformers can be drawn for each of these



$(PhCH_2)(CH_3OOC)N{-}N(COOCH_3)(CH_2Ph)$

58



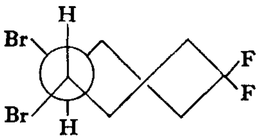
$(CH_3)(EtOOC)N{-}N(COOEt)(CH_3)$

59

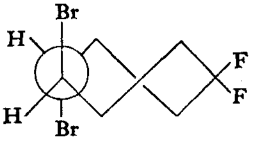
molecules, with the apparent possibility of hindered rotation about the ester C–O bond in addition[58] to the other mechanisms for rotation.

D. Inversion in larger rings

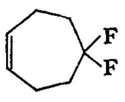
Roberts *et al.* have continued studies on seven-membered carbocyclic rings, which are generally more mobile than their six-membered homologues. The 4,5-*trans*-dibromo-1,1-difluorocycloheptane was considered to adopt the two conformations (**60A**) and (**60B**).[60] The diequatorial conformer (**60A**) is favoured by 74:26 over the diaxial form (**60B**). In the ^{19}F spectrum, observed below −118°C, the fluorine nuclei appear as two single peaks, indicative of the symmetry of the conformers and $\Delta H^{\neq}$ for the inversion is calculated to be 9·8 ± 0·3 kcal/mole. On the other hand the ^{19}F spectrum of



60A



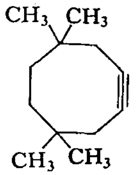
60B



61

5,5-difluorocycloheptene (**61**) gives an AB pattern for the geminal fluorine atoms, indicating non-equivalence. In this case $\Delta H^{\neq}$ was given as 7·4 ± 0·1 kcal/mole.[60]

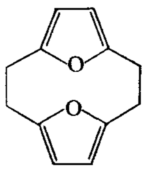
The linear nature of the C≡C triple bond imposes strain on the ring of cyclo-octyne, but does not apparently impart rigidity to it, as the low temperature spectrum of 4,4,7,7-tetramethyl-cyclo-octyne (**62**) implies that the ring is inverting with a free energy of activation $\Delta G^{\neq}_{-18} = 12{\cdot}6 \pm 0{\cdot}5$



62

kcal/mole.[61] This indicates a rather slow inversion rate, probably due to strain in the transition state.

Inversion in bridged aromatic rings has been extensively reported, including heterocyclic analogues of a variety of *meta*-cyclophanes[62–64] including the four compounds (**63** to **66**), 3,2-*meta*-cyclophanes,[65] 7,12-dihydropleiadene and its 1-methoxy derivative (**67**),[66] 1,8-(1′,8′-naphthyl dimethyl) naphthalene (**68**),[67] 1,2,5,6-dibenzocyclooctadienones,[68] doubly bridged biphenyl derivatives (**69**)[69], compounds in the cyclotri- and tetraveratrylene series (**70** to **72**)[70,71] and even the novel 18-membered ring (**73**).[72] The geometry of these rings is very important in determining the extent of mobility in these rings and hence the free energy of activation for inversion. Cyclotriveratrylene itself is conformationally rigid, whilst the tetra derivative can adopt a



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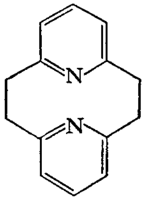

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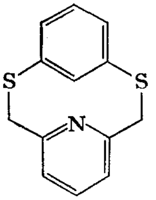

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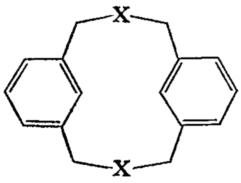
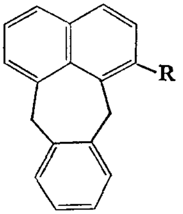


X = S, SO, and SO$_2$

66



R = H, OMe

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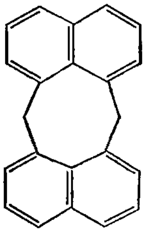

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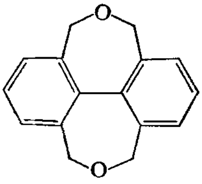

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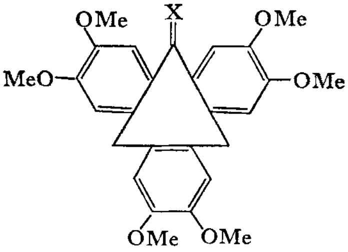
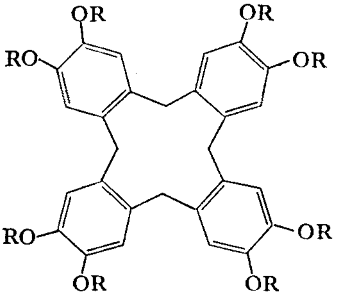


70, X = O

71, X = CH$_2$



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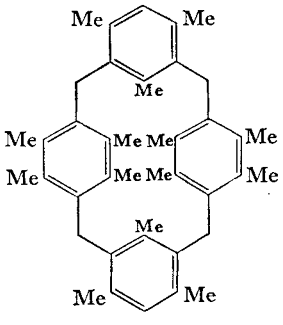
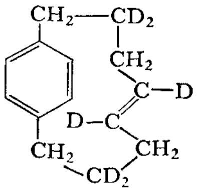


73

"chair" or "saddle" conformation.[71] Finally in this series, the novel *para*-cyclophane (**74**) with a *trans* double bond is not a rigid molecule and has been shown to invert between the two conformers (**74A**) and (**74B**),[73] with an energy barrier $E_a = 13{\cdot}4 \pm 0{\cdot}7$ kcal/mole.



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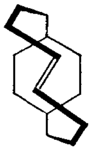
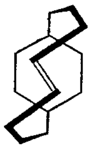


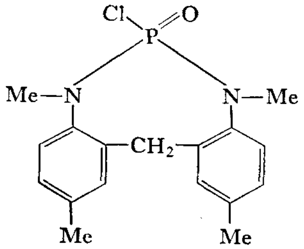
74A



74B

Tri-*o*-thymotide, discussed in the first review in this series,[5] has been shown by X-ray crystallography to adopt the "propeller" conformation in the crystal. A solution, prepared in an NMR tube at low temperature, showed only the peaks due to the "propeller" form in the proton spectrum, but on warming inversion to the "helix" form was observed.[74]

Possible synchronous nitrogen inversion is suggested for the interesting phosphorus-containing ring (**75**), the spectrum of which becomes quite



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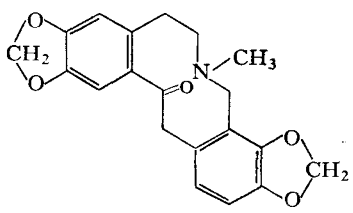
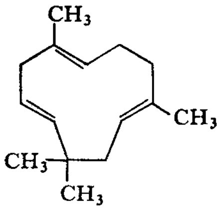


76

complex at low temperatures, due to non-equivalence, and long-range ^{31}P–^{1}H coupling.[75] In the 10-membered ring alkaloid, protopine (**76**) interaction across the ring between the carbonyl group and the nitrogen atom is thought to raise the energy barrier to its observed value (~13 kcal/mole).[76]

Among several large unsaturated rings examined, the four compounds (**77** to **80**) all exhibit temperature dependent spectra for one reason or another, with energy barriers (E_A) of 4·67 and 14·8 kcal/mole for (**77**) and (**78**), and $\Delta G_c^{\ddagger}$ of 10·6 and 15·9 → 16·4 kcal for (**79**) and (**80**) depending on the solvent used.[77,78] Conformations and possible inversion pathways were discussed in the case of (**79** and **80**).



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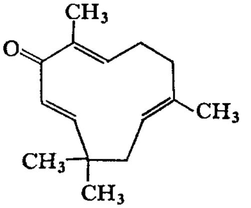

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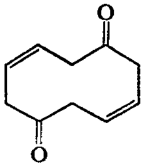

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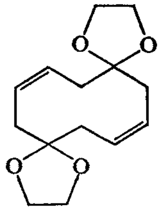

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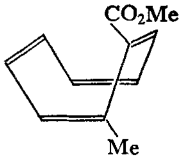
E. Valence tautomerism

The structures of valence-bond tautomers are readily studied by the NMR technique, as the fluctuation of bonds is relatively slow on the NMR time scale. Recent advances in the subject have been reviewed.[79] Also under this heading, azepins, diazepins,[80] their iron tricarbonyl derivatives,[81] cycloheptatriene,[82] benzo-diazepinones[83] and oxepin[84] have been analysed by the NMR variable temperature method, and found to undergo either or both ring inversion and valence tautomerism. Non-rigid cyclopentadienyl rings in molybdenum complexes have been discovered,[85] and also temperature dependent spectra in 1,3,5,7-tetramethyl cyclo-octatetraene tricarbonyl compounds of chromium, molybdenum and tungsten,[86] and in the rhuthenium tricarbonyl complex of cyclo-octatetraene.[87] Most of these systems are amenable to a kinetic treatment, leading to a better understanding of the nature and mechanisms of valence tautomerism.

One of the rare cases in which kinetic parameters can be obtained both from line shape and equilibration studies has been demonstrated, in the study of the bond shift isomers (**81**) and (**82**).[88] Under normal conditions in an equilibrium mixture, the ratio (**81**):(**82**) is 17:1, as measured by integrated intensities in the proton spectrum. Irradiation of the mixture in $CDCl_3$ for six hours at –30° to –50°C provided a mixture with (**82**) now slightly in excess. Following the equilibration gave $\Delta G^{\ddagger} = 18{\cdot}8$ kcal/mole,



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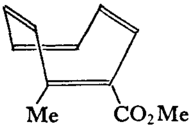

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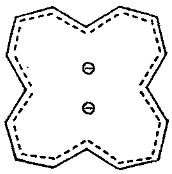
whilst by the normal coalescence method (80° for the CH_3 peaks) a value for $\Delta G^{\ddagger}_{90} \sim 19{\cdot}5$ kcal/mole was obtained in good agreement.

Annulenes and their derivatives have been the subject of much further study. The "ring current" controversy does not enter the scope of this review, but many of the annulenes undergo quite fast valence tautomerism, which can be "frozen out". The large chemical shift differences found for instance in [18]-annulene below coalescence, make kinetic studies particularly interesting. The energy barriers have been determined in this way for a variety of annulene rings,[89] with $\Delta G_c^{\ddagger}$ lying between 8·6 for [16] annulene to 13·4 kcal/mole for [18]-annulene, with the barriers depending very much on the ring size. The dianion of [16]-annulene (**83**) has been shown to adopt the conformation shown, with alternate *cis* and *trans* double bonds.[90] The inner four protons absorb at δ – 8·17 for the dianion, which must be one of the highest field chemical shifts known for non-paramagnetic species. The NMR spectrum is temperature invariant up to 140°C, the dianion being isoelectronic with the stable [18]-annulene. In contrast, the



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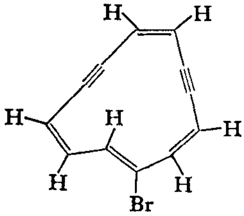
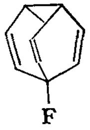


84

PMR spectrum of the "4n" annulene (**84**), adopts the form with one inner proton, which has the extraordinarily low field shift of δ 16·4, some 24 p.p.m. downfield from the inner protons of (**83**).[91]

Bullvalene and its derivatives have received much attention, and have been recently reviewed.[79] The mono-halo-bullvalenes have attracted interest, particularly fluoro-bullvalene, in which the fluorine atom could reside in four chemically and magnetically distinct positions. In fact the symmetrical structure (**85**) is apparently preferred at low temperature.[92]

An elegant use of double resonance in the study of interconverting species



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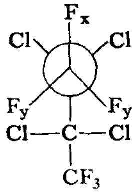
has been demonstrated with [18]-annulene.[93] Irradiation of a multiplet at 20°C, at which temperature slow interconversion is occurring between sites, causes disappearance of the peaks at the other site (in [18]-annulene irradiation of the low field multiplet causes disappearance of the high field peaks). This is attributed to the fact that nuclei are being transferred to the other site before spin relaxation has had time to take place. This phenomenon may have some use in the assignments of peaks in the spectra of rapidly interconverting molecules.

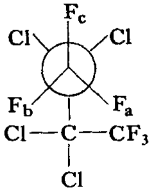
F. Slow rotation in acyclic molecules

With some careful experimental studies of the ^{19}F and ^{1}H spectra of 1,1,2,2-tetrabromofluoroethane, Govil and Bernstein concluded that the average value of J_{HF} in the molecule at temperatures *above* coalescence cannot be used *alone* to calculate the *gauche* and *trans* H–F coupling constants of the separate rotamers.[94] The free energy of activation is shown to be both temperature and solvent dependent, with $\Delta G^{\ddagger}_{93}$ varying from 10·00 in $CFCl_3$ to 10·80 kcal/mole in acetone. The *gauche* and *trans* couplings are also very solvent dependent, and in addition the free energy difference favouring the *gauche* form varies from 422 to 382 cal/mole. It has not yet, however, been proved that vicinal ^{1}H–^{1}H couplings vary to the same degree with temperature and solvent. In rigid molecules, ^{3}J(H–H) has been shown to be almost independent of solvent and temperature within experimental error.[95] Other fluorinated acyclic compounds which have been studied at low temperatures include (i) 1,2-difluorotetrachloroethane, in which $\Delta G^{\ddagger}$ varies from 9·8 at 175°K to 10·3 kcal/mole at 250°K, and the *trans* isomer is favoured by 165 ± 5 cal/mole,[96] and (ii) bis(trifluoromethyl)tetrachloroethane, (**86**) in which slow rotation is observed about all three C–C bonds rendering *all* the fluorine nuclei non-equivalent.[97] Of the two conformations (**86A**) and (**86B**), (**86B**) is shown to be favoured, being present at equilibrium to the extent of 92%. The proof of the conformational preference is based on "through space" coupling constants which are discussed later in this review.

Almost all the examples of slow rotation about C–C bonds in acyclic compounds deal with halogenated ethane derivatives. In most of the reported papers on this theme, fluorine is present, and the ^{19}F spectrum is used to investigate the rotation. In a recent example, internal rotation in



86A

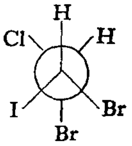


86B

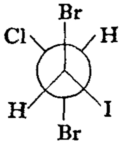
$CF_3 \cdot CCl_2 \cdot CCl_2 \cdot CF_3$

86

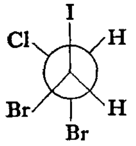
CHClBr.CHBrI was examined using the variable-temperature *proton* spectrum.[98] Of the three possible rotational isomers (**87A, B** and **C**) only the *gauche* isomers **87A** and **87C** were found to be present to any extent, with **87C** being more stable by 303 cal/mole; ^3J(H–H) was found to be 1·8 Hz in (**87C**) and 1·15 Hz in (**87A**). Line shape treatment, over a 30°C range, gave $\Delta G^{\ddagger} = 9{\cdot}6 \pm 0{\cdot}2$ kcal/mole. Anet *et al.*[99] recently reported slow rotation in several *t*-butyl alkanes, the proton spectrum of the *t*-butyl groups at very



87A



87B



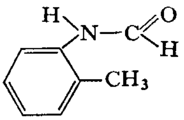
87C

low temperatures (–130° to 160°C) showing 2:1 doublets. The free energy of activation varied from 6·0 to 7·8 kcal/mole, being smallest for *t*-butyl cyclopentane and largest for *t*-butyl cyclo-octane. The results are explained in terms of methyl-β-methylene interactions which are affected by (i) internal ring angle, and (ii) eclipsing of the C_α–$C_{\alpha'}$ bond with the β-methylene bonds.

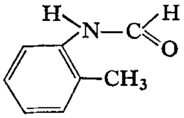
An enormous number of papers has been published in the last two years, dealing with slow rotations about single bonds with partial double-bond character, and single bonds between an sp^3 and an sp^2 carbon atom. The most popular subject studied in this field is the rate of rotation about the C–N bonds of amides and similar compounds, where the energy barrier is conveniently large, and the rotational isomers are two instead of the three found in normal ethane-type fragments.

Dimethyl formamide has been the subject of a great deal of attention in the last few years, with estimates for the barrier to inversion varying from 7 to 25 kcal/mole. Current opinion[100–104] seems to favour the higher end of this range ($\Delta G^{\ddagger} = 20{\cdot}5$ to 21·7 kcal/mole), supported by the results for *N*-benzyl-*N*-methyl formamide,[105] using both line shape and equilibration methods. The internal rotation is, however, not just a simple monomer process, as demonstrated by Rabinowitz and Pines,[103] who showed by quantitive NMR evidence that dimethyl formamide associates as the dimer at low concentration in carbon tetrachloride solution; the free enthalpy for association being $\Delta H_0 = -6{\cdot}0$ kcal/mole. The authors consider that the formyl proton does not participate in hydrogen-bonding, and that the association occurs through the nitrogen and oxygen moieties. Other concentration experiments on the NMR spectra of DMF, and other formamides and acetamides, however, led to the conclusion that hydrogen bonding *is* involved in the interactions between the formamide molecules, and also the thioformamides.[104] Neuman and Jonas have also attempted a full line shape analysis of *N*,*N*-dimethyl acetamide-d_3 in which $\Delta G^{\ddagger} = 18{\cdot}2$ kcal/mole for the neat liquid.[106]

It seems from the results on these compounds, that although amides are attractive molecules for NMR study, care should be taken in attributing too much weight to the kinetic parameters. Such arguments have been voiced by Siddall *et al.*,[107] who isolated and obtained the kinetic parameters for the separate geometric isomers of 2-methyl formanilide (**88A**) and (**88B**).



88A

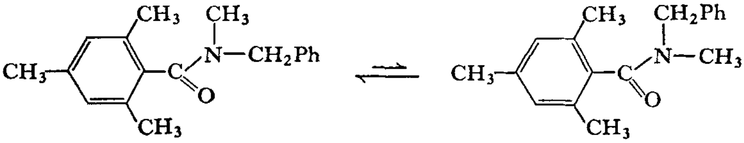


88B

Ortho substituted acetanilides, and related compounds, have been the centre of much activity in recent months.[107–114] Again, particularly with a free N–H proton present, molecular association will be present at the concentrations used in NMR spectroscopy, and therefore the kinetic parameters and conformational preferences obtained by this method are only meaningful on a qualitative basis. In addition, slow rotation about the aryl-N bond may be present, in which case two rotational processes could in theory be frozen out, complicating the issue further.

Among other amide-containing compounds examined, Mannschreck *et al.* compared the kinetic results for both line shape and equilibration techniques for the benzamide derivative (**89A**) and **89B**) and *N*,*N*,2,4,6-pentamethyl benzamide, the parameters agreeing within the error limits.[115] Equilibrium was reached 200 min after the dissolution of the pure crystals of (**89A**). Similar results were found for a formamide derivative.[105]

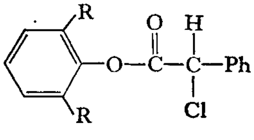
Other results for hindered rotation in amides and thioamides follow on similar lines.[116–123] In *N*-acyl dihydro isoindole derivatives slow rotation renders the two methylene groups non-equivalent, and the spectrum of these protons becomes an AA′BB′ type, from which the cross-ring coupling constants can be obtained (^4J *trans* usually > ^4J *cis*, depending on the substituent R).[116] Siddall and Stewart found additional complications, in that



89A **89B**

slow rotation was also observed about the Ar–CO bond in a benzamide,[122] and slow rotation about the N–Pr. bond in some *N*,*N*-di-*sec*-alkyl amides.[123] Hindered N–CO and N–CS bond rotation is not, of course, confined to amides, and analogous NMR investigations of ureas,[124] thioureas,[125] carbamate esters[126,127] and dithiocarbamate esters[128,129] have been published. Similar hindered rotation is present in so-called "vinylogous" amides and carbamates, in which the nitrogen atom and the carbonyl group are separated by one or more double bonds.[130–134]

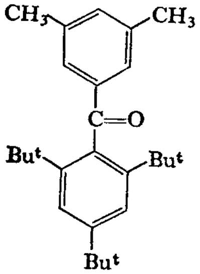
Hindered rotation about Ar–N bonds is either due to partial double bond character (resonance effects), as in adenosine,[135] cytidine[135] and purine,[136] or due to the steric effects of bulky *ortho* substituents.[124,137–139] Analogous Ar–O hindered rotation was observed for the phenol esters (**96**) and (**91**), where the asymmetric centre causes the isopropyl methyl protons in (**91**) to appear as *two* doublets at high temperature, i.e. the 2 and the 6-isopropyl groups, although chemically equivalent at high temperature are rendered magnetically non-equivalent by the inherent asymmetry of the molecule as a whole.[140] At low temperatures, *four* doublets were observed for the isopropyl methyl groups, indicating non-equivalence due to *both* asymmetry and conformational isomerism.



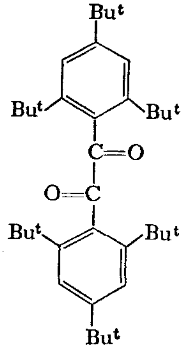
90, R=Me
91, R=Pr^i

The effect of resonance on the rotation about Ar–CO bonds was first reported by Anet and Ahmad[141] for benzaldehyde, and *p*-*N*,*N*-dimethylamino benzaldehyde. The latter compound, deuterated in the *meta* position has been reinvestigated, and $\Delta G_c^{\ddagger}$ shown to be solvent dependent to a significant degree.[142] Steric effects, on the freedom of the Ar–CO bond to rotate, have been shown in the highly substituted benzophenone derivative

(**92**) and the similarly sterically hindered benzil derivative (**93**), in which $\Delta G_c^{\ddagger}$ values are $17{\cdot}2 \pm 0{\cdot}2$ and 16·7 kcal/mole respectively.[143]

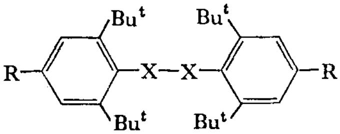


92



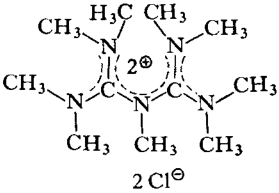
93

As expected, the phenyl groups in triaryl carbinols[144] and tetra-aryl methanes[145] severely hinder rotation about the Ar–C bond, and successful attempts to measure the kinetic parameters have been made. Even the Ar–C bond in substituted benzyl halides,[146] isopropyl benzene derivatives[147] and similar compounds, and also anisyl-di-*t*-butyl-carbinol,[148] has been shown to be strongly affected by steric interactions. The unusual compounds (**94**) and (**95**) are also affected by the bulk of the *t*-butyl groups and slow rotation about the S–S or Se–Se bonds has been measured by coalescence of the *t*-butyl proton peaks and the coalescence of the *meta* protons.[149] $\Delta G_c^{\ddagger}$ varies from 15·5 to 16·3 in the disulphide (**94**) depending on the group R, whereas a much lower value is found for the diselenide (**95**) of 12·5 kcal/mole.



94, X = S
95, X = Se

Also in this series, hindered rotation due to partial double bond character has been demonstrated in a wide variety of nitrogen-containing unsaturated compounds.[150–165] Formamidines,[150–152] benzamidines,[153] arylimines,[154] quinone diimines,[155] enamines and hydrazones,[156] aryl triazenes,[157] *NO*-diacyl hydroxylamines,[158] *O*-(*N*,*N*-dimethyl carbamoyl)oximes,[159] 6-dialkyl amino fulvenes,[160] *N*,*N*-diacyl hydrazines,[158,161] *N*,*N*-dialkylaminophosphines,[162] and other phosphorus–nitrogen-containing compounds,[163,164] have all been extensively discussed in terms of their NMR spectra. With the discovery of "magic" acid ($FSO_3H—SbF_5—SO_2$), carbonium ions are readily observed in the NMR spectrum. As an example of the potential of this technique, the rotational energy barriers in substituted allyl cations have been determined ($\Delta G^{\ddagger} \sim 13$ kcal/mole).[166] In addition, triphenyl methyl carbonium ion, specifically fluorinated in the rings, has been studied by Schuster *et al.*[167] The most favourable mechanism of interconversion of the non-planar propeller conformers is a concerted process in which three rings pass through a plane perpendicular to that defined by the three central carbon to phenyl bonds (three ring flip) ($\Delta H^{\ddagger} \sim 9$ kcal/mole). Finally in the realm of cations, the slow rotation found in guanidines[168] has been also demonstrated in the two biguanide cations (**96** and **97**).[169] In (**96**) all the *N*-methyl groups become equivalent at 190°C; at lower temperatures various coalescences occur, which are discussed in detail.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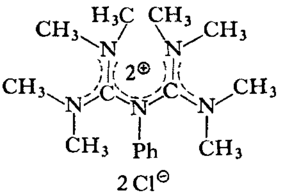
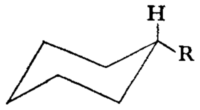

97

Vapour phase NMR temperature experiments have been rarely reported, so worthy of special mention is the work of Harris and Spragg with dimethyl nitrosamine. Coalescence of the methyl groups in the vapour takes place at 158°C ($\Delta G_c^{\ddagger}$ 21·1 kcal/mole), whereas in the liquid coalescence does not occur below 195°C.[170] This area of kinetic measurements clearly can be most useful in the measurement of parameters in the gaseous state.

II. CONFORMATIONAL PREFERENCES OF RING SUBSTITUENTS, AND ROTATIONAL ISOMERS

A. "A" values in substituted cyclohexanes

The validity of the NMR methods of determining the conformational preferences of monosubstituted cyclohexanes has been questioned at length by several groups. There are three well-established basic methods for determining "A" values ($-\Delta G_0$): (i) comparison of the chemical shift of the methine proton in the cyclohexane (**98**) with that in the *cis* and *trans*-4-*t*-butyl derivatives, (**99**) and (**100**), assuming the chemical shift of H_1 in the separate conformers of (**98**) is the same as that in the respective 4-*t*-butyl derivatives, measured under the same conditions; (ii) measurement of the



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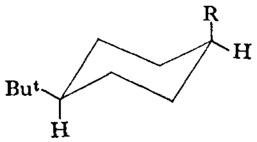

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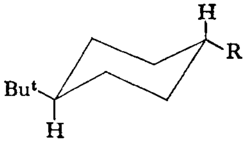


100

"band width" of the H_1 multiplet in all three cases (**98**), (**99**) and (**100**), which is equal to the sum of the coupling constants to that proton, again assuming that the 4-*t*-butyl group has no effect on the coupling constant between the C_1 and C_2 protons; (iii) measurement directly of the areas of the H_1 multiplet in the two conformers, (provided that H_1 has different chemical shifts in the two positions) at a temperature such that interconversion is very slow relative to the NMR time scale (usually $< -60°C$). The latter method is the most direct, providing an accurate value of $-\Delta G_0$ at that temperature, without recourse to model compounds.

Eliel and Martin, following a thorough investigation of the chemical shift method (i) above, concluded that 3-*t*-butyl derivatives are poor models for accurate determinations of ΔG_0, whereas 4-*t*-butyl derivatives, though not exact models, do not induce large errors in the free energy differences obtained.[171] Further conclusions made were that, in the case of heterocyclic compounds and in the use of ^{19}F chemical shifts, large discrepancies can occur, and also, that the low temperature method (iii) was none too accurate, as the chemical shifts of the pure conformers of chlorocyclohexane apparently vary with temperature. On the other hand, Jensen and Beck have strongly criticized the chemical shift method (i), finding errors ~0·1 kcal/mole by this method, due to differences in the chemical shifts of the methine proton in the pure conformers and the 4-*t*-butyl derivatives.[172] In a more recent paper, the same research group carefully measured the "A" values of twenty-two monosubstituted cyclohexanes at low temperature (method (iii)).[173] The results were obtained keeping the conditions of measurement as similar as possible, and are recorded in Table III. Wolfe and Campbell have also examined the effects of 3- and 4-*t*-butyl substituents on the chemical shifts and coupling constants of the remainder of the ring protons.[174] They concluded that the 3-*t*-butyl derivatives are poor models, and that a 4-*t*-butyl group *does* affect the H_1 chemical shift (by ~4 Hz at 60 MHz), and also affects the axial-equatorial coupling between H_1 and H_2 (or H_6). Another interesting point made in the paper by Jensen *et al.*[173] was that the ratio of conformers or the equilibrium constant varied with the increase in RF power used. Apparently the peaks due to the less stable conformer saturate less readily, as the molecules in the latter are replaced more rapidly by unsaturated molecules, than in the more stable conformer. It seems at the

TABLE III

"A" Values at 100 MHz using method (iii)[a]

Substituent	Concn., M	$\nu_{\mathrm{ax}}^{a,b}$, Hz	$\nu_{\mathrm{eq}}^{a,b}$, Hz	$\Delta\nu$, Hz	Temp.,[c] °C	K[d]	$\Delta G_0^{d,e}$, kcal/mole
$H(C_6D_{11}H)$	2·50	..	..	51	–80	1·04	0·015 ± 0·015
HgOAc	0·38[f]	234	298	64	–79	1·00	0·00 ± 0·09
$N\overset{\rightarrow}{=}C$	2·02	333	384	51	–80	1·73	0·210 ± 0·013
$C\equiv N$	2·05	240	292	52	–79	1·88	0·24 ± 0·003
F	2·11	421	465	44	–86	2·10	0·276 ± 0·015
$N{=}C{=}S$	2·01	352	403	51	–79	2·09	0·284 ± 0·013
$C\equiv CH$	2.04	209	271	62	–80	2·90	0·41 ± 0·05
I	1·98	406	479	78	–80	3·39	0·468 ± 0·021
Br	2·15	390	460	70	–81	3·48	0·476 ± 0·013
$N{=}C{=}O$	1·96	318	380	62	–80	3·74	0·506 ± 0·020
OTs	1·00[g]	419	263	43	–80	3·83	0·515 ± 0·021
Cl	2·01	370	440	70	–81	3·99	0·528 ± 0·019
OCD_3	2·13	292	334	42	–82	4·23	0·547 ± 0·019
OSO_2CH_3	1·00[g]	452	496	44	–88	4·63	0·56 ± 0·03
$OC({=}O)H$	2·04	461	500	39	–80	4·62	0·59 ± 0·03
$SiCl_3$	2·13	405	457	52	–80	4·92	0·61 ± 0·04
OAc	2·01	444	482	38	–88	5·95	0·71 ± 0·05
NO_2	1·77	425	444	19	–90	18·0	1·05 ± 0·14
SCD_3	2·02	236	293	57	–79	16·1	1·07 ± 0·04
SH	1·07	257	341	84	–80	21·3	1·17 ± 0·04
SH	2·18	257	341	84	–80	23·0	1·20 ± 0·04
$SC{=}N$	2·08	307	402	95	–79	24·3	1·23 ± 0·05
CO_2CH_3	2·00	214	253	39	–78	29·0	1·31 ± 0·10

[a] Except where indicated the solvent is CS_2-TMS 90:10, by volume.

[b] Measured from TMS (internal standard).

[c] Maximum uncertainty in T = ±4°C.

[d] The uncertainty reported is the maximum observed deviation.

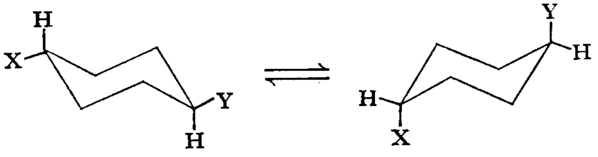
[e] The uncertainty reported is the sum of the effects of the maximum uncertainty in K and T.

[f] Solvent = pyridine-TMS-CS_2, 25:75:67·5 by volume.

[g] Solvent = TMS-CS_2-$CDCl_2$, 4:43:53 by volume.

present time, therefore, that all three methods are open to error, though the errors involved are not excessive, being ~0·1 kcal/mole in method (i) and probably less in the other methods. An example where all three methods have been applied is the study of isocyanato cyclohexane ($C_6H_{11}NCO$).[175,176] The "A" values obtained by methods (i) (ii) and (iii) respectively are 0·37, 0·48 and 0·44 kcal/mole (in favour of the conformer with the substituent equatorial). A fourth method not using NMR spectroscopy, namely equilibration, led to the value of 0·39 kcal/mole, again in good agreement, with the total spread of all four results being only 0·11 kcal/mole. In the same work, the benzoylamino (1·53, 1·7 kcal/mole) and the isobutylidene amino (0·75 kcal/mole) groups were measured.[176] In addition, other monosubstituted cyclohexanes, examined by one or more methods, usually the chemical shift technique (i), have given "A" values for the oxiran group (0·27 kcal/mole favouring the conformer with oxygen axial),[177] the formyl group ($-\Delta G_0 =$ 1·32 to 1·45 depending on solvent and concentration),[178] the trifluoromethyl group (2·4 to 2·5 kcal/mole),[179] and the magnesium substituent in the cyclohexyl Grignard reagent (rather variable values obtained from 0·247 to 0·784 kcal/mole, depending on the substituent, concentration and solvent used).[180]

Cyclohexanol has been re-examined, $-\Delta G_0$ varying from 0·809 to 1·000 kcal/mole in going from cyclohexanone to dimethyl formamide solvent, intermolecular hydrogen bonding being clearly responsible for the variations.[181] Similarly cyclohexylamine has been examined, and the "additivity" rule of $-\Delta G_0$ values found *not* to hold for *cis* 4-methyl cyclohexylamine.[182] The same authors have examined a series of 4,4-disubstituted cyclohexanes, and have proposed ΔG_0, ΔH_0 and ΔS_0 values for OH, Cl, NH_2, OAC and I.[183] Analogous research on 4-hydroxy cyclohexanone and the cyclohexane-1,4-diols has been reported,[184] and should be compared with the results for 4-hydroxy cyclohexanone oxime.[185] Interesting results have been quoted for the *cis* and *trans* isomers of 1,4-dichloro-, 1,4-dibromo- and 1,4-bromochloro-cyclohexanes, all studied at low temperature by PMR spectroscopy.[186] The *cis* isomers of the dichloro and dibromo compounds clearly interconvert between two conformers of identical energy, which are frozen out at ~—70°C. The methine protons appear in the spectrum as two multiplets, one broad (the axial proton at *high* field) and one narrow (the equatorial). In the case of the *cis*-bromochloro compound, three out of the four possible multiplets are visible, with two overlapping and with no particular preference for one conformation or the other. The *trans* 1,4-dihalocyclohexanes can interconvert between two unequal conformations (**101A** and **101B**), the diaxial conformers (**101B**) being of higher energy. The differences in free energy between the "*ee*" and "*aa*" conformers, however, are found to be surprisingly small (0·21 for the dibromo, 0·16 for the dichloro, and 0·17 kcal/mole for the bromochloro derivative). In theory, the energy dif-

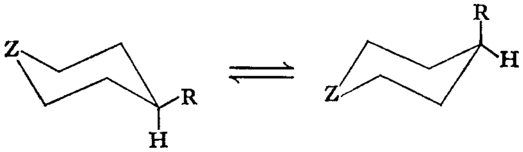


101A **101B**

ferences should be approximately twice the value for the monosubstituted cyclohexane, i.e. ~0·9 for the dibromo, ~1·0 for the dichloro, and ~1·0 kcal/mole for the bromochloro derivative. This effectively demonstrates that "A" values are *not* additive quantities in multi-substituted cyclohexane rings, and that other effects must be considered.

The large chemical shifts found in ^{13}C resonance spectra may well be useful in the determination of free energy differences, particularly in alkyl cyclohexanes. Dalling and Grant, however, found poor precision in the methyl cyclohexanes, with isolated, equatorial methyl carbons appearing ~3·9 p.p.m. downfield from isolated axial methyl carbons.[187] They found it impossible to find a simple set of additive parameters which correlated the shifts of the methyl carbons, which were very sensitive to substituent electronic and steric effects. Buchanan and Stothers appeared to have had more success with hydroxy methyl derivatives of cyclohexane, using the 4-*t*-butyl derivatives as models.[188] In all cases, the axial CH_2OR group appeared at high field, with δ_{ae} being ~5 p.p.m. The $-\Delta G_0$ values quoted were $1{\cdot}4 \pm 0{\cdot}2$ for $R = H$, $1{\cdot}4 \pm 0{\cdot}2$ for $R = CH_3$, and $1{\cdot}8 \pm 0{\cdot}2$ kcal/mole for $R = Ac$.

Prior to 1968, no examples of monosubstituted cyclohexanes had been reported in which the conformer with the substituent *axial* predominated at equilibrium, although the phenomenon was quite common in heterocyclic six-membered rings. Recently, Stolow and Groom found that if strongly electron attracting groups Z were placed in the 4-position, relative to certain substituents, (**102A**) and (**102B**) the equilibrium was changed and in fact reversed in certain cases, with the substituent preferring the axial position (**102B**).[189] As models, *cis* and *trans* 2-*t*-butyl-4-hydroxy-cyclohexanones

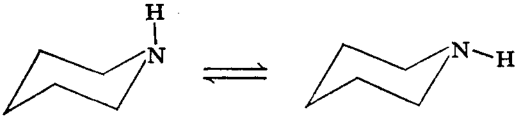


102A **102B**

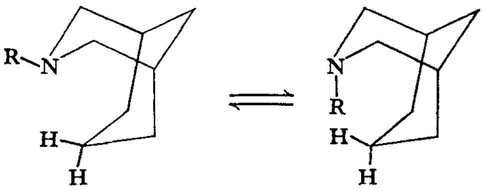
were used, taking the band width of the CHOH proton as the standard. Although this type of model has been found to be dangerously inaccurate as far as chemical shifts are concerned, the error in the band width of the methine proton should not affect the qualitative implications of the results. The "A" value for the hydroxyl group was found to be normal for alkyl substituents in the 4-position, but when $Z = CCl_2$, $-\Delta G_0 = -0{\cdot}1$ kcal/mole and likewise for $Z = CO$ ($-0{\cdot}15$). Much larger effects were discovered for $Z = CF_2$, the free energy difference in 4,4-difluorocyclohexanyl benzoate being $-0{\cdot}35$ kcal/mole.[190] The "A" values for chlorine and hydroxyl are similarly affected, the change from the normal value in each case being ~0·8 to 1 kcal/mole. The effect seems to be polar rather than steric in origin, but is too large to be accounted for by simple dipole–dipole interactions. Further enlightenment is awaited with interest.

B. Nitrogen-containing rings—"lone pair" configurations and conformational effects

The "size" of the lone pair of electrons on nitrogen has been the subject of a great deal of discussion in the last five years, the model compound for examination being piperidine, in which the N–H proton can be axial or equatorial (**103A**) or (**103B**), and interconverts very rapidly between the two positions. Allinger *et al.*[191] dispute the fact that the lone pair has an effective "bulk" at all with regard to non-bonded interactions. They imply that the nitrogen substituent alone defines the preference for equatorial or axial position, and propose, on the basis of Westheimer–Hendrickson–Wiberg calculations, that the conformer (**103A**) is favoured by 0·6 kcal/mole in agreement with the work of Lambert *et al.*,[23] who, using PMR spectroscopy, based their arguments on the chemical shift difference δ_{ae} between the α-methylene protons in piperidine and substituted piperidines (e.g. δ_{ae} for *N*-*t*-butyl piperidine is ~1 p.p.m., whereas in piperidine itself the difference is only 0·5 p.p.m.). Robinson[192] has strongly criticized this work, rejecting δ_{ae} as a good criterion for "lone pair" stereochemistry, and pointed out that substituents on the nitrogen have a considerable effect on the chemical shift of the α protons, the axial proton being more shielded. Some proof of the inadequacy of the "δ_{ae}" criterion was provided in the fixed molecule (**104A**) and (**104B**).[192] It is possible to reverse the position of the N–H group in this compound as shown, by adding methanol to the solution. The change is reflected in the chemical shift of the 7-*endo* proton, whereas no change is observed in δ_{ae}. Further opposition to the proposals of Allinger and Lambert

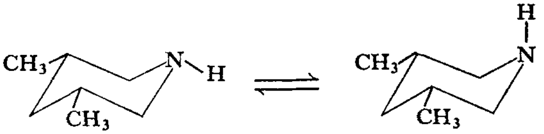


103A **103B**

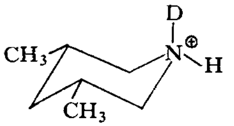


104A **104B**

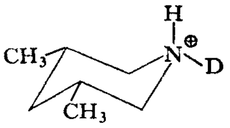
and their co-workers has arisen from infrared[193] and microwave evidence,[194] the former method indicating a preference for N–H equatorial of ∼0·5 kcal/mole (ΔH_0) in both the gas phase and in solution, and the latter method in fair agreement, the equatorial position being favoured by 0·25 ± 0·15 kcal/mole. Booth has used NMR in a different manner, in the study of *cis*-3,5-dimethyl piperidine, which must adopt the conformations (**105A**) and (**105B**), with the N–H flipping independently.[195] The pure dry piperidine, dissolved in trifluoroacetic acid-*d*, provides an NMR spectrum unchanged after two days, consisting in part of a group of peaks at δ2·70, which consist of an overlapping triplet and quartet, due to the α protons in the species (**106A**) and (**106B**) respectively, which couple with either the equatorial N–H proton in (**106A**) or the axial N–H proton in (**106B**), the larger coupling occurring with the axial proton. The relative areas of the triplet and quartet, 54:46, indicate a slight preference of the N–H for the *equatorial* position (by ∼0·1 kcal/mole). Here though, the assumption must be made that deuteration occurs equally rapidly for both conformers, and that nitrogen inversion is much slower than the reaction with $D^{\oplus}$.



105A **105B**

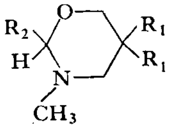


106A



106B

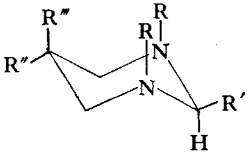
Riddell and Lehn have explored the effect of nitrogen stereochemistry on ^1H–^1H and ^1H–^{15}N coupling constants in substituted tetrahydro-1,3-oxazines (**107**).[196] They found that the chemical shift difference between the α protons is influenced by both the nitrogen substituent *and* the lone pair



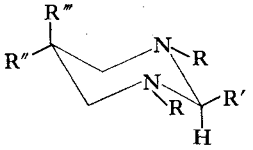
107

orientation, whereas the geminal (two bond) coupling constant is affected only by the orientation of the lone pair. Geminal couplings were used in a similar way in some substituted tetrahydro-1,3-oxazines to assign the configurations of substituents in the ring.[197] Following a review paper on geminal proton–proton coupling constants,[198] a series of papers has appeared dealing with the effects of the "lone pair" on nitrogen, oxygen and sulphur on ^2J(H–H) between the protons on the adjacent methylene groups in five and six-membered rings.[199–202] It was shown that the two-bond coupling, known to be negative in the methylene groups of medium-sized rings, becomes more positive when one of the C–H bonds of the —CH_2— group lies parallel to the nitrogen "lone pair" orbital. This factor has enabled assignments of configuration to be made in a wide variety of heterocyclic rings.

In 1,3-diazines where nitrogen inversion can mean three different conformations (**108A**), (**108B**) and (**108C**), the "Rabbit Ear" effect has been reported to occur.[203] The chemical shifts of the ring protons in a series of substituted diazines (R,R′ etc. normally = CH_3 or H) indicate clearly that not only do *syn*-diaxial *N*-methyl groups repel each other, but also *syn*-diaxial lone pair orbitals also apparently repel each other. Therefore in 1,3-dimethyl-1,3-diazine one methyl adopts the axial configuration and the other adopts the equatorial position as in (**108C**). Similarly, a double "Rabbit Ear" effect has been reported![42] The nitrogen inversion in 1,*cis*-2,6-trimethyl piperidine, when ring inversion is prevented, has been followed by the novel method of examining the proton spectrum for solutions of different pH (0–9).[204] As the basicity is increased from pH 0, the amount of free amine present increases, so that nitrogen inversion, prevented in the protonated species, begins to occur, causing coalescence of the *N*-methyl peaks and the two C–Me doublets at pH = 9. From the results, the rate of nitrogen inversion and the conformational preference of the *N*-methyl



108A



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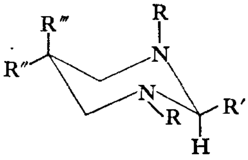
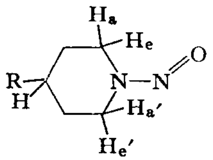


108C

group were obtained. Similar results have been quoted for the more complex situation of 1,2,4,6-tetramethyl piperazine, in which slow nitrogen inversion is again found,[205] said to be due to tightly-bound water molecules of hydration.[206]

In further investigations of protonated piperazine and morpholine derivatives, the effect of protonation on the chemical shifts and coupling constants was investigated.[207,208] Vicinal (^3J) couplings increased on protonation, i.e. become more positive, whereas geminal couplings become more negative. The chemical shifts in *C*-alkyl and *N*-alkyl piperidines have been measured, and conformations of the rings proposed;[209,210] similarly quaternary salts derived from *N*-benzyl[211] and *N*-methyl piperidines[212] have been examined, together with acetals and thioacetals of 4-piperidones.[213] The "A" values for the 3-substituents in 4-piperidone derivatives have also been determined in the usual way.[214,215]

Remarkable deshielding of the ring proton chemical shifts in cyclic amine carbodithioic acid salts have been reported,[216] but even more remarkable effects are found in cyclic *N*-nitroso amines.[217–220] For example, in *N*-nitroso piperidine derivatives of the type (**109**), different chemical shifts are found for all four α protons, with the chemical shift difference $\delta_{ae} \sim 3$ p.p.m., depending on the group R. This must be the largest chemical shift known between protons attached to the same carbon atom. Attempts have been made to calculate theoretically, this large anisotropic effect of the nitroso group[217] and a great many examples have been published.[217–220] It is again remarkable that in *cis*-2,6-dimethyl-1-nitroso-piperidine, the favoured conformation is that with both methyl groups axial (**110**)! This behaviour is also found in the *N*-acyl derivatives[220] and is thought to be caused by steric interaction between the equatorial methyl groups and the N=O or RC=O group.



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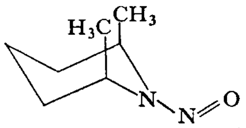
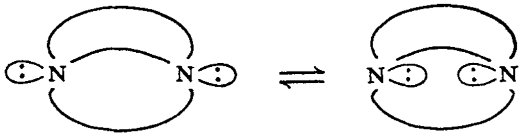


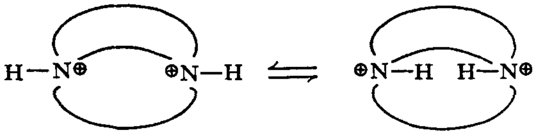
110

Finally, among the enormous number of papers dealing with trigonal nitrogen heterocyclic compounds, the unique properties of "out–in" isomerism have been displayed in the 1, ($k+2$)-diaza-bicyclo[$k.l.m.$]alkanes (**111A**) and (**111B**).[221]

In the parent amine ($k = l = m = 8$), the "lone pair" orbitals can exist either "in" or "out". Below 95°C, the NMR spectrum of the α-CH_2 protons

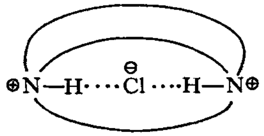


111A **111B**



"out-out" "in-in"

112A **112B**



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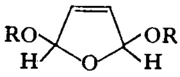
split into two resonances, 0·45 p.p.m. apart, probably due to slow nitrogen inversion ($E_A = 7{\cdot}7$ kcal/mole). The dihydrochloride (**112**) dissolved in 50% TFA/D_2O produces a spectrum which changes with time, the changes being attributed to the N–H protons moving from "out–out" to "in–in". It was also demonstrated that a chloride ion can sit quite comfortably in the cavity, and be trapped there (**113**).

C. Five and six-membered heterocyclic rings containing oxygen

Under this heading, emphasis is placed on important papers in the field of tetrahydrofurans, tetrahydropyrans, 1,3-dioxolans and 1,3 and 1,4-dioxan rings. In addition certain papers dealing with carbohydrates are discussed.

1. *Five-membered rings*

From the PMR spectra of a series of pentofuranose carbohydrates, speculations regarding their conformation have been made.[222,223] Along similar lines the equilibrium between furanoses and pyranoses has been studied in detail.[224] Full analyses of the spectra of 2,5-dihydro- and tetrahydro-furan derivatives both symmetrically and asymmetrically substituted (**114**, **115**) have been performed, and the results discussed with respect to possible conformations.[225]



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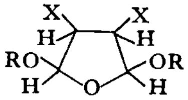
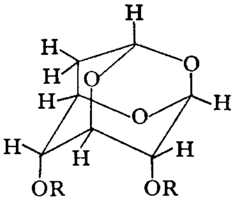


115 X = OH, Br

Both NMR and dipole moment measurements were used in conjunction to predict the conformations of 2-substituted-1,3-dioxolans.[226]

2. *Six-membered rings*

The obvious models for pyranose carbohydrates are derivatives of tetrahydropyran, and a series of papers on this theme has been presented.[227–232] In the NMR study of carbohydrates, one of the problems encountered is the complexity due to overlapping of peaks and strong coupling. The 220 MHz spectrometers are now used successfully in many cases to increase chemical shifts between protons, and thereby reduce the complexity.[233,234] In addition, computer-aided analyses are now common in this field,[235] a good example for this treatment being shown in the rigid pyranose derivative (**116**) in which no less than fifteen different coupling constants are reported.[236]



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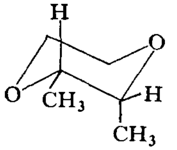
The "half-chair" conformation has been proposed for some 2,3-unsaturated pyranose derivatives,[237] and also a number of 2,3- and 3,4-anhydro pyranosides, in which the epoxide ring introduces some novel conformational effects.[234]

The literature on 1,3-dioxan rings is now voluminous, and fortunately, the situation has been reviewed almost up to the present time, by Riddell,[1] and more recently, by Eliel and Knoeber.[238] The conformational preferences of alkyl groups for the axial or equatorial position in the 1,3-dioxan ring, are substantially different from those in the cyclohexane ring.[238] The $-\Delta G_0$ values for various alkyl groups are quoted as follows: 2-Me $\geqslant$ 3·55, 4-Me = 2·9, 5-Me = 0·8, 5-Et = 0·7, 5-Pr^i = 1·0, 5-Ph = 1·0 and 5-Bu. = 1·4 kcal/mole. This data is rationalized in terms of the shape of the 1,3-dioxan ring, and the "size" of the lone pairs on oxygen. The twist-boat conformation is estimated to be at least 4 kcal/mole greater in energy than the chair form, although the heats of formation of isomeric 2,2,4,6-tetramethyl-1,3-dioxan indicate a smaller difference (~1·6 kcal/mole).[239] However, reported cases of boat conformations in 1,3-dioxan derivatives,[240,241] which have been disputed[242] must be regarded with caution until further evidence is discovered. Recent work on the chemical shifts and coupling constants in a variety of 1,3-dioxan rings has led to further conformational information about this much-discussed system.[243–247]

In 2,3-disubstituted-1,4-dioxans, analysis of the AA'BB' spectrum of the $CH_2 \cdot CH_2$ fragment immediately provides the relative configuration of the two substituents. If in the analysis, $J_{AA'} = J_{BB'}$, *cis* substitution is implied, and *vice versa*. In this manner, the two isomers of 2,3-dimethyl-1,4-dioxan (**117**) and (**118**) have been assigned, with the *trans* isomer having the lower boiling point.[248] The spectra of the two compounds are fully analysed, with an AA'BB' pattern and an $AX_3A'X'_3$ pattern fully recognisable. The coupling constants in the *trans* isomer are in agreement with predominance of the diequatorial conformer (**118**), $J_{AA'}$ being 8·46 Hz.



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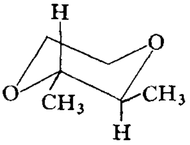

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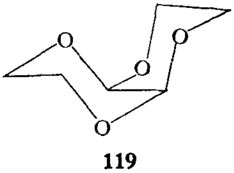
Similarly, the analysis of the spectra of naphthodioxans (**119**), 2,3-diphenyl-1,4-dioxan, and the novel compound (**120**) have established the configurations as *cis*, *cis* and *trans* respectively.[249] Naphthodioxan has been



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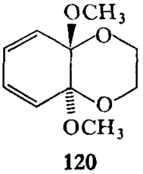

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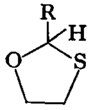
"frozen out" at −104°C, the complex spectra obtained indicating a 3 : 1 ratio of conformers, but no other conclusions were made.[249]

D. Rings containing sulphur atoms

The work of Bushweller on duplothioacetone[31,32] has already been mentioned in conjunction with ring inversion processes, as also have the sulphur analogues of *meta*-cyclophanes.[62–64] Pasto *et al.*[250] have attempted to determine the conformation of the oxathiolan ring system (**121**), and the conformational free energy values for the 2-alkyl substituents. The authors suggest that pseudo-axial protons in such five-membered rings appear at higher field than the pseudo-equatorial protons. This, however, is a dangerous conclusion to make even in six-membered rings where for example, in the 1,3-dithian ring, the axial proton adjacent to sulphur appears generally at *lower* field than the equatorial proton.[251] Therefore, it seems very hazardous to assign specific conformations to five-membered rings containing heteroatoms, which have considerable effects both on chemical shifts and coupling constants. Robertson *et al.* have made similar conclusions with 4-substituted proline derivatives.[252]



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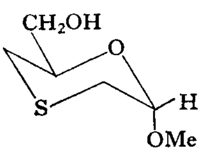
Foster *et al.* claim that sulphoxide configurations in six-membered rings can be assigned from the ring proton chemical shifts.[253,254] An axial S–O bond in a ring significantly *deshields* protons in *syn*-axial positions by ~0·75 to 0·80 p.p.m. The usefulness of this method, however, depends on the flexibility of the ring, which may adopt more than one conformation. By the comparison of the shifts and couplings in 2,6-disubstituted-1,4-oxathian derivatives, and their *S*-oxides (**122**), (**123**) and (**124**), chair conformations were shown to be probable. In addition to the deshielding effect of the axial S–O group, the geminal coupling constants $J_{33'}$ and $J_{55'}$ were shown to increase (become more negative) with the S → O axial.[254]



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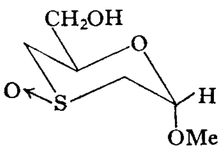

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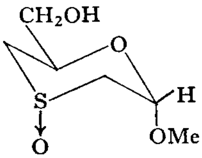

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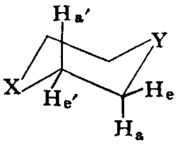
E. "R" values in six-membered rings

Returning to the somewhat safer field of six-membered rings, Lambert and Keske have recently applied the "R" value analysis to a series of six-membered rings (**125**) and from the results proposed the extent of deformation of the chair conformations involved.[255,256] The ratio of $^3J_{trans}$ average to $^3J_{cis}$ average = R, is found to be almost independent of the electro-



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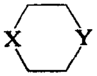
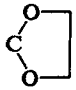
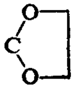
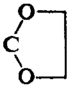
negativity of X and Y. Therefore R is a direct measure of conformational effects.

$$J_{trans} \text{ average} = \tfrac{1}{2}(J_{aa} + J_{ee})$$
$$J_{cis} \text{ average} = \tfrac{1}{2}(J_{ae} + J_{ea}) = J_{ae}$$
$$\therefore \text{R} = \tfrac{1}{2}(J_{aa} + J_{ee})/J_{ae}$$

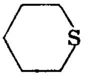
TABLE IV

Average vicinal coupling constants in six-membered rings



X	Y	J_{trans}, Hz	J_{cis}, Hz	R(J_{trans}/J_{cis})
O	O	6.11	2·78	2·20
NH	O	6·66	3·04	2·19
NCH_3	O	6·65	3·05	2·18
NH	NH	6·54	3·04	2·15
$C(CH_3)_2$	$C(CH_3)_2$	8·27	4·03	2·05
		8·34	4·30	1·94
S	O	7·35	2·65	2·77
S	S	8·11	2·40	2·38
Se	Se	8·49	2·43	3·49
C=O	C=O	8·05	6·23	1·29
C=NOH	C=NOH	7·3	6·5	1·12
$C{=}CH_2$	$C{=}CH_2$	7·52	5·31	1·42
C=O	CD_2	8·61	5·01	1·72
C=O	$C(CH_3)_2$	7·81	5·46	1·43
C=O	CPh_2	7·78	5·44	1·43
C=O		8·08	6·25	1·29
S	CH_2	$\alpha\beta$ 8·51	3·26	2·61
		$\beta\gamma$ 8·47	3·28	2·58
$TeBr_2$	CH_2	$\alpha\beta$ 7·8	5·2	1·5
		$\beta\gamma$ 9·21	2·56	3·60

Changes in "R" reflect changes in dihedral angles between the relevant C–H bonds, the near-ideal value for "R" being 2·0. Deviations from this value can be correlated with "flattening", $R > 2$, or buckling ($R < 2$) of the chair form. Compounds existing wholly in the twist-boat conformation have low R values (e.g. for cyclohexane-1,4-dione, $R = 1{\cdot}29$). Results are given in Table IV. More recent results for the thiane (**126**) and dibromo tellurane rings (**127**) indicate a rather puckered conformation for thiane, and a chair form flattened at one end and puckered at the other for the tellurane ring.[255]



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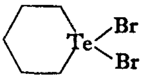

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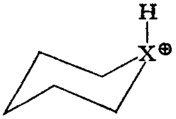

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Finally, an interesting experiment which may have some bearing on the "lone pair" controversy, involves the examination of the conjugate acids of the same six-membered heterocyclic compounds (**128**) in strongly acid solution at low temperatures ($FSO_3H—SO_2$).[257] In each case, the conjugate acid proton appears in the spectrum as a triplet of triplets, due to a large (10 to 14 Hz) and a small (2·1 to 2·4 Hz) coupling to the four α protons. This indicates a clear preference of the proton for the *axial* position, although whether this would hold in less exotic solvents is open to question.

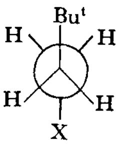
F. Rotational isomerism in acyclic compounds

A factor not always considered in the rotational isomers of three-carbon fragments, is that 1,3-non-bonded interactions between parallel substituents are just as important as in cyclohexane derivatives. Some evidence has been supplied by Sheppard *et al.*, for seventeen chloropropane derivatives, in which **no** cases were found in which two chlorine atoms in the 1,3-positions were parallel to each other.[258] Fortunately, in NMR spectroscopy propane and butane derivatives are normally too complex for conformational conclusions to be made, but such interactions should be considered in work of this kind.

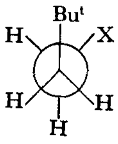
Buys *et al.*[259] have explored the relationship between vicinal coupling constants and dipole moments in 1,1,2-trichloroethane, and the corresponding bromo derivative. Plotting the average coupling constant in various solvents against the square of the corresponding dipole moment, a straight line was obtained, obeying the equation—

$$\mu^2 = -1{\cdot}4J + 11{\cdot}0$$

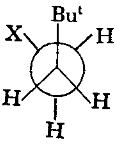
More solvents are required, however, to absolutely verify this relationship, which is most useful in determining energy differences between rotamers. In a more rigorous treatment of 1,1,2-trichloroethane, using electrostatic theory to predict the effect of the medium on the rotamer energy differences,[260] good agreement is found between the calculated and observed energy differences in the liquid and vapour states. In addition, the theory enables the *gauche* and *trans* couplings to be calculated (2·2 and 6·38 Hz respectively). Whitesides *et al.* have examined in detail the rotational isomerism in a large number of 3,3-dimethyl butyl derivatives which adopt the three isomers (**129A**), (**129B**) and (**129C**).[261] The authors assumed only three coupling constants were necessary to describe all the spin–spin interactions in the separate isomers, and thus were able to calculate energy differences between the isomers. In a similar way, the energy differences or preferred conformers were determined for the 3-halogeno-1,1,1-trifluoropropanes,[262] monosubstituted succinic acids,[263] a variety of α-chloro alcohols,[264] epifluorohydrin[265] 1-methoxy-2-hydroxy propane[266] and, in great detail, the complex situation of 2,4-pentanediol,[267] in which the preferred conformation of the racemic compound is found to be (**130A**), and that of the *meso* compound (**130B**). Intramolecular hydrogen-bonding is thought to be important in stabilizing these conformations, and also the preferred conformation in 1-methoxy-2-hydroxy propane.[266]



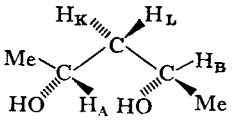
129A



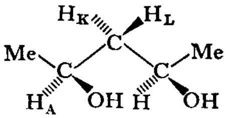
129B



129C



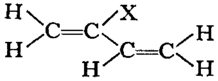
130A



130B

Jablonski and Snyder showed that the rotamer with the bromine atoms *trans* was the more stable in *threo*-ethyl-2,3-dibromopropionate, by careful specific deuteration and comparison of the spectra obtained with that of the undeuterated molecule.[268] The more complex spectra of XCH_2CH_2Y molecules have been fully analysed, and the influence of the substituents on the coupling constants of the individual rotamers determined.[269] It was found that, whereas most of the couplings decreased with increasing electronegativity, the *gauche* coupling in the *trans* isomer increased with increasing electronegativity, contrary to all previous theory. The AA′BB′ spectra of $PhCH_2CH_2X$ were analysed in a similar way, and rotational isomerism investigated.[270]

A series of 1,3-butadienes have been examined by the NMR method, and found to exist mainly in the *s-trans* conformation as far as the haloprenes are concerned (**131**), whereas the trihalobutadienes exist largely in the skew conformation; J_{14} was found to depend on the dihedral angle between the planes of the two double bonds.[271] Other, more highly substituted 3-fluorobutadienes were examined at variable temperatures, and the temperature dependence of ^3J(H–F) used to predict the energy difference between the s-*cis* and s-*trans* conformations.[272]



X = F,Cl,Br and I

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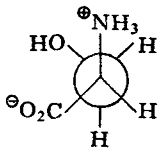
Pentene-2-nitrile derivatives,[273] and *cis* and *trans* but-2-ene derivatives have also been explored by the measurement of the vicinal and long-range coupling constants between the protons. A small difference in $J(CH_3–CH)$ in *cis* and *trans* but-2-ene is interpreted as due to steric interaction between the methyl groups in the *cis* compound,[274] but this is rather speculative, considering the small difference involved (0·16 Hz), and has been criticized by Harris and Howes.[275]

The work of Karabatsos *et al.* on the rotational isomerism in aldehydes and ketones has continued with similar studies on oximes,[276] oxime-*O*-methyl ethers,[277] hydrazones,[278] phenylhydrazones,[279] *N*-alkyl imines[280] and *N*,*N*-dimethylhydrazones.[281] Finally, the PMR spectra of a series of 2-substituted pentan-3-ones was examined, and from the coupling constants, it was clear that the most stable conformation was that with the carbonyl bond eclipsed by the C–CH_3 bond.[282]

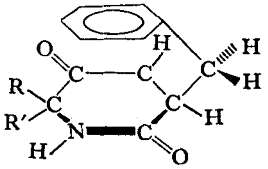
G. Conformations of amino acids and peptides in solution

Cavanaugh has studied phenylalanine in alkaline and neutral solution, at various temperatures between 7° and 99°C, analysing the spectrum for each temperature.[283,284a] The variations of the vicinal coupling constants in the anion with temperature and concentration, indicate that the rotational isomers are the classical staggered conformations, whose relative energies vary with the conditions. In neutral solution, however, the vicinal couplings are almost constant over the temperature range studied. Similar work on serine, $\overset{\oplus}{N}H_3CH(CH_2OH)CO\overset{\ominus}{O}$, showed that the preferred conformer was that with the hydroxyl group gauche to both —$\overset{\oplus}{N}H_3$ and $C\overset{\ominus}{O}_2$ (**132**).[284b]



132

Aruldhas[285] was led to the wrong conclusions in his study of DL-threonine and DL-valine in aqueous solution, due to the presence of impurities in his samples, a fact which was pointed out by three different groups.[286–288] Kopple and Marr have found that cyclic diketo-piperazines containing an aromatic side chain (**133**), adopt preferentially the conformation with the aromatic ring folded over the top of the peptide ring, influencing strongly the chemical shifts of the protons in the 4-position.[289] The folded form appears to be favoured by ~3 kcal/mole. This preference probably stems from the interaction of the two amide dipoles with the polarizable π electrons of the benzene ring.



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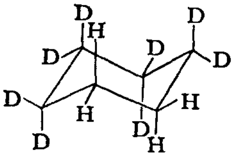
Bystrov and co-workers have explored the conformations of peptides by a study of J(CH–NH) which depends on the dihedral angle between C–H and N–H bonds.[290] They showed that some alanine dipeptide molecules in carbon tetrachloride solution existed 70% of the time in the form of an intramolecularly hydrogen-bonded 7-membered ring. Similar work has been discussed with respect to the DL and LL forms of phenylalanylvalines.[291] The spectra at 220 MHz of porcine and bovine insulin, and the A and B chains of bovine insulin have been discussed, in conjunction with the spectra of twenty-one amino acids, examined separately in CF_3COOH solution, serving to identify certain amino acids in the insulin molecules.[292] Finally, resonances at δ 0·7 to 1·0 have been found in the spectra of the folded forms of lysozyme and cytochrome c at 220 MHz.[293] These high field peaks are caused, apparently, by proximity of the particular protons to the axis of the phenyl ring of phenyl alanyl residues, or other aromatic amino acid fragments.

III. COUPLING CONSTANTS AND STEREOCHEMISTRY IN RING COMPOUNDS

A. Vicinal coupling constants

The dependence of vicinal H–H coupling constants on the dihedral angle between the C–H bonds is now an established fact, as also are the dependencies of ^3J(H–H) on electronegativity, bond angles and strain. Very little data has been available dealing with the coupling constants in the basic, non-substituted rings such as cyclohexane, cyclopentane, etc. Recently, cyclohexane itself, deuterated on all but two adjacent carbon atoms (**134**) was cooled down to –103°C and the proton spectrum obtained with deuterium decoupling.[294] A good analysable AA′BB′ spectrum was obtained, with twenty-two out of the possible twenty-four lines resolved. The results, ^2J(H–H) = –13·05 Hz, ^3J(H–H) = 13·12 (*aa*), 2·96 (*ee*) and 3.65 Hz (*ae*), fit excellently the modified Karplus equation proposed by Barfield and Grant—



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$$J = A\,(\cos^2\phi + n\,\cos\phi)$$

Solving the three equations obtained for A, n and ϕ provides a solution with $\phi = 57°$ for "*gauche*" C–H bonds. Incidentally the "R" value for these results is 2·20, slightly greater than predicted for a perfect chair conformation. The large value for $^3J_{aa}$ probably reflects the extent of substituent participation in substituted cyclohexanes, where it is rare to find axial-axial coupling constants >12 Hz.

Other "pure" rings investigated by either using ^{13}C satellite spectra, or liquid crystal measurements, have been cyclopropane, in which Watts and Goldstein, using ^{13}C satellite spectra, found ^2J(H–H) = –4·31 Hz, ^3J(*cis* H–H) = 8·98 and ^3J(*trans* H–H) = 5·57 Hz;[295] whereas by liquid crystal measurements, the values, $^3J_{cis} = +9·5$ and $^3J_{trans} = +5·5$ Hz were obtained.[296] In analogous liquid crystal experiments, cyclobutane yielded the values:— ^3J(*cis* H–H) = +10·4 ^3J(*trans* H–H) = +4·9 Hz, with the long-range couplings ~0.[296] It is clear that ^{13}C satellite spectra, and/or spectra of deuterated species are necessary for accurate determinations.

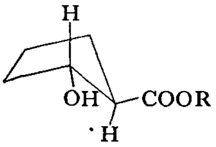
Cyclobutanone has been re-examined by two groups of workers, with good agreement for the vicinal coupling constants (10·0 (*cis*) and 6·3 (*trans*)) and the geminal couplings (–17·6α, –10·9β), but poorer agreement on the long-range couplings (+4·1 and –2·8 to –3·2 Hz).[297,298]

Fleming and Williams have reviewed the NMR spectra of four-membered carbocyclic rings, and given the ranges of vicinal and geminal coupling constants, discussing the effect of ring strain and unsaturation on the coupling constants.[299] Cyclobutene has been re-examined by PMR spectroscopy and the vicinal couplings in the CH_2–CH_2 fragment found to be +4·65 Hz (*cis*) and +1·75 Hz (*trans*).[300]

Returning to larger rings, Altona *et al.* have applied the μ/J relationship previously mentioned,[259] to 1,2-dihalogenocyclohexanes, cyclopentanes and α-halogeno-cyclohexanones and *trans*-1,2-dihalogenoindans,[301,302] finding a linear relationship between the square of the dipole moment (μ^2) and ($J_{AX} + J_{BX}$) in inverting systems, providing a useful technique for measuring energy differences between conformations.

Vicinal H–H coupling constant have also been used to assign the conformational equilibrium in the α-halo cyclohexanones, using the *cis* and the *trans* 4-*t*-butyl derivatives as references, in a variety of solvents.[303] The predominance of the axial conformer became less marked with increase in solvent polarity, and also as the halogen was changed from Br to Cl to F. 2-fluoro-cyclohexanone in acetonitrile (10% axial form) and 2-bromo-cyclohexanone in cyclohexane (89% axial form) represent the two limits in the range of data. Other interesting proposals for cyclohexane conformations using ^3J(H–H) have been made for lactone-bridged cyclohexanes,[304] stereoisomeric 1,3,5-trichlorocyclohexanes,[305] the tetradeutero-cyclohexylchlorides and fluorides, and their cyclohexenyl analogues, [306] a variety of *cis*- and *trans*-2-substituted cyclohexanol derivatives,[307] 2-*t*-butyl-5-hydroxy cyclohexanones, in which it was concluded that non-chair conformations were not appreciable,[308] and 4,4-diphenyl cyclohexanone which was concluded to be in a rather flattened chair conformation.[309]

Baumann *et al.* have attempted to determine the conformational preferences in *cis*- and *trans*-2-carboxy cyclopentanols and the corresponding esters, comparing the results with the corresponding cyclohexanols, by measuring the bandwidth of the spectra of the protons adjacent to the —OH and the —COOR groups.[310] In the *trans* compounds, the conformer (**135**) with the substituents pseudoequatorial seems to be preferred. Also in five-membered rings, the unique feature of the spectra of rings containing heteroatoms and one double bond has been emphasized further in a series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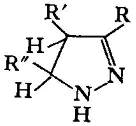
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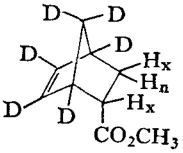
of 2-pyrazolines (**136**), in which the vicinal couplings of the saturated C–C fragment are extremely large, with $^{3}J_{trans} = 9{\cdot}8$ to 10·5 Hz and $^{3}J_{cis} = 11{\cdot}2$ to 13·4 Hz, depending on the substituents present in the ring.[311] In cyclopentene rings, on the other hand, the observed vicinal couplings are much smaller, e.g. in *cis*-3,5-dibromo cyclopentene, J_{34} and $J_{34'}$ are 6·9 and 1·5 Hz respectively, very much smaller and similar to those in cyclopenten-3-one.[312]

The configuration and conformation of δ-lactones have been deduced, again from vicinal coupling constants,[313,314] and also the spectra of fifty γ-lactones have been used to suggest conformational features in these rings.[315]

Coupling constants in rigid systems have often been used as standards for conformational analysis, and it was thought previously that in the rigid bicycloheptane skeleton, $J_{endo\text{-}endo} > J_{exo\text{-}exo}$ by a substantial margin. Anet *et al.* have shown that this is not true, at any rate for the two compounds (**137**) and (**138**), in which analysis of the spectrum indicates $J_{nn} \simeq J_{xx} \simeq 9{\cdot}0$ Hz.[316] Other rigid molecules in which coupling constants have been reported, are the 2,7-dioxabicyclo[2,2,1]heptanes,[317] various substituted bicyclo[2,2,1]heptenes,[95,318,319] norbornene and norbornadiene,[320] and *exo-exo*-3,6-dibromo bicyclo[2,2,1]heptan-2,5-dione.[321]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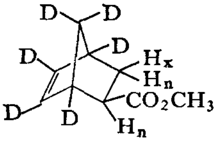
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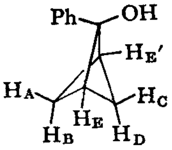
B. Long-range coupling constants

With the constant improvement in instrumentation, a whole host of long-range coupling constants over four or more bonds are coming to light. The largest ^{4}J(H–H) over four saturated bonds so far reported is no less than 18 Hz, between the bridgehead protons (H_E and $H_{E'}$) in a bicyclo[1,1,1]-pentane derivative (**139**).[322] This enormous coupling is said to be caused by extensive overlap of the small lobes of the orbitals directed 180° away from the C–H bond direction, the non-bonded C–C distance being only 1·89 Å.



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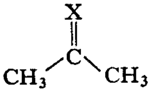
Large four-bond couplings are also found in four membered rings where extensive buckling occurs, with values ranging up to a maximum of ~+7·4 Hz for protons pointing away from each other, preferably with all four atoms H–C–C–H in one plane.[323,324] Such couplings are very common in bicyclic derivatives where the protons have the required rigidity and stereochemistry.

Sardella has discovered a change in sign for the coupling between *gem* dimethyl groups (**140**) depending on the electronegativity of the group X, e.g. ^4J(H–H) is +0·53 Hz in acetone, and –0·49 Hz in 2-methyl propenyl acetate, the coupling *increasing* with increasing electronegativity of the group X.[325] The transition point, when X = NR, shows almost zero coupling, as expected. Couplings between geminal dimethyl groups have also been found by Pascual and Simon,[326] and by Mijs.[244]



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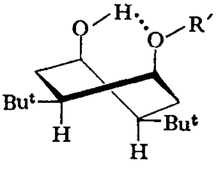
Large five-bond homoallylic coupling constants in the 1,4-cyclohexadiene ring have been assigned,[327] by specific deuteration, to be $J_{cis} = 9{\cdot}63$ Hz and $J_{trans} = 8{\cdot}04$ Hz, and from these figures Garbisch and Griffiths assigned a near-planar conformation to the molecule. A re-evaluation of the steric dependence of allylic coupling constants has shown that to imply that $J_{cisoid} > J_{transoid}$ is unreliable as a basis for structural assignment.[328]

Long-range couplings abound in oxygen heterocyclic compounds, and Anderson[329] and Hall and Manville[330] have attempted to correlate the results for a large number of compounds. Hall[330] has found $^4J_{ee}$ to be positive, +0·8 to +1·6 Hz, $^4J_{ea}$ to be negative (–0·2 to –0·7) and $^4J_{aa}$ to be zero, in accord with Barfield's predictions. The coupling $^4J_{aa}$ has been found, however, to be non-zero in some triterpene derivatives,[331] so the theory does not hold for all cases. These references to long-range coupling, together with many other too numerous to mention here, emphasize the progress made in this section of NMR spectroscopy. It remains for the theory of these coupling constants to be brought up to date in the light of the numerous data now available, the most recent paper by Carey and Ditchfield providing some promising results.[332]

C. Coupling constants through hetero-atoms

Rotamer populations of the hydroxyl group have been estimated using *cis,cis,cis*-2,5-di-*t*-butyl-4-methoxy cyclohexanol (**141**) as a model. The coupling constant $J(H\text{C–O}H)$ depends on whether R′ = H or CH_3, being ~7·0 and ~11.4 Hz respectively, indicating that the OH conformation is slightly different in the two compounds.[333] The HC–OH and HC–C–OH couplings have been observed in the proton spectra of various pyranose derivatives, the long-range coupling being observed *only* for axial —OH groups.[334,335] This is therefore a useful method for assigning the anomeric proton in carbohydrate spectra. The best solvent found for observing the phenomena was a mixture of dimethylsulphoxide-d_6 and acetone-d_6: The use of SO_2—FSO_3H—SbF_5 as a solvent, has enabled the *syn* and *anti* forms of the acetaldehyde conjugate acid to be examined (**142A** and **B**).[336] The HO–CH coupling was found to be 18·5 Hz for the *anti* and 8·5 Hz for the *syn* isomer, reflecting precisely the *trans* and *cis* olefinic coupling constant dependence. The angular dependence of $J(H\text{C–O}H)$ seems to follow the same rules as for H–C–C–H coupling, as might be expected. Similarly $J(H\text{C–N}H)$ also follows a Karplus relationship, varying from 0 to 15 Hz in 58 derivatives of 3-amino acrylic esters.[337]



R′ = H, CH_3

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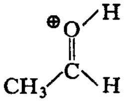
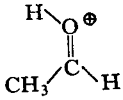


142A



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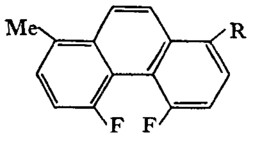
D. Coupling constants involving other nuclei

1. ^{19}F–^{19}F *coupling constants*

Two interesting facts deserve mention as far as conformational analysis is concerned. The low values for vicinal fluorine–fluorine coupling constants in ethane derivatives (3·50 Hz for $CF_3 \cdot CF_3$)[338] are readily explained by the presence in the rotational isomers of two large coupling constants of opposite sign, which tend to cancel each other in the time-averaged spectrum. Vicinal couplings of opposite sign have been found in perfluorocyclobutene,[339] and in halogeno-pentafluorocyclopropanes,[340] among other compounds of this type. The second fact is that "through space" fluorine–fluorine coupling constants, out of favour for many years with theoreticians, seem to be becoming "respectable", with the discovery of many more examples of large coupling constants between spatially-proximate fluorine nuclei, an enormous effect being apparent in (**143**), (J(F–F) = 170 Hz)[341] and clear effects in the rotational isomers of (**144** and **145**).[342] Finally, the full analysis of perfluoromethyl cyclohexane deserves mention, with sixteen coupling constants unravelled from the complex spectrum.[343] It seems unlikely, however, that the spectrum of both conformers is present at ambient temperatures as has been suggested, since an energy barrier of greater than 15 kcal/mole would be required.



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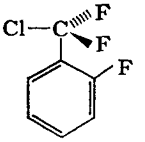

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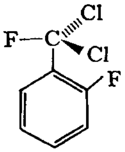

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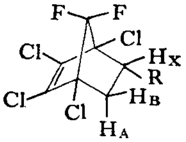
2. ^1H–^{19}F *Coupling Constants*

Williamson *et al.* have thoroughly investigated the angular dependence of ^3J(H–F), and have shown, in addition to a Karplus-type of dihedral angle relationship, that the coupling is very dependent on bond length and also the F–C–C bond angle, varying between 0·9 and 31 Hz for angles of ~118° to ~109° respectively, with the *dihedral* angle held at 0°C.[344] Some interesting results for 7,7′ difluoro bicyclo[2,2,1]heptenes (**146**) indicated that the long-range H–F coupling possessed either sign, varying from +1·12 to −5·44 Hz.[345] Finally some rotational work analogous to that of Jonas *et al.*[342] has been reported for the hindered molecule (**147**).[346] The *t*-butyl



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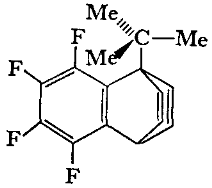
group shows a doublet at 33°C at δ 1·4 (J(F–H) 2·9 Hz) integrating for six protons and a singlet at δ 1·2 (three protons). Free rotation is not complete even at 180°C, indicating the severity of the hindrance. The F–H coupling may be another example of through-space spin interaction.



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3. ^1H–^{31}P *coupling constants*

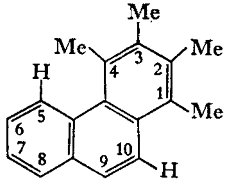
The stereochemical dependencies of ^{31}P–^{1}H couplings have been the subject of a great deal of attention. The two-bond coupling J(P–C–H) has been shown to be sensitive to the orientation of bonds around the phosphorus atom, with J varying between +26 and –6 Hz, depending on the dihedral angle between the two planes defined by the P, C and H atoms and the C–P bond, together with the three-fold axis of the bonds around phosphorus.[347–350] Similarly, $J(POCH)$ in cyclic phosphate esters,[351] some dioxaphosphorinanes,[352] cyclic phosphites,[353–355] and other derivatives,[356] has been shown to have a marked stereochemical dependence. Even five-bond homoallylic ^{31}P–^{1}H couplings have been shown to be dependent on the stereochemistry, i.e. $^5J_{transoid} > {}^5J_{cisoid}$.[357]

Clearly, the stereochemical dependencies of heteronuclear coupling constants are of great value in conformational analysis and the potential is by no means exhausted, and should be extended further, by examining other important nuclei such as carbon-13 in this way.

IV. NUCLEAR OVERHAUSER EFFECTS IN CONFORMATIONAL ANALYSIS

In the period following a paper by Anet *et al.*,[358] in which internal Nuclear Overhauser effects were shown to be advantageous in conformational assignments, further advances have been made. The theory of these effects is beyond the scope of this Review, and it need only be said that in conformationally rigid molecules, where magnetic nuclei are spatially close to each other, direct dipole–dipole interactions can take place, the resulting energy levels of the nuclei being dependent on each other to a certain extent. Double-irradiation of the peak due to one nucleus then causes an *increase* in the intensity of the peak due to the other, the extent of the increase depending on the inter-nuclear distance.

A simple example has been demonstrated with 1,2,3,4-tetramethyl phenanthrene (**148**), in which irradiation of the 4-methyl protons causes a 32% enhancement of H_5, and likewise, irradiation of the 1-methyl group causes an 11% enhancement of H_{10}.[359]



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The method has been used as a conformational aid in a large number of organic compounds, particularly natural products,[360–368] and is clearly useful in assigning ambiguous peaks in a spectrum. Area decreases (negative NOE's) have been noted for two protons separated by an intervening proton, a qualitative mechanism being advanced for the process.[367,368]

V. SUMMARY

In this Chapter, it is abundantly clear that the knowledge of the conformational analysis of heterocyclic compounds has advanced at great speed in the last two years, and shows no sign of abating. 220 MHz instruments are clearly proving to be most helpful in unravelling complex proton magnetic resonance spectra, and variable temperature probes are vital in the study of inversion processes. The advances in the field of conformational analysis using NMR spectroscopy therefore parallel the advances made in instrumental sophistication. Certain techniques, such as Nuclear Overhauser experiments, and the discovery by Pirkle that in racemic mixtures optically active enantiomers can be "resolved" in the NMR spectrum by use of optically-active solvents,[369] are clearly going to be expanded and improved in the near future.

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Nuclear Magnetic Resonance Spectra of Steroids

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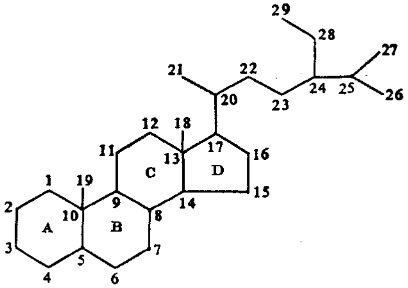
I. INTRODUCTION

ALTHOUGH it is merely ten years since the appearance of Shoolery and Roger's classic paper on the NMR spectroscopy of steroids,[1] NMR spectroscopy is today accepted as one of the most powerful physical methods available to the steroid chemist and is considered to be an essential technique in all steroid laboratories. In order to indicate the omnipresence of NMR spectroscopy in present-day steroid research, we might well invoke Sir Christopher Wren's famous epitaph: "*Si monumentum requiris, circumspice.*" It is standard practice to record the NMR spectra of all new steroids and it is unusual to read a paper describing original work in the steroid field, which does not cite NMR measurements as evidence for chemical structure.

Steroids are compounds containing the perhydrocyclopentenophenanthrene nucleus. They include a wide range of naturally occurring compounds, among which are the steroids proper, the bile acids, the sex hormones, the adrenocortical hormones, the D group of vitamins, the cardiac glycosides and aglycones, various triterpenes, the sapogenins, certain alkaloids and various minor groups. Apart from differences due to the presence of nuclear substituents, the degree of unsaturation and the relative stereochemistry and conformation of rings A, B, C and D, the diverse compounds forming the steroid group arise from variations in the nature of the side-chains, R^1, R^2 and R^3 (cf. **1** and **2**). Side-chain, R^1, may be absent as is the case when ring A and/or ring B are aromatic; R^1 and R^2 are generally methyl groups, although partially oxidized residues such as hydroxymethylene or aldehyde groups are sometimes encountered. Side-chain R^3 may be absent (e.g., oestrane (**2**; $R^1 = R^3 = H$, $R^2 = Me$) and androstane (**2**; $R^1 = R^2 = Me$, $R^3 = H$)) or may comprise two (e.g., pregnane (**2**; $R^1 = R^2 = Me$, $R^3 = Et$)), five (e.g., cholane (**2**; $R^1 = R^2 = Me$, $R^3 = CHMeCH_2CH_2CH_3$)), eight (e.g., cholestane (**2**; $R^1 = R^2 = Me$, $R^3 = CHMeCH_2CH_2CH_2CHMe_2$)), nine (e.g., ergostane (**2**; $R^1 = R^2 = Me$, $R^3 = CHMeCH_2CH_2CHMeCHMe_2$)) or ten carbon atoms (e.g., stigmastane (**2**; $R^1 = R^2 = Me$, $R^3 = CHMeCH_2CH_2CHEtCHMe_2$)); in some steroids (e.g., azasteroids), eight side-chain carbon atoms are associated with an atom of nitrogen, as in solanidine and tomatidine. Substitution by methyl groups of the two hydrogen atoms at carbon-4 and of that at carbon-14 leads to the 4,4,14ξ-trimethyl-steroids or triterpenes.[2]



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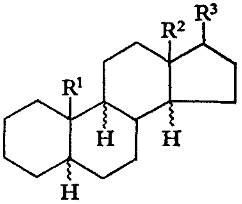

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Since the earlier work on the NMR spectroscopy of steroids has been admirably reviewed by Bhacca and Williams,[3] this article will be largely restricted to a survey of work that has been published during the last four years; a general account of the spectra of naturally occurring steroids has been included. In order to conform with the Editorial decision, chemical shift values have, where necessary, been converted from the tau to the delta scale.

NMR spectroscopy has been used for the identification of individual steroids, the quantitative determination of certain steroids in mixtures, the determination of solvent and of other impurities in steroids and, above all, for the elucidation of the structure of new steroids.

II. EXPERIMENTAL TECHNIQUES

The last four years have been characterized by the wider use of high-resolution 100 MHz spectrometers and by the introduction of simpler 60 MHz spectrometers, suitable for routine use in an organic laboratory. A few measurements on steroids at 220 MHz have been reported[4,5] and use has been made of the nuclear Overhauser effect.

Deuterochloroform is the preferred solvent for steroid measurements, but since many steroids are insoluble in deuterochloroform, hexadeuterated dimethyl sulphoxide[6] and pentadeuteropyridine[7] are frequently used. The structure elucidation of new steroids is often facilitated by observing the change in chemical shift of certain protons in going from a non-aromatic solvent, such as carbon tetrachloride or deuterochloroform, to an aromatic solvent, such as benzene or pyridine.[8] The use of mixed solvents, such as deuterochloroform containing 10% of hexadeuterated dimethyl sulphoxide, although useful for difficultly soluble compounds, should be avoided whenever possible; solvent-shift effects reduce the reliability of comparisons of such spectra with those of reference compounds examined in pure solvents.

Most measurements on steroids have involved proton resonance, but a few fluorine-19 (see Section VC) and carbon-13 measurements have been reported. Weigert, Jautelat and Roberts[9] described the ^{13}C spectrum of cholesterol and, using proton decoupling techniques, were able to distinguish 26 of its 27 carbon atoms.

