CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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IN 1957 the first reports[1a,2] of successful determinations of nuclear magnetic resonance of ^{13}C nuclei in natural abundance appeared and since then, although relatively few investigators have pursued n.m.r. studies of this nucleus, sufficient work has been done to indicate several features which offer new approaches to problems of chemical interest. It is the purpose of this Review to examine the present state of knowledge in this field, to draw attention to some of the major problems, and to indicate potential areas in which the technique should provide rewarding information. The Review is not intended to provide an introduction to n.m.r. spectroscopy in general, since several excellent sources are available.[3] The results which can be obtained directly from carbon spectra are our prime consideration. Consequently we are concerned, for the most part, with the chemical shift which has been called "the most important single parameter to be derived from the n.m.r. spectrum".[3a] Two earlier reviews of this field have appeared.[1b,4]

1. Introduction

Many of the chemical applications of n.m.r. spectroscopy have become routine and several reviews of these have been published, although most are concerned primarily, if not entirely, with the spectra of ^{1}H and ^{19}F nuclei.[3,5] It is therefore appropriate to compare the techniques of ^{13}C spectroscopy and the data therefrom with those of the more familiar cases. Compared with protons, the major differences for ^{13}C are its low natural abundance (1·1%) and smaller magnetic moment. These factors make direct measurements by n.m.r. difficult since at constant field, the signal strength for ^{13}C is $1{\cdot}76 \times 10^{-4}$ relative to unity for ^{1}H. Nevertheless

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[1] (*a*) P. C. Lauterbur, *J. Chem. Phys.*, 1957, **26**, 217; (*b*) *Ann. New York Acad. Sci.*, 1958, **70**, 841.

[2] C. H. Holm, *J. Chem. Phys.*, 1957, **26**, 707.

[3] (*a*) J. A. Pople, W. G. Schnieder, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, 1959; (*b*) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon, New York, 1959; (*c*) H. S. Gutowsky, "Nuclear Magnetic Resonance" in Technique of Organic Chemistry, vol. I, Part IV, 3rd edn., Interscience, New York, 1960; (*d*) W. D. Phillips, "High Resolution H^1 and F^{19} Magnetic Resonance Spectra of Organic Molecules", Ch. 6 in "Determination of Organic Structures By Physical Methods", ed. F. C. Nachod and W. D. Phillips, Academic Press, New York, 1962; (*e*) C. P. Slichter, "Principles of Magnetic Resonance", Harper and Row, New York, 1963.

[4] P. C. Lauterbur, "Nuclear Magnetic Resonance Spectra of Elements Other Than Hydrogen and Fluorine", Ch. 7 in "Determination of Organic Structures by Physical Methods", ed. F. C. Nachod and W. D. Phillips, Academic Press, New York, 1962.

[5] J. B. Stothers, "Applications of n.m.r. Spectroscopy", Ch. IV in "Elucidation of Structures by Physical and Chemical Methods", ed. K. W. Bentley, vol. XI, Technique of Organic Chemistry, Interscience, New York, 1963.

this is within the capabilities of present spectrometers and future developments will no doubt improve the situation. Because of the low sensitivity and long relaxation times, T_1, relatively large samples are required to obtain maximum signal:noise (S/N) ratios and, thus, the attainable field homogeneity is less than that obtained with ^{1}H and ^{19}F. On the favourable side, there are features which tend to compensate for some of the difficulties. Since its nuclear spin, I, is $\frac{1}{2}$, the ^{13}C nucleus has no nuclear quadrupole moment and sharp signals are expected if spin-couplings with other nuclei are resolved, While this is indeed the case for spectra of ^{13}C-enriched compounds, in general, only direct, one-bond interactions (*e.g.*, C–H, C–F, etc.) are resolved in natural abundance spectra. These coupling constants are in the range 120—350 c./sec. The observed bands are broadened by longer range interactions which are usually <10 c./sec. There are no complications due to ^{13}C–^{13}C interactions since the probability of molecules having two adjacent ^{13}C nuclei is very small ($\sim 10^{-4}$). The total variation in ^{13}C chemical shifts (including ionic compounds) is known to be at least 450 p.p.m. (*ca.* 7 kc./sec. at 15·1 Mc./sec.), and spectra consisting of easily identifiable multiplets are obtained. The spectrum of butenone (Fig. 1) provides an example having each of the common multiplets.

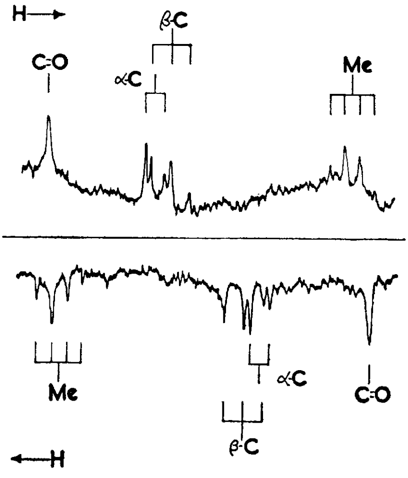

Fig. 1. 15·085 *Mc./sec.* ^{13}C *spectra of butenone*, $CH_2{=}CH{\cdot}COCH_3$.

2. Experimental techniques

(a) **Determination of Spectra.**—Up to the present, rapid-passage dispersion mode conditions using liquid samples have been employed for most studies of natural abundance ^{13}C n.m.r. spectra. In general, conventional high resolution absorption mode operation leads to saturation of the absorbing nuclei because of the high radiofrequency power required for detection of weak signals. Typical results and the basic features of the dispersion mode technique have been discussed[4] and Fig. 1 illustrates these. In particular, it is important to note that the multiplets tend to be skewed and it is essential that measurements be made in *both* sweep directions and averaged to obtain the true peak positions and relative intensities. The skewing of the multiplets is attributed to "magnetisation transfer" during the period of the scan.[4,6] As an example of this effect, consider the four bands assigned to the methyl carbon in Fig. 1. The first transitions recorded in each scan are more intense than the others. When the two traces are combined, it can be seen that the total intensity for each transition very closely approaches the expected 1:3:3:1 binomial ratio. The fact that skewed multiplets are often produced can be helpful for spectral analysis.

For practical purposes, an approximate limit can be placed on the sensitivity of rapid passage, dispersion mode operation at 15·1 Mc./sec. In 15 mm. diameter cells, a carbon nucleus giving rise to a narrow singlet can be detected at a concentration of *ca.* 1 gram-atom per litre, for which case a signal intensity having a S/N ratio of *ca.* 3 can be expected. In general, therefore, molar solutions are required to detect the presence of a specific carbon nucleus. If the nucleus is strongly spin-coupled to other nuclei, more concentrated solutions are of course necessary. As a specific example of the lower limit for detection, the absorption of a fully substituted nucleus, such as a ketonic carbonyl carbon, in a molecule of molecular weight 250 can be measured by use of a 250 mg. sample. These figures are approximate, however, and will vary with the particular spectrometer employed and the breadth of a particular signal, but the values may be used to estimate the applicability of the technique for specific cases. Certain modifications of the usual method directed at improving the S/N ratio have been developed. One interesting, albeit limited, means of overcoming difficulties associated with saturation due to inefficient relaxation of the absorbing nuclei was reported by Forsén and Rupprecht.[7] They employed a flow method whereby the liquid sample contained in a large reservoir in the magnetic field was continuously pumped through the resonance coil. A signal enhancement of *ca.* three-fold relative to that obtained for a stationary sample was realised. While specific applications of this approach may be envisaged its practical limitations are too restrictive for general use. Shoolery[8] demonstrated that better resolution can be observed in the absorption mode using spinning samples and a specially constructed receiver insert, but the sensitivity is not enhanced.

Much more generally useful improvements have arisen from recent developments in double resonance techniques whereby more than one nucleus is excited simultaneously through the use of two (or more) radiofrequencies. If an observed nucleus is spin-coupled to a second nucleus

[6] H. M. McConnell and D. D. Thompson, *J. Chem. Phys.*, 1957, **26**, 958; 1959, **31**, 85; A. Patterson and R. Ettinger, *Z. Elektrochem.*, 1960, **64**, 98.

[7] S. Forsén and A. Rupprecht, *J. Chem. Phys.*, 1960, **33**, 1888.

