ANALYSIS OF HIGH-RESOLUTION N.M.R. SPECTRA

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INTRODUCTION

Several publications have appeared in which the general methods of analysing high-resolution n.m.r. spectra are described¹⁻⁴, and the literature on the details of the subject is very large—not to say too large—in view of the sizeable frequency of duplicated efforts. The progress made since 1960 is certainly sufficient to warrant the writing of an up-to-date treatise on the subject, and in the meantime a cursory appraisal of the present situation may perhaps serve some useful purpose.

Any high-resolution n.m.r. spectrum may (apart from line width considerations) be analysed in terms of the simple spin Hamiltonian:

$$H = - \sum_i \nu_i I_z(i) + \sum_{i < j} J_{ij} \mathbf{I}(i) \cdot \mathbf{I}(j) \quad (1)$$

where $\mathbf{I}(i)$ is the spin operator [with components $I_x(i)$, $I_y(i)$ and $I_z(i)$] operating on particle i .

The Larmor frequencies (chemical shifts) ν_i and the spin coupling constants J_{ij} are often referred to as the phenomenological constants (or parameters). This nomenclature is appropriate because (i) the Hamiltonian (1) was originally derived phenomenologically⁵⁻⁸, and (ii) whereas a strictly quantitative analysis of a given spectrum in terms of the phenomenological parameters is entirely realizable, the further analysis of the parameter values in terms of more fundamental entities must usually take the form of empirical correlations or approximate semi-empirical calculations.

The use of a phenomenological Hamiltonian is commonplace in many branches of spectroscopy. The form of the Hamiltonian may always be justified by incorporating in the quantum mechanical treatment a larger number of variables than those considered to be the primary agents in generating the spectrum. (In high-resolution n.m.r. the primary variables are the nuclear spin coordinates, and the additional variables required for the full treatment are—in the absence of medium effects—the space and spin coordinates of the electrons in the molecule to which the observed nuclei belong. Even the latter approach will, however, yield a spectrum of infinitely sharp lines as long as the calculations are based on the assumptions of a *closed*, stationary system. The broadening of the spectral lines is caused by interactions which were left out from the Hamiltonian. We shall in the following discussion disregard all problems concerning line widths.)

Although high-resolution n.m.r. spectra may become very complex, the form of the Hamiltonian (1) is simple enough to make algebraic calculations—by operator or matrix techniques—seem worthwhile. An outstanding feature of the spin Hamiltonian is that it operates in a finite dimensional

space (the number of dimensions is 2^N if the system comprises N spin $1/2$ nuclei). The eigenvalue problem for a not too large spin system may therefore be solved with any desired accuracy by means of numerical diagonalization. The demands on computer capacity are in fact further relaxed by the universal factorization of the secular determinant according to the total magnetic quantum number M [eigenvalue of $\sum_i I_z(i)$]. Additional factoriza-

tion is obtained (i) if the spin system displays symmetry, (ii) if it contains groups of magnetically equivalent nuclei², or (iii) if it contains groups of weakly coupled nuclei (*cf.* below). Thus, the task of calculating the n.m.r. spectrum for a *given set of phenomenological parameters* represents no problem: the transition frequencies are obtained as eigenvalue differences and the transition probabilities are obtained as the squares of the matrix elements of $\sum_i I_x(i)$ in the representation that diagonalizes the spin Hamiltonian (the eigenvector representation). The experimentalist is, however, faced with the converse problem, *viz.*, that of determining the set (or sets) of parameters that is consistent within experimental error with a given *spectrum*. This is a far more difficult problem and may be tackled by two essentially different methods.

The *direct* methods of analysis are attempts at actually reversing the procedure so as to calculate the parameters from the *observed* spectrum; the procedure in the *indirect* or *iterative* methods is to produce a sequence of *calculated* spectra starting with a set of trial parameters, the values of which are subsequently adjusted by successive approximations until the calculated spectrum finally agrees with the experimentally observed one.

The significance of the words "direct" and "indirect" as used here is different from that intended by Primas *et al.*⁹⁻¹¹, who call any method "indirect" which associates the spectrum with the eigenvalues of the Hamiltonian. In the "direct" approach of Primas *et al.*, the whole spectrum is considered as a single entity described analytically by its correlation function⁹⁻¹¹. Banwell and Primas make abundant use of operator methods and denounce the traditional methods of analysis as not being the most natural ones¹¹. It cannot be denied that methods based on operator algebra are unparalleled in power when it comes to demonstrating general properties of spectra (*cf.* for example the elegant proof of Kummer¹² for an intensity sum rule which had been derived independently by several other authors with considerable labour¹³⁻¹⁵, or the short-cut to treatments of symmetry properties of spectra pointed out by Ernst and Anderson¹⁶, or the proof^{8,17} that spin couplings within a group of magnetically equivalent nuclei² cannot produce observable features in an n.m.r. spectrum). It does not seem likely, however, that the methods indicated by Primas *et al.*⁹⁻¹¹ will become very popular for the actual analysis of experimental spectra, and it is not entirely obvious if this application was ever intended.

DIRECT METHODS OF ANALYSIS—SPECTRAL ASSIGNMENT

When the theoretically calculated transition frequencies and transition probabilities can be given a simple analytical form, an obvious direct

analysis method is to work backwards through the formulae. This approach is practicable in small spin systems, especially spin systems displaying symmetry, where the order of the secular equation may be reduced by factorization into 2×2 determinants^{1,3}. Slight transcriptions of the formulae are often helpful¹⁸.

Among the methods which would here be called direct, the moment methods of Anderson and McConnell¹⁹ is the one which most rightfully deserves the designation. Basically, the moment method requires for its application no information other than that provided by the spectrum itself. This information can be used directly in raw data form, *i.e.*, in the form of transition frequencies and line intensities. In principle, one could measure enough moments to determine all of the chemical shifts and the spin coupling constants of even a very complex molecule. The limitations are however two-fold. Firstly, the equations which relate the phenomenological parameters to the measured moments are implicit in the parameters and become more and more complex with increasing order of moments, thus making the value of the direct approach doubtful. Secondly, the experimental accuracy of the higher moments will be low because the values of these moments depend strongly on the extreme lines of the spectrum which will usually be weaker than the central lines and often so weak as not to be detectable above the noise; while these extreme lines may be of little importance for the lower moments they make an appreciable contribution to the higher moments. In fact the moment method has been used rather sparingly, mainly on account of the difficulty of acquiring sufficiently accurate intensity data to make it comparable in precision with analysis methods based on the transition frequencies alone. Nevertheless the method is quite useful because some chemical information can be obtained directly; information gained from a moment analysis can be very helpful in establishing orders of magnitude, in determining relations between the parameters and as an aid in spectral assignment. Also the moment method may provide useful checks on solutions obtained by other methods of analysis.

