A Thesis

Conformational Analysis
by
Nuclear Magnetic Resonance Spectroscopy.

Submitted to the University of Glasgow
for the degree of Doctor of Philosophy
in the Faculty of Science.

by

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Acknowledgements.

No one who reads a thesis fails to turn first to this page, perhaps in the hope that some indiscretion on the author's part will reveal all that has been suspected in the course of three years. Unfortunately, I harbour few guilty secrets and none are to be declared here. Clearly, though, the work described in this thesis is not the effort of a solitary researcher.

My thanks are due for assistance in this work to many members of the technical staff of the Chemistry Department, especially Mr. James Gall who has shared many a disillusioning hour 'at the controls of the 100'. I would also like to acknowledge the provision of computing facilities (under S.R.C. financing) by the National Engineering Laboratory, East Kilbride, with whom it has been a pleasure 'to do business'.

Many of the ideas developed in this thesis originate with my supervisor, Dr. D.D. MacNicol, who has maintained my enthusiasm, though often driving me beyond distraction, for the duration of these studies. From him I have derived an interest and appreciation of n.m.r. spectroscopy.

The list of persons who have demanded a mention here is almost endless. I do, however, recognise the support provided by 'pie in the sky' and by Budgies attention to the Fuzz and all his other services rendered. To Fred and Consort go my thanks for toleration of three years scrounging. It is my hope that in this thesis, they can see some return for their efforts.

My thanks are due to many other persons, but this thesis is dedicated to Kate for services far beyond the call of duty.

Summary.

Conformational Analysis by Nuclear Magnetic Resonance Spectroscopy.

Nuclear magnetic resonance spectroscopy is a powerful and versatile spectroscopic technique and novel applications are continually being devised for it. This thesis concerns the application of "n.m.r." spectroscopy to the study and definition of both the time dependent and the time independent three dimensional geometries of organic molecules in solution.

The purposes of this thesis are (a) to establish the conceptual background to both n.m.r. spectroscopy and conformational analysis and hence to relate the two fields, (b) to review in varying depth the published results in those areas of chemistry which have been ventured upon in the current research and (c) to present the results and conclusions of the current studies.

To these ends, n.m.r. spectroscopy is first briefly reviewed and the areas of major topical interest touched upon. As n.m.r. spectroscopy is a precisely mathematical subject, the theoretical applications later employed are briefly outlined. The thermodynamic considerations relevent to conformational analysis are then reviewed and this is followed by a discussion of the application of n.m.r. spectroscopy to detailed conformational analysis.

The current studies involve reviewing two discrete fields of conformational analysis. Firstly, n.m.r. studies of conformations in medium ring compounds are reviewed in depth. The results of a study of syn-3,7-dibromo-cis,cis-cycloocta-1,5-diene are recorded in which a definitive statement of the solution conformation (in chloroform) of this molecule is possible. The consistency of the data from other techniques relating to this conformation is remarked upon and the similarity to the solid state conformation determined (F.B. Wilson, Ph.D. thesis, University of Glasgow, September 1971) by an X-ray study is deduced.

Secondly, the vast field of n.m.r. studies in conjugated systems is sketched relatively briefly before the few results relating to aromatic systems are detailed. Work on 9-nitroso, and 9-formyljulolidine rotational barriers for the '9' group are then presented. Extensive electron delocalisation is observed from the nitrogen atom of the quinolizidine unit in these compounds to the '9' group and this is comparable to, or in excess of, that observed in para-substituted dimethylanilines. The rotational barriers for the dimethylamino function in three para-substituted N,N-dimethylanilines are then reported and a Hammett correlation between them is suggested. In this manner, an estimate of the rotational barrier for the dimethylamino function in N,N-dimethylaniline itself is presented. Upon this basis and upon results published for studies of aziridine inversion barriers, an estimate of the resonance energy in dimethylaniline is suggested at 10 ± 1 kcal./mole.