[8] J. N. Shoolery, 3rd Conf. Exptl. n.m.r., Pittsburgh, March, 1962.

which is irradiated simultaneously, the spectrum is perturbed, the effects of the perturbation depending on the relative power level for the second radiofrequency. In 1955, Bloom and Shoolery[9] described the effects of such perturbing radiofrequency fields in some simple systems and the subject has been reviewed recently.[10] Lauterbur demonstrated the potential of the method for ^{13}C spectroscopy several years ago,[4] employing a field sweep technique whereby the ^{13}C spectrum is observed in the normal way while protons spin-coupled to the carbons are irradiated at their resonance frequencies. If the power level for proton irradiation is sufficiently large the ^{13}C–^{1}H interactions are effectively eliminated and the multiplets collapse to form singlets. An additional benefit in these "spin-decoupling" experiments is the occurrence of a positive nuclear Overhauser effect[10] which tends to increase the intensity of the observed singlets over that expected for simple collapse of the multiplet. Very often the enhancement is more than two-fold for normal dispersion mode operation representing a substantial aid for the study of natural abundance spectra. For maximum effect, the perturbing radiofrequency field must be at the resonance frequency of the second nucleus but partial collapse of the original multiplet results if it is close thereto. To illustrate a typical result for a simple system, the ^{13}C spectra of pyridine obtained at three different settings of the proton radiofrequency field are given in Fig. 2(*b*—*d*). Enhancement due to an Overhauser effect is clearly apparent. In practice, complete decoupling cannot be achieved merely by using a sufficiently large radiofrequency field and a residual coupling effect may be observed.[11] This can be largely eliminated, however, by frequency modulation of the second radiofrequency field.[12]

An elegant application of the double resonance method for observing weak spectra has been developed by Baker,[13] employing two frequency synthesisers in combination with a proton-stabilised, frequency-sweep spectrometer. In effect, one source supplying low radiofrequency power is held on the peak of a sharp absorption line of nucleus A while the second source, at higher radiofrequency power output, is used to sweep the frequency through the spectrum of nucleus X. If A and X are spin-coupled, the intensity of the A transition will change as the resonance frequencies of X are traversed. If the power level in the X spectrum is suitably adjusted, these intensity changes of the A line will duplicate the actual X spectrum. The method, termed i.n.d.o.r. (internuclear double resonance) spectroscopy, is without doubt an important advance but, unfortunately, the cost of the instrumentation required will hinder its general application.

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[9] A. L. Bloom and J. N. Shoolery, *Phys. Rev.*, 1955, **97**, 1261.

[10] J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.*, 1963, **63**, 81.

[11] W. A. Anderson and R. Freeman, *J. Chem. Phys.*, 1962, **37**, 85.

[12] W. A. Anderson and F. A. Nelson, *J. Chem. Phys.*, 1963, **39**, 183.

[13] E. B. Baker, *J. Chem. Phys.*, 1962, **37**, 911; R. Freeman and W. A. Anderson, *ibid.*, 1963, **39**, 806.

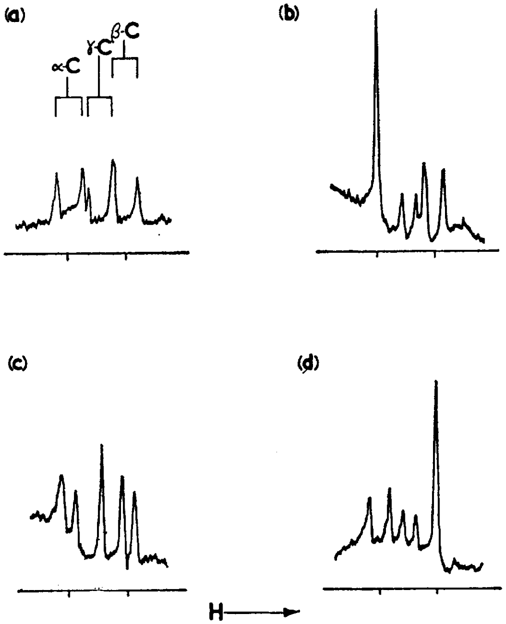

FIG. 2. 15·085 *Mc./sec.* ^{13}C *spectra of pyridine showing effects of simultaneous irradiation at* 60 *Mc./sec.* (*a*) *Normal spectrum,* (*b*) *with α-protons decoupled,* (*c*) *with γ-proton decoupled, and* (*d*) *with β-protons decoupled.*

A more easily realised approach for *both* improved resolution and sensitivity is that described by Paul and Grant,[14,15] utilising absorption-mode operation and proton spin-decoupling with or without sample spinning. An additional benefit of much more accurate chemical shift data can be realised, if the two irradiating frequencies are measured accurately (1 in 10^6) at the instant of maximum decoupling. At present, their technique appears to offer the best approach for n.m.r. study of ^{13}C in natural abundance.

It should be emphasised that conventional high resolution absorption mode conditions are entirely adequate for the study of ^{13}C-enriched compounds and several examples have been published (*e.g.*, see refs. 16, 17).

(b) Calibration.—Audio side-band modulation is the usual means of calibration for a ^{13}C spectrum, with the exception of the newer methods mentioned above. For internal referencing, a strong signal (often a solvent band) may be chosen and the positions of the remaining bands measured relative to it by interpolation. Otherwise, an external reference, preferably

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[14] E. G. Paul and D. M. Grant, 14th Conf. Anal. Chem. Appl. Spec., Pittsburgh, March, 1963.

[15] E. G. Paul and D. M. Grant, *J. Amer. Chem. Soc.*, 1964, **86**, 2977.

[16] K. Frei and H. J. Bernstein, *J. Chem. Phys.*, 1963, **38**, 1216.

[17] D. M. Graham and C. E. Holloway, *Canad. J. Chem.*, 1963, **41**, 2114.

enriched in ^{13}C, can be employed. In the latter case, bulk susceptibility corrections are required for the most precise work unless specially constructed cells are used.[18] If the sample and external reference are contained in concentric spherical cavities, centred in the detector coil, bulk susceptibility differences are eliminated. More commonly, ^{13}C spectra have been obtained using test-tubes (15 mm. diameter) containing several cm. height of liquid to approximate the infinite-length criterion for cylindrical samples[3a] and bulk susceptibility corrections are often neglected because of their small effects on the relatively large chemical shift difference for ^{13}C nuclei. In general the precision of measurement of the line positions is *ca.* 5 c./sec. at 15·1 Mc./sec. and the accuracy of the chemical shift data is of the order 0·3—0·5 p.p.m. for dispersion-mode operation. As noted earlier a marked improvement can be realised by using the optimum conditions described by Paul and Grant[15] for which the shift error is ±0·07 p.p.m. at 15·1 Mc./sec. with the resolution approaching 1·5 c./sec.

The problem of choosing a suitable reference compound has been discussed[4] and it appears that carbon disulphide offers the best compromise for this purpose. Since ^{13}C-enriched CS_2 is not readily available, however, extensive use has been made of secondary reference compounds containing excess of ^{13}C, *e.g.*, methyl iodide, sodium acetate, dimethyl carbonate, and sodium carbonate. The observed data are subsequently converted to a more common scale having either C_6H_6 or CS_2 as an arbitrary zero point. The latter is employed throughout this Review.

(c) **Spectral Analysis.**—As mentioned earlier, first-order patterns generally arise in these spectra and their multiplicities and relative intensities (averaging both sweep directions) provide the primary evidence for the analysis. The first problem is to distinguish the transitions which belong to each of the various multiplets. Spin-decoupling experiments are a valuable aid for this sorting process, particularly for cases in which there are several overlapping multiplets. In the ideal case, one can transform a complex spectrum into a series of singlets, one band for each chemically shifted carbon nucleus, and so reduce the problem to a measurement of these peak positions, *i.e.*, the relative chemical shifts.

