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Nuclear Magnetic Resonance in Liquid Crystals

Liquid crystal solvents have provided a new method for the determination of molecular structure.

Saul Meiboom and Lawrence C. Snyder

Some 5 years ago Saupe and Englert published a series of pioneering papers (l) in which they showed that liquid crystals can serve as oriented solvents for a new kind of high-resolution nuclear magnetic resonance (NMR) spectroscopy. The technique has not only contributed to the understanding of NMR spectroscopy but has also provided a new method for determining molecular structure, particularly for small organic molecules. It is this method which we stress in this review.

The term *molecular structure* is used here to mean the detailed spatial arrangement of the atoms in a molecule. In order to put our subject in perspective, we first enumerate the main techniques of molecular structure determination. We list only those techniques which give relatively direct and detailed information.

1) X-ray diffraction in crystals. Xrays are scattered by the electrons, and thus the results are often in the form of an electron-density map of the crystal.

2) Neutron diffraction in crystals. This is similar to, and complements, the x-ray technique, except that neutrons are scattered by the atomic nuclei rather than by the electron cloud.

3) Electron diffraction in gases. This

technique produces a radial distribution function for the molecule, which is interpreted in terms of interatomic distances.

4) Microwave spectroscopy in gases or in molecular beams. An interpretation of the rotational spectrum gives the moments of inertia of the molecule. Especially if such measurements are made for a number of isotopically substituted species, much information about the structure of relatively simple molecules can be obtained.

5) Nuclear magnetic resonance spectroscopy in liquid crystal solvents is the most recent addition to this list of more or less direct methods. It is unique among the techniques mentioned in that the material studied is in the liquid phase.

We first give some basic facts about NMR spectroscopy and liquid crystals, which, it is hoped, will make the subject comprehensible to the uninitiated; some knowledge of regular high-resolution NMR spectroscopy is assumed.

Basic NMR Spectroscopy

For the sake of simplicity, we restrict the following outline to the NMR spectroscopy of protons in diamagnetic materials. Although much of the discussion applies to other magnetic nuclei as well, the magnitudes of the effects in other nuclei are often quite different. The resonance frequencies exhibited in an NMR spectrum are given by the following equation (2)

 $\omega \equiv \gamma H \tag{1}$

where γ is the magnetogyric ratio of the nucleus and H is the effective magnetic field strength at the nucleus. The effective field H is due to the external magnetic field H_0 modified by small contributions from the substance of which the nucleus is a part. It is these contributions that make NMR spectroscopy interesting, as they give information on the substance investigated. The contributions may be classified, according to their source, into three groups.

1) The contribution from the electrons in the material. In diamagnetic materials the electron cloud has a slight shielding effect on the applied magnetic field H_0 . The magnitude of this effect depends on the details of the electron configuration, and thus varies with molecular species and with the position of the nucleus in the molecule. These differences appear as the well-known chemical shifts in high-resolution NMR spectra. For protons, relative shifts up to a few parts per million in frequency are common.

2) A direct contribution from the magnetic dipole moments of the nuclei. The magnetic field of a proton is far from negligible; at near-neighbor interatomic distances it is of the order of 10 oersteds, resulting in frequency shifts of the protons up to about 50 kilohertz. These fields are dominant in the NMR spectra of solids, where a given nucleus feels fields from a large number of nearby nuclei. This interaction occurs with other nuclei in the same molecule (intramolecular) and with nuclei in other molecules (intermolecular).

From simple magnetostatics the interaction energy of two parallel dipoles is calculated as

$$E = \frac{\mu_1 \mu_2}{r^3} (1 - 3\cos^2 \theta)$$
 (2)

where μ_1 and μ_2 are the magnetic moments of the nuclei, *r* is the length of the vector joining the dipoles, and θ is the angle between this vector and the direction of the dipoles.

The authors are members of the technical staff, Bell Telephone Laboratories, Murray Hill, New Jersey.

In liquids, the molecules move rapidly, and thus the direct dipole-dipole interaction is averaged over all spatial directions of the vector joining a pair of nuclei. If all directions are equally probable, as they are in a normal (isotropic) liquid, then this averaging produces exactly zero. With polar coordinates,

$$\frac{2\pi\mu_{\mu}\mu_{2}}{r^{3}}\int_{0}^{\pi}(1-3\cos^{2}\theta)\sin\theta \ d\theta=0$$

(3)

A corresponding zero result is obtained in a quantum mechanical calculation. It is for this reason that a chemist, when using high-resolution NMR spectroscopy as a routine analytical tool, can always ignore the direct dipole-dipole interactions in interpreting spectra obtained in ordinary solvents.

The point has been elaborated because it is the nonzero average of the direct dipole-dipole interactions that sets NMR spectroscopy in liquid crystal solvents apart from regular highresolution NMR spectroscopy. As discussed below, in liquid crystal solvents the solute molecules will in general tumble anisotropically, and an angledependent weighting function must then be introduced in the integrand of Eq. 3. The resultant intramolecular dipoledipole interaction will thus no longer be zero, and in fact will be the predominant interaction. However, the intermolecular interaction averages to zero as a result of rapid translational diffusion. In this respect the situation in a liquid crystal is intermediate between that in a normal liquid, where all direct interactions average to zero, and that in a solid, where both intraand intermolecular interactions are

present. The power of the liquid crystal technique largely derives from this fact.

