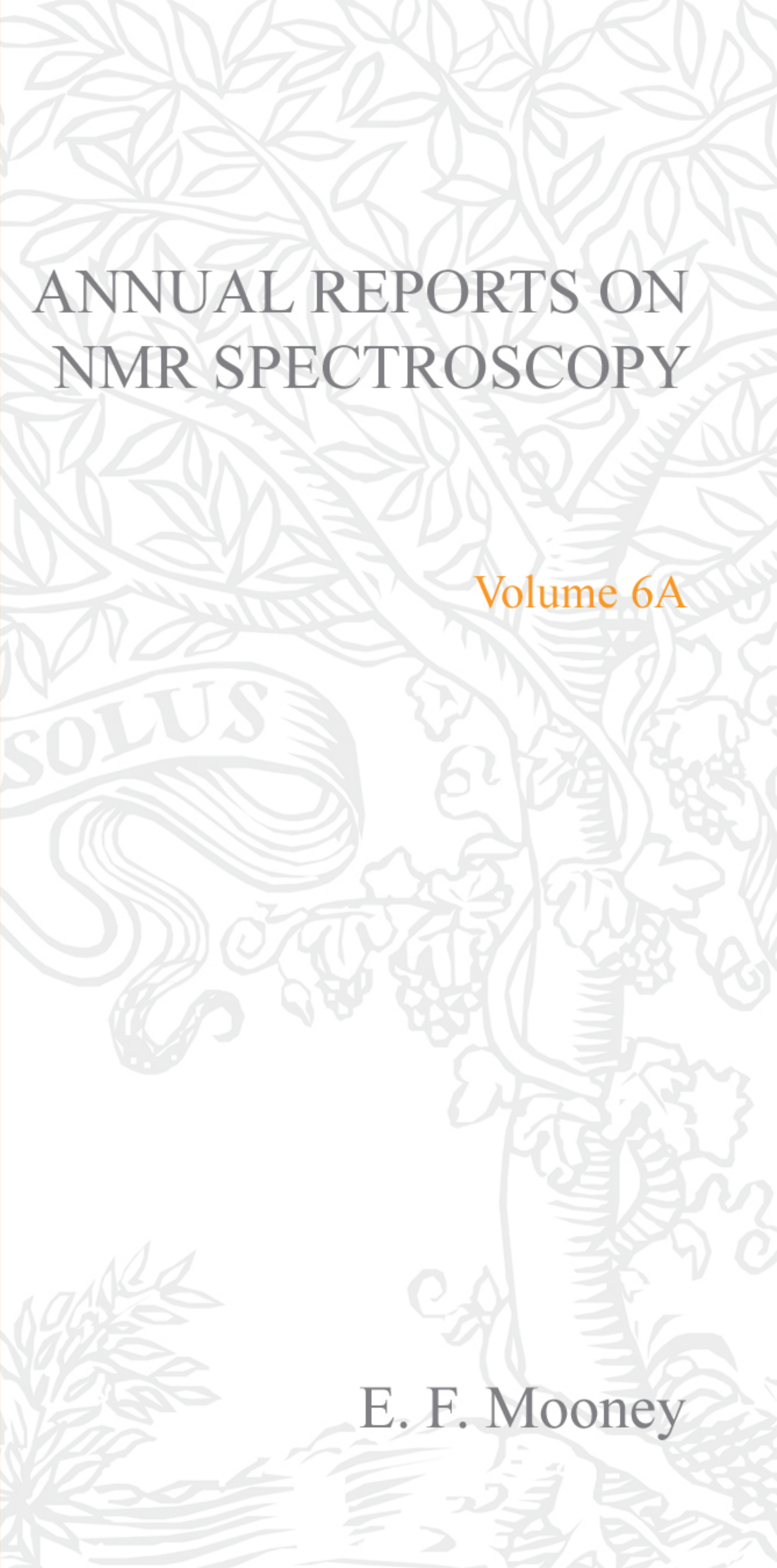

ANNUAL REPORTS ON NMR SPECTROSCOPY

Volume 6A

E. F. Mooney

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NMR SPECTROSCOPY

VOLUME 6A

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NMR SPECTROSCOPY

Edited by

E. F. MOONEY

Anacon (Instruments) Limited, Bourne End, Buckinghamshire, England

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PREFACE

The difficulties experienced by printers, publishers and editors in producing books seem to be growing in magnitude each year. To expedite the publication this Volume has been restricted to four contributions.

Dr. Webb is no stranger to this Series. He has updated his earlier contribution (1970) on NMR of paramagnetic species. The theoretical aspects of contact shifts are briefly considered but the greater proportion of the chapter is concerned with applications, one section being devoted to biological systems. The importance of NMR in biological studies is reflected in that one chapter is devoted entirely to the study of alkaloids.

The general review of NMR deals with four important aspects, chemical shifts, conformation and configurational process, carbon-13 studies and organometallic compounds. The latter section is especially timely in drawing attention to uses of NMR in this field.

The final section deals with an aspect of proton-carbon-13 coupling which has been essentially neglected. The majority of systematic studies of coupling constants have been devoted to single bond ^1H–^{13}C and two bond vicinal ^1H–^1H couplings. This chapter on two bond ^1H–^{13}C couplings will undoubtedly inspire this topic to be further studied.

It will be noted that in an attempt to keep costs down we have omitted an Author Index. In Volume 5A this index occupied forty pages, or over 5% of the total space. We trust that the various authors, whose work has been referred to in this volume, will accept that this is done simply on the basis of economy.

Finally I must express my gratitude to these authors for their efforts in the careful preparation of their manuscripts and to various readers of this Series for their encouragement and appreciation of the usefulness of this series in attempting to summarize various aspects of the chemical applications of NMR Spectroscopy.

Anacon (Instruments) Ltd.,
Bourne End,
Buckinghamshire,
October, 1975

ERIC F. MOONEY

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Nuclear Magnetic Resonance Spectroscopy of Paramagnetic Species

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I. INTRODUCTION

As anticipated four years ago, the number of reported NMR investigations on paramagnetic species has multiplied dramatically during this period. (1) A number of significant advances have been made, the most notable ones being the introduction and extensive use of paramagnetic shift reagents, the study of nuclei other than protons in a paramagnetic environment and the application of more precise theoretical studies to the origins of the interactions produced by paramagnetic species.

Almost all of the areas of investigation reported on previously have produced further data and in some cases new interpretations of older data. The number of reviews (2-11) dealing with various aspects of NMR in paramagnetic systems, published during the last four years reflects the growth in interest of this topic. The present article covers the literature published before the end of 1972, and due to a delay in publication the opportunity has been taken to add references 752-815 which are a selection of the most important papers and reviews appearing on this topic in 1973. In particular two books have been devoted to certain aspects of NMR studies on paramagnetic species, one dealing largely with transition metal complexes, (752) the other with shift reagents. (753) It is to be hoped that this article brings up to date the one written for Volume 3 of this series (1) to which extensive reference is made.

II. THEORETICAL BACKGROUND

Isotropic shifts in the NMR spectra of paramagnetic species may arise from either or both of two different mechanisms, one of which produces contact interactions while the other gives rise to dipolar or pseudo-contact interactions between unpaired electronic and nuclear spins. (1) The expression commonly used to relate the contact shift ΔH, at an applied field H_0, to the hyperfine interaction constant a_N is:

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

where a_N is expressed in gauss, g_e is the rotationally averaged electronic g value, β_e is the Bohr magneton, g_N and β_N are the corresponding nuclear parameters and S denotes the spin of the unpaired electrons. In order that well resolved contact shifted NMR signals be obtained it is necessary for the electronic relaxation time T_{1e} to be sufficiently short such that

$$T_{1e}^{-1} \gg \frac{g_e \beta_e}{h} a_N \tag{2}$$

The factors responsible for producing very small values of T_{1e} are not fully understood in all cases; in general it seems that an orbitally triply degenerate ground term (12) and, or, a spin multiplicity greater than 2 are important contributing factors.

Dipolar shifts may occur in addition to contact shifts. They arise from the direct magnetic dipole–dipole interaction between the unpaired electronic and nuclear spins. For molecules with tetragonal symmetry the dipolar shift is often expressed by:

$$\frac{\Delta H}{H_0} = -\frac{(3\cos^2\theta - 1)}{r^3} \frac{\beta_e^2 S(S+1)}{3\kappa T} F(g) \tag{3}$$

where r is the separation between the resonating nucleus and unpaired electrons, θ is the angle between the vector defined by r and the principal symmetry axis of the molecule and $F(g)$ is an algebraic function of the g tensor components. Many authors have considered that the form of $F(g)$ depends upon the relative magnitudes of the g tensor anisotropy, electronic spin-lattice relaxation time and the correlation time for molecular tumbling. (1) However, it has recently been demonstrated that this is not the case and the same expression for $F(g)$ can be applied to dipolar shifts arising from both solid and liquid samples. (38) Prior to this it has been assumed that contact shifts are the same for a given molecule in the solid and liquid states but that dipolar shifts are different. NMR data on solid and liquid samples of Vanadocene show the same shift in both cases from which it was concluded that the shift is contact in origin. (1) It now seems that this conclusion is not well founded.

Many assumptions have been made in the derivation of equations (1) and (3) which impose limitations on the extent of their application. Four of these assumptions are particularly noteworthy,

(a) contributions to the shift arising from interactions between nuclear spin and electronic orbital angular momenta, are assumed to be accounted for indirectly by means of the g tensor components. This implies that the magnetic moment of the paramagnetic species contains an orbital contribution produced only by spin-orbital coupling. Transition metal complexes with T_1 and T_2 ground terms often have a significant orbital contribution to their magnetic moments but this has been generally ignored in considering their NMR spectra. (12)

(b) In the absence of the applied magnetic field it is assumed that the paramagnetic species has only one thermally populated energy level. The states arising from this level are assigned a spin quantum number S. However, this has been shown to be an inadequate description for some transition metal complexes. (13, 14)

(c) For systems with $S \geqslant 1$ zero field splittings of the states are expected but these have been ignored. ESR data have demonstrated the existence of relatively large zero field splittings in a number of transition metal complexes. (15)

(d) It is assumed in equation (3) that r is sufficiently large for the paramagnetic centre to be treated as a point dipole. The interpretation of some ^{14}N NMR data obtained from iron(III) cyanide complexes suggests that this assumption is not always justified. (16)

In order to obtain realistic estimates of the spin density distribution and geometry of paramagnetic species a theoretical description of the induced shifts is required which is not founded on these assumptions.

A further shortcoming of equation (3) becomes apparent when nuclei other than protons are being considered. For these nuclei a contribution to the dipolar shift may arise from the interaction of the nuclear spin with the orbital angular momentum of unpaired electrons in orbitals centred at the nucleus concerned. (17) Kurland and McGarvey have proposed a general theoretical treatise in which the approximations, responsible for most of the limitations on the use of equations (1) and (3), have been removed. (18)

When chemical exchange may be safely ignored, the interaction between the nuclear spin and the spin and orbital motions of the unpaired electrons is given by:

$$\hat{\mathscr{H}}_N \cdot \hat{I}_N = (\hat{\mathscr{H}}_F + \hat{\mathscr{H}}_D + \hat{\mathscr{H}}_L) \cdot \hat{I}_N \qquad (4)$$

where $\hat{\mathscr{H}}_N$ is the Hamiltonian operator accounting for the nuclear–electronic interaction and $\hat{I}_N$ is the nuclear spin operator. The components of $\hat{\mathscr{H}}_N$ are given by:

$$\hat{\mathscr{H}}_F = \frac{8\pi}{3} g_e\beta_e g_N\beta_N \sum_i \hat{\delta}(\hat{r}_i)S_i \tag{5}$$

$$\hat{\mathscr{H}}_D = g_e\beta_e g_N\beta_N \sum_i \left[\frac{3(\hat{S}_i \cdot r_i)r_i - \hat{r}_i^2 \cdot \hat{S}_i}{r_i^5}\right] \tag{6}$$

and

$$\hat{\mathscr{H}}_L = 2\beta_e g_N\beta_N \sum_i \frac{\hat{L}_i}{r_i^3} \tag{7}$$

where the operators $\hat{S}_i$ and $\hat{L}_i$ represent respectively the spin and orbital angular momenta of the ith electron which is situated at a distance $\hat{r}_i$ from the nucleus and the delta function $\hat{\delta}(\hat{r}_i)$ expresses the probability density for the electron i at the nucleus. The delta function operator is defined by:

$$< \psi \,|\hat{\delta}(r)|\, \psi > = |\psi(o)|^2 \tag{8}$$

where $\psi(o)$ is the wavefunction governing the distribution of the unpaired electrons evaluated at the nucleus. Hence equation (5) describes the contact interaction and

$$a_N = \frac{8\pi}{3} g_N\beta_N |\psi(o)_N|^2 \tag{9}$$

Equation (6) accounts for the dipolar interaction between all of the unpaired electrons and the nuclear spins while the nuclear spin and electron orbital angular momentum interaction is described by equation (7). Thus taken together equations (6) and (7) define the operators which account for the dipolar interactions between nuclei and unpaired electrons.

Kurland and McGarvey have assumed that the interaction described by equation (4) is small compared to the nuclear Zeeman interaction with the applied magnetic field. (18-20) In developing general expressions for the nuclear-electronic interactions they have emphasized the similarity of their approach to that of Van Vleck in the theory of magnetic susceptibilities. (21) This depends upon the existence of a series of states in the absence of an applied magnetic field the nth of which is described by an eigenfunction ψ_n^0 with energy E_n^0. When a field H_0 is applied in the z direction the resulting nuclear-electronic interactions among these states are determined by the operators given in equation (4). In the general case the interactions may be written as:

$$\langle \psi_{nz} | \hat{\mathscr{H}}_N \cdot \hat{I}_N | \psi_{nz} \rangle = m_I [b^0_{nz} + b^{(1)}_{nz} H_0 + \ldots] \qquad (10)$$

In equation (10) m_I is the component of the nuclear spin vector in the direction of H_0 and the coefficients b^0_{nz}, $b^{(1)}_{nz}$ . . . account for the nuclear-electronic interactions among the unperturbed eigenfunctions. Expressions involving b^0_{nz} and $b^{(1)}_{nz} H_0$ are known as first and second order terms respectively. The evaluation of matrix elements of the type depicted by equation (10) are considered separately for the contact and dipolar interactions according to the operators defined by equations (5)–(7).

A. Contact Interactions

For contact shifts the resulting general expression averaged over all molecular orientations is:

$$\frac{\Delta H}{H_0} = -\left[3 g_N \beta_N \sum_n \exp\left(\frac{-E^0_n}{\kappa T}\right)\right]^{-1} \sum_{\alpha = x,y,z} \sum_n \left(\frac{b^0_{n\alpha} E^{(1)}_{n\alpha}}{\kappa T} - b^{(1)}_{n\alpha}\right) \exp\left(\frac{-E^0_n}{\kappa T}\right) \qquad (11)$$

where

$$E^{(1)}_{n\alpha} = \beta \langle \psi^0_n | (L_\alpha + g S_\alpha) | \psi^0_n \rangle \qquad (12)$$

and

$$b^0_{n\alpha} = \langle \psi^0_n | \hat{\mathscr{H}}_F(\alpha) | \psi^0_n \rangle \qquad (13)$$

where $\hat{\mathscr{H}}_F$ is defined by equation (5) and

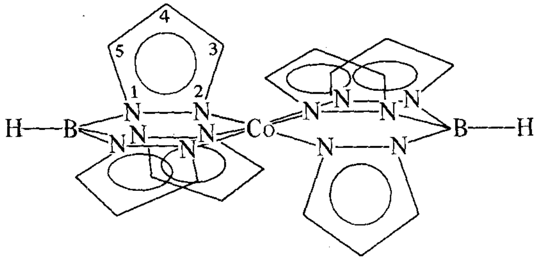
$$b^{(1)}_{n\alpha} = \beta \sum_{m \neq n} [\langle \psi^0_n | \hat{\mathscr{H}}_F(\alpha) | \psi^0_m \rangle \langle \psi^0_m | (L_\alpha + g S_\alpha) | \psi^0_n \rangle + \langle \psi^0_n \, (L_\alpha + g S_\alpha) | \psi^0_m \rangle \langle \psi^0_m | \hat{\mathscr{H}}_F(\alpha) | \psi^0_n \rangle] (E^0_n - E^0_m)^{-1} \qquad (14)$$

Since equation (11) is a general expression for contact shifts it contains more parameters than are necessary for many paramagnetic species. Consequently simplified forms of equation (11) are more suitable for individual cases. In general the contact interaction is not the same for all of the n states included in equation (11). However, metal ions with the electronic configuration $(t_{2g})^1$ can be considered as having the same spin density in all of their thermally populated excited states. The resulting expression for their contact shifts is:

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e \beta_e^2}{g_N \beta_N 6\kappa T}\left\{\frac{(16\kappa T/3\lambda) + [1 - (16\kappa T/3\lambda)]\exp(-3\lambda/2\kappa T)}{2 + \exp(-3\lambda/2\kappa T)}\right\} \tag{15}$$

where λ is the electronic spin-orbital coupling constant.

Neither equation (11) nor (15) predict a Curie Law dependence (i.e. T^{-1}) for the contact shifts. This has been verified by some tetrahedral nickel(II) complexes which have a $^3T_1$ ground term. (20) However, not all molecules with orbitally degenerate ground terms have a non-Curie law dependence of their contact shifts as has been demonstrated by tris(pyrazolylborate)cobalt(II), (19) [1]. McGarvey (19) has written the contact shifts predicted by equation (11) as:



[1]

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e \beta_e}{g_N \beta_N h} F \tag{16}$$

and

$$F = F_1 + F_2 \tag{17}$$

where F_1 and F_2 represent the total contributions to the shifts from the first and second order terms respectively. Previous experimental data has revealed that [1] is trigonally distorted such that the $^4T_{1g}$ ground term is split into $^4A_2$ and ^4E components with the ^4E lying lowest in energy. (13) Values of F_1, F_2 and F have been calculated for the ^4E components and plotted as a function of temperature in Fig. 1 which shows that the first and second order contributions to the contact shifts are almost equal at room temperature for [1]. Although both F_1 and F_2 are temperature

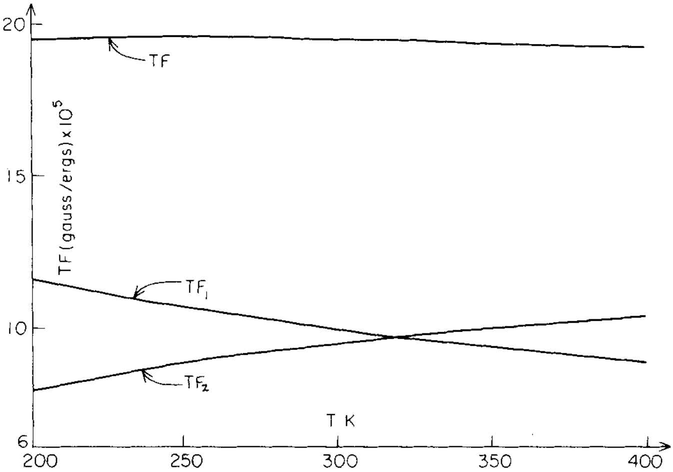


FIG. 1. Plot of the contact contributions times temperature as a function of temperature for the ^{4}E states of [1]. (19)

dependent the total contact shift, as denoted by F, is fortuitously almost independent of temperature over the range 200 to 400 K. The difference in the temperature dependence of the contact shifts for these two cases of triply orbitally degenerate ground terms, tetrahedral nickel(II) and six-coordinate cobalt(II), arises from the extent to which excited and ground states are mixed. This mixing can produce a large contact shift even when the excited states are not extensively populated. Consequently each case must be considered individually.

If all of the thermally accessible states of a given molecule belong to a single spin level with spin S then the appropriate expression for the contact shifts is:

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e}{3 g_N \beta_N}\left[\frac{\chi_{xx}}{g_{xx}} + \frac{\chi_{yy}}{g_{yy}} + \frac{\chi_{zz}}{g_{zz}}\right] \tag{18}$$

where χ_{xx}, χ_{yy} and χ_{zz} are the principal components of the magnetic susceptibility tensor, which contains both first and second order terms. The corresponding components of the g tensor, which contains only first order terms, are g_{xx}, g_{yy} and g_{zz}. For a system with no zero field splitting and no ground state orbital angular momentum,

$$\chi_{\alpha\alpha} = \frac{g_{\alpha\alpha}^2 \beta_e^2 S(S+1)}{3\kappa T} \tag{19}$$

This relatively simple system is described by equation (1) which is obtained by substituting equation (19) into (18) and assuming that the g tensor is isotropic.

The effects of zero field splittings, D, on contact shifts have been discussed for the cases in which $S = 1, \frac{3}{2}$ and $\frac{5}{2}$. It is assumed that the zero field splitting tensor is isotropic and $\kappa T \gg D$. (18) For an axially symmetric molecule with a non-orbitally degenerate ground term, the components of the g tensor parallel and perpendicular to the major symmetry axis are $g_{\parallel}$ and $g_{\perp}$ respectively. The resulting contact shifts are given for $S = 1$ by

$$\frac{\Delta H}{H_0} = -\frac{2a_N g_e^2 \beta_e^2}{g_N \beta_N 3\kappa T}\left[1 - \frac{(g_{\parallel} - g_{\perp})D}{9g_e \kappa T}\right] \tag{20}$$

for $S = \frac{3}{2}$,

$$\frac{\Delta H}{H_0} = -\frac{5a_N g_e^2 \beta_e^2}{g_N \beta_N 4\kappa T}\left[1 - \frac{4(g_{\parallel} - g_{\perp})D}{15g_e \kappa T}\right] \tag{21}$$

and for $S = \frac{5}{2}$,

$$\frac{\Delta H}{H_0} = -\frac{35a_N g_e^2 \beta_e^2}{g_N \beta_N 12\kappa T}\left[1 - \frac{224(g_{\parallel} - g_{\perp})D}{315g_e \kappa T}\right] \tag{22}$$

Since $(g_{\parallel} - g_{\perp})$ is expected to be small for non-orbitally degenerate ground terms it is apparent from equations (20)-(22) that contact shifts significantly different from those predicted by equation (1) will only be produced by zero field splitting when the ratio of D to κT is large. This ratio is expected to be small for the majority of transition metal complexes, therefore the zero field splitting contribution to the contact shifts is not expected to be very significant in most cases.

B. Dipolar Interactions

In the general case the dipolar shifts are given by expressions similar in form to equations (11)-(14), with the operators $\mathscr{H}_D$ and $\mathscr{H}_L$ defined by equations (6) and (7) replacing $\mathscr{H}_F$. These operators represent the total dipolar interaction which consists of two contributions, one from unpaired electrons in orbitals centred at the metal ion, the other from unpaired electrons in orbitals belonging to the ligand nucleus whose NMR spectrum is being considered. These two contributions are denoted by $\Delta H^M/H_0$ and $\Delta H^L/H_0$ respectively. McGarvey (19) has calculated the first order, P_1, and second order, P_2, components of the dipolar shift, P, for [1] from a set of expressions similar to equations (11)–(14). The second order contribution to the dipolar shift has not often been considered, (22, 23) however as shown in Fig. 2 it can be similar in magnitude to the first order contribution. The non-Curie law dependence of the dipolar shift over the temperature range studied is also demonstrated in Fig. 2.

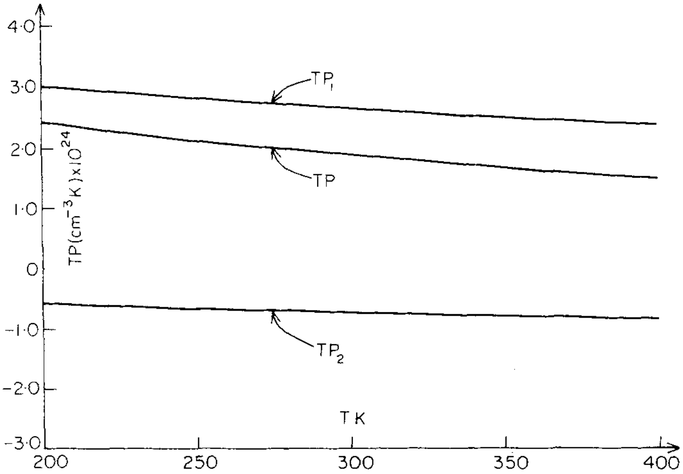


FIG. 2. Plot of the dipolar contributions times temperature as a function of temperature for [1].(19)

Using the point dipole approximation the contribution to the dipolar shifts arising from unpaired electrons on the metal is

$$\frac{\Delta H^M}{H_0} = -\frac{1}{3r^3}\left[(3\cos^2\theta - 1)(\chi_{zz} - \tfrac{1}{2}\chi_{xx} - \tfrac{1}{2}\chi_{yy}) + \frac{3}{2}(\chi_{xx} - \chi_{yy})\sin^2\theta\cos 2\psi\right] \tag{23}$$

where the angles θ and ψ are defined in Fig. 3.

For axial symmetry equation (23) reduces to:

$$\frac{\Delta H^M}{H_0} = -\frac{1}{3r^3}(3\cos^2\theta - 1)(\chi_{\parallel} - \chi_{\perp}) \tag{24}$$

In those cases where the major components of the magnetic susceptibility tensor and molecular geometry have been determined it is possible to calculate dipolar shifts from equation (23) or (24). By comparing the calculated and observed shifts it is possible to evaluate

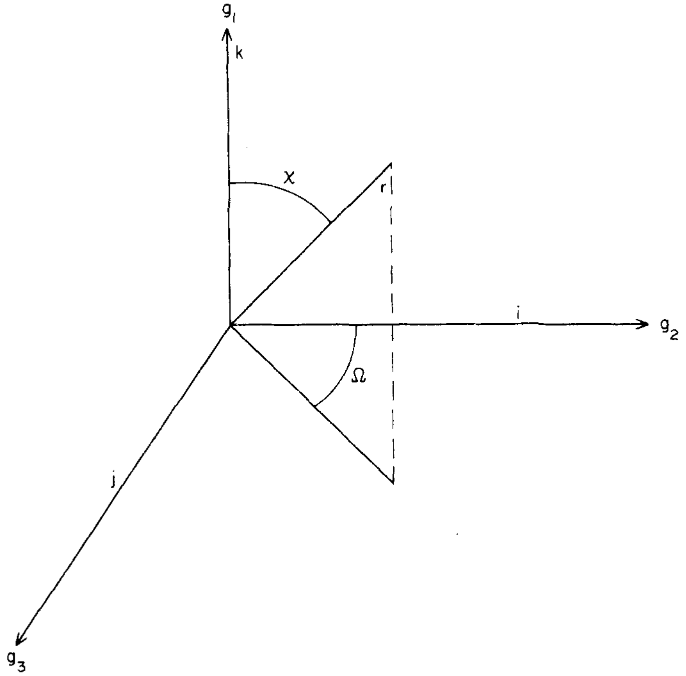


Fig. 3. Definition of angles and g tensor components in rhombic symmetry.

contact contributions to the experimental shifts. This approach has been applied to tris(bipyridyl)cobalt(II) dibromide hexahydrate, (22) bis(dithioacetylacetone)cobalt(II), (24) bis(acetylacetone) bis(pyridine)cobalt(II), (25) dichloro bis(triphenylphosphine)cobalt(II) and nickel(II) (26) and some eight coordinate lanthanide shift reagent adducts. (27) In the latter case the results show that the proton shifts are mainly dipolar in origin and that it is in general unwise to assume that the adducts have axially symmetrical magnetic properties in the solid state. (27)

If zero field splitting is ignored and only one thermally populated multiplet with spin S is considered, then the major components of the magnetic susceptibility tensor can be expressed by equation (19). The corresponding dipolar shifts depend only on first order terms and are given by:

$$\frac{\Delta H^M}{H_0} = -\frac{\beta^2 S(S+1)}{9\kappa T r^3}\left[(3\cos^2\theta - 1)(g_{zz}^2 - \tfrac{1}{2}g_{xx}^2 - \tfrac{1}{2}g_{zz}^2) + \frac{3}{2}(g_{xx}^2 - g_{yy}^2)\sin^2\theta\cos 2\psi\right] \tag{25}$$

and for the case of axial symmetry by:

$$\frac{\Delta H^M}{H_0} = -\frac{\beta^2 S(S+1)}{9\kappa T}\frac{(3\cos^2\theta - 1)}{r^3}(g_\parallel^2 - g_\perp^2) \tag{26}$$

which is the most commonly used form of equation (3). Equations of this form, involving g tensor components, are frequently used in discussions of lanthanide induced dipolar shifts. However, for ions such as europium(III) which have a ground state with zero electronic angular momentum, these equations are meaningless. In such cases the dipolar shifts are due to second order terms arising from the thermal population of excited states, consequently expressions involving the magnetic susceptibility tensor must be used in serious discussions of the dipolar shifts. Unfortunately many authors have overlooked this point in discussing the shifts induced by complexes of europium(III). (28)

For axially symmetric molecules with non-orbitally degenerate ground terms the effects of zero field splittings on the dipolar shifts have been considered when $S = 1$, $\frac{3}{2}$ and $\frac{5}{2}$. (18) Expressions analogous to equations (20)-(22) are obtained by assuming that $\kappa T \gg D$.

For $S = 1$

$$\frac{\Delta H^M}{H_0} = -\frac{2\beta_e^2(g_\parallel^2 - g_\perp^2)}{9\kappa T}\frac{(3\cos^2\theta - 1)}{r^3}\left[1 - \frac{(g_\parallel^2 + \frac{1}{2}g_\perp^2)D}{3(g_\parallel^2 - g_\perp^2)\kappa T}\right] \tag{27}$$

for $S = \frac{3}{2}$

$$\frac{\Delta H^M}{H_0} = -\frac{5\beta_e^2(g_\parallel^2 - g_\perp^2)}{12\kappa T}\frac{(3\cos^2\theta - 1)}{r^3}\left[1 - \frac{4(g_\parallel^2 + \frac{1}{2}g_\perp^2)D}{5(g_\parallel^2 - g_\perp^2)\kappa T}\right] \tag{28}$$

and for $S = \frac{5}{2}$

$$\frac{\Delta H^M}{H_0} = -\frac{35\beta_e^2(g_\parallel^2 - g_\perp^2)}{36\kappa T}\frac{(3\cos^2\theta - 1)}{r^3}\left[1 - \frac{224(g_\parallel^2 + \frac{1}{2}g_\perp^2)D}{105(g_\parallel^2 - g_\perp^2)\kappa T}\right] \tag{29}$$

Equations (27)-(29) each comprise two major terms, the first of which is similar in form to equation (26) and has a Curie law dependence. The second term arises from zero field splitting and has a T^{-2} dependence. Due to the shapes of the relevant equations, the zero field splitting term is expected to play a more significant role in any discussion of dipolar shifts than it does for contact shifts.

Six-coordinate nickel(II) provides an example in which the zero field splitting contribution to the dipolar shifts amounts to approximately 25% of that produced by the first-term in equation (27).

Theoretically a variable temperature NMR study should allow the contributions from the two terms in equations (27)–(29) to be separated. In practice the experimental range of temperatures is often too small and the errors too large to permit it. However, the dipolar component of the shifts exhibited by a high-spin iron(III) complex with an isotropic g tensor has recently been demonstrated to have a T^{-2} dependence on account of the zero field splitting term. (544) The non-Curie law dependence of the shifts of some tetra-(allene)uranium(IV) complexes has also been accounted for by the zero field splitting components given in equations (20) and (27). (601) Further studies of this type aimed at estimating the importance of zero field splitting in determining dipolar shifts, are to be anticipated.

Bleaney (28) has developed expressions for the dipolar shifts of lanthanide ions from a consideration of the magnetic susceptibility tensor. These expressions depend upon the anisotropy of the zero field splitting tensor rather than the g tensor and consequently, by analogy with equations (27)–(29), they show a T^{-2} dependence for the shifts providing that the molecular geometry does not vary with temperature or the number of $4f$ electrons present. This discussion is considered further in Section III. H. 1(i) page 102.

If the unpaired electrons in the paramagnetic species are able to occupy a p orbital centered on the nucleus, whose NMR spectrum is being studied, then a ligand centered contribution to the dipolar shifts may occur. With protons the unpaired electrons are mainly in s orbitals only, however, most other nuclei have p orbitals of the correct symmetry and energy for the ligand centred contribution to be of some significance.

The ligand centred contribution depends on the admixture of metal d and ligand p orbitals resulting in the delocalization of unpaired electrons between the metal and the ligand. Those electrons in a ligand p orbital are able to interact with the nuclear spin and produce a contribution to the dipolar shifts which, for metal complexes with the electronic configuration $(t_{2g})^5$, is given by (18):

$$\frac{\Delta H^L}{H_0} = -\frac{16\beta_e^2 f^2 \langle d^{-3}\rangle p}{45\kappa T}\left[\frac{1 + (11\kappa T/6\lambda)\,[1 - \exp(-3\lambda/2\kappa T)]}{1 + 2\exp(-3\lambda/2\kappa T)}\right] \tag{30}$$

where f is the mixing coefficient for the molecular orbitals formed from the metal $d(t_{2g})$ and ligand orbitals, $\langle d^{-3}\rangle p$ is the average value of d^{-3} for the ligand p orbital concerned and d is the separation of the unpaired electron and nucleus in question. Equation (30) predicts a dipolar shift for molecules with an isotropic g tensor which contrasts strongly with equations (25)-(29) describing the metal centred contribution. This arises from the mixing of spin and orbital states by spin-orbital coupling. (18)

The amount of spin density present in the ligand centred orbitals is expected to be much smaller than in the metal orbitals; however $\langle d^{-3}\rangle p$ is expected to be much larger than r^{-3}. Therefore the contributions to dipolar shifts from metal and ligand centered spin densities may be of comparable magnitude. In the case of the ferricyanide ion the observed ^{14}N shift together with reasonable estimates of λ and $\langle d^{-3}\rangle p$ yield a value of 0·029 for f^2 from equation (30) which corresponds to about 17% covalency in the metal-ligand bonds. Obviously the ligand centred contribution to the dipolar shift is significant in this case but it may not always be. (18) In general it appears that molecules with orbitally degenerate ground terms, which have extensive mixing of spin and orbital states, are most likely to have appreciable ligand centred contributions to their dipolar shifts. Hence each case has to be considered individually.

A convincing demonstration of the necessity of using the equations formulated by Kurland and McGarvey has been presented by La Mar, Jesson and Meakin. (29) They have plotted the temperature dependence of the isotropic shifts of the four different protons in [1], and compared the curves with three different theoretical treatments, one of which is expressed by equations (1) and (3), another by Kurland and McGarvey's equations and the third by a series of comparable equations proposed by Jesson (13) in which only first order terms are considered. The results are presented in Fig. 4. (29)

Although the results obtained from Jesson's equations agree well with the room temperature shifts the deficiencies produced by neglecting the second order terms become apparent when the variable temperature experimental data are considered. Consequently in order to quantitatively interpret the contact and dipolar shifts the approach developed by Kurland and McGarvey must be followed, especially for distorted molecules with orbitally degenerate ground terms.

In a recent consideration of magnetic multipoles it has been reported that the contribution of the quadrupolar term to dipolar shifts may be significant. (30) At a distance of 5 Å from the metal

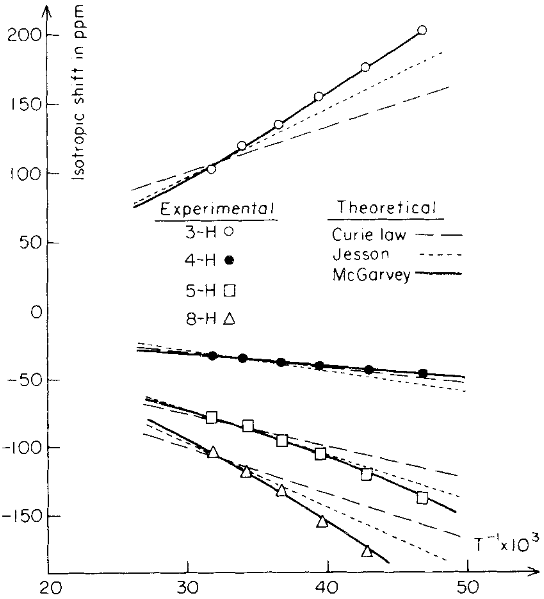


FIG. 4. Temperature dependence of the isotropic shifts of [1] in CD_2Cl_2 compared with curves derived from the Curie Law and the equations of Jesson and of Kurland and McGarvey. (29)

ion in a molecule without a centre of inversion the quadrupolar contribution to the shifts could be approximately 10% (30). In centrosymmetric molecules the corresponding octopolar contribution is estimated to be about 1%.

For transition metal complexes with cubic symmetry this contribution is expected to be too small to distinguish in the presence of a contact term. (754) A similar conclusion is reached for lanthanide complexes. However, if the complex lacks a centre of inversion, mixing of metal and ligand orbitals could produce a significant quadrupolar contribution to the dipolar shifts. (754)

C. Relaxation Phenomena

The relaxation times of nuclei with a spin of one-half depend upon both the dipolar and contact interactions present in a paramagnetic environment. (1) The expressions for the longitudinal, T_1, and transverse, T_2, nuclear relaxation times under these conditions are:

$$\frac{1}{T_1} = \frac{2S(S+1)}{15\hbar^2} g_e^2\beta_e^2 Nn \left[\frac{g_N^2\beta_N^2}{r^6}\left(\frac{3\tau_c}{1+\omega_I^2\tau_c^2} + \frac{7\tau_c}{1+\omega_S^2\tau_c^2}\right) + \frac{5a_N^2\tau_e}{1+\omega_S^2\tau_e^2}\right] \tag{31}$$

and

$$\frac{1}{T_2}=\frac{S(S+1)}{15\hbar^2}g_e^2\beta_e^2 Nn\left[\frac{g_N^2\beta_N^2}{r^6}\left(4\tau_c+\frac{3\tau_c}{1+\omega_I^2\tau_c^2}+\frac{13\tau_c}{1+\omega_S^2\tau_c^2}\right)\right.$$

$$\left.+\,5a_N^2\left(\tau_e+\frac{\tau_e}{1+\omega_S^2\tau_e^2}\right)\right] \tag{32}$$

In equations (31) and (32) the first term represents the dipolar interaction and the second term the contact interaction, where ω_I and ω_S are the Larmor precession frequencies of the nuclear and electronic spins respectively, τ_c is the correlation time for the dipolar interaction and τ_e that for the contact interaction, N is the number of ligand molecules in the first coordination sphere of the metal and n is the concentration ratio of metal to complexed ligands. For a stable molecule N_n becomes unity. Equations (31) and (32) relate to the general case of an isotropic g tensor, modifications are required to incorporate g tensor anisotropy. (31)

It is often reasonable to assume that $\omega_I^2\tau_c^2 \ll 1$ in which case, for stable molecules, equations (31) and (32) become:

$$\frac{1}{T_1}=\frac{2S(S+1)}{15\hbar^2}g_e^2\beta_e^2\left[\frac{g_N^2\beta_N^2}{r^6}\left(3\tau_c+\frac{7\tau_c}{1+\omega_S^2\tau_c^2}\right)+\frac{5a_N^2\tau_e}{1+\omega_S^2\tau_e^2}\right] \tag{33}$$

and

$$\frac{1}{T_2}=\frac{S(S+1)}{15\hbar^2}g_e^2\beta_e^2\left[\frac{g_N^2\beta_N^2}{r^6}\left(7\tau_c+\frac{13\tau_c}{1+\omega_S^2\tau_c^2}\right)+5a_N^2\left(\tau_e+\frac{\tau_e}{1+\omega_S^2\tau_e^2}\right)\right] \tag{34}$$

Now in the limit of rapid isotropic motion, $\omega_S^2\tau_e^2 \ll 1$ and equations (33) and (34) reduce to:

$$\frac{1}{T_1}=\frac{1}{T_2}=\frac{4S(S+1)}{3}\frac{g_N^2\beta_N^2 g_e^2\beta_e^2\tau_c}{\hbar^2 r^6}+\frac{2S(S+1)}{3}\frac{g_e^2\beta_e^2 a_N^2\tau_e}{\hbar^2} \tag{35}$$

For a Lorentzian line the observed linewidth at half-height, Δ, is given by:

$$\Delta=\frac{1}{\pi T_2} \tag{36}$$

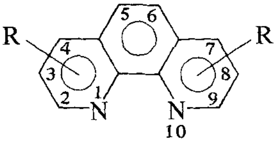
Consequently by measuring the linewidths and induced shifts at a number of magnetically different sites in a paramagnetic species it is often possible to decide whether the dipolar or contact interaction controls the nuclear relaxation times.

The correlation times τ_e and τ_c are related to the correlation times characterizing the rotational motion of the separation vector between the unpaired electron and nucleus under investigation, τ_r, the electron spin-lattice relaxation, τ_s, and the ligand exchange, τ_M, by equations (37) and (38)

$$\frac{1}{\tau_c} = \frac{1}{\tau_r} + \frac{1}{\tau_s} + \frac{1}{\tau_M} \tag{37}$$

$$\frac{1}{\tau_e} = \frac{1}{\tau_s} + \frac{1}{\tau_M} \tag{38}$$

which show that τ_e and τ_c are controlled respectively by whichever of τ_s, τ_M or τ_r, τ_s, τ_M is the shorter. For first transition series metals τ_r varies from about 10^{-9} to 10^{-13} sec, for aquometal ions τ_s is about 10^{-11} sec and τ_M is usually several orders of magnitude larger than either τ_r or τ_s. For some tris(*o*-phenanthroline)chromium(II) dichloride complexes [2] it has been experimentally demonstrated



[2]

that the proton NMR linewidths are controlled by the dipolar term in equation (35). (32) For the molecule with R = H the value of τ_c is estimated to be less than 3×10^{-12} sec which is much smaller than the expected value of $\tau_r \sim 10^{-10}$ sec. Consequently the electron spin-lattice relaxation characterized by τ_s is considered to be the process controlling the proton relaxation in this case. (33) For the corresponding molecule with R = CH_3 the signal for the protons of the methyl groups in positions 4 and 7 is unobservable at room temperature whereas the dipolar term in equation (35) predicts a linewidth of about 50 Hz. At 50°C the methyl signal appears and its width decreases dramatically up to about 70°C (Fig. 5). (33) At higher temperatures bulk ligand exchange contributes to the linewidth. The difference in the slopes of the plots in Fig. 5 for the methyl and aromatic protons indicates the presence of two correlation times with widely different activation energies. To account for this observation it has been proposed that the contact interaction term in equation (35) makes a contribution to the relaxation times. (33) However, only small linewidth differences are expected to occur

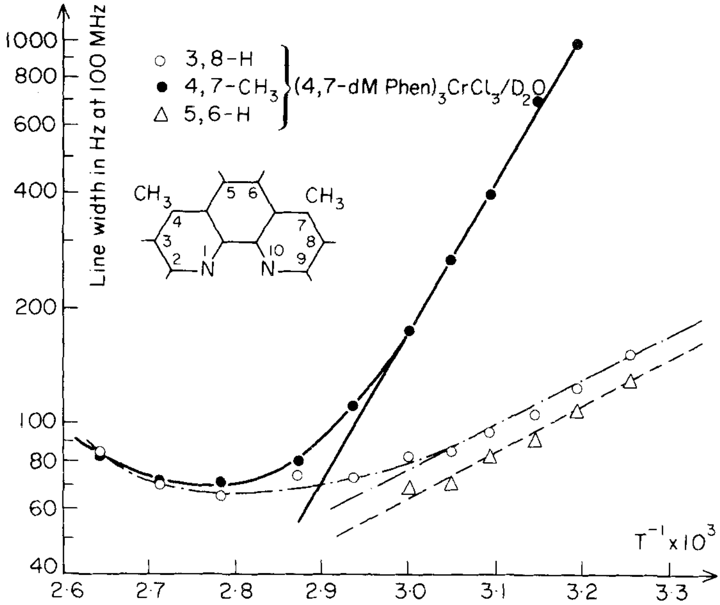


FIG. 5. Dependence of the proton linewidth on temperature for various protons in the tris-4,7-dimethyl complex of [2] with chromium(III) trichloride, in deuterium oxide. (33)

from differences in a_N for the methyl and aromatic protons. When $\tau_s^{-1} \gg a_N$ the protons experience the average spin magnetization which produces the contact shifts but the *average* contact interaction can be modulated by the lifetime of the metal–ligand bond. (34) Consequently rotation of the methyl group is capable of controlling the linewidth of the methyl protons through the contact interaction term in equation (35). Under these conditions equation (38) becomes:

$$\frac{1}{\tau_e} = \frac{1}{\tau_s} + \frac{1}{\tau_M} + \frac{1}{\tau_L} \qquad (39)$$

where τ_L is the rotational correlation time for the methyl group. If the methyl group rotates sufficiently rapidly such that $\tau_s > \tau_L$ then the methyl signal can be narrower than predicted by taking equations (35) and (38) together. Under these conditions measurement of the width of the methyl proton's signal can provide an estimate of the rotation time of the methyl group. This has not yet been estimated for a transition metal complex and is more likely to be found for free radicals which usually have nuclei with larger values of a_N and larger electron spin–lattice relaxation times.

Line broadening is produced as the barrier to the rotation of the methyl group increases. Under these conditions, where ΔH is the observed contact shift,

$$\frac{1}{T_2} = \frac{4g_N^2 \beta_N^2 \Delta H^2}{3\hbar^2} \tau_L \tag{40}$$

for the methyl protons. Consequently, τ_L may be evaluated from the observed width of the methyl proton's signal and the activation energy for rotation, V, estimated from equation (41).

$$\tau_L = \tau_L^0 \exp\left(\frac{V}{RT}\right) \tag{41}$$

Arrhenius plots yield a value of about 18 Kcal/mole for V in the case of (2) with methyl groups in the 4 and 7 positions whereas in the more crowded molecule with $R = CH_3$ in the 3, 4, 7 and 8 positions $V \sim 21$ Kcal/mole for the 4 and 7 methyl groups and about 17 Kcal/mole for those in the 3 and 8 positions. (33, 34) These data are not unreasonable and yield a value of 10^{-12}–10^{-15} sec for τ_L^0 which is consistent with the expected rotation times of unhindered methyl groups. (33, 34)

For nuclei with small values of a_N the dipolar interaction tends to dominate the nuclear relaxation times. Equation (35) shows that this term has an inverse sixth power dependence upon the separation between the nucleus under investigation and the transition metal ion. Consequently the line broadening due to this term attenuates rapidly with distance from the metal ion. This fact has been used in the interpretation of the NMR spectra of paramagnetic species (1) and has led to paramagnetic metal ions being used as broadening agents to remove interfering solvent lines from NMR spectra. (35, 36)

Even in the presence of a small amount of contact interaction the r^{-6} dependence renders the dipolar relaxation very sensitive to changes in r. This has been used to determine electron-nucleus distances for some labile complexes of chromium(III), manganese(II), iron(III), cobalt(II), nickel(II) and copper(II) from line broadening measurements. The values obtained are in good agreement with known structures. (755) Provided that the appropriate NMR signals can be resolved and assigned this method of structural determination can be applied to large molecular complexes and to substrates in the presence of certain lanthanide complexes, (804, 808) (Section III. H. 2(i)).

Equations (31) and (32) show that the nuclear relaxation times depend upon the ratio of metal to ligand concentration, n, in the solution. This has formed the basis of an analytical method for following redox titrations and titrations which produce metal complexes either in solution or by precipitation. (37) The equivalence point is determined by measuring the spin-lattice relaxation time of the nuclei in solution as a function of the added volumetric reagent. The paramagnetic species concerned may be either in the original or the added solutions. (37)

D. Spin Density Distribution in Paramagnetic Species

NMR contact shifts and hyperfine splittings in ESR spectra provide a description of the distribution of the unpaired electrons in paramagnetic species. (1) Equation (9) shows that it is necessary for the unpaired electrons to have some S character in order to produce contact interactions. In studies of the proton NMR spectra of ligands attached to a paramagnetic transition metal ion a_N is usually given by:

$$a_N = \frac{Q\rho}{2S} \tag{42}$$

For π spin delocalization ρ is the spin density in the $2P_\pi$ orbital of the atom to which the proton is bonded and Q is -22.5 Gauss for a single proton and about 27 Gauss for the protons of a methyl group. For σ spin delocalization ρ is the spin density at the proton and Q is 508 Gauss. In either case $2S$ is the total number of unpaired electrons in the molecule (39) rather than the number involved in the particular delocalization mechanism giving rise to the contact shifts. (40)

The smaller values of Q for π delocalization compared with that for σ delocalization reflect the inefficiency of the less direct spin polarization mechanism whereby the unpaired electrons achieve some S character in the former case.

Comparison of the values of a_N found experimentally from contact shifts described by an expression based upon equations (11)-(14) with that obtained from equation (42), following a theoretical estimate for ρ, gives the fraction of unpaired electron, κ, producing the contact shifts in the NMR spectra of the ligands.

$$\kappa = \frac{a_N}{a'_N} \tag{43}$$

where a'_N is the value of the hyperfine interaction constant for one unpaired electron in an S orbital of the nucleus N under investigation. (41) Thus the contact shifts ΔH_N found for nuclei in the same paramagnetic species give the relative amounts of unpaired electrons present at each nucleus according to:

$$\Delta H_N \ \alpha \ \frac{\kappa a'_N}{g_N} \tag{44}$$

Equation (44) may also be used to estimate the relative contact shifts exhibited by different nuclei, each experiencing the same fraction of unpaired electrons in their S orbitals in the same molecule (Table 1). Not surprisingly isotopes of a given element show the same relative contact shifts. However, it is notable that the relative contact shifts given by protons are much smaller than those produced by the same amount of unpaired S electrons at most other nuclei. Consequently when both contact and dipolar interactions occur, the contact interaction plays a more significant role in determining the isotropic shifts of other nuclei than it does for protons (42).

TABLE I

The relative contact shifts for some nuclei in the presence of the same amount of S electron spin density(10, 41)

Nucleus	a'_N	Ratio of contact shifts of nucleus concerned and ^{1}H
^{1}H	508	1·00
^{2}H	78	1·00
^{13}C	1119	8·76
^{14}N	557	15·17
^{15}N	−781	15·17
^{17}O	−1659	24·09
^{19}F	17160	35·91
^{23}Na	224	1·667
^{31}P	3676	17·88
^{35}Cl	1672	33·59

In discussing the unpaired electron distribution in transition metal complexes it is customary to consider the ligand as a free radical formed by the transfer of an electron between the metal and the ligands. In conjugated ligands metal to ligand electron transfer results in unpaired spin density in the lowest antibonding orbital (LAO), and ligand to metal electron transfer produces unpaired spin density in the highest bonding orbital (HBO) of the ligand π network. It is often possible to determine which of the ligand π orbitals contains the unpaired electron by comparing the experimental and theoretical spin density distributions. The latter may be obtained for the LAO and HBO from valence bond or molecular orbital (MO) calculations. The valence bond approach has not been extensively used in this context although, in qualitative terms, its effects are perhaps easier to visualize than those presented by MO calculations. A series of odd and even alternant heterocyclic ligands have been treated by the valence bond method and, provided that ionic structures are considered, the results are found to give a satisfactory account of their contact shifts. (43)

The MO method for calculating spin densities proposed by McLachlan (44) has been applied to many ligand systems. (40, 45-48) This is the simplest form of MO calculation to provide a sign for the spin density. For an aromatic proton comparison of equations (1) and (42) reveals that a positive spin density produces a low frequency contact shift and a negative spin density a high frequency shift. When dealing with spin densities in the HBO the odd electron is in a perturbed MO and the parameterization of the calculation should be adjusted accordingly. (49-52) A serious limitation on the use of the McLachlan procedure is that it deals only with π electron delocalization. Semi-empirical MO calculations including all valence electrons are often performed in order to deal with unpaired σ electrons. An example of this type of calculation is afforded by the Extended Hückel Molecular Orbital (EHMO) approach which has been applied to some σ ligand systems with apparent success. (53-56) However EHMO calculations are unable to predict negative spin densities. Consequently the low frequency shifts, which are sometimes observed in the NMR spectra of σ ligands, are either ignored or attributed to spin polarization or other spin delocalization mechanisms.

Spin densities of either sign are directly available from the Intermediate Neglect of Differential Overlap (INDO) procedure. (57) Computer programs to perform these calculations are now readily available (57) and spin densities calculated by this method have been reported for a number of σ ligands. (58-67) In general good agreement is found between the experimental and theoretical estimates of the relative σ spin densities at different sites in a given radical.

Calculations which include the valence orbitals of the transition metal ion in the basis set have also been reported. (68-72) The results of some self consistent charge and configuration (68) (SCCC) calculations for a series of metallocenes (69, 70) and bis-benzene complexes (71) demonstrate the importance of the involvement of σ orbitals on the ligand rings in the formation of metal-ligand bonds in both series of these formally "π complexes". However, since these calculations are based upon the EHMO method they are unable to account for negative spin densities. The SCCC method can be extended by using Different Orbitals for Different Spins (DODS). This permits the sign of spin densities to be estimated and has been applied in a discussion of the aquo complexes of the first transition series metals. (72) The spin density distribution is found to depend linearly upon the number of unpaired t_{2g} electrons on the metal concerned. This is accounted for by the DODS calculations but not by those based upon McLachlan's method which predicts the incorrect sign for the spin densities. (72)

The application of INDO calculations to model ligand systems has generated considerable interest in the mode of electron delocalization between metal and ligand. For example, following INDO calculations on the benzyl radical it has been claimed that the relatively large negative spin density at the meta position in the phenyl rings of some conjugated ligands is due to the occurrence of σ spin delocalization. (73) It is thought that this arises from a non-planar arrangement of the phenyl rings. However, it has been suggested that mechanisms other than σ delocalization can account for the observed spin density pattern. (50)

Proton contact shifts have been traditionally attributed to π or σ electron delocalization according to three criteria: (1)

(a) If the observed shifts alternate in sign between adjacent sites on a conjugated ligand then π delocalization is proposed. This is consistent with an alternating change in sign of the π spin density in equation (42) as found from Valence Bond and McLachlan type MO calculations. Non-alternation in the sign of the shifts is taken to be typical of σ delocalization.

(b) Attenuation of the shifts with increasing proton–metal separation is thought to be typical of σ delocalization. Whereas non-attenuation with distance is claimed to be a characteristic of π delocalization.

(c) If the replacement of a proton by a methyl group on the ligand results in the NMR signal from the methyl protons being shifted in the opposite sense to that of the replaced proton then π delocalization is claimed. This is consistent with the opposite signs of Q for a single proton and the protons of a methyl group in equation (42).

Recent experimental data on nuclei other than protons, together with INDO calculations, have shown that these criteria may be incorrectly employed in many cases. (42, 66) These developments have also provided a more detailed picture of the spin density distribution in transition metal complexes.

III. APPLICATIONS

Undoubtedly the most prolific growth area during the last four years, in the field of NMR studies on paramagnetic species, has been that dealing with lanthanide shift reagents. A number of reviews (6-11) have recently covered this area, hence it is not dealt with exhaustively in the present article. However, the more important theoretical and experimental aspects of lanthanide shift reagents are covered in some detail in Section III. H. together with some of their applications.

Sections III. A to III. G, cover the growth in interest of the topics reviewed four years ago (1) together with some other applications of NMR to paramagnetic species which have been introduced during the period under review.

A. Electron Distribution and Bonding in Metal Complexes

The presence of covalent bonds between a metal and its ligands provides a pathway for the delocalization of unpaired electrons throughout the molecule. The ensuing contact shifts in the NMR spectra of the nuclei of the ligands may reveal the mode of spin delocalization. However, the identification of either σ or π spin delocalization mechanisms does not necessarily imply a similar mode of metal-ligand bonding. (1) It should also be remembered that many discussions relating contact shifts to spin delocalization have employed equations (1) and (42). As shown in Section II equation (1) provides an inadequate description of some metal complexes, also some users of equation (42) have taken incorrect values of S. (39) Although these oversights produce an error in the magnitude of the delocalized spin density they should not affect the relative values of spin densities at different sites on the same ligand attached to a given metal ion. Consequently discussions relating to the relative amounts of σ and π delocalization at different sites in the same metal complex may remain a valid exercise.

In dealing with a series of isostructural metal complexes, with the same ligands in each case, caution is required in evaluating relative covalencies. (39) The MO, ψ, containing the unpaired electron can be written as:

$$\psi = N(\phi_d - \lambda\phi_L) \qquad (45)$$

where ϕ_d and ϕ_L are the appropriate metal d and ligand orbitals respectively, N is the normalizer and λ is the orbital mixing coefficient. Assuming that the amount of metal-ligand overlap is small and $\lambda \ll 1$, then if the d orbital concerned is singly occupied the amount of metal-ligand covalency is given by λ^2.

In discussing the bonding in octahedral transition metal complexes the e_g subset of the metal d orbitals is considered to be capable of σ bonding with the ligands and the t_{2g} subset to be π bonding. (68) The covalency depends upon the occupation probability of the d orbitals which is related to the amount of spin density present. Consequently the relative covalencies, λ^2, can be obtained from the relative spin densities for a series of octahedral metal complexes with the same ligand provided that either the σ or π delocalization mechanism operates exclusively in all of the complexes considered. Under these conditions:

$$\lambda^2 \; \alpha \, \frac{\ell A}{B} \qquad (46)$$

where A is the degeneracy of the d orbital subset considered, $A = 2$ and 3 for the e_g and t_{2g} subsets respectively, and B is the number of unpaired electrons in that subset. If all of the d orbitals of a given subset are singly occupied then the spin density becomes a direct measure of the relative covalency. (39, 74) An example of a metal ion with each of its t_{2g} orbitals singly occupied is chromium(III). While nickel(II) provides an example for which each of the e_g orbitals is singly occupied.

When each of the d orbitals of a given subset are not singly occupied then relative covalencies can only be found from experimental data by means of equation (46). The ions considered in Table II are hypothetical high-spin, divalent hexahydrides in which only σ delocalization occurs. The values of a_N, ρ and λ^2 are compared with unity for the nickel(II) complex. It is noteworthy that in general neither a_N nor ρ appears to be a valid measure of the metal-ligand covalency. The relative values of a_N give a direct measure of the relative covalencies only for those complexes which have all of their unpaired electrons in the same orbital subset, e.g. nickel(II) and copper(II). The relative values of ρ provide an index of relative covalency for complexes which have the same unpaired spin population for the particular orbital subset involved in the metal-ligand bonding, e.g. manganese(II), iron(II) and nickel(II) for the cases considered in Table II.

Similar arguments apply to the interpretation of contact shift data

TABLE II

Relative values of hyperfine interaction constants spin densities and covalencies for some complexes $[MH_6]^{4-}$ exhibiting identical contact shifts (39)

Metal (II)	Relative value of a_N from equation (1)	Relative value of ρ from equation (42)	Relative value of λ^2 from equation (46)
Cr	$\frac{1}{3}$	$\frac{2}{3}$	$\frac{4}{3}$
Mr	$\frac{8}{35}$	$\frac{4}{7}$	$\frac{4}{7}$
Fe	$\frac{1}{3}$	$\frac{2}{3}$	$\frac{2}{3}$
Co	$\frac{8}{15}$	$\frac{4}{5}$	$\frac{8}{9}$
Ni	1	1	1
Cu	$\frac{8}{3}$	$\frac{4}{3}$	$\frac{8}{3}$

for complexes in which only π delocalization occurs and for molecules with different symmetries. A restriction on the consideration of very low symmetry species exists in that the distinction between σ and π orbitals may not be valid. If both σ and π mechanisms occur simultaneously then it is not possible to unambiguously determine the relative covalencies resulting from either mechanism for a series of complexes. (39) In this case a weighted average of the spin densities in two of the top filled orbitals on the ligand, chosen according to the number of their nodes, must be considered when comparing experimental spin densities with those calculated for the ligand treated as a free radical. (20)

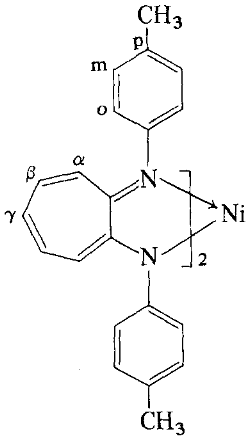
Due to their extensive chemistry and their usually well resolved NMR spectra paramagnetic complexes of nickel(II) and cobalt(II) remain the most commonly reported ones in the NMR literature. (1)

1. *Four-coordinate transition metal complexes*

It has been customary to attribute the isotropic shifts found in the NMR spectra of tetrahedral nickel(II) complexes entirely to contact interactions. (1) Strictly tetrahedral nickel(II) complexes have a triply orbitally degenerate ground term, $^3T_1$, which is expected to result in magnetic anisotropy giving rise to a significant dipolar interaction. (12) McGarvey (20) has shown that small distortions from tetrahedral symmetry can produce large contact shifts in nickel(II) complexes. Experimental confirmation of this point has been provided by the direct evaluation of the dipolar term, using single crystal magnetic susceptibility data, for dichloro bis(triphenylphosphine)nickel(II) (26) and bis(*N*-isopropylsalicylaldimine)-nickel(II). (77)

Tetrahedral complexes of cobalt(II) have a non-orbitally degenerate ground term, in this case magnetic anisotropy can be introduced by spin-orbital coupling. This produces a second order mixing of the ground state with split components of excited terms. (12) Single crystal magnetic anisotropy measurements on the dichloro bis(triphenylphosphine) complexes of cobalt(II) and nickel(II) have demonstrated that the dipolar interactions are opposite in sign for the two complexes with the interaction found for the cobalt(II) complex being approximately four times as large as that of the nickel(II) complex. (26) Consequently in spite of the symmetry of the ground terms involved, when considering the isotropic shifts of comparable tetrahedral complexes of cobalt(II) and nickel(II) it is not too unreasonable in general to assume that the cobalt(II) complexes exhibit large dipolar shifts and the nickel(II) complexes produce small ones.

Natural abundance ^{13}C NMR spectra have been reported for bis[*N*,*N*′-di(*p*-tolyl)aminotroponimine] nickel(II) [3] (75) and some related complexes of *n*-alkyl derivatives. (76) The proton NMR spectra of these and similar complexes of nickel(II) have been interpreted in favour of a dominant contact interaction arising from π spin delocalization. (1) Under these conditions the comparable shifts of a carbon nucleus and its attached proton are predicted to be: (75)



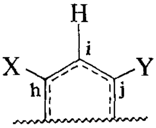
[3]

$$\frac{\Delta H_{^{13}\mathrm{C}_i}}{\Delta H_{^{1}\mathrm{H}_i}} \simeq -6{\cdot}2 + 2{\cdot}5\left(\frac{\rho_{\mathrm{C}_h^{\pi}} + \rho_{\mathrm{C}_j^{\pi}}}{\rho_{\mathrm{C}_j^{\pi}}}\right) \qquad (47)$$

The corresponding expression for the nuclei of a methyl group is:

$$\frac{\Delta H_{^{13}\mathrm{CH}_2}}{\Delta H_{\mathrm{C}^1\mathrm{H}_3}} \simeq -2{\cdot}1 \tag{48}$$

where $\rho_{\mathrm{C}_i}^{\pi}$ is the spin-density in the p_π orbital centred on carbon atom i. (4) The shift ratios predicted by equations (47) and (48) are



[4]

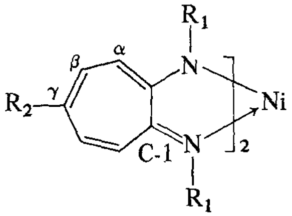
compared with experimental ones in Table III. Although the signs of the theoretical and experimental shift ratios are in agreement, their magnitudes are generally not. Better agreement is forthcoming by

TABLE III

Comparison of some ^{13}C and proton contact shifts for [3], low frequency shifts are positive (75)

	^{13}C shift compared with				
	α-proton	β-proton	ortho-proton	meta-proton	CH_3
Predicted by equations (47) and (48)	−8·4	−18·1	−10·6	−12·0	−2·0
observed	−14·9	−10·5	−16·9	−6·7	−2·3

considering the presence of some σ spin density in the ligand system in addition to the π spin density included in equations (47) and (48). A positive σ spin density at the meta and β positions reduces the predicted low frequency shifts for the carbon nuclei at these positions and increases the high frequency proton shifts thus improving the agreement with the experimental ratios in Table III. The effect of a positive σ spin density at the ortho and α positions is to increase the high frequency carbon shifts and decrease the low frequency proton shifts again providing better agreement with the observed shift ratios. Since the para-methyl group is sufficiently far removed from the nickel atom for σ spin delocalization to be small, the predicted and observed shift ratios are in reasonable agreement at this position. (75) A similar conclusion has been reached for [5a]. (76) However, close agreement between the observed shift ratios and those predicted on the basis of π electron delocalization only is found for [5b]. This is attributed to a strong interaction between the formyl group and the π electrons of the cycloheptatriene ring. (76)

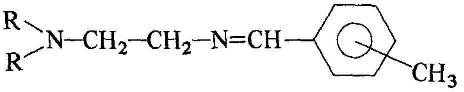


[5a] $R_1 = CH_3; R_2 = H$

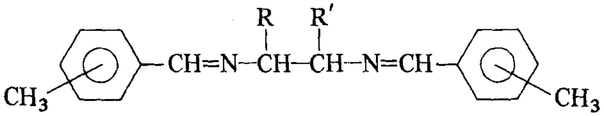
[5b] $R_1 = CH_2CH_3; R_2 = CHO$

From this investigation it appears that σ spin delocalization can play an important role in determining the contact shifts of carbon nuclei but a less important one in the contiguous proton shifts. Consequently ^{13}C NMR spectra of paramagnetic species provide a closer insight into the modes of electron distribution than are available from proton data alone.

The proton NMR spectra of the pseudotetrahedral complexes of nickel(II) with some Schiff bases [6]-[8] of general formula $NiLX_2$,

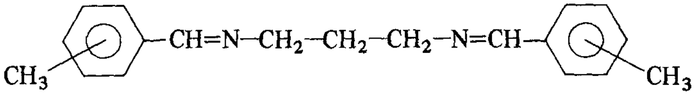


[6]



[7]

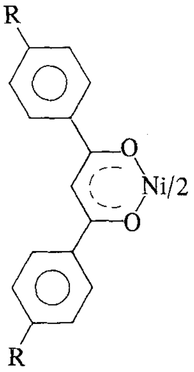
R and R' = H or CH_3



[8]

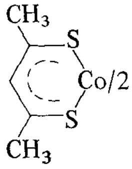
where L is the Schiff base ligand and X = Cl, Br or I, show large shifts. (78) These have been discussed in favour of a dominant π delocalization mechanism together with either a σ delocalization or a dipolar contribution. (78)

The isotropic shifts found in the proton spectrum of [9] show a Curie law dependence. (79) It is claimed that the shifts are contact in origin and by means of equation (1) both σ and π electron delocalization is reported. (79) The cobalt(II) complex [10] is square-planar. Single crystal magnetic susceptibility anisotropy measurements have shown that the dipolar interaction in [10] has a small second order component (24, 80). However, the dipolar interaction dominates the observed proton shifts which have only a small contact contribution. (24) From the known anisotropy of the g tensor of some tetrahedral cobalt(II) dichloride complexes with α, β or γ picoline it is claimed that the dipolar contribution to the proton NMR shifts is negligible. (81) Hence this appears to be a case in which the proton shifts of some tetrahedral cobalt(II) complexes are dominated by a contact mechanism. From a study of the line widths it is reported that the electron spin relaxation rate is determined by the modulation of the zero field splitting by molecular tumbling. (81)



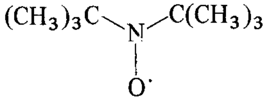
R = H, CH_3

[9]



[10]

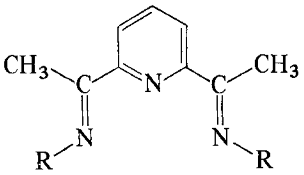
The complex formed between the free radical DBNO [11] and cobalt(II) dibromide gives a proton NMR spectrum very similar to that of the neat free radical. (82) The proton relaxation times of the complex are found to be intermediate between those of the free radical and those normally found for tetrahedral cobalt(II) complexes, suggesting that DBNO is coordinated essentially as a free radical. However, the NMR results are not as definite as they might be. By using DBNO as a solvent for transition metal complexes it is possible that spin exchange between solvent and solute molecules shortens the electronic relaxation times of the solute molecules by averaging their electron spin levels. This interaction has permitted the observation of contact shifts to be made in the proton NMR spectra of bis(acetylacetone)copper(II) and bis(acetylacetone)vanadium(IV) (83) as well as in the ^{19}F spectra of bis(hexafluoroacetylacetone)-copper(II) and bis(trifluoroacetylacetone)copper(II). (84) The ^{19}F NMR spectra are not resolvable in the absence of DBNO. It appears very probable that the spin exchange mechanism involves the formation of labile complexes between the solute molecules and DBNO.



[11]

2. *Five-coordinate transition metal complexes*

Five-coordinate transition metal complexes are usually either trigonal bipyramidal or tetragonal pyramidal in structure. Theoretical arguments favour the latter for nickel(II). However, ligand strain or bulkiness can change the relative energies of the two structures. The NMR spectra of the bidentate ligand, 2,6-diacetylpyridine bis(imine) [12] coordinated to nickel(II) dihalides have large shifts which are Curie law dependent in $CDCl_3$. (85) Consequently it is concluded that these complexes are not exhibiting equilibria. The shifts are



[12]

reported to be largely contact in origin and to involve both σ and π electron delocalization. Comparison of the shifts for the complexes in which the halide and the group R is changed as well as the solvent shows that an increase in the size of R and the halide as well as a decrease in the dielectric strength of the solvent favours the trigonal bipyramid structure for these complexes. (85)

A five-coordinate monopyridine adduct of square-planar bis(*N*-alkyl salicylaldimine)nickel(II) has been detected by means of its NMR spectrum. (86) The diamagnetic square planar complex reacts with two molecules of pyridine to form the paramagnetic di-adduct. If this is the only paramagnetic species present the isotropic shifts will increase monotonically with increasing pyridine concentration. The rather complicated dependence of the shifts on the pyridine concentration has been interpreted in favour of an equilibrium between the diamagnetic complexes and the paramagnetic mono- and di-adducts (Fig. 6), the spin density distribution in the two adducts being significantly different. (86) NMR spectra have been reported for some five-coordinate complexes of nickel(II) with Schiff bases formed from some benzaldimines (87) and ortho-mercapto-

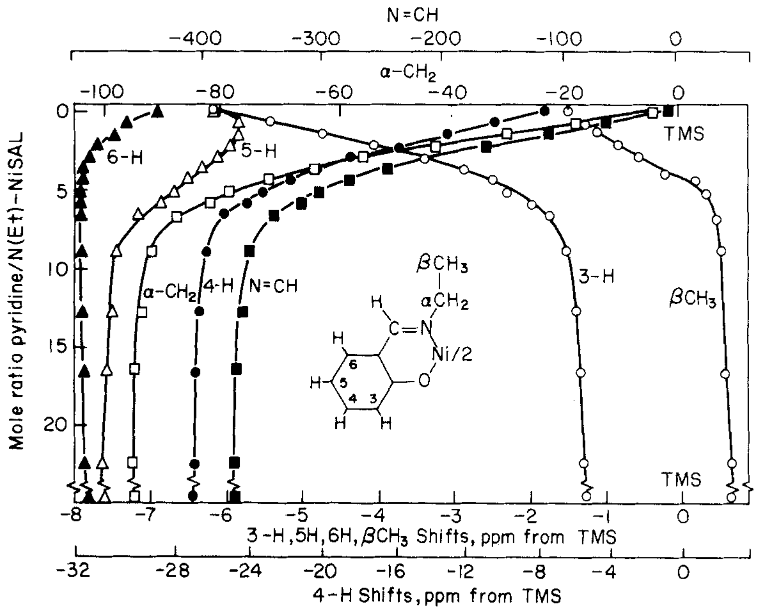
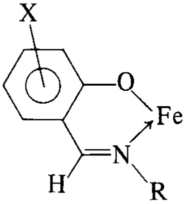


FIG. 6. Dependence of the contact shifts of bis(*N*-ethyl salicylaldimine)nickel(II) in deuterochloroform upon the ratio of pyridine to complex. (86)

benzaldimines. (88) Both σ and π electron delocalization appear to play significant roles in the contact interaction process.

Variable temperature proton NMR data for some binuclear exchange coupled iron(III) complexes with porphyrins (120) and Schiff base ligands (121) [13] have been interpreted in terms of



X = H;
X = Me;

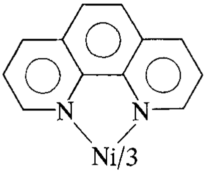
[13]

contact and anti-ferromagnetic exchange interactions. A π contribution to the contact interaction has been claimed from the NMR spectra of [13]. However, it has recently been claimed that these results are based upon the use of invalid assumptions. (544) No doubt further theoretical and experimental studies on the importance of contact interactions in antiferromagnetic systems will be forthcoming.

3. *Six-coordinate transition metal complexes*

Six-coordinate complexes of nickel(II) have non-orbitally degenerate ground terms and are thus expected to experience only contact interactions. (1) By substituting experimental values of D into equation (27) it is found that zero field splitting is unable to produce significant dipolar shifts in the NMR spectra of six-coordinate nickel(II) complexes. (18) In contrast to this the corresponding complexes of cobalt(II) have a triply orbitally degenerate ground term which is expected to produce magnetic anisotropy and dipolar shifts. (1, 19) Hence in comparing the isotropic shifts found for analogous six-coordinate complexes of cobalt(II) and nickel(II) it is often assumed that the differences between the two sets of shifts can be attributed to the dipolar term which contributes to the shifts of the cobalt(II) complex but not to those of the nickel(II) complex. (1) This so called "ratio method" relies upon the nickel(II) complex having no dipolar term and the mode of spin delocalization being identical for the two complexes. Although the amount of unpaired spin delocalization in a given ligand MO may be different for the cobalt and nickel complexes the pattern of spin distribution is expected to be the same. If more than one MO is involved or more than one mode of delocalization is present then the "ratio method" is not strictly applicable. (23, 25, 89-93) It has been claimed that if the change in the ratio of σ to π electron delocalization is relatively small, in going from cobalt to nickel, then the "ratio method" may still be used. (90, 758) Thus caution should be exercised in using the "ratio method" to separate the contact and dipolar interactions for six-coordinate cobalt(II) complexes.

The proton NMR spectra of tris(phenanthroline)nickel(II) [14] and some of its methyl derivatives are reported to show contact shifts produced by a dominant σ delocalization process together with some π delocalization. (90, 94) A similar conclusion has been reached for the six-coordinate complexes of nickel(II) with pyridine and some substituted pyridines. (48, 54, 62) Previously only σ delocalization has been considered for these complexes. (1) Proton hyperfine interaction constants have been calculated by the INDO method for the cations of pyridine and some methylpyridines as well as for the analogous phenyl radicals. (64, 66, 67, 756) Comparison of the proton NMR shifts for six-coordinate nickel(II) complexes with the INDO data shows that the spin transfer process is dominated by a ligand to metal σ spin transfer, as indicated by the shifts of the α and β protons. However the shifts of the γ proton and methyl protons at all positions indicate that π delocalization occurs also, probably due to a σ-π polarization at the nitrogen atom. Thus the earlier conclusion, (1) that σ delocalization alone is able to account for the observed proton shifts, requires modification. (66) It has recently been reported that there is no evidence for any metal-ligand π interaction in these and similar complexes. (756, 757) In general it seems that the phenyl radical model (66) is superior to the pyridine cation model (64, 67) for the INDO calculations on pyridine-type ligands. Discrepancies between observed spin densities and those calculated by either model could arise from the neglect of metal-

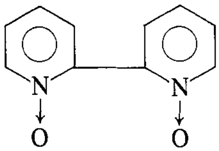


[14]

ligand interactions in the INDO calculations. By including these the unpaired electron is placed in a σ antibonding orbital of the complex rather than in the HBO of the ligand σ electron system, the spin density distribution is expected to be significantly different in the two cases. (67) Hence in order to make significant comments about spin delocalization mechanisms it is necessary to perform all valence electron MO calculations on either the ligand or the entire complex molecule. (54, 67)

Dominant σ delocalization together with a small π contribution has been claimed for a series of complexes ML_4X_2 where M is cobalt(II), iron(II) or nickel(II), L is pyridine or a substituted pyridine molecule and X = Cl, Br, I or NCS. (95, 481) For the cobalt and iron complexes the sign of the dipolar contribution is found to depend upon the nature of X. Dipolar effects are also apparent in the spectra of the free ligand and the solvent $CHCl_3$. (481)

The proton NMR spectra of the hexakis (4-methylpyridine-*N*-oxide)nickel(II) and cobalt(II) cations have been interpreted in favour of delocalization in the π system of the ligands. (91, 93) This is thought to occur through the mixing of the ligand π orbitals with the metal e_g orbitals due to the presence of non-linear metal–oxygen–nitrogen bonding. In these complexes the coefficients of the hydrogen atoms in the highest filled σ MO are very small, thus proton NMR is unlikely to reveal the presence of σ electron delocalization even if it occurs to a significant extent. (91). Carbon or nitrogen NMR data would be very interesting in this context. A dominant π delocalization mechanism has also been claimed for the tris(bipyridine-*N*,*N*′-dioxide)nickel(II) and cobalt(II) cations [15].

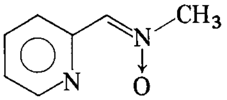


[15]

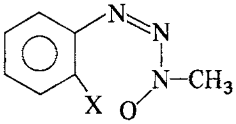
(92) By analogy with the pyridine *N*-oxide ligands MO data should be considered before discussion of σ delocalization is entered into. The dipolar portion of the shifts produced by the cobalt(II) cation [15] indicate that the conjugated rings of the ligand are tipped such that the angle between them is 67°. Stilbenediamine attached to six-coordinate nickel(II) provides a further example of a complex in which the metal–ligand bonding is essentially σ in character but for

which the π mechanism is dominant in deciding the contact shifts of the phenyl protons. (89)

Hexakis(benzamide) (53, 93) and hexakis(diphenylsulphoxide) (96) cobalt(II), nickel(II) and iron(II) complexes produce contact shifts which can be accounted for by σ and π delocalization. A similar conclusion has been reached for [16] (47) and [17] (97) when they are attached to six-coordinate nickel(II).



[16]

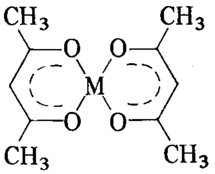


X = OCH_3, OC_2H_5

[17]

On the basis of contact shifts and INDO calculations it has been claimed that ligand to metal σ spin transfer occurs for piperidine and morpholine coordinated to nickel(II) (63) whereas some NMR data for coordinated water, ammonia and some simple aliphatic amines are not well described by INDO calculations. (65)

The NMR spectra of the paramagnetic adducts of bis(acetylacetone) cobalt(II) and nickel(II) [18] have been widely reported.

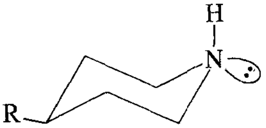


M = Cobalt (II)
Nickel (II)

[18]

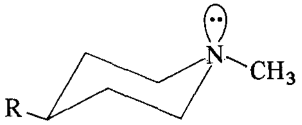
INDO calculations for some attached pyridine *N*-oxides and quinoline *N*-oxides show that ligand to metal β spin transfer in a π orbital is the dominant process in determining the contact shifts. (64, 65) For some adducts with substituted pyridines, quinolines and isoquinolines the INDO data reveal that σ delocalization dominates, but a small π contribution is also present as in the hexa- and tetrapyridine complexes of nickel(II). (60, 62, 64, 66) In the case of the benzonitrile adduct metal to ligand β spin transfer to a π antibonding orbital is postulated (64) which is consistent with the importance of π back-bonding in complexes of benzonitrile.

Comparison of the proton and ^{13}C NMR data (98, 99, 189, 751) with INDO spin densities (66) for the adducts formed between [18] and some pyridine-type bases has been made. It is found that the hyperfine interaction constants for the carbon nuclei do not always attenuate with distance from the nickel(II) ion whilst showing an alternation in sign between adjacent nuclei due to σ delocalization only. A change in sign of the shifts of a proton and of the protons of a substituted methyl group is also found to occur through σ delocalization. Consequently these criteria appear not to be diagnostic of π electron delocalization (66). A number of other adducts formed between [18] and bases have been studied by ^{13}C NMR, including those with aniline, (98) triphenylphosphine, (98, 99) piperidine derivatives [19] [20], (59, 100) quinuclidine [21], (59, 100), 1-azaadamantane [22], (59) quinoline (60) and isoquinoline. (60) Proton NMR data are also available for most of these adducts. (56, 58, 60, 101) The shift patterns found for the aniline adduct are consistent with a π spin delocalization mechanism. (98) For triphenylphosphine the ^{13}C NMR data are consistent with a dominant σ delocalization (98, 99) while the proton spectrum reveals the presence of π spin density in the phenyl rings. These sets of data can be reconciled if the triphenylphosphine assumes a skew conformation in which the orbital containing the phosphorus lone-pair of electrons is nearly parallel to the plane of the phenyl rings. (98)



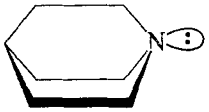
R = H
R = CH_3

[19]

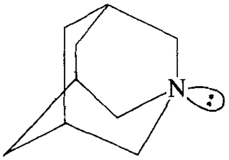


R = H
R = CH_3

[20]



[21]



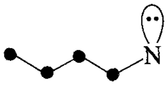
[22]

Comparison of the NMR results with INDO data has led to the suggestion of a ligand to metal σ spin transfer resulting in spin delocalization along a zigzag pathway, [23], for [19] and [22] and a folded pathway, [24], for [20]. (59, 100) Positive spin density reaches the protons through the zigzag pathway [23]; this attenuates slowly with distance. The folded pathway [24] can induce positive or negative spin densities which attenuate fairly rapidly with distance from the nickel ion. (58) Consequently [23] is dominated by σ spin delocalization whereas [24] is subject to spin polarization. The contribution of the carbon 2*s* orbitals to the lone-pair MO is small compared to that from the hydrogen 1*s* orbitals hence the spin polarization mechanism plays a larger role in deciding the carbon contact shifts than it does in deciding the proton shifts. Consequently the folded pathway, [24], is the major one for distributing spin density to the carbon nuclei.

zigzag path

[23]

folded path



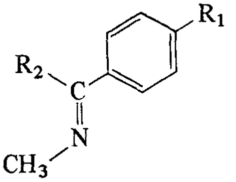
[24]

In the case of quinuclidene [21] the high frequency contact shift experienced by the γ carbon nucleus indicates the presence of positive σ spin density at this position, possibly from a through space spin transfer. (59)

Since nuclear spin-spin coupling arises from electron spin polarization it is reasonable to expect a correlation between spin-spin coupling constants and contact shifts when the shifts are dominated by the spin polarization mechanism. Such a correlation has been found for a number of bases coordinated to the nickel(II) complex [18]. (102)

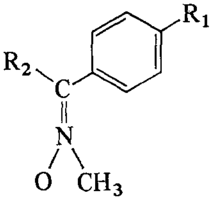
The adducts formed between the nickel and cobalt complexes [18] and some tropones give contact shifted NMR spectra which indicate that the six-membered ring of the tropones is in the semi-planar form. (103) For the comparable adducts with 6 aminobenzonorbornene and 6-aminobenzonorbornadiene the contact shifts are dominated by σ delocalization while the conjugated protons also experience a π contribution. (104)

NMR studies of the adducts formed between [18] and some imines [25] and homologous nitrones [26] reveal that the spin density distribution is mainly in the π network of the bases [25],



[25]

$R_1 = H, CH_3; R_2 = H, CH_3, C_6H_5$.

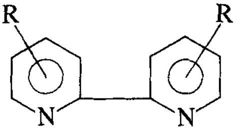


[26]

$R_1 = H, CH_3; R_2 = H, CH_3$.

[26]. (105) However, the distribution is restricted by the non-coplanarity of the phenyl ring with the remainder of the π system. (105) The NMR spectra of the acetylacetone protons of [18] in the presence of a number of different axial groups show that the contact shifts are independent of the nature of the axial group and are mainly due to π delocalization in the nickel complex. (106) Other NMR studies of adducts formed by [18] include ^1H, (107) ^{19}F, (108) ^{14}N (108) and ^{31}P (109) investigations of numerous bases. In general the results are discussed in terms of electron delocalization processes. Similar discussions have been reported, based on proton NMR data, for some adducts formed with square-planar sulphur coordinated nickel(II) chelates. (62, 110, 111)

Cobalt(I) is isoelectronic with nickel(II), consequently only contact shifts are expected in the NMR spectra of six-coordinate cobalt(I) complexes. Experimentally this is supported by some tris(bipyridine)cobalt(I) complexes [27]. Both σ and π electron



R = H, CH_3

[27]

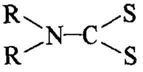
delocalization occur, the dominant π mechanism arises from an excess of α spin density on the ligand. (112) A substantial increase is reported in the relative amount of π bonding for the cobalt(I) complex compared to that for the corresponding nickel(II) complex. (112) This is consistent with the view that ligands of this type, [27], are able to stabilize low valence states due to their superior π acceptor properties.

Proton (32, 113-115) and ^{13}C (116) NMR data have been reported for the low spin tris complexes of iron(III) with bipyridine

[27] and phenanthroline [2]. Considerable controversy has arisen concerning the mechanism of spin delocalization in these complexes. The dipolar interaction has been evaluated from ESR data by means of the first order terms present in an expression similar to equation [25]. (114) Magnetic susceptibility data indicate that second order terms are relatively unimportant for these complexes which have a $^2A_2$ ground term due to the trigonal distortion present. (115) After allowing for the dipolar term the proton shifts can be accounted for if both σ and π delocalization is permitted, it appears that the σ mechanism is not dominant. (115) However comparison with the delocalization mechanisms in the corresponding complexes of cobalt(II) and nickel(II) should be treated with caution since in the iron(II) complexes all of the metal d electrons are confined to the t_{2g} subset. Proton NMR spectra have also been reported for the corresponding complexes of ruthenium(III) and osmium(III) and interpreted in a similar manner. (114) The broad lines found in the NMR spectra of high-spin iron(III) complexes can be made narrower by means of spin exchange coupling. (117) This has been observed in some complexes of [2] and [27] of the type $[Fe_2(ligand)_4O]Cl_4$ which are binuclear and exhibit antiferromagnetic exchange coupling. (118, 119) The dipolar term is thought to be insignificant for these magnetically isotropic molecules and the proton contact shifts are dominated by a σ delocalization mechanism due to the presence of an excess of α spin density on the ligand. From equation (29) it is apparent that the dipolar term could become important through zero field splitting effects which are presumably small in the molecules under consideration.

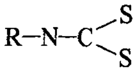
From a temperature dependent study of the proton NMR spectra of some alkoxy bridged β-dicarbonyl dimeric copper complexes, it has been reported that it is possible to distinguish between copper(II) and copper(I) dimers. (759) It is anticipated that these data could be useful in describing the nature of dimeric copper units in proteins. (759)

The proton NMR spectra of the manganese(III) complexes formed with some dithiocarbonates [28], [29] have been studied at a variety of temperatures and compared with those of the corresponding iron(III) complexes. (122) It is found that the electron spin density at the nitrogen atom is greatly reduced upon replacing



R = various aryl groups

[28]



R = various aryl groups

[29]

iron(III) by manganese(III) and the spin density distribution along the alkyl chain, R, is also changed. (122)

A series of tris complexes of chromium(II) with [2] and [27] and various alkyl derivatives have been prepared and their proton NMR spectra investigated. (32-34, 113, 123-125, 478-480) Although these complexes have an orbitally degenerate ground term it is claimed that dipolar interactions do not play a significant part in determining the proton shifts. (32) These are attributed to a contact interaction produced by both π and σ electron delocalization. Both metal to ligand and ligand to metal π charge transfer occur involving different ligand MO's. (113) The net spin transferred is small therefore the hyperfine interaction constants are not realistic indices of metal-ligand π covalency for these molecules. (480) The covalency appears to be sufficiently strong that the ligand MO's are not suitable for quantitatively describing the delocalized spin density. (480)

In some dimethyl derivatives the NMR signal from the methyl protons is anomalously broad due to the modulation of the contact shift by rotation of the methyl group, (33, 34) (Section II, C). By comparison with the proton spectra of the analogous nickel(II) complexes it appears that the restricted methyl rotation is electronic rather than steric in origin. (124) This is probably a characteristic of the unusual π bonding scheme present in the chromium(II) complexes. (124)

Analysis of the non-Curie law dependence of the contact shifts of some mixed ligand chromium(II) complexes with dimethyl derivatives of [2] and [27] reveals whether the ^{3}A or ^{3}B component of the split ^{3}E ground term lies lowest. It is found that this depends upon which mixed complex is formed. (125) Some mixed ligand tris chelate complexes of vanadium(III), with a triply orbitally degenerate ground term, have also been studied. (40) The proton NMR data reveal that electron withdrawing substituents tend to decrease the metal to ligand spin transfer and vice-versa for electron releasing substituents. This is rationalized by considering that an electron withdrawing substituent on a ligand in the xy plane increases the occupancy of the metal d_{xy} orbital which is unable to interact with the π system of the ligand in the xy plane but which forms π bonds with the other ligands in the molecule. (40)

Many transition metals have electronic spin-lattice relaxation times which are too long for well resolved ligand proton NMR spectra to be obtained. Comparison of equations (9), (35) and (36) reveals that, when the nuclear relaxation is controlled by the contact term, improved resolution can be expected in the spectrum of a nucleus whose value of g_N is smaller than that of the proton. The value of g_N for the deuteron is smaller than that of the proton by a factor of about 6.5. Consequently deuteron signals should be narrower than those from protons, under the same paramagnetic conditions, by a factor of $g_H^2/g_D^2 \simeq 42{\cdot}5$. (126, 127) Discounting the lower signal/noise ratio and possible quadrupolar broadening the overall resolution of the deuterium spectrum should be improved by a factor of 6·5 because the contact shifts also depend upon the value of g_N, equation (1). Deuteron NMR spectra have been reported for a number of complexes of deuterated acetylacetone and related ligands. (127-130) In most cases the resolution is significantly enhanced compared with that of the corresponding proton spectrum. However, the expected forty fold decrease in line-width is found only for the chromium(III) tris complex, the results for the titanium(III) and vanadium(III) tris complexes are also in reasonable agreement with expectation. (129) It is anticipated that deuteron NMR will permit the study of bonding and electron distribution to be extended to complexes of many transition metals whose proton signals are too broad to provide the detail required.

INDO calculations on acetylacetone and trifluoroacetylacetone reveal that both metal to ligand and ligand to metal spin transfer may be expected depending upon the electronic configuration of the metal to which the ligands are bonded. (65) Ligand to metal spin transfer is relatively more important in the trifluoroacetylacetonates than in the corresponding complexes with the non-fluorinated ligand which is in agreement with contact shift data. (131)

In the vanadyl(IV) aquo complex π bonding provides the major pathway for spin delocalization to the four equatorial water molecules. (132) Whereas in the 2 : 1 complex formed between vanadyl bis(acetylacetone) and dioxane the dipolar term plays a significant role in determining the proton NMR shifts. (133)

The proton NMR spectra of rhenium(III) complexes with phosphine and arsine ligands show a non-Curie law dependence. (134, 135) This reflects the fact that these complexes become paramagnetic due to the second order Zeeman effect mixing the diamagnetic ground state with paramagnetic excited states. (134)

Paramagnetic metallocenes and related complexes have continued to attract the attention of NMR spectroscopists over the last four years. (1) Usually the dipolar term is not considered to be important for these molecules. This is a reasonable assumption for the vanadium and nickel complexes since they have non-orbitally degenerate ground terms but it may not be valid for the chromium, iron and cobalt complexes. (70) The proton NMR data for metallocenes (69, 136, 137) and a series of bis benzene complexes (70, 71, 138) have been rationalized on the basis of competition between direct σ and indirect π delocalization mechanisms. The highest bonding and lowest antibonding MO's obtained from SCCC calculations on some metallocenes are shown in Fig. 7. Where the symmetries of the orbitals are defined by the conjugated rings, σ orbitals are those which lie in the planes of the rings.

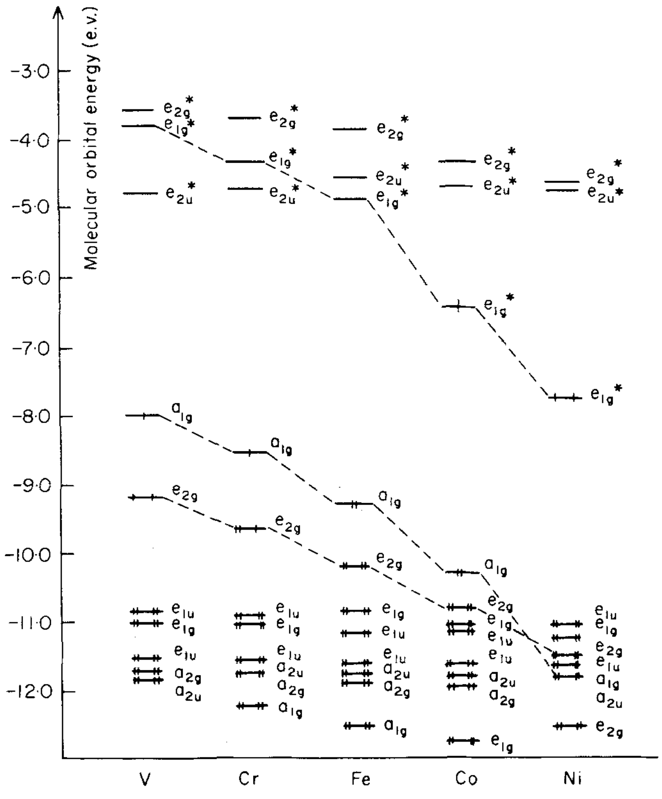


FIG. 7. The highest bonding and lowest antibonding MO's for some metallocenes, obtained from a EHMO calculation. (71)

In the complexes of the earlier transition metals the σ delocalization mechanism dominates the contact shifts due to unpaired a_{1g} electrons. The complexes of the later metals have unpaired electrons in the π antibonding e_{1g} orbitals which produce a controlling π delocalization. A similar conclusion has been reached for the bis-arene complexes (71) Fig. 8. This disagrees with some earlier reports that a direct interaction between the hydrogen 1*s* and metal orbitals

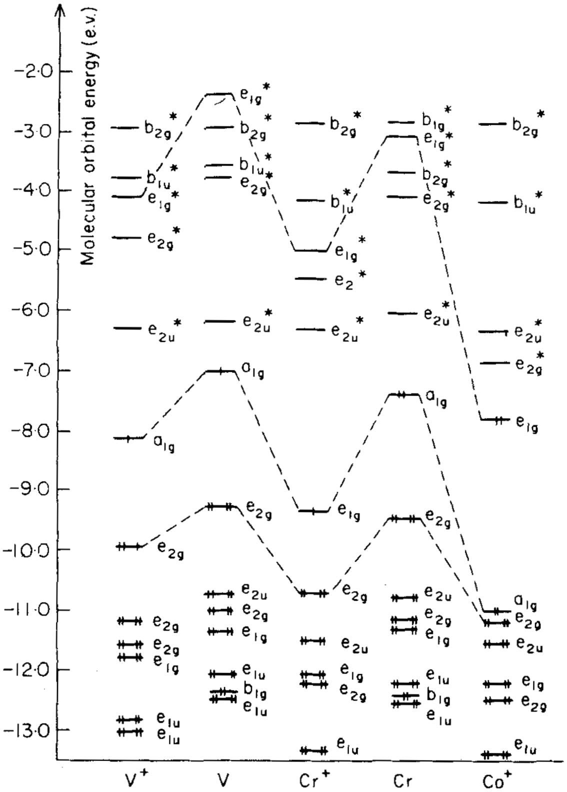
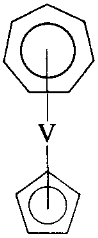


FIG. 8. The highest bonding and lowest antibonding MO's for some bis-arene complexes obtained from a EHMO calculation. (71)

contributes to the shifts. (1, 70) In the mixed ligand complex of vanadium [30] the major pathway for electron delocalization involves the σ orbitals of both rings and the metal d_{z^2} orbital. The interaction with the seven-membered ring is about three times as large as that with the five-membered ring according to both NMR and ESR data. (139) Contact shifts have been found in the ^{13}C NMR

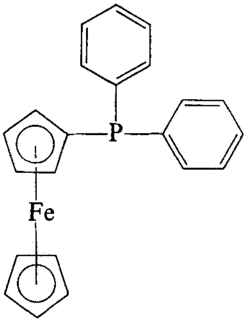


[30]

spectra of some metallocenes (140) and methylmetallocenes. (141) The ratio of the ^{13}C to proton shifts found for the methyl groups of the nickel complex is in close agreement with that predicted by equation (48) showing that π delocalization is dominant at this position in the molecule. It is claimed that exchange polarization dominates the spin transfer to the ring carbon nuclei in the vanadium and chromium complexes producing a net negative spin density, $\sigma-\pi$ polarization then gives a positive spin density at the protons. However ^{13}C NMR data are consistent with the direct delocalization of positive spin density through the σ and π orbitals, which is in contrast to the conclusions reached from proton data. (70, 71)

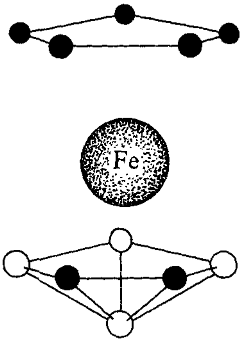
With the exception of the nickel complex the ^{13}C NMR signals are sufficiently narrow to reveal individual reasonances for the non-equivalent ring carbon nuclei in the corresponding proton spectra. This resolution has only been obtained for the cobalt and chromium complexes as well as for some nickelocinium cations (143) and has led to the suggestion of Jahn-Teller distortion for these molecules. (142) The ^{13}C NMR data shows that this proposal is inappropriate because the vanadium complex has a A_{1g} ground term which is not susceptible to a Jahn-Teller distortion. (141)

Bis(π-indenyl) complexes of nickel(II) (144) and cobalt(II) (145)



[31]

have temperature dependent contact shifts which have been interpreted in favour of ring rotation. Ferrocenyldiphenylphosphine [31] interacts through its phosphorus atom with the nickel complex [18] to produce contact shifts in the proton spectrum of [31]. These arise from a predominantly π delocalization process which delivers more spin density to the phenyl than to the cyclopentadiene rings. (146) The carborane sandwich compound [32] has contact shifts in both its proton and ^{11}B spectra which are found to be consistent with the given structure [32]. (147)

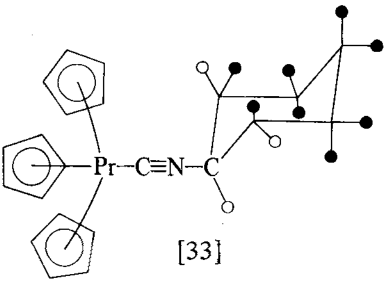


[32]

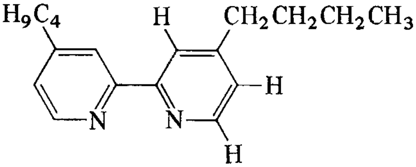
○ = BH, ● = CH

4. *Complexes of the lanthanides and actinides*

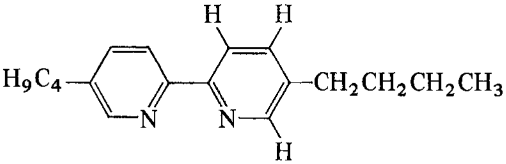
Apart from their extensive use in shift reagents (Section III. H) the lanthanide ions form stable paramagnetic complexes and NMR studies have been instituted on many of them. The dipolar term is usually thought to play a dominant part in determining their isotropic shifts. Some justification for this assumption is forthcoming from the proton and ^{17}O NMR data for the aquo complexes. (148) With the exception of gadolinium(III) all of the paramagnetic trivalent lanthanide ions have orbitally degenerate ground terms which are expected to produce anisotropic magnetic properties. (121) Single crystal magnetic susceptibility measurements have confirmed this in a number of cases. (149-151) By assuming that gadolinium(III) complexes experience only a contact interaction comparison of their shifts with those of the other lanthanides reveals, in most cases, a large dipolar contribution to their shifts. (10) Thus it seems unlikely that complexes which are less symmetrical than the aquo ions will experience significant contact interaction. The shifts observed in the proton spectrum of tris[cyclopentadienyl-(cyclohexylisonitrile)]praseodymium(III), [33], are consistent with this proposal. (152) All of the cyclohexylisonitrile proton shifts are accommodated by means of the geometric factor, $(3 \cos^2 \theta - 1)r^{-3}$, given in equation (3). However, proton data for some lanthanide complexes with *N,N'*-diethyldithiocarbamates, (156) acetates, (157) chloracetates and some substituted bipyridines [34], [35] (158) suggest that both dipolar and contact interactions may be present in these complexes. A more extensive NMR investigation of these molecules appears to be required. Similar studies on tetrakis ethylenediamine complexes of trivalent lanthanide ions suggest that a contact mechanism is responsible for the shifts observed in the complexes formed by the elements from cerium to holmium. The remainder of the rare earths show shifts which are attributed to a dipolar interaction. (762) Depending upon whether the 4*f* shell is more or less than half-filled, ligand to metal electron transfer is



[33]



[34]



[35]

preferentially with β or α spin respectively. Consequently the contact shift contribution is expected to change sign, for a given ligand nucleus, in passing from the first to the second half of the lanthanide series. This change in sign has been observed in the ^{19}F spectra of some solid samples of lanthanide trifluorides showing that the contact interaction is important in this case. (159) Samarium(III) trifluoride is anomalous in this respect but its ^{19}F data may be rationalized by considering the presence of a strong crystal field interaction. (160)

With the exception of those ions with the $4f^6$ configuration, e.g. europium(III) and samarium(II), the trivalent lanthanide ions have ground states with non-zero values of the total angular momentum quantum number J. As shown in Fig. 9, europium(III) becomes paramagnetic at normal temperatures through the population of excited states. This gives rise to a complicated temperature dependence for its dipolar interaction. (28)

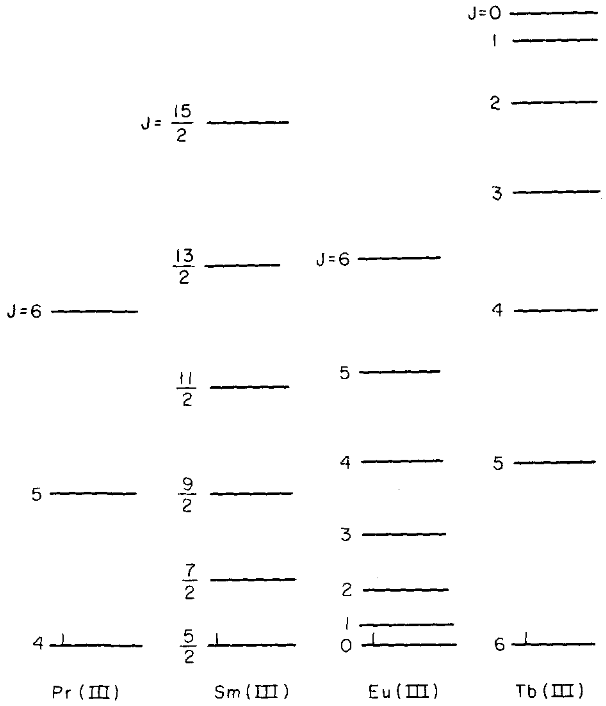


FIG. 9. Grotrian diagrams (21) for the lowest states of praseodymium(III), samarium(III), europium(III) and terbium(III), | = κT at 293 K = 204 cm^{-1}.