The second stage in the analysis is the assignment of a particular band to a specific carbon nucleus. Again, the observed multiplicities and intensities are helpful, combined with a knowledge of chemical shifts for suitable model compounds. The problem of band assignment is simplified considerably by the fact that the effects of substituents on chemical shifts are very often additive. Unequivocal assignments can be made by a comparison of the ^{13}C spectrum of a compound containing deuterium at a specific position with that of the unlabelled material. The effect of substitution of ^{1}H by ^{2}H ($I = 1$) is a greatly increased spin–lattice relaxation time, T_1, for the substituted carbon nucleus with the result that, under the usual experimental conditions, these nuclei are so easily saturated that their signals

[18] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, 1961, **35**, 722.

are not ordinarily observed. Spiesecke and Schneider[19] have demonstrated the utility of this approach and have given some typical spectra.

3. Survey of Results

In the main, the available data have been obtained for relatively simple molecules (<16 carbon atoms), but several examinations of homologous series and series of closely related compounds have revealed certain general trends exhibited by the ^{13}C chemical shifts and ^{13}C–X coupling constants. Sufficient progress has been made to allow an assessment of the principal factors contributing to the shielding of ^{13}C nuclei and to permit one to suggest possible applications. To illustrate the general behaviour of ^{13}C nuclei in various organic molecules some specific results are outlined in this section, after which a discussion of the findings and applications of these is presented. For the common functional groups, ^{13}C nuclei absorb over the range −25 to +200 p.p.m. (relative to CS_2), as illustrated in Fig. 3.

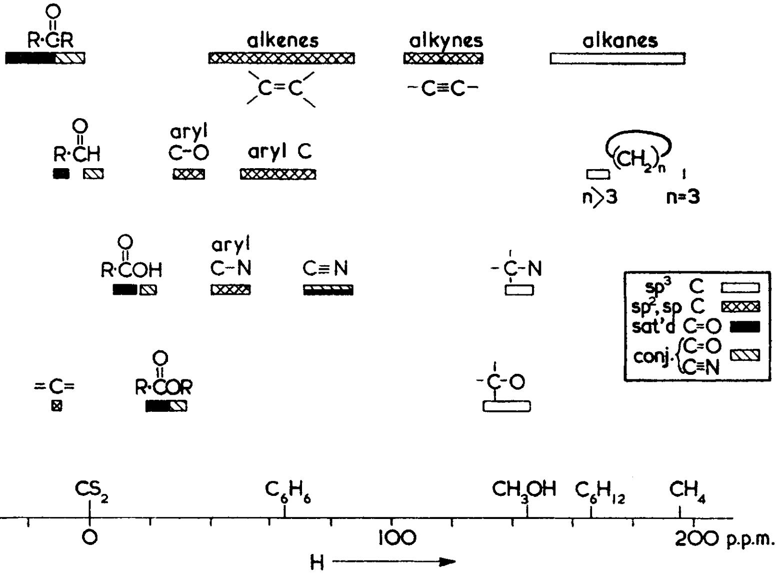

FIG. 3. *Range of ^{13}C chemical shifts for common organic carbon nuclei.*

(a) Chemical Shift Results.—(i) *Aromatic hydrocarbons.* One of the first surveys of a specific family of compounds was that carried out by Lauterbur[20] at 8·5 Mc./sec. for the series: benzene, methylbenzenes, biphenyl, naphthalene, phenanthrene, pyrene, acenaphthylene, fluoran-

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[19] H. Spiesecke and W. G. Schnieder, *J. Chem. Phys.*, 1961, **35**, 731.
[20] P. C. Lauterbur, *J. Amer. Chem. Soc.*, 1961, **83**, 1838.

thene, and azulene. For the alternant hydrocarbons, the carbon shieldings for the nuclei bonded to two other carbons only differ very slightly ($\leqslant 1$ p.p.m.) from that of benzene, 65·0 p.p.m., while the carbon nuclei at ring junctions absorb at appreciably lower field (55—61 p.p.m.). For the non-alternant hydrocarbons, the aromatic nuclei absorb over a much wider range (52—74 p.p.m.) and, even though definitive assignments were not possible, the two types of hydrocarbon exhibit clear differences. Since, theoretically, the significant distinction between the alternant and non-alternant hydrocarbons is that for the former the π-electron density, q_C, at each carbon is very close to unity while for the latter large differences may result at various positions, it follows that ^{13}C shifts in aromatic systems may be governed by the π-electron distribution. For azulene, a more complete assignment of the signals to specific nuclei was accomplished by comparing spectra of some substituted (CH_3 and ^2H) derivatives. From this analysis, the ^{13}C shielding of a specific carbon A, σ_A, was shown to correlate approximately with the π-electron density, q_A. The "best fit" was given by the results of a v.e.s.c.f. treatment. This result led to an expression for the chemical shift (relative to benzene) $\Delta\sigma_A$ of the form,

$$\Delta\sigma_A = \alpha(q_A - 1) \qquad (1)$$

where α is a positive constant of *ca.* 200 p.p.m. Lauterbur[21] obtained another estimate, $\alpha \approx 160$ p.p.m., indirectly from a comparison of the data for several aromatic derivatives (see p. 162). Shortly afterwards, Spiesecke and Schneider[22] published results bearing on this relation and the azulene problem. They measured the ^{13}C shifts for $C_5H_5^-$, C_6H_6, $C_7H_7^+$, and $C_8H_8^{2-}$, for which the π-electron densities are taken as known and obtained the value $\alpha \approx 160$ p.p.m. It is clear, therefore, that aromatic carbon shieldings are strongly dependent on local π-electron densities.

The results for the methyl-substituted benzene series indicated two general features of aromatic ^{13}C shieldings. The more distinctive of these is a pronounced deshielding of *ca.* 9 p.p.m. at an aromatic carbon upon replacement of hydrogen by methyl. The origin of this change is as yet unexplained but it cannot be attributed entirely, or even substantially, to a neighbour-anisotropy effect although this has been suggested. It is particularly interesting that this deshielding influence is approximately constant for a large variety of aromatic derivatives and only for cases in which there is substantial steric interference with the methyl group are marked changes in its magnitude found. The second feature which was recognised, although the differences are small, was that the indirect effects of a methyl group on the other aryl carbons are additive with successive methyl substitution on the ring provided the methyl groups are in *meta* or *para* orientations.

(ii) *Olefinic hydrocarbons.* Although the early ^{13}C results showed that

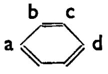
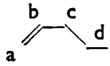
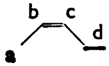
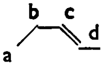
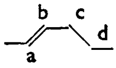
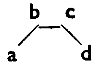
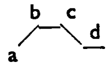
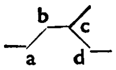
[21] P. C. Lauterbur, *Tetrahedron Letters*, 1961, No. 8, 274.

[22] H. Spiesecke and W. G. Schneider, *Tetrahedron Letters*, 1961, No. 14, 468.

olefinic carbon nuclei absorb in the same region as aromatic carbon,[2] a systematic study of olefins has only recently been reported.[23] Friedel and Retcofsky determined the ^{13}C spectra of several pentenes, hexenes, and heptenes as well as some dienes. Their results demonstrated additional general features of ^{13}C shieldings. From the data for twenty-two mono-olefins which exhibit absorption over the range 40—87 p.p.m. it was apparent that the effects of methyl substitution on or close to the olefinic carbons are approximately additive. Replacement of an olefinic hydrogen tends to deshield the substituted carbon and to shield its doubly-bonded neighbour. These changes were invariably found although their magnitude depends on the location of the double bond in the carbon skeleton. Examples are given in Table 1, together with those for an aromatic system, benzene → toluene,[19] and certain aliphatic systems discussed below.

Friedel and Retcofsky's results have been analysed recently in another way,[24] to show that for simple hydrocarbons the ^{13}C chemical shift

TABLE 1. *Effect of methyl substitution on ^{13}C shieldings in various hydrocarbon skeletons (in p.p.m. relative to parent compound)*

Parent Cpd	Shift due to CH_3 substitution at $C_{(a)}$				
	at $C_{(a)}$	$C_{(b)}$	$C_{(c)}$	$C_{(d)}$	Ref.
	$-9{\cdot}1$	$-0{\cdot}3$	$-0{\cdot}3$	$+2{\cdot}8$	19
	$-10 \pm 0{\cdot}5$*	$+7{\cdot}6 \pm 1{\cdot}2$*	—	—	
	$-6{\cdot}6 \pm 1{\cdot}4$*	$+1{\cdot}1 \pm 1{\cdot}0$*	—	—	
	—	—	$+1{\cdot}6$	$+0{\cdot}2$	23
	$-7{\cdot}2$	$+4{\cdot}4$	—	—	
	$-9{\cdot}35$	$-9{\cdot}51$	$+2{\cdot}45$	$-0{\cdot}51$	
	$-9{\cdot}19$	$-9{\cdot}47$	$+2{\cdot}49$	$-0{\cdot}35$	27
	$-9{\cdot}88$	$-9{\cdot}98$	$+2{\cdot}10$	$-0{\cdot}50$	

* Figures represent ranges observed for several examples.