3) A contribution from the indirect nuclear coupling. This interaction, in which both nuclei and electrons play a role, results in the familiar indirect, or scalar, spin-spin coupling. A simplified physical picture of the origin of this coupling is as follows: the magnetic moment of a nucleus induces a polarization in the surrounding electron cloud, which in turn interacts with the magnetic moment of another nucleus. This electron-coupled interaction is not averaged out by the tumbling of the molecule. The magnitude of protonproton interactions is seldom much over 10 hertz, but it can be much larger for heavier nuclei.

According to a well-known rule in the interpretation of high-resolution NMR spectra, the indirect spin-spin coupling does not cause line splitting if the interacting nuclei are equivalent (that is, have the same frequency). This rule results from the particular (scalar) form of the indirect spin-spin interaction; it does not apply to the direct interaction. Thus the benzene spectrum, which consists of a single line in ordinary NMR spectroscopy because all six protons are equivalent, shows a complex spectrum of some 50 lines in a liquid crystal solvent.

Liquid Crystals

For the general subject of liquid crystals, or the mesomorphic phases as they are often called, we refer the reader to a number of excellent reviews (see 3). Here we discuss only those compounds and properties which are relevant for the NMR work.

1) Nematic liquid crystals. The pioneering NMR work of Saupe and Englert, and much of the later work, has been done with the compound p,p'-di-*n*-hexyloxyazoxybenzene:

At temperatures below 80°C this compound is a crystalline solid; above 125°C it is a normal, clear liquid; but in the intermediate temperature range it is in the nematic mesophase, a low-viscosity, somewhat turbid liquid. Under the polarizing microscope it is seen to be double-refracting, whence the name "liquid crystal," and it exhibits black "threads," whence the name "nematic" (from the Greek word for thread). The "threads" are actually due to discontinuities in the refractive index.

The model we favor for the nematic phase is as follows. Intermolecular forces cause a long-range order, by orienting the long axes of the rodlike molecules parallel but otherwise leaving the molecules free to move relative to each other, very much as they do in the normal liquid. As a result of external disturbances, the nematic liquid is often broken up into a number of domains, each characterized by its own direction of orientation. A moderate magnetic field (of the order of a few hundred oersteds), acting through the anisotropy of the magnetic susceptibility of the domains, is sufficient to rotate the direction of orientation, and thus creates a uniformly oriented, homogeneous, but anisotropic liquid. There is good evidence that in $p_{,p'}$ -di*n*-hexyloxyazoxybenzene and similar compounds the long axes of the mole-



Fig. 1. Nuclear magnetic resonance spectrum of cyclopropane in nematic p,p'-di-*n*-hexyloxyazoxybenzene. The spectrum was obtained at a frequency of 60 megahertz and a temperature of 80°C. Note that the spectrum has a center of symmetry, a consequence of the equivalence of the protons.

cules align parallel to the magnetic field.

In the NMR technique discussed here, the liquid crystal serves as an anisotropic solvent for the compound to be studied. The fact that, in the NMR spectrum, the line width of the solute in the liquid crystal phase is about the same as its line width in the isotropic phase indicates that rapid tumbling and translation of the solute molecules occur in both phases. We think of the situation in terms of a model in which the immediate environment of a solute molecule looks very much the same in the normal and the nematic liquid phases. The rodlike solvent molecules are oriented nearly parallel to each other in both cases, but in the normal liquid a specific orientation persists only for a short distance and a short time, while in the nematic liquid it persists over a long range and, when aided by an external magnetic field, is uniform over the whole sample.

2) Cholesteric liquid crystals. As indicated by its name, this mesomorphic phase appears in many cholesterol derivatives. We picture the cholesteric phase as being derived from the nematic phase by the application of a twist around an axis. In other words, the cholesteric phase has a helical structure characterized by a gradual change of molecular orientation on going in the direction of the twist axis. Friedel suggested as early as 1922 that the cholesteric and nematic phases are closely related. There is now good evidence (4) that the helicity of the cholesteric phase has the same underlying cause as optical activity: the presence of an asymmetric center in the molecule. If in compound I the n-hexyl groups are replaced by optically active pentyl groups, the resulting compound has all the characteristics of the cholesteric phase (4). Conversely, in mixtures of cholesteryl chloride and cholesteryl myristate, which in pure form produce cholesteric structures of opposite helical sense, the helicity can be compensated, and in one critical proportion a nematic phase is produced. This behavior falls in a logical pattern if we realize that, qualitatively, we can think of optically active molecules as comparable to screws. By actually experimenting with a few coarse-threaded screws, one can easily convince oneself that, due to interlocking of their threads, righthanded screws do not stack exactly parallel to each other but, rather, tend to form a right-handed helix and thus 20 DECEMBER 1968



Fig. 2. Molecular model of cyclopropane.

a "cholesteric" structure. Obviously, left-handed screws will form a lefthanded helix, and a "racemic" mixture of left- and right-handed screws will give a "nematic" structure.

The cholesterol derivatives, too, will orient in a magnetic field, but, in contrast to the azoxybenzene compounds, the molecules align with the long axes perpendicular to the field direction, and thus with the axis of the helix parallel to the field (5).

3) Smectic liquid crystals. In this mesophase the molecules are arranged not only parallel to each other but also in layers. Quite a few compounds exhibit both smectic and nematic, or cholesteric, mesophases. The smectic phase always is stable in the lower temperature range. It generally has a high viscosity and, accordingly, produces broad NMR lines; thus it does not seem suitable for the kind of NMR work reviewed here.