Anderson and McConnell derived formulae for the four lowest moments of a high-resolution n.m.r. spectrum by the use of operator algebra (commutation rules and trace relations); the technique was essentially the same as that used earlier by van Vleck for relating the moments of broad electron or nuclear magnetic resonance lines to the dipole and exchange couplings between the spins in a solid²⁰. Anderson and McConnell refined the analysis to make it applicable not only to a whole spectral band but also to *sub*-multiplets based on symmetry or (in the case of magnetic equivalence²) on spin. However, the *sub*-multiplet moments are only good for the analysis of experimental n.m.r. spectra if the different sub-multiplets can be identified as to representation (spin or symmetry); this is tantamount to requiring a partial assignment of the observed lines to transitions between specified energy levels and deprives the moment method of one of its principal merits.

The problem of spectral assignment, *i.e.*, the construction of an energy level diagram of the correct topological structure, is one that enters into almost any method of analysis. Traditionally, this represented the most difficult part in the analysis procedure, but recently methods have been introduced which employ double resonance spectra and multiple quantum

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spectra to reduce the assignment problem almost to triviality. However, even the original spectrum itself contains a considerable wealth of information, that may be put to good use in the process. This information is commonly collected in the form of sum rules.

One sum rule, that is immediately apparent from the very nature of spectroscopy is the rule of repeated spacings:

$$\nu_a - \nu_b = \nu_c - \nu_d \quad (2)$$

or, in a sum rule form:

$$\nu_a + \nu_d = \nu_b + \nu_c$$

which will be fulfilled for any four lines, the corresponding transitions of which form a closed quadrangle in the energy level diagram (*Figure 1*). It is apparent from *Figure 1* that the assignment of the four lines is not unique

Figure 1. Two energy levels of different topological structure which may both give rise to a repeated line spacing

but corresponds to two partial level arrangements of different topological structure. As will be shown presently, the ambiguity can easily be resolved by the use of double irradiation methods.

The structure of the Hamiltonian (1) is such as to make repeated spacings possible in certain cases even for groupings of four lines other than those which satisfy the quadrangle criterion of *Figure 1*. The corresponding sum rules may then be derived by making use of the trace invariance of the submatrices of the Hamiltonian (1) as was first demonstrated by Waugh *et al.*^{14,21}. Sum rules exist not only for the line frequencies but also for the intensities. Intensity sum rules which depend explicitly on the properties of the spin Hamiltonian¹²⁻¹⁵ cannot, as a rule, be applied in other branches of spectroscopy but sum rules based on invariance under unitary transformations (such as the principle of spectroscopic stability^{22,23}) apply to any kind of spectrum, and were in fact often applied in other fields long before they were rediscovered by n.m.r. spectroscopists. Sum rules have been derived by

Kummer¹², Giomousis and Swalen¹³, Castellano and Waugh¹⁴, Whitman¹⁵, Fessenden and Waugh²¹ and Swalen and Waugh²³. Bothner-By and Pople²⁴ have shown that partial *moments* of spectral lines corresponding to transitions between different *pairs* of sub-matrices are also invariants that may be usefully employed both for spectral assignment and for the direct evaluation of the phenomenological parameters.

Whitman¹⁵ maintains that a computer assignment technique is the only effective method that will ensure the inclusion of every possible assignment in the analysis. To keep the number of acceptable assignments manageable, Whitman used both frequency and intensity sum rules, each weighted according to the precision of the experimental measurements. Validity limits were imposed on the sum rules to make up for deviations caused by experimental error. The method has the advantage of eliminating any bias, but may become impracticable for large spin systems, not least because of the difficulties caused by "missing" (unresolved or weak) lines.

One of the most ambitious attacks on the problems of spectral assignment and of direct analysis of a spectrum is that reported in the paper by Castellano and Waugh on the exact analysis of three-spin spectra¹⁴. Castellano and Waugh have evaluated the number of energy level arrangements that are consistent with a given set of transition frequencies and the number of parameter sets that are consistent with the energy level information. The phenomenological parameters are given as explicit functions of the energy levels and may thus be evaluated without recourse to any iterative procedure. The important point about this is that the convergence properties of the iterative programmes are not known in detail; with an exact analysis method at hand one is in a much better position to investigate the different calamities that may befall the iterative procedures. The unsymmetrical three-spin system has in fact become the touchstone for methods of analysing spectra: the number of references pertaining to this subject is quite respectable (*see* references 14, 21 and 25–42 for some of the more important ones). There are several good reasons for this. Firstly, the number of expected lines (15) is low enough to give the experimentalist a reasonable chance of resolving them; secondly, the problem is complex enough to make the test realistic and yet the exact solution is known; thirdly, the problem is not as overdetermined as would be the case for larger spin systems if most of their allowed transitions could be resolved.

Whitman⁴² has suggested an alternative method for the direct analysis of three-spin spectra, and extended the method to more complex spin systems as well. Whitman's approach is to establish algebraic relationships between the phenomenological parameters and the experimental energy eigenvalues. These expressions are derived⁴² by identifying the coefficients of the sub-determinant secular equations with the symmetric functions of the roots of the equations (*i.e.*, the experimental energy eigenvalues). The same approach was indicated by Brügel, Ankel and Krückeberg²⁹ and has earlier been applied in other branches of spectroscopy by, for example, Brown and Parker^{43–46}. The same equations may alternatively be derived by making use of the trace invariance of the Hamiltonian and of its square, cube and higher powers as has been demonstrated by Parker and Brown⁴⁶. Obviously, what is required is a sufficient number of *independent* relationships; any

invariant of the sub-determinants may be employed in the search for these relationships^{14,29,42,47,48}.

