

Laboratoriums- und



Meßtechnik in der Chemie

II. OPTISCHE METHODEN

Applications of High-Resolution Nuclear-Magnetic-Resonance Spectroscopy to Organic Chemistry

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Zusammenfassung

In den letzten Jahren wurde es klar, daß die magnetische Kernresonanzspektroskopie organischer Verbindungen in Lösung oder in flüssigem Zustand eine neue, sehr leistungsfähige physikalische Methode für die qualitative Bestimmung von molekularen Strukturen, insbesondere für die Ermittlung von Art und Anordnung funktioneller Gruppen in einem Molekül ist. Die Gruppen, die so nachgewiesen werden können, enthalten magnetische Kerne, wie Wasserstoff, Fluor, Phosphor, Bor usw. Die reichlich vorhandenen Sauerstoff- und Kohlenstoffisotope beeinflussen das Spektrum nicht, und die Stickstoffspektren sind gewöhnlich so schwach, daß für die Anwendung in der organischen Chemie das Hauptgewicht auf den Wasserstoffresonanzen liegt. Diese geben aber zahlreiche wertvolle Informationen, da die Positionen der Resonanzen von der Art der Elektronenverteilung um den Kern abhängig sind. So können auf dem Gebiete der Kohlenwasserstoffe CH-Bindungen in gesättigter, in Äthylen- und Acetylen-, in aromatischer und Allyl-Stellung gewöhnlich gesondert unterschieden werden. Ihr relatives Zahlenverhältnis kann in günstigen Fällen ebenfalls annähernd bestimmt werden. CH-Bindungen, die mit elektronegativen Atomen, wie Stickstoff, Sauerstoff und Chlor, verbunden sind, können gewöhnlich gut nachgewiesen werden. Methylgruppen sind dank der Stärke der auftretenden Banden besonders leicht zu bestimmen. Die Feinstruktur der Resonanz eines bestimmten Wasserstoffatoms kann auch dazu dienen, die Zahl der umliegenden Wasserstoffkerne zu bestimmen. Zum Beispiel zeigt das Feinstrukturmuster der CH_2 - und CH_3 -Resonanzen einer $-\text{OCH}_2\text{CH}_3$ -Gruppe, daß die Methylengruppe an der Methylgruppe hängt, und umgekehrt. Die Wasserstoffresonanzen von NH- und OH-Gruppen sind ebenfalls imstande, wertvolle Informationen zu liefern, obschon strukturelle Aussagen hier erschwert werden durch die Tatsache, daß die Positionen der Bänder sehr empfindlich auf Wasserstoffbindungen sind. Eine Zahl ausgewählter Spektren wird diskutiert, um einige Anwendungsmöglichkeiten dieser Methode in der organischen Chemie aufzuzeigen.

Nuclear magnetic resonance as a physical phenomenon was discovered in 1946 by BLOCH¹ and PURCELL² in

¹ F. BLOCH, W. W. HANSEN and M. E. PACKARD, *Physic. Rev.* 69 (1946) 127.

² E. M. PURCELL, H. C. TORREY and R. V. POUND, *Physic. Rev.* 69 (1946) 37.

the U.S.A. Despite the fact that only 13 years have passed since the first resonances were observed, and despite the very high precision of the experimental techniques required, this branch of spectroscopy is developing rapidly into a physical method for the determination of molecular structures that has wide application to chemical problems.

Two main types of nuclear magnetic resonance (NMR) experiments are carried out. The so-called 'broad-line' experiments are concerned mainly with the spectra obtained from samples in the solid state. High-resolution or 'narrow-line' experiments are carried out with chemical samples in fluid media, i.e. in the liquid, solution or gas phases. Although some very interesting chemical work has been done with the 'broad-line' technique³ the present and future chemical applications of high-resolution work appear to be much more extensive and I shall confine myself to this aspect of the subject. In this short account I shall discuss some of the applications of the method to organic chemistry.

As its description implies, high-resolution nuclear-magnetic-resonance spectroscopy requires very precise physical measurements to be made in a semi-routine fashion; for this reason the price of suitable equipment is high (about \$ 25,000 to \$ 50,000). Nevertheless most of the work done is carried out with commercially manufactured apparatus and the applications are so extensive that, despite the high cost, we may expect in a few years time to find such equipment installed in most of the larger chemical laboratories of the world. How the word 'larger' is to be interpreted in this context will depend almost entirely on the price at which such equipment can be offered in the future, for it can be said with confidence that every preparative organic chemist (and many of his inorganic colleagues) will wish in the future

³ J. A. V. SMITH, *Quart. Rev.* 7 (1953) 279.

to have access to such equipment in much the same way that today he has access to an infra-red spectrometer.

Let us first of all look at the physical principles involved in nuclear resonance. Many nuclei, like the electron, have an effective spin angular-momentum which we may express as $Ih/2\pi$ where h is Planck's constant. For the electron $I = \frac{1}{2}$, but for different nuclei I may have any one of the half-integral values $0, \frac{1}{2}, 1, \frac{3}{2}$ etc. As a nucleus is associated with a distribution in space of positive charge—even though this is of small volume—then rotation of this charge distribution will give rise to an effective flow of current about the axis of spin. This in turn gives rise to a magnetic moment, μ , directed along the axis of spin as shown by the heavy arrow in Figure 1.