Of the actinide metal ions the one whose paramagnetic complexes have been most extensively studied by NMR is uranium(IV). This has the electron configuration $5f^2$ which produces the orbitally degenerate ground term, $^3H_4$, which is expected to be associated with magnetic anisotropy and dipolar interactions. However, the dipolar term does not appear to dominate the NMR spectra of uranium(IV) complexes, significant contact contributions have been reported for complexes containing cyclopentadiene, (153, 154, 161-166) cyclooctatetraenes, (153, 167) allene (168, 601) and some β-diketones. (169, 170) However the proton spectra of some tris(cyclopentadienyl)-alkoxy uranium(IV) complexes (171) and of the ethylenediaminetetraacetic acid complex of uranium(IV) (172) display shifts which are generally determined by dipolar interactions. On the other hand the ^{17}O data from solid uranium(II) dioxide has been interpreted entirely in favour of a contact interaction which produces a negative spin density on the oxygen nuclei. (173)

Spin-orbital coupling produces a large interaction in the actinide metals and gives rise to a ground state in which the z component of the electron spin is parallel to the direction of the applied field. (167) This is opposite to the situation found in transition metal complexes. Thus for the same type of spin delocalization process the contact shifts produced in *iso*-structural complexes containing metals with $3d$ and $5f$ electronic configurations are of opposite sign if the f shell is less than half filled and of the same sign if the f shell is more than half filled. Both σ and π delocalization occur in bis(cyclooctatetraene)uranium(IV) with the former playing a major role. (167) However, in some β-diketone complexes of uranium(IV) π bonding involving the f orbitals produces a large π delocalization. (169)

In general the proton signals from uranium(V) complexes are too broad to yield satisfactory information about bonding and electron distribution. (174, 175) The hyperfine interaction constant for some tetramethylcyclooctatetraene complexes of uranium(IV) and neptunium(IV) is found to be approximately the same in both cases and to be primarily due to π delocalization. (155) Since neptunium(IV) has one more unpaired electron than uranium(IV) stronger covalency is implied in the uranium complex. It has been proposed that the π electron delocalization arises from ligand to metal spin transfer leaving an excess of positive spin density on the ligand. This conclusion is supported by some simple MO data and the neptunium Mössbauer spectrum. (155)

B. Structural Studies of Metal Complexes

The NMR spectra of molecules with very small structural differences are often almost identical. The presence of a paramagnetic centre tends to amplify slight spectroscopic differences arising from subtle changes in structure. A study of the NMR spectra of paramagnetic species can lead to information on various forms of equilibria and isomerism as well as to other structural data.

1. *Structural equilibria*

Four-coordinate complexes of nickel(II) can exhibit a rapid equilibrium between the diamagnetic square-planar and paramagnetic tetrahedral forms. Large deviations in the observed shifts from a Curie law dependence have been taken to signify such an equilibrium. (1) By assuming that the shifts of the paramagnetic form do follow a Curie law, the observed shifts for the equilibrium are often fitted to equation (49)

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2 S(S+1)}{g_N \beta_N 3\kappa T}\left[\exp\left(\frac{\Delta G}{RT}\right) + 1\right]^{-1} \tag{49}$$

where ΔG is the free energy change for the equilibrium and,

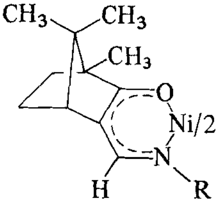
$$\Delta G = \Delta H - T\Delta S \tag{50}$$

However equation (49) is a modified form of equation (1) which is known to be incomplete in many cases (Section III. A). Comparison of the thermodynamic parameters obtained from equation (49), for some four-coordinate nickel(II) complexes, with those derived from a more complete expression based upon equation (11) shows that the differences are not great over the temperature range 200 to 400 K. (20) This is especially true for those complexes with a large distortion. Taking bis[*N,N'*-bis(ethyl)aminotroponeimine] nickel(II) as an example the values $\Delta H = 1180$ Kcal/mole and $\Delta S = 10.2$ e.u. are reported from the more complete treatment compared with $\Delta H = 1250$ Kcal/mole and $\Delta S = 11.3$ e.u. obtained from equations (49) and (50).

Planar-tetrahedral equilibria exist for some tertiary phosphine complexes of nickel(II) of the form $Ni(PR_3)_2X_2$ where X = Cl, Br or I and PR_3 can be a mixed alkyl, aryl phosphine (176-179) or a mixed phenyl, alicyclic phosphine. (482) The latter were chosen in order to investigate the relative importance of steric and electronic effects on the equilibrium. It is found that steric factors are relatively unimportant in deciding the thermodynamics of the equilibria, whereas electronic effects depending upon metal–phosphorus π bonding play an important part. (482) For a given phosphine ligand it is reported that the tetrahedral form becomes more stable as X changes from Cl to Br to I.

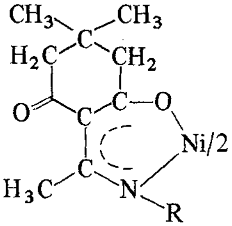
The bis(tertiary phosphine) complexes represent the only series of four-coordinate nickel(II) complexes so far studied in which it is possible to "freeze out" the individual NMR spectra of the diamagnetic and paramagnetic isomers. (176-179) The rates of isomerism have been studied by analysing the proton line shape as a function of temperature over the range from about 190 K to about 320 K. The first order kinetics of the isomerization reveal rate constants of about 10^5 to 10^6 $\sec^{-1}$ at 298 K which depend upon both the halide and the substituted phosphine present. (177, 179)

Rapid equilibria have been reported for a number of four-coordinate nickel(II) complexes and the corresponding thermodynamic data obtained from equations (49) and (50). These include complexes of 3-(*N*-substituted amine) methylene-camphor [36]



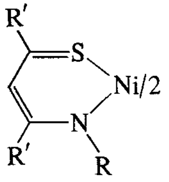
[36]

(180) where R is CH_3, C_2H_5 or $C_6H_5CH_2$, *N*-substituted 2-acetiminodimedone [37] (181) where $R = i\text{-}C_3H_7$, *sec*-C_4H_9 or

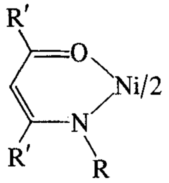


[37]

$C_6H_5CHCH_3$, and some pairs of α, β unsaturated, *N*-substituted β-aminothiones [38] (182) and β-ketoamines [39] (182) where R



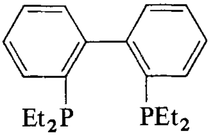
[38]



[39]

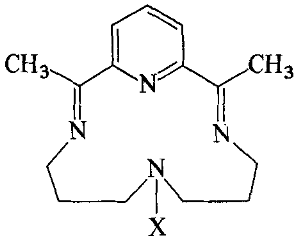
and R' are various substituents. In the latter investigation it was found, from a comparison of the data for complexes of the comparable ligands [38], [39] considered in pairs, that the planar isomer is relatively more stable with the sulphur containing ligand [38] than with the oxygen containing one [39]. (182) The relative equilibrium positions are controlled by enthalpy effects arising from the differences in nickel-oxygen and nickel-sulphur bonding in these pairs of similar complexes. The addition of pyridine to a solution of the nickel complex of [39] with R = phenyl, and R' = CH_3 in $CDCl_3$ shifts the equilibrium towards the square-planar isomer. (48)

Square planar-tetrahedral isomerism has also been reported from the NMR spectra of some nickel(II) dihalide complexes with 2,2'-diphenylenebisdiethylphosphine [40]. It is found that the amount of the tetrahedral isomer increases as the halide is changed from chloride to bromide to iodide. (183).



[40]

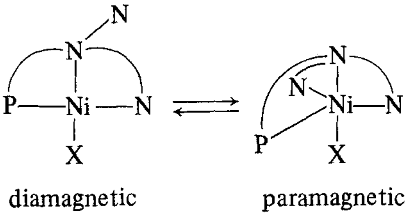
An octahedral-square planar equilibrium has been investigated for some nickel(II) complexes with the optically active ligand 2,3-butylenediamine. (184, 185) The value of ΔG for the complex of the *meso* form is found to be [2150 ± 70 – (7.7 ± 0.2) T] Kcal/mole whereas for the *racemic* form the corresponding complex gives ΔG = [3700 ± 500 – (9.0 ± 1.5) T] Kcal/mole. (185) The relatively large entropy contribution to the value of ΔG is attributed to the expulsion of water from the axial coordination sites of the complex by interaction with the methyl groups of the ligand. A similar equilibrium in a variety of solvents has been found from the proton NMR data of the complexes of nickel(II) with the quadridentate ligand, CR [41]. Changes in the azomethine methyl signal as a function of temperature have been analysed in favour of values of



X = H
X = CH$_3$

[41]

ΔH ranging from −3.27 to 6.39 Kcal/mole and of ΔS in the region from −7.7 to 17.9 e.u. (186) These data are dependent upon the solvent, the anion present and whether X is H or CH$_3$. A square planar-trigonal bipyramidal equilibrium has been investigated for the complexes formed by nickel(II) dihalides and bis(2-ethylaminoethyl) (2-diphenylphosphinoethyl)amine [42]. (187) The proton NMR spectra of the chloro and bromo complexes in CDCl$_3$ have been



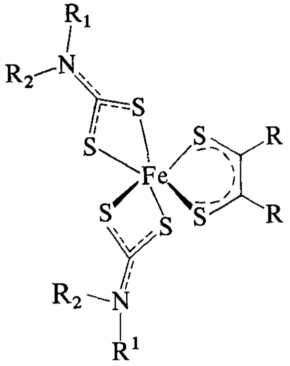
[42]

analysed to give ΔH values of 1.3 and 0.9 Kcal/mole and ΔS values of 7.2 and 6.7 e.u. respectively at 299 K. (187) For the iodo complex only the square planar form is found which suggests that the relative stability of this form increases as the halide changes from chloride to bromide to iodide.

Complexes of cobalt(II) with pyridine and similar bases often exhibit a tetrahedral-octahedral equilibrium in solution, both forms being paramagnetic. It has recently been demonstrated that analysis of the exchange averaged chemical shift data, by a standard fitting procedure, provides values for the isotropic shifts exhibited by both the octahedral and tetrahedral isomers. (188)

2. *Spin equilibria*

The well known (1, 190) spin equilibrium between the diamagnetic $^1A_{1g}$ and paramagnetic $^5T_{2g}$ configurations of six-coordinate iron(II) has been the focus of some further NMR investigations. (191) In addition a new type of spin equilibrium, involving spin singlet and triplet configurations, has been reported for complexes of iron(II) with ligands of the type [43]. (192-194)



$R = CF_3$
$R_1, R_2 = CH_3, CH_3$;
$C_2H_5, C_2H_5; CH_3, C_6H_5$;
$(CH_2)_4, (CH_2)_5$.

$R = CN$
$R_1, R_2 = C_2H_5, C_2H_5$;
CH_3, C_6H_5.

[43]

The observed proton shifts are believed to be largely dipolar in origin, complexes in which $R = CF_3$ give NMR spectra in dichloromethane which have been interpreted in favour of two intramolecular rearrangements in the temperature range 173 to 363 K, differing in rate by about 10^3 Hz at 298 K. Proton and ^{19}F NMR data indicate that the low temperature process is inversion of the molecular conformation probably arising from a twist about the pseudo-three-fold axis of the complex. (193) The high temperature process has been assigned to rotation about the carbon-nitrogen bond. Similar conclusions have been reached for the complexes with $R = CN$. (194) The complex with $R = CN$, $R_1 = R_2 = C_2H_5$ has a higher triplet state population than the corresponding complex with $R = CF_3$. At 223 K this appears to produce a small increase in the rate of the inversion process attributed to the low temperature rearrangement. (194)

3. *Optical isomers*

The NMR spectra of paramagnetic diastereoisomers often show separate signals for each equivalent set of nuclei in the different isomeric species. (1) In a bis-chelate complex of 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. When a *racemic* ligand mixture is used to prepare the complexes the resulting NMR spectra usually show two sets of signals, one set for the *meso* complex and one for the optically active pair of complexes (+, +) and (−, −). The shift differences in the proton NMR spectra of the stereoisomers of four-coordinate nickel(II) complexes are usually largest when the complexes are involved in a rapid square planar-tetrahedral equilibrium. In this case the shift differences are attributed to slight differences in the ΔG values for the equilibria concerned. (180, 182, 195)

For complexes not involved in an equilibrium process the shift differences are thought to arise from different values of the hyperfine interaction constant at corresponding positions in the various isomers.

Examples of diastereoisomeric complexes of nickel(II) which undergo the square planar-tetrahedral equilibrium and which show shift differences for the active and *meso* forms are afforded by [38] where R = *sec*-C_4H_9 or $C_6H_5CHCH_3$ (182) and [36] where R = CH_3, C_2H_5, $C_6H_5CH_2$, 1-adamantyl or (+) or (−)α phenylethyl. (180, 195) In the latter case six diastereoisomers have been detected in the proton spectrum of the complex made from the *racemic* ligand mixture. This is demonstrated by the data presented in Table IV where A, B, C and D are defined in terms of the chiralities of the amine and camphor groups in the ligand, A = (+) camphor (+) amine, B = (+) camphor (−) amine, C = (−) camphor (+) amine and D = (−) camphor (−) amine, thus Ni(AB) denotes a nickel complex containing one A and one B type of ligand.

TABLE IV

Proton NMR data for some diastereoisomers of bis[3(α-phenylethylamino)-methylenecamphor] nickel(II) (195)

Complexes	Relationship	Chemical Shift (Hz)[a]
Ni(AA), Ni(DD)	Enantiomers	62
Ni(AB), Ni(CD)	Enantiomers	90
Ni(AC), Ni(BD)	Enantiomers	67, 102
Ni(BB), Ni(CC)	Enantiomers	97
Ni(AD)	*meso*	89
Ni(BC)	*meso*	105

[a] The shifts are for a methyl signal to low frequency of TMS at 100 MHz and 303 K.

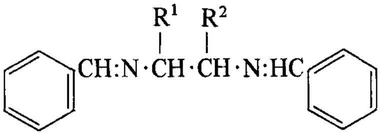
In the tetrahedral forms of these complexes the nickel ion lies at a further asymmetric center which may produce additional diastereoisomers, Δ and Λ, for each of the isomers considered above where Δ

and Λ denote respectively left- and right-handed helicity about the C_2 axis of the complex. However, additional proton signals due to these further isomers have not been detected, for most of the nickel(II) complexes so far discussed, due to the racemization of the Δ and Λ diastereoisomers which is rapid on the NMR time scale. (180, 182, 195)

Complexes formed from [36] with R = 1-adamantyl show a doubling of many of the proton signals due to the relatively slow interconversion of the Δ and Λ diastereoisomers with this rather bulky ligand. (195) A similar effect has been noticed previously in the proton spectra of some salicylaldimine complexes. (1)

The controlling process for the interconversion of the Δ and Λ isomers in the nickel(II) complexes appears to be intramolecular rather than due to ligand exchange. (195)

Differences in the hyperfine interaction constant for the isomeric complexes of nickel(II) with [44] are claimed to be responsible for



[44]

R^1 and R^2 are either H or CH_3

the splitting in their proton spectra since they do not undergo a square planar-tetrahedral equilibrium in solution. (196) A previous case in which differences in the hyperfine interaction constant were claimed to be responsible for proton line splittings, (1) has been invalidated on account of the reported presence of impurities in the sample. (178) Further examples of isomeric nickel(II) complexes which show proton signal splittings due to differences in the hyperfine interaction constant are afforded by the ligands methyl-phenyl-*p*-anisyl phosphine (195) and 2,3-diaminobutane. (184, 185) A thorough investigation of the proton NMR data for the tris(*meso*-2,3-diaminobutane)nickel(II) ion as a function of temperature, (185) has revealed that some previous conclusions (184) relating to this ion are in error. The rate of racemization of the Δ and Λ forms is reported to be $2{\cdot}3 \times 10^3$ sec^{-1} at 323 K with a free energy of activation of 14.0 Kcal/mole at this temperature. (185)

Some six-coordinate complexes of vanadium(III) with derivatives of carvone and pulegone also show diastereoisomeric shift differences but signal overlap has prevented a full analysis of the data. (196)

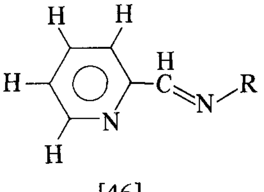
4. *Geometrical isomers*

Six-coordinate tris-chelate complexes of identical unsymmetrical bidentate ligands (A–B) can exist as *cis* and *trans* isomers [45],

cis *trans*

[45]

having C_3 and C_1 symmetry respectively. Consequently a separate signal is expected for a given proton site on each ligand in the *trans* form whilst the *cis* form should give one signal only. (1) Thus NMR provides a simple method of distinguishing between the *cis* and *trans* isomers. The presence of a paramagnetic center in the tris complexes usually facilitates signal resolution. Examples are provided by the tris complexes of unsymmetrically methyl substituted phenanthroline [2] with chromium(II), iron(III), cobalt(II) and nickel(II). (113, 123) Complexes of [46] with iron(II), cobalt(II) and nickel(II), (197) complexes of some unsymmetrical β-diketones with vanadium(III), manganese(III), iron(III) and ruthenium(III), (198) some unsymmetrical β-thioketone complexes of vanadium(III) (198) and some metal complexes of 3-acetylcamphor. (130)



[46]

R = methyl, ethyl, *i*-propyl, phenyl, *p*-tolyl

Variable temperature NMR data on tris-chelate complexes has enabled intramolecular isomerization reactions to be studied, (192-194, 198-201) and in some cases mechanisms have been inferred. (193, 194, 200, 201) Two independent stereochemical processes occur in the intramolecular rearrangement of tris-(*N*-

methyl-*N*-phenyldithiocarbamate)iron(III) (200) and tris-(*N*-methyl-*N*-benzyldithiocarbamate)iron(IV) tetrafluoroborate, (201) where the ligands have structures similar to [28]. The low temperature process is claimed to be a twist about the pseudo-threefold axis of the molecule since this is the only likely mechanism capable of averaging two of the three *trans* resonances leaving the third one unchanged and at the same time not interconverting the *cis* and *trans* isomers, as observed. (200, 201) The high temperature process depends upon a mechanism which randomly scrambles all of the *cis* and *trans* environments; this is probably due to rotation about the carbon–nitrogen bond. (200, 201)

Geometrical isomers have also been detected in the NMR spectra of some complexes of four-coordinate nickel(II) with Schiff base ligands derived from 1,2-diaminoethane and some conjugated ketones (202) as well as some related complexes. (78)

5. *Some other structural investigations*

Conformational studies from NMR data on six-coordinate nickel(II) complexes have been extensively reported. The most frequently studied ligands are simple diamines (55, 185, 203-205) as well as EDTA and related amino acids. (206-213) In general the contact shifts for the axial and equatorial protons of puckered chelate rings are different even though the rings are thought to be in rapid equilibrium between the δ and λ conformations. (203, 213) The equilibrium constants for the conformational interconversion and the contact shifts of the nuclei in the individual conformers may be obtained from variable temperature NMR studies. (185, 204, 205) For example the energy required for the conversion of the δ to the λ conformation of the ligands in tris (*meso*-butylenediamine) nickel(II) is reported to be 530 cal/mole at 300 K compared with 300 cal/mole for the corresponding tris-ethylenediamine complex. (185)

However, in the tris-ethylenediamine nickel(II) cation it has been reported that the conformations of the rings are solvent dependent. (765) In DMSO the ring is claimed to be 7° more puckered than in water and in the solid state it is 23° more puckered than in DMSO. These differences are attributed to solvation effects, primarily due to hydrogen bonding between the solvent and the amino proteins of the complex. (765)

The hyperfine interaction constants for the axial and equatorial protons of the coordinated ethylenediamine molecule may be obtained from their contact shifts and related to the dihedral angle,

θ_N, between the carbon–proton and nickel–nitrogen bonds by equation (51) (214)

$$a_N = (\beta_0 + \beta_2 \cos^2 \theta_N)\rho \tag{51}$$

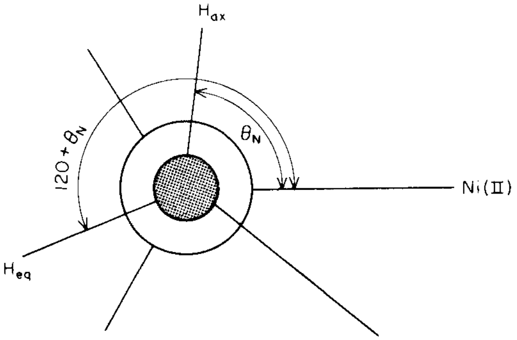


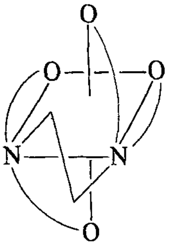
FIG. 10. Definition of the dihedral angle θ_N. (55)

where β_0 and β_2 are constants for a given electronic environment. From a comparison of equations (1) and (51) the ratio for the equatorial to axial proton contact shifts is given by:

$$\frac{\Delta H_{eq}}{\Delta H_{ax}} = \frac{\beta_0 + \beta_2 \cos^2 \theta_{eq}}{\beta_0 + \beta_2 \cos^2 \theta_{ax}} \tag{52}$$

With known values of β_0 and β_2 equation (52) provides a means of estimating the amount of ring pucker in the complexes from contact shift data. It is usually assumed that $\beta_0 \ll \beta_2 \cos^2 \theta_N$ and that tetrahedral angles may be taken between carbon–hydrogen bonds such that $\theta_{eq} = \theta_{ax} + 120°$; this has led to the estimated value of 80° for θ_{ax} in some ethylenediamine ligands. (204, 205) However the assumption that $\beta_0 \ll \beta_2 \cos^2 \theta_N$, is not valid as θ_{ax} approaches 90°. It must also be considered that in general equation (52) has two solutions, one corresponding to a value of θ_{ax} less than 90° and one greater than 90°. EHMO spin density calculations on *N,N'*-dimethylethylenediamine and on the unsubstituted ligand are reconcilable with the contact shifts provided that the value of θ_{ax} is between 97° and 100° for the dimethyl ligand. (55) For the complex with unsubstituted ethylenediamine it appears that the ring is less puckered in solution than in the solid state. (55)

Proton, ^{13}C and ^{17}O NMR data have been reported for EDTA complexes of nickel(II). Any of the structures [47] [48] or [49] could be adopted in solution. The NMR data support the presence of



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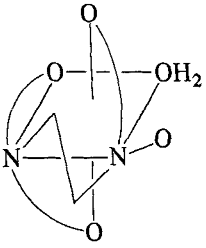

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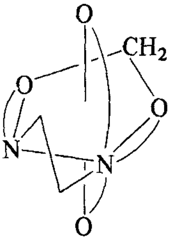
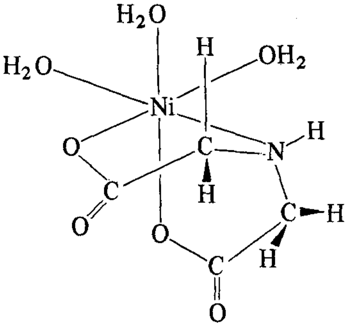


[49]

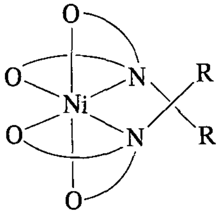
structure [47] in neutral solution and [48] in acid solution. (210) A further ^{17}O NMR study has also led to the suggestion that [47] is present in acidic media but indicates a six-coordinate monoaquo complex in neutral solution in which one unprotonated arm of the EDTA ligand is not coordinated to the nickel(II) ion. (208, 209) Proton NMR results on this and related complexes offer a less distinct interpretation of the dominant species present in solution. (212)

The iminodiacetate ligand is known to be tridentate with nickel(II) ions [50]. The resulting six-coordinate complexes can exist



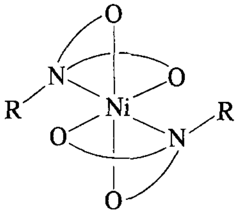
[50]

in two isomeric forms [51], [52] in both of which a *cis* arrangement of the carboxyl groups occurs. (213) The proton NMR spectrum of the complex is consistent with a mixture of the two isomers. (213) After making an allowance for the dipolar term the proton data for some cobalt(II) complexes with aminopolycarboxylate ligands have been interpreted in a similar manner. (215)



[51]

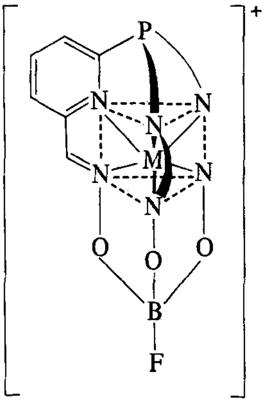
R = H or alkyl



[52]

R = H or alkyl

Six-coordinate chelate complexes can adopt stable structures which show significant distortions from octahedral or trigonal-antiprismatic microsymmetry whilst retaining a true or pseudo three-fold rotation axis. (216-218) Such structures have been found for a number of divalent metals from the first transition series and proton NMR spectra have been reported for nickel(II) complexes with the structures [53]-[56] which show an increasing departure from trigonal prismatic geometry. (218) In general the contact shifts for the four nickel complexes are not very sensitive to the slight



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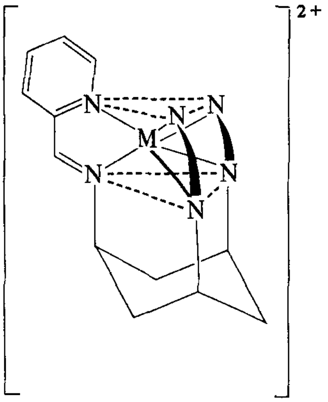

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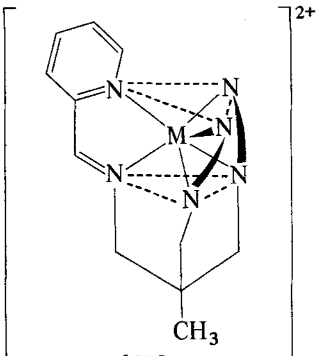

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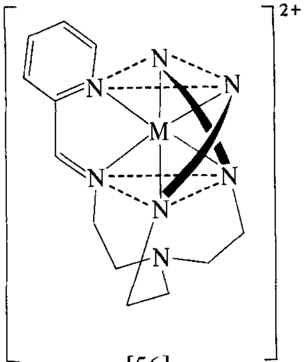
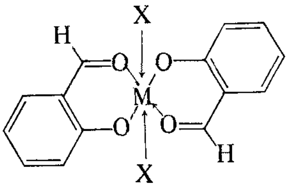


[56]

changes in stereochemistry, however the linewidths are more sensitive and a qualitative model to account for this has been proposed. (218)

Proton NMR spectra have been reported for a series of nickel(II) and cobalt(II) complexes with salicylaldehyde [57]. (219-221) For



M = Co^{II}

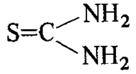
M = Ni^{II}

[57]

the molecule with X = pyridazine variable temperature spectra reveal that the pyridazine ring rotates at about 10^5 Hz at 295 K. (221)

Some cobalt(II) complexes with pyridine type bases have had their proton spectra taken in water/acetone mixtures. (222) For the individual bases considered the dominant species are found to be $[Co(imidazole)_6]^{2+}$, $[Co(pyridine)_3(H_2O)_3]^{2+}$, $[Co(4\text{-methylpyridine})_4(H_2O)_2]^{2+}$, $[Co(4\text{-methylpyridine})_3(H_2O)_3]^{2+}$, $[Co(pyrimidine)_3(H_2O)_3]^{2+}$ and $[Co(purine)_3(H_2O)_3]^{2+}$.

Thiourea [58] forms complexes with cobalt(II) and nickel(II). (223, 224) The proton NMR spectra of these complexes suggest that



$$S{=}C\begin{matrix}\nearrow NH_2\\ \searrow NH_2\end{matrix}$$

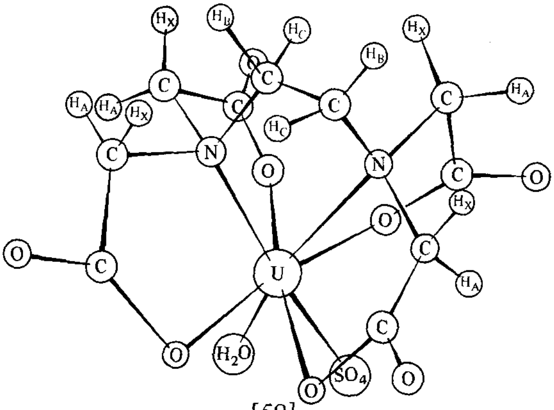
[58]

the thiourea ligands are attached to the metal via the sulphur atom and that rotation about the carbon–nitrogen bond is completely restricted. (223) The barrier to rotation is found to be higher in the complexes than in the free ligands.

In the presence of bis(β-diketone)copper(II) the NMR spectra of pyridine, pyridine *N*-oxide and *N,N*-dimethylformamide (DMF), show large shifts which are consistent with the presence of tetragonally distorted six-coordinate complexes. (131, 225) Line width studies on the proton signals from the two inequivalent methyl groups in DMF show that DMF is bound to the copper ion through its oxygen atom. (225)

Temperature dependent studies on the dipolar shifts observed for tris[cyclopentadienyl-(cyclohexylisonitrile)] praseodymium(III), [33], have revealed that the value of ΔG for the cyclohexyl ring inversion is 282 ± 15 Kcal/mole. (152) In a similar complex of uranium(IV) with cyclohexanol in place of cyclohexylisonitrile the inversion is 282 ± 15 cal/mole. (152) In a similar complex of value of ΔG is 2.3 Kcal/mole. (171)

Following variable temperature proton NMR studies a solution structure for an EDTA complex of uranium(IV) has been reported [59]. (172)



[59]

NMR studies on paramagnetic compounds in the solid state have also been reported. (226, 227) A torsional motion around the copper chlorine bond with a frequency of about 3×10^{12} Hz has been proposed following ^{35}Cl and ^{39}K studies on single crystals of $K_2CuCl_4 \cdot 2H_2O$. (227)

C. Ion-Pair Formation and Second Sphere Solvation of Metal Complexes

The proton NMR spectra of diamagnetic cations in solutions containing paramagnetic anions sometimes show isotropic shifts. (1) These shifts have been attributed to dipolar interactions arising from ion-pair formation. ^{14}N NMR spectra have been reported for the tetrabutylammonium cation in the presence of various paramagnetic anions. (228) These spectra reveal the presence of contact as well as dipolar interactions. The first column in Table V shows the low frequency shifts expected due to the bulk susceptibility differences between diamagnetic and paramagnetic samples. The dipolar terms for all of the nuclei in the cation can be evaluated from the geometric factor $(3 \cos^2 \theta - 1)r^{-3}$. The second column in Table V contains the values of the ^{14}N dipolar shifts estimated from proton data and the final column gives the difference between the experimental shift and that expected for a purely dipolar interaction. (228) The resulting high frequency shift is most probably due to a contact interaction following weak covalent bonding between the cation and anion in the ion-pair. (228) For both the $[NiX_4]^{2-}$ and $[CoX_4]^{2-}$ ions the magnitude of the observed shifts varies with X in the order $[MCl_4]^{2-} < [MBr_4]^{2-} < [MI_4]^{2-}$ which suggests that the nitrogen s orbital does not receive a significant proportion of its spin density from direct overlap with a metal orbital. It is possible that the spin is transferred to the cation through the halogen ligands of the anions. This conclusion is in contrast to that reached from another ^{14}N and ^{31}P NMR study on some of the complexes listed in Table V. (229) It has been claimed that the high frequency shifts arise primarily from direct spin transfer between the metal ion and the nitrogen or phosphorus atom in the cation. (229) However, such a mechanism is unable to account for the observed proton NMR data and has been strongly criticized. (1, 228)

Some six-coordinate complexes of iron(II) and cobalt(II) with benzamide are reported to give only contact interactions in the absence of ion-pairings. However, ion-pair formation apparently produces a distortion resulting in g tensor anisotropy which results in a dipolar contribution to the isotropic shifts. (53)

The complicated solution equilibria which occur for ion-paired systems in various solvents together with a contact contribution to the shifts and some oversimplified assumptions about free rotation in solution implies that estimates of interionic separation obtained from dipolar shifts are at best qualitatively correct. (230-233) However the contact and dipolar portions of the shifts have been separated with reasonable consistency for a series of anionic lanthanide complexes (232) and for some quaternary ammonium cations in the presence of tetrabromo cobalt(II) and tetrabromo nickel(II) anions. (233) The dipolar contribution to the shifts is estimated from a restricted tumbling model (231) in which the anion is permitted to move on a section of a sphere described with respect to a fixed cation position,

TABLE V

^{14}N NMR shift data in ppm for some ion-pairs (228)

Ion-pair	Bulk susceptibility shift	Predicted[a] dipolar shift	Observed shift	Total high frequency shift
$[(n\text{-}C_4H_9)_4N][(C_6H_5)_3PCoI_3]$	5·4	5·9	−9	−20
$[(n\text{-}C_4H_9)_4N][(C_6H_5)_3PNiI_3]$	3·1	−2·8	−10	−10
$[(n\text{-}C_4H_9)_4N]_2[CoCl_4]$	5·8	1·7	1	−6
$[(n\text{-}C_4H_9)_4N]_2(CoBr_4]$	6·1	2·1	−5	−13
$[(n\text{-}C_4H_9)_4N]_2[CoI_4]$	6·2	2·1	−12	−20
$[(n\text{-}C_4H_9)_4N]_2[NiCl_4]$	3·8	−1·3	−6	−8
$[(n\text{-}C_4H_9)_4N]_2[NiBr_4]$	3·8	−0·9	−7	−10
$[(n\text{-}C_4H_9)_4N]_2[NiI_4]$	3·4	−0·1	−12	−15
$[(n\text{-}C_4H_9)_4N]_2[Co(SCN)_4]$	5·3	0	−1	−6
$[(n\text{-}C_4H_9)_4N]_2[MnBr_4]$	9·1	0	−5	−14

[a] Calculated from proton data assumed to be entirely dipolar in origin, and the geometric factor $(3\cos^2\theta - 1)r^{-3}$.

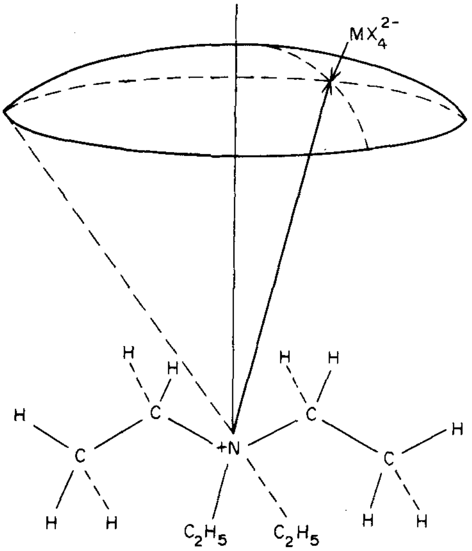


FIG. 11. The restricted tumbling model for tetraethyl ammonium cations and $[MX_4]^{2-}$ anions. (232)

Fig. 11. From a comparison of the shifts produced by $[CoBr_4]^{2-}$ and $[NiBr_4]^{2-}$ it has been claimed that the former is responsible for predominantly contact shifts while the contact and dipolar mechanisms make comparable contributions in the latter case. (233) This is in contrast to the usually considered order of importance of dipolar and contact interactions in determining the isotropic shifts of tetrahedral complexes of cobalt(II) and nickel(II), as discussed in Section III. A (1). Consequently a reconsideration of earlier NMR data on ion-paired systems, (1) in which only dipolar interactions were considered, is called for.

Measurement of the relaxation rate of caesium(I) ions in aqueous solutions containing iron(III) halides and various counteranions indicates that ion-pairs are formed by the caesium(I) and iron(III) halide ions. (234) Other systems in which ion-pairing has been studied by NMR measurements include the hexacyanoiron(III) ion and some biquaternary ammonium cations (235) and the hexafluorosilicate anion in the presence of some aquo transition metal cations. (236) In the latter case ^{19}F NMR data signifies the presence of both contact and dipolar interactions. (236)

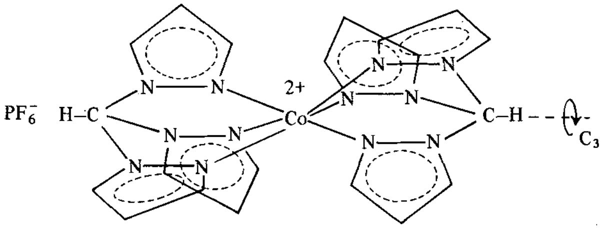
The unusual temperature dependence of some isotropic NMR shifts in various paramagnetic systems could be due to ion-pair formation. (237) Perhaps this should be considered along with the conditions described by equations (11) and (49) as a further possible cause for non-Curie law behaviour.

The determination of the structure of the second coordination sphere of a complex ion in solution is relevant to studies on the mechanisms of its reactions. The average orientation of neutral molecules in the second coordination sphere of chromium(III) has been investigated by a comparison of the nuclear relaxation times of non-equivalent protons of the same molecule in the presence of a stable chromium(III) complex. (238, 239) Equations (35) and (36) show that if the relaxation times are controlled by the dipolar term, then the relative line widths of two non-equivalent protons in the same molecule depend upon the sixth power of their relative separations from the chromium(III) ion. Well defined intramolecular effects are observed by comparing the data from a number of solvents which may be accounted for by an ion-dipole model. (238, 239) Comparison of the NMR data for DMF, *N,N*-dimethylacetamide and methanol in the presence of various transition metal ions with different charges reveals that the orientation of the solvent molecules depends upon the charge on the complex ion. (238) In the case of a series of chromium(III) complexes in methylene chloride it is found that the cations order the second coordination sphere more effectively than the anions. (240)

The solvent line widths of the NMR signals of some tris-α-diimine chelates of chromium(II) and nickel(II) in mixed aqueous-methanolic solutions have been reported. (768) Analysis of the data suggests a preference for water molecules to penetrate within the ionic radius in the cationic chelates of the reducing chromium(II) ion but not for the more redox-stable nickel(II) ion. (768)

The second coordination sphere of some complexes of cobalt(II) has also been studied by NMR measurements. (241-244) In this case it is assumed that dipolar interactions produce the shifts observed in the NMR spectra of the molecules in the second coordination sphere. By means of the geometric factor $(3\cos^2\theta - 1)r^{-3}$ estimates of the structure of this outer sphere have been obtained for aniline and some pyridines in the presence of tris(pyrazolylborate)cobalt(II), [1]. (241, 242) It is found that the dipoles of the bases forming the second sphere are in opposite orientations to those of the first sphere ligands and that the enthalpy change involved in the formation of the second sphere is about 2 to 3 Kcal/mole. (241, 242) Consequently the structure of the second sphere appears to be determined by the electrostatic interactions resulting from the negatively charged ligands in the first coordination sphere. Aniline experiences competition with solvent molecules for a place in the second sphere, the solvent becomes an increasingly effective competitor in the series, carbon tetrachloride, benzene and methylene chloride.

The cobalt(II) cation [60] forms an ion-pair with the hexafluorophosphorus (V) anion in acetonitrile. (243) From the ^{19}F NMR shift data it is concluded that the preferred position of the anion lies close to the three-fold axis of the cation, (243) with dipolar solvent molecules taking up the positions of closest approach to the cobalt(II) ion. This contrasts with the results of studies on second sphere coordination involving neutral molecules.



[60]

It is anticipated that interest in this area of NMR studies will grow rapidly in the hope that an understanding of the detailed mechanisms of the ligand exchange reactions involved in homogeneous catalysis may emerge.

The structures of the second coordination spheres of paramagnetic centers involved in enzymatically catalysed reactions in aqueous media may also be determined and some knowledge of the relevant mechanisms obtained.

D. Formation and Reactions of Metal Complexes

The formation of paramagnetic metal complexes can be studied by means of the shifts and line broadenings observed in the NMR spectra of the ligand molecules. If the rate of exchange between complexed and free ligand molecules is not too rapid it may be possible to observe a separate NMR spectrum for the ligands residing in the first coordination sphere of the metal ion. (1) In this case evaluation of the relative areas of the signals from coordinated and uncoordinated ligands leads to accurate estimates of metal coordination numbers and competitive solvation phenomena. (1)

The importance of water both as a solvent and as a ligand together with its simple NMR spectrum led to a number of early studies of metal ion hydration. (1) When ligand and proton exchange is sufficiently slow to satisfy the relationship:

$$\tau \simeq \frac{1}{2\pi\Delta\nu_M} \tag{53}$$

then a separate proton signal for coordinated water molecules is to be expected. In equation (53) τ is the lifetime of the proton in the solvation sphere of the metal and $\Delta\nu_M$ is the separation of the proton signals from the free and coordinated water molecules in Hz. In order to satisfy equation (53) it is often necessary to use low temperatures. (245-247) Hydration numbers of six have been reported for a number of lanthanides and first transition series metal ions. (245-247) Separate signals have been observed for the hydroxyl protons of methanol coordinated to titanium(III) and in the uncoordinated form, the number of bound methanol molecules is estimated to be about four. (248) In a similar investigation on methanolic solutions containing both nickel(II) and chloride ions, $[Ni(CH_3OH)_6]^{2+}$ and $[Ni(CH_3OH)_5Cl]^+$ have been detected by low temperature NMR measurements. (249)

Often the rate of solvent exchange between the bulk solution and the first coordination sphere of a metal ion is sufficiently rapid that only one set of signals appears in the NMR spectrum. Under these conditions

$$\Delta\nu = P_M \Delta\nu_M \tag{54}$$

where $\Delta\nu$ is the observed isotropic shift for the solvent nuclei in the solution with respect to the pure solvent and P_M is the fraction of solvent molecules coordinated to the metal ion. Proton NMR data from aqueous solutions of chromium(II) have been analysed by means of equation (54) to show that spin transfer to the protons arises mainly from π delocalization. (250) A similar conclusion has been reached from a ^{17}O NMR study of a vanadium(IV) aquo complex. (132) Comparison of the sign, magnitude and temperature dependence of the ^{17}O shifts with the proton data for some aquo complexes of lanthanide metal ions, reveals that the former are mainly due to contact interactions and the latter to dipolar interactions. (148)

Swift and Connick have demonstrated that line width studies on the exchange averaged signals can also provide valuable information. (251, 252) The observed line width depends upon the relaxation time of the nuclei present in the bulk solvent in the absence of paramagnetic ions, T_{2W}, together with a contribution, T_{2P}, from the paramagnetic ions. From equation (36) it follows that:

$$\pi\Delta = \frac{1}{T_2} = \frac{1}{T_{2w}} + \frac{1}{T_{2P}} \tag{55}$$

where

$$\frac{1}{T_{2P}} = \frac{P_M}{\tau_M}\left[\frac{(T_{2M})^{-2} + (T_{2M}\tau_M)^{-1} + \Delta\nu_M^2}{(T_{2M}^{-1} + \tau_M^{-1})^2 + \Delta\nu_M^2}\right] \tag{56}$$

τ_M is the mean lifetime of the ligand molecules in the first coordination sphere of a metal ion and T_{2M} is the relaxation time for a given nucleus in a coordinated molecule.

Experimental data are usually analysed with the help of some limiting conditions. If the rate of ligand exchange is slow and

$$\frac{1}{T_{2M}^2} \gg \frac{1}{\tau_M^2}, \Delta\nu_M^2 \tag{57}$$

then the relaxation rate is controlled by chemical exchange and,

$$\frac{1}{T_{2P}} = \frac{P_M}{\tau_M} \tag{58}$$

for faster exchange, such that,

$$\frac{1}{\tau_M^2} \gg \Delta\nu_M^2 \gg \frac{1}{T_{2M}\cdot\tau_M} \tag{59}$$

then

$$\frac{1}{T_{2P}} = P_M\tau_M\Delta\nu_M^2 \tag{60}$$

and for very fast exchanges,

$$\frac{1}{T_{2M}\cdot\tau_M} \gg \frac{1}{T_{2M}^2}, \Delta\nu_M^2 \tag{61}$$

then

$$\frac{1}{T_{2P}} = \frac{P_M}{T_{2M}} \tag{62}$$

A logarithmic plot of relaxation rate against reciprocal temperature reveals which of the limiting equations (58), (60) or (62) is applicable to a given experiment. Usually chemical exchange has a higher activation energy than other relaxation mechanisms, thus a large negative or a large positive slope indicate respectively a temperature region corresponding to equations (58) and (60).

The variation of τ_M with temperature permits the evaluation of the enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ of activation for the first order exchange reaction from,

$$\tau_M = K^{-1} = \frac{h}{\kappa T} \exp\left(\frac{\Delta H^{\ddagger}}{RT} - \frac{\Delta S^{\ddagger}}{R}\right) \qquad (63)$$

where K is the rate constant for the ligand exchange reaction. Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ have been estimated by means of either equation (58) or (60) together with equation (63) for a number of transition metal complexes including aquo and methanol complexes of the first transition series metal ions (Table VI). Some of the results given in Table VI show significant differences from those given earlier. (1) A deuterium isotope effect on the rate constant has been reported from a study of the acid catalyzed proton exchange between vanadium(IV) and uncoordinated water. (259)

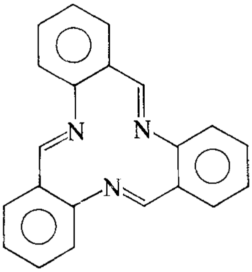
TABLE VI

Some kinetic data for solvent exchange at 298 K

Metal ion	Solvent	K(sec^{-1})	$\Delta H^{\ddagger}$(Kcal/mole)	$\Delta S^{\ddagger}$(eu)	Ref
Ti(III)	H_2O	(1·0 ± 0·1) x 10^5	6·2 ± 0·3	−15 ± 2	248
Ti(III)	CH_3OH	(1·88 ± 0·3) x 10^5	3·3 ± 0·5	−24 ± 2	248
V(II)	H_2O	1 x 10^2	16·4 ± 0·6	5·5 + 1·5	254
V(III)	H_2O	1·67 x 10^3	6·2	−23	255
Mn(II)	H_2O	3·7 x 10^5	6·2	−12	253
Fe(II)	H_2O	5 x 10^4	12	3	253
Fe(II)	H_2O	5·1 x 10^3	10·1	− 8	253
Cu(II)	H_2O	7·4 x 10^7	6·0	− 2·6	257

The rate constants for water exchange with lanthanide metal ions range from 0·3 to 2·6 x 10^{-7} sec^{-1} and they reflect changes in the ionic radii of the lanthanide ions. (256) The upper limit of $\Delta H^{\ddagger}$ is reported to be about 5 Kcal/mole. (256) The predominant relaxation mechanism for ^{17}O nuclei in paramagnetic aquo complexes is reported to be the contact interaction whilst dipolar interactions control the proton relaxation rates. Consequently by considering both proton and ^{17}O relaxation data it is possible to estimate values for the hyperfine interaction constant, a_N, as well as for the correlation times τ_e and τ_c from equation (32). (245, 247, 255, 258, 259).

Reasonable estimates of the electronic relaxation time have also been obtained from NMR studies. (259) In aqueous solutions of metal ions with $S = \frac{3}{2}$ or $\frac{5}{2}$, e.g. chromium(III), manganese(II) or iron(III), the electronic relaxation process is controlled by the modulation of the zero field splitting by collisions between the hydrated complex ion and bulk solvent molecules. Theoretical equations have been derived to incorporate this and the contact controlled relaxation rates for protons, in the hydration shells of these metal ions, obtained from ESR measurements. (258) Comparison of the electronic relaxation times obtained in this manner with those available from NMR data shows good agreement for chromium(III) and iron(III) but only moderate agreement for manganese(II). (258) The kinetic parameters for the exchange of water by metal complexes can be of interest in a consideration of substitution reactions as well as in structural studies. Some kinetic data for water exchange reactions are reported in Table VII for a number of transition metal complexes including the nickel(II) complex of TRI [61]. The results given in Table VII show the effects of various coordinated ligands on the stability of complex water molecules. In the case of nickel(II) the presence of ammonia and ethylene diamine produces a labilizing effect on the remaining water molecules whereas terpyridine, bipyridine [27], CR [41] and TRI [61] produce only slight changes in the water exchange behaviour.



[61]

Comparison of the kinetic data for analogous cobalt(II) and nickel(II) aquo complexes shows that at 298 K the cobalt complexes exchange water approximately one hundred times quicker than the

TABLE VII

Kinetic data for water exchange at 298 K with some transition metal complexes

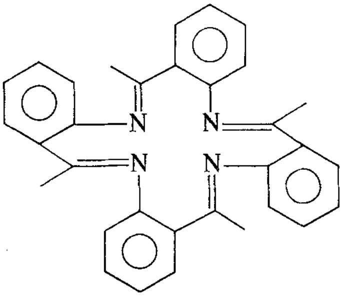
Complex	K($\sec^{-1}$)	$\Delta H^{\ddagger}$(Kcal/mole)	$\Delta S^{\ddagger}$(e.u.)	Ref.
$[Ni(H_2O)_4\,en]^{2+}$	(4·4 ± 0·2) x 10^5	10·0 ± 0·5	10 ± 2	260
$[Ni(H_2O)_2\,en_2]^{2+}$	(5·4 ± 0·3) x 10^6	9·1 ± 0·5	2·6 ± 2	260
$[Ni(H_2O)_5NH_3]^{2+}$	(2·5 ± 0·2) x 10^5	10·6 ± 0·5	1·8 ± 1·5	261
$[Ni(H_2O)_4(NH_3)_2]^{2+}$	(6·1 ± 0·2) x 10^5	7·8 ± 0·3	−6·0 ± 2·0	261
$[Ni(H_2O)_3(NH_3)_3]^{2+}$	(2·5 ± 0·2) x 10^6	10·2 ± 0·5	5·0 ± 1·5	261
$[Ni\,terpy]^{2+}$	(5·2 ± 0·4) x 10^4	10·7 ± 0·4	−1·0 ± 1	262
$[Ni(H_2O)_2CR]^{2+}$	4·5 x 10^4	6·8	−14·4	263
$[Ni(H_2O)_2CRCH_3]^{2+}$	5·2 x 10^4	6·3	−15·8	263
$[Ni(H_2O)\,EDTAH]^-$	(2·0 ± 0·1) x 10^5	9·8 ± 0·3	−1·5 ± 2	209
$[Ni(H_2O)\,EDTA]^{2-}$	(7 ± 0·5) x 10^5	8·0 ± 0·5	−7·0 ± 2	209
$[Ni(H_2O)_4\,bipy]^{2+}$	4·9 x 10^4	12·6 ± 0·5	5·1 ± 2	264
$[Ni(H_2O)_2\,bipy_2]^{2+}$	6·6 ± 10^4	13·7 ± 0·5	9·2 ± 4	264
$[Ni(H_2O)_2\,TRI]^{2+}$	3·8 ± 10^4	10·9	−1·9	269
$[Ni(H_2O)_6]^{2+}$	(3·6 ± 0·2) x 10^4	12·3 ± 0·5	3·6 ± 1·5	261
$[Ni(H_2O)_6]^{2+}$ at pH = 6	(4·4 ± 0·2) x 10^4	10·3 ± 0·5	−5·2 ± 2	260
$[Ni(H_2O)_6]^{2+}$	(3·4 ± 0·1) x 10^4	12·1 ± 0·3	2·9 ± 0·9	262
$[Ni(H_2O)_6]^{2+}$	3·2 x 10^4	12·1 ± 0·5	2·6 ± 2	264
$[Co(H_2O)_5NH_3]^{2+}$	(1·55 ± 0·2) x 10^7	12·6 ± 0·6	17 ± 3	265
$[Co(H_2O)_4(NH_3)_2]^{2+}$	(6·5 ± 1) x 10^7	9·4 ± 1·5	7 ± 5	265
$[Co(H_2O)_4\,malonate]$	2·2 x 10^7	12·9 ± 0·8	18 ± 4	265
$[Co(H_2O)_6]^{2+}$	(2·35 ± 0·2) x 10^6	11·9 ± 0·7	10·6	266
$[Co(H_2O)_6]^{2+}$ at pH = 4·2	(2·24 ± 0·05) x 10^6	10·3 ± 0·2	5·1 ± 0·6	265
$[Mn(H_2O)\,EDTA]^{2-}$	4·4 x 10^8	7·7	7	267
$[Mn\,ATP]^{2-}$	5·0 x 10^7	9·6	8·8	771
$[Mn(H_2O)_2\,NTA]^-$	(1·50 ± 0·8) x 10^9	6·6	6	267
[a] $[Mn(H_2O)_4\,phen]^{2+}$	(1·3 ± 2) x 10^7	9 ± 2	6 ± 7	268
[a] $[Mn(H_2O)_2\,phen_2]^{2+}$	(3·1 ± 3) x 10^7	9 ± 2	8 ± 9	268
[a] $[Mn(H_2O)_6]^{2+}$	(5·9 ± 0·6) x 10^6	8·8 ± 1	5 ± 3	268
[b] $[VO(H_2O)_3Cl]^+$	(2·3 ± 0·6) x 10^4	15 ± 1		270
[b] $[VO(H_2O)_2Cl_2]$	(8·5 ± 0·3) x 10^5	10 ± 1		270
[b] $[VO(H_2O)_4]^{2+}$	(5·9 ± 0·2) x 10^2	15 ± 1		270
[c] $[Cr(H_2O)_5N_3]^{2+}$	1·20 x 10^4	11·7	3	271

[a] Data taken at 273 K. [b] Data taken at 300 K. [c] Data taken at 293 K.

en = ethylenediamine; terpy = 2,2′,2″-terpyridine; phen = structure [2] with R=H; bipy = structure [27] with R=H; CR = structure [41] with X=H; $CRCH_3$ = structure [41] with X=CH_3; TRI = structure [61]; EDTAH = protonated EDTA; NTA = nitrilotriacetate.

nickel complexes although the corresponding values of $\Delta H^{\ddagger}$ are similar or sometimes larger for the cobalt complexes. Crystal field calculations suggest that the value of $\Delta H^{\ddagger}$ should be smaller for cobalt(II) than for nickel(II) complexes, thus it appears that different mechanisms are used by the two metals in exchanging water.

It is possible that four-coordinate cobalt(II) is involved in the process. (265) This is supported by some ^{35}Cl NMR results from aqueous solutions of cobalt(II) chloride. (266, 267) It has also been reported that the exchange of ammonia with cobalt(II) ammines in aqueous solution gives very similar kinetic data to that found in anhydrous ammonia. (273) For the manganese(II) and vanadium(III) complexes reported in Table VII ligand substitution tends to increase the rate of water exchange. It seems likely that the NMR data represents the average of a number of similar exchange mechanisms which require further study.



[62]

The methanol exchange rate constants per coordinated solvent molecule for the methanol molecules *cis* and *trans* to the water in $[Co(CH_3OH)_5H_2O]^{2+}$ have recently been reported. (770) The *cis* and *trans* sites are found to have equal exchange rate constants per coordinated methanol molecule of 609 sec^{-1} at 243 K. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are reported to be 12·8 Kcal/mole and 6·9 e.u. respectively. (770) These results are comparable to those for methanol exchange with $[Co(CH_3OH)_5(CNS)]^+$ where exchange occurs without rearrangement of the complex ion. (296)

The exchange of DMF with various Schiff base complexes of nickel(II), including TAAB [62], have been studied by proton NMR. (263, 274) The resulting kinetic parameters are given in Table VIII. The similarity of the data reported for $[Ni\ TRI(DMF)_3]^{2+}$ and for $[Ni(DMF)_6]^{2+}$ adds further support to the conclusion reached from the water exchange data in Table VII, namely that TRI does not greatly affect the solvent exchange kinetics. (269, 274) This is in contrast to the data reported in Table VIII for other Schiff base ligands. The fast exchange rates and low values of $\Delta H^{\ddagger}$ reported for the final two complexes in Table VIII is thought to reflect either

TABLE VIII

Kinetic data for the exchange of DMF with some Schiff-base complexes of nickel(II) at 298 K

Complex	R(sec^{-1})	$\Delta H^{\ddagger}$(Kcal/mole)	$\Delta S^{\ddagger}$(e.u.)	Ref.
$[Ni(DMF)_3\ TRI]^{2+}$	$5{\cdot}9 \times 10^2$	15·6	6·5	274
$[Ni(DMF)_2\ TAAB]^{2+}$	$7{\cdot}3 \times 10^4$	11·5	2·5	274
$[Ni(DMF)_2\ CR]^{2+}$	$1{\cdot}9 \times 10^6$	9·5	2·2	263
$[Ni(DMF)_2\ CRCH_3]^{2+}$	$2{\cdot}8 \times 10^6$	7·8	−2·9	263

CR = structure [41] with X = H; $CRCH_3$ = structure [41] with X = CH_3; TRI = structure [61]; TAAB = structure [62].

steric interactions or coupling to a diamagnetic-paramagnetic equilibrium. (186, 263, 274)

^{14}N NMR spectra have been used to study DMF exchange with nickel(II), cobalt(II) and manganese(II). (275) Proton data on the exchange of DMF with iron(III) have also been reported. (276) Nitrogen quadrupolar interactions are reported to dominate the nuclear relaxation processes for the nickel and cobalt complexes while isotropic spin exchange plays the major role for the manganese complex. (275)

The exchange reactions of dimethylsulphoxide (DMSO) have also been widely studied by means of NMR spectroscopy. (277-282) The ligand exchange kinetics of the six-coordinate complexes of nickel(II) and cobalt(II) in DMSO and in the mixed solvents DMSO/nitromethane and DMSO/methylenechloride are found to be the same. This is consistent with a dissociative mechanism. (277-279) A five-coordinate intermediate has been postulated for the nickel(II) complex. (281)

Some kinetic parameters for acetonitrile exchange, from proton and ^{14}N NMR data, are reported in Table IX. For the cobalt(II) and nickel(II) complexes listed in Table IX, it is reported that both the protons and nitrogen nuclei relax by the "$\Delta\nu$" process. (251, 252) This arises from a change in precessional frequency when solvent exchange occurs. (285-286) In addition the protons experience a significant dipolar relaxation.

From Table IX it is apparent that the value of K at 298 K decreases from manganese(II) to nickel(II) whereas a reverse trend is noted for $\Delta H^{\ddagger}$. Similar observations have been made for the exchange of water, methanol and ammonia with the same metal ions suggesting a similar mechanism for the four solvents. (285, 291) The

TABLE IX

Kinetic data for the exchange of acetonitrile with some transition metal ions at 298 K

Metal ion	K (sec^{-1})	$\Delta H^{\ddagger}$(Kcal/mole)	$\Delta S^{\ddagger}$(e.u.)	Ref.
^{b}VO(IV)	$2{\cdot}85 \times 10^3$	7·05	−20	287
^{a}Mn(II)	$(1{\cdot}2 \pm 0{\cdot}3) \times 10^7$	7·25 ± 0·25	−1·8 ± 0·8	283
^{a}Fe(II)	$(5{\cdot}5 \pm 0{\cdot}8) \times 10^5$	9·7 ± 0·7	0·3 ± 2·2	284
^{a}Co(II)	$(3{\cdot}2 \pm 0{\cdot}3) \times 10^5$	11·4 ± 0·5	5·0 ± 0·2	285
^{b}Co(II)	$(3{\cdot}5 \pm 0{\cdot}5) \times 10^5$	11·4 ± 0·5	5·2 ± 2·2	285
^{a}Ni(II)	$(2{\cdot}1 \pm 0{\cdot}3) \times 10^3$	16·4 ± 0·5	12·0 ± 2·0	286
^{b}Ni(II)	$(2{\cdot}8 \pm 0{\cdot}5) \times 10^3$	11·7 ± 0·1	−3·6 ± 1·0	288

[a] Data from ^{14}N NMR measurements.
[b] Data from proton NMR measurements.

observed trend in $\Delta H^{\ddagger}$ values is predicted from crystal field calculations, based on a square-pyramidal transition state, for water exchange. (289)

A comparison of solvent exchange rate data for iron(III) and nickel(II) shows that for water, DMSO, DMF and acetonitrile the exchange rates for iron(III) are about 0·6% of the corresponding rates for nickel(II), while for methanol and ethanol the exchange rate for the iron complex is twice that for the nickel complex.

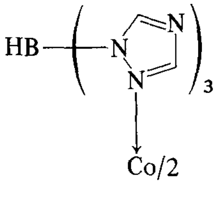
The cobalt(II)-triethylenetetramine(trien) system in acetonitrile has been studied by means of ^{14}N NMR. (290) The predominant species are found to be $[Co(CH_3CN)_6]^{2+}$, $[Co\ trien(CH_3CN)_n]^{2+}$ where n is one or two, $[Co_2(trien)_3]^{4+}$ and $[Co(trien)_2]^{2+}$. Upon coordination of trien the lability of the coordinated acetonitrile increases by a factor in excess of 10^3. A similar effect has been observed for water exchange in the presence of coordinated amines and could be due to the decrease in the effective charge on the metal ion produced by electron donation from the amines. (261, 264, 265)

Spin-echo techniques have been used to study dilute solutions of nickel(II) ions in acetonitrile (292, 293) and cobalt(II) ions in deuteromethanol. (294) This work includes the first reported application of the Carr-Purcell experiment to the study of ligand exchange which depends upon the exchange rate being comparable to the chemical shift difference between the two ligand sites. The spin-echo results are consistent with four exchanging acetonitrile molecules per nickel ion. (292) However, ^{14}N NMR linewidth measurements indicate the presence of four equivalent exchanging molecules and a further two acetonitrile molecules exchanging more rapidly. This is to be expected since it is known that the complex is tetragonally distorted with two long and four short metal-ligand bonds. (293)

For cobalt(II) in deuteromethanol the six ligands exchange at the same rate which is in agreement with earlier high resolution NMR data. (294) In acetonitrile–water mixtures it is found that $[Cr(CNS)_4]^{3-}$ exhibits a strong preference for acetonitrile. (295) The rate at which the first SCN^- ion is removed from the complex ion is reported to be a function of the solvent shell composition.

The ligand exchange kinetics for some picolines, (297, 298) 4-picoline-*N*-oxide (299) and some substituted anilines (300) co-ordinated to bis(β-diketone) complexes of nickel(II) and cobalt(II) similar to [18] have been reported. In general the 4-picoline-*N*-oxide exchange is found to be faster than that for 4-picoline. This probably reflects the lower basicity and greater steric interaction between 4-picoline-*N*-oxide and the chelate rings of the metal complexes. In agreement with previous (1) observations the exchange rates of the cobalt complexes are faster than those of the corresponding nickel complexes.

3-picoline-*N*-oxide exchanges with hexakis (3-picoline-*N*-oxide)nickel(II) in a solvent composed of equal amounts of nitromethane-d_3 and acetone-d_6. (301) The NMR data show that the exchange rate is independent of the concentration of the free ligand. This supports a dissociative mechanism for the exchange reaction (301) rather than strong preferential solvation of the complex by the exchanging ligand. (297) NMR measurements on various nuclei have provided kinetic data for a number of cobalt(II) complexes including those with dimethyl methylphosphonate and trimethylphosphate, (302) halide ions in various solvents, (266, 272, 303-305) thiocyanate ion in aqueous solutions (306) and hydrotris(1,2,4-triazol-1-yl)-borate [63] in a variety of D_2O/D_2SO_4 mixtures. (307) For the cobalt(II) chloride–pyridine system ^{14}N NMR shift data show that the equilibrium constant $K = 2{\cdot}3 \pm 1{\cdot}2$ mole^2 at 303 K, where



[63]

$$K = \frac{[CoPy_2Cl_2]\,[Py]^2}{[CoPy_4Cl_2]} \tag{64}$$

the value of the corresponding thermodynamic parameters are ΔH = 13·0 ± 0·9 Kcal/mole and ΔS = 43·4 ± 2·2 e.u. The mean lifetime of pyridine in $CoPy_4Cl_2$ is reported to be (1·5 ± 0·2) x 10^{-7} sec at 298 K with $\Delta H^{\ddagger}$ = 13·2 ± 0·5 Kcal/mole and $\Delta S^{\ddagger}$ = 17 ± 2 e.u. for the exchange. (305) This is a striking example of the utility of NMR measurements in obtaining both thermodynamic and kinetic data on paramagnetic species in solution.

Further examples of the use of NMR techniques in obtaining information on the solvation of metal ions from the first transition series are afforded by the following:

Vanadium(IV) complexes in methanol and halogen-substituted ethanols, (308) pulsed NMR measurements relating to the association between the manganese(II) and dithionite ions, (309) electron exchange reactions between isonitrile complexes of manganese(II) and manganese(I), (310) the exchange of a substituted phosphoric acid with copper(II) ions (311) and a study of the preferential solvation and relaxation of some chromium(III) complexes. (312, 313) Exchange reaction data have also been reported for some lanthanide metal complexes. (156, 158, 273, 314)

E. Organic Free Radicals

Electronic relaxation times for free radicals are often longer than for transition metal complexes, consequently in order to satisfy equation (2) it is necessary to produce a more rapid relaxation process. This has been achieved by using the liquid radical DBNO [11] as solvent for a number of organic free radicals. Rapid spin exchange between solvent and solute results in a single shifted NMR signal for each set of equivalent nuclei in the solute radical. (1, 315)

In addition to interpreting the observed isotropic shifts it is also possible to determine hyperfine interaction constants from the widths of the shifted signals. In the case of a –C–H fragment a dipole-dipole interaction occurs between the proton and unpaired electron in the $2p_\pi$ orbital of the carbon atom. By assuming that τ_e is shorter than the molecular rotation time equation (35) for the proton becomes:

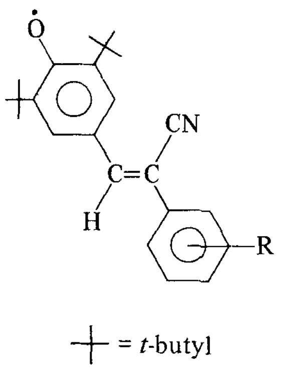
$$\left(\frac{1}{T_2}\right)_H = \frac{4S(S+1)g_N^2\beta_N^2 g_e^2\beta_e^2\rho_c^2\tau_e}{3\hbar^2 r_{\text{C-H}}^6} + \frac{2S(S+1)a_H^2\tau_e}{3\hbar^2} \qquad (65)$$

where ρ_c is the spin density on the adjacent carbon atom. By considering equations (36), (42) and (65) it is apparent that the line widths of the proton signals are proportional to a_H^2.

In the case of a –C–F fragment an additional term is necessary to account for the dipolar contribution to the line width from spin delocalized in the fluorine $2p$ orbitals, equation (35) now becomes:

$$\left(\frac{1}{T_2}\right)_F = \frac{4S(S+1)g_N^2\beta_N^2g_e^2\beta_e^2}{3\hbar^2}\left(\frac{\rho_c^2}{r_{\mathrm{C-F}}^6}+\frac{\rho_F^2}{r_F^6}\right)\tau_e + \frac{2S(S+1)a_F^2}{3\hbar^2}\,\tau_\epsilon \tag{66}$$

where ρ_F is the spin density in the fluorine $2p$ orbital concerned and r_F is the separation between the electron in this orbital and the F nucleus. By using estimates of the various separations in equations (65) and (66) it is possible to obtain the spin density distributions from line width data. This approach has been applied to the study of some fluorinated phenoxy radicals [64]. (315, 316) In contrast to



R = H
R = *ortho* fluoro
R = *meta* fluoro
R = *para* fluoro

[64]

protons the sign of the fluorine hyperfine interaction constant is the same as that of the spin density on the adjacent carbon atom. This has been interpreted in favour of a major contribution from spin density in the fluorine $2p$ orbital to the fluorine hyperfine interaction constant. (315, 317)

NMR studies have been performed on a number of polyradicals. (318-320) Usually dipolar interactions between the unpaired electrons are not averaged at room temperature, by molecular tumbling, and they produce a single broad signal in the ESR spectra of these species from which it is not possible to obtain hyperfine interaction constants. However, in some cases NMR spectra may be used to determine these parameters.

The energy separation between the spin singlet and the triplet states of a biradical is given by the electron spin exchange integral J.

In an isotropic system the corresponding magnetic susceptibility is expressed by equation (19) in the form:

$$\chi = \frac{g_e^2 \beta_e^2 S(S+1)}{3\kappa T} \left[1 + \exp\left(\frac{J}{RT}\right) \exp\left(\frac{-\Delta S}{R}\right) \right]^{-1} \qquad (67)$$

where ΔS is the singlet-triplet entropy separation. In this case the expression for the contact shifts becomes:

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2 S(S+1)}{g_N \beta_N . 3\kappa T} \left[1 + \exp\left(\frac{J}{RT}\right) \exp\left(\frac{-\Delta S}{R}\right) \right]^{-1} \qquad (68)$$

If $RT > J$ and the entropy difference between the singlet and triplet states is entirely due to differences in electronic degeneracy, then equation (68) becomes:

$$\frac{\Delta H}{H_0} = -\frac{a_N g_e^2 \beta_e^2 S(S+1)}{g_N \beta_N \cdot 4\kappa T} \qquad (69)$$

Although it is possible to evaluate the hyperfine interaction constant from equation (69) it does not distinguish between strongly ($J > a_N$) and weakly ($J < a_N$) coupled biradicals. (319, 320) The data obtained from the NMR spectra of some poly radicals are presented in Table X. It is apparent from Table X that the radicals [66], [67], [70] and [71] have singlet ground states while [65] exists in a spin triplet ground state. The conjugated radicals [65]-[67] and [70] have much larger values of the exchange integral than the largely unconjugated radicals [68], [69], [72] and [73] where the electrons are localized in well separated regions of the radical. It is reported that $RT > J$ for the radicals [68], [69], [71]-[76].

A comparison of the hyperfine interaction constants of the biradicals [74]-[76] with those of the corresponding monoradical reveals that the nuclei in the rings connecting the two monoradical halves have hyperfine interaction constants which are the average of those for nuclei in corresponding positions in the monoradical. Nuclei in other parts of the biradicals have hyperfine interaction constants which are about a half of the magnitudes found for the monoradicals. The relative values of the hyperfine interaction constants have been accounted for by both a simple perturbation calculation and INDO data. (320)

Steric effects in some monoradicals, usually dissolved in DBNO, have been studied by means of equation (51). (321-325) In the

TABLE X

Hyperfine interaction constants and singlet-triplet separation data for some polyradicals at 297K (318–320)

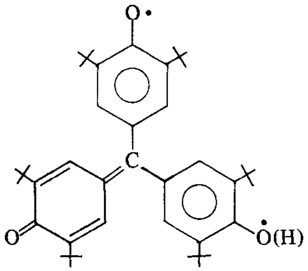
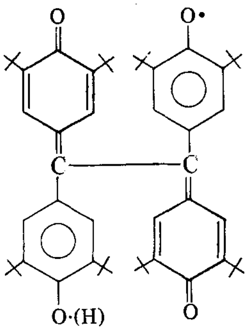
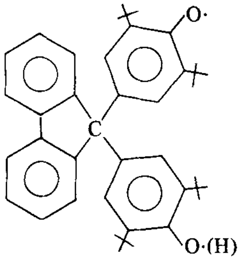
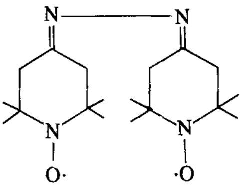
Radical		Group	a_N(Gauss)	J(cal)	ΔS(e.u.)
	[65]	*t*-butyl	0·04	−550	2·18
		m-H	0·93	−1320	2·18
	[66]	*t*-butyl	−0·025	1350	3·3
		m-H	0·72		
	[67]	*m*-H	780		2·18
	[68]	methyl	−0·06		
		methylene	−0·006		

TABLE X—*cont.*

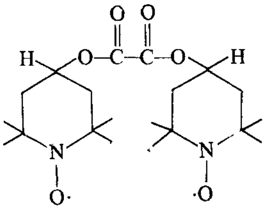
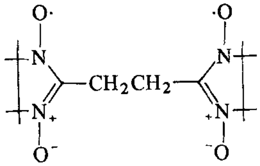
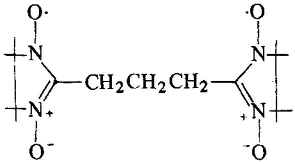
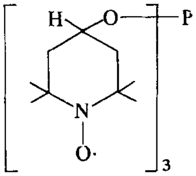
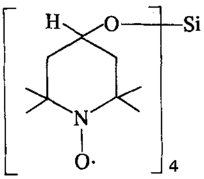
Radical	Group	a_N(Gauss)	J(cal)	ΔS(e.u.)
 [69]	*o*-methyl [1]	−0·20		
	o-methyl [2]	−0·008		
	m-methylene [1]	−0·15		
	m-methylene [2]	−0·24		
	Bridgehead proton	0·04		
 [70]	methyl	−0·112	409	2·84
	methylene	−0·956	340	2·62
 [71]	methyl	−0·103		
	α methylene	−1·01	<200	
	β methylene	0·056		
 [72]	*o*-methyl [1]	−0·14		
	o-methyl [2]	~0		
	m-methylene [1]	−0·098		
	m-methylene [2]	−0·159		
	Bridgehead proton	0·025		
	nitrogen	5·14		
 [73]	*o*-methyl [1]	−0·102		
	o-methyl [2]	~0		
	m-methylene [1]	−0·072		
	m-methylene [2]	−0·116		
	Bridgehead proton	0·019		
	nitrogen	3·89		

TABLE X–*cont.*

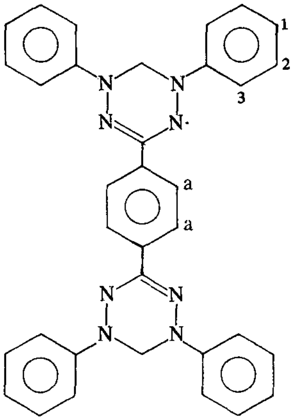
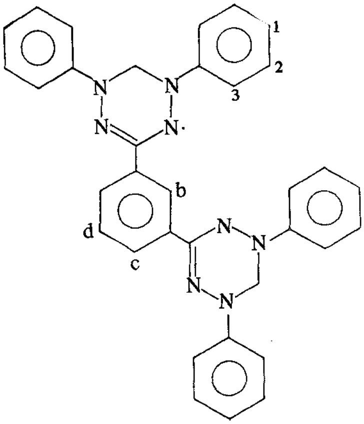
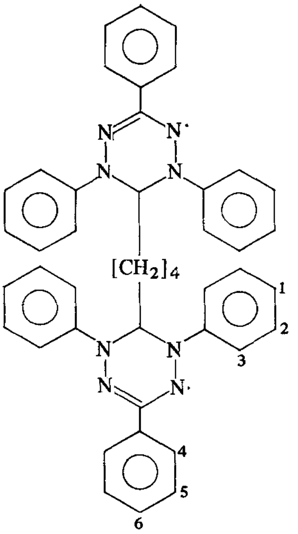
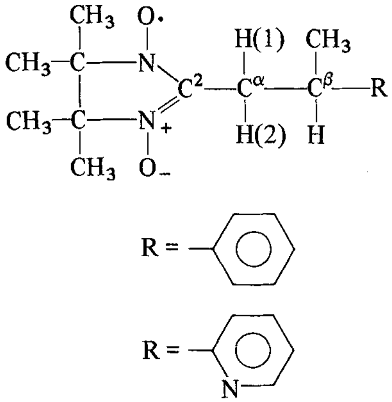
Radical	Group	a_N(Gauss)	J(cal)	ΔS(e.u.)
 [74]	Proton-1	−0·580		
	Proton-2	0·195		
	Proton-3	−0·533		
	Proton-a	0·118		
 [75]	Proton-1	−0·602		
	Proton-2	0·204		
	Proton-3	−0·554		
	Proton-b	0·366		
	Proton-c	0·366		
	Proton-d	−0·167		

TABLE X—*cont.*

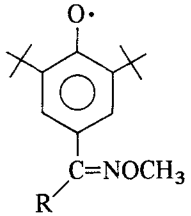
Radical	Group	a_N(Gauss)
 [76]	Proton-1	−0·630
	Proton-2	0·217
	Proton-3	−0·630
	Proton-4	0·217
	Proton-5	−0·076
	Proton-6	0·149

radical [77] the two protons on the α carbon have different values of the dihedral angle θ_N in the various possible conformations. These angles may be evaluated from the separate contact shifted signals which these protons give at room temperature. (322)



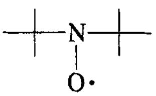
[77]

Yamauchi and Kreilick have concluded that in the series of phenoxy radicals [78] the spin delocalization at the protons on the first carbons of the aliphatic chains results mainly from a hyperconjugation mechanism. (321) On the other hand spin-polarization and direct overlap with the π system contribute to the contact shifts of the other protons. (321) The first direct assessment of both the sign and magnitude of some carbon hyperfine interaction constants has been made by ^{13}C NMR for the series of nitroxide radicals [79]-[82]. (324, 325) The signs of the ^{13}C hyperfine interaction constants are found to alternate between adjacent carbon atoms in the radicals. Spin density on the nitrogen atom produces a negative value for the hyperfine interaction constant of the α carbon due to electron polarization effects. The positive values of a_c found for the β carbon nuclei have an angular dependence described by equation

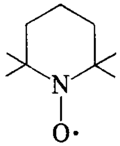


$R = CH_3$
$R = CH_2CH_3$
$R = CH_2CH_2CH_3$
$R = CH_2CH(CH_3)_2$
$R = CH(CH_3)_2$
$R = C(CH_3)_3$

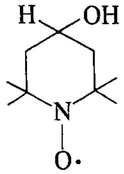
[78]



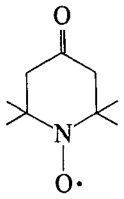
[79]



[80]



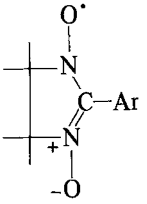
[81]



[82]

(51), the γ carbon hyperfine interactions are small and have a more complicated angular relationship. (325)

Various theoretical procedures for calculating spin density distributions have been compared for a series of nitronyl nitroxide radicals [83]. These are unusual in having a large negative spin density at the

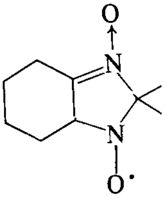


Ar = phenyl
Ar = 2-pyridyl
Ar = 4-pyridyl
Ar = 3-pyridyl

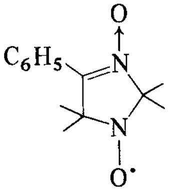
[83]

ortho and *para* positions of the conjugated rings and a small positive spin density at the *meta* position as determined by proton NMR. (52, 320) INDO results as well as a second order perturbation calculation within the framework of the McLachlan procedure are able to account for the signs and relative magnitudes of these spin densities. (52)

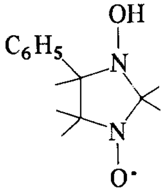
An NMR study of some hydroxyl radicals has revealed relatively large positive spin densities at the *meta* carbons of some conjugated rings. (568) This has been accounted for in terms of significant σ delocalization at these positions resulting from a non-planar structure for the radicals. (73, 568) Proton NMR data have been reported for the iminoxy radicals [84]-[86]. (326) The proton hyperfine interaction constants alternate in sign for protons attached to adjacent aliphatic carbon atoms. From the relative shifts of the protons in the



[84]



[85]

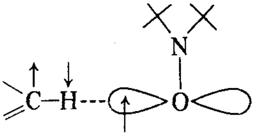


[86]

conjugated regions of the radicals it is reported that spin density is delocalized into the π system in [85] but not in [86]; this is attributed to the absence of π bonding in the imidazoline ring of [86]. (326)

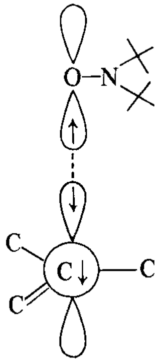
Comparison of the long-range hyperfine interaction constants of a series of free radicals with nuclear spin–spin coupling constants for related molecules shows a satisfactory correlation reflecting the similarity of the origins of these two parameters. (662)

Spin density transfer by weak interaction between free radicals and diamagnetic molecules has been observed in a number of systems. (61, 327-334) The induced contact shifts in the diamagnetic molecules have proven to be useful as a probe for studying hydrogen bonding (327-332) and charge transfer interactions. (61, 333) The contact shifts produced by 2,2,6,6-tetramethyl piperidine-*N*-oxyl [80] at the hydroxyl protons in a number of Lewis acids is thought to arise from hydrogen bonding with a filled MO on [80] which largely consists of an oxygen lone-pair of electrons. (327, 328) DBNO [11] has also been widely used in hydrogen bonding studies. In the X–H- - -DBNO hydrogen bonded system the proton and nucleus X, e.g. ^{13}C, experience a net negative and positive spin density respectively due to spin polarization. (329-332) INDO calculations on model systems have demonstrated that this type of spin delocalization requires the X–M proton to be placed directly above the oxygen p_π lone pair orbital of DBNO. (331) A number of aprotic molecules and hydrocarbons in the presence of DBNO have been studied by means of ^{13}C NMR. (333, 334) In the case of conjugated hydrocarbons both σ-type [87] and π-type [88] interactions with DBNO are possible. In substituted benzenes, e.g.



σ-type interaction

[87]



π-type interaction

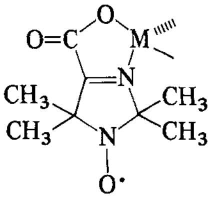
[88]

nitrobenzene and fluorobenzene, the ring carbon nuclei generally experience high frequency shifts in the presence of DBNO whereas the substituted carbon has a low frequency shift. Similarly fused ring hydrocarbons show high frequency ^{13}C shifts for the ternary carbons whilst the bridging carbons exhibit low frequency shifts when DBNO is added. These observations are accounted for by a direct π-type [88] of interaction between DBNO and the substituted or bridging carbon atoms. (334)

In the charge-transfer interaction between halogenated molecules and DBNO positive spin densities are produced at both the halogen atom and the carbon atom directly bonded to it. (61, 333) This is consistent with a direct positive spin transfer from DBNO to the antibonding orbital localized between the carbon and halogen nuclei. INDO calculations have been reported which support this proposal. (61)

A nitroxide radical has been used to distinguish between *cis* and *trans* lactams by means of hydrogen bonding interactions which produce different contact shifts in the NMR spectra of the two isomers. (335)

The interactions which occur between transition metal ions and nitroxide (82-84) and iminoxy radicals [89] (336-338) have been studied by means of NMR. Spin-exchange between the two paramagnetic centres gives rapid electronic relaxation and well resolved NMR spectra. These have been interpreted in favour of a dominant contact interaction at low concentrations and a dipolar interaction at higher concentrations. (338)



[89]

M = Cu(II), Ni(II) or Cr(III)

NMR studies have been reported for a number of the ion-pairs formed between radical anions and alkali metal cations. (339-344) A thorough investigation of some alkali metal-naphthalene ion-pairs has demonstrated that the contact mechanism is responsible for the proton linewidths. A quadrupolar contribution occurs in the deuterium spectra which have narrower lines than those found in the corresponding proton spectra, such as noted for some transition metal complexes. (127-130)

The resonances of the alkali metal nuclei reveal a positive spin density on lithium(I) and sodium(I) and a negative spin density on rubidium(I) and caesium(I) whereas the sign of the spin density on potassium(I) is temperature dependent. (342) This phenomenon has been implied from ESR data also (345) but a satisfactory theoretical explanation of it has yet to appear.

High frequency solvent shifts have been observed in the NMR spectra of ether and glyme in the presence of alkali metal coronene radical ion-pairs. (339-341) These have been attributed to contact shifts originating from the solvent layer around the metal cations. Similar shifts have been found for phenanthrene and triphenylene alkali metal ion-pairs, (339, 340) but not for all of the radical anion systems studied. (339) The reason for this selectivity is not clear.

F. Some Overhauser Phenomena

Although the Overhauser effect is not frequently employed in studies of chemical interest, for the sake of balance and completeness some of its recent chemically orientated applications are included here.

1. *Solutions containing free radicals*

Due to the intermolecular coupling of electronic and nuclear spins in a solution containing free radicals, solvent nuclei can display an enhanced NMR signal amplitude when the free radical ESR transition is saturated. As discussed previously for protons and ^{19}F nuclei both dipolar and scalar contributions to the coupling may be present. (1)

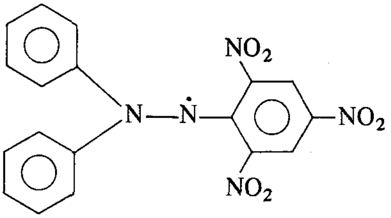
At magnetic fields in the region of 3000 Gauss it is not easy to separate the two contributions to ^{13}C NMR signal amplitude enhancements (346, 347); however this may be achieved at lower fields. A dominant scalar mechanism results in a large positive increase in signal amplitude whereas signal inversion coupled to an increase in amplitude corresponds to a dominant dipolar coupling. (348) ^{13}C NMR data for methyl iodide and benzene taken at several field strengths show that the major contribution arises from the dipolar interaction for both compounds. (349)

The ^{13}C NMR spectra at 74 Gauss of a series of solvents with three different radicals show both negative and positive signal enhancements. The sign of the enhancement appears to depend upon the solvent rather than upon the radical being investigated. (350)

Saturated carbon atoms bonded to chlorine tend to have a positive signal enhancement whereas unsaturated carbon atoms and those bonded to protons have negative enhancements indicating a dominant dipolar contribution to the coupling. (347, 349, 350) This is in contrast to the results obtained from ^{19}F NMR studies which show an increase in the scalar contribution to the coupling when the fluorine is bonded to an unsaturated carbon atom and an increase in the dipolar term when fluorine is bonded to a saturated carbon. (348, 351-353) A change in the strength of the magnetic field often results in a change in sign of the enhancement for ^{19}F nuclei.

^{31}P NMR data show that the sign of the enhancement depends upon the nuclear environment more than upon the choice of radical or magnetic field strength. (354-358)

Equation (42) shows that the scalar hyperfine interaction is proportional to the amount of *s* electron spin density at the nucleus concerned and from Table I it is apparent that ^{13}C shows a smaller hyperfine interaction for a given amount of spin density than do the ^{19}F or ^{31}P nuclei. Calculations have demonstrated that the amount of *s* electron spin density at the nucleus is usually much smaller at the ^{13}C nucleus than at the ^{19}F or ^{31}P nuclei for the system considered. Consequently scalar coupling will only be significant for the ^{13}C nuclei when the dipolar contribution is small. Since the dipolar mechanism depends very critically upon the separation between the unpaired electronic and nuclear spins, peripheral nuclei have a larger dipolar contribution than do those within the body of the solvent molecule. This supports the observation of a dominant scalar coupling for saturated carbon nuclei. (350) Further evidence arises from the ^{13}C NMR spectra of carbon tetrachloride and carbon tetrabromide in DPPH [90] where the shifts are mainly contact in origin. (360) A similar situation occurs for phosphorus nuclei with the exception that the scalar term is larger than it is for carbon, consequently the scalar and dipolar terms are of similar magnitudes



[90]

for phosphorus leading to the observed strong dependence of the enhancement upon chemical environment. (354-358)

For fluorine the relatively large hyperfine interaction constant, Table I, together with the expected large spin density in the *s* orbital ensure that the scalar interaction is usually dominant. (359)

2. *Chemically induced dynamic nuclear polarization* (*CIDNP*)

CIDNP is a study of the enhanced emission or absorption of NMR signals from the diamagnetic products formed from radical pairs. Applications of CIDNP have been widely reported (361-371) and reviewed. (372, 483-485) Closs and his co-workers have shown that the nuclear spin polarization occurs in the product forming steps of a reaction rather than in the formation of the radicals. They have proposed a transverse Overhauser mechanism to explain CIDNP spectra. (373-379)

CIDNP spectra have been reported for some biradicals as well as for the more common radical pairs. (486) In the latter case diffusive separation of the correlated electron spins occurs but not in the former.

3. *Nuclear Overhauser effect* (*NOE*)

The NOE is the basis of a technique employed in diamagnetic systems for obtaining information on the spatial relationships of various groups of nuclei. It depends upon a nuclear–nuclear interaction and is not strictly an example of the Overhauser effect. (380-382)

In ^{13}C NMR spectroscopy NOE can give a signal enhancement up to a factor of 2·988 for dipolar carbon–proton couplings. However, the exact magnitude of the NOE enhancement is very variable for different carbon nuclei in a given molecule, consequently noise decoupled ^{13}C NMR spectra cannot be used in quantitative analysis. This problem has been overcome by the addition of small amounts of paramagnetic species which remove the NOE without significantly broadening the ^{13}C signals. (383-387) Any soluble, nonreactive paramagnetic compound can be used to remove the NOE enhancement.

The NOE enhancement in the noise-decoupled ^{13}C NMR spectrum of dioxane has been removed by DBNO [11] (383) and by some ions of the first transition series, Fig. 12. (384) Transition metal complexes can also be used to reduce long ^{13}C spin-lattice relaxation times and hence provide signal enhancement. (387, 436) Tris(acetylacetone)chromium(III) has been used to achieve shorter

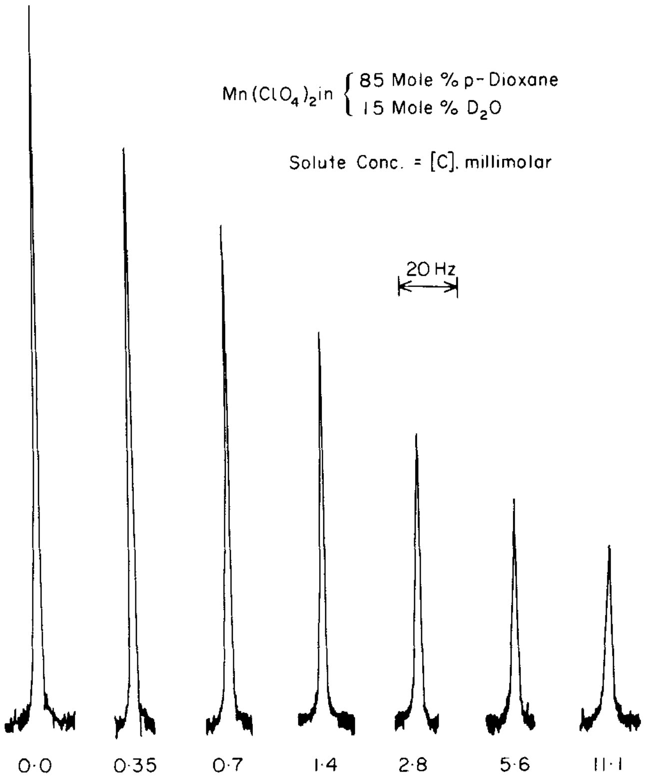


FIG. 12. Single sweep proton-decoupled ^{13}C NMR traces of dioxane as a function of added manganese(II) ions. (384)

nuclear relaxation times. (776) It has a non-orbitally degenerate ground term and consequently no significant dipolar interactions. Since it is kinetically stable it does not react readily when added to a solution under investigation, thus it also produces no contact shifts.

The signal to noise ratio in ^{13}C FT NMR spectra may be improved by the addition of paramagnetic ions. (388) These reduce the NOE and provide an additional relaxation mechanism for saturated signals. The europium(III) shift reagent, [96], has recently been used in this capacity in order to enhance proton and ^{13}C signals. (777, 778)

^{15}N NMR spectroscopy suffers from long ^{15}N spin-lattice relaxation times as well as negative NOE enhancement from nitrogen–proton couplings. (380) Both of these drawbacks can be overcome by the addition of a paramagnetic species as has been demonstrated in the case of benzonitrile. (389)

Apart from the importance of removing NOE enhancement in quantitative analysis, the addition of a paramagnetic centre to a given sample leading to the differential suppression of the NOE at various sites can be useful in ascertaining the binding sites of metal ions or spin labelled molecules.

G. Some Systems of Biochemical Interest

In this section we shall be considering the information obtainable from the NMR spectra of some biochemically significant molecules in the presence of paramagnetic centers.

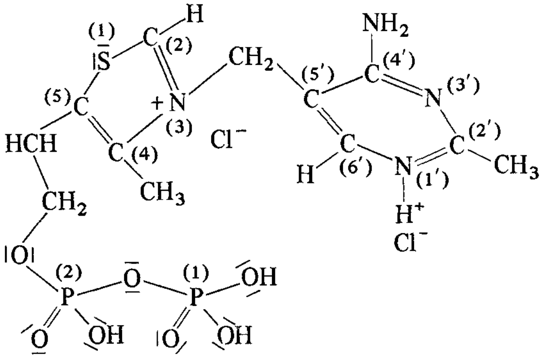
1. *Enzymes*

When a hydrated paramagnetic ion binds to a macromolecule its rotational correlation time usually increases, this leads to an increase in the relaxation rates of the water nuclei. Hence paramagnetic species may be used as probes for the investigation of active sites in enzymes. The principles and applications of this technique have recently been reviewed. (390-393) Typical studies lead to a determination of the number of binding sites, the environment of the bound metal ion, the structure and configuration of the active site and binding constants. (394-396)

As shown by equations (33), (34), (37) and (38) various relaxation mechanisms may be operative and the interpretation of the experimental data in terms of these mechanisms is not always easy. Frequency and temperature dependent studies of T_1 and T_2 are often useful as aids to interpretation. (391, 393) The most commonly used paramagnetic metal ion in metal enzyme binding studies is manganese(II). Frequency dependent measurements of T_1 for the protons of water molecules coordinated to manganese(II) have led to estimates of the number of them exchanging when the metal is bound to an enzyme. In the case of carboxypeptidase A it is one, (397) for transfer RNA it is two, (398) values of two (397) and three (399) have been reported for pyruvate kinase and less than one half for the quaternary complex formed with creatine kinase. (400) In the latter case it has been concluded that a conformational change occurs in the enzyme when the second substrate is added rendering the manganese(II) ion inaccessible to the solvent water molecules. (400)

Relaxation data for ternary metal-substrate-enzyme complexes, which are labile and give four species containing metal ions in solution, have been interpreted by a computer fit. This method appears to be more reliable than the graphical methods used previously. (401) Europium(III) and gadolinium(III) ions have also been used as probes in enzyme systems. (402) These ions are chemically comparable to a number of diamagnetic ions, e.g. europium(II) and calcium(II), and can be useful in the study of the biochemistry of their diamagnetic counterparts. The dominant relaxation process is reported to arise from the rotation of the solvated complexes. (402) In addition to europium(III) and gadolinium(III) other lanthanide ions have been shown to be excellent NMR probes of their environment in enzymes. (437)

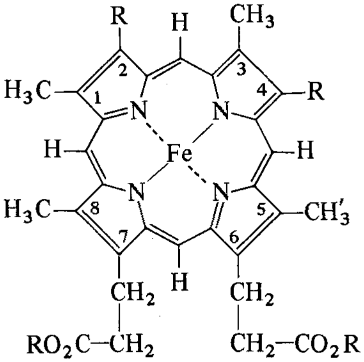
Thiamine pyrophosphate [91] is the cofactor, cocarboxylase, which together with magnesium(II) ions can restore the activity of yeast. Variable temperature proton and ^{31}P NMR measurements on [91], in the presence of cobalt(II) and nickel(II) ions, have been reported. The results indicate that the metals bind to [91] through the pyrophosphate and pyrimidine moieties. Proton NMR studies of the reaction of pyruvate with [91] indicate that the metal complex of [91] acts as a more efficient catalyst in the decarboxylation of pyruvate than [91] alone. (403)



[91]

2. *Hemes and hemoproteins*

Heme groups consist of a porphyrin ring with an iron(II) or iron(III) ion coordinated to the four nitrogen atoms [92]. The iron atom is capable of using either one or both of its axial positions for coordination with suitable ligands. Paramagnetic hemes arise from high-spin or low-spin iron(III) or high-spin iron(II), they usually exhibit resolvable contact shifted NMR spectra. (404) Small conformational changes close to the heme group in iron(III) myoglobin cyanide produce a shift difference of about 200 Hz in the resonance position of the protons of a heme methyl group, X-ray crystallo-



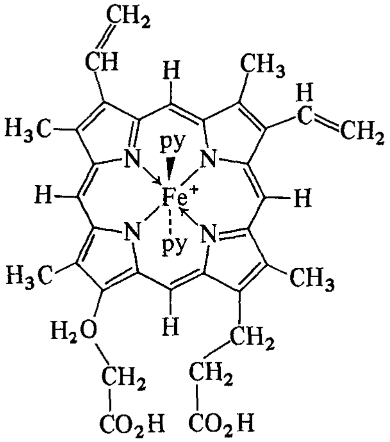
[92]

graphy (411) has been unable to detect the changes producing this shift difference, hence it is apparent that NMR is a more sensitive technique to apply to these paramagnetic systems. (405-410) However six-coordinate low-spin iron(III) can experience dipolar interactions which can render NMR signal assignments uncertain in molecules the size of hemes.

Low-spin iron(III) porphyrins are considered as suitable model compounds for studying the properties, structure and reaction mechanism of iron(III) hemoproteins. Compared with the contact interaction the dipolar contribution to the proton shifts is generally small in porphyrin iron(III) cyanides and is most significant for the four methine bridge protons [92]. (412) A similar conclusion has been reached from a proton NMR investigation of some bis(pyridine)iron(II) protoporphyrin IX complexes [93]. (413, 414) A linear relationship between the basicity of the coordinated pyridine and the shifts of the porphyrin protons is found which is most marked for the peripheral methyl protons [93]. Ligand to metal π charge transfer is claimed to be the main mechanism for spin delocalization onto the pyrrole rings. (413, 414)

Recently the NMR spectra of a series of low-spin iron(III) bis-imidazole complexes of some synthetic porphyrins have been reported. (779) The shifts of the phenyl protons are shown to be due entirely to dipolar interactions by means of equation (25). Deviations in Curie law behaviour are observed probably originating in the dipolar interaction. (779)

The nature of the axial ligand also significantly influences the proton shifts found in the NMR spectra of some high-spin iron(III) deuterohemin esters. (415) A recent investigation of a high-spin iron(III) porphyrin complex has revealed that the dipolar shifts have



[93]

an inverse square dependence on the temperature, as shown in equation (29) this data can be interpreted in terms of the zero field splitting contribution. (544)

The suggestion that metal-imidazole bond rupture may play a critical role in biological processes of cytochrome C has led to an NMR study of imidazole exchange in low-spin iron(III) porphyrins. (418)

Proton NMR data have been recorded and analysed for a number of cobalt(II) porphyrin complexes. (780-782) In general it is concluded that the shifts are dipolar in origin, which is in agreement with ESR data. Some possible solution structures are reported for the molecular complexes, these are derived from the dipolar shifts. (782) In the case of the low-spin planar cobalt(II) complexes a temperature dependent axial field is reported due to solvation. (780) NMR line widths and spin relaxation data have been recorded for some tetra-*p*-tolyl-porphyrins of chromium(III), manganese(III) and iron(III). (783) The line widths are found to decrease as the metal is changed from chromium to manganese and to iron. In favourable cases the line width data can provide an estimate of the zero field splitting. (783)

Proton NMR data have also been reported for some examples of mammalian type ferrocytochrome C which show evidence for methionine coordination to iron, (417) for ferredoxin from *clostridium paesteurionum* (418) and from spinach (419, 784) in both oxidized and reduced forms and for some binuclear oxo-bridged ion(III) porphyrins. (120, 420) Since imidazole does not coordinate axially to the binuclear iron(III) porphyrins it is anticipated that binuclear oxo-bridged hemoproteins do not occur naturally. (420)

In the cases of ferrocytochrome C and metmyoglobin cyanide it has recently been demonstrated that the second order Zeeman effect and in-plane magnetic anisotropy play significant roles in determining the dipolar shifts. (785)

3. Amino acids and proteins

The binding of copper(II) ions to carnosine in deuterium oxide, over the pD range 2 to 12, has been investigated by proton NMR. (421) Comparison of line widths with those predicted from models has led to the conclusion that three pD dependent major constituents are present in solution, Fig. 13. The formation of the tridentate

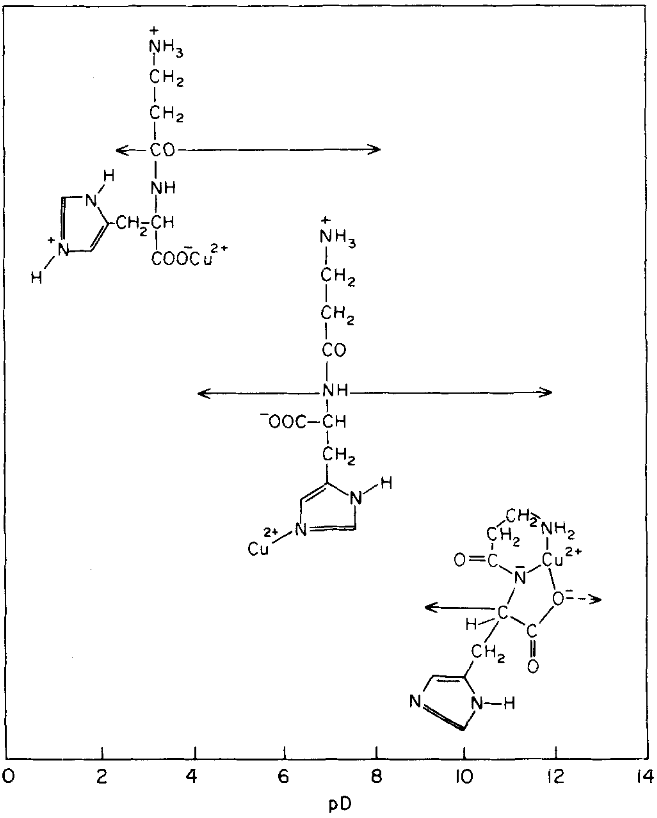


FIG. 13. The distribution of the complexes formed between carnosine and copper(II) ions as a function of pD. (421) The approximate pD ranges for the existence of the complexes are indicated.

complex in alkaline solution is considered to occur in a stepwise process so that additional intermediate species could also be present.

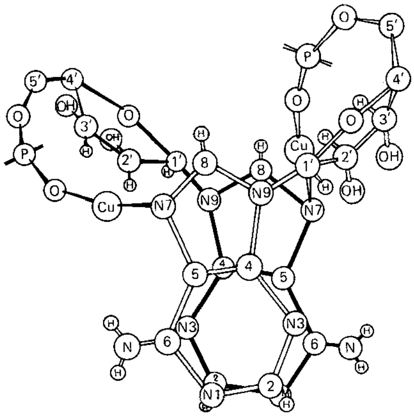
Glycine peptides have been investigated in deuterium oxide solutions containing copper(II) and nickel(II) ions, and some information concerning structures and coordination sites reported. (422, 423)

The addition of cobalt(II) ions to a solution of lysozyme produces large proton shifts which are thought to be mainly dipolar in origin. (424) With this assumption particular resonances have been assigned to constituent amino acid residues. A similar study on gramicidin *S* has employed a free radical to simplify the proton spectrum. (335)

Other NMR studies on amino acids and proteins in the presence of paramagnetic centres include conformational studies on some amino acid complexes of nickel(II), (206, 425, 786) and a reinvestigation of the effects, on the NMR spectra of some amino acids, of the addition of some iron(II) salts. (453) Recent studies on amino acids and proteins have considered the use of various probes and shift reagents in order to obtain conformational information; these include complexes of neodymium(III), (787) the vanadyl(IV) ion, (788) chromium(III), (755) manganese(II), (755, 789) iron(III), (755) cobalt(II), (755) nickel(II), (755) and copper(II). (755, 790)

4. *Nucleic acids and related molecules*

Berger and Eichorn (426) have studied the binding of copper(II) ions to some adenosine nucleotides. In general the copper ions can bind to multiple sites on the adenine base, preference for a given site can be influenced by molecular associations which are governed by the position of the phosphate on the ribose in the different adenosine monophosphate (AMP) monomers. The results for 3′- and 5′-AMP have been interpreted in favour of a binuclear copper-AMP complex [94] in which the two bases are stacked with each copper



ion bound to a phosphate of one AMP unit and N-7 of the other. (426) Proton and ^{31}P NMR spectra of 5′-AMP have been recorded as a function of pD in the presence of low molar ratios of manganese(II), nickel(II), cobalt(II), chromium(III), copper(II), iron(II) and iron(III) ions. (431) It is found that all of these metal ions form complexes with the phosphate moiety and the adenine ring of AMP; however various binding sites on the adenine ring appear to be used. (431)

The influence of manganese(II) ions on the proton decoupled ^{13}C NMR spectra of AMP has been noted. (791) The C-5 and C-8 resonances are broadened more than these from C-2, C-4 and C-6 and it is concluded that the metal ion is bonded close to the N-7 position of the base. (791)

Proton NMR has been used to study the binding of copper(II) ions to ribonuclease A. (427-429) It is reported that histidine-105 and histidine-12 provide stronger binding sites for copper(II) than histidine-119 which in turn is preferred to histidine-48. (429)

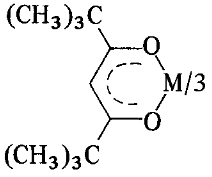
Other reports include the use of lanthanide metal ions as shift and broadening probes which provide quantitative data on the conformation of mononucleotides in solution, (438, 792) a study of the binding of cobalt(II) ions to imidazole, pyrimidine and purine (222) and an investigation by proton NMR of the binding of copper(II), nickel(II) and manganese(II) ions to some dipyrromethenes. (430)

5. *Membranes*

The addition of paramagnetic species effect the NMR spectra of some membranes. (432-435) Free radicals have been employed in studies on detergent micelles (432) and aqueous lecithin dispersions, (433) whereas transition and lanthanide metal ions have been used for lecithins. (434, 435) In this way it has been possible to distinguish between the proton signals from trimethyl-ammonium groups on internal and external surfaces of bilayer vesicles. Doubtless the use of this technique will spread to include other groups, containing several equivalent nuclei, on membranes.