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[23] R. A. Friedel and H. L. Retcofsky, *J. Amer. Chem. Soc.*, 1963, **85**, 1300.
[24] G. B. Savitsky and K. Namikawa, *J. Phys. Chem.*, 1964, **68**, 1956.

may be a constitutive property largely dependent on the immediate chemical environment of a specific nucleus. From the data for olefins, including values for some cycloalkenes and simple alkanes,[18] a set of ten empirical bond parameters was determined from which 70 reported shifts for sp^3 and sp^2 carbons were calculated to within 2 p.p.m.

In contrast to other spectroscopic methods, ^{13}C shieldings are not sensitive to double-bond conjugation in simple dienes. The carbon shifts for buta-1,3-diene are close to those found for the olefinic carbons in pent-1-ene, hex-1-ene, and styrene,[25] with the larger deviation exhibited by the terminal carbons (*ca.* $-3{\cdot}5$ p.p.m.), a difference which is absent from a comparison with penta-1,4-diene and hexa-1,5-diene. A most interesting observation was made for the allenic dienes, for which the central carbon [*e.g.*, $C_{(2)}$ in buta-1,2-diene] absorbs at $\sim$50 p.p.m. to lower field than any other unsaturated nucleus in the hydrocarbon series, in the range $-16{\cdot}7$ to $-13{\cdot}4$ p.p.m. An explanation for this remarkable shift has been offered (see p. 161).

(iii) *Acetylenic hydrocarbons.* A few alkynes have been examined[4,16,23] and the shifts for the *sp*-hybridised carbon atoms were found in the range 104—129 p.p.m. This region is virtually free from other ^{13}C signals and thus acetylenes are readily identifiable.

(iv) *Aliphatic and alicyclic hydrocarbons.* Until very recently, the reported ^{13}C spectra of alkanes[19] included only those for CH_4, C_2H_6, C_3H_8, $CH(CH_3)_3$, and $C(CH_3)_4$ since the chemical-shift differences for saturated carbon nuclei are relatively small in the higher homologues and the signals are not resolved sufficiently by the usual procedures. Using their improved method[15] described earlier, Paul and Grant carefully measured the ^{13}C shieldings for the linear alkanes up to C_{10} and showed[26] the existence of additive substituent effects such that the observed chemical shifts were described by a linear relation.[26] From the results of these spectra and those of the branched hydrocarbons up to C_6, these authors suggested a slightly modified linear expression of the form

$$\delta_C(k) = 131{\cdot}26 + \sum_l A_l n_{kl} \qquad (2)$$

to account for the n-alkane results.[27] In equation (2), the shift of the kth carbon (relative to C_6H_6) is given by the sum of the products of the number of carbons in the lth position (*i.e.*, α, β, γ, δ, or ϵ relative to C_k) and a factor, A, which is an additive parameter for that position, plus a constant 131·26, which is very close to the shift difference between C_6H_6 and CH_4, 130·8 p.p.m. To apply equation 2, five variables were evaluated; the standard deviation of the fit for 30 observed n-alkane shifts was 0·21 p.p.m. For the branched compounds, eqn. (2) does not give satisfactory

[25] K. S. Dhami and J. B. Stothers, *Canad. J. Chem.*, 1965, **43**, 510.
[26] E. G. Paul and D. M. Grant, *J. Amer. Chem. Soc.*, 1963, **85**, 1701.
[27] D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, 1964, **86**, 2984.

results unless eight additional variables are used. To account for the effects of neighbouring groups on the carbon shieldings, an analysis of the neighbour-anisotropy effects of the C–C bonds was attempted using the simple point-dipole model.[28] While it is interesting that a linear relation of the form expected was obtained, the required value for the anisotropy of the magnetic susceptibility of a C–C single bond, $\Delta\chi_{C-C}$, was 416×10^{-6} cm.^{3}/mole, a figure which is *ca.* 10^2 larger than all previous estimates.[29] The last entries in Table 1 illustrate the effect of methyl substitution at the various carbon nuclei in a hydrocarbon chain for comparison with the unsaturated systems.

The cycloalkanes, C_3 to C_{17}, have been examined by ^{13}C n.m.r. spectroscopy[30] and the most striking feature of these data is the remarkably high field position for cyclopropane, 196·3 p.p.m. Its position is virtually the same as that for methane, 195·8 p.p.m.[18] The other members of this series exhibit absorption over the range 164—170 p.p.m. (Fig. 4), variations within which have been ascribed to conformational effects. The shieldings for the medium rings, C_{12}—C_{17}, closely approach the values for long-chain linear alkanes but do not overlap. To explain the high-field position of the cyclopropyl signals Burke and Lauterbur,[30] using a ring-current model, found that a satisfactory accounting for the observed shielding required a current due to 3·5 electrons flowing in a ring of radius 1·10 Å. No suitable method is available for estimating a ring-current contribution in the larger rings.

(v) *Aliphatic derivatives.* In 1958, Lauterbur[1b] published the results of a survey of several series of methane derivatives to show that within a group of closely-related compounds the ^{13}C chemical shifts followed a strikingly regular variation. As examples, a plot of the data for the series $(CH_3)_4Z$, where Z = N, C, Si, Sn, against the Pauling electronegativity of Z gives a straight line as does the plot for the series with Z = Cl, Br, I, but the slopes are different. Nearly linear variations of shift with composition were also found for several other series [such as $Me_xH_{(3-x)}CZ$ and $Z_xCH_{(3-x)}$, for $x = 1,2,3$], although, again, the slopes differ for each. Spiesecke and Schneider[18] later attacked the problem of ^{13}C shieldings in simple alkyl derivatives through an examination of the ^1H and ^{13}C shifts in several CH_3X and $CH_3{\cdot}CH_2X$ molecules and found that all values do not correlate with substituent electronegativity. The greatest deviations were exhibited by compounds having X = I, Br, Cl, S, while the others, X = F, O, N, C, Si, H, showed reasonably linear changes. The deviations were attributed to neighbour-anisotropy contributions of the C–X bonds and the authors concluded that the observations were adequately explained by the interplay of these two factors. Savitsky and Namikawa[31] have

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[28] J. A. Pople, *Proc. Roy. Soc.*, 1957, *A*, **239**, 550; H. M. McConnell, *J. Chem. Phys.*, 1957, **27**, 226.

[29] A. G. Moritz and N. Sheppard, *Mol. Phys.*, 1962, **5**, 361.

[30] J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, 1964, **86**, 1870.

[31] G. B. Savitsky and K. Namikawa, *J. Phys. Chem.*, 1963, **67**, 2430.

recently analysed the figures for the series RZ with R = Me, Et, Pr^i, Bu^t; Z = F, O, N, C, Cl, Br, I, C_6H_5, CO_2H and found that for each Z, except OH, it was apparent that there is a regular change with increasing bulk of the Z group in addition to the trends previously noted. These authors concluded that the additive effects of successive methyl substitution on the α-carbon are related to the C–Z bond distance, suggesting a contribution due to bond hybridisation in addition to the other factors.