A. Qualitative measurements

In order to aid the identification of steroids by comparison of their NMR spectra, Neudert and Röpke[10] have published catalogues containing reference spectra for selected steroids. Unfortunately, Neudert and Röpke's measurements were undertaken at 40 MHz; most observations on steroids are now made at either 60 or 100 MHz. When comparing NMR spectra of steroids, it is important to compare spectra which have been recorded in the same solvent and under the same spectral conditions.

B. Quantitative measurements

NMR spectroscopy is used on an *ad hoc* basis for the quantitative determination of steroids in mixtures. This is usually done by comparing the integrated intensities of the peaks for the angular 10-methyl and 13-methyl protons of the different steroids; the 10-methyl and 13-methyl proton peaks are normally sharp and well-separated.

Solvent and other impurities are readily identified and estimated by NMR spectroscopy. If a resonance peak can be attributed to a known impurity (either a solvent or another steroid), the relative amount of the impurity can be estimated by comparing the height of the integrator step for the impurity peak with that for a peak assigned to a known group in the steroid. The technique is of particular value in following chemical reactions involving steroids and in helping to establish the purity of a steroid.

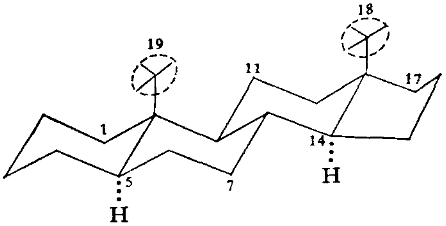
III. METHYL, METHYLENE AND OLEFINIC GROUPS

Shoolery and Rogers[1] showed that although it is not possible, as with molecules of molecular weight less than 200, to assign to particular protons every peak or group of peaks in the NMR spectrum of a steroid, it is relatively easy to identify the sharp peaks associated with methyl groups of various types and in different environments and, further, to assign peaks due to aromatic and olefinic protons and to protons geminal to oxygen and nitrogen atoms. The rigid polycyclic steroid framework is ideal for the evaluation of steric factors affecting coupling constants and for the investigation of long-range effects associated with different functional groups.

A. Methyl groups

The scope of Shoolery and Rogers[1] observation that the frequency shifts of angular methyl protons, induced by different functional groups, are approximately additive has been extended considerably by Zürcher[11,12] and by Cohen and Rock[13] (cf. Bhacca and Williams[14]). Zürcher tabulated the chemical shifts for the 10-methyl and 13-methyl protons in a large number of differently substituted steroids and derived the frequency increments for a wide range of substituents at different positions on the steroid nucleus. By comparing the chemical shift of the angular methyl protons for an unknown steroid with values calculated from Zürcher's tables, possible chemical structures can be readily tested.[12]

Recent work on new types of steroids and on triterpenes has led to many additions to Zürcher's tables and has thrown more light on deviations from the additivity rules. The contribution of a substituent must change if its position and distance relative to an angular methyl group changes. Thus, if introduction of either a double bond or an epoxide group distorts the steroid frame from that of one of Zürcher's four basic skeletons, namely 5α,14α- (**3**), 5α,14β- (**4**), 5β,14α- (**5**) and 5β,14β-androstane (**6**), the calculation will be less accurate. Complications caused by skeletal changes, dipole–dipole interaction, hydrogen-bonding and steric effects may cause additivity deviations greater than one Hz. The cause of and the calculation of proton chemical shifts in non-conjugated steroids have been discussed by Zürcher.[15]



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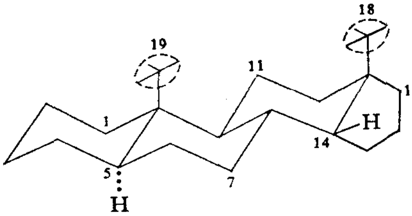

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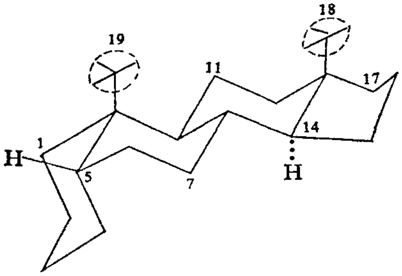

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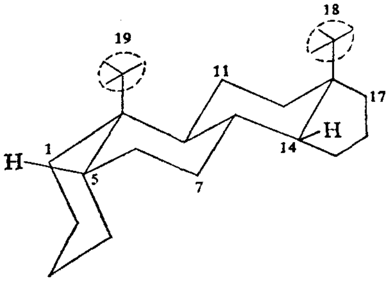


6

Jacquesy and his colleagues[16] have tested Zürcher's rules for other substituents in the A- and B-rings of 5α-cholestanes in deuterochloroform solution and have deduced the chemical shift increments for the 10-methyl protons caused by these substituents (cf. Table I). The chemical shift values for 10-methyl and 13-methyl protons in the four 9,10-stereoisomeric series, 5β,8β,9β,10α- (**7**), 5β,8α,9α,10α- (**8**), 5α,8β,9β,10β- (**9a** or **b**)[17,18] and 5α,8β,9α,10β- (**3**),[19] have been recorded. Substituent additivity values found for steroids with the natural configuration, 8β,9α,10β (**3**), cannot be applied to steroids in other series because of the marked geometric difference between the androstane skeletons, and it is therefore necessary to base the calculation in each series on the appropriate androstane skeleton. The extra chemical shifts of the 10-methyl and 13-methyl protons arising from the introduction of one or more substituents in the various androstane skeletons differ from

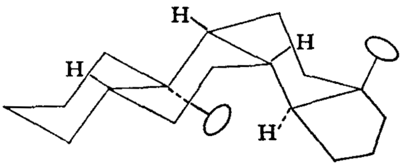
TABLE I

Substituent increments (in Hz) for the chemical shift of the 10-methyl protons of 5α-cholestane in $CDCl_3$ solution at 60 M Hz[a]

Substituents	10-Methyl, Hz
5α-Cholestane	47
1α-OH	−3
1α-CN	6·5
2α-Br	3·5
2β-Br	19
2α-Cl	5
3-Oxo	13
3,3-Ethylenedioxy	2
3α-OH	−1
3β-OH	1
3α-OAc	0·5
3β-OAc	2·5
3α-Me	0·5
3β-Me	−1·5
4α-Me	1·5
4β-Me	2
4β-Ethynyl	15·5
4β-Vinyl	−3
4β-Ph	−11
4α,5α-Epoxy	3
4β,5β-Epoxy	8
5α-OH	11·5
5α-CN	8·5
5α-Cl	16·5
5α-Br	18
5α-Me	8·5
6β-OH	9
6β-OAc	5·5
6β-CN	18
6β-Cl	17·5
6β-Br	18·5
6β-Me	4·5
6β-Et	−0·5

[a] (A positive value denotes a downfield shift caused by a substituent). (From Jacquesy, Jacquesy, Levisalles, Pete and Rudler.[16])

one series to the other. Some typical values are included in Table II. Hammer and Stevenson[20] have listed the chemical shifts for the angular methyl protons of a series of cholestane, ergostane, ergost-22-ene and 22,23-dibromo-



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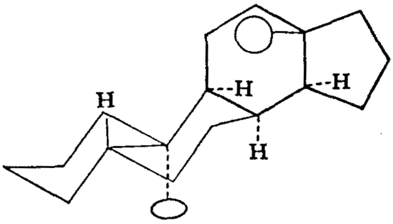

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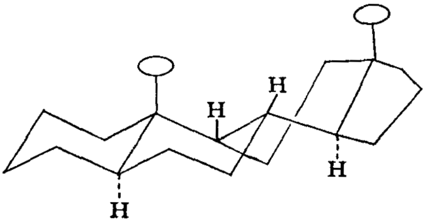

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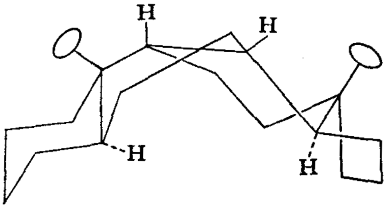

9b

ergostane derivatives and have compared the experimental and calculated values.

Lavie, Greenfield, Kashman and Glotter[21] have tabulated the chemical shifts of the angular methyl protons for one hundred and thirty-one additional steroids and have calculated the additivity increments of substituents, mainly, at carbon-1, -4, -5 and -6 (see Table III). The compounds examined included 4α,5α-, 5α,6α-, 4β,5β- and 5β,6β-epoxy-steroids and dihydrodeoxy-derivatives of the natural steroidal lactone, withaferin A (**10**). The principle of additivity increments was used in helping to establish the stereochemistry of withaferin A derivatives.

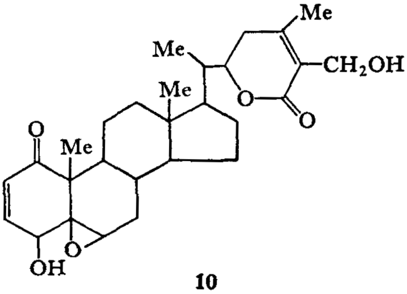

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TABLE II

Substituent increments (in Hz) for the chemical shift of the 10-methyl and 13-methyl protons of four stereoisomeric androstane series in $CDCl_3$ solution at 60 M Hz[a]

	8β,9α,10β		8β,9β,10α		8α,9α,10α		8β,9β,10β	
Substituent	10-Me	13-Me	10-Me	13-Me	10-Me	13-Me	10-Me	13-Me
5α-Androstane	47·0	41·0	57·0	43·0	56·5	50·5	54·5	54·0
3-Oxo-5α-	14·5	2·5	14·5	1·5	13·0	−1·5	13·5	0·5
Δ^{4}-3-Oxo	25·0	4·5	24·5	3·5	24·0	−2·5	24·0	−4·0
$\Delta^{4,6}$-3-Oxo	21·5	7·5	21·5	5·5	18·5	−7·0	22·5	3·0
$\Delta^{1,4,6}$-3-Oxo	25·5	9·0	24·5	5·5	20·0	−8·5	24·5	3·5
$\Delta^{4,7}$-3-Oxo	24·5	−2·5	7·5	−0·5	21·0	−18·5	20·5	−17·0
3β-OAc-$\Delta^{5,7}$	11·0	−1·0	−10·5	−1·0	9·5	−14·0	21·5	−13·0
17-Oxo	1·0	10·0	−2·5	10·0	1·0	11·0	1·0	10·0
17β-OH	0	2·0	−3·0	2·0	−1·0	2·0	−1·0	2·0
17β-C_9H_{17}	−1·0	−2·0	−1·0	−2·0	−1·5	−2·0	−0·5	−2·0
17β-CHMeCHO	−1·0	0·5	−1·0	0	−1·0	0·5	0	0·5
17β-CMe:$CHNC_5H_{10}$	−1·5	−10·5	−1·0	−10·5	−1·5	−11·5	−1·0	−9·5
17β-Ac	−0·5	−5·0	1·5	−5·5	0	−6·0	0	−6·0
17:CMeCHO (*trans*)	0·5	15·0	−1·5	15·0	0·5	15·0	1·5	15·0
17:CMeCHO(*cis*)	0·5	22·0	−1·5	22·5	0·5	22·5	1·5	22·5
17β-Et	−0·5	−8·5	−0·5	−8·5	..	..	..	..

[a] A positive value denotes a downfield shift caused by a substituent. (From Halkes and Havinga.[17])

TABLE III

Substituent increments (in Hz) for the chemical shift of the 10-methyl protons of 5α-cholestane in $CDCl_3$ solution at 60 M Hz[a]

Substituents	10-Methyl, Hz
5α-Cholestane	46·5
1α-OH	0·5
1α-OH-Δ^2	2·0
1α-OAc-Δ^2	0·5
1-Oxo	22·2
1-Oxo (5β)	12·8
1-Oxo-Δ^2	16·9
1,1-Ethylenedithio	24·3
1,1-Ethylenedithio (5β)	26·0
3β-OAc	2·6
3-Oxo	14·1
3-Oxo-Δ^1	14·0
3-Oxo-1α,2α-epoxy	8·0
3-Oxo-Δ^4	23·8
3-Oxo-4α,5α-epoxy	16·5
3-Oxo-4β,5β-epoxy	22·6
Δ^3-5β-OH	11·0
Δ^3-5α-OH	7·5
4,4-Ethylenedithio	9·3
4α,5α-Epoxy	16·5
Δ^4	14·0
4α-OH	0·5
4α-OH-Δ^5	11·8
4α-OAc-Δ^5	15·5
4β-OH-Δ^5	25·5
4β-OAc-Δ^5	21·2
4-Oxo (5β)	11·5
4-Oxo	−2·4
4-Oxo-Δ^5	11·3
4-Oxo-5α-OH	1·6
4-Oxo-5α,6α-epoxy	12·9
4-Oxo-5β-6β-epoxy	13·6
5α-OH	10·5
Δ^5	13·4
5β-OH	−1·3
5α,6α-Epoxy	15·2
6α-OH	0·5
6α-OAc-Δ^4	16·3
6α-OH-Δ^4	13·1
6β-OH-Δ^4	26·0
6β-OAc-Δ^4	18·5
6β-OMe-Δ^4	19·5

TABLE III—*continued*

Substituents	10-Methyl, Hz
6-Oxo-Δ^4	11·5
6-Oxo-4α,5α-epoxy	12·4
6-Oxo-4β,5β-epoxy	13·8
Secondary Contributions	
1β-OH (5β)	3·4
1β-OAc (5β)	3·5 or 8·8
2α-Br	4·8
3β-Cl	2·1
4β-Br	24·4
4α-OAc	1·6
4α-OAc (5β-OH)	2·7
4β-OAc	10·9
4β-OAc (5β-OH)	3·8
4β-OH (5β-OH)	2·3
4β-OMe (6β-OH)	11·0
6β-OMe	7·0
6β-OMe (4β-OH)	10·9
6β-OAc	9·6
6β-OH	12·0
6β-OH (5β-OH)	6·9
6β-Br (4β-OAc)	24·1
6β-Br (4α-OAc)	20·4

[a] A positive value denotes a downfield shift caused by a substituent. (From Lavie, Greenfield, Kashman and Glotter.[21])

The effect of sulphur-containing substituents in ring A on the chemical shifts of the angular methyl protons of 5α-steroids has been evaluated by Tori and Komeno,[22] who showed that, in general, the behaviour of a mercapto and an acetylthiol group is similar to that of a hydroxyl and an acetoxyl group, respectively. Introduction of 2β-sulphur and 4β-sulphur atoms causes distortion of ring A and leads to discrepancies in the additivity rules for the 10-methyl protons.[22] The effect of 5α-azido-, 5α-amino- and 5α,6α-imino- groups on the angular methyl protons has been examined by Snatzke and Veithen.[23]

Pivnitsky and Torgov[24] have listed the 13-methyl proton shifts for a series of 19-nor-, 3-oxo-4,9-diene- and D-homo-androstanes. The chemical shifts given in Table IV show that in the presence of a 5(10)-double bond, ring A substituents, such as 1,3-diene, 2-ene, 3-methoxyl and 3-oxo groups, do not displace the 13-methyl protons; the 13-methyl proton shifts for 19-nor-D-homo-androstanes can be calculated.

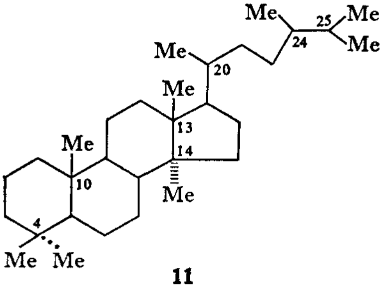
TABLE IV

Substituent increments (in Hz) for the chemical shift of the 13-methyl protons of 5α,14α-D-homoandrostane in $CDCl_3$ solution at 60 M Hz[a]

Substituents	13-Methyl, Hz
5α,14α-D-Homoandrostane	44·5
19-Nor	0
D-Homo	3
3-MeO-$\Delta^{1,3,5(10)}$	2
3-MeO-$\Delta^{2,5(10)}$	2
3-Oxo-$\Delta^{5(10)}$	2
3-Oxo-$\Delta^{4,9}$	9·5
17*a*-Oxo (D-homo series)	21
17*a*β-HO (D-homo series)	3

[a] A positive value denotes a downfield shift caused by a substituent. (From Pivnitsky and Torgov.[24])

Zürcher's additivity rules have been extended to 4,4-dimethyl-14α- and 4,4-dimethyl-14β-androstanes[25] and to steroids of the lanostane series.[26] Cohen, Rosenthal, Krakower and Fried[26] showed that the additivity principle for the chemical shifts of the angular methyl protons holds satisfactorily for eleven nuclear substituents and for eighteen different side-chains and that the contributions of functional groups in "equivalent positions" are in reasonable agreement. The chemical shifts of the methyl protons of lanostane derivatives,[27] 4,4-dimethyl-cholestane derivatives[28] and 4,4-dimethyl-5α- and 4,4-dimethyl-5β-androstan-6-ones[29] have also been discussed.



11

The eburicane (24-methyl-lanostane; **11**) skeleton possesses nine methyl groups, compared with two or three such groups in androstanes and pregnanes, respectively. The problem of assigning the appropriate chemical shifts to the various methyl groups, many of them in similar environments and giving rise to overlapping signals, was solved by analysing the spectra of relatively simple derivatives containing only the nuclear methyl groups and making assignments for the 10-methyl and 13-methyl protons. The signal for the 14-methyl group was then assigned and, from a study of the derivation of the 4,4,14α-trimethyl-androstane series, assignments for the 4α-methyl and 4β-methyl protons were made. Finally, compounds having the various side-chains were analysed until a consistent set of assignments were obtained.[26]

The chemical shifts for the methyl protons of a wide range of natural triterpenes[30,31] and their derivatives, including betulin,[32,33] cucurbitacin,[34] dammarane,[33] euphane, isoeuphane, hopane,[33] glycyrrhetic acids,[35] lupane,[33] lupan-1,3-dione,[36] oleanenes,[37–40] ursene,[41] pentacyclic triterpene hydrocarbons[42] and triterpenes of the ursane, oleanane and lupane series[43] with oxygen functions at carbon-2, -3 and -23, have been reported. Similar results for steroidal sapogenins (spirostans, cf. Table V)[44] and card-20(22)-enolides,[45] derived from cardiac glycosides, have been recorded and will be discussed in Section VI.

Most NMR measurements on steroids have been conducted on solutions in deuterochloroform, but an increasing amount of work is done on solutions in other solvents. This is particularly necessary for corticosteroids, which are often insufficiently soluble in deuterochloroform. Hampel and Krämer examined the spectra of seventy corticosteroids in deuterochloroform and hexadeutero-dimethyl sulphoxide[6] and of over one hundred steroids in deuterochloroform and pentadeutero-pyridine solution[7] and reported the effect of solvent change on 10-methyl, 13-methyl and other methyl protons, on olefinic protons and on protons geminal to hydroxyl groups. The positions of the angular methyl peaks for certain steroids do not shift appreciably in going from deuterochloroform to heptadeutero-dimethyl formamide solution,[46] but show big changes in going from either carbon tetrachloride or deuterochloroform to hexadeutero-dimethyl sulphoxide,[46] pyridine or benzene solution.[8]

Tori and Kondo[47] examined the NMR spectra of a range of hydroxy- and acetoxy-3-oxo-Δ^4-steroids in deuterochloroform and pyridine solution and used the chemical shift values of the angular methyl protons to elucidate the structure of microbiological hydroxylation products of 17α-21-dihydroxy-pregn-4-ene-3,20-dione (**12**; $R^1 = R^2 = OH$) and progesterone (**12**; $R^1 = R^2 = H$). The results for pyridine solutions were important in this study since hydroxy-steroids are frequently sparingly soluble in deuterochloroform and, moreover, the larger shift values for angular methyl protons induced by a hydroxyl substituent provide better evidence for the position of the hydroxyl group. The authors listed the effects of 1-, 2-, 6-, 7-, 8-,

TABLE V

Substituent increments (in p.p.m.) for the chemical shift of the 10-methyl and 13-methyl protons of steroids in deuterochloroform and pyridine solution[a]

Substituent	10-Methyl		13-Methyl	
	$CDCl_3$	Pyridine	$CDCl_3$	Pyridine
5α-14α-Androstane	0·79	0·76	0·69	0·68
5β-14α-Androstane	0·92	0·91	0·69	0·67
5α,25*R*-Spirostan	0·79	0·77	0·77	0·86
5β-25*R*-Spirostan	0·92	0·92	0·76	0·85
1α-OH (5α)	0·02		0·02	
(5β)	0·21	0·37	0·01	0·04
(Δ^4-3-oxo)	0·02		−0·01	
1β-OH (5α)	0·05		0·01	
(5β)	0·15	0·34	0·01	0·00
(Δ^4-3-oxo)	0·03	0·33	−0·01	0·05
2α-OH (5α)	0·04	0·02	−0·01	0·01
(5β)	0·00	0·02	0·00	−0·01
(Δ^4-3-oxo)	0·11	0·13	0·00	0·00
2β-OH (5α)	0·25		0·01	
(5β)	0·03	0·04	−0·01	−0·01
(Δ^4-3-oxo)	0·01	0·14	0·03	0·00
3α-OH (5α)	0·01	0·03	0·01	0·01
(5β)	0·01	0·01	0·01	−0·01
3β-OH (5α)	0·03	0·05	0·00	−0·01
(5β)	0·05	0·09	0·00	0·01
(Δ^4)	0·04	0·04	0·00	0·00
(Δ^5)	0·01	0·03	0·00	0·00
4α-OH (5α)	0·00		0·00	
(5β)	0·01		0·01	
4β-OH (5α)	0·27		0·01	
5α-OH	0·18		0·01	
(3-oxo)	0·17		0·00	
(6-oxo)	0·06		0·01	
5β-OH	0·08	0·25	0·00	0·01
6α-OH (5α)	0·01	0·03	−0·01	0·04
(5β,Δ^4)	−0·01	0·06	0·01	0·00
6β-OH (5α)	0·23	0·55	0·04	0·04
(5β,Δ^4)	0·19	0·49	0·04	0·06
7α-OH (5β,Δ^4)	−0·01	0·09	−0·01	0·06
(Δ^5)	0·00	0·01	−0·01	0·02
7β-OH (5β,Δ^4)	0·03	0·01	0·04	0·02
8β-OH (5α)	0·16	0·42	0·28	0·53
(Δ^4)	0·16	0·42	0·26	0·52
(14β)	0·18		0·18	
9α-OH (Δ^4)	0·15	0·23	0·01	0·08
10β-OH (Δ^4)	. .	. .	0·04	0·06

TABLE V—*continued*

Substituent	10-Methyl		13-Methyl	
	$CDCl_3$	Pyridine	$CDCl_3$	Pyridine
11α-OH (5α,Δ^4)	0·12	0·29	0·03	0·07
(5β)	0·14	0·26	0·01	0·06
($\Delta^{1,4}$-3-oxo)	0·18		0·02	
11β-OH (5α,5β)	0·26	0·53	0·24	0·49
(Δ^4)	0·26	0·57	0·25	0·51
($\Delta^{1,4}$-3-oxo)	0·23		0·21	
12α-OH	−0·04	0·03	−0·01	0·12
12β-OH	0·01	0·01	−0·02	0·21
14α-OH	0·00	0·06	0·12	0·23
14β-OH	0·02		−0·03	
(15-oxo)	0·01		−0·09	
15α-OH (14α)	0·01		0·03	
(14β)	0·00		−0·03	
15β-OH (14α)	0·03	0·07	0·27	0·45
16α-OH (14α)	−0·01		0·02	
17α-OH (14α)	−0·01	0·02	0·06	0·00
17β-OH (14α)	0·00	0·04	0·03	0·20
(14β)	0·01		0·03	
18-OH	−0·01	0·00	..	..
19-OH	..		0·01	
1α-OAc (5α)	0·06	0·05	−0·03	−0·06
(5β)	0·05	0·09	0·00	0·01
(Δ^4-3-oxo)	0·07		0·00	
1β-OAc (5α)	0·15	0·20	−0·02	0·00
(5β)	0·00	0·05	0·01	−0·03
2α-OAc (5α)	0·09	0·07	−0·02	−0·05
(5β)	0·01	−0·01	0·00	0·00
(Δ^4-3-oxo)	0·13	0·13	0·00	0·00
2β-OAc (5α)	0·15		0·00	
(5β)	0·07	0·01	0·00	−0·02
(Δ^4-3-oxo)	0·01	0·06	0·01	0·01
3α-OAc (5α)	0·03	−0·02	0·02	0·00
(5β)	−0·01	−0·02	0·00	−0·01
(Δ^4)	−0·02		0·01	
3β-OAc (5α)	0·05	−0·02	0·00	0·00
(5β)	0·06	0·04	0·01	0·01
(Δ^4)	0·04	0·01	0·01	0·00
(Δ^5)	0·02	−0·02	0·00	0·00
4β-OAc (5α)	0·23		0·00	
(5β)	0·08	0·01	0·00	0·00
5α-OAc	0·20		0·00	
6α-OAc (5α)	0·08		0·00	
(5β,Δ^4)	0·04		0·01	
6β-OAc (5α)	0·18		0·04	
(5β,Δ^4)	0·09	0·22	0·05	0·04

TABLE V—*continued*

Substituent	10-Methyl		13-Methyl	
	CDCl$_3$	Pyridine	CDCl$_3$	Pyridine
7α-OAc (5α)	0·08		0·00	
(5β,Δ^{4})	0·01	−0·03	0·00	0·00
7β-OAc (5β,Δ^{4})	0·05	0·01	0·05	0·03
11α-OAc (5α,Δ^{4})	0·09	0·13	0·06	0·07
(5β)	0·11	0·11	0·04	0·04
($\Delta^{1,4}$-3-oxo)	0·06		0·06	
11β-OAc (5α,5β)	0·07	0·07	0·12	0·14
($\Delta^{1,4}$-3-oxo)	0·05			
12α-OAc	−0·01	−0·02	0·08	0·07
12β-OAc	0·02	−0·02	0·09	0·11
15α-OAc (14α)	0·00		0·07	
15β-OAc (14α)	0·04	0·02	0·23	0·23
16α-OAc (14α)	0·00		0·04	
17α-OAc (14α)	0·01	0·00	0·01	0·00
17β-OAc (14α)	0·00	−0·01	0·08	0·14
18-OAc	0·01	0·02	..	..
1-Oxo (5α)	0·38		0·02	
(5β)	0·22	0·33	0·00	−0·03
Δ^{1} (5α)	0·05		0·02	
(5β)	0·18		−0·02	
Δ^{1}-3-Oxo (5α)	0·25		0·05	
$\Delta^{1,4}$-3-Oxo	0·46	0·32	0·10	0·02
$\Delta^{1,4,6}$-3-Oxo	0·43		0·15	
2-Oxo (5α)	−0·03	−0·08	0·01	−0·06
(5β)	0·15	0·05	0·00	−0·05
Δ^{2} (5α)	−0·02	0·00	0·00	0·00
(5β)	0·05	0·02	0·01	0·00
3-Oxo (5α)	0·24	0·13	0·01	−0·02
(5β)	0·12	0·02	0·04	0·01
Δ^{4}-3-Oxo	0·42	0·27	0·06	0·02
$\Delta^{3,5}$	0·20		0·06	
$\Delta^{3,5}$-7-Oxo	0·37		0·08	
3α-CN (5α)	0·02		0·00	
3β-CN (5β)	0·05		0·00	
4-Oxo (5α)	−0·03		0·02	
(5β)	0·20		0·00	
Δ^{4}	0·25	0·20	0·03	0·02
$\Delta^{4,6}$-3-Oxo	0·33	0·25	0·11	0·02
Δ^{5}	0·23	0·23	0·03	0·00
$\Delta^{5,7}$	0·14		−0·03	
Δ^{5}-7-Oxo	0·39		0·04	
$\Delta^{5(10)}$	..		0·03	
5α-CN	0·15		0·01	
(3-oxo)	0·13		0·00	
6-Oxo	−0·05	−0·01	0·02	−0·01

TABLE V—*continued*

Substituent	10-Methyl		13-Methyl	
	$CDCl_3$	Pyridine	$CDCl_3$	Pyridine
Δ^{6}	−0·03		0·05	
6β-CN	0·33		0·05	
7-Oxo	0·28	0·24	0·01	0·03
Δ^{7}	−0·01		−0·12	
$\Delta^{7,9}$	0·09		−0·15	
$\Delta^{8(9)}$	0·13		−0·08	
$\Delta^{8(14)}$	−0·12		0·18	
$\Delta^{8(9)}$-11-Oxo	0·28		0·03	
8β-CN	0·37		0·38	
$\Delta^{9(11)}$ (5α)	0·14	0·16	−0·07	−0·03
(5β)	0·12	0·12	−0·07	−0·03
$\Delta^{9(11)}$-12-Oxo	0·27	0·18	0·27	0·19
11-Oxo	0·22	0·38	−0·05	−0·03
Δ^{11}	−0·03		0·08	
12-Oxo	0·10	0·03	0·28	0·25
Δ^{14}	0·01		0·25	
15-Oxo (14α)	0·01		0·08	
(14β)	−0·04		0·19	
16-Oxo (14α)	0·02		0·19	
Δ^{16} (14α)	0·03		0·07	
Δ^{16}-17-Ac (14α)	0·02		0·18	
16α-CN (14α)	−0·03		−0·07	
16α-C≡CH (14α)	−0·02		−0·03	
17-Oxo (14α)	0·02	−0·01	0·17	0·10
(14β)	0·02		0·08	
17α-Ac (14α)	0·01		0·20	
(14β)	−0·04		0·25	
17β-Ac (14α)	−0·01		−0·08	
(14β)	0·03		−0·03	
2α,3α-Epoxy (5α)	−0·01	−0·08	0·00	−0·02
6α-Me (Δ^{4})	0·00	0·00	0·00	0·00
23*a*-Br (spirostan)	0·00		0·08	
23*b*-Br (spirostan)	0·00		0·01	
Δ^{24} (spirostan)	0·00		0·00	
$\Delta^{25(26)}$ (spirostan)	0·00		0·00	
$\Delta^{25(27)}$ (spirostan)	0·00	0·00	0·02	0·02
25α-OH (spirostan)	0·00	0·00	0·00	0·00
25β-OH (spirostan)	0·00	0·00	0·00	0·00
27-OH (spirostan)	0·00	0·00	0·02	0·03
27-OAc (spirostan)	0·00	0·00	0·00	0·00
Spirostan side chain	0·00	0·01	0·08	0·18

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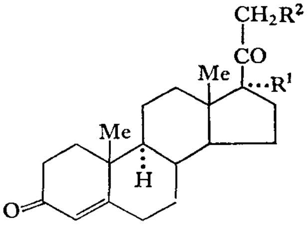
[a] A positive value denotes a downfield shift caused by a substituent. (From Tori and Aono.[44])



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9-, 10-, 11-, 12-, 14-, 15-, 16-, 17-, 18- and 19-hydroxyls and -acetoxyls on the chemical shifts of 10-methyl, 13-methyl and 4-protons; their values for the substituent increments for 10-methyl and 13-methyl protons are included in Table V.

There have been extensions of Zürcher's additivity rules to measurements in solvents other than deuterochloroform. Fétizon and Gramain confirmed the additivity of increment values for the 10-methyl and 13-methyl protons of 5α,10β,13β-, 5α,10α,13β- and 5α,10β,13α-androstanes, containing oxo, hydroxyl, acetoxyl, bromo and methyl substituents,[48,49] and of substituted 5α-androstanes, 4,4-dimethyl-5α,14α-androstanes and 4,4-dimethyl-5α,14β-androstanes in carbon tetrachloride, deuterochloroform, benzene and pyridine solution.[50] The increment values for the angular methyl groups for twenty-five functional groups for steroids dissolved in the four solvents are listed in Table VI.

Recently, Severini Ricca and Russo[51] have discussed the effect of an 11-oxo-group, and of a solvent change from deuterochloroform to pentadeuteropyridine, on the methyl proton signals of the pentacyclic triterpene, olean-12-ene. Wilson and Williams[52] found that in derivatives of the triterpenes, oleanene and lupane, only methyl protons that are close to a polar group show appreciable benzene solvent shifts. In the compounds examined an axial proton, on the same carbon atom as an equatorial acetate group, shows a characteristic downfield shift in benzene. In contrast, an equatorial proton geminal to the oxygen atom of a γ-lactone bridge undergoes an upfield shift in benzene. In general protons that lie in regions of high electron density tend to be deshielded by benzene.

The line-widths at half-height of the NMR signals assigned to tertiary methyl groups are appreciably broadened by the presence of one or more protons at the end of four-bond coupling paths, which can take up configurations favourable to long-range proton spin–spin couplings.[53,54] Thus, in 2-oxosteroids coupling between the axial 1α-proton and the 10-methyl protons and in 11-oxosteroids coupling between the axial 12α-proton and the 13-methyl protons causes broadening of the 10-methyl and 13-methyl signals, respectively. The experimental reliability of line-width measurements

TABLE VI

Substituent increments (in Hz) for the chemical shift of the 10-methyl and 13-methyl protons of 5α-androstane in CCl_4, $CDCl_3$, C_6H_6 and C_5H_5N solution at 60 M Hz[a]

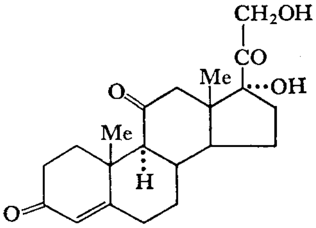
Substituent	CCl_4		$CDCl_3$		C_6H_6		C_5H_5N	
	10-Me	13-Me	10-Me	13-Me	10-Me	13-Me	10-Me	13-Me
5α-Androstane	47·6	41·9	47·6	41·9	47·2	42·9	46·2	41·2
2-Oxo	−3	0	−2·5	−0·5	−12·5	−6·5	−5·5	−3·5
3β-OH	1	0	1·5	0	−4	−1	3·5	0·5
3β-OAc	2	0	2	0	−5·5	−1·5	−0·5	−0·5
3β-OBu^t	1	1	0	−1	−2·5	−1	−1	−0·5
3-Oxo	14	2	14	2	−7·5	−2·5	9	0·5
3-Oxo-Δ^4	24	4	24·5	4	0	−3·6	16·5	1
Δ^5	12	2	12·5	1·5	14·5	0·5	14	0·5
Δ^5(4,4-Dimethyl)	13·5	2·5	14·5	2	16	1	16	1·5
4,4-Dimethyl	4	−1	4·5	−0·5	5	0	5	0
4,4-Dimethyl (Δ^5)	5	−0·5	5	−0·5	7·5	0·5	7	1
4,4-Dimethyl-Δ^5	17·5	1·5	18	1	21·5	1	21	1
3-Oxo-4,4-dimethyl-Δ^5	5	3	5	2·5	−2	−3	4·5	0·5
7-Oxo	15·5	−0·5	15·5	0	−2	−5	11	−1·5
7-Oxo-Δ^5	24	3	23·5	3	6	−2	19·5	2
$\Delta^{8(14)}$	−6·5	10·5	−7	9·5	−3·5	10	−5·5	9·5
Δ^{14}	3	19	2	19	−0·5	21	−0·5	20·5
16α-Br	−1	4	−1	1·5	−5·5	−10·5	−2	−1
16-Oxo	2	11·5	2	11·5	−5·5	−7	−0·5	4·5
17β-Et	−0·5	−9	0	−8·5	0	−8	0	−7·5
17β-OH	0	−0·5	0·5	2·5	−2		1·5	17·5
17β-OMe	0	−0·5	0·5	3·5	−1	10·5	0	8·5
17-Oxo	1	7	1·5	10	−6	−4	−1	7
17,17-Ethylenedioxy	−0·5	5	−0·5	8·5	0	16	−0·5	15
17,17-Ethylenedioxy-Δ^5	2·5	9·5	2	13·5	−0·5	27	1	24

[a] A positive value denotes a downfield shift caused by a substituent. (From Fétizon, Golfier and Gramain.[50])

at half-height has been evaluated and the utility of such measurements as a stereochemical tool established.[55–57] The line-width of the 10-methyl signal for a steroid gives information on the stereochemistry of the A/B-ring junction; the width of the 10-methyl peak at half-height for *trans*-fused rings is larger than is that for *cis*-fused rings.[57]

Shoppee and his colleagues[58] have shown that the difference between the line-width at half-height of the signal investigated and that of the tetramethylsilane, present in the same solution as internal standard, provides a more reliable basis for measurement than does line-width itself. Nevertheless, because of the presence of secondary, non-steric, factors in determining the line-widths of tertiary methyl groups, small, but still appreciable, long-range interactions between protons in "non-W configuration", the presence of special effects in strained systems, the limited accuracy of experimental measurements and second-order effects, such as virtual coupling, special care is needed in the interpretation of line-width measurements.[58] Whenever possible, spin-decoupling experiments and measurements on deuterium-labelled analogues should be undertaken. Lacoume[59] has, by spin-decoupling and deuterium-labelling, demonstrated long-range coupling over four bonds between the axial 1α- and the axial 3α-protons of 3β-substituted 2-oxo-triterpenes and of 3β-substituted 4,4-dimethyl-2-oxo-5α-steroids.

The NMR spectra of 1α-methyl derivatives of compounds related to cortisone (**13**)[60] and of epimeric pairs of 1-methyl-3-oxo-steroids with *cis* and *trans* fused A/B-rings have been reported.[61]



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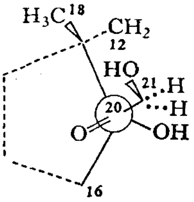
Cross and Beard[62] have pointed out that, because of possible conformational changes in ring D, the assignment of stereochemistry in 16,17-disubstituted steroids on the basis of 13-methyl proton-resonance frequency shifts must be approached with caution. The introduction of a 16β-methyl group can lead to changes in the conformation of ring D and in the orientation of a 17β-acetyl side-chain. In 17-oxo-steroids and in pregnan-20-ones, 16β-methyl protons resonate at a lower magnetic field than do the corresponding 16α-methyl protons;[62,63] in androstan-17β-ols, the situation is reversed.[62]

B. Methylene groups

Cookson, Crabb, Frankel and Hudec[64] have reviewed the factors that influence the geminal spin–spin coupling constants of methylene groups and have listed the different structural types of methylene groups that appear in polycyclic compounds, such as steroids. The value of the coupling constant is sensitive to the conformation of adjacent groups and to strain in adjacent bonds. The behaviour of the geminal 12-protons of 11-oxo-steroids is discussed in Section IVB.

Recently, NMR has been used in conjunction with infrared spectroscopy to deduce the conformation of the side-chain of cortisone (**13**) and related compounds.[65] The decrease in the geminal coupling constants of the 21-protons with increase in the van der Waal's radius of the 21-substituent[66] suggests a preference for the arrangement in which the 21-substituent is approximately eclipsed with the 20-carbonyl group and the ketone group lying over ring D. The dominant conformation of the cortisone side-chain is shown in (**14**).[65]



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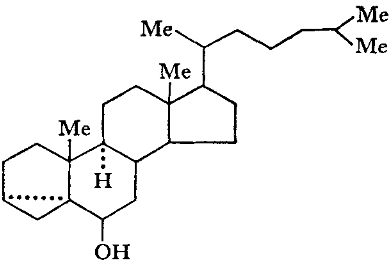
The methylene protons of a cyclopropyl group show a characteristic geminal coupling constant (–4 to –6 Hz) and usually appear at high magnetic field.[64,67] The spectra of various 6-substituted 3α,5-cyclo-5α-cholestanes (e.g., 3α,5-cyclo-5α-cholestan-6β-ol; **15**),[68] 3β,5-cyclo-5β-steroids,[69] 7-methyl-6-oxo-3α,5-cyclo-5α-steroids,[70] 1α,2α-methylene-steroids, 1β,2β-



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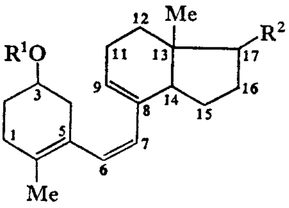
methylene-steroids[71] and 1α,2α:6β,7β-dimethylene-3-oxo-steroids have been described.[72]

C. Olefinic groups

The NMR resonances of protons directly attached to an olefinic double bond in a steroid[73] have been investigated systematically by Cragg, Davey, Hall, Meakins, Richards and Whateley,[74] who recorded the spectra of a series of steroidal mono-olefins free from oxygenated substituents; the series included representatives of all possible endocyclic olefins except the 15-ene isomer. The chemical shift values and coupling constants for the olefinic protons together with the chemical shift values for the angular methyl protons were listed.

NMR spectroscopy has been used to confirm that precalciferol (**16**) and tachysterol (**17**) are *cis* and *trans* isomers, respectively, about the 6(7)-double bond. An *s-trans* configuration is suggested for calciferol (**18**) and a 5(6)-*s-trans*-7(8)-*s-cis* structure for tachysterol (**17**) in deuterochloroform solution.[75] The structure of 25-hydroxy-cholecalciferol, a biologically-active metabolite of cholecalciferol (vitamin D_3; **18**; $R^1 = H$, $R^2 = C_8H_{17}$), has been established.[76]



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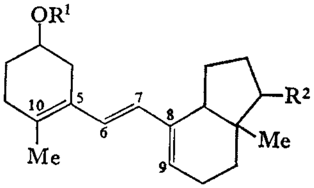

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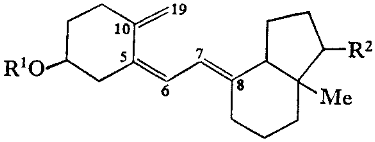

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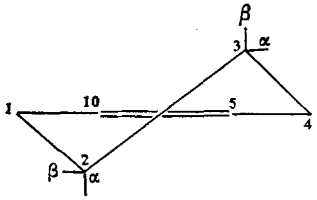
The conformation of steroidal cyclohexene rings has been deduced by NMR.[24,77–79] An unusual type of conformational preference operates in ring A of 3-hydroxy- and 3-azo-oestr-5(10)-enes. It is evident from the spectra of epimeric pairs that the 3α- and 3β- valence bonds are equatorial and axial, respectively, and it is concluded that of the three possible conformational modifications of ring A, (**19**), (**20**) and (**21**), the half-chair conformation (**19**) is preferred;[80,81] the conformational preference of ring A in ring B aromatic steroids, such as neoergosterol, has likewise been studied.[82] Epimeric 16-hydroxy-[83] and epimeric 16-halogeno-pregn-17(20)-enes[84] can be distinguished by NMR.



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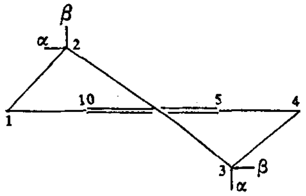

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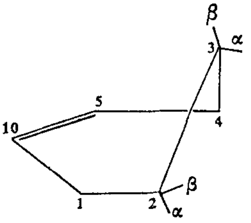

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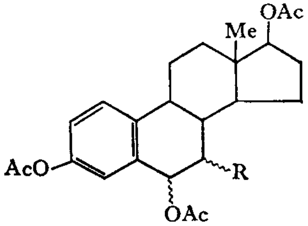
The stability of isolated double bonds in steroids[85] and addition reactions of steroid polyenes, such as the reaction of 7-dehydrocholesteryl acetate with dimethylacetylene dicarboxylate[86] and reactions of the cholesta-5,7,9(11)-triene system,[87] have been studied by NMR. Such measurements[88] have led to revised structures for four maleic anhydride adducts of ergosteryl acetate. One adduct is a normal Diels–Alder product of *endo* configuration, in which dienophilic addition has occurred from the α-side. The other three adducts are formed by an addition–abstraction process, i.e., with addition at carbon-7 and concomitant abstraction of either the 9α- or the 14α-proton to give 7α-succinic anhydride derivatives of 3β-acetoxyergosta-5,8(9),22-triene and 3β-acetoxyergosta-5,8(14),22-triene. The structures of photochemical addition products of ethylene and maleic anhydride to 17β-acetoxy-androsta-4,6-dien-3-one have been established.[89]

An attempt has been made to calculate the chemical shift produced by the introduction of a double bond into a steroid.[90] The McConnell equation[91] was modified to include examples where the distance between the shielding group and the proton observed is small compared to the length of the induced dipole. The principle was established that, in calculating the chemical shift produced by the introduction of a substituent into a molecule, the screening effect of all bonds displaced must be considered as well as that of all bonds introduced. The shift for any distant nucleus in proceeding from an alkane to the corresponding alkene comprises the algebraic sum of the screening constants for the displaced carbon–carbon and carbon–hydrogen bonds and the introduced carbon–carbon double bond and olefinic carbon–hydrogen bonds. In only a minority of the examples considered was the contribution of the double bond to the total shift clearly predominant.

D. Aromatic groups

The substitution pattern of an aromatic steroid is readily identified by NMR spectroscopy;[92] recent work has been directed to an understanding of the conformation of steroids containing aromatic rings.[82]

An NMR study of 6-acetoxy- (**22**; R = H), 6-acetoxy-7-bromo- (**22**; R = Br) and 6,7-diacetoxy-oestra-1,3,5(10)-triene-3,17β-diyl diacetate (**22**; R = AcO) has shown that ring B in fully-acetylated compounds, either unsubstituted at carbon-7 or bearing a 7α-substituent, is in the half-chair form, while that in 7β-acetoxy- analogues assumes a more planar conformation intermediate between half-chair and boat.[93]



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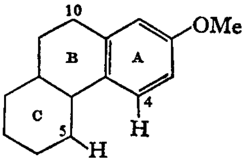
An investigation[94,95] of the steric effect of deshielding of the aromatic 4-proton by a 5-proton in an octahydrophenanthrene (**23**) provided an explanation of the steric compression between the 1-proton and the 11α-proton and, hence, of the greater deshielding of 1- than of 4-protons in simple oestrone derivatives. Fishman and Liang[96] examined the spectra of oestrogen catechol derivatives in deuterochloroform and dimethyl sulphoxide solution and, from the chemical shifts of the aromatic protons, they were able to assign structures to isomeric monomethoxy- and monoacetoxy-derivatives of the oestrogen catechols. The results were used in studies of



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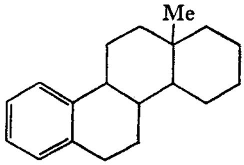
the metabolism of oestrone[96] and of 3,15β,16α,17β-tetra-acetoxy-oestra-1,3,5(10)-triene[97] and to identify the isomeric aryl monosulphates of oestrogen catechols.[98] NMR spectroscopy has helped to establish the structures of the products from the microbiological hydroxylation of oestrone derivatives.[99]

E. Homo, rearranged and abnormal steroids

D-Homo-steroids give characteristic NMR spectra.[100] Pivnitsky and Torgov[24] have reported the 13-methyl proton shifts for certain 19-nor-, 4,9-diene-3-oxo- and 5α,14α-D-homo-androstanes (see Table IV). The effect of 3- and 17*a*-substituents and of 8(9)-, 8(14)-, 9(11)- and 14-double bonds on the 13-methyl protons of D-homooestra-1,3,5(10)-triene (**24**) and of 19-nor-D-homoandrost-4-en-3-one[101] and the behaviour of 17*a*β-hydroxy-17α-methyl-D-homoandrostane derivatives have been discussed.[102]



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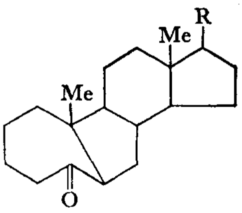
NMR spectroscopy has been employed to assign the preferred conformations of the seven-membered rings in A-homo-B-nor- (e.g., **25**) and A-nor-B-homo-steroids (e.g., **26**)[103] and to help elucidate the structures of 5β-methyl-19-nor-steroids,[104] of 3β-acetoxy-4*a*α-hydroxy-5β-methyl-A-homo-B-nor-steroids and their rearrangement products[105] and of oxetanes, such as 2α,5-epoxy-A-nor-5α-cholestane (**27**) and 2β,5-epoxy-A-nor-5β-cholestane.[106] The technique plays a part in studies of rearranged steroids, such as the ketobicyclo[3,1,0]hexene (**28**), which was formed by the thermal rearrangement of a ketovinyl cyclobutene.[107]



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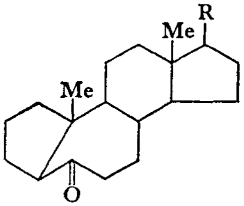

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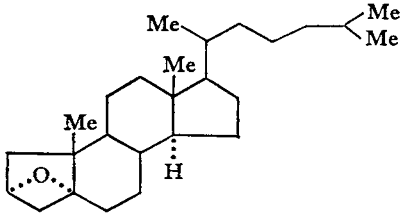
The spectra of several groups of steroids with abnormal configurations, such as 5β,8β,9β,10α- (**7**), 5β,8α,9α,10α- (**8**) and 5α,8β,9β,10β-androstanes



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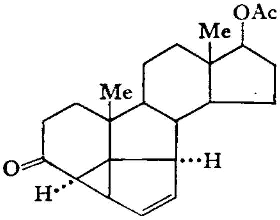

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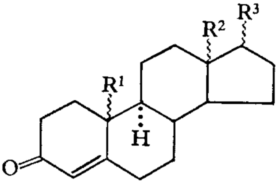
(**9**),[17] 5α,10α,13β- and 5α,10β,13α-androstanes,[48,49] 13α,17α-testosterones (**29**; $R^1 = \beta$Me, $R^2 = \alpha$Me, $R^3 = \alpha$OH),[108] 11β-acetyl-13β-ethyl-steroids,[109]



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5α,14β-androstanes,[110] 4,4-dimethyl-5α,14β-androstanes[50] and des-A-pregnanes[111] have been reported. Recently, a series of epimeric 16-deutero-5α, 13α-androstane-3β,17-diols have been examined and the conformation of ring D in 13α-sterols discussed.[112]

IV. OXYGEN- AND SULPHUR-CONTAINING GROUPS

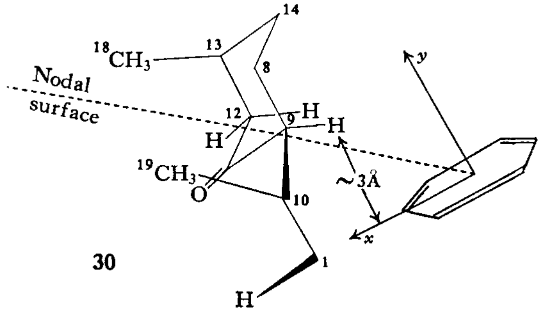
The earlier work on the resonance of protons adjacent to, or associated with, specific oxygen-[113] and sulphur-containing functions[114] has been reviewed by Bhacca and Williams. In this survey only recent developments will be considered.

A. Ketones

The position of a keto group in the steroid nucleus has a strong influence on the chemical shift of the angular methyl protons. Zürcher's original observations[12] of the effect of ketones on the angular methyl protons of steroids in deuterochloroform solution have been extended by measurements on solutions in benzene and pyridine, and Williams and Bhacca[8,115–117] have formulated empirical generalizations relating the solvent shift of the angular methyl protons (i.e., the alteration in chemical shift of the methyl protons on changing solvent) to the spatial arrangement of the methyl and ketone groups.

The solvent shifts ($\Delta = \delta_{\mathrm{CDCl_3}} - \delta_{\mathrm{C_6D_6}}$) for the angular methyl protons of oxo-steroids were attributed to the formation of 1:1 collision complexes between the carbonyl groups and benzene solvent molecules. The solvent shifts associated with 1-, 2-, 3-, 6-, 7-, 11-, 12-, 15-, 16-, 17- and 20-oxo groups were usually dominant, even in the presence of other substituents, and were approximately additive.[116] In general, the solvent shift for a proton resonance in passing from deuterochloroform to benzene solution is positive for protons lying behind a plane drawn at right angles to the carbonyl bond and passing through the carbonyl carbon atom, but will be negative for protons lying in front of this plane; protons lying approximately in the plane undergo a small or a zero solvent shift. Thus axial protons or methyl groups adjacent to a carbonyl group in a cyclohexanone system will have positive solvent shift values (+0·20 to +0·40 p.p.m.), while equatorial substituents will have small positive or negative values (+0·06 to –0·10 p.p.m.). Similar deductions have been made for solvent shifts induced by changes from carbon tetrachloride to pyridine solution.[117]

Originally, benzene was believed to form a collision complex with a ketone, in which the π-electron system of the benzene ring and the positive end of the carbonyl dipole interact in an approximately planar arrangement.[115] Calculations using the Johnson–Bovey data for the magnetic field around a benzene ring could not account, however, for the observed solvent shifts of the 12-protons of 5α-androstan-11-one and, further, steric factors that would prevent planar association, do not drastically change solvent shifts in camphor derivatives.[118] It was, therefore, postulated that the plane of the benzene ring is almost at right angles to the overall plane of the steroid molecule (see **30**).[119] The mechanism of solvent shifts has been further discussed by Ronayne and Williams.[120–123]



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Laszlo and Williams[124] have examined the effect of temperature variation on the chemical shift of proton resonances in six 5α-androstan-11-ones in toluene solution. The changes in the resonance positions of the 1β-, 12α- and 12β-protons and of the 10-methyl and 13-methyl protons of 5α-androstan-11-one in passing from carbon tetrachloride to toluene solution were accentuated on cooling to –80°C, since, with decrease in temperature, the equilibrium,

$$\text{ketone} + \text{toluene} \leftrightarrows \text{complex}$$

is driven towards complex formation. The temperature variation of the equilibrium constant, calculated in terms of a 1 : 1 complex, gave the heat of formation of the complex. The sign of the solvent shifts induced by toluene relative to carbon tetrachloride closely followed those induced by benzene relative to deuterochloroform. Similar measurements have been conducted on α,β-unsaturated oxo-steroids in deuterated toluene.[125] It is, however, now believed that in many cases the concept of a 1 : 1 solute–solvent association as an explanation of the mechanism of aromatic solvent-induced shifts is an over-simplification.[123]

The chemical shifts of the angular methyl protons for twenty-four mono-, di- and tri-oxosteroids, free from other substituents, in carbon tetrachloride, deuterochloroform, benzene and pyridine solution have been studied by Cherry, Cottrell, Meakins and Richards.[126] Benzene caused larger induced shifts than did pyridine and the solvent-shift values ($\Delta = \delta_{CCl_4} - \delta_{C_6H_6}$) of the methyl protons varied characteristically with the position of the ketone groups. With 6-oxosteroids, the solvent shift for the 13-methyl protons appeared to be greater than that for the 10-methyl protons. The solvent shifts for the 10-methyl and 13-methyl protons of 5α- and 5β-androstan-17-one and, likewise, those for the 10-methyl and 13-methyl protons of 5α- and 5β-cholestan-6-one were almost equal, suggesting that the solvent shift is independent of steric environment. The methyl resonances of di- and tri-oxo-5α-androstanes in deuterochloroform solution agreed well with values calculated from Zürcher's tables and the observed solvent shifts were close to those calculated from the shifts for the corresponding monoketones. Similar observations on 13α-androstan-3-ones and -17-ones,[48] and on 5α-androstan-2-ones, -7-ones and -16-ones[50] have been reported. Solvent shift values for the angular methyl protons of 5α- and 5β-androstan-1,6,17-triones,[127] 5α- and 5β-androstan-1-ones,[128] 1-oxo, 4-oxo-, 1,4-dioxo-[129] and 11-oxo-steroids,[130,131] 11-oxo derivatives of olean-12-ene[51] and derivatives of oleanene and lupane[52] have been discussed.

NMR spectroscopy has been used to assign the conformation of steroidal cyclohexanone rings, such as that of ring A in 4,4-dimethylcholest-5-en-3-one.[132]

B. 11-Oxo and other 11-substituents

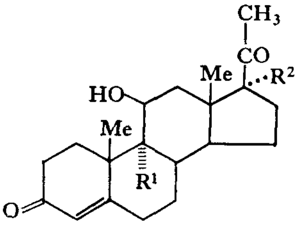
The 12-protons of simple 5α-androstan-11-ones, 5α-pregnane-11,20-diones and 11-oxo-25*R*-spirostans (11-oxo-isosapogenins) in deuterochloroform solution give rise to a two-proton singlet at δ 2·38 to 2·27[119,130–131] and the equatorial 1β-proton, which is deshielded by the 11-oxo group, gives a pair of smeared triplets centred at δ 2·45.[119,131] The singlet formed by the 12-protons is caused by the accidental coincidence of the chemical shifts of the two methylene protons; in benzene solution the signal for the 12α-proton (axial) is displaced upfield, whereas that for the 12β-proton (equatorial) is either barely moved or is displaced downfield, thus forming an AB system and giving rise to a pair of doublets (*J*, –12 to –12·5 Hz).[119,130–131] Similar, but somewhat smaller displacements of the 12-proton signals are observed in pyridine solution.[119,131]

The 12-protons of many 5α,9α- and 5α,9β-ergostan-11-ones and of 5α-pregnane-11,20-diones, substituted at either carbon-16 or carbon-21, give an AB quartet in both deuterochloroform and aromatic solvent solutions, with the 12α-proton (axial) resonating at higher magnetic field than does the corresponding 12β-proton. The geminal coupling constants of the 12-protons of a 9α- and a 9β-ergostan-11-one are about –12 and –16 to –17 Hz, respectively; the 9β-proton, which is deshielded by the 11-ketone, couples with the 8β-proton and gives rise to a doublet centred at about δ 2·87 (*J*, 8 Hz).[131] Introduction of either a 9α-methyl or a 9α-bromine substituent deshields the 12α-proton by 1,3-diaxial interaction so that in deuterochloroform solution, the 12α-proton absorbs at lower field than does the 12β-proton.[119,130]

The 12-protons of simple 17α-substituted pregnane-11,20-diones also form AB quartets in both deuterochloroform and pyridine solution, but the axial 12α-proton, which is deshielded by the pseudo-axial 17α-substituent, now absorbs at lower field than does the equatorial 12β-proton. Introduction of a 9α-halogen leads to further 1,3-diaxial deshielding of the 12α-proton, the degree of deshielding being dependent on the size of the substituent. A 9α-fluorine splits the doublets for the 12α- and 12β-protons giving rise to double doublets (*J*, –12 and 6·5 Hz and –12 and 2 Hz, respectively).[131]

The 12α-protons of 9α-halogeno-11β-hydroxy- and of 9α,11β-dihalogeno-17α-hydroxypregnan-20-ones are also deshielded more than are the corresponding 12β-protons. 9α,11β-Dichloro-17α-hydroxypregnan-20-ones show a pair of doublets in the δ 2·5 region for the 11α-proton and two pairs of doublets at higher field for the two 12-protons. The spectra of the corresponding 9α-halogeno-11β,17α-dihydroxy-steroids are similar, except that in the 9α-fluoro analogue, fluorine couples with the 11α-proton and gives rise to a pair of multiplets; the paramagnetic shift of the 12α-proton signal increases with increasing size of the 9α-halogen atom. The 10-methyl and 11α-protons are displaced to lower field, the size of the displacement being again related to the size of the 9α-halogen atom.[131]

The chemical shifts of protons α, β and γ to halogen atoms in halogenated steroids have been examined further by Lack and Ridley.[133] The chemical shifts of the 2α- (α-proton) and 3β-protons (β-proton) of 2β-halogeno-3α-hydroxy-5α-cholestane and of the 11α-proton (β-proton) of 9α-halogeno-11β-hydroxy-progesterone (**31**; R^1 = halogen, R^2 = H) correlated with electronegativity after allowing for a calculated "carbon–carbon bond shift", but the chemical shift of the 10-methyl protons (γ-proton) in the progesterone derivatives appeared to be controlled by the increasing size of the 9-halogen substituent.



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C. α,β-Unsaturated ketones

α,β-Unsaturated oxosteroids and their derivatives have been the subject of many NMR investigations; these have provided information on the conformations of rings A and B and on long-range coupling effects. NMR spectroscopy has shown that introduction of either a 2β-methyl or a 2β-acetoxyl substituent into a 19-nortestosterone (**29**; $R^1 = \beta H$, $R^2 = \beta Me$, $R^3 = \beta OH$) changes the normal half-chair conformation of ring A to a twist form;[134] the conformation of ring A in 5α- and 5β-Δ^1-3-oxo-19-norsteroids[135] and the effect of a 6-halogen atom in Δ^4-, $\Delta^{1,4}$-, $\Delta^{4,6}$- and $\Delta^{1,4,6}$-3-oxo-9β,10α-steroids have, likewise, been examined.[136]

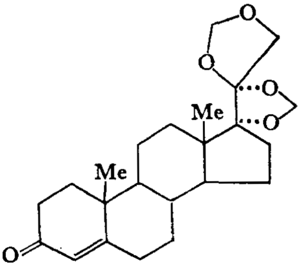
A study of 6-substituted-4-methylcholest-4-enes has revealed that in epimeric 3,3-ethylenedithio-4-methylcholest-4-en-6α- and -6β-ols, homoallylic coupling occurs between the 4-methyl protons and the 6β-proton but not between the 4-methyl protons and the 6α-proton. Similarly, the 4-methyl protons couple with the 6β-proton but not with the 6α-proton in epimeric 6-bromo- or 6-acetoxy-4-methylcholest-4-en-3-ones.[137] The 60 MHz, but not the 100 MHz, spectrum of 7,7-ethylenedithio-cholest-4-en-3-one shows virtual coupling between the 4-proton and the equatorial 6α-proton.[138]

NMR analysis of epimeric pairs of 1-methyl steroids with *cis*-fused A/B-rings and in the Δ^5-series has shown that the A-rings of 1β-methyl-3-oxo-5α- and 1β-methyl-3-oxo-Δ^4-steroids exist in the twist and in the alternative half-chair conformation, respectively.[61] Additional evidence has been obtained to show that ring B in 3-oxo-Δ^4-steroids having a 6β-substituent bulkier than, or equal in size to, chlorine is distorted because of 1,3-diaxial interaction between the 10-methyl group and the 6β-substituent.[139] There was some reservation about the original conclusion, since the values of the coupling constants between the 6α- and 7α-protons and between the 6α-and 7β-protons that led to this conclusion were obtained by a first-order approximation.[140] Measurements at 100 MHz on 6β-bromotestosterone acetate and related compounds in deuterochloroform and deuterobenzene solution confirmed that ring B is distorted.

The chemical shift of the olefinic protons of 6-substituted $\Delta^{4,6}$-3-oxo steroids depends on the size of the 6-substituent. The position of the signal for the 4-proton is approximately proportional to the magnetic shielding parameter of the 6-substituent, but that of the 7-proton depends on the mesomeric effect of the 6-substituent, moving to higher magnetic field in the presence of an electron-donating group. In the 6-ethoxy-, 6-methoxy- and 6-fluoro-analogues, in which the 7-proton signal is displaced to higher field, the 7-proton couples (*J*, 2 Hz) with the 8-proton.[141]

D. Ketals and oximes

NMR spectroscopy has been used to identify ethylenedioxy, naphthodioxan and methylenedioxy groups[142] and can distinguish between the 20*R*- (**32**) and 20*S*- epimers of 17,20:20,21-bismethylenedioxy-steroids (**33**).[143] It has been employed to assign the stereochemistry of 3-hydroxy-4-oxa-5α-cholestane and related hemiacetals[144] and to study cyclic thioketals[145] and oxetanes.[106]



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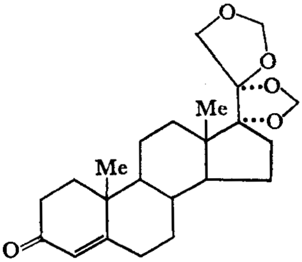

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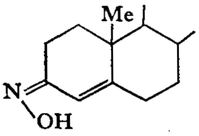
NMR spectroscopy readily distinguishes between the *syn*- (**34**) and *anti*-forms (**35**) of oximes derived from α,β-unsaturated oxo-steroids. The chemical shift of the vinylic proton is affected by the proximity of the



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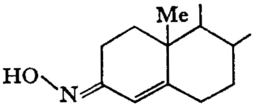

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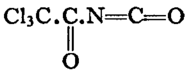
hydroxyl group of the oxime. Thus, the 3-oxime of pregn-4-ene-3,20-dione shows 4-proton peaks at δ 6·43 and 5·77, corresponding to the *syn*- (**34**) and *anti*-forms (**35**), respectively.[146–149] Using a 100 MHz spectrometer, Oka and Hara[150] have identified the peaks for methylene protons adjacent to the oximino carbon atom in the *syn*- and *anti*-forms of saturated 3-oxosteroid oximes. In the *anti*-form, the multiplet for the 2α-proton (equatorial) is deshielded to about δ 3·25 to 3·03, whereas in the *syn*-form the multiplet for the 4α-proton (equatorial) is deshielded to about δ 3·02 to 2·81. The method can be used to assign the geometrical configuration of unsymmetrical saturated oxime and *O*-methyloxime derivatives.

E. Alcohols, esters and ethers

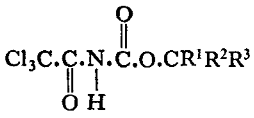
Several NMR methods are available for establishing the configuration and structural environment of a hydroxyl group.[151] In dimethyl sulphoxide solution the hydroxyl protons of primary, secondary and tertiary alcohols give clearly resolved triplets, doublets and singlets, respectively.[152] The rate of hydroxyl proton exchange, which is catalysed by traces of acid present in deuterochloroform (unless the deuterochloroform has been stored over fresh molecular sieves), is reduced sufficiently in dimethyl sulphoxide to permit observation of hydroxyl proton splitting. The characteristic changes in the chemical shift of the proton geminal to the hydroxyl group that occur on esterification[153] and on methylation[154] and in that of the ^{19}F signal that occur on esterification with trifluoroacetic acid[155] have been suggested as the basis of methods for establishing the nature of a steroid hydroxyl group.

Recently, trichloroacetyl isocyanate (**36**) has been introduced as a reagent for the NMR classification of steroid alcohols.[156] The steroid carbamate (**37**) is formed a few minutes after the addition of trichloroacetyl isocyanate to a solution of the steroid alcohol or phenol in carbon tetrachloride or deuterochloroform. Even highly hindered 11β- and 17α-hydroxyl groups form carbamates without noticeable dehydration and the resulting carbamate is often more soluble in deuterochloroform than was the original alcohol. A polyhydroxy-steroid undergoes reaction at each hydroxyl group and the carbamate imide signals appear in the δ 9 to 8 region as distinct singlets, providing a direct indication of the total number of hydroxyl groups. Information on the environment of each hydroxyl group can be obtained by



$Cl_3C.\underset{\underset{O}{\|}}{C}.N{=}C{=}O$

36



$Cl_3C.\underset{\underset{O}{\|}}{C}.\underset{\underset{H}{|}}{N}.\overset{\overset{O}{\|}}{C}.O.CR^1R^2R^3$

37

comparing NMR spectra before and after addition of trichloroacetyl isocyanate; the carbinol protons for primary and secondary alcohols are shifted downfield by 0·5 to 0·9 and 1·0 to 1·5 p.p.m., respectively.[157]

McClenaghan and Sykes[158] have used chloral alcoholates to determine the structure of sterols. Chloral, trichloroacetaldehyde, reacts rapidly at room temperature with certain hydroxy-steroids to give products which display characteristic changes in chemical shifts; the asymmetry of the chloralate gives rise to two products with the *R* and *S* configurations.

The deshielding or shielding effect on protons geminal to a hydroxyl group that occurs when the group is esterified or methylated, respectively, is well established, but the effect on neighbouring protons is less clear. Tori and Komeno[159] examined the spectra of a series of steroids with multiple hydroxyl and thiol groups in ring A and reported the effect on vicinal protons of acetylation. However, since ring A is not rigid Narayanan and Sarma[160] re-investigated the effect in the rigid ring B of 5α-hydroxy-cholestanes and of triterpene alcohols. Esterification of the axial 5α-hydroxyl group deshielded the adjacent equatorial 4α- and 6α-protons by about 1 p.p.m. and the corresponding axial 4β- and 6β-protons by about 0·1 p.p.m.; the significance of the results was discussed.

Steroids have been used as model substances in an NMR method for determining the conformation of primary hydroxyl groups in terpenoids. One of the methyls in a *gem*-dimethyl group or an angular methyl in a triterpene may be oxidized to give a primary hydroxyl group; the two protons of the resulting methylene group show different chemical shifts and a coupling constant of about −11 Hz, indicating that the protons are not freely rotating and have a preferred conformation. This conformation can be deduced by using the observation that methyl protons are deshielded by an adjacent eclipsing hydroxyl group and that in pyridine solution they are deshielded further. Thus, the most stable conformation for an axial 4β-hydroxymethylene group in a normal triterpene with a 10-methyl is that in which the hydroxyl carbon–oxygen bond nearly eclipses the equatorial 4α-methyl group.[161] Narayanan and Bhadane deduced the conformation of 4-carboxylic acids and esters and 4-aldehydes in terpenoids[162] and have examined the effect of solvent-shifts in cyclic ethers, including steroid derivatives.[163] Gaudemer, Polonsky and Wenkert[164] also studied the conformation of hydroxymethylene and acetoxymethylene substituents in triterpenes.

The solvent shifts observed for hydroxy-steroids in changing from deuterochloroform to pyridine solution have been rationalized in terms of specific solute–solvent complexes between pyridine molecules and the polar hydroxyl functions in the solute molecule. In saturated steroids, methyl protons and protons occupying positions 1,3-diaxial, vicinal or geminal to a hydroxyl group are deshielded in pyridine relative to deuterochloroform.

The extent of the deshielding provides information on both the location and the stereochemical nature of protons in the vicinity of hydroxyl functions.[47,165] Wilson, Rivett and Williams[166] have correlated benzene-induced solvent shifts with the structure of certain hydroxy- and methoxy-steroids. Protons attached to the same carbon atom as an oxygen atom exhibit positive solvent shifts (0·05 to 0·25 p.p.m.), but protons in close proximity to the lone pair electrons of an oxygen atom show negative solvent shifts.

Smith[167] (see also Tori and Kondo[47] and Table V) has tabulated the chemical shift values for the angular methyl protons and for protons geminal to hydroxyl and acetoxyl groups in a wide range of positions on the steroid nucleus and has used the information in a systematic approach to the elucidation of the structure of hydroxy-steroids formed during microbiological transformations. The technique has been employed to identify the enzymic hydroxylation products of 16,20-dioxo-steroids[168] (cf. Fishman and Liang[96] and Fishman and Guzik[97]). Recently, the structures of epimeric 3β,7ξ-diacetoxy- and 3β,7ξ-dibenzoyloxy-cholest-5-enes have been assigned on the basis of their 100 MHz spectra,[169] and the 60 MHz spectra of vicinal diacetoxy-cholestanes reported.[170]

Hydrogen-bonding in 9α-halogeno-11β-hydroxyprogesterones has been studied with a view to finding out whether the biological activity of 17α-acetoxy-9α-fluoro-11β-hydroxyprogesterone (**31**; $R^1 = F$, $R^2 = OAc$) could be associated with increased bonding to an enzyme electron donor site. NMR measurements[171] showed that hydrogen-bonding to dioxan and to acetone is increased by the presence of a β-halogen atom, as in 2β-halogeno-5α-cholestan-3α-ol, but that bonding of the 11β-hydroxyl group is probably increased because of steric hindrance to free rotation of the hydroxyl group. Baker and Bartley[172] have used NMR to show that 2-hydroxymethylene-4,4-dimethylcholest-5-en-3-one is completely enolized in solution and that it exists in the hydroxymethylene rather than in the aldo-enol form.

Protons on carbon atoms adjacent to ether and epoxide groups are readily identified by NMR.[173] The spectra of steroid oxetanes, such as 2α,5-epoxy-A-nor-5α-cholestane (**27**),[106] 6β-19-epoxycholanic acid derivatives[174] and various oxa-steroids and related hemiacetals[144] have been reported.

Sheppard and Turner[175] used the technique to assign the conformation of the δ-lactone ring in unstrained steroidal lactones. The spectra of 4-oxa-$\Delta^{1,5(10)}$-3-oxo-steroids (i.e. steroidal δ-lactones) have been recorded.[176]

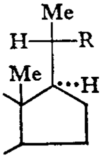
F. 17α- and 17β-substituents

The 17-epimers of 17-hydroxy-, 17-acetoxy-, 17-chloro-, 17-amino- and 17-acetamido-steroids may be distinguished on the basis of the chemical shift and splitting pattern of the geminal 17-proton. A pseudo-axial 17α-proton resonates at higher magnetic field than does the corresponding pseudo-equatorial 17β-proton. The 17-proton for a 17α-substituted steroid is usually a doublet (*J*, 6 to 7 Hz), while that for a 17β-substituted steroid is a triplet (*J*, 8 to 9 Hz); a 17-amino or 17-acetamido group causes additional splitting. In 17α-hydroxy- and 17α-acetoxy-steroids, the 13-methyl proton peak appears upfield of that for the corresponding 17β-epimer; the reverse occurs for 17-amino- and 17-acetamido-steroids.[177] The spectra of 17-chloro-[178] and 17-mercapto-steroids[179] have also been reported and Fishman[180] has discussed the spectra of 16α- and 16β-deutero-derivatives of 17α- and 17β-oestradiols (cf. Cross and Crabbé[181]).

The 17-protons of steroids with 17α- and 17β-acetyl side-chains are not readily distinguished. In simple 5α- and 5β-pregnane-3,20-diones with a 17β-acetyl group, the 13-methyl peak, however, appears at about δ 0·67 to 0·60, whereas in the corresponding 17α-epimer, the 13-methyl protons resonate at lower field (about δ 0·90 to 0·85).[182,183] A 17α-acetyl group does not induce any detectable long-range conformational effects. The spectra of 17α- and 17β-acetyl-steroids with a modified ring B have been reported.[184]

G. 20α- and 20β-substituents

NMR spectroscopy readily distinguishes between 20α-substituted (**38**) and 20β-substituted pregnanes (**39**)[185–188] and between 20α-hydroxy- and



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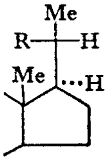

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20β-hydroxy-cholesterol derivatives.[189] In 16,17-unsubstituted pregnanes (**38** and **39**, where R = OH, OAc, NH_2, NHAc, NHMe, NMe_2 or NO_2), the 21-proton signal for the 20α-epimer is shifted downfield by 0·07 to 0·11 p.p.m. relative to that for the 20β-epimer; a similar shift is shown by the 21-proton peak for 20α- and 20β-hydroxy-9β,10β-pregnanes.[190] In 20-hydroxy- and 20-acetoxy-pregnanes, containing either a 16-ene or a 16-epoxide grouping, the 13-methyl proton peak of the 20α-epimer appears at lower field than that for the 20β-epimer.[187] In this way, 20α- and 20β-epimers can be distinguished when both are available for comparison.

The signal for the 13-methyl protons of 20-amino- and 20-hydroxy-pregnanes undergoes a characteristic shift when the 20-substituent is acetylated. On acetylation of the 20-hydroxyl group the 13-methyl peaks for

20α-hydroxy- and 20β-hydroxy-epimers move downfield (about 0·01 p.p.m.) and upfield (about 0·11 p.p.m.), respectively. Acetylation of 20α-amino and 20β-amino groups causes the 13-methyl peaks to move downfield (0·05 to 0·06 p.p.m.) and upfield (0·02 to 0·05 p.p.m.), respectively.[187] The substituent effect of the des-A-9-en-5-one grouping on the chemical shift of 13-methyl protons has been deduced[111] and the effect used to determine the configuration of epimeric 20-hydroxy- and epimeric 20-acetoxy-des-A-pregn-9-en-5-ones.

The configuration of the 20-substituent in 20-oxygenated pregnanes can be established from the coupling constant between the 17α- and 20-protons; 20α- and 20β-substituents are associated with coupling constants of 7·0 to 7·5 and 9·0 to 9·7 Hz, respectively.[191]

Noguchi, Otsuka, Obayashi, Imanishi and Takahashi[192] have reported the spectra of 11β,17α-dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione 17-acylates and have shown that the corresponding $21\alpha_F$-hydroxy- and $21\beta_F$-hydroxy-derivatives can be identified by NMR spectroscopy.

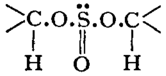
H. Sulphur-containing groups

The NMR behaviour of mercapto and acetylthiol groups, in general, resembles that of hydroxyl and acetoxyl groups, respectively (cf. Bhacca and Williams[114]). Tori and Komeno[22] have reported the effects of mercapto-, acetylthio-, thiocyanato- and epithio-substituents on the 10-methyl and 13-methyl protons of 5α-androstanes and 5α-cholestanes and have, by inspecting the shapes of the signals for protons attached to substituent-bearing carbon atoms, studied the distortion of ring A caused by 2β- and 4β-sulphur atoms. Epimeric 3-acetylthio-,[193] 3-mercapto-[194] and 17-mercapto-groups[179] are distinguished by the shape and the position of the geminal proton signals; an equatorial geminal proton gives a sharper signal and appears at lower magnetic field than does the corresponding axial proton.

The spectra of 16α- and 16β-acylthiopregn-20-ones,[195] 4-ethylthio-Δ^4-3-oxo-steroids and their analogues,[196] acetonides of 2β,3α-mercapto-cholestanols[197] and various cyclic thioketals[145] have been reported and discussed. The equatorial 6α-proton in a 4-ethylthio-Δ^4-3-oxo-steroid is unexpectedly deshielded (about δ 3·78) by the 4-ethylthio function.[196] The conformations of ring A in 4,5-disubstituted 2,2-dimethyl-(1,3)-oxathiolanes fused at the 2- and 3-positions and at the 3- and 4-positions of 5α-cholestane have been deduced.[197]

Jones and his colleagues[198,199] have discussed the spectra of 5α-cholestane 4-methyl sulphides, sulphoxides and sulphones. The 10-methyl protons resonate at lower field in 4β-sulphoxides and 4β-sulphones than in the corresponding 4α-sulphoxides and 4α-sulphones; this behaviour is consistent with the closer proximity of the axial 4β-methyl sulphinyl or 4β-methyl sulphonyl group than of the corresponding 4α-groups to the 10-methyl group. 10-Methyl protons in a (*R*)-4β-sulphoxide or (*R*)-4α-sulphoxide resonate at lower field than in the corresponding (*S*)-epimers; this difference in deshielding of the 10-methyl protons, due to magnetic anisotropy of the sulphoxide bond in pairs of compounds diastereoisomeric at sulphur, is consistent with the difference in the geometrical relationship between the sulphoxide and the 10-methyl groups.

Lack and Tarasoff[200] have examined sulphites of 2β-hydroxy-, 4β-hydroxy- and 4α-hydroxy-5α-cholestane and of 3α-hydroxy-5β-cholestane (cf. **40**) and have demonstrated the non-equivalence of the 2α-, 4α-, 4β- and 3β-protons, respectively, in these derivatives. The spectra of triethyl ammonium salts of steroid sulphates have been reported.[201]



$$>\underset{\overset{|}{\mathrm{H}}}{\mathrm{C}}.\mathrm{O}.\underset{\overset{\|}{\mathrm{O}}}{\ddot{\mathrm{S}}}.\mathrm{O}.\underset{\overset{|}{\mathrm{H}}}{\mathrm{C}}<$$

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V. NITROGEN-, PHOSPHORUS- AND HALOGEN-CONTAINING GROUPS

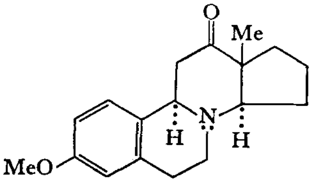
Recently, there has been increased interest in the spectra of aza-steroids and of steroids substituted with nitrogen-containing groups. The spectra of these compounds and of steroids containing halogen and phosphate groups are discussed in this Section.

A. Nitrogen

The proton spectra of a wide range of nitrogen-containing steroids have been described. The spectra of steroidal oximes have been discussed in Section IVD.[146–150] de Ruggieri, Gandolfi and Guzzi[202] studied the spectra of 10β-amino-steroids and Cantrall, Conrow and Bernstein[203] those of amino-oestrone methyl ethers and of 1,11-imino-oestrones. Snatzke and Veithen[23] have examined the effect of 5α-azido-, 5α-amino- and 5α,6α-imino-groups on 10-methyl and 13-methyl protons. The behaviour of 3β-azido-Δ^5- and 6β-azido-3α,5α-cyclo-steroids and of 17α-azido- and 17β-azido-5α-pregna-11,20-diones has been studied by Jarreau, Monneret, Khuong-Huu and Goutarel[204] and by Nathansohn, Winters and Vigevani,[205] respectively.

N-Methyl groups in the hydrochlorides of certain dimethylamino-steroids and of other suitably unsymmetrical alicyclic bases give rise to magnetically non-equivalent pairs in the NMR spectra.[206] The non-equivalence effects are sensitive to the position and orientation of the dimethylamino groups. The spectra of secondary amines and of ketimines formed from 11α-amino-, 11β-amino- and 3β-amino-5α-cholestane with acetone and ethylmethyl ketone have been reported.[207]

The spectra of 3-aza-19-hydroxy-17-oxo-3,19-cyclo-A-homo-5α-androstane and -5β-androstane,[208] various 4-aza-steroids,[209] 6-aza-oestrogens,[210,211] ring-A oxygenated 6-aza-steroids,[212] 8-aza-steroids,[5,213] 11-aza-steroids,[214] 12-aza-11-oxo-steroids,[215] 14-aza-11-oxo-steroids[216] and 17-aza-steroids[217] have been described. An examination[5] of the 220 MHz spectrum of the 8-aza-steroid (**41**) permitted a first order assignment of the configuration at carbon-14. Levine has reported the NMR spectrum of a novel steroidal β-lactam, in which a fused β-lactam replaces ring A.[218]



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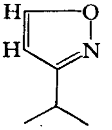
Yamauchi and Moore[219] have described the spectra of 1,2-diazobicyclosteroids. Steroidal α-diazoketones, such as 2-diazo-5α-cholestan-3-one and 2-diazo-4,4-dimethyl-5α-cholestan-3-one, undergo reversible stereospecific protonation in fluorosulphonic acid–deuterochloroform–sulphur dioxide solution; a one-proton peak, which is ascribed to the protonated diazo ketone system, appears at −70°C and disappears on warming to −30°C.[220]

The spectra of heterocyclic steroid derivatives, such as 17β-isoxazolyl (**42**) and 17β-pyrazolyl steroids (**43**) show characteristic features.[221] Low-temperature measurements on derivatives of 2,3-fused diazaheterocycles of oestra-1,3,5(10)-trien-17-one have shown that oestra-1(10),4-dien-(2,3-*c*)-(1′,2′,5′)oxadiazol-17-one 2′-oxide and 5′-oxide are a rapidly equilibrating mixture of (**44**) and (**45**).[222]



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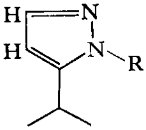

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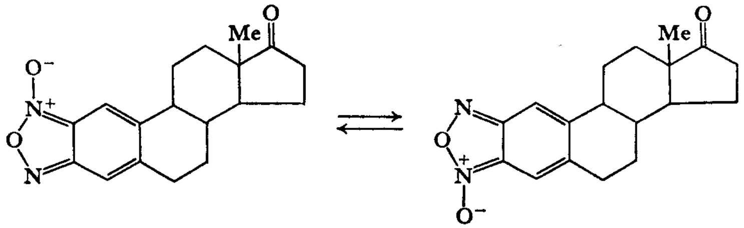


44 **45**

Chemical shifts resulting from the introduction of 1α-cyano and 1β-cyano groups (cf. Bhacca and Williams[223]) have been reported by Glen, Lawrie and McLean.[224]

Hassner and Heathcock[225] have assigned the configuration of 6-nitro-steroids by measuring the half-band width of the 6-proton signal and, from a study of 6α-nitro- and 6β-nitro-testosterones, Tori and Kuriyama[226] have deduced the long-range effects of 6α-nitro- and 6β-nitro- groups on 10-methyl and 4-protons. In a more recent study[227] the spectra of 3-, 4-, 6-, 7- and 17-mononitro-steroids and -dinitro-steroids and of steroids with geminal chloro-nitro, bromo-nitro and chloro-nitroso groups have been examined.

B. Phosphorus

The spectra of steroid phosphate methyl esters in deuterochloroform and benzene solution have been investigated and the values for the proton-phosphorus spin–spin coupling constants discussed.[228–230] Riess[230] has drawn attention to the spectra of certain steroid methyl phosphonates, in which the methoxyl protons show two doublets of almost equal intensity, but in which the protons of methyl groups directly linked to phosphorus do not give the secondary splitting. The effect is attributed to the bulk of the third substituent on the phosphonyl radical, which gives rise to magnetically non-equivalent diastereoisomers.

C. Halogen

The chemical shifts of protons attached to halogen-bearing carbon atoms in many α-halogeno-oxosteroids[231] and -allobetulones[232] have been reported. The effect of 2-halogen and 6-halogen substituents on the 10-methyl and 4-protons of testosterone (**29**; $R^1 = R^2 = \beta Me$, $R^3 = \beta OH$) and other Δ^4-3-oxo-steroids have been discussed[233] and the chemical shifts of protons α, β and γ to halogen atoms in halogenohydrins, such as 9α-halogeno-11β-hydroxy-progesterones (e.g., **31**; R^1 = halogen, R^2 = H), [133,171]examined. The method has been employed to identify the enzymic halogenation products of 11,20-dioxo-steroids and of 15-oxo-1-dehydrotestolactones.[234]

Levisalles and his colleagues investigated the spectra of bromo-derivatives of 4,4-dimethyl-5α-cholestane,[235] lanost-8(9)-ene,[236] 5β-methyl-19-nor-cholestane[237] and 4,4-dimethyl-5α- and 4,4-dimethyl-5β-oestrane.[238]

An examination of the position and splitting pattern of the 16-proton signal provides a good method for identifying each of the four possible isomers of methyl 16-halogenopregn-17(20)-ene-21-carboxylate and of 21-acetoxy-16-halogenopregn-17(20)-ene.[84] The conformations of ring D in epimeric 3β-acetoxy-16-bromo-5α,13α-androstan-17-ones have been assigned on the basis of NMR measurements.[239]

Although considerable attention has been paid to the PMR spectra of fluorinated steroids, particularly to long-range heteronuclear coupling between fluorine and angular methyl protons,[240] there have been relatively few reports[241–245] of ^{19}F NMR spectra of steroids. Boswell recorded the ^{19}F chemical shifts for 5α-fluoro-6-oxosteroids[241] and for a number of mono-, di-, tri-, tetra- and penta-fluoroandrostan-2-ol and -fluoroandrostan-3-one derivatives[242] and Merritt and Stevens[244] studied the direct fluorination of steroidal olefins to give *cis*-vicinal difluorides. The ^{19}F spectra of trifluoro-acetate esters of steroid alcohols have been used to distinguish between different types of steroid alcohols.[155]

The PMR spectra of difluoromethyl ethers of steroids have also been described.[246]

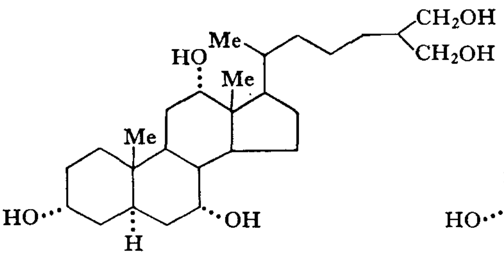
VI. MISCELLANEOUS NATURAL PRODUCTS AND THEIR DERIVATIVES

NMR spectroscopy has during the last five years played an important part in helping to elucidate the structure and stereochemistry of natural products structurally related to steroids; these products show a remarkable range of structural modification. Reference has already been made to the spectra of certain triterpene derivatives and of related 4,4-dimethyl-steroids.[25–43,51,52,59,132,161,162,164] In this Section reference will be made to the spectra of selected groups, such as those of the bile alcohols, the arthropod hormones, certain triterpene derivatives, the steroidal sapogenins and the steroidal alkaloids.