H. Paramagnetic Shift Reagents

The most significant development in organic proton NMR studies during the past four years has been the introduction and extensive use of paramagnetic shift reagents. (6-11) In 1969 Hinckley reported that some bis pyridine tris(β-diketone)lanthanide(III) complexes induce stereospecific shifts in the NMR spectra of organic substrate molecules and reduce second-order NMR spectra to first-order without loss of resolution. (439) Subsequent studies have shown that some of the tris(dipivaloylmethane) complexes, $M(DPM)_3$ [95], and tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) complexes, $M(FOD)_3$ [96], are superior since they produce larger shifts



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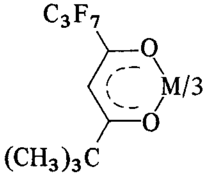


[96]

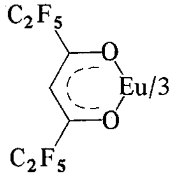
for protons, up to 20 Å from the site of attachment of the organic substrate to the metal ion, without substantial line broadening. (440-442)

Transition metal complexes have also been used as shift reagents for strong Lewis bases. The most common of these are divalent metal complexes with structures similar to [18] as discussed in Section III B. 3. (424, 443-455) They usually produce larger shifts than lanthanide complexes but they suffer from having both contact and dipolar interactions which render them less suitable for structural investigations which only depend upon a dipolar interaction. Transition metal complexes may also produce greater line broadening than lanthanide complexes.

Some accounts of the use of free radicals (335) and radical anions (339-341, 456) as shift reagents have been made. The results have been interpreted in favour of contact interactions.

Ring currents have been used to produce small low frequency shifts in completely diamagnetic systems, tetraarylborates (457-460) and some diamagnetic metal phthalocyanines (461, 462) have been the sources of the ring currents. A theoretical consideration of magnetic octopole contributions has shown that they could make a considerable contribution to the observed shifts in these systems. (754) A proton 4 Å above the centre of a ring of radius 1·4 Å can experience octopolar deshielding which can be as large as one-quarter of the dipolar shielding. (754) It is anticipated that geometrical data on the complexes formed between diamagnetic shift reagents and substrate molecules will be forthcoming as a result of these theoretical studies.

Lanthanide complexes other than those of types [95] and [96] have been used as NMR shift reagents. In general they are found to be inferior in that they frequently produce smaller shifts and/or broader lines. (152, 441, 453-467, 567) Recently a fully fluorinated side chain complex of europium(III) has been reported [97]. (468) As a shift reagent it is claimed that [97] is superior to the europium(III) complex of [96] in that it has no residual side chain protons to interfere with the spectrum of the substrate and it produces larger shifts for protons remote from the complexing site of the substrate. (468)



[97]

The complex $U(FOD)_4$, and related molecules with fluorinated side chains, produces shifts comparable to those of lanthanide reagents. In contrast to the latter it appears that the uranium(IV) complexes are not moisture sensitive. (794)

Recently the question of diamagnetic corrections to lanthanide induced shifts has been considered. (806) It is reported that these may safely be ignored in the majority of cases; however it might be prudent to check this for small, or apparently erroneous, induced shifts.

During 1972 alone over two hundred citations of lanthanide shift reagents have appeared in the literature, many of these are trivial and draw erroneous conclusions. Not all of these are included in this review which concentrates on the major developments in the field. Before discussing experimental aspects of the utilization of lanthanide shift reagents it is propitious to briefly consider quantitatively why they are suitable as shift reagents as well as some possible limitations on the information they can provide.

1. *Quantitative aspects of using lanthanide shift reagents*

Equations (35) to (38) demonstrate that short electronic relaxation times favour narrow NMR lines such as are generally found in complexes of cobalt(II) and nickel(II). However, in these complexes the lines can be sufficiently broad to mask any residual spin-spin coupling fine structure especially for nuclei close to the metal ion.

Many complexes of lanthanide metal ions have shorter electronic relaxation times than found in transition metal complexes. Consequently they produce very narrow lines in the NMR spectra of substrate molecules, and fine structure persists up to a high concentration of metal with respect to substrate.

As a means of expanding complicated NMR spectra, making their interpretation easier, lanthanide shift reagents have a very wide range of application. However many reports have appeared in which structural information has been deduced from proton NMR spectra modified by lanthanide shift reagents.

The following assumptions are implicit in these reports:

(i) The proton shifts are entirely dipolar in origin and the adduct formed in solution, between the substrate and the shift reagents, is axially symmetric. Under these conditions the relative shifts may be interpreted by the geometric factor $(3\cos^2\theta - 1)r^{-3}$.

(ii) The principal magnetic axis of the adduct has a known orientation with respect to the substrate molecules which exist either in a single conformation or as an appropriate average conformation in the adduct.

(iii) Only a single non-isomeric adduct is formed in solution which is in equilibrium with the uncomplexed substrate.

It is important to consider the validity of these assumptions since their violation will probably render the reported geometrical conclusions invalid. We will now consider how the available data agrees or conflicts with these assumptions.

(i) Origin of the shifts and their interpretation. The greater importance of spin-orbital coupling in lanthanide ions than in transition metal ions is reflected in the discussion of magnetic susceptibilities where it becomes necessary to consider the total angular momentum quantum number J rather than L and S for the orbital and spin contributions. Bleaney (28) has shown that in a non-cubic environment the dipolar contribution to the shifts induced by lanthanide ions arises from zero field splitting:

$$\frac{\Delta H^M}{H_0} = -\frac{g_e^2\beta_e^2 J(J+1)(2J-1)(2J+3)}{60(\kappa T)^2 r^3} \times \tag{70}$$

$$[D_{zz}(3\cos^2\theta - 1) + (D_{xx} - D_{yy})\cos 2\theta \sin^2\theta]$$

where D_{xx}, D_{yy} and D_{zz} are the major components of the zero field splitting tensor which is assumed to have the same principal axes as the g tensor. In the case of axial symmetry,

$$D_{xx} = D_{yy} = -\tfrac{1}{2}D_{zz} \tag{71}$$

and equation (70) becomes:

$$\frac{\Delta H^M}{H_0} = -\frac{g_e^2 \beta_e^2 J(J+1)(2J-1)(2J+3)}{60(\kappa T)^2} D_{zz} \frac{(3\cos^2\theta - 1)}{r^3} \tag{72}$$

It is apparent from equation (72) that attempts to describe lanthanide induced dipolar shifts in terms of g tensor anisotropy are without foundation. A significant difference between the shifts predicted by equation (72) and equations (3), (25)–(29) based upon g tensor anisotropy is their dependence upon the inverse square of the temperature. Ions with the configuration $4f^6$, e.g. europium(III) and samarium(II) are exceptions to this since they have ground states with $J = 0$ such that the dipolar shifts they induce are determined by the populations of excited states giving a more complicated temperature dependence. (21, 28, 448)

Temperature dependent shifts produced by shift reagents have been reported for a number of substrates. (489-499) In most cases a Curie law behaviour is reported, but often the relationship is not the same for all of the protons in a given substrate molecule. Cognisance should also be taken of the equilibrium present in solution between complexed and uncomplexed substrate molecules. (499) The temperature dependence of this equilibrium will influence the shifts in a manner similar to that described for contact shifts by equations (49) and (50). The temperature dependence of the shifts observed for dimethoxyethane in the presence of (1 : 1) europium(III) and praseodymium(III) complexes of [95] and [96] follows Curie law behaviour for the europium(III) complexes and a T^{-2} behaviour for the praseodymium(III) complexes. (795) These experimental data strongly support the predictions of Bleaney's theory. However this theory has recently been criticized on the grounds that it does not include systems with non-axial symmetry and assumes that the first order Zeeman contribution to the magnetic anisotropy is absent over the range of temperatures usual for NMR experiments. (796) It has further been claimed that it is necessary to incorporate the entire ground term set of energy levels for each f^n electronic configuration rather than considering levels with particular J values only. (796) The resulting temperature dependence of the shifts is not either Curie law or T^{-2} and magnetic susceptibility data support this prediction. A further criticism of Bleaney's approach is that he has only considered the lowest non-zero crystal field terms in his discussion of magnetic anisotropy. (796) However the incorporation of higher terms under

C_{3h} symmetry are shown to produce deviations of 20% or less. (797)

Further theoretical and careful experimental studies of the temperature dependence of induced shifts are to be expected in order to settle apparently conflicting viewpoints in this fundamentally interesting area.

Equations (70) and (72) show the dependence of the induced dipolar shifts upon the value of J and zero field splitting parameters. By assuming the same geometry for a series of lanthanide complexes the largest dipolar shifts are predicted for terbium(III) and dysprosium(III) which is in agreement with experiment (Table XI). (489, 500, 501)

TABLE XI

Comparison of the relative induced dipolar shifts[a] of the 2 proton of 4-vinyl pyridine in the presence of lanthanide $(DPM)_3$ complexes (500)

	Theoretical relative shifts[b]		
Lanthanide(III) ion	Calculated from equation (72) for the ground state only	Calculated to include excited states occupied at 300 K	Experimental relative shifts
Lanthanum	0	0	0
Cerium	−6·6	6·3	–
Praseodymium	11·4	11·0	20
Neodymium	4·5	4·2	9·5
Promethium	−2·4	−2·0	–
Samarium	−0·5	0·7	2·4
Europium	0	−4·0	−10·0
Gadolinium	0	0	–
Terbium	87	86	91
Dysprosium	100	100	100
Holmium	39	39	71
Ebium	−33	−33	−27
Thulium	−53	−53	−70
Ytterbium	−22	−22	−33
Lutecium	0	0	0

[a] All shifts are scaled to 100 ppm for dysprosium(III).

[b] A positive sign indicates a low frequency shift, only relative signs for the shifts are found from the theoretical calculations. The signs presented here are chosen to give the best agreement with the experimental shifts.

Single crystal X-ray diffraction data has provided information on the solid state structures of some lanthanide shift reagents and their 1 : 1 and 1 : 2 adducts. (469-472, 805) In general a twofold axis is found to be the highest order symmetry axis and the most likely principal magnetic susceptibility axis is not coincident with the lanthanide-substrate bond as is frequently assumed. (473)

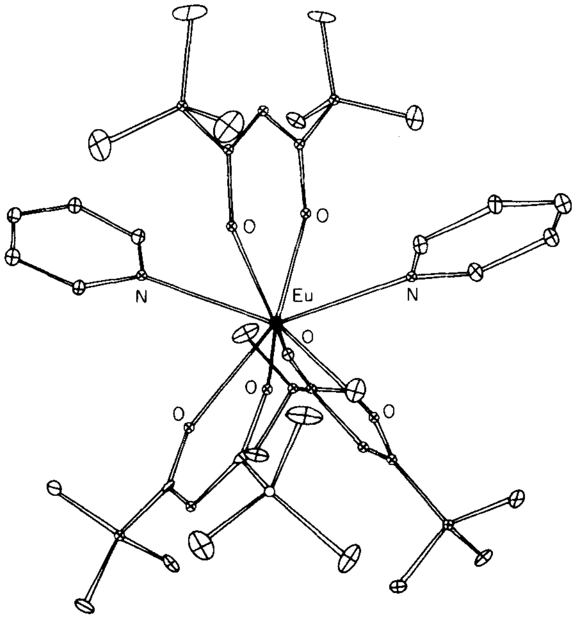
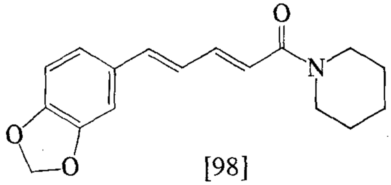


FIG. 14. Structure of Eu(DPM)$_3$ (pyridine)$_2$. (471)

Dipolar shifts for rhombic symmetry are described by equation (23). Single crystal magnetic susceptibility measurements on the bis(4-picoline) adduct of M(DPM)$_3$ for a series of lanthanide metals show that the last term in equation (23) contributes less than 15% to the dipolar shifts in most cases. (27) Therefore using the geometric factor $(3 \cos^2 \theta - 1)r^{-3}$ of the first term of equation (23) is not too unreasonable in this case, but in general this may not be valid. (150, 151, 474, 475) However, under given conditions for internal rotations, $(3 \cos^2 \theta - 1)r^{-3}$ has been shown to be the appropriate geometric factor to use for lanthanide complex-substrate adducts in solution even when the magnetic susceptibility tensor is non-axially symmetric. (476, 477) Rotation about the lanthanide complex-substrate bond is considered to give equal populations to various rotamers, for hindered rotation an additional angle must be specified. (476) Thus the use of the geometric factor $(3 \cos^2 \theta - 1)r^{-3}$ for the dipolar shifts in solution NMR spectra of lanthanide complex-substrate adducts appears to be both theoretically and experimentally justified. (10, 11) Substantial contact contributions have been reported from the proton NMR spectra of some conjugated pyridine *N*-oxides and anilines especially in the presence of the strong Lewis acids $M(FOD)_3$. (487) As shown in Table I protons display much smaller contact interactions than other nuclei for the same amount of unpaired spin density. However dipolar interactions are independent of the nucleus on the substrate concerned, therefore contact interactions are expected to be relatively much more important for other nuclei than for protons. This assumption is supported by proton and ^{17}O NMR data on aqueous solutions of lanthanide perchlorates. (10, 502) It is usually considered that bonding to lanthanide metal ions occurs primarily through the 6*s* orbital rather than the more shielded 4*f* orbital of the lanthanide ion. By comparison with transition metal ions where the *d* orbitals are directly involved in bonding to the ligands, spin density transfer is much less effective for lanthanide ions. A second order perturbation calculation of the spin density, including the effects of spin-orbital coupling and covalent bonding, provides an estimate of the relative contact shifts experienced by nuclei bonded to various lanthanide metal ions. (502) The theoretical estimates are in agreement with ^{17}O and ^{14}N NMR shift data on water and pyridine (503) respectively, both of which are consistent with the presence of a negative spin density on the substrate produced by the transfer of α spin electrons to the 6*s* orbital of the lanthanide ion. Further evidence for contact shifts produced by lanthanide shift reagents is forthcoming from ^{13}C NMR data. The carbon atom of the carbonyl group in piperine [98] shows



[98]

a low frequency shift when $Eu(DPM)_3$ is added. (504) The other ^{13}C resonances show high frequency shifts suggesting the presence of a contact contribution to the shift of the carbonyl group which bonds to the europium ion. Proton and ^{13}C NMR results for the same pyridine bases with added $Eu(DPM)_3$ show contact contributions to the ^{13}C shifts. (505) The proton shifts have been accounted for by an axially symmetric dipolar term, but the ^{13}C data cannot be fitted to this model due to the presence of contact interactions. (506, 609) An analysis of the ^{13}C shifts of isoquinoline, to which various $M(DPM)_3$ complexes have been added, has revealed the percentage contact contributions to the shifts shown in Table XII. The smallest contact contribution arises from $Yb(DPM)_3$ hence this should be a very suitable shift reagent for obtaining structural information about the substrate from the dipolar shifts produced in its NMR spectrum. (464, 489-494, 501, 527-530) $Yb(DPM)_3$ has the added advantage of producing much larger shifts, in the same direction as those produced by $Eu(DPM)_3$, with only small line broadening, as demonstrated in Table XI. (507, 802)

TABLE XII

Percentage contact contributions to the shifts induced in the ^{13}C NMR spectra of isoquinoline in the presence of various lanthanide $(DPM)_3$ complexes (507)

Complex	Percentage ^{13}C contact shift
$Pr(DPM)_3$	15
$Nd(DPM)_3$	70
$Eu(DPM)_3$	80
$Tb(DPM)_3$	21
$Dy(DPM)_3$	13
$Ho(DPM)_3$	19
$Er(DPM)_3$	25
$Yb(DPM)_3$	5

Consequently the assumption that lanthanide metal complexes induce only dipolar shifts in the NMR spectra of substrate molecules is not generally valid, especially for the most frequently used complex $Eu(DPM)_3$. Table XII shows that this reagent produces the largest contact contribution to the shifts of all those included in the relevant study. (507) However it would be prudent to consider each example individually since the size of the contact interaction experienced depends upon the lanthanide metal ion, its ligands and the substrate being investigated as well as the particular nucleus chosen for study. (27, 474, 475, 487, 501, 508-514) Nuclei closest to the metal ion are the ones most likely to experience a significant contact contribution. (508)

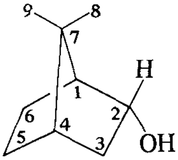
(*ii*) *Magnetic properties and structure of the adduct in solution.* The magnetic susceptibility of $Eu(DPM)_3$ is lower in solution than in the solid state and decreases as the coordinating ability of the solvent or substrate increases. (508) This behaviour is consistent with the presence of dimeric species in solution. (508, 513) As discussed in the previous section the orientation of the principal magnetic axis of the adduct formed between the substrate and lanthanide complex is usually not known in solution. However due to rotation of the substrate group, and molecular motion, it seems to be reasonable in many cases to consider the lanthanide-substrate bond as constituting the major magnetic axis of the adduct, (799) although some authors do not accept this conclusion. (798)

Various physical techniques have been employed to study the nature of the adduct formed in solution including circular dichroism spectra, (515) chromatography, (516) electronic spectra, (674) molecular weight determinations, (676, 801) and calorimetric measurements. (517) Unfortunately the latter study assumes axial symmetry which in the systems investigated appears to be unlikely. The resulting prediction of a contact shift of ~1000 Hz for the α protons of pyridine is therefore unjustified. (517) In general it seems that the $M(DPM)_3$ reagents form 1:1 adducts with typical substrates and $M(FOD)_3$ reagents can form 1:2 adducts. (515, 554, 561, 565, 674, 675) The importance of the angle dependent term, in the geometric factor $(3\cos^2\theta - 1)r^{-3}$, has been demonstrated in a number of cases and neglect of it can produce considerable errors in structural assignments. (676) Positive values of the angle term arise for $0° < \theta < 54{\cdot}7°$ and produce high frequency shifts, while negative values giving low frequency shifts occur when $54{\cdot}7° < \theta < 125{\cdot}3°$. In general $Eu(DPM)_3$ produces high frequency shifts, however low frequency proton shifts have also been observed (437, 518-524) and some aromatic protons are found not to be shifted at all by $Eu(DPM)_3$. (525) The low frequency shifts are attributable to negative values of the angle dependent term while the absence of shifts for certain protons corresponds to the term becoming zero. The maximum sensitivity of the shifts to changes in angle occurs for $\theta = 45°$ and 135° and minimum sensitivity for $\theta = 0°$, 90° and 180°, consequently the angle dependent term is considerably more important for some protons than for others in a given substrate.

A change in sign of the dipolar shift for a given proton can occur by changing the lanthanide ion involved. As shown in Table XI, $Eu(DPM)_3$ and $Pr(DPM)_3$ have opposite signs for the components of the zero field splitting tensor appearing in equation (70). This change in sign of dipolar shifts has been demonstrated in a number of cases. (441, 464)

Due to the third power dependence of the geometrical factor on r differences in the value of r are likely to control changes in the geometrical factor for different protons. This has led some authors to neglect the angle dependent term in discussing shift differences found in the NMR spectrum of a given substrate. (511, 529, 676) The inverse third power dependence of the induced shifts upon r has been demonstrated for a large number of substrates. (439, 526-536) However an inverse square dependence has also been claimed (522, 537-541) together with other powers of r ranging from $-0{\cdot}2$ to $-3{\cdot}0$. (542, 543) In these latter cases it seems likely that contact contributions, changes in the angle dependent term and the separation of the lanthanide ion from the heteroatom of the substrate have to be taken into account. (511)

Several attempts have been made to obtain detailed structural information about the substrate molecules from the geometric factor $(3\cos^2\theta - 1)r^{-3}$ by theoretically varying the position of the lanthanide ion with respect to a fixed substrate molecule until a best fit is obtained between calculated and observed shifts. (470, 501, 505-507, 509, 512, 521, 545-547) The proton shifts induced in the proton NMR spectrum of borneol [99] by $Pr(DPM)_3$ have been fitted to a model by an iterative procedure, by excluding the proton on carbon number two the standard deviation is 5·8%. The same model has been used to account for the ^{13}C NMR data with a standard deviation of 2·7%. The good fit obtained between the theoretical and experimental data, excluding the proton on carbon number two, indicates a contact contribution at this position. The model used has a praseodymium-oxygen separation of 3·0 Å, a Pr–O–C(2) angle of 126° and a dihedral Pr–O–C(2)–H(2) angle of 25°. (545, 546) Comparable distances and angles have been employed in models of some hydroxyoxetons and cyclic alcohols. (521) In order to estimate the agreement between experimental and calculated shifts an agreement factor R has been defined by: (548, 549)



[99]

$$R = \left[\frac{\sum_i (\Delta H^i_{\text{obs}} - \Delta H^i_{\text{calc}})^2 W_i}{\sum_i (\Delta H^i_{\text{obs}})^2 W_i}\right]^{1/2} \tag{73}$$

where $\Delta H^i_{\mathrm{obs}}$ and $\Delta H^i_{\mathrm{calc}}$ are respectively the observed and calculated dipolar shifts for nucleus i with a weighting factor W_i. In this work the lanthanide ion is shifted incrementally over the surface of a sphere whose radius, r, corresponds to the separation of the lanthanide ion from the coordinating atom of the substrate which is placed at the origin. The position of the lanthanide ion on the sphere is described by the angles ρ and ϕ defined in Fig. 15. The dependence of R upon these angles and the distance r is conveniently displayed using contour lines on a map projection as in Fig. 16, which shows the visual description of R for endo-norbornenol [100]. (548) Values of R in the range 0·032 to 0·092 have been reported for a series of substrates containing epoxide, carbonyl and hydroxyl coordinating centres. (548, 549) The significance of various rigid substrate conformations has been discussed in terms of their relative R values.

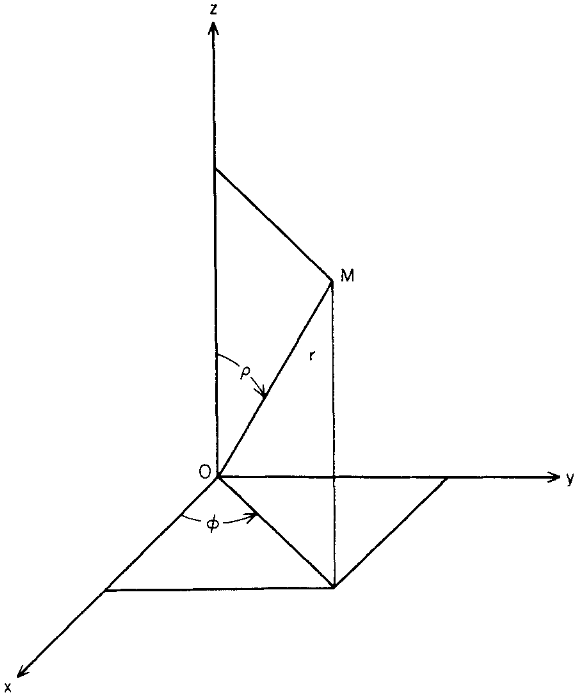


FIG. 15. Definition of the angles l and ϕ and the distance r. (548)

The conformation of flexible molecules in the presence of lanthanide shift reagents has also been considered. (438, 550-557) Obviously

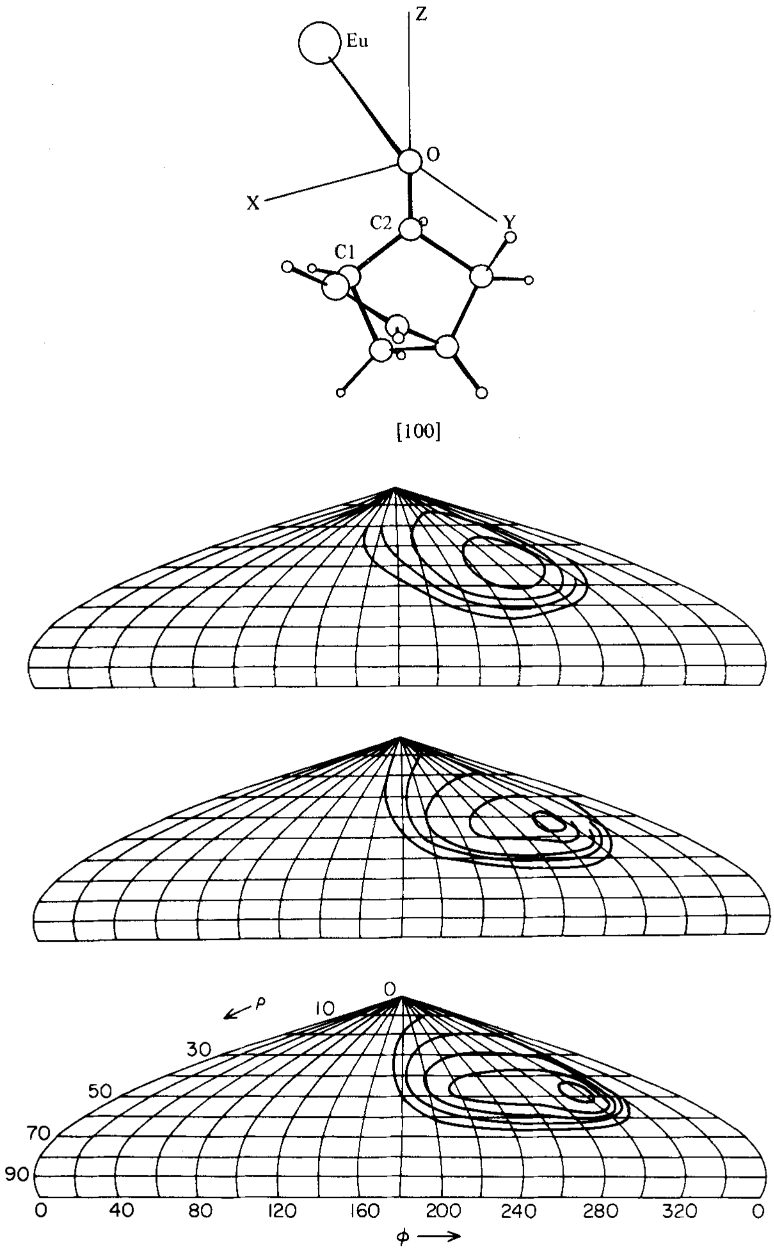


FIG. 16. Plots of the agreement factor R for [100]. From the top diagram to the bottom one the europium(III)-oxygen distances are 2·9, 3·1 and 3·3 Å. In each case the contours are at intervals of 0·02 in R, the outermost contour is at R = 0·12. (548)

a large number of conformations have to be included, this number may be reduced by using line broadening as well as line shift data. As shown by equations (31) to (34) the amount of line broadening depends upon the inverse sixth power of the internuclear separation when the dipolar interaction controls the rate of nuclear relaxation. Consequently the measurement of line widths helps to eliminate some of the possible conformations of flexible molecules and nucleotides. (437, 438)

It may be concluded that in general the assumption that a substrate exists in either a single conformation or as a suitable average conformation is justified by the available experimental data.

(*iii*) *Solution equilibria of the adduct.* The shifts induced in the NMR spectrum of the substrate increase in size as the ratio of the concentrations of the added shift reagent to substrate increases. Consequently rapid exchange occurs, between free and complexed substrate molecules, on the NMR time scale.

Usually the shifts are presented graphically as a plot against the ratio of the concentrations of shift reagent to substrate. (442, 465, 513, 542) In the majority of cases these plots are not linear over the concentration ratio range of 0 to 1. This can be accounted for at low concentration ratios by the presence of other equilibria in the system such as that due to the formation of a complex between the shift reagent and water or other impurities. (496, 513, 520, 542, 558) At high concentration ratios incomplete solution of the shift reagent and association in solution have to be considered. (442, 551) The equations for these coupled equilibria have been solved satisfactorily in a number of cases (552-554) and a lucid account of this work has been presented by Reuben. (10)

A recent report shows that experimental errors in the concentration ratio does not adversely affect the slope of the plot against induced shift. (555)

By extrapolating the observed induced shift to its position in the absence of shift reagent each line in the NMR spectrum can be identified. This may also be performed automatically by means of an algorithm. (556, 602) This approach has obvious utility in the assignment of signals and does not depend upon the nature of the equilibrium taking place in solution. However in studies of molecular structure these equilibria must be determined.

Most of the reported structural determinations from induced proton shift data have employed observed induced shifts, Δ_1, rather than those which would be observed for total complex formation Δ. These are related for 1:1 complex formation by:

$$\frac{1}{\Delta} = \frac{[S_0]}{\Delta_1[M_0]} + \frac{1}{\Delta_1 K_1 [M_0]} \tag{74}$$

where $[S_0]$ is the total concentration of substrate, $[M_0]$ is the concentration of the added shift reagent and K_1 is the equilibrium constant for the 1:1 complex under the conditions $[S_0] \gg [M_0]$. (552, 553) Many data have been fitted to equation (74), by plotting Δ^{-1} against $[S_0]$ at constant $[M_0]$, and this has been taken as evidence of a simple one step formation of a 1:1 complex. (552, 553, 559)

However equation (74) seldom provides a rigorous examination for 1:1 complex formation. (560-562) Almost any mechanism can produce a linear plot under the conditions for which this equation is applicable. (562) In order to determine the actual interaction mechanism taking place the concentrations of all the interactive species must be varied over as wide a range as possible. Shapiro and Johnston have reported the results of an analysis of the concentration dependence of the induced shifts of 3-(*para*-chlorophenyl)-3,5,5-trimethylcyclohexanone with Eu(FOD)$_3$ in carbon tetrachloride at 303 K. (561) Their results are shown in Fig. 17. In their analysis Shapiro and Johnston have considered the two step mechanism for the species MS_2:

$$\begin{gathered} M + S \leftrightharpoons MS \\ MS + S \leftrightharpoons MS_2 \end{gathered} \tag{75}$$

The analysis demonstrates that a four parameter data fit is necessary in order to obtain a reliable estimate of the equilibrium constant. (561) However reliable values of the limiting induced shift, Δ_1, for the MS_2 adduct may be found from equation (74) by plotting Δ^{-1} against $[S_0]$ at constant $[M_0]$ when $[S_0] \gg [M_0]$ and from a plot of Δ against $[M_0][S_0]^{-1}$ at constant $[S_0]$ under the same relative concentration conditions. (552, 553, 559-561)

Consequently quantitative attempts to determine the structure of substrate molecules based upon values of limiting induced shifts from equation (74) are theoretically justified from a consideration of the equilibria taking place in solution even when a two step process occurs. However the corresponding values of the equilibrium constants, determined from equation (74) and similar expressions are probably in considerable error. (513, 526, 554, 561, 563-567, 569) This is especially true for adducts formed with Eu(FOD)$_3$ which tend to be of the 1:2 type rather than the 1:1 type usually found with Eu(DPM)$_3$.

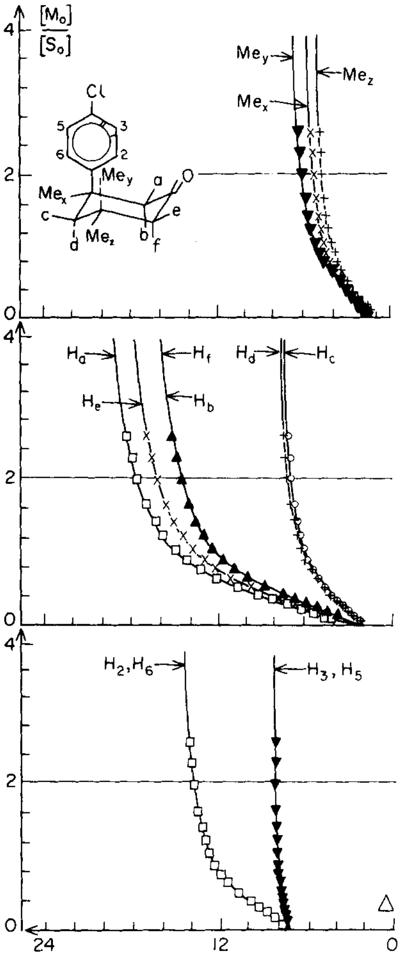


FIG. 17. Results of theoretical fits of the two-step mechanism, equation (75), to the observed induced shifts for 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone at constant $[S_0] = 0{\cdot}15$ molar. (561)

Although the three basic assumptions given on page 102 for the use of shift reagents in structural studies on substrate molecules are not always valid, careful experimental observations can often reveal how close a particular system is to satisfying these assumptions. Thus it is necessary to consider each NMR experiment individually.

2. *Some experimental aspects of lanthanide shift reagents*

Lanthanide shift reagents with the structures [95] and [96] complex with water molecules, thus the reagents should be stored in vacuo and used only with dried solvents. The most commonly used solvent is carbon tetrachloride. Acids tend to decompose the shift reagents hence they should be absent from the NMR sample. Other lanthanide compounds have been used in acidic (570) and basic (438) media.

(*i*) *Choice of lanthanide ion.* The synthesis of complexes with structures [95] and [96] has been described for all of the lanthanide metal ions and most are now available commercially. (571, 572) These series of complexes have been widely examined as shift reagents. (489, 501) As shown in Table XI, complexes of dysprosium(III), terbium(III) and holmium(III) give the largest dipole induced shifts for substrate protons whereas the commonly used europium(III) complexes produce shifts which are an order of magnitude smaller. Figure 18 demonstrates this point for the $M(DPM)_3$ complexes. (501)

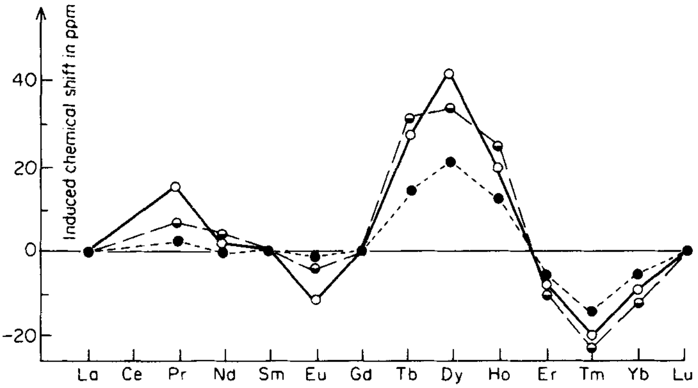


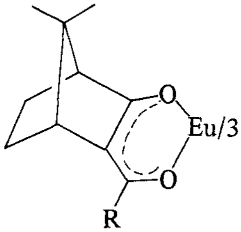
FIG. 18. Some isotropic shifts for solutions of *n*-hexanol(*H*-1,○), 4-picoline-*N*-oxide(*H*-2,●) and 4-vinylpyridine(*H*-2,◒) in the presence of various $M(DPM)_3$ complexes at 303 K in deuterochloroform solution. (501) The ratio of the concentrations of $M(DPM)_3$ to substrate = 0·125.

Due to the very short electronic relaxation times europium(III) and praseodymium(III) induce shifts with very narrow signals in the proton spectra of the substrates whereas larger shifts are usually associated with broader lines. The best compromise appears to be ytterbium complexes, as shown in Table XII. $Yb(DPM)_3$ has a small contact contribution in the shifts it induces in substrates. The wide range of shifts produced by $Yb(DPM)_3$, without undue line broadening, together with the large dipolar contribution indicates that it will be widely used in future investigations. (464, 489-491, 501, 528-530)

The most commonly used shift reagents to date are $Eu(DPM)_3$ and the stronger Lewis acid $Eu(FOD)_3$. It has recently been demonstrated that the former produces larger shifts in the NMR spectra of oxygen containing substrates than the latter. (603) These could arise from differences in geometry, D tensor anisotropy or in the equilibria described by equation (75). A thorough investigation of this matter could result in more selective use of the ligands attached to the lanthanide metal ion as well as of the metal itself.

As demonstrated in equations (31) and (32) the width of a NMR line in the presence of a paramagnetic species depends upon r^{-6}. Gadolinium(III) has a long electronic spin relaxation time and an isotropic magnetic moment, thus it is a very suitable relaxation reagent, producing lines with a r^{-6} width dependence and negligible shifts. Consequently relaxation data obtained from $Gd(FOD)_3$ can provide more reliable structural information than is often available from shift measurements since the interpretation of the line widths lies on firmer theoretical grounds. (804) The two types of measurement have been used to complement each other in deriving solution structures for some substituted pyridines. (804, 808)

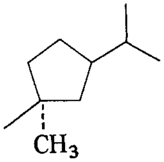
(*ii*) *Chiral shift reagents*. As discussed in Section III. B. 3, the presence of an asymmetric centre in a paramagnetic compound can lead to separate NMR signals for different isomeric species. The chiral shift reagent [101] has been used to produce separate sets of proton signals for stereoisomeric substrate mixtures. Some amine isomers have been identified from their proton spectra taken in the presence of [101] with $R = C(CH_3)_3$. (573) However only a line broadening effect was observed when the same shift reagent was added to racemic bis(phenyl-sulphinyl)methane. (604) By using [101] with $R = CF_3$ it has been possible to obtain separate signals from stereoisomeric mixtures of amines, ketones, esters, alcohols,



[101]

sulphoxides and epoxides. (574-577) The compound with R = C_3F_7 has also been used as a shift reagent on similar mixtures, (495, 574, 578) as well as on benzyl alcohol and related compounds where the benzylic protons have been reported to give separate NMR signals. (578) In this latter case the signal separation must arise from a difference in the geometries of the adducts formed by the substrates. This could also be the case for the stereoisomeric mixtures although a difference in the equilibrium constants of the adducts might be responsible. Similar arguments have been used to account for the shift differences of protons in stereoisomers of alcohols, (605) ketals (606) and lactams (607, 608) produced by $Eu(DPM)_3$ and $Eu(FOD)_3$.

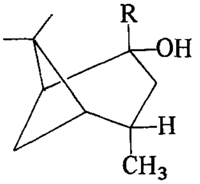
The largest separation of signals from different stereoisomers, due to a shift reagent, so far reported is 1·65 ppm for 1-phenylethylamine in the present of [101] where R = [102]. (579) It seems



[102]

likely that more bulky substituents could produce larger signal separations by influencing both the geometries and the equilibrium constants of the adducts.

(*iii*) *Isotope effects*. The equilibrium constant of the adduct formation between shift reagent and substrate is influenced by deuterium substitution and this is revealed in the NMR spectrum of the substrate. Partially deuterated verbenol [103] in the presence of



[103]

R = H, D

$Eu(DPM)_3$ shows a doubling of all of its proton NMR signals, the relative intensity of the high frequency component of each pair increases as the amount of deuteration increases. (580) Similar effects have been observed with other alcohols. (580, 581) The substitution of a $-CD_3$ group for an α-methyl group in an alcohol also leads to significant isotope effects in the NMR spectra of their adducts. (582)

Isotope effects have also been observed in the NMR spectra of glymes in the presence of $Eu(DPM)_3$ and $Pr(DPM)_3$. (456, 583, 584) It has been claimed that these effects arise from an intramolecular exchange reaction of the lanthanide complex. (584)

It seems most probable that the isotope effects observed in the NMR spectra of shift reagent-substrate adducts arise from an increase in basicity of the heteroatom upon deuteration. The NMR spectrum provides a convenient route for comparing the isotopic equilibrium constants in one experiment.

(*iv*) *Effects on spin coupling constants in the substrate.* Chemical exchange spin decoupling can occur in the presence of a paramagnetic centre, which can lead to a decrease in, or the complete removal of, the spin-spin coupling fine structure in the NMR spectrum of the substrate. (451, 585-591) Theoretically a paramagnetic centre may be treated as a perturbation causing rapid nuclear relaxation such that the condition (76) is not obeyed, where T_1 is the longitudinal relaxation time for either nucleus A or B. The

$$J_{AB} > \frac{\sqrt{2}}{2\pi T_1} \tag{76}$$

decreased values of the quinoline coupling constants, found when $Eu(DPM)_3$ is added, provide an example of chemical exchange spin decoupling. (512) Although other examples of changes in substrate coupling constants, in the presence of shift reagents, have been reported they have not generally been attributed to chemical exchange spin decoupling.

It has often been considered that substrate coupling constants remain unchanged in the presence of a shift reagent. (497, 592, 593) This appears to be a dangerous assumption and should not be used, when conformational arguments based upon coupling constants are being deployed, without a very careful consideration of the system under investigation.

An increase in the values of coupling constants has been reported for a number of substrates in which the electron withdrawing effects of the shift reagent or the favouring of a particular substrate conformation is claimed to be responsible. (594-597) Other changes in coupling constant data due to added shift reagents have also been reported. (598-606)

This adds further support to the contention that molecular conformations based upon coupling constant data, obtained from solutions containing paramagnetic centres, may be incorrect. (600)

3. *Some of the substrates investigated*

Due to the very extensive literature and recent reviews, (6-11) not all of the reports dealing with the use of shift reagents are included in this account. An illustrative selection of the wide range of substrates amenable to study is presented.

(*i*) *NMR spectra of nuclei other than protons.* The range of chemical shifts exhibited by nuclei other than protons is such that they usually produce well resolved first-order spectra. Consequently the use of shift reagents in NMR studies of other nuclei is unlikely to become widespread. Due to the much greater relative importance of contact contributions to the induced shifts experienced by other nuclei, shift reagents are unlikely to provide useful structural data from their NMR spectra.

Apart from protons, reports of ^{13}C NMR spectra in the presence of shift reagents are the most common. The ^{13}C data for borneol [99] in the presence of $Eu(DPM)_3$, $Pr(DPM)_3$ and $Tb(DPM)_3$ has been reconciled in terms of a dipolar mechanism except for carbon number two which shows a contact contribution. (546) A similar conclusion has been reached for piperine [98]. (504)

The ^{13}C NMR spectra of some pyridine type bases in the presence of various shift reagents show considerable contact and dipolar interactions. (505-507, 609) Similar effects are found in the ^{13}C NMR spectra of some primary amines, (610, 803, 810-812) some alcohols, (799, 810) a dioxolane, (611) some cholesterols, (612, 813) quinoline, (613) some cyclopentanols, (614) some ketones, (810, 814) nitriles, (810) phenol, (812) and some pyridine *N*-oxides. (812, 815)

When extensive signal overlap occurs in the proton region, proton-carbon decoupling experiments can be difficult to perform and their results can be uncertain. This problem can be overcome by the use of shift reagents which permit complete ^{13}C signal assignments to be made. Some examples are provided by ribose-5-phosphate, (615, 750) isoborneol (616) and 2,2-dimethyl-1-propanol where the INDOR technique has been applied. (617) ^{14}N chemical shifts have been reported for pyridine in the presence of a number of shift reagents (503) and for various amines and other nitrogen containing substrates with $Eu(DPM)_3$ and $Yb(DPM)_3$ added. (618, 619) In all cases the ^{14}N shifts appear to be dominated by a contact interaction.

^{31}P induced shifts have been observed in some bidentate ligands [104] (620) and some trialkylphosphates. (621) The reported data are consistent with dominant contact contributions.

$$R_2NC_2H_4P(C_6H_5)_2 \qquad R = H, CH_3$$

[104]

Recently the ^{31}P NMR data for cytidine 5′-monophosphate in the presence of lanthanide shift reagents has been analysed and the contact and dipolar contributions to the induced shifts have been separated. (809) The contact contribution is found to be at its largest when europium(III) is used whereas the highest dipolar contribution arises from ytterbium(III) in agreement with the data in Table XII.

Induced shifts have also been recorded in the ^{19}F NMR spectra of 2,4,6-trifluoroaniline (622) and 7-fluoronorbornen-2-ol (623) in the presence of shift reagents. The results appear to favour a substantial contact contribution as expected.

(*ii*) *Proton NMR spectra.* Any substrate with a suitable polar group is potentially able to form an adduct with a shift reagent. In practice the stability of the adduct usually decreases in the following order for mono-functional substrates, (465)

amine > hydroxyl > ketone > aldehyde > ether > ester > nitrile.

For saturated polyfunctional substrates the preferred order of adduct formation is,

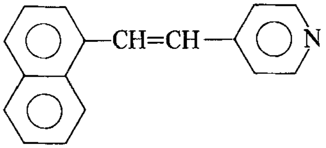
ether > thioether > ketone ≃ ester

the order may be changed in unsaturated substrates. (624)

We will discuss the monofunctional substrates and some of their applications in the above order of decreasing adduct stability.

Amines usually exhibit large induced shifts due to their strong basicity. In the absence of steric and solvent effects the size of the induced shifts at a given position in a series of related amines generally corresponds to the relative basicity of the substrate. (528, 625-627) Shift reagents have been used in the analysis of diamine (628) and *N*,*N*-dimethyl-propylamine derivatives, (634) in the identification of bis(1-amino-2-naphthalene)trisulphide (629) and in the identification of three isomeric 1,3-dimethylcyclohexylamines. (6)

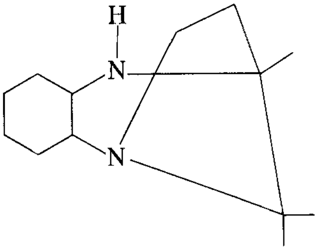
Steric effects are found to be very important in deciding the order of induced shifts in the proton spectra of *azaheterocyclic bases.* (464, 501, 509, 512, 513, 565, 630-632) The vinyl and aromatic proton signals of 4[β(-1-naphthyl)vinyl]pyridine [105] have been separated by the use of Eu(DPM)$_3$ and *cis* and *trans* isomers identified. (633) The conformation of nicotine has been studied by means of the same shift reagent. (635)



[105]

Shift reagents have been used to render the proton spectra of some substituted pyrazines first order and the spin coupling constants have been reported. (592, 672)

In a study on benzo[*b*]-1,4-diazobicyclo[3,2,1]octane [106], it is found that Eu(FOD)$_3$ coordinates exclusively with the bridgehead nitrogen atom. (673)

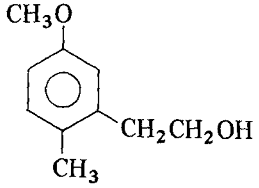


[106]

The *hydroxyl* group was the first to be employed in shift reagent NMR studies. (439-441, 450, 465, 637) The shifted NMR spectra of normal saturated alcohols with up to eleven carbon atoms have been studied. (492, 636) The magnitude of the induced shift is largely determined by the position of the given proton with respect to the alcohol group. Thus the integrated signals of the methyl groups of a mixture of alcohols, in the presence of a shift reagent, can be used to identify the composition of the mixture. (492) This approach has also been used in studies on some 3-hydroxy steroids. (498)

The configurations of some alkenols have been determined by the use of Eu(DPM)$_3$. (638) Cyclic and polycyclic alcohols have also been studied on many occasions. (510, 537, 538, 542, 545, 639-643) The position of deuterium substitution in a number of complicated alcohols has been established from their shifted proton NMR spectra.

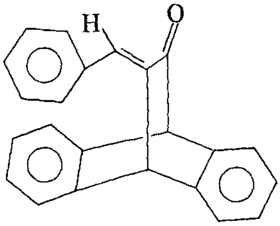
(644-647) A structure has been reported for 3-methoxy-6-methylphenethyl alcohol [107] based upon coupling constant data obtained in the presence of a shift reagent. (648) A number of



[107]

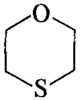
natural products and their precursors containing alcoholic groups have yielded interpretable proton spectra when lanthanide shift reagents have been employed, including steroids, (440, 540, 555, 649, 650, 655) terpenes (651-658) and other miscellaneous alcohols. (640, 659-661, 663-671)

The NMR spectra of *aldehydes* and *ketones* have been frequently studied in the presence of shift reagents. Large induced shifts have been reported in the spectra of a number of common compounds, both cyclic and linear, containing carbonyl groups. (491, 527, 529-531, 603) In addition there are a number of examples of shift reagents being used in structural studies on carbonyl compounds. (524, 536, 677-701) An example being [108] where it is found that



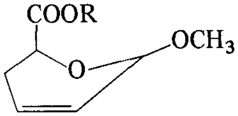
[108]

the shift induced in the vinyl proton is larger than in the aromatic protons which is consistent with the vinyl proton and carbonyl group being *cis* and the shift reagents being coordinated to the carbonyl group. The proton shift data on *ethers* is not as extensive as that on carbonyl compounds. (442, 456, 465, 583, 605, 624, 702, 703) However ethers are found to be stronger donors than *thioethers* (624, 684, 703) as demonstrated by [109], where it is claimed that 70% of the coordination to a shift reagent occurs at the oxygen atom. (703)



[109]

Esters and *lactones* combine relatively weakly with shift reagents and compete unfavourably in the presence of stronger donor groups. (513, 567, 656, 691, 704, 705) However a number of reports have appeared in which shift reagents have been used effectively with these groups. (705-712) An example is [110] in which the *cis* isomer is found to have smaller induced shifts than the *trans* probably due to steric hindrance upon adduct formation.

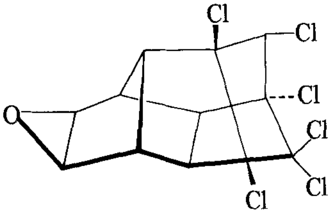


[110]

Nitriles coordinate very weakly with shift reagents and few reports of their induced shifts have appeared. (465, 490, 713, 714) The NMR spectra of a number of *oximes* show that the proton signals of the *anti* isomers are shifted more than the *syn* signals which is consistent with coordination by the nitrogen lone-pair to the lanthanide ion. (715, 716) Not all reports agree with this interpretation, (541) however a close inspection of the anomalous data shows it to be incorrect.

Other nitrogenous groups which have been reported to coordinate with shift reagents are the following, *azo*, (717) *azoxy*, (718) *nitrosamine*, (719) *amine N-oxide* (487, 501, 632) and *amide*. (490, 720, 721) In the latter case adduct formation occurs at the carbonyl group. *Thioamides* (533, 721) which have smaller shifts than the corresponding amides, probably due to coordination by the sulphur atom which has a lower electron density than oxygen, (722) and *lactams*, (539, 637, 638) in which adduct formation occurs through the oxygen atom, have also been studied.

Ketals (703) and *epoxides* (522, 534, 723) also show induced shifts in the presence of lanthanide shift reagents. An example is afforded by photodieldrin [111], where the proton on carbon number twelve has been assigned to a position *syn* to the epoxide function due to the magnitude of its induced shift. (534) However

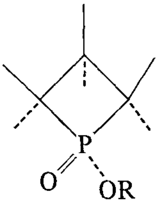


[111]

no account was taken of the angular term in the geometric factor, consequently the analysis should be repeated.

In addition to thioamides and thioethers other sulphur containing groups have been reported to form adducts with lanthanide shift reagents including *sulphoxides*, (523, 532, 724) which attach themselves to the shift reagent through an oxygen atom producing shifts similar in magnitude to those found in the NMR spectra of alcohols. *Dithiolane oxides* (725) and *sulphines* (604, 726) also show large induced shifts which are thought to indicate coordination via a sulphinyl oxygen atom. *Thiosulphinates* have also been studied. (727)

Groups containing phosphorus bonded to oxygen are assumed to be attached to shift reagents through an oxygen atom. Some examples of the use of these groups in producing shifted NMR spectra have been reported for some *phosphine oxides*, (728) *phosphetan oxides* [112] (729) and some *phosphoryl* compounds.



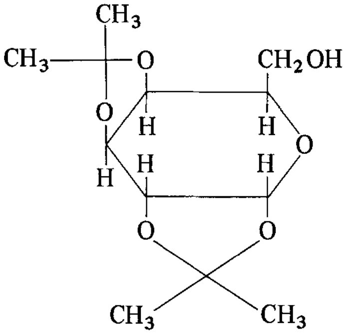
[112]

(598, 599, 730, 731) The *thiophosphoryl* group is found to be a very weak donor and is non-competitive for the shift reagent in the presence of other groups. (731)

Organometallic compounds usually combine with lanthanide shift reagents through a hydroxyl ester or ketone functional group. (732-735) In the case of metal carbonyl complexes terminal carbonyl groups do not interact with the shift reagent whereas the more basic bridging carbonyl groups do interact. (734, 735) Further applications of shift reagents are to be anticipated in organometallic chemistry as aids to structural studies.

Due to the high degree of line overlap found in the NMR spectra of *polymers,* shift reagents are expected to find many applications in polymer chemistry. Poly(methyl methacrylate), (736, 737) poly(ethylene oxide), (736) poly(propylene glycol) (738) and some poly(glycoldimethylethers) (456, 583) are amongst those which have been investigated. In general the proton spectrum is simplified by the addition of the shift reagent and in some cases the polymer tacticity has been determined. (736) Other successful applications of shift reagents to polymer problems include the determination of the composition and various sequences of the trioxocane-dioxolane copolymers, (739) the triad sequence in the trioxane-dioxolane copolymer (740) and the triad tacticity of poly(methylvinyl ether). (741)

Simplification of the proton NMR spectra of *carbohydrates* has been obtained by the use of lanthanide shift reagents. (496, 497, 742-746) In the case of 1,2,3,4-di-*o*-isopropylidene-α-D-galactopyranose [113], the signals from all of the protons have been identified due to complex formation between the CH_2OH group and the shift reagent.



[113]

(743, 744) *Lipids* and their derivatives are another class of compounds usually exhibiting a large amount of signal overlap in their NMR spectra. Simplification and assignment of the protons by means of shift reagents has been achieved for a number of molecules in this class. (465, 747-749)

Although the use of lanthanide shift reagents [95] and [96] in simplifying proton NMR spectra is still increasing dramatically they may not be ubiquitously employed. Acidic media and molecules with acidic and phenolic functions tend to decompose them, also there are many molecules which do not form adducts with the shift reagents. A further experimental problem can be line broadening and chemical exchange spin decoupling which results in the loss of spin-spin coupling data. NOE may also be removed by paramagnetic shift reagents. Most of these shortcomings can be countered with suitable experimental procedures.

In order to obtain reliable structural data from NMR spectra taken in the presence of lanthanide shift reagents the stoichiometry of the adduct formed and the contact contribution to the observed shifts must be accurately known. The choice of metal and ligands in the shift reagent used contains at least part of the answer to this problem which will doubtless be the focus of many chemical NMR spectroscopists attention in the near future.

The rate of growth of the literature dealing with NMR spectra of paramagnetic species over the last four years has been so spectacular that the potential of this field of study has become widely known and appreciated. No doubt the chemical literature during the next four years will reflect this potential and the widespread interest in NMR of paramagnetic species.

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General Review of Nuclear Magnetic Resonance

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I. INTRODUCTION

A complete review of nuclear magnetic resonance publications in the year 1971 is, of course, impractical and an attempt will be made to cover only certain broad areas within the field. These regions were selected on the basis of their importance and potential importance to the future applications of NMR and, consequently, they are not numerically representative of the year's output.

Included are:

1. Factor influencing resonance positions with particular emphasis upon Lanthanide shifts. These inorganic species have dramatically extended the application area from small to medium-large organic molecules and the technique may, in most but not all cases, compete favorably with higher frequency instruments.
2. Conformational and configurational rate processes and this area continues to dominate the various fields of NMR research.
3. Carbon-13 and currently the emphasis appears to consist of extensions to cover not only all aspects of proton spectra, but also additional application areas are now open for investigation. The method has, however, a number of significant drawbacks and the most severe probably concerns the high cost of instrumentation.
4. Organometallic systems and NMR has contributed both qualitatively and quantitatively to the information explosion of the area.

II. FACTORS INFLUENCING CHEMICAL SHIFTS

A. Lanthanide Shift Reagents

1. Types of reagents

Hinckley's (1) report in 1969 of NMR shifts of proton signals by the dipyridine adduct of tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$ dipyridine] was followed in 1970 by the observation of Sanders and Williams (2) that further shifts arose from uncomplexed Eu(DPM)$_3$. It appears that Eu(DPM)$_3$ is adequate for most proton shift studies since Eu(III) results in less or nearly equal line broadening than do other lanthanides and the dipivalomethanate complexes are air stable and soluble in organic solvents. (3) Of alternatives to Eu(DPM)$_3$ as lanthanide proton shift reagents ytterbium (DPM)$_3$ has greater solubility in organic solvents, gives stronger downfield shifts, but slightly increased line broadening. (4-7) The fluorinated ligand tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octane dione)europium(III) or Eu(fod)$_3$ (8) has superior solubility properties and is better at coordinating weakly basic ligands. $Pr(DPM)_3$ and $Pr(fod)_3$ give 1·4 to 3·0-fold greater shifts than $Eu(DPM)_3$ with only slight broadening, but in an upfield direction. (8, 9) $Eu(NO_3)_3 \cdot 6H_2O$ (10) and $Eu(ClO_4)_3$ (11) give upfield shifts in aqueous and polar solutions of substrates too polar to have properties compatible with $Eu(DPM)_3$; $Pr(ClO_4)_3$ and $PrN(CH_2CO_2)_3 \cdot (H_2O)_3$ (11) give complementary downfield shifts. Other lanthanide reagents using Er, Lu, Tm, Dy, Ho, Nd, Sm, Gd, Tb, have been synthesized and investigated. (12, 13) The relative shifts are depicted in Fig. 1.

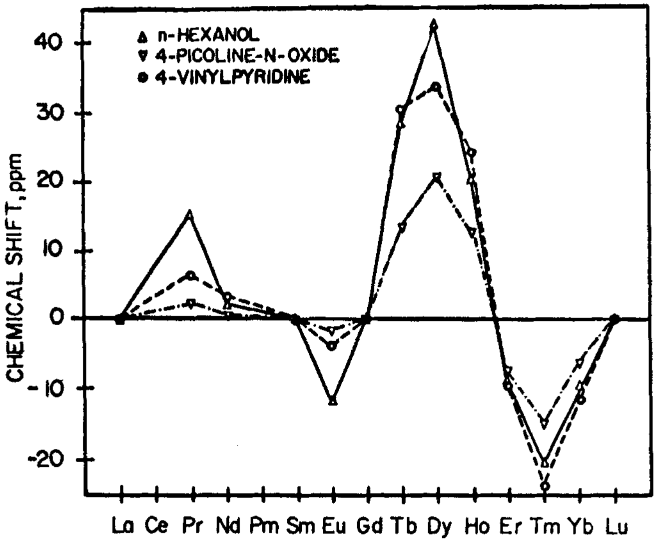


FIG. 1. Observed isotropic shift for the most shifted resonances of 0·8 M solutions of *n*-hexyl alcohol (H-1), 4-picoline *N*-oxide (H-2), and 4-vinylpyridine (H-2), in the presence of various lanthanide complexes. The mole ratio of shift reagent to substrate (R_p) was 0·125 and the shifts were measured at 30° on $CDCl_3$ solutions. (From Horrocks and Sipe. (12))

2. *Relationship between lanthanide shifts and molecular and physical parameters*

Evidence continues to accumulate that paramagnetic $Eu(DPM)_3$ induced proton and carbon-13 shifts result largely, if not exclusively, from pseudocontact interactions (3, 10, 14-16) which depend mainly on distance and geometry, rather than from contact interactions which depend on covalent bonding. However, contact contributions to proton shifts near coordination sites have been suggested by some workers. (17-20) Contact contributions are of importance for ^{14}N shifts in amines and for ^{31}P shifts in phosphates and phosphonates. (21) Pseudocontact contributions to proton and ^{13}C shifts have been best described using the McConnell-Robertson (22) equation (1) for anisotropic pseudocontact interaction, where

$$\Delta\delta_i = D\left(\frac{3\cos^2\theta_i - 1}{R_i^3}\right) \tag{1}$$

$\Delta\delta_i$ is the observed lanthanide induced shift of the ith proton; D, a function of temperature and magnetic properties of the complex, is a constant for a given metal (10) θ_i is the internuclear angle made by the lanthanide–electron donor–ith proton averaged over motions rapid on the NMR time scale, and R_i is the internuclear distance between the lanthanide and the ith proton of the ligand.

The ratio of lanthanide induced pseudocontact shifts can be expressed by equation (2). Using this equation the preferred conformation of two mononucleotides, 9-β-D-ribofuranosyladenine-5′-monophosphate and 1-β-D-deoxyribofuranosylthymine-5′-monophosphate have been determined. With computer aid molecular geometry was varied until values of θ and R giving best agreement with observed shift ratios were found. (10, 23) Using the computer method a europium–oxygen distance of 2·7 ± 0·4 Å has been estimated for a ketone. (23)

$$\frac{\Delta\delta_i}{\Delta\delta_j} = \frac{\dfrac{3\cos^2\theta_i - 1}{R_i^3}}{\dfrac{3\cos^2\theta_j - 1}{R_j^3}} \tag{2}$$

Correlations of observed lanthanide shift ratios with calculated distance and angle factors using the $3\cos^2\theta - 1/r^3$ relationship have proven reasonably successful, even though the McConnell-Robertson equation should correspond to only axially symmetric systems and bound chemical shifts. Horrocks has shown that the bis(4-picoline) adduct of $Ho(DPM)_3$ is not axially symmetric with respect to adduct ligands in the crystal, (12) although it is not known if the adduct approximates axial symmetry in a magnetic sense or in solution.

In order to relate lanthanide induced shifts to internuclear distances, Hinckley (1) has suggested using approximate equation (3) in which θ_i of equation (1) is assumed invariant for all protons. Plots of log $\Delta\delta_i$ versus log R_i should be linear with slopes of -3.

Differences between lines of slope −3 and measured shifts have been attributed to uncertainties in estimating R from models and to small

$$\Delta\delta_i = DR^{-3} \tag{3}$$

$$\log \Delta\delta_i = -3 \log R_i + \log D \tag{4}$$

contact shift contributions. (18) To a good approximation, however, shifts will be angle invariant only when $3 \cos^2 \theta - 1$ is nearly constant for protons being compared. (24) Using Hinckley's approximation equation (5) has been used to compare internal proton shifts. (24)

$$\frac{3R_i}{3R_j} = \frac{\Delta\delta_j}{\Delta\delta_i} \tag{5}$$

Following the suggestion of DeMarco, (25) the quantity Δ La, the lanthanide induced shift at a molar ratio of $La(DPM)_3$ complex to solute of one, has been used to report magnitudes of induced shifts. (3, 4, 9, 26) Since Δ La reflects the lanthanide-substrate complexation constant K (Fig. 2) and is a function of lanthanide-proton distances and angles, meaningful comparisons of Δ La for protons in different molecules can be made only with caution. (26) In order to determine Δ La, a plot of shift ($\Delta\delta_i$) versus lanthanide/substrate mole ratio (L/S) obtained at ratios 0·1–0·15 is extrapolated to mole ratio 1·0. It has been suggested that in comparing induced shifts of two protons, the slope of the line obtained from this plot (ΔG) can be used as a more precise measure of lanthanide-proton distance (9) using equation (6). The slope ΔG which results when all the

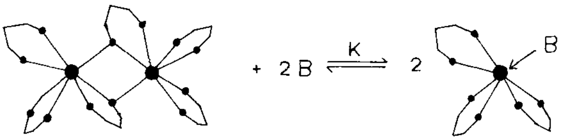


FIG. 2. Schematic diagram based on the structure of $PR_2(thd)_6$ dimer. (From Erasmus and Boeyens. (27))

$$\frac{\Delta G_i}{\Delta G_j} = \frac{R_j^3}{R_i^3} \tag{6}$$

substrate is complexed to lanthanide is termed the bound chemical shift (ΔB). (28) In order to obtain values of R, lanthanide-heteroatom distances have been assigned for which equation (6) will hold.

Typical distances are Eu–O = 2·8 Å in ketones, (25) Yb–N = 3 ± 0·3 Å in amines (5) Yb–O = 1·5 ± 0·2 Å in ketones, (6) Eu–S = 3·0 – 3·5 Å in thioamides. (29) The range of distances is probably a reflection of the approximate nature of equation (6).

Cockerill (30) has suggested that because of the uncertainty in positioning the lanthanide atom, shifts can be better described by equation (7), where r_i is the distance from proton H_i to the periphery of the donor lone pair $n = 2$. Some workers have adopted a value for n which gives the best straight line correlation between log $\Delta\delta_i$ and log r. (31) It has also been suggested that equation (9) be used as a direct method of calculating n from $\Delta\delta$ and r values for any two protons. Values obtained in the direct manner vary from $n = 0{\cdot}2\text{–}3{\cdot}0$, (32) and often differ from values obtained from the graphical method using equation (8).

$$\Delta\delta_i = Dr_i^{-n} \tag{7}$$

$$\log \Delta\delta_i = -n \log r_i + \log D \tag{8}$$

$$n = \frac{\log \Delta\delta_i - \log \Delta\delta_j}{\log r_j - \log r_i} \tag{9}$$

Using equation (8) configurational assignments to stereoisomeric ethers have been made by estimating distances r from molecular models. Where only one stereoisomer gave r values yielding a linear plot of negative slope $n = 2\text{–}3$, a stereochemical assignment was made. (31) Using this approach it has been suggested that oximes coordinate on oxygen (33) but other workers have postulated nitrogen as the coordination site. (34)

Although approximate equations (3) to (8) have found some use, the importance of the angle term of the McConnell-Robertson equation (1) has been recognized in numerous molecules. (10, 31, 35) The most dramatic indications are shown for protons in which θ is between 54·7° and 125·3° for in this region the $3\cos^2\theta - 1$ term of equation (1) is negative and $Eu(DPM)_3$ shifts are upfield. (36-39)

Contact shift contributions have been considered to affect shifts of protons near the coordination site (17) and have been used to explain the variations in shift ratios for different protons using different shift reagents. (20) Also, variations in the Eu(III)/Pr(III) shift ratios for protons in a cyclic ketone indicate that carbonyl anisotropy may change upon complexation. (16)

As mentioned earlier, the shifted spectrum represents a time average of signals from free and complexed solute (40) where at low concentrations of substrate the lanthanide coordinates with a single ligand, although higher coordination numbers may be possible. (13, 41) Greater shift magnitudes at lower temperatures suggest a shift in equilibrium toward complexed solute. (35, 42, 43) The lanthanide-substrate equilibrium is also sensitive to the absolute concentration of substrate. (28, 35, 42) While values for the bound chemical shift ΔB have generally been assumed equal to ΔG as defined for equation (6), different absolute concentrations of substrates yielded different values for ΔG. More reliable values of ΔB can be obtained, if high substrate to lanthanide mole ratios are used, by plotting substrate concentration versus $1/\delta$ at constant lanthanide concentration Lo. A line is obtained whose slope is LoΔB and y intercept is $-(1/K_B +$ Lo), where K_B is the equilibrium binding constant. Representative binding constants for *n*-propylamine, $K_B = 12{\cdot}3$ (liter-mole)$^{-1}$, and neopentanol, $K_B = 6{\cdot}2$ (liter-mole)$^{-1}$, suggest that for a given shift reagent characteristic shift magnitudes for different functional groups may be correlated with binding constants. (28)

The lanthanide shift reagents are sterically hindered weak Lewis acids, so the binding constants and associated induced shifts are dependent upon steric and electronic factors about donor atoms. (44) Inter- and intra- molecular competition experiments of Sanders and Williams (3) have established preferred orders of coordination for functional groups of $NH_2 > OH > C = O > O > CO_2R > CN$ with the basic amines being most shifted. However, others have shown alteration of the above order. Steric effects on coordination at phosphoryl and amide sites have been discovered (45) and coordination at ether oxygen in preference to sterically hindered hydroxyl, (24) at hydroxyl in preference to hindered amine, (46) at ether oxygen in preference to carbonyl, (27) anhydride in preference to amine, (47) and at ketone carbonyl and ester carbonyl about equally, (27) have been observed. Basicity scales as described by protonation correlate linearly with $Eu(DPM)_3$ induced shifts in *p*-substituted anilines, (48) but *N*-methyl anilines are sufficiently sterically hindered that such a correlation fails. Indeed, basicity scales as described by protonation fail in general to correlate with induced shifts. (5, 49) A pronounced steric effect was found in a study of thionocarbamates in which weak coordination with sulfur was suggested. (50) Reportedly, shifts occurred only with the *O*-alkyl esters of methyl-thiocarbamic acid in which the sulfur and methyl are *trans*.

3. *Uses of lanthanide shift reagents*

The lanthanide shift reagents have been used to obtain expanded spectra of molecules with a variety of functional groups. Shifts of alcohols (51-57) have been exploited to simplify spectra of steroids, (3) carbohydrates (34, 57-59) and nucleosides. (56) Shifts of amines (3-5, 14, 60) have been used for aminosteroids (61) and shifts of esters (62-64) for lipids (65) Vitamin A derivatives (66) and synthetic polymers. (67-68) From a clarified spectrum polymer molecular weight has been determined. (69) Simplified spectra of pyrazines (70) ketones (3, 9, 36, 71, 72) ketals (73-75) nitriles (4) ethers (3, 20) sulfoxides (76, 77) phosphine oxides (78, 79) epoxides (80) nitrosamines (81) pyrazoles (82) and amides (4, 56, 83) have been obtained.

Angle and distance dependency of lanthanide shifts have been useful in structural determinations of *Z–E* isomers of alkenols (84) phosphorinanes (85) cyclic esters (63) azetidinols (46) α-benzocyclohexanols (86) oximes (33, 34) phosphetanoxides (87) epoxides (31, 80) amines (41, 60, 88) vinyl- (6, 17) and β-halovinylaldehydes and ketones (89) and ethers. (31, 90) Assignments to *N*-alkyl groups of amides (91, 92) thioamides (29) and thionocarbamates (50) have been made. Proton shifts of a europium oxaloacetate chelate have been used to assign coordination of europium with the oxygens of the carboxylate and α-keto group. (93)

Since lanthanide induced shifts are primarily pseudo-contact in origin, the magnitudes of coupling constants, which are field invariant, are unaffected. Peak broadening, however, may occasionally make determination of coupling *J* values difficult. The conformation of griseofulvin (94) and of carbohydrate derivatives (59) have been determined from coupling information obtained on shifted spectra. Information has been obtained on averaged conformations of bicyclic alcohols (95) hydroxyesters (40) ketones (25, 96) and in a notable effort mononucleotides. (10) Where the shift reagent may affect conformation, assignments should be made with caution. (90)

Since expanded spectra frequently make possible assignment of resonances of many or all protons in a molecule, peaks from diastereotopic groups or diastereomeric molecules can be identified and isomeric compositions determined. An analysis of amine diastereomers (40) and separation of the methyls of iso-, hetero-, and syndiotactic triads in a sample of atactic poly(methylmethacrylate) (67) are examples. Simple methods for determination of optical purities have been applied to sulfoxides, alcohols, ketones, esters, epoxides, and amines utilizing several dissymmetric shift reagents as means of obtaining diastereomeric lanthanide-substrate complexes. (97-99)

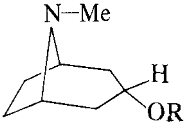
In lanthanide shift studies of heteronuclear resonances, coordination with lone pair donors has proven useful in assignment of ^{13}C shifts. (100-103) The complementary tools of alternately pulsed NMR and proton decoupled spectra in the presence of $Eu(DPM)_3$ has been used to assign ^{13}C signals in isoborneol. (103) Shifts of ^{31}P in phosphates and phosphonates (22) have been reported to result from contact and pseudocontact contributions. A comparative study of lanthanide and actinide $(DPM)_3$ chelates on ^{14}N shifts of pyridine has found $Dy(DPM)_3$ the best high field and $Yb(DPM)_3$ the best low field shift reagents. (104) Shifts of ^{14}N have been related to basicity and steric effects. (105)

B. Metallo-Porphyrin Shift Reagents

A class of porphyrin shift reagents induces diamagnetic shifts as a result of a ring current effect. Using a germanium porphin, a nonlabile germanium-substrate bond has been formed from phenols, acids, or organometallics, molecules where the $La(DPM)_3$ reagents are not applicable. (106) Because of the diamagnetic origin of the induced shifts, paramagnetic line broadening is not observed. Iron(II) and ruthenium(II) phthalocyanine have been found to form donor-acceptor bonds with Lewis bases such as butylamine and thus serve as shift reagents. (107)

C. Contact Shift Reagents

Using proton contact shifts induced by paramagnetic nickel(II) acetylacetonate the mode of electron spin distribution throughout the σ and/or π skeletons of 1,4-dimethyl piperidine and azaadamantane, (111) 6-aminobenzonorbornene and 6-aminobenzonorbornadiene has been studied; (112) and using ^{13}C contact shifts electron spin distribution in piperidine, quinuclidine, and azaadamantane (113) has been determined. On the basis of Co(II) and Ni(II) acetylacetonate induced contact shifts, the semi-planar form has been suggested for tropine benzoate [1A] and homatropine [1B]. (114) $Ni(acac)_2$ and bis(*O,O'*-dialkyl or diphenyl-dithiophosphato) nickel have found use in simplifying spectra of amines. (115, 116)



[1A] R = COPh

[1B] R = COCHOHPh

A correlation between Ni(acetylacetonate)$_2$ contact shifts and nuclear spin coupling constants has been found (117) for molecules where electron spin polarization mechanism determines the magnitude of spin-spin coupling. The pseudocontact contribution to cobalt(II) acetylacetonate shifts has been estimated by comparison of Ni(II) and Co(II) (acac)$_2$ induced shifts of amines. (118)

Proton and ^{13}C contact shifts of protic molecules in the presence of the nitroxide radical have been used to measure the strength of the H-bond interaction. (119) Addition of paramagnetic Cu(II) and observation of contact broadening of certain resonances has been used to study the stoichiometry and bonding sites of aqueous thorium(IV)-diethylenetriaminepentaacetic acid complexes. (120) Downfield shifts of ethereal solvent lines for solutions of phenanthrene, triphenylene, and coronene anions have been discussed in terms of contact interactions and changes in bulk diamagnetic susceptibility. (121)

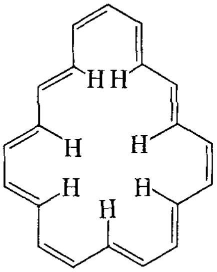
D. Shifts in Protic Media

Shifts induced by protonation have been used to determine relative basicities of the amino groups of $Me_2N(CH_2)n{-}NH_2$, $n = 2{-}5$, (108) and H_2SO_4 induced shifts have been useful in peak assignments of steroids. (109) Pure shifts for water containing alkylammonium ions have been considered diagnostic of water structure phenomena. (110)

E. Correlations of Spectral Parameters with Molecular Structure

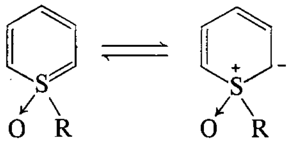
1. *Aromatic molecules*

With the synthesis of 20 annulene [2] the series from 6 to 24 are known. Excepting 8 and 10 annulene which are non-planar, all 4*n* annulenes show paramagnetic ring current and all 4*n* + 2 a diamagnetic current. (122) The 15-membered fully unsaturated carbon cation has been found to have a diamagnetic ring current and a

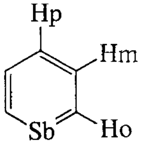


[2]

15-membered oxygen heterocycle a paramagnetic current. (123) Anet and Schenck (124) have devised a method using specific solvent effects to study diamagnetic and paramagnetic ring currents in potentially homoaromatic compounds. In estimating aromatic character, proton shifts of thiabenzene *S*-oxides suggest no appreciable ring current (125) with structure [3B] being of importance in the resonance picture. However, proton shifts in stibenes [4] are consistent with ring currents. (126) Proton H_0 of [4] appears at



[3A] [3B]

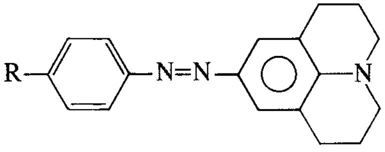


[4]

δ10·7, a result of the magnetic anisotropy of the large heteroatom, awhile H_m and H_p resonate at δ8. On the basis of an empirical reassessment, it appears the effect of ring currents on the deshielding of proton resonances in planar, condensed, benzenoid hydrocarbons has been overestimated by semiclassical theory. (127) Calculated aromatic currents in benz[*b*] thiophenes are comparable with those in benzene and the aromaticity of dibenzothiophenes is like naphthalene. (128, 129)

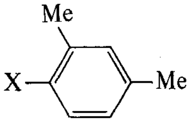
Benzene induced solvent shifts of pyrazines, pyrimidines and their *N*-oxides have been used to establish sites of *N*-oxidation (130) and benzene induced shifts on *N*-*O*-alkyl oximes and methylbenzoic esters have been investigated. (131) Takeuchi (132) has explained benzene solvent shifts by postulating a 1:1 complex formation of the solute dipole with the induced dipole of solvent. Unusual shielding in some 2-phenyl-sulfonamido-*N*,*N*-dialkylanilinium ions has been observed arising from anisotropy of the phenyl ring. (133)

An HMO-E1P treatment of shifts of monosubstituted thiophenes has been found equivalent to the Hammett interpretation of the problem when σ_p is used. (134) A similar linear relation between σ_p and internal shift of aromatic ring protons has been found in 9-phenylazojulolidines [5]. (135) For 2,4-dimethylbenzene deriva-



[5]

tives [6], shifts of protons *ortho* to the substituent X have been correlated with polarizability, bond length and ionization potential of X. (136)



[6]

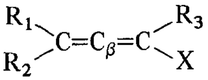
Shifts in fulvene derivatives have been correlated with π-electron densities (137) aromatic ^{13}C shifts have been correlated with SCF-MO charge densities (138-140) and proton shifts for lithium, potassium, and sodium salts of indole have been found to agree with calculations using π-charge density and point anisotropy approximations applied to a free-anion model. (141) The ^{7}Li NMR shifts of series of cyclic conjugated anions (142) and dianions (143) have been used to obtain information concerning ring currents.

2. *Non-aromatic molecules*

ApSimon and Beierbeck (144) have shown by comparison of calculated and experimental shifts that electronic and magnetic anisotropy effects are equally important in long-range proton deshielding by carbonyl. The electric field effect has been discussed in terms of CNDO/2 MO calculations by Hamer and Reynolds. (145) Rosenberg and Drenth (146) have evaluated contributions of various shift parameters to shifts in substituted acetylenes [7]. A linear relationship has been found between the number of alkyl substituents R and the shift πC_B in allenes. (147) Substituent correlations indicate the termination of both π-systems at C_β of [8] is an oversimplification. (147).

$H{-}C{\equiv}C{-}R$

[7]



$$R_1R_2C{=}C_\beta{=}CR_3X$$

[8]

Proton chemical shifts in a number of hydrocarbons have been calculated by Allinger (148) from considerations of bond anisotropy and van der Walls dispersion effects. The spectrum of norbornane is reproduced acceptably, but adamantane and *cis, cis*- and *cis, trans*-1,3,5-trimethylcyclohexane are not. A linear correlation between shifts of substituted aliphatics and charge densities calculated using the MOLCAO method was found for substituents of the same row of the periodic table. (149) Shifts of solvent peaks due to intermolecular anisotropy from edge association with cyclopropanes have been discovered by Anet and Schenck; (150) evidence in favor of ring current theory has been advanced to explain cyclopropane anisotropy. (151, 152)

Shifts for protons in phenylazoalkanes [9] are consistent with conical regions of shielding and deshielding about the azo group; it

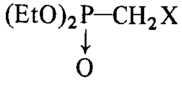
$$\text{Ph—N=N—R}$$

[9]

was concluded from an analysis of shift parameters that some mechanism other than magnetic anisotropy must be responsible for the observed shifts. (153)

The ^{31}P chemical shifts of a series of alkoxyphosphonium compounds could not be explained by the predictions of Letcher and Van Wazer. (154) Alternative empirical suggestions have been advanced. (155) A procedure for calculating chemical shifts of ^{19}F based on Huggins electronegativities has been proposed and extended to fluorine bonded to Sn(IV). (156)

The ^{13}C shifts of phosphonate carbon in compounds [10] reflect the direct electronic effect of the substituent X with no indication of



$$(\text{EtO})_2\underset{\substack{\downarrow\\ \text{O}}}{\text{P}}\text{—CH}_2\text{X}$$

[10]

specific substituent interaction of the $(\text{EtO})_2\text{P(O)}$ groups with X. (157) However, in a study of 2,4-disubstituted adamantanes, it was indicated that in addition to a direct effect of substituents on the chemical shifts of adjacent protons, there is an indirect shift contribution arising from interaction of substituents. (158) An α-alkyl effect similar to that found in ^{13}C resonances has been found for ^{15}N in the methylesters of some amino acids. (159) In a study of aniline derivatives ^{15}N resonances have been found to decrease with increasing substituent electronegativity; (160) ^{119}Sn shifts are affected in a similar manner by substituents. (161) The relationship between inductive effects and conformation of groups attached to boron have been discussed for boron-11 chemical shifts in aminoboranes and borates. (162)

Binding of *N*-trifluoroacetylated aminoacids by chymotrypsin (163) has been investigated using ^{19}F shifts. Stereochemical differences for

^{13}C (164) and ^{19}F (165) resonances in anomeric glucoses have been identified, and ^{13}C shifts have been applied to *Z*/*E* assignments in substituted ethylenes. (166) The importance of substituent stereochemistry in affecting shifts has been evidenced in steroids, (167) azoxybenzoles, (168) cyanoindanylidenes, (169) and additive rules have been proposed by Wollwage and Seib (170) to predict shifts of methylethers of 1,6-anhydroglucopyranoses.

III. CONFORMATIONAL AND CONFIGURATIONAL RATE PROCESSES

A. Introduction

It is well recognized that conformational and configurational rate processes are of prime importance to the successful application of contemporary research in the fields of stereo-, bio-, and organic chemistry. (171) For small molecules, the use of NMR to monitor conformational changes is reasonably well established. The number of small interesting systems in these areas has, however, undergone a significant decrease in recent years. For large molecules, and most of the current problems involve such species, the proton spectrum is usually complex, and this is due in part to the number and types of nuclei involved. A second complication frequently encountered in large systems involves the effects from overlapping processes. Simplification is usually possible by going to: (a) higher frequencies, (b) substitution of protons with deuterium, and (c) changing the physical parameters, i.e., temperature, solvent, and pH. In general, the methods apply to those systems with energies of activation ranging from about 8 to 25 Kcal/mole. This range corresponds to approximately $-150°$ to 200°C, and the limits are imposed by the available instrumentation, as well as the development of new and improved methods for handling materials at these extremes.

B. Theory

The theoretical aspects governing rate measurements by NMR date from the line shape function developed for the two-site exchange by Gutowsky and Holm (172) and the subject was adequately reviewed by Binsch (173) in a recent survey. Most investigators recognize that the matching of experimental and theoretical line shapes (the TLS method) is best accomplished by the use of computers. However, most investigators *do not* use this TLS method, but rather, one of the more simple approximations. The reasons vary and include simplicity, time, money, and the use of resulting data.

Some of the approximations such as,

$$k_{A \to B} = \frac{\pi}{\sqrt{2}} \Delta\nu_{AB}$$

obtained at the coalescence of two singlets, A ⇌ B, of equal population, and

$$k_{A \to B} = \frac{\pi}{\sqrt{2}} [\Delta\nu_{AB}^2 + 4J^2]^{1/2}$$

which corresponds to the rate at the coalescence of an AB quartet, have been found to give reliable estimates of $\Delta F^{\ddagger}$, the free energy of activation, when certain precautions are taken. (174-177) One approximation method (177, 178) the use of $W_{1/2}$ the line width at half height to characterize the line shape, shows considerable promise. It appears to possess an accuracy that is not significantly lower than that obtained by the more elaborate total line shape analysis. Consequently, further discussion of the $W_{1/2}$ technique appears warranted. At this point, it is instructive to examine the behavior of the line shape function, A ⇌ B, in the two limiting cases, when the average lifetimes are long and short. In the first case, if τ is sufficiently large compared with the inverse of the separation $1/2\pi(\nu_A - \nu_B)$, the spectrum will consist of distinct broadened signals in the vicinity of the frequencies ν_A and ν_B, each with widths at one-half height of

$$W_{1/2} = \frac{1}{\pi T_2^{\circ}} + \frac{1}{2\pi\tau} \cdot \tag{10}$$

In the limit of rapid exchange, the spectrum will consist of a single broadened line centered on a mean frequency

$$\bar{\nu} = P_A \nu_A + P_B \nu_B$$

with a width given by

$$W_{1/2} = \frac{1}{\pi T_2^{\circ} - 1} + 4\pi P_A P_B (\nu_A - \nu_B)^2 . \tag{11}$$

Thus, in both extremes the line width is composed of two parts: one due to intrinsic line width, and the other to exchange broadening. Similar results would be obtained if T_2° were replaced by T_2^* throughout. The equation would then obtain the inhomogeneously broadened line widths in place of the natural line widths. Since the line widths can be extracted in the extremes, then it is not unreasonable to leave it out altogether and to compare experimental line widths, corrected for inhomogeneity and natural line widths, with widths computed from the simplified form of the Gutowsky-Holm (172) equation

$$(T_2^{\circ -1} = 0; P_A = P_B = \tfrac{1}{2}),$$

$$G_{(\nu)} = \frac{K\tau(\nu_A - \nu_B)^2}{[\frac{1}{2}(\nu_A + \nu_B) - \nu]^2 + 4\pi^2\tau^2(\nu_A - \nu)(\nu_B - \nu)^2} \qquad (12)$$

A family of curves based upon the above line shape function was generated whereby $W_{1/2}$ is plotted against τ, $k_{A \rightarrow B} = 1/2\tau$ (Fig. 3). Exchange rates obtained by the $W_{1/2}$ method were compared with those derived from a complete line shape analysis and the resulting thermodynamic parameters show good agreement. (177)

There was, however, at least one exception, notably, *N,N*-dimethyl formamide (DMF). For DMF the $W_{1/2}$ method yielded E_a values of 24·9 and 24·1 Kcal/mole at 60 and 100 MHz, respectively, and they do not agree with recent reports (179, 180) E_a = 20·5 Kcal/mole obtained by the total line shape (TLS) method. For neat *N,N*-dimethylacetamide (DMA) and for solutions of DMA in DMSO-d_6 application of the $W_{1/2}$ method yielded parameters E_a, $\Delta H^{\pm}$, and $\Delta S^{\pm}$, which are in excellent agreement with those obtained by the TLS method. In Table I are shown the thermodynamic parameters

TABLE I

Thermodynamic parameters for the exchange of methyl groups in neat *N,N*-dimethylcarbamoyl chloride (177)

$E_a{}^{a}$ Kcal/mole	$H^{\pm b}$ Kcal/mole	$S^{\pm b}$ Cal/deg mole	Method
16·9[c]	–	–	Total line shape
16·4[d]	15·8	–3·2	Total line shape
16·8[e]	16·2	–0·6	$W_{1/2}$ (line-width)
14·0[f]	–	–	Spin-echo

[a] From plot of ln k against $1/T$.

[b] From plot of ln k/T against $1/T$.

[c] Reference 181.

[d] Least squares analysis of data reported by Reference 181.

[e] Reference 177.

[f] Reference 182.

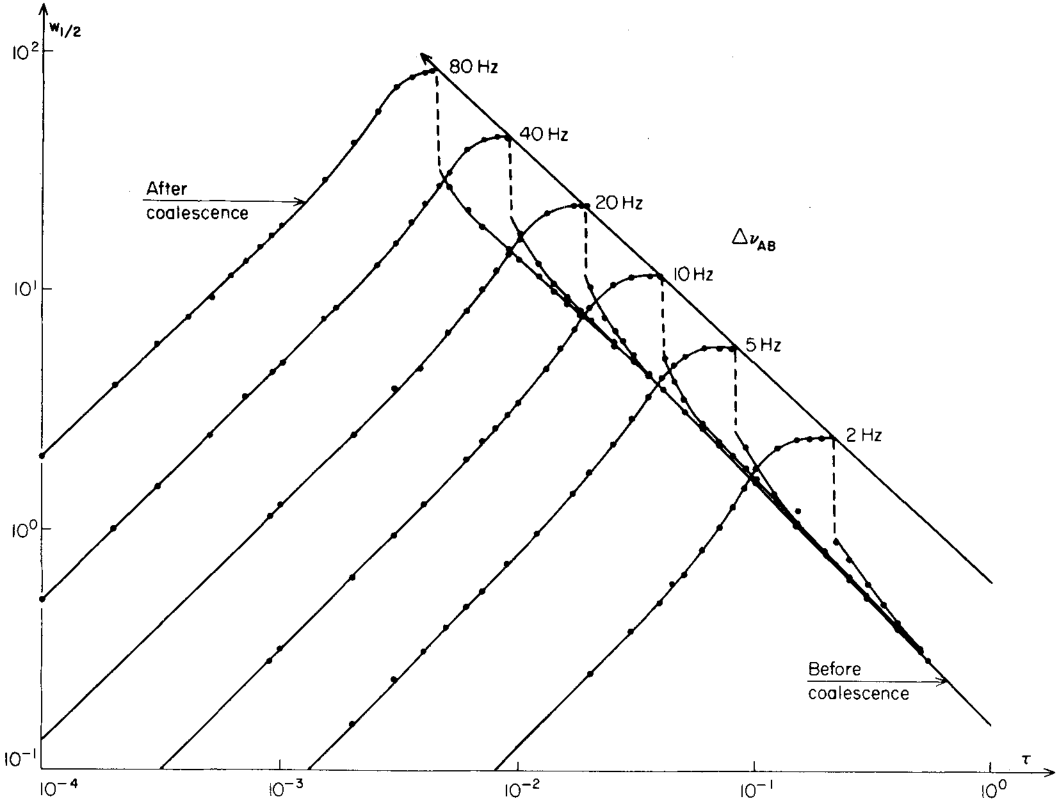

$w_{1/2}$
10^2
10^1
10^0
10^{-1}
After coalescence
80 Hz
40 Hz
20 Hz
10 Hz
5 Hz
2 Hz
$\Delta\nu_{AB}$
Before coalescence
τ
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^0

FIG. 3

for the exchange of methyl groups in *N,N*-dimethylcarbamoyl chloride (DMC). Again, the $W_{1/2}$ and TLS methods yield E_a values in good agreement with each other.

C. Calculation of Thermodynamic Parameters

In most cases only a single rate constant at the coalescence temperature has been determined, or better yet, estimated. This value is then converted to the free energy of activation $\Delta F^{\pm}$ or $\Delta G^{\pm}$ via the well-known Erying equation (183) and the agreement between laboratories is surprisingly good. (184)

$$k_r = \frac{k(k_B T)}{h} e^{-(\Delta F^{\pm}/RT)} \tag{13}$$

Most authors prefer to trust only $\Delta F^{\pm}$ values and this restriction appears warranted for a large fraction of the older data. Unfortunately, some of the more recent data also fall in this class, particularly those involving small $\Delta\nu$ values. This demonstrates the importance of using the highest possible magnetic field for systems with small frequency differences and low activation energies. Perhaps the most important factor contributing to uncertain thermodynamic parameters, so-called systematic errors, arises from neglect of line width changes over the temperature range covered. An associated problem involves the temperature range which should, of course, be as large as possible.

Current practice usually involves an Arrhenius plot, ln k_r against $1/T$ from which the activation energy E_a may be obtained from the

$$\ln k_r = \frac{-E_a}{RT} + \ln A \tag{14}$$

slope and the frequency factor from the intercept. The thermodynamic parameters, $\Delta H^{\pm}$ and $\Delta S^{\pm}$, enthalpy and entropy of activation, may be obtained directly from equation (15) which may be derived from equation (13) and $\Delta F^{\pm} = \Delta H^{\pm}\ T\Delta S^{\pm}$,

$$\ln (k_r/T) = \ln (k_B k/h) + \Delta S^{\pm}/R - \Delta H/RT. \tag{15}$$

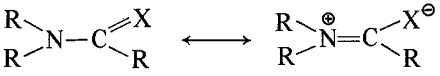
In general, plots of $\ln(k_r)/T$ versus $1/T$ are constructed and a least squares analysis of the data yield $\Delta H^{\pm}$ from the slope and $\Delta S^{\pm}$ from the intercept.

As a general rule the entropy of activation shows the highest sensitivity to systematic errors and as a consequence, most reported values should not necessarily be questioned but, nevertheless, treated with caution.

D. Hindered Rotation

1. *About the C–N bond*

(*a*) *Amides and thioamides.* Restricted rotation about the C–N bond in amides and thioamides are classic examples of the use of NMR to monitor rate processes. For these systems the barrier height, E_a, is principally due to the contribution of the partially double bonded form:

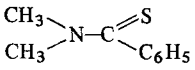
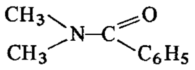
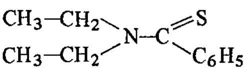
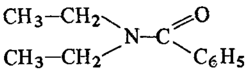


where X = O and S.

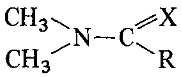
Many amides and thioamides have been investigated and some of the results are reported in Table II. Inspection of the Table leads to the conclusion that only a 2 to 4 Kcal/mole difference exists for the

TABLE II

Activation parameters for hindered internal rotation in some amides and thioamides

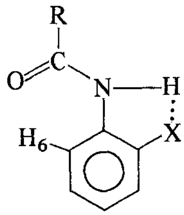
Compound		E_a Kcal/mole	$\Delta H^{\pm}$ Kcal/mole	$\Delta S^{\pm}$ (e.u.)	Method	Ref.
	[12]	19·6	18·9	−1·4	$W_{1/2}$	(177)
	[13]	17·5	16·9	4·9	$W_{1/2}$	(177)
	[14]	19·6	18·9	2·8	$W_{1/2}$	(177)
	[15]	15·6	15·1	4·1	$W_{1/2}$	(177)

barrier, E_a, of amides relative to thioamides. Secondly, and perhaps more significantly, it was suggested that this small difference may be explained on the basis of the larger size of the sulfur atom; thus, the assumption of a greater contribution of the polar form for thioamides is no longer necessary. Similar conclusions were drawn from a collection of previous reports on some amides and thioamides of general structure [11]. (185)



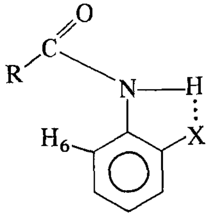
[11]

For X = O and R = CN, F, CH_3, Cl, C_6H_5, OCH_3, and SCH, $\Delta F^{\pm}$ (Kcal/mole) was reported to be: 21·4, 18·2, 17·4, 16·8, 14·8, 15·2, and 15·4. The corresponding values for X = S were also reported: 23·4, – 20·2, 19·1, 18·4, 17·8, and 15·7, respectively. Some of the other factors which contribute to the partial double bond are: steric, dipolar repulsions between π-systems and, in some cases, even hydrogen bonding plays an important role. Typical examples of the latter are anilines of general type [16] which show striking deshielding effects. The downfield shift of H_6 in [16A] is caused indirectly by intramolecular hydrogen bonding (186) between the amide proton and a suitable *ortho* hydrogen bond acceptor, to form either a five- or six-membered ring. This hydrogen bond forces the amide group to be coplaner with the benzene ring. If the acyl group R is large enough, it appears that the preferred configuration about the C–N bond will be the *Z* form. (187) Consequently, proton H_6 will be in a deshielding region of the carbonyl group which accounts for the observed shift. The NH proton resonance is also deshielded since it is involved in hydrogen bonding with the *ortho* substituent. The chemical shifts for the H_6 proton, the NH proton, and the acylation shift (defined as the chemical shift difference in going from an aniline to the corresponding anilide or thioanilide) were reported for 33 compounds. (186) The chemical shifts are quite large: for H_6 they range from about 8 to 9·5; for the NH they vary



Z form

[16A]

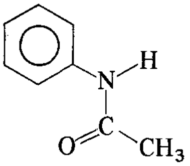


E form

[16B]

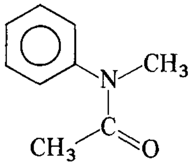
from 8 to 13, and the acetylation shifts extend from 1 to 3. It is interesting to note that the larger shifts are for the thioanilides, which may be taken as further evidence for the greater magnetic anisotropy of the thiocarbonyl group compared to the carbonyl group. (186)

(*b*) *N-Acetyl derivatives of five- and six-membered rings*. For most amides, the steric effects of the two nitrogen groups with each other and with the carbonyl and attached alkyl group determine the isomer populations *E* and *Z*. With acylanilides, however, a combination of steric and electronic factors must be considered. This point is well illustrated by the structures of acetanilide [17]. This amide exists almost completely in the sterically favored *Z* form, while *N*-methyl acetanilide [18] has the carbonyl group orthogonal to the benzene ring and is almost completely in the *E* form. For the latter, the dipolar interactions are at a minimum. In one interesting case compound [19] three isomers, 30 : 65 : 5, corresponding to *ZZ*, *EZ*, and *EE* were observed at ambient temperatures. (188) It is evident that steric factors would favor the *ZZ* form. The dipolar repulsions would be more favorable for the *EZ* form and the small π–π interactions would favor *EE*. The approximate free energy of activation was found to be 16·7 Kcal/moles and was based upon a



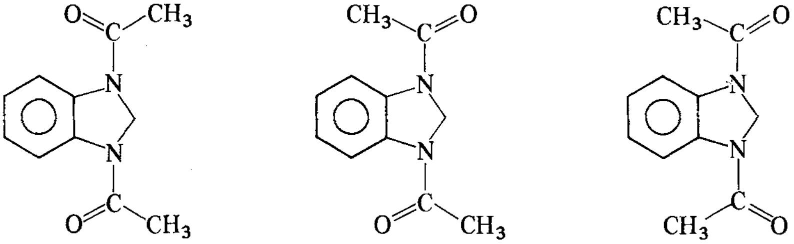
Z-form

[17]



E-form

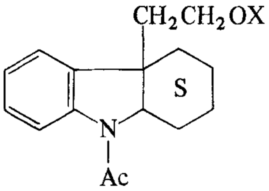
[18]



ZZ *EZ* *EE*

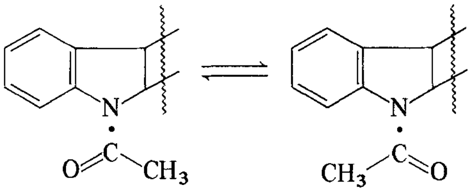
[19]

single rate constant corresponding to the coalescence temperature. (188) Similar results were reported for a series of hexahydrocarbazoles [20]. (189) In this case the investigation was concerned with the complex problem of distinguishing and differentiating configurational and conformational effects in multiple ring systems. They found that no distinction could be made between *cis* and *trans* fused isomers, since the temperature dependent spectra were associated with rotational isomerism of the *N*-acetyl group. It should be noted that the distinction is not always clear and considerable caution should be exercised in the assignment when overlapping processes are possible. An approximate free energy of activation, $\Delta F^{\pm}$, for the interconversion between rotamers [20A] and [20B]



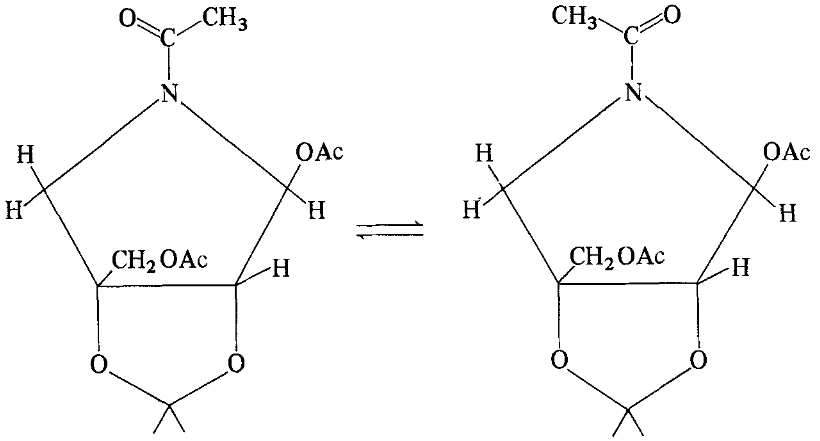
[20]

X = Ac
X = H
X = Ts



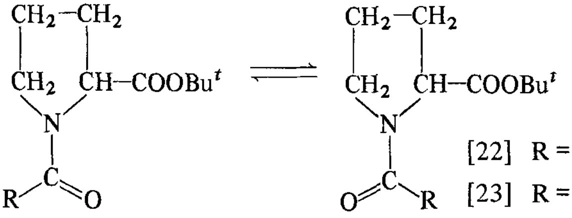
[20A] [20B]

was obtained by observing the C-8 doublet in the slow exchange limit. The latter yielded a value of 15 Kcal/mole in good agreement with the approximation 14 to 15 Kcal/mole obtained from the coalescence temperature. For a similar five-membered ring compound [21] the activation parameters, $E_a = 18{\cdot}8$ Kcal/mole, $\Delta H^{\pm} = 18{\cdot}1$ Kcal/mole, and $\Delta S^{\pm} = 0{\cdot}9$ e.u., were derived from a combination of the TLS and direct thermal equilibration methods for [21A] $\rightleftharpoons$ [21B]. (190) Maia *et al.* (191) reported on a study of the biologically important proline derivatives. For compounds [22] and [23] the *t*-butyl ester group serves as a convenient handle for following the interconversion, A $\rightleftharpoons$ B, and line-widths, peak to valley ratios, and chemical shift differences were utilized in the matching of computed and experimental line shapes. For compound [22] $\Delta F^{\pm}$, $\Delta H^{\pm}$, and $\Delta S^{\pm}$ were found to be 17·3 and 15·9 Kcal/mole, and −4·8 e.u., respectively. The corresponding values for compound [23] were 19·2 and 21·0 Kcal/mole, and 6·1 e.u. Surprisingly, these values suggest that the energy barrier for interconversion of rotamers of the urethan [22] is approximately 5 Kcal/mole less than that for the peptide



[21A] [21B]

[23]. This in turn implies, as reported, that the contribution of the charge separated structure $N^{\oplus}=CRO^{\ominus}$ is less in the urethan than in the peptide. However, the difference in entropy values, approximately 10 e.u., gives rise to questions concerning the accuracy of the $\Delta H^{\pm}$ values.