The necessary practical details of this work are then outlined. The importance of computing facilities in this work is made in the appendices and an original coding of a least squares method due to W.E. Wentworth (J.Chem.Ed., 1965,42,96) is included.

Published papers on this work are then appended.

Introduction.

The basis of the nuclear magnetic resonance (n.m.r.) method is now familiar to every senior undergraduate chemistry student, and indeed in many instances, practical experience of n.m.r. spectrometers is an integral part of their course of studies. In this respect, n.m.r. spectroscopy joins infra-red and ultra-violet spectroscopies in being presented practically at the undergraduate level. In achieving this, considerable disadvantages of price and complexity of instrumentation have been overcome. Significantly, 'bench-top' n.m.r. spectrometers have recently been announced and it is only to be expected that such a teaching and general purpose tool will soon make its appearance in many undergraduate laboratories. There can be little doubt, considering the scope of n.m.r. spectroscopy, that this move will only be to the student's advantage.

It is hoped that the power of the n.m.r. method will be amply demonstrated in the work reviewed in this thesis. However, only a few of very many applications will be treated in any detail. In n.m.r. spectroscopy we have a unique probe into many aspects of molecular behaviour and it is perhaps the almost all-encompassing applications of n.m.r. which illustrate this point so well. There are few branches of chemistry where n.m.r. has not or cannot be applied profitably in elucidating the nature and behaviour of matter at macroscopic and microscopic levels.

In 1924 Pauli[1] put forward the hypothesis of nuclear spin to explain some of the details of hyperfine structure observed in optical atomic spectra. The existence of nuclear spin, though now a commonplace fact, has diverse consequences in physical chemistry[2]. One such consequence was first detected in gaseous matter in the form of directed beams over thirty years ago[3] when nuclear magnetic resonance was first observed. The growth of n.m.r. as a branch of radio-frequency spectros:

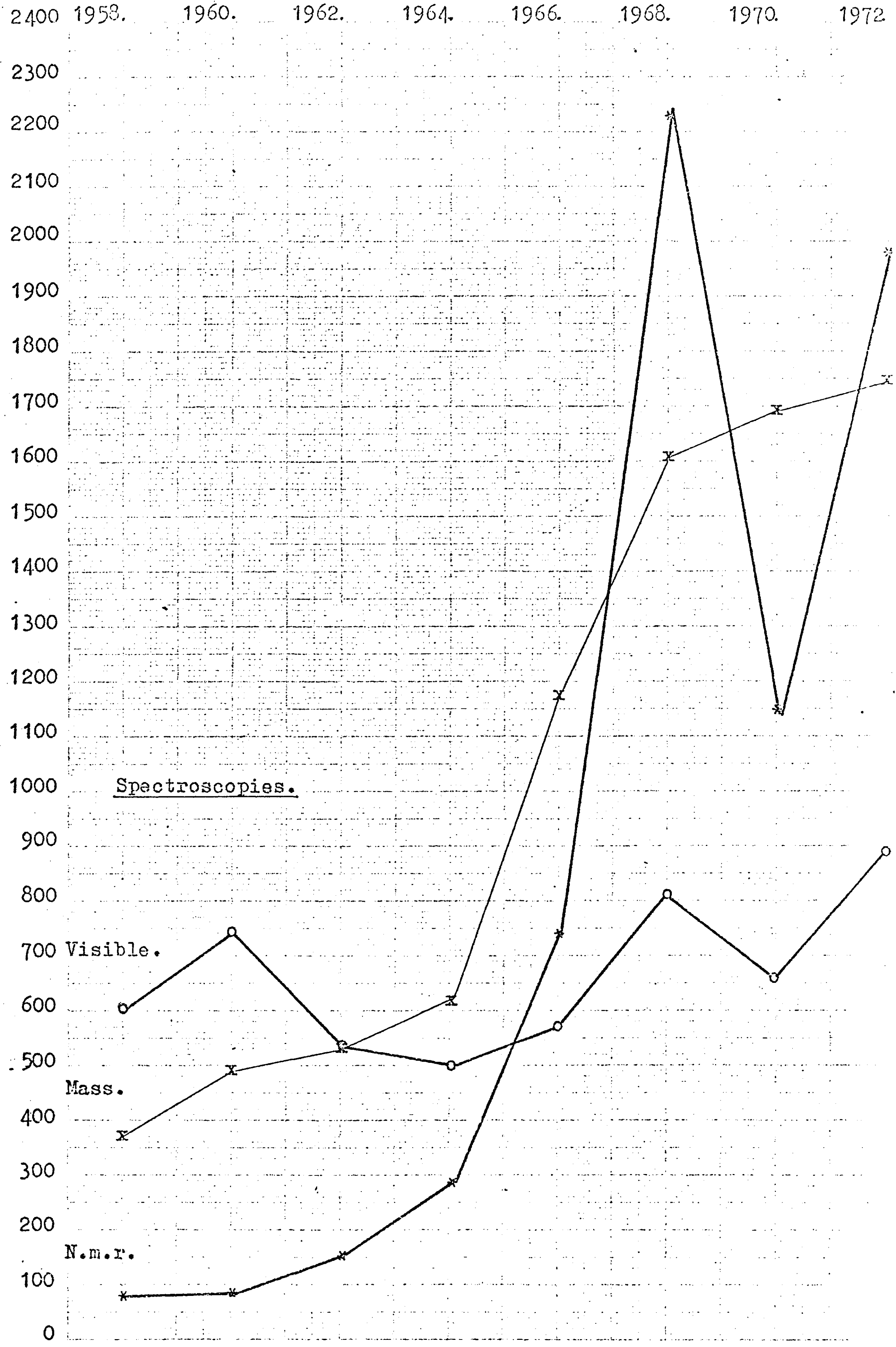
copy was greatly stimulated by its demonstration in condensed phases by Purcell et al.[4] and by Bloch et al.[5] in 1946. In 1950 several authors including Thomas[6] observed a 'chemical shift'[*7] between nuclei in various molecular environments and in 1951 Packard et al.[8] reported separate lines for various chemically different nuclei in the same molecule. When a number of liquids were first examined by n.m.r. spectroscopy, it was found that certain substances showed more lines than were required by simple considerations of the number of non-equivalent nuclei.[*9] These 'coupling'[*10] effects were later interpreted[*11,*12] as arising from interaction between neighbouring nuclear spins.

The term 'high resolution' was applied at this time to measurements which could distinguish individual resonance lines arising from nuclei of the same isotopic species in the same molecule, but differing in magnetic environment. The observation of high resolution spectra depends to a great extent upon the strength and quality[*13] of the magnetic field employed in the measurement. Magnetic resonance experiments are unique in spectroscopy in that the energy of the particular transition observed can be made to vary, simply by changing the strength of the magnetic field in which the sample is situated. At the same time, chemical shifts are sensitive to field strength, the higher the field the larger the shift differences become. The fine structure due to nuclear spin-spin interactions is not field dependent and so increasing field strengths are only a partial solution to resolution[*14] problems. At the same time as increasing the field, we must maintain or increase the magnetic field homogeneity to allow us to separate signals due to small coupling constants.[*15] It is still true, however, that increases which can be made in field strength without sacrificing field homogeneity lead to considerable advantages in n.m.r. spectroscopy.

The first commercial n.m.r. instrument appeared in 1953. As this was only three years after the realisation[16,17] of the significance of n.m.r. to physical chemical studies, this is clear indication of the potential generated very early in the development of the subject. This early machine employed a magnetic field equivalent to a proton resonance frequency of 30MHz. In the ensuing decade both permanent and, to a greater extent, electromagnets were used to advance fields to '100MHz.'. This latter field (23,500gauss, $2.35 Wb.m^{-2}$) is commonly employed nowadays in sophisticated research instruments[*18] even though it was first employed in 1962. This is, however, the limit attainable by electromagnets under the necessary conditions of the n.m.r. experiment. Permanent magnet designs, which have the advantage of not requiring a stabilised power supply, are currently available at 60MHz. and are generally employed in more routine work.