It is significant that the equations derived by Whitman⁴² become more and more involved with increasing complexity of the spin system, and that the functional relationships tend to become implicit in the phenomenological parameters, thus necessitating an iterative method of solution. It appears to be in the nature of the problem that the approach will become less and less "direct" the higher the order of the secular equation, and it seems likely that the indirect methods of analysis will continue to be in demand also for solving analysis problems where analytical (but complex) solutions have been derived by the direct method. The prime reason for this is that an iterative computer programme based on the indirect approach may be made very flexible so as to cover a very large class of spectra. The direct methods will yield a different solution procedure for every new type of spectrum and if a computer analysis is intended this will entail the writing of a new programme for every new symmetry arrangement and separate programmes for two-spin systems, three-spin systems, *etc.*

Miscellaneous aids in spectral assignment

So far we have only dealt with the information contained in a single spectrum. In dealing with complex problems the spectroscopist will seldom be content with this since many aids are available to provide supplementary information. First, the n.m.r. spectrum may be recorded at another spectrometer frequency. Secondly, spectra of isotopically substituted molecules may be obtained; these spectra are related to the original spectrum by well-known rules¹ and although they introduce the complication of an increase in the number of parameters, the additional information obtained is usually worth the effort, not least because the new parameters can more often than not be evaluated almost on inspection. The words isotopic substitution make one think of some lengthy synthesis work. This is not necessarily implied, however, since most of the elements occur as isotopic mixtures. For example, the isotope ¹³C has a natural abundance of *ca* one per cent and this is often sufficient to yield quite acceptable proton resonance spectra from molecules containing ¹³C atoms in unenriched samples. The method of isotopic substitution again is a method which is applicable in many branches of spectroscopy but the ease with which the spectra from molecules of different isotopic composition may be recorded and identified in n.m.r. is not paralleled in many other fields. Accordingly, the method of isotopic substitution—in particular the recording of the "satellite" spectra obtained from naturally occurring species of low abundance—has been very popular ever since its introduction some seven years ago^{49,50}. It probably represents one of the safest methods for obtaining a unique set of parameters in strongly coupled spin systems^{40,41}.

Less reliable information may be obtained by the use of specific medium effects (*i.e.*, by change of solvent⁵¹) and by comparison with structurally related model compounds. The theoretical basis for estimating the phenomenological parameters is not strong enough to permit very wide extrapolations and one is well advised to try to make the changes in composition

by degrees so as to allow the precise correlation with the original spectrum to be made.

Double and multiple irradiation techniques^{52,53} are very powerful aids to the spectroscopist. Not many kinds of spectroscopy can benefit from such techniques to the same extent as n.m.r. and the development of this particular brand of n.m.r. spectroscopy during the last few years is best characterized by the word explosive. A fair appraisal of the achievements is impossible within the limitations of the present communication, and only the most fundamental applications for spectral analysis will be considered. The original use of double resonance was for spin decoupling and many examples, e.g., the use of spin decoupling as an aid in analysing spectra, could be given.

Freeman and Anderson³⁷ have introduced a double irradiation method (colloquially referred to as "tickling") in which the perturbing rf. field is weak enough to affect only a single line in the spectrum. This will produce a coherent mixing of the states involved in the transition and any line that has an energy level in common with the irradiated line will be split by the perturbation. Consequently, the "tickling" technique may be employed for spectral assignment and it was with this particular application in mind that the technique was introduced. The observed double resonance pattern depends not only on whether or not the observed line has a level in common with the irradiated line but also on how the energy of this common level is placed with respect to the interval demarcated by the two other levels involved. Figure 2 is helpful in explaining this. The two transitions that have

Figure 2. Two transitions that have a common energy level are called *connected* transitions. (a) The connection is said to be *progressive* if the energy of the common level is intermediate between those of the two terminal levels and (b) *regressive* if the common level has an energy outside the interval demarcated by the terminal levels

an energy level in common are designated^{39,53} *connected* transitions, and such transitions may be divided into two categories depending on whether the energy of the common level is intermediate between those of the two terminal levels (Figure 2a), when the transitions are referred to as *progressive*, or whether the energy of the common level falls outside the interval demarcated by the two other levels (Figure 2b), when they are referred to as *regressive*. Not only the variations in the double resonance pattern obtained by slightly varying the irradiation frequency but also the line shapes in the observed doublet at a given irradiation frequency depend on whether the lines are

connected in a progressive or in a regressive arrangement. Either of these characteristics may therefore be used to determine the kind of connection (progressive or regressive).

By means of "tickling" experiments one may unambiguously draw the network of energy levels and transitions connecting these levels without recourse to the whole apparatus of frequency and intensity sum rules. These rules may be used as a check after the initial assignment has been made and will still be required if the observed energy levels are to be correlated with the diagonal elements of the Hamiltonian matrix in the original basis representation, as required in most of the direct methods of analysis.

Double resonance methods which are based on population transfer have been suggested by Kaiser⁵⁴ and by Hoffman, Gestblom and Forsén^{55,56} as alternatives to the method of Freeman and Anderson, and yet other double resonance techniques provide information on the energy level arrangements in a less direct fashion⁵³. It appears however that the "tickling" technique will prove to be the most universally applicable double resonance method for spectral assignment. A draw-back of the "tickling" method is that its proper use requires the facilities of a frequency-sweep n.m.r. spectrometer; however this is not a forbidding restriction because frequency-sweep spectrometers are now commercially available and furthermore, as has been shown by Whipple and Chiang³⁸, even field-sweep "tickling" experiments may be quite helpful in the assignment process. Field-sweep "tickling" experiments will produce simple splittings similar to those in frequency-sweep experiments only in the progressive case, however.

The identification of progressively connected lines can be achieved with still simpler apparatus by the use of double-quantum transitions³⁹ if the spectrum is that of a strongly coupled spin system (as it will usually be if the assignment should cause any difficulties). This identification is based on a frequency sum rule, since the double-quantum transition will have a frequency equal to the arithmetic mean of any two frequencies that correspond to a pair of progressive transitions which together span the interval between the levels involved in the double-quantum transition.

ITERATIVE METHODS OF ANALYSIS

The amount of processed information obtainable by the various assignment procedures outlined above will normally be more than sufficient to ensure the convergence of the iterative programmes to the correct solution. If *sufficiently accurate* estimates of the phenomenological parameters are available, even the assignment procedures can be left out because a line by line comparison between the calculated trial spectrum and the observed one will yield an assignment which may be used for the ensuing iterative calculations⁵⁷.

The foregoing statement immediately brings up a number of questions. Firstly, how close to the correct solution must the first estimate be in order to ensure that the process converges? Secondly, suppose that the root mean square deviation (or whatever criterion you may have) has several minima, as it must generally have when only transition frequencies are considered¹⁴ then what are the risks that a set of parameters that was originally in the proximity of the correct set will start drifting away towards one of the

spurious solutions? Thirdly, can one really be sure that the programme will always converge?