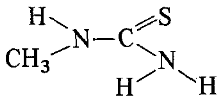


[A] [B]

[22] R = PhCH$_2$O–

[23] R = PhCH$_2$OCONHCH(CH$_2$OBu^t)–

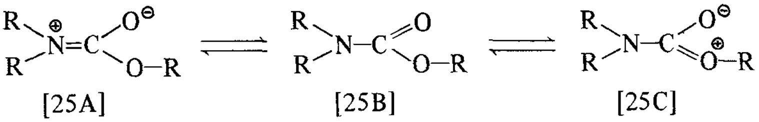
(*c*) *Urea and thiourea.* In general, it appears that rotational barriers around the C–N bonds in alkyl-substituted ureas and thioureas are considerably lower than in comparable simple amides. In one report (192) a TLS study of hindered rotation about the $CH_3NH\nmid CS$ bond of [24] yielded an E_a value of 15·7 Kcal/mole while a strikingly smaller value of 10·2 Kcal/mole was estimated for



[24]

$\Delta F^{\pm}$ from the coalescence temperature for the CS$\nleftarrow$NH$_2$ rotation of [24]. (192) The latter value, although small, is reasonable and similar to those obtained from a TLS study of urea. (193) These systems are, however, difficult to study since they are only soluble in highly polar solvents. Consequently, it is not easy to separate out the hydrogen bonding effects. For the urea study, (193) two solvent systems were used, DMF-DMSO (dimethylformamide and dimethylsulfoxide) and acetone-TMU (tetramethylurea), and the resulting range of $\Delta F^{\pm}$ values was surprisingly small, $\Delta F^{\pm} = 11{\cdot}3 \pm 0{\cdot}5$ Kcal/moles.

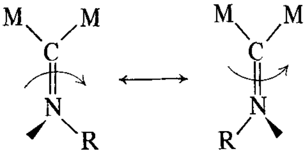
(*d*) *Carbonates.* In contrast with amides, hindered rotation in carbonates has been investigated to a small extent only and some of these reports are contradictory. It has been demonstrated (194) that the barriers to rotation about the C–N bond in carbonates is slightly lower, $E_a = 15{\cdot}5$ Kcal/mole, $\Delta H^{\pm} = 14{\cdot}9$ Kcal/mole and $\Delta S^{\pm} = -3{\cdot}2$ e.u., than that reported for the corresponding amides, and this difference has been attributed to cross-conjugation (194) [25A] ↔ [25B] ↔ [25C].


[25A] [25B] [25C]

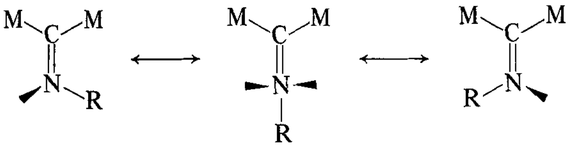
As expected, the technique does not apply to all systems. For example, the *syn* and *unsyn* *N*,*N*-dialkyldithiocarbonates (195) exhibit no splitting of the *N*-alkyl resonances and this was attributed to an extremely small difference in magnetic environments of the groups within the rotamers.

2. *Rotation and inversion about the C=N bond*

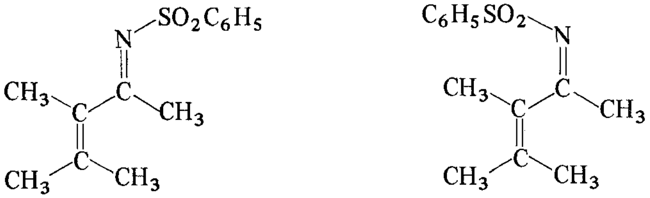
(*a*) *Imines.* There are in principle two possibilities for the isomerization in imines. The first is *rotation* in which the substituent R describes a circle about the axis of the C–N bond. In the second



process, *inversion* or *lateral shift*, the N–R bond swings into the plane of the imine system, i.e., a progressive increase in θ, the CNR



angle, from *ca.* 120° to 180° in the transition state. Numerous reports have been presented supporting both mechanisms. Some of the more pertinent arguments supporting inversion are: (a) the relatively low barrier in imines as compared with normal olefins, and (b) the effects of solvent which appear to be quite small. On the other hand, the torsion mechanism is supported by the effects of heteroatoms which lowers the barrier when attached to the imino carbon atom. Recently (196) an intermediate mechanism encompassing both rotation and inversion was reported for [26]. The process was studied by the TLS, as well as an equilibration method.



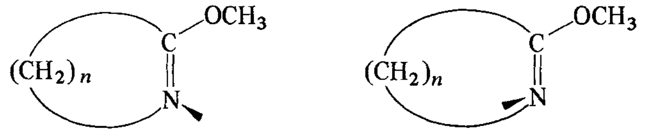
[26]

Surprisingly, the values differ greatly suggesting that inherent or systematic errors are involved in at least one, or possibly both, methods and the former is suspect. From the TLS study a value of E_a = 19·4 Kcal/mole was obtained while a much smaller value of 16·2 Kcal/mole was reported from a combination of the TLS and equilibration methods. The combination of both methods significantly extends the temperature range covered and therein probably lies the source of error in the former. These results also suggest that investigators should utilize, whenever possible, the complete temperature range in which the line shapes are affected by the exchange process.

The order of thermodynamic parameters for inversion may be derived from the aziridines in which only inversion is possible. (197) For *N*-phenylaziridine, a value of $\Delta F^{\pm}$ = 11·7 Kcal/mole was reported. (197) For most imines the values appear to be somewhat larger, which may be interpreted as supporting a mechanism with considerable torsional character.

The large E_a values reported for a series of *O*-methyl imidates

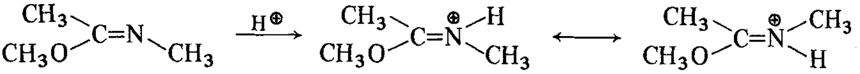
(198) and *S*-methyl thioimidates (199) also support the torsional mechanism on the same basis. For the cyclic *O*-methyl imidates two forms of compounds [27], *anti*(*Z*) and *syn*(*E*), were suggested on the basis of the chemical shift data. However, the *O*-methyl resonance appeared as a sharp singlet throughout the range −100° to 120°, which is indicative of either a low or high barrier. The latter was preferred as based upon a study of their conjugated acids [28]. At room temperature in 100% H_2SO_4 [28] is converted completely to the protonated form; $J(NH\text{-}CH_3) = 5$ Hz. Heating at 80° caused a gradual doubling of the OCH_3, CCH_3 and each of the spin coupled



$n = 2\text{-}8$ $n = 9\text{-}13$

syn or *E* form *anti* or *Z* form

[27]



[28A] [28B]

TABLE III

Activation parameters for cyclic and linear *S*-methyl imidates (199)

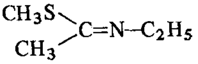
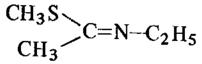
Compound and/or ring size		Isomer ratio				
		Z	*E*	E_a(Kcal/mole)	$\Delta H^{\pm}$(Kcal/mole)	$\Delta S^{\pm}$ e.u.
7	[29]	0	100	–	–	–
9	[30]	0	100	–	–	–
10	[31]	10	90	–	–	–
11	[32]	80	20	18·6	17·9	−2·6
12	[33]	75	25	21·9	21·2	3·8
13	[34]	75	25	19·7	19·0	0·3
16	[35]	50	50	22·4	21·7	3·6
 $(CH_3S)(CH_3)C{=}N{-}C_2H_5$	[36]	50	50	20·2	19·4	−2·2

TABLE IV

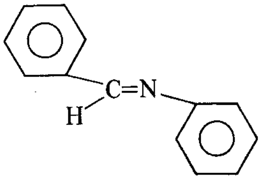
Chemical shifts for proton absorption in cyclic and linear *S*-methyl imidates and their conjugate acids (199)

Ring size	ppm SCH_3		$C = NCH_2$	$N = CCH_2$	Diastereomer ratio (%)		Diastereomer ratio for conjugate acid	
	E	*Z*			*E*	*Z*	*E*	*Z*
7	2·16	–	3·58	2·40	100	–	100	–
9	2·18	–	3·63	2·37	100	–	100	–
10	2·15	2·35	3·60	2·48	90	10	90	10
11	2·21	2·38	3·45	2·45	80	20	80	20
12	2·17	2·38	3·44	2·48	25	75	30	70
13	2·20	2·38	3·43	2·47	25	75	35	70
16	2·20	2·40	3·36	2·50	50	50	50	50

Compound	ppm SCH_3		$C{=}NCH_2$		$N{=}CCH_3$		Diastereomer ratio (%)		Diastereomer ratio for conjugate acid	
	E	*Z*					*E*	*Z*	*E*	*Z*
 $(CH_3S)(CH_3)C{=}N{-}C_2H_5$	2·22	2·40	3·30	3·42	2·27	2·49	60	40	45	55

$NHCH_3$ resonances. While the *Z* diastereomer is the exclusive form for [28], the ratio of A : B at equilibrium is 1 : 2. The preference for the *Z* configuration was attributed to the interorbital electron repulsion in the *E* form between the nonbonding electrons upon the oxygen atom and the lone pair on nitrogen localized in an sp^2 orbital. The cyclic *S*-methyl thioimidates are strikingly different from the cyclic *O*-methyl imidates. For the former, interconverting diastereomers were observed at room temperature and some of the activation parameters and chemical shifts are shown in Tables III and IV.

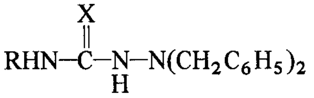
A chemical shift study of benzalaniline [37] and derivatives thereof suggest rapid rotation of the phenyl rings about the C–C and C–N bonds at room temperature. (200) An average dihedral angle of 45° between the H–C=N and ring planes was suggested. This value is consistent with the chemical and physical properties, but contrary to the traditionally accepted view.



[37]

3. Rotation about the N–N bond

(*a*) *Thiosemicarbazides.* Previous data have suggested that the barrier to inversion is somewhat less than that for the corresponding rotational barrier. For example, Dewar and Jennings (201) observed two AB systems for the methylene protons of $R_2\ N{-}N\ (CH_2C_6H_5)_2$ [38] at low temperatures indicating that both inversion and rotation was slow on the NMR time scale. The temperature dependence of the spectra was interpreted in terms of an inversion barrier of approximately 8 Kcal/mole and that the rotational barrier was larger, although an absolute value was not determined. Recently, Svanholm (202) reported the thermodynamic parameters for a series of compounds ([39]–[41] A–E), and some of these are listed in Table V.



$$RHN-\overset{\overset{X}{\|}}{C}-\underset{H}{N}-N(CH_2C_6H_5)_2$$

R = Me Et Bz Pr^i Bu^t

[A] [B] [C] [D] [E]

[39] X = O [40] X = S [41] X = Se

TABLE V

Energy barriers for compounds 39–41 and spectral parameters[a] without exchange of the non-equivalent protons (202)

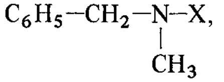
Compound	$\Delta\nu_{AB}$ Hz	J_{AB} Hz	E_a Kcal/mole	$\Delta H^{\pm}$ Kcal/mole	$\Delta S^{\pm}$(e.u.)
[39A]	7·7	12·9	16·5	15·9	−4·7
[39B]	9·6	12·6	15·7	15·1	−7·2
[39C]	9·3	12·8	17·6	14·6	−9·3
[39D]	10·1	12·5	19·1	18·5	−2·2
[39E]	11·9	12·4	19·1	18·5	0·9
[40E]	13·1	12·8	12·9	12·3	−8·3
[41E]	10·0	12·6	18·9	18·3	−0·9

[a] 60 MHz.

The values are of the same order of magnitude as those found for *N,N′*-dibenzylhydrazine, (203) and accordingly they were assigned to hindered rotation about the N–N bond.

4. *Inversion about the C–N bond*

(*a*) *Amines.* For hydroxylamine derivatives of type


$$C_6H_5{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{N}}{-}X,$$

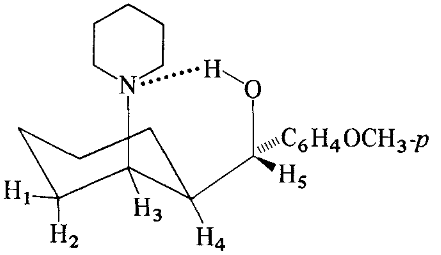
where X = −OH [42] and −OCH$_3$ [43], there has been some controversy on the nature of the equilibrating process. Non-equivalence of the benzyl CH$_2$ protons may arise from restricted rotation about the N–O bond or from restricted pyramidal inversion at nitrogen. E_a values (204) of 13·5 and 8·3 Kcal/mole were reported for the equilibrating process in compounds [42] and [43]. (204) A third compound X = Cl [44] was included which exhibited a non-equivalent quartet for the benzyl CH$_2$ protons. Nitrogen inversion is, of course, responsible for the non-equivalence and an E_a value of 11·8 Kcal/mole was obtained from the TLS method. This value, in turn, suggests that a similar mechanism is reponsible for the equilibrating process for [42] and [43].

E. Ring Inversion Processes

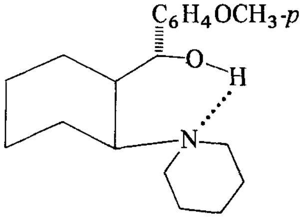
1. *Cyclohexane derivatives*

Conformations of the cyclohexane ring, other than the chair form are quite rare, and this principle is exemplified by the results of a

NMR study of the *cis* isomers of 2-piperidino-α-(*p*-methoxyphenyl)-cyclohexanemethanol. (205) For the *cis*-isomer with a *threo* configuration of the side chain with respect to the adjacent carbon, the conformation of the cyclohexane ring may be either a chair with an axial piperidine [45A] or a twist-boat with piperidine pseudo-equatorial [45B],



[45A]



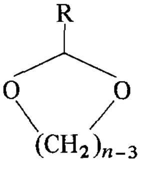
[45B]

These fixed conformations were derived from chemical shift data which suggested strong intramolecular hydrogen bonding. The four remaining hydrogens on the cyclohexane ring and the side-chain carbinol hydrogen of selectively deuterated samples of the two *cis*-isomers exhibit relatively simple resonance patterns which were analyzed in terms of the chemical shifts and coupling constants. These parameters appear to be consistent with the chair form for both isomers. For the isomer with an axial piperidino group, it is suggested that the chair is somewhat distorted as a result of steric interactions.

Ring inversion of a novel monosubstituted cyclohexane *via* a paramagnetic lanthanide ion in the substituent, tris cyclopentadienyl (cyclohexyl isocyanide)-praseodymium(III) [46], yielded from the coalescence temperature a $\Delta F^{\pm}$ value of 282 ± 16 cal/mole. (206) The influence of the large substituent and the relationship of $\Delta F^{\pm}$ to the normal inversion process is, however, not well defined. It seems reasonable to assume that the large praseodymium atom will change the thermodynamic parameters, since the electronic effects have altered the ring proton chemical shifts and the latter is a spatiotomporal effect. This assumption is, however, qualitative in nature since the effects have not been studied in detail.

2. *1,3-Dioxanes and dioxepans*

Similar to cyclohexane, conformations of the 1,3-dioxane ring other than the chair form are quite rare, although the chair-boat energy difference is approximately 3 Kcal/mole for the latter as opposed to about 6 Kcal/mole for cyclohexane. In one report the conformational equilibria in some cyclic acetals was determined which yielded:

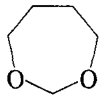


[47] R = Et
[48] R = Me
$n = 6$

[49] R = Et
[50] R = *i*-Pr
$n = 5$

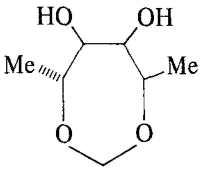
information on the important skew interactions between alkyl groups and oxygen atoms in the absence of double bonds. These values, in turn, led the authors (207) to speculate on the essential structural factors which determine the conformational preferences in simple aldehydes and ketones. (207) They suggested that the major conformational feature concerns the double bond and not the dipole-dipole interactions of the electronegative oxygen atoms.

The conformational properties of 1,3-dioxepan [51] are expected to be similar to those of cycloheptane. (208) For the latter,



[51]

calculations (209) suggest four similar low-energy conformations, twist-chair (TC), chair (C), twist-boat (TB) and boat (B) in order of increasing energies. Stoddart and Szanek (210) reported that the vicinal coupling constants involving C-2, C-3, C-4 and C-5 of 1,6-dideoxy-2,5-*O*-methylene-D-mannitol [52] suggest that the predominant contributors to the conformational equilibrium are three

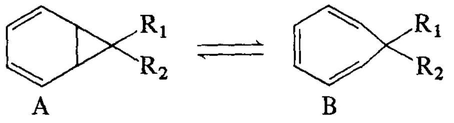


[52]

TC types, one having a C_2 axis of symmetry and two degenerate conformations.

3. Valence tautemerism

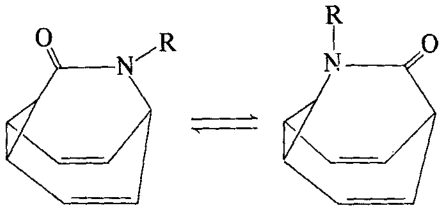
Hall and Roberts (210) reported on an in-depth study of the electrical effects of substituents on the thermodynamic parameter of the equilibrium [53A] ⇌ [53B], [54A] ⇌ [54B], and [55A] ⇌ [55B].



[53] $R_1 = C_6H_5; R_2 = COOCH_3$
[54] $R_1 = p\text{-}C_6H_4NO_2; R_2 = COOCH_3$
[55] $R_1 = p\text{-}C_6H_4OCH_3; R_2 = COOCH_3$

Only time-averaged spectra of the rapidly equilibrating mixtures were accessible, which tends to restrict the accuracy of the parameters. $\Delta H^{\pm}$ and $\Delta S^{\pm}$ for the conversion of [53], [54] and [55] norcaradine [A] to the corresponding cycloheptatriene [B] were found to be 5·4, 3·5 and 2·3 Kcal/mole, and 17, 11 and 7 e.u., respectively. The authors (210) suggested that the effect of the nitro and methoxy groups in lowering the enthalpy of cycloheptatriene relative to norcaradiene is that both increase the polarity of the phenyl substituent and this, in turn, induces a polarity in the carbomethoxy group. This attraction would be expected to decrease the bond angle between them and thus favor norcaradiene as previously proposed by Ciganck. (211)

Considerable interest has been aroused in equilibria of bridged homotropilidenes and we have used both spin decoupling and shift reagent in a study of substituent effects. (212) These techniques indicate that [56] exists predominately in the [A] form. Furthermore, it appears that [A] is several Kcal/mole more stable than

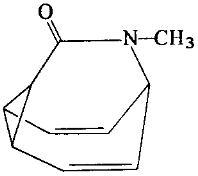
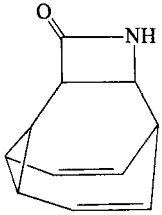
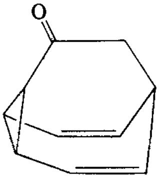
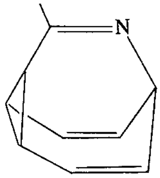


[56A] [56B]

tautomer [B] since the spectrum was invariant with temperature from −70 to +140°C. Similar results were reported for a series of bridged homotropilidenes as depicted in Table VI.

TABLE VI

Position of equilibria[a] of some bridged homotropilidenes

	Favored tautomer	%	$\Delta F^{\pm}$ Kcal/mole	Ref.
[56]		$>94^b$(140°)	$>3{\cdot}7$	(212)
[57]		64 (45°)	0·36	(213)
[58]		90	≈ 2	(214)
[59]		90	$\approx 1{\cdot}8$	(215)

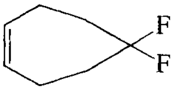
[a] Determined by NMR.

[b] Minimum estimate, no minor isomer was detected.

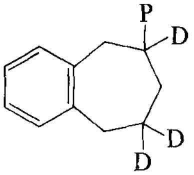
4. Ring inversion in substituted cyclo- heptenes and octenes

In general, the thermodynamic parameters determined for equilibrations that take place at extremely low temperatures, i.e., −150°C or lower, are considerably less reliable than those reported for higher temperature processes. Most of the large ring inversions appear to fall in this category, e.g., a $\Delta F^{\pm}$ value of 7·4 Kcal/mole was reported for

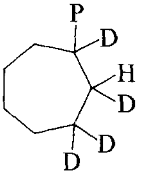
5,5-difluorocycloheptene [60], 10·9 Kcal/mole for 4,4,6,6-tetradeuteriobenzocycloheptene [61] and 5·0 Kcal/mole for 4,4,5,6-6-pentadeuteriocycloheptene [61]. (216)



[60]

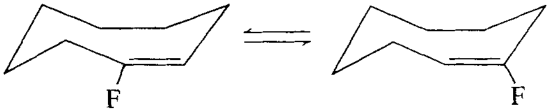


[61]



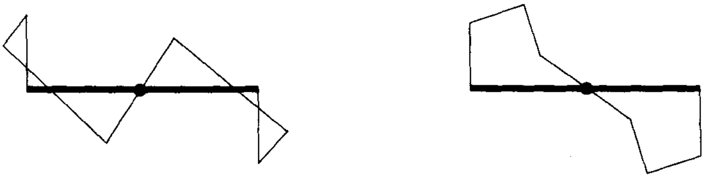
[62]

Similar results were also reported for 1-fluorocyclooctene [63]. (217) A process with a free energy of activation of 6·1 Kcal/mole was reported for the interconversion of the two conformations [63A] ⇌ [63B]. However, it is highly improbable that the large chemical shift difference between the fluorine in the two environments 16·7 ppm can be explained in terms of this process. Consequently, a second low energy equilibration, possibly pseudorotation, is suggested.



[63A] [65B]

Anet and Wagner (218) reported on cyclomonane [64] which shows both ^{1}H and ^{13}C temperature dependent spectra. Their results



TBC (D_3)

TCB (C_2)

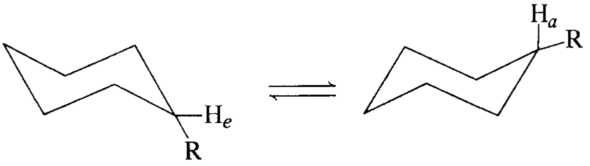
[64]

lend support to the twist-boat-chair (TBC) conformation, D_3 symmetry, in contrast to earlier X-ray studies (219, 220) on somewhat similar compounds which suggest C_2 symmetry, a twist-chair-boat (TCB) conformation. A conformational process involving conversion of the TBC into a boat-chair (BC) and back into a different TBC form was suggested and a free-energy barrier of about 6 Kcal/mole was reported.

F. Conformational Preference of Ring Substituents

1. *Cyclohexane derivatives*

NMR methods for determining conformational preference and the equilibrium constant are well established. (221) For mono-substituted cyclohexanes the band width method ($\frac{1}{4}$-intensity width of the α-proton resonance) is quite popular and gives reliable information on the position of the equilibrium ($[A] \rightleftharpoons [B]$).



[65A] [65B]

It appears that this method was first suggested by Eliel (222) and further developed by Franklin and Feltkamp, (223) among others. It has the advantage of yielding not only populations of conformers, and these are usually obtained at low temperatures where the chair-chair interconversion is retarded to the extent that separate resonance for the form are observable, but also an assignment of the resonances to equatorial or axial protons. The equatorial proton should give rise to a band width approximately equal to a $2J_{ea} + 2J_{ee}$ while the axial proton resonance should have a width corresponding to $2J_{aa} + 2J_{ae}$.

Since J_{aa} is roughly 3 to 4 times as large as the other vicinal couplings which are approximately equal, the axial proton resonance is readily differentiated from the equatorial. Furthermore, the equatorial proton resonance (A) invariably falls at a lower field than the corresponding axial α-proton (B).

The equilibrium constant at any given temperature may, in principle, be calculated from the mole fractions of the two conformations p and $(1 - p)$, where

$$k_r = \frac{p}{(1-p)} e^{-\Delta F^{\pm}/RT}. \tag{16}$$

$\Delta F^{\pm}$ is the free energy difference between the two conformations at temperature T.

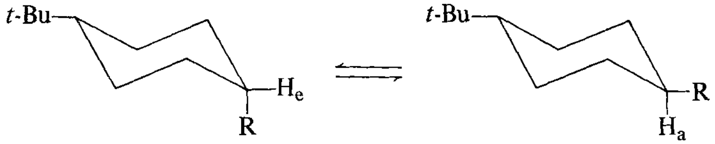
The most serious restriction concerns overlap of the α-proton resonances which negates accurate measurements of the conformers. In general, it appears that the separation of axial and equatorial resonances depends primarily upon the electronegativity of the R substituent. The problem may be surmounted by the use of partially deuterated derivatives, but the cost may be prohibitive in certain cases.

For fast interchange of the two chair conformations A and B, the α-proton resonance will appear at an average position τ which is related to the isomer concentrations p and $(1-p)$ and the chemical shifts τ_a and τ_e by equation (17) and to the rate constant kr by equation (18).

$$\tau = p\tau_a + (1-p)\,\tau_e \tag{17}$$

$$kr = \frac{p}{(1-p)} = \frac{\tau - \tau_e}{\tau_a - \tau}\,. \tag{18}$$

τ_e and τ_a are the chemical shifts of the equatorial and axial α proton resonances in the absence of exchange and these values must be obtained from low-temperature spectra. A second method, although an approximation, involves the 4-*t*-butyl compounds [A′] and [B′],



[A′] [B′]

This method has the advantage of utilizing room temperature spectra, but it has the disadvantage of assuming that the *t*-butyl group has no effect upon the α-proton chemical shifts H_e and H_a, which is not necessarily true. Nevertheless, the method has been used frequently and the results appear reasonable.

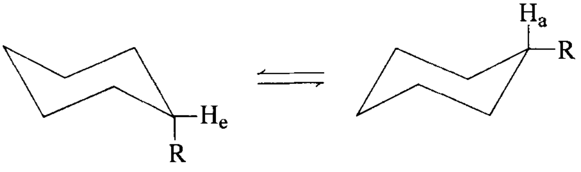
Numerous other methods of approximating the rate constants for interconversion exist and most of these were discussed in detail by Booth. (221) The band width method of the α-proton resonances is probably the most popular technique for estimating the rate constants. The equations are quite similar to those for the chemical shift method previously discussed. W the average width is related to p, W_a and W_e by

$$W = pW_a + (1-p)W_e \tag{19}$$

and to the rate constant by

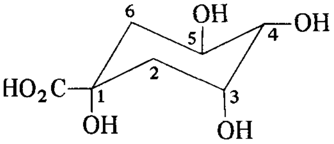
$$kr = \frac{p}{1-p} = \frac{W - W_e}{W_a - W}. \tag{20}$$

W_e is the band width of H_e in [A″] and W_a corresponds to the band width of H_a in [B″]. Similar to the chemical shift method, the 4-*t*-butyl compounds are used to obtain W_a and W_e. The limitation also goes along with the W_a and W_e approximations, but apparently the influence of the 4-*t*-butyl group upon the widths of the α-proton resonances is small relative to the other errors involved and thus reasonably accurate values of $\Delta F^{\pm}$ are obtained.

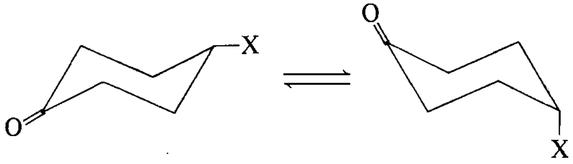


[A″] [B″]

Interesting examples of the more recent methods involve (—)-quinic acid [66] and 4-methoxycyclohexanone [67]. Haslam and Turner (224) used the coupling constant to reverse an older assignment which was based on chemical evidence; namely, that the acid readily forms a α-lactone, quinide. (225) They reported a complete first order analysis (224) of [66] and this includes the methylene protons at positions 2 and 6.



[66]



[e] [a]

[67]

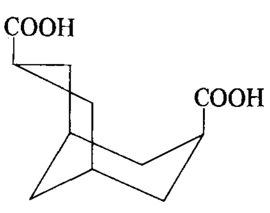
The band width method was used to study [67] and again the data suggests that an older assignment, which was based on dipole moments, was incorrect. (226) Cyclohexanone [68] and methylcyclohexane [69] were used as model compounds for the dipole moment study of [67] and an axial : equatorial (a : e) ratio of 36 : 64 was reported for a benzene solution at 31°. (227) However, this ratio was not consistent with those for a similar compound, 4-hydroxy cyclohexanone, [70] which yielded a 56 : 44 ratio of axial to equatorial isomers. (228) The results for a number of 4-substituted cyclohexanones are collected in Table VII, and they show a predominance of the axial conformation in all cases.

TABLE VII

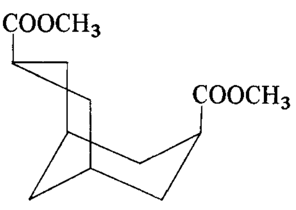
NMR band width data for some 4-substituted cyclohexanes at 30°C

Compound	Solvent	*W*(Hz)	% axial	$\Delta F^{\ddagger}$/Kcal/m	Ref.
(2,2,6,6-d_4)-4-Methoxycyclohexanone [67]	C_6H_6	16·5	73	−0·6	(226)
(2,2,6,6-d_4)-4-Hydroxycyclohexanone [70]	C_6H_6	19·7	56	−0·15	(229)
(2,2,6,6-d_4)-4-Chlorocyclohexanone [71]	$CFCl_3$	18·45	65	−0·38	(226)
	CCl_4	18·05	67	−0·42	(230)
Chlorocyclohexanone [72]	CCl_4	17·5	69	−0·5	(231)
Bromocyclohexanone [73]	C_6H_6	20	54	−0·1	(232)
Iodocyclohexanone [74]	C_6H_6	21	55	−0·1	(232)

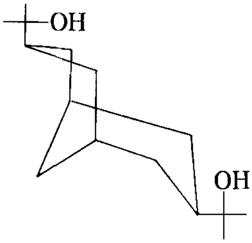
A number of interesting studies involving di- and tri-substituted compounds as well as bicyclo systems were reported. (233-236) Of particular interest are the reported non-chair conformations of some 3α,7α-disubstituted bicyclo[3.3.1]nonanes [75], [76] and [77].



[75]

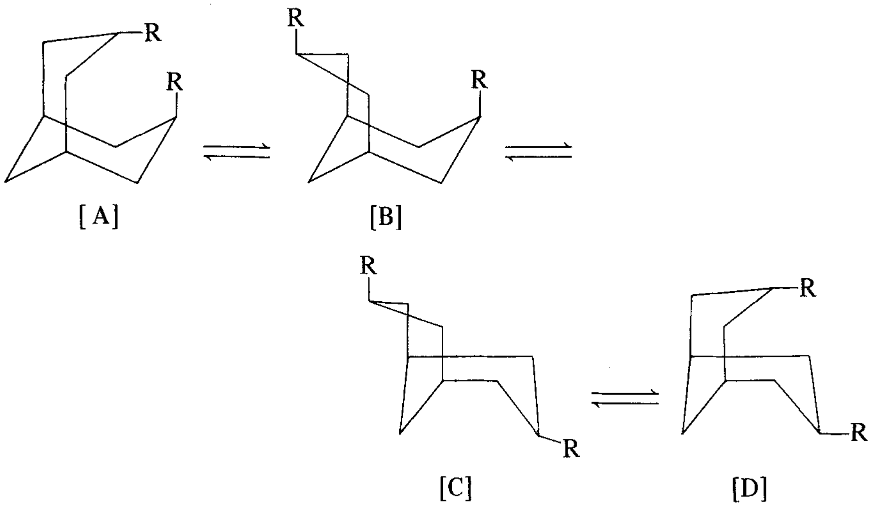


[76]



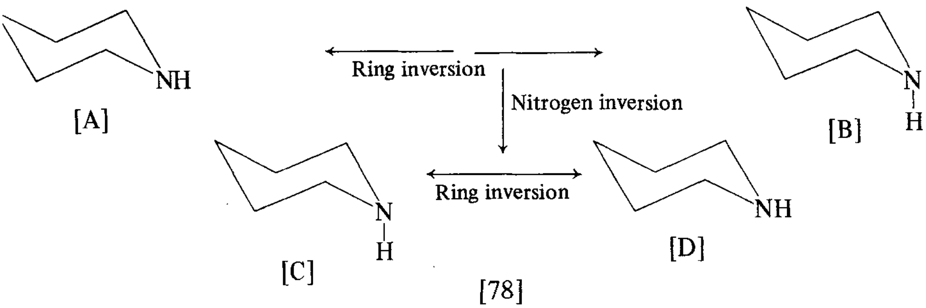
[77]

The possible conformations are [A] through [D], although the large R groups would tend to rule out [A] on steric considerations alone. They found that in all three cases [75], [76] and [77], the spectra were too complex to analyze at 100 MHz and, consequently, Eu $(DPM)_3$ was added until separation between the various multiplets was achieved. The resulting parameter, particularly the splitting patterns of the 2α-, 4α-, 6α and 8α proton resonances, suggest that [C] is the predominant conformation for [77], while [75] and [76] exist as equilibrium mixtures with isomer [D] having significant populations.



2. *Saturated heterocycles containing nitrogen*

Piperidine [78] the simplest six-membered ring containing nitrogen has been subjected to a host of analytical tests, including X-ray (237) IR (238) and microwave spectroscopy (239) and by dipole moments (240) as well as NMR. (241, 242, 243) Collectively these techniques suggest that piperidine exists as a mixture of chair conformations [A] and [D] which are interconvertible by the processes depicted below.

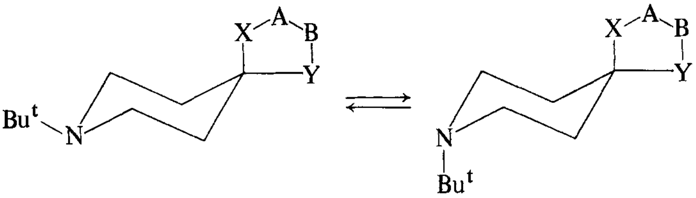


[78]

There has been a lack of uniformity in the NMR interpretation of substituted piperidines, i.e., Lambert and Keske (241) observed that the chemical shift *Δae* for the 2-methylene groups for some substituted piperidines decreased in the series $Bu^t > Me \gg H$, and thus were led to an improbable conclusion that the predominant conformation of piperidine has the NH-group axial. A more detailed study by Halls *et al.*, (243) suggested that, whereas the *Δde* values can be a useful qualitative indication of the orientation of lone pairs, no simple quantitative correlation exists between these quantities.

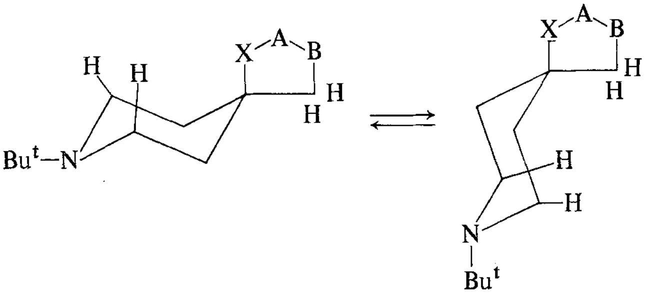
Jones and co-workers (244, 245, 246) reported on an in-depth study of standard interactions which attempts to apportion strain energies among various intramolecular interactions of defined shape. They (244) note and stress the importance of measuring the difference between two well-defined interactions.

Spiro-compounds [79] in which two groups X and Y are connected yield certain advantages.



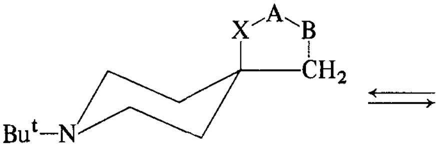
[79A] [79B]

The three-, four-, and five-membered spiro-rings would tend to hold the X and Y groups at a known orientation and distance from the probe of the 1,3-axial interactions. Secondly, in addition to low-temperature NMR spectroscopy, dipole moments may be utilized to determine the equilibrium position. The NMR assignments concern the relative shifts of CH_2-groups in environments [80A] and [80B]



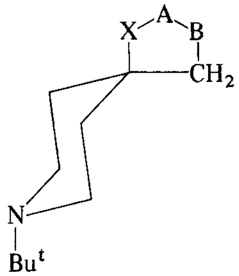
[80A] [80B]

and the authors conclude that the axial CH_2-group occurs at a lower field than the corresponding equatorial group. It should be noted that this assignment is the reverse of the general rule for cyclohexane rings where the axial protons tend to fall at higher yield strengths than equatorial. For [81] both NMR and dipole moment studies suggest that the equilibrium favors [81A], with a free energy difference between conformers of +0·40 Kcal/mole. Similar results were also obtained for [82] and [83]. The preference of conformation [84B] is somewhat surprising since the authors reported



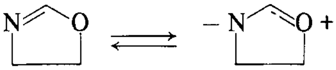
[81A]

[81] (X—A—B = O—CPh=N)
[82] (X—A—B = O—CH$_2$—O)
[83] (X—A—B = O—CMe$_2$—NH)
[84] (X—A—B = N=CPh—O)



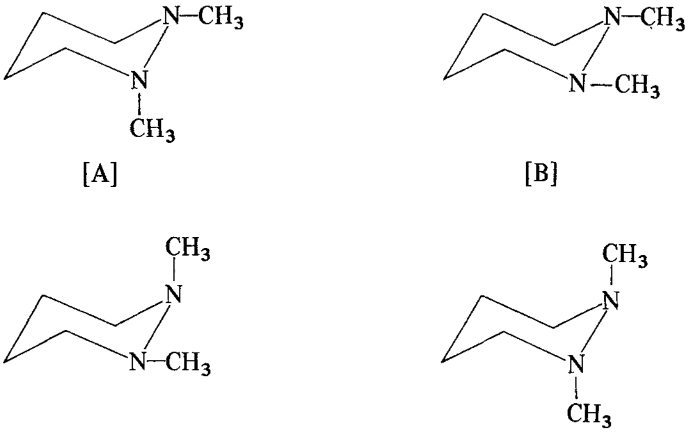
[81B]

that an *sp*^{2} hybridized nitrogen atom has relatively small steric requirements. They suggest, as a possible explanation, a significant contribution from canonical form [85B].



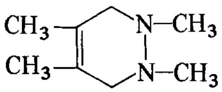
[85A] [85B]

Jones *et al.*, (247, 248) also reported on a number of substituted pyridizines. They used both low temperature NMR and dipole moment data to reverse an older assignment (249) which was based on NMR. For 1,2-dimethylhexahydropyridizine [86] 17, 30, 17 and 36% were reported for conformations A, B, C and D, respectively, whereas the older report had favored the diequatorial conformer [B]. Furthermore, the NMR data for tetramethyltetrahydropyridine [87] were reinterpreted with respect to the populations of conformational isomers, as well as process. Anderson (249) had suggested nitrogen inversion (barrier 12·3 Kcal/mole) as the process responsible for the AB quartet for the methylene protons at −44°. This value is, however, probably more consistent with a rotational barrier as based on previous reports of tetra-substituted hydrazines, e.g., 8 Kcal/mole



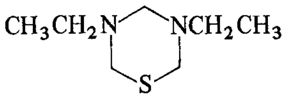
[A] [B] [C] [D]

[86]



[87]

for an inversion barrier and 11 Kcal/mole for a rotational barrier. (250, 251) Similar results were also reported for 3,5-diethyltetrahydro-1,3,5-thiadiazine [88]. At −70° the ring protons of [88] appear as two overlapping AB quartets, the methyl protons remain a simple triplet (suggesting that nitrogen inversion is still fast on the NMR time scale), and the methylene protons of the ethyl groups



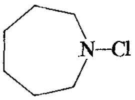
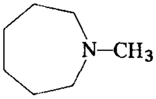
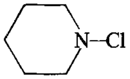
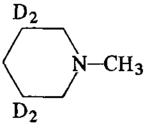
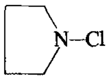
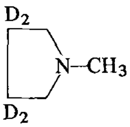
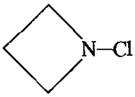
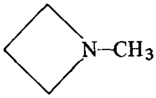
[88]

indicate nonequivalence. From the coalescence temperature of the methylene protons, the free energy of activation for the ring inversion process was calculated to be 12·1 Kcal/mole in good agreement with previous reports for similar processes. (250, 251)

A comprehensive study of pyramidal inversion about nitrogen in saturated cyclic amines containing from four to seven members was reported by Lambert *et al.* (249) They note that incorporation of nitrogen into a ring for inversion studies has one important advantage over open chain systems. Namely, the process of rotation about bonds from nitrogen may not be differentiable from nitrogen inversion. For four- five- and seven-membered azacycles, this problem of differentiation does not exist. Ring puckering and pseudorotational processes do occur, but the rates are much too rapid to influence the spectra (<5 Kcal/mole). For six-membered rings, the problem is complicated by the competitive processes ring reversal and nitrogen inversion. In Table VIII are listed the thermodynamic parameters for a series of compounds involved in an equilibrium process whereby the α-protons are converted from an A_2

TABLE VIII

Activation parameters for nitrogen inversion or ring reversal in cyclic amines[a]

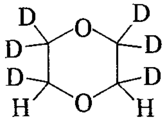
Compound		E_a Kcal/mole	$\Delta H^{\pm}$ Kcal/mole	$\Delta S^{\pm}$ e.u.	$\Delta F^{\pm}$ Kcal/mole
	[89]	11·2	10·6	8·9	9·1
	[90]	–	–	–	6·8
	[91]	17·0	16·4	10·6	13·5
	[92]	14·4	–	–	–
	[93]	13·8	13·2	14·5	10·3
	[94]	10·2	9·6	7·9	8·3
	[95]	–	–	–	13·4
	[96]	12·5	11·9	9·5	10·0

[a] From Ref. 249.

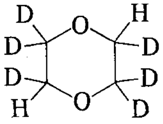
to an AB pattern. These patterns neglect neighboring interactions and this was accomplished by deuteration or spin decoupling of the α-protons. Unfortunately, but as expected, spin decoupling seriously restricts the total line-shape method and this is reflected by the large $\Delta S^{\pm}$ values. The parameters for compounds [89], [91], [93] and [95] are considerably larger than those for compounds [90], [92], [94] and [96] and this appears to be due to the well known rate-retarding effect of chlorine. (253)

3. *Saturated heterocyclics containing oxygen*

The kinetics of ring inversion for most heterocycles containing oxygen are quite similar to those for the corresponding carbon compound. There are, however, a few exceptions, notably 1,4-dioxane [97] for which the NMR spectrum has been reported to be temperature independent. (254, 255) As is frequently the case, deuterated isomers yield simpler spectra and more accurate parameters than those for the fully protonated compound. Anet and Sandstrom (256) examined a mixture of [d_6]-1,4-dioxane isotopic isomers [98] and [99].



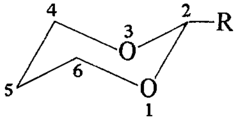
[98]



[99]

The proton spectrum separated into two lines at −97°, $\Delta\nu_{AB}$ = 0·016 ppm and a free energy of activation value of 9·7 Kcal/mole was calculated for the chair-chair ring inversion. Similar results were obtained from the vibrational frequencies in the ground state of 1,4-dioxane. (257) A value of 10·1 Kcal/mole was reported for the chair-to-boat process.

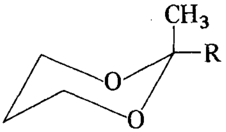
Some generalizations concerning the conformations of 1,3-dioxanes have emerged. The NMR spectra of 2-alkyl-1,3-dioxanes [100] are substantially invariant over wide ranges of temperature



[100]

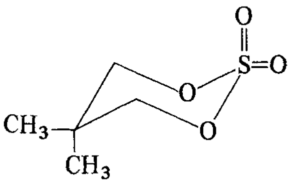
(258) and the patterns exhibited by the ring protons attached to C_4, C_5 and C_6 are quite similar to those observed in the low temperature spectrum of 1,3-dioxane itself. In at least one case, an X-ray study (259) showed the 2-alkyl group equatorially substituted. It is, therefore, generally accepted that the R group occupies the equatorial position and that the molecule exists predominately in a chair conformation.

For 2,2-dialkyl-1,3-dioxane [101] the NMR spectrum sharply contrasts with that of the monosubstituted species and suggest time-averaging, as well as small energy differences between isomers.

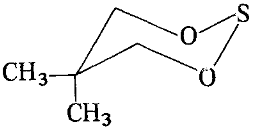


[101]

Some of the factors which influence rotation–inversion barriers in dioxanes, both theoretically (260) and experimentally, have been reported. (261) Examples illustrating some of these factors, i.e., electron pair–electron pair, electron pair–polar bond, etc., are 5,5-dimethyltrimethylene sulfate [102] for which $\Delta F^{\pm} = 8{\cdot}1 - 0{\cdot}4$ Kcal/mole was reported for the chair–chair interconversion (262) and 5,5-dimethyl-1,3-2-dioxathiane [103] for which a strikingly larger value of $\Delta F^{\pm} = 12{\cdot}6$ Kcal/mole was reported. (261)



[102]



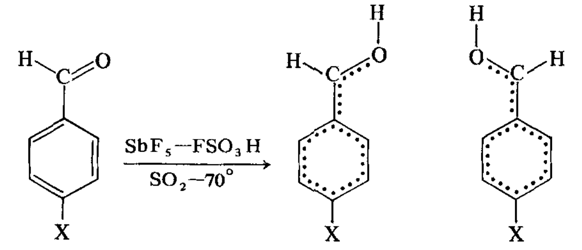
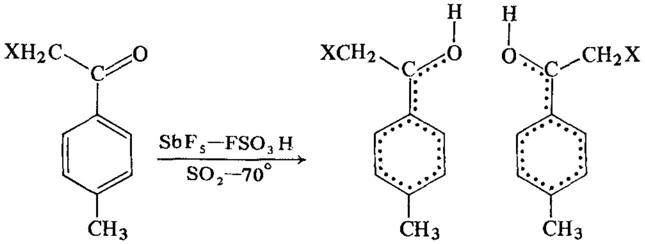
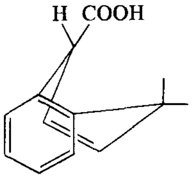
[103]

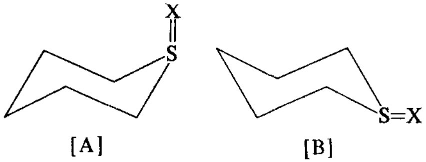
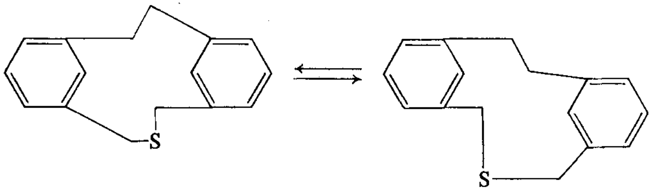
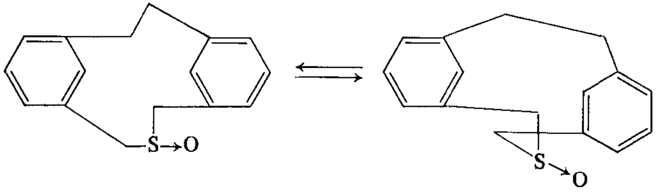
4. Miscellaneous ring systems

In Table IX are listed a variety of compounds and conformational processes. Included are the predominant conformation, as well as thermodynamic parameters whenever available and the method of evaluation.

TABLE IX

Preferred conformations and thermodynamic parameters for some miscellaneous ring systems

Compound and/or Process		Thermodynamic Data, $\Delta F^{\pm}$ Kcal/mole	Method	Ref.
 	[104] X = *p*-Me	16·3	Coalescence	(263)
		16·4	Coalescence	(264)
	[105] X = *p*-Cl	14·8	Coalescence	(263)
		13·9	Coalescence	(264)
	[106] X = *p*-Br	14·8	Coalescence	(263)
		14·0	Coalescence	(264)
		17·9	Coalescence	(264)
 		12·4	Coalescence	(265)
		12·4	Coalescence	(265)
		12·2	Coalescence	(265)
	[107] X = *p*-OCH₃	11·9	Coalescence	(265)
	[108] X = F			
	[109] X = Cl			
	[110] X = Br			
	[111] X = I			
1,4-dihydro-1-naphthoic acid [112]	 	is the preferred isomer as suggested by the NMR parameters, chemical shifts and coupling constants.		(266)

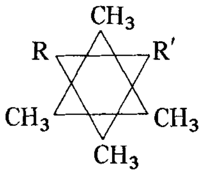
 [A] [B]	[113] X = NH [114] X = NTs [115] X = NBs	NMR Parameters suggest a predominance of isomers [B]		(267)
 [116]		13·1 Kcal/mole	coalescence	(268)
 [117]		16·2 Kcal/mole	coalescence	(268)

G. Conformational Preference of Acyclic Compounds

1. Substituted ethanes

Rotation about C–C bonds in simple molecules, e.g., substituted ethanes, is of considerable interest, and has been the subject of a vast number of recent investigations. (269-281) The great majority of these studies have been concerned with molecules bearing several halogenated substituents, which tends to increase the barrier to rotation and thus simplify the experimental details of measuring the activation parameters. In contrast, only a few investigations of rotational barriers have been reported for substituted ethanes in which alkyl–halogen and alkyl–alkyl interactions are involved.

Roberts and co-workers (273) reported on a series of substituted butanes, compounds [118] through [123], containing both halogen and alkyl substituents. Some trends are apparent in the rotational barriers in Table X. Firstly, substitution of bromine for chlorine



[118] R = Cl; R′ = CH_3
[119] R = Br; R′ = CH_3
[120] R = R′ = Cl
[121] R = R′ = Br
[122] R = Cl; R′ = Br
[123] R = Cl; R′ = $C(CH_3)_3$

TABLE X

Barriers to internal rotation in halogenated butanes

Comp.	Tc	E_A Kcal/mole	$\Delta F^{\pm}$ Kcal/mole	$\Delta H^{\pm}$ Kcal/mole	$\Delta S^{\pm}$ e.u.	Ref.
[118]	−81°	11·8	9·8	11·4	8·1	(273)
[119]	−68°	13·6	10·8	13·2	11·9	(273)
[120]	−61°	10·9	10·8	10·5	−1·6	(273)
[121]	−38°	11·8	12·3	11·4	−3·8	(273)
[122]	−45°	12·3	11·9	11·8	−0·4	(273)
[123]	−71°	10·3	10·9	9·9	−5·0	(273)

results in increased values of $\Delta F^{\pm}$ as expected. Secondly, the gauche halogen–halogen and gauche methyl–methyl interactions are more severe than gauche halogen–methyl interactions. From a comparison of compounds [118] with [120], [118] with [122], [119] with [121] and [119] with [122], an increase in the free energy of activation for rotation is observed when a halogen is substituted for a methyl group. It is, of course, possible to draw a number of other conclusions on the interactions, but the inherent uncertainties in E_a, as well as $\Delta H^{\pm}$ and $\Delta S^{\pm}$, seriously restricts their use.

From a combination infrared and NMR study (274) of chlorinated propanes the most probable conformations were ascertained. They (274) note that the exclusion of isomers with parallel 1 : 3 chlorine–chlorine interactions is the major factor in restricting the number of conformations.

Abraham and Kemp (279) reported on a number of interesting trends in proton and fluorine internuclear coupling constants. For 1,2-difluoro- [124], 1,1,2-trifluoro- [125], and 1,1,2,2-tetrafluoroethane [126] they concluded: (1) increasing fluorine substitution gives a progressive but very nonlinear decrease in J_t^{HH} and J_t^{HF}, and (2) J_t^{FF} is very dependent on the fluorine substitution, varying from −30 to 0 Hz, while J_g^{FF} is relatively constant −13 to −5 Hz.

Bothner-By and Trautwein (282) reported on a conformational study of phosphate esters, centering on rotation about the P–O and C–O bonds. Their results on trimethyl phosphate [127], tris (β-chloroethyl) phosphate [128] and trisneopentyl phosphate [129] suggest that the dependence of ^3J(POCH) upon dihedral angle and substitution is similar to that for the well-known Karplus curve. (283)

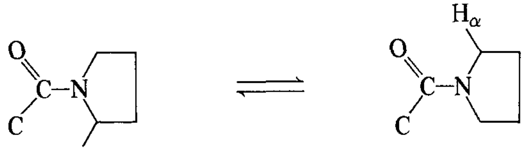
2. *Amino acids, polyamino acids and polypeptides*

Elucidation of structural details of polypeptides or proteins in solution is, of course, quite complex and requires considerable background information on smaller and simpler systems. To this end Newmark and Miller (284) investigated a number of valine [130] and phenylalanine [131] derivatives. For both [130] and [131] they observed a substantial increase in the coupling constant in going from the dipolar ion to the *N*-acetyl ester in aqueous solutions, indicating a change in the relative populations of the conformers. For *N*-acetyl-L-phenylalanine ethyl ester (NAPEE) [132] they concluded that solvent effects could produce small changes in rotomer populations, but that intramolecular interactions are more important than the medium in determining the relative populations of the conformers.

Tonelli and Bovey (285) reported on conformations about the nitrogen-α-carbon bond in random-coil polypeptides. They observed $J_{N\alpha} = 6{\cdot}5$, $6{\cdot}3$ and $7{\cdot}0$ Hz for poly-L-alanine [133], poly-L-methionine [134] and poly(β-benzyl-L-aspartate) [135], respectively; these are in good agreement with calculated values based upon a Karplus-like dependence of $J_{N\alpha}$ on the dihedral angle θ. They conclude that interactions between the side chains and between side chains and solvents which might influence backbone conformations are negligible. Secondly, the conformational characteristics of this class of random-coil poly-L-peptides are adequately described by the energy calculations of Brant and Flory (286) and Brant, Miller and Flory. (287)

In contrast to the above conclusion, Anad, Murthy, Naider and Goodman (288) reported results which suggest that amino acid side chains can have important influences on the backbone conformations of a polypeptide. Specifically, they note that whereas poly-L-lysine hydrobromide [136] and poly(N^{ϵ}-glycol-L-lysine hydrobromide) [137] exist in a random coil conformation in water, both poly(N^{ϵ}-L-phenylalanyl-L-lysine hydrobromide) [138] and poly(N^{ϵ}-L-leucyl-L-lysine hydrobromide) [139] are α-helical. These conclusions were based upon circular dichroism as well as 220 MHz spectra.

Torchia and Bovey (289) reported on a novel study of poly-(L-proline). In particular, they monitored the isomerization of *cis* to *trans* poly(L-proline) [140], [A] ⇌ [B], and arrived at an activation enthalpy of *ca.* 23 Kcal/mole. Resonances for both α-*trans* and α-*cis* protons were found which suggests that the disruption of the ordered poly(L-proline) structure in solution is primarily due to the presence of both *trans* and *cis* peptide bonds randomly distributed along the polymer chain.



cis *trans*

[140A] [140B]

IV. CARBON-13

A. Techniques

The use of carbon-13 nuclear magnetic spectroscopy has lagged behind that of proton magnetic resonance spectroscopy for several reasons. Firstly, the only stable isotope of carbon with a nuclear magnetic moment is ^{13}C ($I = 1/2$) which has a natural abundance of 1·1% compared with the 99·9% abundance of proton nuclei. Also the ^{13}C gyromagnetic ratio, a proportionality constant between the resonance frequency and the field strength, is smaller than that of ^{1}H nuclei by a factor of 0·25. The relative sensitivity for detecting equal numbers of nuclei at a constant field strength is proportional to the cube of the gyromagnetic ratio; and, consequently, the sensitivity of ^{13}C is 0·016 relative to ^{1}H = 1·00. (290) The combination of these factors, holding all others equal, reduces the intensity of the ^{13}C signal by almost 6000 fold over that of proton nuclei. A further serious difficulty in obtaining ^{13}C spectra is the relatively long relaxation time (T_1) of carbon-13.

Even with these difficulties carbon-13 studies are becoming increasingly important. The ^{13}C chemical shift range extends over 200 ppm, compared to about 10 ppm for protons. This, in turn, gives rise to first order spectra and alleviates the need for higher frequency instruments. Further, the carbon atoms are usually imbedded within a molecule where intermolecular interactions are insignificant relative to intramolecular effects.

Several techniques have been developed since 1954 when Royden (291) and then Lauterbur (292, 293) employed adiabatic rapid passage techniques on the dispersion mode to observe the ^{13}C magnetic resonance signal. Among the first to obtain improved ^{13}C spectra were Paul and Grant (294) by using larger NMR tubes 10–15 mm), sample spinning which resulted in better field homogenity, and proton decoupling techniques. The last innovation resulted in signal enhancement due to a nuclear Overhauser effect and an increase in resolution resulting from the multiplet collapse.

A significant contribution was made when Ernst and Anderson (295) introduced the application of Fourier transform spectroscopy to magnetic resonance. (296-298) This, coupled with a digital computer or time-averaging device, allowed large improvements in signal-to-noise (S/N) ratios to be achieved. In order to employ the repetitive scanning of the pulse or continuous wave type, the use of super stabilizers and other sophisticated hardware is necessary. These devices are now commercially available and will do much to open the field. The Fourier-transform technique consists of: the application to the sample of a short intense radiofrequency pulse that excites the entire range of precision frequencies of the chosen nuclear species, and the measurement as a function of time of the resulting free induction signals from the nuclear spins in the sample. Fourier transformation of the free induction signal gives the usual high resolution spectrum. It has been shown that under certain easily satisfied conditions the Fourier transform of this free precision signal is identical with the steady-state slow-passage spectrum. The advantage of this technique, as opposed to continuous-wave spectroscopy, is that the free induction signal is obtained rapidly so that in a given observation time it is possible to apply the pulse repetitively and store the free induction signals in a time-averaging device. The enhancement of the S/N ratio in this case is of the order of the square root of the observation time. The difficulty with this system is that the pulse interval must be long relative to the spin-lattice relaxation time T_1 in order to permit the nuclei to return to equilibrium.

B. T_1 and T_2 Measurements

Since the spin-lattice relaxation time (T_1) of some ^{13}C nuclei is of the order of minutes, the pulse interval and the observation time necessary to obtain a significantly improved signal must be long. The spin-lattice relaxation time is relatively long because the nuclear spin system is only weakly coupled to the other motions of the system. Four mechanisms are known which can contribute to the spin-lattice relaxation rate of ^{13}C spins: the dipolar, and scalar interactions of ^{13}C with the spins of other nuclei or electrons, the spin rotation interaction, and the anisotropic chemical shift. The results of recent investigations show that the intramolecular dipole-dipole interactions provide the predominate spin-lattice relaxation mechanism whenever protons are bound directly to the carbons under investigation. (299-304) However, there is an appreciable contribution to $1/T_1$ from the spin-rotation interaction for small or very symmetric molecules. (302) To circumvent this problem of long observation time, several techniques have been developed. The first procedure is the "driven equilibrium Fourier transform" (DEFT) (296, 305) in which reestablishment of the equilibrium magnetization is achieved in a time much less than T_1 by the application of a refocusing multiple pulse scheme. A second method recently introduced is the spin-echo-Fourier-transform method (SEFT) (306) in which a different pulse sequence is employed to accomplish the same purpose. The enhancement to be expected by the pulsed NMR techniques over that of the continuous wave method is dependent on the ratio of T_1/T_2^* and is lost when $T_2^* \ll T_1$. (307) $1/T_2^*$ is the sum of $1/T_2$, the "natural transverse relaxation time"; and $1/T'_2$, the dephasing contribution from the inhomogenity of the magnetic field.

The key to these enhanced methods is T_1 and the measurement of this parameter has generated considerable interest. One method of studying ^{13}C spin-lattice relaxation times is to make use of proton-decoupled partially-relaxed Fourier transform spectra (PRFT), obtained by means of the 180°-τ-90° pulse sequence. The initial state of the spins is established by a 180° pulse of the type

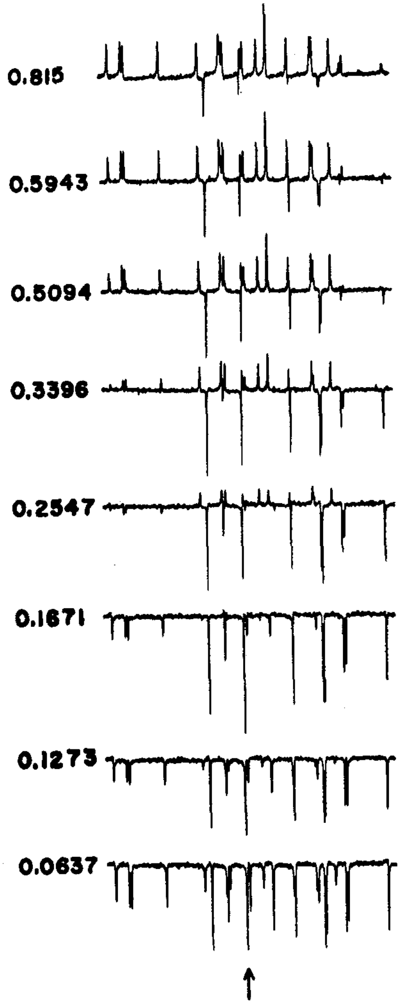


FIG. 4. Proton-decoupled natural abundance carbon-13 partially relaxed Fourier transform NMR spectra of 1M cholesteryl chloride in CCl_4, at 15·08 MHz and 42°C. The number to the left of each spectrum is the interval between the 180° pulse and 90° pulse in seconds. Each spectrum is the result of 128 accumulations, with a recycle time of 21·7 sec. The range 132·2–182·2 ppm upfield from neat CS_2 is shown. (From Allerhand *et al.* (308).)

used in standard T_1 measurements; and then, after a time interval τ, a 90° pulse is applied and a digital signal averager is triggered to record the free induction decay (FID). The sequence is repeated after waiting a period of several multiples of T_1. The resulting time-dependent signal, after a suitable number of accumulations, is Fourier transformed to yield a partially-relaxed frequency domain spectrum. Since the recovery of the perturbed population towards thermal equilibrium is governed by the individual spin-lattice relaxations, the history of the spectrum as a function of τ and the delay time in seconds between the 180° pulse and the 90° pulse give the full unperturbed relaxation behavior (308) as shown in Fig. 4.

If τ is much shorter than the T_1 of a particular resonance a "negative" peak will appear with an amplitude equal to that in the normal spectrum. As τ increases this negative peak decreases in amplitude, goes through a null at $\tau = T_1 \ln 2$, because positive, and for $\tau \gg T_1$ becomes equal to the normal resonance. The intensities obtained from sets of such spectra are used to compute the ^{13}C longitudinal relaxation times using

$$A = A_0 [1 - 2 \exp(-\tau/T_1)] \qquad (21)$$

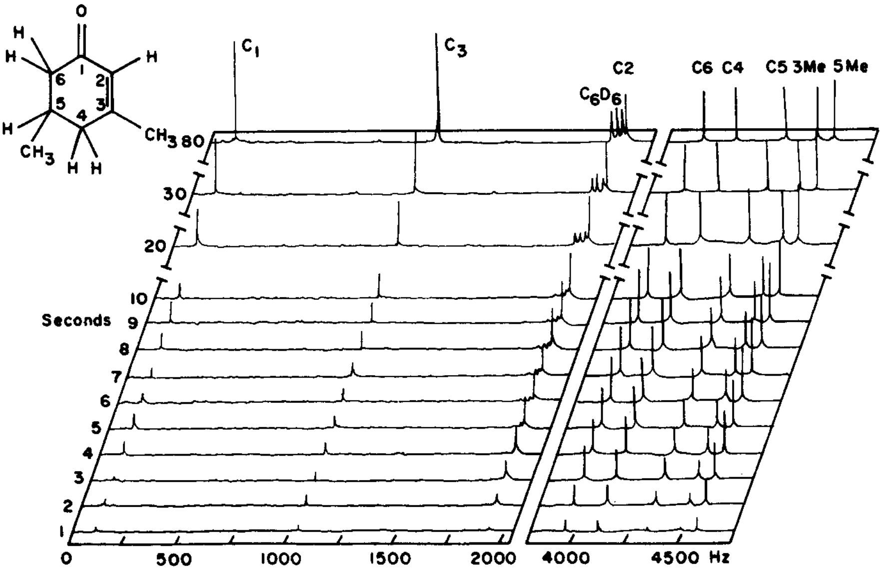


FIG. 5. Spin-lattice relaxation of carbon-13 nuclei in proton-decoupled 3,5-dimethylcyclohex-2-ene-1-one by the progressive saturation method. The spectra were obtained by Fourier transformation of 64 accumulated transient signals in the steady-state pulse regime for each setting of the pulse interval τ seconds. (From Freeman and Hill (309).)

where A_0 is the equilibrium amplitude measured in a PRFT spectrum, and A is the amplitude in a PRFF spectrum. Least squares analysis yield τ values with standard deviations of less than 8% in most cases.

Rather than use the classic inversion-recovery method for measuring spin-lattice relaxation times, a progressive saturation technique has been developed, (309) yielding similar results. A series of spectra measured as a function of τ can be stacked in such a way as to create the impression of a three dimensional diagram-intensity as a function of frequency and τ (Fig. 5). A comparison of the two experimental techniques for measuring T_1 applied to 3,5-dimethylcyclohex-2-ene-1-one is shown in Table XI.

TABLE XI

Comparison of the two experimental techniques for measuring spin-lattice relaxation times applied to 3,5-dimethylcyclohex-2-ene-1-one

Carbon nucleus	T_1 by progressive saturation (sec)	T_1 by inversion-recovery (sec)
Cl	39	37
C3	32	33
3Me	6·0	5·9
C2	5·6	5·4
C5	5·4	5·3
C6	3·2	3·1
C4	3·3	3·1
5Me	2·6	2·7

Separate semilogarithmic plots were made of the experimental data obtained by the 2 different methods and the corresponding time constants were derived independently. (From Freeman and Hill (309).)

In the work cited above, the longest T_1 is only 8 seconds and that is of a nonprotonated carbon. Most of the protonated carbons studied had relaxation times of less than one second. This is the case for large molecules with low symmetry whereas, T_1 for smaller symmetrical molecules is much longer, Table XII.

It was mentioned earlier that the main spin-lattice relaxation mechanism for ^{13}C, when bound to a proton, is *via* the intramolecular dipole–dipole interaction; that this is not always the case was demonstrated for the methyl carbon of toluene.

The spin-lattice relaxation time of the methyl carbon in toluene (311) was calculated and compared (310) with the experimental value. The results suggest that spin-internal-rotation relaxation accounts for about 75% of the total relaxation rate for ^{13}C nucleus

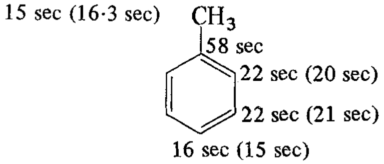
TABLE XII

^{13}C spin-lattice (T_1) relaxation times of various liquids[a]

Molecule	T_1 (sec)	Ref.
$\underline{CH}_3I$	11·1 ± 0·4	(302)
$\underline{CH}_3Cl$	13·1 ± 1·0	(302)
$\underline{CH}_3OH$	13·4 ± 0·8	(302)
$\underline{CH}_3COOH$	10·5 ± 0·5	(302)
$\underline{C}_6H_6$	28	(299)
$\underline{C}_6H_{12}$	21 (23)	(299, 310)
$\underline{C}S_2$	36 ± 1	(299)
C_5H_{12}	24	(299)
$(CH\underline{CH}_3O)_3$	2·6	(299)
$[(\underline{C}HCH_3)_2NH]_2$	1·4	(299)

[a] The T_1's refer to the underlined carbons.

of the methyl group in toluene near room temperature. The calculated T_1's for the ^{13}C of toluene are compared with the experimental values in parenthesis



The measurement of the individual values of carbon-13 spin-lattice relaxation times, T_1, by means of partially relaxed Fourier transform can be utilized to gather information concerning internal motion (312-315) within the molecule. The correlation time for rotational reorientation, T_R, can be calculated from the spin-lattice relaxation time, T_1, when the relaxation is dominated by dipole–dipole interactions with the attached protons. In Fig. 6 is shown the spectra of 1-decanol along with T_1 and T_R. The increase of T_R from 5 psec for the methyl carbon to 36 psec for the CH_2OH carbon represents loss of internal motion caused by intermolecular hydrogen bonding. This increasing chain motion of the terminal groups was also observed for dipalmitoyl lecithin. (313)

While the main effort has been directed at obtaining spin-lattice relaxation times T_1, a Fourier transform method has also been described (316) to measure the transverse relaxation time (T_2) (also called spin-spin relaxation time) for ^{13}C. As can be seen in Table XIII, T_2 is shorter than T_1 for the molecules studied. Such a

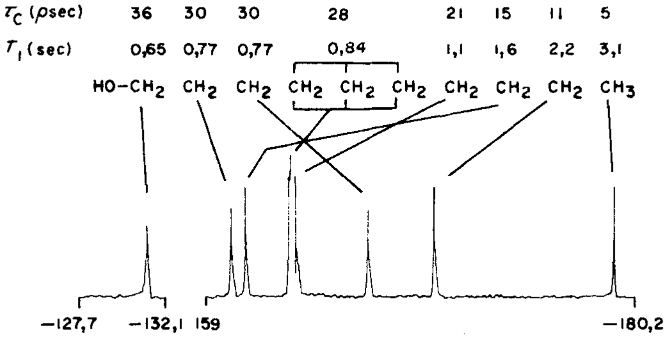


FIG. 6. Normal proton-decoupled natural-abundance carbon-13 Fourier transform NMR spectrum of neat-liquid 1-decanol at 42° and 15·08 MHz, after four accumulations, with a recycle time of 21·7 sec. Horizontal scale is in parts per million upfield from neat carbon disulfide. Spin-lattice relaxation times and effective rotational correlation times are indicated above each carbon. (From Doddrell and Allerhand (313).)

situation can occur when relaxing spin-1/2 nuclei, e.g., protons are coupled to ^{13}C such that:

$$A \equiv 2\pi J \gg R_{1\mathrm{H}}, \qquad (22)$$

TABLE XIII

Relaxation times for 60% ^{13}C-enriched compounds at 25° (317)

	T_1 sec	T_2 sec
$^{13}CH_3I$	13·4	3·9
$^{13}CH_3COOCD_3$	19·2	6·1
$^{13}CS_2$	48	38

where A is the coupling constant in radians and $R_{1\mathrm{H}} = 1/T_{1\mathrm{H}}$. One consequence of this observation is that the advantage predicted by the multiple-pulse refocusing methods will be reduced, since the sensitivity enhancement is based on the assumption that $T_2 \approx T_1$. This will not be the case for small symmetrical molecule where T_1 is large. (See Table XII.)

C. Nuclear Overhauser Effects

As mentioned in the introduction, the use of proton noise decoupling techniques enhanced the S/N ratio by the collapse of the multiplet structure and by the Overhauser effect. The latter effect can provide a S/N enhanced of 2·8888 for dipolar C–H coupling. However, the exact magnitude of the Overhauser enhancement factor is critically dependent on the functionality of the carbon and is, thus, highly variable even for carbons within the same molecule. This variable magnitude destroys the simple relationship between resonance intensity and the number of ^{13}C nuclei. Thus, the use of noise decoupled ^{13}C spectra does not lend itself to quantitative analysis. However, the addition of a paramagnetic substance into the solution will reduce the Overhauser enhancement almost to zero and restore the resonance intensity number of nuclei relationship. (318-320) The usual technique employed to assign ^{13}C resonances of protonated carbons is to employ off-resonance decoupling or single resonance irradiation methods.

D. ^{13}C Chemical Shift

1. *Standards*

Before examining the new carbon-13 chemical shift data that is present in the literature, one must be aware of the fact that a number of "standard" reference compounds are used to measure the relative chemical shift. Historically, all chemical shifts were made relative to external carbon disulfide (CS_2). Now ^{13}C chemical shifts are being reported relative to tetramethylsilane (TMS) with higher frequency (low field) shifts positive. This system is consistent with the δ-scale for protons and has the additional advantage that only one compound is used as a reference for three important nuclei, ^{1}H, ^{13}C, and ^{29}Si. CS_2 is a logical standard for ^{13}C if rapid passage single resonance spectra are being studied; but with the advent of double resonance and frequency sweep techniques, a proton-containing standard is a better choice because it gives a much stronger double resonance signal and can be used for indirect measurement of ^{13}C chemical shifts by various methods of heteronuclear double resonance. Benzene is not suitable because about half of the ^{13}C shifts would be either negative or positive.

To convert ^{13}C chemical shifts which were measured relative to CS_2 to the new TMS scale, the conversion is:

$$\delta_{\mathrm{TMS}} = 193{\cdot}1 - \delta_{\mathrm{CS_2}}.$$

Many investigators measure the chemical shift relative to the solvent and, in turn, relate this to TMS or external CS_2; consequently, a number of relationships abound in the literature. Table XIV contains the chemical shift for the common standards relative to TMS. (321) The solvent effects on the carbon-13 resonance in tetramethylsilane have been measured in a number of aliphatic and aromatic solvents relative to pure TMS. (322)

TABLE XIV

TMS-based ^{13}C chemical shifts for common standards and solvents (321)

	Chemical shift	
Compound (solvent)	Protio compound	Per-deutero compound
Cyclohexane	27·51	26·06
Acetone	30·43	29·22
Dimethylsulfoxide	40·48	39·56
Methylene chloride	54·02	53·61
Dioxane	67·40	
Chloroform	77·17	76·91
Carbon tetrachloride	95·99	
Benzene	128·53	127·96
Acetic acid (*CO)	178·27	
CS_2	192·8	
CS_2 capillary	193·7	

2. *Empirical Methods for Calculating Spectras*

In addition to the experimental observations and assignments, several empirical methods for calculating carbon-13 chemical shifts have been developed. (304, 323, 324) Roberts and co-workers have devised a method for calculating the chemical shifts of any alkene carbon relative to the chemical shift of ethylene. Using a least-squares analyses, a number of additive substituent parameters were calculated based on the chemical shift data of some fifty alkene hydrocarbons. In describing the chemical shifts of alkene carbons, the following substituent effects were considered in the calculation of

$$\underset{\delta}{C}\ \text{-}\underset{\gamma}{C}\ \text{-}\underset{\beta}{C}\ \text{-}\underset{\alpha}{C}\ \text{-}C_A = C\ \text{-}\underset{\alpha'}{C}\ \text{-}\underset{\beta'}{C}\ \text{-}\underset{\gamma'}{C}\ \text{-}\underset{\delta'}{C}.$$

Using this method, the substituent effects experienced by carbon-1 of 2,4,4-trimethyl-1-pentene are: $2\alpha' + \beta' + 3\gamma'$. The least-squares solutions indicated that δ and δ' parameters have very little effect upon the chemical shift of C_A. Nevertheless it was necessary to include several correction terms for α, β and α' to account for non-additivity of the parameters in highly branched systems and a "*cis*" correction term to represent the dependence of the chemical shift on the geometric isomerism of the double bond. The ^{13}C

chemical shift of several methyl ethylenes were similarly measured and two sets of additive parameters were derived from which the chemical shifts of the methyl and vinyl carbons could be predicted. (304) It was found that the vinyl parameters could be explained on the basis of inductive charge effects while the methyl parameters were steric dominated. The expression for the vinyl carbon chemical shifts required six parameters: δ_0 reflect the chemical shift of ethylene, δ_α and δ_β represent methyl substitutions on the vinyl carbon and adjacent vinyl carbon respectively, δ *cis*, δ_α *gem*, and δ_β *gem* represent steric interactions and correction parameters. The predicted values are plotted vs the experimental chemical shift in Fig. 7.

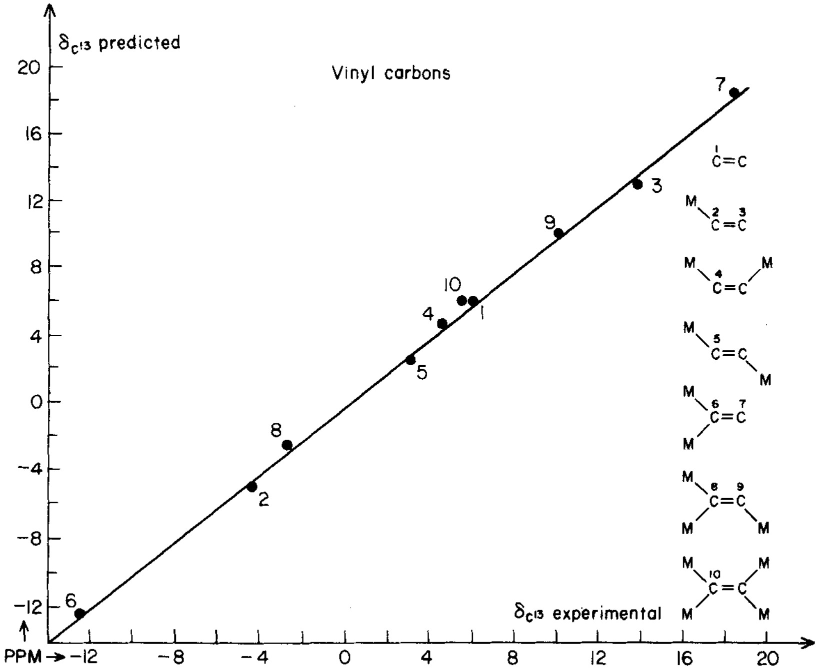


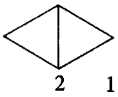
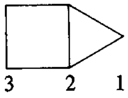
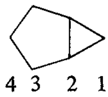
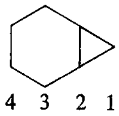
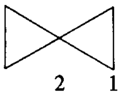
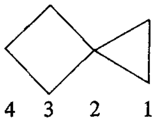
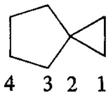
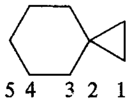
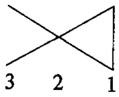
FIG. 7. Plot of the experimental vs. predicted chemical shifts for the vinyl carbons. (From Collins (304).)

3. *Hydrocarbons*

Since the pioneering work of Grant and Paul (325) and Burke and Lauterbur (326) on ^{13}C chemical shifts, the area has expanded and today encompasses a large number of hydrocarbons—particularly the smaller species.

TABLE XV

^{13}C chemical shifts of several bicyclo[*n*.1.0] alkanes and spiro[2.*n*] alkanes (328)

Compound		Experimental chemical shift (rel. to benzene)
	C_1 C_2	132·9 98·0
	C_1 C_2 C_3	112·5 114·6 104·8
	C_1 C_2 C_3 C_4	112·5 111·6 100·6 108·1
	C_1 C_2 C_3 C_4	118·1 118·8 104·4 106·8
	C_1 C_2	122·5 120·0
	C_1 C_2 C_3 C_4	116·4 108·6 97·6 111·5
	C_1 C_2 C_3 C_4	115·6 106·2 92·5 96·1
	C_1 C_2 C_3 C_4 C_5	116·4 109·6 92·5 102·8 102·2
	C_1 C_2 C_3	114·7 117·4 103·1

Lindeman and Adams (327) obtained the ^{13}C chemical shift for all the isomers of C_5 to C_8 paraffins and for many of the C_9 isomers. Several examples of magnetic non-equivalence were detected. The first example was 2,3-dimethyl pentane where the two methyl carbons in the isopropyl group are not equivalent. These experimental chemical shifts were used to test and confirm the Grant and Paul chemical shift parameters for linear and branched paraffins.

The chemical shifts of several bicyclo[*n*.1.0]alkanes and spiro-[2.*n*] alkanes are summarized in Table XV.

As mentioned earlier Roberts and co-workers (323) reported on an in-depth investigation of monoenes and polyenes. Their study includes 1,1-disubstituted-, 1,2-disubstituted-, trisubstituted-, tetrasubstituted alkenes, cycloalkenes, several methylenecycloalkanes, dienes, and several simple terpenes. The primary objective concerned the change in the chemical shift of the trigonal olefinic carbon with the change in local environment. This effect was illustrated and a complete assignment was made for many of the compounds studied. A few representative ^{13}C chemical shifts of the olefinic carbons are presented below.

TABLE XVI

^{13}C NMR chemical shifts of several olefins (323)

Compound	^{13}C chemical shift (ppm rel. to external CS_2)[a]	
Octene-1	$C_1 = 79{\cdot}2$	$C_2 = 54{\cdot}3$
2 methyl-1-heptene	$C_1 = 83{\cdot}5$	$C_2 = 47{\cdot}9$
cis-3-octene	$C_3 = 61{\cdot}9$	$C_4 = 64{\cdot}1$
cis-2-octene	$C_2 = 69{\cdot}9$	$C_3 = 62{\cdot}5$
trans-2-octene	$C_2 = 68{\cdot}8$	$C_3 = 61{\cdot}6$
trans-3-octene	$C_3 = 60{\cdot}9$	$C_4 = 63{\cdot}9$
2,3-dimethyl-2-hexene	$C_2 = 69{\cdot}6$	$C_3 = 65{\cdot}6$
trans cyclooctene	$C_1 = 63{\cdot}3$	
methylenecyclohexane	$C_1 = 44{\cdot}0$	
3,5-*cis*, *cis*-octadiene	$C_3 = 60{\cdot}2$	$C_4 = 70{\cdot}2$

[a] $\delta_{TMS} = 193{\cdot}1 - \delta_{CS_2}$.

Comparison of the ^{13}C chemical shifts of simple olefins with those reported for a series of allenes was reported. (329) The chemical shift of the central (*sp*-σ) allenic carbon falls below, while the other two olefinic carbons (sp^2) are found at fields higher than those for the simple olefins. (329) A few of the reported values are shown below.

TABLE XVII

^{13}C chemical shifts of polysubstituted allenes $R_1R_2C_\alpha = C_\beta = C_\gamma R_3R_4$ (329)

Substituents				^{13}C chemical shifts (ppm)[a]			
R_1	R_2	R_3	R_4	δ_{C_α}	δ_{C_β}	δ_{C_γ}	δ_R
H	H	CH_3	CH_3	121·6	−13·6	100·3	174·2 (CH_3)
CH_3	H	CH_3	H	108·3	−13·4	108·3	
C_6H_5	C_6H_5	C_6H_5	C_6H_5	80·1	−15·8	80·1	56·3 (C_1) 65·3 (Cp) 64·3, 64·4 (Co, Cm)

[a] Rel. to CS_2.

Rosenberg and Drenth (330) investigated a number of acetylenes. Their results indicate the ^{13}C chemical shift of the *sp* hybridized carbon is largely influenced by charge changes that occur in the triple bond upon substitution. They used the sum of the chemical shifts of the two acetylenic carbon atoms, $\delta_{C_1} + \delta_{C_2}$, as an indicator for the charge changes in the acetylenic bond and the difference between the shift values, $\delta_{C_1} - \delta_{C_2}$, as a measure of the polarization of the charge in the acetylenic bond. They concluded, from the results in Table XVIII, that an electronic charge shift from the triple bond to the substituent occurs in phenylethyne, ethylthioethyne, triethynylphosphine, triethynylphosphineoxide and ethynyltriethylgermanium. In 1-alkynyl ethers and amines a charge shift to the triple bond is present.

TABLE XVIII

^{13}C chemical shifts of substituted acetylenes $RC_1{\equiv}C_2R^1$ (330)

Compound		^{13}C chemical shifts (ppm from CS_2)			
R	R^1	δ_{C_1}	δ_{C_2}	$\delta_{C_1} + \delta_{C_2}$	$\delta_{C_1} - \delta_{C_2}$
H	C_4H_9	128·0	111·0	239·0	+17·0
H	C_6H_5	115·7	109·4	225·1	+6·3
H	OEt	170·8	104·6	275·4	+66·2
H	SEt	112·6	121·4	234·0	−8·8
H	Ge(nC$_4$H$_9$)$_3$	101·3	108·0	209·3	−6·7

The difficulty encountered in assigning ^{13}C resonances to particular carbons in symmetrical nonsubstituted organic compounds was demonstrated for a series of fused polycondensed aromatic hydrocarbons (331) containing from two to seven fused benzene rings. Use was made of previously assigned data on naphthalene and phenanthrene, (332) noise off resonance decoupling (NORD) to distinguish the non-protonated carbons from the protonated carbonatons, (333) and selected double resonance based on the fully analyzed ^1H NMR results to assign the individual protonated carbon.

4. *Substituent effects*

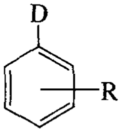
The influence of substituents on the ^{13}C chemical shifts of the carbon atom was studied for all the chlorine (334) and bromine (335) substituted ethanes and ethylenes. The successive substitution of hydrogen directly bonded to carbon by chlorine in an ethane series shifted the ^{13}C resonance to lower fields (relative to CS_2) by about 30 ppm. Similar substitutions in the bromine series gave rise to a 20 ppm downfield shift. In the ethylene series successive chlorine substitution only shifts the ^{13}C resonance about 4 ppm, whereas in the bromine series the shift is of the order of 16 ppm and in the opposite direction.

The additivity increment method of Grant and Paul (325) for calculating the chemical shifts of substituted alkanes was again substantiated for C-1 substituted alkanes C_nH_{2n+1} X ($n = 1$–8 $X = CO_2H$, OH, Cl, Br, I) and 2-, 3-, and 4-substituted octanes $C_8H_{17}X$ (X = OH, Cl, Br). (336)

The ^{13}C NMR shifts of methylcyclopentanes, cyclopentanols and cyclopentyl acetates were obtained. (337) The chemical shift effects produced by the methyl substitution on cyclopentane are in accord with the expected steric interactions. The substituent effects found for the cyclopentane series are similar to those observed for the cyclohexanes.

By studying the ^{13}C NMR spectra of a series of substituted *t*-butyl-1,3-dioxanes, it was possible to determine the effects of: (a) substituent position and (b) conformation of ring, upon the chemical shifts of the ring and substituent. (338) It was suggested that substituent shift correlations could, in most instances, be transferred from cyclohexane derivatives to their heterocyclic analogs provided the deshielding effects of the ring oxygens on axial 5-substituents were taken into consideration.

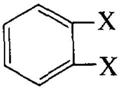
The ^{13}C NMR isotope shifts induced by deuterium in several substituted benzenes were recorded, (339)



	ortho	*meta*	*para*
R =	OMe	OMe	OMe
	Me	Me	Me
	Cl	Cl	Cl
	CN		CF_3.

The results showed that the carbon bearing the deuterium is shifted upfield (0·276 to 0·338 ppm) and the two adjacent carbons are shifted upfield to a smaller extent (0·123 ppm to 0·037). The *meta* carbons are moved upfield by 0·011 ppm. They suggested that the ^{13}C isotope shift is dominated by two factors. The larger effect is the change in the normal vibrational modes of the benzene ring upon deuterium substitution, and the second is the electronic demand of the substituent: an increase in electron density at a given carbon being associated with an increased isotope shift.

The ^{13}C chemical shifts for the symmetrical *ortho*-dihalobenzenes

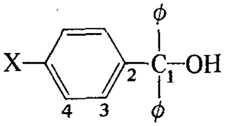


X = F, Cl, Br & I

were determined as well as the long range H–^{13}C coupling constants. (340) The ^{13}C chemical shift of the carbon directly bonded to the substituent (C_s) moves downfield in going from X = F to X = I by about 40 ppm. It appears that the changes in C_s are largely accounted for by inductive and magnetic anisotropy effects of X. The observed trend at the *ortho* carbon (C_o), however, is that the ^{13}C chemical shift moves upfield by 22 ppm with increasing substituent electronegativity.

The ^{13}C chemical shift for the *meta* carbons (C_m) moves downfield by about 6 ppm in going from X = F to X = I. This trend is consistent with the C_m and C_p substituent effects observed in monohalobenzenes (341) and is in accord with resonance effects for electron releasing halogens, which are likely to be important at the *para* position.

The ^{13}C NMR chemical shifts of a number of *para* substituted triphenyl carbinols (342) and the corresponding carbonium ions have



X = H, NO_2, F, Cl, CH_3
OCH_3, $N(CH_3)_2$

been measured. The results, examples of which are shown in Table XIX, are interpreted in terms of charge densities. The agreement between the observed chemical shift and those based on the usual additivity relationships are good for the carbinol series and the corresponding carbonium ions.

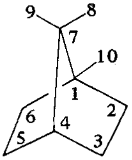
TABLE XIX

^{13}C NMR spectral parameters for *para* substituted triarylcarbinols and corresponding carbonium ions (342)

Substituent	Chemical shifts[a]				
	C_1	C_2	C_3	C_4	C_5
H	113·4	43·6	65·1	65·1	65·1
(ion) H	–	53·5	50·1	62·3	50·1
NO_2	112·8	40·6	64·2	69·9	45·8
ion NO_2	–20·2	48·6	47·3	67·2	37·0
NMe_2	113·2	55·5	64·6	32·0	44·0
ion	16·8	67·3	54·0	80·9	37·6

[a] ppm rel. to CS_2.

Bicyclic ring systems have been extensively investigated by means of NMR in order to study the influence of molecular geometry and polar substituents on chemical shifts and coupling constants. These rigid molecules of known and fixed geometry have been used extensively in the study of field effects, through-space effects, the "W-letter" rule for long-range coupling, and the Karplus relationships. Furthermore, the study of the NMR of bicycloheptanes and bicyclooctanes may be considered as intermediates for the study of natural products and other biologically interesting systems. Therefore, it is not surprising that several reports have recently appeared on these materials. (336, 343, 344) The greater emphasis has been on the bicycloheptane series, [141] and a typical spectrum is shown in



[141]

Fig. 8. The results of the various investigators indicate that the influence on substituents on the ^{13}C chemical shifts are quite regular, additive and predictable. They conclude that the important effects are electronic in nature and that the influence of diamagnetic

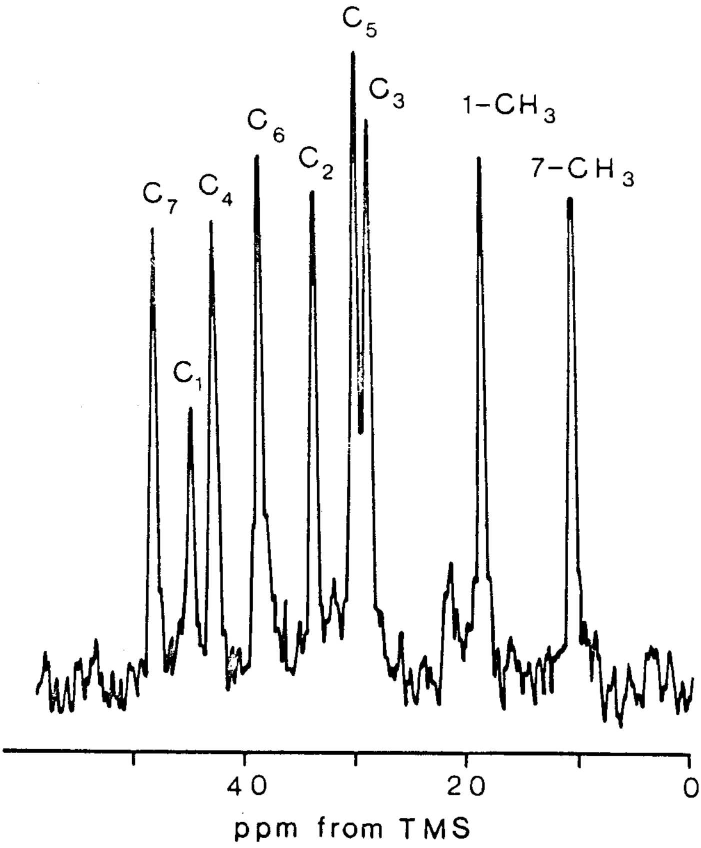
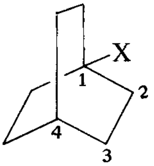


FIG. 8. Proton-decoupled ^{13}C absorption spectrum of 1,7-dimethylnorbornane. (From Lippmaa *et al.* (343).)

anisotropy of nearby groups is negligible: but an important effect, specific for spectra of heavier nuclei, is the gauche 1,4-nonbonded interactions which always leads to diamagnetic shifts (low frequency).

A specific example is norbornyl alcohols in which the introduction of a hydroxyl group causes a 42 to 45 ppm downfield shift in the resonance of the α carbon relative to the unsubstituted carbon and a 6 to 12 ppm downfield shift of the β carbon relative to the unsubstituted carbon. When the hydroxyl group is substituted on the number 2 carbon, the resonance of the C-6 carbon is shifted 9 ppm upfield for an *endo* hydroxyl group and a 5 ppm upfield for the *exo* substituent.

In contrast to the extensive study on bicyclo[2,2,1]heptanes, only a limited amount of work has been reported for the bicyclo[2,2,2]-octanes [142]. (345) The chemical shifts of the number 1 carbon

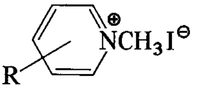


X = H, OCH_3, F, Cl, Br

[142]

upon substitution of X for hydrogen is from 36 to 65 ppm downfield relative to the unsubstituted carbon. The other carbons are affected much less by substitution at the number 1 carbon. A range of 2 to 10 ppm downfield was observed.

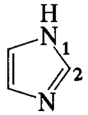
A similar study was made to determine the effect on the chemical shift of the methyl group of *N*-methyl pyridinium iodide (346) by



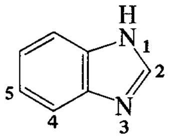
[143]

substitution at the *meta-para* position for a hydrogen. An overall shift of 5·5 ppm relative to the unsubstituted salt was observed. For *para* substituted compounds the shift of the ^{13}C methyl resonance went from +3·49 ppm for $-NH_2$ to $-1{\cdot}06$ ppm for -CN relative to -H. Whereas in the *meta* substituted compounds the range was from $-0{\cdot}40$ ppm in COO Et to 0·44 ppm in $-CH_3$. Excellent shift correlations were obtained with Hammett substituent constants when $\sigma^{\oplus}$ values were used for donor substituents.

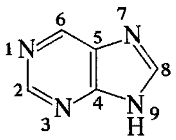
Closely aligned with substituent effects is the influence on the ^{13}C chemical shift of a particular carbon in going from a neutral molecule to a charged species. Detailed studies of chemical shift changes generated by successive protonation of imidazole, benzimidazole, and purine:



[144]



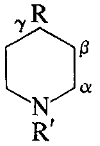
[145]



[146]

confirmed the protonation sites within the molecules. (346) The results indicate tautomeric averaging occurs in purine and that the nearly equal magnitude of the shift values provide little distinction for either N-7 or N-9 as the preferred site for protonation. In aqueous solution the labile proton probably spends equal time at N-7 and N-9. However, successive protonation of purine occurs in the six-membered ring and most probably at the N-1 position. Olah and co-workers (348) have extended their NMR studies of carbocations (carbonium ions) to include ^{13}C spectra of allyl cations. Some of their more recent results are collected in Table XX.

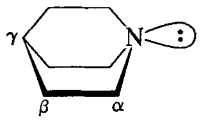
The effect on the ^{13}C chemical shift of several nitrogen heterocycles, when coordinated with nickel(II) acetylacetonate, have been observed for the completely proton-decoupled spectra. (349) The



piperidine derivative

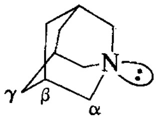
$R = H$ or CH_3

$R^1 = H$ or CH_3



quinuclidine

[147]



azaadamantane

[148]

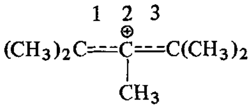
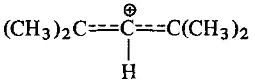
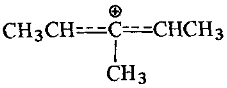
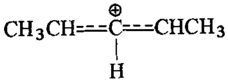
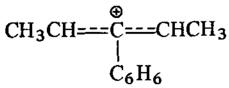
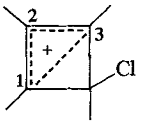
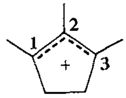
systems studied were piperidine derivatives, quinuclidine, and 1-aza-adamantane. These are σ-electron systems in which the nitrogen lone pair electrons serve as the σ binding site with the paramagnetic nickel(II) acetylacetonate. In every case, alternating ^{13}C contact shifts were obtained for the ligand molecules indicating the relative importance of spin polarization as the mechanism of electron spin transfer through the carbon skeleton. The α and γ carbons were shifted upfield +1·00 ppm (rel.) and 0·1 to 0·2 ppm (rel.) respectively. Whereas, the β carbons are shifted downfield from −0·35 to −1·60 ppm. This range of chemical shifts for the β carbons has been explained on the basis of different conformational preference for the nitrogen lone-pair electrons in the various piperidine derivatives.

5. *Configuration and conformation*

Mention has already been made of the use of ^{13}C spectroscopy to

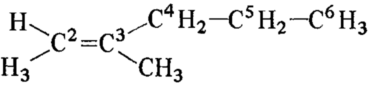
TABLE XX

^{13}C NMR chemical shifts of allyl cations and related reference olefins in SO_2ClF at −70° C (348)

Ion	$^{13}C^a$	
	C_1C_3	C_2
 $\overset{1}{(CH_3)_2C}{=}{=}\overset{\overset{2}{\oplus}}{\underset{\displaystyle CH_3}{C}}{=}{=}\overset{3}{C}(CH_3)_2$	−31·3	+41·3
 $(CH_3)_2C{=}{=}\overset{\oplus}{\underset{\displaystyle H}{C}}{=}{=}C(CH_3)_2$	−41·0	+51·6
 $CH_3CH{=}{=}\overset{\oplus}{\underset{\displaystyle CH_3}{C}}{=}{=}CHCH_3$	−36·0	+33·2
 $CH_3CH{=}{=}\overset{\oplus}{\underset{\displaystyle H}{C}}{=}{=}CHCH_3$	−46·6	+41·9
 $CH_3CH{=}{=}\overset{\oplus}{\underset{\displaystyle C_6H_6}{C}}{=}{=}CHCH_3$	−42·7	+31·8
	−1·6	+16·9
	−54·3	+37·4

^{a} ppm from CS_2.

study configurational effects in bicyclic ring systems with substitution in the *endo* or *exo* positions. Likewise, it was noted that substitution on the olefinic carbons was affected differently depending upon whether the substituent was *cis* or *trans*. A correction term in the empirical calculation must be included to satisfy the different geometrical isomers. Further evidence concerning the effect on the chemical shifts of carbon atoms in spatially crowded alkyl groups was reported. (350) They studied the (*E*) and (*Z*) isomers of the branched disubstituted and trisubstituted ethylenes. It was noted that in (*Z*) conformers of disubstituted ethylenes, α-carbon signals are found invariably at higher fields than the corresponding α-carbon signals in (*E*) conformers. However, in trisubstituted olefins the signal for the methyl carbon, which is on the same carbon as the alkyl group in the (*Z*) conformers (*trans*), is at lower fields than the corresponding α methyl group signal in the (*E*) conformer (*cis*). A case in point is 3-methyl-2-hexene [149] in which $^{13}C_{CH_3}$ in the



E(*cis*)

[149]

(*Z*) conformer is −7·80 ppm downfield from the methyl group in the (*E*) conformer, while $^{13}C_{CH_2}$ is 8·40 ppm upfield in the (*Z*) conformer from that of the *E* conformer. This is essentially the same as that reported by Roberts and co-workers: (323)

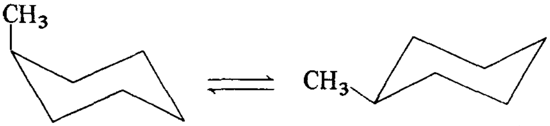
	C_1	C_4	$3CH_3$ rel. to CS_2
cis-3-methyl-2-hexene	180·5	159·8	170·4
trans-3-methyl-2-hexene	180·5	151·3	178·3

The ^{13}C NMR study of some *N*-nitrosamines and *N*-nitrosoanilines demonstrates the *cis-trans* configurational effects. (351) The differences in carbon chemical shifts, $\Delta\delta$, between the corresponding *cis* and *trans* isomers vary from 5·7 to 10·1 ppm for the α carbon, 1·0–4·6 ppm for the β-carbons, and 0·2 to 0·6 ppm for the γ-carbons, with the *trans* isomers giving the lowest field absorptions in the α and β cases.

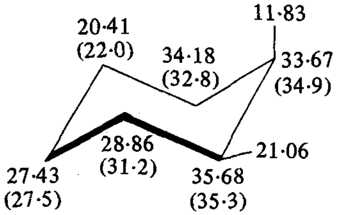
In the case of *N* substituted-*N*-nitrosoaniline, where the substituent is methyl, ethyl, *n*-propyl and *n*-butyl, only one isomer is present which is assigned the *cis* isomer relative to the alkyl and nitroso substituent. In the case of *N*-*t*-butyl-*N*-nitrosoaniline the single isomer is assigned to the *trans* isomer. More significantly, however, the spectrum of *N*-methyl-*N*-nitrosoaniline establishes that rotation around the *N*-phenyl bond is restricted.

Low temperature ^{13}C NMR spectroscopy has been used to observe the different chair conformers of substituted cyclohexanes.

(352, 353) The ^{13}C NMR spectrum of neat methylcyclohexane, at −110°, indicates that the ^{13}C resonance of the axial methyl group is shifted 6 ppm upfield from the equatorial methyl group and that the chemical shifts of the C-3 and C-5 of the axial form are also 6 ppm upfield from those of the equatorial form, as predicted by Dalling and Grant. (354)



The ^{13}C NMR spectra of *cis*-1,2-dimethylcyclohexane [150] were studied as a function of temperature from 160° to 253°K. At lower temperatures both chair conformers were present and the chemical shifts are shown in Fig. 9. (352)



[150]

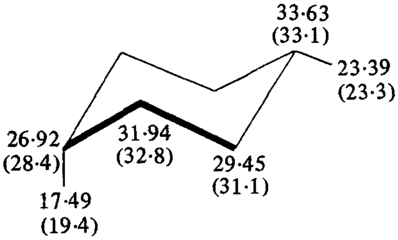


FIG. 9. ^{13}C NMR shifts of *cis*-1,2-dimethylcyclohexane [150] at 158°K and *cis*-1,4-dimethylcyclohexane at 180°K; solvent = CCl_2F_2 + TMS (5 : 1). Values in ppm downfield from TMS. (From Schneider *et al.* (353).)

The temperature dependence of the spectrum of compound [150] yielded $\Delta H^{\pm} = 12$ Kcal/mole and $\Delta F^{\pm} = 9{\cdot}9$ Kcal/mole. Analogous measurements on *cis*-1,4-dimethylcyclohexane produced a similar value, $\Delta F^{\pm} = 9{\cdot}3$ Kcal/mole, for the ring inversion barrier.

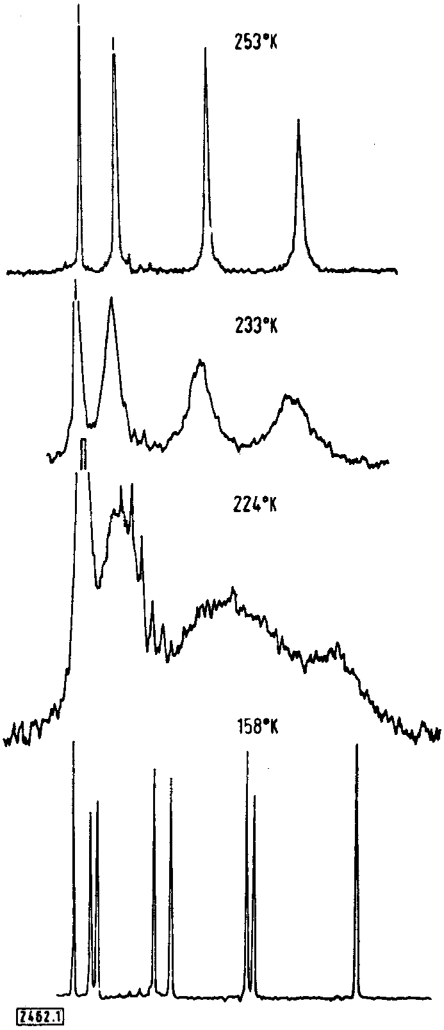
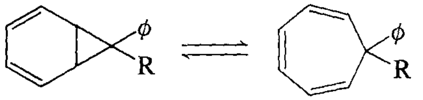
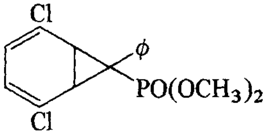


FIG. 10. ^{13}C-NMR spectra of *cis*-1,2-dimethylcyclohexane [150] at different temperatures, measured in CCl_2F_2 + TMS (5:1) using $(CD_3)_2CO$ as lock. (From Schneider *et al.* (353).)