(vi) *Aromatic derivatives.* Much attention has been focused on the ^{13}C shieldings in aromatic systems since the first report[1b] of their dependence on substituent polarity. For the monosubstituted benzenes, Lauterbur[21] noted a correlation with the Hammett σ parameter and compared the variations with those previously found for ^{19}F and ^{1}H resonances in similar compounds.[32,33] The *p*-carbon shifts display the best linear behaviour, and it was suggested that the ^{13}C shieldings may be more simply related to ground-state electron distributions than either those for ^{19}F or ^{1}H. Unequivocal proof for the assignmets of the aryl shieldings was provided by Spiesecke and Schneider[19] by a comparison of the spectra of specifically deuterated derivatives with those of the normal monosubstituted benzenes C_6H_5X [X = F, Cl, Br, I, CH_3, OCH_3, NH_2, $N(CH_3)_2$, CHO, CO_2CCl_3, NO_2]. A total range of 60 p.p.m. is found for the aryl shieldings with the largest variation shown by the $C_{(1)}$ nucleus. The 18 p.p.m. variation for the $C_{(4)}$ shifts exhibits a good linear dependence on the Hammett σ_p parameter, while the *meta*-carbon atoms ($C_{(3)}$ and $C_{(5)}$) are little affected by the substituent, appearing over a total range of only 2·6 p.p.m. As noted above, ^{19}F shieldings appear to depend on the σ parameter and are correlated by an expression[34]

$$\delta^{para} = \alpha\sigma_I + \beta\sigma_R \qquad (3)$$

Taft has found that, except for + *R* groups, eqn. (3) is applicable to ^{13}C data by using the constants α = 6·0, β = 23·0, both of which differ somewhat from those required for ^{19}F data. Lauterbur[35,36] has systematically examined the ^{13}C aryl shifts for a variety of methyl-substituted benzene derivatives, $(CH_3)_nC_6H_{4-n}X$ [X = OH, OCH_3, I, NH_2, $N(CH_3)_2$, NO_2] and found that successive substitution of methyl groups on the aromatic ring causes additive variations in the aryl shieldings. Thus, if the substituents are not *ortho*, the aromatic ^{13}C shifts in polysubstituted cases are given by the algebraic sum of the effects observed for the monosubstituted benzenes. In these cases and others,[37] the agreement between observed and calculated values is often ~1 p.p.m. and, generally, the deviations are less than 2 p.p.m. If the substituents are *ortho*, larger deviations are usually

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[32] R. W. Taft, *J. Phys. Chem.*, 1960, **64**, 1805 and earlier references.
[33] R. R. Fraser, *Canad. J. Chem.*, 1960, **38**, 2226.
[34] R. W. Taft, 3rd Ann. Conf. Soc. App. Spect. Cleveland, Sept. 1964.
[35] P. C. Lauterbur, *J. Amer. Chem. Soc.*, 1961, **83**, 1846.
[36] P. C. Lauterbur, *J. Chem. Phys.*, 1963, **38**, 1406, 1415, 1432.
[37] G. B. Savitsky, *J. Phys. Chem.*, 1963, **67**, 2723.

found. Lauterbur has refined the treatment of substituent effects in the polysubstituted cases to account for the various patterns exhibited in an effort to extract more information from the available data, although interpretations of small deviations from additivity in terms of π-electron distributions are questionable before solvent effects are better understood.[37] For structural analysis, however, the simple additivity relation should prove useful on its own.

(vii) *Carbonyl compounds.* Since the carbonyl carbon nucleus absorbs at low-field in a region relatively free of other signals, this grouping is well suited for n.m.r. study. In the usual conditions, a singlet is observed for all carbonyl carbons except that of the formyl group for which a well defined doublet arises, J_{C-H} = 165—205 c./sec. Surveys of carbonyl resonance positions have been reported[38,39] to show that these signals are found over a range of *ca.* 70 p.p.m. and that some of the effects encountered in the infrared and ultraviolet spectra for this grouping are manifest in their ^{13}C spectra. These results indicated that ^{13}C carbonyl data would prove to be useful adjuncts to other physical measurements.

The normal absorption regions for the common carbonyl groups are included in Fig. 3. From the available data, interfering signals in this portion of the ^{13}C spectrum are restricted to those of some olefinic carbons,[4,23,40] the central allenic nucleus,[23] oximes,[4] and CS_2. For reasons noted below, it seems probable that solvent effects could be used to distinguish carbonyl signals from these others, although in any case the presence of a carbonyl group may be confirmed by the infrared spectrum.

The major factors contributing to carbonyl shieldings include substitution, conjugation, hydrogen-bonding, and ring size in cyclic systems.[39] Alkyl groups on or near C_α, the carbonyl carbon, produce changes directionally similar to those found for the hydrocarbons although the magnitude is much reduced, *ca.* −5 p.p.m. Clearly a neighbour-anisotropy effect cannot be the sole reason for this general trend but its origin is not obvious. Substitution by an electronegative atom on the carbonyl carbon gives the opposite effect. For example, replacing a directly bonded carbon or hydrogen by oxygen, nitrogen, or chlorine invariably produces a high field shift of the carbonyl peak. One possible explanation of this change is that the substituent alters the electronic configuration of the C=O bond such that a net increase in π-electron density at the carbonyl carbon results. Simple HMO calculations support this.[41] To judge from the data for several aliphatic polychlorinated compounds, further substitution at the α-position enhances this effect. The changes due to increased chlorine substitution have been examined[39] in several carbonyl series and have been found to be qualitatively similar although there are quantitative differences. Not

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[38] P. C. Lauterbur, Abst. 138th Meeting Amer. Chem. Soc., New York, 1960, p. 22B.
[39] J. B. Stothers and P. C. Lauterbur, *Canad. J. Chem.*, 1964, **42,** 1563.
[40] D. H. Marr and J. B. Stothers, *Canad. J. Chem.*, 1965, **43,** 596.
[41] S Forsén, *Spectrochim. Acta*, 1962, **18,** 595.

unexpectedly, the α-hydroxyl group does not give the same result, because of hydrogen-bonding. The very pronounced deshielding caused by intramolecular hydrogen bonding was first noted in the study of substituted methyl benzoates[1b] and has been found to be quite general for carbonyl carbon.[39,42] Note that *meta*- and *para*-substituents in aromatic carbonyl compounds do not affect the carbonyl shieldings appreciably (see Table 2).

TABLE 2. *Substituent effects on carbonyl shieldings in various compounds (in p.p.m. from* CS_2*)*

R	R·CHO	R·CO·CH_3	R·CO_2H	R·CO_2·CH_3
H–	—	−6·8	27·0	(33·0)*
CH_3–	−6·8	−12·3	15·6	23·0
CH_2=CH–	0·4	−4·4	20·5	29·2
C_6H_5–	1·8	−3·2	20·2	26·7
4–NO_2–C_6H_4–	(4·0)†	−3·3	—	27·6
4–MeO–C_6H_4–	2·6	−2·9	—	27·2

* Value for ethyl ester.
† *m*-NO_2 derivative.

Perhaps the most interesting trend is that exhibited by conjugated systems relative to the corresponding saturated analogues. In general, conjugated carbonyl carbons absorb at the higher field. This difference has been observed for all types of carbonyl function examined although its magnitude differs somewhat in each series. In addition, the results show that, although not precisely the same, the effects of a double bond and an aryl ring are comparable. The data for a few carbonyl functions are given in Table 2 to illustrate these points.

In alicyclic systems, the carbonyl carbon shielding depends on the ring size but does not follow the behaviour displayed by the cycloalkanes (see Fig. 4). An interpretation of the results illustrated in Fig. 4 presents a difficult problem. The most puzzling feature is the remarkably low-field position of cyclopentanone and other five-membered ring carbonyl compounds.[39] A similar difference is found for certain ketonic derivatives including dimethyl ketals, dioxolans, and dithiolans.[43] Significant, although lesser, differences from the others are exhibited by the eight- and nine-membered rings as well. Minor contributions due to conformational effects may account for the relatively small changes in the remaining examples, the behaviour of which is analogous to the hydrocarbons except that the observed shifts are comparable to those found for acyclic ketones.

(viii) *Carbonium ions.* ^1H and ^{19}F n.m.r. spectra have proved to be valuable for the positive identification of aliphatic carbonium ions[44]

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[42] G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, 1964, **68**, 437.
[43] M. Anteunis, D. A. Ross, and J. B. Stothers, unpublished observations.
[44] N. C. Deno, *Chem. Eng. News*, 1964, Oct. 5, p. 88; N. C. Deno, C. V. Pittman, and M. J. Wisotsky, *J. Amer. Chem. Soc.*, 1964, **86**, 4370; D. M. Brouwer and E. L. Mackor, *Proc. Chem. Soc.*, 1964, 147.