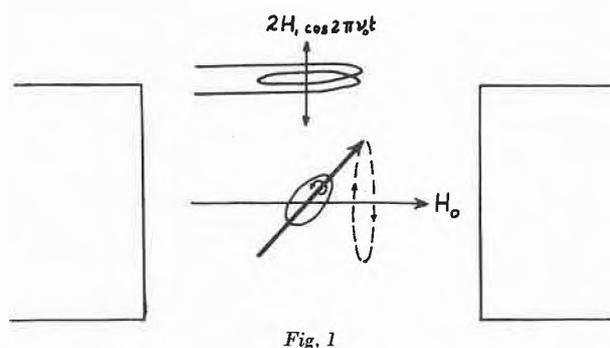


Fig. 1

Next let us suppose that we place this magnetic nucleus in an applied magnetic field, H_0 . In terms of classical physics we should expect the nucleus to experience a couple (or torque) which will tend to line it up with the field. However, because the nucleus is spinning, its gyroscopic motion tends to oppose any change in orientation and the net effect is—as when a torque is applied to a gyroscopic top—that the axis of spin takes up a precessional motion about the direction of H_0 . The frequency, ν_0 , of this precessional motion is the frequency that we measure in the nuclear-magnetic-resonance experiment and it can be shown to have the value

$$\nu_0 = \frac{1}{2\pi} \gamma H_0 = \frac{\mu}{h I} H_0,$$

where γ is the magnetogyric ratio of the nucleus.

This precessional motion can be detected by applying an oscillatory magnetic field, H_1 , at right angles to H_0 , in the form of electromagnetic radiation generated by a radiofrequency oscillator with a tuned coil wound around the sample. If this oscillatory field has the correct frequency and phase the nucleus will be tilted more and more from alignment with H_0 on each precessional cycle and, in the simplest case, the consequent absorption of energy is measured as a change in impedance of the coil. The spectrum may be scanned either by keeping H_0 fixed and varying the radio-frequency or, more

usually and conveniently, by keeping the radio-frequency fixed and varying H_0 . As the amount of energy absorbed corresponds to only a small fraction of the voltage applied to the radio-frequency coil, it is necessary to enhance sensitivity of a single coil apparatus by balancing off most of the applied voltage in frequency and phase with a bridge circuit. An alternative method is to have separate transmitter and receiver coils at right angles to each other so that the receiver coil detects magnetic field changes resulting from the tilting of the nuclei from alignment. This is the method used in the induction type of spectrometer shown diagrammatically in Figure 2.

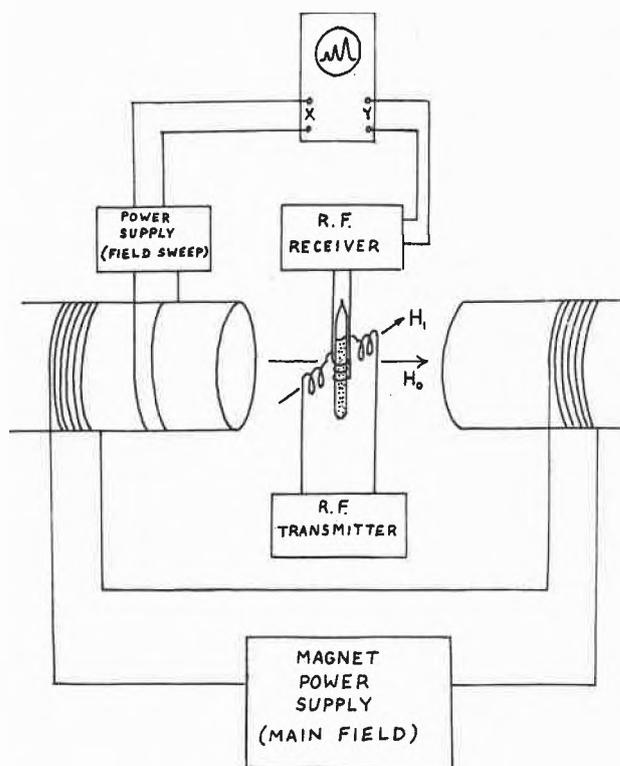


Fig. 2. Nuclear magnetic resonance (induction) spectrometer

The above description of nuclear magnetic resonance is, in outline, the description of the phenomenon according to classical mechanics. According to the concepts of quantum mechanics it is not possible for the nucleus to take up a continuous range of orientations with respect to the magnetic field but instead—for nuclei of spin $\frac{1}{2}$ —two preferred angular orientations which are conventionally termed the parallel and antiparallel orientations. Transitions between the corresponding two energy levels lead to a frequency which is the same as quoted above for the classical case.

The next point of interest concerns which nuclei are capable of giving strong nuclear-magnetic-resonance spectra. There is a family of nuclei for which $I = 0$; as their charge distributions are not in rotation they have

zero magnetic moments. Included in this category are the naturally abundant nuclei ^{12}C , ^{16}O , ^{28}Si , and ^{32}S , where the number represents the mass of the particular isotope. Magnetic-resonance spectra cannot be obtained from these nuclei, nor from any other nucleus that has both an even mass number and an even charge (or atomic) number.