4) Finally, we must mention two quite different systems, which are interesting possibilities as anisotropic solvents. Lawson and Flautt (6) have described lyotropic mesophases, a typical one having the composition 36 percent sodium decyl sulfate, 7 percent *n*-decyl alcohol, 7 percent sodium sulfate, and 50 percent water (or heavy water). These mesophases orient in a magnetic field and show the "threaded" microscopic structure and birefringence typical of the nematic phase. The other system is a solution of polybenzyl



Fig. 3. Comparison of (top) experimental and (bottom) computed spectra of cyclopropane. Only the left portion of the spectrum is shown.



Fig. 4. The central part of the cyclopropane spectrum, recorded at much higher sensitivity than the spectrum of Fig. 3. The bottom spectrum is experimental, the top one calculated. Lines w, x, and y correspond to w, x, and y of Fig. 3; the cross indicates the center of the spectrum. The small peaks, indicated by capital letters, are due to the presence of molecules containing one ¹³C nucleus. In natural isotopic abundance the fraction of such molecules is 3 percent.

glutamate in methylene chloride or similar solvent. The mesomorphic character of such solutions was first described by Robinson, and they have been studied in recent NMR work by Sobajima, by Panar and Phillips, and by Samulski and Tobolsky (7). The solutions are presumably cholesteric.

Experimental Aspects

The only basic difference between the liquid crystal technique and ordinary high-resolution NMR spectroscopy lies in the use of a suitable liquid crystal, rather than a normal liquid, for the sample solvent. In principle, any high-resolution NMR spectrometer will do, although some may require modification to allow the larger sweep widths (often a few kilohertz) required. However, a number of factors are more critical in liquid crystal work than in regular NMR spectroscopy and require attention if high quality spectra are desired.

1) A high degree of temperature stability and uniformity over the active part of the sample is essential. In liquid crystal solvents, temperature variation affects the degree of solute orientation, and thus the magnitude of the dipoledipole interaction. Nonuniformity of temperature typically results in increasing line broadening toward the outermost lines of the spectrum.

2) Intensities are often low, due to limited solute concentration and the multitude of lines in a typical spectrum. Time-averaging techniques are therefore often required.

3) In many cases, though not all, spinning of the sample will destroy the



Fig. 5. Cyclobutane spectra. The top three spectra are calculated, for the three molecular structures idicated. The bottom spectrum is experimental. Only one side of the spectra is given; the complete spectra have a center of symmetry similar to that of the cyclopropane spectrum of Fig. 1.

macroscopic orientation of the solvent (8). The spectrometer therefore must have good resolution (preferably better than a few hertz) even without sample spinning.

4) In choosing liquid crystal solvents one looks for low viscosity (in order to obtain narrow solute lines), a high degree of orientation in a magnetic field, sufficient solubility of the compounds that are to be studied, and absence of disturbing solvent lines. Paradoxically, this last condition is met by choosing a liquid crystal which has a large number of protons. The number of lines in the NMR spectrum of the solvent is then so large that the lines overlap extensively and form a uniform background for the high-resolution solute spectrum. Thus, the solvent p,p'di-n-hexyloxyazoxybenzene (structure I) does not produce any detectable narrow lines, whereas the analog compound with methyl instead of hexyl groups (p-azoxyanisole) does produce a disturbing background.

Until now, much of the published work has been done with p,p'-di-nhexyloxyazoxybenzene, which proves to be a good solvent for hydrocarbons. For polar molecules, such as alcohols, the compound p-n-octyloxybenzoic acid has been used (9). The nematic state is presumable made up of the dimer



A drawback of both these compounds is the fact that their nematic mesophase occurs at temperatures well above room temperature. To facilitate attainment of the required temperature stability and homogeneity, a compound whose liquid crystal phase occurs at room temperature would be very desirable. The best course seems to be the use of eutectic mixtures of liquid crystals (10). However, other systems, such as those mentioned in the preceding section, hold promise.

Theory

The NMR spectrum of a compound dissolved in a liquid crystal solvent is much more complex than the spectrum of the same compound dissolved in an isotropic solvent and cannot be easily understood intuitively. The familiar multiplet rules of high-resolution NMR spectroscopy, whose validity depends on the accuracy of a first-order perturbation treatment of the interactions, are seldom applicable in liquid crystal spectra because the interactions are large. In all but the simplest cases, numerical diagonalization of the spin Hamiltonian (\mathcal{H}) is necessary. The procedure is the same as that for ordinary high-resolution NMR spectra (2) except that additional terms representing the direct dipole-dipole interactions must be included in the spin Hamiltonian (11). The latter, in frequency units, is written as follows:

$$\begin{aligned} \mathcal{H} &= \sum_{i} \gamma_{i} H_{0}(1-\sigma_{i}) I_{zi} + \\ &\sum_{i>j} J_{ij}(I_{xi}I_{xj} + I_{yi}I_{yj} + I_{zi}I_{zj}) + \\ &\sum_{i>j} D_{ij}(-\frac{1}{2}I_{xi}I_{xj} - \frac{1}{2}I_{yi}I_{yj} + I_{zi}I_{zj}) \end{aligned}$$

$$(4)$$

The first term at the right-hand side of Eq. 4 represents the Zeeman energy. Here H_0 is the applied magnetic field, γ_i is the magnetogyric ratio, σ_i is the screening constant (relative chemical shift), and I_{xi} , I_{yi} , and I_{zi} are the components of the angular momentum operator of the *i*th nucleus. The second term accounts for the indirect spin-spin interactions, characterized by the coupling constants J_{ii} between the *i*th and the *j*th nuclei. The first two terms are all that are needed for interpretation of NMR spectra in ordinary liquids. The third term allows for the direct interactions in the case of liquid crystal solvents.