These are questions that arise in all methods based on successive approximations and full answers cannot be given in very general terms. A good deal can be learnt, however, from specific examples and a few general statements can probably be made. In his thesis¹², Kummer raised the question whether any idealized (perfect) spectrum is ever in exact agreement with more than one set of parameters and reached the conclusion that the only variables left undetermined are (i) the labels of the nuclei (*i.e.*, the structural assignment) and (ii) the absolute signs of the spin couplings. The mathematical apparatus used by Kummer¹² to demonstrate the correctness of this theorem is rather esoteric and most n.m.r. spectroscopists (including myself) will probably have to accept it on the strength of his words.

Castellano and Waugh¹⁴ and others refer to cases where convergence of an iterative solution could not be obtained at all, and to other cases where two entirely different sets were found by accident, which were all consistent with the observed spectrum within ordinary experimental error. Which set is actually obtained is an accidental result of the particular set of trial parameters originally chosen and the criteria used to effect convergence. In any indirect method there is a very real possibility that the correct solution may be missed if it happens to be different from the one expected. However, Cavanaugh³⁴ has drawn attention to the fact that a similar misfortune could be encountered even with a direct approach. Cavanaugh presented the spectral data for 2-iodo-thiophene (at 40 Mc/s) as an illustration of this. The spectrum was analysed by the direct method of Castellano and Waugh¹⁴ and a set of parameters was obtained that reproduced the intensities of the 11 observed lines to within an average deviation of 1.5 per cent of the total intensity. (It is in the nature of the Castellano-Waugh approach that the calculated frequencies agree exactly with the input data which appear in the form of *adjusted* frequencies.) In the case referred to, the amount of adjustment was very modest giving an average mean deviation between observed and adjusted frequencies of only 0.016 c/s as compared with the three times larger uncertainty in the experimental values³⁴. By using a different set of adjusted frequencies, which fitted the experimental values equally well, Cavanaugh obtained only complex parameter values, all having a minor imaginary part. Such solutions would normally be rejected for obvious reasons, but Cavanaugh found that these complex parameters were actually closer to the correct solution than the ones first obtained³⁴.

Since an experimental spectrum will always be subject to random errors no matter how refined the techniques can become, the questions just raised may perhaps most properly be reformulated as follows: how ill-behaved (from the numerical analysis point of view) can the matrices of the spin Hamiltonian become in actually encountered situations? Experience alone can provide the answer* (*see* the Addendum, p. 558).

† Some of the experience already acquired is rather disheartening. Swalen has found that as many as 1000 iteration cycles may be required to effect convergence to an acceptable solution. In a series of test calculations on the spectrum of a fictitious three-spin system (with assumed parameter values of $\nu_A = -11.72$ c/s, $\nu_B = +5.55$ c/s, $\nu_C = +6.17$ c/s, $J_{AB} = -0.04$ c/s, $J_{BC} = 18.03$ c/s, $J_{AC} = +20.71$ c/s), Swalen found that convergence could not be obtained at all if the trial values of one of the chemical shift parameters (*e.g.* ν_C) differed by more than 0.08 c/s (*sic*!) from the parameter value of the correct solution.

The task of actually setting up an iterative scheme may be tackled in several different ways, most of which boil down to a linearization of the problem. That a linearization is in general possible follows from the fact that a well-behaved solution to the eigenvalue problem will be a linear function of the parameters in a neighbourhood of the original set of trial parameters⁵⁸. The *pedestrian* approach would be to solve the eigenvalue problem for one set of trial parameters and then for all sets obtained from the original one by a small variation in one of the parameters. In this manner one obtains the eigenvalue variation ΔE_i upon the variation of parameter p by Δp and the difference quotient $\Delta E_i/\Delta p$, which is a first approximation to the partial derivative that occurs as the coefficient of parameter p in the linearized equation. If n parameters are involved, the pedestrian approach will require n full diagonalizations to evaluate all the partial derivatives. Although this involves a large waste of computation time, the pedestrian approach may have the merit of giving a more rapid convergence than the methods to be described presently, when the linear approximation becomes insufficient.

The problem faced in any indirect method of analysis is that of solving the eigenvalue problem under variation of the parameters. This problem is related⁵⁹ to the problems of perturbation theory, and the approach indicated by Hoffman⁵⁸, and Hoffman and Gronowitz⁶⁰ is nothing more than a first order perturbation expansion in the parameter variations. Only one full diagonalization is required to obtain the linearized equations in this method: the coefficients are obtained from the eigenvectors belonging to the first trial set of parameters.

Bothner-By *et al.*⁶¹⁻⁶³ derived independently the same set of equations by calculating the partial derivatives of the matrix equation:

$$\Lambda = S^{-1}\mathbf{H}S \quad (3)$$

retaining only the diagonal elements. In equation (3), Λ represents the diagonal energy matrix, $\mathbf{H}$ the Hamiltonian matrix in the basis representation and S the transformation matrix, composed of the eigenvectors of $\mathbf{H}$, that reduces $\mathbf{H}$ into the diagonal form Λ .

Both Hoffman⁵⁸ and Bothner-By *et al.*⁶³ solve the iterative equations for the transition frequencies, *i.e.*, for the eigenvalue *differences*.

In the approach developed independently by Swalen and Reilly²³ and by Alexander⁶⁴ the iteration procedure involves only the *eigenvalues*. It has been demonstrated by Hoffman⁵⁸ that the two methods are in principle equivalent, but that the approach which utilizes the eigenvalues should offer possibilities for economizing the actual computational labour.

Bothner-By *et al.*⁶³ and Swalen and Reilly²³ have written widely used FORTRAN programmes (designated LAOCOON II and NMRIT, respectively) which translate their ideas into computer language. Several other authors have described alternative computer programmes for iterative analysis procedures, usually however in far less detail.

In the approaches described so far, the actual iteration cycles are based on only that part of the experimental information which is derived from the observed transition frequencies. The intensity information may have been

used in the assignment procedure and will always have to be used in the final assessment of the soundness of the fit, but it is virtually lying idle during the crucial step in the parameter evaluation. The same weakness is inherent in almost every direct analysis procedure. Allegedly, this truncation is to protect the evaluated parameters from being detrimentally influenced by inaccurate data, but it seems more than likely that the decision was largely dictated by considerations of computational convenience.

Arata, Shimizu and Fujiwara³⁶ have outlined an iterative scheme which employs all the observed transition frequencies and line intensities, each observable being weighted according to the precision with which it is known. Unfortunately the computer they used did not have sufficient capacity to cope with the problem, and they had to leave out the intensities in the iteration cycles. It seems, therefore, that the possibility of using the intensity information for iteration cycles has not yet been exploited in any practical case.