Those nuclei with $I = \frac{1}{2}$ give spectra which can be most easily interpreted and these include ^1H , ^{19}F and ^{31}P . Nuclei with spin $I = 1$ include ^2H and ^{14}N . The relative signal strengths to be obtained from these, and a number of other useful nuclei, are shown in Figure 3.

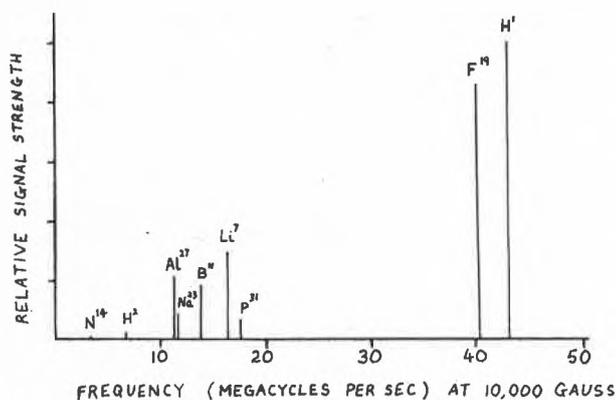


Fig. 3

Some nuclei with $\mu = 0$, $I = 0$ ^{12}C , ^{16}O , ^{24}Mg , ^{28}Si , ^{32}S
 Some nuclei with $\mu \neq 0$, $I = \frac{1}{2}$ ^1H , ^{13}C , ^{15}N , ^{19}F , ^{31}P

It is seen that much the strongest signals, nucleus for nucleus, are obtained from hydrogen and fluorine and it may be immediately concluded that NMR spectroscopy is of great importance to chemists working with these two types of nuclei. As hydrogen nuclei are located in different positions in nearly all organic molecules, it is here that the major application to organic chemistry lies, and probably more than 90% of the total volume of work done has been concerned with hydrogen (i.e. proton) resonances. Useful organic chemical work is also done with the ^{31}P nucleus but, at the present stage, signals from ^{14}N nuclei are so weak that the practical applications are relatively few. It might appear that it is very unfortunate for the organic chemist that both the ^{12}C and ^{16}O nuclei do not give spectra. In fact if these were magnetic nuclei their spectra, and those of hydrogen nuclei attached to them, would probably be too complex to interpret in any but the simplest cases.

The resonance experiment so far described is purely an experiment in physics—no chemical factors affecting the resonance have yet been mentioned. The original experiments were done by physicists and their aim was to determine, from the observed resonance frequencies, the magnetogyric ratios for the various nuclei. On increasing the precision of their measurements to 5 or 6 significant figures they found that the resonance position for a given type of nucleus depended slightly on the

chemical surroundings—for example the resonant magnetic field of protons at a given frequency differed when these occurred in a sample of water as compared to a sample of paraffin hydrocarbon. The differences in resonance position are referred to as *chemical shifts*, a term which was originally an expression of annoyance from the physicist who had then reached the limit of precision with which magnetogyric ratios could be measured from readily available samples.

The cause of these chemical shifts is that the electrons surrounding the nucleus whose resonance is being studied shield it to some extent from the applied field, H_0 , as a result of currents set up in the electron distribution by the magnetic field. Because hydrogen nuclei in chemically different locations in a molecule have different electron surroundings, so the shielding effect is different for each type of chemical location. If ν is the resonance frequency actually observed for a nucleus within a molecule we may now write

$$\nu = \frac{\mu}{h I} H_0 (1 - \sigma')$$

where the resonance is seen to differ from that of a bare nucleus, ν_0 , by an amount dependent upon the shielding constant, σ' . Ideally σ' should be defined relative to a bare nucleus, but as such measurements are difficult to make it is usually referred to a standard chemical location such as, for hydrogen nuclei, that of protons within a water molecule.

It might be anticipated that the shielding constants, σ' , would be small in value and this is so. For hydrogen nuclei they are so small that it is customary to use shielding constants σ such that $\sigma = \sigma' \times 10^6 = \frac{H - H_{ref}}{H_{ref}} \times 10^6$ where H is the field at which a given nucleus gives resonance, and H_{ref} is the field at which the nucleus in the reference surroundings gives resonance at the same frequency.

These shielding constants, and the differences between them which are the chemical shifts with the symbol δ , e.g. $\delta_{12} = \sigma_1 - \sigma_2$, are only detectable because the resonance lines are extremely sharp and can hence be resolved from each other. Even so, it is only by exceedingly careful design of the magnet and of the electronic circuits that field uniformity and frequency stability can be ensured that will make these measurable with the amazing present day accuracy of about 1 part in 10^8 . All of this precision is of use in studying the chemical implications of the NMR spectra of hydrogen atoms, although useful information can still be achieved at a resolution of 1 part in 10^7 ; for many other nuclei less (sometimes considerably less) precision is acceptable.

Not only do different types of location for hydrogen atoms within a given molecule give rise to different resonance positions but also, within limits, the same type of chemical location of a hydrogen nucleus in *different* molecules gives the same resonance position with res-

pect to a suitably chosen common reference. For this reason in favourable cases it is possible to infer those types of hydrogen-containing chemical groupings which are present in a molecule from the positions of the observed resonances, in an analogous fashion to the way that different functional groups can be detected by their characteristic frequencies in infra-red spectra. The precision with which this can be done varies from case to case, for certain frequency ranges may be common to more than one type of hydrogen-containing functional group. Nevertheless it is a very useful property of NMR spectra, and this method can be exceedingly powerful when chemical and other physical techniques have reduced the possible structures for the molecule to only a few alternatives.