With the Hamiltonian (Eq. 4) one can interpret the NMR spectrum in terms of the following parameters: chemical shifts σ_i , indirect couplings J_{ij} , and direct couplings D_{ij} (12). Our main interest here is in the direct coupling constants D_{ij} , which are dependent on the geometry of the molecule through the equation

$$D_{ij} = K \left\langle (1 - 3\cos^2 \theta_{ij}) r_{ij}^{-3} \right\rangle \quad (5)$$

Here r_{ij} is the length of the vector connecting nuclei *i* and *j*, and θ_{ij} is the angle between this vector and the direction of the applied field H_0 ; *K* is a known constant and equals 120,067 Hz Å³ for protons. The angular brackets indicate that the enclosed expression must be averaged over the motions of the molecule. Here we consider the molecule to be rigid—that is, we average over the molecular tumbling only. The influence of molecular vibrations (mentioned below) is small.

Equation 5 relates quantities derived from the NMR spectrum with the structure of the molecule and is the basis

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for obtaining structural information, provided we know how to take the required average. This last qualification may appear to be a serious difficulty, because we do not know the actual probability distribution over the orientations of the tumbling molecule, a quantity by which the dipolar interaction must be weighted when the average is computed. Actually, a detailed knowledge of this function is not needed. The averaging process can be characterized by at most five parameters (11), which we call motional constants. Because the angular factor in Eq. 5 is a seconddegree spherical harmonic, the relevant part of the probability distribution is a linear combination of the five seconddegree spherical harmonics. In fact, the number of parameters is often further reduced by symmetry of the molecule: only those spherical harmonics that are invariant under all symmetry operations of the molecule have nonzero coefficients. Thus, for the important case of molecules having a threefold or higher axis of symmetry, only one parameter is needed.

From *n* different objects, n(n-1)/2different pairs can be formed. Accordingly, the number of measured pair interactions, D_{ij} , will increase more rapidly than the number of nuclei. Therefore, if the number of magnetic nuclei in a molecule is not too small, the number of Eqs. 5 will be larger than the number of unknowns, and it should be possible to obtain the molecular structure, as well as the motional constants, from a knowledge of the D_{ij} 's—that is, from the NMR spectrum. A closer look at this argument reveals that, in suitable cases, it is indeed possible to obtain quite detailed structural information on the shape of the molecule. However, it is impossible to obtain the molecule's absolute size from the NMR spectrum, for the following reason. If Eq. 5 is written out in terms of spherical harmonics, as discussed above, then the motional constants multiplying each term will always appear in combination with a factor r_{ij}^{-3} , and therefore cannot be calculated separately. What all this boils down to is that one has to adopt the absolute value of one internuclear distance as obtained by other methodsfor instance, electron diffraction. Once this is done, other distances and angles in the molecule can, in principle, be obtained from the NMR spectrum.

In practice the analysis of an experimental spectrum is a trial-and-error Table 1. Parameters of the spin Hamiltonian for cyclopropane (in hertz) (14). The last two rows refer to molecules containing one ¹⁸C atom.

Atom pair* (<i>i</i> , <i>j</i>)	J_{ij}	D_{ij}			
(1,2)	+ 9.5	- 194.51			
(1,4)	- 7.0	+974.00			
(1,5)	+ 5.5	+ 4.35			
(C,1)	+ 162.0	+651.78			
(C,3)	0.0	- 33.95			

* See Fig. 2.

process: one guesses a molecular geometry, motional constants, chemical shifts, and indirect interactions, and computes a spectrum. The parameters are then varied till the calculated and experimental spectra closely agree. Except for the simplest cases, the amount of computation involved in this process is so great that the use of a digital computer is essential. Computer programs have been written which compute and plot the theoretical spectra for any set of input parameters (13).

As a simple example we discuss here the analysis of the NMR spectrum of cyclopropane in a nematic solvent (14). The spectrum is shown in Fig. 1. We begin by assuming that cyclopropane has a plane of symmetry containing the carbon atoms, and a threefold axis. Therefore only one motional constant is required. The positions of the protons are determined by the distances a and b of Fig. 2. With reasonable assumptions for a and b and a guess concerning the motional constant, a set of $D_{i,i}$'s and a theoretical spectrum were computed. The latter was in rough qualitative agreement with the experimental spectrum. Next the value of the motional constant was adjusted to give a correct overall width of the spectrum, and the D_{ij} 's (ratio of a to b) were

Table	2.	Cyclo	propane	geor	netry	', a	s de	eter-
mined	by	NMR	spectros	сору	and	by	elec	tron
diffract	tion	l.						

Method	Dista (angstr	Angle HCH	
	C-C	СН	(degrees)
NMR Spec- troscropy †		••••••	
$D_{12}D_{15}$	(1.510)	1.122	113.6
$D_{14}D_{15}$	(1.510)	1.107	114.4
$D_{12}D_{14}$	(1.510)	1.123	114.4
Electron diffraction ‡	1.510	1.089	115.1

* Values in parentheses are electron diffraction results. \dagger Results obtained by fitting the D_{ij} 's indicated (see 14). D_{C1} has been fitted in all cases. \ddagger See 15.