FACTORIZATION AND SYMMETRY

The largest sub-matrix of the spin Hamiltonian (1) will in the simple product representation of an N spin- $1/2$ system have a dimension of $\binom{N}{N/2}$. It is therefore obvious that the solution of the eigenvalue problem for a system composed of even a moderate number of coupled spins will be time-consuming and costly, notwithstanding the impressive capacity of a modern high-speed computer. Therefore all possibilities for factorization in addition to the universal factorization according to M should be exploited.

Two recurring examples are the factorization according to symmetry and the factorization caused by large chemical shifts (weak coupling). The word symmetry here implies the symmetry of the Hamiltonian (1) rather than the symmetry of the molecule. What matters therefore, is the group of spin permutations which leave the Hamiltonian invariant. (It may be noted, however, that the factorization according to M may be derived by considering the fact that a *rotation* around the Z -axis leaves the Hamiltonian invariant). A particular kind of symmetry is that displayed by a group of magnetically equivalent nuclei². This will yield a factorization according to the total spin of the group, as may be obtained by using symmetry adapted product functions⁶⁵. The matrix elements involved are, however, calculated with much less effort by making use of the general properties of angular momentum operators^{2,3,66-69} (the "composite particle" approach^{67,68}). That this simple stratagem is apparently still unknown to many n.m.r. spectroscopists must be ascribed to an unfortunate lapse by Pople, Scheider and Bernstein in their otherwise excellent presentation of analysis methods¹. However, the use of a symmetry-adapted basis set will always effect the factorization, and probably represents the most fool-proof method.

The factorization of the Hamiltonian is the basis for any *sub*-spectral analysis method^{1-3,8,19,66-76}. Diehl and others⁷²⁻⁷⁶ have gone to great lengths in exploiting this approach. The procedure is to pick out from the total spectrum certain groups of lines, which together form a sub-spectrum. A sub-spectrum will often display a pattern identical in appearance to the

entire spectrum of a simpler spin system. If the sub-spectrum is analysed according to one of the methods applicable to the simpler system, a set of parameters may be evaluated, which by a so-called sub-spectral transformation is related to the parameter set of the actual system.

The n.m.r. study of symmetrical molecules has been exceedingly popular in recent years and only one more aspect of the problem will be dwelt upon, *viz.*, the occurrence of deceptively simple spectra^{35,77,78}. Such spectra may also be encountered with spin systems which display no symmetry whatsoever, but they are particularly prevalent in the study of symmetrical molecules for reasons that may be illustrated by the example of *p*-difluorobenzene. The spectrum of this compound, which has been studied by Paterson and Wells⁷⁹, and also by Rodmar, Gestblom and Hoffmann⁸⁰, consists essentially of a fluorine quintet and a proton triplet. Thus the spectrum closely resembles that of two groups of magnetically equivalent nuclei one containing two spin 1/2 nuclei and the other containing four spin 1/2 nuclei. Now, magnetic equivalence can occur only if the *ortho* and *meta* proton-fluorine spin couplings are equal, and it is known that they are not. The strong *ortho* proton-proton spin couplings create, however, a tendency for the protons to act as a single unit^{35,57}, and hence to overcome the magnetic non-equivalence. In fact, any spectral structure additional to that reported must rest on the non-vanishing magnitude of $J_{\text{HF-ortho}} - J_{\text{HF-meta}}$ and, as Paterson and Wells point out⁷⁹, "a n.m.r. spectrum which avoids degeneracy by dependence on the finite value of a single parameter collapses more rapidly than the parameter tends to zero". Their observation can be rationalized by consideration of the fact that a finite value of the parameter in the present case implies a finite degree of mixing between states with different total proton spin. Without this mixing no additional structure could arise; hence such additional structure must be of *second* order in the parameter. The rule just quoted is obviously not applicable to such first order features as long-range coupling in weakly coupled spin systems.

The ubiquitous second power of the parameters in the denominators of the Abraham-Bernstein conditions⁷⁸ for deceptive simplicity is symptomatic, and it is characteristic also that the dependence on the finite value of a *single* parameter was encountered only in the A_2X_2 case, *i.e.*, the case in which the Hamiltonian displayed symmetry.

Symmetry factorization is only one of the possible factorization schemes. The most general approach to the problem is by group theory and consists in finding the group of all operators that *commute* with the Hamiltonian.

The division of an observed spectrum into sub-spectra according to symmetry is seldom a very straightforward procedure because the appearance of the spectrum will not reveal the symmetry representation to which the different lines belong except in very particular cases^{81,82}.

On the other hand, the spectroscopist is always alert towards regularities in the spectrum and one particularly striking regularity is the symmetry of an observed *spectrum*. Such symmetries can generally be traced to the existence of an operator which *anti-commutes* with the Hamiltonian^{16,83}. A (linear or anti-linear) operator which anti-commutes with the Hamiltonian (or with one term H_A of the Hamiltonian if this term H_A *commutes* with the Hamiltonian) will always tell us that a symmetric grouping of energy levels exists.

If, in addition, the operator is either unitary or anti-unitary, then the observed spectrum will also show a corresponding symmetric grouping of lines. This theorem has proved particularly useful for discussions of the dependence of n.m.r. spectra on the signs of spin coupling constants⁵³.

PERTURBATION METHODS

Where exact factorization of a sub-determinant is no longer obtainable, a perturbation expansion may be the answer as long as the degree of mixing is low. Perturbation calculations in n.m.r. have been confined almost exclusively to large-shift (weak coupling) approximations, and this has led Banwell and Primas to point out that there are several perturbation methods which do not rely on the smallness of a coupling constant. The success of the iterative schemes may, in view of what has been said earlier, be taken as a demonstration of this.

Nevertheless, if a complete theoretical spectrum is to be given in closed form by expressions derived from perturbation expansions, it seems that some assumptions concerning the magnitudes of the phenomenological parameters will have to be made. This does not necessarily mean, however, that one has to work along the traditional lines. To find suitable alternatives one will probably have to look for basic sets of a different type than that of symmetrized simple product functions, which is almost exclusively used at present. One radically different set has been suggested by Waugh and Dobbs⁶⁹, and their approach will most likely be suitable for perturbation approximations in strongly coupled spin systems.