It should be mentioned that NMR spectroscopy has been used to study the interaction of phospholipids and cholesterol.[247] Thus, the spectrum of an egg yolk lecithin dispersion in heavy water solution is modified when cholesterol is added.

A. Bile alcohols

The bile of sharks, frogs and toads contain polyhydric steroid alcohols, which are usually present as the sodium salts of sulphuric acid esters. The chemical structures of typical bile alcohols, such as cyprinol (**46**),[248] ranol (**47**)[249] and myxinol (**48**),[250] which are isolated from species of fish,



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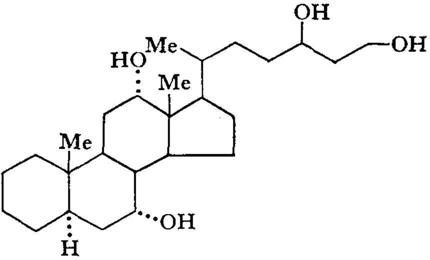

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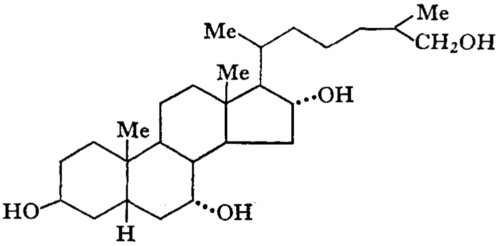

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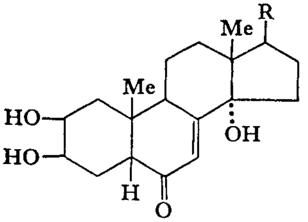
frog and hag fish, respectively, have been established by NMR measurements.

NMR studies have also confirmed that fucosterol, which is obtained from marine brown algae, is 24-ethylidenecholest-5-en-3β-ol.[251]

B. Arthropod hormones

NMR spectroscopy has helped to clarify the structures of the ecdysones, the hormones responsible for the moulting phenomena in insects; these compounds are, with interesting structural modifications, widely distributed in arthropods and in certain plants.

Hoffmeister, Rufer, Keller, Schairer and Karlson[252] have discussed the spectra of various α,β-unsaturated oxosteroids related to ecdysone, which has been assigned the structure (**49**).[253] Among the many analogues of ecdysone, for which NMR measurements have been reported, are 20,26-dihydroxy-ecdysone,[254] ponasterone A (**50**),[255] ponasteroside A (a glycoside of ponasterone A),[256] ponasterone B, ponasterone C,[257] 2-deoxycrustecdysone,[258] crustecdysone (ecdysterone or 20-hydroxyecdysone),[259,260] pterosterone,[261] capitasterone (**51**),[262] cyasterone (**52**),[263,264] shidasterone (a stereoisomer of ecdysterone),[265] podecdysone A,[266] makisterone A,[267]



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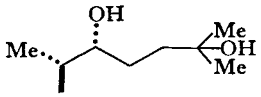
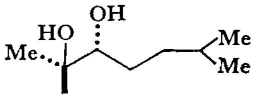
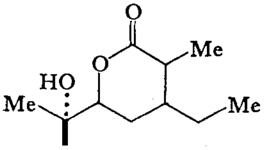


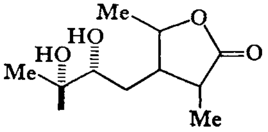
50 R =



51 R =



52 R =



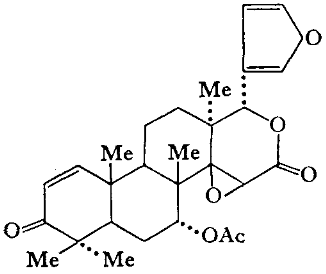
53 R = =O

makisterone B, makisterone C,[268] lemmasterone (24-ethyl-ecdysterone),[269] and ajugasterone.[270] Rubrosterone (**53**) is believed to be a metabolite of insect-moulting substances in plants.[271]

C. Triterpene derivatives

Reference has already been made to the spectra of certain triterpene derivatives.[25–43,51,52,59,132,161,162,164]

Ohochuku *et al.*[272] used the line-width of the peaks for the 15- and 17-protons to establish long-range coupling and, hence, confirm the



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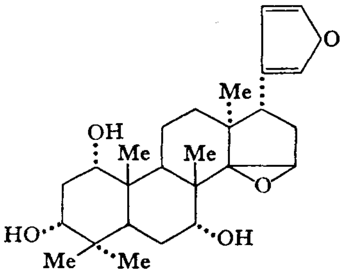

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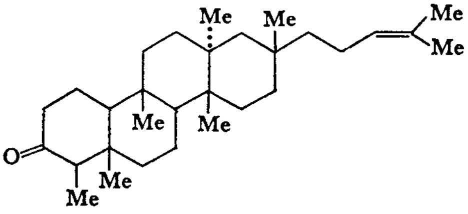
structure of gedunin (**54**) and of related limonoids. Other limonoids that have been examined include havanensin (**55**),[273] methyl 6-hydroxy- and methyl 6-acetoxy-angolensate[274] and 11β-acetoxykhivorin.[275]

NMR spectra have been reported for shionone (**56**),[276] melianone (**57**),[277] alnincanone (**58**),[278] the camelliagenins,[279] barrigenol,[280] the saikogenins,[281] odoratol,[282] and arundoin and related triterpenes.[283] The technique has been used to establish the stereochemistry of ceanothic acid[284] and to elucidate the structure of triterpenes obtained from the saponin ,"Aescin".[285]



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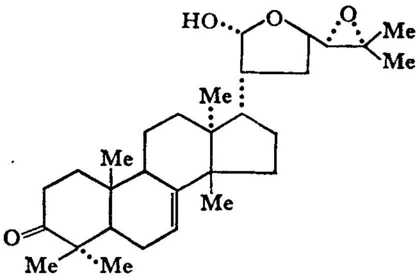

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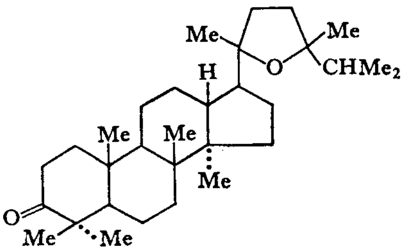

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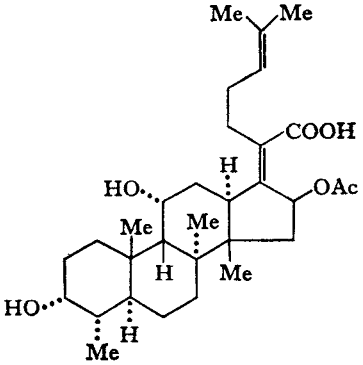
The fusidic acid (**59**), helvolic acid (**60**) and cephalosporin P_1 group (**61**) are of interest, since although derived from different sources, they have related structures. The general similarity of fusidic acid, helvolic acid and cephalosporin P_1 was first indicated by an NMR examination of their degradation products.[286] Further examination of the spectra of the parent substances and of related compounds revealed the stereochemistry of fusidic acid[287] and the structures of cephalosporin P_1[288,289] and helvolic acid.[289,290] The inter-relation of fusidic and helvolic acids has been confirmed by chemical and microbiological transformations supported by NMR measurements.[291,292]



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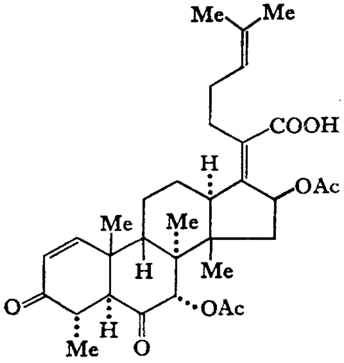

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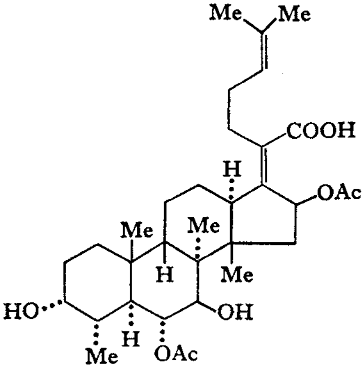

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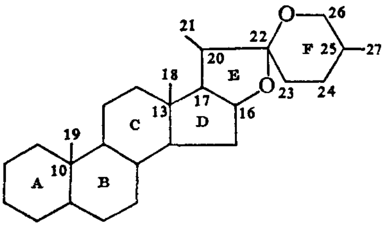
D. Steroidal sapogenins

The steroidal sapogenins, which are spirostans (**62**), are obtained from



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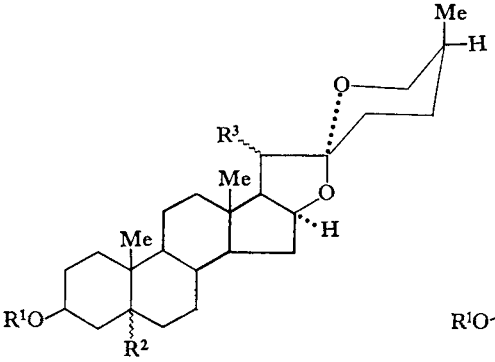
saponins, plant glycosides, by hydrolysis with acid or enzymes; they give characteristic spectra which can be used to establish the stereochemistry of rings E and F. Certain steroidal sapogenins, e.g. hecogenin and diosgenin, are of commercial importance as starting materials for the manufacture of corticosteroid drugs.

Spirostans possess a spiroketal side-chain, which can theoretically exist in eight isomeric forms, differing in configuration about centres at carbon-20, carbon-22 and carbon-25. Sarsasapogenin (5β,25*S*-spirostan-3β-ol; **63**; $R^1 = H$, $R^2 = \beta H$, $R^3 = \alpha Me$) and smilagenin (5β,25*R*-spirostan-3β-ol; **64**; $R^1 = H$, $R^2 = \beta H$, $R^3 = \alpha Me$) are examples of the normal (20*S*,22*R*,25*S*) and isosapogenin (20*S*,22*R*,25*R*) series, respectively, and the semi-synthetic isomers, cyclopseudosarsasapogenin (5β,20*R*,22*S*, 25*S*-spirostan-3β-ol; **63**; $R^1 = H$, $R^2 = \beta H$, $R^3 = \beta Me$) and cyclopseudosmilagenin (5β,20*R*,22*S*,25*R*-spirostan-3β-ol; **64**; $R^1 = H$, $R^2 = \beta H$, $R^3 = \beta Me$) represent two further types.†



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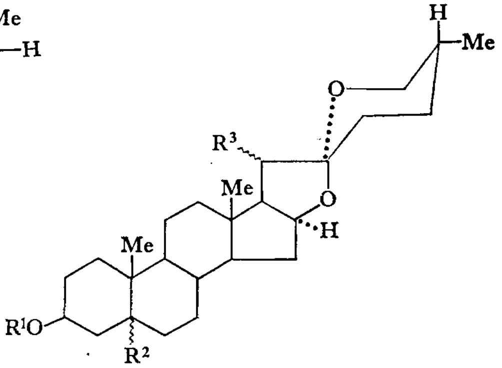

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The four isomers can be distinguished empirically by infrared spectroscopy, but NMR indicates more specific differences. Rosen, Ziegler, Shabica and Shoolery[293] first recorded the spectra of a series of steroidal sapogenins in deuterochloroform solution and reported a difference in the chemical shifts of the equatorial 25*R*-methyl and axial 25*S*-methyl protons and of 20*S*-methyl and 20*R*-methyl protons. In the 25*R*-methyl series, 25-methyl protons resonate at higher field than the 20-methyl protons; further, 25*R*-methyl protons resonate at higher field than the corresponding 25*S*-methyl protons (see Table VII). In pyridine solution, the spectral differences between the 25*R*-methyl and 25*S*-methyl series become greater so that the method readily establishes the stereochemistry of the 25-methyl group.[294] These observations have been confirmed by Tori and Aono,[44]

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† See revised tentative rules for nomenclature of steroids: *Biochim. Biophys. Acta*, 1968, **164**, 453.

who reported measurements on 155 steroidal sapogenins and their derivatives in deuterochloroform and pyridine solution. They examined the effect of substituents on the positions of the proton signals for the four methyl groups and showed that the displacements followed the same general additivity rules as those proposed by Zürcher[12] (cf. Table V). Likewise, as for simple steroids, factors, such as changes in configuration at carbon-5 and carbon-14 and conformational changes caused by the introduction of a double-bond, substitution at carbon-11, carbon-12 and carbon-17 and polysubstitution in the same ring need special consideration.

The solvent shift (see Table VII) for a given proton in going from deuterochloroform to pyridine or from deuterochloroform to benzene solution ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) is approximately constant provided that the position of the proton relative to polar sites in the molecule is unchanged.[295,296] Thus the double doublet for the 16α-proton of steroidal sapogenins, in which the polar environment in rings B, C, D, E and F is unchanged, shows a small range of solvent-shift values (–0·17 to –0·19 p.p.m.) in going from deuterochloroform to benzene solution. The solvent shifts for the protons of the 25-methyl group, however, depend on its equatorial (0·09 to 0·12 p.p.m.) or axial nature (about –0·02 p.p.m.). The change in solvent shift reflects the change in spatial relationship between the 25-methyl protons and the other features of rings E and F. Similar inferences as to the stereochemistry of the 20-methyl group may be deduced.

The downfield displacements (cf. Table VII)[295,296] of the 13-methyl and 20-methyl proton peaks of cyclopseudotigogenin acetate (**64**; $R^1 = Ac$, $R^2 = \alpha H$, $R^3 = \beta Me$) in deuterochloroform solution relative to those of tigogenin acetate (**64**; $R^1 = Ac$, $R^2 = \alpha H$, $R^3 = \alpha Me$) in the same solvent suggest a change in the electronic environment of the 13-methyl and 20-methyl groups, the deshielding being due to mutual steric interaction. The solvent shift ($\Delta = -0{\cdot}04$ p.p.m.) of the 13-methyl group of cyclopseudotigogenin acetate in going to benzene solution, however, suggests that the position of the group relative to the basic steroid skeleton is the same as that in tigogenin acetate ($\Delta = -0{\cdot}04$ p.p.m.), but that the 20-methyl protons of cyclopseudotigogenin have a different orientation ($\Delta = 0$) with respect to rings E and F to that existing in tigogenin acetate ($\Delta = -0{\cdot}23$ p.p.m.). The spectral results, therefore, suggest that, in the conversion of tigogenin acetate to cyclopseudotigogenin acetate, epimerization occurs at carbon-20 and the 20-methyl group moves into the region of the 13-methyl group.

The 17α-protons of 12-oxo (**65**) and 12β-substituted, but not of 12α-substituted 25*R*-spirostans, appear as single-proton multiplets, centred at δ 2·80 to 2·75 and 3·07 to 2·63 in deuterochloroform and benzene solution, respectively. The 17α-proton, which couples with the 16α- and 20β-protons to give two overlapping doublets (*J*, 6·5 to 7·5 and 8·5 to 9 Hz), is deshielded

TABLE VII

Proton resonance lines (δ values) and solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) for steroidal sapogenins[a]

Compound	Solvent	10-Me	13-Me	16α-H	20-Me	25-Me	26-H
Tigogenin acetate	$CDCl_3$	0·84	0·76	4·39	0·95	0·79	3·44
(**64**; R^1 = Ac, R^2 = αH,	C_6H_6	0·67	0·80	4·58	1·18	0·67	3·55
R^3 = αMe)	Δ	0·17	−0·04	−0·19	−0·23	0·12	−0·11
Cyclopseudo tigogenin acetate	$CDCl_3$	0·83	0·93	4·42	1·13	0·78	3·47
(**64**; R^1 = Ac, R^2 = αH,	C_6H_6	0·66	0·97	4·58	1·13	0·68	3·62
R^3 = βMe)	Δ	0·17	−0·04	−0·16	0·0	0·10	−0·15
Smilagenin acetate	$CDCl_3$	0·98	0·76	4·40	0·94	0·76	3·44
(**64**; R^1 = Ac, R^2 = βH,	C_6H_6	0·90	0·80	4·57	1·24	0·67	3·60
R^3 = αMe)	Δ	0·08	−0·04	−0·17	−0·30	0·09	−0·16
Sarsasapogenin acetate	$CDCl_3$	1·00	0·77	4·40	1·00	1·08	3·30/3·95
(**63**; R^1 = Ac, R^2 = βH,	C_6H_6	0·91	0·82	4·63	1·22	1·10	3·38/4·14
R^3 = αMe)	Δ	0·09	−0·05	−0·23	−0·22	−0·02	−0·08/−0·19

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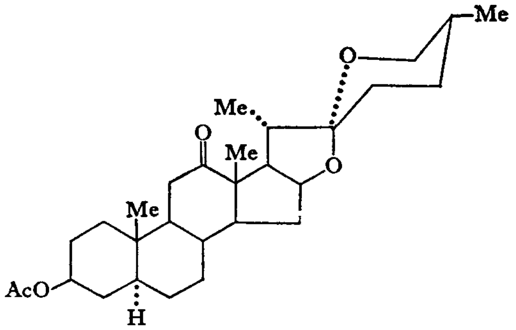
[a] From Williams and Bhacca[295] and Green, Page and Staniforth.[296]



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by either an axial 12α-substituent or a 12-oxo-group, but not by an equatorial 12β-substituent. The 20α-protons of cyclopseudosapogenins, but not the 20β-protons of normal and isosapogenins, give rise to double quartets (*J*, 8 and 9·5 Hz) centred at about δ 2·41 and 2·70 in deuterochloroform and benzene solution, respectively.[296]

Solvent changes sometimes lead to unexpected reversals in the order of the resonance lines for the angular methyl protons of steroidal sapogenins.[296] Such reversals can only be identified with certainty by observing the positions of the methyl peaks in the spectra of sapogenin solutions in mixed solvents, in which the relative proportions of deuterochloroform and benzene are varied systematically from 0 to 100%; the effect for hecogenin acetate (**65**) is shown in Fig. 1.

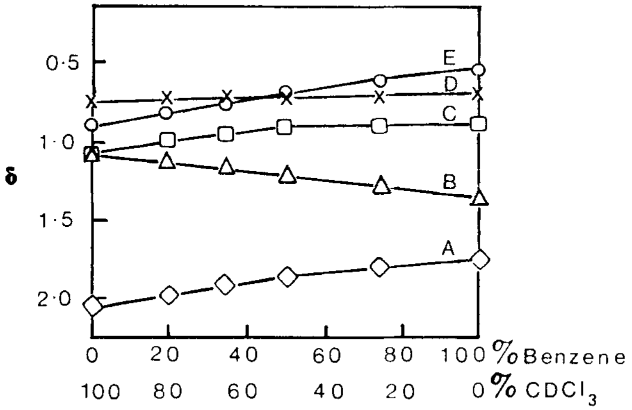

FIG. 1. The effect on the methyl proton resonances of hecogenin acetate (7% solution) of varying the proportions of deuterochloroform and benzene in the solvent A, 3-AcO; B, 20-Me; C, 13-Me; D, 25-Me; E, 10-Me (from Green, Page and Staniforth[296]).

NMR spectroscopy has helped to establish the structure and stereochemistry of the bromo-steroidal sapogenins. Bromination of a 25*R*-spirostan gives rise to two series of monobromo-isomers which were designated 23*a*-bromo- and 23*b*-bromo-isomers and were, on infrared spectroscopic evidence, believed to be equatorial and axial bromo epimers, respectively.[297,298] NMR measurements eliminated other possible bromination sites, confirmed the infrared assignments[299] and, further, showed that in dibromo-compounds both bromine atoms are at carbon-23 and that in monobromo 25*S*-spirostans, the bromine atom is also at carbon-23 and is equatorial.[300]

Introduction (cf. Table VIII) of an equatorial 23-bromine has little effect on the doublets for the 20-methyl and 25-methyl protons of either 25*R*- or 25*S*-spirostans, but an axial 23-bromine displaces downfield by about 0·22 p.p.m. the 20-methyl doublet, but not the 25-methyl doublet, of a 25*R*-spirostan. Dibromination increases the effect on the 20-methyl doublet of a 25*R*-spirostan and also displaces downfield the 20-methyl and axial 25-methyl doublets of a 25*S*-spirostan; the equatorial 25-methyl doublet of a 25*R*-spirostan is not affected.[300]

The single-proton multiplets centred at δ 4·09 and 4·30 in the spectra of 23*a*-bromotigogenin and 23*a*-bromoneotigogenin acetate, respectively, consist of two broad doublets indicating axial coupling with the 24-protons and confirming that the bromine atoms are equatorial. In the 23*b*-bromo-isomer, the single-proton peak at δ 4·12 is relatively sharp indicating that the proton is equatorial and that the geminal bromine atom is axial.[300]

The long-range shielding effects of substituents in the sapogenin side-chain on the protons of the angular 10-methyl and 13-methyl groups are, as for simpler steroids, largely additive. Substitution in the sapogenin side-chain has little effect on the chemical shift of the 10-methyl protons, but it has an important effect on the 13-methyl protons. An equatorial 23-bromine, but not an axial 23-bromine atom, shifts downfield by about 0·12 p.p.m. the 13-methyl peaks for 25*R*- and 25*S*-spirostans; dibromination doubles the effect (cf. Table VIII).[300]

NMR spectroscopy has helped to establish the structure of 25-hydroxy-

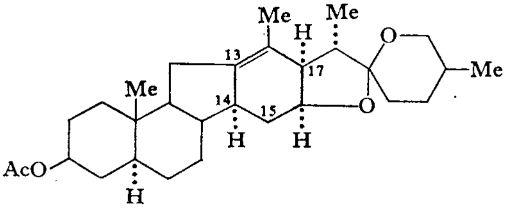

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TABLE VIII

Proton resonance lines (δ values) for steroidal sapogenin derivatives in deuterochloroform solution[a]

Compound	10-Me	13-Me	20-Me	23-H	25-Me	26-H
Tigogenin acetate (**64**; R^1 = Ac, R^2 = αH, R^3 = αMe)	0·84	0·76	0·95	1·58	0·80	3·44
23*a*-Bromotigogenin acetate	0·84	0·88	0·94	4·09	0·80	3·43
23*b*-Bromotigogenin acetate	0·85	0·80	1·17	4·12	0·82	3·52
23,23-Dibromotigogenin acetate	0·86	1·00	1·27	..	0·86	3·53
Neotigogenin acetate (**63**; R^1 = Ac, R^2 = αH, R^3 = αMe)	0·84	0·77	0·97	1·75	1·08	3·96, 3·28
23*a*-Bromoneotigogenin acetate	0·85	0·89	0·96	4·30	1·12	3·98, 3·28
23,23-Dibromoneotigogenin acetate	0·85	1·02	1·30	..	1·43	3·38, 2·75

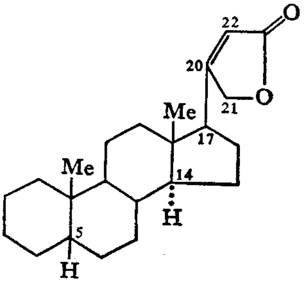
[a] From Callow, James, Kennard, Page, Paton and Riva di Sanseverino.[300]

spirostans (e.g., isoreineckiagenin[301]), 27-hydroxy-spirostans (e.g., igagenin[302]) and 2β,3α,4β-trihydroxy-spirostans (e.g., diotigenin[303] and isodiotigenin[304]). Coxon, Hartshorn and Kirk[305] have revised the structure of the C-nor-D-homo-endocyclic olefin (**66**) derived from hecogenin and have deduced the structures of other sapogenin rearrangement products.[306]

E. Steroidal alkaloids

The spectra of several groups of steroids derived from cardiotonic glycosides and aglycones have been described.

Tori and Aono[45] studied the spectra of sixty-five 5β,14α,17β-card-20(22)-enolides (**67**) and 5β,14β,17α-card-20(22)-enolides of known structure in deuterochloroform and (or) pyridine solution and observed the additivity of the additional shift values for the angular methyl protons caused by the introduction of various substituents. The additivity rule did not hold for 7β-substituted or 7-oxo-steroids with a 14β-hydroxy-group, since mutual interaction occurs, for 12-substituted steroids, which, particularly in 14β-analogues, are affected by 17-substituents, for certain 11-substituted 5β, 14β-steroids and for certain steroids poly-substituted in the same ring.



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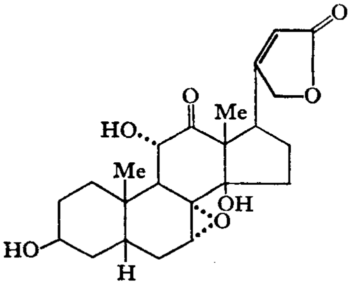
The spectra of 19-halogeno-card-20(22)-enolides[307] and of sarverogenin (**68**)[308] and alloglaucotoxigenin (**69**)[309] have been reported. Recently, NMR



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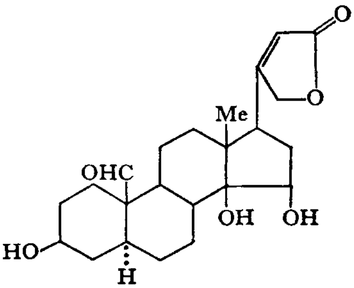

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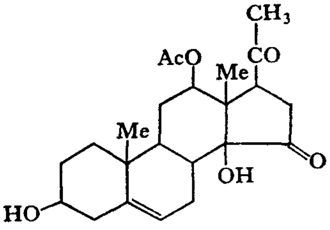
has been used to determine the position of acetyl groups in partially acetylated derivatives of the cardenolide, digoxin.[310]

NMR measurements have been invoked to support the structure of digacetigenin (**70**), the aglycone of the glycoside, digacetinin, from *Digitalis*



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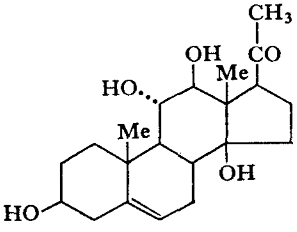

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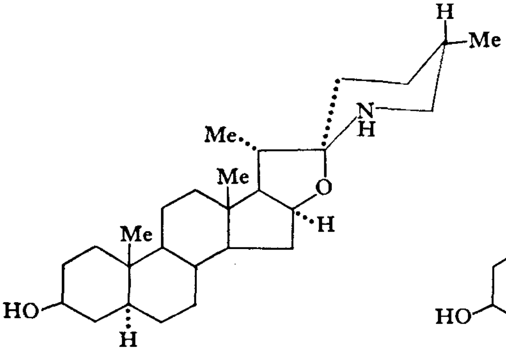
purpurea.[4,311–313] The spectra of drevogenin P (**71**) and its derivatives have been reported.[314]

Lavie and his colleagues[21] compiled the chemical shifts for the angular methyl protons of steroids related to dihydroxy-deoxy-withaferin A and used the information to deduce the stereochemistry of derivatives of withaferin A (**10**)[21,315] and of analogues, such as jaborosalactones A and B.[316]

Many bufadienolides have been examined and the structure of cinobufaginol assigned.[317]

Naturally occurring azasteroids comprise compounds in which nitrogen forms an integral part of the steroid nuclear skeleton, with or without alteration of ring size, and compounds in which nitrogen appears in a side-chain. The spectra of synthetic azasteroids were discussed in Section VA.

The side-chain stereochemistry of the spiroaminoketal alkaloids, which are related to the steroidal sapogenins, has been established by NMR



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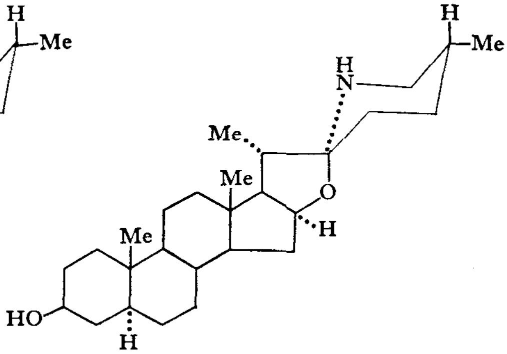

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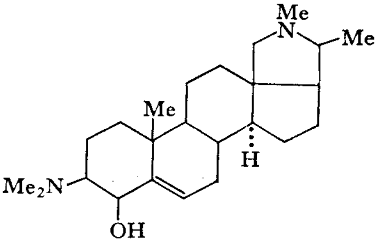
measurements.[318] The known absolute configuration at carbon-25, together with the equatorial conformation of the 25-methyl group, as obtained from proton spectra, allowed the assignment of the configuration at carbon-22. Tomatidine (**72**) and 5α-solasodan-3β-ol (**73**) were given the structures, 5α-22*S*,25*S*-spirosolan-3β-ol and 5α-22*R*,25*R*-spirosolan-3β-ol, respectively.[318,319] The spectra of *N*-methylsolasodine in deuterochloroform and benzene solution have been reported and the conformation of the isomers assigned.[320]

Toldy and Radics[321] separated and, using NMR spectroscopy, identified the two rotational isomers formed by restricted rotation about the nitrogen–carbon bond of the *O*,*N*-diformate of 5α-solasodanol. Such isomers are frequently recognised in NMR spectra, but are rarely separated chemically.

α-Hydroxyconessine (**74**)[322] and various buxus alkaloids[323–325] are representatives of other groups of nitrogen-containing steroid alkaloids which have been studied.



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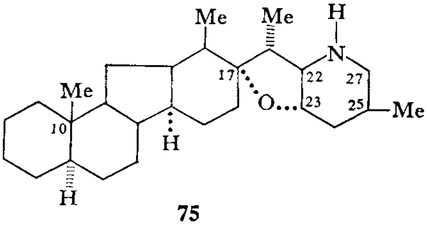
The spectra of sixty-five derivatives of 22,27-imino-17,23-oxidojervane, which has the skeleton (**75**), have been described; it has been shown that the additivity principle for the additional chemical shifts induced by different substituents holds for the 10-methyl protons of C-nor-D-homo-steroids.[326]



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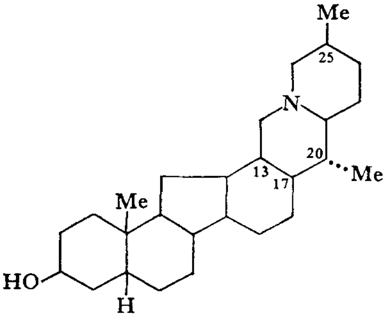
Measurements on thirty-seven veratrum alkaloids, which have structures based on the skeleton (**76**), produced evidence supporting earlier proposals for the β-configuration of the 25-methyl group and for A/B-ring fusion in sabine derivatives. Changes in the chemical shift values for the 20-methyl



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protons suggested that the conformation of ring D changes on introducing *ortho*-diacetate groups in ring D.[327] NMR studies have led to a revised configuration for veratramine and jervine.[328]

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Nuclear Magnetic Resonance Spectroscopy of Paramagnetic Species

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I. INTRODUCTION

THE PRESENCE of any paramagnetic centre will influence the NMR spectrum of a resonating nucleus.[1] In terms of chemical applications the most significant effects of the interaction between unpaired electrons and nuclei are revealed by the isotropic hyperfine shifts,[2] the changes in nuclear relaxation times[1] and by nuclear spin polarization which gives rise to the Overhauser effect.[3] The first two of these effects can provide much information relating to the electronic and geometrical structures of paramagnetic species and the way in which they react. Consequently this review is largely concerned with these two effects, for the sake of balance and completeness some of the recent chemically interesting applications of the Overhauser effect are included in Section IIIF(3).

In the past five years much interest has been shown in the NMR spectra of paramagnetic species and several review articles have been published.[4–7] The present article is intended to be a comprehensive current survey of the effects of paramagnetism on NMR spectroscopy and their chemical interpretation. Not all of the classes of work described are exclusive to paramagnetic compounds. In those cases, however, where data from diamagnetic systems are also available the introduction of a paramagnetic centre usually produces larger shifts and facilitates interpretation.

II. THEORETICAL BACKGROUND

The isotropic hyperfine shifts may arise from two different mechanisms, one of which produces contact interactions and the other pseudo-contact interactions between the unpaired electrons and nuclei.[8] The former of these may be interpreted in terms of electronic structure whilst the latter contains information relating to the geometric structure of the sample molecules.

A. Contact interactions

To account for some of the fine structure observed in the electronic spectra of atoms containing unpaired s electrons Fermi proposed a direct nucleus–electron magnetic interaction,[9] which is quite distinct from the classical dipole–dipole interaction. The Fermi interaction energy for a proton in a large magnetic field may be expressed by the Hamiltonian $\mathscr{H}$, where

$$\mathscr{H} = a_N g_e \beta_e \sum_K S_{KZ} I_{NZ} \tag{1}$$

a_N is the hyperfine interaction constant expressed in gauss, g_e and β_e are the electronic g value and Bohr magneton, S_{KZ} is the Z component of the spin of the Kth electron and I_{NZ} is the Z component of the spin of proton N.

The hyperfine interaction constant, a_N in gauss, may be expressed as

$$a_N = \frac{8\pi}{3} g_N \beta_N |\psi(0)_N|^2 \tag{2}$$

where $\psi(0)_N$ is the wavefunction governing the distribution of the unpaired electron evaluated at the nucleus N, and g_N and β_N are the nuclear g value and magneton respectively. From equation (2) it is apparent that finite values of a_N exist only for species with electrons whose wave-functions are nodeless at the nucleus so that a direct "contact" between electron and nucleus may occur. Consequently Fermi interactions are frequently referred to as contact interactions. Since only s atomic orbitals are nodeless at the nucleus, it is necessary for the unpaired electron to have some s character if the contact shift mechanism is to be operative. Some ways in which this might occur are discussed in Section IID.

One effect of the interaction described by equation (1) is to produce the well-known hyperfine structure observed in the solution ESR spectra of free radicals. In principle the same splitting might be expected to occur in the NMR spectrum of nucleus N (Fig. 1). So far it appears that the hyperfine structure has not been resolved in an NMR spectrum. This is no doubt due to the fact that in practice the reciprocals of the electronic relaxation time T_1 and/or the electronic exchange time T_e are much larger than the hyperfine splitting described by a_N.

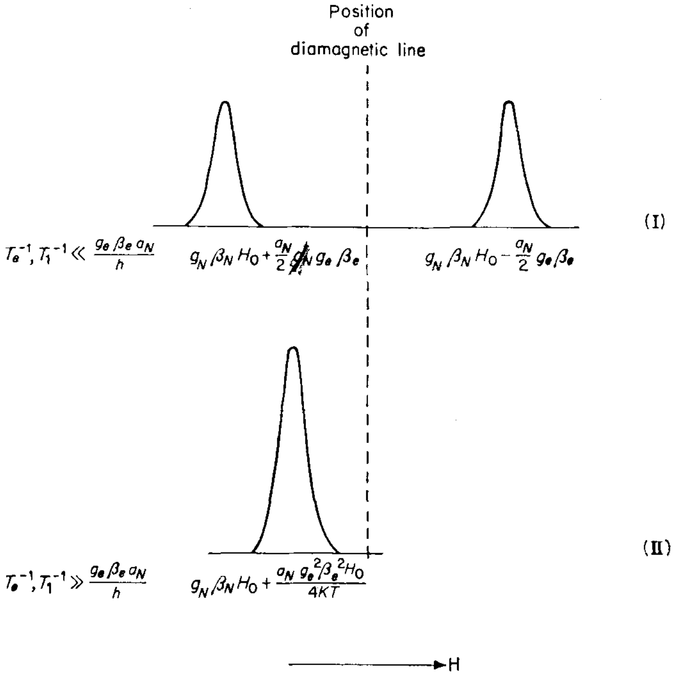


FIG. 1. Schematic representation of the line positions and transition energies for a nuclear transition in the presence of an unpaired electron, assuming slow electronic relaxation or exchange (I) and rapid electronic relaxation or exchange (II) respectively.

$$T_e^{-1}, T_1^{-1} \gg \frac{g_e \beta_e}{h} a_N \tag{3}$$

When the conditions expressed by equation (3) are fulfilled the nucleus N senses an average hyperfine field from the paramagnetic centre. Its resonance position is then contact shifted by an amount dependent upon this average field. The contact shifted line is produced by the collapse of the two lines given in Fig. 1. Its position is at the mean of their positions weighted according to the thermal populations of the electronic energy levels $m_s = \pm\frac{1}{2}$ producing the hyperfine splitting. In the simple case of a rapidly tumbling isotropic paramagnetic molecule the position of the averaged NMR line of a proton arising from the conditions described in equation (3) may be considered by analogy with the equations for rapid site exchange.[10] Let ν_M be the frequency of the line produced by the collapse of the lines of frequencies ν_A and ν_B corresponding to sites with fractional populations P_A and P_B.

$$\nu_M = P_A \nu_A + P_B \nu_B \tag{4}$$

where

$$P_A = \frac{\tau_A}{\tau_A + \tau_B} \quad \text{and} \quad P_B = \frac{\tau_B}{\tau_A + \tau_B} \tag{5}$$

and τ_A, τ_B are the mean lifetimes for a stay at sites A and B. The energy E_M corresponding to ν_M is given by:

$$E_M = P_A E_A + P_B E_B \tag{6}$$

If site A corresponds to that in which $m_s = -\frac{1}{2}$ and site B to that of $m_s = +\frac{1}{2}$ then with a_N expressed in gauss

$$E_M = P_{-1/2}\left(g_N \beta_N H_0 + \frac{a_N g_e \beta_e}{2}\right) + P_{+1/2}\left(g_N \beta_N H_0 - \frac{a_N g_e \beta_e}{2}\right) \tag{7}$$

The mean lifetimes $\tau_{-1/2}, \tau_{+1/2}$ are dependent upon a Boltzmann distribution between the $m_s = \pm\frac{1}{2}$ states, therefore,

$$\tau_{-1/2} \propto \exp\left(\frac{\frac{1}{2}g_e \beta_e H_0}{kT}\right) \quad \text{and} \quad \tau_{+1/2} \propto \exp\left(\frac{-\frac{1}{2}g_e \beta_e H_0}{kT}\right) \tag{8}$$

For simplicity we can write

$$X = \frac{g_e \beta_e H_0}{2kT} \tag{9}$$

and

$$E_M = \frac{\left(g_N \beta_N H_0 + \frac{a_N g_e \beta_e}{2}\right)\exp(X) + \left(g_N \beta_N H_0 - \frac{a_N g_e \beta_e}{2}\right)\exp(-X)}{\exp(X) + \exp(-X)} \tag{10}$$

For experiments at normal temperatures with a magnetic field strength of 10 or 20 k/gauss, $g_e \beta_e H_0 \ll 2kT$, so that $\exp(X) \approx 1 + X$ and $\exp(-X) \approx 1 - X$, consequently equation (10) may be written as

$$E_M = g_N \beta_N H_0 + \frac{a_N g_e^2 \beta_e^2 H_0}{4kT} \tag{11}$$

If the hyperfine coupling constant a_N is a positive quantity then the contact shifted line appears at the low energy side of its position in the corresponding diamagnetic compound by an amount given by—

$$\frac{a_N g_e^2 \beta_e^2 H_0}{4kT} \tag{12}$$

At a constant value of the applied H_1 field this corresponds to a low field shift ΔH in terms of the magnetic field H_0 as is indicated by the negative sign in equation (13).

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2}{g_N \beta_N 4kT} \tag{13}$$

The general case of the Fermi contact interaction between a proton and an electron has been treated by quantum mechanics.[2, 5, 8] This considers a spin system characterized by the inequalities given in equation (3) in an applied magnetic field H_0. The energy of the average magnetic field experienced by proton N is given by the spin Hamiltonian—

$$\mathscr{H} = -g_N \beta_N I_{NZ} \left(H_0 - \frac{a_N g_e \beta_e \langle S_Z \rangle}{g_N \beta_N} \right) \tag{14}$$

where $\langle S_Z \rangle$ denotes the weighted average of the Z component of the electron spin. The corresponding shift of the nuclear spin energy levels with respect to the diamagnetic case is given by δE where

$$\delta E = a_N g_e \beta_e \langle S_Z \rangle I_{NZ} \tag{15}$$

By using the high temperature limit approximation for systems obeying the Curie law $\langle S_Z \rangle$ is evaluated—

$$\langle S_Z \rangle = \frac{\sum\limits_{-S}^{+S} S_Z \exp\left(\frac{-g_e \beta_e H_0}{kT} \right)}{\sum\limits_{-S}^{+S} \exp\left(\frac{-g_e \beta_e H_0}{kT} \right)} \simeq \frac{-g_e \beta_e H_0 S(S+1)}{3kT} \tag{16}$$

By substituting for $\langle S_Z \rangle$ in equation (15) we obtain the following expression for δE—

$$\delta E = -\frac{a_N g_e^2 \beta_e^2 H_0 S(S+1) I_{NZ}}{3kT} \tag{17}$$

The corresponding change in the transition energy ΔE between the two proton spin states $I_{NZ} = \pm\frac{1}{2}$ is given by—

$$\Delta E = -\frac{a_N g_e^2 \beta_e^2 H_0 S(S+1)}{3kT} \tag{18}$$

which produces a change ΔH in the value of the magnetic field H_0 at resonance, where ΔH is given by

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2 S(S+1)}{g_N \beta_N . 3kT} \tag{19}$$

For the case of one unpaired electron, $S = \frac{1}{2}$, equation (19) reduces to equation (13) which we obtained from the simple rapid relaxation model. The most significant aspect of this model is that it illustrates the necessity of a short electronic relaxation and/or exchange time for the observation of contact shifted lines. Since a_N does not, however, describe a small perturbation in the spin system ($a_N = 508$ gauss for the gaseous hydrogen atom) it is necessary to consider the interaction of all of the spins in the general case. Consequently the more rigorous quantum mechanical derivation of equation (19) is to be preferred. In transition metal complexes it is often necessary to include the effects of spin-orbit coupling in a description of the electronic energy levels. A description of the variation of ΔH with temperature for octahedral transition metal complexes including spin-orbit coupling has been published by Golding.[11]

B. Pseudo-contact interactions

In addition to the contact shift interaction there is the possibility of pseudo-contact interactions occurring in both the solid state and in solution.[8] These arise from the direct magnetic dipole–dipole interaction between the spins of the unpaired electrons and those of the nuclei. The pseudo-contact shifts are isotropic because, to a first approximation, they are independent of the orientation of the molecule with respect to the applied magnetic field. For a molecule with tetragonal symmetry the pseudo-contact shift in the solid is given by—

$$\frac{\Delta H}{H_0} = -\frac{(3\cos^2\theta - 1)}{r^3}(g_\parallel^2 - g_\perp^2)\frac{\beta^2 S(S+1)}{9kT} \tag{20}$$

where $g_\parallel$ and $g_\perp$ are the components of the g tensor parallel to and perpendicular to the principal axis of the molecule, r is the separation between the unpaired electrons and the resonating nucleus and θ is the angle between this distance vector and the principal molecular axis.

Due to rapid tumbling of the molecules in solution the electron spin becomes quantized in the direction of the applied magnetic field in spite of the anisotropy of the g tensor. Depending upon the relative magnitudes of the g tensor anisotropy, the correlation time for molecular tumbling τ_c and the electron spin-lattice relaxation time T_{1e} there are four limiting descriptions of the pseudo-contact interaction.[12] It should be noted that T_{1e} includes the longitudinal relaxation processes described by both T_l and T_e.

If $\tau_c^{-1} \ll |g_\parallel - g_\perp|\beta H\hbar^{-1}$ and $T_{1e} \ll \tau_c$, then the Boltzmann distribution between the spin levels is preserved over the rotation of the molecule and the pseudo-contact term is the same as for the case of the solid, given by equation (20).

If $\tau_c^{-1} \gg |g_\parallel - g_\perp|\beta H\hbar^{-1}$ and $T_{1e} \ll \tau_c$ then,

$$\frac{\Delta H}{H_0} = \frac{-(3\cos^2\theta - 1)}{r^3}(3g_\parallel + 4g_\perp)(g_\parallel - g_\perp)\frac{\beta^2 S(S+1)}{45kT} \tag{21}$$

If $\tau_c^{-1} \gg |g_\parallel - g_\perp|\beta H\hbar^{-1}$ and $T_{1e} \gg \tau_c$ then,

$$\frac{\Delta H}{H_0} = \frac{-(3\cos^2\theta - 1)}{r^3}(g_\parallel + 2g_\perp)(g_\parallel - g_\perp)\frac{\beta^2 S(S+1)}{27kT} \tag{22}$$

If $\tau_c^{-1} \ll |g_\parallel - g_\perp|\beta H\hbar^{-1}$ and $T_{1e} \gg \tau_c$ then an average population of the spin levels is maintained during the rotation of the molecule. The resulting expression for the pseudo-contact shift is only available in a rather complicated form.[12] Since the expressions for the pseudo-contact shift are dependent upon the relative magnitudes of T_{1e}, τ_c and the g tensor anisotropy these have to be estimated before the expressions can be used quantitatively.[13]

By comparing equations (20), (21) and (22) it is apparent that pseudo-contact shifts can be different for the same sample depending upon whether it is a solid or in solution. This difference may be used to distinguish pseudo-contact shifts from contact shifts since the latter are not directly dependent upon the state of the sample. Measurements on vanadocene[14] in solution and in the solid state have suggested that the shift is contact in origin. This method of investigating the origin of isotropic shifts has not been widely used due to the difficulties encountered in obtaining sufficiently well resolved solid state spectra.

In those cases where it is possible to obtain bond lengths and angles from X-ray studies and estimates of the principal values of the g tensor from ESR data, the pseudo-contact shift may be calculated. In the case of the cobalt(II) trispyrazolylborate and trispyrazolylmethane complexes Jesson[12, 15] has demonstrated that, by comparing the calculated shifts with the observed ones, it is possible to distinguish between contact and pseudo-contact shifts. A further means of distinguishing between these two types of shift could be the study of the nuclear relaxation times T_1 and T_2. From equations (23) and (24) it is apparent that T_1 and T_2 have a different dependence upon the hyperfine interaction constant a_N, however it appears that investigations of this type have so far received little attention.[4]

C. Relaxation phenomena

The relaxation of nuclei with a spin of one-half in a paramagnetic environment depends upon both dipole–dipole and contact interactions.[16] [17]

Equations (23) and (24) describe respectively the longitudinal (T_1) and the transverse (T_2) nuclear relaxation times. In these equations the first term represents the dipole–dipole interaction between electrons and nuclei and the second term the contact interaction.

$$\frac{1}{T_1}=\frac{2S(S+1)}{15\hbar^2}g_e^2\beta_e^2\frac{Nn}{N_p}\left[\frac{g_N^2\beta_N^2}{r^6}\left(3\tau_c+\frac{7\tau_c}{1+w^2\tau_c^2}\right)+\frac{5a_N^2\tau_e}{1+w^2\tau_e^2}\right] \tag{23}$$

$$\frac{1}{T_2}=\frac{S(S+1)}{15\hbar^2}g_e^2\beta_e^2\frac{Nn}{N_p}\left[\frac{g_N^2\beta_N^2}{r^6}\left(7\tau_c+\frac{13\tau_c}{1+w^2\tau_c^2}\right)+5a_N^2\left(\frac{\tau_e}{1+w^2\tau_e^2}+\tau_e\right)\right] \tag{24}$$

Where N is the molar concentration of paramagnetic ions, n is the number of nuclei in the solvation sphere of the paramagnetic ion, N_p is the molar concentration of the nuclei under consideration, w is the Larmor precession frequency of the electron and τ_e is the correlation time for the contact interaction. These equations deal with the general case in which solvent molecules randomly enter and leave the coordination sphere of the paramagnetic species which is assumed to have an isotropic g tensor. Under these conditions Nn/N_p is the probability that a given nucleus will be in the coordination sphere of the paramagnetic species, in the case of a stable entity such as a coordination compound this becomes unity. If the paramagnetic species has an anisotropic g tensor equations (23) and (24) require modification to include this.[18]

The r^{-6} dependence of the dipole–dipole contribution to $1/T_1$ and $1/T_2$ produces a rapidly attenuating effect whereby those nuclei nearest to the paramagnetic centre exhibit the broadest lines in the spectrum. Large values of a_N are also expected to produce broad lines in the NMR spectrum. Species with large values of a_N may, however, exhibit sharp lines if τ_e is short, and this can arise from rapid electron relaxation and/or rapid exchange as has been demonstrated for the case of electron transfer between diamagnetic and paramagnetic species.[19] Some of the sharpest lines that have been reported for paramagnetic species are those of some nickel(II) complexes with line widths of 2 to 5 Hz.[20] LaMar[21] has shown that electron relaxation times of $\sim 10^{-13}$ sec are necessary to account for the observed NMR spectra of some pseudotetrahedral cobalt(II) and nickel(II) complexes. The major process producing these very short electronic relaxation times appears to be the coupling of the zero-field splitting to the tumbling of the complex in solution. A similar conclusion has been reached in the case of some octahedral nickel(II) complexes[22] but for the corresponding cobalt(II) complexes the orbitally degenerate ground term[23] makes the situation more complicated.

It is often difficult to observe the ESR spectra of complexes with a short electronic relaxation time. This may be overcome in some cases by carrying out the ESR studies at helium temperatures so that both NMR and ESR spectra of the same complex become available. This is often required in deciding the contribution of the pseudo-contact interaction to an observed isotropic shift.

The usually narrow ESR lines of organic free radicals indicate longer electronic relaxation times than those found in transition metal complexes. This often means that in solution the NMR lines of organic radicals are too broad for accurate detection. In the solid state intermolecular exchange effects can lead to line narrowing making NMR studies more feasible. The intermolecular electronic exchange time T_e is related to the viscosity of the solvent η, the temperature T of the solution and the concentration of the radical C by equation (25).

$$T_e \propto \frac{\eta}{CT} \tag{25}$$

Consequently it appears that the most favourable circumstances for observing the NMR spectra of free radicals in solution are those of low viscosity, high concentration and high temperature.[24] A small value for the hyperfine interaction constant is also conducive to the observation of contact shifted spectra as can be seen from the inequalities of equation (3).[25] Recently Canters and de Boer[26] have shown that radicals with large hyperfine interaction constants ($a_N > 5$ gauss) can also give well resolved spectra provided that the electronic spin lattice relaxation time is sufficiently short ($\leqslant 10^{-8}$ sec).

D. Spin density distribution in paramagnetic species

It is apparent from equation (2) that the observation of contact shifts in the NMR spectrum, and hyperfine splitting in the ESR spectrum, of paramagnetic species depends upon the unpaired electrons having some s character. In a π radical, such as $C_6H_6^{\ominus}$, the unpaired electron is considered to be in a network of delocalized p_π orbitals which have nodes in the plane of the six hydrogen atoms. If we are interested in discussing the proton NMR spectrum of this radical we have to relate the spin density at the proton to the spin densities in the π molecular orbitals, which are theoretically predicted to contain the unpaired electron. If we consider a C–H fragment of the radical (Fig. 2), it is apparent that the electron–nucleus contact interaction most probably occurs via a π–σ interaction between the p_π spin density centred on the carbon atom and the pair of σ electrons comprising the C–H bond.[2, 27–29] Qualitatively we may consider the contact shift to arise from an exchange interaction between the unpaired p_π electron and the σ electron with parallel spin in the C–H bond. The consequent spin polarization of the electrons in the C–H bond produces a resultant spin density in the hydrogen 1s orbital which is antiparallel to the spin of the unpaired p_π electron. The antiparallel nature of this spin density is reflected in the negative value of the proportionality constant Q between a_N and the spin density ρc centred on the p_π orbital of the carbon atom[2,30] as given by equation (26).

$$a_N = Q\rho c \tag{26}$$

Both theory and experiment have shown that Q is approximately $-22{\cdot}5$ gauss for all aromatic protons.[29,31–33] By definition, the sum of the spin densities on all of the carbon atoms in the radical is equal to the number of unpaired electrons present.

By combining equations (19) and (26) we can see that aromatic protons bonded to carbon atoms having a positive spin density experience a high field contact shift whereas negative spin densities lead to low field shifts. Consequently the NMR spectrum gives directly the sign of the spin density whereas the ESR spectrum usually provides its numerical value only. The determination of the signs of spin densities can provide a valuable means of testing some of the predictions of theoretical calculations. Some non-alternant and odd-alternant radicals have been predicted to have positive and negative spin densities at different sites which has now been experimentally confirmed.[34]

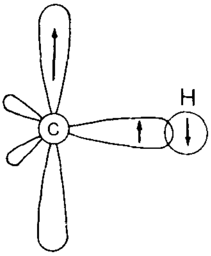


FIG. 2. σ and π bonding orbitals in a $\dot{C}$–H fragment.

Electron correlation effects, arising from coulomb repulsion and spin exchange interactions, have been included in a number of theoretical calculations.[35] In order to obtain quantitative agreement with experimental values of spin densities sophisticated calculations are necessary. Qualitative agreement, however, is often sufficient to extract chemically important information from a spectrum, and there are two simple types of calculation commonly used for this purpose. One of these is the valence bond method which makes allowance for spin correlation by its very nature, the other is the extended Hartree-Fock procedure developed by McLachlan[36] and recently extended by Nowakowski.[37] This type of calculation employs a single determinantal wave function which includes different orbitals for electrons with opposite spins. Spin correlation is included by taking slightly different coulomb integrals for the electrons with opposite spins. Recently semi-empirical molecular orbital calculations, using the INDO approximation, have been successful in predicting spin densities.[38,39]

Contact shifts, of course, arise from atoms and groups other than the protons of aromatic $\dot{\mathrm{C}}$–H fragments. Protons in methyl groups and fluorine atoms attached to aromatic carbon atoms have been studied and relationships similar to equation (26) have been reported for them.[40–43] In the case of methyl protons the spin density is transferred by a hyperconjugative mechanism giving direct delocalization to the hydrogen 1*s* orbitals. Consequently a positive spin density on the aromatic carbon atom produces a positive spin density at the proton. So that for a given carbon p_π spin density the contact shifts of the protons in the two fragments $\dot{\mathrm{C}}$–H and $\dot{\mathrm{C}}$–$\mathrm{CH_3}$ are in opposite directions. This has been demonstrated by NMR studies on a number of transition metal complexes, the earliest of which was on the tris complexes of acetylacetone and methylacetylacetone with vanadium(III).[44]

It has been suggested that fluorine atoms may participate in conjugation with a π system,[41,43] hence the effect of spin density in the p_π orbital of fluorine has to be included in any relationship between the hyperfine interaction constant and the appropriate spin density. A modified form of the Karplus–Fraenkel equation[45] appears to be applicable.

$$a_F = Q^F_{CF}\,\rho^\pi_C + (Q^F_{FC} + S^F)\,\rho^\pi_F \tag{27}$$

where ρ^π_C is the spin density in the p_π orbital of the carbon atom adjacent to the fluorine atom, ρ^π_F is the spin density in the p_π orbital of the fluorine atom, Q^F_{CF} is the spin polarization parameter of the 2*s* electrons of the fluorine atom which accounts for the effect of spin density at the adjacent carbon atom, Q^F_{FC} and S^F are the spin polarization parameters of the fluorine 2*s* and 1*s* electrons respectively which account for the effect of spin density in the fluorine p_π orbital. An expression similar to equation (27) has been used to account for the hyperfine splitting constant of nitrogen atoms.[56]

Aliphatic and σ bonded compounds have generally received less attention than π electron systems. Spin densities in σ electron systems have been treated theoretically,[47] and attempts to calculate the hyperfine interaction constants of σ radicals by means of the semiempirical extended Hückel procedure have recently been reported.[48–52] Reasonable agreement with experimental values of a_N is reached in most cases although the extended Hückel treatment does not incorporate the concept of negative spin densities.

III. APPLICATIONS

Compared to the chemical shifts and spin coupling constants observed in the spectra of diamagnetic compounds, contact shifts are very large. The spectra of paramagnetic compounds are usually first order with one line for each chemically distinct group of nuclei as shown in Fig. 3. Contact shifts have been reported for the ligand atom nuclei of many transition metal complexes, generally the widths of the resonances are very dependent upon the metal ion. Sharp proton resonances are most commonly found for complexes of cobalt(II) and nickel(II). Consequently complexes of these metals have received the most attention to date.

A. Electron distribution and bonding in metal complexes

If covalent bonds are formed between a metal ion and its ligands then it is possible for some of the metal ion's unpaired electrons to become delocalized throughout the complex. The contact shifts produced by these unpaired electrons can then be related to the covalency of the metal-ligand bonds.

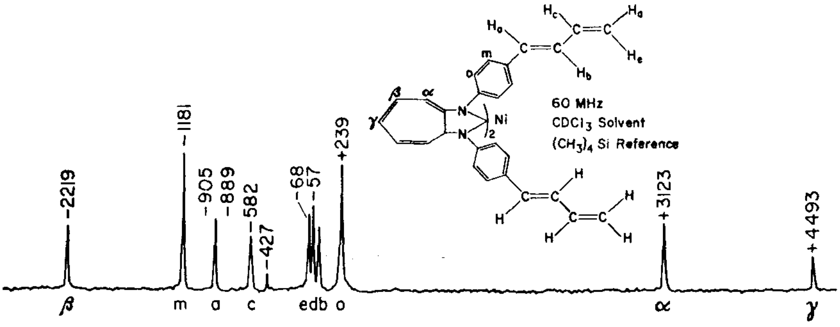


FIG. 3. Proton spectrum of Ni(II) *N*,*N*′-bis-(*p*-1,3-butadienylphenyl)aminotroponeimineate at 60 MHz $CDCl_3$ solvent, $(CH_3)_4Si$ reference, 25°C. (From Eaton and Phillips, p. 124.[4])

1. *Six coordinate complexes*

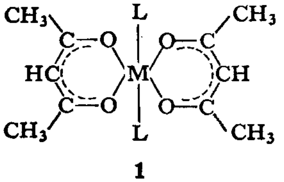
Before attempting to relate an observed isotropic resonance shift to unpaired spin density it is necessary to ascertain the nature of the interaction causing the shift. The difference between the isotropic proton shifts of analogous six coordinate complexes of cobalt(II) and nickel(II) is usually explained by the presence of a pseudo-contact interaction contribution to the shifts of the former but not to the latter.[53–55] The absence of a pseudo-contact contribution for the nickel(II) complexes implies that they are magnetically isotropic in agreement with the presence of an orbital singlet ground term, whereas the cobalt(II) complexes have a triply orbitally degenerate ground term producing magnetic anisotropy.[23]

By assuming that the extent of electron delocalization is the same in analogous complexes of cobalt(II) and nickel(II) the pseudo-contact contribution to the former is estimated from the difference in the position of analogous proton lines in the spectra of the complexes of the two metal ions. This factoring procedure has been criticised and it has been demonstrated that the spin delocalization mechanisms can be different in six coordinate complexes of cobalt(II) and nickel(II).[56] This difference can be accommodated[57] by expressing the isotropic shift of proton i in a cobalt complex $\Delta H^{i}_{\mathrm{Co}}$ in terms of the shift of the comparable proton in the analogous nickel complex $\Delta H^{i}_{\mathrm{Ni}}$ as described by equation (28),

$$\Delta H^{i}_{\mathrm{Co}} = K\Delta H^{i}_{\mathrm{Ni}} + P(T,g_{\parallel},g_{\perp})\cdot f(\theta,r)_i \tag{28}$$

where K is the delocalization ratio between the two complexes, $P(T,g_{\parallel},g_{\perp})$ is a constant factor for all of the protons in the molecule and $f(\theta,r)$ is the geometric factor $(3\cos^2\theta_i - 1)r_i^{-3}$ of nucleus i for an assumed geometry. The appropriate geometry is that which gives agreement between the K and P values for all of the protons. For complexes with O_h, D_{4h} or D_3 microsymmetry, the difference in the amounts of electron delocalization between analogous cobalt(II) and nickel(II) complexes, as expressed by K, most probably arises from the fact that cobalt(II) has unpaired electrons in d orbitals which are capable of π bonding whereas nickel(II) does not.

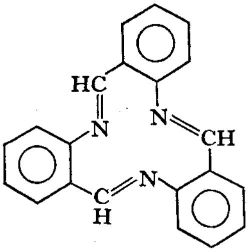
Electron delocalization may occur by a π mechanism or σ mechanism or even both.[55] Unpaired electrons in orbitals with σ symmetry usually produce a rapidly attenuating positive spin density at each proton site,[58] from equation (19) we can see that this produces a low field shift for all protons. In contrast a positive spin density in the π network gives rise to a high field shift. For even alternants this implies a high field shift for all protons, whereas for odd alternants and non-alternants alternate high and low field shifts are expected for neighbouring proton sites. Hence it is possible to rationalize a given contact shift in terms of σ and π electron delocalization. This has been discussed for a number of pyridine type ligands,[55, 59–61] some six coordinate complexes of cobalt(II) and nickel(II) with salicylaldimines[62] and salicylaldehyde,[63] and a variety of ligands, L, octahedrally coordinated to bis-acetylacetonates and substituted bis-acetylacetonates of cobalt(II) and nickel(II) (**1**). The coordinated ligands include some pyridines,[55] triarylphosphines,[64] arylisonitriles,[64] arylnitriles,[65] heterocyclic amine-N-oxides,[53,54,57,66] substituted anilines,[67] aliphatic amines,[68] and some aldehydes and ketones.[69]



$M = Co^{II}$ or Ni^{II}

1

In strictly octahedral nickel(II) complexes the unpaired metal electrons are in e_g orbitals which have σ symmetry so that a direct transfer of spin density to ligand π orbitals is not expected. To account for the observed contact shifts of nickel(II) complexes with substituted pyridines,[55] substituted aromatic amines[67,70] and salicylaldimines[62] an indirect σ–π interaction has been suggested. Hence delocalization of metal electrons in the π system of the ligands should not be taken as direct evidence for metal–ligand π bonding. LaMar[71], however, has rejected the possibility of indirect σ–π interactions in nickel(II) complexes, arising from polarization by the unpaired e_g electrons of either the paired metal π electrons or the π electrons of the ligands, in favour of reducing the symmetry of the complexes below octahedral whereby the e_g orbitals may have a non-zero overlap with the ligand π system.[72,73] This proposal has been applied to some salicylaldimine complexes of nickel(II) and the complex with the macrocyclic ligand tribenzo[*b*,*f*,*j*][1,5,9]triazacycloduodecine (TRI) (**2**) which has a propeller-like distortion.[74] Both of the rejected indirect σ–π interactions predict a negative spin density on the ligand whereas the NMR spectra are only consistent with a positive spin density, in agreement with the direct transfer of e_g electrons.



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It appears, however, that either one of the σ–π polarization interactions or the mixing effect of spin-orbit coupling is to be preferred in discussing the contact shifts of the more structurally regular complexes of nickel(II) such as the hexabenzonitrile,[65] the hexammino[75] and the hexaaquo complexes,[76,77] where both σ and π spin densities are required to account for the proton spectra of the ligands.

Acetonitrile coordinates through its nitrile group which is capable of both σ and π bonding. The contact shifts produced by dissolving various transition metal salts in acetonitrile have been studied.[78–80] The spin density found at the methyl proton nuclei in solutions containing salts of cobalt(II), nickel(II) and copper(II) is negative which is accounted for on the basis of σ bonding between the metal and ligand, the spin reaching the nitrile carbon atom by a σ–π interaction whereby it undergoes a change in sign. For solutions containing Ti^{III} ions a positive spin density is observed at the methyl proton nuclei which agrees with a direct π delocalization mechanism without spin reversal. From the relative magnitudes of the observed shifts it appears that the direct π transfer mechanism is the more effective one. Comparable conclusions have been reached from a study of the ^{13}C and ^{14}N contact shifts of the hexacyanides of some of the metal ions of the first transition series.[81,82]

The NMR spectra of most ligands that have been studied are consistent with the presence of unpaired electrons in the π network. An exception to this are the pyridine type ligands which have a relatively large amount of σ spin density.[54,55,59,61,83,84] This has been reconciled with the fact that the highest bonding orbital in this type of ligand has been shown from extended Hückel molecular orbital calculations to have σ symmetry.[61,83,85] In hemin and related compounds contact shift data also indicate a spin transfer into the σ bond system of the porphyrin ring,[86] which could be of importance in understanding electron transfer mechanisms in these biologically interesting molecules.

In some cases the contact shifts arising from π spin density can be due to either ligand to metal or metal to ligand spin transfer. Consequently the unpaired spin may populate either the highest bonding orbital (HBO) or the lowest antibonding orbital (LAO) of the ligand π network.[85] Which π orbital contains the unpaired spin can often be decided by comparing the experimental spin densities with those calculated by valence bond or molecular orbital procedures for the HBO and LAO. In this manner it has been demonstrated that the unpaired spin lies in the HBO for some six coordinate complexes of nickel(II) with heterocyclic *N*-oxides,[54] isonitriles and triarylphosphines[64] indicating that ligand to metal spin transfer predominates in these complexes. Whereas metal to ligand spin transfer is required to account for the spectrum of the complex formed with 4-nitropyridine-1-oxide.[65] Metal to ligand spin transfer has also been reported to be the dominant mechanism in some tris complexes of vanadium(III) with β-diketones,[87,88] salicylaldehyde[89] and salicylaldimines.[89]

The proton NMR spectra have been reported for a series of complexes formed between transition metal ions and the ligands acetylacetone and some aminotroponeimines including some mixed ligand complexes.[85,90] It is found that for the tris acetylacetone complexes between 1% and 10% of an electron is delocalized and that both metal-to-ligand and ligand-to-metal spin transfer occurs, with the latter becoming more important as the atomic number of the metal increases.

These results are consistent with the fact that at the beginning of the first transition series the metal *d* orbitals are comparable in energy to the LAO of the acetylacetone ligand and with the fact that as the atomic number of the metal increases the energy of its *d* orbitals tends to decrease such that towards the end of the transition series the energy of the *d* orbitals approaches that of the ligand HBO. This is in agreement with the ease of oxidation of those metals for which metal-to-ligand spin transfer predominates, e.g. titanium-(III), whereas those that are more readily reduced are the ones favouring ligand-to-metal spin transfer, e.g. iron(III). The HBO in the aminotroponeimines is considerably higher in energy than it is in acetylacetone; consequently ligand-to-metal spin transfer is favoured in complexes with aminotroponeimines. The overall results from the complexes with aminotroponeimines and from the mixed complexes with acetylacetone are consistent with this picture, generally it is found that the spin transfer characteristics of the two sets of ligands are complementary and that for the later transition metals ligand-to-metal spin transfer dominates.

Contact shifts have been reported for several metallocenes and related complexes.[14,91–96] In unsubstituted metallocenes all of the protons are equivalent and a single line occurs in the NMR spectrum. The spectra of the cobalt and nickel compounds exhibit a shift to lower frequency† which could arise from either metal-to-ligand or ligand-to-metal spin transfer. The corresponding compounds of vanadium and chromium[14,94] and the ferrocinium cation,[93] however, produce a resonance which is shifted to higher frequency. Neither metal-to-ligand nor ligand-to-metal spin transfer causing spin pairing is able to account for this.[4] The possibility of a pseudo-contact contribution has been dismissed on the basis of NMR measurements made on the solid and liquid phases.[94] To account for the observed shifts Levy and Orgel[97] have proposed a spin polarization mechanism whereby the non-bonding a_{1g} and e_{2g} vanadium and chromium electrons polarize the strongly bonding e_{1g} ligand electrons, in a similar manner to the polarization of the σ bonding electrons by the unpaired π electrons in the $\dot{C}$–H fragment. This proposal appears able to account for the observed shifts of the aromatic protons of the dibenzenechromium and ditoleunechromium cations,[98] since it causes the transfer of a negative spin density to the carbon atoms of the ligand, which corresponds to the observed higher frequency proton shifts.[4] By comparison, the unpaired metal electrons in the cobalt and nickel compounds are in e_{1g} orbitals which are able to interact directly with the ligand producing positive spin densities at the carbon atoms and low frequency proton shifts. The spin polarization mechanism, however, predicts that the proton signal of a substituted methyl group will move in the opposite sense to the signal of the replaced proton. Contact shift studies on some dimethylmetallocenes demonstrate that this does not always occur.[91,92,96] To account

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† Shifts to low and high frequency correspond to shifts to high and low field respectively.

for their results Fritz *et al.*[96,99] have suggested that the unpaired spin density is transferred directly from the metal to the ring protons producing the higher frequency shifts, but that when more than six *d* electrons are present the normal spin π delocalization processes occur giving rise to the low frequency shift in the cobalt and nickel compounds.

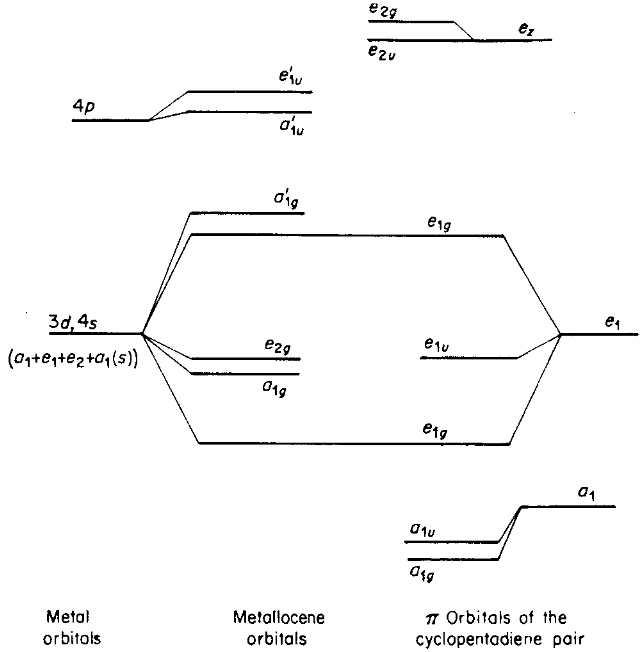


FIG. 4. Energy level diagram for metallocenes.

NMR studies on complexes formed by transition metals of the second series indicate that pseudo-contact interactions become increasingly important[85,90] and they are probably dominant in rare earth complexes with acetate,[100] water,[100] acetylacetone[85] and related ligands.[101] In the case of complexes with an aromatic amine, it is, however, claimed that contact shift interactions are predominant.[102] Doubtless those complexes with an orbitally degenerate ground term are the ones with the largest pseudo-contact contribution.

Some complexes of osmium(IV) and rhenium(III) halides with tertiary-phosphines and arsines exhibit "contact" shifted proton spectra in spite of having diamagnetic ground terms.[103] The very small magnetic moments of these d^4 complexes are thought to be due to a second order Zeeman effect,[23] the same effect could also account for their small "contact" shifts.

2. *Four coordinate complexes*

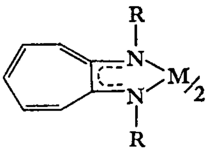
Tetrahedral nickel(II) complexes and octahedral cobalt(II) complexes have orbitally degenerate ground terms,[23] hence it is to be expected that tetrahedral nickel(II) complexes will have an anisotropic g tensor and thus exhibit pseudo-contact shifts comparable to those observed in octahedral cobalt(II) complexes.[59,98,104] In practice, however, the NMR spectra of tetrahedral and slightly distorted tetrahedral nickel(II) complexes are often interpreted in favour of a contact shift interaction only. This may produce an error in the magnitude of the spin density but should not affect the relative values of spin densities at different sites on the same ligand.[12] An example of some reported data is furnished by some bis(triarylphosphine) complexes of cobalt(II) and nickel(II) dihalides. It is claimed that the spectra of the nickel(II) complexes show only a contact interaction whereas both contact and pseudo-contact interactions contribute to the shifts of the cobalt(II) complexes.[105] Although it now seems unlikely that this is the correct interpretation of the origin of the isotropic shifts, the discussion of the π spin density distribution being due to d_π–d_π bonding between the occupied nickel and empty phosphorous d orbitals is still valid.[106]

The increased facility for π bonding in tetrahedral as compared to octahedral complexes has been demonstrated by the interpretation of the contact shifts of some pyridine type ligands coordinated to cobalt(II). These indicate that σ delocalization dominates in the octahedral complexes whereas the π delocalization mechanism is the more important one in the tetrahedral complexes.[59,107,108] The situation in similar complexes of nickel(II) appears to be less decisive since π delocalization only becomes important at the γ position of the pyridine ring.[83]

Data on nickel(II) chelates formed with aminotroponeimines,[4,20] pyrrole-2-aldimines,[109] salicylaldimines,[110] β-ketoimines[111] and β-diimines[112–115] show that the unpaired spin lies in the HBO, indicating an excess of ligand-to-metal spin transfer in these chelates. The reverse situation applies to the pyrromethene and porphyrin chelates of nickel(II), where metal-to-ligand spin transfer is favoured by a low lying LAO in the ligand π system.[116]

The investigation of the contact shifts of a series of complexes of the type CoL_2X_2 (where L = pyridine or a substituted pyridine and X = chloride, bromide or iodine) has led to a controversy over the relative importance of steric effects and covalency in determining the contact shifts.[108,117–119] Studies are reported in which both the pyridine and halogen substituents are varied but it appears that the shifts are not as yet well understood. Better wave functions for the substituted pyridines would no doubt assist in finding an understanding.[118]

Amongst the most extensively investigated proton contact shifts of four coordinate metal complexes are those of the aminotroponeimines (**3**). These



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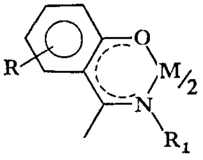

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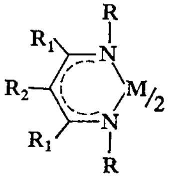
form d_π–p_π bonds with metals, resulting in about 10% delocalization of an electron. A thorough review of this work has been published by Eaton and Phillips.[4] Some of the nickel(II) bis-aminotroponeiminates have contact shifted lines of only 2 Hz width and due to the narrow lines it has been possible to evaluate spin coupling constants that are not readily available from the very complicated spectrum of the free ligand.[120]

A similar system exhibiting sharp contact shifted spectra is that of the *N*-sec-alkylsalicylaldimines and related compounds (**4**).[121] These generally give smaller shifts than are observed in the aminotroponeimineates and have approximately 3% of an electron delocalized in their π networks, which appears to be due to d_π–p_π bonding.[62,110,122,123] This work has recently been reviewed together with that on the closely related β-ketoamine complexes by Holm, Everett and Chakravorty,[124] and will therefore not be mentioned in greater detail here.

The NMR spectra of some metal complexes of β-diimines (**5**) have recently been reported.[112–115,125] These are of interest both from the point of view of



$R_1 = R_2 = H$
or
$R_1 = CH_3$ and $R_2 = H$

5

metal–ligand bonding and their biochemical properties. The cobalt(II) and nickel(II) complexes have contact shifted spectra corresponding to the β spin transfer of about 6% of an electron from the ligand to the metal.[112,114,115] By comparing this with the amount of spin transferred in related ligand complexes we find that the relative π bonding tendencies to the same π acceptor, namely nickel(II) in a pseudo-tetrahedral state, decrease in the order aminotroponeimine > β-diimine > β-ketoamine >

salicylaldimine. Hence the ligand systems presenting four nitrogen donor atoms to the metal are more effective in delocalizing π spin density than are those with two nitrogen and two oxygen donor atoms. To be certain that this trend in π delocalization is not predominantly a function of the geometry of the complex a series of mixed ligand complexes should be studied. This would enable a comparison of the spin densities with those in the unmixed ligand complexes to be made. Comparable data are reported for complexes of the type NiL_1L_2, where L_1L_2 are respectively different salicylaldimines[122] and different aminotroponeimines.[126] It is reported that the spin density becomes distributed asymmetrically between the two different ligands. The differences in spin density distribution are related to the electron withdrawing or donating properties of the substituents on the ligands, and may be interpreted by considering a competitive situation whereby spin is only delocalized onto one ligand at a time. This arises under C_{2v} symmetry because the π bonding metal orbitals belong to the irreducible representations b_1 and b_2 which are not suitably orientated for maximum π bonding with both ligands simultaneously.[127] From this model it should be possible from spin density determinations to decide the order of the π bonding ability of a series of related ligands.

The variations in spin density transfer, as a function of coordination number and of the atomic number of the metal ion, have been reported. A study of complexes of nickel(II) with the salicylaldimine fragment has demonstrated that, although ligand-to-metal spin transfer is predominant in the four coordinate complex, the relative importance of metal-to-ligand spin transfer increases as the coordination number increases to five and six.[71] The four coordinate complexes formed between metal ions of the first transition series and hexamethylphosphoramide show increasing covalency as the atomic number of the metal increases.[128] These examples demonstrate that the mechanism of spin transfer is very dependent both upon the relative energies of the metal and ligand orbitals and upon the symmetry of the complex.

B. Structural studies of metal complexes

NMR spectra having isotropically shifted lines may be used to obtain information on the structure of paramagnetic species. We will consider how these spectra can provide structural information on compounds participating in structural and spin equilibria, and various forms of isomerism as well as other structural data.

1. *Structural equilibrium*

Contact shifted spectra have been reported for molecules taking part in a rapid equilibrium between a diamagnetic ground state and a thermally accessible paramagnetic state. Under these conditions the contact shifts do not show a Curie law dependence and equation (19) has to be modified to include the equilibrium as shown in equation (29)[129]

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2}{g_N \beta_N} \frac{S(S+1)}{3kT}\left[\exp\left(\frac{\Delta G}{RT}+1\right)\right]^{-1} \tag{29}$$

where ΔG is the free energy change for the equilibrium, which is found from the temperature dependence of the contact shifts. Unfortunately many of the early workers in this field[4] used an incorrect form of equation (29) resulting in ΔG values too high by $RT\ln 3$ and ΔS values too low by $R\ln 3 = 2{\cdot}2$ e.u.; fortunately the value of a_N is unaffected by this error.[129]

The contact shifts of four coordinate complexes of nickel(II) have been most numerously interpreted on the basis of equation (29). Many of these complexes in solution exhibit an equilibrium between the square planar (diamagnetic) and tetrahedral (paramagnetic) forms. It has often been suggested that this equilibrium is responsible for the sharp NMR lines shown by these complexes.[4] La Mar, however, has demonstrated that the rate of interconversion between the two forms is too slow for this process to be decisive in line width arguments.[21] The nickel complexes that are reported to exhibit this equilibrium include those with aminotroponeimines,[4,20,41,43,120,126,130] salicylaldimines,[62,110,122,124] naphthaldimines,[123] β-ketoamines,[111,124,131] pyrrole-2-aldimine[109] and a ditertiaryphosphine in which the two phosphorus atoms are separated by three carbon atoms.[132] Since the observed lines are usually between 2 and 20 Hz wide the rate of interconversion between the two forms in equilibrium is considered to be in excess of 10^9 to 10^{10} per sec.

In general it is found that the free energy difference between the square planar and tetrahedral forms can be varied by the appropriate substitution on the parent ligand system. Data on a series of complexes with comparable substituents indicate that the order of increasing stabilization of the tetrahedral form relative to the square planar form is pyrrole-2-aldimine (8·5% tetrahedral) < salicylaldimine (50% tetrahedral) < β-ketoamine (100% tetrahedral).[109] The contact shifts of a series of nickel(II) complexes of β-ketoamines and corresponding -aminothiones have shown that the ligands containing the sulphur donor atoms produce a greater stabilization of the planar stereochemistry than do those with oxygen donor atoms.[133]

Complexes of nickel(II) with Schiff bases formed from salicylaldehydes and *N*,*N*-disubstituted ethylenediamines have been shown from NMR data to exist in solution as an equilibrium mixture of the diamagnetic square planar form and two paramagnetic forms, one of which is five coordinate and the other six coordinate.[72,134]

A square planar, tetrahedral solution equilibrium has also been reported for four coordinate cobalt(II) complexes.[131,135,136] However, both forms are now paramagnetic and the equilibrium cannot be studied by means of equation (29). Free energy changes for the structural interconversion have been evaluated from NMR measurements of the temperature dependence of the solution susceptibility.[137] ΔG is given by—

$$\Delta G = RT\ln\left[\frac{\mu_t^2 - \mu_o^2}{\mu_o^2 - \mu_p^2}\right] \tag{30}$$

where μ_t and μ_p are the magnetic moments of the tetrahedral and square planar forms taken from measurements on the solid and μ_o is the observed magnetic moment of the solution. The results indicate that, for a given ligand, the relative stability of the tetrahedral form is greater with cobalt(II) than with nickel(II), in agreement with crystal field stabilization energy arguments.

A variable temperature study of the NMR spectra of some copper(II) complexes has indicated an equilibrium between tetrahedral and other forms.[138,139] The variation of the line width with temperature has been interpreted in favour of increasing stability of the tetrahedral form of bis(*N*-isopropyl-salicylaldimato)copper(II) with increasing temperature.[139]

2. *Spin equilibrium*

All metals with the electronic configuration d^6 are theoretically capable of exhibiting a spin equilibrium between a diamagnetic term $^1A_{1g}$ and a thermally accessible paramagnetic term $^5T_{2g}$. It has been demonstrated for a series of iron(II) poly(1-pyrazolyl)borates[140,141] that the spin equilibrium may be studied by following the temperature dependence of the proton contact shifts of the ligands. The results obtained from this study are in qualitative agreement with the conclusions reached from magnetic data. The thermodynamic parameters relating to the spin equilibrium may be interpreted by an equation comparable to equation (29) after due allowance has been made for the g tensor anisotropy of the $^5T_{2g}$ term. Each level of the split $^5T_{2g}$ term requires an individual Boltzmann averaging which makes the expression for the temperature dependence of the contact shift rather complicated.

Proton and ^{19}F NMR data have been reported for some iron(III) complexes with substituted dithiocarbamates.[142,143] These complexes exhibit a spin equilibrium between the terms $^6A_1$ and $^2T_2$ both of which are paramagnetic. From the NMR and magnetic susceptibility data it has been possible to determine the ratio of the molecular vibrational partition functions corresponding to the two terms.[143] Recently the proton "contact" shift of uranium(IV) tetracyclopentadienyl has been reported.[144] It is claimed that, since the ground term is a spin singlet, the "contact" shift arises from the thermal population of an excited spin triplet term.

3. *Optical isomers*

The contact shifts of paramagnetic species are frequently between 1 and 10 KHz. The magnitude of these shifts means that it is sometimes possible to detect very subtle differences in molecular structure which lie beyond the limit of resolution in diamagnetic systems. An example of this is the estimation of the differences in π bonding abilities of different ligands in the same complex as discussed in Section IIIA(2). A further example lies in the detection of diastereoisomers.[87] In a bis complex with a ligand containing an asymmetric centre it is possible to have three isomeric species, namely (+,+) and (–,–) both of which are optically active and (+,–) the *meso* form. Comparison of the proton spectra of the *meso* form with that of either of the active forms of a series of bis-salicylaldimine complexes of nickel(II) shows that a splitting of up to 10 Hz occurs in some of the signals of the former indicating the difference between the (+) and (–) forms of the ligand.[110,124,145] The temperature dependencies of the sets of signals for the active and *meso* isomers are found to be different. Thus it is possible to interpret the observed spectra in favour of a difference in the free energy changes for the structural equilibria of the active and *meso* forms, ΔG_{active} and ΔG_{meso}.

$$\text{Square Planar } (+,+) \text{ or } (-,-) \xrightleftharpoons{\Delta G_{active}} \text{Tetrahedral } (+,+) \text{ or } (-,-)$$

$$\text{Square Planar } (+,-) \xrightleftharpoons{\Delta G_{meso}} \text{Tetrahedral } (+,-)$$

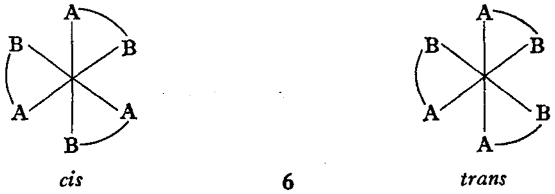
Further studies have been reported on four coordinate nickel(II) complexes with salicylaldimine type ligands having two or more asymmetric centres and a further centre of asymmetry at the metal.[121,146–149] In favourable cases the absolute configuration at the metal Δ,Λ is not racemized in the square planar, tetrahedral equilibrium. In this case it has been possible to detect the three diastereoisomers, $\Delta(+,+)\equiv\Lambda(-,-)$, $\Delta(-,-)\equiv\Lambda(+,+)$ and $\Delta(+,-)\equiv\Lambda(+,-)$, by virtue of three distinct signals for certain proton sites.[149] This has been verified by the further doubling of each proton line when the spectrum is taken in an optically active solvent.

In the case where a structural equilibrium is not proposed, contact shift differences between optically active and inactive forms have been attributed to differences in the hyperfine splitting constant for a given proton in the two forms.[62,146,150] Some four coordinate complexes of nickel(II) and cobalt(II) with an unsymmetrical phosphine ligand appear to be an example of this case.[150]

4. *Some other structural investigations*

In metal complexes of amino acids the nature of the metal binding sites is often of biological significance. Small, pH dependent, structural changes of amino acids coordinated to transition metal ions have been detected from contact shift measurements.[151–153] The interpretation of these shifts leads to a better understanding of the metal binding sites. The binding site may be localized by noting which of the protons exhibit the largest shift, since for either σ delocalization of a pseudo-contact interaction these protons are the ones which are closest to the metal ion. It has been reported that the biologically important metal cobalt(III) forms four different types of complexes with histidine in different pH ranges.[153] The spectra reported for the 2:1 complex formed from a racemic mixture of histidine have been interpreted in favour of an octahedral structure.[153]

Cis and *trans* isomers are possible for tris-chelate complexes (**6**) containing an unsymmetrical chelate ring. The *trans* isomer has no symmetry whilst the *cis* isomer contains a C_3 symmetry axis. Consequently we expect a separate proton signal for a given proton site on each chelate ring in the *trans* form and a single line for the *cis* form. This criterion has been applied in deciding the stereochemistry of vanadium(III) complexes with β-diketones,[87] β-ketoamines,[88] salicylaldehydes[89] and salicylaldimines.[89]



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A comparison of the contact shifts recorded for a series of *N*,*N*-dimethylamides and lactams hexacoordinated to nickel(II) has resulted in the identification of the methyl groups which are either *cis* or *trans* to the carbonyl oxygen atom in the free amide.[154] The results show that the *cis* methyl group is the more shielded one. This agrees with previous assignments of the free amide based on coupling constants, but is at variance with theoretical predictions of the magnetic anisotropy of the carbonyl group.

The formation of hydrogen bonds between chloroform and some complexes of nickel(II) and cobalt(II) has been claimed following the observation of the contact shifted chloroform proton signal.[155] It appears that the contact interaction is dominant in producing the observed shift so the results indicate a degree of covalency in the hydrogen bonded complex.