Fig. 6. Molecular model of bicyclobutane.

varied to improve the agreement. Next, values for the indirect spin-spin coupling constants, taken from the literature for isotropic solvents, were introduced. The signs of these approximate couplings were varied for a sign determination. After a process of refinement on all the parameters had been completed, an excellent agreement, illustrated in Fig. 3, was obtained. The final parameters are given in the top three rows of Table 1.

The spectrum discussed above is that of molecules containing only the nonmagnetic ¹²C isotope. In fact, the natural abundance of the magnetic ¹³C isotope is about 1 percent. Thus, 3 percent of the cyclopropane molecules contain one ¹³C nucleus. These molecules give a proton spectrum richer in lines than that of molecules containing only 12C-one which bears no resemblance to it and is, of course, of much lower intensity. Part of this spectrum is shown in Fig. 4. Its interpretation is of interest, as it gives the positions of the carbon nuclei in the molecule. The

parameters used are identical to those used for the ¹²C molecules, complemented with two additional parameters given in the last two rows of Table 1. Incidentally, the success of such an interpretation provides an independent check on the correctness of the original parameters.

The final step in the interpretation is the correlation of the D_{ii} 's with the geometry of the molecule. The latter can be characterized by three distances—a, b, and c in Fig. 2. As discussed above, one can get only ratios of these quantities, not their absolute values. Thus we have adopted, from electron diffraction results (15), a value of 1.510 angstroms for the carboncarbon distance. There remain three parameters to be determined, two distances and one motional constant. The spectrum analysis gives the five D_{ii} 's of Table 1. An estimate of the consistency of the interpretation may be obtained by comparing the results obtained in using different D's. This comparison is summarized in Table 2.

Results

We next review some of the structural results obtained from NMR spectroscopy in liquid crystal solvents. The structure of the simplest molecules discussed is well known, and an analysis serves as a check on the method. In other cases quantitative structural information is obtained.

The first compound for which a complete quantitative analysis was made was benzene (16). The structure, in which there is a hexagonal arrangement of the protons, is characterized by a single motional constant and a single distance. As discussed in the preceding section, only one adjustable parameter, together with three indirect interactions which play a minor role, is used in calculating the spectrum. The spectrum could be simulated within the limits of experimental accuracy on the basis of this parameter.

Similarly, the spectrum of cyclobutadiene iron tricarbonyl was analyzed by assuming that the protons occupy the corners of a square (17) and that the molecule has an effective fourfold axis of symmetry. The rather complicated spectrum of monofluorobenzene was analyzed by assuming a reasonable structure and then varying the two motional constants (11). The structure of monofluoromethane was likewise confirmed (18).

The fact that quantitative structural information can be deduced from these spectra was shown in the original publication by Saupe and Englert (1, 19). They found that in 2,3,5,6-tetrachlorotoluene, the ratio of (i) the distance between the aromatic and methyl protons to (ii) the separation of the protons in the methyl group is 3.225 \pm 0.025.

Saupe, Englert, and Povh (9) have determined the HCH angle of the methyl groups of acetonitrile, methanol, and methyliodide. For each of



Fig. 7. Spectrum of bicyclobutane. The top spectrum is theoretical, calculated with the parameters of Table 6. The bottom spectrum is experimental.

Table 3. HCH angles in methyl groups as determined by NMR spectroscopy in liquid crystal solvents and by microwave spectroscopy.

Method	CH ₃ CN	CH ₃ OH	CH ₃ I
NMR spectroscopy*	109°2′ 土 2′	110°3′±8′	111°42′±2′
Microwave spectroscopy †	109°16′	109°2′±45′	111°25′

* See 9. † See 25, 26, and 27, respectively.

Table 4. Ratios of proton-proton distances for methyl acetylene, methyl diacetylene, and dimethyldiacetylene as measured by NMR spectroscopy in liquid crystal solvents and by other methods.

Method	Distance ratio						
	$\begin{array}{c} \text{H-C} \equiv \text{C-CH}_3 \\ (R/r) \end{array}$	$ \begin{array}{c} H-C \equiv C-C \equiv C-CH_3 \\ (R/r) \end{array} $	$CH_{3}-C \equiv C-C \equiv C-CH_{3}$ (ϵ_{0}/ρ)				
NMR spectroscopy* Other †	$\frac{2.353 \pm 0.003}{2.352}$	3.711 ± 0.011 3.757	$7.035 \pm 0.02 \\ 7.396$				

* See 20. † See 28, 29, and 30, respectively.

Table 5. Structure of cyclobutane, as determined by NMR spectroscopy and by electron diffraction.

	Distance (Angles (degrees)			
Method	C-C	C–H	нсн	Dihedral	Methylene tilt*
NMR spectroscopy † Electron diffration §	(1.548) 1.548 ± 0.003	$\frac{1.171 \pm 0.02}{1.092 \pm 0.010}$	108.5 ± 2 110	35 ± 2	2.5 ± 2 0 (assumed)

^{*} The angle between the bisector of angle HCH and the plane through the nearest carbon nuclei. The direction of tilt is such that the distance between axial protons on the same side of the ring is increased. \ddagger See 31. \ddagger Electron diffraction result. \$ See 32.

these molecules, one motional constant is required. The angle is, of course, equivalent to the ratio of two distances. The results of Saupe and his associates are summarized in Table 3.