In certain cases, the most suitable approach will be suggested by the appearance of the spectrum. This is definitely true for the large shift approximation and is also the case for spectra of the so-called $(AB)_2$ type studied in some detail by Gestblom, Hoffmann and Rodmar⁸⁴. *Figure 3* shows one of their spectra, *i.e.*, that of thieno[3,2-*b*]thiophene⁸⁴. It is seen that this spectrum has an appearance, which strongly resembles that of an AB spectrum with some additional fine structure. This suggests the use of the AB eigenfunctions as a basis for the perturbation expansion. A similar structure may be discerned in the spectra of *para*-disubstituted benzenes, though less obviously so, indicating that here the perturbation expansion will converge more slowly⁸⁴.

If a spectrum consists of several independent but interpenetrating sub-spectra, the best approach to a perturbation expansion will not be so obvious from the appearance of the spectrum. This is well illustrated by the work of Gestblom and Rodmar⁸⁵ on the n.m.r. spectra of *para*-substituted fluorobenzenes (*see* the spectrum of *p*-chloro fluorobenzene in *Figure 4*).

To sum up, one is probably correct in saying that the possibilities of the perturbation methods have been far from fully exploited.

FUTURE PROSPECTS

The line of future development which is most likely to yield reward is that concerned with data handling and data processing. As it is at present, only a small fraction of the information content of an observed spectrum is ever used. This is as it should be in cases where more is not needed, but often a

Figure 3. The A_2B_2 proton magnetic resonance spectrum of a 11.7 per cent acetone solution of thieno[3,2-*b*]thiophene at 60 Mc/s⁸⁴. The appearance of the spectrum is that of an AB spectrum with some additional fine structure and indicates the feasibility of an $(AB)_2$ perturbation method of analysis⁸⁴

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pressing problem is incapable of solution because the spectrum is either not resolved well enough, or too complex to be dealt with, or because some relevant part may be lost in the noise. Many of these obstacles can be surmounted by the use of more powerful techniques recently developed or still in the course of development. Firstly, the actual information content may be substantially increased. At the cost of considerable spectrometer time the signal-to-noise ratio can be greatly enhanced by the use of time-averaging techniques⁸⁶. For practical reasons an enhancement factor of the order of 100 probably represents the absolute upper limit to this method when applied to a high-resolution n.m.r. (proton resonance) spectrum, but preliminary investigations of more sophisticated methods have been reported⁸⁷. Secondly, the information from a given spectrum may be supplemented with other spectral data obtained by slight variations in the experimental conditions. The methods of varying spectrometer frequency, specific medium effects, isotopic substitution and, last but certainly not least, double and multiple resonance, already discussed in connection with problems of spectral assignment, are all relevant in this context. Thirdly, the information at hand could be made more manageable so as to allow the processing of it to the stage of a complete analysis.

Signal-to-noise improvement by computer smoothing^{88,89} represents a technique in which the actual information content is reduced, but cast in a form which simplifies the extraction of the remainder.

Resolution enhancement is often badly needed and is in fact obtainable both by digital and analogue devices^{90,91}. The traditional approach to the problem has not been very satisfactory. From the appearance of an unresolved line (its "knees" and "shoulders") an educated guess as to the number of component lines, their frequencies and intensities is made; the correctness of the estimate is then checked by comparison with a theoretical spectrum calculated from trial parameters. This is obviously a highly subjective approach, in particular if the theoretical data are represented in "needle" diagrams that take no account of the experimental line widths. Several spectroscopists have refined the technique and present their output data in the form of Lorentz-shaped curves^{23,92,93}. Even so the procedure is impaired by subjectivity as long as the soundness of the fit is judged by inspection. A more satisfactory approach is to convert the *observed* data into digital form. Ideally, these would be given as a list of centre frequencies and normalized intensities of all the lines in the spectrum that contribute significantly to its structure. In high-resolution n.m.r. the component lines have more often than not all the same width, and this makes the programme outlined possible provided that the line shapes are reproducible enough, *i.e.*, provided that the signal-to-noise ratio is high and that the non-repro-

Figure 4. The proton and fluorine n.m.r. spectra of a 24 per cent carbon disulphide solution of *p*-chlorofluorobenzene⁸⁵. The ¹H spectrum was obtained at 60 Mc/s and the ¹⁹F spectrum at 40 Mc/s. The theoretical spectra were calculated by complete numerical diagonalization with parameters identical to those obtained in the (AB)₂X analysis⁸⁵

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Figure 5. Digital fit to a partial spectrum of overlapping lines in the A_2B_2 n.m.r. spectrum of 3-chloroethane. The broken-line curves are digitally fitted and the dots represent experimental data obtained by digitizing the observed spectrum

ducible wiggles are of low amplitude. Figure 5 shows the digital fit obtained by Lusebrink and Sederholm to one band of overlapping lines in the spectrum of 3-chloroethane. The line shape function employed in the procedure was a step function obtained by digitalizing the observed profile of a well resolved line. One might think that the number of overlapping lines in each unresolved band must be known in advance, or else the computer would improve the fit by adding more and more lines. However, this is not necessarily so. Lusebrink and Sederholm report that the improvement of the fit after the correct number of lines has been found becomes only marginal and arises in part through the introduction of new lines with negative intensities⁹⁰. On the whole, no difficulties were encountered in asserting the correctness of the solution, at least not in the moderately complex cases studied so far.

ADDENDUM

Some recent studies of very strongly coupled unsymmetrical three-spin systems have shed new light on the problem of the uniqueness of analysis procedures.

Castellano and Bothner-By⁹⁴ have observed a spectrum which could be fitted with any set of n.m.r. parameters that belong to a particular curve in the five-dimensional parameter space of an ABC spin system. This behaviour is in general to be expected in very strongly coupled three-spin systems as may be inferred from recent work by Bishop⁹⁵.

In his analysis of very strongly coupled ABC spectra, Bishop uses basis functions which are appropriate to a spin system with vanishing chemical shift differences and he introduces the small but finite chemical shifts as a

perturbation term. Bishop found by carrying the perturbation expansion up to second order that the transition frequencies of all the 15 theoretically possible transitions are given by only four independent auxiliary parameters, these being simple algebraic functions of the five phenomenological n.m.r. parameters.

From Bishop's results one may draw the following conclusion: If the spectrum of an unsymmetrical three-spin system does not reveal structural features of higher order than the second in the chemical shift differences, then the set of n.m.r. parameters used to fit the spectrum must remain arbitrary to within one degree of freedom.

The foregoing result is not altogether unexpected since it is well-known that the spectrum obtained with vanishing chemical shift differences is collapsed into a single line; the loss of structural information as the spectrum approaches this limit might be expected to be gradual on the grounds of physical continuity. What is new and somewhat unexpected about the result is that even a spectrum in which the frequencies of all 15 transitions are known may contain insufficient information for the establishment of a unique parameter set. Hence this lack of uniqueness may not be referred to one of the well-known categories of spectra with "missing lines" or "deceptively simple" spectra. Work is now in progress in this Institute to explore whether similar situations are to be encountered in n.m.r. spectra of other spin systems also.