It has also been shown (355) that ethyl 7-phenyl-cycloheptatriene-7-carboxylate [151] and dimethyl-7-phenylcycloheptatriene-7-phosphate [152] exist in valence-tautomeric equilibrium with the corresponding norcaradiene forms, whereas dimethyl 2,5-dichloro-7-phenylnorcaradine-7-phosphonate [153] exists solely in the bicyclic form.



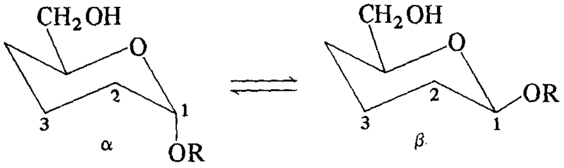
[151] [152]

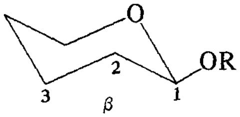


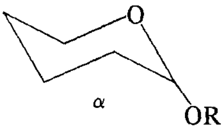
[153]

R = $COOC_2H_5$
= $PO(OCH_3)_2$

The orientation of the substituent at the C-1 atom in anomeric glycosides is very important in carbohydrate chemistry and has received considerable attention. (356-358)



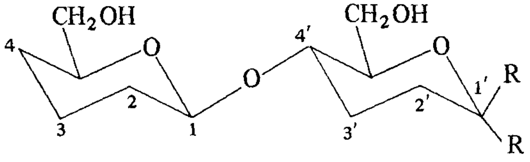




R = CH_3, $C_6H_4NO_2$ O,M,P, C_6H_5

The ^{13}C-signal of the C-1 carbon atom appears between 100 and 107 ppm downfield from TMS. Secondly, the ^{13}C resonance for C-1, with the substituent in the axial position (α), appears at a higher field strength, 2 to 4 ppm, than when the substituent is in the equatorial position (β).

A number of disaccharides have also been investigated in which particular attention was made to the configuration of the glycosidic linkage, (359, 360) as well as the configuration at the anomeric carbon (C-1′). When the hydroxyl group is in the axial (α) position,



the chemical shift of the C-1′ carbon is about 4 ppm upfield from C-1′ for which the hydroxyl group is in the equatorial (β) position.

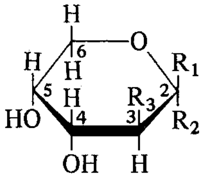
It was also found the linked anomeric carbon in an α (axial) position falls at a higher field strength than the corresponding β (equatorial) linked isomer.

TABLE XXI

^{13}C-1′ NMR chemical shifts for disaccharides (359, 360)

	Chemical shift C-1′ (rel. to CS_2)
Methyl α-D-glucopyranoside	93·4
Kojibiose (1,2α)	96·1
Nigerose (1,3α)	93·4
Maltose (1,4α)	92·4 (92·8)
Sucrose (1,4α)	100·6
Methyl β-D-glucopyranoside	89·3
Sophorose (1,2β)	88·2
Laminaribiose (1,3-β)	89·7
Cellobiose (1,4-β)	89·7 (90·2)
Lactose (1,4-β)	89·7

The use of carbon-13 pulse Fourier transform (PET) NMR has made it possible to study mutarotation of sugar and even observe minor components in the anomeric mixtures which were not observed using the continuous wave (CW) technique. (361, 362) ^{13}C NMR spectra of D-glucose, D-trehalose, cellobiose and maltose, obtained immediately after preparation, indicates only one isomer (Fig. 11). The spectra are, however, time dependent and soon gives rise to resonances for both anomers. A parallel reaction is observed when commercial β-D-fructose is dissolved in H_2O. Two isomers are indicated by the initial ^{13}C spectrum, whereas the equilibrium system corresponds to four components. Based primarily upon chemical shifts, the latter species were identified as the α and β anomers of D-fructopyranose:



$R_1 = CH_2OH, R_2 = OH$ D-fructose [154]
$R_1 = OH, R_2 = CH_2OH$ D-fructose [155]

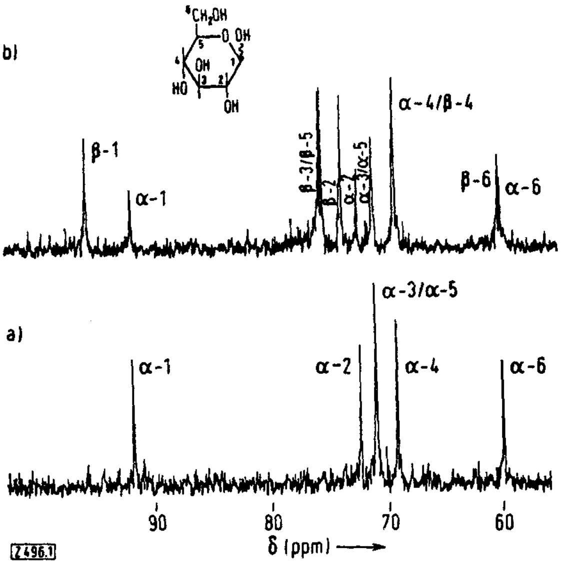
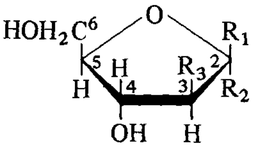


FIG. 11. PFT ^{13}C NMR spectra of D-glucose, 0·5 M in D_2O, 512 pulses, pulse interval 0·8 s; (a) immediately, (b) 3 days after preparation of solution (ppm values relative to external TMS=O). (From Voelter *et al.* (361).)

and the α and β anomers of D-fructofuranose:



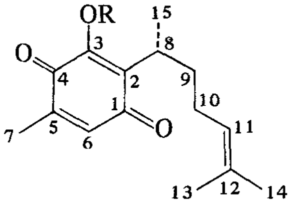
$R_1 = CH_2OH, R_2 = OH$ fructose [156]

$R_1 = OH, R_2 = CH_2OH$ fructose [157]

Measurement of integrated and peak intensities yielded the following equilibrium composition at 36°: 3 ± 1% α-D-fructopyranose, 57 ± 6% β-D-fructopyranose, 9 ± 1% α-D-fructofuranose and 31 ± 3% β-D-fructofuranose.

6. *Natural products*

The application of ^{13}C NMR for the elucidation of structural details of natural products is of considerable interest and importance. Most of the systems are quite large and, as a consequence, they present numerous problems. Nevertheless, complete assignments of the ^{13}C shifts have been reported. Examples include perizone [157] and derivatives thereof. (363) For the more difficult assignments,



R=H

[157]

both noise and specific decouplings are necessary, and typical spectra are shown in Fig. 12.

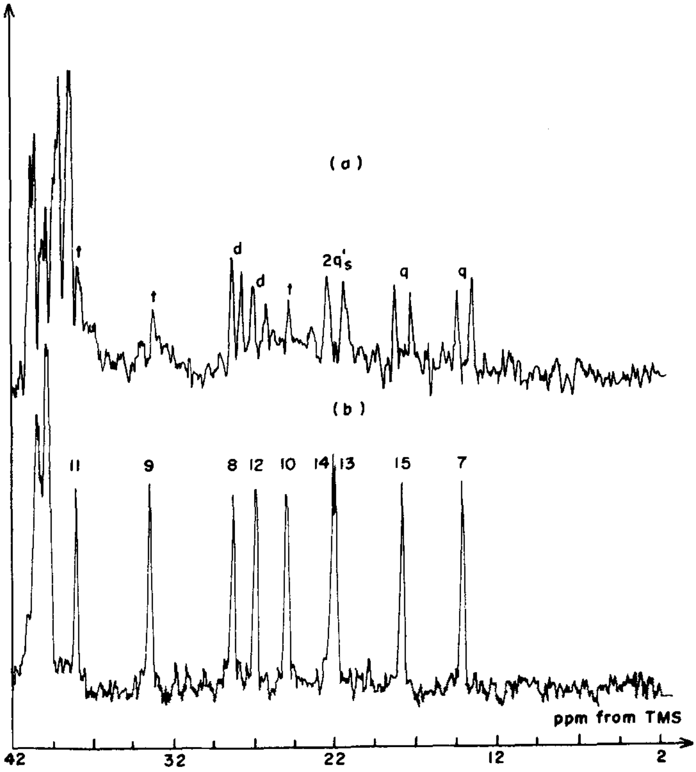
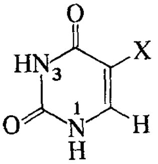


FIG. 12. ^{13}C NMR spectra of dehydroperezone [158]. The top trace, a- was obtained using off-resonance CW decoupling, while b, the lower trace, was obtained using proton noise decoupling.

The ^{13}C spectrum of vitamin B_{12} (cyanocobalamin) (364) and vitamin B_2 (riboflavin) (365) were recorded and assigned. In both cases the assignments were aided by reference to model compounds and selective and off-resonance decoupling.

The ^{13}C spectra of several biologically important heterocyclic bases have been determined. (366) Shifts for uracil [159] thymine [160] and the 5-halouracids have been obtained and were correlated with π and total electron charge densities calculated with extended-Huckel theory.



X = H – uracil [159]
= CH_3 thymine [160]
F
Cl
Br
I

Spectra of amino acids and peptides, containing the natural abundance ^{13}C isotope, were reported. (367-369) In general, the ^{13}C signal of the carboxyl group carbon is found between 170 to 183 ppm downfield from TMS, the C_α signal is found between 40 and 62 ppm downfield, C_β signal between 17 and 60, the C_γ and C_δ signals are found between 17 and 50 ppm downfield, and aromatic carbon signals are found between 110 to 140 ppm. A typical spectrum, *N*-acetyl-L-cysteine [161], is shown in Fig. 13. (367)

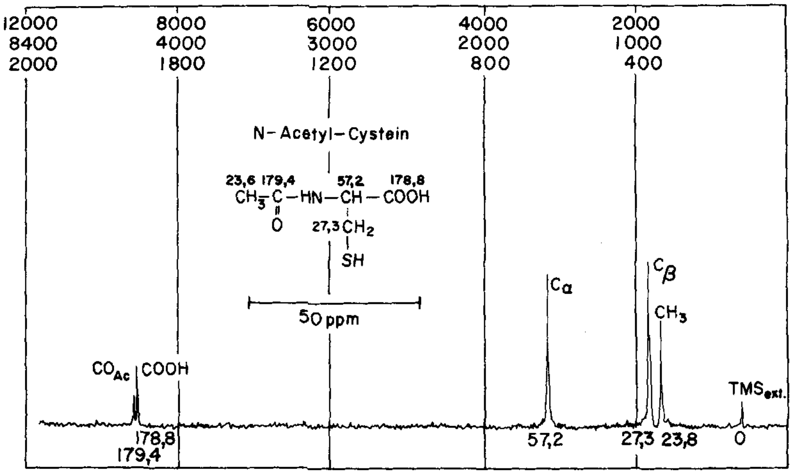
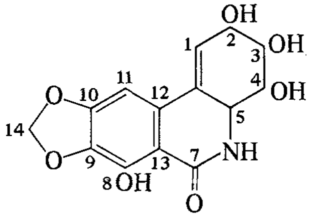


FIG. 13. ^{13}C-chemical shift of *N*-acetyl-L-cysteine [161]. (From Voelter (367).)

^{13}C NMR has proven quite useful in alkaloid studies, e.g., the revised structure for narciclasine (370) [162] was based primarily



[162]

upon ^{13}C and ^{1}H spectra. The previously proposed structure had the hydroxyl groups at the C-1, C-2 and C-3 positions and the double bond at C-5, C-6 position.

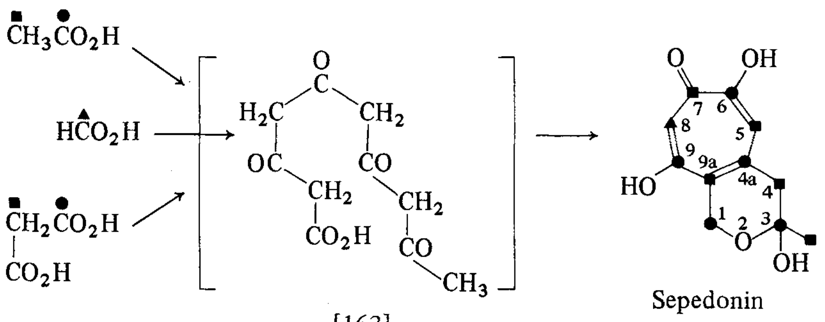
Roberts and co-workers (371) have made the assignments of nearly all the resonances of nicotine, quinine and several amaryllidaceae and veratium (372) alkaloids. Use was made of noise decoupling, both total and specific, and the shifts from a number of derivatives.

A number of interesting ^{13}C steroid studies were reported. (373, 374) Some of the systems investigated were: conessine, dihydroconessine, conanines, 5α-cholestane and 5α-ergostane.

7. ^{13}C *Tracer studies*

The study of biosynthetic pathways by ^{13}C tracer studies is a well known and well documented technique. However, the application of ^{13}C NMR in elucidating a biosynthetic pathway is a new technique. (375-378)

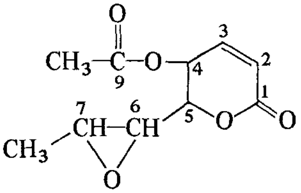
By analyzing the individual ^{13}NMR spectra of sepedonin [163] labeled by $^{13}CH_3CO_2H$, $CH_3\ ^{13}CO_2H$, and $H^{13}CO_2H$, and noting



[163]

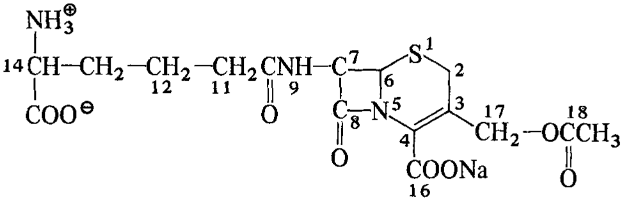
which signals were enriched by the appropriate labeled precursors, it was proposed (375) that sepedonin is formed by the insertion of the formate carbon atom between the third and fourth carbon atoms of a ten-carbon polypeptide chain derived from acetate [163].

Similar biosynthetic studies were carried out on asperlin (376) [164] and cephalosprin C (377) [165] using sodium 2-^{13}C-acetate and sodium 1-^{13}C acetate as labeling species. The ^{13}C spectra for the labeled aspulin showed increased intensity from the signals of C_2, C_4, C_6, C_8 and C_{10}.



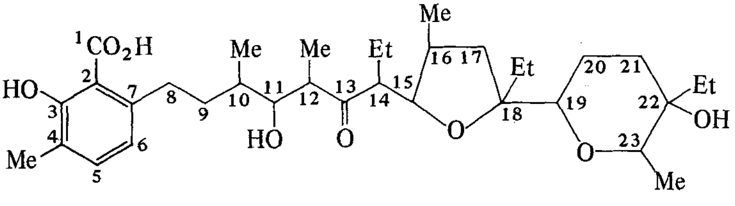
[164]

For Cephalosporin C, the use of $CH_3{}^{13}COONa$ resulted in enrichment of the ^{13}C signals of the C_{10}, C_{15} and C_{18}, and the use of $^{13}CH_3COONa$ resulted in enhancement of the signals of C_{11}, C_{12}, C_{13}, C_{14} and C_{19}.



[165]

Incorporation experiments (378) with ^{13}C labeled substrates revealed that the carbon-skeleton of antibiotic X-537A [166] is assembled from acetate, propionate, and butyrate units.



[166]

The use of sodium[1-^{13}C]butyrate in X-537A fermentations, followed by ^{13}C NMR, demonstrated that all three ethyl groups are derived from butyric acid. In addition, similar experiments with [1-^{13}C]propionate confirmed that the *C*-methyl groups at C-4, 10, 12 and 16 are propionate derived.

8. *Polymers*

Numerous ^{13}C NMR investigations of vinyl polymers have been reported. (379-384) Typical data for poly(vinyl chloride) (PVC) illustrating sensitivity, resolution and tacticity are shown in Figs. 14 and 15.

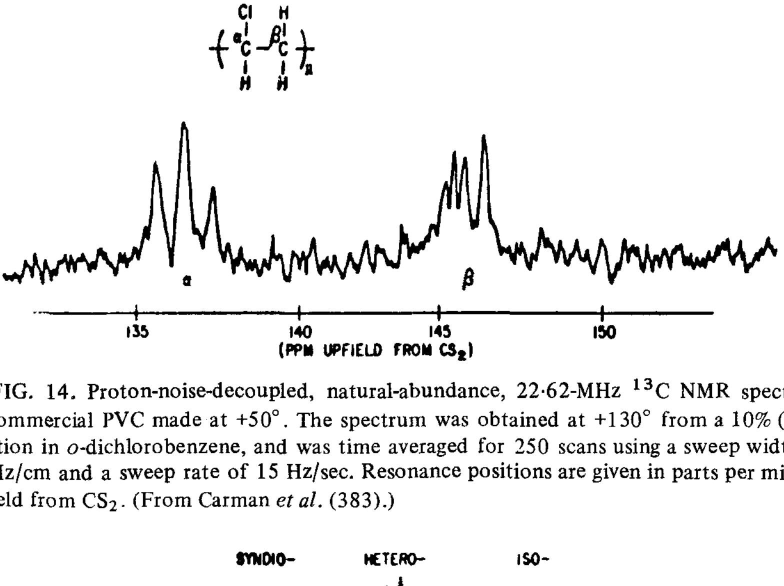


FIG. 14. Proton-noise-decoupled, natural-abundance, 22·62-MHz ^{13}C NMR spectrum of commercial PVC made at +50°. The spectrum was obtained at +130° from a 10% (w/v) solution in *o*-dichlorobenzene, and was time averaged for 250 scans using a sweep width of 10 Hz/cm and a sweep rate of 15 Hz/sec. Resonance positions are given in parts per million upfield from CS$_2$. (From Carman *et al.* (383).)

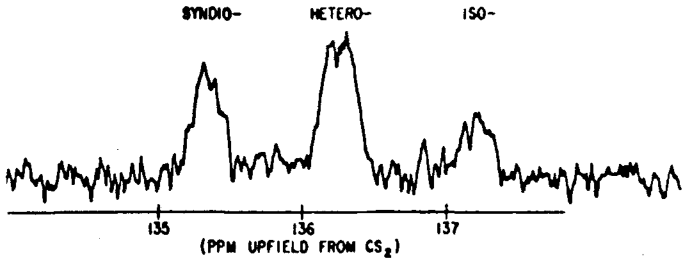


FIG. 15. Proton-noise-decoupled, natural-abundance, 22·62-MHz ^{13}C NMR spectrum of the methine carbons in a commercial PVC made at +50°. The spectrum was obtained at +130° from a 10% (w/v) solution in *o*-dichlorobenzene, and was time averaged for 400 scans using a sweep width of 2·0 Hz/cm and a sweep rate of 3 Hz/sec. Resonance positions are given in parts per million upfield from CS$_2$. (From Carman *et al.* (383).)

9. *Organometallics*

^{13}C NMR investigations of organometallics are of considerable interest and importance, particularly with respect to bonding types. (385-391) Representative data are illustrated in Table XXII.

TABLE XXII

^{13}C chemical shift for some organometallic complexes (385)

Compound	Chemical shift (rel. to TMS) (ppm)	
$(CO)_9Co_3Br$	CO	186·2
$(CO)_3W(\pi C_5H_5)CH_3$	(*cis*)CO	239·2
$(CO)(\pi C_5H_5)Fe(CN^{\ominus})K^{\oplus}$	C_5H_5	82·6
$(\pi C_5H_5)TiCl_2$	C_5H_5	121·3
$(CO)_3W(\pi C_5H_5)(CH_3)$	CH_3	−28·9
$(CO)_2(\pi C_5H_5)FeCO(CH_3)$	CH_3	+52·0

The ^{13}C chemical shift of the carbon atoms of a number of methyl substituted organometallic compounds have been obtained (385-389) and studied as a function of the other ligands bonded to the metal. In the case of a series of methyl platinum complexes, the ^{13}C chemical shift of the methyl carbon varies from −28 ppm to +2·0 ppm (TMS) in going from *trans*-$Pt(CH_3)Cl(AsMe_3)_2$ to *fac*-$Me_3Pt(AsMe_3)_2I$, respectively. In a series of linear, branched, and cyclic methyl siloxanes, a 12 ppm chemical shift range is observed for the methyl carbon is going from $(CH_3)Si(OCH_3)_3$ to $(CH_3)Si[(Si(CH_3)_3]_3$. Whereas a 10·3 ppm chemical shift of the methyl carbon is observed for a series of methyl tin compounds in the successive replacement of the methyl group of $(CH_3)_4$ Sn for $-SCH_3$.

V. ORGANOMETALLIC COMPOUNDS

A. Introduction

The study of complex and highly reactive organometallic species presents a number of interesting problems to the spectroscopist. The primary complications are: handling, sampling, and interpretation, with emphasis upon the last. Most investigations to date have been concerned with structural details and this is, of course, the necessary starting point. As a general rule, the conformational and associative processes exhibited by numerous organometallics seriously restricts the interpretation and thus, necessitates additional experimental details. Because of the vast array of bonding types and energies, the organometallic systems provide interesting examples for which relationships may be developed between reactivity and structure. A comprehensive survey of studies of dynamic organometallic compounds of the transition metals by means of NMR was conducted by Vrieze and Van Leeuwen. (392) As a consequence, these flexible systems will be treated only sparingly in this report.

The most popular organometallic system for study since 1900 has evolved around Grignard compounds and a relatively simple picture has emerged in which the composition is pictured as an equilibrium involving R_2Mg, MgX_2 and RMgX species. Numerous investigators have anticipated that NMR would be the ideal tool for studying such systems, but both nuclear magnetic resonance and infrared have met with only limited success. Recent data, however, indicates that the tide may have changed. Parris and Ashby (393) reported direct observation of RMgX and R_2Mg species individually in ether solution. Their results are consistent with earlier presentations of the composition of Grignard reagents by the Schlenk equilibrium:

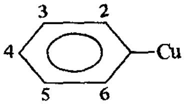
$$R_2Mg + MgX \rightleftharpoons 2RMgX.$$

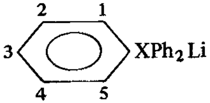
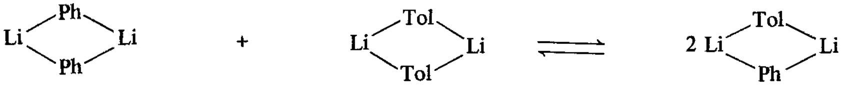
The relationship between NMR parameters and reactivity is also of considerable interest and importance, and has been the subject of numerous investigations. There has, however, been a significant paucity of usable data on the subject, particularly from proton spectra. The probability of detecting such a relationship is enhanced considerably if ^{13}C spectra are considered and this assumption is based primarily upon the extended range of ^{13}C resonances. There are, however, a number of restrictions, e.g., low solubility and low signal-to-noise of conventional ^{13}C spectra. The latter may be partially overcome by pulsed Fourier and a recent report by Clark and co-workers (394) is encouraging. They found a direct relationship between ^{13}C parameters, *trans*-influence, and ligand reactivity for a series of methylplatinum compounds.

This portion of the survey will be concerned with NMR parameters used in arriving at the various structures. Organometallic compounds of Groups I through VIII are presented in Tables I through IV. For Groups I to IV most of the values correspond to averaged spectra and whenever possible the equilibrium constants are included.

TABLE XXIII

NMR parameters for groups I and II organometallic compounds

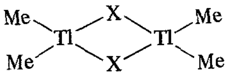
Compounds	Chemical shift (ppm)						Comments	Ref.
	H_2	H_3	H_5	H_6	CH_3			
[167] *o*-Tolylcopper				7·9	2·8			(395)
[168] *p*-Tolylcopper	7·9	7·0	7·0	7·9	2·3			(395)
[169] *o*-Anisylcopper		6·2		8·6	2·3			(395)
[170] 2,4-Dimethylphenylcopper				7·9	2·7			(395)
[171] $CH_3Au \leftarrow P(CH_3)_3$	CH_3-Au = 0·4					J(H-C-Au-P) = 8·7 J(H-C-P) = 8·9	Rapid ligand exchange at 30° with rate dependent upon concentration of free ligand	(396)
[172] $(CH_3)_3Au \leftarrow P(CH_3)_3$	CH_3-Au-*trans* CH-Au-*cis*				0·9 0·0	J(H-C-Au-P *cis*) = 7·8 J(H-C-Au-P *trans*) = 9·7 J(H-C-P) = 10·1	Ligand exchange was not detectable at 30°	(396)
[173] $AgBF_4$·Norbornene							K = 420	(397)
[174] $AgBF_4$·Cyclohexene							K = 2·6	(397)
[175] $AgBF_4$·1-Methylcyclohexene							K = 0·5 Ag + olefin ⇌ [Ag·olefin]$^{\oplus}$ For equal molar concentration $K = \dfrac{\dfrac{\Delta\ \text{obsd}}{\Delta\ \text{max.}}(\text{complex})}{\dfrac{\Delta\ \text{max} - \Delta\ \text{obsd}}{\Delta\ \text{max}}(\text{complex})^2}$	(397)

	$H_{1,5}$	$H_{2,4}$	H_3	J_{12}	J_{13}	J_{14}	J_{15}		
[176] X = C	7·3	6·5	5·9	8·3	1·2	0·4	1·8		(398)
[177] X = Si	7·3	7·0	6·9	7·3	1·4	0·7	1·3		(398)
[178] X = Ge	7·4	7·0	6·9	7·2	1·4	0·6	1·2		(398)
[179] X = Sn	7·5	6·9	6·9	7·0	1·5	0·5	0·9		(398)
[180] X = Pb	7·8	6·9	6·8	6·9	1·5	0·6	0·8		(398)
 [181] [182] [183]								Li resonance appears as a singlet at room temperature, but splits into a doublet at 212°K. $E_a \approx 29{\cdot}5$ KJ/mole	(399)

	^{199}Hg	$J(^{199}Hg-^{19}F)$	$^3J(^{199}Hg-H_o)$	
[184] $(o\text{-}CF_3{\cdot}C_6H_4)_2Hg$	17·89347 MHz	26·5	110	(400)
[185] $(o\ CF_3{\cdot}C_6H_4)HgBr$	17·88698 MHz	28·8	199	(400)
[186] $(m\text{-}CF_3{\cdot}C_6H_4)_2Hg$	17·89600 MHz	9·5	108	(400)
[187] $m\text{-}CF_3{\cdot}C_6H_4HgBr$	17·88817 MHz	18·3·	202	(400)

TABLE XXIV

NMR parameters for groups III and IV compounds

Compounds	Chemical shift (ppm)	Coupling constant (Hz)	Comments	Ref.
				
[188] X = OEt	–	$^2J(\text{Tl–H}) = 371$		(401)
[189] X = OPh	–	$^2J(\text{Tl–H}) = 368$		(401)
[190] X = SO_2Me	–	$^2J(\text{Tl–H}) = 426$		(401)
[191] $(CH_3)_3SnI$	0·72	$J(^{117}\text{Sn–C–H}) = 56{\cdot}2$ $J(^{119}\text{Sn–C–H}) = 58{\cdot}8$		(402)
[192] $(CH_3)_3SnBr$	0·58	$J(^{117}\text{Sn–C–H}) = 57{\cdot}2$ $J(^{119}\text{Sn–C–H}) = 59{\cdot}6$		(403)
[193] $(CH_3)_4Pb$	0·73	$J(^{207}\text{Pb–C–H}) = 61{\cdot}4$		(403)
[194] $Br(CH_3)_2Sn\text{–}Mn(CO)_5$	1·08	$J(^{114}\text{Sn–C–H}) = 45{\cdot}3$		(404)
[195] $(CH_3)_3Sn\text{–}Mn(CO)_5$	0·5	$J(^{119}\text{Sn–C–H}) = 48{\cdot}9$		(404)

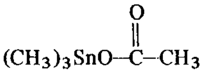
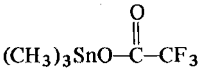
X-$Bu_2SnOSnBu_2X$				
[196] X = F	$^{119}Sn = +168$		Rel. to $Sn(CH_3)_4$	(405)
[197] X = Cl	$^{119}Sn = 145$ and 94		Rel. to $Sn(CH_3)_4$	(405)
[198] X = Br	$^{119}Sn = 141$ and 87		Rel. to $Sn(CH_3)_4$	(405)
[199]  $(CH_3)_3SnO{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$	(Sn-C-H) = 0·51	$J(^{117}Sn\text{-}C\text{-}H) = 55{\cdot}9$ $J(^{119}Sn\text{-}C\text{-}H) = 58{\cdot}4$		(406)
[200]  $(CH_3)_3SnO{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CF_3$	(Sn-C-H) = 0·68	$J(^{117}Sn\text{-}C\text{-}H) = 57{\cdot}4$ $J(^{119}Sn\text{-}C\text{-}H) = 60{\cdot}0$		(406)
[201] $(CH_3)_3SnC_6H_5$	–	$J(^{117}Sn\text{-}C\text{-}H) = 50{\cdot}5$ $J(^{119}Sn\text{-}C\text{-}H) = 52{\cdot}9$		(407)
[202] $(CH_3)_3SnC_6H_5\text{-}Cr(CO)_3$	–	$J(^{117}Sn\text{-}C\text{-}H) = 53{\cdot}0$ $J(^{119}Sn\text{-}C\text{-}H) = 55{\cdot}4$		(407)
[203] $(C_6H_5)_2Sn(acac)_2$	–		Single acetylacetonate CH_3 resonance ($\delta = 2{\cdot}0$) observed at 30°, suggesting equilibration of ligands	(408)

TABLE XXV

NMR parameters for groups V and VI organometallic compounds

Compounds	Chemical shift (ppm)	Coupling constant (Hz)	Comments	Ref.
[204] NbF_5–SbF_5–SO_2ClF			Broad lines are observed at room temperature suggesting fast fluorine exchange	(409)
[205] $(4\text{-}FC_6H_4)_3As$	$^{19}F = 112{\cdot}8$	$^3J(^{19}F\text{–}H) = 8{\cdot}6$	Chemical shift relative to $CFCl_3$	(410)
[206] $TaF_5 \cdot Et_2O$	$^{19}F = -157{\cdot}7$ ppm	$^4J(^{19}F\text{–}H) = 5{\cdot}8$	Chemical shift relative to external CF_3COOH	(411)
[207] NbF_5	$^{19}F = -288$ ppm		Chemical shift relative to aqueous HF	(411)
[208] $((CH_3)_3Ge)_3Sb$–$Cr(CO)_5$	Ge–C–H = 0·06			(412)
[209] $(CO)_5CrC(CH_3)$–$N(C_6H_5)_2$	$CH_3 = 2{\cdot}84$ $C_6H_5 = 7{\cdot}60$			(413)
[210] $Mo(CO)_2Cl_2$–$(AsCH_2As)_2$	$CH_2 = 5{\cdot}74$	$J_{AB} = 11$, $\Delta\nu_{AB} = 109$	For bidentate As–CH_2–As group	(414)
		$J_{AB} = 14$, $\Delta\nu_{AB} = 47$	For monodentate As–CH_2–As group	(414)
[211] $W(CO)_2Cl_2$–$(AsCH_2As)_2$	$CH_2 = 5{\cdot}59$	$J_{AB} = 11$, $\Delta\nu_{AB} = 21$	For bidentate As–CH_2–As group	(414)
		$J_{AB} = 13$, $\Delta\nu_{AB} = 59$	For monodentate As–CH_2–As group	(414)

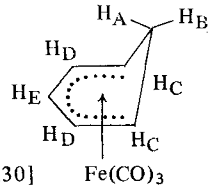
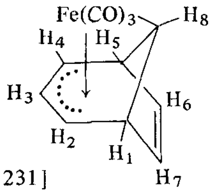
TABLE XXVI

NMR parameters for group VIII organometallic compounds

Compounds	Chemical shift (ppm)	Coupling constant (Hz)	Comments	Ref.
Q = di-*t*-butylphosphine				
[212] *trans*-RhCl(CO)Q_2		J(P–H) = 347 J(P–P) = 321 J(P′–H) = 0		(415)
[213] *trans*-IrCl(CO)Q_2		J(P–H) = 357 J(P–P) = 315 J(P′–H) = –8		(415)
[214] *trans*-NiI_2Q_2		J(P–H) = 352 J(P–P) = 355 J(P′–H) = 0		(415)
[215] *trans*-PdI_2Q_2		J(P–H) = 349 J(P–P) = 515 J(P′–H) = 0		(415)
[216] *trans*-PtI_2Q_2		J(P–H) = 374 J(P–P) = 447 J(P′–H) = –11		(415)
[217] $HCo[(PhO)_3P]_4$	Co–H = –14·5		Quintet at 30° which collapses to a singlet at –55°, suggesting a non-rigid model	(416)
$IrHCl_2(PBu^t{}_2R)_2$				
[218] R = CH_3	Ir–H = –50·5		The *t*-butyl resonance forms a 1:2:1 triplet showing that J(P–P) is large and that the phosphines are probably *trans*	(417)
[219] R = CH_2–CH_3	Ir–H = –49·6			
[220] R = CH_2–CH_2–CH_3	Ir–H = –50·0			

TABLE XXVI—*cont.*

Compounds	Chemical shift (ppm)	Coupling constant (Hz)	Comments	Ref.
[221] $HCo(PF_3)_4$	Co–H = −12·7 ^{19}F = −64·7	J_{HP} = 5·0 J_{HF} = 9·7	Chemical shifts rel. to $CClS_2H$. Low temperature spectra yield axial and equatiorial resonances	(418)
[222] $HRh(PF_3)_4$	Rh–H = −9·9 ^{19}F = −67·6	J_{HP} = 57·0 J_{HF} = 16·5 J_{HPh} = 5·5	Chemical shifts rel. to $CClS_2H$. Low temperature spectra yield J_{HP} *trans* = 215 H_2, and axial and equatorial resonances	(418)
[223] $HRu(Pme_2Ph)_3$–(CO)Cl *cis* H,Cl; *trans* Cl, CO	Ru–H = −6·6			(419)
[224] *trans*-$HRu[C_2H_4\text{–}(PEt_2)_2]_2Cl$	Ru–H = −21·8			(419)
[225] *trans*-$HFe(C_2H_4\text{–}(PEt_2)_2)_2Cl$	FeH = −33·8			(419)
[226] *trans*-$[HRh(C_5H_5N)_4\text{–}Cl]^{\oplus}$	Rh–H = −18·6			(419)
[227] *cis*-$[PtCl_2(Bu_3P)((PhO)_3P)]^2$	P = −7·8 P′ = −62·8	J(Pt–P) = 3159 J(Pt–P′) = 6304 J(P–P) = 20·5	Chemical shifts rel. to 85% H_3PO_4	(420)

[228] *trans*-$[PtCl_2(Bu_3{}^nP)((PhO)_3P)]$	P = −4·6 P′ = −88·9	J(Pt–P) = 2570 J(Pt–P′) = 4116 J(P–P′) = 715	Chemical shifts rel. to 85% H_3PO_4	(420)
[229] $H–C{\equiv}C–C(OH)(CH_3)_2$ $Pt(Ph_3P)_2$	(PH) = 7·30 (CH_3) = 1·32 (CH) = 6·24	J(Pt–C≡C–H) = 59·5		(421)
 [230]	δ_A = 2·08 δ_B = 3·10 δ_C = 4·35 δ_D = 5·87 δ_E = 7·37	J_{AC} = 6·5 J_{BC} = 0		(422)
 [231]	$\delta_{1,5}$ = 3·10 $\delta_{2,4}$ = 4·70 δ_3 = 4·30 $\delta_{6,7}$ = 6·30 δ_8 = 0·60	J_{12} = 5·5 J_{18} = 6·3 J_{17} = 1·5 J_{28} = 1·4 J_{32} = 6·1 J_{31} = 1·2 J_{75} = 1·1		(423)

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Nuclear Magnetic Resonance of Alkaloids

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I. INTRODUCTION

Papers demonstrating the power of NMR spectroscopy in the elucidation of alkaloid structures first appeared in 1958 and 1959 and a survey of this early work (covering the literature to June 1960) has been made. (1) A comprehensive compilation of NMR data of alkaloids studied before 1963 has been published (2) and a second volume in preparation will cover alkaloids described in 1964 and 1965. A discussion of some of the NMR work published subsequent to this period may be found in later volumes of "The Alkaloids". (3)

This article describes characteristic features of the NMR spectra of alkaloids, illustrated by examples taken predominantly from papers published during the period January 1969–June 1972. In many of these papers alkaloid structures have been assigned using NMR-structure correlations established prior to the period under review and in some cases this work has been included.

The classification of the alkaloids into groups follows that adopted in the Chemical Society specialist report on alkaloids (4) and in the recent comprehensive book, (5) so as to facilitate the reading of this review in conjunction with these works dealing largely with the chemistry of the alkaloids. The classification occasionally differs from that in alkaloid texts in that on the basis of the volume of NMR data available a relatively small alkaloid group may be allotted a full sub-section and an important family incorporated into a related group. In addition if NMR spectral similarities between certain alkaloids are great enough then these alkaloids are discussed together even though this necessitates removal of the alkaloid from its "natural" section. Steroidal alkaloids are not included in this review since these were covered in the article on the NMR spectra of steroids contained in Volume 3 of this series (6) and peptide alkaloids are better covered in a review on the NMR spectra of peptides. However, some simple parent systems, products of alkaloid degradation (with the exception of non-nitrogenous products), and some intermediates obtained during an alkaloid synthesis are included in the review.

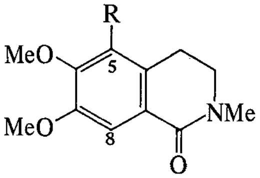
Throughout the review NMR spectral data on alkaloids mentioned in the text are given with the structural formulae and unless otherwise indicated the quoted chemical shifts (δ) are those of the protons.

II. THE ISOQUINOLINE ALKALOIDS

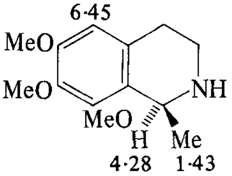
A. *Simple Isoquinoline Alkaloids*

N-Methylthalidaldine ([1], R = MeO) and *N*-methylcorydaldine ([1], R = H) (7) are characterized by the low field absorption of the 8-aromatic proton (δ 7·43 and δ 7·58 respectively) arising from the deshielding influence of the amido group [cf. δ 6·58 for 5-H in ([1], R = H)]. The *N*-methyl protons also absorb at lower field (δ 3·10) than in *N*-methyltetrahydroisoquinoline (δ 2·32). Unlike the situation in the aporphine alkaloids (section IID) all three methoxyl group protons in ([1], R = MeO) absorb at similar field (δ 3·83, 3·86, 3·88).

The NMR spectrum of *O*-methylanhalonidine (8) [2] provides an example of the values of chemical shifts observed in the simple tetrahydroisoquinoline alkaloids. Comparison of this spectrum with that of [3] (9) shows identical chemical shifts for the single aromatic

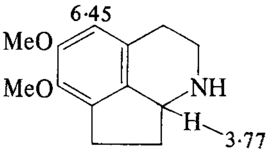


[1]



MeO 3·87, 3·87, 3·97
(in $CDCl_3$)

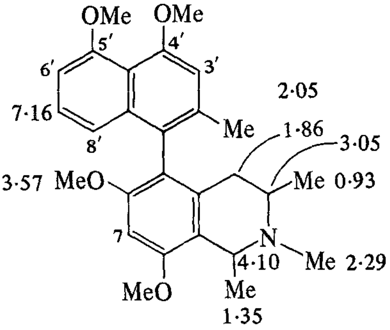
[2]



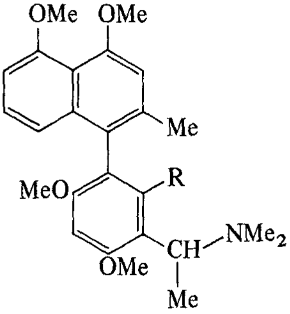
(in $CDCl_3$)

[3]

proton in both compounds even though protons *para* to methoxyl are normally shielded. In addition the angular Ar*CH*N proton in [3] absorbs 0·51 ppm to higher field of the 1-proton in [2]. In *O,N*-dimethylancistrocladine [4] (10) attachment of the naphthalene nucleus at the 5-position was suggested by the unusual shielding of the olefinic methyl protons (δ 1·28) in the derived methine ([5], R = CH=CHMe) and of the corresponding methyl protons (δ 0·53) in ([5], R = CH_2CH_2*Me*).



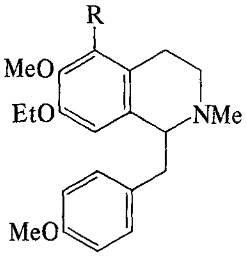
MeO at C(8), C(4′), C(5′), 3·89, 3·95, 3·98,
3′-H and 7-H, 6·47, 6·78; 6′-H and 8′-H, 6·85, 6·74
(in $CDCl_3$)
[4]



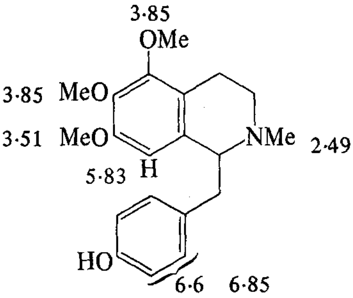
[5]

B. Benzylisoquinoline Alkaloids (including Emetine group)

In benzylisoquinolines the 8-aromatic proton is shielded by the benzylic aromatic ring. This is clearly illustrated by the chemical shifts (δ 6·09 and 6·58) of the 5- and 8-protons in ([6], R = H) [the singlet at δ 6·58 being absent in the spectrum of [6], R = D (11)].



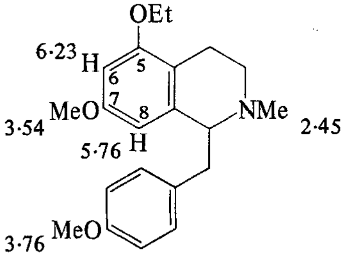
[6]



(in $CDCl_3$)

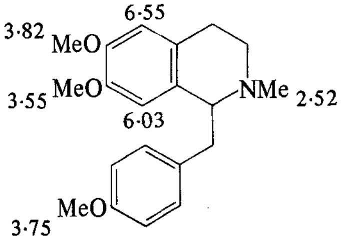
[7]

Use of this criterion aided the assignment of structures to thalifendlerine [7] (12) and the ethoxydimethoxybenzylisoquinoline [8] (13) (δ 8-H 5·83 and 5·76 respectively; cf. δ 6·23 for 6-H in [8]).



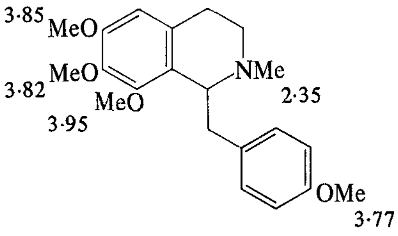
[8]

The *N*-methyl protons in [7] and [8] absorb "normally" at δ 2·49 and δ 2·45 but the 7-*O*-methyl protons in [7] absorb (δ 3·51) to higher field of the other *O*-methyl protons (δ 3·85) and this effect is also noted in the spectrum of [8] in which the *O*-methyl protons in the benzyl group aromatic ring absorb at lower field (δ 3·76) than those in the isoquinoline ring (δ 3·54). (13) Effects such as these have been studied in detail (14) and discussed in terms of the orientation of the benzyl ring with respect to ring A. Thus [9] showing the upfield shift of the 8-aromatic proton (0·52 ppm with respect to 5-H) and of the 7-*O*-methyl protons (0·27 ppm with respect to the 6-*O*-methyl protons) must adopt the conformation shown with the benzyl ring shielding 8-H and the 7-*O*-methyl protons. In contrast [10] does not show the shielding of the 7-*O*-methyl protons and must exist in the conformation shown as a result of interactions arising from the presence of the 8-methoxyl group. Conformation [10] is supported by the upfield shift (δ 2·35) for the *N*-methyl protons in [10] (cf. 2·52 in [9]). That the *N*-substituent is able to influence the preferred conformation is



(in $CDCl_3$)

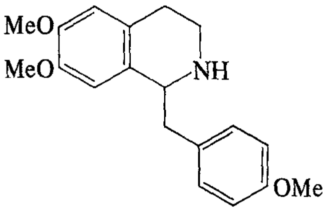
[9]



(in $CDCl_3$)

[10]

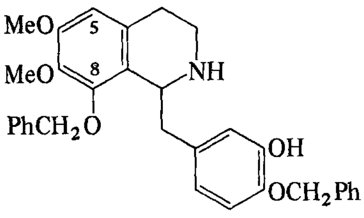
shown by [11] in the NMR spectrum of which no shielding of 8-H is observed.



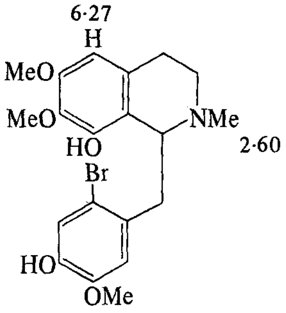
MeO 3·83, 3·80, 3·78,
5-H, 8-H, 6·63, 6·58
(in $CDCl_3$)
[11]

In the benzylisoquinoline [12] (15) the two benzylic methylene groups may be distinguished since the 8-benzyloxymethylene protons absorb as an AB quartet (δ 5·25 and 4·88, $J = -11$ Hz) as a consequence of restricted rotation.

Structures [13] and [14] were assigned (16) to the isomeric diphenolic isoquinolines from the different chemical shifts (δ 6·27 in [13]; δ 6·45 in [14]) of the 5-aromatic protons since previous work had shown similar chemical shift differences in isomeric 6,7,8-hydroxy, dimethoxy-1,2,3,4-tetrahydroisoquinolines. The difference in chemical shift between the ring A aromatic protons in [16] is much smaller (0·08 ppm) than in [15] (1·05 ppm). (17)

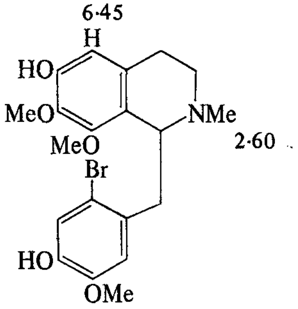


[12]



MeO:	3·82	3·84	3·85
Aromatic protons	6·87	7·00	

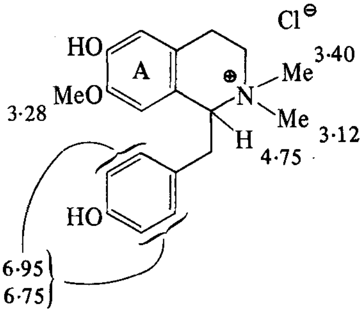
(in $CDCl_3$)
[13]



MeO:	3·76	3·79	3·80
Aromatic protons	6·88	6·99	

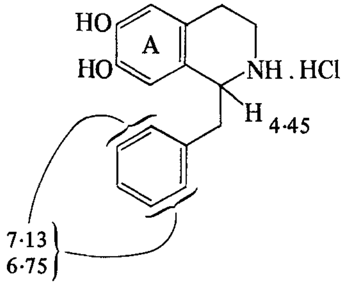
(in $CDCl_3$)

[14]



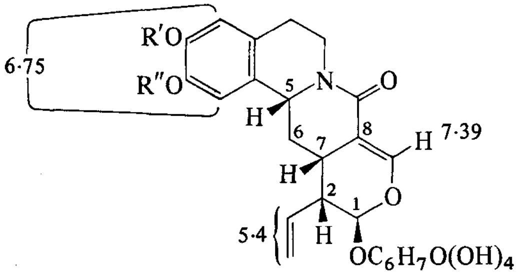
Ring A aromatic protons 6·70, 5·65

[15]



Ring A aromatic protons 6·60, 6·52

[16]



MeO: 3·79

(R′ or R″ = Me or H)

(in DMSO-d_6)

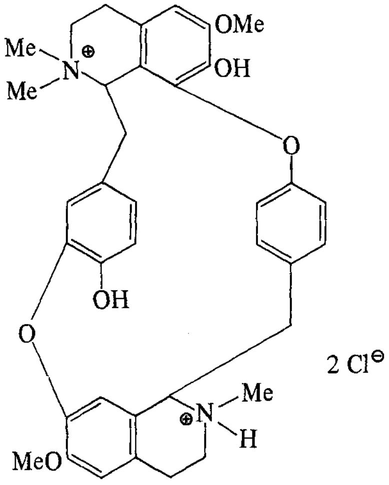
[17]

Chemical shifts for the emetine type compound alangiside (18) are shown in [17].

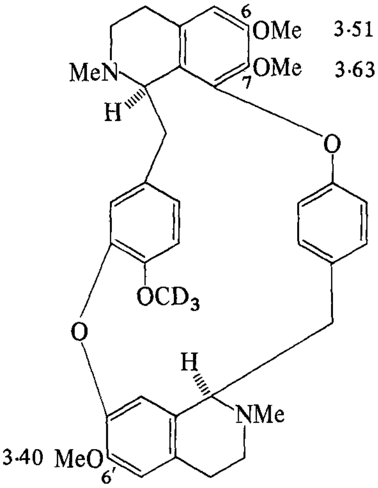
C. *Bisbenzylisoquinoline Alkaloids (including Benzylisoquinoline-Aporphine Alkaloids)*

The long accepted structure for tubocurarine has been shown (19) to be incorrect. The structure [18] is consistent with the NMR results: three *N*-methyl signals one of which (non-quaternary) moves 56 Hz to high field on the addition of NaOD.

The NMR spectrum (C_6D_6) of *O*-trideuteriomethylchondrofoline (20) [19] showed the 6- and 6′-methoxyl group protons at δ 3·51 and δ 3·40 and the 7-methoxyl protons (situated between the two ether substituents) at δ 3·63. From a study of the spectra of related systems (e.g. [20] and [21]) (20) it was possible to distinguish between the two diastereoisomeric series from the position of the *N*-methyl proton resonances. Thus for ([21]; 1,1′ = *S,S* or *R,R*) very similar δ values (e.g. 2·28 and 2·24) were observed as compared with δ values of *ca.* 2·28 and 2·03 for ([20]; 1,1′ = *S,R* series). In these compounds the 4″-methoxyl protons resonate at higher field and the 7-methoxyl protons at lower field than the 6″-methoxyl protons.

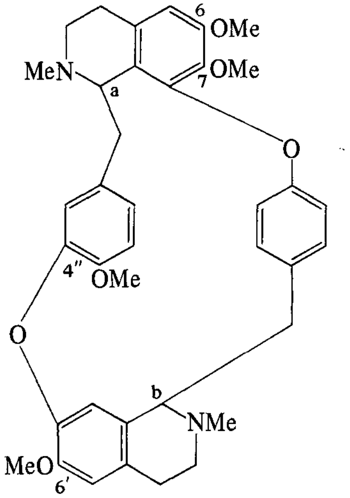


[18]



MeN: 2·27, 2·24
(in C_6D_6)

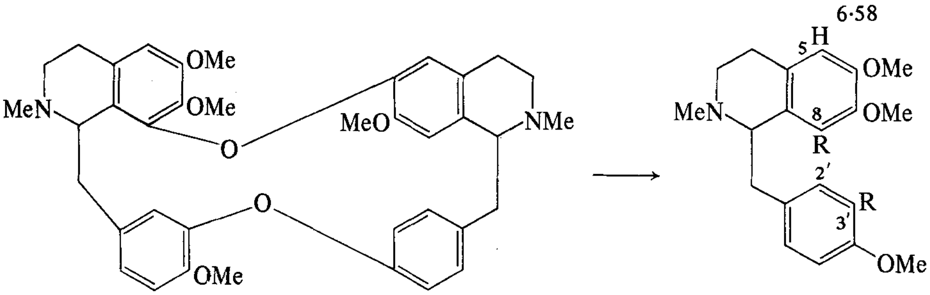
[19]



(a, b = *S*,*R*) (in C_6D_6)
7-MeO 3·63; 6- and 6′-MeO 3·47; 4″MeO 3·43
MeN 2·28, 2·03
[20]

(a, b = *R*,*R* or *S*,*S*) (in C_6D_6)
7-MeO 3·62; 6 and 6′ MeO 3·52, 3·42; 4″ MeO 3·30
MeN 2·28, 2·24
[21]

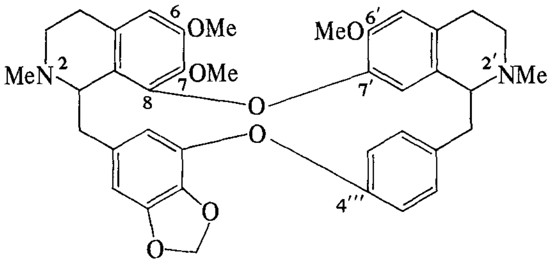
Cleavage of *O*-methylisothalicberine [22] by sodium in trideuterioammonia gave ([23]; R = D). ([23]; R = H) showed the 8-proton at δ 6·58 and the 5-proton at δ 6·09 and it was the latter



[22] [23]

signal which was reduced in intensity in ([23]; R = D). In addition the four proton multiplet between δ 7·16 and 6·76 in the spectrum of ([23]; R = H) changed in that of ([23]; R = D) to an absorption pattern in which the higher field signals were reduced in intensity. (11) In these 4′-*p*-methoxybenzylisoquinolines the 2′-aromatic proton absorbs at lower field than the 3′ protons. Related studies on deuterated *O*-methyloxyacanthine have been carried out and the spectra of the derived deuterated armepavine and 4′-*O*-methyl-*N* methylcoclaurine published. (21)

In the spectra of biscoclaurine type alkaloids the 7-methoxyl protons absorb at *ca.* δ 3.17 in those compounds possessing ether linkages between 8 and 7′ and between 4‴ and 3″ (or 4″ and 3‴). In the 3″, 4‴ ether type there is high field absorption of one of the *N*-methyl group protons (*ca.* δ 2·30). (22) On this basis isotenuipine was assigned the structure ([24]; 1*R*,1′*S*). (23) The difference in the chemical shifts of the 6′-methoxyl protons in isotenuipine and in tenuipine ([24]; 1*S*,1′*S*) is marked and is indicative of the change in stereochemistry.

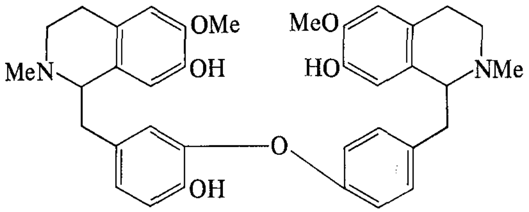


(1*R*, 1′*S*): 6-MeO 3·75; 6′-MeO 3·60; 7-MeO 3·16
2′-MeO 2·58; 2-MeN 2·30

(1*S*, 1′*S*): 6-MeO 3·78; 6′-MeO 3·33; 7-MeO 3·18
2′-MeN 2·63; 2-MeN 2·32

[24]

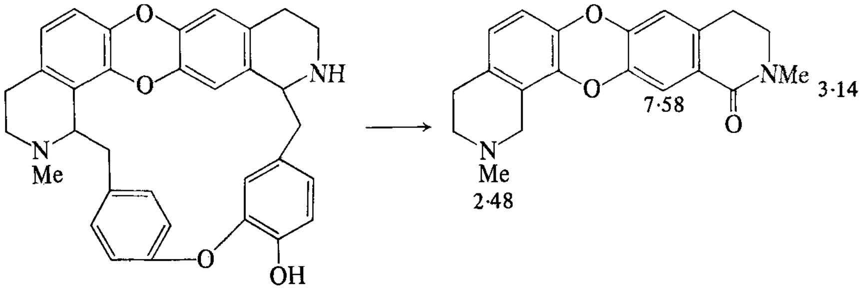
The NMR spectra ($CDCl_3$) of berbamunine ([25]; 1*R*,1′*S*) and its diastereoisomer are as shown under the structures. The 8-protons of the tribenzyl derivatives of these appeared as two singlets (e.g. δ 6·22, 6·25 for tribenzylberbamunine) but on recording the spectra after *ca.* 20 days a singlet absorption was observed (δ 6·11). (24)



(1*S*, 1'*S*)	OMe 3·81 NMe 2·43, 2·48 8-H 6·24, 6·29
(1*R*, 1'*S*)	OMe 3·82, 3·84 NMe 2·44, 2·49 8-H 6·22, 6·33

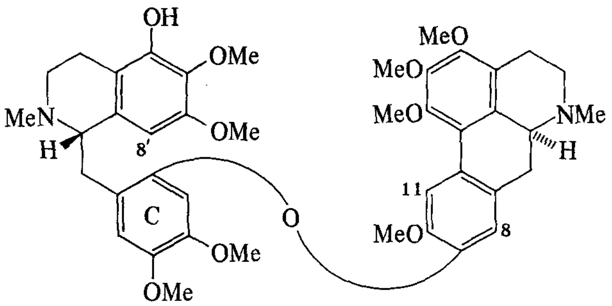
[25]

Micranthine [26] may be converted to the aminolactam [27] in the spectrum of which the *N*-methyl and amido-*N*-methyl protons absorb at δ 2·48 and δ 3·14 respectively. A similar conversion of *O*-methyl, *N*-trideuteriomethyl micranthine produces the aminolactam the NMR spectrum of which shows the reduction in intensity of the δ 3·14 signal and proves the structure [26]. (25)



[26] [27]

The chemical shifts of the aromatic protons in thalminelin (26) are in accord with the structure [28]. The 11-proton in the aporphine (see section IID) is relatively deshielded and the 8'-proton in the benzylisoquinoline is shielded (see Section IIB).



MeO 3·47 3·70 3·73 3·76 3·83 3·89

Aromatic protons 8′-H 5·71 Ring C 6·43, 6·48

8-H 6·66 11-H 7·98

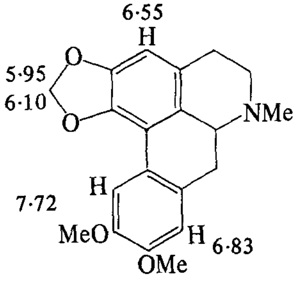
(in $CDCl_3$)

[28]

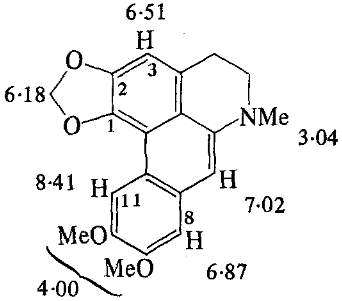
D. Aporphine, Oxaaporphine and Proaporphine Alkaloids

1. Aporphines

Early work on the NMR spectra of the aporphine alkaloids has been reviewed. (27) The non-equivalence of the methylenedioxy protons in dicentrine [29] and bulbocapnine resulting from the non-planarity of the two aromatic rings has been known for some time. (28, 29) These protons show a geminal coupling constant of 1 to 2 Hz which is only slightly different from that of the 2-protons in monocyclic 1,3-dioxolans (0 to 0·8 Hz). (30) In dehydrodicentrine [30] (31) these methylenedioxy protons absorb as a singlet and the



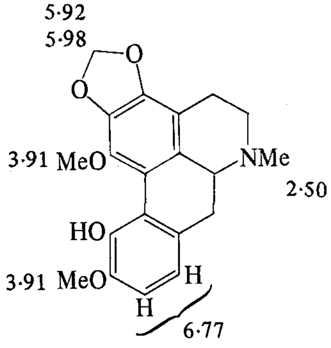
[29]



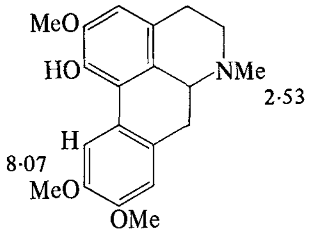
[30]

low field absorption (δ 8·41) of an aromatic proton (11-H) and of the *N*-methyl protons (δ 3·04, cf. δ 2·57 in dicentrine (32)) in this alkaloid are characteristic of the dehydroaporphines. Similar 11-proton and *N*-methyl proton parameters to those in [30] are shown by dehydroocopodine (33) (structure identical to dehydrodicentrine but with C(8)H replaced by methoxyl). In ocokryptine [31] (31) the two aromatic protons absorb as a singlet whereas in *O*-methylocokryptine an AB quartet (J = 8 Hz) is observed. This change appears to be general for these systems so that singlet absorption for these two aromatic protons implies a phenolic function at C(10) or C(11), and an AB quartet implies C(10) and C(11) methoxyls. (34)

In aporphines the 1- and 11-methoxyl group protons normally absorb at higher field (δ 3·40 to 3·72) than other methoxyl group protons (δ 3·72 to 3·90) [compare shielding of 7-methoxyl group protons in benzylisoquinolines (IIB)] and the 11-proton at lower field than the other aromatic protons. (35) The NMR spectrum of thaliporphine [32] (13) showed absorption from one aromatic proton (11-H) at δ 8·07 and absorption for its three methoxyl group protons at δ 3·89 and δ 3·83 in accord with structure [32]. The chemical shifts of the 8- and 11-protons in 1,2,3,10-tetramethoxy-9-hydroxyaporphine (36) (δ 6·84 and 7·96 in $CDCl_3$) and in 1,9,10-trimethoxyaporphine (37) (δ 6·83 and δ 8·0 in $CDCl_3$) also show the shielding of the 11-proton.



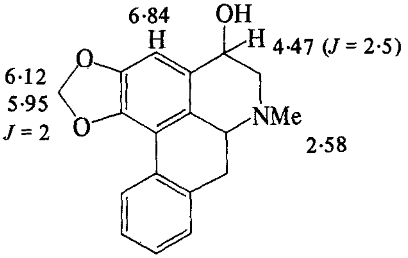
[31]



[32]

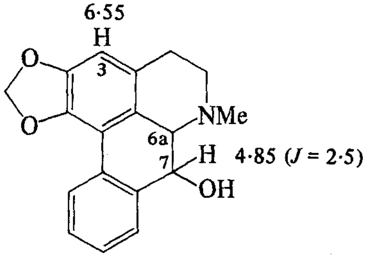
In agreement with expectations the NMR spectrum of *O*-methylocokryptine (*O*-methyl [31]) shows the 11-methoxyl protons to absorb at higher field (δ 3·63) than the 1- and 10- methoxyl protons (δ 3·86 and δ 3·97). However, in the spectrum of 1,9,10-trimethoxyaporphine all three methoxyl groups possess similar chemical shifts (δ 3·87, 3·92, 3·92) and both methoxyl group protons in ocokryptine [31] absorb at δ 3·91. Thus, although it is reasonable to expect a shielding of the 1-methoxyl group protons in the aporphines, other structural features may affect the chemical shifts so that this criterion must be used with caution.

The chemical shifts of the C*H*OH protons and of the 3-aromatic protons in steporphine [33] and in ushinsunine [34] are markedly different (38) and aid the establishment of structures to systems of this type. In the NMR spectrum of 7-hydroxynoraporphine (39) the 7-proton absorbs at δ 4·56 and shows $J_{6a,7}$ to be 3·5 Hz.



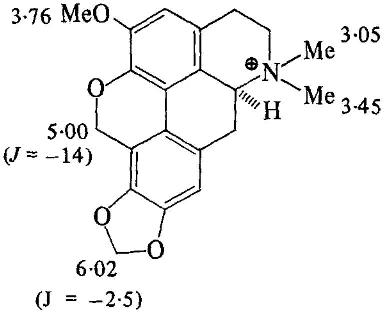
(in $CDCl_3$)

[33]



(34)

Thalphenine [35] (40) provides some NMR data not normally encountered in the aporphines. J_{gem} for the Ar—CH_2—O protons (AB quartet centred at δ 5·00) in this alkaloid was found to be −14 Hz and the methylenedioxy group protons (AB quartet centred at δ



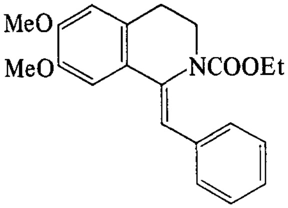
Aromatic protons 6·82, 6·79

(in DMSO-d_6)

[35]

6·02) showed a rather large value of J_{gem} ($|2{\cdot}5|$ Hz) for protons in this environment.

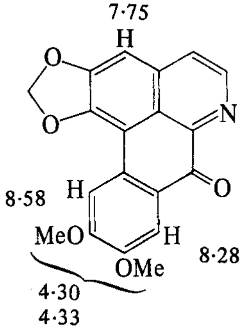
The chemical shift (δ 0·8) of the methyl group in compounds of type [36] (41, 42) (intermediates in synthesis of aporphines) indicates the *trans*-configuration of the aromatic rings about the double bond.



[36]

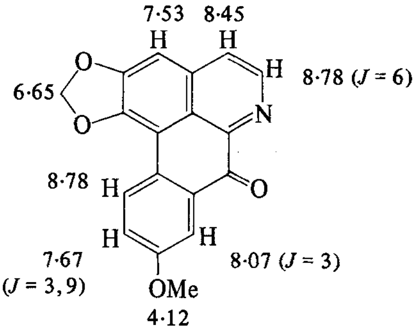
2. *Oxaaporphines*

In trifluoroacetic acid solution the chemical shift of the protons in decentrinone (33) are as in [37] showing the influence of the carbonyl group on the chemical shift of the 8-proton.



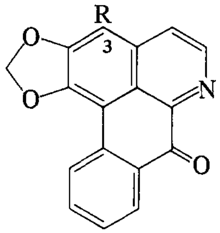
[37]

Comparison of the proton chemical shifts in oxoxylopine (43) [38] with those in liriodenine ([39]; R = H) (44) and in atherospermidine ([39]; R = OMe) (44) suggested the structure [38] or [40]. Establishment of the structure [38] for oxoxylopine then showed that the structure for lanuginosine must be [40] and not [38] as previously proposed. (45) The rather low field absorption of the methoxyl proton in ([39]; R = OMe) is not observed in [41], possibly as an effect arising from the presence of the 4-methoxyl. In addition the ring A methoxyl proton resonances are not significantly



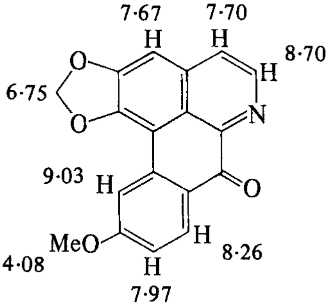
(in TFA)

[38]



R = H; 3-H 7·63
R = MeO; 3-MeO 4·55
R = H; (in TFA)
R = MeO; (in TFA)

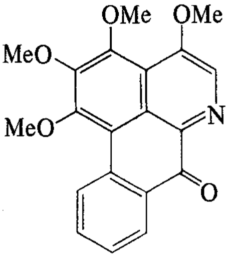
[39]



(in TFA)

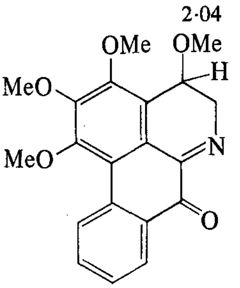
[40]

altered by hydrogenation of the 4,5 double bond (cf. [41] and [42]). (46)



MeO 4·05 4·10 4·15 4·25

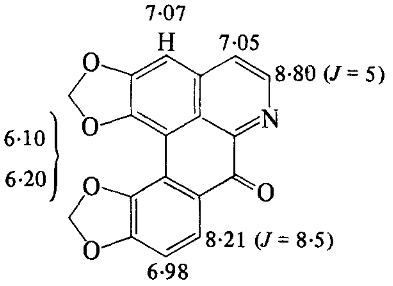
[41]



MeO 4·09 4·13 4·22

[42]

The chemical shifts ($CDCl_3$) in hernandonine [43] (47) are significantly different from those of the analogous protons in oxoxylopine (trifluoroacetic acid).

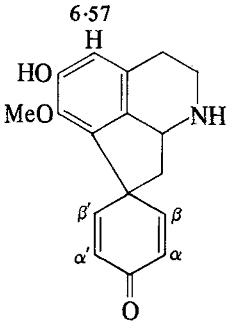


(in $CDCl_3$)

[43]

3. *Proaporphines*

The early work on the NMR spectra of the proaporphine alkaloids has been reviewed. (48) The absorptions for the protons in the cyclohexadienone system are characteristic for alkaloids of this type (e.g. crotonosine [44]) (49) and 1-methoxyl group protons normally absorb at higher field than 2-methoxyl group protons [e.g. pronuciferine (*O,N*-dimethyl crotonosine) 1-methoxyl, δ 3·57; 2-methoxyl, δ 3·78]. On the basis of the NMR spectrum a half chair cyclohexene ring with a pseudoaxial OH has been suggested for roemeramine [45]. (50)



(in DMSO)

[44]

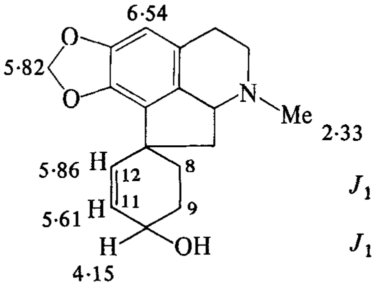
$\beta\beta'$ δ 7·04

$\alpha\alpha'$ δ 6·20

$J_{\beta\beta'} = 2·5$

$J_{\alpha'\beta'} = 10$

$J_{\alpha\alpha'} = 1·5$



$J_{10,11} = 3·1$

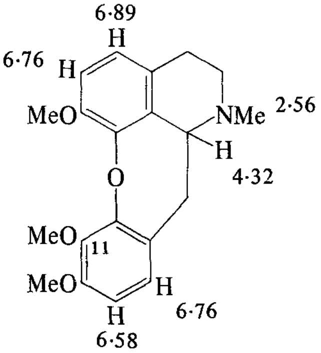
$J_{12,10} = 1·2$

(in $CDCl_3$)

[45]

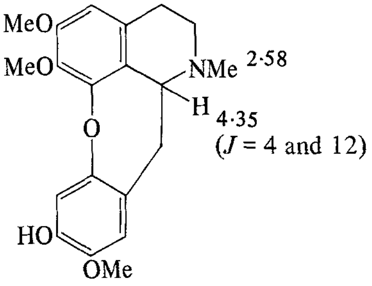
E. Cularine Alkaloids

The NMR spectra of the cularine type compounds [46] (51) and [47] (16) have been reported. It must be noted that when the C(11) methoxyl group is replaced by OH an AB quartet for the aromatic 8- and 9-protons is observed so that the rule (13) discussed above for the aporphine system does not apply to this type of alkaloid. The coupling constants and chemical shift of the angular NC*H* proton in [47] is characteristic of the cularine alkaloids.



(in $CDCl_3$)

[46]



MeO 3·76, 3·80, 3·87

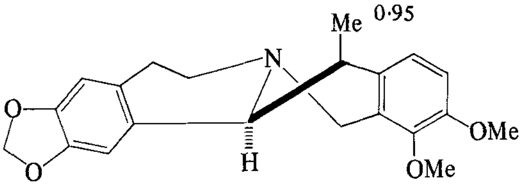
Aromatic protons 6·49 (2H), 6·87

(in $CDCl_3$)

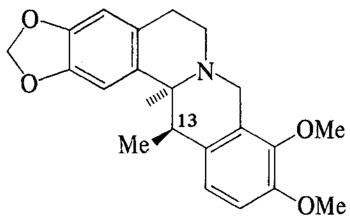
[47]

F. Protoberberine and Protopine Alkaloids

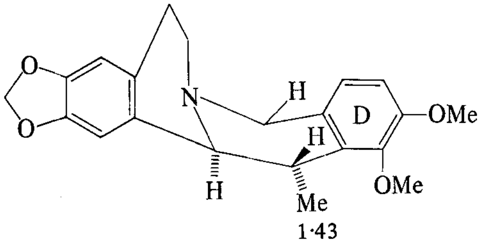
The *trans* fused ring conformation [48] adopted by [49] and the *cis* fused ring conformation [50] adopted by [51] has been correlated with the "chemical shifts" (centre of the methyl doublets) of



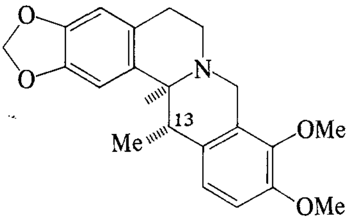
[48]



[49]

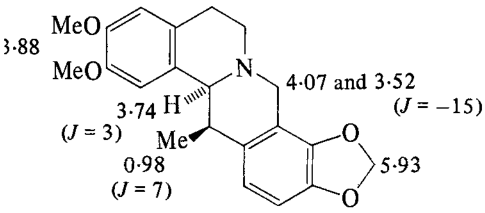


[50]



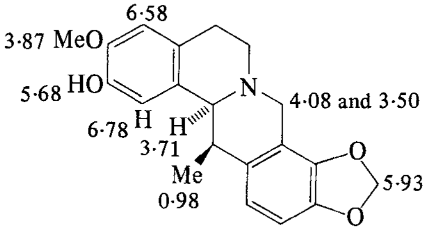
[51]

the 13-methyl group protons (δ 0·95 in [48], δ 1·43 in [50]. (52) Similar results have been described for the isomeric 2,3-dimethoxy-10,11-dibenzyloxy-13-methyltetrahydroprotoberberines. (53) A more detailed NMR examination of the tetrahydroprotoberberine system (in particular of cavidine, apocavidine and thalictrifoline has been carried out (54) and the results summarized in [52], [53] and [54]). [52] and [53] adopt the *trans* fused ring conformation and are characterized by δ 0·98 (13-Me) and a large chemical shift difference between the 8-methylene protons (0·55 ppm). The *cis* fused ring compound thalictrifoline [54] shows δ 1·48 (13-Me) and a difference in chemical shift between the 8-methylene protons of only 0·13 ppm in keeping with a geometry such that the nitrogen lone pair bisects the methylene group. The aromatic proton chemical shifts and the relative position of the OH and methoxyl in apocavidine were established by double irradiation and nuclear Overhauser effects.



(in $CDCl_3$)

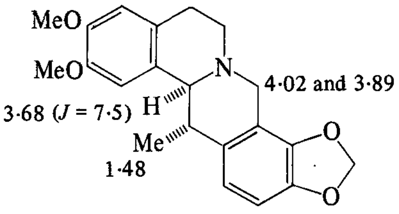
[52]



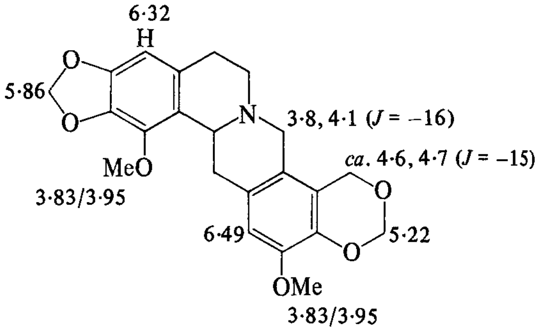
(in $CDCl_3$)

[53]

The NMR spectrum of orientalidine [55] (55) shows a similar J_{gem} (−16 Hz) for the N—CH_2Ar protons to that in thalictrifoline but the difference in chemical shift is 0·3 ppm. The presence of the



[54]

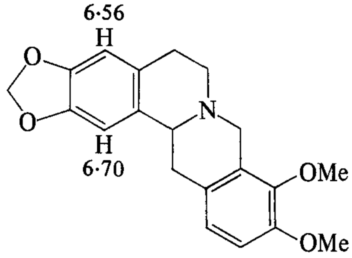


(in CDCl$_3$)

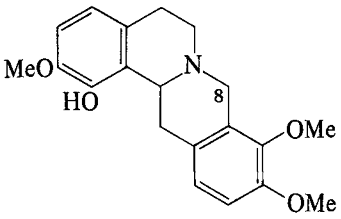
[55]

1,3-dioxan system in this alkaloid (not normally encountered in benzylisoquinoline alkaloids) provides some other NMR data (J_{gem} = −15 Hz for ArCH_2O) and the shielding influence of the methoxyl group in ring A on the chemical shift of the *para* aromatic proton may be seen from a comparison of [55] and [56].

The doublet (from one of the 8-protons) in the spectrum of caseanadine [57] (56) is typical of tetrahydroprotoberberines



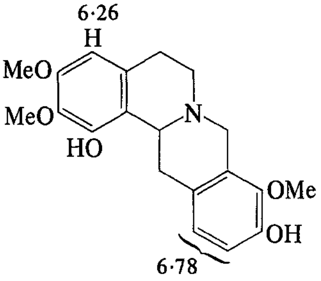
[56]



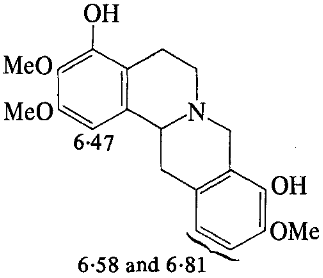
[57]

carrying an oxygen substituent at C(9). (57) In tetrahydroprotoberberines unsubstituted at C(9) a broad singlet is observed for the 8-methylene protons but substitution at C(9) of an oxygen substituent produces an upfield shift of the 8_{ax}-proton and a downfield shift of the 8_{eq}-proton. (57)

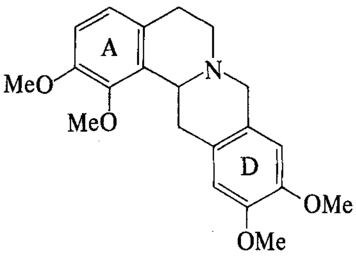
Comparison of the NMR spectra of caseanadine [57] (56) and its *O*-acetate shows the marked downfield shift (0·4 ppm) of the 4-proton (*para* to phenolic OH) occurring as a result of acetylation. The coupling of the 4-protons in these compounds with the 5-benzylic protons aided the determination of the ring A substitution pattern. A related method for determining substitution pattern has been described for capaurimine [58]. (58) Heating capaurimine in deuterium oxide with potassium *t*-butoxide resulted in loss of the δ 6·26 signal (the 4-proton *para* to phenolic OH) and a reduction in intensity of the δ 6·78 signal (from the 11- and 12-protons; 11-H *ortho* to phenolic OH) by half. The NMR spectrum of a position isomer of capaurimine is shown in [59] (59) and that of caseadine methyl ether (60) in [60]. In the spectrum of bisjatrorrhizine [61] (61) the high field absorption of one of the benzylic methylene



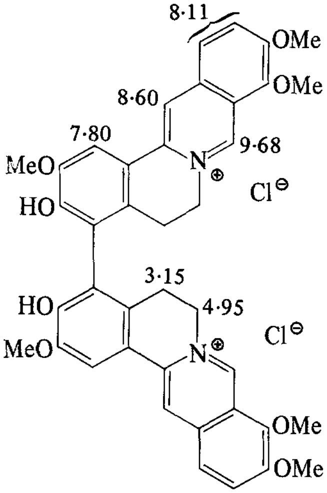
MeO 3·81 3·85 3·93
(in $CDCl_3$)
[58]



MeO 3·69 3·79 3·79
(in DMSO-d_6)
[59]



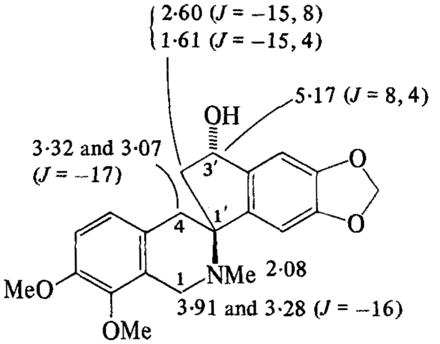
Aromatic protons 6·18 (ring D)
6·87 (ring A)
[60]



(in TFA)
[61]

protons indicates substitution at C(4) and since no exchange occurs on heating the alkaloid with DCl the absence of protons *ortho* and *para* to the phenolic group is indicated.

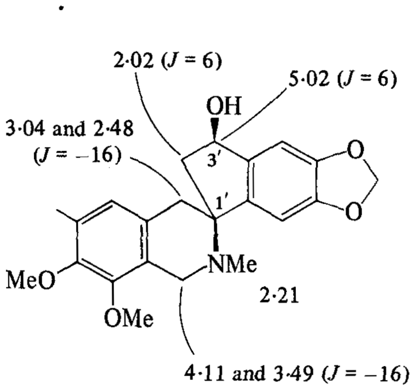
The NMR spectra of the compounds [62] to [65] derived from an anhydroprotopine have been described in detail. (62) The J_{gem} value (−15·4 Hz) for the 4-methylene protons in [65] is different from that (−16 to −17 Hz) in the other three compounds, suggesting



Aromatic protons 6·71 6·81 6·76

(in $CDCl_3$)

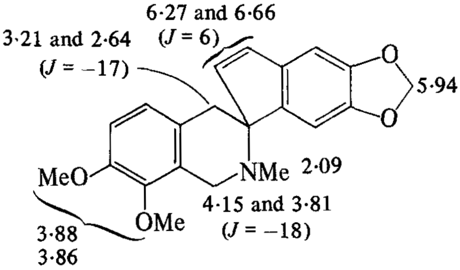
[62]



Aromatic protons 6·73 6·79

(in $CDCl_3$)

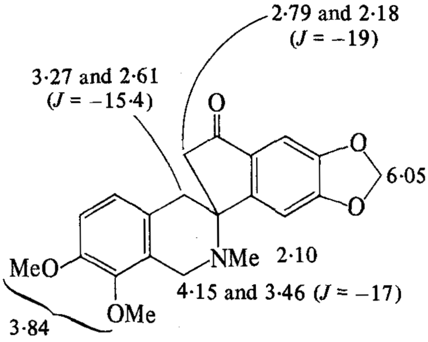
[63]



Aromatic protons 6·76

(in $CDCl_3$)

[64]



Aromatic protons 7·05 6·98 6·73

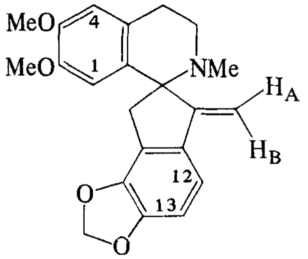
(in $CDCl_3$)

[65]

a small change in geometry of the methylene group with respect to the plane of the benzene ring. The absorption of the *N*-methyl protons in [63] [C(3′)OH *cis* to C(1)–N) is at lower field than in [62] [C(3′)OH *trans* to C(1)–N].

G. Spirobenzylisoquinoline Alkaloids

The structure [66] was proposed (63) for ochotensimine partially on the basis of its NMR spectrum: exocyclic methylene (δ 5·63 and 4·90, $J = 0$ Hz), 9-methylene (AB quartet centred at δ 3·20, $J = -18$ Hz), *N*-methyl (δ 2·13), *O*-methyl (δ 3·83 and 3·62) aromatic protons (1-H and 4-H δ 6·30 and 6·53; 12-H and 13-H AB quartet centred at δ 6·96).



[66]

Nuclear Overhauser effects observed (64) in this alkaloid are summarized in Table 1. A linear relationship is observed between the reciprocal of the effect and r^6 and such a relationship should assist the determination of internuclear distances (r) in unknown structures.

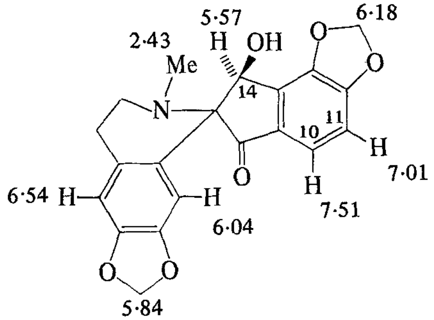
TABLE I

Nuclear overhauser effects on ochotensimine ($CDCl_3$) (64)

Proton irradiated	Proton observed	N.O.E. (%)	Internuclear distance (Å) (r)
H_A	H_B	40	1·82
13-H	H_B	8	2·40
H_B	13-H	24	2·40
12-H	13-H		2·42

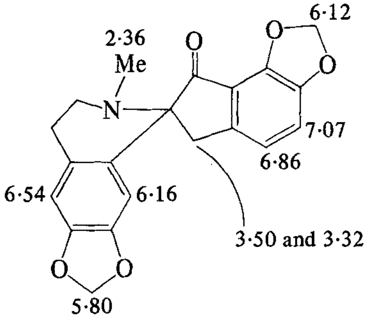
A very detailed NMR study, utilizing double irradiation and nuclear Overhauser effects, on sibiricine [67] (65) and fumariline

[68] (66, 67) has been published. The chemical shifts of the 10-aromatic protons in these compounds are strongly influenced by their orientation with respect to the carbonyl group and provide a ready means of distinguishing between the two structures. The large nuclear Overhauser effect observed at 14-H when the *N*-methyl proton signal is irradiated proves the configuration of the OH in sibiricine. In [68] an effect on the 10-proton when the 9-protons are saturated places one of the methylendioxy groups in the 12,13 position and in the alkaloid ([68]; with the 2,3 methylenedioxy group replaced by methoxyls) similar effects enabled the assignment of the chemical shifts to the methoxyl group protons to be made (3-MeO, δ 3·82; 2-MeO, δ 3·57). (67) Ochrobirine and diacetylochrobirine [69] have also been carefully studied. (68) Irradiation of the δ 6·55 signal (14-H) in [69] decoupled the δ 6·73 (13-H) signal (*ortho* benzylic coupling) and irradiation of the δ 6·36 signal (9-H) decoupled the δ 6·86 (12-H) signal (*para* benzylic coupling). This experiment demonstrated the application of the known variation in value of the coupling of benzylic protons (69) with *ortho*-, *meta*- and *para*- protons to an alkaloid problem.



(in $CDCl_3$)

[67]

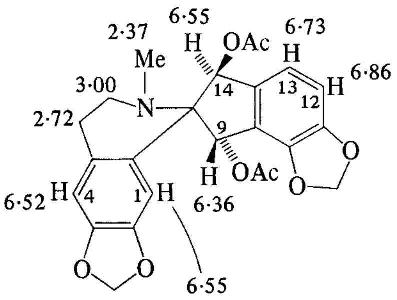


(in $CDCl_3$)

[68]

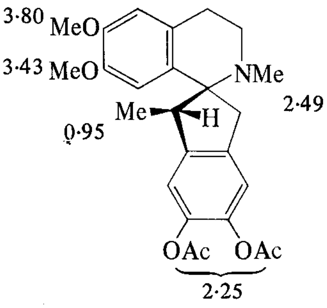
There is a large difference in chemical shift (1·23 ppm) between the acetyl group protons in diacetylochrobirine. One of these must be strongly shielded by an aromatic ring. In ochrobirine itself the 9-proton signal is sharper than that of the 14-proton.

Some synthetic spirobenzylisoquinolines bearing the *exo*-methylene group have been prepared (53) and show the upfield shift for the *N*-methyl protons (δ 2·10 in $CDCl_3$) and the characteristic J_{gem} (8-methylene protons) of −19 Hz. In [70] (53) the *N*-methyl



OAc 2·12 and 1·89
(in $CDCl_3$)

[69]



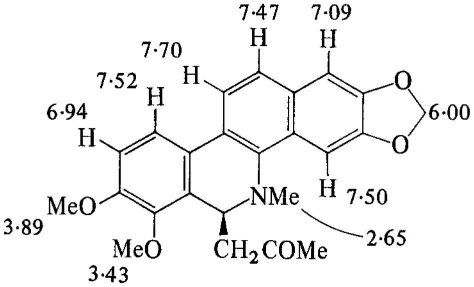
(in $CDCl_3$)

[70]

protons absorb "normally" (δ 2·49 in $CDCl_4$) and the *C*-methyl protons appear at δ 0·95 ((*J* = 6·5 Hz).

H. Benzophenanthridine Alkaloids

One of the major NMR spectral problems associated with this group of alkaloids has been the assignment of the aromatic protons; this has now been solved utilizing the nuclear Overhauser effects. In this way assignment of all the aromatic proton signals in the NMR spectrum of 11-acetonyldihydrochelerythrine, as shown in [71] has been made. Thus the δ 7·50 signal was assigned to the 10-proton on the basis of an effect with the *N*-methyl proton, the δ 6·94 signal to the 3-proton on the basis of an effect with the methoxyl protons (δ 3·89) and the δ 7·47 signal to the 6-proton on the basis of an effect with the 7-proton (δ 7·09). The remaining signals were assigned from coupling constant data. (70) Similar assignments have been made to the related alkaloids dihydronitidine, dihydroavicine,

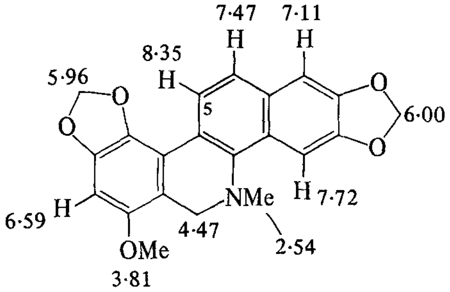


[71]

and bocconoline. (71) This latter alkaloid [71]; CH_2COMe replaced by CH_2OH) shows an ABX system for the $CHCH_2OH$ moiety (δ 3·09, 3·47, 4·65; J −10·5, 10·5, 5 Hz).

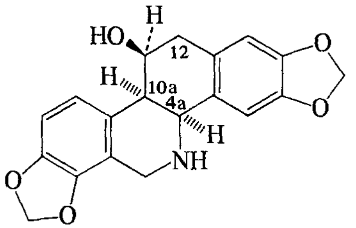
NMR and nuclear Overhauser effect measurements show (72) the structure [72] for dihydrobocconine. The effect of the ring A methylenedioxy group on the δ value of the 5-proton (compare [71] and [72]) is marked.

The coupling constants ($J_{4a,10a}$ = 3·5 Hz, $J_{10a,11}$ = 2 Hz) are in accord with the stereochemistry [73] for norchelidonine. (73)



(in $CDCl_3$)

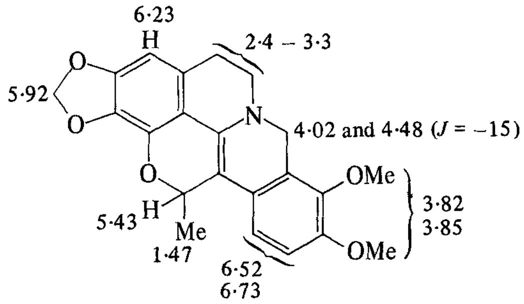
[72]



[73]

I. Phthalideisoquinoline Alkaloids (including Rhoeadine type)

The structure [74] for a compound derived from α-narcotine has been established (74) from a study of its NMR spectrum. Since this compound differs from the protoberberines (discussed in Section IIF), essentially in the presence of the double bond in ring C, it is worth comparing its spectrum with those of [52] to [56]. In particular comparison of [74] and [55] shows the similar shielding effect of the heterocyclic oxygen atom in [74] on the *para* aromatic hydrogen to that exerted by the 8-methoxyl group in [55] and the

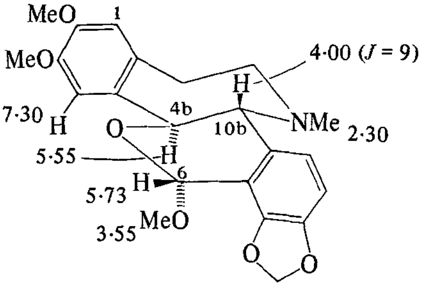


(in $CDCl_3$)

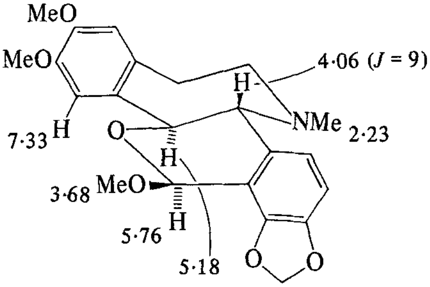
[74]

lower field chemical shifts of the NCH_2Ar protons in [74] which may in part arise from the incorporation of nitrogen lone pair in orbitals involving the double bond system.

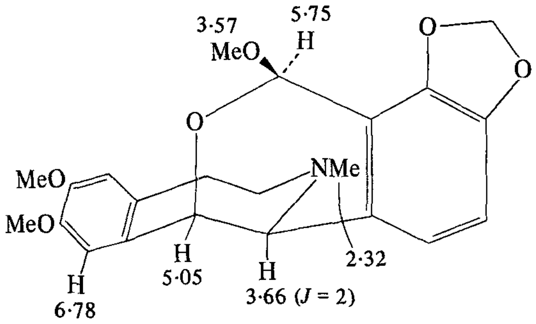
In the establishment of the stereochemistry of the rhoeadine alkaloids evaluation of the chemical shifts of the 4-methoxyl-, the 4b-, and of the 1-aromatic protons as well as $J_{4b,10b}$ has proved of importance, and a full discussion of these NMR-stereochemical correlations has been published. (75) Comparison of the NMR data obtained for epiglaudine [75] and glaudine [76] show the higher field absorption of the axial anomeric methoxyl protons than of the equatorial methoxyl protons and the low field absorption of the 4b-proton in [75] consequent upon its *syn* axial relationship with the methoxyl group. In [75] and [76] the aromatic 4-proton absorbs at much lower field than that in oreodine [77] since in the former pair of alkaloids the oxygen atom is close to 4-H. In oreodine [77] (*cis*-fused) the 4b-proton is at higher field than in the *trans*-fused alkaloid, but that it is under a deshielding influence from the



[75]

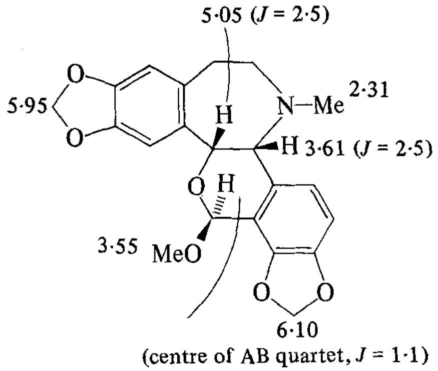


[76]

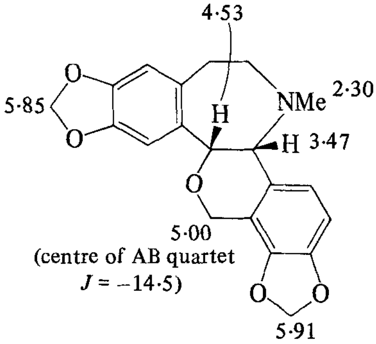


[77]

anomeric methoxyl group is shown by the movement to high field of the proton in going from rhoeadine [78] to demethoxyrhoeadine [79]. (76). One further means of distinguishing between *cis* and



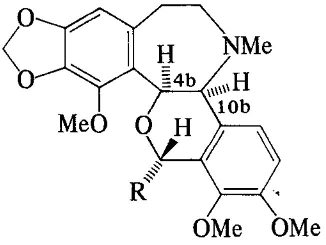
[78]



(in $CDCl_3$)

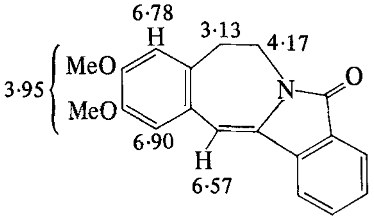
[79]

trans fused rhoeadines is provided by the observation of a $J_{4b,10b}$ of 9 Hz in *trans* fused compounds [75] and [76] and of a $J_{4b,10b}$ of 2 Hz in *cis* fused compounds [77]. Arguments such as these have been utilized in the establishment of the structures of related rhoeadines. (77, 78) In the pair of compounds ([80]; R = OMe) and ([80]; R = OH) $J_{4b,10b}$ is 4 Hz and <1 Hz respectively, reflecting a change in the dihedral angle between 4b-H and 10b-H brought about by the change in the C(6) substituent. (78) In an approach to the synthesis of rhoeadine type alkaloids the NMR spectra of [81] and [82] have been reported. (79) These show the greater deshielding of the CH_2 NCO proton in [81] over than in [82] as a result of fixing the conformation by construction of ring B.



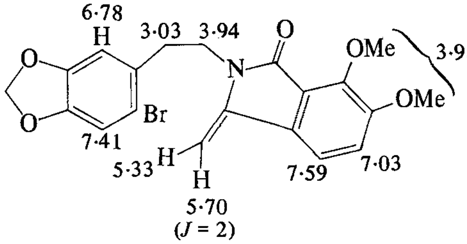
(in $CDCl_3$)

[80]



(in $CDCl_3$)

[81]

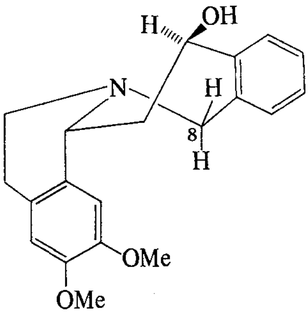


(in $CDCl_3$)

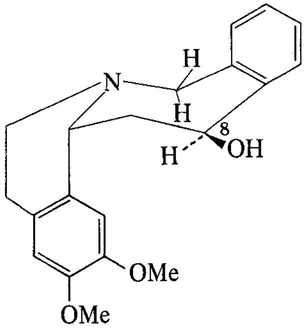
[82]

J. Phenethylisoquinoline Alkaloids

From the chemical shifts of the 8-methylene protons in the hydroxyhomoprotoberberines [83] (δ 4·24) and [84] (δ 4·81) the structures shown have been assigned. (80) It has been argued that



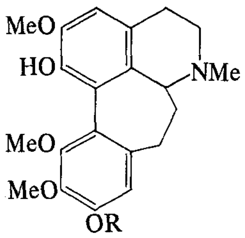
[83]



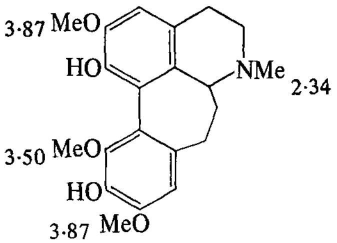
[84]

since [84] is more rigid than [83] the 8-equatorial proton in [84] is held more firmly in the plane of the aromatic ring giving rise to the observed deshielding. Other deshielding or shielding influences were not considered. The J_{gem} (8-methylene) in both isomers was −14·5 Hz. If 8-H_{eq} in [84] lies in the plane of the aromatic ring there would be a nil contribution from the aromatic ring to J_{gem} which would then be less than the observed value. These observations make the detailed stereochemistry shown open to objection.

The methoxyl group protons in kreysigine ([85]; R = Me) absorb at δ 3·83, 3·86, 3·86 and 3·59 and in floramultine ([85]; R = H) at 3·89, 3·84 and 3·55. (81) The high field absorption of one of these methoxyl group protons is evidence for a 12-methoxyl group. Similar methoxyl proton resonances are shown by multifloramine [86]. (82)

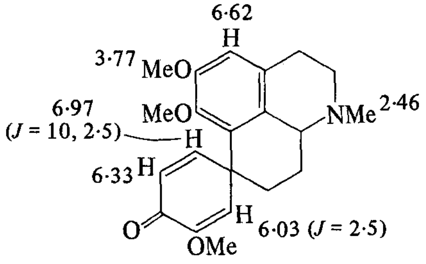


[85]



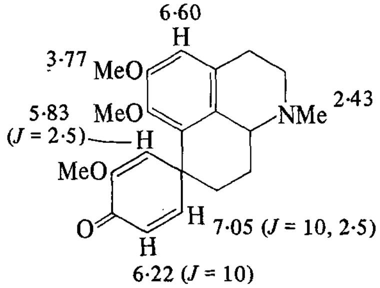
[86]

Typical NMR data for homoproaporphines are shown in [87], [88], (82) [89] (83) and [90]. (84) The position of the methoxyl group with respect to the aromatic proton in [90] has been established by nuclear Overhauser effects and in these compounds the 1-methoxyl group protons appear at higher field than the other



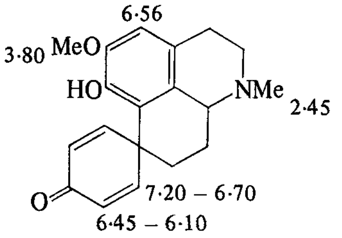
MeO 3·52, 3·56
(in CDCl$_3$)

[87]



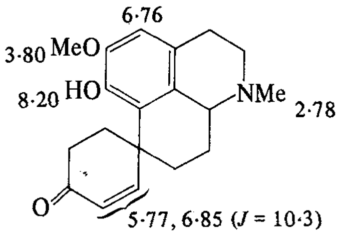
MeO 3·51, 3·63
(in CDCl$_3$)

[88]



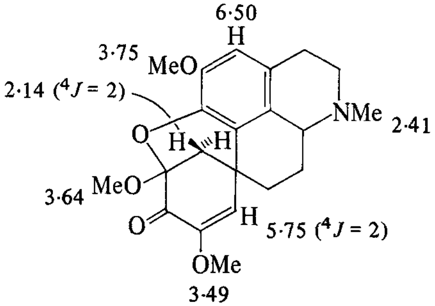
(in $CDCl_3$)

[89]



(in $CDCl_3$-DMSO-d_6)

[90]



(in $CDCl_3$)

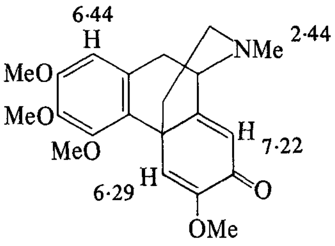
[91]

aromatic ring methoxyl protons. The relatively high field absorption of the olefinic methoxyl group in [91] has been attributed to the diamagnetic anisotropy of the aromatic ring. (81) The influence of an adjacent methoxyl group on the chemical shifts of the olefinic protons in these systems is quite marked. (Compare [87] and [88] shielding of *ca.* 1·0 ppm.) Comparison of the NMR spectrum of [89] with that of [87] and [88] shows that replacement of the 1-methoxyl by phenolic OH has little effect on the chemical shifts of the 2-methoxyl group protons or of the cyclohexadienone ring protons.

NMR data on some 1-phenethylisoquinoline alkaloids from *Colchicum cornigerum* (85) and on *C*-norandrocymbine [92] has been obtained. (86)

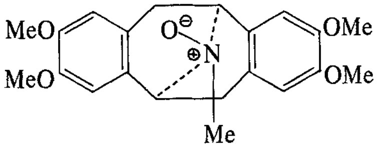
K. Pavine and Isopavine Alkaloids

Marked downfield shifts of two methoxyl group protons and of two aromatic protons were observed in the NMR spectrum of argemonine *N*-oxide [93] in deuterium oxide as compared with



MeO 3·78, 3·82, 3·82, 3·98
(in $CDCl_3$)

[92]



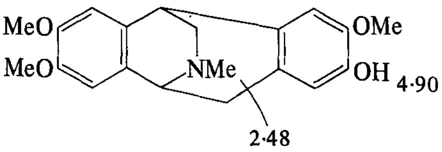
$CDCl_3$ (TMS) MeO 3·78, 3·78, 3·82, 3·88
Aromatic protons 6·50, 6·54, 6·65, 6·65
NMe 3·35

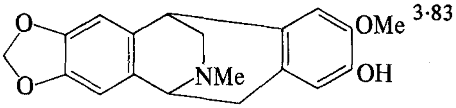
D_2O (TTS) MeO 3·80, 3·85, 4·22, 4·28
Aromatic protons 6·68, 6·79, 7·36, 7·36
NMe 3·62

[93]

shifts in deuteriochloroform. The origin of these shifts is under investigation. (87)

All three methoxyl group protons in thalisopavine [94] absorbed at δ 3·86 and in *O*-methylthalisopavine the additional methoxyl appeared at δ 3·77. Comparison of these values with those of the methoxyl proton resonances in amurensine [95] and in amurensi-





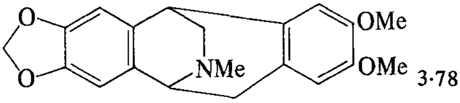
[95]

MeO 3·86
Aromatic protons 6·75(2H), 6·61, 6·54

[94]

mine [96] aided the assignment of structure [94] to thalisopavine. (88)

Aromatic protons *ortho* and *para* to the phenolic OH in argemonine derivatives undergo an upfield shift on changing solvent from $CDCl_3$ to DMSO whereas the *meta* protons experience a downfield

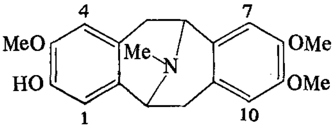
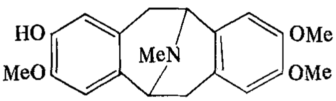
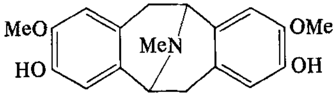


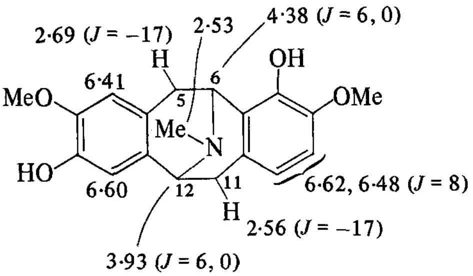
[96]

shift (Table 2). (89) This solvent shift aided the assignment of aromatic ring protons in munitagine [97]. Recording the NMR spectra of these compounds in DMSO and then in solutions containing successive amounts of NaOD in D_2O show the greater upfield shift of the protons *ortho* to OH expected by the application of the

TABLE II

Chemical shifts of aromatic protons in $CDCl_3$ and DMSO-d_6 of some argemonine derivatives (89)

		Chemical shifts			
	Solvent	1-H	4-H	7-H	10-H
	$CDCl_3$	6·62	6·42	6·62	6·42
	DMSO	6·56	6·45	6·73	6·50
Norargemonine					
	$CDCl_3$	6·59	6·47	6·59	6·47
	DMSO	6·70	6·36	6·71	6·51
Isonorargemonine					
	$CDCl_3$	6·57	6·42	6·63	6·40
	DMSO	6·53	6·45	6·68	6·33
Bisnorargemonine					



MeO 3·82, 3·76

5′-H, 11′-H 2·56, 3·51 ($J_{5'6} = J_{11'12} = 6$)

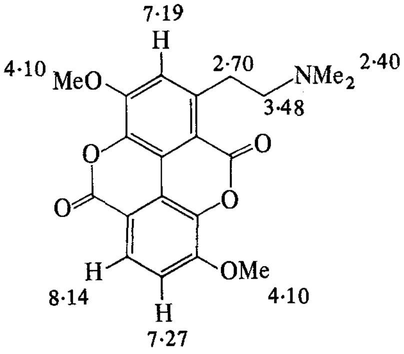
(in $CDCl_3$)

[97]

technique. (90) The lowest field Ar–CH–N proton in munitagine was assigned to 6-H since this is close to the C(7) OH group which exerts a deshielding influence.