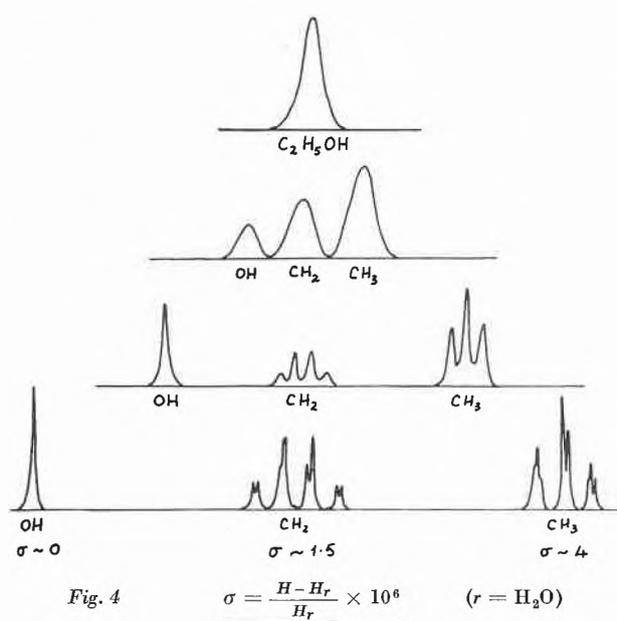


Figure 4 shows the NMR spectrum of ethyl alcohol, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{OH}$, as observed under different degrees of resolving power. In the first spectrum all the hydrogen resonances occur as a single unresolved peak. In the second spectrum the resonances of the CH_3 , CH_2 and OH groups have been resolved from each other, and it is seen that the relative intensities of the three resonances vary as 3 to 2 to 1, *i.e.* as the number of hydrogen nuclei involved in each case. This is a second important property of NMR spectra, namely that the intensities of the various resonances due to the same type of nucleus in different chemical surroundings are dependent only on the number of nuclei involved. Various practical difficulties make the measurements of relative band intensities difficult in some cases, *e.g.* when a sharp single band has to be compared with a broad band of complicated structure, but much progress has recently been made with automatic integration methods that overcome some of these difficulties. A consequence of this intensity situation is that the resonances of CH_3 groups

are usually strong and readily picked out from the spectra. These are in many ways the most readily located groups in NMR spectra.

The third and fourth spectra of ethyl alcohol on Figure 4 show the CH_2 and CH_3 resonances split into several fine-structure components. These fine-structure patterns are caused by interaction (the so-called spin-spin interaction) between the magnetic hydrogen nuclei of the CH_2 and CH_3 groups via the intervening electron distribution. The simplest case of such a splitting would occur with a molecule containing two adjacent CH bonds of the type $\text{X}_2\text{CH}-\text{CH}'\text{Y}_2$ which, because of differences in the substituents X and Y , gives rise to separate resonances for the H and H' nuclei. In this case the two hydrogen nuclei are sufficiently close in the molecule that spin-spin interaction can occur, and each resonance will be split into a doublet of the same spacing. In qualitative terms we may say that the resonance frequency of nucleus H depends slightly on whether H' is oriented parallel or antiparallel with respect to the magnetic field. When this type of reasoning is applied to more complicated cases it is found that if a given hydrogen or other magnetic nucleus of spin $\frac{1}{2}$ (or chemically equivalent set of hydrogen nuclei) has n equivalent neighbours of spin $\frac{1}{2}$, then its resonance will be split into $(n+1)$ fine-structure lines whose relative intensities are given by the numerical coefficients of the various terms of a binomial expansion of the type $(x+y)^n$, *e.g.* 1, 2, 1 for $n=2$.

A simple and symmetrical splitting pattern of this type will be observed only so long as the coupling constant, J —which is given by the magnitude of the spacing between the fine structure lines—is much less than the chemical shift, δ , between the two resonances. If J and δ are comparable much more complex patterns are obtained which have to be analysed by appropriate calculations of the energy levels and spectroscopic transitions. However recognisably simple patterns are observed in many cases and these lead to important information about the number of hydrogen atoms on the adjacent carbon or nitrogen atoms. Neighbouring hydrogen atoms attached to an oxygen atom, and sometimes to a nitrogen atom, often do not cause fine-structure splittings because of exchange processes which involve relatively rapid breaking of OH bonds. Under these conditions a given pair of nuclei are connected together for too short a period for the spin-spin interaction to be operative.

With saturated hydrocarbon groupings the spin-spin coupling constants are sufficiently great to be resolved in the observed spectrum if the adjacent interacting hydrogen atoms are attached to the same or immediately neighbouring carbon atoms, *i.e.* if the nuclei are separated by two or three bonds only. Longer-range interactions usually only give rise to resolvable splittings when double or triple bonds form part of the intervening electron distribution. Even then these splittings are usually sufficiently small that they can be recog-

nised as such. Finally it should be noted that chemically equivalent hydrogen nuclei (for which $\delta = 0$) do not cause mutual splitting of each other's resonance; this is because of the operation of a selection rule that reduces the intensities of all fine-structure lines but the central one to zero. For this reason isolated CH_2 and CH_3 groups give sharp and strong resonances in the spectra.