The ^{17}O and ^{35}Cl NMR spectra of cobalt(II) chloride in solutions containing a range of concentrations of hydrochloric acid from 0·4 to 16 molar have shown that the important species in solution are $Co(H_2O)_6{}^{2\oplus}$, $CoCl(H_2O)_5^{\oplus}$, $CoCl_2(H_2O)_2$, $CoCl_3(H_2O)^{\ominus}$ and $CoCl_4{}^{2\ominus}$. The tetrahedral $CoCl_4{}^{2\ominus}$ ion predominates at high concentrations of hydrochloric acid.[156,157] The magnitude of the hyperfine interaction for the ^{17}O and ^{35}Cl nuclei makes the pseudo-contact interaction insignificant in hydrochloric acid solutions containing cobalt(II) and iron(III).[156,158] Whereas the proton spectra of these and analogous systems require a pseudo-contact contribution for accurate interpretation.[159]

The proton spectra of a series of aqueous solutions containing varying amounts of nickel(II) chloride and ethylenediamine show that the signal of the $—CH_2—$ protons is split into a doublet when the nickel-trisethylenediamine species is present.[160] The position of the proton signal corresponding to the mono- and bis-ethylenediamine nickel(II) species lies midway between the split components of the signal of the tris complex indicating that a rapid conformational equilibrium takes place in the former species.

The competitive equilibria for coordination sites on nickel(II) have been investigated from the NMR spectra of solutions of $Ni(pyridine)_4Cl_2$ in $CDCl_3$ containing various amounts of pyridine, α,β or γ-picoline, γ-picoline oxide and triphenylphosphine or triphenylphosphine oxide.[161] The results show that pyridine and β and γ-picoline have approximately the same affinity for hexacoordinate nickel(II), which is many times greater than the affinities of the other ligands. This is in agreement with coordinating abilities of the ligands as deduced from their electronic structures.

C. Ion-pair formation in solution

Isotropic shifts have been observed in the proton NMR spectra of diamagnetic cations when in solutions containing paramagnetic anions. These shifts have been attributed to pseudo-contact interactions arising from ion-pair formation.[98,104,162–167] The single resonance line for each equivalent set of protons in the cation may be produced by rapid tumbling of the cation at a fixed distance from the metal ion,[98] or by exchange between free cations and those in ion pairs at a rate in excess of 10^3 sec^{-1}.[164] This latter proposal is supported by the dependence of the shifts upon the concentration of cation. LaMar[98,104] has reported isotropic shifts for the butyl protons in complexes of the type $[(Butyl)_4N][(C_6H_5)_3PMI_3]$ where M is either Co^{II} or Ni^{II}, in $CDCl_3$ solutions. All of the butyl protons in the cobalt complex are shifted to lower frequency, the protons of the methylene group adjacent to the nitrogen atom being shifted farthest. The shift decreases along the butyl chain such that the terminal methyl protons are only slightly shifted from their diamagnetic position. In the corresponding nickel complex all of the butyl protons are shifted to higher frequency, again the magnitude of the shift decreases along the butyl chain. The shifts have been interpreted in terms of equations (21) or (22) depending upon the relative magnitudes of T_{1e} and τ_c. The opposite signs of the shifts in the analogous cobalt and nickel complexes are thought to arise from different signs in the g tensor anisotropy, $g_\perp > g_\parallel$ for the former and $g_\parallel > g_\perp$ for the latter.[98]

On the assumption of free internal rotation within the cation the ratio of the pseudo-contact shifts for two inequivalent sets of protons may be calculated as a function of the interionic separation along the C_3 axis of the distorted tetrahedral anion (Fig. 5). A comparison of the observed and calculated ratios has provided an estimate of the equilibrium interionic distance of 3·8 ± 0·2 Å for both of the complexes discussed above. The corresponding ionic radius of the cation is estimated as 3·1 ± 0·2 Å, which is compatible with the n-butyl chains being folded. Hence it is reasonable to suppose that the terminal methyl groups are farthest from the metal ion in the ion-pair, as is suggested by their small isotropic shift.

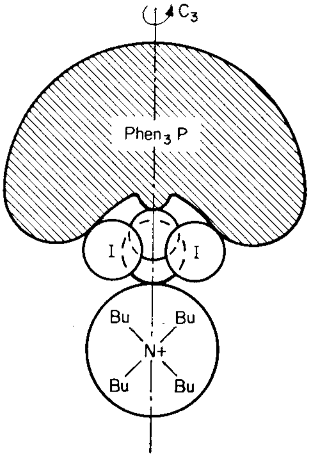


FIG. 5. Model for the ion pair $[Bu_4N]^{\oplus}[(Phen_3P)MI_3]^{\ominus}$. (From LaMar, p. 236.[104])

An alternative interpretation of the shifts of the butyl protons is that they arise from a direct spin transfer from the metal ion to the nitrogen atom of the cation.[101,168] This mechanism appears to be supported by the observation of high frequency ^{14}N signals for a number of cations in ionic complexes.[168] However it also postulates that the spin will be transferred to the protons in the alkyl chain which should produce shifts of lower frequency in all cases for complexes of cobalt(II) and nickel(II). Whilst the butyl protons in the cobalt(II) complex described above have shifts in agreement with this proposal, the protons in the corresponding nickel(II) complex exhibit shifts at higher frequency, which invalidates the spin transfer mechanism for these complexes.[167]

The proton spectrum of the cation in the complex $[(C_6H_5)_4As]$-$[(C_6H_5)_3PCoI_3]$ has been interpreted in favour of the cation occupying a site on the C_3 axis of the anion, with an interionic separation of 9·0 ± 0·8 Å.[163] A similar model has been employed to analyse the spectra of $[(C_4H_9)(C_6H_5)_3P][(C_6H_5)_3PMX_3]$, where M is either Co^{II} or Ni^{II} and X is bromide or iodide.[167] In the cobalt(II) anions containing iodide the interionic separation is found to be about 0·5 Å greater than in the corresponding bromide complex. This is in agreement with the differences in the Van der Waals radii of the bromine and iodine atoms. For the cobalt triiodide anion the interionic distance is estimated to be 8·1 Å which, considering the smaller size of the phosphorus atom and the smaller steric requirements of the butyl group, is in good agreement with the work on $[(C_6H_5)_4As][(C_6H_5)_3PCoI_3]$. This lends support to the dipolar model of ion-pairing which, although it may not accurately predict interionic distances, does give meaningful comparisons of sizes of related species.

Two of the assumptions that are made in applying the dipolar model are that the ions are spherical and that the ion-pairs in equilibrium with solvated ions are the only significant species present in solution. If the cation is non-spherical, as seems likely for $[(\text{Butyl})_4N]^{\oplus}$, then the calculated interionic distances will be too small. In low dielectric solvents such as chloroform higher ionic aggregates are to be expected which will produce further complications.[162,163,169]

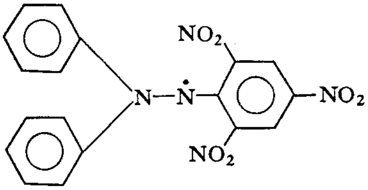
From the proton spectra of a series of $[(\text{Butyl})_4N][MX_4]$ complexes in 0·25M dichloromethane solutions, where M is Fe^{II}, Co^{II} or Ni^{II} and X is a halide, ion-pairing has been reported.[166] The isotropic shifts are found to be at lower frequencies for the iron(II) and cobalt(II) salts and to higher frequency for the nickel(II) salts. Since the anions are expected to be cubic in solution the *g* tensor should be isotropic, consequently a pseudo-contact interaction is not anticipated. To account for the observed shifts it is assumed that the anion is distorted and that the shifts may be correlated with the magnitude of this distortion.

Recently the NMR spectra of alkali metal nuclei have been employed to demonstrate the existence of positive and negative spin densities on the metal nuclei when they form ion-pairs with aromatic radicals.[170]

D. Organic free radicals

NMR studies on organic radicals in the solid state were first reported in 1958. The dipole–dipole coupling produces short nuclear relaxation times in the solid state, consequently the observed resonances are broad. From equation (19) it is apparent that low temperatures enhance the contact shift interaction. Hence contact shifts in excess of the line width for the solid samples have been obtained by observing their spectra at liquid helium temperatures.[4,5]

Reasonable agreement has been obtained between the spin densities derived from the solid state contact shifts, the solution ESR spectra and theoretical calculations for α,α-diphenyl-β-picrylhydrazyl (DPPH, **7**)[171,172]



DPPH **7**

and potassium pyrenide.[173] The signs of the hyperfine interaction constants were found for DPPH, which provided the first direct evidence of negative spin densities on carbon atoms in odd alternant π systems, and consequently the inadequacy of the Hückel molecular orbital theory in estimating spin densities in this type of radical.

Hyde and Maki first observed ENDOR spectra of radical solutions and hence indirectly studied the nuclear resonances.[174,175] ENDOR is, however, not an improvement upon ESR either with regard to resolving small interaction constants or the determination of their signs.

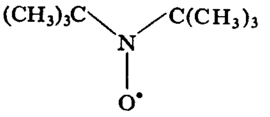
In radicals containing methylene or methyl groups the π spin density at a ring carbon atom may be transmitted to the aliphatic protons by two effects, hyperconjugation and spin polarization.[176] It is considered from ESR data that the hyperconjugative effect is the most important and that an additional small contribution from spin polarization may be present in many radicals.[176–178]

Electron transfer between a neutral molecule and its paramagnetic anion modifies the NMR spectrum of the molecule by broadening and shifting its resonances. Information relating to the rate of electron exchange may be found from the line broadening (Section IIIF(2)) and the unpaired electron spin density at the nucleus may be derived from the line shift.[5] This procedure has been used to study the spin density distribution of alkyl substituted naphthalene anions[179] and some 1- and 1,4-alkyl substituted benzene anions in solution.[19,180,181]

ESR studies on 1- and 1,4-alkyl substituted benzene anions have revealed that the lowest antibonding orbital is antisymmetric with respect to the plane passing through carbons 1 and 4 and perpendicular to the molecular plane.[182] The next antibonding orbital is slightly higher in energy and is symmetric with respect to this plane. Vibronic interaction or thermal mixing between these states can produce positive spin densities in the lowest antibonding orbital at the 1 and 4 positions, whereas configuration interaction between the ground and excited states will produce negative spin densities at these positions. The negative spin densities at the protons on the α carbon atom of the anions of *p*-xylene and *p*-diethylbenzene indicate that the configuration interaction mechanism appears to be dominant in this case.[16,176] The NMR data for *p*-xylene, 1-ethyl-4-methylbenzene, 1-isopropyl-4-methylbenzene and 1-tertiarybutyl-4-methylbenzene in the presence of their anions indicate that the spin density on the protons of the methyl group in position 4 changes sign along the series of anions. This is thought to be due to a decrease in the energy difference between the two lowest states upon passing along the series. In this manner an increase in the vibronic and thermal effects occurs leading to increased positive contributions to the spin density at the 4 position.

The NMR spectra of the anions of ethylbenzene and isopropylbenzene show that the spin densities at all of the ethyl protons in the former and at the single C–H proton of the isopropyl group in the latter are positive. This may be accounted for by noting that in the monosubstituted benzene anions vibronic coupling between the ground and first excited state is more important than in the dialkyl substituted benzene anions.[183] The available variable temperature NMR and ESR data on the monosubstituted benzene anions lend support by showing that the hyperfine interaction constant is temperature dependent whereas for the 1,4 disubstituted anions it appears to be temperature independent.[181]

In addition to those systems exhibiting rapid electron transfer, reasonably sharp NMR lines are expected for highly concentrated radical solutions in low viscosity solvents at high temperatures as described by equation (25). Using the appropriate conditions Kreilick[184] and Hausser *et al.*[25] first reported contact shifted proton spectra for solutions of the radicals di-tertiarybutylnitroxide (DBNO, **8**), tertiarybutyl 2,6-dimethoxyphenylnitroxide (DMPNO, **9**), tritertiarybutylphenoxyl (TBP, **10**) and Coppingers radical (CR, **11**). These radicals have the added advantage of containing a small number of different types of inequivalent protons with a relatively large number of protons of each type. In most cases the spectra allow the estimation of the sign and magnitude of the hyperfine interaction constants. Good agreement with values found from ESR data are reported.[20,184] In addition some small interaction constants which are unavailable from ESR spectra, due to inferior resolution, have been evaluated.



DBNO

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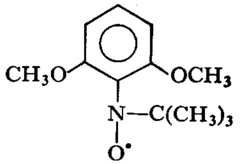

DMPNO

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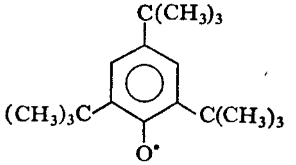

TBP

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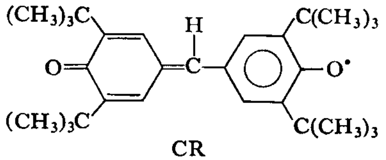

CR

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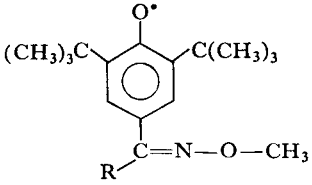
The positive values for the hyperfine interaction constants of the *ortho*-tertiarybutyl protons in TBP and CR indicate a hyperconjugative transfer of positive spin density from the aromatic carbon atom to the butyl protons. In DBNO the interaction constant of the protons is negative whilst the spin density on the nitrogen atom is positive indicating that the hyperconjunction mechanism alone is unable to account for the transmission of spin density through alkyl chains.

If a radical is dissolved in a paramagnetic solvent rapid spin exchange between solute and solvent may allow the NMR spectrum of the solute to be observed in relatively dilute solutions, large values of the hyperfine interaction constant may also be resolved by this means. Kreilick has used this rapid spin exchange to study the NMR spectra of a series of phenoxy radicals dissolved in DBNO.[185–188] Good agreement was obtained in most cases between the values of the hyperfine interaction constant derived from ESR and NMR data. In some cases the ESR spectrum has been computer simulated using the interaction constants determined from NMR data.[185,188] From the NMR spectra of the DBNO solutions of the substituted phenoxy radicals (**12**; R = H, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,



12

cycloheptyl) lines for both the *syn* and *anti* conformations have been reported for those radicals with cyclic substituents.[187,188] The spectra have been assigned on the assumption that the favoured conformation is the one in which the methoxy group is *anti* to the phenoxy ring. From the spectra of the substituents R, it is found that the interaction constant of the proton on the carbon atom bonding R to the remainder of the radical is very dependent upon the size of R, it decreases as R becomes larger. This suggests that hyperconjugation plays a significant part in determining the magnitude of the interaction constant for this proton since, with the hyperconjugative mechanism, the interaction depends upon the angle between the proton and the p orbital of the carbon atom containing the unpaired spin.[189] The interaction constants, for the protons in the substituent R, are smaller and not so dependent upon the size of R and show an alternation in sign and attenuation with distance. This could be accounted for by a spin polarization mechanism with alternating signs for the polarization constant Q in equation (26). These smaller interaction constants are not obtainable from the ESR data.

Proton NMR spectra have been reported for some cyclic aliphatic azoxy radicals[190] and some cyclic aliphatic nitroxides.[191] Alternation in the sign of the hyperfine interaction constant for protons attached to adjacent aliphatic carbon atoms occurs for both series of radicals. The azoxy radicals show separate temperature dependent resonances corresponding to different ring conformations but, due to the rapid interconversion of conformers, the nitroxide radicals have not shown separate resonances over the temperature range studied.

Only a small number of investigations of spin delocalization through aliphatic chains based upon contact shifts have been reported to date. The theoretical understanding of the results is not as well developed as it is for π spin densities. Further NMR data on solutions of σ radicals are expected to assist in the interpretation and understanding of spin delocalization in aliphatic systems.

E. Solvation phenomena

Ideally the study of solvation effects by NMR should provide separate resonance signals for solvent molecules in the bulk of the solvent medium and for those attached to an ion. In practice rapid solvent exchange ensures that this situation does not arise.[192] Assuming that the inequalities of equation (3) are satisfied, the ratio between the lifetime of the solvent molecule in the coordination shell and the reciprocal of the separation between the two sets of signals determines whether or not the sets of signals appear as separate resonances.

Since water is a solvent of great interest to many areas of chemistry and biology much attention has been paid to the study of the hydration shells of paramagnetic ions. In addition to the problem of rapid site exchange the proton signals of water molecules coordinated to a paramagnetic centre are broad such that the shift between bonded and free water is not always large when compared to the line width. Separate proton signals for water molecules in an aqueous solution of a paramagnetic salt have only recently been reported[193] using concentrated solutions of $Co(ClO_4)_2$ (Fig. 6). From the dependence of the relative signal intensities upon solution composition the low field line is assigned to coordinated water. A primary hydration number of six, which is independent of temperature and solution composition, is suggested for cobalt(II) from the proton signal intensities. Earlier proton NMR spectra of aquous solutions of paramagnetic metal ions have shown only the exchange averaged shift from which values of the hyperfine interaction constant are available.[76,77,100] When the rapid exchange of solvent molecules between the coordination sphere and the bulk solvent occurs, the observed isotropic shift $\Delta\nu$, which is the difference between the resonance frequency observed for the solution and the pure solvent, is given by—

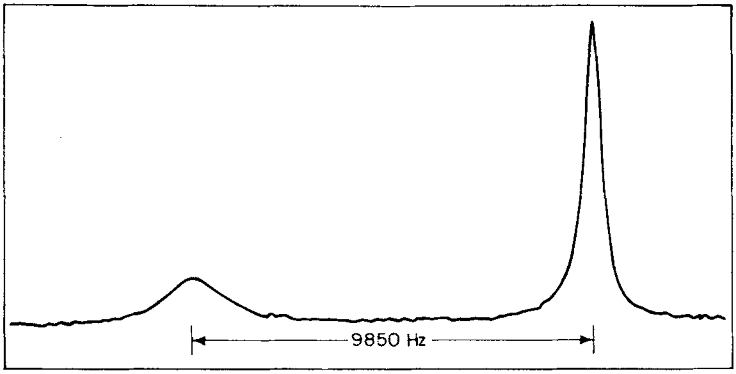


FIG. 6. Proton magnetic resonance spectrum (100 MHz) of a 3·2 M solution of $Co(ClO_4)_2$ in water at −60°C. The magnetic field increases from left to right. (From Matwiyoff and Darley.[193])

$$\Delta\nu = pq\Delta\nu_M \tag{31}$$

where $p = [M]/[\text{Solvent}]$, $\Delta\nu_M$ is the difference in the resonance frequencies for a nucleus in a coordinated and a non-coordinated solvent molecule, and q is the number of solvent molecules coordinated to the metal M. The validity of values of q found by this method depends upon $\Delta\nu_M$ being constant within a series of analogous complexes. Alternatively, if q is known, the hyperfine interaction constant may be found from the contact shift, denoted by $\Delta\nu_M$, by combining equations (19) and (31) to obtain

$$\Delta\nu = pq\Delta\nu_M = -pq\nu_0\, a_N \frac{g_e^2\beta_e^2 S(S+1)}{g_N\beta_N . 3kT} \tag{32}$$

Agreement between the values of the interaction constants found in this manner is not very convincing, especially in the case of solutions containing iron(III).[76,77] This could reflect the incomplete averaging of the line shift, in such cases the kinetic parameters for the exchange process must be taken into account when evaluating a_N.[77]

The ^{17}O chemical shift difference between coordinated and solvent water molecules in a paramagnetic environment is about 10^5 Hz at room temperature. Although the ^{17}O line width can be $\sim 10^4$ Hz in a paramagnetic solution the larger shift compared to that of protons has led to hydration studies employing ^{17}O NMR spectra.[195–198] The first successful observation of an ^{17}O NMR signal from water in the hydration sphere of a paramagnetic metal ion was reported for the Ni^{II} ion which appears to have a coordination number of four or six.[195] Further investigations have dealt with aqueous solutions of cobalt(II), for which a coordination number of six is reported.[196,197] In general the ^{17}O data are in agreement with the results obtained from proton spectra. From relaxation studies on the hydrated Ni^{II} ion it appears that the ^{17}O nucleus relaxes via the scalar hyperfine interaction whereas the protons are relaxed through dipolar coupling. In the former case the relaxation time is dependent upon a_N but independent of the Ni–O separation, whereas in the latter it is very dependent upon the Ni–H distance.[195]

The rate of solvent exchange, between the solvation shell and the bulk solvent, is temperature dependent. By using methanol as solvent the solutions may be cooled to a much lower temperature than aqueous solutions, thus the chances of reducing the exchange rate sufficiently to observe separate resonances are increased. Proton and ^{17}O spectra of methanol coordinated to Ni^{II},[199,200] Co^{II}[197,201] and Ti^{II}[202] ions have been reported. In general, the coordination number of these ions in methanol appears to be six but definite conclusions concerning the structures of the complex ions are not available.[200]

From proton NMR data obtained on aqueous solutions of cobalt(II), containing various monodentate ligands, Horrocks and Hutchinson have suggested that pseudo-contact interactions cannot be ignored.[159] They also demonstrate that earlier work on cobalt(II) methanol-water complexes may be interpreted in a similar manner.[4,199,201] Thus changes in the first coordination sphere of cobalt(II) in solutions containing potential ligands may not be accurately determined from NMR solvent shifts.

Solvation numbers of six have been reported for cobalt(II) and nickel(II) perchlorates in *N,N*-dimethylformamide (DMF),[203] dimethylsulphoxide (DMSO)[204] and acetonitrile.[79,80] It appears that DMF is coordinated to cobalt(II) via its oxygen atom and the Co–O–C angle is non-linear.[203] The tetrafluoroborate salts of cobalt(II) and nickel(II) in acetonitrile have essentially the same solvation data as the corresponding perchlorates indicating complete dissociation of these salts.[205] The hexammino Ni^{II} ion in liquid ammonia has been studied by ^{14}N NMR.[206–208] The ^{14}N data are consistent with the existence of a single solvated metal species over a wide range of temperature and solution composition.

The outer coordination sphere has also been investigated by NMR studies. From ^{17}O data on enriched water solutions of hexaaquo chromium(III), in the presence of perchlorate ion, Alei has concluded that the perchlorate ion enters into the second coordination sphere of the $Cr(H_2O)_6{}^{3\oplus}$ ion.[209] The ratio of perchlorate to water in this coordination sphere is similar to that in the bulk solution. A ^{19}F study on fluoride and $PF_6^{\ominus}$ ions in solutions containing $Cr(H_2O)_6{}^{3\oplus}$ ions with various ligands has revealed that the nature of the ligands in the first coordination sphere influences the degree of second sphere coordination.[210] Generally the degree of outer sphere coordination increases with increasing charge on the inner sphere complex.

F. Relaxation studies

In this section we shall be considering the chemically interesting information available from rate processes and relaxation phenomena of paramagnetic systems.

1. *Kinetics of chemical exchange processes*

In a chemically stable system the line shape of an NMR spectrum is described by the Bloch equations. These have been modified to include the possibility of chemical exchange by McConnell.[211] Further modifications to include the conditions present in dilute aqueous solutions containing paramagnetic metal ions have been reported by Swift and Connick.[194,212]. Half of the line width at half height $\delta\omega$, expressed in rad/sec, is equal to the reciprocal of the apparent nuclear transverse relaxation time T_2.[213] The actual line width is a function of the relaxation time of the nuclei in the bulk solvent T_{2W} which occurs in the absence of paramagnetic ions, and a contribution T_{2P} from the paramagnetic ions. These are related by equations (33) and (34).

$$\delta\omega = \frac{1}{T_2} = \frac{1}{T_{2W}} + \frac{1}{T_{2P}} \tag{33}$$

$$\frac{1}{T_{2P}} = \frac{1}{T_2} - \frac{1}{T_{2W}} = \frac{1}{\tau_W}\left[\frac{(T_{2M}^{-2}) + (T_{2M}\tau_M)^{-1} + \Delta\omega_M^2}{(T_{2M}^{-1} + \tau_M^{-1})^2 + \Delta\omega_M^2}\right] \tag{34}$$

where τ_W and τ_M are the lifetimes of water nuclei with respect to chemical exchange, in the bulk of the solution and coordinated to the metal ion respectively, T_{2M} is the transverse relaxation time of a water nucleus in the solvation shell and $\Delta\omega_M$ is the difference in precessional frequency of the water nucleus between the bulk water and coordinated water molecules. By considering various relaxation mechanisms and limiting cases of the factors that contribute to T_{2M}[214,215] it is possible to evaluate τ_M and hence the appropriate rate constant.[194,216] For solutions with broad lines and poor signal to noise ratios computerized complete line shape techniques have been used to obtain the kinetic parameters.[217] Direct measurement of nuclear relaxation times have been reported for ligands with only one type of proton such as water[218–220] and DMSO,[221] from which τ_W and τ_M may be evaluated.

The variation of τ_M with temperature allows the enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ of activation, for the water exchange between the coordination sphere and the bulk of the solution, to be evaluated from equation (35).

$$\tau_M = \frac{h}{kT} \exp\left[\frac{\Delta H^{\ddagger}}{RT} - \frac{\Delta S^{\ddagger}}{R}\right] \tag{35}$$

Water enriched in ^{17}O has been widely used in exchange studies making use of the ^{17}O NMR spectra.[195,222–224] A comparison of the ^{17}O and proton NMR data on hexaaquo metal ions in aqueous solution makes it possible to decide whether proton exchange occurs via proton ionization or the complete exchange of a water molecule. The similarity of the kinetic parameters from the ^{17}O and proton data suggests that the complete exchange of water molecules occurs in aqueous solutions of Mn^{II}, Co^{II}, Ni^{II} and Cu^{II} ions, whereas in solutions containing $VO^{2\oplus}$, Cr^{III} and Fe^{III} ions the acid dissociation of the hydrated metal ion appears to be the most probable mechanism for proton exchange.[4,77,158,195,225–227] The similarity in the kinetic data derived from the methyl and hydroxyl protons for methanol in the presence of Mn^{II}, Co^{II} and Ni^{II} ions indicates that the exchange between the bulk solvent and solvation shell involves whole methanol molecules and that there is no significant contribution from hydroxyl proton exchange.[199,201,228] Comparable results have been obtained from ^1H and ^{14}N data on $Ni(NH_3)_6^{2\oplus}$ in an aqueous-ammonia medium, showing that the exchange rate of the individual proton is no greater than that for the exchange of complete ammonia molecules.[207,208,229]

The rates of elimination of water molecules from the first coordination sphere of vanadyl ions in aqueous solutions have been determined from ^{17}O data.[223,224,230] The slow rate of water exchange, compared to other doubly charged metal ions, led to the conclusion that the high positive charge on $V^{4\oplus}$ is important in deciding the bonding of the four equatorial water molecules in the first coordination sphere, whilst the water molecule in the axial position undergoes rapid exchange.[230] By comparing the NMR data on the vanadyl ion in a DMF solution at 25°C with that for aqueous solutions it is found that the rate constants for water and DMF exchange are very similar, but that the activation energy for DMF exchange is much smaller indicating that it is a weaker ligand than water. The values for the entropy of activation suggest that the transition state is more disordered for water exchange possibly due to increased hydrogen bonding between water and the vanadyl ion.[231] NMR data on a series of vanadyl chelates demonstrate that the exchange rate of water from a coordination site can be influenced by the ligands coordinated to adjoining positions.[225] This should be compared with the results obtained from ^{17}O and ^{14}N NMR data on aquothiocyanato complexes of nickel(II), from which it is concluded that the exchange processes of the water and thiocyanate ligands proceed independently.[222]

Proton and ^{14}N data have been reported for aqueous-amine solutions containing copper(II) and various ethylenediamines.[232,233] The kinetic parameters derived from the spectra are consistent with the exchange of an ethylenediamine molecule in its entirety between the first coordination sphere of copper(II) and the bulk solvent.

The values of the kinetic parameters relating to the exchange of acetonitrile in solutions containing Co^{II} and Ni^{II} ions are listed in Table I. The more rapid rate of the solvent substitution reaction for the cobalt(II) complex, relative to that for the nickel(II) complex, is largely due to the difference in activation enthalpy for the two reactions. This relative decrease in the stability of octahedral cobalt(II) complexes, compared to those of nickel(II), have been observed in other donor solvent systems[203,204,234] and has been critically discussed in terms of crystal field stabilization effects.[203,234]

TABLE I

Kinetic data from NMR studies on solutions of acetonitrile with metal ions

Metal ion	10^{-4} K, sec^{-1}, at 25°C	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$ e.u.	Ref.
Ni^{II}	1·24	11·8 ± 0·8	−0·2 ± 2·5	205
Ni^{II}	0·39	10·9	−8·8	79
Ni^{II}	0·24	11·7 ± 0·1	−3·6 ± 0·1	80
Co^{II}	15	8·4 ± 0·6	−7 ± 2	205
Co^{II}	14	8·1 ± 0·3	−7·5 ± 2	79

Recently the kinetics of ligand exchange have been investigated in tetrahedral complexes as well as octahedral ones.[216,217,235–237] Proton NMR data are reported for complexes of the type ML_2X_2 where M can be Fe^{II}, Co^{II} or Ni^{II} and the exchanging ligand L can be triarylphosphine,[216,235,236] 2-picoline[217] or hexamethylphosphoramide[237] and X is a halogen. With the exception of the cobalt(II) hexamethylphosphoramide complexes, which exchange by a mixture of first and second order kinetics, all of the complexes studied show only second order kinetics in their ligand exchange reactions. The necessity of a first order term for the hexamethylphosphoramide ligand has been rationalized in terms of the steric hindrance produced by its size which increases the tendency for the ligand to dissociate from the complex.[237] In the triarylphosphine series of ligands it appears that the lability of the complex is not very dependent upon the nature of the phosphine, but that within a given series the lability increases slightly in the order I < Br < Cl. This order does not appear to be very dependent upon $\Delta H^{\ddagger}$ values alone but upon a combination of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ effects. The order does not reflect the π bonding ability of the halide since π bonding differences are expected to run parallel with differences in $\Delta H^{\ddagger}$ values.[216] The effect of the metal upon the lability follows the order Co < Ni < Fe as shown in Table II.[236] This order is the same as that for the ground state stability predicted by ligand field stabilization arguments. Similar arguments can, however, be used to suggest that a pentacoordinate transition state of iron(II) will be less stable than that of cobalt(II) and nickel(II), in which case the order of lability would be Co, Ni > Fe. Simple ligand field arguments alone are obviously inadequate in assessing the relative reaction rates for the complexes studied, however it may be concluded that the relative *d* orbital populations are important in understanding the relative lability of tetrahedral transition metal complexes.

TABLE II

Kinetic data for the exchange of ligand L with complexes of the type ML_2Br_2

Complex	K_2, sec^{-1}, at 25°C	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, e.u.
L = Triphenylphosphine			
FeL_2Br_2	$2{\cdot}0 \times 10^5$	$3{\cdot}8 \pm 0{\cdot}5$	-22 ± 3
NiL_2Br_2	$6{\cdot}9 \times 10^3$	$4{\cdot}7 \pm 0{\cdot}4$	-25 ± 2
CoL_2Br_2	$8{\cdot}7 \times 10^2$	$7{\cdot}7 \pm 0{\cdot}5$	-19 ± 3
L = Tri-*p*-tolylphosphine			
FeL_2Br_2	$6{\cdot}3 \times 10^5$	$4{\cdot}0 \pm 0{\cdot}8$	-19 ± 5
NiL_2Br_2	$6{\cdot}1 \times 10^3$	$5{\cdot}2 \pm 0{\cdot}8$	-24 ± 4
CoL_2Br_2	$1{\cdot}8 \times 10^3$	$5{\cdot}5 \pm 0{\cdot}9$	-25 ± 4

[a] The value of K_2 is estimated to within $\pm 0{\cdot}5 \times 10^n$.

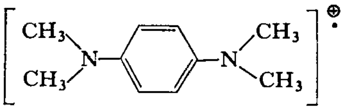
2. *Electron and proton transfer studies*

If an electron is transferred from a paramagnetic to a diamagnetic species the NMR spectrum of the latter is affected by the paramagnetic pulses generated by the unpaired electron. The effect of these pulses on the spectrum of the diamagnetic molecule depends upon their magnitude, duration and frequency. The magnitude of the pulses is dependent upon the hyperfine interactions between the spin of the transferred electron and the nuclei of the newly produced radical. The duration and frequency of the pulses are a function of the kinetics of the electron transfer reaction. Consequently analysis of the NMR spectrum may provide information on the spin density distribution from the line positions and of the kinetics of the transfer process from the line shapes.[19]

The theoretical derivation of the expressions used in the analysis of the NMR spectra, resulting from electron transfer reactions and the basically similar hydrogen atom transfer reactions, has recently been discussed by DeBoer and his co-workers.[5,19] A number of applications of these reactions have also been reviewed.[5,238] It is not proposed to cover this area of NMR in depth here, but for reasons of balance a few of the chemical applications of electron and proton transfer reactions are included.

The line shape analysis of the proton spectra of a number of diamagnetic iron(II) complexes, in the presence of the corresponding paramagnetic iron(III) species, has produced limiting values for the bimolecular rate constant for electron transfer. The lower limits for the rate constants are of the order of 10^5 M^{-1} sec^{-1} for iron complexes of cyclopentadiene,[239] 1,10-phenanthroline[239] and a number of dimethyl substituted 1,10-phenanthrolines.[240,241] The rate of electron transfer between ferricyanide and ferrocyanide ions has been determined from ^{14}N data taken in the presence of a number of alkali metal and alkaline earth cations in aqueous solutions.[242] The cations have a marked catalytic effect on the reaction rate, the effect increasing from $H^{\oplus}$ to $Cs^{\oplus}$ and from $Ca^{2\oplus}$ to $Sr^{2\oplus}$. However the detailed mechanism of the transfer of electrons in the presence of cations is not completely understood.

The first electron transfer reaction studied by NMR was that between Wursters blue (**13**) and its diamagnetic precursor in D_2O.[243] The rate



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constant is found to be very pH dependent increasing from $1{\cdot}5 \times 10^4$ M^{-1} sec^{-1} at pH $= 2{\cdot}68$ to $2{\cdot}9 \times 10^6$ M^{-1} sec^{-1} at pH $= 5{\cdot}03$ at room temperature.[244] The dependence is thought to be due to the variation in the concentration of the neutral diamine with pH, since electron transfer most probably occurs between species containing free amine groupings. This is supported by the measured value for the rate constant in acetonitrile which is (2·0 ± 1·0) × 10^8 M^{-1} sec^{-1}.[245]

The rate constant K_T for the transfer of an electron between *p*-xylene and the potassium-*p*-xylene ion-pair in 1,2-dimethoxyethane has been determined as a function of temperature.[19] It is found that K_T is $10^{12} \exp(-6200/RT)$ M^{-1} sec^{-1}. This is a smaller value than those reported for the electron transfer process between dissociated negative ions and their diamagnetic precursors which is to be expected.[246] It is also reasonable to expect the rate constants for hydrogen atom transfer reactions to be considerably smaller than those for electron transfer; this is experimentally correct. Kreilick and Weissman have reported NMR data on the hydrogen transfer reactions in some phenol-phenoxy and hydroxylamine-nitroxide systems.[247,248] They found conclusive evidence for the presence of short-lived reaction intermediates indicated by the reaction,

$$\text{RO}\cdot + \text{HOR} \underset{K_{21}}{\overset{K_{12}}{\rightleftharpoons}} \text{ROHOR} \underset{K_{12}}{\overset{K_{21}}{\rightleftharpoons}} \text{ROH} + \cdot\text{OR}$$

In the case of the tri-2,4,6-tertiarybutylphenol and its phenoxy radical in CCl_4 at 300°K, $K_{12} = (6{\cdot}6 \pm 1{\cdot}0) \times 10^2$ M^{-1} sec^{-1}, and $K_{21} = (6{\cdot}7 \pm 1{\cdot}2) \times 10^8$ sec^{-1}, whilst for 2,2′,6,6′-tetratertiarybutylindophenol and its phenoxy radical under the same conditions $K_{12} = (1{\cdot}4 \pm 0{\cdot}3) \times 10^3$ M^{-1} sec^{-1} and $K_{21} = (8{\cdot}3 \pm 0{\cdot}4) \times 10^8$ sec^{-1}. These data support the idea of the presence of intermediates whose lifetimes are about 10^{-9} sec.

3. *Structural data from relaxation effects*

The dipolar contribution to the reciprocal of the nuclear relaxation times is inversely proportional to the sixth power of the separation of the nucleus and the unpaired electron, as shown by equations (23) and (24). By using this relationship the binding sites of transition metal ions in molecules of biological interest have been studied, including ATP, RNA, ribosomes, amino-acids and peptides.[4] Proton and ^{31}P data have been reported for solutions containing ATP and Mn^{II}, Co^{II}, Ni^{II}, and Cu^{II} ions. The data on the solutions containing Mn^{II} and Co^{II} ions have been interpreted in favour of the formation of complexes in which the metal ion is simultaneously bound to the adenine ring and to the three phosphate groups.[249,250] The average time for which the Mn^{II} ion sticks to ATP at room temperature is found to be 5 × 10^{-6} sec.[250] In the case of AMP and RNA similar data suggest that Mn^{II} and Co^{II} ions bind to the phosphate groups almost all of the time.[251]

If a hydrated paramagnetic ion becomes bound to a large molecule in solution, the increase in its rotational correlation time causes the metal ion to become more efficient in processes which lead to the relaxation of the protons of the water molecules. Under these circumstances an enhancement factor ϵ for the relaxation rate of the protons has been defined[252]—

$$\epsilon = \frac{\frac{1}{T_1^*}(\mathrm{M}) - \frac{1}{T_1^*}(\mathrm{O})}{\frac{1}{T_1}(\mathrm{M}) - \frac{1}{T_1}(\mathrm{O})} \tag{36}$$

where $\frac{1}{T_1^*}(\mathrm{M})$ and $\frac{1}{T_1}(\mathrm{M})$ are the proton relaxation rates for a solution containing the large coordinating molecules and for a known metal ion concentration in pure water respectively, $\frac{1}{T_1^*}(\mathrm{O})$ and $\frac{1}{T_1}(\mathrm{O})$ are the corresponding relaxation rates in the absence of the metal ions. In the case of DNA the magnitude of ϵ depends upon whether the metal ion is bound to an interior or exterior site of the molecule. Consequently these alternative binding sites may be distinguished from experimental values of ϵ. By studying the dependence of ϵ on metal ion concentration it is possible to calculate the metal binding equilibrium constants and the concentration of binding sites on the macromolecule. For 1 mg of DNA the number of available binding sites was found to be 7×10^{17} for $\mathrm{Mn^{II}}$ and $\mathrm{Cr^{III}}$ ions and 8×10^{17} for $\mathrm{Fe^{III}}$ ions.[252] This technique has been used to study the bonding of $\mathrm{Mn^{II}}$ ions to bovine serum albumin,[253] nucleic acids[254] and the enzymes, enolase,[255] pyruvate kinase,[256–258] and creatine kinase.[259–261] Cohn has shown[261] that the enzymes studied fall into two classes, the first of which have a larger value of ϵ for ternary enzyme–manganese–substrate complexes than for binary enzyme–manganese complexes, whilst in the second class the order of the complexes with the largest value of ϵ is reversed. Creatine kinase is an example of the first class and pyruvate kinase an example of the second. Enzymes of the first kind only bind to the metal ion in the presence of a substrate while, by comparison, the metal ion is bound directly to the protein with enzymes of the second class. In the case of pyruvate kinase it appears that the enzyme binds two $\mathrm{Mn^{II}}$ ions per molecule.

The role of $\mathrm{Mn^{II}}$ ions in enzyme catalysis has been studied for samples of creatine kinase[259,260] and the metalloenzyme carboxypeptidase A.[262] A similar study has been reported on copper(II) containing metalloenzyme dopamine-β-hydroxylase, which catalyses the conversion of dopamine to norepinephrine.[263] It is found that the substrate does not bind directly to the copper ion although it is on the surface of the enzyme.

By investigating the nuclear electron double resonance (Overhauser effect)[264] of liquids containing free radicals it is possible to study the solvent-radical interaction between the nuclei of the solvent and the unpaired electrons of the radicals; these interactions may have a dipolar and a scalar component.[264] Hubbard has proposed two basically different models for the scalar interaction termed the sticking and diffusion models.[265] It appears that the latter is the more suitable for discussing many solvent-radical interactions.[266,267] From ^1H and ^{19}F data it has been possible to estimate the distance of closest approach of the electron to nuclei of the solvent molecules *d*; some values are reported in Table III.

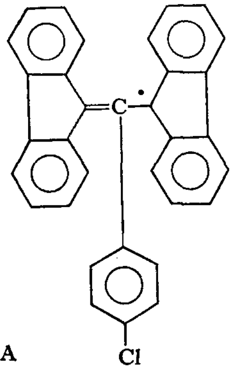
TABLE III

Some estimated values of the distance of closest approach, *d*, of the electron of a solute radical to a solvent nucleus

Solvent	Radical	*d*, Å	Ref.
C_6H_6	DPPH	4·1	267
C_6H_6	DBNO	4·2	267
C_6H_6	DPPH	4·6	268
C_6H_6	CR	4·6	268
C_6H_6	TBP	4·6	268
C_6H_6	CR	5·7	264
C_6H_6	TBP	3·6 ± 0·3	266
C_6F_6	DPPH	3·7	267
C_6F_6	TBP	3·1 ± 0·4	266
C_6F_6	TBP	3·9	268
C_6F_6	CR	3·9	268
$C_6H_5CH_3$	DPPH	4·3	268
$C_6H_5CH_3$	BPA (**14**)	4·3	268
$C_6H_5CH_3$	CR	4·3	268
$C_6H_3F_3$	DPPH	4·3[a]	267
$C_6H_3F_3$	DBNO	3·1[b], 4·2[c]	267
p-$C_6H_4F_2$	TBP	3·6 ± 0·3[b]	266
		4·1 ± 0·3[c]	266
CF_3CCl_3	TBP	4·8 ± 0·5	266
$(C_2H_5)_2O$	DPPH	4·1	268
$(C_2H_5)_2O$	CR	4·1	268
$(C_2H_5O)_2C_2H_4$	DPPH	4·5	268
$(C_2H_5O)_2C_2H_4$	BPA	4·5	268
$(C_2H_5O)_2C_2H_4$	CR	4·5	268

[a] From both ^1H and ^{19}F data.
[b] From ^1H data.
[c] From ^{19}F data.

The ^1H data have been interpreted in terms of dipolar interactions, whereas the ^{19}F results show that the scalar interaction is dominant. It is anticipated that the study of dipolar and scalar interactions between unpaired electrons and nuclei will continue to provide both qualitative and quantitative information of chemical interest in the future.



BPA

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Doubtless in five years time the extent of the data available from NMR studies on paramagnetic species will make the present coverage appear rather narrow.

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Fluorine-19 Nuclear Magnetic Resonance Spectroscopy

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I. INTRODUCTION

THIS REVIEW covers the years 1967 and 1968 and is intended as an extension of the earlier review in Volume 1 of this Series.[1] It will be evident that the amount of published work involving the fluorine-19 nucleus is increasing exponentially. The prime motivation for this is that the larger range of fluorine-19 chemical shifts makes the resonance a very sensitive means of monitoring conformational, electronic and solvent effects.

The situation regarding the reference standard for measurement of chemical shifts is now complicated by the realization that the broad resonance signal of trichlorofluoromethane arises from the isotopic effect of the chlorine atoms. While it had been realized that CCl_3F was not a good standard, because of the breadth of the resonance signal, it nevertheless had the two major advantages that the signal was (*a*) at higher frequency (low field) of the majority of the resonance signals of fluorocarbons and (*b*) was sufficiently volatile for easy recovery of the sample. It is evident that considerable argument will prevail for some time until another universal standard is found. This will certainly be difficult but, for the purposes of a review article, it is satisfactory to quote all chemical shifts on a standard basis and consequently these will be converted to the CCl_3F scale with reference signal at zero. In this present Volume it is the fluorine shifts which are more drastically affected by the new notation for the chemical shift scale. The majority of the resonances of fluorocarbons are to lower frequency (higher field) of CCl_3F and are therefore quoted as negative values on the delta scale ($\delta_{CCl_3F} = 0$).† It is worth mentioning, at this point, that this is the convention which has been used by Brugel in his compilation of ^{19}F NMR data.[2]

The basic sections of this Chapter will be essentially the same as used in Volume 1. Due to unavoidable circumstances which delayed the proposed chapter on the stereospecific nature of F–H coupling constants, a short section has been included on this topic. It is expected, however, that the more detailed consideration of this aspect will be published in a later Volume.

II. FLUOROHYDROCARBONS

A. Fluorinated Aliphatic Hydrocarbons

The spectra of n-alkyl fluorides have been measured and that of the n-propyl fluoride discussed at some length in relationship to the rotational isomerism.[3] The ^{19}F spectra are septets in every case with the lines in approximate ratio 1:2:3:4:3:2:1; this is because the vicinal H–F coupling is approximately one half the geminal H–F coupling. Each component of the signal is broad ~2 Hz and consequently accurate values of coupling constants cannot be obtained from the ^{19}F spectra. In all cases the shifts are $-218{\cdot}7 \pm 0{\cdot}4$.

A series of some thirty-four substituted ethanes of the type $X.CF_2.CH_2F$ have been studied at ambient temperature.[4] The shift of the $CF_2\!<$ and $>\!CF$ groups were naturally dependent upon the nature of X. The *geminal* H–F coupling constants of the CH_2F group were fairly constant, 46·0 to 47·5 Hz, while the *vicinal* F–F couplings were more variable, 15·7 to 24·6 Hz.

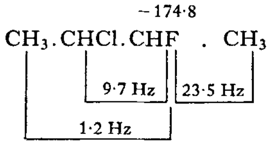
---

† The chemical shifts have been converted to the CCl_3F scale, where necessary, by taking the following shift values for the reference materials used—

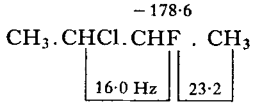
CF_3CO_2H	−78·5	$C_2F_2Cl_4$	−67·3
C_6F_6	−162·9	$(CF_2CCl_2)_2$	−114·1
$C_6H_5CF_3$	−63·9		

It was found that there was a linear relationship between the modulus of the mean *vic* H–F coupling constant and the Huggins electronegativity of X. A similar linear relationship for the *vic* F–F coupling and electronegativity X was found except for the case of X=H when there was considerable discrepancy. A number of other miscellaneous fluoroethanes, many of the form $XCF_2.CFYZ$, where X, Y and Z were halogens other than fluorine, were also investigated. By including the information from the $XCF_2.CH_2F$ compounds it was found that there was a linear relationship between the *vic* F–F coupling and the sum of the electronegativities of the substituents—the relation being given by $|J vic(\mathrm{F{-}F})| = 135{\cdot}3 - 5{\cdot}95\Sigma_\chi$. Again the value for $HCF_2.CH_2F$ did not correlate (see also p. 407).

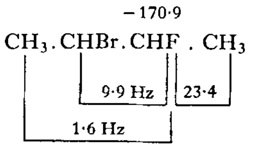
During the study of the formation of carbonium ions from 1-fluoro-2-methylpentanes the ^{19}F data of the parent alkanes were reported.[5,6,7] The ^{19}F chemical shifts of the alkanes $(CH_3)_2CX.(CH_2)_3F$ were −218·8 ± 0·1 for X = OH, Br and F; the shift of the tertiary F in the latter compound was −138·9.[5] The ^{19}F shifts of 1-fluoro-2-haloethanes of the type $FCH_2.CH_2X$, where X = Cl, Br and I, fall in the range −209·4 to −211·1



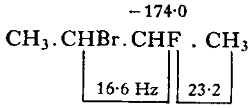
^2J(H–F) = 46·5 Hz
erythro-DL-
1



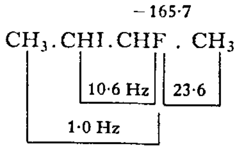
^2J(H–F) = 46·4 Hz
threo-DL-
2



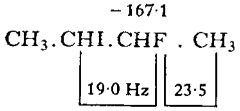
^2J(H–F) = 46·8 Hz
erythro-DL-
3



^2J(H–F) = 46·4 Hz
threo-DL-
4



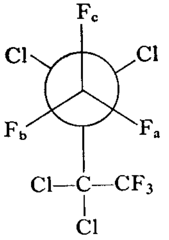
^2J(H–F) = 47·0 Hz
erythro-DL-
5



^2J(H–F) = 47·0 Hz
threo-DL-
6

with *gem* H–F couplings of 46 to 47 Hz and *vic* H–F couplings of 18·5 to 23 Hz.[6] In 2-fluoro-1-halopropanes, XCH_2CHFCH_3, where X = Br and I, the ^{19}F shift is in the range −163 to 170 with *gem* H–F couplings 47 to 48 Hz, and *vic* F–CH_3 and F–CH_2X couplings of ~23 Hz and ~1·8 Hz respectively. The data for *erythro* and *threo*-DL-2-fluoro-3-halobutanes, $CH_3CHX.CHF\,CH_3$, where X = Cl, Br and I, are shown in **1** to **6**. In each case the ^{19}F shift of the $>$CHF group is to higher field in the *threo*-isomer. The *gem* (H–F) and *vic* (CH_3–F) couplings are fairly constant being 46·4 to 47 Hz and 23·2 to 23·6 Hz respectively. The *vic* (F–CHX) coupling is, however, very much more variable being 9·7 to 10·6 Hz in the *erythro*- but 16·0 to 19·0 Hz in the *threo*-isomers.[6] The ^{19}F shifts of the tertiary fluorine atoms in 2-fluoro-3-halogeno-2-methylbutane, $(CH_3)_2CFCHX.CH_3$, where X = Cl, Br and I, fall in the range −135·1 to −141·8.[7] The vicinal F–H couplings of fluorine to the *gem*-dimethyl groups was 21 Hz while that of fluorine to the $>$CHX group was 9 Hz. The tertiary fluorine in 1-halo-2-fluoro-2-methylpropanes, $XCH_2.CF(CH_3)_2$, where X = Cl, Br and I, also has a similar shift of −132·5 to 140·5; the F–$(CH_3)_2$ coupling is the same as in the butanes but the vicinal FC–CH_2X coupling constant is larger being 15 to 16 Hz.[7]

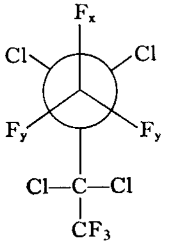
The analyses of the spectra of 1-halogeno-3,3,3-trifluoropropanes, $CF_3CH_2CH_2X$ (where X = Cl, Br and I), have been studied with the problem of rotational isomerism in mind.[8] The spectra were analysed as $AA'BB'X_3$ spin systems and the coupling constants calculated.



$\delta F_a = -69{\cdot}8$
$\delta F_b = -73{\cdot}5$
$\delta F_c = -61{\cdot}1$

$J_{ab} = 105$ Hz
$J_{ac} = 124$ Hz
$J_{bc} = 116$ Hz
$J_{aa'} = 75$ Hz

7



$\delta F_x = -61 \pm 2$
$\delta F_y = -73 \pm 2$

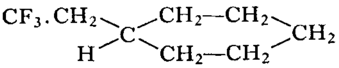
8

The conformational equilibrium of 1,2-bis(trifluoromethyl)tetrachloroethane has been studied over the temperature range of −73° to −150°C.[9] At −112°C rotation about the C–CF_3 bond is slow in the gauche isomer (**7**) but fast in the *trans* isomer (**8**). At −150°C rotation about all the carbon bonds is slow and the calculated parameters for this temperature are shown below each structure. The presence of only one large five-bond coupling (aa′), which is between two fluorine atoms in close proximity, implies that the dominant effect may be that through space rather than through bonds. This is the first direct case in which the *geminal* F–F coupling of a trifluoromethyl group has been measured and also the first example of the slow rotation about a C–CF_3 bond in a saturated system.

The rotational isomerism in 1,1,2,2-tetrabromofluoroethane has been studied and the thermodynamic parameters calculated.[10]

Trifluoromethylcarbene, formed photolytically from 2,2,2-trifluorodiazoethane, reacts with hydrocarbons in the liquid phase to give insertion products.[11] The shifts of the CF_3 groups in a variety of products are shown in **9** to **17**; the latter two compounds were prepared by similar reaction with dimethylamine and methanol in place of a hydrocarbon.

−65·1



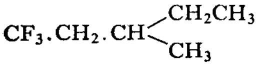
9

−64·9

$CF_3(CH_2)_4CH_3$

10

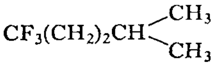
−68·7



$CF_3.CH_2.CH{<}^{CH_2CH_3}_{CH_3}$

11

−68·3



$CF_3(CH_2)_2CH{<}^{CH_3}_{CH_3}$

12

−61·0

$CF_3.CH_2.C(CH_3)_3$

13

−55·8

$CF_3.CH_2.Si(CH_3)_3$

14

−71·1

$CF_3(CH_2)_2SiH(CH_3)_2$

15

−72·4

$CF_3.CH_2.N{=}N{-}N(CH_3)_2$

16

−76·9

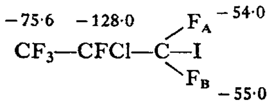
$CF_3.CH_2.O.CH_3$

17

The ^{19}F parameters of some iodo-perfluoroalkanes, used in the preparation of substituted allene, have been given.[12] These data are shown in structures **18** to **20**.

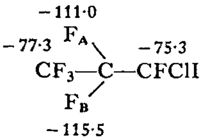
During the course of the study of the reaction of bis(trifluoromethyl)diazomethane or bis(trifluoromethyl)diazirine with the hydrocarbons, cyclohexane, neopentane and n-butane, a number of fluorinated alkanes were isolated.[13] The compounds were all of the general form $RCH(CF_3)_2$, where $R = C_6H_{11}$—, $(CH_3)_3C.CH_2$—, $CH_3CH_2.CH(CH_3)$— and $CH_3(CH_2)_3$—, and although the shifts of the trifluoromethyl groups were slightly variable these all fell in the range of −62·0 to −68·5 with $^3J(CF_3–CH)$ of about 9 Hz.

The ^{19}F spectrum, including the ^{13}C satellite spectra, of perfluorobutane has been examined in great detail by Harris and Woodman.[14] The shift of the CF_3 and CF_2 groups were −83·13 and −126·89 respectively; these values are slightly different from those reported by Hopkins[15] but this could be due to solvent effects. The spectra of the CF_3 and CF_2 groups were



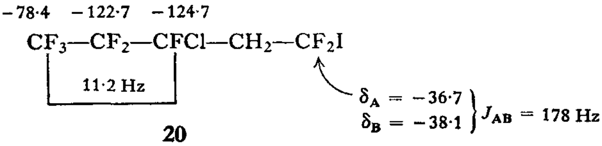
$^2J(F_A\text{–}F_B) = 201{\cdot}0$ Hz $^3J(CF_3\text{–}CFCl) = 6{\cdot}7$ Hz
$^4J(CF_3\text{–}F_A) = 11{\cdot}9$ Hz $^3J(CFCl\text{–}F_A) = 13{\cdot}0$ Hz
$^4J(CF_3\text{–}F_B) = 10{\cdot}1$ Hz $^3J(CFCl\text{–}F_B) = 9{\cdot}0$ Hz

18



$^2J(F_A\text{–}F_B) = 270{\cdot}4$ Hz
$^3J(CF\text{–}F_A) = 13{\cdot}3$ Hz
$^3J(CF\text{–}F_B) = 14{\cdot}5$ Hz
$^4J(CF_3\text{–}CFCl) = 10{\cdot}7$ Hz

19



20

insufficiently resolved and the data obtained from the ^{13}C satellite spectra were used to calculate the additional parameters.

B. Derivatives of fluorinated aliphatic hydrocarbons

1. *Ethers*

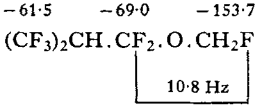
Fluorinated ethers have been prepared by the reaction of a perhalogenated ketone or acid fluoride with a metal fluoride, an olefin and a halogen;[16] only partial ^{19}F data was quoted although it was stated that the products were identified by NMR.

−68·0 −75·6
$(CF_3)_2CBr.CF_2.O.CH_3$

21

−65·8 −72·5 −118·2
$(CF_3)_2CBr.CF_2.O.CHF.CH_3$

22



23

−63·2 −68·5 −119·6
$(CF_3)_2CH.CF_2.O.CHF.CH_3$

24

−63·0 −67·0 −75·0 −72·7
$(CF_3)_2CH.CF_2.O.CClF.CCl_2F$

25

−63·6 −67·9 −84·6
$(CF_3)_2CH.CF_2.O.CClF.CCl_3$

26

−63·6 −69·4 −72·5
$(CF_3)_2CH.CF_2.O.CCl_2.CCl_2F$

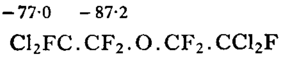
27

−63·6 −67·3 −85·4 −76·4
$(CF_3)_2CH.CF_2.O.CF_2.CCl_2F$

28

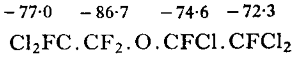
Yuminov *et al.*[17, 18] have published two papers on the preparation of fluorinated ethers by the reaction of bromine trifluoride in bromine with unsaturated ethers at ~0°C. At higher temperatures further fluorination of $—OCH_2$ and $—OCH_3$ groups occurs. Alternatively bromine trifluoride reacts with polychloroethers to afford the mixed chlorofluoroalkyl ethers. The ^{19}F NMR parameters of the ethers prepared are shown in **21** to **31.**

Perfluorovinylmethyl ether has been obtained from the flow pyrolysis of perfluoro-(1-dimethylamine-2-methoxycyclobutane) at 600°C and the ^{19}F shifts of this ether and of the brominated product are shown in **32** and **33**;[19] precise assignments of the two β-fluorine atoms of **32** were not given.



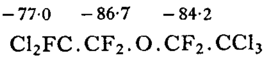
$\overset{-77\cdot0}{Cl_2FC}.\overset{-87\cdot2}{CF_2}.O.CF_2.CCl_2F$

29



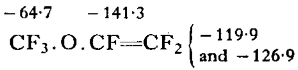
$\overset{-77\cdot0}{Cl_2FC}.\overset{-86\cdot7}{CF_2}.O.\overset{-74\cdot6}{CFCl}.\overset{-72\cdot3}{CFCl_2}$

30



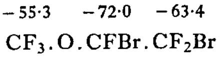
$\overset{-77\cdot0}{Cl_2FC}.\overset{-86\cdot7}{CF_2}.O.\overset{-84\cdot2}{CF_2}.CCl_3$

31



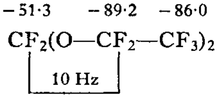
$\overset{-64\cdot7}{CF_3}.O.\overset{-141\cdot3}{CF}{=}CF_2\left\{\begin{matrix}-119\cdot9\\ \text{and } -126\cdot9\end{matrix}\right.$

32



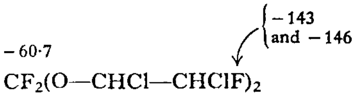
$\overset{-55\cdot3}{CF_3}.O.\overset{-72\cdot0}{CFBr}.\overset{-63\cdot4}{CF_2Br}$

33



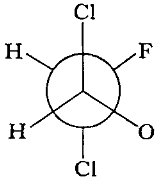
$\underbrace{\overset{-51\cdot3}{CF_2}(O\text{—}\overset{-89\cdot2}{CF_2}}_{10\text{ Hz}}\text{—}\overset{-86\cdot0}{CF_3})_2$

34

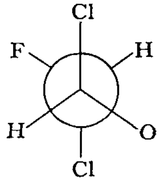


$\overset{-60\cdot7}{CF_2}(O\text{—}CHCl\text{—}\overset{\left\{\begin{matrix}-143\\ \text{and } -146\end{matrix}\right.}{CHClF})_2$

35



36



37

The reaction of bis(fluoroxy)difluoromethane with tetrafluoroethylene gave the perfluorodiethoxymethane (**34**) and with *trans*-1,2-dichloroethane gave bis(1,2-dichloro-2-fluoroethoxy)difluoromethane (**35**); the ^{19}F data of these compounds were as shown.[20] Two separate signals for the —CHClF group in **35** arise from the two different *cis*- and *trans*- addition products (**36** and **37**); there was no alteration in the appearance of the spectrum over the temperature range –40° to 60°C.

2. *Alcohols*

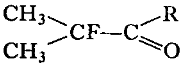
The ^{19}F shifts of the CF_3 groups of hexafluoropropane-2,2-diol and the corresponding mono-alkali metal salts have been quoted as occurring in the range δ –81·5 to –83·5.[21] The corresponding data for the di-lithio salt and the 2,2-bis(trimethylsiloxy) compound fall within the same range.[22]

The alkali metal salts of the perfluoro-ethoxides, propoxides and butoxides have been prepared by reaction of the metal fluoride with the perfluoroacyl fluoride or with hexafluoroacetone.[23] As the salts were soluble in propionitrile the formation was followed by ^{19}F NMR in solution.

The ^{19}F shift of 2,2,2-difluoronitroethanol and some of its derivatives falls into the range of –91 to –93.[24]

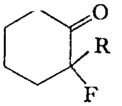
3. *Ketones and aldehydes*

A general method for the synthesis of α-fluoro-carbonyl compounds has been described.[25] The shifts for tertiary fluorine in **38** and **39**, R = Me, are



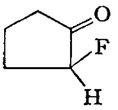
R = H or Me

38

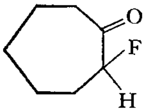


R = H or Me

39



40



41

in the region δ –154 to –159 while those of the >CHF group in **39**, R = H, and **40** to **42** are in the range –186 to –194; the latter resonances showing the typical *gem* H–F coupling of 49 to 52 Hz. The four bond H–F coupling across the carbonyl group (**38**, R = Me, and **42**) is 5 Hz.

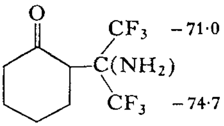
The ^{19}F data for trifluoromethyl- and pentafluoroethyl- trifluorovinylketones has been reported.[26] The ^{19}F shift of the fluorine atom in 5-fluoropentan-2-one was –216·6; a value very similar to that found in 1-fluoro-2-methylpentanes (p. 263).[5]

A number of the ketones containing the $(CF_3)_2CHCO$— group have been prepared using bis(trifluoromethyl)ketene, and in every case the shifts of CF_3 groups were in the region –64 to –66.[27] In the ketones having an α-bromine atom to the carbonyl group, two CF_3 resonance signals were observed due to rotational isomerism.

Cyclohexanone and hexafluoroisopropylidenimine react to give the

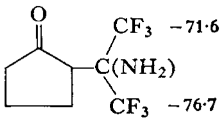
$CH_3.CH_2.CHF.CO.CH_3$

42



^4J(F–F) = 9 Hz

43



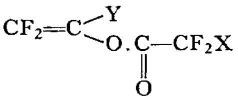
^4J(F–F) = 9 Hz

44

corresponding 2-(hexafluoro-isopropylamino)cyclohexanone (**43**);[28] a similar reaction occurred with cyclopentanone (**44**).

4. *Acids, esters and amides*

During the course of the preparation of bromodifluoromethyl ketones several acids and esters were obtained as by-products and were of the general form **45** and **46**; the shifts of the C(O)CF_2X group were –61 to –63·5 for X = Br and –129 for X = H.[29] The shifts of the vinylic fluorine atoms are not given here as these give rise to AB spectra and each line of the quartet is quoted as a chemical shift value in the paper; further, since the frequency used is not given, it was not possible to recalculate these. The shifts of the CF_2 group in the lactone and hydroxy acid isolated are shown in **47** and **48**.



$CF_2{=}C(Y)O.C(O){-}CF_2X$

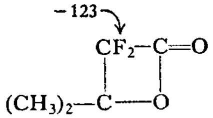
X = H or Br; Y = Cl or Br

45

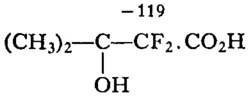
XCF_2CO_2Me

X = H or Br

46

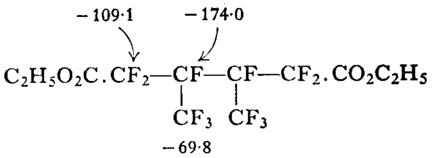


47



$(CH_3)_2{-}\underset{OH}{C}{-}CF_2.CO_2H$

48



$C_2H_5O_2C.CF_2{-}\underset{CF_3}{CF}{-}\underset{CF_3}{CF}{-}CF_2.CO_2C_2H_5$

49

Several new esters of ω-nitroso-perfluorinated carboxylic acids have been synthesized[30] and although the ^{19}F chemical shifts are given in the paper precise assignments could not always be made.

The sensitivity of ^{19}F chemical shifts has been utilized to study the micelle formation of the sodium salts of perfluoro- caprylate and propionic acids.[31] The shifts of the CF_3 and α-CF_2 were measured as a function of concentration and the intersection of the two separate lines (Fig. 1) give the critical micelle concentration. The results of this work are compared with previous work of Muller and Birkhahn,[32] who had considered the correlation of ^{19}F shifts of ω-fluoro-caparate, laurate and tridecanoate ions.

It has been found that the bromoperfluoroalkane carboxylic esters, which are relatively easily prepared, were conveniently condensed via the active bromine site by irradiation in the presence of mercury to give the α,ω-dicarboxylic esters.[33] For example, ethyl 3-bromoperfluorobutanoate gave the diester **49**; the ^{19}F shifts were as shown.

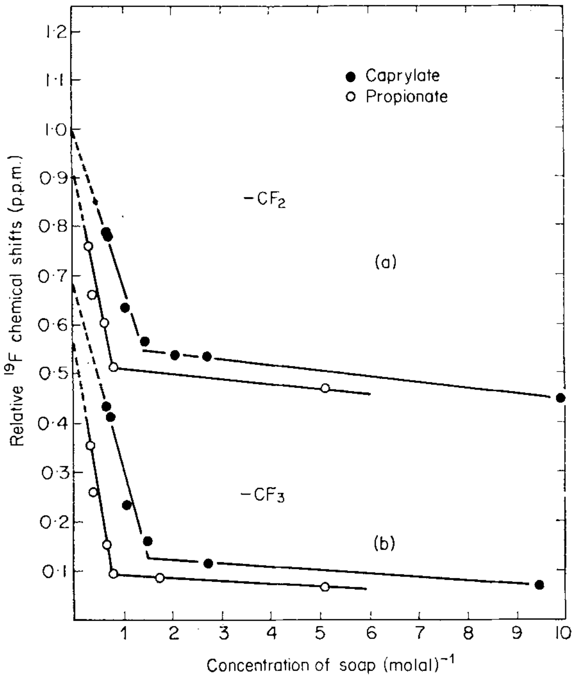


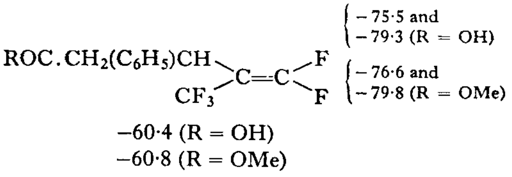
FIG. 1. Plot of ^{19}F chemical shifts of (a) the —CF_2 peak and (b) —CF_3 peak against the inverse concentration of the sodium salts of perfluoropropionic and caprylic acids. (From Haque.)[31]

A series of carboxyl derivatives of the general structure **50** were prepared from bis(trifluoromethyl)ketene.[27] Due to rotational isomerism arising from the asymmetric centre two CF_3 resonance signals were observed, the first in the range −62·9 to −64·3 and the second between −65·3 to −66·3. The

$(CF_3)_2CH.CH(C_6H_5)CH_2COX$

X = OH, OMe, F

50



$ROC.CH_2(C_6H_5)CH(CF_3)C{=}CF_2$

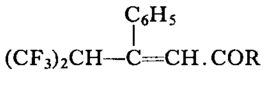
51

fluorine shift of the acid fluoride derivative **50** was at 42.1. Two further acids (and derivatives), **51** and **52**, were also prepared.

It has been demonstrated that there is a linear correlation of the ^{19}F shift of the acyl fluoride with the number of methyl groups attached to the αC atom in the compounds RR′CHC(O)F, where R and R′ = H or CH_3.[34a] For convenience, however, this aspect will be considered in relationship to the similar effects experienced in fluorophosphonates (see p. 353).

Hexafluoroisopropylidenimine reacts with compounds containing active methylene groups.[28] Hence diethyl malonate and methyl cyanoacetate afford the two amine esters **53** and **54** respectively. It will be observed that the shifts of the CF_3 groups in the —$C(CF_3)_2.NH_2$ entity are similar to those of the aromatic compounds (p. 275).

The ^{19}F shifts of the amides *N*-trifluoromethyl-α,α-dihydroxy-β,β,β-trifluoropropionamide (**55**) and *N*,*N*′-bis(trifluoromethyl)oxamide (**56**) were quoted together with the data for the *N*,*N*′-bis(trifluoromethyl)urea (**57**).[34b] It is of note that the *gem*-diol form of the pyruvamide is stable; this is analogous to the stability of the *gem*-diol form of hexafluoroacetone.



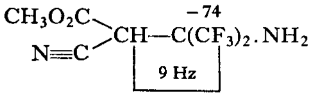
$(CF_3)_2CH{-}\overset{C_6H_5}{\overset{|}{C}}{=}CH.COR$

−61·2 (R = OMe)
−62·9 (R = NHC_6H_5)

52

$(CH_3O_2C)_2CH.\overset{-74\cdot4}{C(CF_3)_2}.NH_2$

53



54

$\overset{-57\cdot8}{CF_3}NH.CO.C(OH)_2.\overset{-83\cdot3}{CF_3}$

55

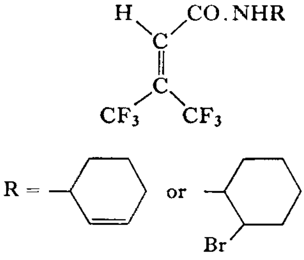
$\overset{-57\cdot7}{CF_3}NH.CO.CO.NHCF_3$

56

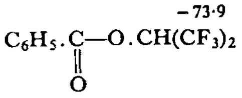
$\overset{-56\cdot2}{CF_3}NH.CO.NHCF_3$

57

During the course of the study of the addition of hexafluoroacetone to ketenimines two hexafluoroisopropylideneacetamides of cyclohex-2-ene and 2-bromocyclohexane (**58**) were isolated.[35] The two CF_3 groups are



58



$C_6H_5.\underset{\underset{O}{\|}}{C}{-}O.\overset{-73\cdot9}{CH(CF_3)_2}$

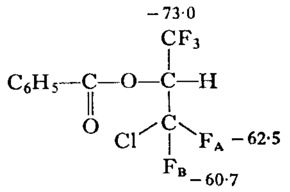
$^3J(H\text{-}F) = 6\cdot3$ Hz

59

non-equivalent and have resonance signals in the ranges −59·5 to −60·5 and −63·5 to −65·9, with ${}^4J$(F–F) = 7·0 Hz and ${}^4J$(F–H) = 1·0 to 1·5 Hz.

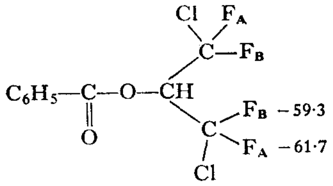
Hydrolysis of the α,α-difluorofluoramine, $C_6H_5CF_2NFCH(CH_3)CH_2CH_3$, gave the *N*-fluoro-*N*-sec-butylbenzamide, $C_6H_5C(O)NFCH(CH_3)CH_2CH_3$, with ^{19}F shift of −88·9. The signal appeared as a doublet due to coupling to the α-CH proton, ${}^3J$(F–H) = 42 Hz.[36]

The free-radical addition of benzaldehyde to fluorinated ketones gave good yields of the benzoates. Thus hexafluoro-, pentafluoro- and α,α,α′,α′-tetrafluorodichloro- acetones gave **59** to **61** respectively.[37] In compounds **60** and **61** there is magnetic non-equivalence of the fluorine atoms of the —CF_2Cl groups.



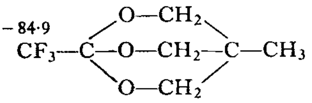
${}^2J(F_A–F_B)$ = 177 Hz
${}^3J(CF_3–H)$ = 5·9 Hz
${}^3J(F_A–H)$ = 9·0 Hz
${}^3J(F_B–H)$ = 6·7 Hz
${}^4J(CF_3–F_A)$ = ${}^4J(CF_3–F_B)$ = 9·0 Hz

60

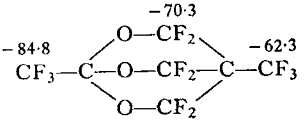


${}^2J(F_A–F_B)$ = 168 Hz
${}^3J(F_A–H)$ = 9·8 Hz
${}^3J(F_B–H)$ = 6·3 Hz

61



62



${}^4J(CF_3–C–CF_2)$ = 9·3 Hz

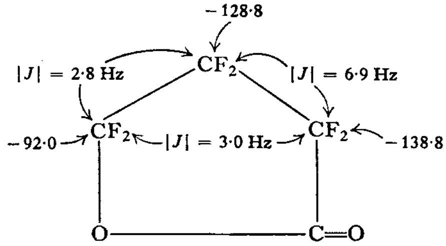
63

Fluorination of the ortho ester (**62**) resulted in the formation of the fully fluorinated 1,4-bis(trifluoromethyl)-2,6,7-trioxabicyclo[2.2.2]octane (**63**) with bicyclic structure still intact.[38]

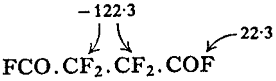
A series of α-fluoro esters have been examined by Fraisse-Jullien and Thoi-Lai.[39] The ^{19}F shift of the single fluorine atom in ethyl fluoroacetate is at −231·2. In the α-fluoro- propionate and phenylacetate the shift is at −185·0 and −182·2 respectively, while in longer chain esters the shift is in the range −189·7 to −192·3. In esters with a methyl substituent also in the α-position, i.e. with a CF(Me)— group, the shift is −155 to −157·5 and with a phenyl group, —$CF(C_6H_5)$, the shift is −165·3 to −167·3.

The ^{19}F data of ethyl ω-bromoperfluoropropionate has been given[40] as an example of a series of bromoperfluorocarboxylates prepared. The shift of the $BrCF_2$— group and of the —$CF_2.CO$ group were −66·74 and −115·48 respectively.

The ^{19}F spectrum was used to identify the product of the reaction of disilver perfluoroglutarate and iodine as perfluoro-γ-butyrolactone (**64**), perfluorosuccinyl fluoride (**65**) and perfluorosuccinyl anhydride (**66**); the shifts were as shown.[41] The spectrum of the lactone was deceptively simple. The isomerization of the lactone to perfluorosuccinyl fluoride, by heating with anhydrous potassium fluoride, was monitored by ^{19}F NMR.

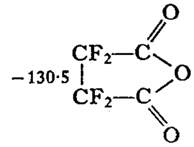


64



$FCO.CF_2.CF_2.COF$

65



66

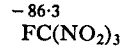
The rate of esterification of alcohols with trifluoroacetate acid was found to be dependent upon the nature of the alcohol and the number and relative disposition of the hydroxyl groups.[42] Thus the degree of conversion to ester decreased in the order isopropanol, pentan-2,4-diol and heptan-2,4,6-triol, and the rate is depressed by the presence of α-hydroxyl groups. It was also found that *meso*-molecules react more slowly than the racemic molecules. Each of the five individual esters (mono-, di-, and tri-) gave rise to discrete CF_3 resonance signals and this could have application in the study of conformational problems.

The absolute configuration of optically active α-hydroxy-α-trifluoromethylphenylacetic acid and its methyl ether could not be determined from ORD measurements because of the oppositely signed Cotton effects. The investigation of these compounds in optically active solvents has, however, solved this problem.[43] Using (+)α-(1-naphthyl)ethylamine as solvent the carbomethoxy resonances of the enantiomers of methyl-α-hydroxy-α-trifluoromethylphenyl acetate, methyl mandelate, methyl atrolactate and methyl-α-hydroxy-α-trichloromethylphenyl acetate were correlated. The ^{19}F data were similarly used and it was concluded that the methyl ether exhibited the anomalous Cotton effect.

5. *Nitroalkanes*

Sulphur tetrafluoride reacts smoothly with nitro-alcohols to afford nitrofluoroalkanes;[44] the ^{19}F shift for the $>CH_2F$ group in 2,2-dinitrofluoro- and 2,2-dinitro-1,3-difluoro- propanes was δ −230 to −235.

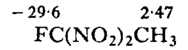
A number of fluoro-nitroalkanes have been synthesized by the direct fluorination of the nitronate salts in aqueous solution; the NMR data was reported for the compounds shown in **67** to **72**.[45] It is of interest that in fluorotrinitromethane the ^{14}N–^{19}F coupling is clearly resolved, $J = 9{\cdot}8$ Hz, while in the 1-fluoro-1,1-dinitroethane, although more than nine lines were observed in the ^{19}F spectrum, this coupling could not be precisely measured. This indicates that the field gradient around the nitrogen atom in these instances is very symmetrical.



$\overset{-86\cdot3}{F}C(NO_2)_3$

$J(^{19}F\text{–}^{14}N) = 9{\cdot}8$ Hz

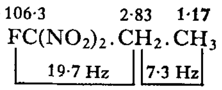
67



$\overset{-29\cdot6}{F}C(NO_2)_2\overset{2\cdot47}{CH_3}$

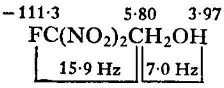
$J(^{19}F\text{–}^{1}H) = 17{\cdot}7$ Hz

68



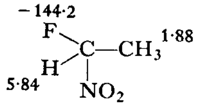
$\overset{-106\cdot3}{F}C(NO_2)_2.\overset{2\cdot83}{CH_2}.\overset{1\cdot17}{CH_3}$

69



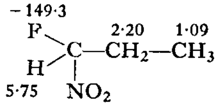
$\overset{-111\cdot3}{F}C(NO_2)_2\overset{5\cdot80}{CH_2}\overset{3\cdot97}{OH}$

70



$^2J(H\text{–}F) = 51$ Hz
$^3J(F\text{–}CH_3) = 21$ Hz
$^3J(H\text{–}H) = 6{\cdot}3$ Hz

71



$^2J(F\text{–}H) = 52$ Hz
$^3J(F\text{–}CH_2) = 22{\cdot}5$ Hz
$^3J(CH_2\text{–}CH_3) = 7{\cdot}5$ Hz

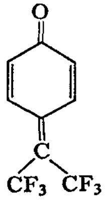
72

6. *Aromatic alkyl substituent groups*

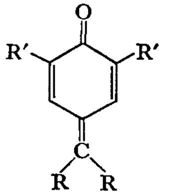
In this section will be included the available data on fluoroalkyl groups when either directly attached to an aromatic nucleus (either hydrocarbon or fluorinated) or when attached by a single atom, e.g. oxygen or sulphur, or a group, e.g. amido.

The ^{19}F data for α-bromo-α-fluorotoluene, which is used for the formation of phenylfluorocarbene,[46] has been reported. The shift of the —CFHBr group is at δ −130·8 with $^2J(H\text{–}F)$ of 49 Hz.

The 7,7-bis(trifluoromethyl)quinonemethide (**73**), unlike 7,7-dialkyl compounds, was found to be stable.[47] Normally 2,6-dialkyl substituents are required to be present to afford the compounds any useful lifetime. The shift of the CF_3 groups was at δ −57·6 with a coupling to the *ortho*-protons of 0·7 Hz. Sheppard[48] had earlier reported the stability of the 2,6-disubstituted compounds and subsequently presented the data of these and a number of precursors. In the quinonemethide compounds (**74**) the shifts for the CF_3 group were –54·2 ± 0·1, while that for the CF_2Cl group was –43·3. In the precursors of the general type **75** and **76** the resonance of the group R = CF_3 is –75·9 to –76·7 for X = —O—, –70·9 ± 0·1 for X = Cl, –68·7 ± 0·3 for X = —N— and –66·4 for X = H. For R = CF_2Cl, the the shift is –60·4 for X = —O— and –54·5 for X = Cl.

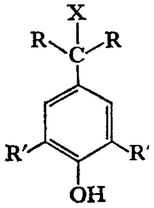


73

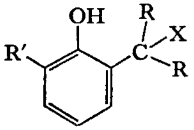


74

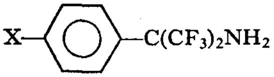
a. R = CF_3, R′ = CH_3
b. R = CF_3, R′ = $C(CH_3)_3$
c. R = CF_2Cl, R′ = CH_3



75

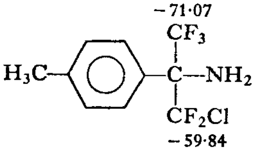


76

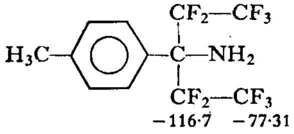


77

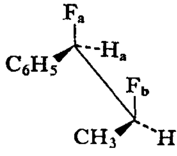
α,α-Bis(fluoroalkyl)benzylamines have conveniently been prepared by the Friedel–Crafts interaction of fluoroimines and aromatic hydrocarbon derivatives.[28] Since however the ^{19}F data is primarily concerned with fluoroalkyl groups attached to an aromatic ring the compounds will be considered in this section. The shifts of the trifluoromethyl group in the general environment **77** fall in the range –71 to –77. One example of each of the $C.(CF_3)(CF_2Cl).NH_2$ and $C(CF_2CF_3)_2.NH_2$ groups are also given and the shifts are as shown in **78** and **79**; it will be noticed that the shift of



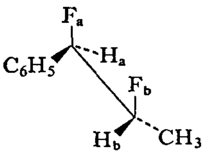
78



79



80



81

the CF_3 group in **78** falls within the general range of compounds of the type **77**. The shift of the CF_3 groups in two of the acetamides formed from the benzylamines, thus containing the $—C(CF_3)_2.NHCOCH_3$ group, were in the region −67 to −69·5.

Fluorination of *cis*- and *trans*-propenylbenzenes in non-polar solvents leads to the formation[49] of DL-*erythro*- (**80**) and DL-*threo*-1,2-difluoro-1-phenylpropanes (**81**); the ^{19}F parameters are tabulated below:—

	80	**81**
δF_a	−193·5	−186·8
δF_b	−182·5	−183·8
$J(F_a\text{–}H_a)$	48 Hz	48 Hz
$J(F_a\text{–}F_b)$	~15 to 16 Hz	~15 Hz
$J(F_a\text{–}H_b)$	~15 to 16 Hz	~15 Hz
$J(F_b\text{–}H_a)$	~14 Hz	~14 Hz
$J(F_b\text{–}CH_3)$	~23 Hz	~23 Hz
$J(F_a\text{–}CH_3)$	~1·6 Hz	<0·5 Hz

Fluorination in methanol resulted in the formation of the DL-*erythro*- and DL-*threo*- 1-methoxy-1-phenyl-2-fluoropropanes; both isomers showed a single ^{19}F resonance signal at −178·5.

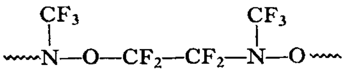
For convenience the data of fluoroalkyl groups attached to the pyridine ring will be included in this section.

Pyridine *N*-oxide reacts with hexafluoropropene to give presumably *O*-alkylation, which rearranges to yield the 2-(1,2,2,2-tetrafluoroethyl) pyridines. The shifts of the —CFH group were in the range −198 to −200, while those of the terminal $—CF_3$ group fell in the limited range −79·2 ± 0·2.[50]

7. *Polymers*

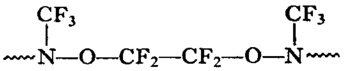
Using the two model compounds, $CH_2Cl—CHCl—CFCl—CH_2—CH{=}CFCl$ and $CH_2Cl—CH(CFCl_2)—CH_2—CH{=}CFCl$, resonance signals at −49·4 and −107 to −116 were assigned to $—CFCl_2$ and —CFCl— groups respectively.[51] The polymer obtained from fluorodichloropropene showed four intense lines at δ −104, −106, −111 and −115, indicating CFCl groups in different environments; only a very weak peak at −47·0 ± 1·5 could be detected for the $—CFCl_2$ group and integration indicated greater than 90% linear $[—CH_2—CHCl—CFCl—]_n$ rather than branched $[—CH_2—CH(CCl_2F)—]_n$ structure, implying that extensive 1,2 migration of chlorine had occurred. In constrast difluorochloropropene does not rearrange and the polymer shows only a single strong resonance line at −52·0 due to the $—CF_2Cl$ group in the $[—CH_2—CH(CF_2Cl)—]_n$ chain.

The ^{19}F spectra of poly(vinyl trifluoroacetate) polymers have been investigated but it was impossible to correlate the ^{19}F shifts of the CF_3 groups with any stereoregularity in the polymer chain.[52] The trifluoroacetylation of polyvinyl alcohol has been compared with other model alcohols,[42] but little useful information resulted; the ^{19}F signals observed



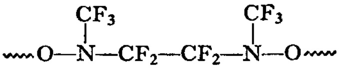
$\sim\overset{CF_3}{\overset{|}{N}}-O-CF_2-CF_2-\overset{CF_3}{\overset{|}{N}}-O\sim$

82



$\sim\overset{CF_3}{\overset{|}{N}}-O-CF_2-CF_2-O-\overset{CF_3}{\overset{|}{N}}\sim$

83



$\sim O-\overset{CF_3}{\overset{|}{N}}-CF_2-CF_2-\overset{CF_3}{\overset{|}{N}}-O\sim$

84

would be at least consistent with a random orientation along the polymer chain.

The ^{19}F spectra of nitroso rubber copolymers, being copolymers of tetrafluoroethylene and trifluoronitrosomethane, have been examined and compared with the spectrum of perfluoro-(2-methyl-1,2-oxazetidine).[53] The two spectra are shown diagrammatically in Fig. 2. There are three ways in which polymerization can occur, that shown in **82** being the predominant; the strong lines shown in Fig. 2 are due to this orientation. The small signal near the main $—CF_2O—$ signal is due to form **83** and that near the main $—CF_2N\Big<$ signal due to form **84**.

C. Fluoro-olefins and acetylenes

The spectra of 3,4,4-trifluoro-4-bromo-2,3-dichloro-1-butene (**85**) have been examined in some detail.[54] The three fluorine atoms constitute an ABX spin system and the two individual sets of signals are illustrated in the paper. The allylic H–F couplings were found to be positive and this aspect has been discussed in general terms regarding the mechanism of coupling.

The pure *trans*-2*H*-heptafluoro-2-butene has been isolated and the ^{19}F shifts of this isomer compared with those of the corresponding *cis*-isomer.[55] The shifts are as shown in **86** and **87**; the stereochemical implications for the formation of the *trans*-isomer, from hexachlorobutadiene and potassium fluoride in *N*-methyl-2-pyrrolidene, involving a conformationally preferred carbonium ion, has been discussed.

The reaction of phenylmagnesium bromide with 1,1-bis(chlorodifluoromethyl)ethylene afforded a number of products, three of which were isolated; the migration of fluorine atoms was rationalized by an S_N2' reaction.[56] The shifts of the 3-phenyl fluoropropenes obtained are shown in Table I.