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References

- ¹ J. A. Pople, W. G. Schneider, and H. J. Bernstein. *High-resolution Nuclear Magnetic Resonance*, chapter 6. McGraw-Hill, New York (1959).
- ² W. A. Anderson. In *NMR and EPR Spectroscopy* (Ed. Varian Staff and Consultants), p. 151. Pergamon, Oxford (1960).
- ³ P. L. Corio. *Chem. Rev.* **60**, 363 (1960).
- ⁴ J. D. Roberts. *An Introduction to the Analysis of Spin-Spin Splitting in High-resolution Nuclear Magnetic Resonance Spectra*. Benjamin, New York (1961).
- ⁵ E. L. Hahn and D. E. Maxwell. *Phys. Rev.* **84**, 1246 (1951).
- ⁶ H. S. Gutowsky, D. W. McCall, and C. P. Slichter. *Phys. Rev.* **84**, 589 (1951).
- ⁷ E. L. Hahn and D. E. Maxwell. *Phys. Rev.* **88**, 1070 (1952).
- ⁸ H. S. Gutowsky, D. W. McCall, and C. P. Slichter. *J. Chem. Phys.* **21**, 279 (1953).
- ⁹ H. Primas. *Spectrochim. Acta* **14**, 17 (1959).
- ¹⁰ H. Primas and H. H. Günthard. *Helv. Phys. Acta* **31**, 413 (1958).
- ¹¹ C. N. Banwell and H. Primas. *Mol. Phys.* **6**, 225 (1963).
- ¹² H. Kummer. "Beitrag zur Analyse Komplizierter Protonenresonanz Spektren," *Thesis ETH, Zürich*, p. 59. Juris Verlag, Zürich (1963).
- ¹³ G. Giomousis and J. D. Swalen. *J. Chem. Phys.* **36**, 2077 (1962).
- ¹⁴ S. Castellano and J. S. Waugh. *J. Chem. Phys.* **34**, 295 (1961).
- ¹⁵ D. R. Whitman. *J. Chem. Phys.* **36**, 2085 (1962).
- ¹⁶ R. Ernst and J. M. Anderson. *J. Chem. Phys.* **40**, 3737 (1964).
- ¹⁷ A. Abragam. *The Principles of Nuclear Magnetism*, p. 481. Oxford University Press, Oxford (1961).
- ¹⁸ R. A. Hoffman and S. Gronowitz. *Arkiv Kemi* **16**, 501 (1960).
- ¹⁹ W. A. Anderson and H. M. McConnell. *J. Chem. Phys.* **26**, 1496 (1957).
- ²⁰ J. H. van Vleck. *Phys. Rev.* **74**, 1168 (1948).

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- ²¹ R. W. Fessenden and J. S. Waugh. *J. Chem. Phys.* **31**, 996 (1959).
- ²² E. U. Condon and J. H. Shortley. *The Theory of Atomic Spectra*, p. 20. Cambridge University Press, Cambridge (1935).
- ²³ J. D. Swalen and C. A. Reilly. *J. Chem. Phys.* **37**, 21 (1962).
- ²⁴ A. A. Bothner-By and J. A. Pople. Communication presented at the *Sixth Experimental NMR Conference, Mellon Institute, Pittsburgh, Pennsylvania, 25-27 February 1965*.
- ²⁵ H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams. *J. Am. Chem. Soc.* **79**, 4596 (1957).
- ²⁶ H. J. Bernstein, J. A. Pople, and W. G. Schneider. *Can. J. Chem.* **35**, 65 (1957).
- ²⁷ R. A. Hoffman and S. Gronowitz. *Arkiv Kemi* **15**, 515 (1960).
- ²⁸ C. N. Banwell and N. Sheppard. *Mol. Phys.* **3**, 351 (1960).
- ²⁹ W. Brügel, Th. Ankel, and F. Krückeberg. *Z. Elektrochem.* **64**, 1121 (1960).
- ³⁰ C. A. Reilly and J. D. Swalen. *J. Chem. Phys.* **32**, 1378 (1960).
- ³¹ C. N. Banwell and N. Sheppard. *Proc. Roy. Soc. (London)* **A263**, 136 (1961).
- ³² S. Castellano and J. S. Waugh. *J. Chem. Phys.* **37**, 1951 (1962).
- ³³ J. R. Cavanaugh. *J. Chem. Phys.* **39**, 2378 (1963).
- ³⁴ J. R. Cavanaugh. *J. Chem. Phys.* **40**, 248 (1964).
- ³⁵ J. I. Musher and E. J. Corey. *Tetrahedron* **18**, 791 (1962).
- ³⁶ Y. Arata, H. Shimizu, and S. Fujiwara. *J. Chem. Phys.* **36**, 1951 (1962).
- ³⁷ R. Freeman and W. A. Anderson. *J. Chem. Phys.* **37**, 2053 (1962).
- ³⁸ E. B. Whipple and Y. Chiang. *J. Chem. Phys.* **40**, 713 (1964).
- ³⁹ W. A. Anderson, R. Freeman, and C. A. Reilly. *J. Chem. Phys.* **39**, 1518 (1963).
- ⁴⁰ R. T. Hobgood Jr., R. E. Mayo, and J. H. Goldstein. *J. Chem. Phys.* **39**, 2501 (1963).
- ⁴¹ R. Freeman. *J. Chem. Phys.* **40**, 3571 (1964).
- ⁴² D. R. Whitman. *J. Mol. Spectry.* **10**, 250 (1963).
- ⁴³ L. C. Brown and P. M. Parker. *Phys. Rev.* **100**, 1764 (1955).
- ⁴⁴ L. C. Brown and P. M. Parker. *J. Chem. Phys.* **27**, 1108 (1957).
- ⁴⁵ L. C. Brown and P. M. Parker. *J. Chem. Phys.* **30**, 909 (1959).
- ⁴⁶ P. M. Parker and L. C. Brown. *Am. J. Phys.* **27**, 509 (1959).
- ⁴⁷ B. Dischler and W. Maier. *Z. Naturforsch.* **16a**, 318 (1961).
- ⁴⁸ B. Dischler and G. Englert. *Z. Naturforsch.* **16a**, 1180 (1961).
- ⁴⁹ A. D. Cohen, N. Sheppard, and J. J. Turner. *Proc. Chem. Soc. (London)* **1958**, 118.
- ⁵⁰ N. Sheppard and J. J. Turner. *Mol. Phys.* **3**, 168 (1960).
- ⁵¹ T. Schaefer and W. G. Schneider. *Can. J. Chem.* **38**, 2066 (1960).
- ⁵² J. D. Baldeschwieler and E. W. Randall. *Chem. Rev.* **63**, 81 (1963).
- ⁵³ R. A. Hoffman and S. Forsén. In *Progress in NMR Spectroscopy* (Ed. L. Sutchcliffe). Pergamon Press, Oxford, in the press.
- ⁵⁴ R. Kaiser. *J. Chem. Phys.* **39**, 2435 (1963).
- ⁵⁵ R. A. Hoffman, B. Gestblom, and S. Forsén. *J. Chem. Phys.* **40**, 3734 (1964).
- ⁵⁶ R. A. Hoffman, B. Gestblom, and S. Forsén. *J. Mol. Spectry.* **13**, 221 (1964).
- ⁵⁷ R. A. Hoffman. *Arkiv Kemi* **17**, 1 (1960).
- ⁵⁸ R. A. Hoffman. *J. Chem. Phys.* **33**, 1256 (1960).
- ⁵⁹ P. O. Löwdin. *J. Mol. Spectry.* **13**, 326 (1964).
- ⁶⁰ R. A. Hoffman and S. Gronowitz. *Arkiv Kemi* **15**, 45 (1960).
- ⁶¹ A. A. Bothner-By and C. Naar-Colin. *J. Am. Chem. Soc.* **84**, 743 (1962).
- ⁶² A. A. Bothner-By, C. Naar-Colin, and H. Günther. *J. Am. Chem. Soc.* **84**, 2748 (1962).
- ⁶³ S. Castellano and A. A. Bothner-By. *J. Chem. Phys.* **41**, 3863 (1964).
- ⁶⁴ S. Alexander. *J. Chem. Phys.* **32**, 1700 (1960).
- ⁶⁵ H. M. McConnell, A. D. McLean, and C. A. Reilly. *J. Chem. Phys.* **23**, 1152 (1955).
- ⁶⁶ W. A. Anderson. *Phys. Rev.* **102**, 151 (1956).
- ⁶⁷ D. R. Whitman. *Ph.D. Thesis, Yale University* (1957).
- ⁶⁸ D. R. Whitman, L. Onsager, M. Saunders, and H. E. Dubb. *J. Chem. Phys.* **32**, 67 (1960).
- ⁶⁹ J. S. Waugh and F. W. Dobbs. *J. Chem. Phys.* **31**, 1235 (1959).
- ⁷⁰ J. A. Pople and T. Schaefer. *Mol. Phys.* **3**, 547 (1960).
- ⁷¹ P. Diehl and J. A. Pople. *Mol. Phys.* **3**, 557 (1960).
- ⁷² P. Diehl, R. G. Jones, and H. J. Bernstein. *Can. J. Chem.* **43**, 81 (1965).
- ⁷³ P. Diehl. *Helv. Chim. Acta* **48**, 567 (1965).
- ⁷⁴ R. G. Jones, R. C. Hirst, and H. J. Bernstein. *Can. J. Chem.* **43**, 683 (1965).
- ⁷⁵ P. Diehl and R. C. Hirst. Communications presented at the *Sixth Experimental NMR Conference, Mellon Institute, Pittsburgh Pennsylvania, February 1965*.