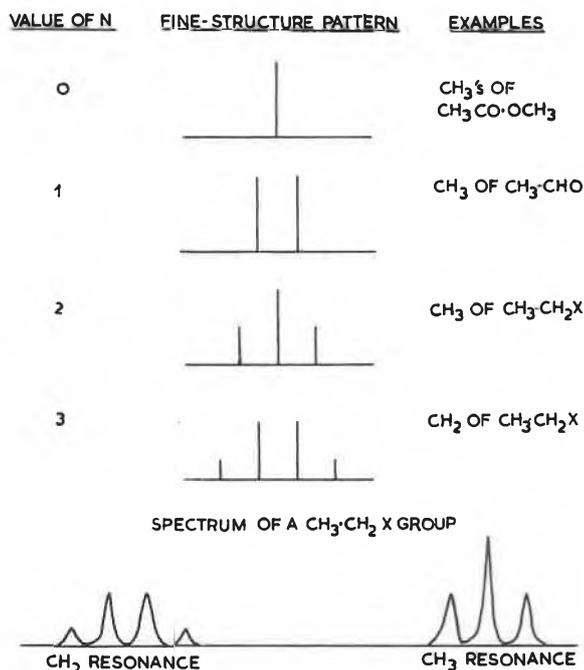


Fig. 5. Simple fine-structure patterns caused by interaction of the resonating nucleus with N equivalent adjacent nuclei of spin $\frac{1}{2}$

Figure 5 shows some of these simple splitting patterns and illustrates, as an example, the characteristic patterns of lines of the OCH_2CH_3 group which we have already seen in the spectrum of ethyl alcohol, and which occurs in the spectra of all molecules containing this group.

The operation of the various factors that have been discussed so far—the chemical shifts and spin-spin splittings—are illustrated by the series of spectra of typical organic molecules shown in the next few Figures. These spectra were obtained some years ago under uniform conditions which were not those of the highest resolving power. They are however adequate for the present purpose. The 'zero' of the chemical shift scale is that of water; the resonances were actually measured against cyclohexane ($\sigma = +3.9$) used as an internal reference.

Figure 6 shows the spectra of a representative series of hydrocarbons and illustrates how CH bonds in saturated hydrocarbon groups give differently located resonances from those of olefinic CH groups ($\text{C}=\text{C}-\text{H}$), and that these in turn are generally distinguishable from aromatic CH groups. This latter distinction is one which is not often so readily made by other spectroscopic methods. Another very useful NMR rule is that CH

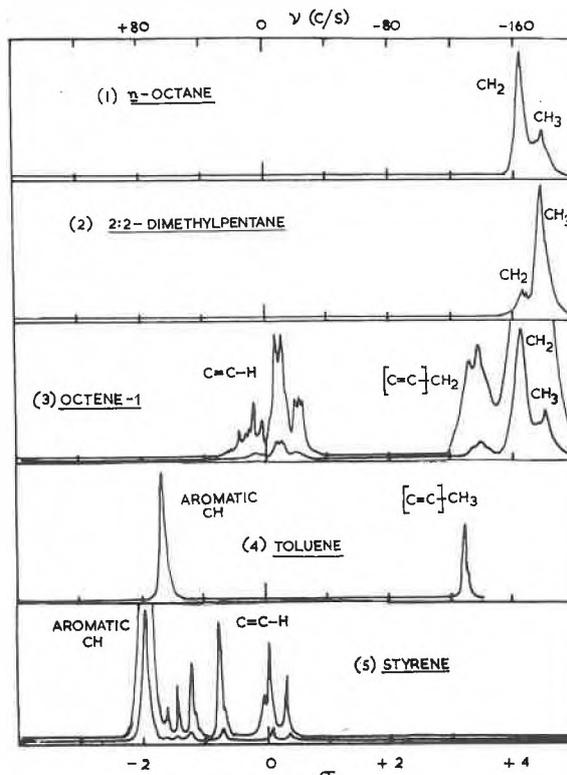


Fig. 6

groups attached to saturated carbon atoms can be distinguished from those attached to $\text{C}=\text{C}$ groups (i.e. in allylic positions) or to benzene rings.

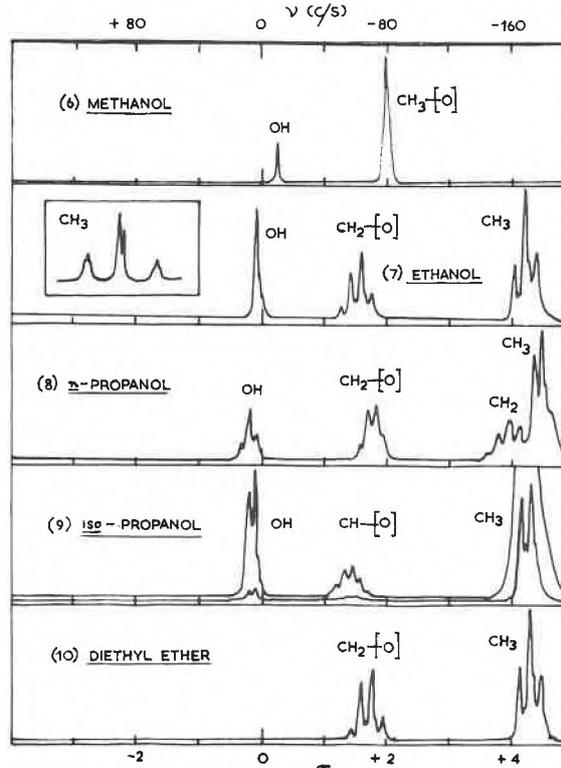


Fig. 7

Figure 7 shows three main series of bands caused by (a) CH groups attached to saturated carbon atoms (b) CH groups attached to oxygen atoms and (c) OH groups. In general OH resonances vary much more widely in position than is apparent here owing to changes in the strength of hydrogen-bonding.