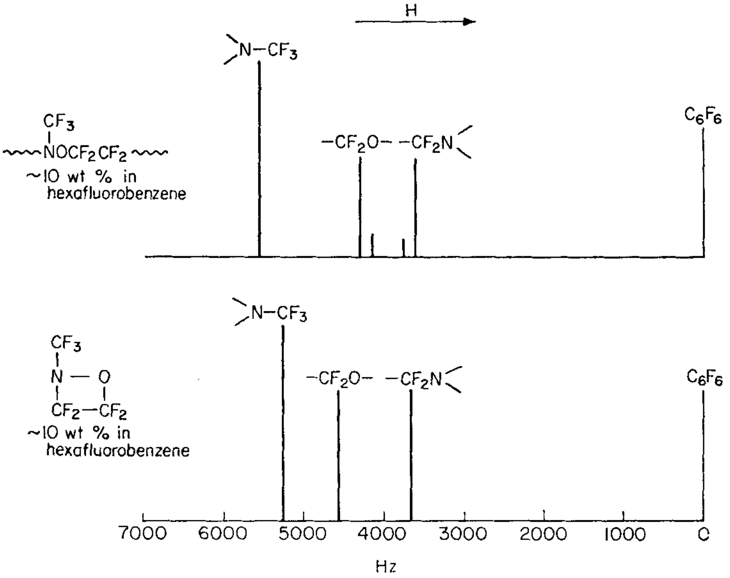
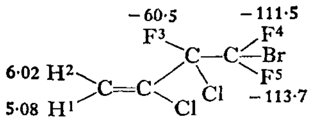


FIG. 2. Diagrammatic comparison of the ^{19}F shifts of the $CF_3NO/CF_2{=}CF_2$ copolymer and of perfluoro(2-methyl-1,2-oxazetidine). (From Lawson and Ingham.)[53]

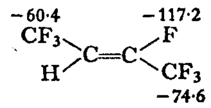
The shifts of the *cis*- and *trans*- cinnamic acids, their ethyl esters, and the corresponding styrenes have been quoted. The notation used for describing the *cis*- and *trans*- cinnamic isomers is slightly ambiguous and the data are therefore not included here.[57]

Two monohydro-chloro-octafluoropentenes have been prepared and characterized by the ^{19}F NMR spectra.[12] In one, the 2*H*-3-chloro-octafluoropent-1-ene, complete analysis was not attempted owing to the complexity arising from the asymmetric centre. The parameters of these two pentenes are shown in **88** and **89**.



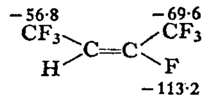
$^2J(H^1–H^2) = -2{\cdot}72$
$^4J(H^1–F^3) = 5{\cdot}24$
$^5J(H^1–F^4) = 0{\cdot}51$
$^5J(H^1–F^5) = 0{\cdot}0$
$^4J(H^2–F^3) = 2{\cdot}41$
$^5J(H^2–F^4) = <0{\cdot}05$
$^5J(H^2–F^5) = 0$
$^3J(F^3–F^4) = -10$
$^3J(F^3–F^5) = -12$
$^2J(F^4–F^5) = 171$

85



$^5J(CF_3–CF_3) = 1$ to 2 Hz

86

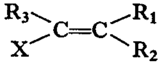


$^5J(CF_3–CF_3) = 10{\cdot}2$ Hz

87

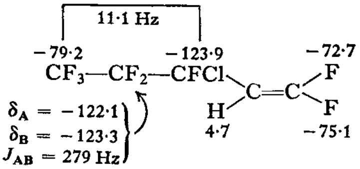
TABLE I

The ^{19}F shifts of fluoro olefins

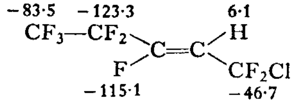


X	R_1	R_2	R_3	Chemical shift, δ R_1	R_2	R_3	Ref.
$C_6H_5CH_2$	F	F	CF_2Cl	−82·8	−76·0	−47·1	56
$C_6H_5CH_2$	F	Cl	CF_3	−67·3	..	−60·8	56
$C_6H_5CH_2$	Cl	F	CF_3	..	−65·4	−60·1	56
$C_6H_5CH_2$	F	F	CF_3	−82·4	−78·2	−61·2	61
p-$CH_3C_6H_4$	F	F	CF_3	−78·4	−76·7	−60·8	61
p-ClC_6H_4	F	F	CF_3	−80·6	−78·9	−61·6	61
CH_3	F	F	CF_3	−84·7	−80·3	−64·2	62
CH_3	F	F	CF_2H	−89·6	−88·2	−118·1	62
CH_3CH_2	F	F	CF_3	−84·6	−79·2	−63·2	62

The ^{19}F spectra of a number of perfluorovinyl derivatives have been examined in some detail.[58] The compounds essentially fell into two types. Firstly, three 3-substituted-5-fluoropropilidene-1,2,4-oxadiazoles (**90**) were examined and the ^{19}F spectra were all identical to within ±0·2 Hz, i.e. the spectra were unaffected by the nature of the 3-substituents. The experimental and calculated spectra for each of the four sets of signals have shown in the paper and the shifts and coupling constants are given below.



88



$^{3}J(\mathrm{CF_3{-}CF_2}) = 1{\cdot}9$

$^{4}J(\mathrm{CF_3{-}F}) = 6{\cdot}3$

$^{3}J(\mathrm{CF_2{-}F}) = 12{\cdot}7$

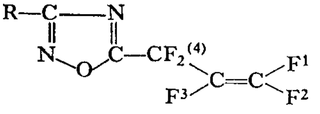
$^{5}J(\mathrm{CF_2{-}CF_2Cl}) = 2{\cdot}0$

$^{3}J(\mathrm{F{-}H}) = 28{\cdot}0$

$^{3}J(\mathrm{CF_2Cl{-}H}) = 10{\cdot}0$

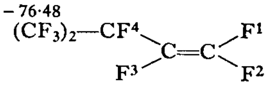
$^{4}J(\mathrm{CF_2Cl{-}F}) = 21{\cdot}7$ Hz

89



R = $C_6H_5CH_2$-, *m*-$CH_3C_6H_4$-
and *p*-$CH_3C_6H_4$-

90



91

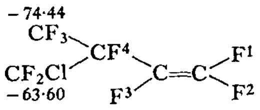
Secondly fluorinated isopropylethylenes, perfluoro-isopropylethylene (**91**) and perfluoro-1-methyl-1-vinylethyl chloride (**92**), were examined and the shifts and coupling constants of these two compounds are shown below (for convenience the trifluoromethyl and chlorodifluoromethyl groups are omitted—but see structures—and the numbering system is different to that used by authors)—

	90	**91**	**92**		**90**	**91**	**92**
$\delta(\mathrm{F}^1)$	–106·07	–107·08	–106·77	$J(1,2)$	±55·86	±57·7	±57·4
				$J(1,3)$	∓117·23	±117·5	∓116·1
$\delta(\mathrm{F}^2)$	–91·24	–89·48	–89·58	$J(1,4)$	±26·22	±43·5	±44·4
				$J(2,3)$	±37·86	±39·3	±39·1
$\delta(\mathrm{F}^3)$	–188·44	–188·51	–186·87	$J(2,4)$	±6·57	±2·7	±2·0
				$J(3,4)$	∓18·66	∓13·0	∓12·8
$\delta(\mathrm{F}^4)$	–102·72	–187·51	–179·46				

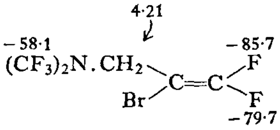
The ^{19}F chemical shifts of chlorodifluorovinylamines have been calculated for the *cis*- and *trans*-1,2- and *gem*-1,1-difluoro isomers and these results compared with these calculated for the system.[59]

The spectra of the two isomeric *cis*- and *trans*- β-fluorostyrene have been analysed at low frequency (21·35 MHz for ^{19}F).[60] The comparison of the spin-coupling data was made with other fluoroethylenes.

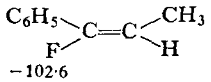
A number of fluorovinylamines were prepared by the reaction of *N*-bromobistrifluoromethylamine with olefins followed by dehydrohalogenation or dehalogenation.[19] Although extensive NMR analysis was not carried out the chemical shift data was sufficient to permit structural assignment. The chemical shifts are shown in Table II. Other bis(trifluoromethyl)vinylamines have been reported and the data for these compounds are also included in Table II. The data for one bis(trifluoromethyl)allylamine (**93**) have also been included in this paper.



92

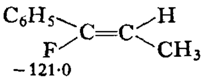


93



$^3J(\mathrm{F{-}H}) = 22$ Hz
$^4J(\mathrm{F{-}CH_3}) = 2{\cdot}2$ Hz

94

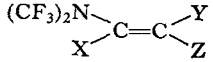


$^3J(\mathrm{F{-}H}) = 36$ Hz
$^4J(\mathrm{F{-}CH_3}) = 2{\cdot}5$ Hz

95

TABLE II

The ^{19}F shifts of fluorovinylbis(trifluoromethyl)amines[a]



			Chemical shifts, δ				
X	Y	Z	$(CF_3)_2N$—	X	Y	Z	Ref.
F	F	F	−61·0	−114·0	−147·8	−100·7	19
F	Cl	F	−59·3	−111·0	. .	−97·5	19
F	F	Cl	−59·3	−111·1	−125·7	. .	19
F	H	F	−59·0	−111·3	(6·58)	−149·1	19
F	F	H	−58·5	−136·5	−165·1	(7·06)	19
H	F	F	−62·4	(5·16)	−93·0	−83·5	19
Br	F	F	−59·7	. .	−79·8	−81·7	19
Br	H	$N(CF_3)_2$	−58·9	. .	(6·64)	−59·7	63
Br	H	H	−58·9	. .	(6·55)	(6·41)	63
H	H	CF_3	−58·1	(6·82)	(5·60)	−64·1	63
I	H	CF_3	−55·9	. .	(6·84)	−61·8	63
I	CF_3	H	−58·4	. .	−63·1	(6·80)	63
H	H	Br	−58·4	(6·48)	(6·68)	. .	63
H	Br	H	−58·6	(6·49)	. .	(6·81)	63

[a] Proton shifts are shown in parentheses.

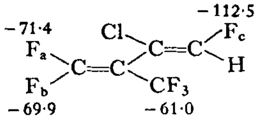
The dehydrofluorination of the 1,2-difluoro-1-phenylpropanes (see p. 276) afforded *cis*- and *trans*-1-fluoro-1-phenylpropene; the ^{19}F data are shown in **94** and **95**.[49]

The reaction of perfluoroketones with difluoromethylenetriphenylphosphorane has provided a general method for the preparation of β-substituted perfluoroolefins.[61] The ^{19}F shifts of three of the olefins are included in Table I. The *gem* F–F coupling was rather variable being in the range 9·1 to 19·5 Hz; the *cis*- and *trans*- CF_3–F coupling constants were more constant in value 20·8 to 24·5 and 10·6 to 11·7 Hz respectively. It will also be noted from Table I that the shift of a trifluoromethyl group attached to a C=C group lies in the comparatively narrow range of −60·1 to −61·6.

Terminal perfluoromethylene olefins containing the group $F_2C{=}C\langle$ have been synthesized by reaction of lithium aluminium hydride with highly halogenated olefins of the form $RHC{=}C(CF_2X)_2$, where R is a hydrocarbon chain or H and X is Cl or F.[62] The ^{19}F shifts of three of the compounds described are included in Table I.

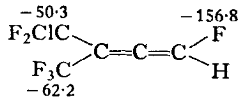
Thermal isomerization of allene **97** gave the butadiene **96**; the ^{19}F shifts and coupling constants were as shown.[64]

The spectra of 1,1-dibromo- and 1,1-dichloro- 3-fluorobuta-1,3-diene have been studied in detail over a range of temperatures from –130° to 39°C.[65] The temperature dependence of the *vic* (H–F) coupling, of the C=CF—CH=C group, which varies from 17 Hz at 39°C to ~24 Hz at –130°C is interpreted in terms of *s-trans* and skew conformations. It was deduced that the value of this coupling was ~+25 for the *s-trans* form and ~–1·9 for the skew form.



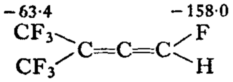
$^2J(F_a–F_b) = 5·1$
$^5J(F_a–F_c) = 1·9$
$^5J(F_b–F_c) = 2·8$
$^4J(F_a–CF_3) = 10·3$
$^4J(F_b–CF_3) = 21·1$
$^5J(F_c–CF_3) = 0·7$
$^2J(F_c–H) = 77$

96



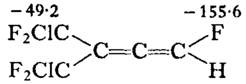
$^2J(F–H) = 76·6$
$^5J(CF_2Cl–F) = 5·8$
$^5J(CF_3–F) = 5·5$
$^5J(CF_2Cl–H) = 1·2$
$^5J(CF_3–H) = 1·1$

97



$^2J(F–H) = 77$
$^5J(CF_3–F) = 5·4$
$^5J(CF_3–H) = 1·2$

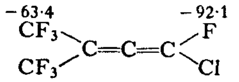
98



$^2J(F–H) = 77$
$^5J(CF_2Cl–F) = 5·8$
$^5J(CF_2Cl–H) = 1·1$

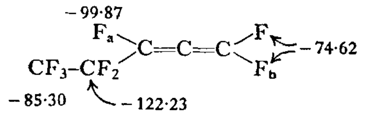
99

Reaction of acetylenic alcohols with sulphur tetrafluoride resulted in the formation of fluorinated allenes.[64] Although the ^{19}F data were not recorded in every instance, the data for some of the compounds are shown in **97** to **100**.



$^5J(CF_3–F) = 3·5$ Hz

100



$^4J(CF_3–F_a) = 5·8$
$^3J(CF_3–CF_2) = 2·9$
$^3J(CF_2–F_a) = 23·0$
$^5J(CF_2–F_b) = 6·0$
$^4J(F_a–F_b) = 37·9$

101

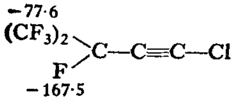
Perfluoropenta-1,2-diene, one of the few perfluoroallenes isolated, has been prepared by a number of different routes and fully characterized;[12] the ^{19}F data is as shown in **101**. The four-bond F–F coupling across the allenic double bond system is of the usual characteristic value of ~40 Hz.

One of the simplest perfluoroacetylenes, namely tetrafluoromethylacetylene, has been isolated;[66] the ^{19}F parameters are shown in **102**. The ^{13}C satellite spectra of the CF_3 group was examined and the direct-bond ^{13}C–^{19}F coupling was found to be 259·0 Hz, while the two-bond F_3C–^{13}C coupling was 57·7 Hz.

$$\overset{-50\cdot8}{CF_3}\text{—}C\equiv C\text{—}\overset{-203\cdot0}{F}$$

$^4J(F\text{–}F) = 4\cdot3$ Hz

102



$^3J(F\text{–}F) = 10\cdot0$ Hz

103

$$\overset{-62\cdot4}{(CF_3)_2N}\text{—}C\equiv \overset{2\cdot74}{CH}$$

104

$$\overset{-59\cdot4}{(CF_3)_2N}\text{—}C\equiv C\text{—}\overset{-51\cdot7}{CF_3}$$

105

$$\overset{-62\cdot3}{(CF_3)_2N}\text{—}C\equiv C\text{—}N(CF_3)_2$$

106

Treatment of acetylenic alcohols with sulphur tetrafluoride normally gave allenes, however, in two cases fluorinated acetylenes were obtained.[64] The ^{19}F data for one of these two acetylenes is shown in **103**.

The ^{19}F data of three bis(trifluoromethyl)amino acetylenes have been reported;[63] the shifts of these compounds are shown in **104** to **106**.

D. Fluorinated cyclo hydrocarbons

1. *Saturated systems*

The small ring cycloalkanes, cyclo-propane and -butane, are ideal model compounds for the study of coupling constants. A detailed study[67] of derivatives of the type **107**, the shifts and coupling constants of which are shown in Table III, has shown that $|^3J(H\text{–}F)|$ of the F–C–CHF$_2$ group is dependent upon the number of methyl groups *cis* to the CHF_2 group. The value of the coupling constant increases from approximately 7 to 8 Hz in the absence of *cis* methyl groups to 13 to 14 Hz for one and 17 to 18 Hz for two *cis* methyl groups. This type of correlation has obvious use in the assignment of geometrical isomers. In the same context it is only when the two *cis* groups are dissimilar that the two fluorine atoms of the —CHF_2 group are non-equivalent.

Two papers[68,69] have been concerned with the values of the F–F coupling constants in halogeno-fluorocyclopropanes, **108** and **109**, and the shifts and coupling constants are collated in Table IV. In both series of compounds the *trans* vicinal F_A–F_X coupling constant is markedly affected

TABLE III

^{19}F parameters of 1-difluoromethyl-1-fluorocyclopropane derivatives (107)

				Shifts		Coupling constants of 1–CF–CF_2H group, Hz[b]		
X	Y	P	Q	CF_2H[a] $\nu_A - \nu_B$ p.p.m.	1–F, δ	FF *gem*	FF *vic*	FH *vic*
H	H	H	H	0	−224·5	See note[c]	12	7
Me	H	H	H	0	−221·5	See note[c]	10	8
H	Me	H	H	4·9	−201·5	295	10	13
Me	Me	H	H	5·0	−214·5	301	9,11[d]	13
H	Me	Me	H	4·7	−218·5	291	11,10[d]	13
Me	H	Me	H	0	−232·5	See note[c]	9	7
H	Me	H	Me	0	−200·5	See note[c]	11	17
Me	Me	Me	H	5·1	−227·5	301	10,12[d]	14
Me	Me	H	Me	0	−213·5	See note[c]	13	17
Me	Me	Me	Me	0	−224·5	See note[c]	13	18

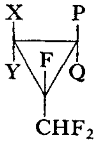
[a] The mean chemical shift 1/2 ($\nu_A + \nu_B$) for all compounds falls in the narrow range −128·5 ± 2.

[b] The value of ^2J(F–H) of the —CF_2H falls in the range 51 to 56 Hz.

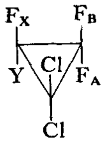
[c] J_{AB} not measured due to magnetic equivalence of the two fluorine atoms of —CF_2H group.

[d] The first value refers to the *gem*-fluorine atom resonating at higher frequency (lower field).

by the nature of the substituent Y. Williamson and Braman[68] assigned F_A and F_B in **108** on the basis of the marked dependence of the shift of F_A upon the electronegativity of Y; the shift of F_B and F_X are more constant

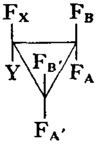


107



Y = Cl, Br, I

108



109

in value. A similar marked variation in the shifts of F_A and $F_{A'}$ in **109** is also observed. It was assumed that the sign of the *gem* F–F coupling is positive and double resonance studies showed[68] that J_{AX} and J_{BX} were of the opposite sign to J_{AB} and therefore presumably negative. The authors found that all three F–F coupling constants were dependent upon the electronegativity of Y, but, as with the chemical shift, the value of J_{AX} was

TABLE IV

^{19}F parameters of 1-halogeno-pentafluoro- and 1,1,2-trihalogeno-trifluorocyclopropanes (108 and 109)

		Shifts, δ			Coupling constants, Hz					
		δ_A	δ_B	δ_X	J_{AB}	$J_{AB'}$	$J_{AA'}$	$J_{BB'}$	J_{AX}	J_{BX}
108	Cl	−136·2	−143·2	−149·8	155·0	..	..	..	−1·3	−4·1
108	Br	−131·0	−143·2	−148·6	153·0	..	..	..	−5·4	−5·4
108	I	−122·9	−142·7	−148·8	150·5	..	..	..	−10·0	−6·8
109	Cl	−151·6	−158·4	−175·0	189·04	0·88	4·87	10·73	−5·82	8·27
109	Br	−145·1	−157·1	−175·1	185·72	2·42	1·91	10·41	−10·13	6·59
109	I	−134·6	−154·4	−189·1	181·44	4·34	−1·29	9·78	−15·44	4·72

the most affected. The dependence of J upon dihedral angle was discussed and no simple relationship could be discerned. Barlow *et al.*[69] also assumed the *gem* F–F coupling to be positive and found that the *vicinal* F–F coupling could be of either sign and in **109** the sign of $J_{AA'}$ changes from positive to negative in charging Y from Cl and Br to I. It is noticeable that the *cis* BX *vicinal* F–F coupling is negative in **108** but positive in **109**; this may arise as a substituent effect of the vicinal CCl_2 and CF_2 groups.

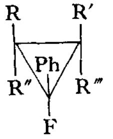
Two independent groups have dealt with the addition of phenylfluorocarbene to olefins. Moss[46] has considered addition to tetramethylethylene, *iso*-butene and *trans*-butene; the tertiary fluorine of the adduct (**110 a** to **c**) has a shift in the region δ −170 to −180. It was observed that in every case there was long-range four-bond coupling of the fluorine to all the methyl protons present. Ando *et al.*[70] also considered the addition of the carbene to tetramethylethylene, *cis*-butene, 2-methyl-2-butene, 2-methyl-2-pentene and cyclohexene to give adducts (**110 d** to **k**). The stereochemistry was based upon earlier observations that in cyclopropane derivatives J(*cis*H–F) > J(*trans*H–F), and that the fluorine atom is shielded by *cis* but deshielded by *trans* alkyl substituents. The ^{19}F shifts of these compounds are summarized in Table V.

The same basis of the magnitude of the coupling constants was used to confirm the *exo*- and *endo*- structures of the addition of chlorofluorocarbene to 2,3-dihydro-4*H*-pyran to give the 7-chloro-7-fluoro-2-oxanorcarene (**111a**).[71] Reduction of **111a** gave the 7-fluoro-2-oxanorcarene **111b**; the shifts and coupling constants of these compounds are shown in Table VI. In each case the *cis* H–F coupling constants were of greater magnitude.

Three isomeric cyclobutane derivatives are formed from the dimerization of the perfluoropenta-1,2-diene and two have been identified by ^{19}F NMR

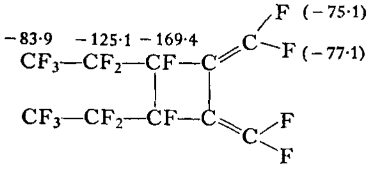
TABLE V

The ${}^{19}F$ shifts of the fluorine atom in 1-fluoro-1-phenyl cyclopropanes (110)

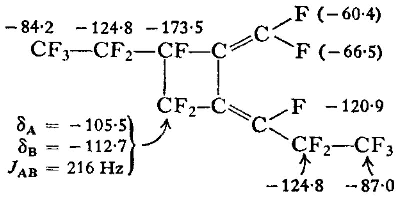


110

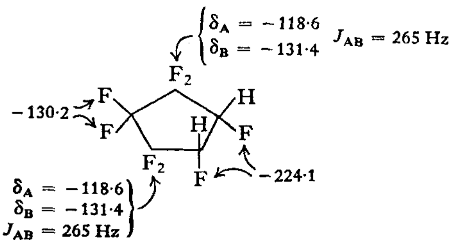
	R	R′	R″	R‴	Chemical shift, δ	Ref.
(a)	CH_3	CH_3	CH_3	CH_3	−170·2 −171·0	46 70
(b)	CH_3	H	CH_3	H	−174·5	46
(c)	CH_3	H	H	CH_3	−179·7	46
(d)	CH_3	CH_3	H	H	−148·6	70
(e)	H	H	CH_3	CH_3	−214·8	70
(f)	CH_3	H	CH_3	CH_3	−186·0	70
(g)	CH_3	CH_3	CH_3	H	−157·0	70
(h)	CH_3	H	CH_3	C_2H_5	−188·0	70
(i)	CH_3	C_2H_5	CH_3	H	−168·2	70
(j)	—$(CH_2)_4$—		H	H	−139·3	70
(k)	H	H	—$(CH_2)_4$—		−205·0	70



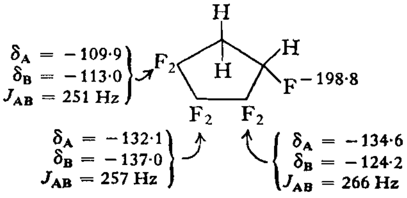
112



113



114

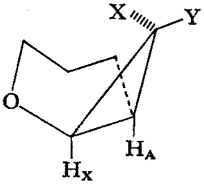


115

as the perfluoro-(1,2-diethyl-3,4-dimethylenecyclobutane) (**112**) and perfluoro-(1-ethyl-2-methylene-3-propylidenecyclobutane) (**113**);[12] the ^{19}F

TABLE VI

The ^{19}F parameters of 7-fluoro-2-oxanorcarane derivatives



111

a. X or Y = Cl or F
b. X or Y = H or F

X	Y	^{19}F chem. shift, δ	Coupling constants, Hz J(H$_A$–F)	 J(H$_X$–F)	 ^2J(H–F)
Cl	F	–136·7	22	12	..
F	Cl	–168·5	6	2	..
H	F	–213·6	26·6	12·0	61·5
F	H	–243·5	13·2	0	64·5

parameters are as shown in the formulae. Three 2,2-bis(trifluoromethyl)-cyclobutanone derivatives have been prepared from bis(trifluoromethyl)-ketene and styrene.[27] The CF_3 resonances were in the region –65·0 to –69·5.

During the study of the hydrogenation of perfluorocyclopentene dihydro- and trihydro-perfluorocyclopentanes were obtained.[72] The shifts of the 1*H*,2*H*-octafluoro- and 1*H*,1*H*,2*H*-heptafluoro-cyclopentanes are shown in **114** and **115** respectively.

The differentiation of 1,2- and 1,4-addition products of perfluorocyclopentadienes has been established[73] by the shift of the —CF_2 group which in the former occurs in the region of –114, in the latter at –140. Some of the data for the 1,4 addition products are shown in Table VII.

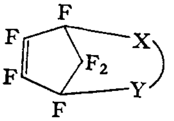
During the study of the irridation of perfluoro-*N*-fluoropiperidine in the presence of perfluorocyclobutene, perfluorobicyclobutyl (**116**) was obtained.[74]

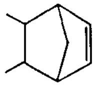
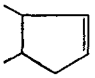
The resonance data of 2,3-bis(trifluoromethyl)bicyclo[2.2.2]octa-2,5,7-triene (**117**) has been given and the structures of the three rearranged products (**118** to **120**), obtained on photolysis of **117**, have been determined from the NMR spectra.[75]

Although the fluorine-19 resonance spectrum of perfluoromethylcyclohexane **121** has received much attention the same compound has again been

TABLE VII

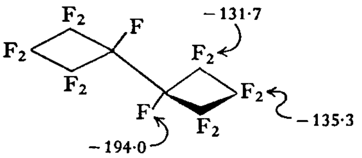
^{19}F parameters for 1,4-Diels–Alder addition products of perfluorocyclopentadiene



X—Y	Chemical shift, δ			*J* gem
	—CF_2—	—CF=CF—	$>$C—F	F–F, Hz
MeO_2C—C=C—CO_2Me	−134·7	−155·3	−212·1	See note[a]
—CH_2—CH_2—	−146·8	−160·4	−208·9	177
—CH=CH—	−136·5	−159·0	−210·9	See note[a]
HO_2C—CH—CH—CO_2H	−141·3	−150·8	−208·5	175
CH_2=CH—CH—CH_2—	−143·9	−153·9 −160·3	−207·9 −209·9	180
 Isomer 1	−137·5	−150·0	−205·4	175
Isomer 2	−135·9	−148·3	−203·9	175
	−139·9	−153·9 −154·9	−207·3	179
CF_3.N—O	−143·5	−149·0 −155·6	−173·9 −185·7	172

[a] Two fluorine atoms of $>CF_2$ group are equivalent.

considered in some depth.[76] It is perhaps natural that this compound has been so extensively examined, as it is the simplest of the fluorinated cyclohexanes which is conformationally rigid. The coupling between CF_3–CF_{1a} is both temperature and solvent dependent while those couplings between the CF_3 group and the fluorine atoms 2,6(*a* and *e*) and 3*e* and 5*e* are not affected. Perhaps one of the most notable coupling constants is the long-range 4-bond coupling between 1*a* and 3*a* and 5*a* which has the large value of 25·5 Hz. The *cis* coupling between 1*a* and 2*e*, 6*e* is larger (14·5 Hz) than



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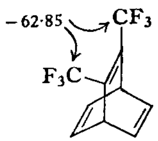

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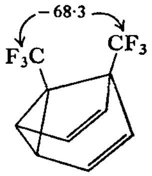

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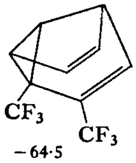

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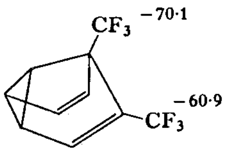

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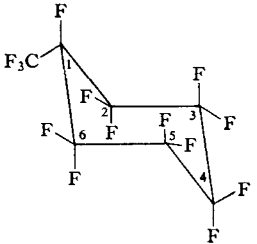
the *trans*-vicinal coupling between 1*a* and 2*a*, 6*a* (2·6 Hz), and no coupling of F_{1a} with either of the equatorial fluorine atoms at C3 or 5, or the fluorine atoms on C4, could be detected. The following generalizations, related to the F–F coupling constants, were made from analysis of the spectrum of the ring fluorine atoms—

$$J_{1,2}\ gauche \sim 14\ \text{Hz};\ J_{1,2}\ trans \sim 1\ \text{to}\ 2\ \text{Hz}$$

$$J_{1,3}\ ax\text{-}ax \sim 25\ \text{Hz};\ J_{1,3}\ eq\text{-}eq \sim 6\ \text{Hz}$$

$$J_{1,3,}\ ax\text{-}eq \sim 2\ \text{Hz}$$



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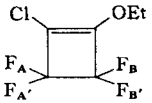

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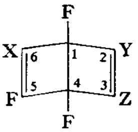
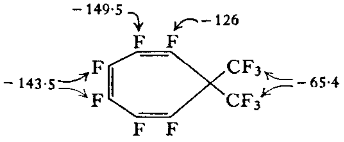


X, Y, Z = F or OEt

123



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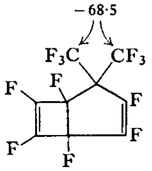
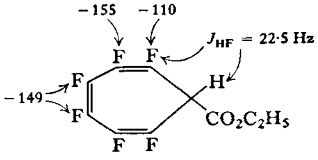


$\geq$CF at −178 and −180
=CF at −120, −126, −143 and −148
(assignments not made)

125



126

It was suggested that the large value of $J_{1,3}$ *ax-ax* arose from the close spatial proximity of the two nuclei involved.

2. *Unsaturated systems*

Although the chemical shifts of perfluorocyclobutene have been recorded several times no serious attempt has been made to obtain the coupling constants. Harris and Ditchfield[77] have considered the $[AA'X]_2$ spin system of perfluorocyclobutene, although even at 94·075 MHz the chemical shifts between the two types of nuclei are not really sufficiently large to make the $[AA'X]_2$ treatment valid. Using the composite particle approach, however, the coupling constants were computed. The coupling constants were slightly dependent upon the experimental conditions under which the spectra were recorded. The coupling constants were also compared to those of other fluorinated cyclobutenes and "Dewar benzenes" (bicyclo-[2.2.0]hexa-2,5-dienes).

Newmark[78] has considered the signs of coupling constants in fluorocyclobutenes using 2-chloro-1-ethoxy tetrafluorocyclobutene (**122**) as a model compound. Assuming that the *geminal* F–F coupling constants were positive then the signs and magnitude of the *vicinal* coupling constants were $^3J(F_A–F_B) = +25·2$ Hz and $^3J(F_A–F_{B'}) = -16·7$ Hz. The signs of the couplings were checked by spin-tickling experiments on the first-order spectrum of 1,4-dichloro-3,3,4-trifluorocyclobutene which gave the two *vicinal* couplings of +26 and –12 Hz relative to the *geminal* F–F coupling of +188 Hz. The signs of the two *vicinal* ^3J(F–F) coupling constants in perfluorocyclobutene were also found to be of opposite sign.[77]

The chemical shifts of a series of fluorinated cyclohexenes and cyclohexadienes have been collated[79] and shift ranges for the olefinic fluorine atoms, the CF_2 and attached CF_3 groups were given as an aid to the identification of similar compounds.

The data in the perfluorobicyclo[2.2.0]hexa-2-5-diene and the diethoxy derivatives (**123**) have been discussed[80] and the shifts and coupling constants are shown in Table VIII.

Thermolysis of bis(trifluoromethyl)diazomethane in excess hexafluorobenzene gave perfluoro-7,7-dimethyl-1,3,5-cycloheptatriene (**124**), which on irradiation gave perfluoro-2,2-dimethyl bicyclo[3.2.0]hepta-3,6-diene (**125**).[81] Irradiation of the diazomethane and hexafluorobenzene gave ethyl 2,3,4,5,6,7-hexafluoro-2,4,6-cycloheptatrienecarboxylate (**126**). The shifts are as shown in the structural formulae.

Irradiation of diazocyclopentadiene in the presence of hexafluorobenzene gave a product for which structure **127** was suggested;[82] the shifts were certainly similar to those observed in **124**. On heating **127** it rearranges to

TABLE VIII

^{19}F parameters of bicyclo[2.2.0]hexa-2,5-diene derivatives (123)

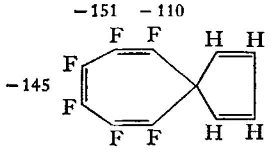
X	Y	Z	Shifts, δ						
			F_1	F_2	F_3	F_4	F_5	F_6	
F	F	F	−191·0	−122·8	−122·8	−191·0	−122·8	$\overset{\curvearrowleft}{-122{\cdot}8}$	
F	OEt	OEt	−185·1	..	..	−185·1	−124·3	$\overset{\curvearrowleft}{-124{\cdot}3}$	$J = \pm 9{\cdot}1$ and $\pm 8{\cdot}4^a$ $J_{14} = 14{\cdot}6$ $J_{56} = 4{\cdot}2$
OEt	OEt	F	−180·0	..	−133·9	−192·0	−133·9	..	$J_{13} = J_{15} = 11{\cdot}6$ $J_{14} = 14{\cdot}4$ $J_{34} = J_{45} = 4{\cdot}4$
OEt	F	OEt	−185·7	−136·1	..	−185·7	−136·1	..	$J_{13} = J_{46} = \pm 11{\cdot}1$ $J_{16} = J_{34} = \pm 4{\cdot}0$

[a] The cross-ring and *vic* F–F couplings cannot be assigned with certainty.

give the new product which shows six fluorine resonance signals; the structure of this latter compound is rather uncertain.

3. *Conformational equilibria*

The use of fluorine-19 resonance spectra in the study of conformational equilibria has continued to grow. The basis of this subject was considered



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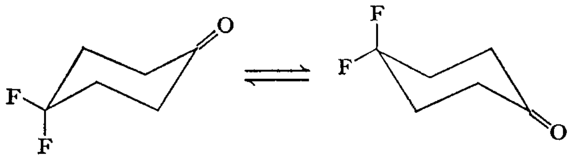
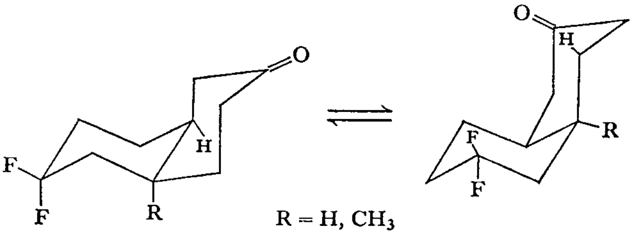


128 **129**



R = H, CH_3

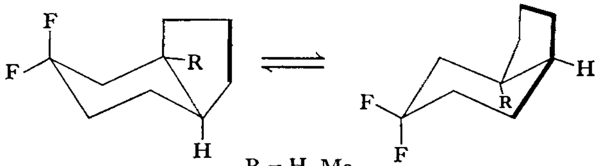
130 **131**

in Volume 1 of this series.[83] More recent work and the derivation of the thermodynamic parameters has been further considered in this Volume.[84]

Roberts *et al.*[85] have used the ^{19}F spectra of 4,4-difluorocyclohexanone, 6,6-difluoro- and 10-methyl-6,6-difluoro-*cis*-decal-2-one in the study of the equilibria between forms **128** and **129** and **130** and **131** respectively. To determine the magnitude of the shift difference between the two *geminal* fluorine atoms 2-bromo-4,4-difluorocyclohexanone, which possessed a conformational preference, was used, especially for the temperature variation of δ_A–δ_B (which varied from 264 Hz at –2°C to 374 Hz at –109°C). There was a very slight increase in the magnitude of J_{AB} at low temperature. From these studies it was deduced that the free energy of activation of 4,4-difluorocyclohexanone is small, 2·3 kcal. or less. Alternatively, the ring may exist preferentially in a twist-boat form with the two F atoms equivalent because of the two-fold symmetry axis, or it may undergo inversion by a pseudorotation via a form having a two-fold axis. The experimental and calculated temperature variable spectra of the two decal-2-one derivatives are shown in the paper.

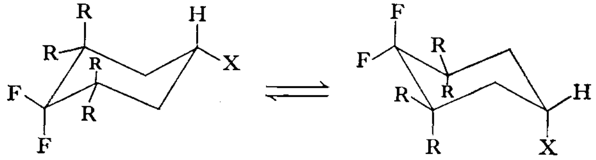
Roberts *et al.*[86] have extended their studies to the substituted 1,1-difluorocyclohexanes and 1,1,2,2-tetrafluorocyclohexane. At 35°C the ^{19}F spectrum of 4,4-dimethyl-1,1-difluorocyclohexane consists of a pentet, while at –80°C an AB spectrum is obtained, in which the lower frequency part, assigned to the axial fluorine as in similarily related systems, is considerably broader. In 4-methyl, 4-ethyl and 4-chloro-1,1-difluorocyclohexanes the fluorine resonance signals are basically an AB quartet at 35°C. At low temperature two AB quartets are observed, one from each conformer. The ^{19}F spectra of 3-methyl-, 4-methyl- and 4-*t*-butyl-1,1-difluorocyclohexanes are temperature invariant due to the conformational preference of the alkyl group for equatorial disposition.

Lack and Roberts[87] have used the *gem*-difluoro-label to investigate the conformational equilibria in the 5,5-difluoro- and 9-methyl-5,5-difluoro-*cis*-hydrindans. Both compounds gave rise to AB spectra over a range of temperatures due to the rapid interconversion of the two forms **132** and **133**. The kinetic parameters of the 5,5-difluoro-*cis*-hydrindan and 2,2-difluoro-*cis*-decalin derivatives were compared, and the effect of the angular methyl groups on the energies of the ground and transition states were considered.



132 R = H, Me **133**

Roberts *et al.*[88] have also pointed out that substitution by fluorine in polar flexible molecules significantly alters the conformational equilibria because of electrostatic interactions between the polar substituents and the fluorine atoms. These authors have studied 4,4-difluorocyclohexane derivatives **134** and **135** to evaluate the transannular interactions. At low temperature two separate AB spectra are observed due to the two conformers **134** and **135**. The higher-frequency equatorial components are sharper and the relative intensities of these were used to ascertain the relative proportions of the conformers. In the benzoate the major conformation is **135b** and is present to the extent of 74 ± 2% and, by comparison with cyclohexyl acetate, the change in ΔG° on introducing the *gem* difluoro group is about 1.1 kcal./mole. In 4,4-difluorocyclohexanol the conformer proportions are approximately equal and, from the comparison of ΔG° for cyclohexanol, it is inferred that there is significant stabilization of the equatorial conformer **134c** compared to the axial conformer **134d**. By similar considerations it was shown that there was significant stabilization of the axial conformation **135e**, but in both cases the stabilization was too large to be accounted for by simple dipole–dipole interactions.

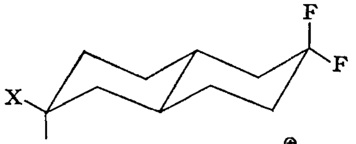


134 **135**

a. R = H; X = OBz
b. R = D; X = OBz
c. R = H; X = OH
d. R = D; X = OH
e. R = H; X = Cl

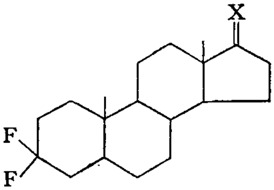
The validity of the NMR method for determining conformational equilibria has been examined by Eliel and Martin,[89] both from the point of view of proton and fluorine-19 studies. It was emphasized that the ^{19}F data for rigid molecules cannot be used to calculate conformational equilibria in mobile analogues. It is significant that in the 3-alkyl substituted derivatives the axial fluorine resonance occurs to higher frequency than in the 4-alkyl derivatives. It is not clear whether this arises from long-range anisotropy or distortion of the cyclic structure. Using ^{19}F resonance data in the study of the conformational equilibria of *cis* and *trans* 3- and 4-*t*-butylcyclohexyl fluorides, correction factors were applied.[90] Even so, meaningful data for the 3-*t*-butyl isomers could not be computed.

While considerable attention has been given to the correlation of ^{19}F shifts in systems where π-electron mechanisms are operative little has been done on purely inductive effects. Dewar and Squires[91] considered the effects on ^{19}F shifts in decalin and andrastane. In decalin derivatives **136** the equatorial fluorine at C-2 is shielded by $+I$ substituents in position 6 while the effect on the axial fluorine is usually very small. It was stated that if substituents interact by electrostatic polarization of C–F σ bonds the effect on the equatorial fluorine would be greater than on the axial fluorine, although the shift would be expected in the opposite direction. Also it was observed that there was no effect between the 3 and 17 position of androstane (**137**), although the distance is comparable with that between the 3 and 4″ positions of terphenyl. The effects in decalin cannot be due to electrostatic polarization because greater differences would be expected in **136**, where $X = NH_2$ and $\overset{\oplus}{N}H_3$ and $X = OH$ and $O^{\ominus}$. The authors suggest that the effects are stereochemical rather than electronic due to conformational distortion of the decalin ring.



$X = -OH, -O^{\ominus}Na^{\oplus}, NH_2, \overset{\oplus}{N}H_3Cl^{\ominus}$

136

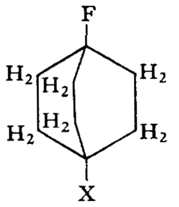


$X = H_2$ or $=O$

137

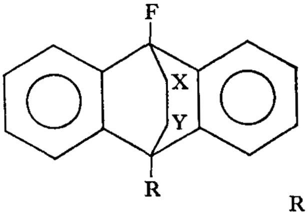
In a related paper Anderson and Stock[92] considered the same problem but as model compounds they chose species having a bridgehead fluorine atom. The shifts to lower frequency found for more highly strained compounds were not in agreement with the prediction that increase in *s* character should produce a high frequency shift. The shifts are, however, in keeping with the prediction that the bond order is increased in the strained molecules due to interaction between nonbonding electrons of the fluorine atom and the endocyclic carbon–carbon bonds with enhanced *p* character. It was similarly observed that there were marked effects upon the ^{19}F shift on charging the nature of the 4-substituent in the bicyclo[2.2.2]octane derivatives (**138**). The observed effects may be rationalized in terms of a repulsive interaction between the electropositive bridgehead carbon atoms of the disubstituted bicyclic compound which gives rise to an elongation of the structure and an increase in the *p* character of the endocyclic carbon–carbon bonds. The authors point out that if these deductions are correct then the ^{19}F resonance shift provides a valuable probe for detecting small changes in structure. This assumption would seem to be supported by the variation of ^{19}F shifts in maleic anhydride and ethylene adducts of anthracene (**139**).

Included in the study of conformational equilibria has been the use of the trifluoromethyl group. Della[93] considered the conformational preference of the trifluoromethyl group by (*a*) comparing chemical shifts between conformationally homogenous systems, e.g. *cis* and *trans* 4-*t*-butyl-trifluoromethylcyclohexanes, and mobile systems, e.g. *cis*-4-methyl trifluoromethylcyclohexane, and (*b*) freezing the equilibrium of the latter compound. The chemical shift method would appear to be very useful for an equatorial CF_3 group, e.g. in *trans*-4-*t*-butyl-1-trifluoromethylcyclohexane has a shift of −74·78, while that of an axial group, e.g. in the *cis*-isomer, is −67·4. This concept has been extended[94] to the *cis*-3-substituted trifluoromethylcyclohexanes (**140**) in which both substituents are equatorial. In agreement with the observations of Dewar,[91] it was shown that substituents have little effect upon the chemical shifts. Irrespective of the nature of X the shift of the equatorial CF_3 group falls in the range −74 ± 1.



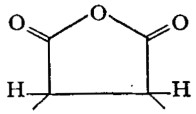
X = H, F or CO_2Et

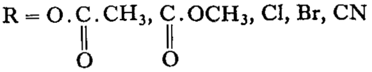
138



139

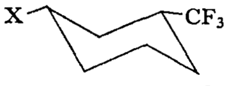
X–Y = CH_2—CH_2 or





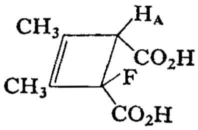
$$R = O.\underset{\displaystyle O}{\underset{\|}{C}}.CH_3,\ \underset{\displaystyle O}{\underset{\|}{C}}.OCH_3,\ Cl,\ Br,\ CN$$

$NHCOCH_3$ or NO_2



X = Me, NH_2, $NH_3^{\oplus}$, OH or $CONH_2$

140



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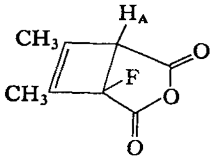


142

4. *Stereospecific dependence of H–F coupling constants*

Williamson *et al.*[95] have represented some data which was published earlier[96] and was considered in Volume 1 of this Series.[1] Two new compounds were included, the 1,2-dimethyl-3-fluoro-cyclobutene *cis*-3,4-dicarboxylic acid and anhydride (**141** and **142**). The dihedral angle between H_A and F in each case was 0° and the coupling constant was 6·25 and 0·9 Hz respectively. It was clear that J_{vic}(H–F) was dependent upon some factor other than dihedral angle for, with a constant angle of 0°, the *vicinal* coupling varied from 0·9 to 30·8 Hz. The coupling constants are dependent upon the bond lengths and are also effected by substituent parameters. The dependence of the *vicinal* H–F coupling upon dihedral angle is shown in Fig. 3, the equation for the coupling being given by—

$$J_{HF} = \begin{cases} 31\cos^2\phi & 0^\circ \leqslant \phi \leqslant 90^\circ \\ 44\cos^2\phi & 90^\circ \leqslant \phi \leqslant 180^\circ \end{cases}$$

Rather more attention has been paid to the angular dependence of the H–F coupling constants in carbohydrates. In the 3,4,6-tri-*O*-acetyl and 3,4,6-tri-*O*-benzoyl derivatives of 2-deoxy-α-D-arabinohexopyranosyl fluoride the vicinal di-axial H–F coupling was 38·2 ± 0·2 Hz while the axial F-equatorial H coupling was 5·2 ± 0·2 Hz.[97] These same authors also considered the H–F coupling constants of the 2-halogeno- and 2-acetoxy-2-deoxy-α-D-manno-, (**143**) -α-D-gluco- (**144**) and β-D-glyco-(**145**) hexopyranosyl fluoride triacetates.[98] The axial-fluorine-axial-H(2) couplings in **144** were large, 23·8 to 38·0 Hz, the axial fluorine-equatorial H(2) couplings

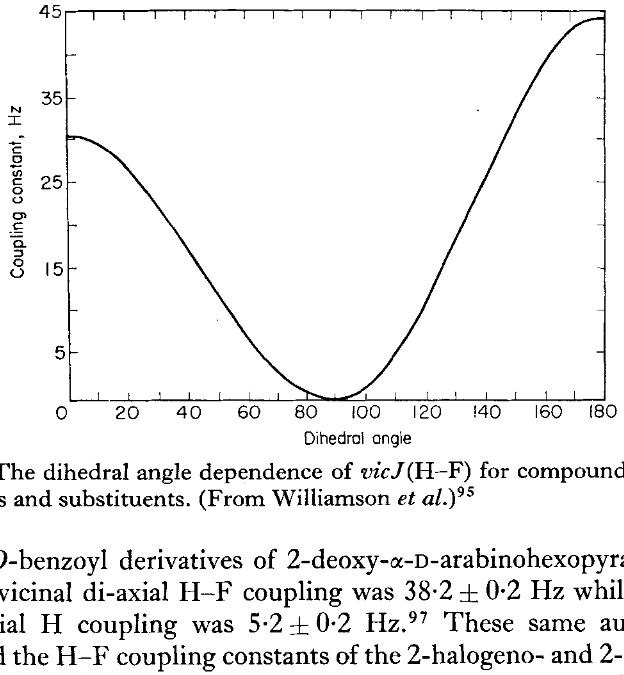
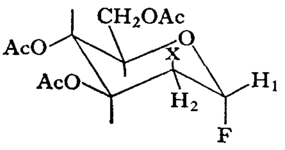


FIG. 3. The dihedral angle dependence of *vic*J(H–F) for compounds of similar bond angles and substituents. (From Williamson *et al.*)[95]



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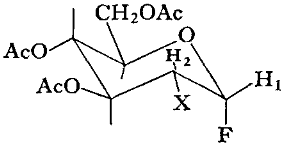

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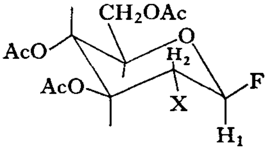
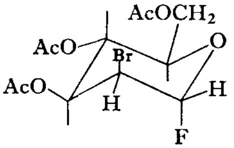


145

X = H, I, Br, Cl or OAc

in **143** were small, 1·5 to 5·3 Hz, while the equatorial F-axial H(2) couplings in **145** were intermediate, 9·3 to 12·0 Hz. It was also of significance that the ^{19}F shifts exhibited an angular dependence effect. The authors found an approximately linear relationship between the *vicinal* H–F coupling constant and the substituent electronegativity.

X-ray data on 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-mannopyranosyl fluoride (**146**) showed[99] that the bromine atom was *trans* diaxial to the fluorine atom; this was consistent with the axial fluorine-equatorial proton coupling constant of 2·7 ± 0·3 Hz.



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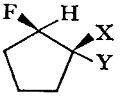
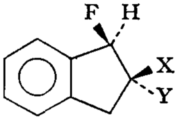
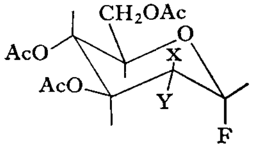


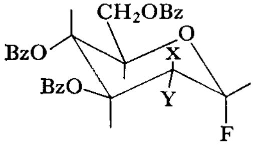
a. X = OH; Y = H
b. X = H; Y = OH
147



a. X = OH; Y = H
b. X = H; Y = OH
148

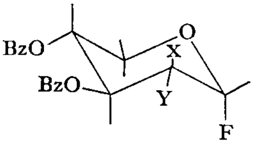


a. X = OAc; Y = H
b. X = H; Y = OAc
149

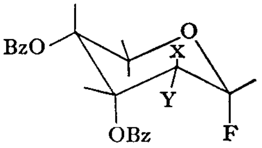


a. X = OBz; Y = H
b. X = H; Y = OBz
150

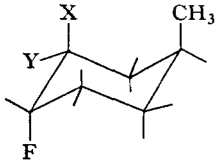
Jullien and Stahl-Larivière[100] considered the problem of the effect of the conformation of substituents on fluorine-19 chemical shifts. In the two 1-fluoro-2-hydroxy-cyclopentane derivatives **147** and **148** the ^{19}F shift of the *cis* configuration is to lower frequency (δ = –192 ± 4) than that of the *trans* isomer (δ = –178 ± 2). In four sets of carbohydrate derivatives (**149** to **152**) the shift of the fluorine atom *trans* diaxial to the substituent acetate or benzoate group was to higher frequency (δ = –60 ± 2) than the *cis* axial-equatorial conformation (δ = –70 ± 3). A similar correlation was found in monofluoro-methylcyclohexane derivatives (**153** to **155**) in which



a. X = OBz; Y = H
b. X = H; Y = OBz
151

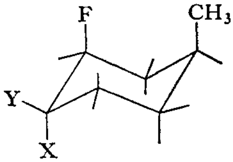


a. X = OBz; Y = H
b. X = H; Y = OBz
152



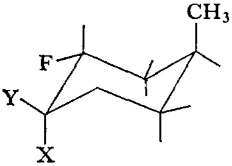
a. X = OH; Y = H
b. X = OAc; Y = H
c. X = H; Y = OH
d. X = H; Y = OAc

153



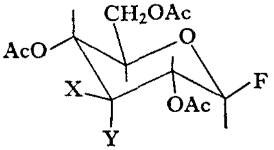
a. X = OH; Y = H
b. X = OAc; Y = H
c. X = H; Y = OH
d. X = H; Y = OAc

154



a. X = OH; Y = H
b. X = OAc; Y = H
c. X = H; Y = OH
d. X = H; Y = OAc

155

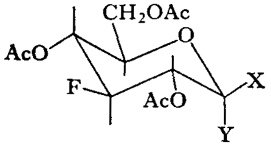


a. X = H; Y = OAc
b. X = OAc; Y = H

156

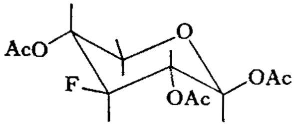
the shift of the fluorine atom in the *trans* diaxial conformation was at higher frequency ($\delta = -182{\cdot}5 \pm 4$) than the *cis* axial fluorine-equatorial X arrangement ($\delta = -200 \pm 6$). In 3-fluoro-1-methylcyclohexane derivatives (**155**), in which the fluorine atom is equatorially orientated, the shifts are not as clearly differentiated. The shift in the equatorial fluorine-axial X conformer is to lower frequency ($\delta = -187{\cdot}7 \pm 0{\cdot}1$) than for the di-equatorial arrangement ($\delta = -185{\cdot}8 \pm 0{\cdot}4$); the problem of enhanced steric interactions in 3-fluoro-methylcyclohexanes was fully realized during the study of conformational equilibria in these compounds.[90]

The long-range ^4J(H–F) coupling constants have also been shown[101] to have a steric dependence in carbohydrate derivatives. β-D-Allopyranosyl fluoride tetraacetate (**156a**) exhibits a long-range coupling of +3·6 Hz between F_{1e} and H_{4e} while the corresponding β-D-glucopyranosyl fluoride tetraacetate (**156b**) shows no similar coupling; a four bond coupling of 1·1 Hz between F_{3e} and H_{5a} is, however, resolved. Similarily 3-fluoro-3-deoxy-α-D-glucopyranose tetraacetate (**157a**) shows $^4J(F_{3e}\text{–}H_{1e})$ of 4 Hz while the corresponding β-anomer (**157b**) shows no similar coupling. The $^4J(F_{3e}\text{–}H_{5e})$ coupling of +4·2 Hz is present in 3-fluoro-3-deoxy-β-D-xylopyranose triacetate (**158**) while there is no coupling between F_{3e} and H_{5a}. The four-bond F_e–H_a couplings have been resolved in 2-chloro-2-deoxy-β-D-glucopyranosyl fluoride triacetate (**159**) and $^4J(F_{1e}\text{–}H_{3a}) = -0{\cdot}8$



a. X = H; Y = OAc
b. X = OAc; Y = H

157



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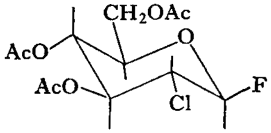
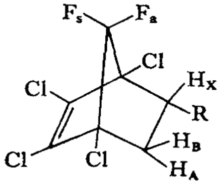


159



R = OAc, OH, Cl, C_6H_5, CO_2H or CN

160

Hz and $^4J(F_{1e}–H_{5a}) = 0{\cdot}7$ Hz. These results indicate that the long-range four-bond coupling occurs preferentially between nuclei having a 1,3-diequatorial disposition. A five-bond $F_{3e}–H_6$ coupling in **157b** was also reported.

Williamson and Fenstermaker[102] have also studied the geometrical dependence of the four-bond H–F coupling using 5-substituted-7,7-difluoro-1,2,3,4-tetrachlorobicyclo[2.2.1]heptenes (**160**) as model compounds. The ^{19}F shifts and coupling constants involving the fluorine atoms are shown in Table IX. The signs of coupling were not determined by double resonance techniques but were based upon the correlation of the J values with substituent electronegativity; this method was additionally assisted by

TABLE IX

^{19}F parameters of 5-substituted 7,7-difluoro-1,2,3,4-tetrachlorobicyclo-[2.2.1]-hept-2-enes (160)

	Chemical shifts, δ		Coupling constants, Hz							
R	F_s	F_a	F_aF_s	F_aH_X	F_aH_B	F_aH_A	F_sH_X	F_sH_B	F_aH_A
OAc	−141·7	−123·0	179	−3·24	−3·46	−1·89	+0·56	−0·76	−5·44
OH	−138·2	−122·8	182	−3·21	−3·48	−1·95	+0·36	−0·45	−5·38
Cl	−138·9	−121·9	178	−3·56	−3·21	−1·56	+0·81	−0·68	−5·27
C_6H_5	−140·5	−124·0	169	−3·04	−2·51	−0·90	+1·04	+0·39	−4·95
CO_2H	−143·2	−123·9	174	−2·81	−2·72	−1·42	+0·93	+0·89	−5·14
CN	−143·6	−123·4	174	−2·32	−2·74	−1·40	+1·12	−0·32	−4·87

the observation of variation in the appearance of the proton resonance spectrum which seemed to be sensitive to the signs of the H–F coupling constants. The authors also considered the geometrical dependence of the four-bond H–F coupling constants.

E. Fluoroaromatics

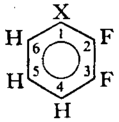
1. *General considerations*

The full spectral analysis of fluoroaromatics still continues to demand attention. Goldstein *et al.*[103] have examined the spectra of a number of *ortho*-, *meta*- and *para*-halogenofluorobenzenes and obtained the complete set of parameters by exhaustive analysis of the spectra. The H–F couplings have been compared with the corresponding couplings in the parent fluorobenzene and correlated these with the substituent electronegativity. In the *ortho*- and *meta*-substituted fluorobenzenes it was found that the *para* H–F coupling constants, although small, were of opposite sign to the *ortho* and *meta* H–F coupling constants which in turn are both of the same relative sign as the H–H couplings.

The same authors had earlier studied in some detail the spectrum of fluorobenzene,[104] especial consideration being given to the concentration dependence of both the chemical shifts and coupling constants. In this work the H–H and H–F couplings were assumed to be positive although, in view of the above later work, that of the *para* H–F coupling may need revision. Page[105] has considered the same compound in some detail and similarly found that the shifts and coupling constants were dependent upon concentration; a different solvent was used by Goldstein.[104] The ^{13}C shifts and direct ^{13}C–^{1}H coupling constants were also considered and the two bond ^{19}F–C–^{13}C coupling observed. The author states that the "unusual asymmetry" of the ^{19}F spectrum was used to establish that all the ^{1}H–^{19}F and ^{1}H–^{1}H coupling constants are of the same sign.

The spectra of both *ortho*-[106] and *meta*-[107, 108] difluorobenzenes have been examined in some detail. The analysis of *ortho*-difluorobenzene was effected by sub-spectral analysis. The H–H and *meta* and *ortho* H–F coupling constants were positive while the *ortho* F–F and *para* F–H couplings were found to be negative. Both authors[107, 108] recorded the spectra at 100 MHz (proton) and 94·1 MHz (fluorine), although those shown in ref. 108 are of better quality. There were variations in the precise values of the coupling constants but the spectra were recorded under different conditions: Mohanty[107] used neat liquid while Macdonald[108] used a 30% solution in carbon tetrachloride. There was, however, basic agreement in the signs of coupling, all being positive with the exception of the *para* H–F coupling.

As an extension to the study of *ortho-* and *meta-* difluorobenzene, Abraham *et al.*[106,109] have studied the spectra of 1-substituted 2,3-difluoro-[161] and 2-substituted 1,3-difluoro[162]-benzenes in order to establish the signs of the coupling constants. In a series of compounds of type **161** the *para* H–F couplings were negative, while all others were positive and in most cases the magnitude of the coupling constant was dependent upon the nature of X. Similarly the *para* H–F couplings in a series of compounds of type **162** were negative. A significant aspect of this later work was the very considerable variation in the magnitude of the *meta* F–F coupling, varying from 0·0 in **162**, where X = CN, to 12·1 Hz where X = NH_2.



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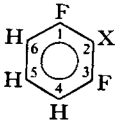


162

The variation in the values of *meta* and *para* F–F couplings have been considered in greater detail,[110a] following two earlier preliminary reports.[110b,c] The authors found that the magnitude and sign of each F–F coupling constant could be determined by additive substituent contributions. The couplings were found to vary over the following ranges +5 to +18 Hz (*para*) and –20 to +20 Hz (*meta*). This overlap of the magnitudes of *ortho* (~20 Hz), *meta* and *para* F–F coupling constants leads to ambiguities when determining the position of substitution in aromatic rings (see p. 332).

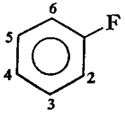
The ^{13}C–^{1}H and ^{13}C–^{19}F coupling constants of *ortho-*, *meta-* and *para-*substituted fluorobenzenes have been determined;[111] while the ^{13}C–^{1}H couplings could be related to the Hammett substituent constants no such similar correlation could be found for the ^{13}C–^{19}F coupling constants.

Kumar[112] has analysed the spectrum of 1,3-difluoro-4,6-dinitrobenzene and considered the solvent effects on both the chemical shifts and coupling constants. The spectrum of 1,2,4-trifluorobenzene has also been analysed,[113] using iteration methods to match all 197 lines. The H–F coupling constants that displayed considerable variation were the *ortho* H–F couplings, covering the range 7·64 to 10·3 Hz, and the *meta* H–F couplings, over the range 3·26 to 8·71 Hz. The overlap found for these couplings now precludes the criterion of the magnitude of the H–F couplings in assigning the position of substituents in aromatics.

Subspectral methods have been used to analyse the spectrum of 1,2,3,4-tetrafluorobenzene.[114] As the molecule contained both *ortho* H–H and *ortho* F–F couplings, the relative signs of these two coupling constants could be determined. Both *ortho* H–F and H–H were found to be positive while the *ortho* F–F coupling was negative.

TABLE X

^{19}F shifts of fluorinated aromatics



Substituent on positions					Chemical shift, δ						
2	3	4	5	6	F(1)	F(2)	F(3)	F(4)	F(5)	F(6)	Ref.
H	H	F	F	F	–139·8	..	..	–139·8	–156·8	–156·8	119a
H	COOMe	F	F	F	–134·9	..	..	–138·8	–148·7	–154·6	120
H	F	H	F	F	–132·2	..	–114·2	..	–132·3	–166·6	119a
H	F	F	H	F	–139·8	..	–139·8	–139·8	..	–139·8	119a
H	F	F	OMe	F	–140·7	..	–140·7	–158·4	..	–158·4	119a
R[a]	F	F	F	F	–158·1	..	–158·1	–165·3	–163·1	–165·3	123
CN	CN	F	F	F	–127·9	..	..	–127·9	–143·5	–143·5	119a
CN	F	F	CN	F	–130·6	..	–130·6	–130·6	..	–130·6	119a
COOH	COOH	F	F	F	–138·6	..	..	–138·6	–152·2	–152·2	119a
COOH	F	F	COOH	F	–140·4	..	–140·4	–140·4	..	–140·4	119a
COOEt	COOEt	F	F	F	–138·0	..	..	–138·0	–151·2	–151·2	119a
COOEt	F	F	COOEt	F	–140·1	..	–140·1	–140·1	..	–140·1	119a
COCl	COCl	F	F	F	–131·5	..	..	131·5	–138·0	–138·0	119a
COCl	F	F	COOH	F	–136·4	..	–136·4	–138·9	..	–138·9	119a
COCl	F	F	COCl	F	–137·6	..	–137·6	–137·6	..	–137·6	119a
CF$_3$	H	F	H	CF$_3$	–123·3	(–64·1)	..	–116·1	..	(64·1)	121
OH	F	OMe	F	F	–166·0	..	–160·1	..	–166·0	–172·7	122
OH	F	OCH$_2$CF$_3$	Cl	F	–161·5	..	–158·7	(–76·4)	..	–151·0	122
OH	F	F	OMe	F	–166·0	..	–166·0	–161·2	..	–161·2	122

OH	F	F	OCF_3	F	−165·7	..	−165·7	−156·1	(−61·3)	−156·1	122
OH	F	F	Cl	F	−163·0	..	−163·0	−144·6	..	−144·6	122
OH	Cl	F	F	OCH_2CF_3	−160·1	..	..	−146·3	−166·1	(76·4)	122
OH	Cl	F	Cl	F	−161·6	..	..	−120·6	..	−139·0	122
OMe	F	OMe	Cl	F	−161·0	..	−153·6	..	..	−145·2	123
OMe	F	F	Cl	F	−160·8	..	−160·8	−147·0	..	−147·0	123
OCH_2CF_3	F	OCH_2CF_3	Cl	F	−155·6	(−76·4)	−149·7	(−76·4)	..	−142·0	123
OCH_2CF_3	F	F	OCH_2CF_3	F	−158·9	(−76·2)	−158·9	−158·9	(−76·2)	−158·9	123
OCH_2CF_3	F	F	F	F	−158·9	(−76·1)	−158·9	−165·7	−164·2	−165·7	123
OCF_3	F	F	OMe	F	−156·1	(−61·0)	−156·1	−159·6	..	−159·6	123
OCF_3	F	F	F	F	−154·3	(−60·8)	−154·3	−164·6	−158·1	−164·6	123
$OCCl_3$	F	F	F	F	−148·4	..	−148·4	−164·4	−157·4	−164·4	123
$OCCl_3$	F	F	Cl	F	−145·6	..	−145·6	−141·1	..	−141·1	123
OEt	OEt	F	F	F	−160·1	..	..	−160·1	−166·9	−166·9	80
OEt	F	F	OEt	F	−159·4	..	−159·4	−159·4	..	−159·4	80
OEt	F	F	F	OEt	−151·3	..	−159·3	−166·9	−159·3	..	80
F	F	CF_3	F	CF_3	−128·1	−163·5	−128·1	(−59·0)	−116·8	(−59·0)	121
F	F	Cl	OH	Cl	−138·4	−165·8	−138·4	..	..	..	122
Cl	R[a]	Cl	OH	Cl	−114·8	..	..	..	..	..	122
Cl	R[b]	Cl	OH	Cl	−113·9	..	..	..	..	..	122
Cl	OCH_2CH_2F	Cl	R[a]	Cl	−113·8	..	(−138·5)	..	..	..	123
Cl	F	Cl	R[a]	Cl	−114·2	..	−114·2	..	..	..	123
Cl	F	Cl	OH	Cl	−114·1	..	−114·1	..	..	..	122
Cl	Cl	F	F	OH	−112·9	..	..	−135·9	−155·2	..	122
Br	CO_2Me	F	F	F	−128·5	..	..	−138·7	−154·6	−150·8	120
Br	F	F	Br	F	−131·7	..	−131·7	−131·7	..	−131·7	119a
I	I	F	F	F	−104·1	..	..	−104·1	−151·5	−151·5	119a

[a] $R = —OCH_2(CF_2)_3CF_2H$.

[b] $R = —OCH_2(CF_2)_5CF_2H$.

The pentafluoroaromatics still continue to be investigated and among those examined in some depth during the past two years were pentafluorobenzene,[115, 116] pentafluoroanisole[117] and pentafluoroiodobenzene.[118] In the case of the pentafluorobenzene two sets of parameters were obtained by iterative methods and the correct one selected by using spin-tickling methods.

Dean and McFarlane[116] have used heteronuclear double resonance techniques to determine the relative signs of coupling in pentafluorobenzene. Assuming that the *ortho* F–F coupling is negative, all the other couplings except the *para* H–F were positive. The signs obtained by Bernstein *et al.*[115] would therefore appear to be in error. There was, however, fairly good agreement with the relative magnitudes of the coupling constants. This work, which shows that the H–F coupling is negative, together with work on other fluorobenzenes would tend to indicate that the *para* H–F coupling, although of variable magnitude, is probably always negative.

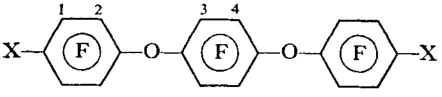
Sub-spectral analysis was used to study the spectrum of pentafluoroanisole and it was found that both the chemical shifts and coupling constants were solvent dependent. The authors[117] point out the advantage of using sub-spectral methods for this type of investigation as a number of parameters are quickly obtained without recourse to full analysis. The study of the pentafluoroiodobenzene was carried out at the surprisingly low frequency of 6·14 MHz. Moniz and Lustig[118] point out the advantage of measuring ^{19}F spectra at low fields since the relative signs and precise assignment of coupling constants can then be made; this is not possible at higher fields due to the "first-order" character of the spectra. Thus the F(2)–F(6) and F(3)–F(5) coupling constants were found to be –4·95 and –1·22 Hz respectively; the third *meta* coupling, F(2)–F(4), was found to be +2·08, thus the relative signs of all *meta* couplings were obtained.

The chemical shifts and some of the coupling constants of a whole series of pentafluorobenzene derivatives have been tabulated,[119a] although many of these compounds had previously been reported by various authors. The same paper also gave the shifts of various disubstituted tetrafluorobenzenes; some of these are tabulated in Table X. The author also refers to the correlation of the chemical shift of the *para*-fluorine atom F(4) with the F(2)–F(4) coupling constant in which two lines were obtained[119b] depending upon the electron-attracting or -donating property of the substituent. Bruce,[119a] however, points out that this becomes a single straight line if there is a change in the sign of the *meta*-F(2)–F(4) coupling constant. Even if the author is correct, and there appears some ground to support the reversal in sign, the comparison of $|J[F(2)–F(4)]|$ with the chemical shift of F-4 provides a qualitatively useful indication of the electron withdrawing or donating properties of the substituent groups. The ^{19}F spectra of many of these same pentafluorobenzene derivatives were also reported independently and the shifts correlated with the Taft reactivity parameters.[119c]

Recently some ^{19}F data on 1,3-bis(trifluoromethyl)-2,4,5,6-tetrafluoro- and 2,5-difluoro- benzenes have been published.[121] This work was, however, done at 30·107 MHz and it is not clear as to the precise accuracy of the coupling constants; the shifts are however included in Table X.

TABLE XI

^{19}F shifts of derivatives of 1,4- and 1,3-dihydroxy tetrafluorobenzenes[124]



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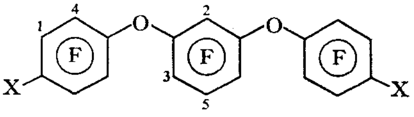

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Cpd.	X	Chemical shifts, δ F(1)	F(2)	F(3)	F(4)	F(5)		
163	CN	−138·0	−161·1	−162·1	−162·1	..	..	..
163	CF_3	−141·4	−155·4	−156·1	−156·1	..	δ(CF_3)	−57·5
164	CN	−135·6	−152·1	−154·9	−158·1	−165·5	..	..
164	CF_3	−143·9	−151·9	−155·5	−158·5	−165·5	δ(CF_3)	−57·3

The chemical shifts of fluorinated phenols and phenyl ethers, obtained by reaction of the fluorobenzenes with alkoxide ions,[122, 123] have been

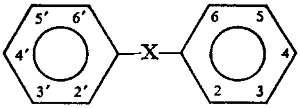
TABLE XII

^{19}F chemical shifts of pentafluorophenyl iminosulphur dihalides[125] and sulphurdiimide,[126] $C_6F_5N{=}X$

	X: SF_2	SCl_2	S=O	=S=N—C_6F_5
δF(2,6)	−147·8	−145·7	−141·7	−145·2
δF(3,5)	−164·5	−162·1	−164·0	−164·6
δF(4)	−159·5	−155·5	−156·7	−158·7
$J(F_3–F_4)$	20·5	20·4	19·3	19·3
$J(F_2–F_4)$	2	1·1	1·2	..
$J(F_2–SF_2)$	13	..	..	..

TABLE

^{19}F shifts of fluorinated



X	Substituted on position									
	2	3	4	5	6	2′	3′	4′	5′	6′
..	H	F	F	F	F	H	F	F	F	F
..	H	F	F	OMe	F	H	F	F	F	F
..	H	F	F	OMe	F	H	F	F	OMe	F
..	F	F	F	F	F	OMe	H	H	H	H
..	F	F	F	F	F	OH	H	H	H	H
..	F	F	H	F	F	OMe	H	H	H	H
..	F	F	H	F	F	OH	H	H	H	H
..	F	F	CF_3	F	F	OMe	H	H	H	H
..	F	F	F	F	F	CH_2Br	H	H	H	H
..	F	F	F	F	F	H	H	H	H	H
..	F	F	F	F	F	H	Me	H	H	H
..	F	F	F	F	F	H	Cl	H	H	H
..	F	F	F	F	F	H	Br	H	H	H
..	F	F	CF_3	F	F	F	F	CF_3	F	F
C=O	OMe	F	F	F	F	F	F	F	F	F
C=O	F	F	F	F	F	F	F	F	F	F
O	F	F	C_4H_9	F	F	F	F	CO_2H	F	F
O	F	F	F	F	F	F	F	F	F	F
S	F	F	F	F	F	F	F	F	F	F

included in Table X. The shifts of some fluorinated derivatives of 1,4-dihydroxytetrafluorobenzene are shown in Table XI.[124]

Pentafluoroaniline and sulphur tetrafluoride gave the imino sulphur difluoride[125] and with sulphur dichloride gave imino sulphur dichloride or the sulphurimide;[126] the shifts of the pentafluorophenyl entity are shown in Table XII. The shifts of a number of substituted diphenyls, diphenyl ethers and sulphides and benzophenones have also been reported in a number of papers. The shifts of these compounds have been collected in Table XIII.

The fluorine chemical shifts and the F–F coupling constants of a series of 4,5-difluorophenanthrenes have been investigated.[127] The magnitude of the F–F coupling and its independence of the ^{19}F chemical shifts have been explained in terms of the coupling occurring via non-bonding electrons. The chemical shifts and F–F coupling constants in acetone-d_6 are shown in

XIII

diphenyl derivatives

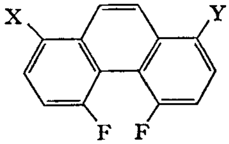
Chemical shift, δ										
F(2)	F(3)	F(4)	F(5)	F(6)	F(2′)	F(3′)	F(4′)	F(5′)	F(6′)	Ref.
..	−140	−156	−156	−140	..	−140	−156	−156	−140	401
..	−142	−151	..	−134	..	−140	−156	−156	−140	401
..	−140	−149	..	−134	..	−140	−149	..	−134	401
−140·65	−163·95	−156·9	−163·95	−140·65	..	..	..	..	..	403
−140·55	−164·4	−157·95	−164·4	−140·55	..	..	..	..	..	403
−141·3	−141·3	..	−141·3	−141·3	..	..	..	..	..	403
−139·5	−140·8	..	−140·8	−139·5	..	..	..	..	..	403
−139·8	−143·0	(−57·0)	−143·0	−139·8	..	..	..	..	..	403
−139·65	−161·6	−154·1	−161·6	−139·65	..	..	..	..	..	403
−146·5	−166·0	−159·5	−166·0	−146·5	..	..	..	..	..	404
−146·0	−166·5	−160·0	−166·5	−146·0	..	..	..	..	..	404
−143·5	−165·5	−158·0	−165·5	−143·5	..	..	..	..	..	404
−146·0	−165·5	−158·0	−165·5	−146·0	..	..	..	..	..	404
−135·2	−138·4	(−56·1)	−138·4	−135·2	−135·2	−138·4	(−56·1)	−138·4	−135·2	406
..	−155·2	−150·0	−162·9	−143·6	−142·0	−160·9	−148·4	−160·9	−142·0	120
−141·6	−160·3	−146·5	−160·3	−141·6	−141·6	−160·3	−146·5	−160·3	−141·6	120
−160·1	−146·9	..	−146·9	−160·1	−158·8	−141·7	..	−141·7	−158·8	405
−156·2	−162	−159·4	−162	−156·2	−156·2	−162	−159·4	−162	−156·2	402
−133	−161	−151	−161	−133	−133	−161	−151	−161	−133	401

Table XIV; while the chemical shifts appear to be solvent dependent the F–F coupling constants were invariant with change of solvent. The coupling between the 4- and 5-fluorine atoms is exceptionally large for a five-bond coupling and certainly would appear to be the largest five-bond coupling constant reported to date. The authors also suggest that "through-space" coupling might be differentiated by the insensitivity of the coupling constant with the nature of the substituents. The ^{19}F spectrum of 9-fluorophenanthrene shows a doublet of doublets at −123·6, the larger coupling of 11·7 Hz arising from *ortho* H–F coupling and the smaller, 2·0 Hz, coupling arising from interaction with H(4) or H(5).[128]

Partial ^{19}F data of the tetrafluorobenzyne adducts with aromatic hydrocarbons have been discussed, although the paper was primarily concerned with the proton spectra.[129]

TABLE XIV

The ^{19}F shifts and F–F coupling constants of 4,5-difluorophenanthrenes[127]



X	Y	Chemical shift, δ F_4	Chemical shift, δ F_5	Coupling constant, $^5J(F_4–F_5)$, ±2 Hz
CH_3	CH_3	−103·68	−103·68	. .
CH_3	CH_2Br	−98·18	−103·42	170
CH_3	CH_2OH	−101·96	−103·85	170
CH_3	CO_2Et	−92·62	−103·67	167
CH_3	NH_2	−115·22	−103·50	167

2. ^{19}F *shifts of fluorinated aromatics and the study of electronic interactions*

The realization that the larger chemical shifts of the fluorine-19 nucleus makes this a very useful probe for investigation of the mesomeric/inductometric interaction has led to a surge of papers dealing with all types of compounds. In this section the metallic derivatives will not be considered and the reader is referred to p. 340 *et seq.* for this aspect.

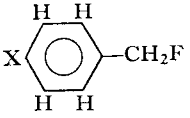
In pentafluoroaromatics it is often the *para*-fluorine shift which is most markedly affected. This aspect was emphasized by Beckert and Lowe[130a] who, during the course of Friedel–Crafts alkylation of pentafluorobenzene, found that there was a 450 Hz shift between the 4-fluorine in 2,3,4,5,6-pentafluorotoluene and tris(2,3,4,5,6-pentafluorophenyl)methane; those of (2,3,4,5,6-pentafluorophenyl)phenyl methane and bis(2,3,4,5,6-pentafluorophenyl)methane were of intermediate value.

The shift of the fluorine atom in *m*- and *p*-fluorophenylalanines have been used to study the enzyme (chymotrysin)-inhibitor interaction in solution.[130b] This work also afforded a further example of the preferential solvent effects upon enantiomers. Addition of chymotrysin to a solution of *N*-acetyl-DL-*p*-fluorophenylalanine resulted in the appearance of two overlapping multiplets of the 4-fluorine; use of the pure D- and L-isomers separately showed that the L-isomer is less strongly bound to the enzyme.

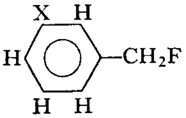
Taft *et al.*[131] have used the *para*-fluorine shift as a label to study hydrogen bonding between *p*-fluorophenol and the three bases tetrahydrofuran, pyridine and dimethylformamide. By using proton decoupling it was possible to use low concentrations of the phenol (less than 0·01 M) which ensured that the phenol was present in the monomeric state; the results were also directly comparable to the results for the hydrogen bonding obtained by the infrared technique. An additional feature is that using the *p*-fluorine label it was possible to determine the extent of proton-transfer in the H-bonded complex. The chemical shift difference for the 4-fluorine atom of *p*-fluorophenol in carbon tetrachloride and the *p*-fluorophenoxide ion in dimethyl sulphoxide solution was 14 p.p.m.; consequently the % proton transfer $\simeq 100\Delta/14$, where Δ is the shift between the free and complexed fluorophenol.

Certainly the most systematic work on the study of the fluorine shifts in *p*- and *m*- fluorophenyls as a means to study electronic interactions has been undertaken by Taft and his coworkers. One of the first attempts to determine the π-charge density at a carbonyl carbon atom before and after reaction has been the study of 4-fluorobenzophenone derivatives and the complexes with Lewis acids.[132] The shifts obtained for the complexes were additionally used to calculate the enthalpy of formation; in most cases there was good agreement with the calorimetrically determined values.[133]

Pews[134] has used the ^{19}F chemical shifts of *m*- and *p*- fluorophenylcyclopropanes, oxiranes, thiranes, ethylenimines and oxaxiridines to calculate the inductive and resonance substituent constants from the linear relationships developed by Taft and his coworkers.



165



166

Beguin[135] employed the fluorine shift of the substituted benzyl fluorides **165** and **166** to determine the mesomeric interaction of the substituent with the aromatic ring. An essentially linear plot, between the ^{19}F shift and the σ^+ constant of Brown and Okamoto, was found. The ^{19}F shift of the —CH_2F group differed by 15·9 p.p.m. on changing X in **165** from —NO_2 to —OCH_3; this again indicates the sensitivity of the fluorine-19 shifts.

Gale and Krespan[28] have found that the shift of the CF_3 groups in substituted α,α-bis(trifluoromethyl)benzylamines **77** could be correlated with the Taft function, σ_{R°, of the *para*-substituent X. By comparison of the shift of the *para*-fluorine atom (X = F in **77**) with that of fluorobenzene (−1·72 p.p.m.), it was suggested that the hexafluoroisopropylamino group is slightly less electron withdrawing than the hexafluoroisopropanol group in the corresponding compound *p*-$FC_6H_4C(CF_3)_2OH$ (*p*-F 2·00 p.p.m. from fluorobenzene). This difference was thought to be due to the differences in electronegativity of oxygen and nitrogen.

The ^{19}F shifts of 2,3,5,6-tetrafluoro-*p*-benzoquinone and of 1,4-dicyano-2,3,5,6-tetrafluorobenzene have been used to measure the equilibrium constants for the electron-donor-acceptor complexes between these two fluoroaromatics and various methyl-substituted benzenes; the benzoquinone forms stronger complexes than the 1,4-dinitrile. The effect of solvent upon the equilibrium complex was also studied.[136] The ^{19}F shifts of both 2,3,5,6-tetrafluoro-*p*-benzoquinone and the complexes with methylbenzenes were found to be temperature dependent.[137] The temperature variations of the shifts were approximately the same and the general trend for the association constant for various quinone complexes was maintained at each given temperature investigated.

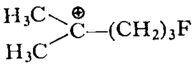
F. Fluorocarbonium ions

1. *Alkyl carbonium ions*

A number of fluoroalkyl carbonium ions have been observed by dissolving *gem*-difluoroalkanes in antimony pentafluoride–sulphur dioxide solution at –60°C.[138] The dimethylfluorocarbonium ion, $CH_3\overset{\oplus}{C}FCH_3$, has a resonance signal at 182·0 with ^3J(H–F) of 26 Hz (compare shifts of parent compound $CH_3CF_2CH_3$ at –81·5 with ^3J(H–F) of 19 Hz). The same ion was obtained by protonation of 2-fluoropropene in fluorosulphuric acid–antimony pentafluoride. The phenylmethylcarbonium ion, $C_6H_5\overset{\oplus}{C}FCF_3$, has been prepared and has a ^{19}F resonance signal at 51·3 (compared to parent compound $C_6H_5CF_2CF_3$ at –89·2). It is suggested that in both of these ions there is considerable back-donation from the fluorine into the vacant sp^2-carbon orbitals, i.e. $\overset{\oplus}{F}{=}C{-}R_2$ resonance forms stabilize the cation and account for the very considerable deshielding of the fluorine resonance.

1-Fluoro-2-methyl-propan-2-ol dissolved in fluorosulphuric acid, antimony pentafluoride and sulphur dioxide afforded the carbonium ion, $CH_3CH_2\overset{\oplus}{C}FCH_3$, which had a shift of 170·2 and the two vicinal H–F coupling constants were both in the region of 22 to 26 Hz; the shift of the parent alcohol was –224·8.[7]

Attempts to obtain fluoronium ions by ionization of 1-fluoro-4-hydroxy- and 1-fluoro-4-chloro- 4-methylpentanes in fluorosulphuric acid–antimony pentafluoride–sulphur dioxide afforded only protonated cyclic carbonium ions.[5] The 4-chloro-compound, however, was thought to initially yield the ion in antimony pentafluoride–sulphur dioxide but rearrangement eventually occurred. The carbonium ion (**167**) was obtained from the 1,4-difluoro-4-methylpentane. The proton NMR data of this ion and that

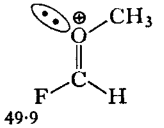


$(H_3C)_2\overset{\oplus}{C}{-}(CH_2)_3F$

167

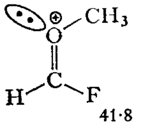
from 5-fluoro-pentan-2-one were given but no ^{19}F data. The ^{19}F shifts of only the parent compounds were given (see p. 263).

The hypothesis that the ions obtained from α,α-dichlorodimethylether existed in two conformational forms was proved by examination of the corresponding methoxyfluorocarbonium ion, obtained from α,α-difluorodimethylether.[139] The ion existed as *cis* and *trans* isomers **168a** and **b** and both exhibiting high-frequency resonances compared to the parent ether



$^2J(F\text{–}H) = 98$ Hz

168a



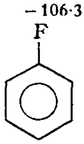
$^2J(F\text{–}H) = 98$ Hz
$^4J(F\text{–}CH_3) = 0{\cdot}7$ Hz

168b

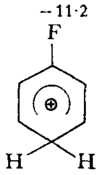
CH_3OCHF_2 with a shift of −89·7 and $^2J(H\text{–}F)$ of 75 Hz; the increased *gem* H–F coupling certainly supports the sp^2 character of the —CFH group. The fact that two conformations of the ion are observed also indicates the importance of contributions to the structure as are shown in **168a** and **b.**

2. *Aromatic carbonium ions*

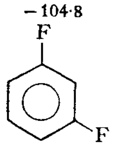
The protonation of mono-, di-, tri- and tetra- fluorobenzenes in fluorosulphuric acid–antimony pentafluoride solution give stable fluorobenzenonium ions (fluorocyclohexadienyl cations).[140] The ions can only be observed in neat fluorosulphonic acid–SbF_5 mixture as dilution with liquid SO_2 resulted in sulphonylation occurring. Consequently the viscosity of the solutions, especially at the low temperatures used to reduce the exchange rates, caused the spectra to be poorly resolved. The shifts of the parent benzenes and the ions, together with the F–F coupling constants are, for convenience, shown in **169** to **174**. This work has been extended to the study[141] of mono-, di-, tri- and tetra- fluorotoluenes as well as the mono- di- and tri- fluoromesitylenes; in this latter work the more stable ions could be diluted with liquid sulphur dioxide. Again the chemical shifts and the significant coupling constants are shown in **175** to **183**. The ^{19}F spectra readily permit the structure of the carbonium ion to be determined since fluorine atoms *meta* to the $>CH_2$ or $>CHCH_3$ group occur



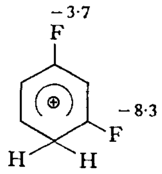
169a



169b

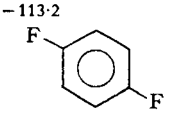


170a

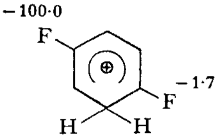


^4J(F–F) = 80 Hz

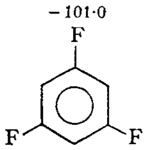
170b



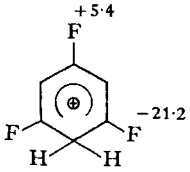
171a



171b

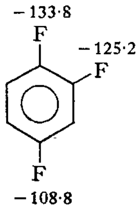


172a

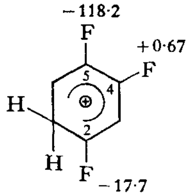


^4J(F–F) = 80 Hz

172b



173a

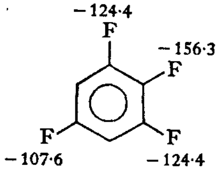


^3J[F(4)–F(5)] = 20 Hz
^4J[F(2)–F(4)] = 80 Hz

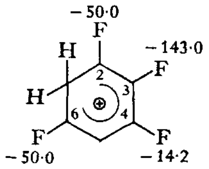
173b

in the range −100 to −143 p.p.m., while the *ortho* and *para*-fluorine atoms occur at higher frequency (*ortho* −1·7 to −54·6 and *para* +5·4 to −19·3 p.p.m.). The greater sensitivity of the fluorine shifts may again permit a greater understanding of the charge distribution in the ions. A particularly interesting aspect of this work is the realization of the extremely large *meta* four bond F–F coupling of some 70 to 80 Hz.