L. Other Isoquinoline Alkaloids

The structure [98] has been assigned to Taspine. (91)



(in $CDCl_3$)

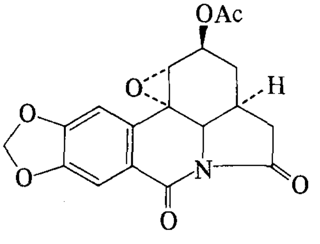
[98]

III. AMARYLLIDACEAE ALKALOIDS

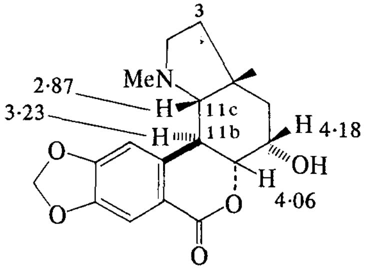
A. Lycorine and Lycorenine Type Alkaloids

The observation (92) of a zero coupling constant between the 1- and 2-protons in [99] established the α-configuration of the oxide ring since this gives a dihedral angle between C(1)-H and C(2)-H of *ca.* 90°.

Coupling constant data has established the stereochemistry [100] for clivonine. (93) In the acetate of clivonine the 5-proton signal moves to δ 5·35 and irradiation of this signal gave values for $J_{5,5a}$ (3·0 Hz) and $J_{5a,11b}$ (12·5 Hz) which enabled the stereochemistry to be established. Unexpectedly, the 11-proton in this compound absorbs to lower field of the 8-proton, even though the proton is deshielded by the carbonyl group. This must arise by a deshielding from the nitrogen atom which is close to the 11-proton. (The lower field aromatic proton signal was assigned to the 11-proton by comparison with the chemical shifts observed in a compound of similar structure to clivonine in which the C=O group has been replaced by CH_2.) In the NMR spectrum of [101] the corresponding aromatic protons absorb at δ 6·82 and δ 6·85 and the *N*-methyl protons absorb at unusually high field (δ 1·84) suggesting a conformation in which the *N*-methyl group lies over the aromatic ring.

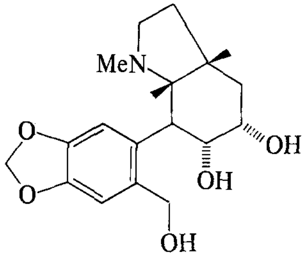


[99]



[100]

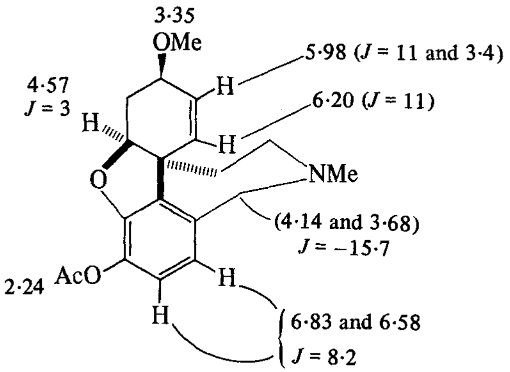
$J_{4\alpha 4\beta} = -15{\cdot}5$
$J_{4\alpha 3\alpha} = 3{\cdot}5$
$J_{4\beta 3\alpha} = 6{\cdot}5$
$''J''_{11b,11c} = 9{\cdot}5$
$''J''_{11b,5a} = 12{\cdot}5$
$''J''_{11c,3a} = 5{\cdot}8$



[101]

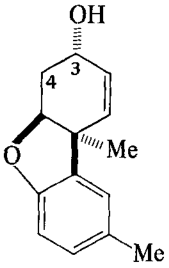
B. Galanthamine Type Alkaloids

In connection with work on *O*-acetylchlidanthine [102] (94) the NMR spectra of [103] and of its 3-hydroxy epimer were studied.



(in $CDCl_3$)

[102]

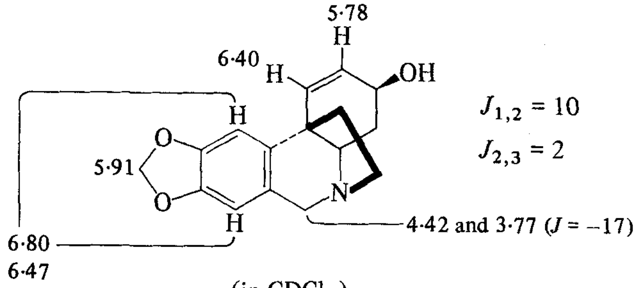


[103]

The appearance of the C(4) methylene proton signals as fourteen lines (δ 2·9–1·5) was seen to be characteristic of the configuration depicted in [103] and first order analysis of these gave for [103] 4e-H δ 2·61 (*J* = 4·5, 13·7) and 4a-H δ 1·76 (*J* = 2·9, 13·7, 9·8). In the spectrum of the C(3) epimer of [103] the 3-proton absorbed at δ 4·14 ($CDCl_3$) with a *J*(C*H*–O*H*) of 10·2 Hz (O*H* δ 2·4) indicating intramolecular hydrogen bonding, whereas in DMSO-d_6 *J*(C*H*–O*H*) was 5·8 Hz (O*H* δ 4·67) consonant with a freely rotating OH group.

C. Crinine Type Alkaloids

In the NMR spectra of alkaloids of the crinine type the AB pattern for the 6-methylene protons is quite distinctive, although the upfield proton signals are often obscured. The near bisecting geometry of the 6-methylene H–H internuclear axis with the plane of the aromatic ring and with the nitrogen lone pair produces the rather negative value of −17 Hz for these protons. Examples are provided by epicrinine [104] (95) and 2-methoxy-3-oxocrinine [105]. (96,

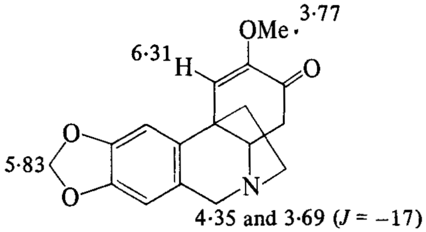


(in $CDCl_3$)

[104]

97) Other NMR parameters typical of these systems are shown in [104], (95) [105], [106] (96, 97) and [107]. (98)

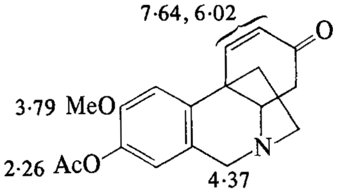
The NMR spectrum ($CDCl_3$) of [108], an intermediate in the synthesis of crinine, (99) shows the deshielding of the 7-proton by the amido group (δ 7·7 cf. δ 6·65 for 10-H) and there is a large difference in chemical shift between the benzylic methylene group protons (δ 5·44 and δ 4·4, $J = -16$ Hz).



Aromatic protons 6·80 and 6·41

(in $CDCl_3$)

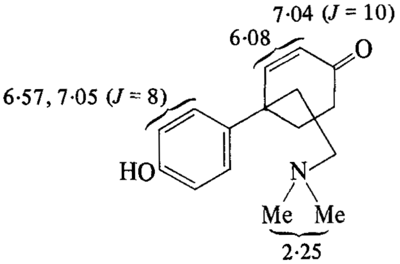
[105]



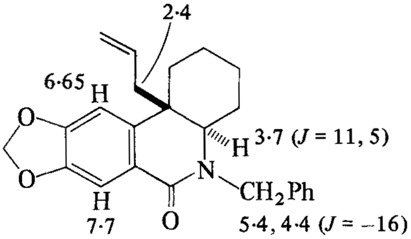
Aromatic protons 6·93 and 6·66

(in $CDCl_3$)

[106]

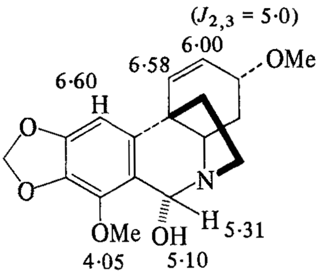


[107]



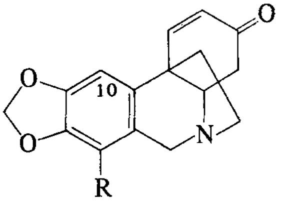
[108]

The 10-proton in 6-hydroxybuphanidrine [109] (100) absorbs at δ 6·60 and, on hydrogenation of the C(1)–C(2) double bond, this



[109]

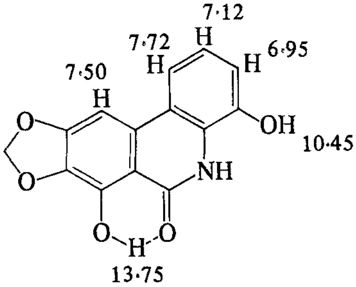
proton undergoes an upfield shift (δ 6·38) illustrating the deshielding effect of the double bond on the 10-proton. The α-orientation of the OH group in 6-hydroxybuphanidrine was established by the chemical shift (δ 5·31) of the benzylic proton since in the β hydroxy series this proton absorbs at *ca.* 0·6 ppm to lower field. The upfield shift (0·24 ppm) of the aromatic 10-proton in going from oxocrinine ([110]; R = H) to oxopowelline ([110]; R = OMe) has been recorded. (101)



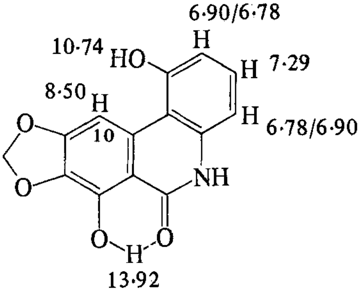
[110]

D. Narciprimine and Narciclasine Alkaloids

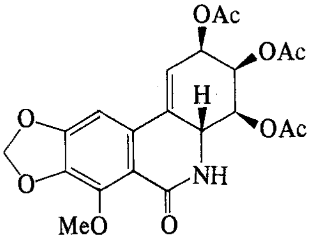
Comparison of the NMR spectrum of narciprimine [111] with that of the phenanthridone [112] established the structure shown. (102) The deshielding effect of the OH on the chemical shift of the 10-proton in [112] is marked. A detailed study of the NMR spectrum of *O*-methyl narciclasine triacetate (proposed structure [113]) suggested the stereochemistry shown [114], (102) whereas the X-ray study (103) on narciclasine tetraacetate gives the structure [115], epimeric with the proposed structure at C(2). However, the value of $J_{2,3}$ (2·4 Hz) may be consistent with a coupling between pseudoequatorial 2-H and pseudoequatorial 3-H (in [115] since the



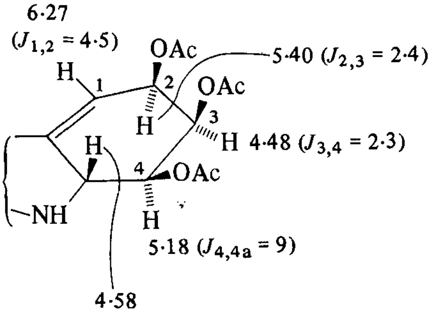
[111]



[112]



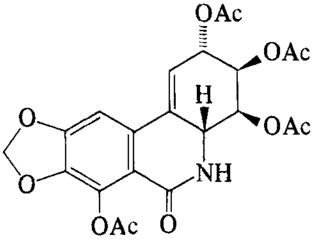
[113]



$J_{1,4a} = 2{\cdot}2$ $J_{1,3} = 1$

$J_{2,4a} = 1{\cdot}2$

[114]

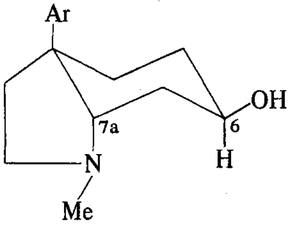


[115]

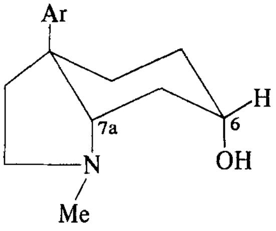
effect of acetate substituents on J_{vic} in systems such as CH–CH–C(OAc), where OAc lies in the plane of one of the coupled protons, is known to be quite marked and results in a decrease in J_{vic}. (104)

E. Mesembrine and Related Alkaloids

The NMR parameters for the 6- and 7a- protons in mesembranol and epimesembranol are in accord with the structures [116] and [117]. (105) 6ax-H in [116] absorbs (δ 4·08) to lower field of

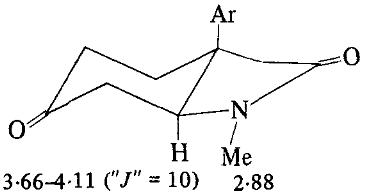


[116]

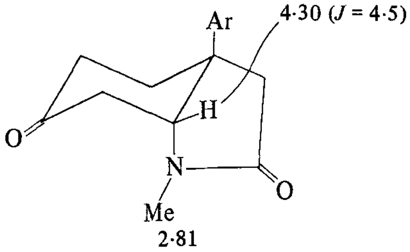


[117]

6eq-H (δ 4·00) in [117] and this is more clearly seen in the case of the corresponding acetates (δ 5·10 and δ 4·88 respectively in benzene solution). This reversal of the usual trend probably arises from the influence of the nitrogen group. Variation in the apparent coupling constants obtained from the 7a-H signals suggest a distorted chair in *O*-acetylepimesembranol. (105) The *N*-methyl proton absorptions in mesembranol and its acetate are similar to that of the *N*-methyl protons in *N*-methylpyrrolidine (δ 2·36), whereas in epimesembranol and its acetate the *N*-methyl group protons absorb at δ 2·46 and δ 2·26 respectively. Similar axial aryl-equatorial 7a-H conformations have been established for related systems. (106) The spectra of the octahydroindol-2,6-diones [118] and [119] have also been recorded. (107)

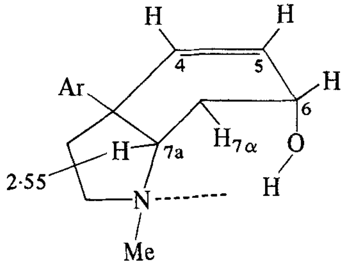


[118]



[119]

On the basis of coupling constants shown in [120] the conformation of 6-epimesembrenol was defined. In mesembrenol the coupling constants were similar with the exception of $J_{4,6}$ which was



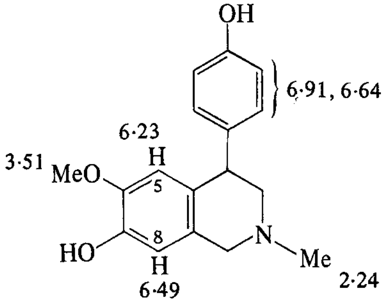
[120]

$J_{4,5} = 10{\cdot}5$
$J_{5,6} = 5{\cdot}5$
$J_{4,6} = 0 (\phi = 0^\circ)$
$J_{4,7a} = 1{\cdot}5$
$J_{5,7\alpha} = 1{\cdot}0$

now 1·8 Hz (cf. 0 Hz in epimesembrenol). The values of these allylic couplings in the two compounds are consistent with dihedral angles of 0° for epimesembrenol and 90° for mesembrenol. (108) Similar results have been described for *N*-demethylmesembrenol. (109)

F. 4-Phenyltetrahydroisoquinoline Alkaloids

In the NMR spectrum (DMSO-d_6) of cherylline [121] (110) the 5-proton was assumed to absorb at higher field than the 8-proton because of the shielding effect of the aromatic ring. On the addition of D_2O–NaOD both aromatic singlets moved upfield to δ 6·06 and since the resultant chemical shift difference is greater for the 8-proton the phenolic function was located at C(7).



(in DMSO-d_6)

[121]

G. Carbon-13-NMR Spectra of Amaryllidaceae Alkaloids

The ^{13}C NMR spectra of some amaryllidaceae alkaloids are summarized in Table 3. In the spectrum of narciclasine tetraacetate (111) the multiplicities do not agree with the previously proposed structure (OH group at 1,2,3 and a 5,6 double bond). In the tabulation of chemical shifts of the other five alkaloids (112) assignment of some very similar δ values may need to be reversed.

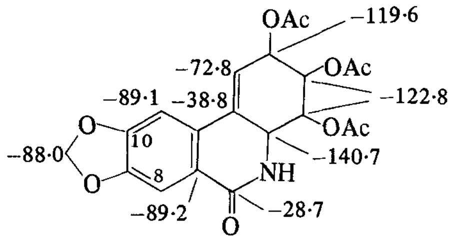
IV. ERYTHRINA AND RELATED ALKALOIDS

A. Erythrina Alkaloids

Utilizing decoupling and INDOR techniques a complete analysis of the NMR spectrum of erythristemine [122] has been made. (113) Irradiation of the 17-proton produced a slight narrowing of the δ 3·94 signal indicating it to be the 11-proton. The vicinal coupling involving the 4-methylene protons show the 5-methoxyl to be pseudo-equatorial. In erythristemine and in erythrinine [123] (114) the geminal coupling constant between the 10-methylene protons is

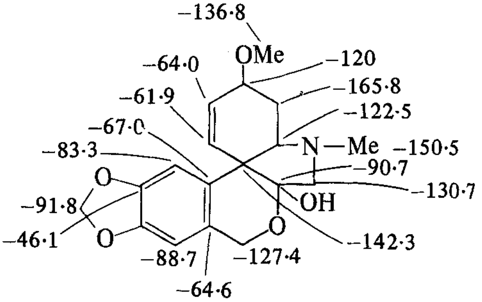
TABLE III

^{13}C NMR spectra (ppm upfield from CS_2) of some amaryllidaceae alkaloids (111, 112)

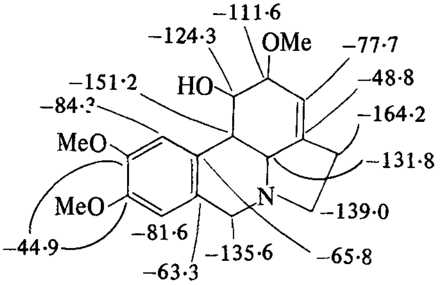


C8, C9, C10, C12 – 56·7

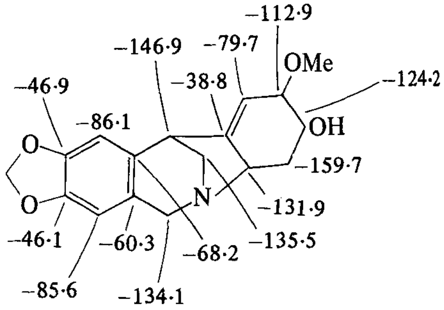
Narciclasine tetraacetate



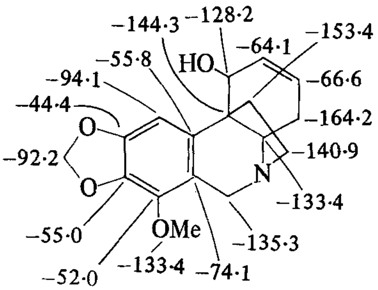
Tazettine



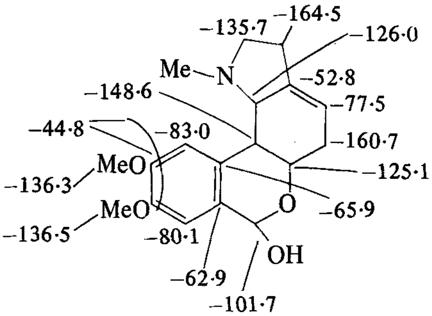
Galanthine



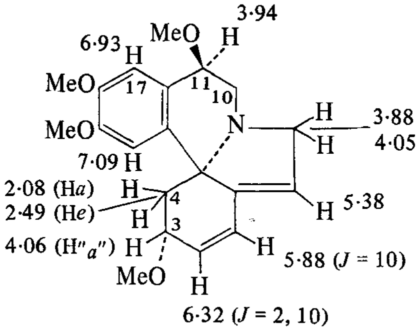
Montanine



Buphanamine



Lycorenine

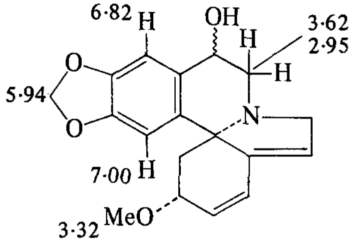


MeO 3·43 (6H), 3·21, 3·02

(in C_6D_6)

[122]

$J_{3,4a}$	10·5
$J_{3,4e}$	5·5
$J_{4a,4e}$	−10·5
$J_{4e,7}$	1 to 1·5
$J_{4e,1}$	1 to 1·5
$J_{8,8'}$	−15
$J_{10''a'',10''e''}$	−14
$J_{10''a'',11}$	4
$J_{10''e'',11}$	4

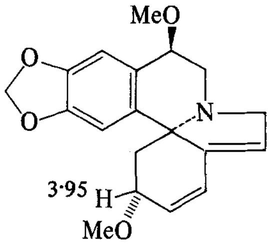


[123]

−14 and −13·5 Hz respectively indicating a conformation in solution such that the nitrogen lone pair bisects the 10-methylene. In erythrinine [114] the 11-proton absorbs at δ 4·73 (*J* = 4·5 Hz) and the 10-protons at δ 3·62 and δ 2·95. The couplings (both of 1 to 1·5 Hz) between 4e-H and 1-H and 7-H in erythristemine are noteworthy.

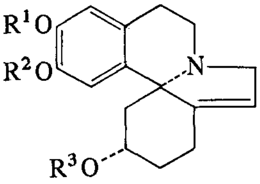
With the exception of the chemical shift of the 3-proton (δ 3·95; cf. δ 4·06 in erythristemine), the NMR parameters for 11-methoxyerythraline [124] (115) are very close to those observed for erythristemine. (113) Dreiding models show 3-H to be closer than 11-H to the aromatic ring so that changes induced by the substitution of the methylenedioxy group for the two methoxy groups should affect the chemical shift of the 3-proton more than that of the 11-proton (δ 3·92 in 11-methoxyerythraline, δ 3·94 in erythristemine).

In erysodine [125], erysovine [126] and erysonine [127] (116)



(in C_6D_6)

[124]

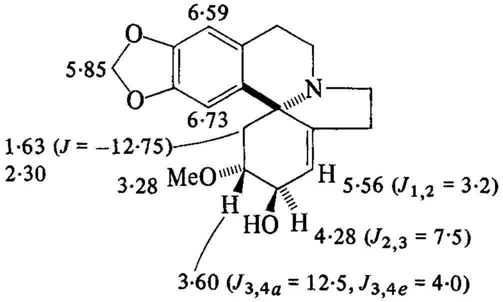


[125] (R^1=H, R^2, R^3=Me)

[126] (R^1, R^3=Me, R^2=OH)

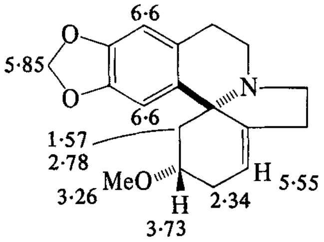
[127] (R^1, R^3=H, R^2=Me)

the 17-proton (δ 6·65) was coupled to the benzylic methylene. Deuteration of erysodine (D_2O-base) removed this signal from the spectrum (*ortho* to OH) but the 14-proton signal remained (δ 6·76). This result, together with other chemical data, enabled the structure to be assigned to these three alkaloids. NMR spectra of erythratine [128] and erythramine [129] were in accord with the structures



(in $CDCl_3$)

[128]

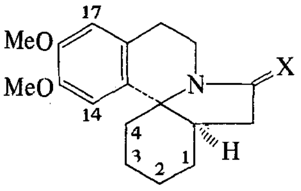


(in $CDCl_3$)

[129]

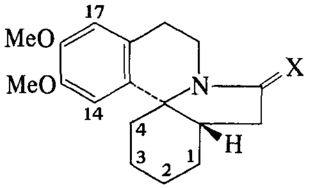
shown. In epierythratine [epimeric at C(2)] $J_{2,3}$ is 3 to 4 Hz and in erythratine benzoate the methylenedioxy protons became non-equivalent (J = 1·4 Hz).

Observation of the chemical shifts of the 14- and 17-protons in compounds possessing the erythrinane skeleton has proved of value in elucidating the stereochemistry (e.g. [130] or [131]) of the CD ring fusion. Dreiding models show a close approach of 14-H to 1-H and 3-H in the *trans*-erythrinane series [132] and this steric effect must be responsible for the deshielding of the 14-proton observed in the *trans* compounds. (117) Two examples illustrating the importance of this effect are shown in Table 4 and the correlation is applicable to more complex derivatives. Thus in the *cis*-CD compound ([133]; R = OH, R′ = H) (118) the aromatic protons absorb at



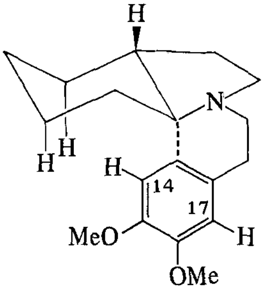
cis-Erythrinane

[130]



trans-Erythrinane

[131]



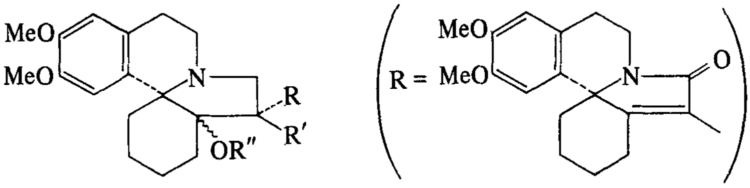
[132]

TABLE IV

Chemical shifts ($CDCl_3$) of 14-H and 17-H in [130] and [131] (117)

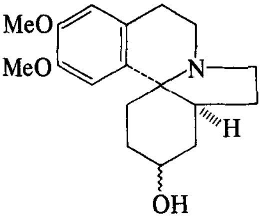
Compound	14-H	17-H	Δ	14-H	17-H	Δ
X = O	6·93	6·63	0·30	7·22	6·66	0·56
X = H_2	6·71	6·50	0·21	7·18	6·63	0·55

δ 6·95 and δ 6·78, whereas in the *trans*-CD compound ([133]; R = H, R′ = OH) one of the aromatic protons absorbs at lower field (δ 7·21, 6·83, 6·75, 6·6).

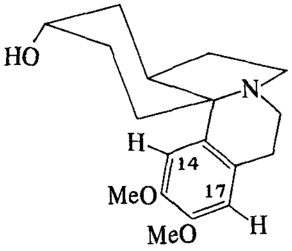


[133]

A related deshielding effect is observed (119) in the α-epimer of compound [134]: the aromatic protons in [134] (α OH) absorb at δ 6·97 (14-H) and δ 6·60 (17-H) whereas in [134] (β OH) the 14-proton absorbs at δ 6·71 and the 17-proton at δ 6·58. Reference to models [135] of the α-hydroxy compound shows the proximity of the OH to C(14)-H responsible for the relative deshielding.

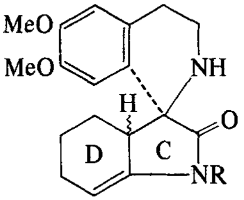


[134]

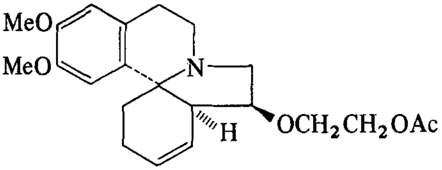


[135]

Perhaps less readily attributable to one cause is the deshielding of the 17-proton in the *cis* (the methine proton on the same side as the aromatic ring A) spiroisoquinoline [136] (δ 6·33) compared with δ 6·13 in the *trans* isomer. (120) In the *cis* fused acetate [137] the

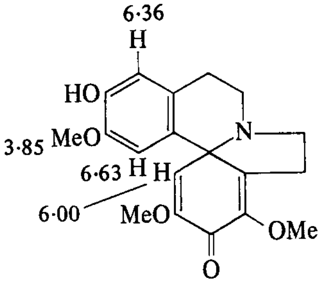


[136]



[137]

chemical shift of the acetate protons (δ 2·02) showed no influence from the aromatic ring and accordingly the side chain was assigned (121) the β orientation. Chemical shifts of the aromatic and methoxy protons in an erythrinadienone are as shown in [138]. (122)

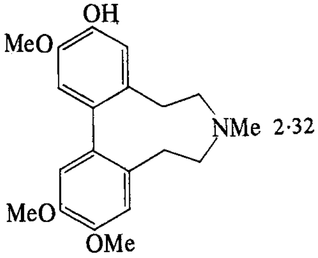


MeO 3·72 and 3·62

(in $CDCl_3$)

[138]

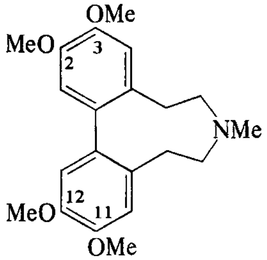
Comparison of the positions of methoxyl proton resonances in erybidine [139] (123) with those in related ethers ([140] and [141]) suggested the methoxylation pattern shown. The methine



MeO 3·92, 3·87, 3·87

(in $CDCl_3$)

[139]



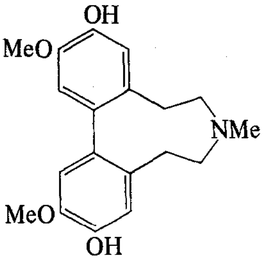
MeO 3·92, 3·92, 3·86, 3·86

[140]

[142] derived from erybidine showed the typical ABX pattern for the olefinic protons and it is noteworthy that the *N*-methyl protons in this compound absorb (δ 2·09) to higher field than those in erybidine (δ 2·32).

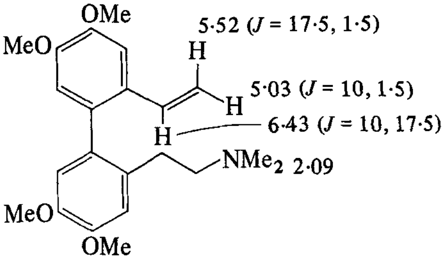
B. Cephalotaxine Alkaloids

NMR parameters for cephalotaxine are shown in [143]. The methoxyl proton absorption at δ 3·70 is typical for such a group



MeO 3·85, 3·85

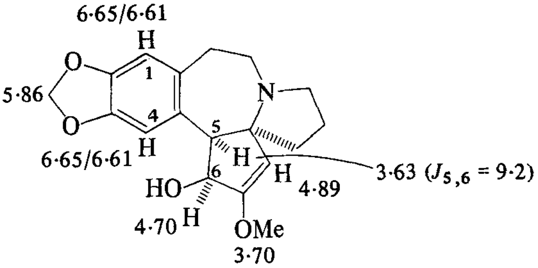
[141]



MeO 3·84, 3·88, 3·94, 3·96

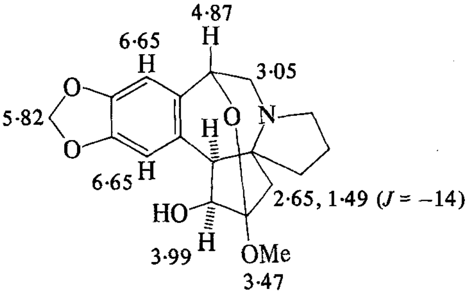
[142]

attached to a double bond and the 6-proton shows the expected low field shift (1·10 ppm) as a result of the acetylation of [143]. The related compound [144] shows an isolated methylene [at C(8)] with a fairly large Δ_{AB} (1·16 ppm, $J = -14$ Hz). (124) In this compound the 6-proton absorbs at higher field (0·71 ppm) than in [143]. The



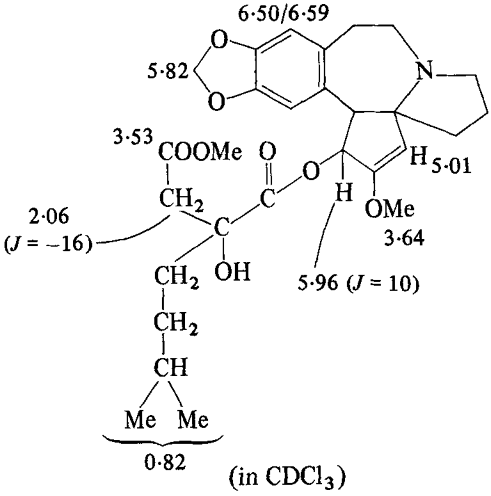
(in CDCl$_3$)

[143]

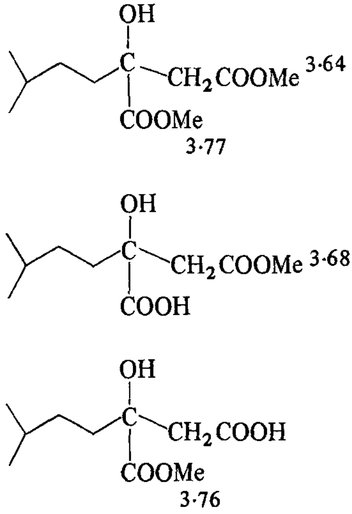


[144]

structure [145] was assigned to deoxyharringtonine (125) on the basis of its NMR spectrum and comparison of the side chain ester methyl chemical shifts with those in the model compounds [146].



[145]

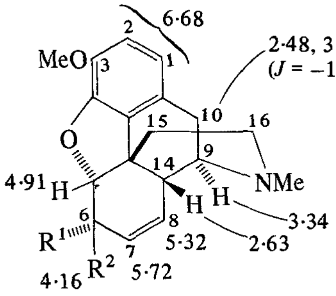


[146]

V. MORPHINE ALKALOIDS

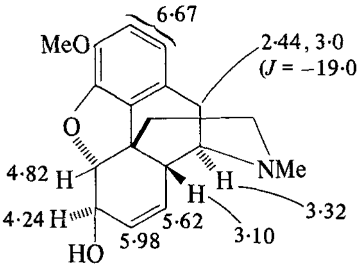
A. Alkaloids Containing the 4,5-Oxide Bridge

A detailed study of the NMR spectra of many of the morphine alkaloids has been made (126-128) and the main spectral features of codeine, isocodeine, pseudocodeine and neopine (126) are shown in [147] to [150] and in Table 5. Ring C geometry for codeine is favourable for homoallylic ($J_{6,14}$ = 2·6 Hz) and allylic ($J_{6,8}$ = 2·9 Hz) couplings whereas in isocodeine these couplings are zero. The small difference in $J_{8,14}$ in codeine and allocodeine is presumably a result of a change in ring C necessary to reduce the magnitude of the flagpole OH–14-H interaction in isocodeine. Pseudocodeine also shows allylic and homoallylic couplings involving 8-H which are absent in allopseudocodeine [epimeric at C(8)]. In neopine and isoneopine [epimeric at C(6)] the 6-protons absorb at δ 4·22 and δ 3·62 respectively as a result of their differing spatial relationship with the 8,14 double bond. The large value of $J_{10\alpha,10\beta}$ in these compounds

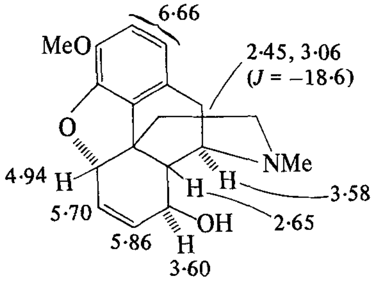


(in CDCl₃)

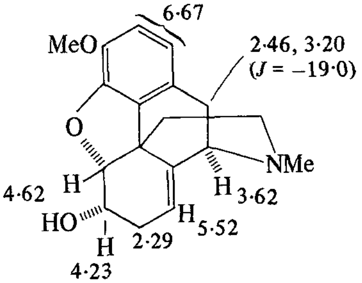
[147]



[148]



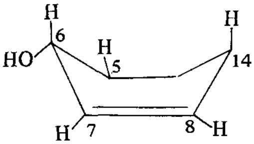
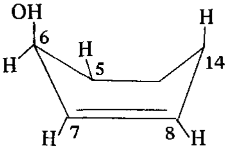
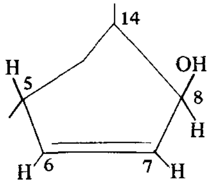
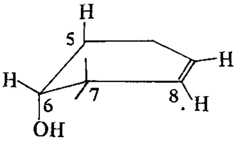
[149]



[150]

TABLE V

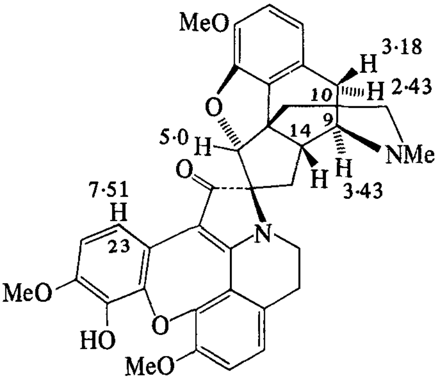
Coupling constants of ring C protons in some morphine alkaloids

 Codeine	$J_{5,6} = 6{\cdot}4$ $J_{6,7} = 1{\cdot}8$ $J_{6,8} = 2{\cdot}9$ $J_{6,14} = 2{\cdot}6$	$J_{8,14} = 2{\cdot}5$
 Isocodeine	$J_{5,6} = 1{\cdot}2$ $J_{6,7} = 5{\cdot}7$ $J_{6,8} = 0$ $J_{6,14} = 0$	$J_{8,14} = 1{\cdot}8$
 Pseudoceine	$J_{5,8} = 1{\cdot}2$ $J_{6,8} = 1{\cdot}8$ $J_{7,8} = 1{\cdot}2$	$J_{8,14} = 9{\cdot}6$
 Neopine	$J_{5,6} = 4{\cdot}2$	

(−18·6 to −19·0 Hz) indicates the bisecting geometry between the plane of the aromatic ring and the 10-methylene group.

The presence of a large section of the codeine molecule in cancentrine [151] (129) was demonstrated by the almost identical couplings involving the 9-, 10- and 14- protons in the two compounds. The location of the OH group in cancentrine was established by acetylation when the 23-proton (*para* to OH) moved upfield from δ 7·51 in [151] to δ 7·88 in the acetate of [151].

Full details of the NMR spectra of thebaine [152], dihydrothebaine [153], codeinedimethylketal [154] and some of their deuterated derivatives have been published. (127) The deuteration



$J_{gem} = -18{\cdot}5$

$J_{10\beta,9} = 1{\cdot}0$

$J_{10\alpha,9} = 6{\cdot}0$

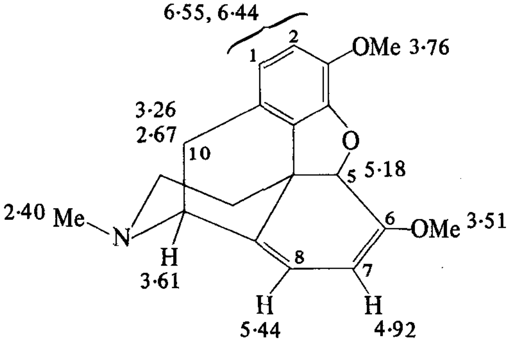
$J_{9,14} = 1{\cdot}5$

MeO at 3·91, 3·76, 3·85

[151]

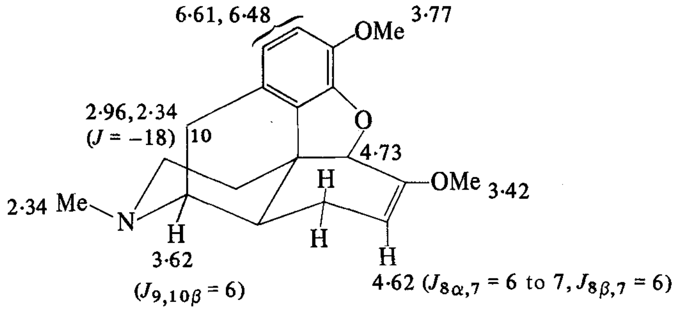
experiments have permitted the assignment of the methoxyl proton signals in [152] and [153] and of the axial and equatorial methoxyls in the ketal. The effect of the ring C double bonds on the chemical shifts of the 10-methylene protons may be observed by a comparison of the spectra of thebaine and dihydrothebaine, and the high field absorption of the acetal methoxyl protons *cis* to the aromatic ring in [154] is worthy of note.

The NMR spectra ($CDCl_3$) of 6-deoxy-7α-methoxy- [155] and 7β-methoxy- neopine [156] have been described. (131) The NMR spectra of both compounds are very nearly identical with the exception of the chemical shifts and coupling constants of the 8-olefinic proton. The 7-methoxyl protons have identical chemical



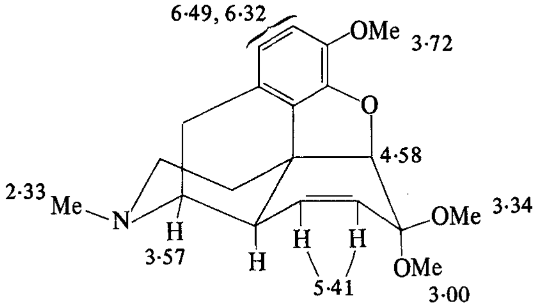
(in $CDCl_3$)

[152]

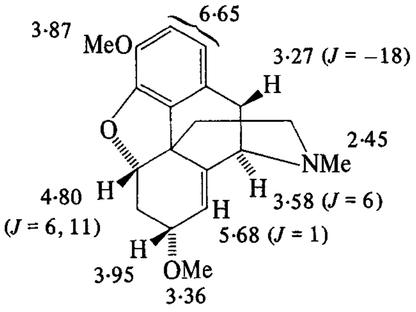


(in $CDCl_3$)

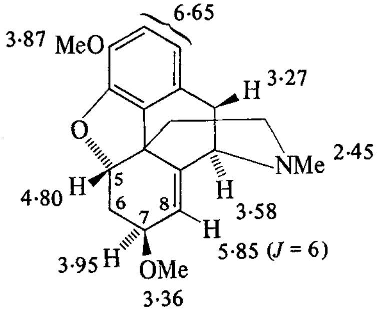
[153]



[154]

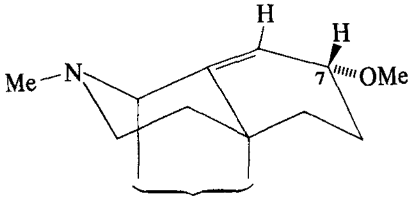


[155]



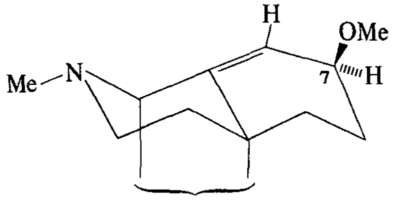
[156]

shifts in various solvents and, although the 7-proton signals overlap the 3-methoxyl proton signals so that coupling constants were not extractable from the spectra, the 7-proton chemical shifts in both compounds are not very different. This is unexpected in view of the different stereochemistry [157] and [158]. Models (see partial structures [157] and [158] show dihedral angles between 7-H and 8-H of *ca.* 85° for the 7α-methoxy compound and 35° for the 7β-methoxy compound consistent with the vicinal couplings shown in [155] and [156]. The 8-proton absorbs at lower field in the β-methoxy compound [156] than in [155]. A dihedral angle of 30° between the nodal plane of the aromatic ring and the benzylic methylene is consistent with the observed J_{gem} of −18 Hz. NMR parameters for the related compound 7β-hydroxyneopine are summarized in [159]. (132)



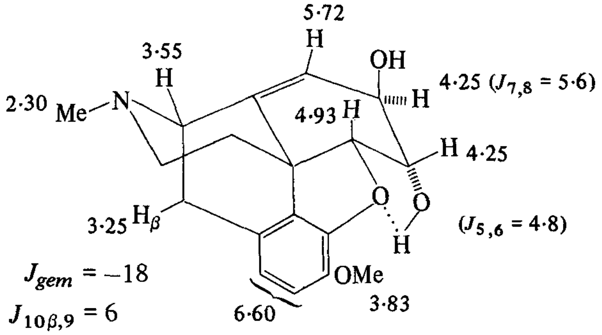
$\theta = 85°$

[157]



$\theta = 35°$

[158]

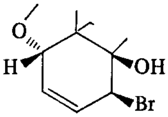
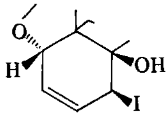
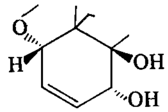
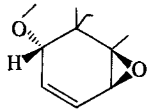
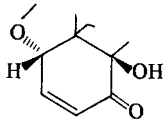
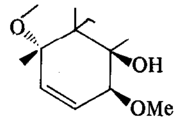


[159]

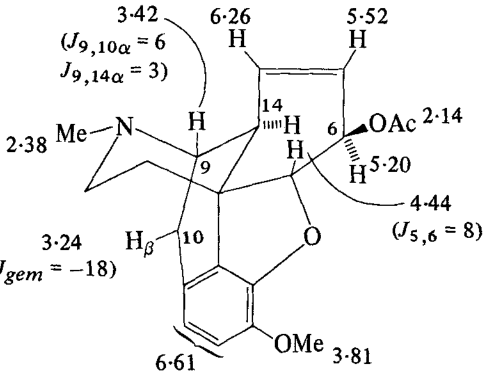
The spectra ($CDCl_3$) of the epimeric pair of B/C *trans* morphine structures [160] and [161] (133) show many similarities to the spectra of the normal B/C *cis* morphines. The acetate protons in the α- acetate [161] are at much higher field (δ 1·75) than in [160] (δ 2·14) as a consequence of their spatial relationship with the aromatic ring. A useful compilation of 5β-H chemical shifts in Δ^6-morphine derivatives has been made (Table 6). (134) The signals for this proton appear as a quartet showing coupling to both olefinic protons.

TABLE VI

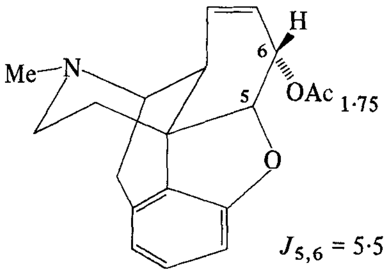
Chemical shifts of the 5β-H proton in some Δ^6-morphine derivatives (134)

Compound	δ 5β-H	$J_{5\beta,6}(= J_{5\beta,7})$
	5·04	5
	5·05	5·5
	4·92	3·6
	4·79	3·5
	5·15	4·3
	4·86	4

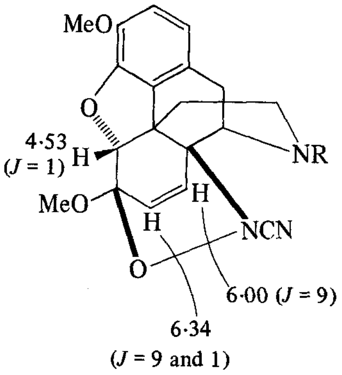
The NMR spectrum ($CDCl_3$) of the thebaine adduct [162]; R = Me) (135) clearly shows the ^4J of 1 Hz between the 7- and 5-protons. In compound ([162]; R = CH_2CN) it is claimed that the signal from the *N*-methyl protons present in ([162]; R = Me) is replaced by a methylene quartet (δ 3·80 and 3·65, $J = -11$). This is a most unexpected value of J_{gem} since in acetonitrile J_{gem} is $-16·9$ Hz. The olefinic proton in [163] (136, 137) absorbs ($CDCl_3$) at much lower field than in e.g. [155] or [156], suggesting the *syn* configuration of the oxime group, and one of the 6-methoxyl protons



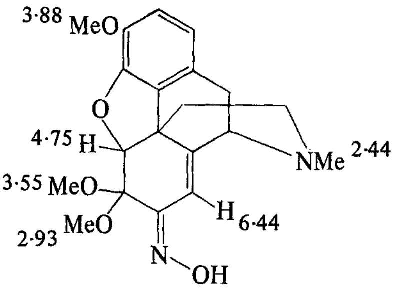
[160]



[161]



[162]

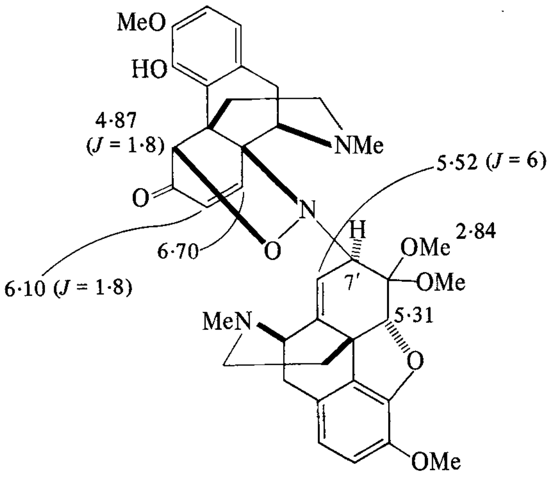


(in $CDCl_3$)

[163]

absorbs at δ 2·93 (compare [154]). From the same set of nitrosation experiments (137) as that producing [163] the Diels–Alder adduct [164] was obtained. The presence of the signals at δ 4·87 and δ 5·31 showed two CH–O linkages to be present, even though the phenolic function had been liberated. Again one of the acetal methyl protons absorbed at high field (δ 2·84, cf. [154]) and the 7′-β configuration was established from the value (6 Hz) of $J_{7'8}$ which is similar to that in simple 7β-substituted neopinone acetals. (138)

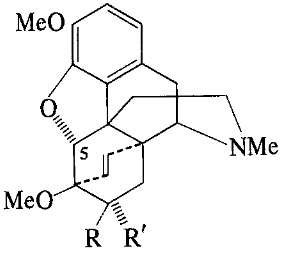
In the spectrum ($CDCl_3$) of the pair of isomers ([165]; R = H, R′ = SO_2Et) and ([165]; R = SO_2Et, R′ = H) the 5-proton absorbed at δ 4·41 and δ 5·53 respectively enabling the C(7) configuration to be assigned (139) assuming that the NMR-structural correlation established for related compounds containing 7β-electron attracting



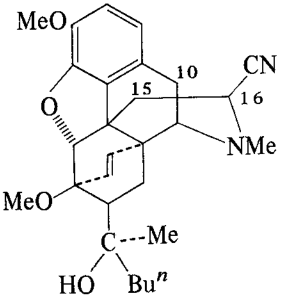
NMe 2·50, 2·41
MeO 3·86, 3·77, 3·56
(in $CDCl_3$)

[164]

groups may be applied to this system. (140) The 16β-proton signals (δ 3·89, $J_{eq\text{-}eq} = J_{eq\text{-}ax} = 5$ Hz) in the spectrum of the 16α-nitrile ([166]; αCN) confirmed the axial orientation of the 16α-nitrile

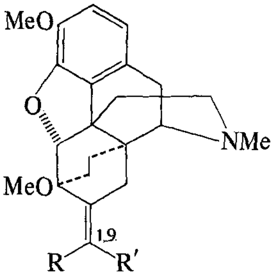


[165]



[166]

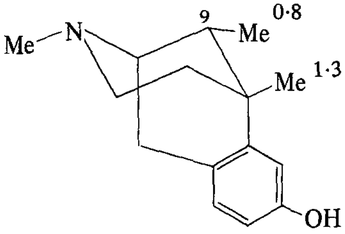
group and since the 10β-proton lies in the deshielding zone of this group it absorbs at relatively low field (δ 3·6). (141) In the corresponding 16β-nitrile ([166]; βCN) the 16α-proton absorbed at δ 3·43 (J = 7, 10 Hz). The structures ([167]; R = H, R′ = Me) and ([167]; R = Me, R′ = H) were assigned (142) from the observation of



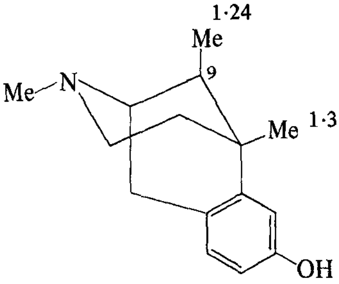
[167]

a downfield shift of the 19-methyl group protons (δ 1·85) in the spectrum of ([167]; R = Me, R′ = H) as a result of deshielding by the 6-methoxyl group (cf. δ 1·65 in the isomer).

The chemical shifts ($CDCl_3$) of the 9-methyl protons in the 5,9-dimethyl-6,7-benzomorphans [168] and [169] (143) are different and this may be a result of their differing stereochemistry with



[168]

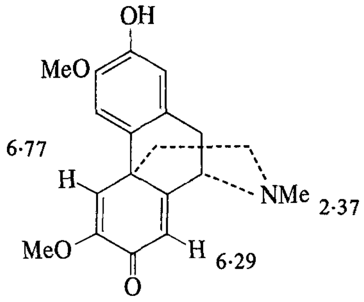


[169]

respect to the aromatic ring and the nitrogen atom. The methiodide of [168] shows the $\overset{\oplus}{\mathrm{N}}\mathrm{Me}_2$ signals at δ 3·36 and δ 3·24 (DMSO-d_6) whereas in the methiodide of [169] absorption is at δ 2·83 and δ 3·13. The δ 2·83 signal suggests a skew boat for the piperidine ring in this compound so that one of the *N*-methyl groups lies in the shielding zone of the aromatic ring.

B. Alkaloids Possessing the Morphine Skeleton but Lacking the 4,5-Oxide Bridge

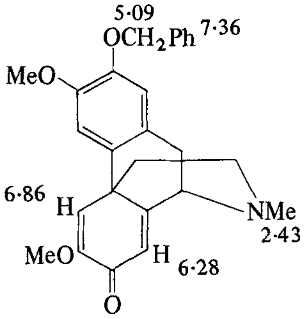
The NMR spectrum of pallidine (144) is summarized in [170] and naturally the spectrum of *O*-benzylisosalutaridine [171] (145) is almost identical with the exception of those signals arising from the *O*-benzyl group. In the related compound [172] (146) the 5-olefinic proton absorbs at lower field than in [170] and [171].



MeO	3·79, 3·89
Aromatic protons	6·33, 6·68

(in $CDCl_3$)

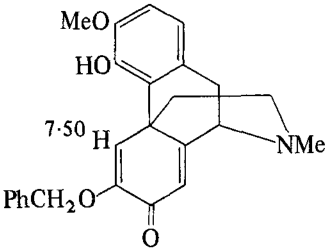
[170]



MeO	3·80, 3·88
Aromatic protons	6·38, 6·67

(in $CDCl_3$)

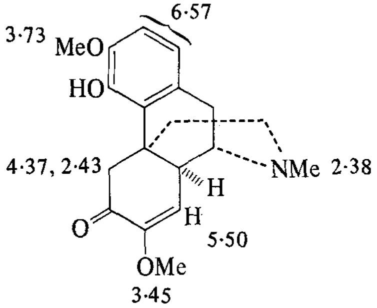
[171]



(in $CDCl_3$)

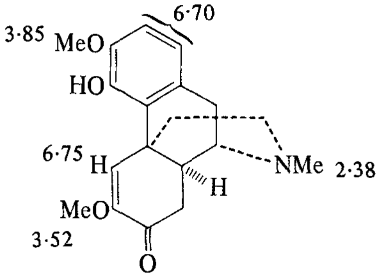
[172]

The chemical shifts of the olefinic protons in sinomenine [173] and isosinomenine [174] clearly differentiate between the two isomers. (147)



(in $CDCl_3$)

[173]

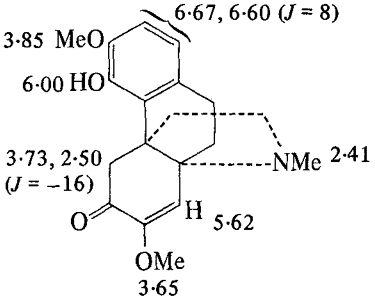


(in $CDCl_3$)

[174]

C. Alkaloids Possessing Hasuban Skeleton

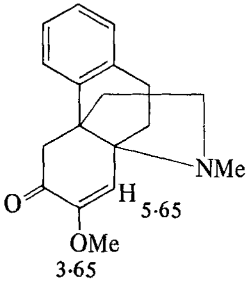
The chemical shift of the olefinic proton is cepharamine [175] (148) is similar to that in sinomenine and in the model compound



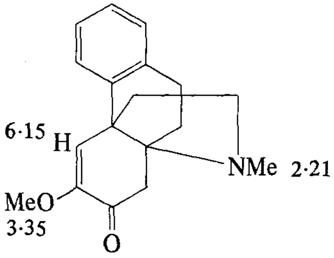
(in $CDCl_3$)

[175]

[176] (149) and comparison of the olefinic proton chemical shifts in [177] (149) and [174] shows the deshielding effect of the C(4)-OH on the 5-proton in these systems. In this connection it should be

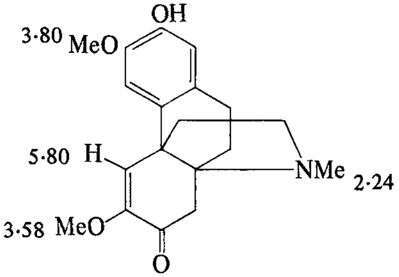


[176]

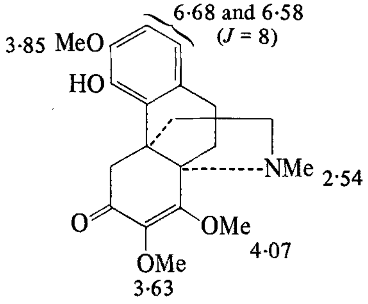


[177]

noted that the chemical shifts of the olefinic protons and of the methoxyl group proton signals in [177] and in [178] (150) differ more than would be expected, although this may be a solvent effect (no solvent recorded for [178]). The change in structure (position of attachment of *N*-methyl) from sinomenine [173] to cepharamine [175] results in a shielding of one of the 5 methylene protons. The NMR parameters of the four related alkaloids are shown in [179] to [182]. (151) The J_{gem} of −16·5 Hz recorded for the C(5) methylene group protons in [182] is consistent with a bisection of this group

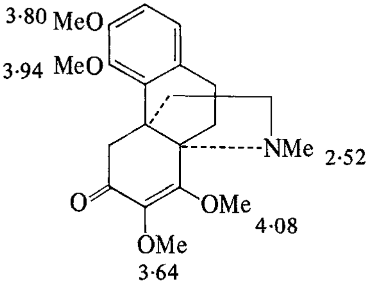


[178]



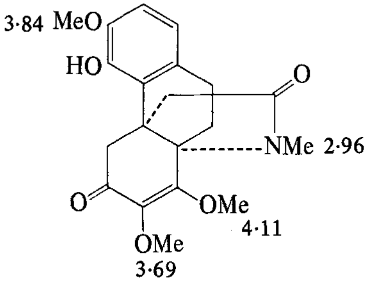
Aknadinine (in $CDCl_3$)

[179]



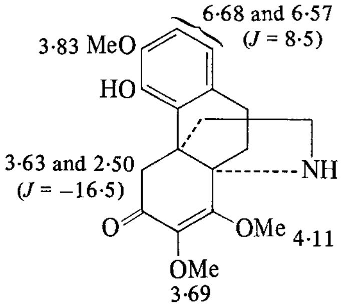
Hasubanonine (in $CDCl_3$)

(180)



Aknadilactam (in $CDCl_3$)

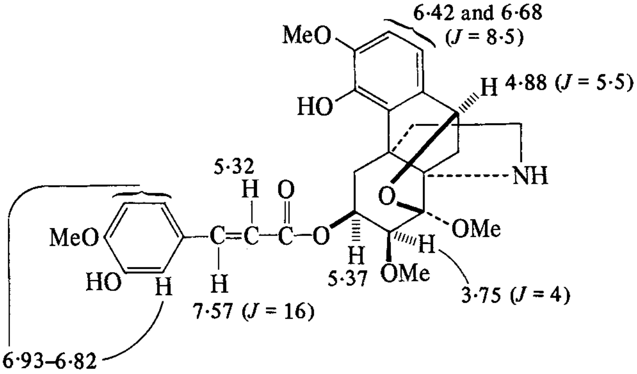
[181]



Aknadicine (in $CDCl_3$)

[182]

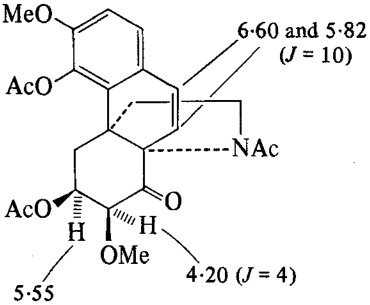
by the nodal plane of the carbonyl group. The NMR spectra of stephisoferuline and one of its degradation products are summarized in [183] and [184]. (152)



MeO 3·92, 3·57, 3·40

(in $CDCl_3$)

[183]



MeO 3·80, 3·47

AcO 2·33, 2·13, 1·70

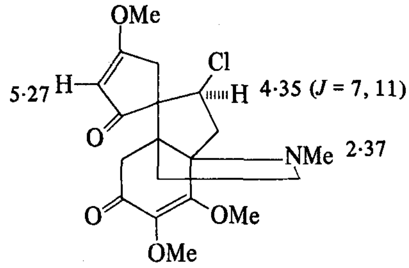
(in $CDCl_3$)

[184]

D. Acutumine and Related Alkaloids

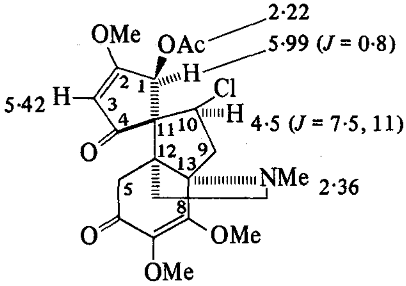
In the NMR spectrum of acutuminine [185] (153) the proton geminal to the chlorine atom absorbs at δ 4·35 and shows vicinal couplings of 7 and 11 Hz. The NMR spectrum (deuterobenzene) of acetylacutumine [186] (154) enables further analysis of the 9- and 10-proton signals to be made (δ 3·10, 2·47, 4·58 with J_{vic} = 12·5

MeO at 4·11, 3·88, 3·71



[185]

MeO at 3·70, 3·91, 4·11



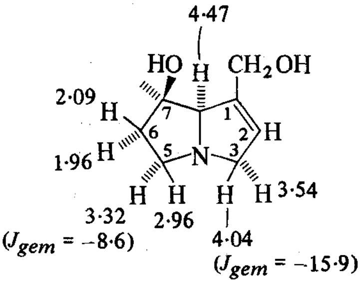
(in $CDCl_3$)

[186]

and 7, J_{gem} −12·5 Hz). In this solvent the 5-methylene protons also appear as an AB system (δ 2·72 and 2·10, J = −16 Hz). The allylic coupling (0·8 Hz) between the 3- and 1-proton in acetylacutumine is clearly shown. (154)

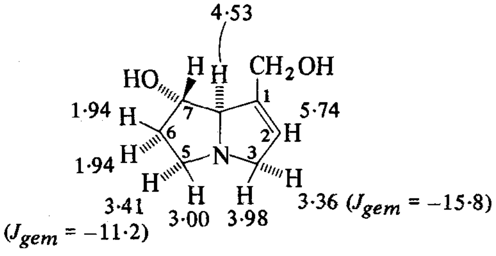
VI. PYRROLIZIDINE AND PYRROLE ALKALOIDS

The NMR spectra of the pyrrolizidine alkaloids has been extensively studied and a comprehensive review is available. (155, 156) The chemical shifts (pyridine solution) for retronecine and heliotridine are summarized in [187] and [188] and some of the vicinal



(in pyridine)

[187]



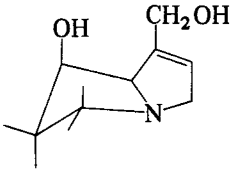
[188]

coupling constants in Table 7. These coupling constants are best interpreted in terms of an *exo*-buckled pyrrolizidine ring for retronecine [189] and for an *exo* ⇌ *endo*-buckled ring conformational equilibrium for heliotridine [190]. An *endo*-buckled conformation is

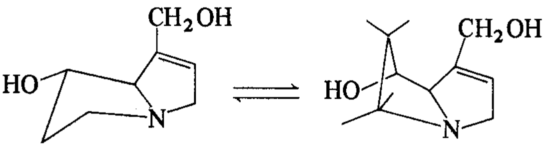
TABLE VII

Vicinal coupling constants in Heliotridine and Retronecine (155)

Heliotridine	Retronecine
$J_{5\alpha6\alpha}$ 5·7	$J_{5\alpha6\alpha}$ 7·2
$J_{5\alpha6\beta}$ 8·4	$J_{5\alpha6\beta}$ 1·2
$J_{5\beta6\alpha}$ 5·7	$J_{5\beta6\alpha}$ 12·0
$J_{5\beta6\beta}$ 5·7	$J_{5\beta6\beta}$ 6·0
$J_{7\beta8\alpha}$ 3·4	$J_{7\alpha8\alpha}$ 3·9



[189]

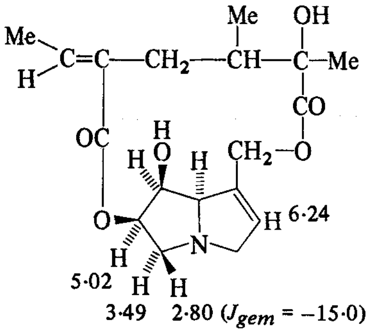


exo-buckled *endo*-buckled

[190]

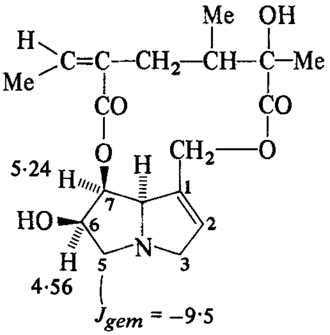
characterized by a more negative J_{gem} [C(5) methylene protons] than an *exo*-buckled ring conformation (J_{gem} = −11·2 Hz for heliotridine; J_{gem} = − 8·6 Hz for retronecine).

The difference in J_{gem} [C(5) methylene protons] in madurensine (−15·0 Hz; indicating *endo*-buckled ring) and in anacrotine (−9·5 Hz; indicating *exo*-buckled ring) suggested (157) that the previously proposed structure (158) for the former alkaloid was incorrect since such a difference should not be a result of a small change in the structure of the esterifying acid. Irradiation of the C*H*OCOR signals in the two alkaloids showed the differing positions of attachment of the side chain and the structures of the alkaloids are shown in [191] and [192]. The J_{gem} of −15·0 Hz in madurensine is the most negative J_{gem} yet observed for methylene group protons adjacent to tertiary nitrogen and may arise from the electron withdrawal by the C(6) oxygen function in addition to the loss of the positive contribution to J_{gem} from the nitrogen lone pair caused by the *endo*-buckled conformation. A detailed analysis of the NMR spectrum of heliotridene [193] has been made (159) and results are consistent with an *endo* ⇌ *exo*-buckled conformational equilibrium. The homoallylic couplings ($J_{5\alpha8\alpha}$ = 3·6 Hz, $J_{5\beta8\alpha}$ = 5·0 Hz) are unusually large and are reduced to normal values on protonation of the nitrogen.



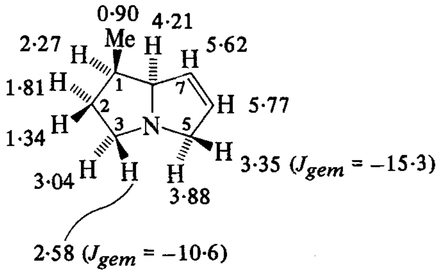
Madurensine (in $CDCl_3$)

[191]



Anacrotine (in $CDCl_3$)

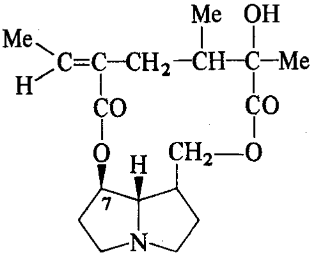
[192]



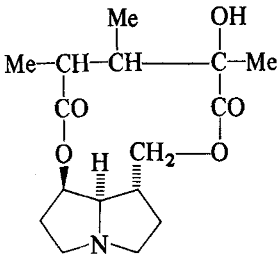
(in $CDCl_3$)

[193]

The 7-proton in hastacine [194] (160) comes at unusually high field (δ 4·46) (cf. retusine [195] δ 7-H 5·21). The low field absorption in retusine and similar systems is on account of 7-H lying



[194]

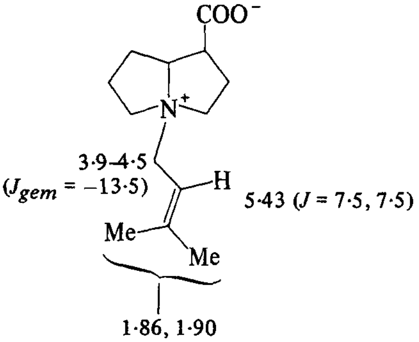


[195]

in the plane of the ester carbonyl. The geometry must be disturbed in [194] by changes in the macrocyclic structure. The NMR spectra of other pyrrolizidine derivatives have been discussed. (161) In

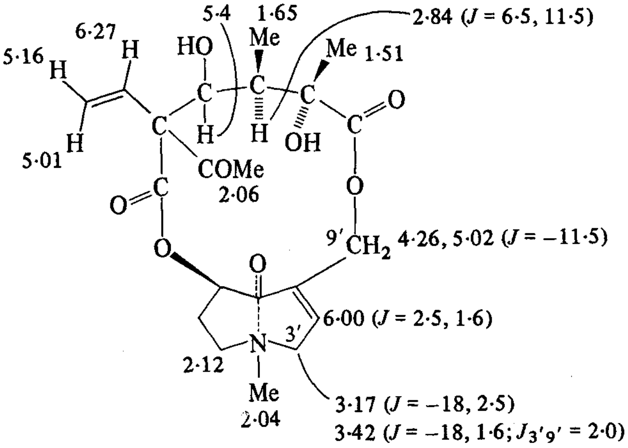
3,5-dioxopyrrolizidine and related systems the 1β-protons exhibit an upfield shift relative to the 1α-protons [δ(1β-H) = 1·7 and δ(1α-H) = 2·4].

The NMR parameters of anodendrine, (162) clivorine (163) and ligularine (164) are summarized in [196], [197] and [198]. The



Anodendrine (in $CDCl_3$)

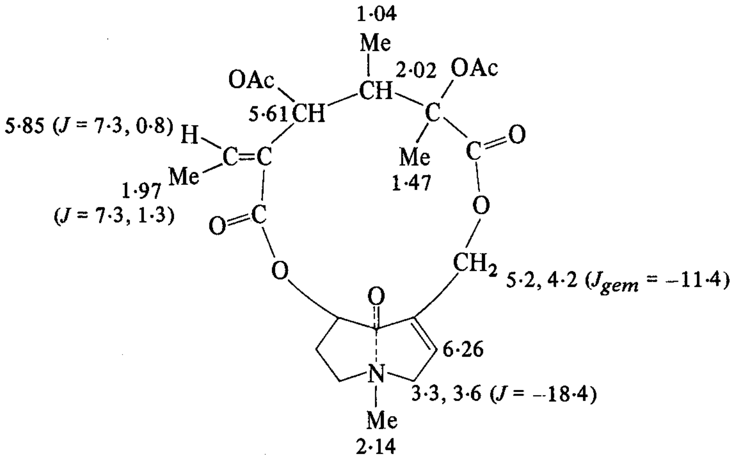
[196]



Clivorine (in $CDCl_3$)

[197]

values of the geminal coupling constants for the $N^{\oplus}CH_2C{=}C$ protons in anodendrine and for the $OCH_2C{=}C$ protons in clivorine and ligularine are all rather large for protons situated adjacent to a π bond. The NMR parameters given for the heterocyclic ring protons in anado-



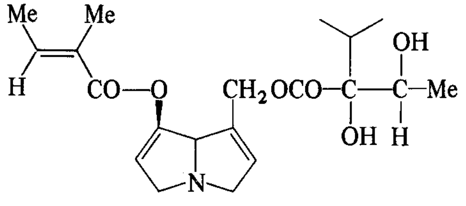
OAc 2·01, 2·09

Ligularine (in $CDCl_3$)

[198]

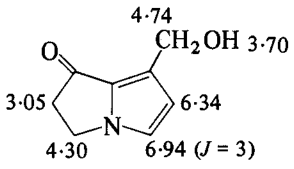
line [199] (165) are not in accord with the structure shown. In particular the 3-methylene protons are said to absorb as a quartet (δ 4·02, 4·20, J = 9 Hz) which is of the wrong magnitude for a J_{gem} for $NCH_2C{=}C$ protons, and the 5-methylene protons at δ 2·1 and δ 2·40 which are also incorrect chemical shifts for protons in such an environment.

NMR parameters for the pyrrole alkaloid loroquin (166) are as shown in [200].



(in $CDCl_3$)

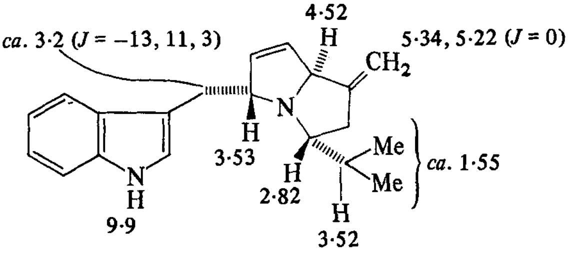
[199]



(in $CDCl_3$)

[200]

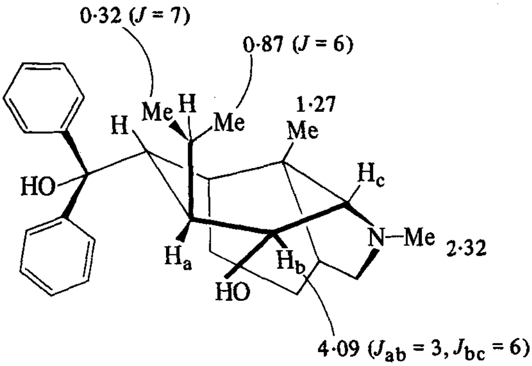
On the basis of the 200 MHz NMR data summarized in [201] the structure shown has been assigned (167) to peduncularine. The low field absorption of the isopropyl methine proton is in accord with an



[201]

eclipsing relationship between this proton and the nitrogen lone pair. (168) The J_{gem} value (−13 Hz) of the indolylmethylene protons indicates a conformation in which the π orbitals of the indole near bisect the methylene group, and the smaller J_{gem} (−17 Hz) of the pyrrolidine ring methylene protons indicates a dihedral angle of 30° between the π orbital of the *exo*methylene group and the C–H bonds.

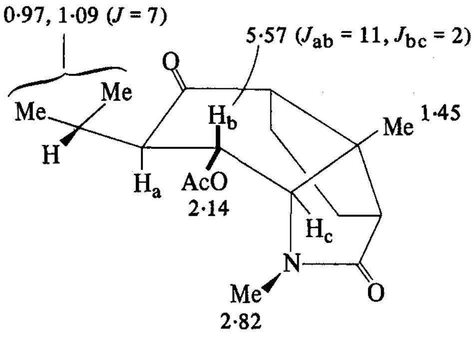
In studies relating to dendroline (169) interesting NMR results were obtained on compounds [202] and [203]. In particular the



(in $CDCl_3$)

[202]

large difference in chemical shift between the isopropyl protons (δ 0·32 and δ 0·87) in [202], implying a conformation such as that shown so that one of the methyl protons is shielded by the aromatic ring, and the unusual observation of different J_{CHMe} coupling constants in an isopropyl moiety is worthy of note. Other data are given in the structures.

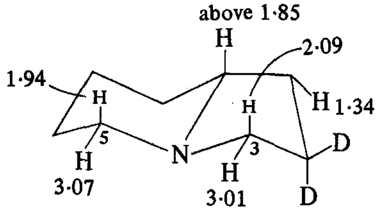


(in $CDCl_3$)

[203]

VII. INDOLIZIDINE ALKALOIDS

The NMR spectrum of 3,3-dideuterioindolizidine (170, 171) shows the geminal coupling constant of the 3-methylene protons (−9·5 Hz) to be larger than that of the 5-methylene protons (−11·0 Hz), in agreement with the previously proposed (172) relationship between J_{gem} in NCH_2 groups and the nitrogen lone pair -CH dihedral angle (Dreiding models: ϕ 5-H 180°; ϕ 3-H < 180°). Other NMR data obtained on this compound is shown in [204]. Coupling constants in *N*-acetylslaframine hydrochloride [173] (D_2O) are $J_{5a,5e} = -13$ Hz (typical of α-methylene protons in *N*-protonated piperidines), $J_{5a,6e} = 2{\cdot}8$ Hz (smaller than in [204]) and $J_{1,8a} = 6{\cdot}5$ Hz, and the chemical shifts of the 1- and 6-protons in the spectrum of *N*-acetylslaframine [205] (174) and its isomers are as shown in Table 8.



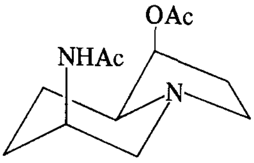
$J_{5e,5a} = -11{\cdot}0$

$J_{5a,6a} = 11{\cdot}0$

$J_{5a,6e} = 4{\cdot}0$

$J_{3e,3a} = -9{\cdot}5$

[204]



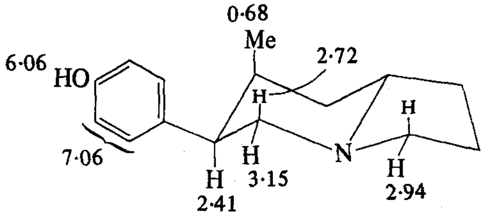
[205]

TABLE VIII

NMR spectra of isomers of *N*-acetylslaframine (174)

Stereochemistry of isomer		Chemical shifts 1-H	Chemical shifts 6-H
trans 1H, 8*a*H	*eq* OAc	4·84	–
trans 1H, 8*a*H	*ax* OAc	4·76	4·25
cis 1H, 8*a*H (*N*-acetylslaframine)	*ax* OAc	5·31	4·24
cis 1H, 8*a*H	*eq* OAc	5·32	4·12

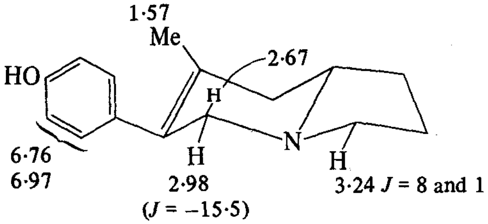
The value of $J_{5a,5e}$ observed in the NMR spectrum of dihydroipalbidine [206] (175) is close to that in indolizidine [204], but unexpected is the low value (4 Hz) of $J_{5a,6a}$ in [206] (cf. 11·0 Hz in [204]) which must be a result of conformational distortion. The chemical shift of the 5*ax*-proton is at much lower field in [206] than in [204] as a result of deshielding by the *syn*-axial methyl group. Two reports on the NMR spectrum of ipalbidine [207] have been



$J_{5a,5e} = -11·2$
$J_{5a,6a} = 4·0$
$J_{5e,6a} = 1·9$

(in $CDCl_3$)

[206]

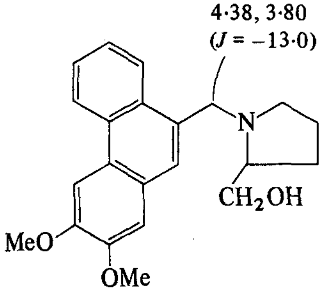


(in $CDCl_3$)

[207]

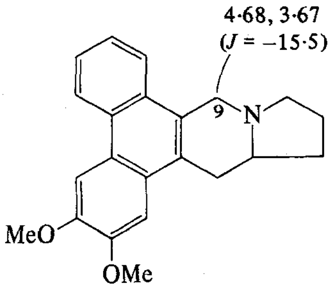
published. (175, 176) If the whole of the difference in $J_{5a,5e}$ (ΔJ = 4·5) on going from [206] to [207] is a result of a negative contribution from the double bond then the nodal plane of this bond must be situated so as to bisect the C(5) methylene group. (177)

Cyclization of the phenanthrylmethylproline [208] to the phenanthroindolizidine [209] resulted in a decrease of 2·5 Hz in the Ar-CH_2-N coupling constant, (178) This coupling constant for the C(9) methylene protons is similar in the indolizidine [209] and in the quinolizidine cryptopleurine [210]. It has been argued that in [209] and [210] the C(9) methylene group is orientated such that there is an approach to bisection of the methylene by the nodal plane of the aryl system which permits a negative contribution to J_{gem}. (177) When a Dreiding model of [209] is twisted such that the plane of the aromatic ring bisects the C(9) methylene group the nitrogen lone pair is brought into a position such that it is near eclipsing one of these CH bonds and in this conformation the positive contribution to J_{gem} from the nitrogen lone pair in [210]



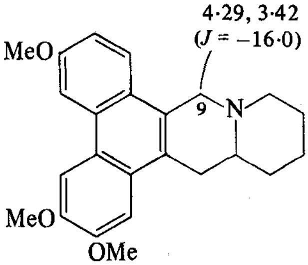
(in CDCl$_3$)

[208]



(in CDCl$_3$)

[209]

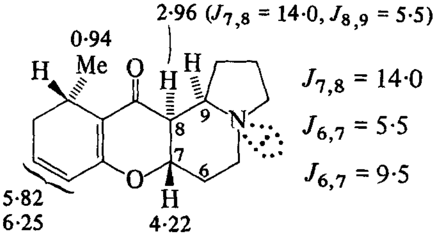


(in CDCl$_3$)

[210]

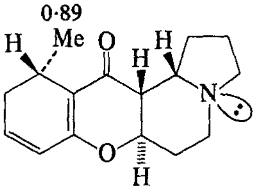
would then almost cancel the negative contribution from the aryl system. It would seem therefore that the conformation of [209] differs from this and it is probable that the orientation of the C(9)-methylene with respect to the aromatic ring is not the same in [209] and [210]. The greater shielding of 9*ax*-H in [210] than in [209] and the greater deshielding of 9 *eq*-H in [209] also indicates differing orientations of the C(9)-H bonds to the aromatic system and to the nitrogen lone pair.

NMR data ($CDCl_3$) on a number of elaeocarpus alkaloids have been reported (179, 180) ([211], [212] and [213] and isomers of



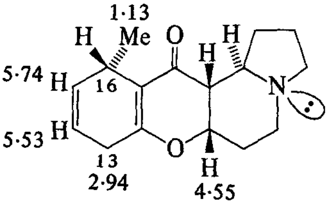
Epialloelaeocarpiline

[211]



Alloelaeocarpiline

[212]

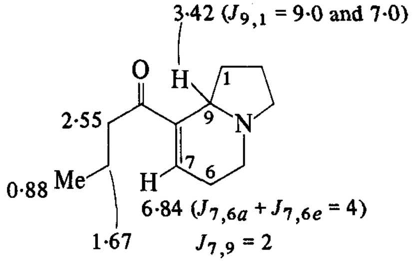


$J_{14,15} = 10$
$J_{13,14} = 3$
$J_{15,16} = 4$

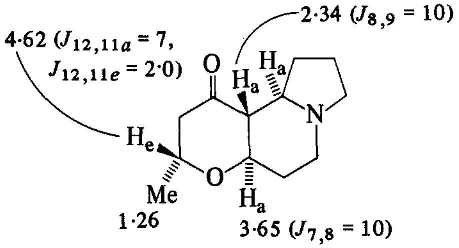
Pseudoepi-isoelaeocarpiline

[213]

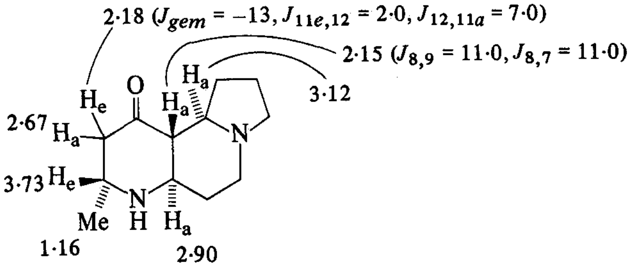
[211] and [212]). The difference in the chemical shift of the 16-methyl protons in epialloelaeocarpiline and in alloelaeocarpiline is a result of the differing configurations of the methyl group with respect to the 8,9 bond. Other stereochemically informative NMR data is summarized in [211] and [212] and that of some related alkaloids in [214], [215] and [216]. (181) In the spectrum ($CDCl_3$) of elaeocarpine [217] (182) the 7-proton signals could not be analysed because of the similar chemical shifts of the 6-methylene protons and of the 5*ax*-protons. Accordingly the spectrum was run in deuterioacetic acid, which resulted in deshielding of the 5-protons, so that the multiplet arising from the 7*a*-proton could be analysed ($J_{7,8}$



Elaeokanine A (in $CDCl_3$)
(*trans*-fused)
[214]

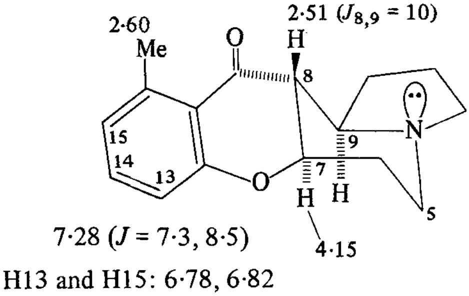


Eliokanine D
[215]



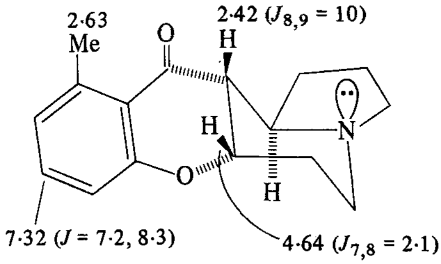
Eliokanidine A
[216]

= 11·8 Hz). [217] and [218] were clearly differentiated by the NMR parameters of the 7-proton. The upfield shift of the *C*-methyl protons and the deshielding of the 8-proton (δ 3·80, cf. δ 2·51 in elaeocarpine) suggests the conformation [219] for isoelaeocarpicine.



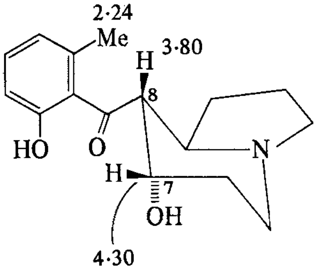
(in $CDCl_3$)

[217]



(in $CDCl_3$)

[218]

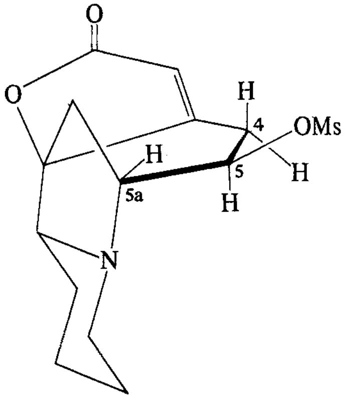


(in $CDCl_3$)

[219]

NMR spectra of other elaeocarpine alkaloids have been described. (183)

On the basis of the coupling constants shown in [220] the



$J_{5\alpha,4\beta} = 9{\cdot}5$
$J_{5\alpha,4\alpha} = 5{\cdot}0$
$J_{5\alpha,5\beta} = 2{\cdot}0$

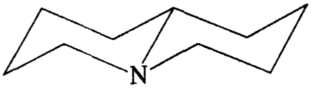
[220]

stereochemistry, containing a near boat conformation, was assigned (184) to the mesylate of securinol B.

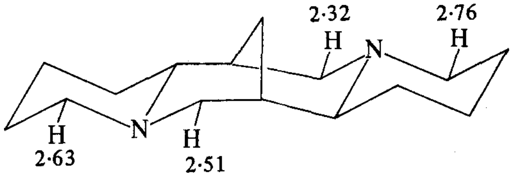
VIII. QUINOLIZIDINE ALKALOIDS

The chemical shifts of the protons ajacent to the nitrogen atom in quinolizidine derivatives are of diagnostic importance in structural studies. Decoupling experiments (185) gave a Δ*ae* (difference in chemical shift between the axial and equatorial 4-methylene protons) in quinolizidine itself of 0·93 ppm measured in CDCl$_3$. More recently (186) measurement of Δ*ae* in 3,3-dideuterioquinolizidine gave a value of 0·87 ppm (δ 4*eq*-H 2·77 and δ 4*ax*-H 1·90) and the 100 MHz NMR spectrum of 4,6-tetradeuterioquinolizidine (187) showed the angular proton to absorb at δ 1·7. The mechanism for the shielding of the 4*ax*-H proton in quinolizidine has been the subject of controversy (188) but must arise from both the shielding effect of the *anti*-nitrogen lone pair and of the gauche C(6) methylene and, providing allowance is made for other shielding influences, a large Δ*ae* in a quinolizidine derivative implies a *trans*-fused ring conformation [221].

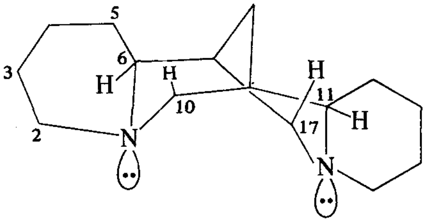
The value of these observations is illustrated with reference to spartein [222] and β-isospartein [223]. (189) In spartein there are



[221]



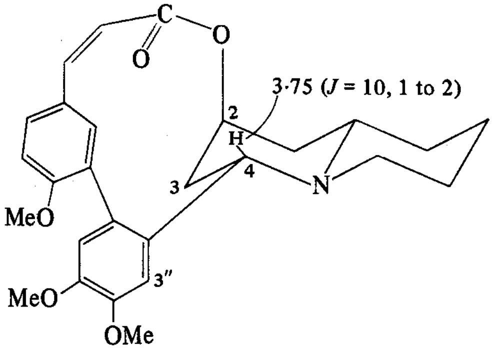
[222]



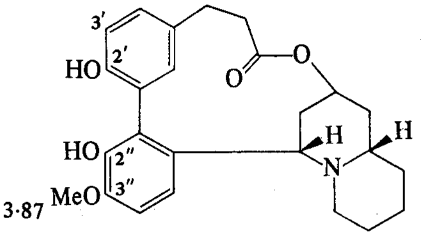
[223]

two *trans* fused quinolizidine moieties and in accord with this only four protons absorb below δ 2·8. In β-isospartein there are six protons gauche to the lone pairs and two (10*ax*-H and 17*ax*-H) *trans* diaxial. The 6- and 11-protons are found to absorb at δ 3·00 and the remaining gauche protons at δ 2·79, 2·48 and 2·26. The 10*ax*- and 17*ax*- protons absorb at δ 2·15 (at lower field than in quinolizidine itself) because of the deshielding influence of appropriately orientated ring A and D methylene groups. (190) As has been pointed out (4) the recent challenge to the structure [223] on IR evidence (191) does not appear reconcilable with the NMR data.

The NMR spectrum of methyllythrine [224] (192) corresponds to the structure shown since vicinal couplings of 10 Hz and 1 to 2 Hz may be extracted from the signals arising from the 4*ax*-proton (δ 3·75) and the half width of the 2-proton signals is 7·5 to 9 Hz. Methylvertine is shown to be enantiomeric with methyllythrine at C(10) (i.e possesses *cis*-quinolizidine moiety) by, *inter alia*, the lower field chemical shift of 4*ax*-H (δ 4·60). When both of these compounds are hydrogenated the 4*ax*-H signals move upfield by *ca.* 0·60 ppm possibly as a result of changes in the torsional angle between the phenyl rings. The H3″ proton in these series of alkaloids is deshielded by *ca.* 1·0 ppm on converting the alkaloids to the *N*-oxides. In decodine [225] (192) the methoxyl group protons



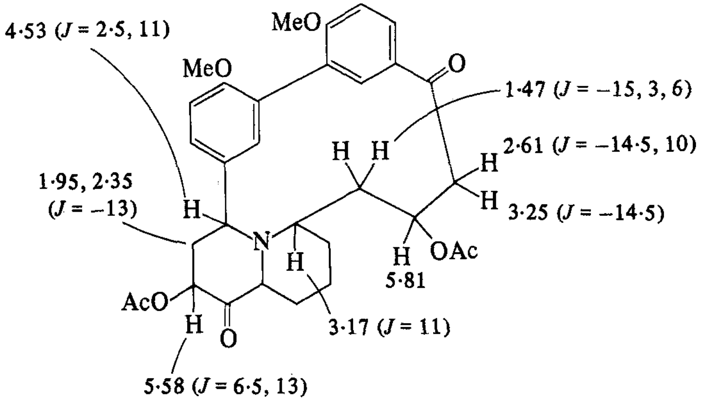
[224]



[225]

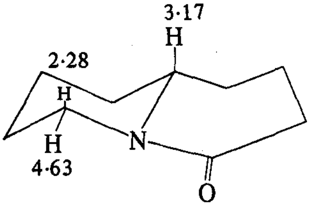
absorb at δ 3·87 whereas in dimethyldecodine absorption occurred at δ 3·87, 3·69 and 3·69 indicating, by their high field absorption, that the two introduced methoxyls are at 2″ and 2′ (see discussion in section IID on aporphines).

A detailed examination of the NMR spectrum of the diketone [226] obtained by oxidation of lythrancine-II has been made. (193) The coupling constants involving the 1-proton (2·5 and 11 Hz) show its axial nature and since its chemical shift is at rather low field (δ 4·53) it is tempting to assign the *cis*-fused quinolizidine stereochemistry.

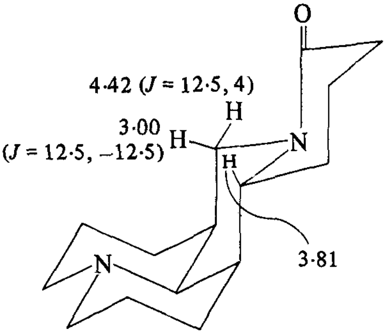


[226]

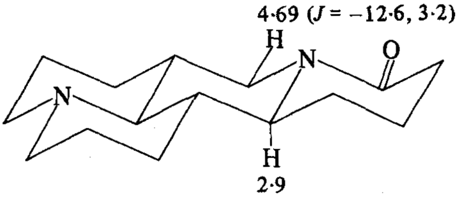
Many quinolizidine alkaloids contain the quinolizidin-4-one moiety [227] and these are characterized by the very low field absorption (194, 186) of the 6*eq*-proton since this lies in the plane of the amido carbonyl group. Typical examples illustrating the importance of this effect are matrine [228] and allomatrine [229]. In



[227]

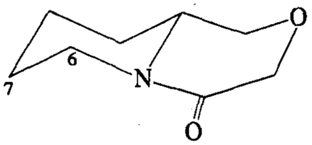


[228]



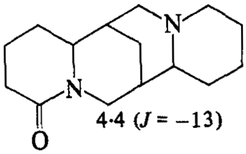
[229]

matrine the axial protons absorb at lower field than in [227] perhaps on account of the proximity to the nitrogen lone pair. To provide more information regarding the spectra of compounds related to matrine, a detailed study of the NMR spectra of a series of substituted hexahydropyrido[2,1-*c*][1,4]oxazin-4(3*H*)-ones has been made (186) and typical values of the coupling constants involving the 6-methylene protons are shown in [230]. Comparison of the NMR spectra of lupanine [231], aphyllidine [232] and 5,6-dehydrolupanine [233] shows the effect of introducing a ring A double bond on the chemical shift of the proton *peri* to the amido carbonyl group. (195) A related deshielding effect to that in [227] is seen in the phenanthraquinolizidinone [234] (196) in which the 8-aromatic proton absorbs at δ 9·65. The NMR spectrum of the dilactam [235] provides a value for the chemical shift of a proton situated adjacent to the nitrogen atom of an amido function. The

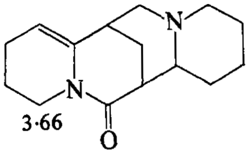


[230]

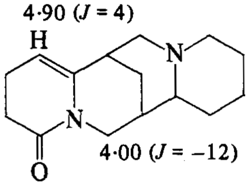
$J_{6ax\,6eq}$	−13·0
$J_{6ax\,7ax}$	11·8
$J_{6ax\,7eq}$	3·0
$J_{6eq\,7ax}$	3·0
$J_{6eq\,7eq}$	2·0



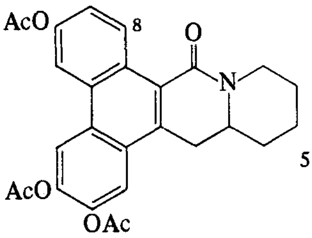
[231]



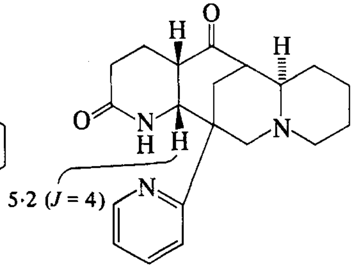
[232]



[233]



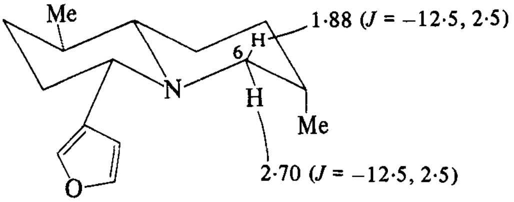
[234]



[235]

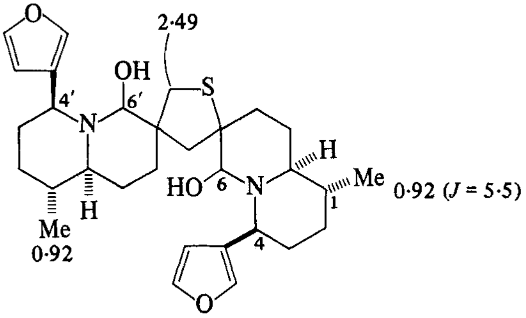
J_{vic} of 4 Hz involving this proton demonstrates the *cis*-A/B ring fusion. (197)

Other assignments have been based on the differing NMR parameters of the *C*-methyl protons in methylquinolizidines. Thus, it has been demonstrated (198) that axial methyl group protons absorb at lower field with a larger apparent *J* than equatorial methyl group protons (e.g. in 3-methylquinolizidines, δ Me(*ax*) 1·08, δ Me(*eq*) 0·82). This is illustrated by the chemical shifts (benzene) of the methyl group protons in deoxynupharidine [236] (199) (δ Me(*ax*) 1·10, δ Me(*eq*) 0·89). This correlation does not hold for 4-methyl group protons (in 4-methylquinolizidines, δ Me(*ax*) 0·93, δ Me(*eq*) 1·00). (198) Coupling constants involving the 6-methylene protons in deoxynupharidine have been given [236] (200) and NMR spectral data on 6,6′-dihydroxythionuphlutine [237] published. (201) The formyl proton in [238] gives rise to two singlets ($CDCl_3$) at δ 8·23 and 8·14. (202)



[236]

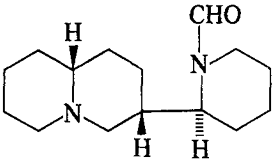
The carbinol carbon proton chemical shifts in the epimeric alcohols [239] (203) were δ 4·12 and δ 3·51 and on this basis the axial and equatorial OH respectively were assigned to these from comparison of data obtained on epimeric hydroxyquinolizidines. (204)



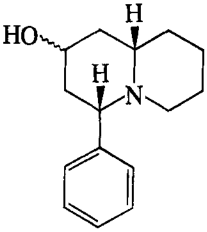
3·61 H4 or 4'
3·74 H4 or 4'
4·1 *CH*OH
4·33 *CH*OH
6·50 βH furan 2H
7·48 αH furan 4H

6,6'-Dihydroxythionuphlutine A (in $CDCl_3$)

[237]



[238]

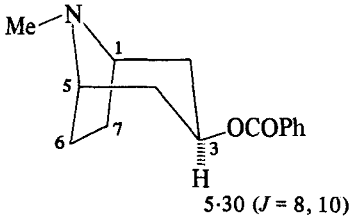


[239]

IX. PIPERIDINE (INCLUDING TROPANES) AND PYRIDINE ALKALOIDS

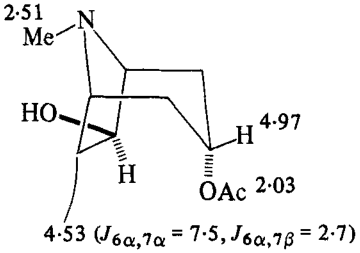
Tropanes

In the NMR spectra of the tropanes the 3α-proton signals are at lower field than the 3β-proton signals (205) and this observation has been utilized in establishing the stereochemistry of the tropanes [240], [241], [242] (206) and [243]. (207) The absorption of the 3α proton in the NMR spectrum of 3-benzoyloxytropane (tropacocaine) [240] (206) as a triplet of triplets (*J* = 8 and 10 Hz) at δ 5·30 is characteristic of 3β-benzoyl-3αH-tropane derivatives and the position of absorption (δ 4·97) of the 3-proton in the spectrum of [241] indicates a 3βH-tropane derivative. Similarly in the spectrum of the tropane-3β-ol [242] the 3α proton absorbs at lower field (δ 3·91) than the axial C*H*OH in *trans*-4-*t*-butyl-cyclohexanol (δ 3·51). The coupling constants involving the 6-methylene protons in [241] are similar to those in valeroidine (208) (structure as in [241] with OAc



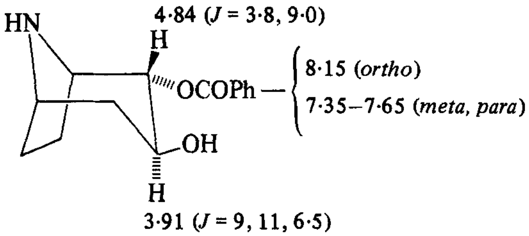
(in $CDCl_3$)

[240]

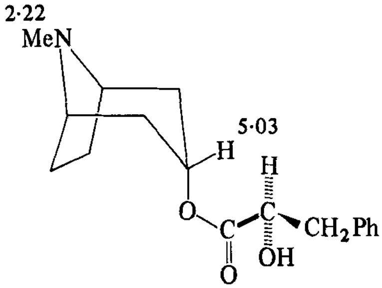


3α-Acetoxy-6β-hydroxytropane (in $CDCl_3$)

[241]



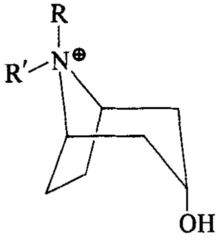
[242]



[243]

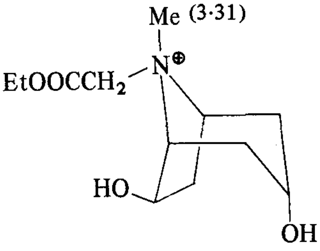
replaced by $OCOCH_2CHMe_2$) and the $PhCH_2CH(OH)$ protons in littorine [243] (207) constitute an ABX system with δ_A 3·09, δ_B 2·96, δ_X 4·37 ($J_{AB} = -13{\cdot}8$, $J_{AX} = 7{\cdot}9$ and $J_{BX} = 4{\cdot}8$).