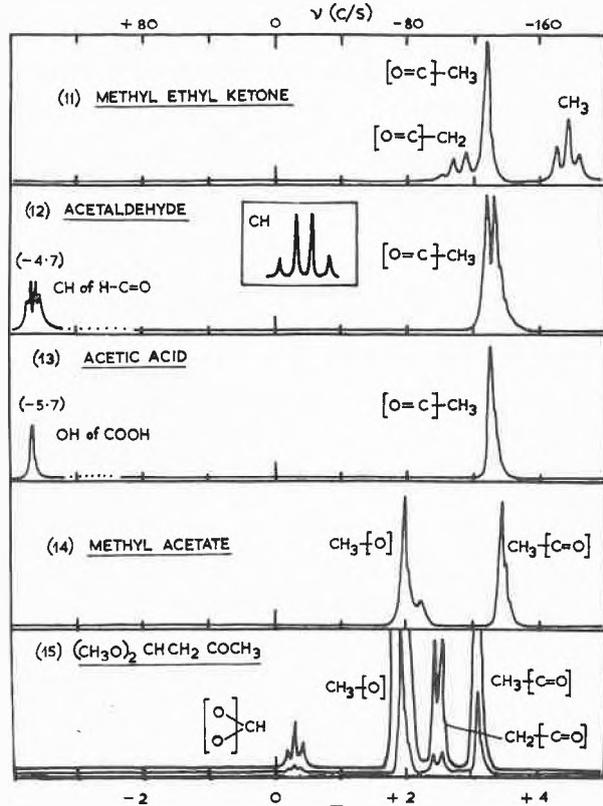


Fig. 8

In Figure 8 it is seen that CH_3 or CH_2 groups next to a carbonyl group, e.g. $\text{CH}_3\text{-[C=O]}$ have a characteristic region of absorption, and that aldehyde CHO groups and $\text{CO}\cdot\text{OH}$ groups give very low hydrogen chemical shifts. The carboxylic OH resonance is lower than that of alcohol OH groups illustrated in Figure 7 because of the stronger hydrogen-bonding occurring in the acid dimers.

Figure 9 shows the positions of various CH-[N] and NH resonances.

Some of these characteristic group frequency ranges for CH groups are summarized diagrammatically in Figure 10. This shows how readily distinctions can be made between the different types of CH groups in hydrocarbon groupings, and also how pronounced are the effects of neighbouring electronegative atoms such as oxygen and nitrogen on CH_3 resonances. The resonances of CH_2 and CH groups attached to the same type of nuclei usually occur at slightly lower σ values than those of CH_3 groups. The pronounced effect of electronegative atoms means that, although the resonances of these atoms themselves cannot be studied directly,

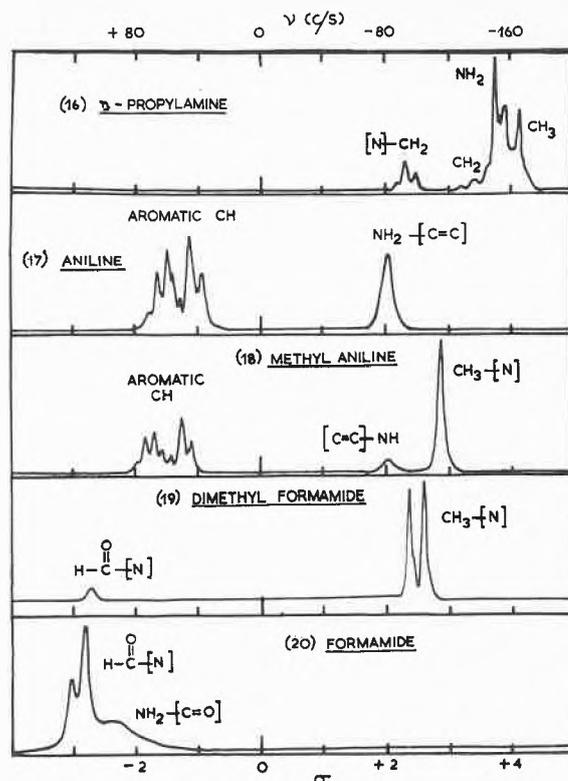


Fig. 9

nevertheless a great deal can be inferred about the presence of such groups from the hydrogen spectra. In our experience OCH_3 and NCH_3 (as well as $\text{C}-\text{C}-\text{CH}_3$) groups

can be very readily located by NMR methods. NMR spectra are particularly useful in analysing the structure of ether-type groups involving C-O bonds, which are not susceptible to ready analysis by infra-red spectroscopy.