Tris(pentafluorophenyl)carbinol in fluorosulphonic acid, or the acid with

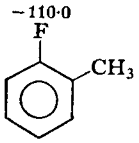


174a

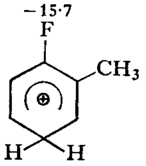


^4J[F(2)–F(4)] = 70 Hz
^3J[F(2)–F(3)] = 20 Hz
^3J[F(3)–F(4)] = 20 Hz

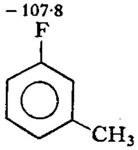
174b



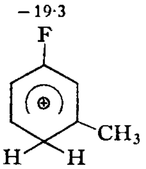
175a



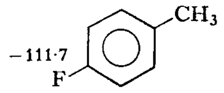
175b



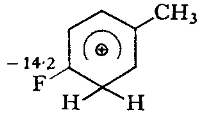
176a



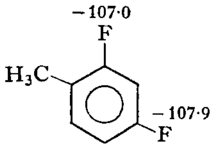
176b



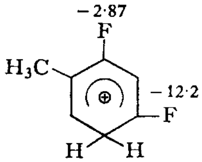
177a



177b

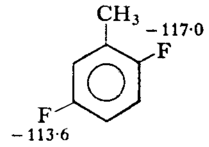


178a

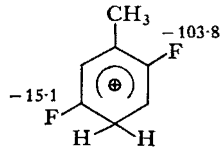


^{4}J(F–F) = 82 Hz

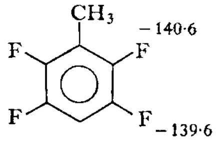
178b



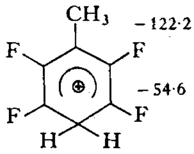
179a



179b



180a



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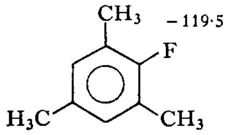
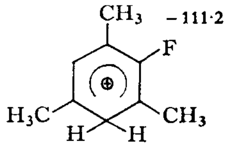
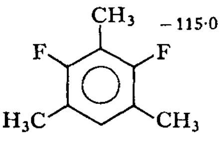


181a

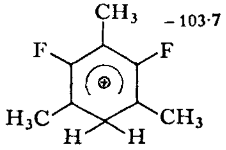


181b

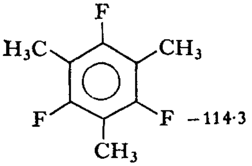
antimony pentafluoride, affords the tris(pentafluorophenyl)-carbonium ion; the former solvent is the more satisfactory as in the presence of antimony pentafluoride the Sb–F resonance masks the signal of the *para*-fluorine atom.[142] In the ion the greatest deshielding occurs in the *ortho* (14·7 p.p.m.) and *para* (40·1 p.p.m.) positions implying considerable charge delocalization into these positions (**184**). The ion from bis(pentafluorophenyl)methyl alcohol is less stable and cannot be obtained in neat fluorosulphonic acid,



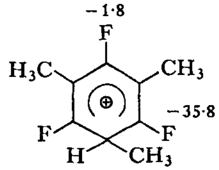
182a



182b



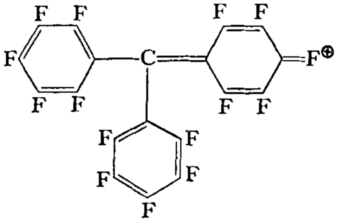
183a



^4J(F–F) = 70 Hz
^3J(H–F) = 6 Hz

183b

the usual $FSO_3H–SbF_5–SO_2$ mixture being required. The pentafluorophenylmethyl carbonium ion was obtained from pentafluorobenzyl fluoride in antimony pentafluoride–liquid sulphur dioxide solution, again the considerable deshielding of the *ortho*- and *para*-fluorine atoms implies



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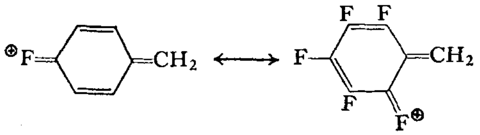

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TABLE XV

Shifts of carbonium ions derived from pentafluorophenyl alcohols and pentafluorobenzyl fluoride[142]

	Chemical shifts, δ					
	Parent compound			Ion		
	ortho	*meta*	*para*	*ortho*	*meta*	*para*
$(C_6F_5)_3C.OH$	−140·98	−161·54	−152·22	−126·25	−154·29	−112·12
$(C_6F_5)_2CHOH$	−144·17	−162·28	−153·69	−111·61	−153·86	−100·36
$C_6F_5CH_2F$[a]	−143·57	−162·53	−152·27	−103·18	−151·53	−74·89

[a] —CH_2F, δ = −211·74.

contribution from canonical forms as in **185**. The shifts of the parent compounds and ions are shown in Table XV.

The ^{19}F spectra of the 3-fluoro-, 3,3′-difluoro-, 3,3′,3″-trifluoro, 4-fluoro-, 4,4′-difluoro-, and 4,4′,4″-trifluoro-triphenylmethyl carbonium

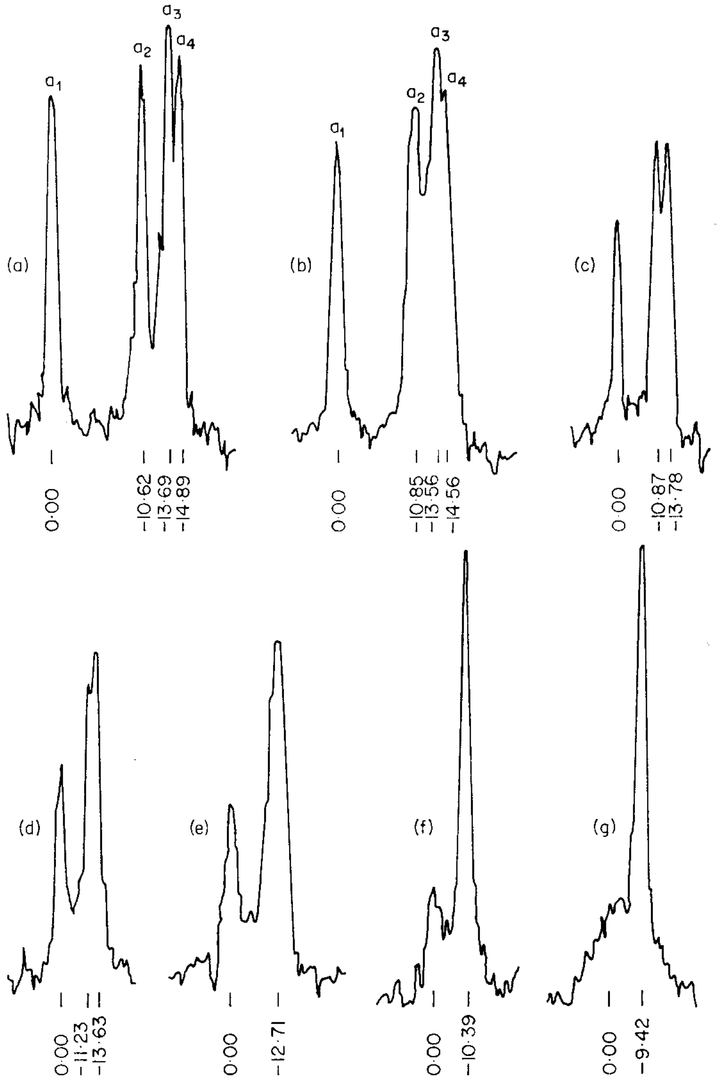


FIG. 4. Variable-temperature ^{19}F spectra of the 3,3′-difluoro triphenylmethyl cation. (From Schuster, Colter and Kurland.)[143]

ions have been measured in liquid hydrogen fluoride as solvent.[143] Low-temperature, spin-decoupled ^{19}F spectra were able to establish the propellor conformation of the cations. Detailed study of the temperature dependence of the spectra of the 3,3′- and 3,3′,3″-fluoro derivatives showed that the most favourable mechanism of interconversion of the propellor conformers is that in which the three phenyl rings pass through a plane perpendicular to the plane defined by the three central carbon to phenyl bonds, i.e. a three ring flip. The temperature variable ^{19}F spectra of the 3,3′-difluoro-triphenylmethyl cation are shown in Fig. 4. The chemical shifts of the six ions and those of the monofluorophenyl dihydroxymethyl cations are shown in Table XVI.

TABLE XVI

Shifts of fluorophenyldihydroxy- and fluorotriphenylmethyl carbonium ions[143]

	δ		δ
$3\text{-}FC_6H_4\overset{\oplus}{C}(OH)_2$	−113·8	$4\text{-}FC_6H_4\overset{\oplus}{C}(OH)_2$	−97·8
$(3\text{-}FC_6H_4)\overset{\oplus}{C}(C_6H_5)_2$	−113·2	$(4\text{-}FC_6H_4)\overset{\oplus}{C}(C_6H_5)_2$	−88·3
$(3\text{-}FC_6H_4)_2\overset{\oplus}{C}(C_6H_5)$	−112·5	$(4\text{-}FC_6H_4)_2\overset{\oplus}{C}(C_6H_5)$	−87·7
$(3\text{-}FC_6H_4)_3\overset{\oplus}{C}$	−111·8	$(4\text{-}FC_6H_4)_3\overset{\oplus}{C}$	−87·2

III. HETEROCYCLIC COMPOUNDS

A. Nitrogen heterocyclics

1. *General*

An increasing amount of chemical shift data is becoming available on fluorinated pyridines. While 4-substituted tetrafluoropyridines were readily obtained from pentafluoropyridine, the corresponding 2-isomers have to be synthesized by a more elaborate route.[144] The chemical shifts of a number of derivatives have been reported (Table XVII) as have a series of derivatives of perfluorodipyridyl[149] (Table XVIII). It is a noticeable characteristic that in all these compounds the nitrogen atom causes a marked deshielding of the α-fluorine atoms and the quadrupole broadening of the resonance signal of the α-fluorine often precludes complete abstraction of the coupling constants. In the 2-substituted tetrafluoropyridines given[144] in Table XVII the majority of the coupling constants could be obtained. The largest coupling was that of the *para* coupling between F_3 and F_6 and tended to be variable in the range 22·7 to 28·1 Hz. The *ortho* F–F coupling constants vary depending upon the position of the fluorine atoms, thus the $^3J(F_3\text{–}F_4)$ and $^3J(F_4\text{–}F_5) = 17{\cdot}6 \pm 0{\cdot}6$ Hz while $^3J(F_5\text{–}F_6) = 24{\cdot}8 \pm 0{\cdot}8$ Hz; the former are smaller and the latter larger than the normal aromatic *ortho* F–F coupling constants. The *meta* $^4J(F_4\text{–}F_6)$ was also rather large being in the range 17·0 to 20·0 Hz, only three values were given for the other *meta* $F_3\text{–}F_5$ coupling –10·1, 4·6 and 4·7 Hz, insufficient data for any generalizations. Banks *et al.*,[147] from the analysis of the spectrum of 4-iodo-2,3,5,6-tetrafluoropyridine, have also found a very large *para* $F_2\text{–}F_5$ coupling of 28·3 Hz which is again considerably larger than the *ortho* $F_2\text{–}F_3$ coupling of 20·4 Hz.

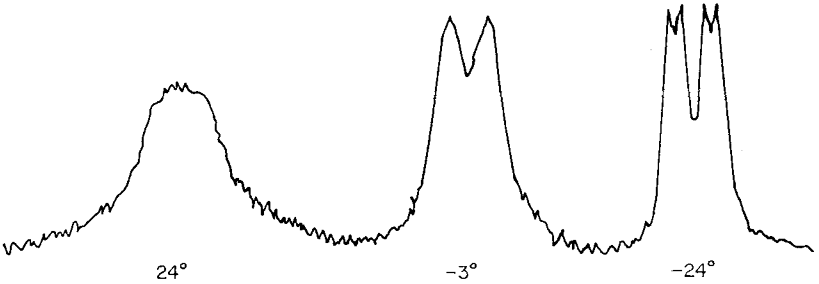
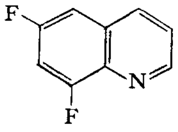


FIG. 5. The temperature dependence of the resolution of the fluorine signal of 2-fluoroquinoline. (From Franz, Hall and Kaslow.)[153]

Cunliffe and Harris[152] have considered the problem of broadened ^{19}F



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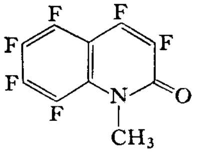
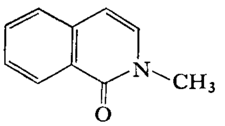


188



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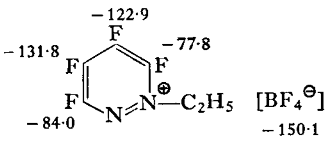

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TABLE XVII

^{19}F shift of fluorinated pyridine derivatives

Substituted on position					Chemical shift, δ					
2	3	4	5	6	F-2	F-3	F-4	F-5	F-6	Ref.
Me	F	Me	F	F	..	–128·7	..	–144·2	–90·9	151
n-Bu	F	Me	F	F	..	–130·6	..	–144·3	–90·7	151
$CH_3.CH{=}CH—$	F	Me	F	F	..	–132·9	..	–145·2	–90·8	146
$CH{=}NOH$	F	Me	F	F	..	–128·3	..	–131·7	–89·9	146
CF_3	F	F	F	F	..	–141·5	–134·9	–149·4	–80·9	144
$CF(CF_3)_2$	F	$CF(CF_3)_2$	F	F	..	(–112·3)[a]	..	(–122·7)[a]	–82	145
C_6F_5	F	F	F	F	..	–154·7	–138·2	–140·2	–81·2	144
$—(CF_2)_3CN$	F	F	F	F	..	–129·5	–134·9	–148·9	–79·7	144
$2\text{-}C_5F_4N$	F	F	F	F	..	–142·0	–137·5	–153·8	–81·7	149
$—(CF_2)_3C_6F_4N$	F	F	F	F	..	–129·5	–136·1	–150·5	–80·6	144
NH_2	F	Me	F	F	..	–145·8	..	–160·1	–94·9	151
NH_2	F	NH_2	F	F	..	–164·1	..	–175·2	–96·4	151
NH_2	F	I	F	F	..	–122·9	..	–140·7	–94·1	147
OH	F	I	F	F	..	–125·4	..	–136·8	–95·1	147
OMe	F	$—CF(CF_3)_2$	F	F	..	–134·9	..	–147·1	–91·5	145
OMe	F	I	F	OMe	..	–135·5	..	–135·5	..	147
OMe	F	I	F	F	..	–122·3	..	–132·7	–92·6	147
OEt	F	Me	F	OEt	..	–152·5	..	–152·5	..	151
OEt	F	Me	F	F	..	–144·3	..	–154·1	–95·1	151
F	$3\text{-}C_5F_4N$	F	F	F	–68·5	..	–110·7	–161·2	–76·3	149
F	F	$—CF(CF_3)_2$	F	F	–87·3	–135·1	..	–135·1	–87·3	145
F	F	CF_2CF_3	F	F	–87	–112	..	–112	–87	145
F	F	Me	F	F	–96·0	–147·8	..	–147·8	–96·0	146
F	F	$(C_6H_5)_2COH$	F	F	–91·5	–137·7	..	–137·7	–91·5	147
F	F	C_6H_5CHOH |	F	F	–93·4	–145·8	..	–145·8	–93·4	147

TABLE XVII—*continued*

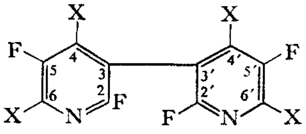
Substituted on position					Chemical shift, δ					
2	3	4	5	6	F-2	F-3	F-4	F-5	F-6	Ref.
F	F	CN	F	F	−90·7	−188·1	..	−188·1	−90·7	146
F	F	CONH$_2$	F	F	−89·7	−142·1	..	−142·1	−89·7	148
F	F	—CONHNHCOC$_5$F$_5$N	F	F	−88·6	−140·8	..	−140·8	−88·6	148
F	F	CH$_2$Cl	F	F	−89·7	−143·1	..	−143·1	−89·7	151
F	F	CHCl$_2$	F	F	−87·8	−140·7	..	−140·7	−87·8	151
F	F	CCl$_3$	F	F	−87·1	−140·1	..	−140·1	−87·1	151
F	F	CH$_2$Br	F	F	−89·8	−143·0	..	−143·0	−89·8	151
F	F	CHBr$_2$	F	F	−88·1	−139·9	..	−139·9	−88·1	151
F	F	CHO	F	F	−90·4	−146·8	..	−146·8	−90·4	151
F	F	CHO	F	F	−91·7	−148·9	..	−148·9	−91·7	146
F	F	COF	F	F	−86·4	−135·7	(+48·8)[b]	−135·7	−86·4	148
F	F	—COCF(CF$_3$)$_2$	F	F	−85·6	−158·5	..	−158·5	−85·6	148
F	F	4-C$_5$F$_4$N	F	F	−90·6	−139·2	..	−139·2	−90·6	149
F	F	4-C$_5$F$_4$N	F	F	−87·6	−138·5	..	−138·5	−87·6	150
F	F	C$_6$H$_5$	F	F	−91·3	−145·5	..	−145·5	−91·3	150
F	F	C$_6$F$_5$	F	F	−88·7	−139·0	..	−139·0	−88·7	150
F	F	n-Bu	F	F	−91·9	−144·2	..	−144·2	−91·9	151
F	F	NC$_5$F$_5$	F	F	−91·5	−140·5	..	−140·5	−91·5	147
F	F	NH$_2$	F	F	−95·9	−161·7	..	−161·7	−95·9	149
F	F	NH$_2$	F	F	−95·0	−165·0	..	−165·0	−95·0	150
F	F	OMe	F	F	−92·9	−161·7	..	−161·7	−92·9	149
F	F	—OCH(CH$_3$)$_2$	F	F	−91·6	−158·4	..	−158·4	−91·6	149
F	F	F	F	OMe	−91·4	−171·9	−140·9	−164·9	..	149
F	F	Me$_3$Si	F	F	−94·2	−131·9	..	−131·9	−94·2	147
F	F	I	F	F	−89·6	−123·2	..	−123·2	−89·6	147
F	Cl	I	F	F	−73·6	..	..	−122·5	−92·2	147
Br	F	F	F	F	..	−155·4	−133·6	−129·7	−80·3	144

[a] Assignments may be reversed.

[b] Shift of —COF group.

TABLE XVIII

^{19}F shifts of 3,-3′-perfluoropyridyl derivatives



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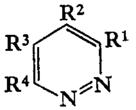
Substituent X				Chemical shifts, δ							
4	6	4′	6′	F-2	F-4	F-5	F-6	F-2′	F-4′	F-5′	F-6′
OMe	F	F	F	−72·1	. .	−164·2	−84·9	−68·5	−112·1	−166·9	−83·5
F	OMe	F	F	−69·8	−119·9	−168·1	. .	−68·4	−112·2	−166·1	−82·4
OMe	F	OMe	F	−73·4	. .	−165·0	−86·7	−73·4	. .	−165·0	−86·7
OMe	F	F	OMe	−73·4	. .	−165·0	−86·7	−71·4	−120·6	−172·3	. .
F	NH_2	F	F	−76·6	−122·5	−160·1	. .	−68·2	−113·0	−164·9	−80·5
F	Me	F	F	−67·3	−119·5	−151·7	. .	−67·3	−112·2	−166·0	−81·6
OPr^n	F	F	F	−72·1	. .	−167·2	−84·7	−67·5	−111·7	−163·3	−82·5
F	OPr^n	F	F	−70·1	−120·4	−157·6	. .	−67·9	−112·1	−163·7	−82·9
OPr^i	F	F	F	−73·6	. .	−165·5	−86·3	−70·8	−114·1	−168·6	−84·2
F	OPr^i	F	F	−71·9	−122·4	−169·1	. .	−69·8	−114·1	−168·6	−84·2

resonance signals due to quadrupolar effect of the ^{14}N nucleus as in 3,4,5-trichloro-2,6-difluoropyridine. It was concluded that the coupling constants could only be obtained from measurement of band-shape when there were departures from Lorentzian line-shape. The N–F coupling was obtained by observation of the ^{15}N satellites in the ^{19}F spectrum and the values for the spin-lattice relaxation time for the ^{14}N nucleus as a function of temperature.

The chemical shifts and coupling constants of fluorinated quinolines have been studied.[153] In 2-fluoroquinoline the ^{19}F resonance, at δ −61, is very broad at room temperature (24°C). On cooling to −24°C (Fig. 5) the signal sharpens and the coupling is readily resolved to give $^3J(F_2–H_3) = 8·5$ Hz

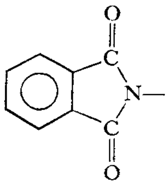
TABLE XIX

The ^{19}F shifts of tetrafluoropyridazine derivatives[408, 409]



R^1	R^2	R^3	R^4	Chemical shifts, δ F(1)	F(2)	F(3)	F(4)
F	F	F	F	−91·2	−144·8	−144·8	−91·2
F	OMe	F	F	−89·2	..	−147·9	−97·4
F	OMe	OMe	F	−92·3	..	..	−92·3
F	OMe	OMe	OMe	−97·3	..	..	..
F	—SC_6H_5	—SC_6H_5	F	−75·0	..	..	−75·0
F	—SC_6H_5	—SC_6H_5	—SC_6H_5	−79·4	..	..	..
F	$C_8H_4O_2N^a$	$C_8H_4O_2N^a$	F	−81·5	..	..	−81·5
F	NH_2	F	F	−92·1	..	−154·9	−102·8
F	Et_2N	F	F	−83·0	..	−148·0	−103·0
F	F	F	OMe	−98·2	−153·8	−148·0	..
F	F	OMe	OMe	−104·4	−156·9	..	..
F	OMe	F	OMe	−96·2	..	−151·1	..
OMe	F	F	OMe	..	−155·1	−155·1	..
OMe	F	OMe	OMe	..	−153·8	..	..

$^aC_8H_4O_2N \equiv$



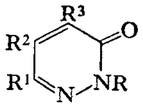
and $^4J(F_2–H_4) = 2{\cdot}9$ Hz. The line broadening was ascribed to small $^{14}N–^{19}F$ coupling which is removed by more effective quadruple relaxation of the ^{14}N at lower temperatures. In 6,8-difluoroquinoline (**187**) the two fluorine resonance signals are basically triplets, the authors state that the three *ortho* H–F coupling constants, namely $^3J(H_5–F_6)$, $^3J(H_7–F_6)$ and $^3J(H_7–F_8)$, and the *meta* F–F coupling are of equal magnitude; the *para* $H_5–F_8$ coupling is zero. The spacings of the components of the triplet are unequal and the authors state that this is possibly due to "virtual coupling". It seems more likely that second-order perturbation owing to the similarity of the shifts of H_5 and H_7 account for the asymmetry. It was claimed that the ^{19}F spectrum of 5,8-difluoroquinoline was also another example of virtual coupling as the two fluorine shifts seemed to be coincident! The shifts of 5-chloro-8-fluoro- and 5,6,7,8-tetrafluoro-quinoline were also recorded. Two five-bond H–F couplings were observed between $H_4–F_6$ and $H_4–F_8$ of $1{\cdot}5 \pm 0{\cdot}1$ Hz.

Musgrave *et al.*[154] have used the ^{19}F resonance data to show the presence of tautomerism in the quinoline and isoquinoline derivatives (**188** and **189**) which could exist in the enol form. Although the shifts were given, full assignments were not made.

Two papers by Musgrave *et al.*[408, 409] have dealt with the substitution of tetrafluoropyridazine and the ^{19}F shifts of these derivatives are shown in Table XIX. Hydrolysis of the fluoropyridazines in strong acid solution leads[409] to the formation of the 1*H* or 1-alkyl-pyridazin-6-ones; the shifts

TABLE XX

^{19}F shifts of polyfluoro-1*H*-pyridazin-6-one derivatives



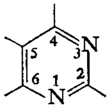
				Chemical shifts, δ		
R	R¹	R²	R³	F(1)	F(2)	F(3)
H	F	F	F	−103·3	−146·3	−139·4
H	F	F	OMe	−106·8	−149·8	. .
H	F	OMe	F	−101·0	. .	−143·3
H	F	OMe	OMe	−102·9	. .	. .
Me	F	F	F	−104·4	−148·1	−138·7
Et	F	F	F	−103·7	−148·2	−137·8
Me	F	F	OMe	−106·3	−150·8	. .

of the compounds obtained are shown in Table XX. It was proved that this latter reaction proceeded via the protonated species as the ^{19}F shifts of tetrafluoropyridazine were −77·2 and −119·5, while those of 3,5,6-trifluoro-4-methoxypyridazine were −76·1, −87·1 and −136·8 (both recorded in concentrated sulphuric acid). The shifts of the resonance signals to low field compared to those of the compounds recorded in neutral solvents (see Table XIX) were a certain indication of protonation. That the pyridazinium ion was formed was further proved by the isolation of the *N*-alkyl-tetrafluoropyridazium tetrafluoroborate salt; the ^{19}F shifts of the *N*-ethyl salt are shown in **190.**

The ^{19}F parameters of a number of fluoropyrimidines have been recorded,[155] and the assignment based upon the deshielding effects of the nitrogen atom; that of F_2 being most strongly deshielded. The chemical

TABLE XXI

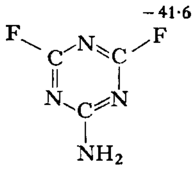
^{19}F chemical shifts of fluoropyrimidines



191

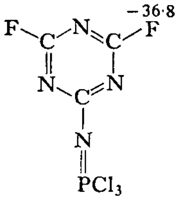
Substituent at				Chemical shift, δ			
2	4	5	6	F(2)	F(4)	F(5)	F(6)
F	F	F	F	−47·9	−74·7	−177·5	−82·3
F	F	H	F	−43·3	−54·5	..	−54·5
H	F	F	F	..	−80·5	−171·9	−80·5
F	H	F	F	−50·5	..	−161·5	−77·0
F	HO	F	F	−53·1	..	−181·5	−86·3
F	MeO	F	F	−48·9	..	−180·3	−84·1
F	NH_2	F	F	−50·9	..	−181·7	−89·7
F	NHMe	F	F	−50·1	..	−184·1	−93·1
F	NMe_2	F	F	−48·5	..	−176·9	−88·3
F	PhNH	F	F	−48·7	..	−179·7	−88·5
F	F	Cl	F	−44·7	−57·5	..	−57·5
F	H	F	H	−53·7	..	−148·4	..
F	OMe	F	OMe	−48·7	..	−181·1	..
F	NH_2	F	NH_2	−53·7	..	−185·7	..
F	NHMe	F	NHMe	−51·9	..	−188·7	..
F	NMe_2	F	NMe_2	−50·5	..	−170·7	..
F	PhNH	F	PhNH	−49·9	..	−179·3	..
MeO	MeO	F	MeO	..	..	−189·7	..

shifts are shown in Table XXI. As in the case of the pyridine derivatives the *para* F_2–F_5 coupling was large being in the range 24·8 to 28·2 Hz, while the *ortho* F_4–F_5 and F_5–F_6 couplings were smaller than in fluoroaromatics, or the F_5–F_6 coupling in fluoropyridines, being in the range 16·4 to 17·9 Hz; both comparable to the value of the F_3–F_4 and F_4–F_5 coupling in 2-substituted fluoropyridines. It would therefore seem dangerous to assume that the coupling between fluorine atoms α and β to a nitrogen atom are necessarily of increased magnitude. The width of the resonance signal of F_2 precluded measurement of any of the *meta* F_2–F_6 coupling constants.



192

Cyanic fluoride $(F—C{=}N)_3$ and ammonia react to give the monoamide (**192**) which, with phosphorus pentachloride, gives the compound **193** which in turn on treatment with formic acid is oxidized to the phosphoryl compound (**194**). The amide **192** also reacted with sulphur tetrafluoride, in the presence of caesium fluoride, to give the iminosulphur compound **195**.[156] The shifts of the fluorine atoms in these cyclic compounds are as shown.



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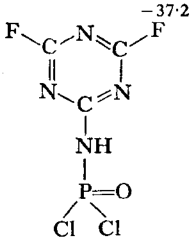

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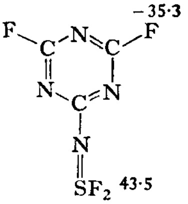


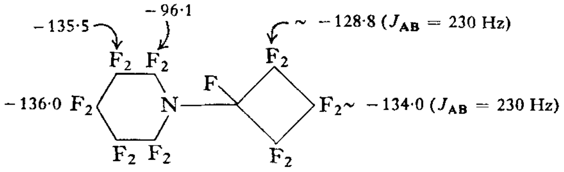
195

The ^{19}F NMR data of a number of fluoroalkyl substituted *s*-triazines have been reported.[157] Basically the carbon atoms had fluorine, trifluoromethyl, perfluoroisopropyl, perfluoropropyl, 2-cyano-hexafluoropropyl, 2,3-dichloropentafluoropropyl, perfluoroallyl and 2-iodo-hexafluoropropyl substituent groups. The ranges of chemical shifts for the different groups were as follows—

$\mathrm{F{-}C}\!<$	−20·8 to −33·5	
$\mathrm{F_3C{-}C}\!<$	−71·5 to −73·2	
$\mathrm{(F_3C)_2CF{-}C}\!<$	−182·1 to −187	(CF)
	−73·4 to −75·6	(CF_3)
$\mathrm{F_3C.\overset{\beta}{C}F_2.\overset{\alpha}{C}F_2{-}C}\!<$	−103·5 to −107	(αCF_2)
	−124·5 to −129·5	(βCF_2)
	−79 to −83·5	(CF_3)
$\mathrm{F_3C.CF(CN).CF_2{-}C}\!<$	−118·8	(CF_2)
(one example only)	−167·8	(CF)
	−79·0	(CF_3)
$\mathrm{ClCF_2.CFCl.CF_2{-}C}\!<$	−111 to −115	(CF_2)
	−128 to −132	(CFCl)
	−61·8 to −63·7	(CF_2Cl)
$\mathrm{CF_2{=}CF{-}CF_2{-}C}\!<$	−97·5	($=CF_2$)
(one example only)	−167	($=CF$)
	−105	(CF_2)
$\mathrm{CF_3.CFI.CF_2{-}C}\!<$	−72·6 to −72·9	(CF_3)
	−143 to −144·3	(CFI)
	−103 to −103·8	(CF_2)

Irradiation of perfluoro-*N*-fluoropiperidine and perfluorocyclobutene gave perfluoro-(*N*-cyclobutylpiperidine) (**196**) and perfluoro-*N*,*N*′-bipiperidyl (**197**);[74] although the authors state that the $>CF_2$ groups of perfluorocyclobutyl give AB spectra the full analysis is not given and only the band centre is given. Pyrolysis of **196** gave the perfluoro-(*N*-vinylpiperidine) which, on treatment with bromine, gave perfluoro-(*N*-(1,2-dibromoethyl)piperidine) (**198**). Irradiation of the perfluoro-*N*-fluoropiperidine in the presence of oxygen gave a product, which on heating, gave perfluoropentamethylene nitroxide which in turn with nitric oxide afforded perfluoro-*O*-nitrosopentamethylenehydroxylamine (**199**) and with polystyrene gave perfluoropentamethylenehydroxylamine (**200**).

Pyrolysis of perfluoro-oxazine derivatives (see p. 331) gave rise to a number of four and five-membered ring nitrogen heterocyclics.[407] The chemical shifts of the products so obtained, perfluoro-(1-methylazetidine) (**201**), perfluoro-(1-methyl-2-pyrrolidone) (**202**), perfluoro-(1-methyl-2-oxo-3-pyrroline) (**203**) are as shown. Chlorination of **203** gave the perfluoro-



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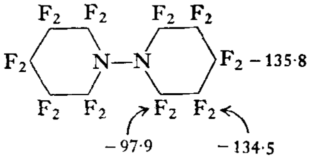

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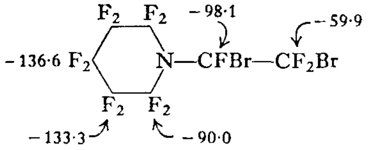

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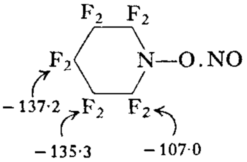

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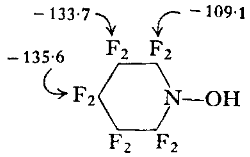
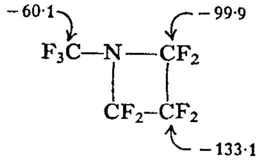


200

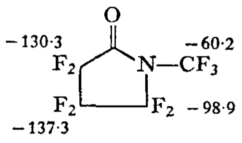
(3,4-dichloro-1-methyl-2-pyrrolidone) (**204**) which, from the ^{19}F spectrum, was concluded to be the *trans*-isomer. Both **202** and **203** showed four bond F–F coupling of the *N*-CF_3 group to the α CF_2 group of 8·5 and 6·7 Hz respectively, and **203** also showed five-bond coupling of the *N*-CF_3 group to the two olefinic fluorine atoms.

Perfluoropiperidine was conveniently prepared from the *N*-fluoro-compound by reaction of the latter with manganese pentacarbonyl-hydride;[158] the shifts of perfluoropiperidine and the *N*-nitro isomer are shown in **205** and **206**.

Perfluoro-(1,4,5-trimethyl-3-imidazoline) (**207**) was prepared by the reaction of fluoride ions on perfluoro-(3,4-dimethyl-2,5-diazahexa-2,4-diene).[159]



201



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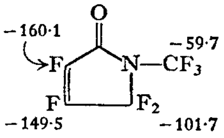

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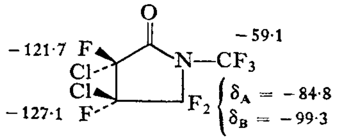

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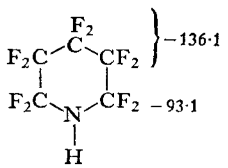

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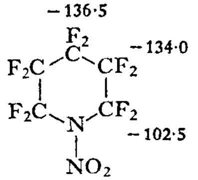
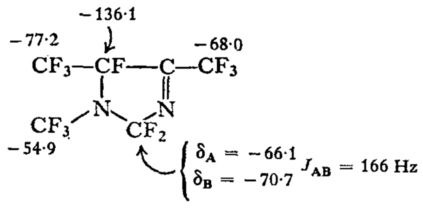


206

Treatment of 1,2-bis(difluoroamino)-1-acetoxycyclopentane with concentrated sulphuric or fluorosulphuric acid gave 3-difluoroamino-2-fluoro-2-azacyclohexanone (**208**) which on dehydrofluorination gave a mixture of



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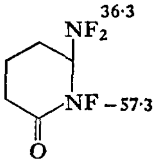

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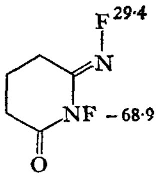
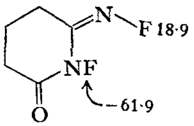
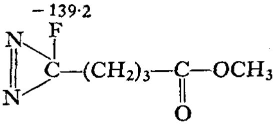


209a



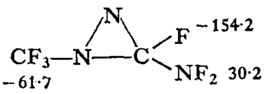
J(F–F) = 96 Hz

209b

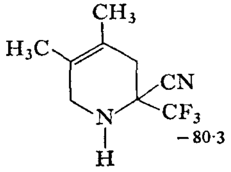


^3J(F–H) = 8 Hz

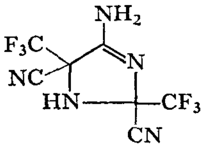
210



211



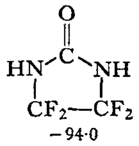
212



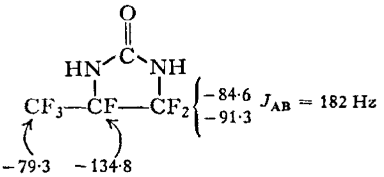
δCF3 *cis* isomer −76·1 and −81·9 [J(F–F) = 2·7 Hz]

δCF3 *trans* isomer −76·3 and −82·0

213



214



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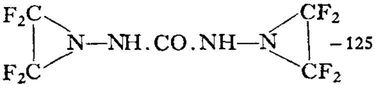


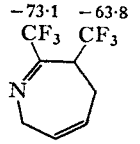
216

syn and *anti* isomers of the fluorimine (**209**); this in turn with sodium methoxide gave 3-fluoro-3-(3-carbomethoxypropyl)diazirine (**210**).[160]

Tetrafluoroformamidine is reduced by dicyclopentadienyl iron to give difluorodiazirine and similarly the 1,1-bis(difluoroamine)perfluoro-2-azapropane gave the derivative **211**.[161]

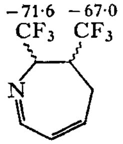
The α-iminoperfluoronitriles react with 2,3-dimethyl-1,3-butadiene to give a tetrahydropyridine derivative (**212**) and with base to give the imidazoline derivative (**213**).[162]

Hydrolysis of perfluoro-(2,4-diazapenta-1,4-diene) and perfluoro-(3-methyl-2,5-diazahexa-1,5-diene) give the 4,4,5,5-tetrafluoro- and 4-trifluoromethyl-4,5,5-trifluoro-2-imidazolidenes (**214** and **215** respectively); the ^{19}F shifts were as shown. The same paper also included the ^{19}F data of the urea derivative **216**.[13]



^{3}J(F–H) = 9·6 Hz
^{5}J(F–F) = 5 Hz

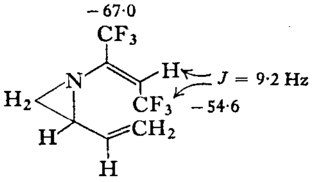
217



^{3}J(F–H) = 9·5 Hz
^{5}J(F–F) = 5 Hz

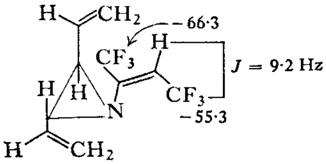
218

2-Vinylaziridine reacted with hexafluorobut-2-yne not to afford the 1,2-divinylaziridine but the isomeric azepine **217**; this was based upon observation of both ^{1}H and ^{19}F resonance spectra.[163] After 24 h at 25°C approximately 30% of the unconjugated azepine was converted to the conjugated isomer **218** by prototropy. When the addition of the hexafluorobut-2-yne was carried out below −76°C a fairly good yield of the aziridine



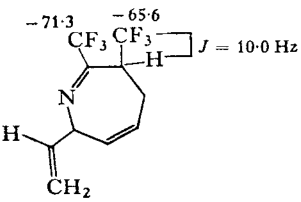
^{5}J(F–F) = 1·5 Hz

219



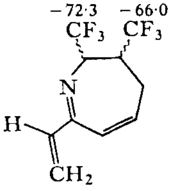
^{5}J(F–F) = 1·5 Hz

220



^{5}J(F–F) = 5·5 Hz

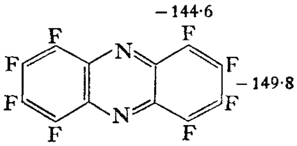
221



^{5}J(F–F) = 5 Hz
^{3}J(F–H) = 9·5 Hz

222

219 was obtained. The relative conformation of the two CF_3 groups was based upon the fact that *trans* CF_3–CF_3 coupling is weaker than that of *cis*-coupling. Treatment of the *trans*-2,3-divinylaziridine with hexafluorobut-2-yne at –78°C afforded the aziridine **220** which again, because of the magnitude of the F–F couplings, was assigned the *trans*-configuration. On standing for several hours at room temperature **220** isomerized to the azepine **221** which in turn after 6 h at 23°C had been converted to about 40% of the conjugated isomer **222**. The rate of rearrangement of **220** and **221** was conveniently followed by ^{19}F NMR and was shown to follow first-order kinetics. It is a striking feature that the trifluoromethyl group closest to the nitrogen atom in all this work has been assigned at highest field. There would seem little doubt, except possibly in the conjugated azepines, that this assignment is correct.



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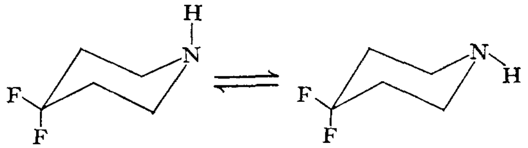


224 **225**

Preliminary ^{19}F NMR data on octafluorophenazine has been given.[164] The shifts are as shown in **223**.

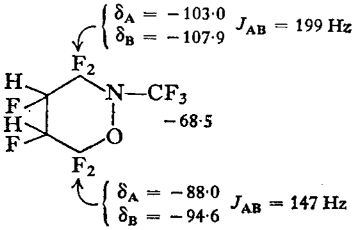
2. *Conformational equilibria*

As an extension of the use of ^{19}F resonance to the study of the conformational equilibria in saturated carbocyclic compound Yousif and Roberts[165a] have measured the rates of inversion of 4,4-difluoropiperidine. The original work on *N*-fluoroperfluoropiperidine was interpreted in terms of either inversion of the *N*-fluoro nitrogen atom being fast on NMR time scale, even at –115°C at which temperature ring inversion should be slow, or that nitrogen inversion is considerably faster than ring inversion and that there is a marked conformational preference for the *N*-fluoro group. There was a marked solvent effect and both conformers **224** and **225** could be seen in acetone solution; the reasons for this are discussed in some detail, but the full significance of the interpretation of the results is not clearly evident. It is, however, clear that the rate of ring inversion and the rate of inversion of the nitrogen atom must firstly be differentiated.

Lee and Orrell[165b] have also carried out a more detailed investigation of the temperature dependence of the ^{19}F spectra of both perfluoro-*N*-fluoropiperidine and perfluoro-*N*-fluoromorpholine over the range –74° to 20°C. The changes observed were interpreted on the basis of changing rate of chair-to-chair inversion; it was concluded that at a given temperature the rate of inversion was greater for the morpholine than for the piperidine ring. The spectra of the perfluoro-(*N*-fluoromethylpiperidines) are, however, independent of temperature over the range –90° to 100°C, implying conformationally rigid structures. The variation of the *geminal* F–F coupling of the ring $>CF_2$ groups and the variation of the chemical shift of the axial and equatorial fluorine atom is considered in some detail.

B. Mixed nitrogen–oxygen heterocyclics

Haszeldine and coworkers have examined the chemistry of perfluoro-oxazine derivatives. The shifts of 4*H*,5*H*/-hexafluorotetrahydro-2-trifluoromethyl-1,2-oxazine (**226**), and 4*H*,4*H*,5*H*- (**227**) and 4*H*,5*H*,5*H*-pentafluorotetrahydro-2-trifluoromethyl-1,2-oxazines (**228**) have been measured.[72] Dehydrofluorination of the oxazine (**226**) afforded the two isomeric 4*H*- and 5*H*- pentafluoro-3,6-dihydro-2-trifluoromethyl-2*H*-1,2-oxazine derivatives **229** and **230** respectively; the shifts are also shown in the structures. In all cases, as in the *N*-trifluoropyrrolines, there is a



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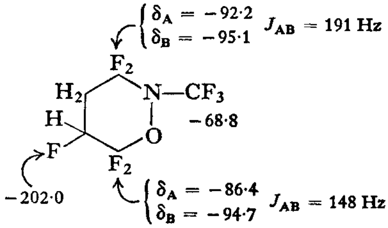

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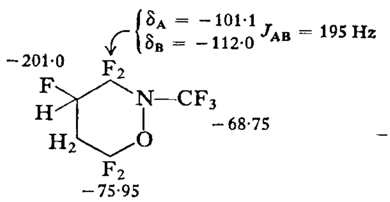

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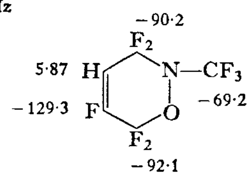

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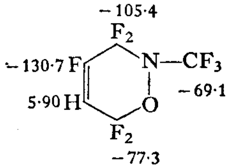

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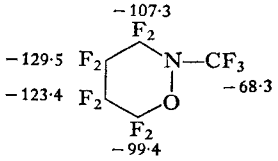

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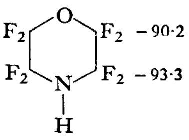

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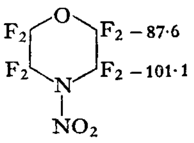

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characteristic coupling between the *N*-CF_3 and adjacent CF_2 groups of the order of 11 to 12 Hz. In neither **229** nor **230** are AB spectra obtained for the $O.CF_2$ or $N.CF_2$ groups and fairly characteristic F–F allylic coupling constants of 12 to 14 Hz and vicinal CF_2—CF= coupling constants of 17 to 19 Hz are found. In both sets of compounds, **227** and **228**, and **229** and **230**, the position of the hydrogen atoms is readily ascertained from the chemical shifts; in each case the presence of the hydrogen causes a marked deshielding of the adjacent CF_2 group.

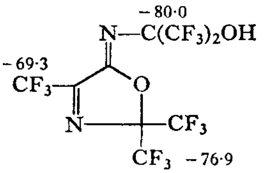
Direct fluorination of the partially unsaturated compound gives[407] the fully fluorinated compound, perfluoro(tetrahydro-2-methyl-2*H*-1,2-oxazine) (**231**), and the ^{19}F spectrum of this compound was remarkably simple, showing no AB subspectra under the conditions used for recording the spectrum. The shifts are as shown in **231**.

A significant point arising from this work is that when the two *gem* fluorine atoms of a CF_2 group adjacent to a hetero atom are non-equivalent the value of the AB coupling constant is a valuable key to the assignment. Thus, in the present instance, the *geminal* F–F coupling constants for an $N.CF_2$ group of 185 to 200 Hz are larger than those for an $O.CF_2$ group of 148 to 159 Hz.

Perfluoromorpholine was conveniently prepared from the *N*-fluoro derivative by reaction with manganese pentacarbonyl hydride;[158] the shifts of this compound and the *N*-nitro derivative are shown in **232** and **233**.

α-Iminoperfluoronitriles react with perfluoroketones to give oxazoline derivatives; the shifts of some of the compounds prepared are shown in **234** to **237**.[162]

Hexafluoroacetone and sodium cyanide form the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidine which, on acidification or on alkylation, gives oxazolidine or its derivatives.[166] The ^{19}F parameters



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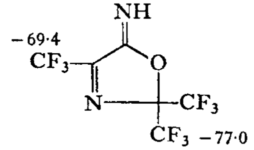

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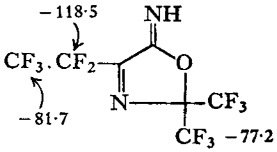

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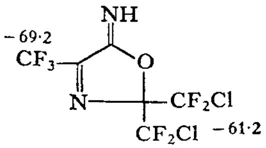

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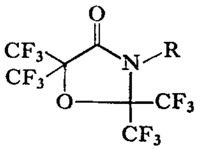
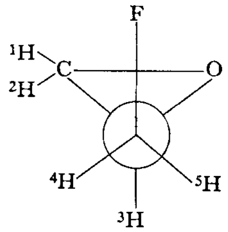


238

quoted in the paper do not specify the shifts of the two types of *gem*-CF_3 groups in **238** but the CF_3 groups occur in two regions −73 to −74 and ~−78.

C. Oxygen and sulphur heterocyclics

The chemistry related to benzofuran and dibenzofuran has been actively investigated and, because of the similarity of the systems and therefore the spectral features, the corresponding sulphur analogues will be considered together for convenience.



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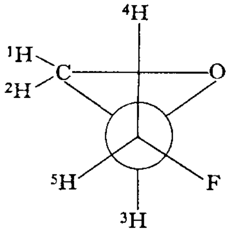

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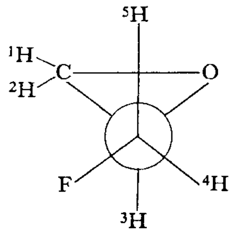


241

The shifts of some of the benzo- furan and thiophen derivatives are given in Tables XXII and XXIII. A feature which has been identified in both the fluorodibenzofuran and fluorobenzo[*b*]thiophen derivatives is the large *para* F–F coupling of 16 to 19 Hz, and is therefore, in some cases, similar in magnitude to the *ortho*-F–F coupling constants.

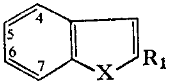
The spectra of epifluorohydrin has been examined in a number of solvents and the parameters rationalized in terms of the rotational isomers **239** to **241**.[170] In all three rotamers H-4 and H-5 are non-equivalent and from the value of J[H(3)–H(4)] of 5·83 to 6·51 Hz it was inferred that H-3 and H-4 prefer a *trans*-configuration, i.e. **240** the most populated isomer. If, however, the assignment of H-4 and H-5 were reversed then **241** would be most populated rotamer. The former was preferred based upon the polarity considerations and the increase in $J_{3,4}$ and decrease in $J_{3,5}$ on changing from non-polar to polar solvent. The value of J[H(3)–F], ~12·0 Hz, is also reasonable for rotamer **240** as in **239** the coupling should be large (25 to 55 Hz).

The ^{19}F spectrum has been used to differentiate between the two isomers **242** and **243** formed by the addition of furan to 2,2′-dilithio-octafluorodiphenyl.[171]

The reaction of sulphide ion with cyclic, acyclic terminal and non-terminal olefins having two replaceable halogens leads to the formation of fluorinated cyclic sulphide or dithiole ring systems.[172] The chemical shifts of some of the compounds thus obtained are shown in **244** to **250**. Two polysulphides

TABLE XXII

^{19}F chemical shifts of benzo-furan and thiophen derivatives

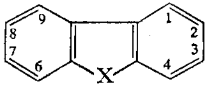


Substituent on						Chemical shifts, δ				
X	R_1	4	5	6	7	F(4)	F(5)	F(6)	F(7)	Ref.
O	H	F	F	F	F	−148·0	−162·3	−164·8	−162·3[a]	167
O	H	F	F	OMe	F	−149·0	−156·8	. .	−159·4[a]	167
O	H	OMe	F	F	F	. .	−160·4	−163·6	−165·0	167
O	H	F	F	F	OMe	−150·8	−166·4	−158·3	. .	167
S	CH_3	F	F	F	F	−146·9	−162·8	−161·7	−143·1[a]	168
NPh	CH_3	F	F	F	F	−161·4	−170·4	−167·8	−152·6[a]	168
S	H	F	F	F	F	−145·18	−160·18	−160·19	−141·66	169
S	H	H	F	F	F	. .	−137·15	−164·29	−136·3	169
S	H	F	H	F	F	−120·37	. .	−140·0	−145·3	169
S	H	F	F	H	F	−148·78	−140·36	. .	−117·4	169
S	H	F	F	OMe	F	−146·47	−155·5	. .	−136·06	169
S	H	F	F	OH	F	−146·92	−160·86	. .	−142·73	169
S	H	F	F	$—NHNH_2$	F	−147·87	−155·69	. .	−136·20	169
S	CO_2H	F	F	F	F	−142·77	−159·80	−156·83	−141·68	169
S	CO_2H	H	F	F	F	. .	−136·97	−161·23	−137·35	169
S	CO_2H	F	H	F	F	−117·38	. .	−136·13	−145·75	169
S	CO_2H	F	F	H	F	−147·01	−139·5	. .	−117·0	169

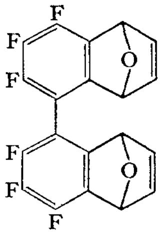
[a] Precise assignments uncertain.

TABLE XXIII

^{19}F shifts of dibenzo-furans and thiophens



Substituent on									Chemical shift, δ								
X	1	2	3	4	6	7	8	9	F(1)	F(2)	F(3)	F(4)	F(6)	F(7)	F(8)	F(9)	Ref.
S	F	F	F	F	F	F	F	F	−141	−156	−158	−134	−134	−158	−156	−141	401
S	F	OMe	F	F	F	F	F	F	−134	..	−153	−136	−134	−158	−156	−141	401
S	F	OMe	F	F	F	F	OMe	F	−134	..	−153	−135	−135	−153	..	−134	401
O	F	F	F	F	F	F	F	F	−138	−160·7	−153·7	−159·4	−159·4	−153·7	−160·7	−138	402
O	F	F	OMe	F	F	F	F	F	−139	−155	..	−154	−159	−154	−160	−138	402
O	F	F	OMe	F	F	OMe	F	F	−140·6	−156·0	..	−154·7	−154·7	..	−156·0	−140·6	402
O	F	F	F	F	H	H	H	H	−147·4	−164·6	−157·9	−161·5	..	..	..	..	403
O	F	F	H	F	H	H	H	H	−149·0	−143·1	..	−138·2	..	..	..	..	403
O	F	F	SH	F	H	H	H	H	−148·0	−148·0	..	−136·5	..	..	..	..	403
O	F	F	SMe	F	H	H	H	H	−147·8	−138·2	..	−133·5	..	..	..	..	403



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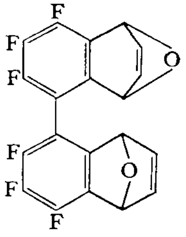
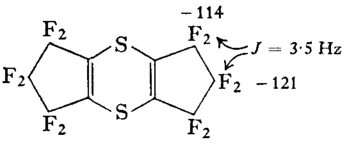


243

$(CF_3)_3C.S_x.C(CF_3)_3$, x = 3 and 4, were also obtained; the shift of the trifluoromethyl groups were –63·3 in each case.

The ^1H and ^{19}F spectra of both 2- and 3-fluorothiophene have been analysed in great detail.[173] The ^{13}C–^{19}F coupling constants of the 2-C–F



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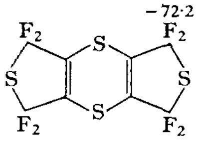

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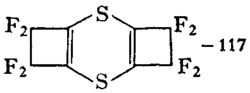

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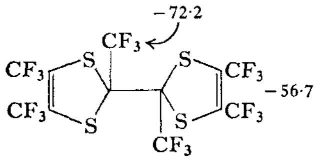

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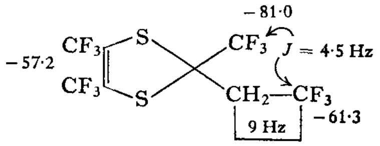

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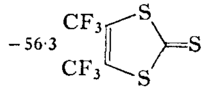

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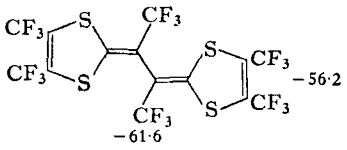


250

bond adjacent to the heteroatom are larger (285 Hz) than for the 3-C–F bond (256 Hz). An isotopic shift of the fluorine nucleus due to sulphur-34 was observed in 2-fluorothiophene.

IV. SOME THEORETICAL CONSIDERATIONS

While the essential purpose of this review is to bring together much of the scattered information which is of considerable importance for structural determination it would, however, be incomplete without giving some thought to the data which are biased towards the purely physical aspects. These aspects will be but briefly considered.

The spectra of hydrogen fluoride have been investigated in the gas phase by two groups of workers.[174, 175] Only a single line is observed for the ^{19}F resonance indicating that rapid exchange was occurring. Both groups of workers have also investigated the temperature dependence of the shifts and the resonance spectra of the D–F species, both groups have interpreted the results in terms of the formation of ring polymers. The variation of the ^{19}F shifts with concentration of hydrogen and deuterium fluorides dissolved in various solvents has been investigated.[176] Hydrogen fluoride has also been studied in aqueous solution in the presence of varying amounts of potassium fluoride.[177] From the study of the $HF–KF–H_2O$ and $HF–KF–D_2O$ systems the chemical shifts of the species $F^{\ominus}(H_2O)_x$, HF, $HF_2{}^{\ominus}$, $F^{\ominus}(D_2O)_x$, DF and $DF_2{}^{\ominus}$ were obtained by consideration of the concentration dependence of the exchange averaged ^{19}F shift. Isotopic substitution of hydrogen by deuterium results in high-field shifts of several parts per million. These authors have used the varying ^{19}F shift of potassium fluoride in H_2O/D_2O mixtures as a method for determining the percentage of water in heavy water.[178] Extension of this study to a variety of alkali fluorides in mixtures of light and heavy water showed that the ^{19}F shift of the fluoride ion is essentially insensitive to the nature of the cation, concentration of the salt and temperature.[179] There was again a linear variation of shift with isotopic composition of the solvent with approximately 3 p.p.m. shift in going from H_2O to 100% D_2O. The results were interpreted in terms of alterations in the vibrational energy of the hydrated fluoride ion, $F^{\ominus}(H_2O)_x$, which results from the isotopic substitution, and this causes a change in the average excitation energy $\langle \Delta E \rangle$. Since this term occurs in the expression of the paramagnetic contribution to the nuclear magnetic shielding constant there is a shift to high field with the heavier isotope. Similar effects were found for solutions of potassium fluoride in deuterated alcohols.

The theory of vibrational effects on nuclear shielding and spin-rotation constants for a diatomic molecule has been outlined. Corrections for these effects have been calculated theoretically for the ^{19}F nuclei in hydrogen fluoride and the calculated isotopic shift between DF and HF is in good agreement with the zero pressure experimental value, $2{\cdot}5 \pm 0{\cdot}5$ p.p.m.[180]

The ^{19}F chemical shift of the salts KHF_2, NH_4HF_2, $NaHF_2$, KF, NH_4F and NaF have been measured as a function of the concentration in water.[181] The changes in the chemical shift observed for KHF_2 was interpreted in terms of the equilibrium $HF_2{}^{\ominus} \rightleftharpoons HF + F^{\ominus}$ and the equilibrium constant was calculated. The chemical shifts of the three hydrated species $HF_2{}^{\ominus}(H_2O)_x$, $HF(H_2O)_y$ and $F^{\ominus}(H_2O)_z$ were compared.

The effect of copper(II) ions on the relaxation times, T_1 and T_2, of the fluoride ion in aqueous solution has been measured over a range of fluoride ion concentration over the pH range of 0·5 to 6.[182] The measurement of nuclear spin-lattice relaxation in $KMnF_3$[183] and its temperature dependence in SF_6, SeF_6 and TeF_6[184] have been studied. The spin-relaxation time has also been measured for $Eu^{2\oplus}$ ions in barium fluoride and for $Mn^{2\oplus}$ ions in both barium and strontium fluoride.[185]

The nuclear relaxation of formyl fluoride, CHFO, has been investigated over the temperature range of –142° to –20°C; the relaxation processes are induced by both intra- and inter-molecular interactions.[186] The deuterated compound, as the neat liquid and as solutions in acetone-d_6, has also been investigated. The ^{19}F nuclear magnetic relaxation measurements of polytetrafluoroethylene have been measured in an attempt to interpret the results in terms of molecular motional mechanisms.[187]

The experimental values for the ^{19}F nuclear shielding anisotropies obtained from solid state, nematic phase and molecular beam measurements have briefly been reviewed[188] and certain discrepancies pointed out. The results of CNDO/2 molecular orbital calculations for fluoromethanes and fluorobenzene were used for a qualitative discussion of the anisotropies. It has been pointed out that small shifts between the nematic and isotropic phases of a liquid crystal solution cannot easily be related to shielding anisotropy owing to change in the environment of the solute.[189] It was stated that an internal reference of high symmetry, e.g. CF_4 or SF_6, was preferred for evaluating the shielding anisotropies, although care must still be exercised in the interpretation of small shifts as changes in the environment could affect the solute and reference to different extents. The high-resolution spectra of 3,3,3-trifluoropropyne in different liquid crystals has been reported and the relative geometry of the molecule agrees with the microwave data.[190] The anisotropies of the fluorine chemical shifts have been measured and are comparable in sign and magnitude with the values for similar compounds; the sign of J(H–F) was found to be negative.

The fluorine NMR spectra of 1,3,5-trifluorobenzene has been examined in the nematic phase and the fluorine chemical shift anisotropy was 104 p.p.m.[191a] The absolute signs of the indirect spin–spin couplings were: H–H, F–F and H–F (*ortho*) all positive and H–F (*para*) negative.

Although the ^{13}C–^{1}H direct bond coupling constant has been shown theoretically to be positive, there has been no experimental verification of this. From spectra of methyl fluoride in nematic phase the absolute sign of ^{13}C–H and ^{13}C–F direct bonded coupling constants were found to be positive and negative respectively.[191b]

The spectrum of perfluorodimethylacetylene has also been studied in the nematic phase.[192] Considerable improvement in the resolution of the outer lines was observed on spinning, the effect being most marked at 220M Hz using a superconducting magnet in which the magnetic field and the axis of spinning are parallel. The long-range indirect F–F coupling was +2·2 Hz and the FCF angle was found to be 110·5 ± 0·5° compared with an earlier estimated value of 107·5°. The anisotropy of the chemical shift of the C–F bond was about 145 p.p.m.

The chemical shift anisotropy of trifluoroacetic acid has also been measured in the nematic phase.[193] The anisotropy of the fluorine magnetic shielding ($\sigma_{\parallel} - \sigma_{\perp}$) for the C–F bonds in trifluoroacetic acid was 235 ± 3 p.p.m.

The molecular-beam magnetic resonance study of fluorobenzene has led to an estimate of the paramagnetic contribution to the ^{19}F nuclear shielding of 284 ± 10 p.p.m.[194] It was also concluded that the ^{19}F nucleus is more shielded when the applied magnetic field is directed along the C–F bond axis. The anisotropy of the magnetic shielding tensor ($\sigma_{\parallel} - \sigma_{\perp}$) was 160 ± 30 p.p.m.

Using CNDO/2 calculations fairly good agreement was obtained between the calculated and experimental chemical shift parameters in a series of fluorobenzenes and fluoronitrobenzenes; evidence for an "*ortho*" effect was also obtained.[195]

Emsley[196a] has compared the magnitudes of the chemical shifts of the fluorine atom *para* to a substituent group in fluorobenzenes and pentafluorobenzenes with the π-electron densities calculated from a semi-empirical SCF-LCAO-MO method. A linear relationship was found between the ^{19}F shift and the π-electron density on the fluorine atom, or the attached carbon, and that the order of shielding constants for the fluorine nuclei are correct. The changes produced by substituent groups are, however, too small and the possible reasons for this discrepancy are discussed.

The attempts to correlate chemical shifts with the localized π-electron density on fluorine atoms in fluoroaromatics were unsatisfactory as the correlation depended upon the number of atoms *ortho* to the fluorine atom;[196b] similar results were obtained in methods which included all the valency electrons. Consideration of the Karplus–Das–Prosser–Goodman treatment for calculation of chemical shifts suggested that this "*ortho*-effect" arose because long-range interactions were being neglected. A method of treatment to include these interactions was developed and good agreement was obtained between calculated and experimental shift values in nearly one hundred fluoroaromatics.

Brownlee and Taft[197] have also considered the advantages of the CNDO/2 calculations and have shown that the empirically related σ_{R^0} scale of substituent π-delocalization can be related to the $\Sigma\Delta q_{(\pi)}$ or $\Delta q^{\mathrm{p}}_{(\pi)}$ terms, where $\Delta q_{(\pi)}$ is the excess π charge density at each ring carbon atom and the summation is taken over all six carbon atoms in a mono-substituted benzene and $\Delta q^{\mathrm{P}}_{(\pi)}$ is the excess π charge density at the *para* position; both these terms are obtained automatically from the calculation. The slope of the graph of $\Delta q^{\mathrm{P}}_{(\pi)}$ vs. σ_{R^0} was of the same order as that estimated from consideration of the *para*-fluorine shifts.

It has also been shown that the ^{19}F shifts of a number of 1- and 2- fluoronaphthalenes could be correlated by a modified FM treatment.[198] The authors point out, however, that the polarization of the C–F bond will demand a vectorial, rather than a scalar, dependence and this is considered in relationship to the 7-substituted 1-fluoro- and 8-substituted-2-fluoronaphthalenes.

Spin coupling constants

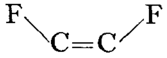
Some data on spin–spin coupling constants is now becoming available from the study of symmetrical compounds in nematic phase (see earlier). Some data on F–F and H–F coupling has also been obtained during the course of the study of P–F coupling constants in phosphines (p. 400). Although there is still a certain amount of mystique associated with the magnitude of coupling constants involving fluorine more information is certainly now available on the signs of these constants.

Murrell *et al.*[199] have calculated the coupling constants of fluoromethanes and other first row fluorides. Fairly good agreement was obtained for the ^{1}J(C–F) values by using a *k* scaling factor of 0·75 instead of 1·0, but poor agreement was obtained for geminal H–F and F–F couplings; reasons for this were discussed.

Love,[200] however, has found a remarkable linear correlation of the direct bonded ^{13}C–F coupling of trifluoromethyl derivatives, F_3C–X, with the C–X bond length; the relationship is–

$$^{1}J(^{13}\mathrm{C{-}F}) = -(106r_{\mathrm{C{-}X}} + 115)$$

Unlike the correlation for C–H coupling there is no dependency upon the electronegativity of the group X. The author predicted that the ^{13}C–F coupling constants of $(CF_3)_3B$, $(CF_3)_3As$ and $(CF_3)_4Pb$ would be –282, –333 and –360 Hz respectively!

Kaiser and Sarka[201] have pointed out discrepancies which have arisen in the signs of F–F coupling constants, especially for hexafluorobenzene in nematic phase and trifluorobenzenes by double resonance, more especially that the *cis* fragment  of two *ortho* fluorine atoms of a fluorobenzene should have a positive sign of coupling. To clarify the situation these authors have studied *cis* and *trans* 1,2-difluoro-1,2-dichloroethylene using ^{13}C double resonance especially since there is no argument that the direct-bonded C–F coupling is negative. The results are summarized below–

	cis	*trans*
^3J(F–F)	+37·9	–129·7
^1J(^{13}C–F)	–299·0	–291·0
^2J(^{13}C–C–F)	+37·0	+54·5

These results certainly confirmed the positive sign of the *cis* F—C=C—F fragment and it is still difficult to reconcile the negative value for the *ortho* coupling in hexafluorobenzene.

The solvent dependence of ^2J(H–F), *cis* ^3J(H–F) and *trans* ^3J(H–F) have been observed in both trifluoroethylene and vinyl fluoride.[202] It was concluded that the orientation of the solute dipole was a critical factor, even possibly the main controlling factor, in determining the solvent dependence of geminal coupling constants.

V. ORGANO-METALLIC AND METALLOID COMPOUNDS

Group I

Copper

From the relative ^{19}F chemical shifts in *m*- and *p*-fluorophenylcopper (0·05 and –5·37 p.p.m. respectively from fluorobenzene) it was concluded[203] that the copper atom exerted little inductive effect but a relatively large resonance effect, possibly by *p*-π interaction involving the empty 4*p* orbitals of copper.

Group II

Magnesium

The larger range of fluorine-19 shifts makes the study of the fluorophenyl derivatives attractive for the investigation of the equilibrium between the diaryl magnesium and the arylmagnesium halide. Evans and Khan[204] have used the pentafluorophenyl-, 4-fluorophenyl- and 4-fluoronaphthyl-magnesium compounds for this purpose and, by studying the resonance spectra over a range of temperatures, it was possible to slow the exchange and thus distinguish unambiguously between the ArRX and Ar_2Mg species.

Mercury

The ^{19}F resonance data for the 3- and 4- fluorophenyl and benzyl-mercurials of the type R_2Hg and RHgX, where X is a halide, have been reported.[205] The results for the fluorophenyl mercurials do not give any evidence for direct aryl-mercury conjugation and the second mercuri-substituent similarly exerts little electronic influence. On the other hand the ^{19}F shifts for the fluorobenzyl mercurials indicates a pronounced *ortho-para* donating effect for the mercuri-methyl group —$HgCH_2$.

McFarlane[206a] has used heteronuclear double resonance studies to determine the signs of the ^{199}Hg–F couplings in bis(pentafluorophenyl)-mercury and the pentafluorophenylmercury acetate, all of which were found to be positive. The values of the chemical shifts and coupling constants for these two compounds are shown in Table XXIV. The *ortho*, three-bond, F(2)–F(3) coupling is rather larger than is normally found in the pentafluorophenyl group. The most interesting point, however, is the large variation in the Hg–F coupling constants and reasons for the variation are discussed. It is perhaps of interest to note that in work on the bis(3-bromo-2,4,5,6-tetrafluorophenyl)mercury the Hg–*ortho*-F couplings are different for F(2) and F(6), being 454 and 516 respectively.[206b] The Hg–F couplings for the compound bis(4-bromo-2,3,5,6-tetrafluorophenyl)mercury are very similar to those given by McFarlane for the bis(pentafluorophenyl) compound.

TABLE XXIV

^{19}F NMR parameters of pentafluorophenylmercury derivatives, C_6F_5—Hg—X[206]

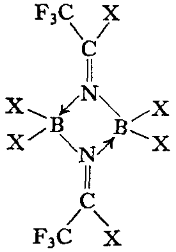
			X		
	C_6F_5—	—$O_2C.CH_3$		C_6F_5—	—$O_2C.CH_3$
δ(2,6)	−117·3	−117·2	*J*(2–3)	−26·0	−25·9
δ(3,5)	−160·5	−160·6	*J*(2–4)	+1·4	+1·0
δ(4)	−153·5	−156·6	*J*(2–5)	+10·3	+9·7
J(Hg–F(2))	+443·0	+597·0	*J*(2–6)	−7·2	−7·3
J(Hg–F(3))	+116·0	+215·0	*J*(3–4)	−18·9	−19·5
J(Hg–F(4))	+14·4	+29·0	*J*(3–5)	−1·7	−1·7

Group III

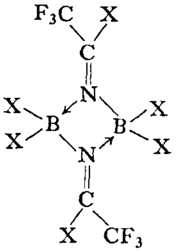
Boron

Trifluoromethyl nitrile reacts with both boron tribromide and trichloride to give an addition compound but, because of the presence of two CF_3 resonance signals, it was suggested that the adduct dimerized to give two isomers **251** and **252**.[207]

Two isomeric methyltrifluoromethylphosphinoboranes have been isolated.[208] One isomer had a ^{19}F shift of −59 and P–F coupling of 68 Hz while the second isomer had a ^{19}F shift of −71 and P–F coupling of 61 Hz; neither showed B–F coupling. The bis(trifluoromethyl)phosphinopentaborane(9), with a ^{19}F shift of −49·9 and P–F coupling of 71·3 Hz, did however exhibit B–F coupling of 6·0 Hz; the ^{19}F spectrum of the latter compound was illustrated in the paper.



251



252

δCF_3: X = Cl, −67·9 and −68·1
X = Br, −60·8 and −61·0

The ^{19}F spectrum of *B*-tri(trifluorovinyl)-*N*-trimethylborazole was used to confirm the structure of the compound.[209] The resonance signals were not assigned, although the expected three signals were found, and it was suggested that the coupling constants were consistent with those expected for a trifluorovinyl group. The authors did not state if there was any broadening of the resonance signals due to ^{11}B–^{19}F coupling.

Aluminium

The ^{19}F shifts of some pentafluorophenyl derivatives of aluminium have been recorded[210] and are shown in Table XXV. The difference in the *para* F resonance of $(C_6F_5AlBr_2)_2$ and the etherate $C_6F_5AlBr_2,Et_2O$ was taken as evidence that the dimer is stabilized by p-π bonding from aluminium to the pentafluorophenyl group as well as by bromine bridging.

TABLE XXV

^{19}F shifts of pentafluorophenylaluminium compounds[210]

	Chemical shifts		
	δ (*ortho*)	δ (*meta*)	δ (*para*)
$(C_6F_5AlBr_2)_2$	−121	−159·5	−147·2
$C_6F_5AlBr_2,Et_2O$	−121	−161·0	−151·5
$(C_6F_5)_2AlBr$	−121	−159·7	−148·5

Group IV

Jolley and Sutcliffe[211] have carried out a systematic study of a number of pentafluorophenyl derivatives of Group IV. All these compounds exhibited a very large *ortho*-effect and these shifts could be rationalized by using either the Van der Waals electric field theory or the bond theory of Houska *et al.* Based upon the assumptions of Parshall the value $|\delta_p - \delta_m|$ should give a measure of the π-bonding. In the case of the four tetrakis-pentafluorophenyl compounds ($(C_6F_5)_4M$, $M = Si$, Ge, Sn and Pb), consideration of the $|\delta_p - \delta_m|$ values indicated the following order of electronegativity or π-acceptor ability: Si > Ge ~ Sn > Pb. The π-acceptor strengths of substituent groups, based upon the same criterion, may be placed in the order $C_6F_5 > C_6H_5 > CH_3$. The chemical shifts of these compounds are shown in Table XXVI. The only coupling constant which warrants mention is the F(2)–F(3) *ortho* coupling which tends to have a larger value than is usual, e.g. in $C_6F_5Pb(Me)_3$ the value is as high as 29·3 Hz.

The apparent resolution in these compounds varied considerably. The loss of resolution of the expanded spectra in the tetrakis-compounds was

TABLE XXVI

^{19}F shifts of pentafluorophenyl derivatives of Group IV elements[211]

$(C_6F_5)_xMX_{4-x}$

M	X	x	Chemical shift $\delta(o)$	$\delta(m)$	$\delta(p)$
Si	. .	4	−127·2	−160·1	−146·9
Ge	. .	4	−127·8	−159·7	−148·1
Sn	. .	4	−122·2	−157·6	−146·2
Pb	. .	4	−121·6	−157·3	−147·3
Sn	CH_3	3	−122·1	−158·2	−148·1
Sn	C_6H_5	3	−120·8	−158·6	−148·3
Ge	Cl	3	−127·8	−160·5	−145·8
Ge	Br	3	−127·8	−158·5	−145·7
Ge	OH	3	−129·2	−158·9	−146·8
Ge	C_6H_5	2	−124·5	−159·9	−150·0
Sn	CH_3	2	−122·1	−159·7	−150·7
Sn	C_6H_5	2	−119·9	−159·0	−149·7
Ge	C_6H_5	1	−121·9	−160·5	−151·2
Sn	CH_3	1	−118·1	−160·3	−151·5
Sn	C_6H_5	1	−122·1	−160·6	−152·6
Pb	CH_3	1	−120·3	−161·0	−154·8
Pb	C_6H_5	1	−117·1	−159·3	−152·3

explained in terms of steric hindrance to free rotation about the M–C(1) bond. This phenomenon was earlier reported by the same authors[212] and the effect upon the *meta*-fluorine resonance of $(C_6F_5)_2Ge(C_6H_5)_2$, compared with that of the mono-pentafluorophenyl compound, $(C_6F_5)Ge(C_6H_5)_3$, was discussed; it appears that steric hindrance is only absent in compounds of the latter type. The use of the correlation of J_{24} with δ_4 and the value of $|\delta_3 - \delta_4|$ has also been used to investigate the π-electronic interaction of the pentafluorophenyl group with silicon in compounds of the type $(C_6F_5)_x SiX_{4-x}$.[213]

The ^{19}F shifts of a series of 4-fluorophenyl stannes of the type $[(p\text{-}FC_6H_4)_nSnCl_{4-n}]$ have been interpreted[214] in terms of $p_\pi - d_\pi$ bonding between the aromatic π-orbital and the empty $4d$ orbital of tin when $n \geqslant 2$. The complications involved in analysing the A_2B_2X spin system are considered in some detail; since the shift between the *ortho* and *meta* protons is ~20 Hz only mean values of the H–F couplings can be obtained.

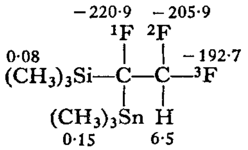
Trimethyl- and dimethyl- tin hydrides react with the trimethyl- and dimethyl- trifluorovinylsilanes to afford compounds of the type **253** and **254**; the NMR parameters are as shown.[215]

The photochemical chlorination of γ-trifluoropropyltrichlorogermane and the dehydrochlorination of the products obtained have been studied;[216] the ^{19}F shifts of the trifluoromethyl group was dependent upon the nature of both the α and β substituents.

Clark *et al.*[217] have discussed the spectra of the 1,1,2,3,3,3-pentafluoropropyl trimethyltin in some detail, especially in respect of the rotational isomers of this compound. The data for this compound (**255**) and for 1,1,2,2-tetrafluoroethyl trimethyltin (**256**) were as shown. Partial data was also given for the two compounds $(CH_3)_3SnCF_2(CF_2)_2CF_2H$ and $(CH_3)_3SnCF_2CF(CF_3)Sn(CH_3)_3$. It would appear that the ^{119}Sn–^{19}F coupling in a Sn—CF_2 group is of the order of 220 to 250 Hz.

Although precise chemical shift data was not given the ^{19}F spectra were, however, used to substantiate formation of a 1:1 or 1:2 adduct of tributyltin methoxide with 1,1,3-trichloro-1,3,3-trifluoropropan-2-one.[218] The 1:1 adduct **257** has a centre of asymmetry and consequently the two fluorine atoms of the —CF_2Cl group are non-equivalent. The ^{19}F spectrum is therefore an ABX system with $J_{AB} = 160$ Hz with $J[(AB)\text{-}(X)] = 17$ Hz. Tributyltin oxide reacts with two moles of the ketone to give the 1:1 adduct **258** which has now no asymmetry and a first order A_2X spectrum is found with $J[(A)\text{-}(X)] = 16$ Hz. Further reaction of **258** with the ketone gives the 1:2 adduct **259** in which rotational non-equivalence again gives rise to an ABX spectrum.

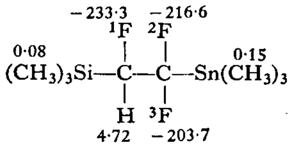
Fluorinated ketones were found to cause silicon–sulphur bond fusion in cyclic silthianes.[219] Various telemeric products were obtained but the



$$\underset{0\cdot08}{(CH_3)_3Si}-\overset{\overset{-220\cdot9}{^1F}}{\underset{\underset{0\cdot15}{(CH_3)_3Sn}}{C}}-\overset{\overset{-205\cdot9}{^2F}}{\underset{\underset{6\cdot5}{H}}{C}}-\overset{-192\cdot7}{^3F}$$

$J(H{-}^1F) = 10\cdot9$ $J(^1F{-}^2F) = 20$
$J(H{-}^2F) = 58\cdot5$ $J(^1F{-}^3F) = 27$
$J(H{-}^3F) = 57\cdot6$ $J(^2F{-}^3F) = 290$

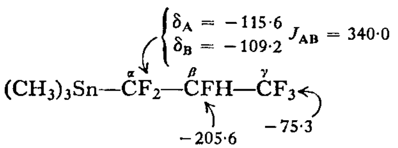
253



$$\underset{0\cdot08}{(CH_3)_3Si}-\overset{\overset{-233\cdot3}{^1F}}{\underset{\underset{4\cdot72}{H}}{C}}-\overset{\overset{-216\cdot6}{^2F}}{\underset{\underset{-203\cdot7}{^3F}}{C}}-\overset{0\cdot15}{Sn(CH_3)_3}$$

$J(H{-}^1F) = 43\cdot1$ $J(^1F{-}^2F) = 8\cdot4$
$J(H{-}^2F) = 36$ $J(^1F{-}^3F) = 9\cdot6$
$J(H{-}^3F) = 9\cdot6$ $J(^2F{-}^3F) = 312$

254

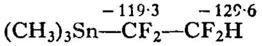


$$\left\{\begin{array}{l}\delta_A = -115\cdot6\\ \delta_B = -109\cdot2\end{array}\right. J_{AB} = 340\cdot0$$

$$(CH_3)_3Sn-\overset{\alpha}{C}F_2-\overset{\beta}{\underset{-205\cdot6}{C}FH}-\overset{\gamma}{\underset{-75\cdot3}{C}F_3}$$

$^2J(H_\beta{-}F_\beta) = 45\cdot9$ $^3J(F_\beta{-}F_\gamma) = 11\cdot75$
$^3J(H_\beta{-}F_\alpha) = 13\cdot9$ $^4J(F_\alpha{-}F_\gamma) = 6\cdot5$
$^3J(H_\beta{-}F_\alpha) = 11\cdot3$ $^4J(F_\alpha{-}F_\gamma) = 11\cdot0$
$^3J(H_\beta{-}F_\gamma) = 6\cdot5$ $^2J(^{119}Sn{-}F_\alpha) = 222\cdot0$
$^3J(F_\alpha{-}F_\beta) = 7\cdot1$ $^1J(^{13}C{-}F_\gamma) = 302\cdot0$
$^3J(F_\alpha{-}F_\beta) = 6\cdot5$

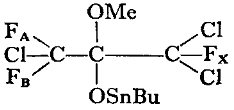
255



$$(CH_3)_3Sn-\overset{-119\cdot3}{CF_2}-\overset{-129\cdot6}{CF_2H}$$

$^2J(^{119}Sn{-}F_\alpha) = 249\cdot5$
$^2J(^{117}Sn{-}F_\alpha) = 237\cdot6$
$^3J(^{119}Sn{-}F_\beta) = 10\cdot0$

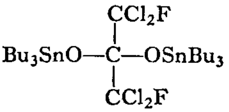
256



$$ClCF_AF_B-\overset{OMe}{\underset{OSnBu}{C}}-CCl_2F_X$$

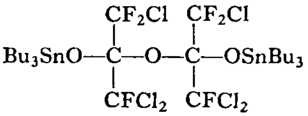
257

—O—C(CF$_3$)$_2$—S— and —O—C(CF$_2$Cl)$_2$—S— groups in isolation had shifts of –74·9 and –56·5 to –58·7 respectively. The mixed group —O—C(CF$_3$)(CF$_2$Cl)—S— in isolation had shifts of –72·6 (CF$_3$) and –60·1 (CF$_2$Cl). Shifts to higher field were found when the groups were in closer proximity; thus in —O—C(CF$_3$)$_2$—S—C(CF$_3$)$_2$—O— the shift was –77·9 and in —O—C(CF$_3$)(CF$_2$Cl)—S—C(CF$_3$)(CF$_2$Cl)—O— the shifts were –75·3 (CF$_3$) and –63·2 (CF$_2$Cl).



$$Bu_3SnO-\overset{CCl_2F}{\underset{CCl_2F}{C}}-OSnBu_3$$

258



$$Bu_3SnO-\overset{CF_2Cl}{\underset{CFCl_2}{C}}-O-\overset{CF_2Cl}{\underset{CFCl_2}{C}}-OSnBu_3$$

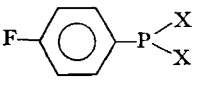
259

Group V

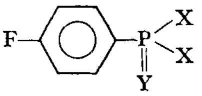
Phosphorus

The relationship $|\delta_m - \delta_p|$ of the pentafluorophenyl group in a series of pentafluorophenylfluorophosphonitriles, $N_xP_x(C_6F_5)F_{2x-1}$ ($x = 3$ to 8), have been used[220] to consider the electronic interaction between the pentafluorophenyl group and the phosphonitrilic ring. The large value of $|\delta_m - \delta_p|$ (14·7 to 16·1 p.p.m.) indicates a strong π-electron withdrawal from the pentafluorophenyl entity; compare the corresponding value of $|\delta_m - \delta_p|$ for pentafluorobenzonitrile of 15·7 p.p.m.

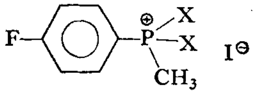
Schindlbauer[221] has employed the 4-fluorophenyl label, and hence the chemical shift of F(4), to investigate the electronic interaction between the



260



261

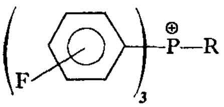


262

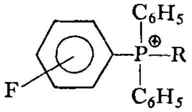
X = H, Cl, CH_3, OEt, Ph, p-FC_6H_4—; Y = O or S

other substituent groups and the phosphorus atom in compounds of the type **260** to **262**. There was a linear relationship between the shift of F(4) and the substituent constant for X.

Using the principles adopted by Taft, the 4-fluorophenyl label has been used to obtain the $\int_{m-X}^{p-X}$ values, where $\int_{m-X}^{p-X} = \int_{H}^{p-X} - \int_{H}^{m-X}$ and in turn $\int_{H}^{p-X}$ and $\int_{H}^{m-X}$ are the ^{19}F chemical shifts of the *para-* and *meta*-substituted fluorobenzene respectively measured with respect to fluorobenzene, for a range of derivatives of tris(fluorophenyl) phosphines (**263** and **264**).[222] From the consideration of the three $\int$ values, it was evident that inductive interactions are dominant in systems of this type and conjugative ($p_\pi - d_\pi$) interactions of tetravalent phosphorus with the adjacent anionic centre would appear to exclude any substantial conjugation between phosphorus and the attached aromatic ring.



263



264

R = CH_3, $\overset{\ominus}{C}H_2$, $O^{\ominus}$

The spectral parameters of tris(4-fluorophenyl) phosphine oxide (**261**, X = p-FC_6H_4 and Y = O) and of the dimethyl 4-fluorophenylphosphonate (**261**, X = OMe and Y = O) have been obtained.[223] The chemical shift difference between the *ortho* and *meta* protons was sufficiently large ~0·5 p.p.m. to give two well-resolved signals for the resonance of each type of proton. There were slight differences in some of the values of the H–F couplings obtained separately from the ^1H and ^{19}F spectra and this may be due to the closeness of the two shifts of the *ortho* and *meta* protons. It has been our experience that to obtain true H–F couplings from the ^{19}F spectra the shifts of *ortho* and *meta* protons of the 4-fluorophenyl group have to be of the order of 200 Hz, i.e. 2 p.p.m. at 100 MHz.

The reactions of triphenylphosphine with a variety of transition metals have been the source of some intensive studies and more recently fluorinated derivatives have been utilized to serve as a means of studying the electronic interactions between the phosphorus and metal atoms. It is therefore more convenient, despite the variety of metals used, to include this work in the section on phosphorus compounds.

The triphenylphosphines $(C_6F_5)_xPPh_{3-x}$ react with the hydrate of rhodium chloride to give the complex $[(C_6F_5)_xPPh_{3-x}]_4Rh_2Cl_2$ which, on reaction with carbon monoxide, affords the complexes *trans*-$[(C_6F_5)_x PPh_{3-x}]RhCOCl$ ($x = 1$, 2 or 3).[224] The ^{19}F shifts of the phosphines and complexes are shown in Table XXVII and the shift of the *para*-fluorine resonance to higher frequency in the metal complexes is in agreement with $d_\pi \rightarrow d_\pi$ donation from the metal to phosphorus atom.

The phosphine $[(C_6F_5)_3P]$ and potassium tetrachloroplatinate(II) react to give the complex of the form $[(C_6F_5)_3P]_2MX_2$, where M = Pt and X = Cl.[225] Similar complexes have been made with M = Pt, X = Br and I and M = Pd, X = Cl and Br. At room temperature the ^{19}F spectra of the pentafluorophenyl entity showed the normal three sets of signals except that the resonance signal of the *ortho*-fluorine atoms was very broad. On cooling to lower temperature two or three bands appear for the *ortho* signal while those of the *para*- and *meta*-fluorine atoms remain unaffected. Two physical motions must be considered, namely the rotation of the rings and rotation about the phosphorus–metal bond. If the rings are rotating and there is no rotation about the phosphorus–metal bond then one of the three rings becomes non-equivalent and a 4:2 ratio for the *ortho*-signals would be expected, as is observed in the complex $[(C_6F_5)_3P]_2PtCl_2$ at –40°. If there is no rotation about either of the rings or about the P–metal bond then there are three pairs of non-equivalent *ortho*-fluorine atoms and signals in ratio of 2:2:2 would be expected as is found $[(C_6F_5)_3P]_2PtBr_2$ and $[(C_6F_5)_3P]_2PtI_2$. There is thus clear indication of steric hindrance between the *ortho*-fluorine atoms and the metal atom; the shifts of these compounds are included in Table XXVII. The ^{19}F spectra of some complexes of pentafluorophenyl phosphines with the carbonyls of iron, ruthenium and molybdenum afforded no unexpected features.[226] There was no evidence for the non-equivalence of the *ortho*-fluorine atoms in these complexes and the chemical shifts are also included in Table XXVII.