In the pair of compounds ([244]; R,R′ = Me, Et) (209) axial methyl protons absorb at lower field than equatorial methyl protons,

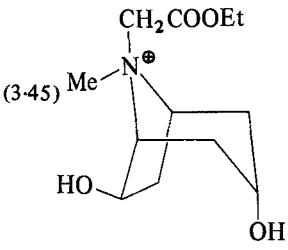


[244]

and similar results have been obtained (210) on 3-oxotropanium salts (e.g. δ Me(*ax*) 3·50, δ Me(*eq*) 3·55 for the pair of isomeric *N*-ethyl-*N*-methyl-3-oxotropanium salts). This trend is reversed in [245] and [246] illustrating the deshielding effect of the C(6)-OH in

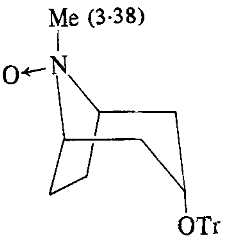


[245]

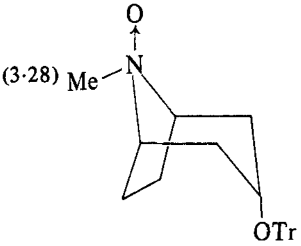


[246]

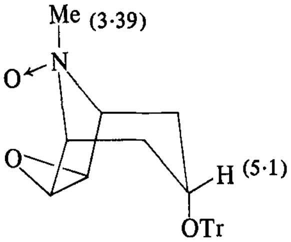
[246] on the *N*-methyl group protons. (209) The group of compounds [247] to [250] (211) (Tr = tropoyloxy) show a similar variation in *N*-methyl proton chemical shifts (spectra recorded in D_2O) in which the deshielding effect of the epoxide group on the *N*-methyl protons in [250] is marked. A *β*-hydroxy methyl group at C(2) also deshields axial *N*-methyl protons. The chemical shifts of a number of tropane alkaloids have been tabulated. (5)



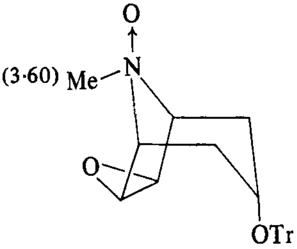
[247]



[248]



[249]



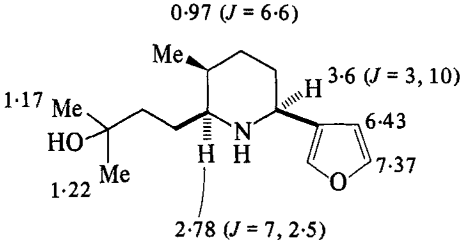
[250]

Alkaloids containing the piperidine nucleus

The NMR spectrum of 3-epinupharamine (212) establishes the stereochemistry shown in [251]. The vicinal coupling constant of

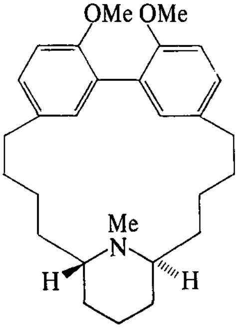
2·5 Hz between the 2- and 3- protons is close to that observed (213) for $J_{2ax,3eq}$ in 2,4,6 trimethyl(*eq*)piperidine.

Comparison of the N-C*H* chemical shifts ($CDCl_3$) in bisdeoxy-*N,O*-dimethyl-lythranidine [252] (δ 2·68) and in the synthetic compound [253] possessing the *cis*-5,9-H configuration (δ 2·30) showed the *trans* relationship of H-5 and H-9 in the lythranidine derivatives. (214) In [253] both hydrogen atoms α to the nitrogen are *trans* diaxial with the nitrogen lone pair and are accordingly shielded. In lythramine [254] (215, 216) the geminal coupling constant for the NCH_2O protons of −11 Hz suggest the *cis* fused ring system with the nitrogen lone pair bisecting the methylene group. (217)

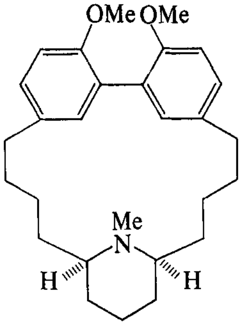


(in $CDCl_3$)

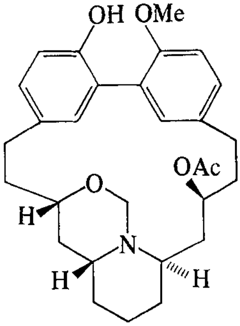
[251]



[252]

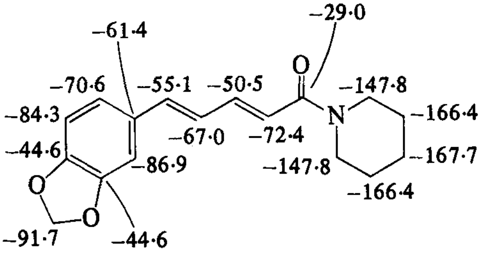


[253]

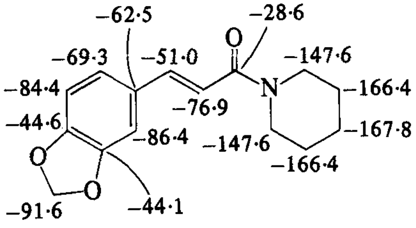


[254]

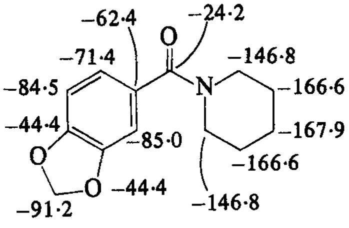
The carbon-13 NMR spectrum of piperine [225] has been studied [218] but in order to differentiate between certain of the chemical shifts the aid of $La(dpm)_3$ and $Eu(dpm)_3$ was required. The data of two model compounds are shown in [256] and [257].



[255]



[256]

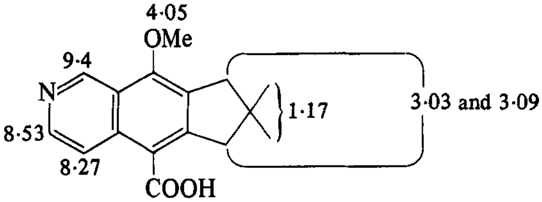


[257]

^{13}C shifts (ppm from CS_2)

Alkaloids containing the pyridine nucleus

The chemical shift of the aromatic protons in illudinine (219) [258] are typical of the pyridine ring protons in an isoquinoline (220) and those of the pyridine protons in maytoline [259] (221) are similar to those in nicotinamide. (222)

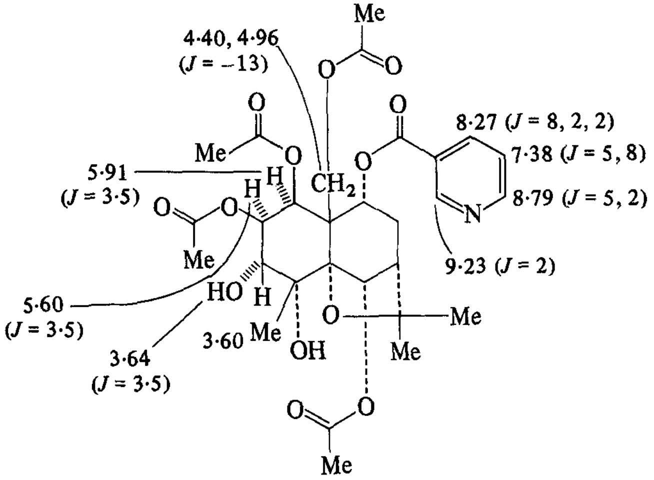


(in DMSO-d_6)

[258]

Similar NMR data aided the assignment of structure to sceletium alkaloid-A_4 [260] (223) and to tortuosamine (224) (similar structure to [260] but with pyrrolidine ring opened).

One of the acetyl methyl group protons in maytoline is shielded



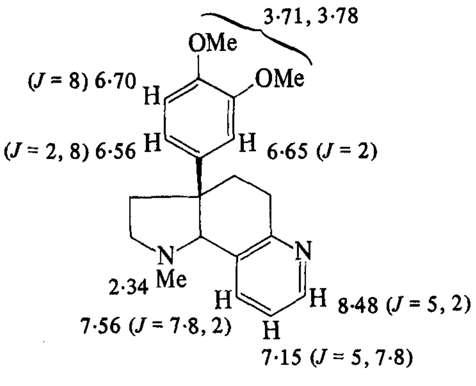
CMe: 1·54, 1·54, 1·61, 1·65

C(O)Me: 2·15, 2·18, 2·30

*CH*OCOR: 5·49 (J = 7·5), 6·16(s)

(in $CDCl_3$)

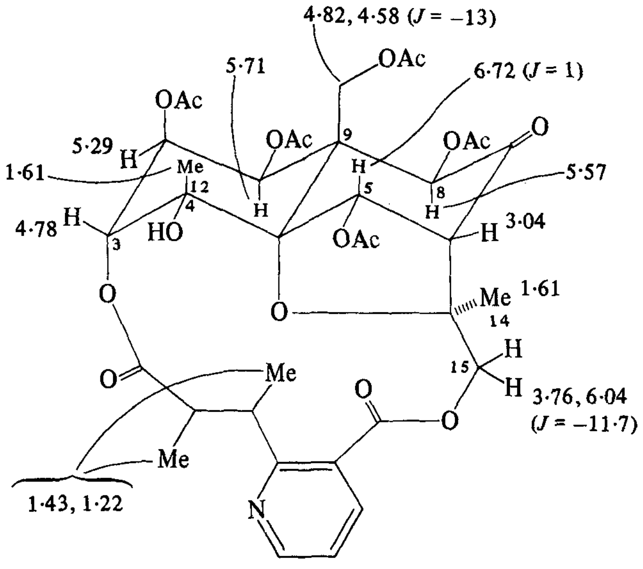
[259]



(in $CDCl_3$)

[260]

(δ 1·54 to 1·65) and this must be the C(1) acetyl methyl since the X-ray study shows this to come under the shielding influence of the nicotinoyl ring. (221)



AcO, 2·23, 2·15, 2·10, 2·05, 1·89

(in $CDCl_3$)

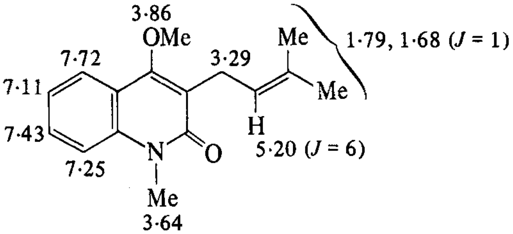
[261]

The NMR spectrum of evonine [261] has been described in detail (225, 226) and nuclear Overhauser effects (227) between H-3 and 12-Me, H-5 and 12-Me, and between H-8 and 14-Me in derivatives of this alkaloid established some of the stereochemistry shown in [261]. In the NMR spectrum of [261] the 5-proton absorbed at unusually low field (δ 6·72) presumably as a result of deshielding by the C(12)-methyl and by the 9-methylene group, and the difference in chemical shift (2·28 ppm) between the 15-methylene protons must be a result of one of them lying in the plane of the nicotinoyl carbonyl group.

The NMR spectrum of evozine ([261] with C(8)- and C(5)-OH groups in place of OAc) has been discussed in relation to that of evonine and it has been pointed out that the nuclear Overhauser effects discussed above are not unequivocal concerning the stereochemistry at C(4) and C(5). In addition the chemical shift of the 12-methyl protons might indicate a 1,3 diaxial relationship between 12(Me) and OAc. (228).

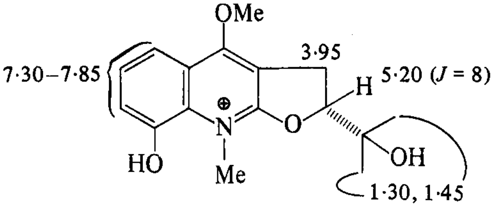
X. QUINOLINE, ACRIDONE AND QUINAZOLINE ALKALOIDS

The presence of the isopentenyl unit in quinoline alkaloids of type [262] (229) is readily determined from a study of the NMR spectrum of the alkaloid and the chemical shifts shown for the *O*-methyl and *N*-methyl protons are typical of this system [cf. δ 3·92, 3·84 in ptelecortin (230)] [(262) with 6,7-methylenedioxy group).



[262]

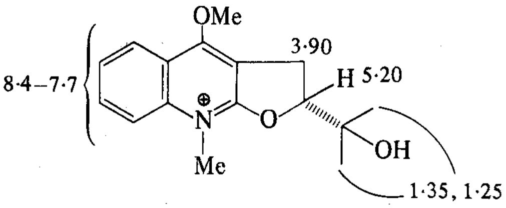
Comparison of the chemical shifts of the *O*-methyl and *N*-methyl protons in [263] (231) and [264] (232) permits assignment of the δ



NMe, OMe 4·40, 4·50

Pteleatinium chloride (in CD_3OD)

(263)



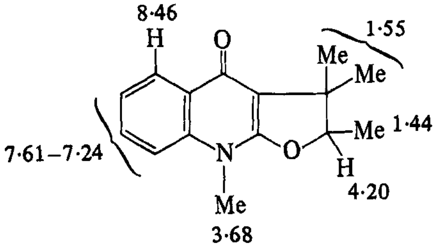
NMe, OMe 4·55, 4·05

Platydesminium metho-salt (in DMSO-d_6)

[264]

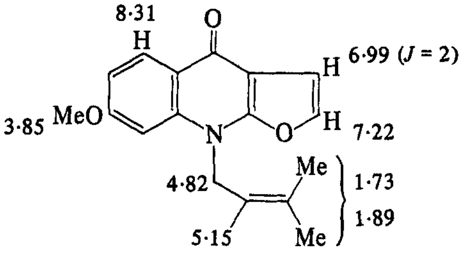
4·05 signal in the NMR spectrum of [264] to the *N*-methyl group protons and illustrates the marked deshielding effect of the C(8)-OH on the *N*-methyl protons. The chemical shifts of the other protons are very similar in both compounds showing the very small effect of the solvent change.

The NMR spectrum of ifflaiamine [265] (233) and of acrophylline [266] (234) show the low field signal (δ 8·46 and δ 8·31 respectively) corresponding to the aromatic proton *peri* to the carbonyl group and this characteristic chemical shift enables a distinction to be made between linear furoquinolines and angular furoquinolines. (235)



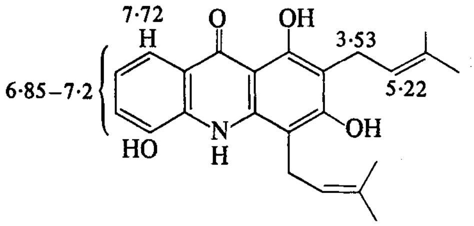
(in $CDCl_3$)

[265]



[266]

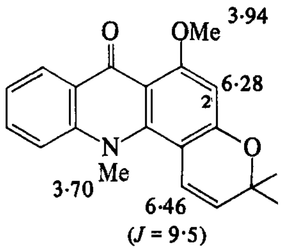
The spectrum of atalaphylline [267] showed signals for the two isopentenyl units but the chemical shift of the aromatic proton *peri* to the carbonyl group (236) is not to such low field as in [265] and this must be a result of its *para* relationship with the phenolic group. Nuclear Overhauser effects have established (237) the proximity of the *N*-methyl to one of the protons (δ 6·46) of the chromene ring and the *ortho* relationship of the methoxyl group and C(2)-H in acronycine [268].



Me: 1·70, 1·78, 1·80, 1·97 NH,OH: 10·28, 8·95

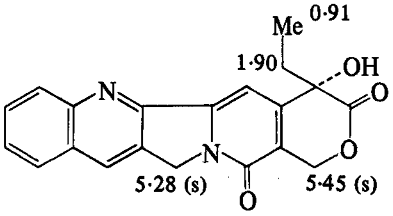
(in $CDCl_3$)

[267]



[268]

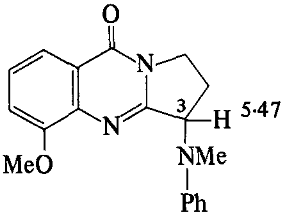
In the spectrum of camptothecin [269] the ArCH_2N and ArCH_2O proton signals are observed as two singlets, whereas in the acetate the δ 5·45 singlet present in camptothecin is replaced by an AB quartet ($J = -17$ Hz). (238)



(in DMSO-d_6)

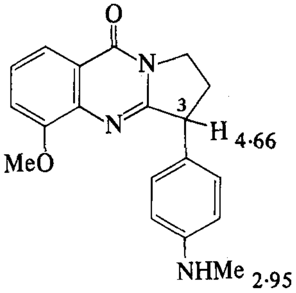
[269]

Comparison of the NMR data (239) (in particular the chemical shift of the 3-proton) obtained from the synthetic compound [270] with that of sessiflorine shows the previously proposed structure to be incorrect and that sessiflorine has structure [271]. The differing



(in CDCl$_3$)

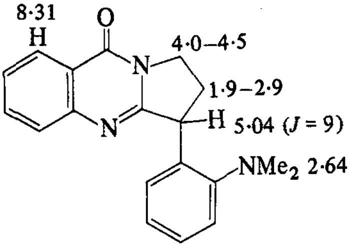
[270]



Sessiflorine

[271]

chemical shifts of the *N*-methyl protons show the position of the *N*-methyl in sessiflorine to be different from that in vasicolinone [272]. (240)

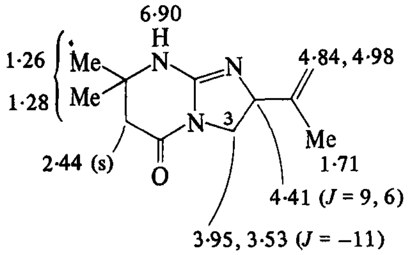


Vasicolinone (in CDCl$_3$)

[272]

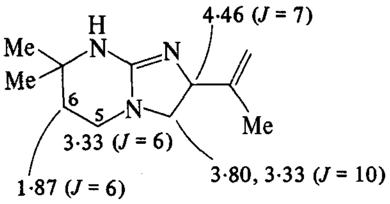
XI. IMIDAZOLE AND GUANIDINE TYPE ALKALOIDS

The NMR spectra of the four compounds [273] to [276] (241, 242) show some interesting features. Thus the deshielding of the



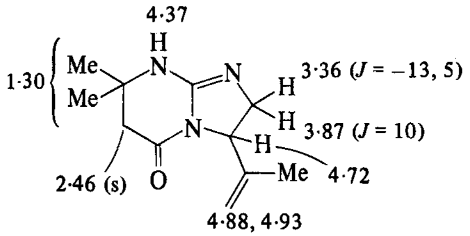
Alchornine (in CDCl$_3$)

[273]



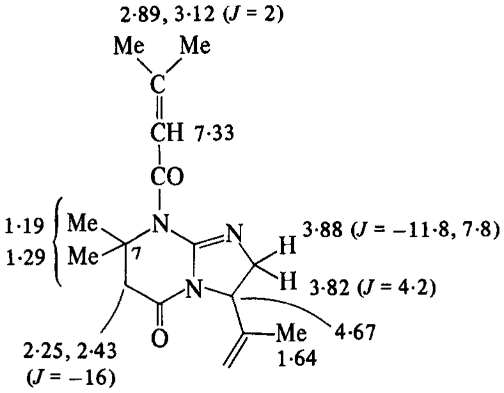
5-Deoxyalchornine (in CDCl$_3$)

[274]



Isoalchornine (in CDCl$_3$)

[275]

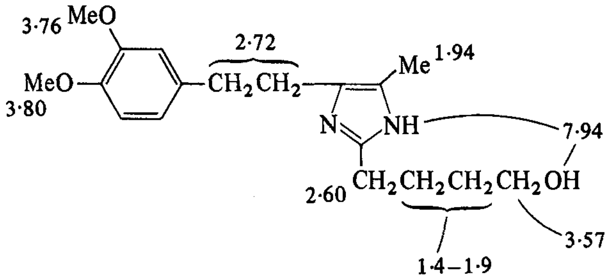


Alchornidine (in CDCl$_3$)

[276]

C(3) methylene by the amido-carbonyl (compare [273] and [274]) is not as great as might have been expected and the geminal coupling constant for the C(3) methylene protons in [273] is only −11 Hz. The change in chemical shift of the 6-methylene protons on going from [273] to [274] was evidence for the structure [273] and the rather different chemical shifts of the 7-methyl protons in [276] for location of the amido side chain at N(8). In the latter compound the 6-methylene protons are also non-equivalent.

The signal at δ 3·57 in the spectrum of cypholophine [277] (243) shifts 0·45 ppm downfield in the spectrum of its acetate showing the presence of the primary CH_2OH group.



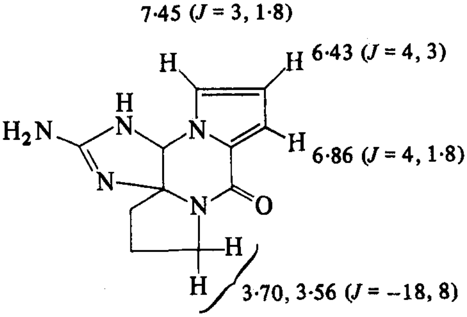
(in CDCl$_3$)

[277]

In contrast to the J_{gem} observed for the 3-methylene protons in

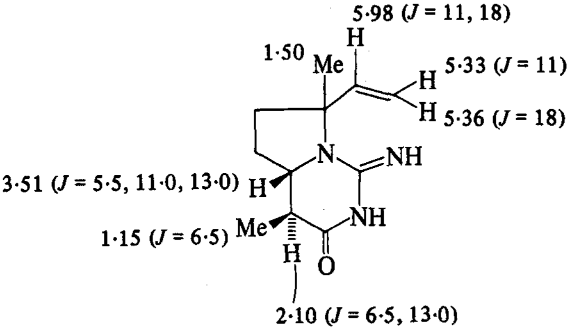
[273] is the extremely negative value (−18 Hz) of J_{gem} for the similarly situated $C(O)NCH_2$ protons in phakellin hydrochloride [278]. (244) It appears from these results and others on model systems (245) that there is a strong stereochemical dependence of the value of J_{gem} on methylene protons adjacent to amido-nitrogen.

A combination of ^1H NMR [279] and ^{13}C NMR [280] spectroscopy enabled the structure of arenaïne to be determined. (246)



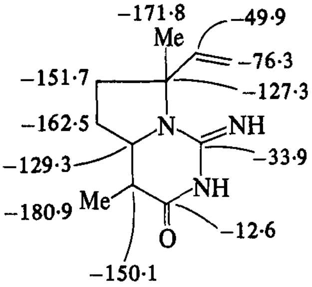
Phakellin (data of hydrochloride)

[278]



Arenaïne (^1H data)

[279]



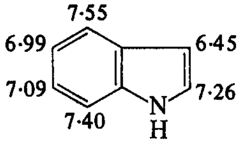
^{13}C data of arenaïne (ppm upfield from CS_2)

(280)

XII. INDOLE ALKALOIDS

A. Indoles and Carbazoles

The NMR spectra of a variety of methyl- (247–249) and hydroxy-indoles (250) have been described and, as examples, the data for indole and 5-methylindole are shown in [281] and [282] and of particular interest are the magnitudes of the long range couplings. The importance of these in the assignment of structure is illustrated by [283] and [284] (251). Here $J_{4,\mathrm{NH}}$ but not $J_{3,7}$ is observed in the spectrum of [283] and both couplings are observed in that of [284].



$J_{4,5} = 7{\cdot}8$ $J_{5,6} = 7{\cdot}1$

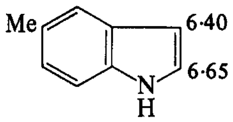
$J_{4,6} = 1{\cdot}2$ $J_{5,7} = 1{\cdot}3$

$J_{4,7} = 0{\cdot}9$ $J_{6,7} = 8{\cdot}1$

$J_{4,\mathrm{NH}} = 0{\cdot}8$

(in acetone)

[281]



$J_{2,3} = 3{\cdot}2$

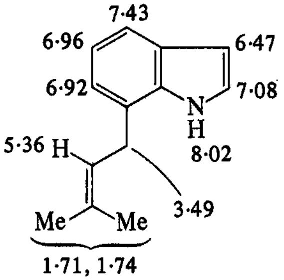
$J_{2,\mathrm{NH}} = 2{\cdot}4$

$J_{3,\mathrm{NH}} = 2{\cdot}0$

$J_{3,7} = 0{\cdot}6$

(in CCl_4)

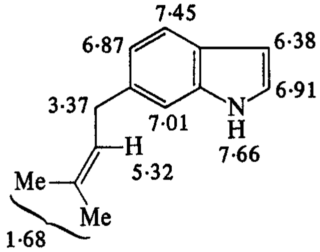
[282]



$J_{4,\mathrm{NH}} = 0{\cdot}80$

[in $CDCl_3$ (HMDS)]

[283]



$J_{4,\mathrm{NH}} = 0{\cdot}75$

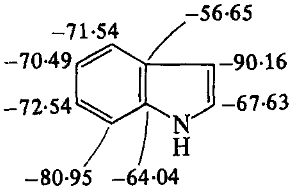
$J_{3,7} = 0{\cdot}95$

[in $CDCl_3$ (HMDS)]

[284]

It has been found (252) that dilution of a carbon tetrachloride solution of an indole with tetrahydrofuran causes a selective downfield shift of the signals arising from a proton or methyl group protons located at the 2- or 7- positions. Thus, the spectrum of 2-methylindole shows δ 3-H 6·00, δ Me 2·03 (carbon tetrachloride) and δ 3-H 6·07, δ Me 2·35 (tetrahydrofuran) and the spectrum of 3-methylindole δ 2-H 6·45, δ Me 2·22 (CCl_4) and δ 2-H 6·89, δ Me 2·28 (tetrahydrofuran).

The ^{13}C NMR spectrum of a series of methyl substituted indoles have been studied in detail (253) and incremental changes in chemical shift with methyl substitution tabulated. The ^{13}C data of indole (ppm upfield from CS_2) are summarized in [285].

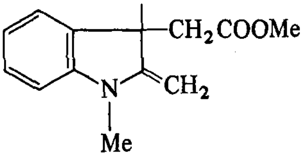


^{13}C shifts of indole

(ppm from CS_2)

[285]

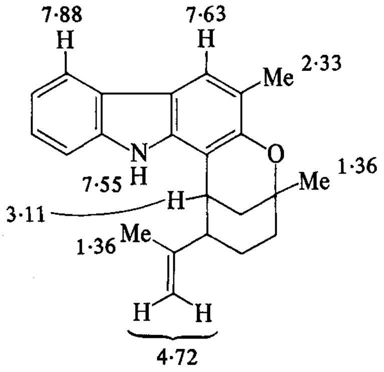
The anomalously high chemical shift (δ 3·80) of the exocyclic methylene protons in [286] has been noted. (254)



[286]

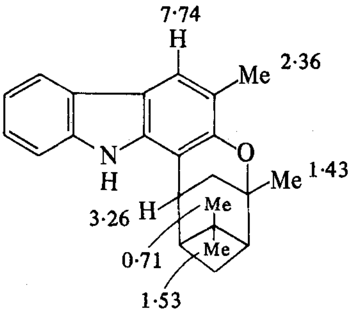
The NMR parameters of a range of carbazole alkaloids are summarized in structures [287], [288], [289], (255) [290], (256) [291] and [292]. (257) In *N*-methylcyclomahanimbine (*N*-methyl derivative of [287]) the benzylic methine proton absorbs at 0·85 ppm to lower field than in [287] and the methyl group protons of the ethylidene side chain absorb at 0·16 ppm to higher field than in [287]. The *N*-methyl protons in *N*-methylcyclomahanimbine absorb at δ 3·86. Moderately large differences in chemical shift between the *gem* dimethyl group protons in [288] and [289] presumably arise from their different orientations with respect to the aromatic system.

In *N*-methylisomahanimbine (*N*-methyl derivative of [291]) the 10-proton absorbs at δ 7·11 [deshielding of 0·61 ppm compared to corresponding signal in isomahanimbine (256)] and the 11-proton chemical shift is very close to that in [291]. A similar deshielding is observed on going from koenimbidine [292] (10-H δ 6·78) to



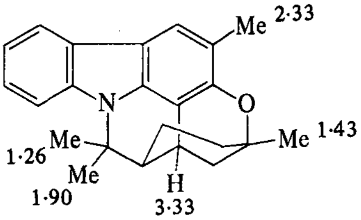
Cyclomahanimbine

[287]



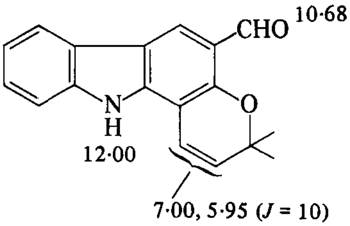
Bicyclomahanimbine (in CDCl$_3$)

[288]



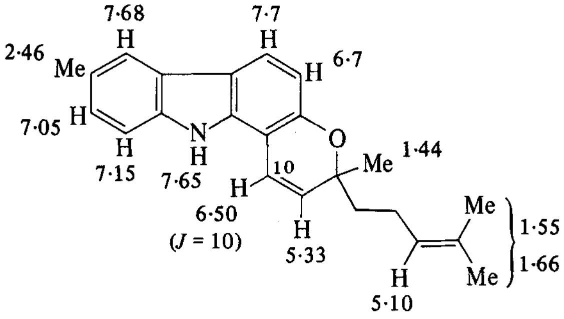
Mahanimbidine (in CDCl$_3$)

[289]



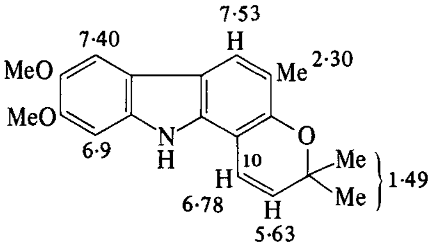
Murrayacine (in DMSO)

[290]



Isomahanimbine (in CDCl$_3$)

[291]



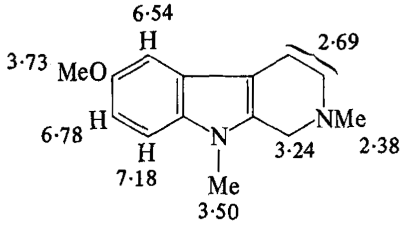
Koenimbidine (in CDCl$_3$)

[292]

N-methylkoenimbidine (10-H δ 7·22) and this provides a method for recognizing angular fusion of the Δ^3-pyran ring to the carbazole nucleus in these systems.

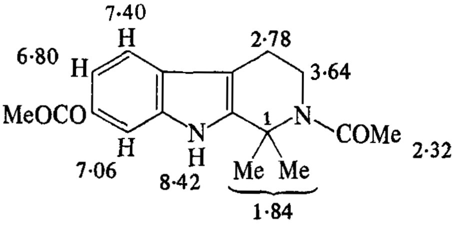
B. Simple Derivatives of Tryptophan and Tryptamine

The proton chemical shifts in the NMR spectrum of a typical tetrahydro-β-carboline are as shown in [293]. (258) To investigate the marked deshielding (δ 1·84) of the 1-methyl protons in [294] (259) (cf. δ 1·34 for the 1-methyl protons in [259]) the pair of compounds ([296]; R = H) and [296]; R = COMe) were prepared The observation of the chemical shifts (δ 1·46 and δ 1·81 respectively) of the methyl protons in the NMR spectra of these compounds showed the *N*-acetyl group to be responsible for the observed deshielding in [294]. In (295) the low field absorption (δ 5·65) of the 1-proton shows it to lie in the plane of the amido group so that the 1-methyl group is removed from this deshielding influence. However, in [294] both methyl group protons will experience the deshielding influence of the amido grouping.



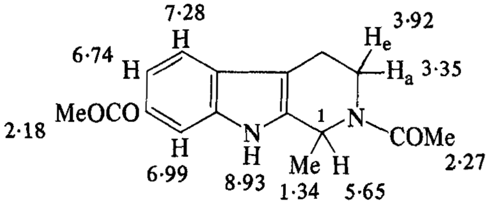
(in CCl_4)

[293]



(in $CDCl_3$)

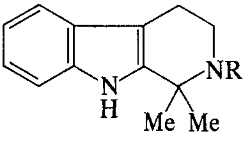
[294]



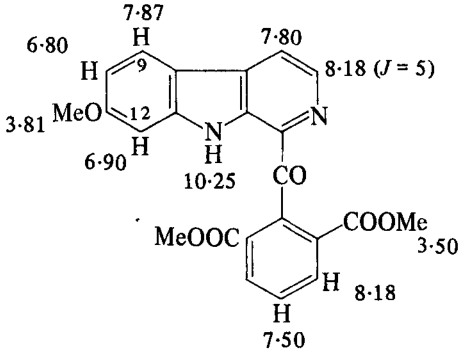
(in $CDCl_3$)

[295]

In the NMR spectrum of the fully aromatic carboline alkaloid alstonilidine [297] (260) the 9-aromatic proton absorbs at signifi-



[296]



(in $CDCl_3$)

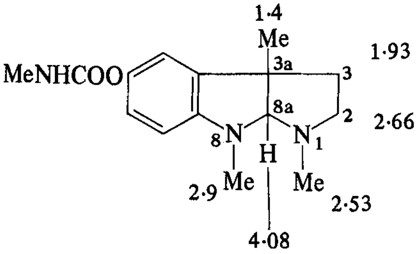
[297]

cantly lower field than the 12-proton and this is typical of carbolines and carbazoles.

C. Physostigmine and Related Alkaloids

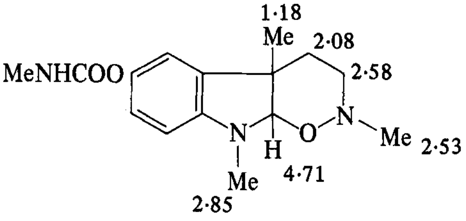
In the NMR spectrum of physostigmine [298] the intensity of the 8a-proton signal was enhanced when either the *N*(8)-methyl or the angular *C*-methyl signal was irradiated. (261) This application of the nuclear Overhauser effect establishes the *cis* nature of the ring fusion in the alkaloid.

Geneserine, previously thought to be the *N*-oxide of physostigmine has now been assigned (262) the structure [299] from a



(in $CDCl_3$)

[298]



(in $CDCl_3$)

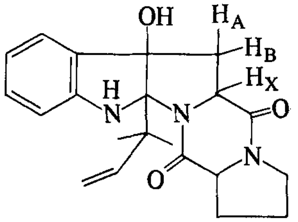
[299]

comparison of its NMR spectrum with that of physostigmine and model compounds. In particular on going from physostigmine to geneserine the angular 8a-proton signal moves from δ 4·08 to δ 4·71, consonant with a change in environment from N-C*H*-N to N-C*H*-O.

If geneserine were the *N*-oxide then comparison of the chemical shifts in *N*-methylpyrrolidine [δ ($CDCl_3$): NMe 2·35; 2-H 2·47; 3-H 1·77] and its *N*-oxide [δ ($CDCl_3$): NMe 3·33; H-2 3·50; H-3 2·16] with those in geneserine suggests that its *N*-methyl resonance and that of the methylene protons α to nitrogen should be at lower field than its actually observed. Finally, the chemical shifts of the NMe (δ 2·47) and of the 3-H protons (δ 2·60) in *N*-methyltetrahydro-1,2-oxazine were found to be close to those of the corresponding protons in geneserine.

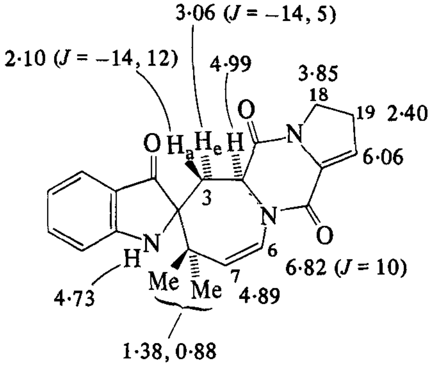
D. Brevianamides and Related Compounds

The presence of the amido group in compounds of this type (e.g. brevianamide [300] (263) and austamide [301] (264)) produces a marked deshielding of those protons lying in the plane of the amido group and particularly of those *cis* to the C=O. This is shown in the NMR spectrum of austamide by the low field absorption of 3*eq*-H (δ 3·06, compare δ 2·10 for 3*ax*-H), of the olefinic 6-proton (δ 6·82, compare δ 5·60 in enamines) and of the 18-methylene protons (δ 3·85, compare δ 2·82 for 2,5 protons in pyrrolidine). The values of the vicinal coupling constants involving the 3-methylene protons in austamide established their orientation with respect to the angular proton, but differed from J_{AX} and J_{BX} in brevianamide. In particular J_{BX} in brevianamide was 8 Hz whereas in austamide the corresponding coupling was 5 Hz. Models show that fusion of the five- and six- membered rings, as in brevianamide, produces dihedral angles between H_A and H_X and between H_B and H_X of less than 180° and less than 60° respectively, whereas in austamide the corresponding angles are *ca.* 180° and 60° consonant with the



$J_{AB} = -13, J_{AX} = 11, J_{BX} = 8$

[300]

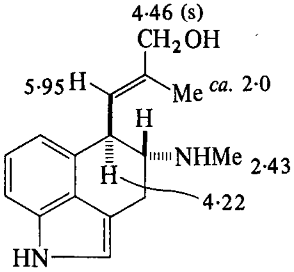


[301]

observed vicinal couplings. Thus the difference in coupling constants may be correlated with the structural change.

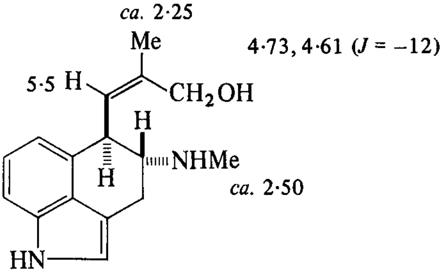
E. Ergot Alkaloids

The CH_2OH group in chanoclavine-I [302] is less hindered than in isochanoclavine-I [303] (265) and this is reflected in the singlet absorption for the CH_2OH protons in the NMR spectrum of [302]



(in C_5D_5N)

[302]

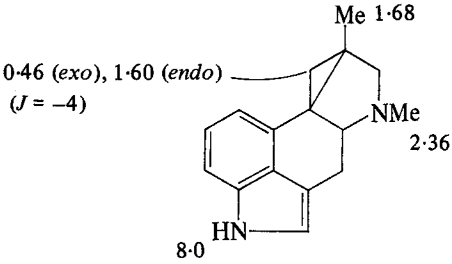


(in C_5D_5N)

[303]

and the AB quartet observed in that of [303]. The difference in chemical shift of the vinyl protons in the spectra of these two isomers is quite large (0·45 ppm) and this, together with the differing position of absorption of the vinyl methyl protons, is diagnostic of the stereochemistry about the double bond. Thus chanoclavine-I-aldehyde (266) was assigned the structure ([302]; CH_2OH replaced by CHO) since the vinyl methyl posessed the same chemical shift as in [302]. In this compound the aldehyde proton absorbed at δ 9·6 and the δ 5·95 vinyl proton signal present in [302] was now shifted downfield.

One of the cyclopropane ring protons in cycloclavine [304] (267)



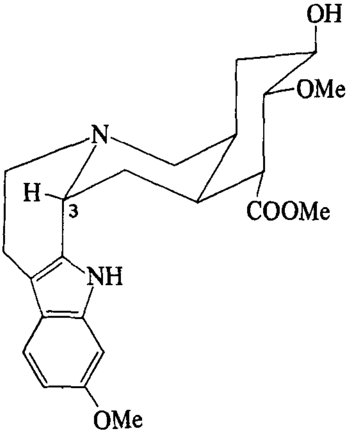
(in $CDCl_3$)

[304]

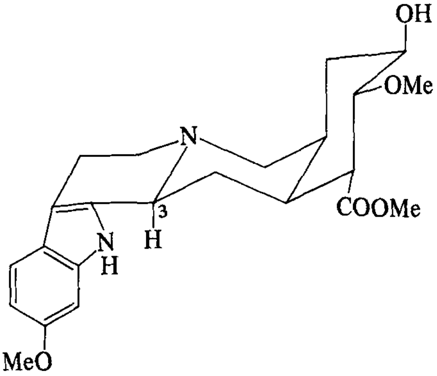
absorbs (δ 0·46) "normally" for such a proton but the other is markedly deshielded (δ 1·60). This deshielded proton must be the *endo* proton since this lies close to the nitrogen lone pair of electrons.

F. Yohimbine, Corynantheine, Picraline and Related Alkaloids

The establishment of the stereochemistry of the CD ring fusion in alkaloids of this type is aided by locating the signal for the angular 3-proton in the NMR spectrum. In alkaloids, in which this proton is gauche with respect to the nitrogen lone pair (i.e. *cis* CD ring fusion), the 3-proton absorbs at much lower field than when it is situated *trans* and axial with respect to an axial nitrogen lone pair (i.e. *trans* CD ring fusion). Thus in methyl reserpate [305] (268) this proton absorbed at δ 4·45 and in methyl 3-isoreserpate [306] to higher field of *ca.* δ 3·3. This chemical shift-stereochemical correlation has been shown to be general for other benzo- and indolo- quinolizidines [269] and typical examples are provided by the compounds [307] and [308]. (270) In [307] (*trans* fused) the angular proton absorbs to higher field of δ 3·2 whereas in the *cis* fused [308] this proton absorbs at δ 4·13. In the latter case the narrow width of the signal established the *cis* fusion shown. In a similar manner a *trans* CD fusion was assigned to the related compound DL-10-desoxy-18,19-dihydro-15-*epi*-hunterburnine (271) and *cis* (angular proton δ 3·96) and *trans* (angular proton δ > 3·5) conformations to the isomeric 2-benzoyl octahydroindolo[2,3-*a*]quinolizines. (272)

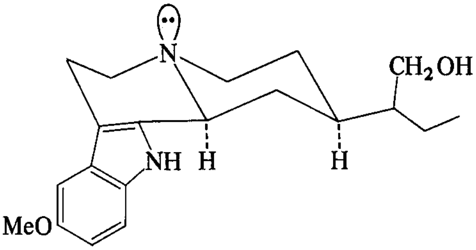


[305]

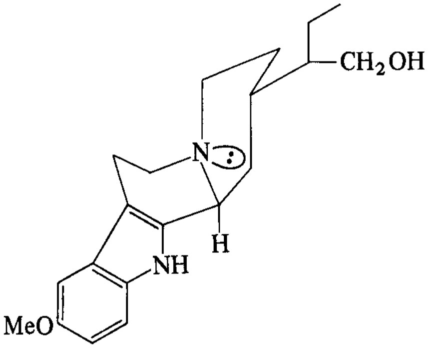


[306]

Methylation of [307] and [308] gave methiodides showing $\overset{\oplus}{N}Me$

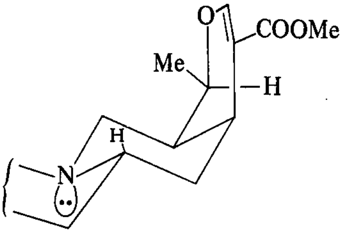


[307]

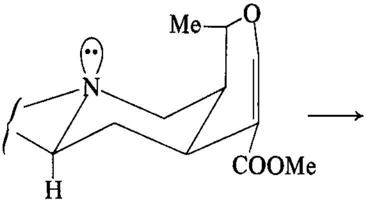


[308]

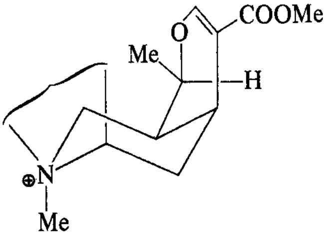
absorptions of δ 3·08 and δ 3·35 respectively. (270) This indicates *trans* fused and *cis* fused structures since in quinolizidine methiodides it has been established that $\overset{\oplus}{N}$Me protons absorb at higher field in *trans* fused structures than in *cis* fused structures. This criterion has established conformational changes occurring as a result of *N*-methylation. Thus isoraunitidine [309] (*trans* CD) on methylation gives a *trans* CD fused methiodide ($\overset{\oplus}{N}$Me δ 3·31) whereas raunitidine [310] (*trans* CD) gives methiodide showing $\overset{\oplus}{N}$Me absorption at lower field (δ 3·49) consonant with a *cis* CD junction [311]. (273) Observation of the $\overset{\oplus}{N}$Me resonances in systems related to [307] and



[309]



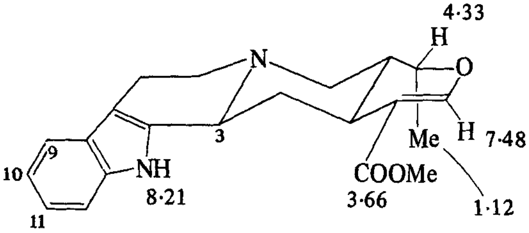
[310]



[311]

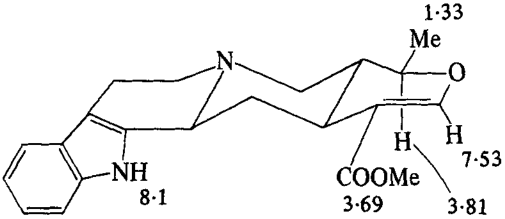
[308] (e.g. ochrosandwine (274)) has aided configurational assignments.

The influence of stereochemistry on the chemical shifts of the 19-proton and of the C(19)-methyl protons in ajmalicine and related structures is shown in [312]–[314] (273) together with other NMR data. (275) In ajmalicine [312] the methyl group protons absorb at δ 1·12 and the 19-proton at δ 4·33, whereas in [313] the corresponding chemical shifts are δ 1·33 and δ 3·81. These



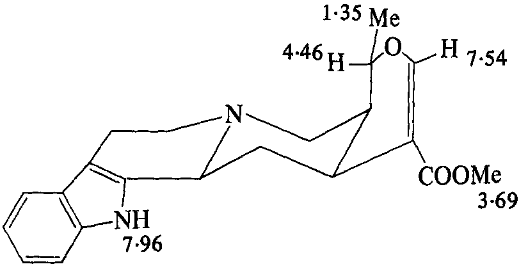
Ajmalicine (in $CDCl_3$)

[312]



19-Epiajmalicine

[313]

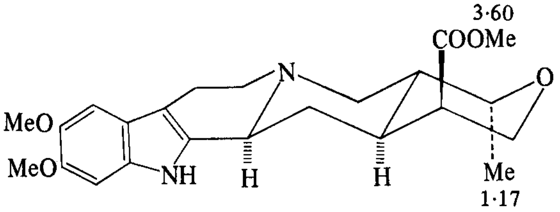


3,4,5,6-Tetrahydroalstonine

[314]

results show the marked shielding of the C(19) α substituent (see also oxindole alkaloids). Similar considerations established (276) the *trans* DE structure for isomitrajavine (9-methoxyajmalicine). In the *cis* DE compound [314] the 19-proton absorbs at very low field (deshielding by nitrogen lone pair) but the methyl proton chemical shift is close to that in [313].

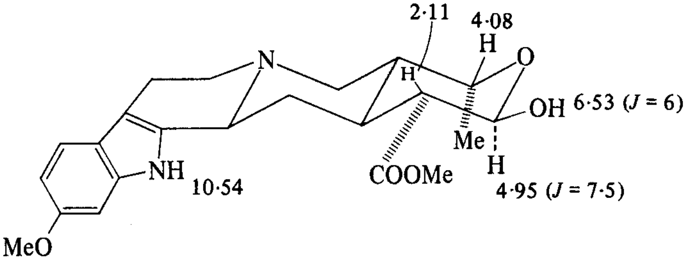
In the dihydroheteroyohimbine herbaceine [315] (277) the 19-methyl protons absorb at δ 1·17 (cf. δ 1·12 in ajmalicine [312])



Herbaceine

[315]

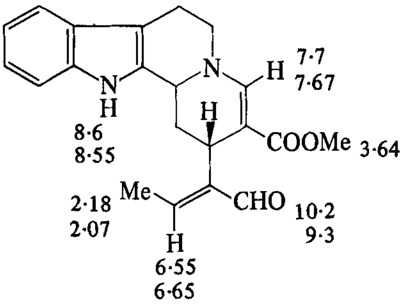
establishing the α-orientation of the methyl group. The methoxycarbonyl group methyl protons in herbaceine and in *epi*-[C(19)] herbaceine absorbed at δ 3·60 and δ 3·69 which seems to be an indication of axial and equatorial COOMe groups respectively since similar shift changes (δ 3·56 to δ 3·78) are observed on going from corynantheine (carbocyclic E ring; axial COOMe) to yohimbine (carbocyclic E ring; equatorial COOMe). A detailed analysis of the NMR spectrum of another dihydroheteroyohimbine tetraphylline has been made leading to the stereochemistry shown in [316]. (278)



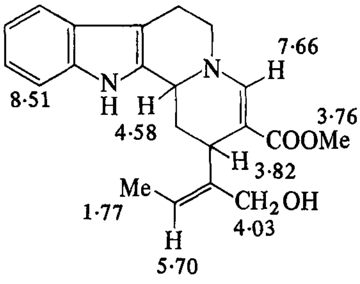
Tetraphylline (in DMSO-d_6)

[316]

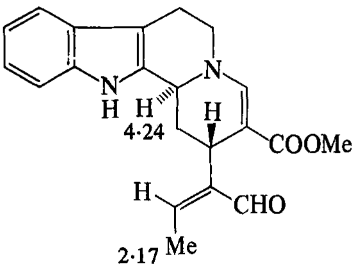
The NMR spectrum ($CDCl_3$) of vallesiachotamine [317] showed doubling of signals arising from restricted rotation and accordingly a detailed analysis of the NMR spectrum of dihydrovallesiachotamine, which was free from this complication, was made and the results are summarized in [318]. (279) Isovallesiachotamine [319] (280) has been obtained from strictosidine [320] and in this isomer the angular 3-proton absorbs ($CDCl_3$) at δ 4·24 (cf. δ 4·44 in vallesiachotamine) and the ethylidene methyl protons (δ 2·17) are homoallylically coupled (J = 1·0 Hz) to the 15-proton. The NMR spectra of a series of related compounds of the type [321] and [322] showed that the 3α-series is characterized by δ (3H) $<$ 3·8 and the 3δ-series by δ (3H) $>$ 3·8 showing the respective *cis* and *trans*



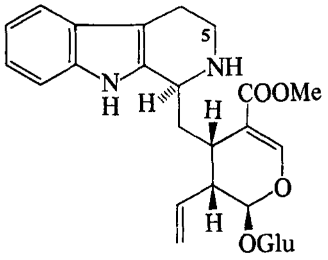
[317]



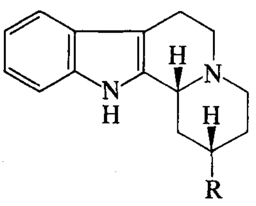
[318]



[319]

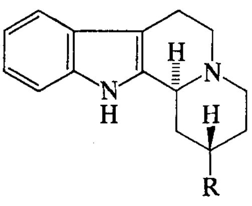


[320]



3β series δ 3H $>$ 3·8

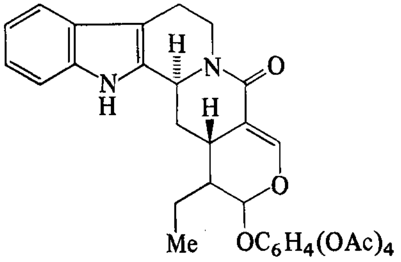
[321]



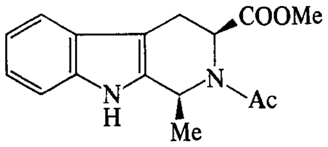
3α series δ 3H $<$ 3·8

[322]

nature of the ring fusion and the results confirmed the 3α stereochemistry in [318] and [319]. The tetra-acetate of 18,19-dihydrostrictosamide [323] is characterized by an unusually high field acetate proton signal (δ 1·22) absent from the spectrum of the 3β-epimer, presumably reflecting the influence of the aromatic ring on the acetate protons in the *cis* fused 3α series. In order to establish the C(3) stereochemistry of 5α-carboxystrictosidine the 3α,5α isomer [324] was prepared and the low field signal (δ 6·1), present in the spectrum of this compound as a result of deshielding of the 5*eq*-proton by the amide C=O, was absent from the spectrum of its C(5) epimer. (281) The characteristic low field signal was present in the 5α-strictosidine derivatives and accordingly the 3α,5α stereochemistry was suggested.



[323]

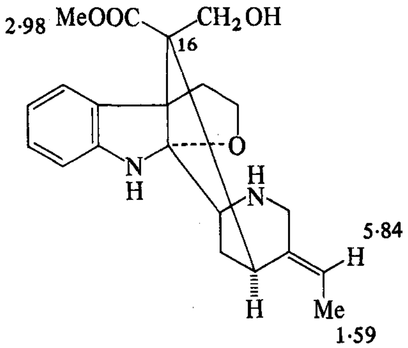


Rotamer 1: H5 δ 6·1, H3 δ 5·1

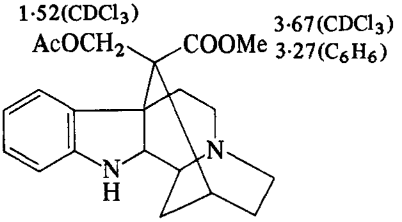
Rotamer 2: H5 δ 4·9, H3 δ 5·6

[324]

The ester methyl protons in lonicerin [325] (282) (16-*epi*-aspidodasycarpine) are much more shielded (δ 2·98) than in aspidodasycarpine (δ 3·72) as a result of their *cis* relationship with the aromatic ring. Similar results have been described for picraline [326] (283) in which the acetyl methyl protons are at high field.

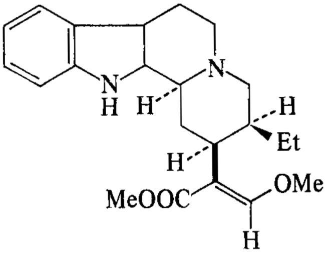


[325]



[326]

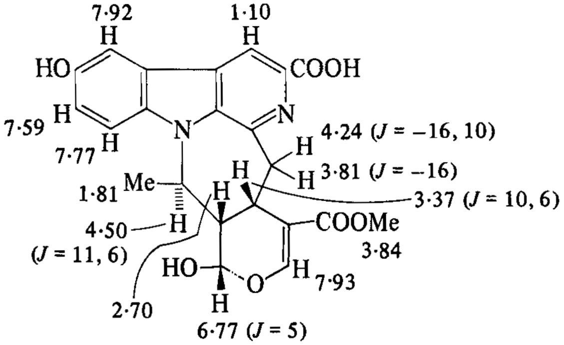
A structure-NMR correlation establishing the axial/equatorial nature of the ethyl group in alkaloids related to corynantheidine [327] has been described. (284) Thus in corynantheidine the ethyl group is axial and therefore *cis* to the nitrogen lone pair so that the



[327]

$\mathrm{C}H_2\mathrm{CH}_3$ protons are deshielded relative to equatorial $\mathrm{C}H_2\mathrm{CH}_3$ protons. This leads to the observation of better resolved "triplets" for the $\mathrm{CH}_2\mathrm{C}H_3$ protons in axial ethyl isomers than in equatorial ethyl isomers.

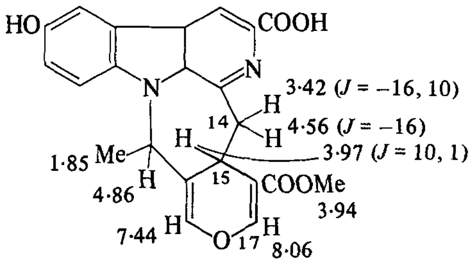
The 220 MHz NMR data of adifoline and anhydroadifoline are summarized in [328] and [329]. (285) In anhydroadifoline the 15-proton is coupled to the 17-proton but only with one of the 14-protons indicating a dihedral angle of 90°.



(in TFA)

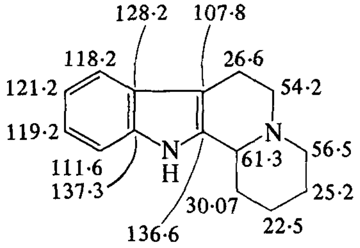
[328]

^{13}C NMR parameters have been reported (286) for the octahydroindolo[2,3-*a*]quinolizine [330]. The chemical shifts of the $^{13}\mathit{C}$N nuclei are fairly readily observable so that these should be useful in stereochemical studies on systems of this type.



(in TFA)

[329]

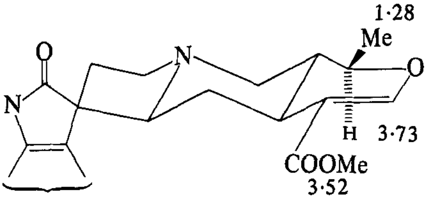


^{13}C NMR data in $(CD_3)_2CO$ ppm downfield from TMS)

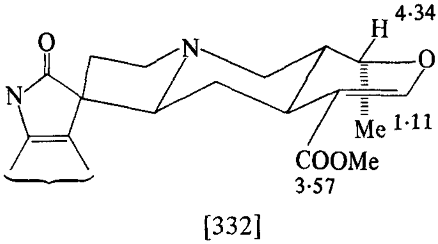
[330]

G. Oxindole Alkaloids (Pentacyclic and Gelsemine Type)

The main features of the pentacyclic oxindole alkaloids are shown in structures [331] to [334]. Mitraphylline [332] shows a higher field chemical shift (δ 1·11) for the 19-methyl protons (α-orientated) than does formosamine [331] (δ 1·28), whereas the reverse direction of chemical shifts is noted for the 19-protons (δ 3·73 in [331], δ 4·34 in [332]). These results show the marked shielding of α-orientated groups in this series of alkaloids. (287) In rauniticine-allo-oxindole-A [333] the 19-methyl protons absorb at very low field (δ 1·44) showing their proximity to the nitrogen lone pair and the *allo*



[331]



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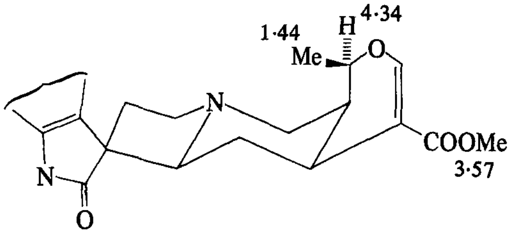
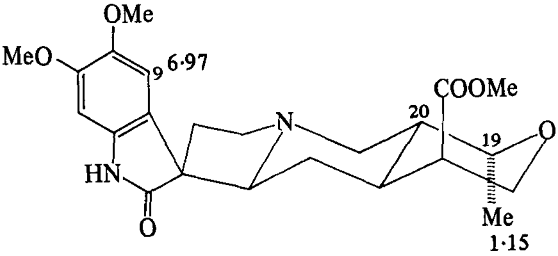


[333]



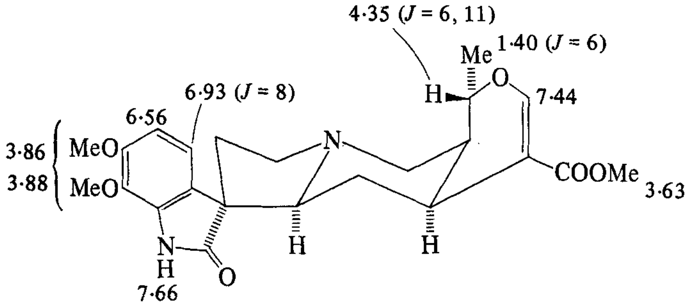
$J_{19,20} = 5{\cdot}7$
(in $CDCl_3$)

[334]

stereochemistry of the alkaloid. (287) Herbaline [334] (277) (a dihydro pentacyclic oxindole alkaloid) shows a 19-methyl chemical shift of the order expected for an α-methyl and the value of $J_{19,20}$ of 5·7 Hz shows a deviation of ring E from chair geometry (a similar effect is noted in [333]).

In *anti*-oxindoles (oxindole carbonyl *anti* to nitrogen lone pair) the C(9)-aromatic protons absorb at δ 6·90 to 7·02, whereas in the *syn*-oxindoles chemical shifts of δ 6·71 to 6·76 have been observed. Once again this effect arises from the proximity of the 9-proton to N(6) in the *anti* series and use of this correlation established the *anti* stereochemistry for herbaline (δ 6·97 for 9-H).

Considerations such as these established the stereochemistry shown in [335] for elegantine. (288) Thus, the low field 19-proton and 19-methyl proton absorptions indicate the presence of the heterocyclic oxygen atom and since *cis* DE alkaloids of this type show absorption for the 19-methyl protons at lower field than in *trans* DE alkaloids the *cis* DE fusion in elegantine (δ 19-Me 1·40) is established, while the δ 6·93 absorption for the 9-proton indicates the *anti* oxindole carbonyl-(N)*b* geometry. Uncarine D and uncarine

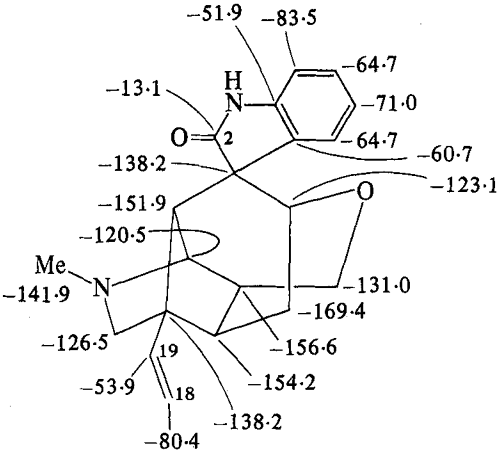


(in $CDCl_3$)

[335]

F (289) possess *cis* DE ring fusion but differ from the other alkaloids so far described in the *cis* nature of the CD ring fusion. Here the carbomethoxy methyl proton signals are characteristic of stereochemistry [δ 3·32 in uncarine D (*cis* oxindole aromatic ring) and δ 3·60 in uncarine F (*cis* to oxindole carbonyl)]. (289)

The assignment of all the ^{13}C chemical shifts in the spectrum of gelsemine [336] has been made. (290) Comparison with the ^{13}C NMR spectrum of 18,19-dihydrogelsemine, 2-deoxo-2,2,18,19-tetrahydrogelsemine and oxindole aided these assignments.

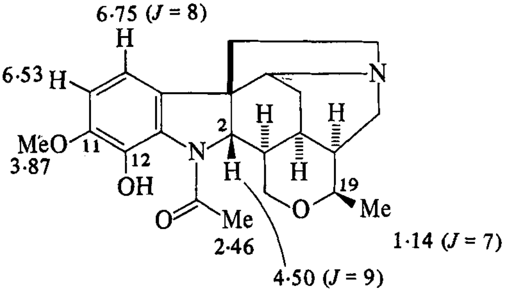


^{13}C data of gelsemine (ppm from CS_2)

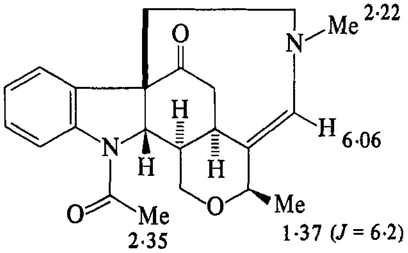
[336]

H. Strychnine, Akuammicine, Uleine and Related Alkaloids

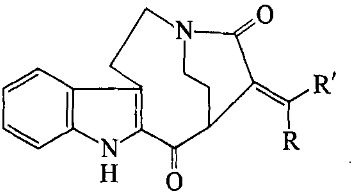
In the spectrum of 12-hydroxy-11-methoxyspermostrychnine [337] (291) the chemical shift of the 19-methyl group protons (δ 1·14) indicates its β-orientation. The 2-proton signal (δ 4·50) is sharper in this compound than in spermostrychnine ([337]; aromatic ring unsubstituted) as a result of fixing the acetyl group by hydrogen bonding to the phenolic OH. In strychnobrasiline [338] the 19-methyl protons are deshielded by the introduction of the 20,21 double bond and particularly of note in this compound is the deshielding of the enamine proton (δ 6·06) which in "normal" enamines absorbs at δ 4·40. This deshielding arises from the trans-annular interaction between the double bond and the C(3) carbonyl and between the nitrogen atom and the carbonyl. In neostrychnine the enamine proton absorbs at δ 5·75. The deshielding effect of an amido-group on the proton *cis* to the amido-carbonyl group is exemplified by the shifts of the *exo*cyclic olefinic proton in the pair of isomers ([339]; R′ = H, R = Me δ 6·41) and ([339]; R′ = Me, R, = H, δ 5·87). (292).



[337]

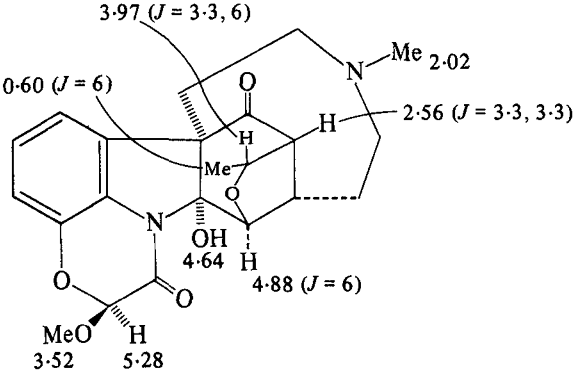


[338]



[339]

A wealth of information concerning dichotine and its transformation products has been published (293) and some of this is summarized in [340] to [343]. In dichotine [340] the *N*-methyl protons absorb (δ 2·02) at higher field than in "normal" saturated amines (cf. *ca.* δ 2·20 in *N*-methylpiperidines) but construction of the oxygen bridge in [343] results in a deshielding of these protons (δ 2·50).

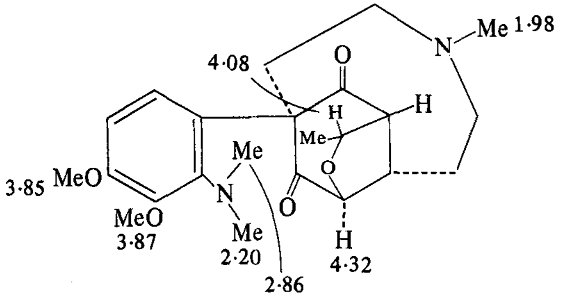


δ 1·76 (*J* = 14, 14)
δ 3·23 (*J* = 4·6, 12·6, 13·6)

Dichotine

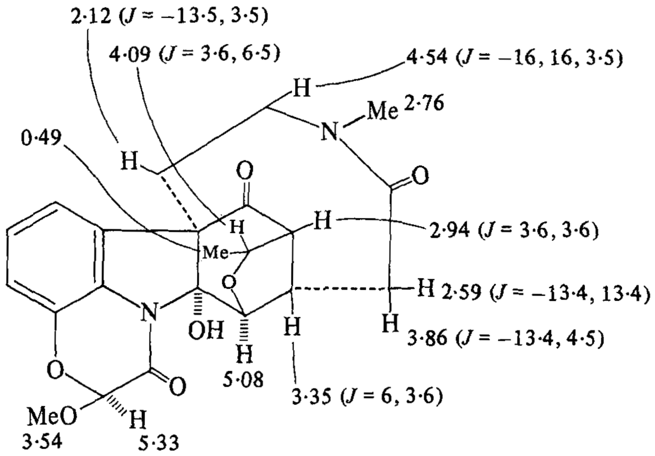
[340]

The O—CH*Me* protons in dichotine [340] and dichotinamide [342] absorb at rather high field (δ 0·60 and δ 0·49) for such protons and this is probably a shielding effect from the aromatic ring. In the dimethylaniline type compound [341] there is a large difference in chemical shift between the two *N*-methyl group protons



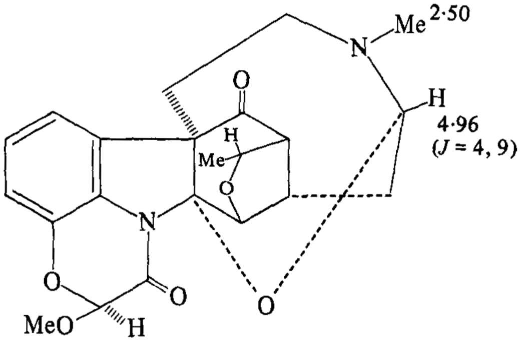
[341]

(δ 2·20 and δ 2·86) which must be a consequence of restricted rotation. The spectrum of dichotinamide exhibits some unusual



Dichotinamide (in $CDCl_3$)

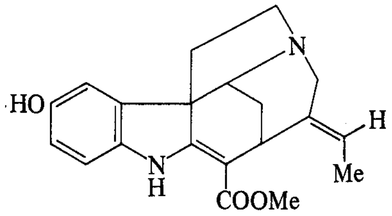
[342]



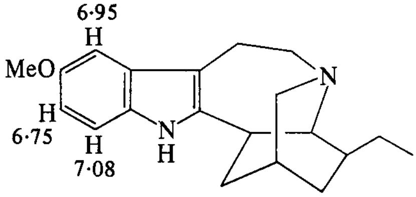
[343]

features in respect of the geminal coupling constants in the $H_{A\,B}CNMeC(O)CH_{X\,Y}$ moiety. $J_{A\,B}$ and $J_{X\,Y}$ are reported as −16 Hz and −13·4 Hz respectively whereas theory and results on similar systems containing this grouping at first sight suggest a reversal of these assignments. However, the chemical shifts of the protons adjacent to the amido function are as expected and the presence of the amido group in dichotinamide in a nine-membered ring therefore gives rise to values of the geminal coupling constants which differ markedly from those observed in simple six-membered ring systems. (293)

The phenolic function in sewarine [344] was located (294) by comparison of the chemical shifts (CD_3OD) of the aromatic protons in the spectrum of sewarine hydrochloride (δ 6·98, 6·70, 6·83) with those in that of ibogaine [345] and vindoline (see Section XIIJ [371]).



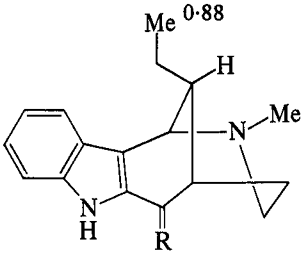
[344]



(in $CDCl_3$)

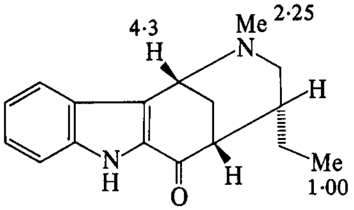
[345]

The influence of the indole ring on the chemical shifts of the $-\mathrm{CH_2C}H_3$ protons in alkaloids of the uleine type is marked. Thus in uleine [346] ($-\mathrm{CH_2C}H_3$ over the indole ring) the methyl group protons absorb at δ 0·88, whereas in epiuleine absorption occurs at δ 1·08. (295) In the spectra of isodasycarpidone [347] (296) and its corresponding epimer the effect is less marked (δ 1·1 in epimer) but the shielding in the synthetic intermediate [348] (297) is very pronounced. Similar effects have been noted in the spectra of the pair of isomers [349] and [350] and in [351]. (298) Compound [352] exhibits a related shielding effect on the protons of an acetyl methyl group. The NMR spectra of these *N*-formyl derivatives show the presence of two rotamers and structures were assigned to these (e.g. [353] and [354]) by comparison with the shifts observed (299)

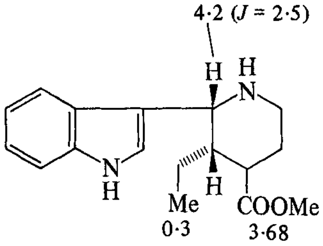


Uleine (R = CH_2)
Dasycarpidone (R = O)

[346]



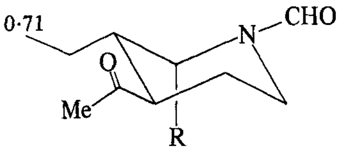
[347]



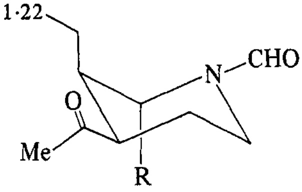
(in $CDCl_3$)

[348]

in *N*-formyl piperidines. (Compounds [349] to [354] are intermediates obtained in a synthesis of uleine and epiuleine; R = 3-indolyl).



[349]



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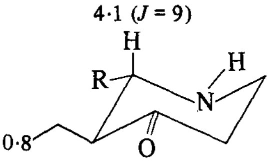
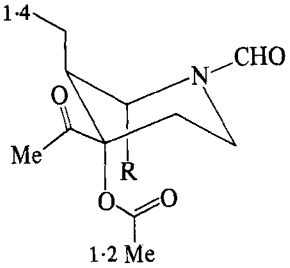
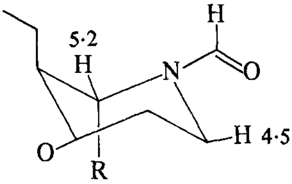


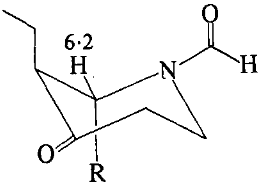
[351]



[352]



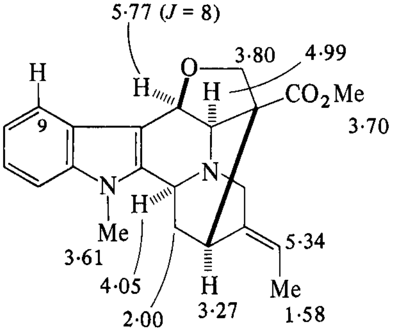
[353]



[354]

I. Sarpagine–Ajmaline Group

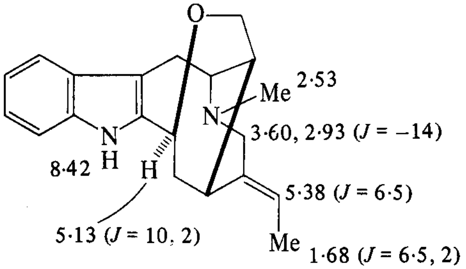
The NMR spectrum of dehydrovoachalotine [355] has been described in detail, (300) and the suggestion that the observed low field aromatic proton signal is that of the 9-proton [deshielded by C(6)-O] was confirmed by the observation of a nuclear Overhauser effect between the 6-proton and the deshielded proton. (301) Additional nuclear Overhauser effects on dehydrovoachalotine (301) show an increase in area of the 15-proton signals when the 18-methyl signal is irradiated demonstrating their *cis* relationship. A similar experiment on gardnutine ([355]; 11 MeO) has been described. (302)



(in $CDCl_3$)

[355]

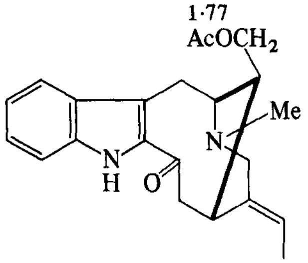
The J_{gem} of −14 Hz for the $NCH_2C{=}C$ protons in taberpsychine [356] (303) suggests a conformation of the piperidine ring such that



(in $CDCl_3$)

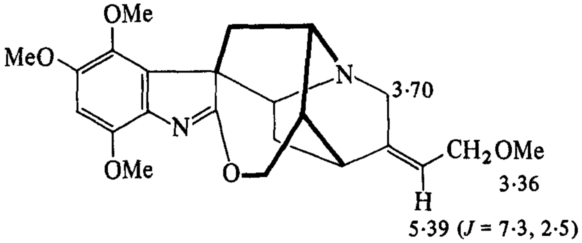
[356]

the π orbital of the double bond makes a dihedral angle of *ca.* 60° with the equatorial CH bond of the methylene. The splitting of 2 Hz observed in the signals of the ethylidene methyl group protons was identified as a coupling between the methyl and the low field $NCH_2C{=}C$ signal (δ 3·60). The high field absorption of the acetyl methyl protons (δ 1·77) in *O*-acetylaffinine [357] (304) indicates



[357]

the stereochemistry at C(16), and some NMR data on gardneramine are shown in [358]. (305)

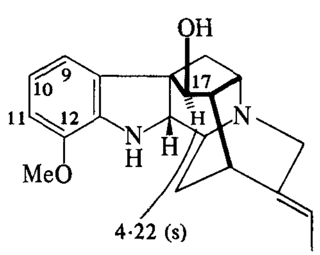


Aromatic MeO: 3·95, 3·90, 3·85

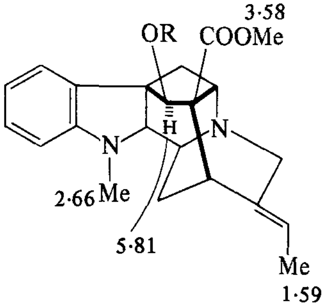
(in $CDCl_3$)

[358]

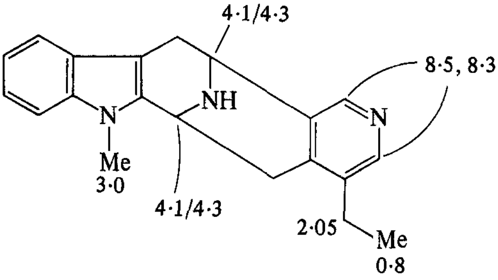
In the spectrum of *N*(*a*)-demethylseradamin [359] (306) the singlet absorption at δ 4·22 for the 17-proton shows its α-orientation since in the 17-*epi*-series a doublet ($J \simeq 9$ Hz) would be observed. A similar singlet (δ 5·30) was observed for the 17-proton in the spectrum of majoridine (307) (as [359] with NMe, OAc, and 10-MeO in place of 12-MeO) and in ([360]; R = *O*-3,4,5-trimethoxycinnamoyl). (260) NMR shifts for suaveoline are as in [361]. (308)



[359]



[360]

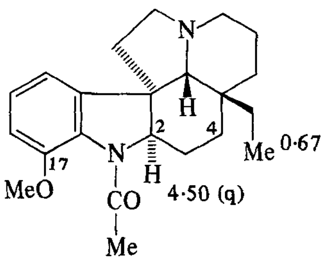


(in $CDCl_3$)

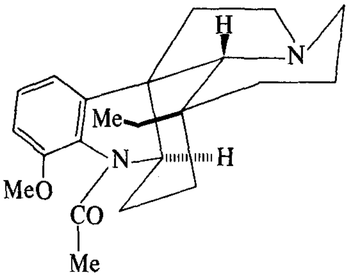
[361]

J. Aspidospermine and Ibogamine Group

One of the most striking features of the NMR spectrum of aspidospermine [362] is the high field (δ 0·67) chemical shift of the $-CH_2CH_3$ protons. This is a direct consequence of its stereochemistry (363) since the *cis* CD ring fusion holds the angular ethyl group over the shielding region of the aromatic ring. In isomers not possessing this stereochemistry, e.g. the synethetically obtained isomer of aspidospermine [364] (309) the CH_2CH_3 protons absorb "normally" (δ 0·94 in [363]) as in 7β-ethyl-5-desethylaspidospermidine (310) (7-ethyl group more distant from the aromatic ring). This is a recurrent theme in papers describing the NMR spectra of alkaloids and related synthetic compounds of this type and is exemplified by [365] (311) (in which there is an even greater shielding effect than in [362]) and by the chemical shift of the $COCH_3$ protons (δ 1·96) in ([366]; R = H). There is a small downfield shift of this latter signal on going to the corresponding



[362]



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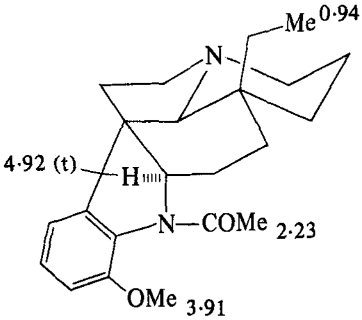
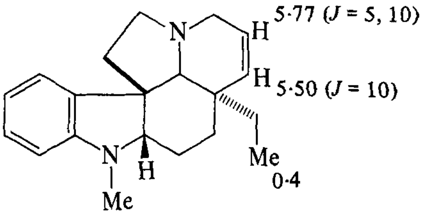
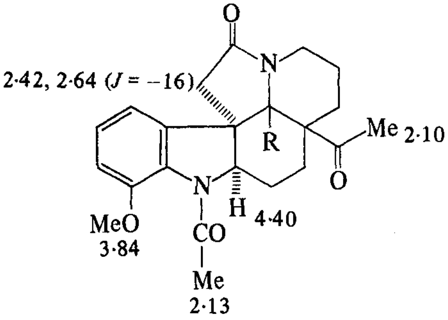


[364]



[365]

hydroxy compound ([366]; R = OH). In the compound related to ([366], (312) but with the angular C(O)Me replaced by CH_2COOMe, the methylene group protons of this substituent absorb as an AB quartet (δ 2·19 and δ 2·59, J_{gem} = −16 Hz). One of these protons absorbs at rather high field and perhaps this angular side chain adopts a preferred conformation such that this proton points towards the

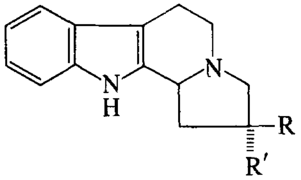


δ values refer to structure with R=OH

[366]

aromatic ring. In any event the J_{gem} of -16 Hz suggests a predominant conformation for this substituent since free rotation about the carbon–carbon bond linking the methylene to the carbomethoxy group would give rise to a J_{gem} of *ca.* -14 Hz.

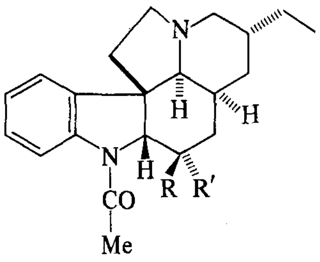
An effect related to the ethyl shielding occurs in the pair of isomers ([367]; R = Et, R′ = $(CH_2)_3OH$) and ([367]; R′ = Et, R = $(CH_2)_3OH$] (313) in which the chemical shifts of the CH_2CH_3 protons are δ 0·85 and δ 0·7 respectively. (These compounds are discussed in this section since they are intermediates en route to aspidosperma alkaloids and both are *cis* fused (δ 4·14 and δ 4·22 for angular proton).



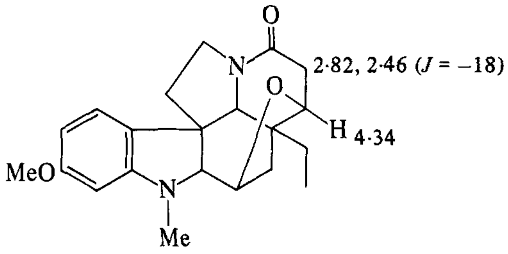
[367]

One final variation on this theme (in this section) is provided by the chemical shifts (δ 3·58 and δ 3·17 respectively) of the COO*Me* protons in the pair of isomers ([368]; R = COOMe, R′ = H) and ([368]; R = H, R′ = COOMe) (314) in which the shielding of these protons in the latter case arises from the axial orientation of the COOMe so that it lies in the aromatic shielding zone.

Geminal coupling constant data in these compounds is provided by [366] and [369] (315) both showing the couplings adjacent to lactam carbonyl, with one example of the methylene in a five- and the other in a six- membered ring.

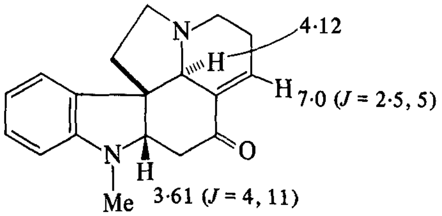


[368]



[369]

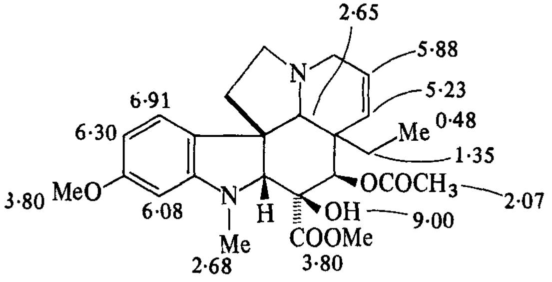
Other features of the spectra of these systems are the rather deshielded 17-methoxyl group protons when situated in an *N*-acetyldihydroindole moiety and the characteristic 2-proton resonances in the same class of alkaloid. In the unnatural aspidospermine [364] the 2-proton is more deshielded than in aspidospermine [362] and this may result from the greater steric crowding in [364]. When the *N*-COMe is replaced by *N*-Me (as for example in [370] (311))



[370]

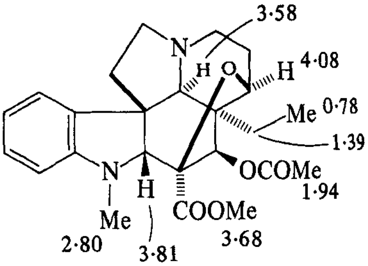
the 2-proton signal moves upfield. The compound [370] also shows a very deshielded olefinic proton (effect of C=O) and a deshielded 19-proton (δ 4·12).

Vindoline [371] (316) has been extensively studied and the spectral parameters are as shown in the structure. Comparison with the spectrum of cathanneine [372] (317) shows the effect of



(in CDCl$_3$)

[371]



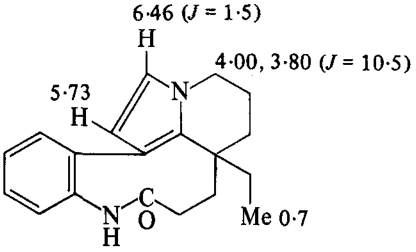
(in CDCl$_3$)

[372]

forming the ether bridge on the shift of the C(19)-proton (δ 3·58). Comparison with ([368]; R = H, R′ = COOMe) might suggest a similar shielding of the COOMe protons in cathanneine but the COOMe protons in this compound absorb (δ 3·68), at similar field to that (δ 3·06) in ([368]; R′ = COOMe, R = H). This does not rule out the operation of a shielding influence since replacement of the

N-COMe in [368] by *N*-Me in [372] will also influence the chemical shift of the COOMe protons. The nuclear relaxation times of individual protons in vindoline have been measured by an audiofrequency NMR spectrometer. (318)

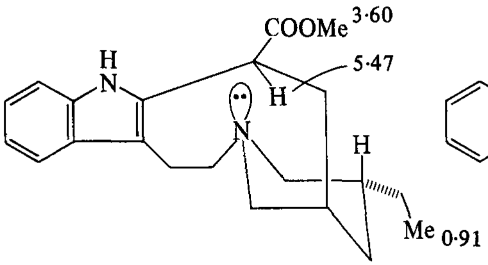
The NMR data of rhazinilam [373] (319) showing the absorption characteristic of the pyrrolo-protons, are shown in the structure.



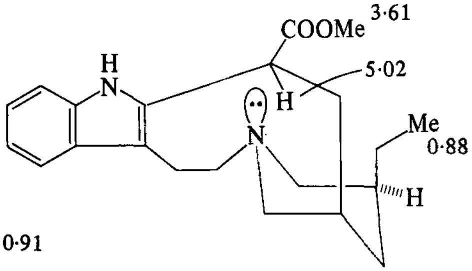
(in $CDCl_3$)

[373]

In the NMR spectra ($CDCl_3$) of two ([374] and [375]) of the four isomeric carbomethoxydihydrocleavamines [374] to [377]



[374]



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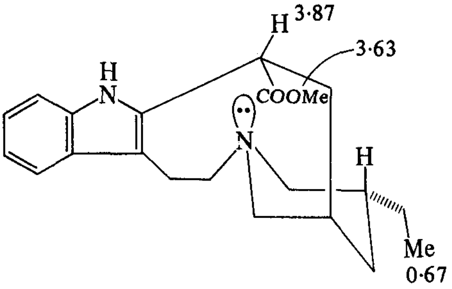
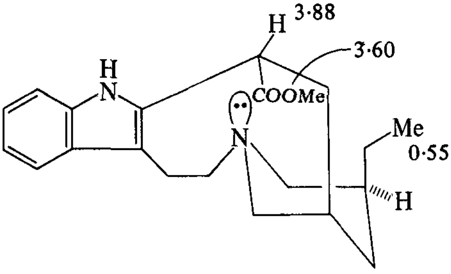


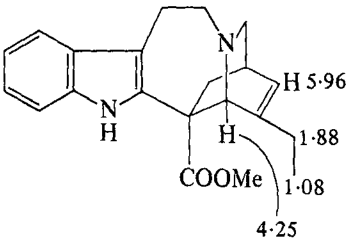
[376]



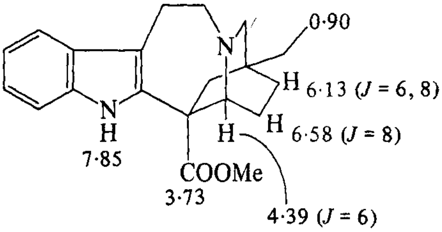
[377]

(320) the C*H*COOMe is very deshielded (δ 5·02, δ 5·47) compared to the corresponding proton in [376] and [377] (δ 3·87, δ 3·88) and this has been explained as a result of the close approach in [374] and [375] of this proton to the nitrogen lone pair. The difference in chemical shift between this proton in [374] and [375] has not been explained but perhaps, in order to relieve the non-bonded interaction in [375] brought about by the presence of the axial ethyl group, the distance between the proton and the nitrogen lone pair is increased.

Differences between the NMR parameters of catharanthine and allocatharanthine are summarized in [378] and [379]. (321, 322)



[378]

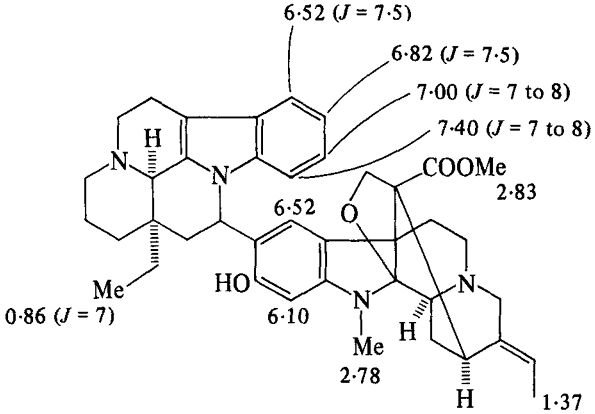


(in $CDCl_3$)

[379]

K. Bisindole Alkaloids

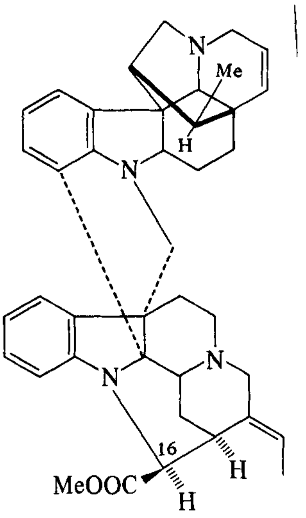
The excellent review (4) on the bisindole group of alkaloids contains a considerable amount of NMR data and it is not necessary to discuss this group in detail here. For the sake of the completeness it should be mentioned, however, that as a result of their "dimeric" nature the spectrum of a bisindole is not simply a superposition of the spectra of the two "halves". Thus umbellamine [380] (323) shows absorption for the COOMe protons at rather high field as a



(in $CDCl_3$)

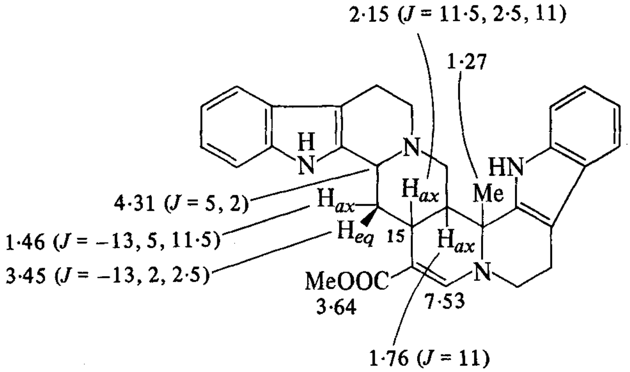
[380]

result of shielding by the dihydroeburnamenine component and pycnanthine [381] (324) a 16-proton signal 1 ppm to lower field of that in 2,7-dihydropleiocarpamine (lower "half" of [381]) as a result of deshielding by the benzene ring of the dehydrotuboxenine "half".



[381]

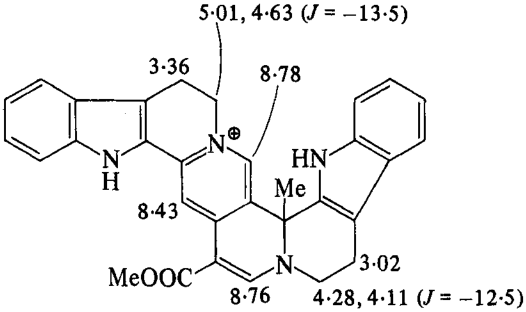
The results of the careful study (325) of the NMR spectrum of roxburghine-D and dehydroroxburghine-D are summarized in [382] and [383] respectively.



NH: 9·72, 10·08

(in acetone-d_6)

[382]



NH: 12·0, 11·55

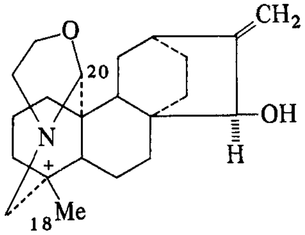
(in acetone-d_6)

[383]

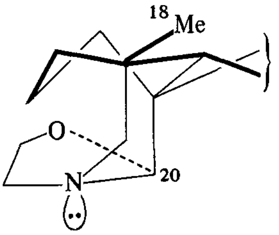
XIII. DITERPENE ALKALOIDS

A comprehensive review (326) of the diterpenoid alkaloids has been published which contains the most important NMR data published up to 1968, and a very detailed review (327) on the NMR spectra of forty-four diterpene alkaloids is available. One of the most interesting features of the NMR spectra of this group of alkaloids is the appearance of the signals from the 18-Me protons in atisine [384] and related systems as two singlets of unequal intensity with the area of the lower field signal twice that of the high field signal (δ 0·75 and δ 0·70 in atisine); at 85° in benzene solution these singlets coalesced. These observations were interpreted as indicating the conformational equilibrium [385] $\rightleftharpoons$ [386]. (327) This explanation has been challenged and as an alternative an interconversion of configurational isomers [387] and [388] has been suggested. (328) In addition two singlets have been noted for the 20-proton. (328) This problem has been briefly reviewed (4) but more data are required before the matter can be settled.

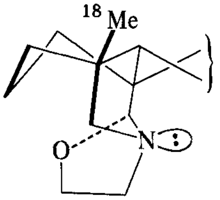
The presence of the cyclopentene-1-carboxaldehyde unit in lycoctamone [389] (329) has been deduced from the chemical shift (δ 9·75) of the aldehyde proton since it has been shown (330) that the



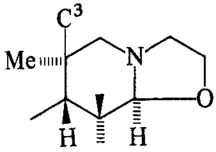
[384]



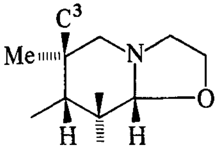
[385]



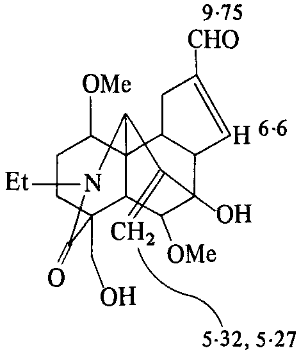
[386]



[387]



[388]

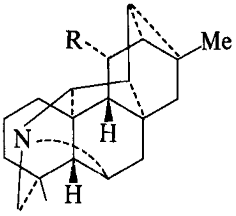


[389]

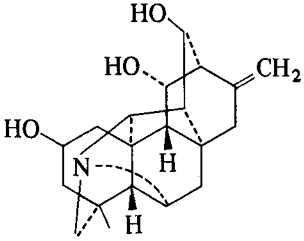
shift of such a proton varies with ring size (cyclopentene-1-carboxaldehyde δ 9·72; cyclohexene-1-carboxaldehyde δ 9·33). In the spectrum of dihydrolycoctamone the aldehyde proton absorbs at δ 9·50 (J = 3 Hz). One other feature of interest in the spectrum of this compound is the rather low field chemical shifts (δ 5·32 and δ 5·27) of the *exo*cyclic methylene protons.

The chemical shifts of the *C*-methyl protons in the spectra of ([390]; R = OH) (δ 0·93 and δ 1·18) and of ([390]; R = OAc) (δ 0·95 and δ 1·2) show a more deshielded methyl than is encountered in the hetesine series [391] illustrating the effect of the cyclopropane system on the chemical shift of the 17-methyl protons. (331)

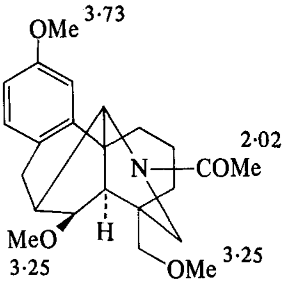
The spectra of the pair of isomers [392] and [393], obtained as intermediates in the synthesis of compounds related to delphinine, showed different chemical shifts for the secondary methoxyl protons (δ 3·25 and δ 3·07 for [392] and [393] respectively). Models of [393] show the methoxyl group to lie in the shielding region of the aromatic ring accounting for the observed chemical shift. (332)



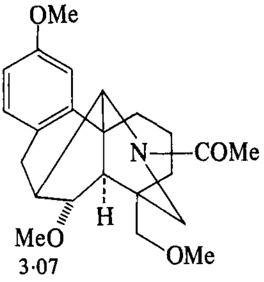
[390]



[391]

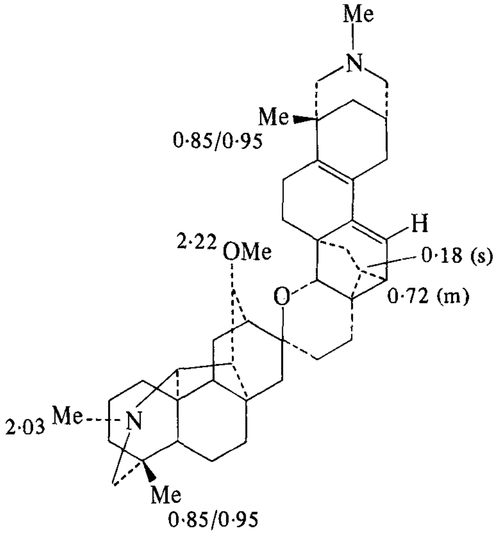


[392]



[393]

The NMR spectrum of staphisine [394] (333) shows a very shielded methoxyl group and in the spectrum of staphisine (1 M)



(in C_6D_6)

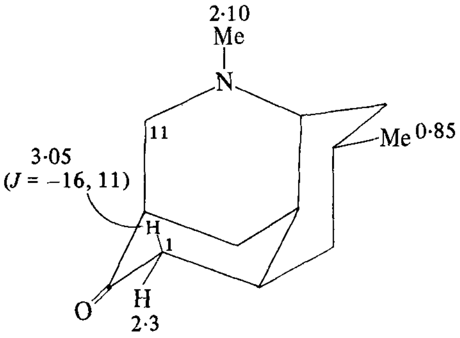
[394]

containing $Eu(thd)_3$ (2 M) in CS_2 the methyl signals (6H) originally present at δ 2·00 separate to two singlets, at δ 2·99 and δ 3·28, whereas the methoxyl group singlet is not shifted.

XIV. LYCOPODIUM ALKALOIDS

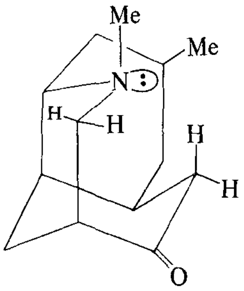
Interesting NMR spectral data obtained on some lycopodium alkaloids and related compounds have been described. The spectrum of luciduline [395] (334) clearly shows the 1 *ax*-proton signals at δ 3·05 and the corresponding equatorial proton signals were located by double irradiation. It was suggested that the low field absorption of the 1-*ax* proton is a result of deshielding by the nitrogen lone pair but deshielding by the two *syn* axial methylenes would also account for this. Rather disturbingly J_{gem} for the NCH_2 proton in luciduline was reported as −13 Hz whereas in the suggested conformation [396] J_{gem} should be −11·5 Hz. However, X-ray results indicate distortion of rings A and C so that this seemingly anomalous J might be a consequence of this.

Alopecurine [397] has also been shown (335) to possess distorted rings and the NMR spectrum, particularly the small (for $J_{ax\text{-}ax}$) value (7·5 Hz) of the vicinal coupling constant, suggests a twisted piperidine ring. J_{gem} for the NCH_2 methylene protons is very negative



(in $CDCl_3$)

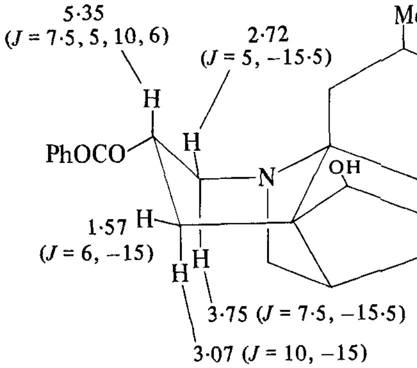
[395]



[396]

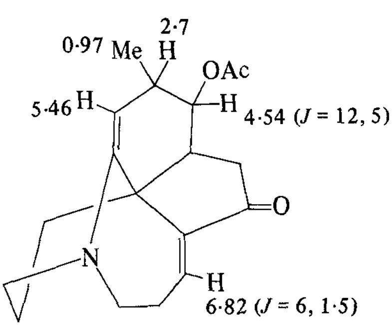
−15·5 Hz and points to a conformation with the nitrogen lone pair bisecting the methylene group. (172)

The absorption of the enamine proton (δ 5·46 in $CDCl_3$) in alolycopine (336) (acetyl alolycopine [398]) is shifted 0·8 ppm downfield in trifluoroacetic acid solution. "Normal" enamine protons absorb at δ 4·5 so that the δ 5·46 absorption in this compound is an effect arising from the non-overlap of nitrogen lone pair and enamine double bond orbitals.



(in $CDCl_3$)

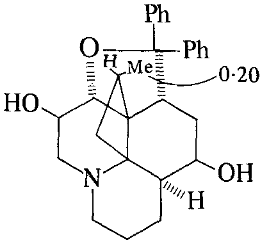
[397]



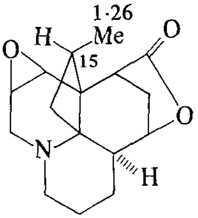
(in $CDCl_3$)

[398]

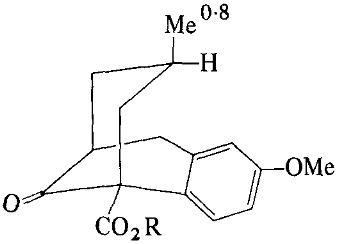
Two examples of unusual shielding effects are provided by diphenylannotinine [399] (337) (compare annotonine [400]) and the synthetic compounds [401] and [402]. (338) The very large shielding of the 15-methyl protons in diphenylannotinine (δ 0·20)



[399]



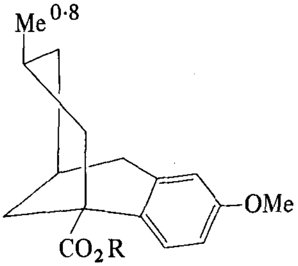
[400]



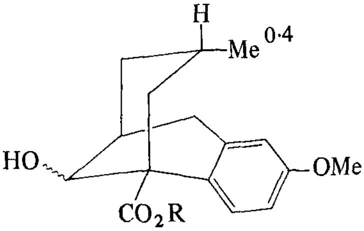
[401]

shows it to be pointing towards ring B so as to suffer shielding by the β phenyl ring.