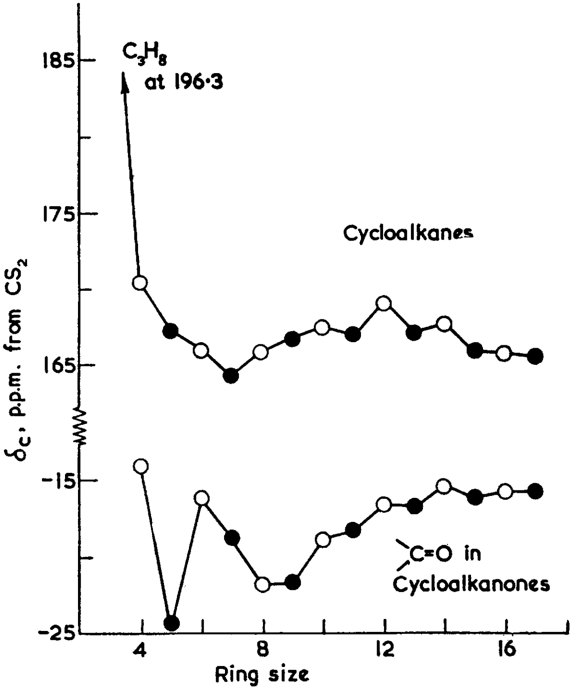

FIG. 4. *Variation of* ^{13}C *shieldings with ring size for cyclohexanes (upper) and carbonyl carbon nuclei in cycloalkanones (lower.)*

and, more recently, ^{13}C spectroscopy has been utilised as well.[45] For example, the ^{13}C spectrum of $CH_3{\cdot}CO^+SbF_6^-$ shows clearly that a partial positive charge is located on the carbonyl carbon. Employing the i.n.d.o.r. method (see p. 147) and ^{13}C-enriched material,[45a] the carbonyl carbon signal was found at —45·4 p.p.m. relative to that in $CH_3{\cdot}COF$. Larger low-field ^{13}C shifts have been observed for other cations including $(CH\text{-})_3C^+$ (—273 p.p.m. from Bu^tCl)[45b] and $(C_6H_5)_3C^+$ (—129·6 p.p.m. from $Ph_3C{\cdot}OH$).[45c] Although some of these changes may be due to solvent effects (these alkyl cations were examined in SbF_5 and H_2SO_4 solutions, respectively), the pronounced deshielding in the cations clearly indicates a concentration of positive charge on carbon and an effect of delocalisation over the aromatic rings is apparent. It is unfortunate that the low concentration of these ionic complexes precluded measurements of the other shieldings which must await technical advances.

(b) Coupling Constants.—Since the prime aim of this Review is an examination of ^{13}C shielding results, only the important features of ^{13}C

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[45] (*a*) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastein, and E. B. Baker, *J. Amer. Chem. Soc.*, 1963, **85**, 1328; (*b*) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastein, *ibid.*, 1964, **86**, 1360; (*c*) G. A. Olah, E. B. Baker, and M. B. Comisarow, *ibid.* p. 1265.

spin-coupling interactions are noted in this section to acquaint the reader with current developments and to provide key references. Normally direct one-bond ^{13}C–X coupling interactions are well-resolved in natural abundance spectra but the precision of measurement is low ($\sim \pm 3$ c./sec.). Thus, better data ($\sim \pm 1$ c./sec.) are obtainable from ^{13}C satellite spectra.[46] In addition, longer-range interactions are resolved in the latter. The $J_{^{13}C-^{1}X}$ parameter shows promise for both practical and theoretical problems, particularly the relatively large one bond J's (120—250 c./sec.). For these, Muller and Pritchard[47] first noted that $J_{^{13}C-^{1}H}$ values correlate with bond properties, specifically the hybridisation of the C–H bond, and hence the bond length. They suggested equation (3) to account for their observations for several hydrocarbons

$$\rho_{C-H} = 0{\cdot}20 J_{C-H} \tag{4}$$

where ρ_{C-H} is the percentage of s character of the bonding C orbital. Their results indicated that bond polarity is relatively unimportant. Later Malinowski[48] showed that the effects of substituents on $J_{^{13}C-^{1}H}$ in several substituted methanes are very nearly additive and a theoretical interpretation was offered.[49] For the halogenomethanes, an evaluation by the maximum overlap orbital treatment has been given.[50] Since eqn. (3) was suggested, several reports of the apparent linearity of ρ_{C-H} with J_{C-H} have appeared and some workers have assigned values for the s character of specific bonds in various structures. The latter step seems premature in view of the steadily increasing number of exceptions found recently.[51] It is clear that more study is essential and some pertinent suggestions have been made.[51b] A more detailed review, citing major references, should be consulted for further details.[52]

The question of the signs of coupling constants has attracted interest and on the assumption (now known to be true) that ^{13}C–H interactions are positive, the relative signs of other coupling constants were deduced.[52,53] Direct ^{13}C–^{13}C couplings have received only limited attention[16,17] since such studies require doubly labelled compounds to obtain satisfactory S/N ratios for ^{13}C spectra. A detailed study of several examples has revealed[17] that there is no simple general correlation with bond distance except for C–C single bonds, but J_{C-C} is proportional to the product of the s charac-

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[46] N. Sheppard and J. J. Turner, *Proc. Roy. Soc.*, 1959, *A*, **252**, 506.

[47] N. Muller and D. E. Pritchard, *J. Chem. Phys.*, 1959, **31**, 768, 1471; N. Muller, *ibid.*, 1962, **36**, 359.

[48] E. R. Malinowski, *J. Amer. Chem. Soc.*, 1961, **83**, 4479.

[49] H. S. Gutowsky and C. S. Juan, *J. Amer. Chem. Soc.*, 1962, **84**, 307.

[50] J. H. Goldstein and R. T. Hobgood, *J. Chem. Phys.*, 1964, **40**, 3592.

[51] (*a*) N. Muller and P. I. Rose, *J. Amer. Chem. Soc.*, 1962, **84**, 3975; (*b*) G. J. Karabatsos and C. E. Orzech, *ibid.*, 1964, **86**, 3574; 1965, **67**, 560.

[52] D. M. Grant, *Ann. Rev. Phys. Chem.*, 1964, **15**, 489.

[53] P. C. Lauterbur and R. J. Kurland, *J. Amer. Chem. Soc.*, 1962, **84**, 3405; F. A. L. Anet, *ibid.*, 1962, **84**, 3767; S. S. Danyluk, *ibid.*, 1964, **86**, 4504; G. V. D. Tiers, *J. Phys. Chem.*, 1963, **67**, 928; K. A. McLauchlan, *Chem. Comm.*, 1965, 105.

ters of the carbon atoms forming the various types of C–C bonds and appreciable π-bond contributions to J_{C-C} are indicated.

4. Discussion of results

(a) General Considerations.—Before considering specific applications of ^{13}C techniques to problems of chemical interest, the general features of ^{13}C shieldings can be examined in terms of current theory of nuclear screening. For a specific nucleus A, the chemical shift depends on the field H_A experienced at that nucleus and which is given by $H_A = H_0 (1 - \sigma_A)$ where H_0 is the applied field. Following Saika and Slichter,[54] we may write the total screening constant σ_A as the sum of three separate quantities: (i) σ_d, a diamagnetic contribution due to local electron currents; (ii) σ_p, a local paramagnetic term involving mixing of electronic states by H_0; and (iii) a term, σ', for contributions by circulations on all other atoms of the molecule, including the effects of neighbouring anisotropic atoms, bonds, or ring structures.

For all nuclei except protons, σ' is relatively unimportant. Neighbour-anisotropy effects appear to be of the order of a few p.p.m. for ^{13}C shieldings. σ_d is given by the well-known Lamb formula and depends on the electron density about A. With Slater atomic orbitals the increase in σ_d caused by the addition of a $2p$ electron is 14 p.p.m. Because of the large differences observed, therefore, the paramagnetic term σ_p is the dominant contribution to ^{13}C shieldings. It is also related to the electron density at A.

The first attempts to correlate ^{13}C shieldings with substituent electronegativity or polarity have been described above, and it is clear that electron-density changes at a particular carbon are reflected by its chemical shift. A linear relation might be expected within a series of compounds for which the σ_d and σ_p contributions change regularly, while σ' remains constant. The simple aromatic derivatives in which the substituent is well removed from the centre of interest apparently afford suitable systems, to judge from the p-carbon shielding results. In aliphatic compounds substituents must be much closer to exert appreciable effects and it seems likely that variable σ_p and σ' contributions owing to the substituent group are responsible for deviations. As noted before, linear changes are observed in closely related aliphatic series with different substituents producing different slopes in the various series.