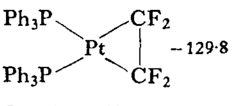
Tetrakis(triphenylphosphine)platinum reacts with fluoroolefins to afford complexes which, from consideration of the ^{19}F spectra, involve the formation of the three-membered ring of platinum with two carbon atoms.[227]

TABLE XXVII

^{19}F chemical shifts of complexes of pentafluorophenylphosphine

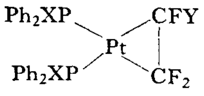
		Chemical shifts, δ			
		ortho	*meta*	*para*	Ref.
$(C_6F_5)_3P$	(in $CHCl_3$)	−131·0	−160·8	−149·1	224
	(in C_6H_6)	−131·5	−160·5	−147·9	. .
$(C_6F_5)_2PC_6H_5$	(in $CHCl_3$)	−129·3	−161·3	−150·6	224
	(in C_6H_6)	−130·3	−161·6	−150·6	. .
$(C_6F_5)_2PC_6H_5,BCl_3$		−125·8	−159·9	−145·3	224
$C_6F_5P(C_6H_5)_2$		−127·9	−161·4	−150·9	224
$[(C_6F_5)_3P]_2RhCOCl$		−126·7	−159·0	−145·5	224
$[(C_6F_5)_2PC_6H_5]_2RhCOCl$		−125·3	−160·0	−147·6	224
$[C_6F_5P(C_6H_5)_2]_2RhCOCl$		−125·2	−161·2	−149·7	224
$[(C_6F_5)_3P]_2PdCl_2$		−126·1	−159·0	−143·9	224
$[(C_6F_5)_2PC_6H_5]_2PdCl_2$		−124·8	−160·2	−146·6	224
$[C_6F_5P(C_6H_5)_2]_2PdCl_2$		−125·3	−161·2	−149·3	224
$[(C_6F_5)_3P]_2PtCl_2$		−126·1	−158·9	−143·7	225
	(at −40°)	−121·4, −130·1	−158·4	−143·3	. .
$[(C_6F_5)_3P]_2PtBr_2$		broad	−159·0	−144·0	225
	(at −20°)	−118·0, −126·7, −130·8	−158·9	−144·0	. .
$[(C_6F_5)_3P]_2PtI_2$		broad	−159·3	−144·1	225
	(at −20°)	−116·8, −124·3, −131·1	−159·0	−144·5	. .
$[(C_6F_5)_3P]_2PdCl_2$		−126·1	−158·8	−143·7	225
$[(C_6F_5)_3P]_2PdBr_2$		broad	−158·7	−143·8	225
$(C_6F_5)_2PFe(CO)_2\pi\text{-}C_5H_5$		−127·1	−162·0	−154·4	226
$(C_6F_5)_2PMo(CO)_3\pi\text{-}C_5H_5$		−126·4	−162·1	−153·3	226
$[(C_6F_5)_2PFe(CO)_3]_2$		−123·8	−158·8	−147·4	226
$[(C_6F_5)_2PRu(CO)_3]_2$		−123·0	−158·1	−147·1	226

The compounds obtained from tetrafluoro-, chlorotrifluoro-, bromotrifluoro- ethylenes, perfluoroprop-1-ene, perfluorobutadiene and perfluorocyclo- butene and hexene are shown in **265** to **270**; the chemical shifts and



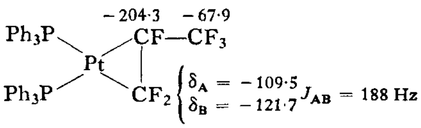
J(Pt–F) = 278 Hz

265



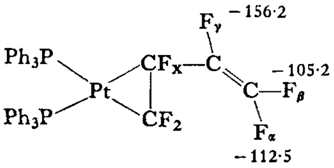
X = Ph or CH_3; Y = Cl or Br

266



J(Pt–CF_3) = 105 Hz

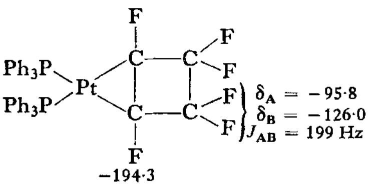
267



268

$J(F_\alpha\text{–}F_\gamma) = 110{\cdot}0$
$J(F_\beta\text{–}F_\gamma) = 27{\cdot}2$
$J(F_\alpha\text{–}F_\beta) = 67{\cdot}3$
$J(F_\alpha\text{–}F_X) = 29{\cdot}5$
$J(F_\beta\text{–}F_X) = 7{\cdot}2$
$J(F_\gamma\text{–}F_X) = 23$

$J(\text{Pt–}F_\gamma) = 265$
$J(\text{Pt–}F_\beta) = 40{\cdot}0$
$J(\text{P–}F_\alpha) = 8{\cdot}5$
$J(\text{P–}F_\beta) = 16{\cdot}0$
$J(\text{P–}F_\gamma) = 2{\cdot}5$



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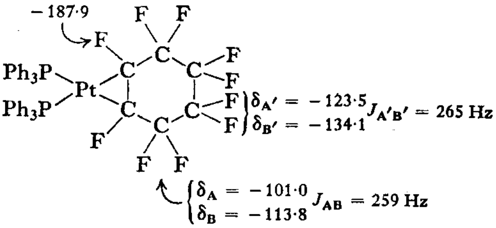


$J(\text{Pt–}F_A) = 200$ Hz
$J(\text{Pt–}F_B) = 100$ Hz

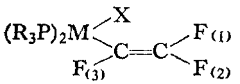
270

the more useful coupling constants are shown. In the compound **266** the full AB analysis of the $>CF_2$ is not given and from a cursory glance at the Table shown in the paper it might, at first instance, appear that the two fluorine atoms of the CF_2 were equivalent. Care must be taken in this respect as there is a growing tendency for many chemists to quote δ values by taking the band centre; this is especially true in the case of AB, A_2B_2 and $[AB]_2$ spectra. It is of significance that the increase in ring size, in **267**, **269** and **270**, is accompanied by an increase in the value of J_{AB}. The appropriate values are as shown which correlate with those found in perfluorocyclo-propanes, butanes and hexanes. On heating the complexes **265** to **268** in butanol the *trans*-$(Ph_2PX)_2Pt(CF{=}CF_2)X$ complexes are obtained; the shifts of these and some *cis*-compounds given in the paper[227] are listed in Table XXVIII.

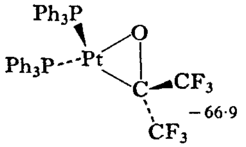
Hexafluoroacetone reacts with the zero-valent compounds $[Ph_3P]_4M$, $M = Pt$ or Pd to afford the complexes $[Ph_3P]_2M[(CF_3)_2CO]$; the compounds $[Ph_3P]_2Pt[(CF_2Cl)_2CO]$ and $[Ph_2MeP]_2Pt[(CF_3)_2CO]$ have also been prepared.[229] The ^{19}F spectra of these compounds indicated the presence of a three-membered ring involving the metal atom, shown in **271** to **273**; the shifts and the relevant coupling constants are also shown. Reaction of excess trifluoroacetonitrile with bis(triphenylphosphine)-platinum *trans*-stilbene gave the complex bis(triphenylphosphine)platinum

TABLE XXVIII

^{19}F chemical shifts and coupling constants of:

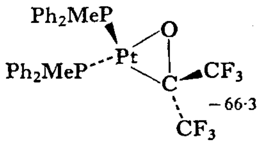


	Chemical shifts			Coupling constants, Hz						
	$\delta(1)$	$\delta(2)$	$\delta(3)$	J_{12}	J_{13}	J_{23}	$J(P–F_{(1)})$	$J(P–F_{(2)})$	$J(P–F_{(3)})$	Ref.
trans-$(Ph_3P)_2Pt(CF{=}CF_2)Cl$	−101·2	−128·7	−147·0	98	31·0	105	5·6	3·5	..	227
trans-$(Ph_2PMe)_2Pt(CF{=}CF_2)Cl$	−100·6	−128·7	−148·9	101	31·1	106	5·8	3·8	..	227
trans-$(Ph_3P)_2Pt(CF{=}CF_2)Br$	−101·4	−128·3	−145·6	101	32·0	105	5·8	3·8	..	227
trans-$(Et_3P)_2Pt(CF{=}CF_2)Cl$	−100·6	−135·3	−153·6	120	35·6	120	4·8	..	..	227
cis-$(Et_3P)_2Pt(CF{=}CF_2)Br$	−98·6	−127·0	−155·1	104	34	104	23	0	34	227
cis-$(Et_3P)_2Pt(CF{=}CF_2)_2$	−101·1	−131·8	−161·4	104	33	104	17	0	33	227
trans-$(Et_3P)_2Ni(CF{=}CF_2)Br$	−89·9	−132·2	−158·8	107	36	107	7·0	7·0	5·5	228
trans-$(Et_3P)_2Ni(CF{=}CF_2)_2$	−91·4	−134·1	−170·8	112	32	112	..	..	..	228
trans-$(Et_3P)_2Pd(CF{=}CF_2)_2$	−95·8	−133·6	−166·1	109	40	104	6·0	4·5	1·0	228
trans-$(Et_3P)_2Pt(CF{=}CF_2)Br$	−99·8	−129·5	−145·5	107	34	107	..	..	..	228
cis-$(Et_3P)_2Pt(CCl{=}CF_2)_2$	−92·2	−80·0	..	65	..	..	..	..	..	228
trans-$(Et_3P)_2Pt_2(CCl{=}CF_2)_2Br_2$	−91·1	−80·6	..	64	..	..	..	..	..	228
$(Et_3P)pyPt(CCl{=}CF_2)Br$	−96·3	−81·3	..	66	..	..	1·0	2·0	..	228
trans-$(Et_3P)_2Pd_2(CCl{=}CF_2)_2Br_2$	−93·9	−80·4	..	69	..	..	4·0	4·0	..	228



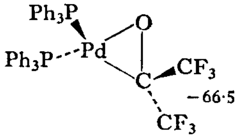
J trans ($P-CF_3$) = 11·3 Hz
J cis ($P-CF_3$) = 1·3 Hz
$J(Pt-CF_3)$ = 70·5 Hz

271



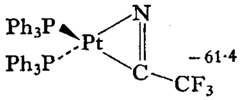
J trans ($P-CF_3$) = 11·3 Hz
J cis ($P-CF_3$) = 1·0 Hz
$J(Pt-CF_3)$ = 68·8 Hz

272



J trans ($P-CF_3$) = 11·6 Hz
J cis ($P-CF_3$) = 6·2 Hz

273



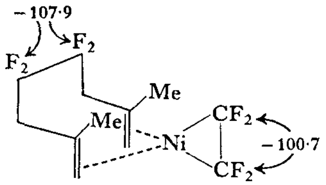
$J(Pt-F)$ = 57·3 Hz
$J(P-F)$ = 6·7 Hz

274

(trifluoroacetinitrile) **274**; the shifts and couplings are shown in the formulae.[230] It is perhaps opportune to emphasize the importance of obtaining the maximum NMR information as in these cases the phosphorus–fluorine and metal–fluorine coupling constants give very valuable information concerning the structure of the complexes.

Similar reactions to those described above have been reported for the reaction of tetrafluoroethylene with bis(cyclooctadiene)nickel and bis(methallyl)nickel,[231] the latter affording the new compound **275**. The former compound reacts with hexafluoroacetone and 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietan to afford the complexes **276** and **277**. The cyclo-octa-1,5-diene entity is easily displaced from complexes **276** and **277** by reaction with phosphines or phosphites to give the complexes **278** and **279** (the data for the triphenyl phosphite are given).

The ^{19}F spectra of some new complexes of the type *cis*- and *trans*-$(Et_3P)_2M(CF{=}CF_2)X$, where M is Ni, Pt or Pd and X = Br or $CF{=}CF_2$ have been discussed[228] together with some new data on *cis*-$(Et_3P)_2Pt(CCl{=}CF_2)$ and *trans*-$(Et_3P)_2Pt_2(CCl{=}CF_2)_2Br_2$; the bridging in the latter compound is cleaved on the addition of pyridine. The chemical shifts and the F–F and P–F coupling constants are shown in Table XXVIII. The magnitude of the platinum–fluorine coupling constants in these compounds warrants some comment. In pentafluorophenylplatinum compounds the three-bond platinum-*ortho*-fluorine coupling is in the range 300 to 500 Hz, while in the trifluorovinyl complexes the similar three-bond platinum–F(2) coupling is only of the order of 50 Hz, but is larger, ~90 Hz, in the 1-chloro-2,2-difluorovinyl compounds. The *trans*-platinum–F(1) coupling in the



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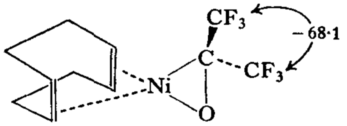

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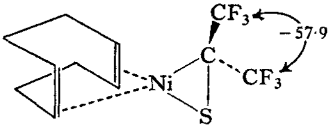

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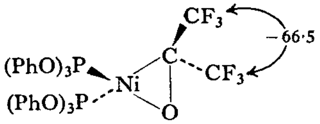
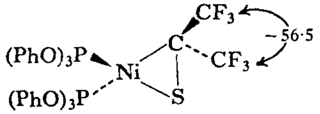


J cis (P–CF_3) = 3·4 Hz
J trans (P–CF_3) = 12·2 Hz

278



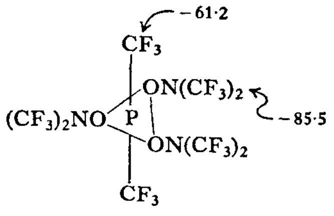
J trans (P–CF_3) = 12·0 Hz
J cis (P–CF_3) = 1·0 Hz

279

trifluorovinyl derivatives is larger, 167 to 188 Hz, but smaller, 140 to 145 Hz, in the 1-chloro-2,2-difluorovinyl derivatives; the two bond platinum–F(3) coupling is in the range 348 to 395 Hz.

The square planar complexes of palladium(II) and platinum(II) with trifluoromethyldiphenylphosphine were investigated in order to evaluate the large *trans* phosphorus–phosphorus coupling constants.[232] The ^{19}F NMR parameters of these complexes were compared to those of the related fluorophosphine and alkylphosphine complexes and the reason for the decrease in the value of $|J(P–CF_3)|$ on complex formation is discussed.

On the basis of the ^{19}F spectrum the product obtained from the interaction of bis(trifluoromethyl)phosphine and bis(trifluoromethyl)nitroxide was



$^2J(CF_3–P)$ = 119 Hz

280

thought to have the conformation shown in **280**.[233] Trifluoromethyl dichlorophosphine, CF_3PCl_2, was found to react quantitatively with nitrogen dioxide to afford the new compound trifluoromethylphosphonyldichloride, $CF_3P(O)Cl_2$.[234] The ^{19}F resonance shift of the latter compound was found to be –74·1 and the ^{19}F–^{31}P coupling constant was 151 Hz.

By consideration of shielding parameters on the ^{19}F shifts of fluorophosphates it was considered that the ^{19}F shifts of dialkylfluorophosphines should be at lower fields whereas in reality these occur to high field.[34a] This effect could not be explained in terms of hyperconjugative effects from the αC–H bonds, but was explained in terms of the number of methyl groups attached to the α-carbon atom (**281** to **283**). This idea was also extended to consideration of acid fluorides and Fig. 6 shows a plot of the ^{19}F shift against the number of methyl groups. The shift of the fluorophosphine groups are shown in Table XXIX. Sheluchenko *et al.*[235] have

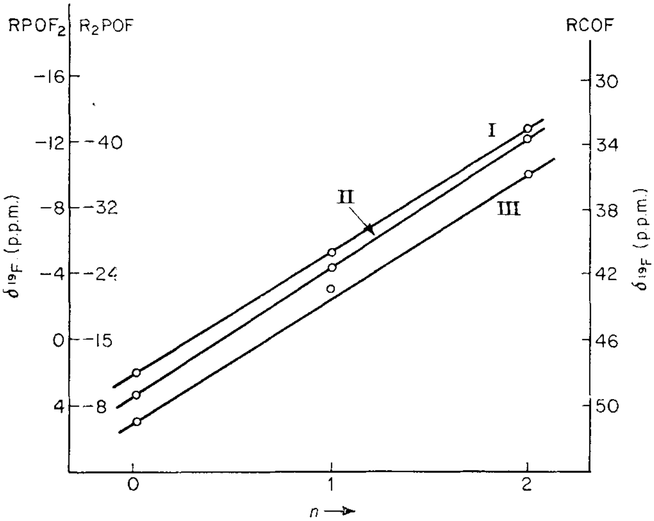
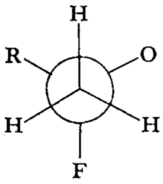
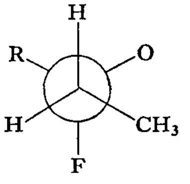


FIG. 6. The dependence of the ^{19}F shift on the number of methyl groups in (I) $(CH_3)_n(CH_{3-n})POF_2$, (II) $(CH_3)_n(CH_{3-n})COF$, and (III) $(CH_3)_n(CH_{3-n})POF$. (From Neimysheva and Knunyants.)[34a]



281



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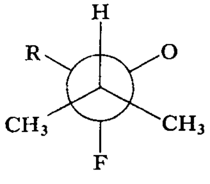

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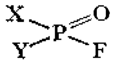
TABLE XXIX

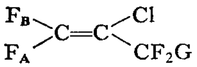
^{19}F shifts of the fluorophosphine group in compounds of the type:



X	Y	δ	X	Y	δ
C_2H_5—	C_2H_5	–83·6	$(CH_3)_2CH$—	$(CH_3)_2CH$—	–99·7
$(CH_3)_2CH.CH_2$—	$(CH_3)_2CH.CH_2$—	–75·4	$CH_3(CH_2)_2$—	$(CH_3)_2CHO$—	–66·6
CH_3	CH_3O	–63·4	$(CH_3)_2CH$—	$(CH_3)_2CHO$—	–72·7
CH_3	C_2H_5O—	–60·5	CH_3	C_2H_5S—	–41·4
CH_3	$(CH_3)_2CHO$—	–58·4	CH_3	$ClCH_2CH_2S$—	–40·4
C_6H_5—	CH_3O—	–67·3	CH_3CH_2	$CH_3(CH_2)_2S$—	–51·3
C_6H_5	C_2H_5O—	–65·4	$CH_3(CH_2)_2$	$CH_3(CH_2)_2S$—	–48·4
C_6H_5	$(CH_3)_2CHO$—	–64·9	$CH_3(CH_2)_2O$—	$CH_3(CH_2)_2O$—	–83·1
C_2H_5	$CH_3(CH_2)_2O$—	–68·6	$(CH_3)_2CH.CH_2O$—	$(CH_3)_2CH.CH_2O$—	–83·3
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2O$—	–65·4	C_6H_5O—	C_6H_5O—	–79·1
C_2H_5	CH_3S—	–53·9	F	F	–93·2
C_2H_5	$(CH_3)_2CH.S$—	–49·5	F	Cl	–47·0
C_2H_5	CH_3O—	–71·1	CH_3—	F	–61·6
C_2H_5	C_2H_5O—	–68·5	F	OH	–87·0
C_2H_5	$(CH_3)_2CHO$—	–66·4	$(CH_3)_2CH$—	F	–76·5
CH_3O—	CH_3O—	–87·1	Cl	Cl	–13·2
C_2H_5O—	C_2H_5O—	–82·3	$ClCH_2$	Cl	–60·1
$(CH_3)_2CHO$—	$(CH_3)_2CHO$—	–78·2	$(CH_3)_2CH$	Cl	–50·0
CH_3	$(CH_3)_2N$—	–61·4	CH_3	OH	–60·1
CH_3	$(C_2H_5)_2N$—	–55·2	CH_3O	Cl	–47·1
CH_3—	CH_3—	–65·8	C_2H_5O	Cl	–44·6
CH_3—	$CH_3(CH_2)_3$—	–72·2	C_2H_5O	OH	–82·2
C_6H_5—	CH_3CH_2—	–77·1			

also measured the ^{19}F shift of a number of fluorophosphine derivatives and these are included in Table XXIX. In all cases the ^{19}F–^{31}P coupling constants were in the range 950 to 1190 Hz.

The tetramer $(CF_3P)_4$ and dimethylphosphine were found to react to afford the novel triphosphine, $CF_3P[P(CH_3)_2]_2$, the structure of which was substantiated from the ^{19}F spectrum which consisted of a doublet of triplets with ^2J(P–CF) of 40·2 Hz and ^3J(P–PCF) of 6·4 Hz.[236] The temperature dependence of the ^{19}F spectrum of the pentamer $(PCF_3)_5$ has been studied.[237] At 147°C the fine structure is blurred and has vanished by 165°C. At 202°C the two main bands broaden and start to merge; during the same temperature range the spectrum of the tetramer (which was present) remained fairly sharp. A motion which scrambles the CF_3 groups at high temperature was ascribed to a pseudo-rotation, i.e. a cyclic interchange of phosphorus atoms, and hence CF_3 groups, round the ring via torsional vibration.



G = —$P(O)(OCH_3)_2$, —$POCl_2$, —$P(O)(C_6H_5)_2$,
—$PHCH_3$, —PHC_2H_5, —PHC_6H_5 and —$P(C_6H_5)_2$

284

2-Chlorotetrafluoroallylphosphorus compounds (**284**) have conveniently been prepared by the reaction of 2,3-dichlorotetrafluoropropene with phosphites, phosphinide ions and phosphines.[238] The shifts of the compounds containing trivalent phosphorus fall into fairly narrow ranges: CF_2= –78·0 to –80·7, and CF_2P –89·4 to –94·7. (More detailed analysis of these compounds is being undertaken.) The data for the phosphorus(V) compounds are, however, shown in Table XXX. The coupling constants of F$_A$ and F$_B$ to the —CF_2G group are fairly constant in magnitude

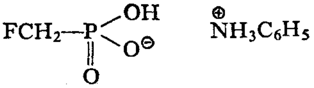
TABLE XXX

^{19}F parameters of 2-chlorotetrafluoroallylphosphoryl compounds (284)

	Chemical shift, δ			Coupling constants, Hz			
G	F$_A$	F$_B$	—CF_2P	J_{AB}	J(P–CF$_2$)	J(P–F$_A$)	J(P–F$_B$)
$P(O)(OCH_3)_2$	–77·0	–74·8	–108·0	19·0	109	6·9	9·8
$P(O)Cl_2$	–72·1	–69·3	–104·7	6·6	146	11·6	16·2
$P(O)(C_6H_5)_2$	–76·4	–74·8	–105·9	14·8	88	5·5	7·5

[$J(F_A\text{–}CF_2G)$ = 27·3 to 28·4 Hz and $J(F_B\text{–}CF_2G)$ = 7·2 to 7·5 Hz]; the data were compared with that for the 2,3-dichlorotetrafluoropropene (**284**, G = Cl) and the 2-chloropentafluoropropene (**284**, G = F).

The ^{19}F parameters for a series of perfluoropropylphosphines have been reported.[239] The shifts of the α and β CF_2 and CF_3 groups fall into the ranges –108 to –116, –122·4 to –123·4 and –80·1 to –81·2 respectively. The phosphorus–fluorine coupling constants also fall into fairly characteristic ranges: (P–αCF_2) = 41·7 to 57·2 Hz, (P–βCF_2) = 24·8 to 33·9 Hz and (P–γCF_3) = 7·5 to 9·5 Hz. As is usual in fluoropropyl derivatives the four-bond F–F couplings, between the α-CF_2 and γ-CF_3, are larger (9·8 to 10·5 Hz) than the three-bond vicinal F–F couplings. The two compounds, bis(trifluoromethyl)heptafluoropropylphosphine and the oxide, afford excellent additional examples of the effect of the valency of the phosphorus on the ^{19}F parameters. The shift of the CF_3 group in the phosphine is at lower field –48·2 than in the phosphine oxide, –64·6; the CF_3–P coupling in the oxide is also larger (112 Hz) than in the phosphine (86 Hz). The ^{19}F shifts of the perfluoropropyl group are little affected but there is a substantial increase in the P–αCF_2 coupling in the oxide (86·0 Hz), but a decrease in the P–βCF_2 and P–γCF_3 coupling constants (2·2 and 2·8 Hz respectively, see above). In both compounds the CF_3–P group couples to both the αCF_2 and βCF_2 group, 7·4 to 8·8 and 4·8 Hz respectively.



$$FCH_2\text{—}P(=O)(OH)O^{\ominus}\quad \overset{\oplus}{N}H_3C_6H_5$$

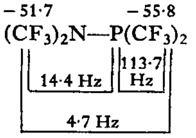
285

The ^{19}F resonance signal of the anilinium salt of fluoromethanephosphonic acid (**285**) is at –239·5 and is a doublet of triplets due to coupling to phosphorus of 61 Hz and to the methylenic protons of 46·3 Hz.[240]

A number of mixed trifluoromethyl -methyl diphosphine, diarsine and phosphino-arsine compounds have been prepared and identified by NMR spectra.[241] The ^{19}F shift of the $(CF_3)_2P$— group in $(CF_3)_2P.P(CH_3)_2$ and $(CF_3)_2P.As(CH_3)_2$ was –47·0 to –47·4 and the two-bond P–F coupling was 64·2 and 61·5 Hz respectively; the longer range F–P–P coupling in the former compound was 7·8 Hz. In the diarsine $(CF_3)_2As.As(CH_3)_2$ and phosphino-arsine $(CF_3)_2As.P(CH_3)_2$ the shift of the $(CF_3)_2As$ group was –42·9 to –43·8; the three-bond F–As–P coupling in the mixed compound was 7·5 Hz. In all cases the five-bond H–F coupling was small being ~0·7 Hz. In the perfluoromethyl phosphino-arsine, $(CF_3)_2P.As(CF_3)_2$ the shifts of the $(CF_3)_2P$ and $(CF_3)_2As$ groups were –44·9 and –42·0 respectively, the two-bond P–F coupling was 65·1 Hz and the three-bond P–F coupling was larger than in the previous examples being 12·3 Hz. The five-bond

F–F coupling was 3·4 Hz, a larger value than that found for the compounds $(CF_3)_2P.X.CF_3$, X = S or Se, and "through space" coupling mechanism is invoked to explain this larger value.

The *N*-chloro- or *N*-bromo-bistrifluoromethylamine underwent a stepwise substitution reaction with tris(trifluoromethyl)phosphine to give



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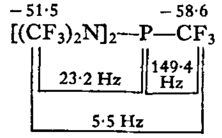

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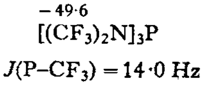


288

compounds of the form $[(CF_3)_2N]_nP(CF_3)_{3-n}$, n = 1, 2 or 3.[242] The shifts and coupling constants of these aminophosphines are shown in **286** to **288**. It should again be noted that the five-bond F–F coupling is fairly large, 4·7 to 5·5 Hz.

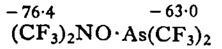
Arsenic

The ^{19}F shifts of the tetramer, $(C_6F_5As)_4$, were found to be δ(*ortho*) −125·9, δ(*para*) −152·1 and δ(*meta*) −161·8, and the *ortho*-F resonance signal showed evidence of ^{75}As quadrupolar broadening.[243] Attempts to prepare the tetrakis compound, $(C_6F_5)_2AsAs(C_6F_5)_2$, gave a product which showed five ^{19}F resonance signals, but on sublimation two isomers were isolated. These are suggested to be rotamers having *gauche* and *trans* configuration; the shifts of the two rotomers were—

Isomer I	δ(*ortho*)	−133·5	δ(*para*)	−152·0	δ(*meta*)	−162·8
Isomer II		−133·5		−146·6		−160·0

The tetrakis compound $(C_6F_5)_2AsAs(C_6F_5)_2$ reacts with $[\pi\text{-}C_5H_5Fe(CO)_2]_2$ or $[\pi\text{-}C_5H_5Mo(CO)_3]_2$ to give the monomeric complexes $(C_6F_5)_2AsFe(CO)_2\pi\text{-}C_5H_5$ or $(C_6F_5)_2AsMo(CO)_3\pi\text{-}C_5H_5$ respectively.[226] The shifts of these compounds, together with the iron and ruthenium tricarbonyls, are shown in Table XXXI.

Bis(trifluoromethyl)arsine and bis(trifluoromethyl)nitroxide gave the trivalent arsenic derivative **289** (compare reaction with the corresponding phosphine, p. 352). A long-range coupling of 1·4 Hz over six-bonds, between the two types of CF_3 groups, was observed.[233]



$$\overset{-76\cdot4}{(CF_3)_2N}O\cdot\overset{-63\cdot0}{As(CF_3)_2}$$

289

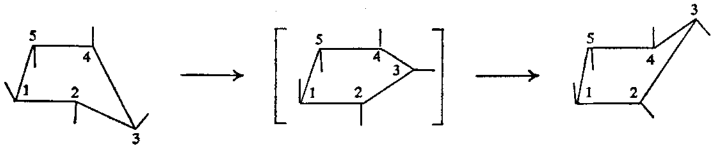
The data for certain diarsines and phosphino-arsines have, for convenience, been included in the section on phosphorus compounds (see above).

TABLE XXXI

^{19}F shifts of pentafluorophenyl derivatives of arsenic[226]

	Chemical shift, δ		
	ortho	*meta*	*para*
$(C_6F_5)_2AsFe(CO)_2\pi\text{-}C_5H_5$	−124·2	−161·6	−153·9
$(C_6F_5)_2AsMo(CO)_3\pi\text{-}C_5H_5$	−124·1	−161·6	−153·1
$[(C_6F_5)_2AsFe(CO)_3]_2$	−122·0	−157·4	−146·2
$[(C_6F_5)_2AsRu(CO)_3]_2$	−121·7	−156·2	−146·1

The pseudo-rotation in the pentamer of trifluoromethylarsenic $(CF_3As)_5$ has also been investigated [see above for discussion regarding $(CF_3P)_5$].[244] If the structure were as in the solid state each CF_3 group should give rise to a discreet resonance signal but three lines, in ratio 2:2:1, are observed. A butterfly wagging motion is suggested to account for the simplified spectrum (**290**). This process must be very fast as there was no alteration in the spectrum down to −130°.



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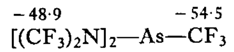


$$\overset{-48\cdot9}{[(CF_3)_2N]_2}\text{—As—}\overset{-54\cdot5}{CF_3}$$

^5J(F–F) = 4·8 Hz

291

The reaction of tris(trifluoromethyl)arsine with *N*-chloro- or *N*-bromo-bistrifluoromethylamine only resulted in the replacement of two of the trifluoromethyl groups of the arsine to give compounds **289** and **291**; compare reaction with corresponding phosphine (p. 357).[242] The five bond F–F coupling (3·7 to 4·8 Hz) is of the same order as that found in the diarsines and phosphino-arsine.

Pentafluorophenylmercapto-metal complexes

It is convenient to consider the compounds in which the aryl group is attached to a sulphur atom separately, as there has been considerable amount of work published in this field involving bonding to a variety of metal atoms.

The complex anions $[M(SC_6F_5)_4]^{2\ominus}$ where $M = Co^{II}$, Pd^{II}, Pt^{II}, Zn^{II}, Cd^{II}, Hg^{II} and $[M(SC_6F_5)_2]^{\ominus}$ where $M = Cu^{I}$, Ag^{I}, Au^{I}, have been prepared[245] and the shifts are shown in Table XXXII.

TABLE XXXII

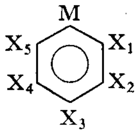
^{19}F shifts of anions of pentafluoromercapto metal complexes

	Chemical shifts, δ			
	ortho F	*meta* F	*para* F	Ref.
C_6F_5SH	−138·2	−164·0	−160·5	245
$[Ph_3P]_2[Pd(SC_6F_5)_2]$	−137·0	−169·3	−168·7	245
$[Ph_3P]_2[Pt(SC_6F_5)_2]$	−136·3	−168·4	−168·4	245
$[Et_4N]_2[Pd(SC_6F_5)_4]$	−132·4	−170·4	−170·4	245
$[Et_4N]_2[Pt(SC_6F_5)_4]$	−131·9	−168·1	−168·1	245
$[Et_4N][Cu(SC_6F_5)_2]$	−135·4	−168·9	−170·7	245
$[Et_4N][Ag(SC_6F_5)_2]$	−136·5	−169·1	−171·1	245
$[Et_4N][Au(SC_6F_5)_2]$	−134·9	−167·8	−167·8	245
$[Et_4N][Zn(SC_6F_5)_4]$	−133·9	−170·1	−171·9	245
$[Et_4N]_2[Cd(SC_6F_5)_4]$	−134·3	−169·8	−172·1	245
$[Et_4N]_2[Hg(SC_6F_5)_4]$	−134·4	−169·0	−170·4	245
$Na[SC_6F_5]$	−140·7	−172·5	−179·5	245
$K[SC_6F_5].H_2O$	−140·5	−170·3	−177·5	245
$[Et_4N]_2[Co(SC_6F_5)_4]$	37·8	−81·2	~172·9	245
$[C_6F_5S.Fe(CO)_3]_2$	−126·7	−159·4	−152·1	246
$C_6F_5S.Fe(CO)_2(\pi\text{-}C_5H_5)$	−132·2	−164·5	−159·3	246
$C_6F_5S.Ni(PPh_3)(\pi\text{-}C_5H_5)$	−131·7	−166·6	−164·3	246
$[C_6F_5S.Rh(CO)_2]_2$	−126·4	−158·2	−150·2	246
$C_6F_5S.Rh(CO)(PPh_3)_2$	−135·5	−172·0	−171·2	246
$C_6F_5S.CH_3$	−135·8	−164·4	−157·2	119a, 246
$Zn(SC_6F_5)_2$	−133·5	−166·4	−164·1	247
$Cd(SC_6F_5)_2$	−133·0	−164·5	−161·4	247
$Hg(SC_6F_5)_2$	−132·9	−165·3	−160·8	247
$Pb(SC_6F_5)_2$	−133·3	−165·4	−163·0	247
$Bi(SC_6F_5)_3$	−130·3	−165·2	−158·2	247
$Ph_3Pb(SC_6F_5)$	−132·3	−166·1	−162·3	247
$C_6F_5S.SC_6F_5$	−134·1	−162·9	−151·3	247
$n\text{-}Bu_3SnSC_6F_5$	−132·2	−163·8	−159·3	248
$n\text{-}Bu_2Sn(SC_6F_5)_2$	−131·7	−162·5	−156·5	248
$Ph_3SnSC_6F_5$	−130·5	−163·7	−158·1	248

Dodecacarbonyltri-iron reacts with either dipentafluorophenyl disulphide or pentafluorothiophenol to afford a single isomer of the complex $[C_6F_5S.Fe(CO)_3]_2$.[246] Extension of this reaction with π-cyclopentadienyliron

TABLE XXXIII

^{19}F shifts of metal carbonyl derivatives of fluoroaromatics



						Chemical shift, δ					
M	X_1	X_2	X_3	X_4	X_5	F(1)	F(2)	F(3)	F(4)	F(5)	Ref.
$Mn(CO)_5$	F	F	F	F	F	−104·3	−161·2	−157·5	−161·2	−104·3	119
$Mn(CO)_5$	F	CN	CN	F	F	−69·1	. .	. .	−135·4	−85·7	119
$Re(CO)_5$	F	F	F	F	F	−101·4	−163·3	−159·9	−163·3	−101·4	119
$Re(CO)_5$	F	F	$C{\equiv}CH$	F	F	−101·9	−138·3	. .	−138·3	−101·9	119
$Re(CO)_5$	F	CN	CN	F	F	−66·2	. .	. .	−134·6	−83·2	119
π-$C_5H_5Fe(CO)_2$	F	F	F	F	F	−106·7	−164·3	−161·7	−164·3	−106·7	119
π-$C_5H_5Fe(CO)_2$	F	F	H	F	F	−109·3	−142·0	. .	−142·0	−109·3	119
π-$C_5H_5Fe(CO)_2$	F	F	CN	F	F	−105·1	−139·4	. .	−139·4	−105·1	119
π-$C_5H_5Fe(CO)_2$	F	F	CF_3	F	F	−104·9	−144·2	. .	−144·2	−104·9	119

π-$C_5H_5Fe(CO)_2$	F	F	CH_3	F	F	−109·3	−145·9	. .	−145·9	−109·3	119
π-$C_5H_5Fe(CO)_2$	F	F	$CH{=}CH_2$	F	F	−108·6	−145·9	. .	−145·6	−108·6	119
π-$C_5H_5Fe(CO)_2$	F	F	$CH_2.CH{=}CH_2$	F	F	−108·8	−146·9	. .	−146·9	−108·8	119
π-$C_5H_5Fe(CO)_2$	F	F	CO_2Et	F	F	−108·2	−142·8	. .	−142·8	−108·2	119
π-$C_5H_5Fe(CO)_2$	F	F	OMe	F	F	−108·3	−158·2	. .	−158·2	−108·3	119
π-$C_5H_5Fe(CO)_2$	F	F	$\pi C_5H_5Fe(CO)_2CH_2$	F	F	−108·4	−142·9	. .	−142·9	−108·4	119
π-$C_5H_5Fe(CO)_2$	F	H	H	F	F	−84·1	. .	. .	−143·8	−101·5	119
π-$C_5H_5Fe(CO)_2$	F	CN	CN	F	F	−69·8	. .	. .	−136·0	−86·8	119
π-$C_5H_5Fe(CO)_2$	F	CO_2Et	CO_2Et	F	F	−83·3	. .	. .	−144·3	−97·3	119
π-$C_5H_5Fe(CO)_2$	F	F	H	F	H	−112·1	−135·9	. .	−119·5	. .	119
π-$C_5H_5Fe(CO)_2$	F	H	F	F	H	−84·0	. .	−143·6	−146·4	. .	119
π-$C_5H_5Fe(CO)_2CH_2$	F	F	F	F	F	−144·2	−162·9	−157·0	−162·9	−144·2	119
π-$C_5H_5Fe(CO)_2C{\equiv}C$	F	F	F	F	F	−140·8	−165·6	−162·0	−165·6	−140·8	119
π-$C_5H_5Fe(CO)_2SO_2$	F	F	F	F	F	−140·5	−161·6	−153·4	−161·6	−140·5	119
π-$C_5H_5Fe(CO)_2CH{=}CH$	F	F	H	F	F	−138·4	−138·4	. .	−138·4	−138·4	119
π-$C_5H_5Fe(CO)_2$	F	F	SCH_3	F	F	−109	−137·7	. .	−137·7	−109	246
π-$C_5H_5Fe(CO)_2$	F	F	SPh	F	F	−107·3	−138·4	. .	−138·4	−107·3	246
$Re(CO)_5$	F	F	SCH_3	F	F	−102·1	−136·5	. .	−136·5	−102·1	246
π-$C_5H_5Fe(CO)_2$	F	F	F	F	F	−107·3	−163·6	−160·3	−163·6	−107·3	249
π-$C_5H_5Ru(CO)_2$	F	F	F	F	F	−104·25	−164·3	−162·5	−164·3	−104·25	249
π-$C_5H_5Fe(CO)_2$	F	CN	CN	F	F	−69·8	. .	. .	−136·0	−86·8	249
π-$C_5H_5Ru(CO)_2$	F	CN	CN	F	F	−68·9	. .	. .	−136·35	−85·9	249

carbonyl, nickelocene, and various chloro-rhodium carbonyl complexes leads to a variety of compounds. The ^{19}F resonance data of these compounds are included in Table XXXII. In the pentafluoro thiophenolate ion it is noticeable, as in the pentafluoroanisole, that the shift of F(4) is to lower frequency and implies considerable p_π–p_π delocalization from the sulphur into the aromatic ring. This general tendency would seem to persist in the majority of ions as the shift of the F(4) nucleus is similar, or to lower frequency of the *meta*-fluorine resonance.

The new compounds $M(SC_6F_5)$, where M = Cs, Tl, Cu, Au and Ph_3Pb, $M(SC_6F_5)_2$, where M = Pb, Cd, Hg, Ni, Pt, $M(SC_6F_5)_3$, where M = As or Bi and $Sn(SC_6F_5)_4$, have been prepared from pentafluorothiophenol and the metal ions in aqueous solution.[247] The ^{19}F chemical shifts of the pentafluorothiophenyl entity reported for some of these compounds are included in Table XXXII. Peach[248] has also reported the ^{19}F shifts of the same group in tin derivatives of the type $R_3SnSC_6F_5$ (R = Bu and Ph) and $R_2Sn(SC_6F_5)_2$ [R = Bu], these are included in Table XXXII.

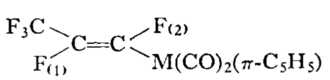
Group VII and VIII

There has been very extensive interest in the study of the reactions of the π-cyclopentadienyl iron carbonyl $[(\pi\text{-}C_5H_5)Fe(CO)_2^{\ominus}]$ ion with fluoroaromatics

Bruce[119] has given a fairly detailed account of the spectra of the products of the anion with fluoroaromatics. The chemical shifts of the compounds discussed are shown in Table XXXIII. Other than the profound deshielding effect of the metal carbonyl group the most significant point is the very large *ortho* F–F coupling between F(1) and F(2) and/or F(4) and F(5) which are in the range 28 to 34 Hz, considerably larger than the range of the *ortho* F–F coupling constants in fluoroaromatics. The author uses the shielding parameters obtained in the routine study to elucidate the structure

TABLE XXXIV

^{19}F shifts of complexes of perfluoropropene[249]



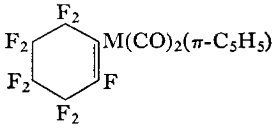
	Chemical shifts, δ			Coupling constants, Hz		
M	CF_3	F(1)	F(2)	$J[CF_3\text{–}F(1)]$	$J[CF_3\text{–}F(2)]$	$J[F(1)\text{–}F(2)]$
Ru	−65·6	−85·3	−163·9	22·25	13·05	134·5
Fe	−66	−86	−166	22	13	131

of the compounds obtained by reaction of the anion with pentafluorobenzonitrile and 1,2-di-iodotetrafluorobenzene. During the course of the study of thiophenol derivatives of metals some derivatives of 4-thiomethyl tetrafluorophenyl-iron and rhenium carbonyl derivatives were prepared for comparison purposes.[246] The ^{19}F chemical shifts of these compounds are shown in Table XXXIII; again the larger *ortho* F(1)–F(2) coupling (29 to 31 Hz) was in evidence.

The ^{19}F NMR parameters of dicarbonyl-π-cyclopentadienyl-ruthenium fluorocarbon complexes have been considered by Stone and his coworkers.[249] The shifts of the metal carbonyl derivatives of the fluoroaromatics are included in Table XXXIII and those of perfluoropropene and perfluorocyclohexene are shown in Tables XXXIV and XXXV respectively.

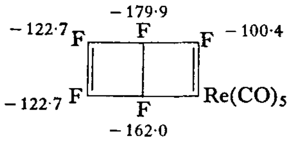
TABLE XXXV

^{19}F shifts of complexes of perfluorocyclohexene[249]



	Chemical shifts, δ				
M	F(2)	F(3)	F(4)	F(5)	F(6)
Ru	−96·3	−116·6	−134·6	−132·3	−92·6
Fe	−104·5	−124·1	−143·5	−141·1	−99·0

Stone *et al.*[250] have examined the interaction of "Dewar hexafluorobenzene", hexafluorobicyclo[2.2.0]hexa-2,5-diene, with various metal carbonyl anions and, because of the variety of compounds obtained, the shifts of the fluorine atoms are shown in the structural formulae **292** to **299**. It was thought that attack on the bicyclo compound occurred on the *exo*-side and that the structure of the complexes of the type **294** to **296** were of the form shown in **300**. The ^{19}F spectra were, however, rather complex for full analysis of the spin system and the final confirmation of the structure might have to await X-ray studies. The structures of products obtained by reaction of the $[\pi\text{-}C_5H_5Fe(CO)_2]^{\ominus}$ and $[Re(CO)_5]^{\ominus}$ anions with hexafluorobut-2-yne have been investigated by the same school.[251] The complexes obtained, together with the spectral parameters, are shown in



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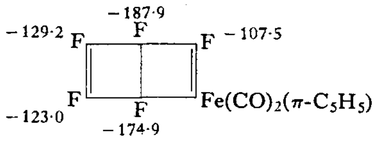

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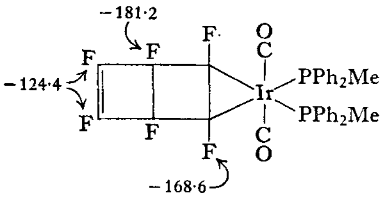

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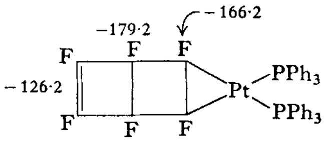
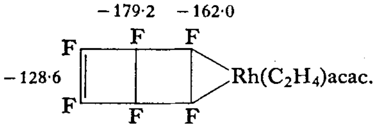


295

301 to **303**. Some consideration is given to the effect of the AB part of the spectrum on an ABX and ABX_3 spin system as found in **303**.



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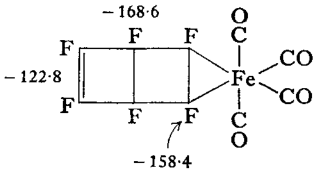

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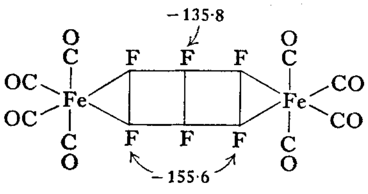

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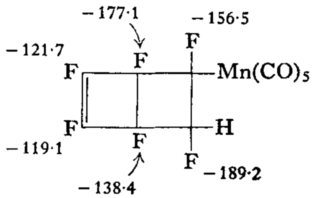

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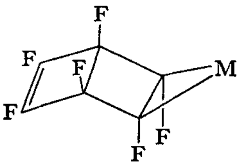
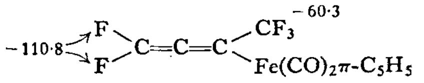


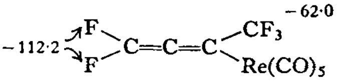
300

Perfluorobut-2-ene reacts with octacarbonyldicobalt to give the complex **304**, this on reaction with triphenylphosphine, triphenylarsine or 1,2-bis(diphenylphosphino)ethane gives the complexes **305** to **306** respectively;



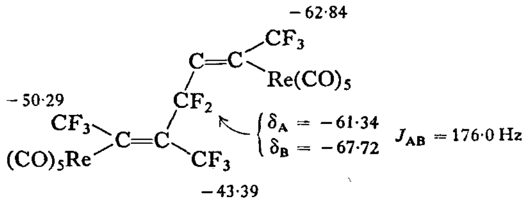
^5J(F–CF_3) = 4·0 Hz

301



^5J(F–CF_3) = 4·0 Hz

302



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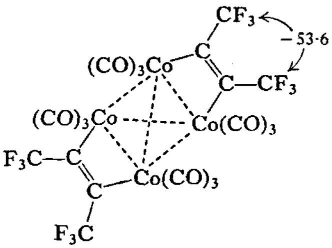

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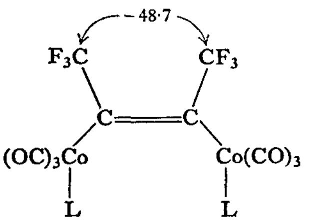
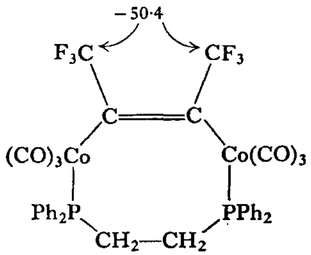


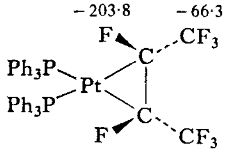
L = PPh_3, $AsPh_3$

305



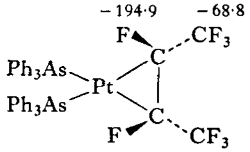
306

the shifts of the CF_3 groups are shown.[252] The reaction of the fluoro-olefin with zero valent complexes of platinum and palladium give complexes as



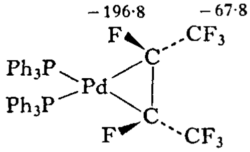
J(Pt–CF_3) = 77·6 Hz
J(P–CF_3) = 9·2 Hz

307



J(Pt–CF_3) = 93·0 Hz

308

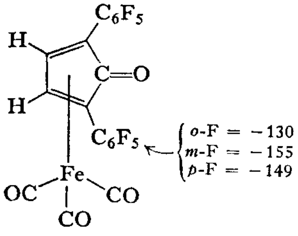


J(P–CF_3) = 9·5 Hz

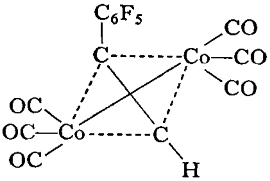
309

shown in **307** to **309**, the coupling of the CF_3 group to platinum and phosphorus can be obtained, but the low solubility of the complex precluded observation of the similar couplings involving the tertiary fluorine.[252]

Pentafluorophenylacetylene and pentacarbonyliron give the bis-2,5-(pentafluorophenyl)cyclopentadienone tricarbonyliron **310** and with octacarbonylcobalt give the complex **311**. Octacarbonylcobalt with excess acetylene gave the new complex **312** and a similar complex was prepared

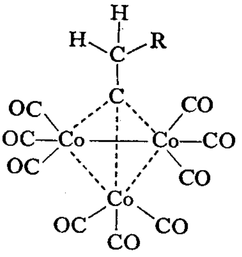


310



Shifts o-F −138, m-F −162, p-F −155

311



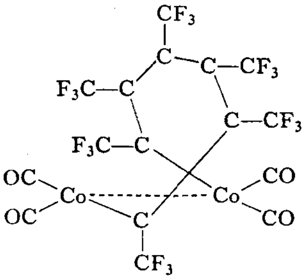
R = C_6F_5 or CF_3

Shifts: (a) C_6F_5 o-F −144, m-F −162, p-F −156

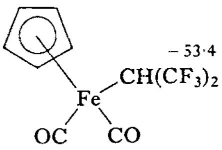
(b) CF_3 −66

312

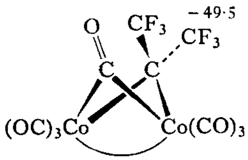
from 3,3,3-trifluoropropyne and the same cobalt carbonyl. Octacarbonyldicobalt and hexafluorobut-2-yne at high temperature gives the complex **313** which showed three sets of CF_3 resonances at −53·2, −56·5 and −60·4, but no precise assignments were given.[253]



313



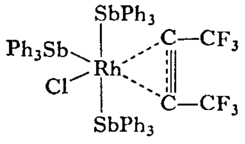
314



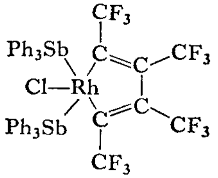
315

Bis(trifluoromethyl)diazomethane reacts with the π-cyclopentadienyldicarbonyliron dimer to give the complex **314** and with octacarbonyldicobalt to give the complex **315**. The diazomethane reacts exothermically with pentacarbonylmanganese hydride and with chlorobis(triethylphosphine) platinum hydride at 120°C to give products in which the $C(CF_3)_2$ group is inserted between the metal and the hydrogen atom as in **314**.[254]

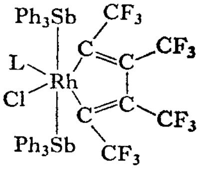
The ^{19}F NMR parameters of a number of new perfluoropropylcobalt derivatives of the type $C_5H_5Co(CO)C_3F_7X$, X = Cl and Br, $(C_5H_5CoC_3F_7SCN)_3$ and $(C_5H_5CoC_3F_7XY)^{\ominus}$, where X = Y = I or CN and X = I, Y = F, all prepared from $C_5H_5Co(CO)C_3F_7I$ have been reported.[255]



316



317



318

Tris(triphenylstilbine)chlororhodium(I) reacts with hexafluorobut-2-yne at room temperature to give the complex shown in **316** in which the two CF_3 groups are nonequivalent (shifts −51·1 and −54·0).[256] At higher temperature the complex **317** is formed (three CF_3 resonances in ratio 1:1:2 at −49·2, −50·3 and −56·8) which readily forms adducts, of form **318**, with carbon monoxide, pyridine and trifluorophosphine.

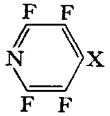
The ^{19}F resonance spectra have, in appropriate cases, been used to supplement the proton magnetic data in the determination of the structure of the rhodium chelates of hexafluoroacetylacetone,[257] and the stereochemistry of the vanadium(III) complexes of β-diketones[258] and β-ketoamines.[259]

The metal carbonyl derivatives react with silver perfluorocarboxylates to afford carboxylate derivatives, e.g. $R_FCO_2M(CO)_5$, where $R_F = CF_3$, C_2F_5, C_3F_7 and M = Mn and Re.[260] The shifts of the groups in the perfluorocarboxylates were: trifluoroacetate CF_3, −74·0 to −76·4; pentafluoropropionate CF_3, −83·3 to −83·7, and CF_2, −118·8 to −120·9; heptafluorobutyrate α-CF_2, −116·2 to −119·5, β-CF_2, −127·0 to −127·7, and CF_3, −81·4 to −81·6. In the perfluoroalkyl cobalt complexes, e.g. $C_2F_5CO_2Co(CO)(C_3F_7)(C_5H_5)$ the α-CF_2 resonance signal of the $Co(C_3F_7)$ group could not be detected, possibly owing to line broadening from coupling to the ^{59}Co nucleus ($I = 7/2$). A similar difficulty was experienced in the perfluorocarboxylates of manganese pentacarbonyl, $R_FCO_2Mn(CO)_5$, as the αCF_2 or CF_3 group of the R_FCO_2 group could not always be detected, although in $R_F = CF_2CF_3$ and $CF_2CF_2CF_3$ the other resonance signals of the β-CF_2 or β or γ-CF_3 groups could be easily seen. The coupling of the α-group to the ^{55}Mn nucleus ($I = 5/2$) may be sufficient to broaden the resonance signal.

The spectra of the iron and ruthenium carbonyl complexes of 2,3,5,6-tetrafluoropyridine have been examined and the shifts are shown in Table XXXVI.[249] There was no appreciable increase in the magnitude of J[F(2)–F(3)] or J[F(2)–F(5)], the *meta* F(2)–F(6) coupling was, however, rather smaller than usual. The formation and ^{19}F spectral parameters of a number of nitrogen heterocyclics have been discussed by Stone *et al.*[261]; the parameters of the 4-metal carbonyl derivatives of 2,3,5,6-tetrafluoropyridine are included in Table XXXVI. The shifts of the metal carbonyl derivatives of

TABLE XXXVI

^{19}F NMR parameters of metal carbonyl derivatives of 2,3,5,6-tetrafluoropyridine



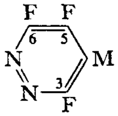
	Chemical shifts, δ		Coupling constants, Hz				
	F(2, 6)	F(3, 5)	*J*(2, 3)	*J*(2, 5)	*J*(2, 6)	*J*(3, 5)	Ref.
$Fe(CO)_2(\pi\text{-}C_5H_5)$	−104·0	−114·2	29·6	26·8	13·6	0·5	249, 261
$Ru(CO)_2(\pi\text{-}C_5H_5)$	−98·7	−111·2	28·9	26·4	11·7	2·5	249
$Mn(CO)_5$	−99·5	−111·8	30·0	24·4	12·7	2·4	261
$Mn(CO)_4PPh_3$	−100·4	−112·2	. .	. .	. .	. .	261
$Re(CO)_5$	−98·0	−110·5	30·3	25·6	13·4	3·8	261

perfluoropyridazine discussed by the same authors[261] are shown in Table XXXVII; similarly it was found that for some complexes of cyanuric fluoride (**319**) the ^{19}F shifts were in the range −41·8 to −42·9.

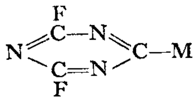
Reaction of 4,4′-octafluorobipyridyl, 4-phenyl-, 4-pentafluorophenyl-, 4-amino- or 4-bromo-tetrafluoropyridine with the ions $[Re(CO)_5]^\ominus$ and $[\pi\text{-}C_5H_5Fe(CO)_2]^\ominus$ results in substitution at the α position to the ring nitrogen atom, or in the 4-aryl derivative at the 4′ position of the aryl

TABLE XXXVII

^{19}F Spectral parameters of the metal carbonyl derivatives of perfluoropyridazine[261]



M	Chemical shifts, δ			Coupling constants, Hz		
	F(3)	F(5)	F(6)	*J*(3, 5)	*J*(3, 6)	*J*(5, 6)
$Fe(CO)_2(\pi\text{-}C_5H_5)$	−55·9	−98·6	−109·2	19·7	32·0	32·0
$Mn(CO)_5$	−53·1	−96·4	−107·1	16·9	31·0	31·0
$Re(CO)_5$	−53·7	−93·8	−106·6	16·9	32·0	32·0
$Mn(CO)_4PPh_3$	−52·5	−95·4	−109·0	16·9	28·2	28·2



M = Mn(CO)$_5$, Re(CO)$_5$,
Mo(CO)$_3$(π-C$_5$H$_5$),
Fe(CO)$_3$(π-C$_5$H$_5$).

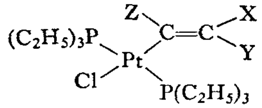
319

ring.[150] As in the case of the aryl derivatives there is a considerable enhancement of the *ortho*-F(2)–F(3) and *para* F(2)–F(5) couplings in pyridines on substitution by a metal carbonyl entity.

The intermediate π-complex was isolated from the reaction of *trans*-[(C$_2$H$_5$)$_3$P]$_2$PtHCl with tetrafluoroethylene; this was an exceptional product as in most other cases fluorovinyl compounds are formed.[262] That the complex was of the π-type was confirmed by ^{19}F NMR as a single resonance signal at −150·7 was observed and there was no indication of coupling to either phosphorus or platinum. In a subsequent paper these same authors reported the NMR data for the fluorovinyl compounds;[263] the ^{19}F parameters of these compounds are shown in Table XXXVIII. It will be observed that the two-bond Pt–^{19}F coupling is fairly large, 479 to 564 Hz; the values of the remaining Pt–F coupling constants are also variable.

TABLE XXXVIII

The NMR parameters of fluorovinylplatinum(II) complexes[263]



			Chemical shift			Coupling constants, Hz		
X	Y	Z	δX	δY	δZ	J_{XY}	J_{XZ}	J_{YZ}
F	F	F	−102·5	−137·2	−155·5[a]	120	35·6	120
F	F	CF$_2$H	−124·9	−126·2	−125·5[b]	26·5	..	..
F	CF$_3$	F	−153·6	−65·3	−86·77[c]	15·3	12·8	9·29
CF$_3$	F	F	−66·3	−175·6	−101·3[d]	13·3	21·3	124
CF$_3$	H	CF$_3$	−57·8	(6·50)	−52·8[e]	9·6	12·2	0

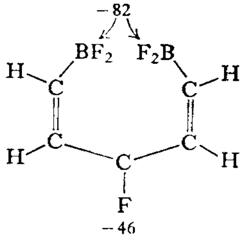
[a] J(Pt–F$_Z$) = 574 Hz; J(Pt–F$_Y$) = 62·4 Hz; J(Pt–F$_X$) = 59·7 Hz.
[b] J(Pt–F$_Z$) = 240 Hz.
[c] J(Pt–F$_Z$) = 479 Hz; J(Pt–CF$_3$) = 13.45 Hz; J(Pt–F$_X$) = 12·8 Hz.
[d] J(Pt–F$_Z$) = 501 Hz; J(Pt–F$_Y$) = 186·1 Hz; J(Pt–CF$_3$) = 5·82.
[e] J(Pt–(CF$_3$)$_Z$) = 142·3 Hz; J(Pt–(CF$_3$)$_X$) = 5·82 Hz.

VI. FLUORINATED DERIVATIVES OF THE ELEMENTS

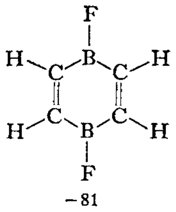
Group III

Boron

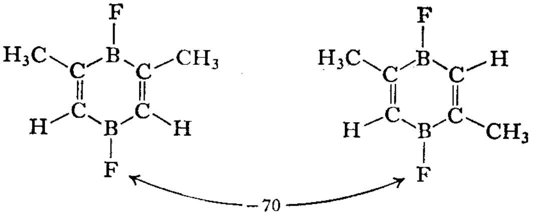
Boron monofluoride reacts with acetylene to afford a polymer and several volatile compounds; the ^{19}F shifts of some of the volatile products are shown



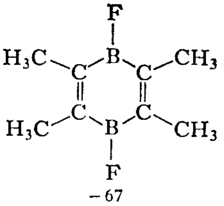
320



321



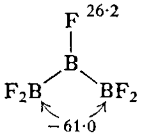
322 **323**



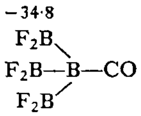
324

in **320** to **324**.[264] Condensation of boron monofluoride with diboron tetrafluoride gave triboron pentafluoride (**325**), while condensation in the presence of carbon monoxide or phosphorus trifluoride gave the complexes (**326** and **327**); the ^{19}F shifts are as shown.[265] Triboron pentafluoride reacts with tetrafluoroethylene to give the bis(boron difluoride) **328**.

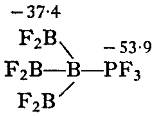
A simple correlation has been found between the ^{19}F chemical shift of the mixed boron halides BF_nZ_{3-n} ($Z = Cl$ or Br, $n = 1, 2$ or 3) and the sum of the electronegativities of the substituents $\Sigma\chi_i$.[266] A plot of $\delta^{19}F$ against $\Sigma\chi_i$ gives a straight line graph (Fig. 7).



325

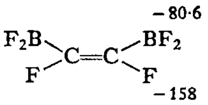


326



$J(^{31}P-^{19}F) = 1350$ Hz

327



328

Laurent *et al.*[267] list the ^{19}F shifts and ^{11}B–^{19}F coupling constants of n-butyl, n-pentyl and n-hexyl-boron difluorides: the shifts were in the range –74·8 to –75·6 and the coupling being 80 ± 5 Hz. The ^{19}F shifts of the trimeric alkoxyboron difluorides $[ROBF_2]_3$ have been measured[268] and were dependent upon the nature of the alkyl group; the ^{11}B–^{19}F coupling was less than 2 Hz.

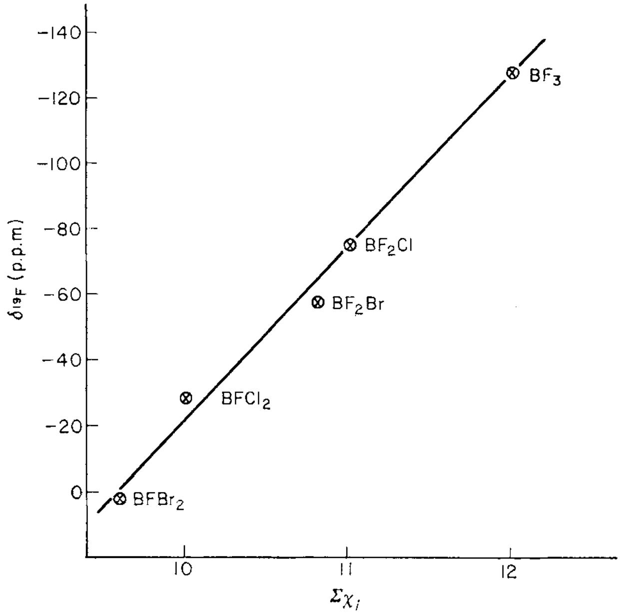


FIG. 7. Relationship of the ^{19}F shifts of mixed boron fluorides with the sum of the electronegativities ($\Sigma\chi_i$) of the halogen atoms. (From Muller, Niecke and Krebs.)[266]

The study of the boron trifluoride complexes of various bases has still continued to attract interest. A detailed study of the boron trifluoride complexes of acetone, methyl ethyl ketone, methyl isopropyl ketone and pinacolone has been made.[269] The following deductions were made: (*a*) only 1:1 complexes were formed which were not appreciably dissociated, (*b*) BF_3 exchange is fast on NMR time-scale but can be slowed at low temperature to give discrete signals of complexed and free BF_3 and (*c*) the loss of the ^{10}B–^{11}B isotope shift (0·066 p.p.m.) at higher temperatures indicated a second exchange process involving exchange of the fluorine atoms. The ^{19}F shifts of the complexes were all about –148. A similar study of a wider range of ketones showed,[270] however, that the variation of the ^{19}F shifts was meaningful and was related to the steric requirements of the complexes. The correlation of both the carbonyl frequency shifts and the

B–O stretching frequencies of the complexes with the ^{19}F shifts was discussed.

The double complexes of ureas, $[BF_3(MeNH)_2CO]_2CdCl_2$, $[BF_3(PhNH)_2CO]_4NiBr_2$ and $[BF_3(PhNH)_2CS_2]_4NiBr_2$, all showed two ^{19}F resonance signals, a broad peak at $-148{\cdot}5 \pm 5$ and a sharp peak at $-150{\cdot}5 \pm 1$.[271] As the relative intensities of the two peaks were both solvent and temperature dependent the authors have tentatively suggested that the two signals arise from associated and unassociated species.

It was demonstrated, by low temperature ^{19}F NMR, that boron trifluoride-monohydrate is formed in acetone solution. If the concentration of water is less than that of boron trifluoride then ^{11}B–^{19}F coupling is observed; with water in excess no coupling is seen due to rapid proton exchange.[272]

Group IV

Silicon

Coyle *et al.*[273] have measured the ^{19}F shifts and the ^{29}Si–^{19}F coupling contrasts in a range of fluorosilanes. The shifts for silicon tetrafluoride in different solvents were compared to that in the gaseous phase; there was considerable variation in the δ values. The shifts of the other compounds were measured with respect to SiF_4, both as an internal and an external reference. There was, however, considerable deviation between the two sets of values, sometimes as much as 10 to 14 p.p.m. The overall values of ^1J(Si–F) ranged from 167·6 Hz in Si_2OF_6 to 384·9 Hz in Si_2Cl_5F. The effect of substituents on both the ^{19}F shifts and ^{29}Si–^{19}F coupling constants were considered in detail. The spectrum of pentafluorophenyl trifluorosilane has also been considered in the same paper. The —SiF_3 group couples to the *ortho*-ring fluorine atoms $J(SiF_3\text{–}o\text{F}) = 8$ Hz and, from the magnitude of the *ortho–para* F–F coupling, these authors suggest that the —SiF_3 group acts as a strong π-acceptor.

The ^{19}F shifts and the H–F and Si–F coupling constants in six methylfluorosilane derivatives have been discussed by Frankiss.[274] The fluorine shifts of the compounds examined lie within a remarkably narrow range ~40 p.p.m. and there is a similar lack of variation in ^{29}Si–^{19}F coupling constants 280 ± 13 Hz. The author compares both the *vic* H–F and geminal H–F coupling in these compounds with those of the corresponding methane derivatives; in general the *vic* H–F coupling of the silanes is very much smaller (4 to 8 Hz) than that of the methanes (12 to 25 Hz). The ^{19}F shift for the simple compounds, $(CH_3)_nSiF_{4-n}$ have also been measured independently[275] and the values are basically in agreement with those given above.[274]

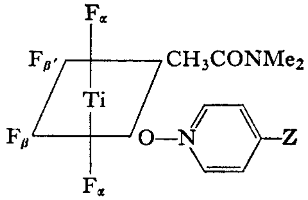
The spectrum of the $SiF_4.(\alpha,\alpha'$-dipyridyl) complex displayed[276] an A_2X_2 spectrum, the shifts being −123·5 and −145·9 with J(F–F) = 12·0 Hz, confirming the *cis*-structure of the complex.

Germanium

The complexes of germanium tetrafluoride with 6-hexanolactam, δ-valerolactam and 2,6-dimethyl-γ-pyrene are of the form $GeF_4.2L$.[276] The ^{19}F shift of GeF_4 in chloroacetonitrile at −11°C was at −120·2 but at −30°C the resonance was shifted downfield to −80·2 indicating that complex formation between GeF_4 and the solvent occurred at this temperature. The complexes all displayed broad resonances at room temperature but at lower temperatures two triplets of an A_2X_2 spectrum appeared corresponding to the *cis*-isomer, clearly at room temperature exchange occurs. Similar results for the tetramethylurea complex were obtained but tetramethylenediamine and α,α′-bipyridyl only formed 1:1 complexes the ^{19}F spectra of which showed A_2X_2 spectra at room temperature as expected for the *cis* complexes of bidentate ligands. In all complexes the F–F couplings were in the range 50 to 66 Hz. The ^{19}F spectrum of $GeF_4.2L$, where L = valerolactam, in aqueous solution was of an AX_4 system, indicating the possible formation of the $[GeF_5(OH)]^{2\ominus}$ species.

Titanium

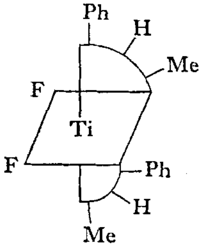
The stereochemistry of the complexes of titanium tetrafluoride have been extensively studied using ^{19}F NMR. From the ^{19}F spectrum it was shown that the complex $TiF_4.2D$ (D = dimethylacetamide) underwent exchange on addition of a 4-substituted pyridine oxide (D′) to give the mixed complex $TiF_4.DD'$ (**329**).[277] The variation of the shifts of F_α, F_β and $F_{\beta'}$ were considered to be dependent upon the nature of the 4-substituent (Z). There was no variation within the series of the three F–F coupling constants: $\alpha\beta = 39$, $\alpha\beta' = 35$ and $\beta\beta' = 48$ Hz. The factors which determine the magnitude of the F–F coupling constants have, however, been further studied.[278] In a series of complexes of the type $TiF_4.2D$ the nature of D has been varied from pyridine oxides, alcohols, amides and ureas and the



329

total range of the F–F coupling was only 34 to 41 Hz. It was concluded that the F–F coupling occurred via a "through-space" mechanism; the apparent lack of through-bond coupling being ascribed to the high ionic character of the Ti–F bond. The temperature dependence of the *cis* complex $TiF_4.2D$ has been further investigated,[279] and as the temperature is raised the two triplets of F_α and F_β broaden and then collapse to a single resonance signal. The coalescence temperature was determined as a function of concentration of D (diethylformamide) in acetonitrile solution. The mechanism of the exchange process was discussed.

The variable temperature ^{19}F spectra have also been used to study the stereochemistry of the difluorobis(1-phenyl-1,3-butanediono)titanium-(IV).[280] At room temperature a single line is observed at δ 232·8, while at –85°C an AB spectrum, together with two other singlet lines, are observed.



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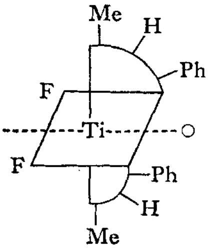

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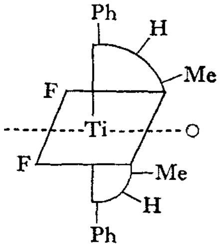


332

The AB spectrum is assigned to the two fluorine atoms in the *cis,cis,cis*-isomer **330**; the other two lines are assigned to the *cis,cis,trans*- and *cis,trans, cis*-isomers **331** and **332** respectively. These results were confirmed by variable temperature proton studies.

Group V

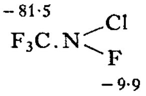
Nitrogen

The amount of work concerning the fluoramino and fluorimine groups has increased very significantly over the past two years.

Fluorination of cyanogen chloride afforded a number of relatively simple fluorinated products;[281] the shifts of these compounds are shown in **333** to **336**. Trifluoroamine oxide, F_3NO, has been fully characterized[282] and over the temperature range of –110 to –65°C a 1:1:1 triplet was observed at δ 363 $\pm$ 2 with $^1J(^{14}N–^{19}F)$ of 136 Hz. Certain aspects of the chemistry of difluoraminocarbonyl fluoride (**337**) and the preparation of perfluorourea (**338**) and difluoraminocarbonyl chloride (**339**) have been discussed.[283] The shift of **337** measured[284] using internal CCl_3F has been reported as being δ NF_2 = 41·8, a slightly different value to that found using an external

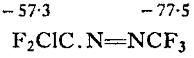
$F_2ClC.NF_2$

333



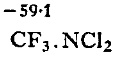
$F_3C.NClF$

334



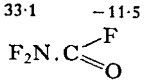
$F_2ClC.N{=}NCF_3$

335



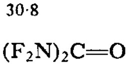
$CF_3.NCl_2$

336



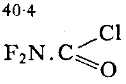
^3J(F–F) = 19 Hz

337



$(F_2N)_2C{=}O$

338



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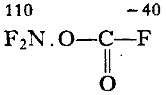
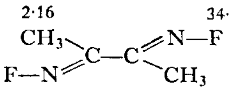


^1J(N–F) = 158 Hz
J(F–F) ≈ 3 Hz

340

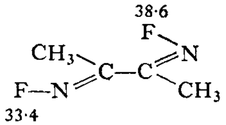
standard.[283] The spectrum of *N*,*N*-difluoro-*O*-fluorocarbonylhydroxylamine (**340**) has also been discussed.[285]

Three isomers of 2,3-bis(*N*-fluorimino)butane have been isolated and characterized[286] as being the *syn*,*syn*-, *syn*,*anti*- and *anti*,*anti*-isomers (**341** to **343**) respectively. The ^1H–^{19}F coupling could be obtained from the ^1H spectra but not from the ^{19}F spectra, due to the quadrupole broadening from the nitrogen.



$J(^1H–^{19}F)$ = 2·5 Hz

341



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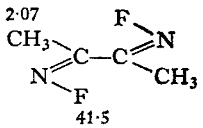
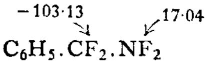


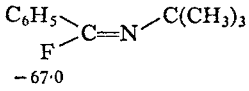
$J(^1H–^{19}F)$ = 1·75 Hz

343



$C_6H_5.CF_2.NF_2$

344



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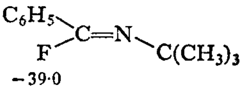
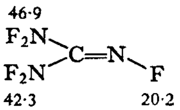


346

Fluorination of benzilidene-t-butylamine afforded α,α-difluorobenzodifluoramine (**344**) and the *syn*- and *anti*-α-fluoro-benzilidene-t-butylamine (**345** and **346**).[36] The *anti*-isomer could not be isolated pure but the compound was identified in the mixture by ^{19}F NMR. Using mild conditions of fluorination an α,α-difluoramine, $C_6H_5CF_2NFR$, was isolated which was stable when pure. These compounds were obtained with a variety of alkyl groups R = t-Bu, *iso*-Bu and *iso*-Pr and the shift of the α-CF_2 group was in the range −87·3 to −97·0 and of the —NF group −73·0 to −105·2, the CF_2—NF coupling being rather variable, 8 to 23 Hz. In those cases where the alkyl group R contained an asymmetric centre, e.g. R = *sec*-Bu, 2-pentyl and 1-phenylethyl, the two fluorine atoms of the CF_2 were non-equivalent even though 2-bonds removed from the asymmetric centre. The shifts of the CF_2 group in these cases fell into the ranges −82 to −87 and −93 to −96; the shift of the NF group was slightly larger to that above, namely −107 to −110. The value of the F_A–F_B *gem* coupling constant was 190 to 192 Hz and that of F_A to NF was 18 to 20 Hz; that of F_B to NF was variable, being less than 1 Hz for R = *sec*-butyl and 2-pentyl but was 10 Hz for 1-phenylethyl. In all cases there was an unusually large three-bond F–H coupling, between the NF and the α-CH group of R, of 31 to 43 Hz.



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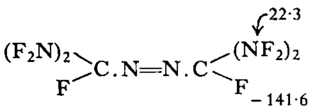

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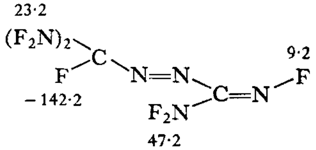

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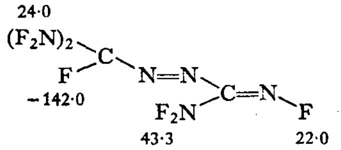

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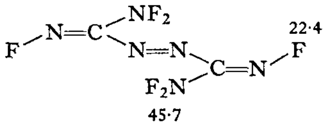
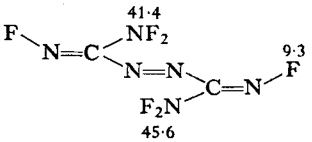


351

trans-Stilbene and tetrafluorohydrazine give a mixture of the *meso*- and DL-α,α′-bis(difluoramino)dibenzyl;[287] the spectra of the two isomers are discussed in some detail. Dehydrofluorination gave the α,α′-bis(fluorimino)-dibenzyl as a mixture of *syn*- and *anti*-isomers and because of the similarity of the ^{19}F shifts no further assignments could be made.

The reaction of difluoramine with acetals has provided a new synthetic route to the α-difluoramino ethers. For example, tetramethoxybut-2-ene afforded the 1,4-bis(difluoramino)-1,4-dimethoxybut-2-ene, F_2NCH



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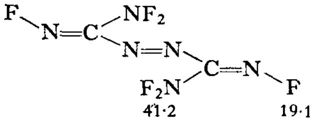

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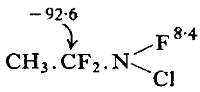
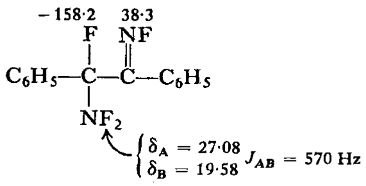


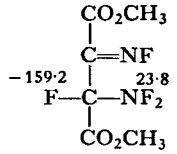
$J(CH_3–CF_2) = 16$ Hz

354


$C_6H_5\text{—}CF(NF_2)\text{—}C(=NF)\text{—}C_6H_5$

$J(F_A\text{-}CF) = J(F_B\text{-}CF) = 8{\cdot}0$ Hz
$J[F_A\text{-}(C{=}NF)] = 5{\cdot}0$ Hz
$J[CF\text{-}(C{=}NF)] = 4{\cdot}0$ Hz

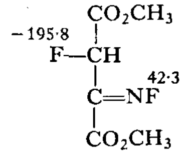
355


$CH_3O_2C\text{—}C(=NF)\text{—}CF(NF_2)\text{—}CO_2CH_3$

356

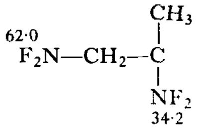
$(OCH_3)CH{=}CHCH(OCH_3)NF_2$. The shift of the —$NF_2$ group was 25·5 and the vicinal F–H coupling was 18·5 Hz.[288]

Pentafluoroguanidine (**347**) has been prepared by direct fluorination by heating guanidine hydrofluoride with excess sodium fluoride in a stream of fluorine; the ^{19}F assignments were as shown.[289] Using the same method for fluorination a series of highly fluorinated azo compounds have been prepared,[290] these compounds are shown in **348** to **353**, together with the chemical shifts. The assignments were made by comparison with the


$CH_3O_2C\text{—}CHF\text{—}C(=NF)\text{—}CO_2CH_3$

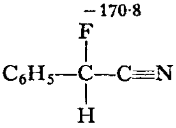
$^2J(H\text{-}F) = 40$ Hz

357


$F_2N\text{—}CH_2\text{—}C(CH_3)\text{—}NF_2$

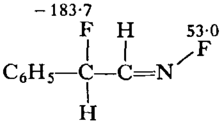
$^3J(F_2N\text{-}CH_2) = 24$ Hz

358


$C_6H_5\text{—}CHF\text{—}C{\equiv}N$

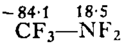
$^2J(F\text{-}H) = 48$ Hz

359

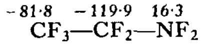

$C_6H_5\text{—}CHF\text{—}CH{=}NF$

$^3J(CH\text{-}NF) = 66$ Hz
$^2J(F\text{-}H) = 48$ Hz
$^3J(CF\text{-}CH) = 4$ Hz

360

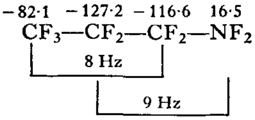

$CF_3\text{—}NF_2$

361

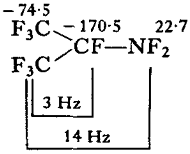

$CF_3\text{—}CF_2\text{—}NF_2$

$^4J(CF_3\text{-}NF_2) = 10$ Hz

362


$CF_3\text{—}CF_2\text{—}CF_2\text{—}NF_2$

363


$(F_3C)_2CF\text{—}NF_2$

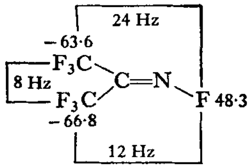
364

published data for **347** since in this compound the shift of the $=N-F$ group *syn*- to a difluoramino group could be obtained as being ~20. Thus, together with the data from **348** to **353**, the shift of the $=N-F$ group is ~20 when *syn*- and ~10 when *anti*- to the $-NF_2$ group.

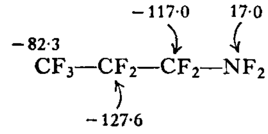
Acetonitrile has been chlorofluorinated using chlorine(V) fluoride (ClF_5), to give *N*-chloro-*N*-fluoro-1,1-difluoroethylamine (**354**) as the major product.[291]

Tetrafluorohydrazine reacts with acetylenes to afford α-fluoro-α-difluoramino fluorimines, which appears to be formed due to the rearrangement of the initial adduct, i.e. α,β-bis(difluoramino)ethylenes.[292] Tolane and N_2F_4 gave the product **355**, with dimethyl acetylenedicarboxylate the major product was **356** and a minor product (**357**) was also isolated; the spectrum of **355** was examined in some detail.

Isopropenylacetylene and the N_2F_4 gave a mixture of the olefin adduct **358** and rearranged 1:4 adduct, the latter consisting of a mixture of *cis* and *trans* isomers (the precise assignments were not given for the two adducts). β-Bromostyrene and N_2F_4 gave three products, 1-fluorobenzylnitrile (**359**), a fluorimine derivative (**360**) and dibromo(difluoramino)phenylethane.

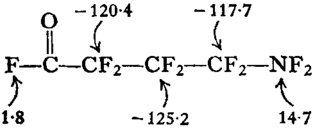


365



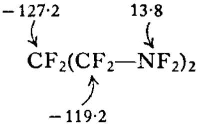
$CF_3-CF_2-CF_2-NF_2$

366



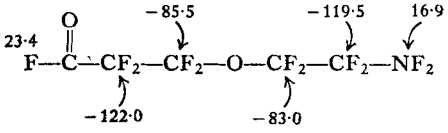
$F-C(=O)-CF_2-CF_2-CF_2-NF_2$

367



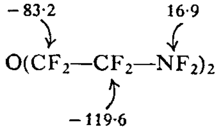
$CF_2(CF_2-NF_2)_2$

368



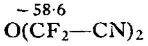
$F-C(=O)-CF_2-CF_2-O-CF_2-CF_2-NF_2$

369



$O(CF_2-CF_2-NF_2)_2$

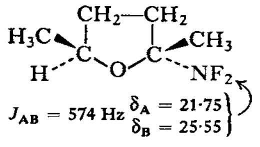
370



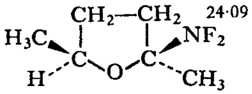
$O(CF_2-CN)_2$

371

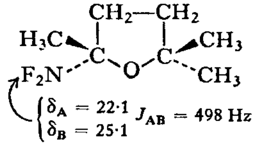
The direct fluorination of nitriles has afforded the perfluoroalkyl difluoramines (**361** to **363**).[293] The corresponding *N*,*N*-difluoroperfluoroisopropylamine (**364**) was obtained by fluorination of 2-imino hexafluoropropane, $(CF_3)_2C{=}NH$; partial fluorination gave the *N*-fluorimino derivative (**365**). Photolysis of perfluoroacyl fluorides in the presence of tetrafluorohydrazine have also yielded *N*,*N*-difluoramine derivatives and the shifts of the derivatives formed are shown in **366** to **370**; dehydrofluorination of **370** using triphenylphosphine gave the dinitrile **371**.[294]



372



372a



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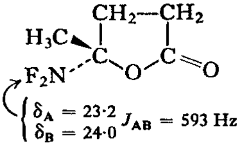

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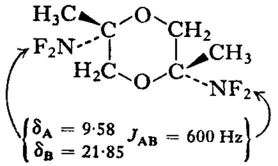

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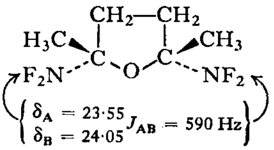

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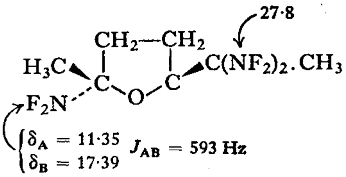
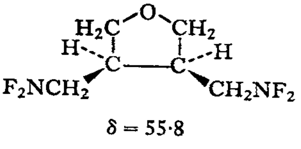


377

Difluoramine reacts with ketones and aldehydes[295] and diallyl ether[410] to afford the bis(difluoramino) compounds; the compounds with carbonium ion precursors in suitable positions gave difluoramino-lactones, tetrahydrofurans and dioxanes. The shifts of the difluoramino groups in alkanes are shown in Table XXXIX while the data of the cyclic compounds are shown in **372** to **378**. Difluoramine also reacts with acetylenes in the presence



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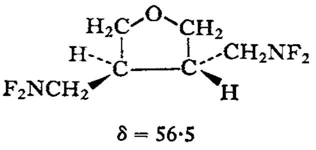
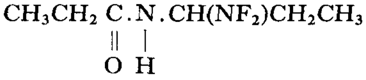
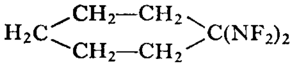
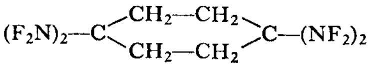
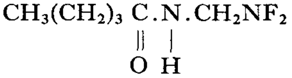
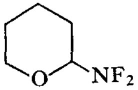
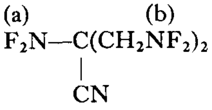
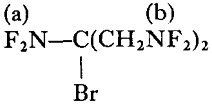
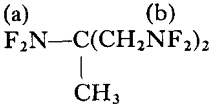
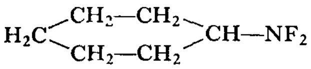
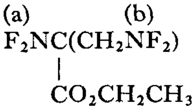
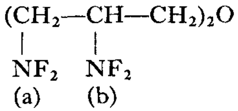


378b

TABLE XXXIX

^{19}F shifts of the NF_2 group in *N*,*N*-difluoroamino alkanes

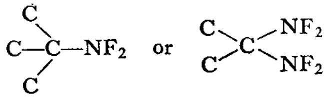
	δ	Ref.		δ	Ref.
$(CH_3)_2C(NF_2)_2$	27·9	295	$CH_3(CH_2)_2CF(NF_2)CH_2CH_3$	16·7	296
$CH_3C(NF_2)_2(CH_2)_5CH_3$	26·69	295	 $CH_3CH_2\underset{\overset{\Vert}{O}}{C}.\underset{\overset{\vert}{H}}{N}.CH(NF_2)CH_2CH_3$	30·5	296
	22·79	295	$CH_3(CH_2)_3CF(NF_2)CH_3$	19·1	296
	25·22	295	 $CH_3(CH_2)_3\underset{\overset{\Vert}{O}}{C}.\underset{\overset{\vert}{H}}{N}.CH_2NF_2$	40·82	296
$CH_3C(NF_2)_2CH_2Cl$	27·8	295	$CH_3(CH_2)_2C(NF_2)_2CH_2CH_3$	28·5	296
$CH_3C(NF_2)_2(CH_2)_3CO_2Et$	28·4	295	$CH_3(CH_2)_3C(NF_2)_2CH_3$	27·6	296
$CH_3C(NF_2)_2(CH_2)_3NO_2$	26·94	295	$(C_6H_5)_3C.NF_2$	32·4	298
$CH_3CH_2CH(NF_2)_2$	36·3	295	$(C_6H_5)_2CHNF_2$	48·6	298
$CH_3C(NF_2)_2CH_2CH_2C(NF_2)_2CH_3$	26·6	295	$C_6H_5CCl_2NF_2$	43·5	298
$F_2N.CH_2.CH_2.CO_2Me$	53·64	295	$(CH_3)_3C.NF_2$	27·1	298
$F_2N.CH_2.CH_2.CO_2H$	53·15	295	$C_2H_5C(CH_3)_2NF_2$	25·1	298
$CH_2{=}CH{-}CH_2NF_2$	53·7	297	$(CH_3O)_2CH.NF_2$	23	298
$CH_2{=}C(CO_2CH_2CH_3)CH_2NF_2$	54·25	297	$CH_3.C(OCH_3)_2.NF_2$	18·7	298
$CH_2{=}C(CN)CH_2NF_2$	54·02	297		28·1	298

$CH_2{=}CBrCH_2NF_2$	53·62	297
$CH_2{=}C(CH_3)CH_2NF_2$	53·91	297
$CH_2{=}C(C_6H_5)CH_2NF_2$	54·63	297
 $\overset{(a)}{F_2N}-\underset{CN}{C}(CH_2\overset{(b)}{NF_2})_2$	34·61(a) 59·62(b)	297
 $\overset{(a)}{F_2N}-\underset{Br}{C}(CH_2\overset{(b)}{NF_2})_2$	34·86(a) 56·04(b)	297
 $\overset{(a)}{F_2N}-\underset{CH_3}{C}(CH_2\overset{(b)}{NF_2})_2$	34·21(a) 56·18(b)	297
	41·1	299
$F_2NCH_2(CH_2)_4CH_2NF_2$	55·4	299
$CH_3CH_2CH_2CH_2NF_2$	54·6	299
$(CH_3)_3C.NF_2$	27·2	299
$\overset{(a)}{F_2N}.CH(CH_2\overset{(b)}{NF_2})_2$	38·4(a) 55·05(b)	297
 $\overset{(a)}{F_2N}\underset{CO_2CH_2CH_3}{C}(CH_2\overset{(b)}{NF_2})$	33·45(a) 60·0(b)	297
 $(\underset{\underset{(a)}{NF_2}}{CH_2}-\underset{\underset{(b)}{NF_2}}{CH}-CH_2)_2O$	56·8(a) 42·0(b)	410

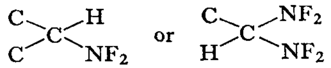
of boron trifluoride–phosphoric acid complex or sulphuric acid to give difluoramino derivatives, the shifts of the —NF_2 groups are included in Table XXXIX.[296] *N*,*N*-Difluoro-amines have also been prepared by the interaction of difluoramine with carbonium ions, the shifts of the compounds obtained are also shown in Table XXXIX.[298]

Tetrafluorohydrazine and cyclic olefins give normal adducts as major products but α-substitution also occurs to give the mono(difluoramines);[300] the shifts of the —NF_2 group are not shown in Table XXXIX as it was not clear in the paper whether AB or the ABX analysis had been carried out.