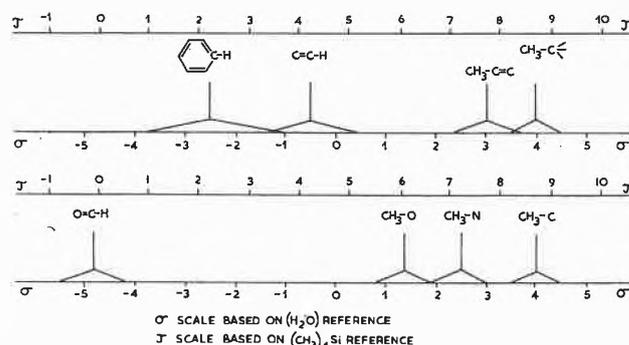
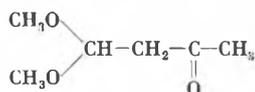


Fig. 10. Characteristic chemical shift values for the hydrogen resonances of various types of CH groups

Useful work can also be done with hydrogen resonances from OH and NH groups, but in some cases the variability of the positions of these with different strengths of hydrogen-bonding makes them less useful

for the determination of molecular structures. In amide groups and in unsaturated heterocyclic nitrogen-containing rings the NH resonance is often so broad as to be difficult to detect (compare the spectrum of formamide in Figure 9). This broadening is caused by the quadrupole moment of the nitrogen nucleus.

As a more detailed example of the type of structural analysis that can be made let us consider the NMR spectrum that was obtained in order to confirm the structure of a newly prepared compound, thought to be



In terms of chemical shifts we can expect to find hydrogen resonances for the molecule at roughly the positions listed below given in σ units (relative to the resonance of H_2O as a reference zero) with the indicated relative intensities. Square brackets indicate neighbouring groups whose properties effect the σ values.

	σ value	Intensity
$\text{CH}_3-\text{[C=O]}$	~ 3	3
$\text{CH}_2-\text{[C=O]}$	~ 2.5	2
$2 \times \text{CH}_3-\text{[O]}$	~ 1.5	6
$\text{CH} \begin{array}{l} \text{[O]} \\ \text{[O]} \end{array}$	~ 0.5	1

The resonances of $\text{CH}_3-\text{[O]}$ and $\text{CH} \begin{array}{l} \text{[O]} \\ \text{[O]} \end{array}$ groups are lower in value than the other CH_3 and CH_2 resonances because of the electronegative oxygen atoms that are adjacent to the CH bonds. Considering next the fine-structure patterns to be expected because of spin-spin splittings, we see that the three methyl groups should all give strong and sharp resonances because there are no hydrogen atoms on the adjacent carbons to cause splittings. The CH_2 and CH groups are, however, adjacent to each other and should give, by mutual interaction, a triplet for the CH resonance and a doublet of the same separation for the CH_2 resonance.

The actual NMR spectrum of this substance is the last one illustrated in Figure 8 and shows all the expected features. The spectrum is therefore seen to provide a stringent test of the details of the structure of this molecule. Although this is a somewhat favourable case in that the chemical shifts of the different groups are well separated from each other, in nearly all cases that we have studied it has been possible to check directly on at least some of the structural groups present in even large organic molecules. For smaller and medium sized molecules it is quite commonly possible, as in the example just given, to assign every resonance to a separate structural group.

All of the spectra that have been illustrated so far are of substances which occur as liquids at room temperature. However most larger organic molecules are solids, and solvents have to be found for them in order to obtain NMR spectra of the type that we have been considering. It is important to consider the extent to which the solubility requirement sets a limitation to the application of the NMR method. Ideal solvents for work with hydrogen resonances are, of course, those such as CCl_4 , CS_2 and C_2Cl_4 which do not themselves contain hydrogen nuclei. However others which have only one chemical type of hydrogen atom will mask only a small part of the overall spectral region; these include many excellent solvents such as chloroform, dioxan, acetone, water, and hydrocarbons such as benzene and cyclohexane. Finally deuterated solvents such as CDCl_3 and D_2O are available at moderate prices and these are becoming widely used. It may be concluded that the solvent situation is a fairly satisfactory one (it is certainly a much more favourable position than in infra-red spectroscopy; perhaps not quite so favourable as for ultra-violet spectroscopy). Even those compounds which are not soluble in a suitable solvent can often be made so by slight modification of the chemical structure, e.g. replacement of OH groups by OCH_3 or $\text{O}\cdot\text{CO}\cdot\text{CH}_3$ usually enhances solubility in chloroform. Nevertheless there remain a few cases where a suitable solvent cannot be found, and more where solubility is sufficiently limited that the spectrum is weak. Although many very successful spectra have been obtained for organic molecules as large as steroids, it remains true, because the solubility of large molecules is less in terms of gram-molecules per litre than for smaller ones, that their spectra are relatively considerably weaker. This is a limitation of the method which must be taken into account.

As a final example we shall consider briefly the NMR spectrum of a large and biologically important molecule, the plant hormone gibberellic acid, which has the property of causing plants to grow to considerably greater heights than usual.