- ⁷⁶ P. Diehl, R. G. Jones and S. Walker. Communications presented at the *Eighth European Congress on Molecular Spectroscopy, Copenhagen, August 1965*.
- ⁷⁷ D. M. Grant and H. S. Gutowsky. *J. Chem. Phys.* **34**, 699 (1961).
- ⁷⁸ R. J. Abraham and H. J. Bernstein. *Can. J. Chem.* **39**, 216 (1961).
- ⁷⁹ W. G. Paterson and E. J. Wells. *J. Mol. Spectry.* **14**, 101 (1964).
- ⁸⁰ S. Rodmar, B. Gestblom, and R. A. Hoffman. Unpublished results.
- ⁸¹ G. W. Flynn and J. D. Baldeschwieler. *J. Chem. Phys.* **38**, 226 (1963).
- ⁸² G. W. Flynn, M. Matsushima, J. D. Baldeschwieler, and N. C. Craig. *J. Chem. Phys.* **38**, 2295 (1963).
- ⁸³ H. V. McIntosh. *J. Mol. Spectry.* **8**, 169 (1962).
- ⁸⁴ B. Gestblom, R. A. Hoffman, and S. Rodmar. *Acta Chem. Scand.* **18**, 1222 (1964).
- ⁸⁵ B. Gestblom and S. Rodmar. *Acta Chem. Scand.* **18**, 1767 (1964).
- ⁸⁶ L. C. Allen and L. F. Johnson. *J. Am. Chem. Soc.* **85**, 2668 (1963).
- ⁸⁷ R. Ernst. Communication presented at the *Sixth Experimental NMR Conference, Mellon Institute, Pittsburgh, Pennsylvania, February 1965*, *Rev. Sci. Instr.*, in the press.
- ⁸⁸ A. Savitzky. Communication presented at the *Sixth Experimental NMR Conference, Mellon Institute, Pittsburgh Pennsylvania, February 1965*.
- ⁸⁹ A. Savitzky. Communication presented at the *Eighth European Congress on Molecular Spectroscopy, Copenhagen, August 1965*.
- ⁹⁰ T. R. Lusebrink and C. H. Sederholm. Communication presented at the *Sixth Experimental NMR Conference, Mellon Institute, Pittsburgh Pennsylvania, February 1965*.
- ⁹¹ L. C. Allen, H. M. Gladney, and S. H. Glarum. *J. Chem. Phys.* **40**, 3135 (1964).
- ⁹² C. S. Johnson Jr., M. A. Weiner, J. S. Waugh, and D. Seyferth. *J. Am. Chem. Soc.* **83**, 1306 (1961).
- ⁹³ P. R. Story, L. C. Snyder, D. C. Douglass, E. W. Anderson, and R. L. Kornegay. *J. Am. Chem. Soc.* **85**, 3630 (1963).
- ⁹⁴ S. Castellano and A. A. Bothner-By. Private communication.
- ⁹⁵ E. O. Bishop. Communication presented at the *Meeting of the British NMR Discussion Group, Brighton, September 1965*; *Mol. Phys.*, in the press.