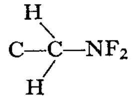
It is now possible to give tentative chemical shift ranges for the —NF_2 group in different environments—



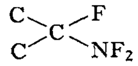
δ 22 to δ 33



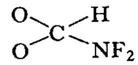
δ 30 to δ 43



δ 40 to δ 53



δ 16 to δ 20

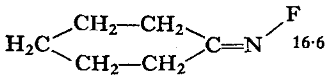


δ 23 to δ 28

Tetrafluorohydrazine reacts with halogenated olefins, tetrafluorobutadiene, 2,5-dimethylfuran and norbornadiene to give a variety of products depending upon the substrate.[301] Reaction of the difluoramino radical and allylic bromides and iodides results in elimination of the halogen with the formation of allylic difluoramine. Further reaction of the allylic difluoramine with tetrafluorohydrazine affords the 1,2,3-tris(difluoramines).[297] The ^{19}F shifts of the —NF_2 groups in the allylic compounds are shown in Table XXXIX.

Alkylamines have been fluorinated in bicarbonate buffered solution to give the *N*,*N*-difluoroalkylamines; the shifts of the —NF_2 groups are also included in Table XXXIX.[299] Dehydrofluorination of the *N*,*N*-difluorocyclohexylamine gave the *N*-fluorocyclohexylimine (**379**).

Nitroanilines are fluorinated in liquid hydrogen fluoride and acetonitrile to afford the *N*,*N*-difluoroanilines.[302] While the general range of ^{19}F shifts



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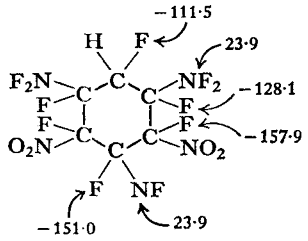

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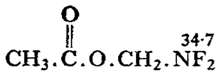
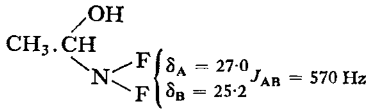


$CH_3.C(=O).O.CH_2.NF_2$ 34·7

381

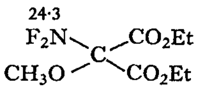


$^3J(H\text{-}F_A) = 16$ Hz
$^3J(H\text{-}F_B) = 24$ Hz

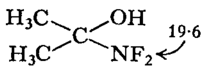
382

29·9
$HOCH_2.NF_2$

383



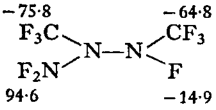
384



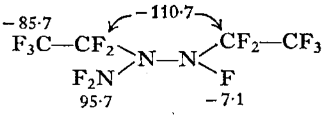
385

31·3
$O(CH_2.NF_2)_2$

386



387



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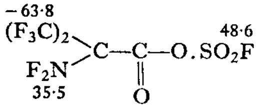

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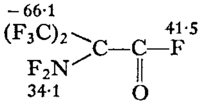

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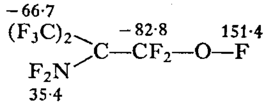


391

of the difluoramino group was 60 to 68 the shift was found to be dependent upon the nature of the two *ortho* substituents—

two *ortho*-nitro groups	$\delta = 61{\cdot}3$ to 63·5
ortho-F and *ortho*-NO_2	62·6 to 63·4
ortho-H and *ortho*-NO_2	65·8 to 68·3

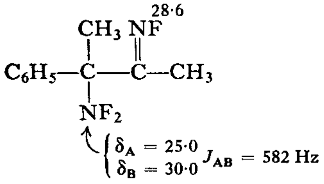
The NF_2 group also couples to *ortho*-fluorine atoms (~21 Hz) and to *ortho*-hydrogen atoms (~2 Hz). Fluorination of 1,3,5-triamino-2,4-dinitrobenzene gave the expected tris(difluoramino)dinitrobenzene but in addition afforded the 1,3,5-tris(difluoramino)-2,4-dinitro-1,2,3,4,5,6-hexafluorocyclohexane (**380**).

Difluoramine and aliphatic aldehydes and ketones give the α-difluoraminocarbinols;[303] these carbinols react with anhydrides to form amino carboxylates. The shifts of the compounds formed are shown in **381** to **386**. The 2-difluoraminopropan-2-ol (**385**) readily dissociates above 9°C to give acetone and difluoramine.

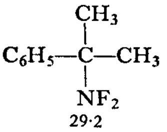
UV irradiation of tetrafluorohydrazine with the perfluoroazoalkanes gives the *N*-difluoramino substituted hydrazines; those from hexafluoroazomethane and decafluorazoethane are shown in **387** and **388**. Tetrafluorohydrazine and difluoraminofluorosulphate add across the carbon-carbon double bond of bis(trifluoromethyl)ketene;[304] the shifts of the products **389** to **391** were given.

A number of mixed difluoramino and fluorimino compounds have been prepared, which undergo rearrangement in fluorosulphuric acid and the shifts are shown in **392** and **393**.

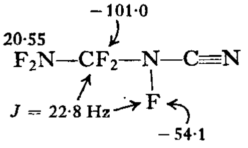
The direct fluorination of sodium dicyanamide, $NaN(CN)_2$, gave the compound **394** in over 90% yield.[305] Fluorination of cyanoguanidine, $H_2NC(NH)NHC{\equiv}N$, gave a number of products some of which were previously known. Two, 1-[(difluoramino)difluoromethyl]-1,2,3,3-tetrafluoroguanidine (**395**) and *N*-[(difluoramino)difluoromethyl] -*N*,*N'N'*, *N''*,*N''*-1-hexafluoromethane triamine (**396**) were new; the shifts of these compounds, which formed the basis of identification, are as shown.



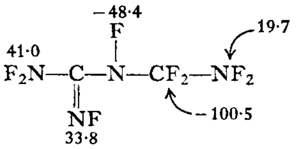
392



393

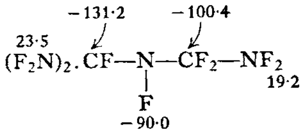


394



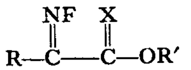
$^3J(CF_2\text{-}NF) = 22{\cdot}8$ Hz

395



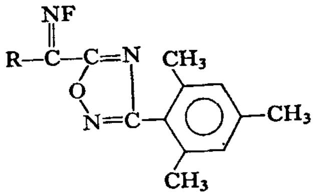
396

N-fluoriminonitriles can be converted into methyl α-fluoriminoimidates (**397**, X = NH, R′ = CH_3) and α-fluorimino esters (**397**, X = O); the shifts of the =NF group are shown in Table XL.[306] The *N*-fluoriminonitriles and 2,4,6-trimethylbenzonitrile oxide gave the 3-mesityl-5(α-fluorimino)-1,2,4-oxadiazoles (**398**) and the ^{19}F shifts of the =N—F group occur in the range 42 to 43 for R = C_6H_5, 4-ClC_6H_4 and Buⁿ while for R = OBuⁿ



$R{-}\overset{\overset{NF}{\|}}{C}{-}\overset{\overset{X}{\|}}{C}{-}OR'$

397



398

two isomers, *syn* and *anti*, were detected with $\delta = -35{\cdot}6$ and $-24{\cdot}4$ respectively.

Perfluoro-α,ω-bisazomethines isomerise in the presence of fluoride ions to give terminal trifluoromethylbisazomethines, the geometrical isomers of

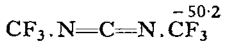
TABLE XL

^{19}F shifts of the fluorimino group in α-fluoriminoimidates and α-fluorimino esters[306] (397)

R	R′	X	δ(=NF)
C_6H_5	CH_3	NH	27·3
4-ClC_6H_4	CH_3	NH	28·3
BuO	CH_3	NH	−47·7 (*syn*, i.e. *cis* F and O) −38·2 (*trans*)
C_6H_5	CH_3	O	27·7
C_6H_5	C_2H_5	O	28·2
4-ClC_6H_4	CH_3	O	30·0
4-ClC_6H_4	C_2H_5	O	29·0
BuO	CH_3	O	−48·4 (*syn*) −30·6 (*anti*)

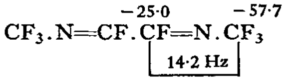
which were differentiated by the ^{19}F spectra.[159] The ^{19}F parameters are shown in **399** to **406**.

Photolysis of perfluoroacyl fluorides in the presence of perfluoro-2,3-diazabut-1,3-diene gave trifluoromethyl isocyanate, carbonyl fluoride and the corresponding perfluoroazomethine. The shifts of compounds obtained are shown in **407** to **410**.[307] The spectrum of perfluoro-3-methyl-2-azabut-1-ene was found to be temperature dependent and at room temperature (25°C) the $N{=}CF_2$ resonance was two broad peaks and not the usual characteristic AB spectrum. At higher temperature (78°C) the two peaks coallesced into one, fairly sharp, peak while at −63°C a clear AB spectrum was observed. This behaviour was attributed to the stereoisomerization about the C=N bond and the data shown in **411** are for the spectrum at −63°C; this had previously been reported.[308]



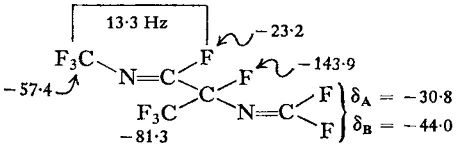
$CF_3.N{=}C{=}N.CF_3$

399

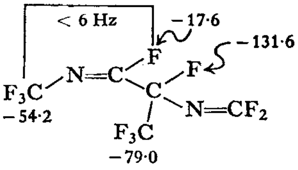


$CF_3.N{=}CF.CF{=}N.CF_3$

400



401



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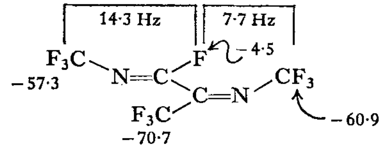

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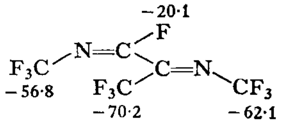

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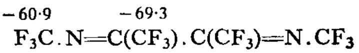
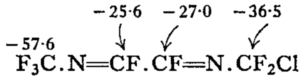


$F_3C.N{=}C(CF_3).C(CF_3){=}N.CF_3$

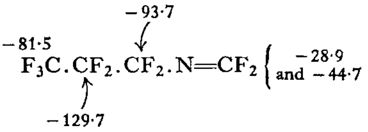
405



$F_3C.N{=}CF.CF{=}N.CF_2Cl$

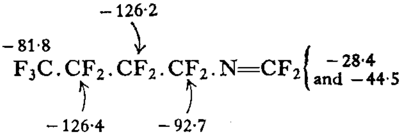
406

Bis(trifluoromethyl)diazomethane, $(CF_3)_2C{=}N{=}N$, reacts with cyclohexane and adamantane to give both an azo compound (**412**) and a hydrazone (**413**) (an alkane derivative is also formed, see p. 265).[13] Bis(trifluoromethyl) diazirine, $(CF_3)_2\overline{C{-}N{=}N}$, also reacts with cyclohexane to yield *N*-cyclohexylhexafluoroisopropylidenimine (**414**); the temperature dependence of the spectrum was reported. Neopentane and n-butane react similarily to give the amines (**415**) with shifts of the CF_3 groups very similar to those of



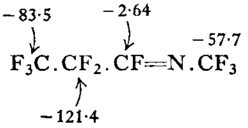
$F_3C.CF_2.CF_2.N{=}CF_2$

407



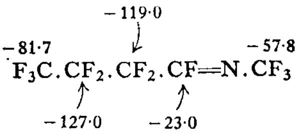
$F_3C.CF_2.CF_2.CF_2.N{=}CF_2$

408



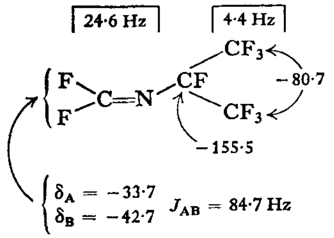
$F_3C.CF_2.CF{=}N.CF_3$

409

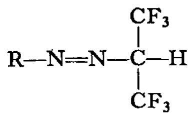


$F_3C.CF_2.CF_2.CF{=}N.CF_3$

410



411



$R{-}N{=}N{-}C(CF_3)_2{-}H$

a. $R = C_6H_{11}—$, b. $R = C_{10}H_{15}—$
$\delta(CF_3) = -71$ (a) and $-73{\cdot}3$ (b)

412

$R—NH—N{=}C(CF_3)_2$
a. $R = C_6H_{11}—$; b. $R = C_{10}H_{15}—$
$\delta(CF_3) = -67{\cdot}2$ (a) and $-64{\cdot}6$ (b)

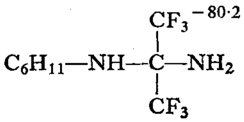
413

$C_6H_{11}—N{=}C(CF_3)_2$
$\delta(CF_3)$; 25° $-64{\cdot}2$ and $-71{\cdot}2$
$^4J(F–F) = 7{\cdot}5$ Hz
150° $-67{\cdot}8$

414

$R—N{=}C(CF_3)_2$
a. $R = (CH_3)_3C.CH_2—$
b. $R = CH_3.CH_2.CH.CH_3$
c. $R = CH_3.CH_2.CH_2.CH_2—$

415

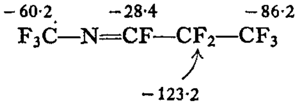


$C_6H_{11}—NH—C(CF_3)_2—NH_2$

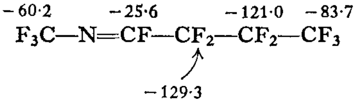
416

414; there was, however, some alkyl rearrangement in the case of n-butane to give the isomer **415b**. Either reaction of hexafluoroacetone imine with cyclohexylamine or reaction of **414** with ammonia afforded the diamine (**416**).

The ^{19}F data of two perofluoro-2-azapent-2-enes (**417** and **418**) and a perfluoro-2-azahex-2-ene (**419**), obtained by pyrolysis of perfluoroamino-cyclobutanes, have been reported. Although the data for **417** has previously been reported,^{310} it has, as in the paper, been included for purposes of comparison of the shifts of the three compounds. The —CF=N group is characterized by the very low field shift and must be one of the lowest field shifts recorded for a fluorine atom attached to carbon.



417



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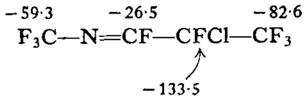
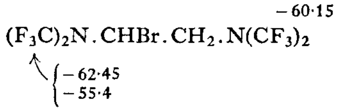
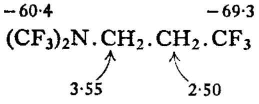


419



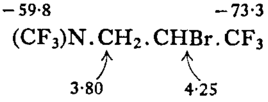
420

The shift of the *N*-trifluoromethyl groups in a series of vinyl- and haloethyl- amines all fall in the range –56·5 to –60·5.[309] The only compound which warrants further mention is that of 1,2-di(bistrifluoromethylamino)-1-bromoethane (**420**) as the two CF_3 groups, of the bistrifluoromethylamino entity, attached to the asymmetric centre are non-equivalent. A similar non-equivalence of the CF_3 groups of the bistrifluoromethylamino group has been reported for other derivatives, although in the 1-bistrifluoromethylamino-1,2-dibromoethane (**423**) only a single, but broad, CF_3 resonance signal was observed.[63] The shifts of these halogeno- ethyl and propyl bistrifluoromethylamines are shown in **421** to **425**. In all these cases, the non-equivalence of the trifluoromethyl groups arises because of the slow inversion of the nitrogen atom adjacent to the asymmetric centre.



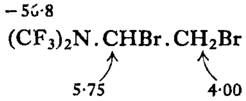
$\overset{-60\cdot4}{(CF_3)_2N}.\underset{3\cdot55}{CH_2}.\underset{2\cdot50}{CH_2}.\overset{-69\cdot3}{CF_3}$

421



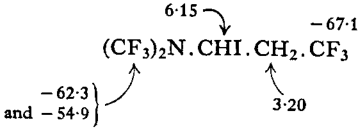
$\overset{-59\cdot8}{(CF_3)N}.\underset{3\cdot80}{CH_2}.\underset{4\cdot25}{CHBr}.\overset{-73\cdot3}{CF_3}$

422



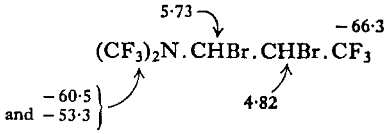
$\overset{-56\cdot8}{(CF_3)_2N}.\underset{5\cdot75}{CHBr}.\underset{4\cdot00}{CH_2Br}$

423



$\underset{-62\cdot3 \text{ and } -54\cdot9}{(CF_3)_2N}.\overset{6\cdot15}{CHI}.\underset{3\cdot20}{CH_2}.\overset{-67\cdot1}{CF_3}$

424



$\underset{-60\cdot5 \text{ and } -53\cdot3}{(CF_3)_2N}.\overset{5\cdot73}{CHBr}.\underset{4\cdot82}{CHBr}.\overset{-66\cdot3}{CF_3}$

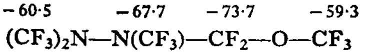
425

The ^{19}F data of three hydrazines (**426** to **428**) and a diaminodifluoromethane (**429**) have also been described.[311] The resonance signal of the N.COF group in **428**, expected at *ca* δ 1, was not observed; the presence of this group was claimed to have been established by IR.

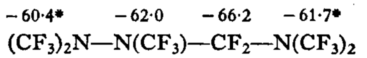
Hexafluoroisopropylidenimine reacted with a number of olefins to give unsaturated amines of the form $R—C(CF_3)_2NH_2$, where $R = CH_2{=}CH.CH_2—$, $CH_3CH{=}CH.CH_2—$ and $C_6H_5—C({=}CH_2)—CH_2—$ and diamines of the form $H_2N.C(CF_3)_2—X—C(CF_3)_2NH_2$, where $X = —CH_2.CH{=}CH.CH_2.CH_2.CH{=}CH.CH_2—$ and $—CH_2C({=}CH_2)CH_2—$.[28] The shifts of the CF_3 groups of the hexafluoroisopropylidenimine entity were in the range –75·5 to –76·9; a range similar to that found for the CF_3 group in α,α-bis(trifluoromethyl)benzylamines (see p. 275).

The photolysis of perfluoro-2,3-diazabuta-1,3-diene affords the hexafluoro-2,4-diazapenta-1,4-diene, $CF_2{=}N—CF_2—N{=}CF_2$, the ^{19}F spectrum of which consists of an AB pattern centred at –41·5, $J_{AB} = 82$ Hz, due to the $CF_2{=}N—$ groups and a broad signal at –60·4 due to the $N—CF_2—N$ group.[312] In the presence of fluoride ion the diazapentene isomerises to give bis(trifluoromethyl)carbodi-imide, $CF_3—N{=}C{=}N—CF_3$, which shows a single ^{19}F resonance signal at –50·2.

N,*N*-Bis(trifluoromethyl)hydroxylamine reacts with acyl or allyl chlorides, in the presence of caesium fluoride, to give *N*,*N*-bis(trifluoromethyl)-nitroxide derivatives (**430**).[313] The shift of the *N*-CF_3 groups in each case was −68·8. The course of this reaction has been studied rather more extensively.[314] *N*,*N*-Bis(trifluoromethyl)hydroxylamine, with a ^{19}F shift of −69·0, forms a 2:1 solid adduct with caesium fluoride, with the ^{19}F resonance now at −67·6. This adduct reacts with COF_2 to give products **431** and **432** and with trifluoroacetyl and heptafluoropropionyl chlorides to give compounds **433** and **434**. In each case the products, as above, have a resonance signal due to the $(CF_3)_2N$ entity in the range −68·2 to −68·8.

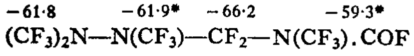

$\overset{-60\cdot5}{(CF_3)_2N}\text{—}\overset{-67\cdot7}{N(CF_3)}\text{—}\overset{-73\cdot7}{CF_2}\text{—}O\text{—}\overset{-59\cdot3}{CF_3}$

426

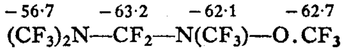

$\overset{-60\cdot4^{*}}{(CF_3)_2N}\text{—}\overset{-62\cdot0}{N(CF_3)}\text{—}\overset{-66\cdot2}{CF_2}\text{—}\overset{-61\cdot7^{*}}{N(CF_3)_2}$

* These two assignments may be reversed.

427


$\overset{-61\cdot8}{(CF_3)_2N}\text{—}\overset{-61\cdot9^{*}}{N(CF_3)}\text{—}\overset{-66\cdot2}{CF_2}\text{—}\overset{-59\cdot3^{*}}{N(CF_3).COF}$

428

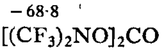

$\overset{-56\cdot7}{(CF_3)_2N}\text{—}\overset{-63\cdot2}{CF_2}\text{—}\overset{-62\cdot1}{N(CF_3)}\text{—}\overset{-62\cdot7}{O.CF_3}$

429

The ^{19}F shifts of the *N*-trifluoromethyl groups in *N*-trifluoromethyl-

$R\text{—}O\text{—}N(CF_3)_2$
$R = H_2C{=}CH.CH_2\text{—}$,
$CH_3C(O)\text{—}$ or $C_2H_5C(O)\text{—}$

430


$\overset{-68\cdot8}{[(CF_3)_2NO]_2CO}$

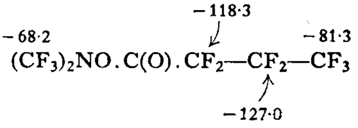
431


$\overset{-68\cdot8}{(CF_3)_2NO}.\overset{-28\cdot3}{C(O)F}$

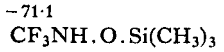
432


$\overset{-68\cdot6}{(CF_3)_2NO}.\overset{-73\cdot9}{C(O)CF_3}$

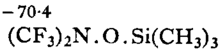
433


$\overset{-68\cdot2}{(CF_3)_2NO}.C(O).\overset{-118\cdot3}{CF_2}\text{—}\underset{-127\cdot0}{CF_2}\text{—}\overset{-81\cdot3}{CF_3}$

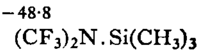
434


$\overset{-71\cdot1}{CF_3NH}.O.Si(CH_3)_3$

435


$\overset{-70\cdot4}{(CF_3)_2N}.O.Si(CH_3)_3$

436


$\overset{-48\cdot8}{(CF_3)_2N}.Si(CH_3)_3$

437

(**435**) and *N*,*N*-bis(trifluoromethyl)- (**436**) -O-trimethylsilylhydroxylamines have been reported.[321] In the bis(trifluoromethyl)amino trimethylsilane (**437**) the shift of the CF_3 group is to lower field.[322]

The preliminary ^{19}F data on the perfluoroammonium salts of antimony and arsenic hexafluorides have been confirmed,[315, 316] the shift of the $NF_4^{\oplus}$ group being at δ 213·5 to 214·7 (depending upon the anion) with $^{1}J(^{19}F\text{–}^{14}N)$ of 231 to 234 Hz. The fluorammonium salts $FNH_3^{\oplus}$ have also been prepared and the ^{19}F data reported.[317] Thus $[FNH_3]^{\oplus}[HSO_4]^{\ominus}$ shows a quartet at δ $-115{\cdot}3$ with $^2J(^{19}F{-}^1H)$ of 38 Hz. and $[FNH_3]^{\oplus}[ClO_4]^{\ominus}$ similarily shows a quartet at δ $-110{\cdot}8$ with $^2J(^{19}F{-}^1H)$ of 44 Hz when recorded is concentrated sulphuric acid. The spectrum of $[FNH_3]^{\oplus}$ $[ClO_4]^{\ominus}$ in acetonitrile, however, shows only a singlet at δ $-122{\cdot}4$ thus indicating that proton exchange occurs in acetonitrile but not in sulphuric acid solution. The methylfluoroammonium ion $[CH_3NH_2F]^{\oplus}$ was also prepared and the ^{19}F spectrum consisted of an incompletely resolved triplet at δ $-49{\cdot}0$ with $J(^{19}F{-}NH) = 42$ and $J(^{19}F{-}CH_3) = 28$ Hz.

Tetrafluorohydrazine and arsenic pentafluoride react to give the ionic compound $[N_2F_3]^{\oplus}[A_5F_6]^{\ominus}$.[318] The evidence for the formation of the $[N_2F_3]^{\oplus}$ ion is supported by the ^{19}F resonance spectra which shows three broad signals at δ 122, 146 and 180; no fine structure could be resolved.

Reaction of the difluoramino compound **393** with boron trifluoride led to the formation of the *N*-phenyl-*N*-fluoroisopropylidenimmonium fluoroborate, $[C_6H_5\overset{\oplus}{N}F{=}C(CH_3)_2][BF_4]^{\ominus}$, the ^{19}F spectrum of which showed resonance signals at δ $90{\cdot}7$ ($\overset{\oplus}{N}F$) and $-150{\cdot}4$ ($BF_4{}^{\ominus}$).[319] A similar salt was prepared from the 4-chlorophenyl compound, the ion showing resonances at $91{\cdot}5$ ($\overset{\oplus}{N}F$) and $-150{\cdot}9$ ($BF_4{}^{\ominus}$).

The first example of a stable (at -60°C) alkyldiazonium ion, in which the nitrogen atom is directly attached to an sp^3 hydridized carbon atom, has been claimed on the basis of the ^1H and ^{19}F NMR studies of trifluoromethyldiazomethane, CF_3CHN_2, in fluorosulphonic acid.[320] The diazomethane in chloroform-*d* shows a ^{19}F resonance signal of the CF_3 group at $-54{\cdot}45$ with $^3J(F{-}H)$ of $4{\cdot}0$ Hz. In fluorosulphonic acid at -60°C the CF_3 resonance occurs at $-64{\cdot}58$ and is a triplet with $^3J(H{-}F)$ of $6{\cdot}1$ Hz due to the diazonium ion $[CF_3CH_2N_2]^{\oplus}$. The ion very slowly decomposes in the solution to afford the 2,2,2-trifluoroethyl fluorosulphate (δ CF_3 $-75{\cdot}76$ and δ OSO_2F $36{\cdot}98$ with $^5J(F{-}F)$ of $2{\cdot}5$ Hz). (It should perhaps be noted that in this paper the authors quoted negative delta values for ^1H shifts to maintain the same sense in signs of ^1H and ^{19}F shift data.)

Phosphorus, arsenic and antimony

Reaction of caesium fluoride with phosphoryl fluoride gave the caesium difluorodioxophosphate, $Cs^{\oplus}[PF_2O_2]^{\ominus}$, the ^{19}F shift of which occurred at $-78{\cdot}4$ with $J(P{-}F)$ of 952 Hz.[323] The corresponding thiophosphate, prepared from potassium fluoride and thiophosphoryl chloride, had a shift of $-2{\cdot}4$ and $J(P{-}F)$ of 1164 Hz. The larger coupling in the latter ion was thought to be due to the enhanced electron density in the P–F bond of the thiophosphate.

As in the case of the mixed boron fluorides (p. 370) a linear relationship has been found for the ^{19}F shifts of both the fluorophosphoryl and fluorothiophosphoryl halides and the $\Sigma\chi_i$ term (Fig. 8).[266] While the relationship of ^{19}F against $\Sigma\chi_i$ is linear for phosphorus(V) compounds the same is not true for the phosphorus(III) halides (see Fig. 8). It is suggested that the deviation in these latter compounds arises because the shifts are primarily determined by the polarity of the P–F bond.

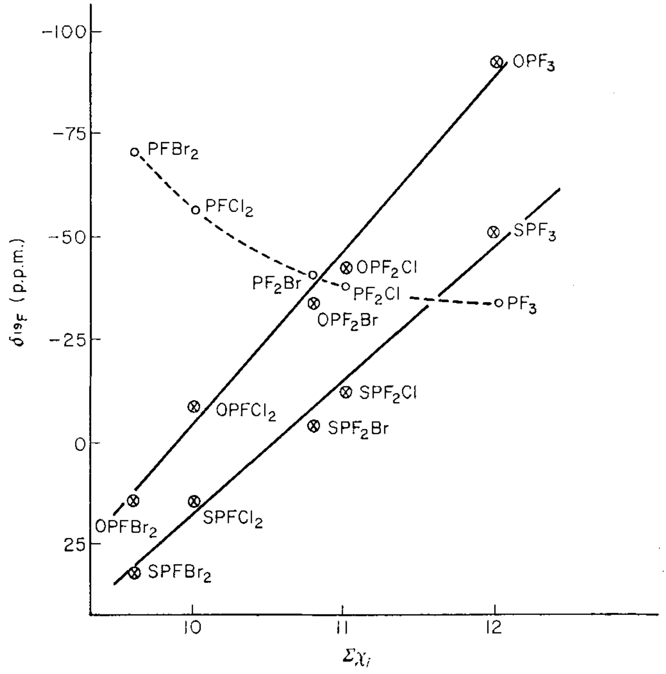


FIG. 8. Relationship of the ^{19}F shifts of the mixed phosphorus(III), phosphoryl and thiophosphoryl halides with the sum of the electronegativities ($\Sigma\chi_i$) of the halogen atoms. (From Muller, Nieche and Krebs.)[266]

The fluorine exchange in phosphorus pentafluoride has been re-examined and the experimental data presented is additional evidence for an intramolecular exchange process to be occurring.[324]

The study of metal complexes with fluorophosphines continues to attract attention. Reddy and Schmutzler[325] have carried out a systematic study of coordination compounds of zerovalent nickel and molybdenum of the type $Ni(CO)_2L_2$, NiL_4 and $Mo(CO)_3L_3$, where $L = MePF_2$, $PhPF_2$, Et_2NPF_2, Pr^nOPF_2 and PF_3. It is found that the ^{19}F shift on complex formation is to higher frequency (lower field) and there is a decrease in the $^{31}P-^{19}F$ coupling constant. These studies lead to the following conclusions—

(*a*) The paramagnetic contribution to the screening of fluorine is increased on complex formation; the contribution is larger in molybdenum than in nickel complexes.

(*b*) The data was interpreted as providing evidence to support the view that there is appreciable $d_\pi-d_\pi$ bonding between the phosphorus and metal atoms; the extent of bonding being larger in the nickel than in the molybdenum complexes.

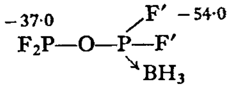
The NMR parameters of the adduct difluorophosphine-borane F_2HP, BH_3 are compared with those of the trifluorophosphine and phosphine adducts of borane.[326] The ^{19}F data for the fluoro-compounds are summarized in Table XLI. The adduct of difluorophosphine is, contrary to predictions, more stable and reasons for this are discussed which requires the F–P–F angles of HPF_2 be smaller than those of PF_3. Although no definite structural evidence is available for HPF_2 the P–H and P–F coupling constants would certainly tend to support this. Thus the P–H and P–F couplings in HPF_2 are close to those for PH_3 (183 Hz) and F_2PNR_2 (1194 Hz) respectively, where the HPH angle is 93·3° and the FPF angle is 92·5°, than to PF_3 (1400 Hz) in which FPF angle is 98·2 ± 0·6°.

TABLE XLI

^{19}F parameters for the borane adducts of difluoro- and trifluoro-phosphines[326]

	$F_3P.BH_3$	$F_2HP.BH_3$
δF	−58·6	−57·0
^1J(P–F)	1406 Hz	1151 Hz
^3J(F–P–B–H)	18	26
^2J(F–P–H)	. .	55
^2J(F–P–B)	6	. .

μ-Oxo-bis(difluorophosphine), F_2POPF_2, forms only a 1:1 adduct with



$$F_2P{-}O{-}P(F')_2{\cdot}BH_3$$

^1J(P–F) = 1387 Hz
^1J(P–F′) = 1328 Hz
^3J(F′–BH) = 17 Hz

438

borane and no complex with boron trifluoride.[327] The NMR data of the borane complex confirmed that P → B co-ordination had occurred and the data are shown in **438**. Action of hydrogen bromide on F_2POPF_2 gave the compound F_2HPO with δ −65·0 and ^2J(H–F) = 115 Hz, ^1J(P–F) = 1113 Hz and ^1J(P–H) = 880 Hz. This compound slowly disproportionated at room temperature to give trifluorophosphine and the new acid monofluorophosphorus acid, $FHPO_2H$. This acid has a ^{19}F resonance shift of −62·9 and ^1J(P–F) = 1030 Hz, ^2J(H–F) = 114 Hz and ^1J(P–H) = 783 Hz.

Nixon[328] has also carried out a detailed investigation of the complexes NiL_4, where L = PF_3, CF_3PF_2, $(CF_3)_2PF$, Cl_3CPF_2, Et_2NPF_2 and $C_5H_{10}NPF_2$, and the ^{19}F spectra are discussed. In every case there was again a shift of the signal of the P–F group on complex formation to high frequency and a decrease in the value of the direct ^{31}P–^{19}F coupling constant.

Phenylphosphonic difluoride reacts with boron trichloride to give the phosphonic dichloride, the reaction proceeding via the intermediate phosphonic fluoride chloride;[329] the course of the reaction was followed by both ^{19}F and ^{31}P resonance studies.

Tebbe and Muetterties[330] have questioned the suggestion of the autoionization of complexes of metal pentafluorides and the acetonitrile, CH_3CN,MF_5 (M = P, As and Sb), and trimethylamine complexes, $(CH_3)_3N,MF_5$ (M = P or Sb), have been reinvestigated by NMR methods. There was no evidence for autoionization of the nitrile complexes in acetonitrile solution. The hexacoordinate species, $F_5AsNC.CH_3$, is sensitive to hydrolysis and on addition of water, or an aqueous base, the hexafluoroarsenate ion is formed.

Iodothiophosphoryl difluoride (SPF_2I) has been prepared (^{19}F shift of δ 64·6 with $^1J(^{19}F–^{31}P)$ of 1290 Hz)[331] and is the first example of a thiophosphoryl compound containing both iodine and fluorine. The two new difluorodithiophosphoric acids (HPS_2F_2 and DPS_2F_2) have been prepared and the ^{19}F resonance consists of a doublet at δ 15·8 to 15·9 with $^1J(^{19}F–^{31}P)$ of 1212 Hz.[332] The methyl- and ethyl-hydridotrifluorophosphoranes have been prepared by exchange reactions between the alkyltetrafluorophosphorane with trimethyltin hydride.[333] Both the ^1H and ^{19}F spectra have been considered in detail over a range of temperatures and the spectra were interpreted in terms of an equatorial-substituted trigonal-bipyramidal structure. The ^{19}F shifts of the equatorial fluorine were −92·9 (Me) and −103·8 (Et), while those of the axial fluorine were −174·4 (Me) and −177·4 (Et); the coupling between the axial and equatorial fluorine atoms was 19 (Me) and 22·7 (Et) Hz. The coupling of the axial fluorine to the phosphorus was ~800 Hz and that between the equatorial fluorine and phosphorus was ~ 970 Hz.

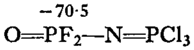
The ^{19}F parameters of the two mixed bromofluoro phosphoryl compounds, OPF_2Br and $OPFBr_2$, have been measured and compared with other fluorophosphoryl compounds.[334] The ^{19}F shifts and coupling constant were—

$$O=PF_2Br \quad \delta\,-32{\cdot}5 \quad {}^1J({}^{31}P-{}^{19}F) = 1203\ Hz$$
$$O=PFBr_2 \quad \delta\,-16{\cdot}1 \quad {}^1J({}^{31}P-{}^{19}F) = 1263\ Hz$$

The two fluorophosphoranes, PF_4Cl and PF_4Br, have been prepared by interaction of the dimethylamino-tetrafluorophosphorane and the anhydrous hydrogen halide.[335] The ^{19}F data of the new bromo-compound was discussed.

Difluorophosphorylamide and phosphorus pentachloride give the trichlorophosphazophosphoryldifluorido (**439**) which in turn with formic acid gives the *N*-phosphoryl chloride–phosphoryldifluorimide (**440**); the shifts of the two compounds were as shown.[336]

The ^{19}F spectra of trifluoromethylphosphorylfluoride, $CF_3P(O)F_2$, has been considered in some detail.[337] The shifts of the CF_3 and PF_2 group were at δ $-72{\cdot}5$ and $-79{\cdot}3$ respectively. The coupling constants were $^1J(P-F) = 1215$, $^1J(P-CF_3) = 162$ and $^3J(F-F) = 11$ Hz. The ^{19}F spectra of dimethyltrifluoro- and trimethyldifluoro- phosphoranes have similarly been discussed.[338a] The spectra of the dimethyltrifluorophosphorane could not be interpreted unambiguously although the results were consistent with a trigonal bipyramidal structure. In the trimethyldifluorophosphorane

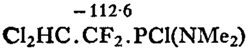


$\overset{-70{\cdot}5}{O{=}PF_2}{-}N{=}PCl_3$

439

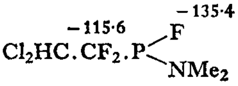
$\overset{-75{\cdot}5}{O{=}PF_2}{-}NH{-}PCl_2{=}O$

440



$Cl_2HC.\overset{-112{\cdot}6}{CF_2}.PCl(NMe_2)$

441



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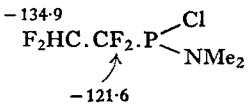

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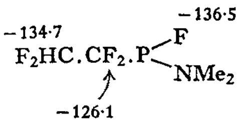

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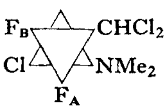

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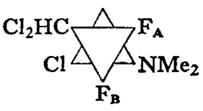


447

only a single ^{19}F resonance signal was found at δ −4·8 with $^1J(^{19}F-^{31}P) = 541$ and $^3J(^{19}F-CH_3) = 12$ Hz; these data are also consistent with the trigonal-bipyramidal structure with three equatorial methyl groups.

The spectra of *N*,*N*-dimethyl-2,2-dichloro-1,1-difluoroethylphosphonamidous chloride and related compounds have been considered[338b] and

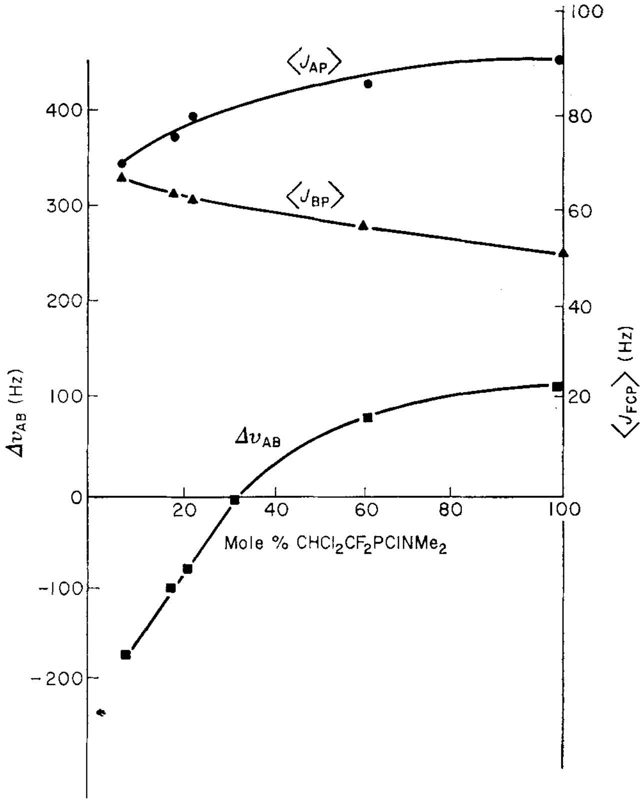


FIG. 9. The concentration dependence of $\Delta\nu_{AB}$, $\langle J_{AP}\rangle$ and $\langle J_{BP}\rangle$ in *N*,*N*-dimethyl 2,2-dichloro-1,1-difluoroethylphosphonamidous chloride in $CFCl_3$ solution. (From Goldwhite and Rowsell.)[338b]

the average ^{19}F shifts are indicated in **441** to **444**. The paper dealt at some length with the problem of rotational isomerism about the P–C bond. This paper also contains another lesson regarding the possible solvent interaction involving trichlorofluoromethane. In Fig. 9 the effect of dilution with CCl_3F on $\Delta\nu_{AB}$, $\langle J(F_A-P)\rangle$ and $\langle J(F_B-P)\rangle$ are shown, where F_A and F_B are the two fluorine atoms of the α-CF_2 group in the rotatomers **445** to **447**;

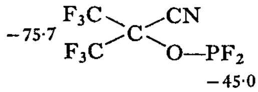
the effect is surely most striking and may indicate that care should be exercised in using CCl_3F as a reference compound.

The ^{19}F parameters of a number of fluorophosphoranes containing thioalkyl, thio- phenyl and phenoxy groups have been reported (Table XLII).[339] The same workers have also considered the low-temperature ^{19}F spectra of alkylthio- and arylthio-substituted fluorophosphoranes.[340] At room temperature there is exchange between the axial and equatorial fluorine atoms and on cooling a fluorophosphorane, e.g. R_2NPF_4, the axial

TABLE XLII

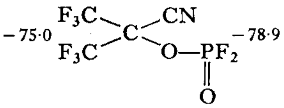
^{19}F parameters of fluorophosphoranes of the type[339] $R_nPF_{4-n}(SR')$ and $R_nPF_2(OPh)_{3-n}$

	δF	^1J(P–F)	^2J(F–F)
$PhPF_3SMe$	−15·0 (ax)	942 (ax)	60·5
	−71·9 (eq)	1042 (eq)	
$PhPF_3SEt$	−15·7 (ax)	938 (ax)	59·3
	−71·3 (eq)	1049 (eq)	
$PhPF_3SPh$	−13·6 (ax)	970 (ax)	60·0
	−71·3 (eq)	1060 (eq)	
Ph_2PF_2SMe	−25·0	760	..
Ph_2PF_2SEt	−25·2	752	..
Ph_2PF_2SPh	−23·5	796	..
$MePF_2(OPh)_2$	−18·1	825	..
$PhPF_2(OPh)_2$	−35·0	829	..
$Ph_2PF_2(OPh)$	−33·3	797	..



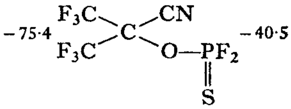
^1J(P–F) = 1380 Hz
^5J(F–CF) = 1·5 Hz
^4J(P–CF) = 6·0 Hz

448



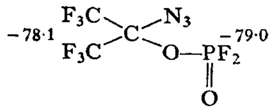
^1J(P–F) = 1064 Hz
^5J(F–CF) = 1·0 Hz
^4J(P–CF) = 0·4 Hz

449



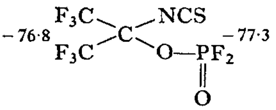
^1J(P–F) = 1176 Hz
^5J(F–CF) = 1·5 Hz
^4J(P–CF) ≐ 0·4 Hz

450



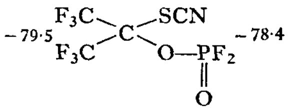
^1J(P–F) = 1048 Hz

451



^1J(P–F) = 1056 Hz
^5J(F–CF) = 1·2 Hz
^4J(P–CF) = 0·34 Hz

452



^1J(P–F) = 1062 Hz

453

and equatorial fluorine atoms were distinguished. With the alkylthio- and arylthio- tetrafluorophosphoranes a further effect is noted at low temperature probably due to restricted rotation about the P–S bond. Therefore, instead of two equivalent equatorial and two equivalent axial fluorine atoms, two non-equivalent axial and two equivalent equatorial fluorine atoms are observed; a similar effect is found in the ethylthio trifluorophosphorane, $EtSP(Ph)F_3$. The ^{19}F parameters are shown in Table XLIII.

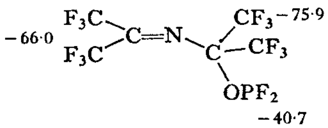
TABLE XLIII

^{19}F parameters of alkythio- and arylthio- fluorophosphoranes

	Temperature	F	Coupling constants, Hz
$MeSPF_4$	–100°C	–14·1(ax – 1)	$^1J(P\text{–}F_{ax-1}) = 930$
		–19·2(ax – 2)	$^1J(P\text{–}F_{ax-2}) = 1088$
		–66·1(eq)	$^1J(P\text{–}F_{eq}) = 1075$
			$^2J(F_{ax-1}\text{–}F_{ax-2}) = 18{\cdot}6$
			$^2J(F_{ax-1}\text{–}F_{eq}) = 104$
			$^2J(F_{ax-2}\text{–}F_{eq}) = 91$
$EtSPF_4$	–70°C	–13·4(ax – 1)	$^1J(P\text{–}F_{ax-1}) = 871$
		–21·4(ax – 2)	$^1J(P\text{–}F_{ax-2}) = 1051$
		–70·5(eq)	$^1J(P\text{–}F_{eq}) = 1049$
			$^2J(F_{ax-1}\text{–}F_{ax-2}) = 34$
			$^2J(F_{ax-1}\text{–}F_{eq}) = 62$
			$^2J(F_{ax-2}\text{–}F_{eq}) = 62$
$PhSPF_4$	–80°C	–13·9(ax – 1)	$^1J(P\text{–}F_{ax-1}) = 1071$
		–16·9(ax – 2)	$^1J(P\text{–}F_{ax-2}) = 943$
		–65·0(eq)	$^1J(P\text{–}F_{eq}) = 1064$
			$^2J(F_{ax-1}\text{–}F_{ax-2}) = 18{\cdot}1$
			$^2J(F_{ax-1}\text{–}F_{eq}) = 113{\cdot}6$
			$^2J(F_{ax-2}\text{–}F_{eq}) = 95{\cdot}9$
$EtSP(Ph)F_3$	–60°C	–13·4(ax – 1)	$^1J(P\text{–}F_{ax-1}) = 871$
		–21·4(ax – 2)	$^1J(P\text{–}F_{ax-2}) = 1015$
		–70·5(eq)	$^1J(P\text{–}F_{eq}) = 1049$
			$^2J(F_{ax-1}\text{–}F_{ax-2}) = 32$
			$^2J(F_{ax-1}\text{–}F_{eq}) = 62$
			$^2J(F_{ax-2}\text{–}F_{eq}) = 62$

A number of new μ-oxo-fluorophosphorus compounds have been synthesized by reaction of 2-halogeno-iodoperfluoro-isopropoxide anion with phosphorus bromide difluoride or phosphoryl bromide difluoride.[341] The ^{19}F parameters of these compounds are shown in **448** to **454**.

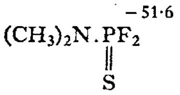
The ^{19}F data have been given for the methylaminothiophosphoryl fluorides **455** and **456**.[342] The ^{19}F spectra were also used to investigate the



$^1J(P–F) = 1396$ Hz
$^5J(F–CF_3) = 8·3$ Hz
$^4J(P–CF) = 40$ Hz
$^6J(F–F) = 1·8$ Hz

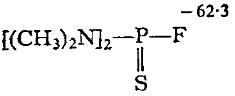
454

aminolysis of the thiophosphoryl fluoride especially in the identification of complex ions, such as $PS_2F_2^{\ominus}$ and $PSF_5^{\ominus}$, in the solid residues.


$(CH_3)_2N.PF_2{=}S$

$^1J(P–F) = 1079$ Hz

455

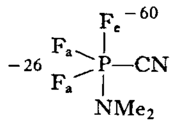

$[(CH_3)_2N]_2—P(=S)—F$

$^1J(P–F) = 1016$ Hz

456

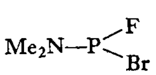
The ^{19}F NMR data has been used to establish the structure of methylaminodifluorophosphine, CH_3NHPF_2, which has a ^{19}F shift of −70·6 and coupling constant of $^1J(P–F) = 1191$ Hz, $^3J(F–H) = 10·2$ Hz and $^4J(F–H) = 2·0$ Hz.[343]

Copper(I) chloride forms a complex with dimethylaminodifluorophosphine, $\{CuCl[(CH_3)_2NPF_2]\}_4$, with a ^{19}F shift of −53; the P–F coupling constant (1194 Hz) is the same as in the uncomplexed phosphine.[344] Copper(II) chloride, however, oxidizes the phosphine to the phosphorane $(CH_3)_2NPF_2Cl_2$, the structure of which was established by NMR. The ^{19}F shift of the phosphorane was 54·3 with $^1J(P–F)$ of 949 ± 8 Hz, an intermediate value between that for $(CH_3)_2NPF_2$ of 1194 Hz and of $(CH_3)_2NPF_4$ of 836 Hz.



$^1J(P–F_a) = 780$ Hz
$^1J(P–F_e) = 950$ Hz
$^2J(F_a–F_e) = 63$ Hz

457

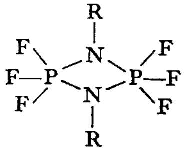


$^1J(P–F) = 1172$ Hz
$^4J(F–H) = 3·1$ Hz

458

Cyanogen bromide reacts with dimethylaminodifluorophosphine to give the two new compounds **457** and **458**.[345] Mitsch[346] found that difluorodiazirine reacts with trivalent phosphorus compounds to form *N*-cyanophosphorus imides and difluorophosphoranes. From the ^{19}F data it was concluded that all the difluorophosphoranes processed the two fluorine atoms in axial positions. The ^{31}P–^{19}F coupling constants, obtained from the ^{31}P resonance spectra, have also been used to determine the structure of difluorophosphoranes.[347]

Harris and Rudner[348] have pointed out that the preference for compounds of the type $(RNPX_3)_n$ to exist as dimers rather than trimers or tetramers raises interesting points regarding the bonding. The formation of cyclic phosphorus–nitrogen bonds, from one axial and one equatorial bond of a pentacovalent phosphorus trigonal bipyramid, should give a strain-free N–P–N bond of 90°. There should then be two equatorial and one axial fluorine atoms in **459** and these should be readily distinguished from the ^{19}F spectrum. The spectra of the compounds examined (**459**, $R = n\text{-}C_3H_7$, C_6H_5—, 2,4-$Me_2C_6H_3$— and 2,6-$Me_2C_6H_3$—) only showed one ^{19}F resonance signal indicating that the atoms were rapidly equilibrating. The ^{19}F–^{31}P coupling constant observed, 897 to 918 Hz, were also intermediate for those required for equatorial (950 to 990 Hz) and axial (~800 Hz) phosphorus–fluorine coupling constants.



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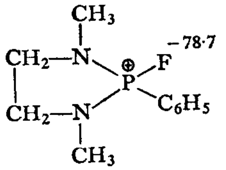
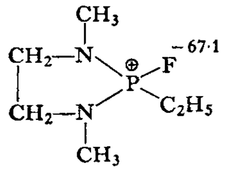


$J(^{31}\overset{\oplus}{P}-^{19}F) = 1136$ Hz

$[C_6H_5PF_5]^{\ominus}$
δF(eq) = −57·4
δF(ax) = −61·0
J[P–F(eq)] = 820 Hz
J[P–F(ax)] = 691 Hz
J[F(eq)–F(ax)] = 37 Hz

460



$J(^{31}\overset{\oplus}{P}-^{19}F) = 1168$ Hz

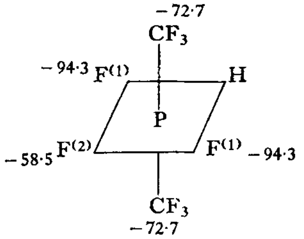
$[C_2H_5PF_5]^{\ominus}$
δF(eq) = −56·0
δF(ax) = −57·4
J[P–F(eq)] = 850 Hz
J[P–F(ax] = 680 Hz
J[F(eq)–F(ax)] = 32 Hz

461

The reaction of tetrafluorophosphoranes with cyclic aminosilanes did not yield the expected monomeric cyclic aminofluorophosphoranes but, on the basis of the ^{19}F spectrum, gave the phosphonium pentafluorophosphates.[349] The data for the compounds formed from phenyl- and ethyltetrafluorophosphoranes are shown in **460** to **461**; the data for the phenylpentafluorophosphate had previously been reported.[350]

The direct addition of potassium bifluoride to bis(trifluoromethyl)-fluorophosphine to form hexa-coordinate phosphorus salts has been reported.[351] The structure shown in **462** is favoured from the consideration of the ^{19}F resonance spectra.

The signs of P–F coupling constants have been investigated by several groups of workers. Manatt *et al.*[352] have carried out double resonance studies on a number of compounds; the relative signs were established using transitory selective irradiation experiments, tickling measurements or partial collapse of multiplet structures using larger irradiation fields. The absolute signs were based upon the assumption that ^1J(P–H) was positive and that ^3J(F–C–C–F) and ^4J(F–C–C–C–F) were negative and positive respectively. The following results were obtained—



$^1J[P–F^{(1)}] = 725$ Hz
$^1J[P–F^{(2)}] = 834$ Hz
$^2J[P–CF_3] = 132$ Hz
$^3J[F^{(1)}–CF_3] = 12·5$ Hz
$^3J[F^{(2)}–CF_3] = 15·5$ Hz

$^2J[F^{(1)}–F^{(2)}] = 25·0$ Hz
$^2J[F^{(1)}–H] = 70$ Hz
$^2J[F^{(2)}–H] = 18$ Hz
$^3J[CF_3–H] = 9·5$ Hz
$^1J[P–H] = 622$ Hz

462

^1J(P–F) −ve; ^2J(F–C–P) +ve; ^2J(F–C–F) +ve;
^3J(F–C–P–H) +ve; ^3J(F–C–P–F) −ve; ^3J(F–C–C–P) +ve;
^3J(F–C–C–F) −ve; ^3J(F–C–P–P) +ve; ^4J(F–C–C–C–P) +ve;
^4J(F–C–C–C–F) +ve and ^5J(F–C–P–P–C–H) +ve.

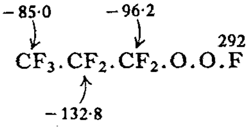
The negative sign for ^1J(P–F) has also been found by Dean and McFarlane[353] in di-isopropyl fluorophosphate, $[(CH_3)_2CHO]_2P(O)F$. Harris *et al.*[354] have also determined the relative signs for the one, two and three bond P–F coupling and three and five bond F–F coupling in the two compounds $(CF_3)_2PSCF_3$ and $(CF_3)_2PF$. The results are in accord with those given by Manatt above. It has been emphasized that the value of the two-bond phosphorus–fluorine coupling constant is dependent upon the valency of the phosphorus atom. Thus in phosphorus(III) compounds the value is 77 to 89 Hz, while in phosphorus(V) compounds it is larger, having values in the range 113 to 193 Hz.[355]

Group VI

Oxygen

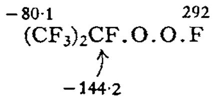
The ^{17}O and ^{19}F NMR studies of the oxygen fluorides have been reported very frequently especially over the existence of some of the intermediate species.

Solomon *et al.*[356] have carried out a detailed study of the ^{17}O and ^{19}F spectra of the suspected O_3F_2, although the ^{19}F spectra were hardly under high-resolution conditions since the line widths were of the order of 10 KHz. It was concluded that O_3F_2 did not exist but was a mixture of O_2F_2 and O_4F_2 in equilibrium with O_2F which, on increasing the temperature, decomposes into O_2F_2 and oxygen. Independently, and about the same time, Nebgen *et al.*[357] considered the relation of the chemical shifts of fluorine and the three oxides OF_2, O_2F_2 and O_3F_2 and, because of the very considerable difference, it was suggested that the bonding in these compounds was very different. It was further suggested that O_3F_2 was O_2F_2 with "interstitial" oxygen. The ^{19}F shift of dioxygen difluoride have still further been considered by Turner *et al.*[358] Finally Solomon *et al.*[359] have substantiated the presence of the equilibrium and that O_3F_2 is a mixture of O_2F_2 and $(OOF)_n$.



$\overset{-85\cdot0}{CF_3}.\underset{-132\cdot8}{CF_2}.\overset{-96\cdot2}{CF_2}.O.O.\overset{292}{F}$

463



$\overset{-80\cdot1}{(CF_3)_2}\underset{-144\cdot2}{CF}.O.O.\overset{292}{F}$

464

Dioxygen difluoride and perfluoropropene react to give a mixture of the 1- and 2- fluoroperoxyperfluoropropanes **463** and **464**; the shifts are as shown.[360] Bis(fluorocarbonyl)peroxide reacts with fluorine to afford the fluorocarbonyl hypofluorite, FC(O)OF, and the shifts, measured with respect to SF_6, were compared with those of other hypofluorites.[361] The hypofluorite can be further oxidized to give bis(fluoroxy)difluoromethane. The ^{19}F shifts of this latter compound have been reported by Hohorst and Shreeve, and are shown in **465**.[362] The reaction of dioxygen difluoride with sulphur dioxide gives, among other products, the fluorosulphuryl hypofluorite, FSO_2OOF; the ^{19}F–^{17}O coupling was greater than 430 Hz.[363] The ^{19}F–^{17}O coupling in acetyl fluoride has been reported to be 39 ± 6 Hz.[364]

The ^{19}F data for fluorocarbonyl trifluoromethyl peroxide has been reported and is shown in **466**;[365] the shifts are compared with other simple compounds containing the fluorocarbonyl and trifluoromethylperoxy group. The catalytic fluorination of bis(fluorocarbonyl)peroxide gave the new compound bis(difluorofluoroxymethyl)peroxide, $FO.CF_2.O.O.CF_2.OF$, the ^{19}F spectrum of which showed a triplet at δ 158·6 due to the FO. group and a doublet at –80·9 from the $O.CF_2.O$ group. The F–F coupling was 36 Hz.[366] The new class of compounds, the bis(perfluoroalkyl)trioxides, have been described[367] and the ^{19}F shifts of the dimethyl and ethylmethyl ethers, peroxides and trioxides are compared (Table XLIV). In general the

TABLE XLIV

Comparison of the ^{19}F shifts and coupling constants of bis(trifluoromethyl) and pentafluoroethyltrifluoromethyl ethers, peroxides and trioxides

	$R = R^1 = CF_3$,		$R = CF_3$, $R^1 = CF_2CF_3$			
	δCF_3	δCF_3O.	$\delta O.CF_2$	$\delta C.CF_3$	$^{3+n}J(CF_3OCF_2)$	^3J(F–F)
$R.O.R^1$	–58·3	–56·2	–91·2	–87·6	9·2	2·2
$R.O.O.R^1$	–69·0	–68·7	–95·7	–83·2	4·3	1·5
$R.O.O.O.R^1$	–68·7	–68·7	–96·4	–83·8	< 1·0	1·5

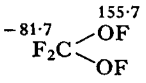
CF_3 resonance of the trifluoromethyl group in ethers occurs in the range –55 to –58, while in higher oxides occurs at lower frequency in the range –68 to –69. A similar, but smaller effect is observed for the —$O.CF_2$— group. The bis(trifluoromethyl)trioxide has been prepared independently by the addition of carbonyl fluoride to oxygen difluoride; the shift of the CF_3 group at –78°C was reported to be –72.4.[368]

Sulphur

The mechanism for fluorine exchange in sulphur tetrafluoride has continued to cause controversy and two further short papers on this subject have been published by the two principle groups of workers.[369, 370] There is, however, still no precise mechanism for the exchange process.

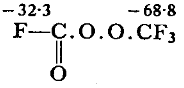
The sulphur isotope effects in the ^{19}F spectra have been realized in the compounds $S_2O_5F_2$, $S_2O_6F_2$, $S_3O_8F_2$ and HSO_3F; the spectra of $S_2O_5F_2$ and HSO_3F are shown in the paper.[371]

N-Cyaniminosulphoxydifluoride and sulphur tetrafluoride gave the *N*-imino sulphur difluoride-*N*′-imino sulphoxy fluoride difluoromethane **467**;[125] the shifts, recorded at –15°C, are shown. Pentafluoroaniline and sulphur tetrafluoride afforded the corresponding iminosulphurdifluoride, $C_6F_5N{=}SF_2$. The ^{19}F shift of the SF_2 group is 66·3; the shifts of the pentafluorophenyl entity are included in Table XII. The *N*-sulphur



^3J(F–F) = 38·6 Hz

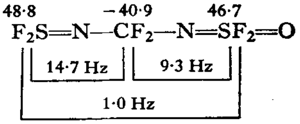
465



$F{-}C(=O).O.O.CF_3$

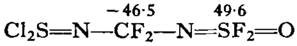
^5J(F–F) = 1·7 Hz

466



$F_2S{=}N{-}CF_2{-}N{=}SF_2{=}O$

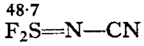
467



$Cl_2S{=}N{-}CF_2{-}N{=}SF_2{=}O$

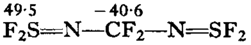
^4J(F–F) = 9 Hz

468



$F_2S{=}N{-}CN$

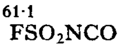
469



$F_2S{=}N{-}CF_2{-}N{=}SF_2$

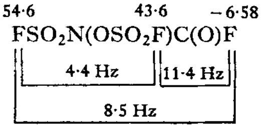
^4J(F–F) = 14·5 Hz

470



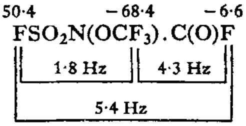
FSO_2NCO

471



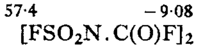
$FSO_2N(OSO_2F)C(O)F$

472



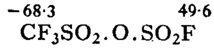
$FSO_2N(OCF_3).C(O)F$

473



$[FSO_2N.C(O)F]_2$

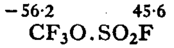
474



$CF_3SO_2.O.SO_2F$

^5J(F–F) = 2·1 Hz

475



$CF_3O.SO_2F$

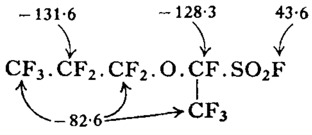
^4J(F–F) = 6·8 Hz

476

difluoride derivative (**467**), on treatment with silicon tetrachloride, gave the corresponding *N*-sulphur dichloride compound (**468**).[126] Sulphur tetrafluoride has similarly been used to fluorinate cyanamide to give *N*-cyanoimino sulphur difluoride (**469**), and further treatment with SF_4 gives *N*,*N*′-iminosulphur difluoride difluoromethane (**470**);[372] the shifts shown were measured at –30° and –50°C respectively.

Fluorosulphuryl isocyanate reacts with fluorine fluorosulphate, trifluoromethyl hypofluorite and fluorine to give a new class of compounds containing the $FSO_2NC(O)F$ group;[373] the shifts of some of these compounds are shown in **471** to **474**. The preparation of trifluoromethyl pyrosulphuryl fluoride (**475**) has been described,[374] and the shifts of this compound and of CF_3OSO_2F (**476**) were given and the shifts of the CF_3 group compared to that of $(CF_3)_2S_2O_5$ (δ –74·02).

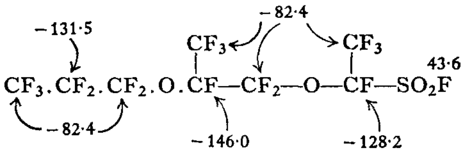
Sulphuryl and sulphonyl fluorides have been found to react with fluoroolefins;[375] the shifts of some of the sulphonylfluorides described are shown



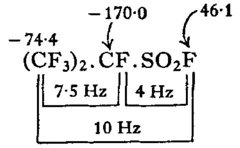
$CF_3.CF_2.CF_2.O.CF(CF_3).SO_2F$

477

in **477** to **479**. The reaction of iminosulphur difluorides with fluoro-olefins has also led to the formation of new derivatives;[376] the shifts are shown

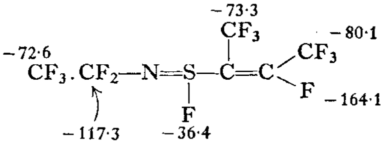


478

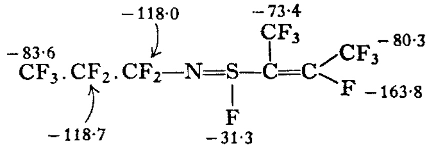


479

in **480** to **482**. The shifts of trifluoromethylsulphonyl fluoride have been reported by Lawless and Harman[377] and by Ratcliffe and Shreeve.[378] The former authors found only one broad resonance signal at –30°C for the SF_3 group at δ 30, while the latter authors were able to resolve the two separate resonance signals of the SF (δ –49·6) and SF_2 (δ 47·4) environments. The shifts of the sulphonyl fluorides given in the paper[378] are shown in **483** to **485**.



480



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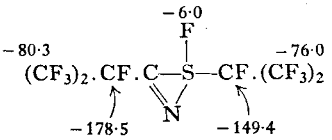

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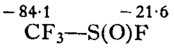
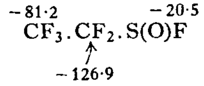


CF_3—S(O)F

^3J(F–F) = 8 Hz

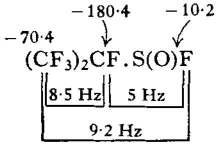
483



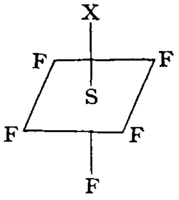
$CF_3.CF_2.S(O)F$

^4J(F–F) = 12 Hz

484



485

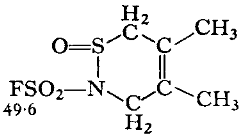


X = C(O)F, O.C(O)F, O.O.C(O)F

486

Despite the fact that many pentafluorosulphur derivatives have been discussed these compounds are still receiving attention. Finer and Harris[379] have given a detailed account of the analysis of bis(pentafluorosulphur)-peroxide, SF_5OOSF_5, and disulphur decafluoride, $F_5S.SF_5$, as $AB_4B_4'A'$ systems. Some new pentafluorosulphuroxy- alkanes and alkenes have been prepared by reaction of pentafluorosulphur hypofluorite and alkenes.[380] There is an aspect of the data presented in this paper which warrants comment. Normally the ^{19}F shifts of the $—SF_5—$ groups occur to low field of the CCl_3F; however, Place and Williamson[380] state that these shifts are to high field of CCl_3F! The rotational isomers of the compounds SF_5OCH $ClCHClF$ and $SF_5OCH_2CCl_2F$ are discussed in some detail. Three other new derivatives, the carbonyl fluoride, fluoroformate and peroxofluoroformate (**486**), have also been described.[381] All the shifts of the pentafluorosulphur group are to low field of CCl_3F; the spectra are reproduced in the paper.

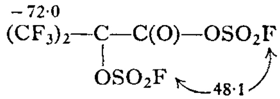
The azyldifluorosulphoxy anion $[NSF_2O]^{\ominus}$ has been prepared and in the tetraphenyl-phosphonium salt the ^{19}F resonance occurs at δ 67·0.[382] The ^{19}F parameters of a number of oxydifluorides,[382] and fluorosulphonyl compounds,[304,319,383,384] have been reported and the shifts of the $—SF_2—$ compounds are shown in Table XLV, while those of the various fluorosulphonyl groups are shown in **487** to **498**.



487

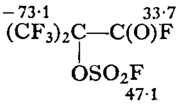
$(CH_3)_3SiNHSO_2F$

488



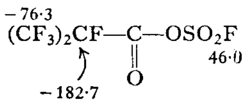
$(CF_3)_2—C(OSO_2F)—C(O)—OSO_2F$

489



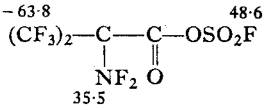
$(CF_3)_2C(OSO_2F)—C(O)F$

490



$(CF_3)_2CF—C(=O)—OSO_2F$

491



$(CF_3)_2—C(NF_2)—C(=O)—OSO_2F$

492

The ^{19}F resonance data on a number of new sulphenyl compounds has been published.[385] The data for the trifluoromethyl-fluorodithioformate (**499**) and bis(trifluoromethyl)trithiocarbonate (**500**) are as shown. The shifts of the trifluoromethylmercapto-halofluoromethansulphonyl halides or pseudohalides, $F_3CS—CFX—SY$, where X = Cl or Br and Y = Cl, Br, CN, SCN or NCO, fall into characteristic ranges: −38·0 to −39·1 for $CF_3S—$, −48·5 to −58·3 for CFX and the $CF_3—CF$ coupling is in the range 9·8 to 11 Hz. The shifts of the SCF_3 groups in bis(trifluoromethylmercapto)-halomethanesulphonyl halides, $(F_3C.S)_2.CX—SX$, where X = Cl or Br, fall in the range −39 to −40 while the shifts of the $C.CF_3$ groups in bis-

TABLE XLV

^{19}F shifts of the SF_2 group in compounds of the type $X{=}SF_2{=}Y$

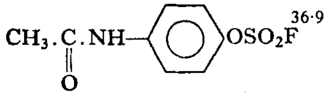
X	Y	δ
$CF_3N{=}$	$={NCF_3}$	57·2[a]
O=	=NCN	48·5
O=	$={NCF_3}$	47·5[b]
O=	=NCOF	46·0
O=	=NCl	43·0
O=	=NF	37·3
O=	=O	−34·0

[a] δCF_3 −48·3, $J(CF_3\text{–}SF_2)$ = 8 Hz.

[b] Shift quoted as 47·3 in text; δCF_3 −48·3, $J(CF_3\text{–}SF_2)$ = 8 Hz.

(trifluoromethyl)chloromethanesulphenyl halide or pseudohalides, $(F_3C)_2C.Cl{-}SX$, where X = Cl, CN or SCN, are in the range −69 to −71.

The ^{19}F shifts of the dimer of trifluoromethanesulphenyl isocyanate were found to be essentially invariable under a range of conditions, the shift being −51·27.[386] This shift was similar to that of many other $CF_5{-}S{-}N{-}$



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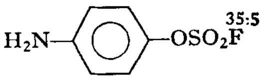

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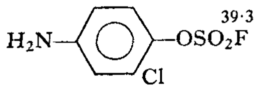

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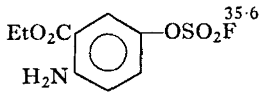

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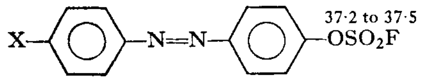
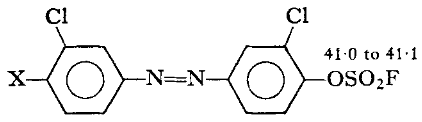


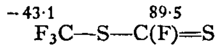
X = NH_2, Cl, Br, CH_3 or H

497



X = NH_2 or H

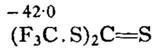
498



$$\overset{-43\cdot1}{F_3C}{-}S{-}\overset{89\cdot5}{C(F)}{=}S$$

^4J(F–F) = 18 Hz

499

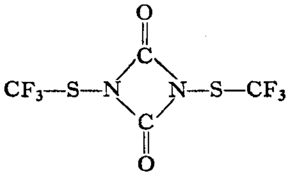


$$(\overset{-42\cdot0}{F_3C}.S)_2C{=}S$$

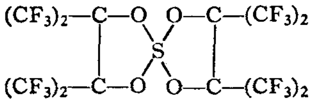
500

compounds and the ^{13}C–^{19}F coupling of 314 Hz was also consistent with this group. The structure of the dimer proposed was that of the 4-membered cyclic uretidine-1,3-dione (**501**).

During the study of a series of fluoroethanes, Dean and Lee[4] also examined a series of fluoroethane sulphur compounds of the form XCF_2.



501



502

CFYZ, CF_3CHFZ and $X_2CF.CF_2Z$, where X and Y was chlorine or bromine (X may also be OMe) and Z was SCl, SO_2Cl or SO_2F.

Reaction of the disodium salt of perfluoropinacol gave the perfluoropinacol orthosulphite (**502**) which showed two sets of CF_3 resonance peaks at –68·0 and –66·3.[387] Two different environments for the CF_3 groups would be expected for **502** due to the pyramidal configuration about the sulphur atom.

Selenium

The fluoroselenates, $RO.SeO_2F$, were prepared by disproportionation reaction of $(RO)_2SeO_2$ and selenium oxyfluoride.[388] The ^{19}F shifts of the methyl and ethyl ester were δ 44·5 and 55·5 respectively and the direct ^{77}Se–^{19}F coupling was 1450 ± 10 Hz. The long-range H–F coupling was also observed, $^4J(^{19}F\text{—Se—OC}H)$ being 1·4 to 1·45 Hz and $^5J(^{19}F\text{—Se—O.C.CH})$ being 0·8 Hz.

The Hammett σ functions obtained from the ^{19}F chemical shifts of the $—SeCF_3$ groups of *m*- and *p*-fluorophenyl trifluoroselenides have been measured and compared with the pKa values obtained for the corresponding carboxylic acids. Although the ^{19}F shifts of the $SeCF_3$ and ring fluorine atoms are given the reference used is not stated.[389]

Tungsten

Tungsten hexafluoride was found to react with dimethyl ether to give the tungsten oxytetrafluoride complex **503**.[390] Diethyl sulphide and selenide on the other hand from 2:1 complexes with tungsten hexafluoride (**504** and **505**); the shifts are shown.

$\overset{62\cdot8}{WOF_4.OEt}$

$J(^{183}W–^{19}F) = 68$ Hz

503

$\overset{70\cdot8}{WF_6.2Et_2S}$

504

$\overset{143\cdot7}{WF_6.2Et_2Se}$

505

VII. COMPLEX FLUORIDE ANIONS

The nuclear spin-lattice relaxation times T_1 and relaxation times along the r.f. field ($T_{1\rho}$) have been measured for the ^{19}F nucleus in ammonium tetrafluoroberyllate [$(NH_4)_2BeF_4$].[391]

The ^{19}F spectra have been used to study the aqueous solutions of the salts NH_4MF_5, $(NH_4)_2MF_6$ and $(NH_4)_3MF_7$, where M = Zr or Hf.[392] The heptafluoro salts have additionally been studied over the range of temperatures from −10 to 80°C. The solutions studied showed rapid exchange of the fluorine atoms and, in addition to intermolecular exchange, rapid reorientation of the ligands in the coordination sphere takes place.

The ^{19}F spectra of the hexafluoroniobate ion have also been investigated over a range of temperatures.[393] Using computer methods for fitting the observed line shapes it was shown that both quadrupole-induced transitions between the spin-states of the ^{93}Nb nucleus and chemical exchange of the fluorine atoms effect the line shapes by modulating the ^{93}Nb–^{19}F scalar coupling. The unusual temperature dependence of the observed ^{93}Nb relaxation rates was explained in terms of a simple model. Because of the unusual shape of the resonance signal the variation of this with temperature is shown in Fig. 10.

Dean and Evans[394] have studied the ^{19}F spectra of hexafluoro-anions of Group IVA and IVB and concluded that the predominant species in aqueous solution are the octahedral $AF_6^{2\ominus}$ ions (except for A = Pb). $(NH_4)_2GeF_6$ in aqueous solution shows a single sharp ^{19}F resonance line with small satellites due to coupling to ^{73}Ge isotope; $J(^{73}Ge–^{19}F) = 98 \pm 0{\cdot}5$ Hz. A 0·1M solution of $(NH_4)_2GeF_6$ in 0·5N perchloric acid was shown, by FMR, to be 70% decomposed. In the solution of $(NH_4)_2SnF_6$, coupling of the fluorine atoms to all three tin isotopes was recognized $J(^{119}Sn–^{19}F) = 1557 \pm 1$, $J(^{117}Sn–^{19}F) = 1487 \pm 1$ and $J(^{115}Sn–^{19}F) = 1363 \pm 2$ Hz. The couplings, however, are solvent dependent and for tetraalkylammonium salts the ^{119}Sn–^{19}F coupling varies from 1557 to 1605 Hz in going from aqueous to chloroform solution. The $TiF_6^{2\ominus}$ ion shows coupling to both the ^{47}Ti and ^{49}Ti isotopes; the value of $J(^{49}Ti–^{19}F)$ being $33{\cdot}0 \pm 0{\cdot}2$ Hz. The ^{19}F spectrum showed that there was very little hydrolysis in solution. Both the $ZrF_6^{2\ominus}$ and $HfF_6^{2\ominus}$ ions show rather broad resonance signals especially for the latter ion and on addition of ammonium fluoride the peaks broaden further and the resonance moves to lower frequency. It is thus evident that fluoride ion exchange is occurring very rapidly, e.g. in a solution 0·25 M in $ZrF_6^{2\ominus}$ and 1·5 M in $F^{\ominus}$ the half-width of the signal was ~1550 Hz and the shift was approximately the mean of the two separate ions.

The shifts of the Group IVA ions ($TiF_6^{2\ominus}$ 73·7; $ZrF_6^{2\ominus}$ −4·6 and

$HfF_6^{2\ominus}$ −45·5) are to higher frequency than the corresponding ions of the Group IVB elements ($SiF_6^{2\ominus}$ −129·5; $GeF_6^{2\ominus}$ −124·9 and $SnF_6^{2\ominus}$ −157·8).

Schaeffer *et al.*[395] have studied the ^{19}F spectra of a 1M solution of ammonium tetrafluoroberyllate, the temperature dependence of which indicated fluoride ion exchange occurring. At −5°C two signals at −164·4 and −166·6 were found, the former due to the $BeF_4^{\ominus}$ ion and the latter to the $H_2O.BeF_3^{\ominus}$ ion; the ^9Be–^{19}F coupling was $33{\cdot}2 \pm 1{\cdot}2$ Hz. In the presence of excess ammonium fluoride a well-resolved quartet at −163·4 was found at room temperature indicating that, under these conditions, no fluoride ion was occurring. The system of aqueous solutions containing beryllium and fluoride ions has, however, been studied in more detail by Reeves *et al.*[396] These studies indicated the presence of both the BeF_3

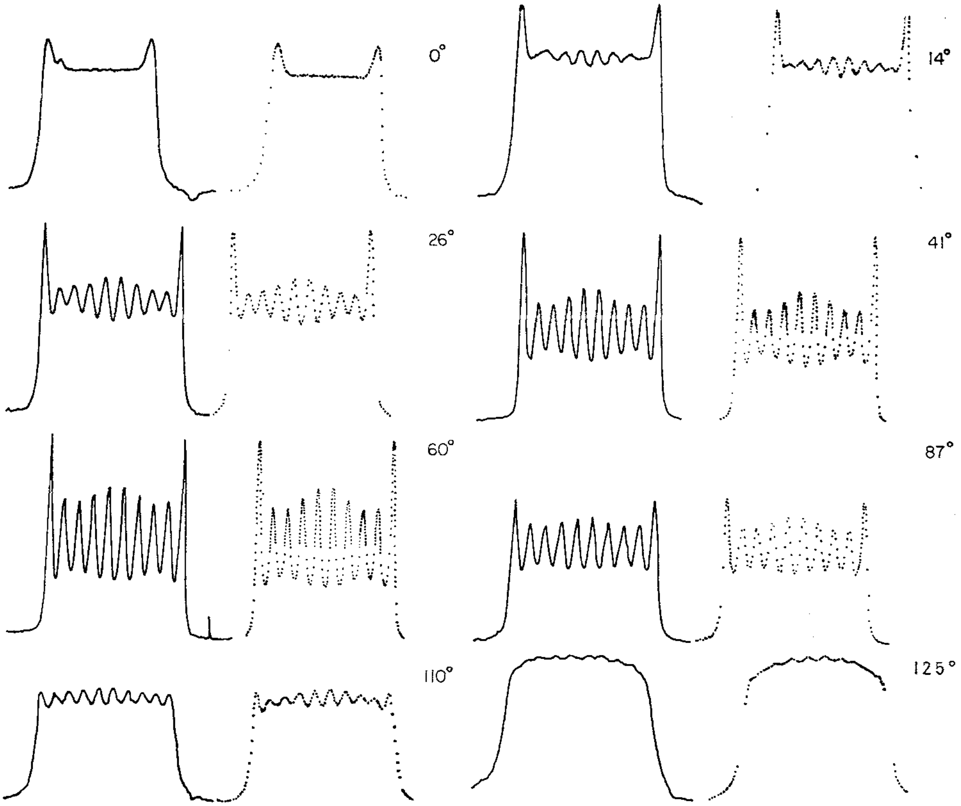


Fig. 10. The temperature dependence of the ^{19}F resonance signal of the hexafluoroniobate ion. In each case the observed spectrum is shown on the left and the calculated spectrum shown on the right. (From Aksnes, Hutchison and Packer.)[393]

$(H_2O)^{\ominus}$ and $BeF_2(2H_2O)$ species. The reduced coupling constants of the isoelectronic series $BeF_4{}^{2\ominus}$, $BF_4{}^{\ominus}$, CF_4 and $NF_4{}^{\oplus}$ were found to correlate with the atomic number.

The ^{19}F spectra of the fluorosilicate ions $SiF_5{}^{\ominus}$, $RSiF_4{}^{\ominus}$ (R = alkyl or aryl) and $(C_6H_5)_2SiF_3{}^{\ominus}$ have been examined both as a function of temperature and of solvent polarity.[397] It was concluded that, in solvent of low polarity, the ions exist as pentacoordinate entities. The low temperature spectra of the $SiF_5{}^{\ominus}$ and $RSiF_4{}^{\ominus}$ anions exhibit a single resonance line implying rapid intramolecular exchange, while that of $(C_6H_5)SiF_3{}^{\ominus}$ shows two different resonance signals corresponding to axial and equatorial environments. Upon the addition of fluoride anion the resonance became considerably broadened and this observation is considered to indicate rapid intermolecular exchange of the type—

$$RSiF_4{}^{\ominus} + F^{*\ominus} \rightleftharpoons RSiF_3F^{*\ominus} + F^{\ominus}$$

The ^{19}F shifts of the $RSiF_4{}^{\ominus}$ anion (R = Me, Bu^n or Ph) all fall in the range –110 to –120, and ^1J(Si–F) is in the range 205 to 223 Hz.

A very extensive study of the complex salts of tin of the type $[SnF_{6-n}X_n]^{2\ominus}$ has been undertaken by Dean and Evans,[398] and the ^{19}F shifts of nearly 100 anions have been tabulated, as have the ^{119}Sn–^{19}F and ^{19}F–^{19}F coupling constants. It perhaps serves as a very useful example to illustrate how the ^{19}F spectra may be used to determine the type of anion present and the type of spectra to be expected are shown in Table XLVI. The shift for the complex ions was found to be related by the expression $\delta = pC + qT$, where C and T are constants characteristic of the ligands X and p and q are the number of substituents *cis* and *trans* to the fluorine atoms respectively. Using the data of mixed ions of the type $[SnX_nY_yF_{6-(n+y)}]^{2\ominus}$, e.g. $[SnBrClF_4]^{2\ominus}$, there was good agreement between the experimental and calculated values. The solvent dependence of the ^{19}F shifts and the ^{119}Sn–^{19}F coupling constant of the hexafluorostannate ion, $[SnF_6]^{2\ominus}$, were also considered.

TABLE XLVI

The spectra characteristic of complex salts of the type $(SnFnX_{6-n})^{2\ominus}$.[398]

SnF_5X	AX_4 or AB_4
cis-SnF_4X_2	A_2X_2 or A_2B_2
trans-SnF_4X_2	Single line
cis-SnF_3X_3	Single line
trans-SnF_3X_3	AX_2 or AB_2
cis-SnF_2X_4	Single line
trans-SnF_2X_4	Single line
$SnFX_5$	Single line

The complex salts containing the anions $[CF_3PF_5]^{\ominus}$, $[(CF_3)_2MF_4]^{\ominus}$ and $[(CF_3)_3MF_3]^{\ominus}$, where M = P and As, have been prepared and the ^{19}F spectra discussed.[399] The spectra of the bis- and tris- (trifluoromethyl)-fluorophosphates indicate a *trans* configuration of the CF_3 groups. No fine structure was observed in the spectra of the fluoroarsenate ions due to the quadrupole broadening from the ^{75}As nucleus.

It was found that the hexafluorophosphate ion and boron trifluoride or phosphorus pentafluoride undergo rapid fluorine exchange in methylene dichloride solution.[400] The exchange rates were measured using the ^{19}F resonance spectra.

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