Englert, Saupe, and Weber (20) have deduced relative distances in methyl acetylene, methyl diacetylene, and dimethyldiacetylene. For the first two molecules they found the ratio R/r, where R is the distance between a methyl proton and the acetylenic proton and r is the distance between protons in the methyl group. For dimethyldiacetylene they found the ratio ε_0/ρ , where ε_0 is the distance between the planes containing the methyl group protons and ρ is the distance of the methyl protons from the threefold axis. Their findings are summarized in Table 4. The agreement of structures obtained with the NMR technique with those obtained by other methods is good for the first two molecules, but an appreciable difference is found for the longest molecule (dimethyl acetylene). This is probably an effect of vibrations. As has been noted by others, linear molecules have out-of-plane vibrations. These tend to bring the ends of a molecule closer together. This is shown by the NMR value for the end-to-end proton distance, which is averaged over these motions. On the other hand, the electron-diffraction value for end-to-end distance given in Table 4 under "Other" is the sum of the bond lengths between neighboring atoms and thus is not changed by these vibrations.

In all the studies referred to above, the molecular geometry was so simple that it could be characterized by one ratio of lengths. In more complicated cases the complete determination of molecular structure requires the values for several ratios. We have been working toward the determination of structure in this general case.

The simplest structure we have determined—that of cyclopropane—is discussed above. Cyclobutane is a rather more complex case. The shape of cyclobutane is fixed by five ratios of coordinates. We have been able to establish four of these; the remaining one was fixed by assuming that the two types of C-H bonds are of equal length. Our difficulty in fixing the fifth coordinate of the carbon atoms reflects the fact that this coordinate is defined by rather weak couplings to the protons on the other side of the ring. The region of the spectrum of cyclobutane containing ¹³C, which is sensitive to these couplings, is obscured by the NMR spectra of cyclobutane molecules containing no ¹³C. We are able to analyze and simulate the observed NMR spectrum only if we assume that the molecule is rapidly flipping between two equivalent bent conformers. This is illustrated in Fig. 5, in which calculated spectra for different conformations are compared with the observed spectrum. The degree of bending is specified by the dihedral angle between two planes, each defined by three carbon atoms. Our structure for cyclobutane is given in Table 5. Again for cyclobutane we find that the C-H bonds determined by the NMR method are too long relative to the C-C bond, for which we have taken the length determined by electron diffraction (20a).

Of all the molecules we have studied so far, bicyclobutane is the one whose structure is the most difficult to determine (21). Eight ratios of distances must be determined to establish its shape. We have succeeded in fixing seven, but we have some difficulty with the eighth: it, again, depends on the interaction of ¹³C at the 2-position with the proton attached to the other carbon atom. Again, the corresponding interaction affects the spectra of molecules bearing ¹³C (at the 2-position) only in regions which are strongly overlapped by spectra of bicyclobutane without ¹³C. Minor features of the NMR spectrum permit us to fix this difficult coordinate within wide limits. Our structure for bicyclobutane is given in Table 6. The coordinates used are defined in Fig. 6, and a comparison of calculated and experimental spectra for the coordinates of Table 6 is given in Fig. 7. For bicyclobutane, as for the other

Table 6. Structure of bicyclobutane, as determined by NMR spectroscopy and by electron diffraction.

Method	Angles (degrees)*			Distance (angstroms)*					
	α	β	γ	δ	C1C2	C2C3	C1-H2	C1H4	С2-Н6
NMR spectroscopy † Electron diffraction §	120.2 ± 2 122.8	110.2 ± 1 116.0	128.0 ± 2 125.5	$\sim \frac{126.3 \pm 1}{122}$	(1.507)‡ 1.507	$\begin{array}{c} 1.507 \pm 0.07 \\ 1.502 \end{array}$	1.167 ± 0.02 ~ 1.106	1.194 ± 0.02 ~ 1.106	1.142 ± 0.02 1.108

* See Fig. 6. † See 21. ‡ Electron refraction result. § See 33.

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molecules discussed, we find fairly close agreement with the structure as determined by electron diffraction. However, in the NMR values the C–H bonds are too long relative to the C–C bonds, if the C1–C2 bond length is given the electron diffraction value of 1.507 angstroms.

Limitations

We believe that the major source of inaccuracy in the structure determinations is our failure to account for molecular vibrations. An accurate correction requires knowledge of the amplitudes of the different vibrational modes as well as knowledge of their anharmonicity. We have as yet made no attempt at a systematic accounting, and give only some qualitative remarks on the effect of vibrations.

The structures we have determined for cyclopropane, cyclobutane, and bicyclobutane differ in a systematic way from those determined by electron diffraction: our C–H bonds are too long relative to our C–C bonds.

Two aspects of molecular vibrations contribute to our error. The first is the anharmonicity of the C-H stretching vibration. This makes the mean C-H distance about 0.015 angstrom longer that the equilibrium distance. The effect of anharmonicity of C-C bond stretching on bond lengths in much less, due to the greater mass of carbon atoms. This would cause C-H bonds to appear too long relative to C-C bonds. We should also note that it is the mean value of $1/r^3$ that is being measured, thus even a harmonic molecular vibration tends to shorten the apparent distance between atoms.

Second, out-of-plane vibrations tend to shorten the mean end-to-end distance of a linear molecule to a value less than the sum of the bond distances for the atoms joined (15). This effect has been noted in electron diffraction studies. We feel that this reduces the distances we find between protons across a ring, and thus contributes to the reduction of C--C distances relative to C-H lengths.