Attempts to rationalise deviations from linearity for "δ_C against electronegativity" plots in terms of neighbour-anisotropy effects seem likely to fail since unduly large values for the $\Delta\chi$ term in the point-dipole model are required. Even though the model is oversimplified very appreciable effects should be observed for the proton shifts in these molecules since anisotropic contributions would only be slightly modified by the geometric factors. A suitable model is yet to be suggested which will account for the

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[54] A. Saika and C. P. Slichter, *J. Chem. Phys.*, 1954, **22**, 26.

observations. The general trends found in both aromatic and aliphatic derivatives, however, indicate that the local electron density at a specific carbon nucleus has a major influence on the resonance position of that carbon atom. Inability to account for the trends quantitatively is compensated by the general observation of additivity of substituent effects in related compounds.

(b) Applications.—In this section, several chemical applications of ^{13}C n.m.r. spectroscopy are described but the published results represent only the preliminary stages. In no case can it be said that the method has been fully developed and, consequently, some of the following comments are conjectural. Certain areas appear to warrant detailed study and some suggestions have been advanced on the basis of the limited data presently available.

(i) *Theory of chemical shifts.* Because of the large shift differences, ^{13}C shieldings offer an excellent means of examining the factors contributing to nuclear shielding. Compared with proton results for which the major factors, σ_d and σ_p, exert quantitatively similar but opposite effects and, hence, the calculated shieldings represent a small difference between two approximate quantities, the observed differences for ^{13}C nuclei allow one to separate the variables more successfully. Although there are apparent anomalies, one can unravel the major influences in a qualitative manner. Pople has developed[55] an approach based on molecular orbital theory of the diamagnetic currents induced in a molecule by an external magnetic field. He showed that the σ_p term must be a major contributing factor to ^{13}C shieldings and, as a first approximation, was able to estimate σ_p contributions for carbon–carbon multiple bonds and the carbonyl group. The calculated effects are less than those observed by a factor of *ca.* 2—3. It is interesting that this method predicts a marked low-field shift for the central carbon in an allene, as observed (see p. 153). More recently, Karplus and Pople[56] have examined the problem of ^{13}C shifts in conjugated molecules and formulated a molecular orbital theory giving reasonable agreement with experiment but clearly illustrating the need for further studies, both experimental and theoretical. They showed that σ_p must be the dominant factor and developed a general expression (6) for the shielding of a carbon, A, (relative to C_6H_6) having a charge density q_A close to unity and free valence F_A, close to the benzene value of 0·399;

$$\sigma_A = (86{\cdot}7 + 46{\cdot}0\ \lambda_H)(q_A - 1) + 46{\cdot}0\ (F_A - 0{\cdot}399) \qquad (6)$$

where $\lambda_H = 0$ for carbon bonded to three other carbons. Equation (6) was obtained from expressions of the form (7) developed for the σ_p term:

$$\sigma_p = -\left[\frac{e^2h^2}{2m^2c^2\,\Delta E}\right] <r^{-3}>2p \left[2 + \frac{8}{27}\lambda_H + \frac{4}{9}(\sqrt{3} - F_A)\right] \qquad (7)$$

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[55] J. A. Pople, *Discuss. Faraday Soc.*, 1962, **34**, 7; *Mol. Phys.*, 1964, **7**, 301.
[56] M. Karplus and J. A. Pople, *J. Chem. Phys.*, 1963, **38**, 2803.

From (7), it is evident that the paramagnetic term depends on the π-electron density only through the polarity term λ_H for C–H bonds, but three other factors enter as well: (i) the mean excitation energy for the molecule ΔE, (ii) the dimensions of the $2p$ orbital, r, and (iii) the free valence. These factors were discussed in detail and the method was illustrated with four alternant hydrocarbons and buta-1,3-diene. Further refinements can be anticipated with the appearance of more ^{13}C results.

(ii) *Estimations of π-electron distributions.* As noted earlier remarkably good agreement between experiment and theoretical calculations is given by equation (1) for the correlation of ^{13}C shieldings with π-electron densities. Several examples are discussed by Lauterbur,[36] and, at present, the approach appears to be capable of providing as reasonable estimates as those obtained by various theoretical calculations. It has been shown[55] however that σ_d cannot be the major factor responsible for this charge dependence but, rather, the main contribution must arise from changes in the σ_p term, in agreement with a similar conclusion drawn by Saika and Slichter for ^{19}F shieldings.[54] Wu and Dailey[57] have concluded that observed substituent effects result from the combined effect of at least two separate additive mechanisms, one of which is π-electron variation, both contributing to the shielding to an approximately equal extent.

For organic chemists, one of the most important applications of ^{13}C spectroscopy is to provide direct evidence for ground-state electron distributions which have previously been surmised on the basis of chemical reactivity only. As an example we may consider cyclohex-2-enone for which it is generally assumed that a polarised form makes a significant contribution to the ground state. Comparison of its carbonyl and olefinic shieldings with those for cyclohexanone and cyclohexene (Fig. 5*a*) bears

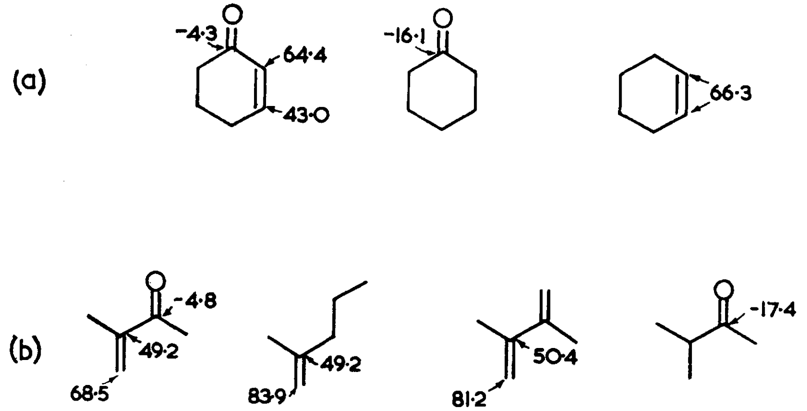

FIG. 5. ^{13}C *shieldings of olefinic and carbonyl carbon nuclei in* (*a*) *alicyclic cases and* (*b*) *acyclic examples. Values given in p.p.m. from* CS_2.

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[57] T. K. Wu and B. P. Dailey, *J. Chem. Phys.*, 1964, **41**, 2796.

out the general assumption clearly. The β-carbon is significantly deshielded while the carbonyl carbon is shielded, as expected for an appreciable polarisation of the π-electron system by the electron-attracting oxygen atom. The analogous comparison for the acylic series illustrated in Fig. 5(*b*) leads to a similar conclusion. It is significant that the diene shieldings do not differ greatly from those of the mono-olefin but the effect of the oxygen atom in the conjugated system is pronounced. Both observations are in complete agreement with current conclusions regarding the structures of these molecules. Thus the variation of ^{13}C shieldings with π-electron distributions may be employed qualitatively although the quantitative inter-relation of these is not yet known with certainty.