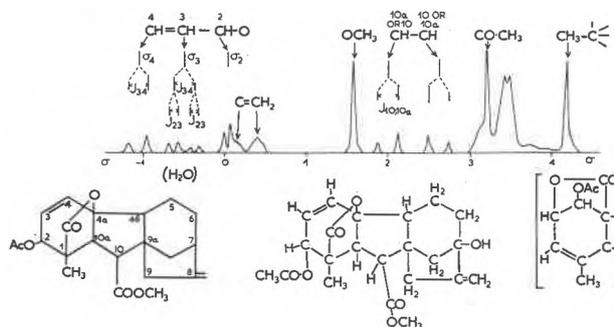


Fig. 11. The hydrogen (proton) nuclear-magnetic-resonance spectrum of methyl monoacetyl-gibberellate

The spectrum illustrated in Figure 11 is that of the acetyl derivative of the methyl ester of gibberellic acid. This derivative, rather than the acid itself, has been

studied because of its enhanced solubility in chloroform. The detailed formula for this molecule is shown in the centre of the bottom part of the Figure. An abbreviated formula on the left shows only the carbon and oxygen skeleton and the numbering of the carbon atoms. The main features of the structure of this molecule were worked out through much chemical and infra-red work by Mr. J. F. GROVE and Dr. B. E. CROSS of Imperial Chemical Industries Ltd., Welwyn (England), but NMR spectroscopy assisted considerably in settling a number of the important final details⁴.

Reading from left to right in the spectrum of Figure 11, the three strongest and sharpest bands correspond to the three methyl groups of types $\text{CH}_3\text{-[O]}$, $\text{CH}_3\text{-[CO·O-]}$,

and $\text{CH}_3\text{-}\left[\begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C}-\text{C} \\ \diagdown \quad \diagup \\ \text{C} \end{array}\right]$. The sharpness of these resonances is

caused by the lack of hydrogen nuclei on the next carbon atom which might otherwise cause fine-structure splitting. In brackets on the right hand side of the formulae is shown an alternative structure for the first ring, ring A, which could not at first be ruled out on chemical grounds. However in this formula the third methyl group

is of type $\text{CH}_3\text{-[C=C]}$ rather than $\text{CH}_3\text{-}\left[\begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C}-\text{C} \\ \diagdown \quad \diagup \\ \text{C} \end{array}\right]$ and the resonance would then have occurred at $\sigma \sim 3$, rather than at 4.2 as observed.

The considerable amount of fine structure found in the region from $\sigma = 0.5$ to $\sigma = -1.5$ must be associated with olefinic CH resonances of the CH=CH group of ring A, the C=CH_2 group of ring C and the resonance of the [C=C]-CH-[O] group, also in ring A. From the spectra of other derivatives of gibberellic acid it is found that the C=CH_2 group causes two broad resonances, one at $+0.4$, and the other overlapping the sharp doublet at $\sigma \sim +0.1$. The remainder of the 8-line spectrum in this region can be subdivided into a doublet (centred at $\sigma = +0.05$), a quartet (centre at $\sigma = -0.5$) and another doublet (-1.1). In fact this is just the type of pattern expected from the 3-hydrogen system CH=CH-CH-[O] in ring A. The two doublets are caused by the outer hydrogen atom whose resonances are split to different degrees by the central hydrogen, and the quartet is the doubly split resonance of the latter. Because the chemical shifts are comparable with the fine-structure splittings the intensities of all the fine-structure lines are not equal, but the general pattern is clear and provides strong confirmatory evidence for the postulated structure of ring A.

The aim of the above discussion has been to show with examples how effective a tool NMR spectroscopy of hydrogen nuclei can be for checking and determining organic structures. There are, however, a number of limitations to the present-day technique on which work still requires to be done.

⁴ N. SHEPPARD, *J. Chem. Soc.* 1960 (in press).

The best resolution of present-day spectrometers is probably adequate for most work on organic molecules. Although further advances in resolution would be welcome the present situation is satisfactory. However, as has already been mentioned, a major limitation at present is the weakness of spectra, particularly from substances of limited solubility; these are often the higher molecular-weight organic substances. Solubility itself can often be enhanced by working with samples above room temperature and equipment for this type of work is becoming available. Another possibility for future advance is the use of higher magnetic fields, for the strength of spectra are approximately proportional to the square of H_0 ; it seems probable that advances in this direction will come from the further development of spectrometers using electromagnets. Furthermore, although the information obtainable from NMR spectra makes it imperative that the technique should be developed as a really routine tool, it is at present only in the semi-routine stage. The main limitations here are temperature-dependent drifts that occur in the magnitude and the homogeneity of the magnetic field. Because of these the accurate measurement of line positions has to be done by techniques which are time-consuming, and further time is lost recovering good field conditions. Recent work has shown that there are possibilities for overcoming both of these difficulties; it is possible that spectrometers with permanent magnets may have advantages in providing stable routine operation conditions. It is clear from the above remarks that the techniques of NMR spectroscopy are still developing. It seems appropriate to end by paying tribute to chemists such as GUTOWSKY⁵ and SHOOLERY who have pioneered this method as a tool for determining molecular structure, and to the electrical engineers and physicists, many of them working with Varian Associates, who have made the exceedingly precise equipment readily available. Without their efforts nuclear-magnetic-resonance spectrometers would still be curiosities used by a limited number of physicists and physical chemists, rather than tools widely used for the analysis of molecular structure.

Bibliography

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- Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* by L. M. JACKMAN; this is an excellent systematic account of the applications to organic chemistry.

⁵ L. H. MEYER, A. SAIKA, and H. S. GUTOWSKY, *J. Amer. Chem. Soc.* 75 (1953) 4567.