The bicyclo[3.3.1]nonane [401] and the corresponding alcohol, obtained by borohydride reduction, both showed the methyl proton signals at δ 0·8 (J = 6 Hz) in their NMR spectra. However, the 11-methyl protons in the 11-*epi*-compound [402] also absorb at δ 0·8 ($J = 6$ Hz) whereas in the corresponding alcohol [403] the methyl protons are shielded (δ 0·4). The shielded methyl in the alcohol [403] is in accord with expectations since it lies in the shielding zone of the aromatic ring so that [402] must exist in the



[402]



[403]

boat conformation [403] with the methyl group out of this region. Presumably the chair conformation is adopted by [403] to relieve unfavourable flagpole interactions.

Acknowledgement

The author is indebted to Mrs. Jean McCulloch for her very careful typing of the manuscript.

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Two-Bond Coupling Between Protons and Carbon-13

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I. INTRODUCTION

There is at present a rapidly expanding interest in the field of ^{13}C NMR spectroscopy. This is the direct result of a recent and continuing increase in the number of instruments now operational and devoted primarily to ^{13}C spectroscopy. With the advent of the Fourier Transform mode of operation and the consequent saving in time the determination of a ^{13}C spectrum, at natural abundance, has now become a routine process, and, in the United Kingdom at least, such routine ^{13}C facilities are now available to all NMR spectroscopists through the service provided under the auspices of the Science Research Council. The very near future will see further expansion in such facilities in many laboratories.

The bulk of the work on the ^{13}C resonance in the past has been concerned with chemical shifts largely because of the usual procedure of determining spectra with complete proton decoupling. The reasons for using such a procedure are well known but much valuable information about ^{13}C–H coupling constants, particularly long-range coupling constants, is thereby lost. It seems likely that much greater attention will be paid in the future to obtaining these coupling constants (although this will undoubtedly often involve the analysis of complex second order spectra) and that these parameters will become of widespread interest.

Some idea of the potential usefulness of ^{13}C–H coupling constants, both to the NMR spectroscopist and the theoretical chemist, may be obtained from the following comparison with proton couplings. For the relatively simple molecule toluene, there are four one-bond couplings [^1J(C–H)], seven two-bond couplings [six ^2J(C–H) and one (unmeasurable) ^2J(H–H)], nine three-bond couplings [seven ^3J(C–H) and two ^3J(H–H)] and nine four-bond couplings [five ^4J(C–H) and four ^4J(H–H)], i.e., twenty-two couplings between carbon and a proton compared to only seven between protons. This is by no means an extreme example and indicates that J(C–H) must be an even more sensitive probe than J(H–H) of the subtleties of electronic and steric interactions within molecules, and of the interaction of molecules within the medium.

Previous reviews (1-3) of ^{13}C spectroscopy have concentrated mainly on chemical shifts and on one-bond couplings between carbon and hydrogen since these are the most easily available parameters, the former from proton decoupled ^{13}C spectra and the latter from the natural abundance ^{13}C satellites in proton spectra. Two-bond coupling ^2J(C–H)† has been dealt with only very briefly (1b, 2b) usually together with other long-range ^{13}C couplings and it is the purpose of this review to collect together all available experimental data on this coupling and to survey the theoretical and empirical studies in this area.

The available body of data on ^2J(C–H) does no more than highlight the great potential of this geminal coupling constant and it is hoped that this survey will indicate the many areas which are ripe for investigation. Three bond couplings between carbon and hydrogen have not been included since there is much less data on this parameter and, unlike the situation for proton–proton coupling, the

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† In this review we are concerned only with the coupling $J(^{13}C–C–H)$ in which the intervening atom is always carbon and the abbreviated notation ^2J(C–H) is adopted throughout.

geminal coupling ^2J(C–H) will precede the vicinal coupling ^3J(C–H) as a parameter of general usefulness. Information on heteronuclear coupling constants is not easily extracted from the literature since in many cases these parameters have been determined only incidentally and their presence in a paper is not indicated in the title or the summary. We have attempted a comprehensive coverage of the literature through to March 1972 and hope that no important work has been missed.

II. THEORETICAL STUDIES

Significant advances have come about in the last few years in the whole field of theoretical chemistry and some of the stimulus for this upsurge has undoubtedly come from the availability of a molecular parameter, the nuclear spin-spin coupling constant, which is a much more intimate measure, than most other parameters, of the state of the electronic organisation in a molecule. Not surprisingly, theories of nuclear spin–spin interactions have been largely evaluated in terms of proton–proton couplings, the most accessible parameter, and other couplings have tended to be treated in a more incidental manner. Hence, it is appropriate here to outline very briefly the development of general theories of spin–spin coupling since this will embrace the early work on ^2J(C–H). No attempt will be made to review the quantum mechanical background to theoretical calculations since this has been covered in the authoritative reviews by Murrell (4) and by Barfield and Grant. (5)

A. Quantitative Calculations of ^2J(C–H)

In 1953 Ramsey (6) formulated a general perturbation theory of nuclear spin–spin coupling and this has formed the basis of virtually all subsequent work. Ramsey recognized two modes of interaction between nuclei and electrons by which nuclear spin information could be transferred viz. a nuclear magnetic moment–electron orbital interaction and a nuclear magnetic moment–electron spin dipolar interaction. In addition, the perturbation Hamiltonian must include a third term representing the direct nuclear spin–electron spin interaction at the nucleus, the so-called Fermi contact term. The mathematical formulation (4) of these three terms in the perturbation Hamiltonian need not be reproduced here. For proton–proton coupling the dipolar and orbital terms are negligible (4) and this also appears to be the case for spin coupling of hydrogen with many other nuclei including carbon. (4, 7, 8) Nearly all theoretical calculations of ${}^2J$(C–H) have been concerned with the contact term and the other two terms have been explicitly (7, 8) or implicitly neglected.

Evaluation of the contact term requires knowledge of the energies of the wave functions of all excited states in the system of interest. Since adequate excited state wave functions were not easily determined for even a very simple molecule like methane, McConnell (9) developed a general molecular orbital (MO) theory of contact coupling which invoked a mean energy as an approximation to the sum over excited states. Within this approximation the coupling constant is given in terms of the usual MO wave functions by expression (1)

$$J_{\mathrm{AB}} = C(\Delta E)^{-1} \sum_{i}^{\mathrm{occ}} \sum_{j}^{\mathrm{occ}} \psi_i(\mathrm{A})\psi_j(\mathrm{A})\psi_i(\mathrm{B})\psi_j(\mathrm{B}) \tag{1}$$

where C contains accumulated constants for the nuclei A and B and ΔE is the mean excitation energy. If the usual LCAO approximation is used, then expression (1) becomes

$$J_{\mathrm{AB}} = C'(\Delta E)^{-1} s_{\mathrm{A}}^2(0) s_{\mathrm{B}}^2(0) P^2_{s_{\mathrm{A}} s_{\mathrm{B}}} \tag{2}$$

where $s_A^2(0)$ and $s_B^2(0)$ are the valence s-electron densities at the respective nuclei and $P_{s_A s_B}$ is the MO bond order between the s-orbitals of nuclei A and B. This expression for J has the major drawback that all coupling constants are predicted to be positive, a result at variance with a large body of experimental data. The use of a constant value of ΔE for the calculation of ${}^1J$(C–H) and ${}^2J$(C–H) has been criticized. (10)

Barfield (11) has shown that negative geminal coupling constants [${}^2J$(H–H), ${}^2J$(C–H)] may be obtained from a MO treatment of spin–spin coupling in terms of the density matrix formalism and the average energy approximation. However, the magnitude of ${}^2J$ (Table I, entry 1) is dependent on a reasonable choice of pivotal parameter. (11)

The mean energy approximation has also formed the basis of the valence bond (VB) approach to the calculation of J since VB wave functions for excited states are not easily obtained. (5) Ranft (12, 13) has investigated ${}^2J$(C–H) in the simple hydrocarbon fragment H–C–C with sp^3 and sp^2 hybridization at carbon, using a variety of VB methods. With the formalism of Karplus and Anderson (14) negative ${}^2J$ values were obtained for ethane and ethylene (Table I, entry 2) but the absolute magnitude was too small in both cases.

TABLE I

Calculated ^{2}J(C–H) values (Hz) for simple hydrocarbons

Entry	Method[a]	Ethane	Ethylene	Acetylene	Ref.
1	Density matrix (MO)	0 to −9·6[b]			
2	Valence bond	−6·9	−9·2		12
3	Valence bond	−4·6	−7·0		12
4	Valence bond	−3·2 to −4·2[c]	−1·8 to −2·1[c]		13
5	Valence bond	−5·4		+18·0	16
6	Independent electron[d]	+9·57	+18·77	+55·10	20
7	Independent electron[d]	+9·51	+19·9	+60·0	7
8	Independent electron[d]	+8·3	+15·2	+39·5	22
9	Extended Hückel[d]	−4·0	−8·0	−5·9	23
10	Extended Hückel[d]	−3·7	−7·8	−7·4	22
11	Non-empirical[d]	+4·8	+11·1	+32·9	26
12	Modified Hückel[d]	−2·2	−1·0	+27·1	25
13	Full SCFMO		+6·1		29
14	Full SCFMO + CI		−3·7		29
15	Full SCFMO + CI[e]		−4·3		29
16	Full SCFMO			−4·85	30
17	Full SCFMO + CI			+13·3	30
18	CNDO/2	0·0	+0·86	+4·89	31
19	CNDO/2 + CI	−0·72	−0·39	+12·99	31
20	CNDO/2 + CI[f]	−1·21	−0·63	+21·29	31
21	CNDO/2[g]	+0·17	+1·14	+5·52	8
22	CNDO/2 + CI[g]	−0·80	−0·53	+5·86	8
23	INDO[g]	+0·42	+1·87	+7·79	8
24	INDO + CI[g]	−1·66	−1·27	+7·46	8
25	INDO[f]	+0·24	+2·17	+15·19	32
26	INDO + CI[f]	−2·90	−2·66	+30·92	32
27	PMO[h]/CNDO/2	−2·56	−3·86	+5·51	35
28	PMO[h]/INDO	−7·20	−11·57	+2·52	35
	Experimental	−4·5, −4·8	−2·4	+49·3, 49·7	56, 57

[a] The method used to evaluate the wave function coefficients. For MO methods the usual descriptive labels are used.

[b] Value depends on magnitude of pivotal parameter.

[c] Value depends on parameterisation.

[d] Using the Pople–Santry approximation. (18)

[e] With inclusion of a dipole–dipole contribution.

[f] s-Electron density at carbon treated as a parameter.

[g] Using variable integrals.

[h] Pople–McIver–Ostlund finite perturbation method. (35)

Much improved values were calculated by the VB method of Hiroike (15) (Table I, entry 3), especially for ethane. In a more extensive analysis (13) of the variation of ^{2}J(C–H) with VB parameterization a wide range of values was found. The best set (Table I, entry 4) agrees remarkably well with the experimental values (Table I, final entry). A VB calculation by Sackmann and Dreeskamp (16) based on the Dirac-vector method of Alexander (17) gave ${}^2J$(C–H) values with the correct sign for ethane and acetylene (Table I, entry 5) although in the latter case the magnitude was much too small.

A serious problem with both MO and VB methods of estimating coupling constants in the average energy approximation is the severe cancellation of numerical terms which occurs. (7, 18) This is also the case for the more sophisticated MO treatments described below and leads to calculated values of J which in many cases are sensitive to the method and the parameterization used in the calculation. It should be borne in mind when evaluating the data and methods summarized in Table I that ${}^2J$(C–H) is only *one* measure of a procedure for calculating the contact term and that methods which perform badly for this particular parameter may do very much better in the wider context of estimating ${}^1J$(C–H), ${}^2J$(H–H) and ${}^3J$(H–H) values.

Several workers have developed MO methods of calculating coupling constants which avoid the mean energy approximation in its crudest form. Within the formalism of a one electron Hamiltonian Pople and Santry (18) considered only a relatively limited number of excited states arising from single excitations between molecular orbitals derived from a minimum basis set of atomic orbitals. Triplet excitation energies are then the differences in orbital energies and the coupling constants may be given (expression 3) in terms of π_{AB}, the atom–atom polarizability. (19)

$$J_{AB} = C'' s_A^2(0) s_B^2(0) \pi_{AB} \tag{3}$$

To calculate π_{AB} Pople and Santry applied (20) their independent electron theory of hydrocarbons. (21) In this theory the molecular orbitals are derived most conveniently in terms of interactions between carbon sp^3 hybrid orbitals. Expressions were derived in terms of these various orbital interactions for the π_{AB} appropriate to ${}^2J$(C–H) in ethane, ethylene and acetylene. The calculated ${}^2J$(C–H) values are given in Table I, entry 6. Although the trend of ${}^2J$ with the amount of s character in the carbon bonding orbitals is nicely reproduced [cf. experimental ${}^2J$(C–H) values in the final entry of Table I], the absolute values are much too positive for ethane and ethylene. This can be attributed in part to neglect of overlap and even more to neglect of electron correlation. Similar ${}^2J$(C–H) values have been found by other workers (7, 22) using the Pople–Santry method with some parameter modification (Table I, entries 7 and 8).

Jameson and Damasco (7) extended a modified Pople–Santry theory to all combinations of sp^3, sp^2 and sp hybridization at both the carbon atoms in the fragment H–C_1–C_2. Although again the ^2J values were too positive this work convincingly demonstrated that C_1 hybridization is the dominant factor. Only a narrow range in ^2J(C–H) was found for the variation of hybridization of C_2 but nonetheless ^2J did become more positive with increasing *s* character of C_2 orbitals, e.g., for $C_1(sp^3)$ then $^2J = +9{\cdot}51$ Hz for $C_2(sp^3)$, 11·29 Hz for $C_2(sp^2)$ and +17·49 Hz for $C_2(sp)$. Calculations of ^2J(C–H) by Fahey *et al.* (23) and de Jeu and Beneder, (22) using the extended Hückel theory of Hoffmann (24) to obtain π_{AB}, were little more successful than those of Pople and Santry. Although the absolute value of ^2J(C–H) for ethane and ethylene was good (Table I, entries 9 and 10), the normal trend of ^2J was not reproduced. The values for acetylene are particularly bad. However, the Hoffmann method appears to be generally better than the independent electron method for most other coupling constants. (22)

Polezzo *et al.* (25) have used non-empirical molecular orbitals with the Pople–Santry equation (3) and again found a reasonable trend in ^2J(C–H) but very poor absolute values for ethane and ethylene (Table I, entry 11). Rather more success was achieved by Kato *et al.* (26) using a modified Hückel MO method to evaluate π_{AB} (entry 12). Both the sign of ^2J and the trend in ^2J with *s* character for the simple hydrocarbons are correct and this is clearly the best set of ^2J(C–H) values based on the Pople–Santry approximation to the sum over excited states when evaluated by empirical MO methods. A VB method for direct calculation of the sum over excited states has been proposed by Barfield (27) but this method has not been applied to the estimation of ^2J(C–H).

With self consistent field (SCF) molecular orbitals substantial improvement might be expected over the empirical independent electron method, particularly if the set of excited states is not limited to those associated with a minimum basis set of molecular orbitals. This was indeed the case for the calculated value of ^2J(H–H) in methane (28) where a value of the correct sign was obtained. A similar full SCF calculation (29) for ethylene produced the ^2J(C–H) values given in Table I (entries 13–15). The first value is again of the wrong sign but with the inclusion of configuration interaction (CI) an extremely good value is obtained, which is not improved by inclusion of a dipole–dipole contribution (Table I, entry 15). These results clearly show the necessity of considering electron correlation. These workers (29) also found that ^2J values are sensitive to the positions of the nodes in the wave functions. Although a similar change of sign was found for ^2J(C–H) in acetylene when CI was included in a full SCF MO treatment (30) the final absolute value was poor (Table I, entries 16 and 17). This was also the case for most other coupling constants calculated in this work.

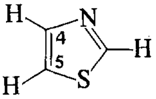
Since *ab initio* calculations are difficult for all but the simplest molecules the usefulness of approximate SCF MO methods in the calculation of ^2J has been extensively explored. Two groups of workers (8, 31, 32) have applied the CNDO/2 and INDO MO methods developed by Pople and his co-workers (33, 34) to the calculations of ^2J(C–H), and many other coupling constants, and their results for the simple hydrocarbons are given in Table I (entries 18–26). It may at once be seen that the inclusion of configuration interaction almost invariably improves the calculated ^2J(C–H) value and that the INDO method is superior to the CNDO/2 method which often produces values of the wrong sign. Ditchfield (32) and Murrell (31) have treated the *s*-electron density at the carbon nucleus ($s_C^2(0)$) as a parameter and obtained some improvement in ^2J (Table I, entry 20) particularly for *sp* hybridized carbon. A different approach to scaling the calculated constant term was used by Towl and Schaumburg. (8) These workers performed calculations firstly with fixed values for the integrals in the perturbation sum and secondly with integral values varying with the SCF atom populations. This later procedure produced negligible improvement for ^2J(C–H) and was only marginally better for ^1J(C–H).

Pople, McIver and Ostlund (35) have recently developed a different approach to the calculation of coupling constants which has had considerable success in accounting for the experimentally observed trends in ^1J(C–H), (36, 37) ^1J(C–C), (38) ^2J(H–H), (39) ^3J(H–H) (40, 41) in a very wide range of compounds. Explicit consideration of excited states is avoided (34, 35) by calculating unrestricted wave functions in the CNDO/2 or INDO approximations in the presence of a finite contact perturbation. Within this framework (which we shall call the PMO method) a coupling constant is given by expression (4) where $\rho_{s_A s_A}$ is the diagonal spin density

$$J_{AB} = C'''s_A^2(0)s_B^2(0)\left[\frac{\partial}{\partial h_B}\rho_{s_A s_A}(h_B)\right]_{h_B=0} \qquad (4)$$

matrix element for the valence *s*-orbital of nucleus A subjected to a contact perturbation h_B arising in nucleus B. Although absolute J values calculated by the PMO method are often relatively poor, experimental trends are confirmed. This is borne out by the data for ^2J(C–H) (Table I, entries 27, 28). The inclusion of one-centre exchange integrals (the INDO method) is less successful for the PMO method when applied to ^2J(C–H), giving poorer J values than are obtained in the CNDO/2 approximation but this is not the case for most other coupling constants. (35)

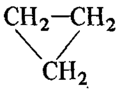
Calculation of ^2J(C–H) in compounds other than the three simple hydrocarbons in Table I has been attempted in a rather fragmentary way with the exception of some very recent work. (42, 43) Using the Pople–Santry equation ^2J(C–H) in benzene has been calculated as −6·9 (23) and −5·9 Hz (44) compared with PMO results (35) of −0·17 (in the CNDO/2 approximation) and −4·9 Hz (in the INDO approximation); experimental values are +1·0 Hz (44) and +1·13 Hz. (45) Similar values are reported for three ^2J couplings in pyrene, (46) from a CNDO SCF calculation. Weigert and Roberts (47) used extended Hückel MO theory with the Pople–Santry approximation to try to reproduce experimental trends of ^2J(C–H) in heterocycles, with little success. Calculated ^2J values (−4·9 to −6·6 Hz) had the wrong sign and showed little correlation with experimental values. Rather better results were reported (48) for CNDO/2 calculations of $J(C_4–H_5)$ (+2·45 Hz) and $J(C_5–H_4)$ (+4·95 Hz) in thiazole [1]. Both the sign and the relative magnitudes of the couplings agree with the observed values (see Table XV).



[1]

For ^2J(C–H) in acetonitrile SCF calculations with CI (32) showed the usual improvement between the CNDO/2 (0·3 Hz) and INDO (−3·6 Hz) approximations although this latter result is still poor compared with the experimental value (−9·83 Hz). (49) Using a VB method Sackmann and Dreeskamp (16) obtained excellent values for ^2J(C–H) in several compounds in which the hydrogen atom was attached to sp^3 hybridized carbon viz. (experimental value in brackets) acetaldehyde $^2J = -7·0$ (−6·6 Hz), dichloroacetaldehyde $^2J = +2$ (0·0 Hz), 1,1,2,2-tetrachloroethane $^2J = +3·8$ (−1·1 Hz) and 1,1-dichloropropene $^2J = +3·3$ (+3·2 Hz).

Various MO methods have been used (23, 43) to obtain ^2J(C–H) in the small ring compounds, cyclopropane [2], oxirane [3] and aziridene [4] (Table II). Lack of experimental values makes this data difficult to assess but, although the extended Hückel calculation of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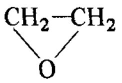
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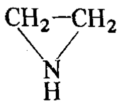
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TABLE II

Calculated ^2J(C–H) values in three-membered ring compounds

Method	^2J(Hz)			Ref.
	[2]	[3]	[4]	
Extended Hückel[a]	−3·3			23
Extended Hückel[a]	−2·79	−4·38	−3·86	43
PMO[b] CNDO/2	−1·87	−1·89	−1·39	43
PMO[b] INDO	−4·47	−4·75	−4·14	43
Experimental	−2·55			58

[a] Using the Pople–Santy approximation. (18)

[b] Pople–McIver–Ostlund finite perturbation method. (35)

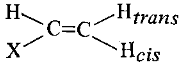
Gopinathan and Narasimhan (43) gives the best absolute value for cyclopropane, the PMO/INDO results may better reflect the trend in ^2J.

Using two different modifications to the extended Hückel method, within the Pople–Santry approximation, Yonezawa *et al.* (42) have obtained ^2J(C–H) values for various substituted ethylenes (Table III). Experimental values were not available to these workers but the recent data of Crecely *et al.* (50) (see Table XI) indicate that these calculated values do broadly reproduce the experimental trends although the absolute values are in most cases relatively poor.

In aldehydes the two-bond coupling to the aldehydic hydrogen is dominated by just two excited states, both involving the non-bonding orbital of the oxygen. (51) A similar situation exists for the ^2J(H–H) coupling in formaldehyde. Yamamoto *et al.* (51) have investigated this ^2J(C–H) coupling using a CNDO/2 method and have obtained values for acetaldehyde (+22·5 Hz), acrolein (+17·8 Hz) and propargyl aldehyde (+26·8 Hz) in very reasonable agreement with the experimental values (26·7, 26·9, 33·2 Hz respectively). The calculated value (51) for fluoroacetaldehyde was +28.0 Hz indicating a positive increment in ^2J for substitution by an electronegative group. A very poor value (+4·2 Hz) has been obtained for acetaldehyde from a VB calculation. (16) The characteristically large positive value of ^2J(C–H) in aldehydes arises from substantial delocalization of the

TABLE III

Calculated ^2J(C-H) values in substituted ethylenes (42)



Substituent	^2J(C-H$_{cis}$)(Hz)		^2J(C-H$_{trans}$)(Hz)	
	A[a]	B[a]	A[a]	B[a]
None	−0·1	+3·5	−0·1	+3·5
CN	−0·4	+1·7	+0·4	+8·1
CH_3	−0·3	+2·2	+0·2	+4·4
COOH	−0·3	+1·2	+0·2	+7·8
CHO	−0·04	+2·3	+0·1	+5·7
Cl	−0·9	+0·3	+2·5	+14·7
OCH_3	−0·9	−0·5	+7·2	+24·4
F		−1[b]	+8·6	+25·1
trans-di-Cl	−0·6	+6·1		
cis-di-Cl			+4·1	+21·8

[a] A and B correspond to different modifications of the Extended Hückel MO method.

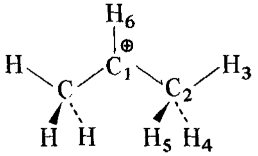
[b] This value is estimated from a plot in the original paper. (42) Actual value has been omitted from the published table.

oxygen non-bonding electrons through a 'pseudo-π-orbital' combined with a low excitation energy from the non-bonding orbital. (51)

A crucial factor in any MO calculation is just how sensitive the calculated parameters are to the geometry of the molecule under consideration, particularly because exact geometries are often unavailable and standard values of bond length and bond angle must be used. A significant dependence of coupling constants on molecular geometry has been demonstrated for calculations on two quite different compounds. For ^2J(C–H) in ethylene (calculated using a CNDO/2 approximation with configuration interaction) Towl and Schaumberg (8) found the following variation.

R(C–C) = 1·336 Å, R(C–H) = 1·085 Å, HCH angle = 116·8°;
$^2J = -0{\cdot}532$ Hz
R(C–C) = 1·35 Å, R(C–H) = 1·06 Å, HCH angle = 120·0°;
$^2J = -0{\cdot}493$ Hz
R(C–C) = 1·34 Å, R(C–H) = 1·08 Å, HCH angle = 120·0°;
$^2J = -0{\cdot}628$ Hz

These results indicate an appreciable sensitivity to geometry even over the relatively narrow range in this case which extends from the standard values of bond length and bond angle to the corresponding experimentally determined values. Even more dramatic sensitivity to geometry is apparent in the study of the isopropyl carbonium ion [5].† For this model species Maciel (52) has calculated ^1J(C–H) and ^2J(C–H) (by the PMO method using INDO molecular orbitals) for variations in bond length, bond angle and dihedral angle and some of the data for the two ^2J couplings are given in Table IV.



[5]

The average coupling between the central carbon and the methyl hydrogens, $J(C_1-H_{345})$ is strongly dependent on the centre bond angle $C_2C_1H_6$ but not very sensitive to bond lengths or dihedral angle. However, the individual coupling $J(C_1-H_3)$ is, not unexpectedly, very sensitive to dihedral angle varying from −7·618 Hz at 0° through +1·760 Hz at 90° to −6·813 Hz at 180°. Although the magnitude of the range is clearly related to the presence of a vacant *p* orbital on C_1 with which a methyl hydrogen is able to conjugate, similar trends can be expected with other types of conjugation centre. Variation of ^2J with dihedral angle has also been noted (12, 13) for the ethanic fragment H–C–C–H. (12, 13) In this case the range is much smaller (*ca.* 0·3 Hz) than that calculated for [5] and better represents the intrinsic dependence on dihedral angle in the absence of conjugation effects. Similar VB calculations (13) for the H–C(sp^3)–C(sp^2) fragment indicated a larger range in ^2J(C–H) (*ca.* 0·6 Hz), reflecting the presence of a conjugating centre. A dependence on bond angle, bond length and dihedral angle has also been demonstrated theoretically for ^2J(H–H) by PMO calculations for methanol and acetaldehyde. (39)

It is clearly essential in the calculation of ^2J that due consideration be given to the dihedral angles involved in the molecular fragment containing the coupling nuclei, particularly when electronegative atoms or conjugation centres are present. Bond angle and bond length are less important and the variation in ^2J from this source cannot be regarded as very significant compared with the general uncertainties inherent in the present methods of calculating

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† The vacant *p* orbital is perpendicular to the plane defined by $C_2C_1H_6$.

TABLE IV

Effect of changes in geometry on calculated ^2J(C–H) values (Hz) in the isopropyl cation [5] (52)

Bond angle $C_2C_1H_6$	$^2J(C_2-H_6)$	$^2J(C_1-H_{345})^a$	Dihedral angle $H_6C_1C_2H_3$	$^2J(C_2-H_6)$	$^2J(C_1-H_{345})^a$	R(Å)	$^2J(C_2-H_6)$	$^2J(C_1-H_{345})^a$
120	−1·762	−2·801	0	−1·762	−2·801	1·49[b]	−2·112	−2·971
118	−1·803	−1·658	20	−1·857	−2·782	1·52[b]	−1·762	−2·801
116	−1·806	−0·457	40	−2·049	−2·746	1·54[b]	−1·549	−2·712
114	−1·768	+0·810	60	−2·144	−2·730	1·07[c]	−1·731	−2·761
112	−1·683	+2·158	80	−2·049	−2·746	1·08[c]	−1·762	−2·801
110	−1·539	+3·582	100	−1·857	−2·782	1·09[c]	−1·795	−2·844
Tetrahedral	−1·490	+3·972	120	−1·762	−2·801			

[a] $^2J(C_1-H_{345})$ is the mean of $^2J(C_1-H_3)$, $^2J(C_1-H_4)$, $^2J(C_1-H_5)$.

[b] $R = R(C_1-C_2)$ for constant $R(C_1-H_6) = 1{\cdot}08$ Å.

[c] $R = R(C_1-H_6)$ for constant $R(C_1-C_2) = 1{\cdot}52$ Å.

J. However, the more sophisticated the calculation, the more important do these factors become.

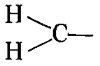
The final point to be considered in this section is the contribution to ^2J(C–H) from σ–π interactions. Little theoretical consideration has been given to this contribution to ^2J although its importance for longer range couplings is widely recognized. (53) Obviously for fragments involving only sp^3 hybridized carbon the π-contribution must be zero but Jameson and Damasco (20) have calculated, using MO methods, ^2J(C–H)(π) for the various possible fragments involving sp^2 and sp hybridization at carbon. Typical values include −1·68 Hz for ethylene and −4·98 Hz for acetylene. Ranft (54) estimated ^2J(C–H)(π) as −1·6 to −2·3 Hz for ethylene from VB calculations and −5 Hz has been similarly estimated (55) for acetylene. Because this π-contribution to ^2J is negative, neglect of this term cannot account for the consistently low calculated values for acetylene (Table I).

B. Theoretical Treatment of Substituent Effects

Very little progress has been made in the development of a comprehensive quantitative theory of substituent effects for ^2J(C–H). This is not surprising considering the relatively poor and very variable results obtained for the simple unsubstituted hydrocarbons (cf. Table I) and reflects the general problem of satisfactorily extending MO and VB methods to include substituents particularly when the atoms concerned have d orbitals to be included in any reasonable atomic orbital basis set. This problem is general to all coupling constants and a valuable approach to substituent interaction has been through qualitative theories. For ^2J(H–H) Barfield and Grant (59) have investigated the effect of an adjacent π-bond using an empirical VB method. This work indicated a strong angular dependence with the negative increment in ^2J at a maximum when the H–H line was parallel to the p-orbitals of the π-bond. A rather more general MO theory of substituent effects has been developed by Pople and Bothner-By (60) (PBB theory) to cope with both inductive and hyperconjugative interactions and their effect on ^2J(H–H). Both Barfield-Grant and PBB theories have been widely used (61-65) but we shall discuss only the PBB approach since it is the more relevant to ^2J(C–H).

Using a localized MO treatment for the symmetric H–C–H fragment [6] Pople and Bothner-By (60) have shown that the electronic structure can be described in terms of two bonding and two antibonding orbitals. Each pair may be further classified as symmetric or antisymmetric about reflection in the plane bisecting the H–C–H angle. The result of substituent interaction with these four orbitals may, in a purely qualitative way, be summarized in two rules: (a) withdrawal of electrons from symmetric orbitals leads to a positive change in the coupling constant. This is generally an inductive effect operating on the symmetric bonding orbital; (b) withdrawal of electrons from unsymmetrical orbitals leads to a negative change in the coupling constant. This is generally a hyperconjugative effect operating on the bonding or antibonding orbitals. Electron donation in either case has the opposite effect on the coupling constant. Hyperconjugative effects have a strong angular dependence very similar to that found by Barfield and Grant (59) i.e., the maximum effect occurs when the *p*-orbital of the conjugating bond or centre is parallel to the H–H line in the H–C–H fragment [7]. The predicted effects of substituents on ${}^2J$(H–H) have recently been confirmed by quantitative calculations using the PMO method. The calculated angular dependence of hyperconjugative effects in methanol and acetaldehyde are completely in accord with the qualitative reasoning of Pople and Bothner-By. (60)

Extension of the PBB qualitative model to the fragment H–C_1–C_2 [8] must take account of two serious changes in the nature of the system. Firstly the localized molecular orbitals obviously do not have a plane of symmetry as they do in [6] and their classification into symmetric and antisymmetric is strictly not a valid one. (66, 67) Secondly substitutions in the fragment can occur not only at the middle atom C_1 but also at C_2 and in this latter case quite different conformational considerations must apply. (67) In spite of these drawbacks PBB theory has obvious attraction for a qualitative approach to trends in ${}^2J$(C–H) and will undoubtedly be of continuing value in this field. The available examples of its application will now be discussed.



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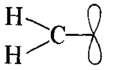

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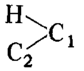
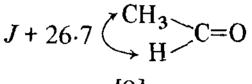


[8]

An empirical relationship between ${}^1J$(C–H) and ${}^2J$(C–H) has been proposed by McLauchlan and Schaefer (68) and this is described in more detail in the next section. It is sufficient here to note that these workers could rationalize deviations from this relationship for acetaldehyde and vinyl cyanide in terms of hyperconjugative interactions of the substituent on C_1, producing electron donation in the former case and electron withdrawal in the latter.

Application of PBB theory to the H–C_1=C_2 fragment (42, 50, 69) can account for the observed trend in ^2J(C–H) in olefins substituted at C_1. An increase in ^2J with increase in substituent electronegativity is the result of increasing inductive withdrawal from the symmetric bonding orbital. PPB theory cannot, however, be applied to substitution at C_2 in H–C_1=C_2. (42, 66)

In aldehydes the fragment H–CO–C_2 can only be substituted at C_2 but the large increase in ^2J(C–H) for aldehydes over that for olefins (in which C_1 is also sp^2 hybridized; compare [9] and [10])



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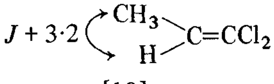
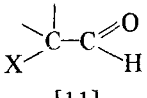


[10]

can be accounted for by regarding the oxygen atom as a C_1 substituent. (51, 67, 68) Inductive withdrawal by the electronegative oxygen atom and hyperconjugative donation from an oxygen lone-pair both provide a positive contribution to ^2J(C–H). Analogous effects are responsible for the very large positive value of ^2J(H–H) in formaldehyde. Substitution of a halogen atom (X) at C_2 of the aldehydic fragment [11] presents a more difficult problem (51, 67) to rationalize in terms of PBB theory. The observed ^2J(C–H) values increase with decreasing halogen electronegativity contrary to what would be expected if only an inductive effect is operating. Ewing (67) has suggested that there is in addition a hyperconjugative donation from halogen lone-pair electrons and that this is the dominant factor for the halogen series. Since a hyperconjugative interaction will increase with the size and polarizability of the halogen atom the net result is a positive increment in ^2J(C–H) in [11] as X changes from Cl to I. Furthermore there is evidence that this hyperconjugative interaction is dependent upon the conformation of the fragment and is at a maximum when the halogen atom is *trans* to the hydrogen atom [12].



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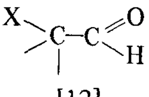
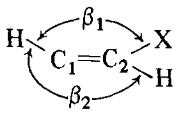


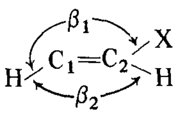
[12]

Gil and co-workers (70, 71) have also attempted to derive a qualitative theory of substituent effect on ^2J(H–H) by incorporating substituent orbitals into the calculation of the atom–atom polarizability (π_{AB} in equation 3). Their results parallel those of Pople and Bothner-By but are less successful for ^2J(C–H). Considering substitution at C_2 in the $H-C_1=C_2$ fragment these workers (70) predicted an increase in ^2J(C–H) for a *cis* substituent and a decrease for a *trans* substituent contrary to experimental data. (50, 72)

An extensive analytical study (7) of ^2J(C–H) for all combinations of the state of hybridization at both C_1 and C_2 has been discussed in the previous section. In this work Jameson and Damasco (7) have also examined in detail the behaviour of the conformation dependent integrals β_1 and β_2 in the expression for ^2J for the olefinic fragment [13] and provided a tentative rationalisation of the changes in ^2J(C–H) induced by the substituent. The effect of an electronegative atom X in [13] and [14] is to increase the magnitude of β_1 and decrease the magnitude of β_2. Since β_1 changes sign between a *cis* and *trans* relationship the net effect is to give a positive increment to $^2J(C_2-H_{trans})$ [14] and a negligible or negative increment to $^2J(C_2-H_{cis})$ [13] in complete agreement with experimental data (see Table XI). This qualitative approach may be quite useful if it can be extended to include the effect of hyperconjugation centres substituted at C_2.



[13]



[14]

III. EMPIRICAL CORRELATIONS

Extensive use has been made of empirical correlations for interproton coupling constants and this has been naturally extended to couplings involving carbon. A widely discussed (26, 36) relationship for both ^1J(C–H) and ^2J(C–H) is that between the coupling constants and what is loosely termed, the *s* character of the carbon bonding orbitals. Whilst the *s* character of an orbital is clearly related to the state of hybridization of the atom concerned there has been a tendency to lose sight of the fact that hybridization is a mathematical and conceptual convenience and not a physical phenomenon. A theoretical basis can be found for a direct dependence of ^1J(C–H) and ^2J(C–H) on the *s* character of the carbon bonding orbital, in the McConnell expression for J (equation 2). An assumed constancy of the terms ΔE, $s_A^2(0)$ and $s_B^2(0)$ leaves J dependent on $P_{s_A s_B}^2$, the bond order between the valence *s*-orbitals of the coupling nuclei, and hence in particular on the amount of *s* character in the carbon orbital. For one-bond coupling this dependence of J on s character was first propounded by Muller and Pritchard (73) and has been uncritically applied by many workers. Extension to coupling in $H\text{-}C_1\text{-}C_2$ has led to the suggestion that $^2J(C\text{-}H)$ is proportional to the s character of the C_1 orbitals (13, 68, 74, 75) and/or the C_2 orbital (7, 13, 16, 76) and that in some cases $^1J(C\text{-}H)$ and $^2J(C\text{-}H)$ may be linearly related. (76, 77) Other studies (51, 78, 79) have found clear evidence that $^2J(C\text{-}H)$ is not linearly related to s character.

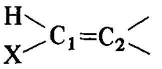
This anomalous situation can be better understood when we consider that equation (2) embodies only a relatively simple MO representation of the coupling between nuclei A and B and the assumed constancy of the above terms is open to severe criticism. (80-82) [Correlation of $^1J(C\text{-}H)$ with s character has also been criticized on the basis of a VB approach. (83)] Saika (81) has shown that allowing for variation in ΔE for the series methane and halogeno-methanes gives distinct improvement in calculated $^1J(C\text{-}H)$ values and for the same compounds other workers (84) have found that inclusion of an appreciable ionic character in the carbon-halogen bond is essential to obtain a good fit with experimental couplings. In some studies, (31, 32) the term $s^2(0)$ for carbon has been treated as a parameter (rather than assume the SCF value) resulting in improved calculated values of $^1J(C\text{-}H)$ and $^2J(C\text{-}H)$ and there seems no reason why this factor should not vary (80) between molecules.

Calculations using a separated electron pair approach (85) have also demonstrated that substituents directly effect the magnitude of $^1J(C\text{-}H)$, not only the s character of the bond. More extensive studies (80) using the Pople-Santry expression (3) indicate that $^1J(C\text{-}H)$ does not have a *direct* proportionality with π_{AB} even for simple hydrocarbons. With the more sophisticated PMO finite perturbation method (35) in the INDO approximation, calculated (36, 37) $^1J(C\text{-}H)$ and the corresponding bond order $P^2_{s_C s_H}$ both appear to parallel the experimental couplings when the only structural changes involved are changes in hybridization and/or bond angle at the carbon atom in a series of hydrocarbons. This supports a qualitative relationship of $^1J(C\text{-}H)$ to $P^2_{s_C s_H}$ within this narrow limitation but when substituent effects are present the trend in experimental $^1J(C\text{-}H)$ values is less well reproduced and the correlation with bond order is even poorer. Even less encouraging results were found for the carbonium ion [5] in which $^1J(C_1\text{-}H_6)$ was very sensitive to the magnitude of the bond angle $C_2C_1H_6$ whereas $P^2_{s_C s_H}$ was virtually unchanged. Furthermore $^1J(C_2\text{-}H_{345})$ increased significantly as the centre bond angle increased but the corresponding bond order decreased slightly. For the ^2J(C–H) coupling in [5] there appears to be no simple relationship with the bond order of the C_1–C_2 bond.

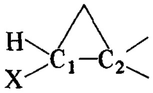
The present picture is still not clear for ^1J(C–H) but it seems fairly certain that ^2J(C–H) is not *linearly* related to *s* character or to ^1J(C–H) except perhaps under very limited conditions and that the broad correlation of ^2J(C–H) with hybridization at C_1 in the fragment H–C_1–C_2 has no more than qualitative significance. Superimposed on this general trend will be the effect of changes in bond angle and bond length, changes in bond polarity when substituents are present, and hyperconjugative interactions with π-centres and non-bonding electron pairs. The hybridization of C_2 is much less important (7, 78) and other effects will also operate at this position. McLauchlan and Schaefer (68) have shown that a plot of ^1J(C–H) against ^2J(C–H) for ethane, ethylene and acetylene produces a smooth curve upon which fit the points for vinylene carbonate, vinyl bromide and 1,1,2,2-tetrabromoethane. These workers argue that both ^1J(C–H) and ^2J(C–H) reflect *s* character in the bonding orbitals and that both couplings are sensitive to inductive withdrawal or donation by substituents on C_1 whereas only ^2J(C–H) is sensitive to hyperconjugative effects. Hence deviation from the reference curve may be taken to represent the kind of hyperconjugative interactions which were proposed by Pople and Bothner-By for ^2J(H–H) (see Section II, B). Acetaldehyde and vinyl cyanide show deviations from the curve in positive and negative directions respectively and this is in agreement with the expected hyperconjugative donation in the former case and withdrawal in the latter case. Deviations were also apparent for some chloro-olefins but these could not be rationalized on the basis of PBB theory. Other workers (75, 86) have also found compounds where the points for a ^1J(C–H) against ^2J(C–H) plot fall on or very close to the reference curve of McLauchlan and Schaefer. (68) Nonetheless the number of compounds which will fit this correlation is probably very limited.

Correlations of ^2J(C–H) with substituent electronegativity (E_X) have been observed for several types of compound including substituted ethylenes, benzenes, and cyclopropanes. In nearly all cases the compounds have fixed geometry and conformational problems do not complicate the picture. When substitution occurs at C_1 then, on the basis of PBB theory, ^2J is expected to increase with increasing E_X owing to electron withdrawal from a symmetric orbital. This trend has been noted for $^2J(C_2$–H) in ethylene [15], (42, 50) cyclopropane [16] (58) and the five-membered heterocyclic ring

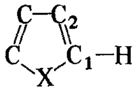
[17]. (47) Substitution at C_2 presents a more complex situation and ^2J(C–H) has been found to both increase (50, 58, 87, 88) and decrease (50, 58, 67, 88, 89) with E_X in a range of compounds. The significance of some of these correlations is obscure. Good *linear* correlations of E_X and ^2J(C–H) are claimed in only certain of the above cases, but a linear relationship may be general for a closely related group of substituents such as the halogens, particularly for substitution at C_1.



[15]



[16]



[17]

^2J(C–H) has also been correlated with both geminal and vicinal proton coupling constants. Karabatsos and co-workers (76, 91, 92) have suggested that J(C–H) = xJ(H–H) where coupling is over the same number of bonds. The value of x varies with the state of hybridization of the carbon atom. In the original work three-bond couplings were examined principally but a reasonable value of ^2J(C–H) in benzene has been calculated in this way. (44) McKinnon and Schaefer (75) have examined the relationship between ^2J(C–H) and the *cis* vicinal proton coupling in certain unsaturated compounds. A reasonable linear correlation is found but separate lines are required for olefinic and aromatic systems. Only a relatively small number of compounds were included and the generality of these correlations remains to be established. The theoretical significance of this relationship is not obvious especially when it is considered that Goldstein and co-workers (50) have found equally good linear plots of ^2J(C–H) in olefins against the *average* of the *cis* and *trans* vicinal proton coupling or even against the *inverse* of ^3J(H–H). In the case of substituted cyclopropanes (58) where a ^2J(C–H) can also be regarded as a ^3J(C–H) the best correlation was obtained with a linear combination of ^2J(H–H) and ^3J(H–H). At present these correlations have no theoretical basis but may have considerable practical value in assigning complex ^{13}C spectra.

IV. EXPERIMENTAL WORK

A. Techniques

Although ^1J(C–H) may readily be measured from the appropriate ^{13}C satellites in the proton spectrum this is not possible for ^2J(C–H) except for a few classes of compound where this coupling is large e.g., aldehydes and acetylenes. In most other cases the inner satellites corresponding to two bond coupling to ^{13}C are swamped by the main signal particularly when these satellites are not simple singlets. To some extent this problem can be overcome using ^{13}C enriched compounds (56, 74, 89, 91, 92), but this often involves laborious and costly syntheses. Certain other special techniques have been described for proton spectra, using double resonance methods (93, 94), the Indor technique, or the modulated double resonance procedure of Freeman. (95) Ziessow and Lippert (96, 97) have recently derived coupling constants from examination of the transient nutations (Torrey oscillations) of ^{13}C resonances, which occur when the proton decoupling irradiation is switched off. None of the above rather special techniques have been widely applied.

Most $^2J(C-H)$ values have been determined from undecoupled ^{13}C spectra obtained by the usual continuous wave technique where, unless enriched compounds are available (49, 98) spectrum accumulation is essential and time consuming. Pulsed Fourier transform spectrometer systems, which give a free induction decay signal, have recently become available and these are bound to prove popular since each spectrum can be obtained in, at most, a few seconds and accumulation times are much shorter than for continuous wave spectra. An additional advantage is that field and frequency stability is less critical for these systems, and clean high resolution spectra can readily be obtained. A good example of a spectrum determined in this way is given in reference 99. However, a larger computer is essential to accommodate the Fourier transform program which converts the free induction decay signal into the normal continuous wave spectrum and to provide for the larger number of data points. Farrar and Becker (100) have discussed Fourier transform spectroscopy in detail.† Gansow and Schittenhelm (101) have recently described a modified Fourier transform method which seems very promising. Broad band proton decoupling is applied using a pulsed source which gives the usual Overhauser enhancement of the intensity of the ^{13}C resonances with concomitant loss of carbon-proton coupling. However, this coupling returns immediately the decoupler is pulsed off and a normal observing pulse then gives a free induction decay signal which shows no appreciable loss of the Overhauser enhancement. Hence alternate pulsing of the proton and ^{13}C resonances gives an enhanced undecoupled spectrum using very

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† See also Volume 5A of this series.

short accumulation times. High resolution spectra obtained using this technique readily show long-range carbon-proton couplings. (101)

Sign determination for ^2J(C–H) often presents serious problems. This information cannot be obtained directly from first order carbon or proton spectra and in many cases no attempt has been made to determine the sign of measured couplings. For second order spectra the signs of the couplings usually follow from the analysis of the spectrum although a unique solution (50) cannot always be found. For simple spectra decoupling techniques (20, 93, 102, 103) can be used for sign determination but these methods have been reviewed in detail elsewhere (104, 105) and will not be discussed here.

B. Data

The available values of ^2J(C–H) exhibit a wide range of experimental precision and the picture is further confused by unrealistic estimates of the accuracy of measured couplings. Most of the very early work relied on spectra of much poorer quality than can be routinely obtained at present and furthermore it is not always clear whether due regard has been given to deviations from a first order splitting pattern. In the majority of cases the sign of ^2J(C–H) has not been determined and although in certain cases it can safely be assumed there are other cases where a clear experimental determination of the sign of ^2J is crucial for the data to have real value. A further problem is the effect of the medium on the value of a coupling constant. At the time of early work on ^2J(C–H) the importance of medium effects was not fully appreciated and hence the tendency was to use neat liquids (particularly advantageous of course for compounds containing only the natural abundance of ^{13}C). Whilst such a procedure has some validity for a group of closely related compounds, in general the variation in properties such as dielectric constant and complexing ability through a series of solutes presents just as serious a problem as does the variation in the properties of solvents. There is now clear evidence that ^2J(C–H) is sensitive to medium (see Section VI) and hence ^2J(C–H) values determined for neat liquids must be interpreted with caution. Related experimental variables, which are largely ignored, include the temperature of the solution and the concentration of the solutes. Ideally low concentrations should be used but this has only recently become a practical prospect. Suitable instrumentation is probably not yet widely available and measurements will continue to be made at high solute concentration.

It is safe to say that many of the ^2J(C–H) values recorded in

Tables V–XVIII will have to be remeasured with greater regard to standardization of experimental conditions. Research workers in this area are strongly urged to use low concentrations in non-polar solvents whenever possible and to record realistic error limits in all cases.

In order to make the data in the Tables as valuable as possible the following conventions have been adopted.

(a) The solvent is indicated in the Tables (as footnotes in some cases) for all ^2J values where the experimental details are clearly reported. In cases where experimental details are not clear or are not reported it is assumed that neat liquids were used. Many workers of course explicitly indicate neat liquids but in this context it is important to realize that neat samples often contain a substantial amount (up to 25%) of a reference compound particularly where the mode of spectrometer operation requires a strong lock signal. In these cases the reference compound has not been regarded as a solvent.

(b) Experimental errors are given in all cases where these are explicitly indicated by the original workers or can be inferred from other reported details. That is not to say that reported error limits are always realistic.

(c) Where different values have been reported for the same coupling under apparently the same conditions all values are given in the Tables since it is not always possible to assess their individual reliability. Occasionally very approximate or clearly erroneous data have been omitted.

(d) The sign is given only for those values of ^2J(C–H) for which it has been explicitly determined.

(e) Although some of the values of ^2J(C–H) are not very reliable very little published data has been omitted. The paucity of accurate data does not truly reflect the range of compounds studied and inclusion of the less accurate values provides a much better basis upon which to examine the apparent trends. The inadequacies of some of the available values of ^2J(C–H) should serve to stimulate more elaborate studies of these compounds.

V. COUPLING CONSTANTS FOR SPECIFIC BONDING SITUATIONS

It is convenient to tabulate values of ^2J(C–H) according to the hybridization at C_1 and C_2 in the fragment H–C_1–C_2. Grouping together all compounds with the same hybridization at carbon permits an easier assessment of trends in substituent effects. An interesting but so far unexplained general observation (44, 47, 72, 88, 89, 92) is that ^2J(C–H) is in nearly all cases smaller than the corresponding ^3J(C–H). The following discussion of the experimental data in the Tables is brief since there is not yet a sufficiently large body of data to warrant a detailed analysis or to permit the rationalization of the coupling constants in any particular compound as can be done (123, 125) for the much more intensively investigated geminal proton coupling, ^2J(H–H). It should be remembered that unusual values for ^2J(C–H) may be the result of a wrong assignment or an erroneous analysis.

A. Coupling in H–C(sp^3)–C(sp^3)

A particular problem for acyclic compounds (Table V) is the existence of more than one stable conformation in most cases. Even if the relative populations of the various conformers were known in all cases it would still be a formidable problem unravelling the substituent interactions and this cannot be done at present. Lack of a sign determination is a further complication for couplings with a magnitude close to zero.

Substitution at C_2 by electronegative groups has only a small effect on ^2J, the first fifteen entries in Table V showing a range of about 2 Hz around the value for ethane. Substitution at C_1 with one or two atoms of chlorine, bromine or oxygen produces a positive increment of 2·5 to 3·3 Hz as predicted by an extension of the qualitative PBB theory (see Section III), but halogen substitution at both C_1 and C_2 gives a complex pattern of results. A generally positive trend in ^2J can be seen and in the heavily substituted compounds the coupling becomes positive.

Cyclic aliphatic compounds are potentially much more interesting particularly when the structure is rigid or partly so. Very few compounds of this type have been examined (Table VI) and little useful discussion is possible. In the cyclobutene [19] both couplings involve methyl group protons and should be similar to the value for ethane. Ring strain and a 90° bond angle at C_2 may account for the low (negative) value. Exactly the opposite effect can be observed when the coupling proton is directly attached to a strained ring as in the bicyclobutane [18] where some couplings are considerably more positive than in ethane. These effects will only be better understood when much more data are available.

The unusually low value of ^2J in β-hexachlorocyclohexane cannot be rationalized on electronegativity grounds. (116) Unusual too are

TABLE V

^2J(C-H) in H-C(sp^3)-C(sp^3): acyclic compounds

Compound	^2J(Hz)	Solvent	Ref.
$H{-}CH_2{-}CH_3$	−4·5 ± 0·3	CCl_4	56
	−4·8 ± 0·1	neat[a]	57
$H{-}CH_2{-}CH_2Cl$	4·2 ± 0·5	neat	78
$H{-}CH_2{-}CHCl_2$	5·1 ± 0·5	neat	78
$H{-}CH_2{-}CCl_3$	5·9 ± 0·5	neat	78
$H{-}CH_2{-}CH_2Br$	4·0 ± 0·5	neat	78
$H{-}CH_2{-}CHBr_2$	5·0 ± 0·5	neat	106
$H{-}CH_2{-}CH_2I$	−5·0 ± 0·5	C_6H_6	107
$H{-}CH_2{-}CH_2CN$	4·28 ± 0·05	neat	49
$H{-}CH_2{-}CH(CH_3)CN$	4·2 ± 0·1	neat	49
$H{-}CH_2{-}C(CH_3)_2CN$	4·08 ± 0·01	neat	49
$H{-}CH_2{-}C(CH_3)(C_2H_5)OH$	4·1 ± 0·1	CCl_4	92
$H{-}CH_2{-}C(CH_3)(C_2H_5)Cl$	3·9 ± 0·1	neat	92
$H{-}CH_2{-}C(CH_3)_3$	3·7 ± 0·1; 6·5	neat	108, 109
$H{-}CH_2{-}CH_2NO_2$	3·7 ± 0·5	neat	78
$H{-}CH_2{-}CH(C_6H_5)OH$	4·1 ± 0·2	neat	110
$H{-}CHCl{-}CH_3$	2·6 ± 0·5	neat	78
$H{-}CCl_2{-}CH_3$	<1·2 ± 0·5	neat	78
$H{-}CHBr{-}CH_3$	2·1 ± 0·5	neat	78
$H{-}CBr_2{-}CH_3$	<1·3 ± 0·5	neat	106
$H{-}C(C_6H_5)OH{-}CH_3$	2·0 ± 0·2	neat	110
$H{-}CH(CH_3){-}CD_2OH$	4	CCl_4	92
$H{-}CH(CH_3){-}CD(C_2H_5)OH$	4·0 ± 0·1	CCl_4	92
$H{-}CH(CH_3){-}C(CH_3)_2OH$	4·0 ± 0·2	CCl_4	92
$H{-}CH(CH_3){-}C(C_2H_5)_2OH$	3·8 ± 0·2	CCl_4	92
$H{-}CH(CH_3){-}C(CH_3)_2Cl$	3·7 ± 0·1	neat	92
$H{-}CHCl{-}CH_2Cl$	<2·0 ± 0·5	CCl_4	78, 111
	−3·4	neat	16
$H{-}CHCl{-}CHCl_2$	<2·0 ± 0·5	neat	78, 111
$H{-}CHCl{-}CCl_3$	3·2 ± 0·5	neat	111
$H{-}CCl_2{-}CH_2Cl$	2·5 ± 0·5	neat	78
$H{-}CCl_2{-}CHCl_2$	1·2; 2·0 ± 0·5	neat	16; 111
$H{-}CCl_2{-}CCl_3$	1·5 ± 0·5	neat	111
$H{-}CHCl{-}CH_2Br$	4·3 ± 0·5	neat	78
$H{-}CHBr{-}CH_2Cl$	4·3 ± 0·5	neat	78
$H{-}CHBr{-}CH_2Br$	−4·2; 4·6 ± 0·5	neat	16; 78
	3·93 ± 0·04[b]	CS_2/C_6H_{12}[c]	112
	4·22 ± 0·1[d]	CS_2/C_6H_{12}[c]	112
$H{-}CHBr{-}CHBr_2$	4·0	neat	106
$H{-}CHBr{-}CBr_3$	<1·5	CCl_4	106
$H{-}CBr_2{-}CH_2Br$	1·2	neat	106
$H{-}CBr_2{-}CHBr_2$	+1·1; 1·0	neat	93; 106
$H{-}CBr_2{-}CBr_3$	2·7	neat	106
$H{-}CHI{-}CH_2I$	−4·7	$CDCl_3$	113

[a] At −70°.

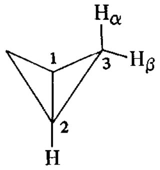
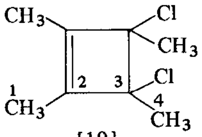
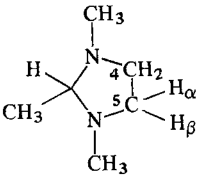
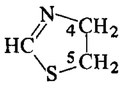
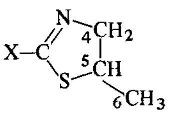
[b] From proton spectrum.

[c] 1:1 Carbon disulphide/cyclohexane.

[d] From ^{13}C spectrum.

TABLE VI

^2J(C—H) in H—C(sp^3)—C(sp^3): cyclic compounds

Compound	^2J(Hz)	Solvent	Ref.
 [18]	$J(C_1{-}H_2)$ 3·3 ± 0·2 $J(C_2{-}H_\alpha)$[a] 0·0 $J(C_2{-}H_\beta)$[a] 3·3 ± 0·2 $J(C_3{-}H_2)$ 5·3 ± 0·2	$CDCl_3$	114
 [19]	$J(C_2{-}H_1)$ 6·0 $J(C_3{-}H_4)$ 6·0	CCl_4	115
β-hexachlorocyclohexane[b]	−5·72 ± 0·04	neat	116
	$J(C_4{-}H_\alpha)$ −4·5 ± 0·4 $J(C_4{-}H_\beta)$ −4·9 ± 0·4	neat	117
 [20]	$J(C_4{-}H_5)$ 17·6	neat	118
 [21]	X = H $J(C_4{-}H_5)$ 16 $J(C_6{-}H_5)$ 9 X = C_2H_5 $J(C_4{-}H_5)$ 15 $J(C_6{-}H_5)$ 9	neat	118

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[a] These assignments may be reversed.

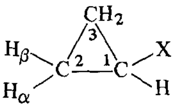
[b] All protons are equatorial in this compound.

the very large unsigned ^2J values in [20] and [21]. These values are reminiscent of the large positive couplings in *cis* disubstituted olefins (see Tables XI and XII) but there is a possibility that these couplings are wrongly assigned and are actually three bond couplings.

Nominally at least cyclopropane has sp^3 hybridized carbon atoms but the value (58) of $-2{\cdot}55$ Hz for ^2J (Table VII) suggests a rather higher *s* character in the bonding orbitals. Some positive increment in ^2J may come from the changes in bond angle (relative to tetrahedral carbon) (cf. Section II, A). Substitution at C_1 gives the expected positive trend in ^2J with increasing electron withdrawal, but substitution at C_2 involves a more complex interaction, with ^2J showing a positive trend with E_X when X is *trans* to the coupling proton and a negative trend when X is *cis*. These trends are similar to those observed for olefins (see below) and indicate the involvement of some factor dependent on geometry. One difficulty with cyclopropane is that each long-range coupling has available both a two-bond and a three-bond pathway and Goldstein and co-workers (58) have found excellent correlations of ^2J(C–H) with a linear combination of geminal and vicinal proton couplings.

TABLE VII

^2J(C–H) in H–C(sp^3)–C(sp^3): cyclopropanes[a]



Substituent	$^2J(C_1-H_\alpha)$	$^2J(C_1-H_\beta)$	$^2J(C_3-H_\alpha)$	$^2J(C_3-H_\beta)$	$^2J(C_2-H_1)$
H	−2·55				
I	−2·3	−5·5	−2·75	−2·85	−1·1
Br	−1·55	−5·35	−2·9	−2·85	−0·75
Cl	−1·15	−5·05	−3·05	−2·75	−0·55
NH_2	−1·0	−4·0	−2·9	−2·7	+0·65
COCl	−2·2	−3·2	−2·35	−2·5	−1·25

[a] All substituted cyclopropanes were examined as neat liquids and the parent compound as a 15% solution in CS_2. All ^2J values are in Hz and the error in all cases is ± 0·1 Hz. (58)

B. Coupling in H–C(sp^3)–C(sp^2)

For most compounds in this category (Table VIII) the sp^2 hybridized carbon lies in a carbonyl group and the variation in ^2J is

TABLE VIII

^2J(C–H) in H–C(sp^3)–C(sp^2)

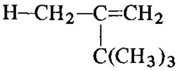
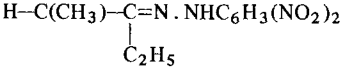
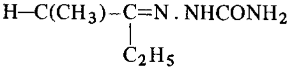
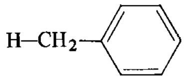
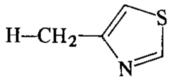
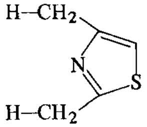
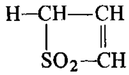
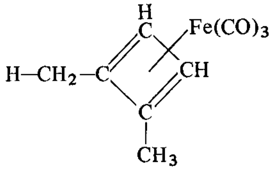
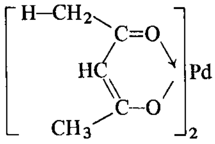
Compound	^2J(Hz)	Solvent	Ref.
$\mathrm{H{-}CH_2{-}CHO}$	−6·6 ± 0·2	neat	16, 78, 98, 119, 120
$\mathrm{H{-}CCl_2{-}CHO}$	0·0	neat	16
$\mathrm{H{-}CH_2{-}CO\,.\,CH_3}$	5·85 ± 0·2; 5·9 ± 0·1	neat	78, 79, 95, 119; 98
$\mathrm{H{-}CH_2{-}CO\,.\,C_6H_5}$	5·7; 6·2 ± 0·1	neat	120; 110
$\mathrm{H{-}CH(CH_3){-}CO\,.\,C_2H_5}$	5·7 ± 0·1	neat	92
$\mathrm{H{-}C(CH_3)_2{-}CO\,.\,CH(CH_3)_2}$	4·1 ± 0·1	neat	91
$\mathrm{H{-}CH_2{-}COCl}$	7·3 ± 0·5; 7·45 ± 0·05; 7·58	neat	78; 98; 79
$\mathrm{H{-}CHCl{-}COCl}$	7·7 ± 0·5	neat	78
$\mathrm{H{-}CH_2{-}COBr}$	7·5 ± 0·1; 7·6 ± 0·5	neat	98; 78, 79
$\mathrm{H{-}CH_2{-}COI}$	7·3; 7·5 ± 0·1	neat	79; 98
$\mathrm{H{-}CH_2{-}CONH_2}$	6·01	neat	79
$\mathrm{H{-}CH_2{-}CON(CH_3)_2}$	5·95 ± 0·03	neat	98
$\mathrm{H{-}CH_2{-}COOH}$	6·7 ± 0·04; 6·75 ± 0·2	neat neat	96, 98; 78, 79, 95, 119
$\mathrm{H{-}CH(CH_3){-}COOH}$	6·4 ± 0·2	$\mathrm{CCl_4}$	92
$\mathrm{H{-}C(CH_3)_2{-}COOH}$	5·2 ± 0·1	neat	91
$\mathrm{H{-}CHCl{-}COOH}$	−4·2 ± 0·3	neat	96
$\mathrm{H{-}CCl_2{-}COOH}$	−2·1 ± 0·3	neat	96
$\mathrm{H{-}CH_2{-}COONa}$	5·82 ± 0·03; 5·9	$\mathrm{H_2O}$	98; 120
$\mathrm{H{-}CH_2{-}COOCH_3}$	6·9	neat	120
$\mathrm{H{-}CH(CH_3){-}COOCH_3}$	6·5 ± 0·3	neat	92
$\mathrm{H{-}CH_2{-}COCH{=}CH_2}$	7 ± 1	neat	121
$\mathrm{H{-}CH_2{-}COOC_2H_5}$	6·0 ± 0·1; 6·79 ± 0·03	$\mathrm{CCl_4}$; neat	92; 98
$\mathrm{H{-}C(CH_3)_2{-}COOC_2H_5}$	5·6 ± 0·1	neat	91
$\mathrm{H{-}CH_2{-}COOC_6H_5}$	7·0	neat	79
$\mathrm{H{-}CH_2{-}COOC_6H_4NO_2\text{-}(}p\mathrm{)}$	7·16	neat	79
$\mathrm{H{-}CH_2{-}COOC_6H_4OCH_3\text{-}(}p\mathrm{)}$	7·0	neat	79
$\mathrm{H{-}CH_2{-}COOCOCH_3}$	7·4 ± 0·5	neat	78
$\mathrm{H{-}CH_2{-}CH{=}CCl_2}$	−7·2	neat	16
$\mathrm{H{-}CHBr{-}CH{=}CH_2}$	−6·0	neat	102
 $\mathrm{H{-}CH_2{-}\underset{\large C(CH_3)_3}{\underset{\mid}{C}}{=}CH_2}$	6·4	neat	79
 $\mathrm{H{-}C(CH_3){-}\underset{\large C_2H_5}{\underset{\mid}{C}}{=}N\,.\,NHC_6H_3(NO_2)_2}$	6·5 ± 0·3	$\mathrm{C_6H_5NO_2}$	92
 $\mathrm{H{-}C(CH_3){-}\underset{\large C_2H_5}{\underset{\mid}{C}}{=}N\,.\,NHCONH_2}$	4·0 ± 0·2	$\mathrm{CHCl_3}$	92

TABLE VIII—*cont.*

Compound	^2J(Hz)	Solvent	Ref.
	6·0 ± 0·1	neat	110, 120
	7·3	neat	123
	6·1 7·9	neat	123
	6·0	neat	99
	4·8 ± 0·3[a]	CCl_4	122
	5·6	$CDCl_3$	74

[a] Same value of ^2J was found for corresponding trimethyl- and tetramethyl- cyclobutadiene iron tricarbonyl compounds. (122)

small. All values are probably negative although this has been experimentally confirmed in only a few cases. Chloro- and dichloroacetic acid and dichloroacetaldehyde are examples of compounds with electronegative substituents at C_1 and all show the usual substantial positive change in ^2J. No trends are apparent in the data for compounds substituted at C_2.

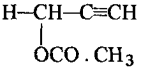
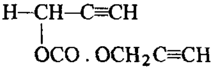
Those compounds where the sp^2 hybridized carbon is olefinic or aromatic constitute a rather heterogeneous collection and more work is required in this area.

C. Coupling in H–C(sp^3)–C(sp)

This interesting class of compounds (Table IX) includes only derivatives of methylacetylene and methyl cyanide and, with one exception, exhibits only a small range of ^2J. However, absence of conformational variation in these compounds allows greater significance to be attached to small changes in ^2J. Comparing an acetylene with a nitrile i.e., changing the C_2 substituent from $\equiv$CH to $\equiv$N, a small positive increment (~0·6 Hz) is found reflecting some electron withdrawal by nitrogen. Other substituent variation at C_2 in the acetylene series (in which the substituent is necessarily one atom removed from C_2) produces negligible change except for the two conjugated diacetylenes where a negative increment of 0·8 Hz is observed. Possibly this indicates a slight increase in the hyperconjugative withdrawal which is already present in methyl acetylene and which may account in part for the large negative change (6·1 Hz) in ^2J(C–H) relative to ethane.

TABLE IX

^2J(C—H) in H—C(sp^3)—C(sp)

Compound	^2J(Hz)	Solvent	Ref.
$H{-}CH_2{-}C{\equiv}CH$	−10·6 ± 0·1	neat	55, 124
$H{-}CHCl{-}C{\equiv}CH$	8·2 ± 0·2	neat	119
$H{-}CHBr{-}C{\equiv}CH$	7·9 ± 0·2	neat	119
 $H{-}\underset{\underset{\displaystyle OCO.CH_3}{\vert}}{CH}{-}C{\equiv}CH$	7·8 ± 0·2	neat	108
 $H{-}\underset{\underset{\displaystyle OCO.OCH_2C{\equiv}CH}{\vert}}{CH}{-}C{\equiv}CH$	7·8 ± 0·2	neat	108
$H{-}CH_2{-}C{\equiv}CC_6H_5$	−10·5 ± 0·1	neat	96, 110
$H{-}CH_2{-}C{\equiv}COC_6H_5$	10·8 ± 0·5	neat	77
$H{-}CH_2{-}C{\equiv}CSeC_6H_5$	10·4 ± 0·5	neat	77
$H{-}CH_2{-}C{\equiv}C{-}C{\equiv}CSC_2H_5$	11·4 ± 0·5	neat	77
$H{-}CH_2{-}C{\equiv}C{-}C{\equiv}CSC_6H_5$	11·4 ± 0·5	neat	77
$H{-}CH_2{-}C{\equiv}N$	9·87 ± 0·04	neat	49
	9·9 ± 0·2; 10·1 ± 0·1		119; 120
$H{-}CF_2{-}C{\equiv}N$	72	neat	125
$H{-}CH(CH_3){-}C{\equiv}N$	9·83 ± 0·05	neat	49
$H{-}C(CH_3)_2{-}C{\equiv}N$	9·16 ± 0·05	neat	49

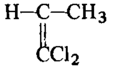
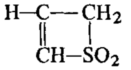
Electron withdrawal by substituents (Cl, Br and O) at C_1 is indicated by a positive change in ^2J but the results do *not* parallel the substituent electronegativity. The remarkably large value for ^2J in difluoroacetonitrile is completely unexplainable by current theories. Such an unusual value clearly requires confirmation and further study of similar compounds may prove interesting.

D. Coupling in H-C(sp^2)-C(sp^3)

This type of coupling is almost entirely restricted to compounds where the sp^2 hybridized carbon lies in a carbonyl group i.e., the coupling involves an aldehydic proton. Only two examples of olefinic compounds are available. A value of +3·2 Hz for ^2J in dichloropropene is interesting since this is considerably more positive (by ~5·6 Hz) than the value for ethylene where, of course, both carbon atoms are sp^2 hybridized. Some positive contribution may come from the two electron withdrawing chlorine atoms although these substituents are one bond removed. Equally interesting is the large (presumably positive) value in thiete sulphone. In this compound there is a combination of ring strain and direct substituent inter-

TABLE X

^2J(C–H) in H–C(sp^2)–C(sp^3)

Compound	^2J(Hz)	Solvent	Ref.
$H{-}CO{-}CH_3$	+26·7 ± 0·1	neat	16, 51, 119
$H{-}CO{-}CH_2 . CH_3$	+25·2 ± 0·1	neat	51
$H{-}CO{-}CH_2 . C_2H_5$	24·8 ± 0·1	neat	51, 67
$H{-}CO{-}CH_2 . CH_2C_6H_5$	24·7 ± 0·1	neat	51
$H{-}CO{-}CH(CH_3)_2$	23·6 ± 0·1	neat	51
$H{-}CO{-}CH(C_2H_5)_2$	22·1 ± 0·1	neat	51
$H{-}CO{-}CH_2Cl$	32·5 ± 0·1	neat	51
$H{-}CO{-}CHCl_2$	+35·2 ± 0·1; +35·8 ± 0·2	neat	51; 16
$H{-}CO{-}CCl_3$	+46·3 ± 0·1	neat	51, 126
$H{-}CO{-}CBr_3$	51·6 ± 0·1	neat	51
$H{-}CO{-}CHCl . C_2H_5$	26·5 ± 0·2	neat	67
$H{-}CO{-}CHBr . C_2H_5$	27·6 ± 0·2	neat	67
$H{-}CO{-}CHI . C_2H_5$	28·9 ± 0·2	neat	67
 $H{-}\underset{\underset{CCl_2}{\|}}{C}{-}CH_3$	+3·2	neat	16
 $\begin{array}{l} H{-}C{-}CH_2 \\ \;\;\|\;\;\;\; \vert \\ \;CH{-}SO_2 \end{array}$	14·2	neat	99

action at C_2 both of which may provide a positive contribution to ^2J. A value for cyclobutene itself would be very interesting.

Delocalization of oxygen non-bonded electrons, which is responsible for the characteristically large value of ^2J in aldehydes, has been discussed in Section II. An understanding of substituent interactions at C_2 is complicated by the existence of at least two stable conformations (141, 142) for these compounds. Generally alkyl groups produce a negative change in ^2J consistent with electron donation and halogen atoms give rise to a positive change indicating electron withdrawal. Successive substitution by chlorine or bromine gives successive positive increments but the trend in ^2J does not parallel the substituent electronegativity. A rationalization of this inverse trend has been offered (67) in terms of an additional hyperconjugative interaction (see Section III).

E. Coupling in H–C(sp^2)–C(sp^2)

Compounds with both carbon atoms sp^2 hybridized form the largest group in our classification and a convenient subdivision has been adopted.

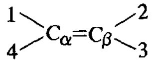
1. *Coupling in the olefinic fragment* H–C_1=C_2

Fairly extensive studies have been made of ^2J in simple olefins (Table XI) including some cyclic compounds (Table XII) where the double bond is essentially localized. A wide range of positive and negative values is found with some variation in reported data for certain compounds. A normal increase in ^2J occurs with increasing electronegativity (E_X) of substituent at C_1, X ranging from $Si(C_2H_3)_3$ through H to OC_2H_3 with a corresponding range of 16·75 Hz in ^2J(C–H) [$J(C_\beta - H_4)$ for the formula in Table XI]. This trend is in agreement with the qualitative extension of PBB theory discussed in Section III. For monosubstitution at C_2 two different trends are found depending upon the position of the substituent X. With X *trans* to the coupling proton, $J(C_\alpha - H_3)$ shows a positive trend with E_X, although the range in ^2J is smaller (10·1 Hz) than for $J(C_\beta - H_4)$, and when X is *cis* to the coupling proton $J(C_\alpha - H_2)$ shows a negative trend with E_X. A qualitative rationalization of these two trends has been given by Jameson and Damasco (7) on the basis of approximate MO calculations (see Section II, B). Some contribution to ^2J(C–H) from dipolar or orbital terms has been suggested for halogenocyclopropanes. (58)

Di and tri- substituted olefins show an approximate additivity of individual substituent effects on ^2J(C–H) and for chloro- and bromo-

TABLE XI

^{2}J(C—H) in H—C(sp^2)—C(sp^2): substituted olefins



Substituents	$^{2}J(C_\alpha$—$H_2)^a$	$^{2}J(C_\alpha$—$H_3)^a$	$^{2}J(C_\beta$—$H_4)^a$	Solvent	Ref.
None	−2·4 ± 0·2			CCl_4; neat^b	56; 57
1-$Si(C_2H_3)_3$			−7·0	neat	50
1-$SiCl_3$	−0·8	−2·5	−6·85	neat	50
1-CH_2Br	2·9 ± 0·2	1·0 ± 0·3		neat	102
1-CN	−4·42 ± 0·01	+0·29 ± 0·01	−3·67 ± 0·01	neat	94
1-COOH	−4·55	+1·55	−0·6	neat	50
1-$COOCH_3$			−0·6	neat	50
1-$COCH_3$			−0·35	neat	50
1-CHO	−3·4	+1·8	+0·25	neat	50
1-I	−7·8	+4·15	+4·0	neat	50
1-Br^c	−8·2	+6·75	+6·25	neat	50
	−8·5 ± 0·5	+7·5 ± 0·5	+5·8 ± 0·2	neat	103
1-Cl^c	−7·9	+7·5	+6·9	$(CH_3)_2CO$	50
	−8·3	+7·1	+6·8	neat	69
1-$OCOCH_3$	−7·9	+7·6	+9·65	neat	50
1-OC_2H_3			+9·75	neat	50
1,2-di-Cl		+15·4; 15·7 ± 0·3		neat	69; 127
		+16·0; +16·5 ± 0·5		neat	128; 78, 111
1,2-di-Br		+14·7; 15·0 ± 0·5		neat	69; 106
1,2-di-I		+11·0 ± 0·1		C_6H_{12}	129
1,2-di-COOH		+3·36		$(CH_3)_2CO$	50
1,2-di-$COOC_2H_5$		1·5 ± 0·3; +3·07		neat	127; 50

TABLE XI—*cont.*

Substituents	$^2J(C_\alpha{-}H_2)^a$	$^2J(C_\alpha{-}H_3)^a$	$^2J(C_\beta{-}H_4)^a$	Solvent	Ref.
1,3-di-Cl[d]	0; <0·3; +0·8 <2; <1·8 ± 0·5			neat neat	127; 69; 128 78; 111
1,3-di-Br	<−0·4; <2·0 ± 0·5			neat	69; 106
1,3-di-I	−1·4 ± 0·5			C_6H_{12}	129
1,3-di-$COOC_2H_5$	−2·77; 4·4 ± 0·3			neat	50; 127
1,4-di-Cl	<0·6; −0·9 ± 0·3 <1·3 ± 0·5			neat neat	69; 96 111
1,4-di-Br	1·3 ± 0·5			neat	106
1-C_6H_5, 3-$COOC_2H_5$			−3·3 ± 0·1	neat	110
1-C_6H_5, 4-Cl	+5·6	−6·3		neat	66
1,2,3-tri-Cl			8·4 ± 0·2; 8·46 ± 0·04 8·5 ± 0·5; 8·9	neat neat	119; 96 78, 111; 69
1,2,3-tri-Br			7·8; 8·0	neat	69; 106
1,2-di-Cl, 3-F[d]			5·1 ± 0·2	C_6H_6	86
1,3-di-Cl, 2-F[d]			11·0 ± 0·2	C_6H_6	86

[a] In Hz.

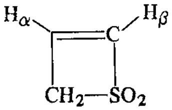
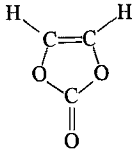
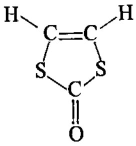
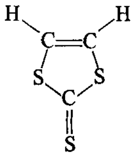
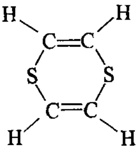
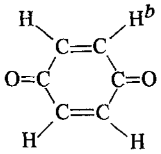
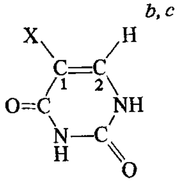
[b] At −70°.

[c] Values have been reported for these compounds, calculated on a first order basis. (106, 111) These are quite different from the values in the Table and are acknowledgely wrong. (106)

[d] For solvent studies on this coupling constant see Section VI.

TABLE XII

^2J(C–H) in H–C(sp^2)–C(sp^2): cyclic olefins[a]

Compound	^2J(Hz)	Solvent	Ref.
	J(C–H$_\alpha$)[b] 7·2 J(C–H$_\beta$) 2·0	neat	99
	17·40; +17·5 ± 0·12	neat	97; 68
	+3·97 ± 0·02	CS_2	75
	+4·66 ± 0·02	CS_2	75
	+8·15	neat	130
	−2·4; −2·5 ± 0·3	neat	131; 132
	X=H <1 CH_3 <1 F 4·2 ± 0·1 Cl 2·3 ± 0·1 Br 1·8 ± 0·1 I <1	DMSO	87

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[a] Compounds in which the double bond is not delocalized.

[b] Coupling is through the double bond.

[c] Couplings given in the Table are ^2J(C$_1$–H); for X = H, ^2J(C$_2$–H) = 4·1 ± 0·1 Hz.

ethylenes ^2J values predicted on a simple additivity rule agree reasonably well with experimental values. (66, 69) Positive ^2J values for the cyclic compounds (Table XII) are characteristic of *cis* disubstitution and the negative value for benzoquinone is anomalous. Correlations of ^2J(C–H) in olefins with ^2J(H–H) and ^3J(H–H) are discussed in Section III.

2. *Coupling through an aromatic double bond*

In the present context the concept of an aromatic double bond has been interpreted as any bond in a cyclic delocalized ring system. Studies of ^2J(C–H) over a delocalized benzenoid double bond have been largely restricted to benzene and halogenobenzenes (Table XIII). Some approximate values [^2J(C–H) $\approx$ 1 Hz] have been reported for naphthalene. (143) From the data for the monohalogenobenzenes substituent parameters may be derived (149) for each of the halogen atoms. With these parameters, and assuming additivity of substituent effects in dihalogenobenzenes, excellent agreement has been found (149) between experimental and calculated coupling constants over one, two, three and four bonds. The ^2J values are particularly good in this respect showing deviations barely greater than the experimental uncertainty. In those compounds where the single substituent is attached directly to the end carbon of the coupling fragment the ^2J(C–H) values show a slight negative trend (149) with E_X, similar to that observed in olefins. However, in the case of more distant substituent effects more complex variations occur and positive, negative and negligible trends with E_X are found depending upon the distance from the substituent(s) of both the proton and the carbon involved in the coupling constant. (88, 89, 149)

Table XIV lists some compounds containing a pseudo-aromatic ring, in all cases complexed to a transition metal. These couplings are all probably positive although no experimental sign determination has been made. Since benzene has a ^2J(C–H) value of +1·1 Hz all compounds in Table XIV show a positive increment which probably arises from a combination of a decreased bond angle and electron withdrawal by the metal atom. (133)

A number of simple heterocyclic compounds have been studied (Table XV) but only for thiophen can substituent effects on ^2J be examined. Even in this case coupling to the substituted carbon atom has not been measured and the more distant substituent effects show no obvious trends. A problem here is the availability of two different pathways by which, for instance, a 2-substituent in thiophen can

TABLE XIII

^2J(C–H) in H–C(sp^2)–C(sp^2): substituted benzenes[a]

Substituent	$^2J(C_1–H_2)$ (Hz)	$^2J(C_1–H_6)$ (Hz)	Solvent	Ref.
None	+1·0	+1·0	neat	44
	+1·11 ± 0·1	+1·11 ± 0·1	$(CH_3)_2CO$	149
	+1·13 ± 0·03	+1·13 ± 0·03	CCl_4	45
1-COCl	7·2 ± 0·1[b]	7·2 ± 0·1[b]	neat	110
1-Cl	−3·39 ± 0·1	−3·39 ± 0·1	$(CH_3)_2CO$	149
2-Cl		+1·41 ± 0·1	$(CH_3)_2CO$	149
3-Cl	+0·29 ± 0·1	+1·55 ± 0·1	$(CH_3)_2CO$	149
4-Cl	+0·87 ± 0·1	+0·87 ± 0·1	$(CH_3)_2CO$	149
1-Br	−3·34 ± 0·1	−3·34 ± 0·1	$(CH_3)_2CO$	149
2-Br		+1·44 ± 0·1	$(CH_3)_2CO$	149
3-Br	+0·44 ± 0·1	+1·60 ± 0·1	$(CH_3)_2CO$	149
4-Br	+0·86 ± 0·1	+0·86 ± 0·1	$(CH_3)_2CO$	149
1-I	−2·41 ± 0·1	−2·41 ± 0·1	$(CH_3)_2CO$	149
2-I		+1·55 ± 0·1	$(CH_3)_2CO$	149
3-I	+0·74 ± 0·1	+1·44 ± 0·1	$(CH_3)_2CO$	149
4-I	+0·82 ± 0·1	+0·82 ± 0·1	$(CH_3)_2CO$	149
1,2-di-Cl		−3·53 ± 0·1	$(CH_3)_2CO$	89
1,3-di-Cl	−4·25 ± 0·1	−3·18 ± 0·1	$(CH_3)_2CO$	88
2,3-di-Cl		+1·89 ± 0·1	$(CH_3)_2CO$	89
2,4-di-Cl		+1·32 ± 0·1	$(CH_3)_2CO$	88
3,4-di-Cl	−0·02	+1·11 ± 0·1	$(CH_3)_2CO$	89
3,5-di-Cl	+0·67 ± 0·1	+0·67 ± 0·1	$(CH_3)_2CO$	88
1,2-di-Br		−3·24 ± 0·1	$(CH_3)_2CO$	89
1,3-di-Br	−3·91 ± 0·1	−2·94 ± 0·1	$(CH_3)_2CO$	88
2,3-di-Br		+2·05 ± 0·1	$(CH_3)_2CO$	89
2,4-di-Br		+1·36 ± 0·1	$(CH_3)_2CO$	88
3,4-di-Br	+0·30 ± 0·1	+1·10 ± 0·1	$(CH_3)_2CO$	89
3,5-di-Br	+0·78 ± 0·1	+0·78 ± 0·1	$(CH_3)_2CO$	88
1,2-di-I		−1·80 ± 0·1	$(CH_3)_2CO$	89
1,3-di-I	−2·94 ± 0·1	−2·14 ± 0·1	$(CH_3)_2CO$	88
2,3-di-I		+1·98 ± 0·1	$(CH_3)_2CO$	89
2,4-di-I		+0·99 ± 0·1	$(CH_3)_2CO$	88
3,4-di-I	+0·50 ± 0·1	+1·23 ± 0·1	$(CH_3)_2CO$	89
3,5-di-I	+0·95 ± 0·1	+0·95 ± 0·1	$(CH_3)_2CO$	88
2,3,4,5-tetra-Cl		+0·4	neat	128

[a] ^{13}C atom taken to be position 1.

[b] This value is probably a three-bond coupling.

affect $^2J(C_4–H_5)$ or $^2J(C_5–H_4)$. If the heteroatom is regarded as a substituent at C_1 in the $H–C_1–C_2$ fragment then the ^2J values [$J(C_4–H_5)$ in Table XV] show a positive change through the series Se, S, N, O. (47) This positive trend with heteroatom electronegativity parallels the trend found in simple olefins and falls in line

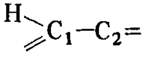
TABLE XIV

^2J(C–H) in H–C(sp^2)–C(sp^2): pseudo-aromatic compounds

Compound	^2J(Hz)	Solvent	Ref.
Ferrocene	6·30 ± 0·03	CS_2	133
Cobaltocene chloride	6·26 ± 0·03	H_2O	133
Ruthenocene	6·30 ± 0·03	$CHCl_3$	133
CBD-Fe(CO)$_3$[a]	4·2 ± 0·3	CCl_4	122
1-Phenyl-CBD-Fe(CO)$_3$[a]	3·7, 4·7	CCl_4	134
1,2-Diphenyl-CBD-Fe(CO)$_3$[a]	4·2 ± 0·3	CCl_4	135
1,2-Dimethyl-CBD-Fe(CO)$_3$[a]	4·2 ± 0·3	CCl_4	122
1,2,3-Trimethyl-CBD-Fe(CO)$_3$[a]	4·2 ± 0·3	CCl_4	122
1-Acetyl-CBD-Fe(CO)$_3$[a]	4·0, 4·9	$CDCl_3$	136

[a] CBD = cyclobutadiene. In these complexes this ring is pseudo-aromatic and many of the couplings are equivalent – see original papers for assignments.

with the general predictions of PBB theory discussed in Section II, A. No trend can be seen in $^2J(C_5-H_4)$ where the heteroatom is now regarded as a C_2 substituent, but when two heteroatoms are present, as C_1 and C_2 substituents, their effects are additive to some extent. Of the two values reported for $^2J(C_4-H_5)$ in 1,3-thiazole the larger (15·2 Hz) seems anomalous and is probably the result of a wrong assignment.

3. *Coupling in the fragment*  $H{>}C_1-C_2=$

The coupling pathway in this case is through a nominally single bond between two conjugated double bonds, one of which is always carbonyl in all of the compounds studied up to the present. Table XVI gives the couplings for compounds where C_1 is a carbonyl carbon i.e., the coupling involves an aldehydic hydrogen atom and has the characteristically large value associated with the delocalization of non-bonding electrons on oxygen through C_1. Substitution of an alkyl group at the C_2 position of the unsaturated aldehydes produces a small negative change in ^2J(C–H) consistent with inductive donation. A halogen substituent at C_2 increases ^2J(C–H) by ~15 Hz, a surprisingly large increment which may reflect both inductive and hyperconjugative contributions. (67) For the aromatic and heterocyclic aldehydes substituents cannot operate directly at C_2 and not surprisingly have only small effects on ^2J(C–H). No detailed rationalization of these small variations is available but the generally smaller value of ^2J(C–H) for *ortho*-substituted aldehydes

TABLE XV

^2J(C–H) in H–C(sp^2)–C(sp^2): heterocyclic compounds[a]

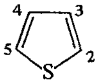
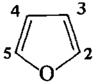
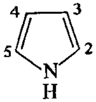
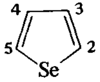
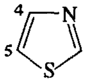
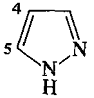
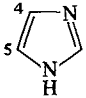
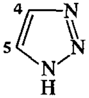
Compound	Substituent	$^2J(C_3–H_4)$	$^2J(C_4–H_3)$	$^2J(C_4–H_5)$	$^2J(C_5–H_4)$	Solvent	Ref.
	None	5·9	5·9	4·7	7·4	neat	47
	$2-CH_3$	5·8	5·6	3·8	9·8	neat	47
	2-Br	5·6	4·2	3·4	5·6	neat	128
		6·1 ± 0·3	4·0 ± 0·3	4·0 ± 0·3	6·6 ± 0·3	neat	72
	2-I	6·1 ± 0·3	3·8 ± 0·3	3·8 ± 0·3	6·9 ± 0·3	neat	72
	$2-COOCH_3$	5·0 ± 0·3	4·5 ± 0·3	4·5 ± 0·3	7·5 ± 0·3	neat	72
	2-CHO	5·0 ± 0·3	4·5 ± 0·3	4·5 ± 0·3	7·5 ± 0·3	neat	72
	$2-OCH_3$	5·9 ± 0·3	3·1 ± 0·3	3·1 ± 0·3	5·6 ± 0·3	neat	72
	$3-CH_3$			5·5	8·95, 7·5	neat	47, 72
	3-Br			5·7 ± 0·3	5·8 ± 0·3	neat	72
	3-I			5·0 ± 0·3	6·6 ± 0·3	neat	72
	3-COOMe			4·7 ± 0·3	6·7 ± 0·3	neat	72
	3-CHO			4·5 ± 0·3	6·3 ± 0·3	neat	72
	$3-OCH_3$			4·6 ± 0·3	5·9 ± 0·3	neat	72
	None	4·0	4·0	14·0	7·0	neat	47
	2-Me[b]	4·0	4·2	13·1	7·2	neat	47
	None	4·6	4·6	7·8	7·6	neat	47
	$2,5-di-CH_3$	4·6	4·6		7·3	neat	47
	None	6·0	6·0	4·5	7·0	neat	47

TABLE XV—*cont.*

Compound	Substituent	$^2J(C_3\text{—}H_4)$	$^2J(C_4\text{—}H_3)$	$^2J(C_4\text{—}H_5)$	$^2J(C_5\text{—}H_4)$	Solvent	Ref.
	None			15·2	15·8	neat	123
				7·2 ± 0·2	16·4 ± 0·2	CS_2[c]	48
	2,4-di CH_3			2·1		neat	123
	2-NH_2			6·1 ± 0·1	14·26 ± 0·1	CD_3OD	48
	None	6·5	9·5	9·5	6·5	neat	47
	3-Me	6·7		9·65	7·5	neat	47
	None			13·0	13·0	neat	47
	None			13·4	13·4	neat	47

[a] In some cases these ^2J values are the average value for several couplings and in many cases the assignments are uncertain. All values are in Hz.

[b] $J(C_2\text{—}H_3) = 6·8$ Hz.

[c] At −30°.

TABLE XVI

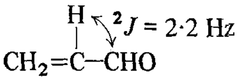
^2J(C–H) in H–C(sp^2)–C(sp^2): aromatic, heterocyclic and unsaturated aldehydes

Compound	^2J(Hz)	Solvent	Ref.
C_6H_5.CHO	24·1 ± 0·1	neat	16, 51, 126
2-CH_3.C_6H_4.CHO	23·4 ± 0·1	neat	51
2-Cl.C_6H_4.CHO	23·6 ± 0·1	neat	16, 51
2-CH_3O.C_6H_4.CHO	22·5 ± 0·1	neat	51
2-OH.C_6H_4.CHO	19·8 ± 0·15; 20·0 ± 0·1	neat	16, 126; 51
	20·7 ± 0·15	$(C_2H_5)_3N$	16
2-NO_2.C_6H_4.CHO	25·4 ± 0·1	neat[a]	51
2-CHO.C_6H_4.CHO	25·2 ± 0·1	neat[a]	51
3-CH_3.C_6H_4.CHO	24·2 ± 0·1	neat	51
3-Cl.C_6H_4.CHO	25·0 ± 0·1	neat	51
3-Br.C_6H_4.CHO	25·1 ± 0·1	neat	51
3-NO_2.C_6H_4.CHO	25·7 ± 0·1	neat[a]	51
4-Br.C_6H_4.CHO	24·8 ± 0·1	neat[a]	51
4-CH_3O.C_6H_4.CHO	23·8 ± 0·2; 24·1 ± 0·1	neat	16, 119; 51
4-$(CH_3)_2N$.C_6H_4.CHO	23·3 ± 0·1	neat	16
	22·9 ± 0·1	CF_3COOH	16
2-OH, 3-CH_3O.C_6H_3.CHO	19·8 ± 0·1	neat[a]	51
2,3-$(CH_3O)_2$.C_6H_3.CHO	23·2 ± 0·1	neat[a]	51
2,4-$(CH_3O)_2$.C_6H_3.CHO	22·3 ± 0·1	neat[a]	51
3,4-$(CH_3O)_2$.C_6H_3.CHO	24·4 ± 0·1	neat[a]	51
3,4-OCH_2O–C_6H_3.CHO	25·0 ± 0·1	neat[a]	51
naphthyl-1-CHO	24·1 ± 0·1	neat	51
pyridyl-2-CHO	22·7 ± 0·1	neat	51
pyridyl-3-CHO	24·3 ± 0·1; 24·8 ± 0·1	neat	51; 16
pyridyl-4-CHO	25·2 ± 0·1; 25·4 ± 0·1	neat	16; 51
furanyl-2-CHO	32·1 ± 0·2	neat	16
CH_2=CH–CHO	26·6; 26·9 ± 0·1	neat	50; 51
CH_2=C(CH_3)–CHO	25·2 ± 0·1	neat	51
trans-CH_3.CH=CH–CHO	+25·4 ± 0·1	neat	51
trans-C_6H_5.CH=CH–CHO	26·1 ± 0·1	neat	51
trans-CH_3.CH=CCl–CHO	40·4 ± 0·1	neat	51
C_3H_7.CH=C(C_2H_5)–CHO[b]	23·6 ± 0·1	neat	51

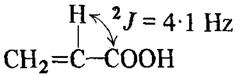
[a] At +80°.
[b] Unknown geometry.

has been ascribed (51) to a steric effect with an additional hydrogen bonding interaction for the hydroxyl group.

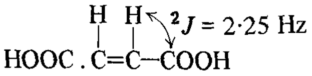
There is a second possible type of coupling across a single bond between carbonyl and olefinic double bonds in which C_2 is the carbonyl carbon i.e., the fragment $=\overset{\overset{\displaystyle H}{|}}{C}-C=O$. The few examples of this coupling are in acrolein [22], acrylic acid [23], maleic acid [24] and diethylmaleate [25], for which the couplings were determined on neat liquids. (50) Two further examples of this coupling are in compound [26] (in DMSO) (87) and the palladium complex [27]


$CH_2{=}\overset{H}{C}{-}CHO$

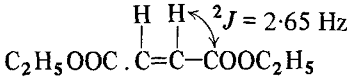
[22]


$CH_2{=}\overset{H}{C}{-}COOH$

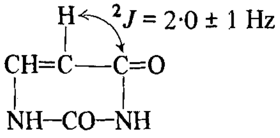
[23]


$HOOC.\overset{H}{C}{=}\overset{H}{C}{-}COOH$

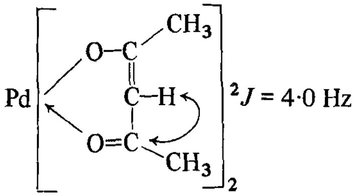
[24]


$C_2H_5OOC.\overset{H}{C}{=}\overset{H}{C}{-}COOC_2H_5$

[25]



[26]

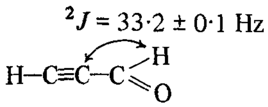


[27]

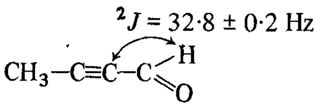
(in $CDCl_3$). (74) These six values show that electron delocalization from carbonyl is not important when operating through C_2.

F. Coupling in H-C(sp^2)-C(sp)

Only two examples of this type of coupling have been reported; propargyl aldehyde [28] (51) and the corresponding methyl derivative [29]. (16) Both couplings are for the neat liquids.



[28]



[29]

The influence of the *sp* hybridization at C_2 can be seen in the increase (~8 Hz) in ^2J(C-H) for this system over the corresponding system with sp^2 hybridization at C_2.

G. Coupling in H-C(sp)-C(sp)

This, the last type of coupling pathway, is by definition restricted to mono-substituted acetylenes and gives a characteristically large positive coupling (Table XVII). This coupling also has the largest

TABLE XVII

^2J(C—H) in H—C(*sp*)–C(*sp*): substituted acetylenes

X—C≡C—H

Substituent	^2J(Hz)	Solvent	Ref.
None	+49·3 ± 0·3	CCl_4	56
	+49·7 ± 0·2	neat[a]	57
CH_3	+50·8 ± 0·1	neat	108, 124
$ClCH_2$	50·0 ± 0·2	neat	119, 137
$BrCH_2$	50·0; 50·5 ± 0·2	neat	137; 119
HOOC	50·2 ± 0·2	neat	119
CH_3OCH_2	49·0	neat	137
$CH_3.COOCH_2$	50·0 ± 0·2	neat	108
$C_3H_3OCO.OCH_2$	49·9 ± 0·2	neat	108
$(CH_3)_3CC{\equiv}C$	52	neat	137
C_6H_5	49·6 ± 0·2; 49·8 ± 0·5	neat	119; 77
	49·9; 50	neat	110; 137
CHO	47·9 ± 0·1	neat	51
$(CH_3)_3Si$	42·0 ± 0·5	neat	77
$(C_6H_5)_3Si$	42·5 ± 0·5	neat	77
$(C_2H_5)_3Ge$	42·5 ± 0·5	neat	77
$(C_6H_5)_3Sn$	41·0 ± 0·5	CCl_4	77
$(C_6H_5)_2N$	55·5 ± 0·5	CCl_4	77
$C_6H_5.NCH_3$	55·6 ± 0·5	neat	77
$(C_6H_5)_2P$	45·8 ± 0·5	neat	77
$(n\text{-}C_3H_7)_2P$	45	neat	137
$(s\text{-}C_4H_9)_2P$	46	neat	137
$HC{\equiv}CP(s\text{-}C_4H_9)$	45	neat	137
$(HC{\equiv}C)_2P$	48	neat	137
$(i\text{-}C_3H_7)_2P{=}S$	46	CCl_4	137
C_6H_5O	61·0 ± 0·5	neat	77
C_6H_5S	51·6 ± 0·5	neat	77
I	51·6 ± 0·5	neat	138
Br	56·0 ± 0·5	neat	138
Cl	60·5 ± 0·5[b]	neat	138
F	65·5 ± 0·5[b]	neat	138

[a] At −70°.
[b] At −90°.

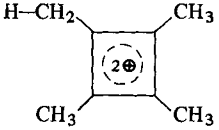
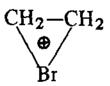
range, from 41·0 to 65·5 Hz. Substitution can only occur at C_2 but there is scarcely any validity in applying PBB theory to this type of coupling since it has no analogy in geminal proton coupling. However, a clear positive trend is apparent with increasing substituent electronegativity and moreover a linear correlation of ^2J(C–H) with ^1J(C–H) has been noted (77, 138) for these compounds.

H. Coupling in Carbonium Ions

Table XVIII gives ^{2}J(C–H) values for various carbonium ions which are gathered together not only because of the common factor of a positive charge but also because in some cases the state of hybridization of C_2 is ambiguous–when an oxygen atom is present the species may exist as an oxonium ion. No signed values of ^{2}J are available but all values are probably negative.

TABLE XVIII

^{2}J(C—H) in carbonium ions[a]

Species	^{2}J(Hz)	Solvent system	Ref.
$H\text{—}CH_2\text{—}\overset{\oplus}{C}HCH_3$	3·3 ± 0·2	$FSO_3Cl\text{—}SbF_5$	90
$H\text{—}CH_2\text{—}\overset{\oplus}{C}(CH_3)_2$	3·6 ± 0·2	$FSO_3Cl\text{—}SbF_5$	90
$H\text{—}CH_2\text{—}\overset{\oplus}{C}HOH$	6·1 ± 0·2	$FSO_3Cl\text{—}SbF_5$	90
$H\text{—}CH_2\text{—}\overset{\oplus}{C}(OH)_2$	6·5 ± 0·2	$FSO_3H\text{—}SbF_5$	90, 139
$H\text{—}CH(CH_3)\text{—}\overset{\oplus}{C}(OH)_2$	6·2	$FSO_3H\text{—}SbF_5$	139
$H\text{—}CH_2\text{—}\overset{\oplus}{C}(CH_3)OH$	7·0 ± 0·2	$FSO_3H\text{—}SbF_5\text{—}SO_2$	90, 140
$H\text{—}CH_2\text{—}\overset{\oplus}{C}{=}O$	9·3 ± 0·2	$FSO_3H\text{—}SbF_5$	90, 139
	8·96 ± 0·04	Oleum	49
$H\text{—}CH(CH_3)\text{—}\overset{\oplus}{C}{=}O$	9·3 ± 0·2	$FSO_3H\text{—}SbF_5$	90, 139
$H\text{—}CH_2\text{—}\overset{\oplus}{C}{=}NH$	9·8	$FSO_3H\text{—}SbF_5$	90
	6·0	$FSO_3H\text{—}SO_2$	115
	0·0	$FSO_2Cl\text{—}SbF_5$	90

[a] These ionic species have been studied at low temperatures in "super acid" solution. In some cases the species may be an oxonium ion.

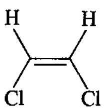
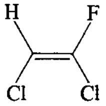
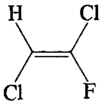
VI. SOLVENT EFFECTS ON ^{2}J(C-H)

There is extensive evidence (144, 145) that in principle all coupling constants have an intrinsic solvent dependence. Most work has dealt with ^1J(C–H) and ^2J(H–H) and it is clear that the phenomenon of a solvent effect is a complex one. Reaction field (146-148) and dispersion effects (109, 146) certainly contribute to the perturbation of bonding electrons and hence to J but other more specific effects (147) may operate particularly for halogen substituents. (146)

Only two studies of the variation of ^2J(C–H) with solvent have appeared although several other instances of variation can be noted in the Tables. Three compounds have been investigated, *cis*-dichloroethylene, and *cis*- and *trans*- dichlorofluoroethylene; the ^2J(C–H) values are given in Table XIX. For the first two compounds ^2J(C–H) increases with increasing solvent dielectric constant indicating a reaction field effect. This will operate for these two compounds (86) so as to increase the polarity of the C–H bond and hence to increase the *s* character of the carbon bonding orbital producing a con-

TABLE XIX

Solvent effect on ^2J(C—H) in some olefins

Compound	^2J(Hz)[a]	Solvent	Ref.
 [b]	16·0	Neat	128
	14·6	Acetonitrile	
	14·6	Carbontetrachloride	
	14·0	Dioxan	
	13·3	Cyclohexane	
 [c]	7·5	Acetonitrile	86
	5·6	Acetone	
	6·0	Chloroform	
	5·1	Isopropyl ether	
	5·3	Carbon disulphide	
	5·1	Benzene	
 [c]	11·7	Dimethylformamide	86
	11·1	Acetonitrile	
	11·1	Acetone	
	11·1	Chloroform	
	11·1	Isopropyl ether	
	11·0	Carbon disulphide	
	11·0	Benzene	

[a] All values are positive.
[b] 50% v/v solutions.
[c] 33% v/v solutions. Error is ± 0·2 Hz.

comitant increase in ^2J. It is not clear why the variation in ^2J for *trans*-dichlorofluoroethylene is so small since this compound will be more polar than the corresponding *cis* isomer. Obviously a simple rationalization of these trends is not possible and other simpler model compounds should be studied. Solvent effects may prove a very useful method of establishing the sign of a ^2J(C–H) coupling.

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SUBJECT INDEX

Asterisks indicate the pages on which the topic is discussed in detail.