(iii) *Stereochemical problems.* The first indication that ^{13}C data might be useful for stereochemical studies was the fact that substituent effects on aromatic shieldings in *ortho*-substituted derivatives are not additive. Lauterbur[36] noted this for substituted dimethylanilines, nitrobenzenes, and iodobenzenes and attributed it to steric inhibition of resonance. Support for the interpretation was provided by the changes in *para*-carbon shieldings and their correlation with other measures of steric interference. Analogous results have been observed for side-chain carbon nuclei and a detailed study of aromatic ketones has been presented.[58,59]

In contrast to those of aromatic nuclei, the shieldings of carbon atoms bonded directly to aromatic rings are not dependent on the nature of the substituents. For many examples of *meta*- and *para*-substitution, the shieldings of the α-carbon atom of toluenes,[1b,35,36] acetophenones,[58,59] alkyl phenyl ketones,[60] methyl benzoates,[61] benzaldehydes,[61] and styrenes,[25] are virtually unaffected; apparently, conjugative interactions dominate. Appreciable deviations from the small range of shifts exhibited by the above derivatives are found, however, for the *ortho*-substituted cases and these deviations show a dependence on the size of the substituent[57] rather than its polarity, strongly suggesting the existence of steric interactions. From the spectra of more than fifty acetophenones, an empirical expression relating the observed carbonyl shielding with the angle of twist, θ, of the carbonyl grouping was proposed[58] and tested.[59] Without exception, reasonable values of θ were obtained, some of which are listed in Table 3 together with estimates obtained by analyses of other results. The ^{13}C method seems to have certain advantages over the others, not the least of which is the absence of grossly abnormal estimates. An extension of the method to other aromatic ketones has also been presented.[60] While refinements are no doubt required, the problems involved are not insignificant.[59,60] In aliphatic conjugated systems, it appears that ^{13}C carbonyl shieldings also depend on the planarity of the system and a clear distinction between planar S-*cis* and non-planar conformations is possible,[40] although these

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[58] K. S. Dhami and J. B. Stothers, *Tetrahedron Letters*, 1964, No. 12, 631.

[59] K. S. Dhami and J. B. Stothers, *Canad. J. Chem.*, 1965, **43**, 479.

[60] K. S. Dhami and J. B. Stothers, *Canad. J. Chem.*, 1965, **43**, 498.

[61] K. S. Dhami, Ph.D. thesis, Univ. of Western Ontario, 1964.

TABLE 3. *Angles of twist in some hindered acetophenones as estimated by various physical methods*

Substituents	^{13}C n.m.r.*	Ultraviolet spectra†	Dipole moments†	Kerr constant‡
2-CH_3	28°	40°	34°	—
2,3-$(CH_3)_2$	32°	—	—	—
2,4-$(CH_3)_2$	25°	24°	—	—
2,5-$(CH_3)_2$	25°	35°	—	—
2,6-$(CH_3)_2$	50°	55°	—	—
2,4,6-$(CH_3)_3$	51°	63°	62°	90°
2,3,5,6-$(CH_3)_4$	57°	—	—	90°

* Ref. 59.
† E. A. Braude and F. Sondheimer, *J.*, 1955, 3754
‡ M. J. Aroney, M. G. Corfield, and R. J. W. Le Fèvre, *J.*, 1964, 698.

systems do not exhibit large differences by other physical measurements.

Since the basis for employing carbonyl shifts to measure steric interference rests on the absence of polar effects, further support for the simplified, if not naïve, interpretation of the results was required. Originally it was suggested that the carbonyl shielding is independent of substituent polarity because of its non-terminal position in the resonance system.[39] To confirm this point a study of the vinyl carbon shieldings in several substituted styrenes was made.[25] It was found that while the β-carbon shieldings are strongly dependent on substituent polarity the α-carbon shifts are not, in accord with the simple model.

(iv) *Solvent effects.* It has been recognised for some time[18] that significant effects on ^{13}C shieldings are exerted by various solvents, but only a few preliminary reports have been presented.[39,40,59–62] Most of these have been concerned with carbonyl and hydroxylic solutes in hydrogen-bonding solvents. The effects, while pronounced at the carbon bearing oxygen, are rapidly attenuated along the carbon skeleton as some typical results listed in Table 4 show. Undoubtedly the polarisation of the solute is changed by these interactions but shielding changes which would reflect this are small, *e.g.*, at $C_{(4)}$ in acetophenone and phenol. It follows, therefore, that the local electronic environment at the carbonyl is altered appreciably and it is pertinent that the solvent effects correlate with the changes in energy of the $n \rightarrow \pi^*$ transition.[61] Attempts to correlate the solvent shifts with the common solvent polarity scales reveal a reasonably linear relation with Y-values.

(v) *Potential applications.* The use of ^{13}C spectroscopy for structural elucidations may be anticipated although little has appeared in the formal literature. As more experimental results become available, the potential areas of application multiply. At present, it is clear that carbonyl reson-

[62] (*a*) G. E. Maciel and G. C. Rubin, *J. Amer. Chem. Soc.*, 1963, **85**, 3903; (*b*) G. E. Maciel and R. V. James, *ibid.*, 1964, **86**, 3893.

TABLE 4. *Effect of solvent on ^{13}C chemical shifts (given in p.p.m. from CS_2)*

		Solvents							
Compound	Carbon	Nil	CCl_4	C_6H_{12}	C_6H_6	$C_4H_8O_2$*	$CH_3 \cdot OH$	DMSO†	Ref.
Phenol	C-1	—	38·0	38·1	37·1	36·1	—	35·2	62b
	C-4	—	71·9	72·9	—	74·4	—	73·9	
Acetophenone	C=O	−3·2	−2·1	—	−2·9	−3·1	−6·3	—	39
	C-1	56·7	55·4	—	56·4	55·8	55·9	—	
	C-4	61·2	60·4	—	61·2	61·5	59·7	—	
	CH_3	167·9	167·4	—	167·4	167·8	167·5	—	
Acetone	C=O	−12·3	−11·0	−9·3	−11·5	−12·3	−16·0	—	62a
Cyclohex-2-enone	C=O	−4·3	−3·6	—	—	—	−7·0	—	40
	C-2	64·4	63·1	—	—	—	63·8	—	
	C-3	43·0	43·7	—	—	—	41·0	—	

* 1,4-Dioxan.
† Dimethyl sulphoxide.

ances may be particularly valuable. A rich potential field is the characterisation of organic compounds lacking H or F and of fully substituted groups. Another interesting facet is the study of bond parameters *via* ^{13}C coupling interactions and several workers have attacked this problem showing that while the approach is promising certain features require careful study (see p. 159).

Throughout this Review several outstanding problems as well as potential avenues of investigation have been mentioned and the results of more detailed studies, some of which are under way, may be awaited with interest. There seems little doubt that ^{13}C spectra should improve our insight into the theory of chemical shifts and spin-coupling interactions as well as a number of aspects of molecular structure. There is a clear need for more experimental data from which to build, but even the limited available evidence points to the fact that ^{13}C spectroscopy can be helpful for many problems through the use of empirical correlations in a manner similar to that of optical spectroscopy.

Kinetic studies are a natural extension of ^{13}C methods and since the chemical shifts are relatively large the study of moderately rapid reaction rates represents an area awaiting attention. Temperature effects on ^{13}C spectra are virtually unexplored although several interesting possibilities are apparent from the foregoing discussion and by analogy with the results of n.m.r. studies of more abundant nuclei. Both of these aspects become even more inviting if one considers the use of suitably labelled reactants.

A valuable and exciting practical application of ^{13}C techniques will be isotopic tracer studies, since a compound enriched in ^{13}C could be followed throughout a reaction or reaction series without disturbing the system. Substances which are unstable or not easily isolable could be readily detected, degradations to isolate the labelled centre would be unnecessary in many cases and an "instantaneous" record of the progress of a reaction would be available. These represent distinct advantages over conventional studies with radioactive tracers. Although no reports of such studies have appeared, there is activity in this direction in several laboratories. A particularly interesting application is the study of biological processes by use of ^{13}C techniques. Biogenetic problems appear to offer an excellent means for an evaluation of the method. An important feature for tracer studies is that enrichment of a few percent. would suffice for many systems. If highly enriched material were used, conventional high-resolution n.m.r. techniques could be employed and the variety of applications now commonplace for ^{1}H and ^{19}F nuclei would be possible.

5. Conclusions

Without question, the major obstacle to widespread use of ^{13}C spectroscopy is the need for increased sensitivity. Hence, a most eagerly awaited technical development is that of magnets with superconducting coils, suitable for high resolution work. For ^{13}C studies, higher magnetic fields would make accessible the spectra of a much wider range of substances. Fortunately, present developments[63] indicate that in the not too distant future homogeneous fields much higher than those presently employed will be available. On the basis of recent reports, it appears that the limit of detectability for ^{13}C in natural abundance may be lowered by an order of magnitude (see p. 146). Thus the future of ^{13}C spectroscopy is assured and the technique should provide valuable assistance for the expansion and refinement of both theoretical and practical considerations.

[63] *Chem. Eng. News.*, 1964, June 8, 55.