So far we have found no evidence that the anisotropic environment experienced by the solute molecule changes the molecule's shape to a significant degree. In order to study such possible changes, we have observed the NMR spectra of protons in neopentane and tetramethyl silane. Because of the tetrahedral symmetry of these molecules, we expect all their motional constants to be zero. This expectation would imply that their proton NMR spectra be single lines in both cases. We find, instead, a triplet of lines with a splitting of 6 hertz (22). We have interpreted these spectra in terms of a change of 0.1 degree in the HCH angle as the molecule rotates in the nematic solvent. This should be one of the larger spectral effects to be observed because of the proximity of the protons in a methyl group.

'It seems that the NMR method will be limited to the study of relatively



Fig. 8. (Top) Nuclear magnetic resonance spectrum of racemic 3,3,3-trichloropropylene oxide dissolved in a mixture of cholesteryl chloride and cholesteryl myristate. (Bottom) Spectrum of the same compound dissolved in p,p'-di-n-hexyloxyazoxybenzene. The line-doubling in the top spectrum is the result of a differentiation of the two enantiomers.

simple molecules. At present we will not even consider for analysis molecules that have more than nine magnetic nuclei. Beyond this limit the spectrum becomes exceedingly complex, and extensive overlap of lines occurs. Also, the number of nuclear states is so large that diagonalizing the matrices of the Hamiltonian becomes too expensive. Group theory is of some help, but does not fundamentally change this problem. It may be possible to deuterate subsets of proton positions and, by means of double irradiation at the deuteron frequency, obtain NMR spectra of the remaining protons. By determining the structure of successive subsets it may be possible to obtain the structure of a large molecule.

Optically Active Solvents

In cholesterol derivatives and their nearly compensated mixtures, a solute molecule experiences an environment which is both anisotropic and helical, For that reason one may expect that optical enantiomers will be oriented differently and will exhibit different NMR spectra. We observed this in the NMR spectrum of racemic 3,3,3-trichloropropylene oxide in a nearly compensated mixture of cholesterol derivatives (23). The bottom trace in Fig. 8 shows the spectrum of this compound when dissolved in nematic p-p'-di-n-hexyloxyazoxybenzene, while the top trace shows the spectrum when the solvent is made up of cholesterol derivatives. The doubling of each peak in the top spectrum is apparent. This spectrum is in fact the superposition of two independent, slightly different spectra, one due to the levo- component of the racemic solute, and the other to the dextro- component.

Other Results

The main theme of this article is the use of NMR spectroscopy in liquid crystal solvents for determining molecular structure. The technique, however, has provided other information of interest. This is mainly of two kinds: results that contribute to a more complete understanding of nuclear magnetic resonance and results relating to liquid crystal structure and intermolecular forces. In this section we briefly touch on these aspects.

In ordinary (isotropic solvent) NMR spectra the assignment of chemical shifts and indirect interactions to specific nuclei is often a matter of conjecture. In appropriate cases liquid crystal spectra can give an unambiguous answer. The high-resolution spectrum of bicyclobutane in an ordinary liquid, for example, is interpreted as due to three pairs of equivalent protons, but their correspondence to the structural pairs can only be guessed at. The liquid crystal spectrum provides an unambiguous assignment.

The absolute signs of the indirect spin-spin interactions is another piece of information which ordinary NMR spectra cannot provide. Again, liquid crystal spectroscopy can be of help, provided the direction of preferred orientation of the solute molecule can be inferred from its shape.

Despite its importance for chemical applications of NMR spectroscopy, the theory of chemical shifts is still in an unsatisfactory state. Contributions related to the anisotropy of the shifts are probably important, and thus some attempts have been made to measure this anisotropy from liquid crystal spectra (17, 18, 20). The basic idea is that the observed chemical shift, like the direct dipole-dipole interaction, is the weighted average over all orientations of the anisotropically tumbling molecule. Therefore, a comparison of the chemical shifts in an anisotropic solvent with those in an isotropic solvent should give the magnitude of the anisotropy of the shift. In practice the method has run into difficulties, as the result has been found to be strongly dependent on the reference substance used. Uncertainties in accounting for solvent susceptibility in the anisotropic solvent are probably at the root of the problem.

Information on intermolecular forces between solute and solvent can be obtained from a study of the variations in motional constants for a number of related molecules. An example is the work of Saupe on a series of chlorobenzenes (24).

Summary and Conclusion

Nuclear magnetic resonance spectroscopy in liquid crystal solvents can give much information not obtainable from high-resolution NMR spectroscopy in ordinary solvents. Specifically, it gives the direct nuclear dipole interactions, which are simply related to the geometry of the solute molecule. It thus provides a technique for obtaining detailed molecular structures. Although the method cannot give absolute size, it can give angles and ratios of distances to an accuracy comparable to that of other methods. Achievement of the highest accuracy will require a careful accounting for the molecular vibrations.

Up to now the method has been applied to small organic molecules, containing up to eight protons. Deuterium substitution may make the method applicable to larger molecules, but the feasibility of this approach has not yet been explored.

In addition to providing structural information, NMR spectroscopy is a useful tool in the study of the liquid crystal solvents and their interactions with solute molecules.

References and Notes

- 1. A. Saupe and G. Englert, Phys. Rev. Letters 11, 462 (1963). For a key to later papers of this group see G. Englert, A. Saupe, J. P. Weber, Z. Naturforsch. 23a, 152 (1968).
- Weber, Z. Naturforsch. 23a, 152 (1968).
 A good general reference book is still J. A. Pople, W. G. Schneider, H. J. Bernstein, High-Resolution Nuclear Magnetic Resonance (McGraw-Hill, New York, 1959).
 I. G. Chistyakov, Usp. Fiz. Nauk, 89, 563 (1966) [Soviet Phys. Usp. English Trans. 9, 551 (1967)]; A. Saupe, Angew. Chem. 80, 99 (1968). For a review of NMR spectroscopy in liquid crystal solvents see G. R. Luckhurst, Quarterly Rev. London 22, 179 (1968).
 M. G. Friedel, Ann. Phys. Paris [IXenne Ser.] 18, 273 (1922); G. Durand, Compt. Rend. 264, 1251 (1967); E. Sackmann, S. Meiboom, L. C. Snyder, J. Amer. Chem. Soc. 89, 5981 (1967).
- (1967)
- (1967).
 5. E. Sackmann, S. Meiboom, L. C. Snyder, A. E. Meixner, R. E. Dietz, J. Amer. Chem. Soc. 90, 3567 (1968).
 6. K. D. Lawson and T. J. Flautt, *ibid.* 89, 5489
- 1967) 7. C. Robinson, Tetrahedron 13, 219 (1961); S.
- Sobajima, J. Phys. Soc. Japan 23, 1070 (1967); M. Panar and W. D. Phillips, J. Amer. Chem. Soc. 90, 3880 (1968); E. Samulski and A. V. Tobolsky, paper presented at the 9th Experi-

mental NMR Conference, Pittsburgh, March

- 8. Spinning about an axis parallel to the static magnetic field (H_0) will not destroy the alignment. This procedure is not practical in conventional spectrometers, but it is usual in spectrometers in which a superconducting sol-
- enoid is used for the generation of H_0 . A. Saupe, G. Englert, A. Povh, Advan. Chem. Ser. 63, 51 (1967). 9.
- 10. D. Demus, Z. Naturforsch. 22a, 285 (1967); H. Spiesecke and J. Bellion-Jourdan, Angew.
- H. Spiesecke and J. Bellion-Jourdan, Angew. Chem. Intern. Ed. Engl. 6, 450 (1967).
 11. L. C. Snyder, J. Chem. Phys. 43, 4041 (1965). A somewhat different but mathematically equivalent treatment has been given by A. Saupe, Z. Naturforsch. 19a, 161 (1964); see also A. D. Buckingham and J. A. Pople, Terme Exceeding Soc. 60, 81 (1962). Trans. Faraday Soc. 59, 81 (1963). 12. An angular dependence of the indirect cou-
- pling will result in a contribution to the D_{ij} 's. For protons this contribution is expected to be very small, and we disregard it here,
- The NMR spectrum simulation programs were written by R. L. Kornegay of Bell Telephone Laboratories.
- 14. L. C. Snyder and S. Meiboom, J. Chem. Phys.
- 47, 1480 (1967).
 15. O. Bastiansen, F. N. Fritsch, K. Hedberg, Acta Cryst. 17, 538 (1964).
- A. Saupe, Z. Naturforsch. 20a, 572 (1965);
 L. C. Snyder and E. W. Anderson, J. Amer. Chem. Soc. 86, 5023 (1964).
- C. S. Yannoni, G. P. Caesar, B. P. Dailey, J. Amer. Chem. Soc. 89, 2833 (1967).
 R. A. Bernheim and B. J. Lavery, *ibid.*, p. 1997.
- 1279. 19. G. Englert and A. Saupe, Z. Naturforsch, 20a,
- 1401 (1965)
- and J. P. Weber, *ibid.* 23a, 152 (1968).
 20a. Note added in proof. We are at present engaged in a critical revision of the earlier results given in Table 5. Although it is too early to give final results, it now appears that the dihedral angle is rather smaller, about 28 degrees
- 21. L. C. Snyder and S. Meiboom, "Molecular structure of bicyclobutane from NMR in a liquid-crystal solvent," paper presented at a meeting of the American Physical Society,
- Berkeley, California, March 1968.
 ..., J. Chem. Phys. 44, 4057 (1966).
 E. Sackmann, S. Meiboom, L. C. Snyder, J. Amer. Chem. Soc. 90, 2183 (1968).

- Amer. Chem. Soc. 50, 2185 (1968).
 24. A. Saupe, Mol. Cryst. 1, 527 (1966).
 25. L. F. Thomas, E. I. S. Sherrard, J. Sheridan, Trans. Faraday Soc. 51, 619 (1955).
 26. P. Venkatesvalu and W. Gordy, J. Chem. Phys. 23, 1200 (1955)

- 27. S. L. Miller et al., ibid. 20, 1112 (1952).
 28. C. C. Costain, ibid. 29, 864 (1958).
 29. L. F. Thomas, J. S. Heeks, J. Sheridan, Arch. Sci. Geneva 10, 180 (1957).
- Sc. Geneva 19, 160 (1977).
 A. Almenningen, O. Bastiansen, T. Munthe-Karr, Acta Chem. Scand. 10, 261 (1956).
 S. Meiboom and L. C. Snyder, J. Amer. Chem. Soc. 89, 1038 (1967).
- 32.
- A. Almenningen, O. Bastiansen, P. N. Skancke, Acta Chem. Scand. 15, 711 (1961); P. N. Skancke, thesis, Institute for Theoretical Skancke, thesis, Institute for Theoretical Chemistry, Norges Tekniske Høgskole, Trond-heim, Norway. 33. O. Bastiansen, private communication
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