It has been on instruments such as these that the broad and substantial basis of n.m.r. empirical results has been established. It is not possible here to provide a survey of these years of development. Such a task would require at the very least a small monograph to convey a valid impression of the results achieved.[*19] However, as an illustration of the rate of growth during this period, the following diagram should suffice (see next page). The drop in citations for the two years up to 1970 was in response to a request from the series editor to curtail references to those of immediate significance. Yet by 1972, the three authors of 'Nuclear Magnetic Resonance Spectrometry'[20h] despaired of there ever being another such review due to the impracticability of selecting material for inclusion within the confines of a single review. In this light it is interesting to quote from the author of the corresponding review published in 1960.[20b]

" The casual reader of the literature (or even the careful one) might get the impression that NMR is as generally applicable a tool as infrared, ultraviolet, or mass spectrometry. But this reviewer believes that such is not yet the case, and, furthermore, that it is unlikely to be at least until intensity information can be obtained more reliably and interpreted with more confidence. Even then it is not at all clear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Spectroscopies.
Visible.
Mass.
N.m.r.

that NMR will be as generally useful as the other spectroscopic tools mentioned. This belief stems from the following considerations: In the author's experience, it is all too frequent that NMR spectra of samples to which the technique ought to be applicable, are of little use for the analytical problem at hand. The most common reason for this is that the samples are not sufficiently pure. The impurities, for example, may be small amounts of paramagnetic ions, oxygen, or simply isomers of the main component. The resulting NMR spectra will then often consist of a relatively small number of bands instead of a large number of sharp lines usually obtained from sufficiently pure compounds of low molecular weight. In such cases, a useful analysis will still be possible if it depends only on chemical shift information. On the other hand, a useful analysis may not be possible at all if spin-spin coupling information is also needed. For example, the band positions and intensities expected from two postulated structures may not be sufficiently different to allow a decision to be made. Samples prepared by distillation rather than by crystallisation seem to be more subject to the effects of impurities. The spectra of compounds of higher molecular weight tend to consist more of bands than of sharp lines, and may not show sufficient detail to be very useful. This is the primary reason, for example, for the limited applicability of high resolution NMR to the study of the structure of polymers. However, NMR spectroscopy can be a very rapid and powerful tool for the identification and study of suitable samples of relatively simple compounds."

Several of these objections were refuted by the author of the following review in this series/[20c] partly on the basis of differing opinions but more significantly on a basis of advancement in technique in the intervening two years. The work of the last decade makes such objections now appear almost ridiculous and certainly amusing. It is convenient, in the light of these comments, to remark briefly on the many advances currently being made in n.m.r. spectroscopy and to consider the major fields of application of these new techniques and possible future developments.

The advantages of operating n.m.r. spectrometers at ever increasing field strengths have attracted considerable attention recently, particularly with the advent of commercial superconducting magnet systems capable of fields equivalent to proton irradiation at 200 to 300 MHz. One of the major advantages of such high fields is the resolution of second order effects in spectra[*21]. The simplification resulting from the use of very high magnetic fields allows fairly ready analysis of the spectrum for the spectral parameters without resort to considerable computer work, which is both time consuming and expensive.

The availability of highly homogeneous fields from superconducting magnets in recent years has opened up large areas of chemistry to study by n.m.r. spectroscopy. Many complex molecules, particularly polymers of both synthetic and biological origins, are extremely difficult to analyse at ordinary field strengths. The type of results obtainable, even from relatively simple molecules, can be dramatically simplified as Johnson's article[22] illustrates well. The spectral simplification attained at 300 MHz. in very many instances results in nearly first order spectra from systems which exhibit extreme second order effects at 100 MHz. (figs. 1,4-10 of ref. 22.)

The use of high field systems is of course not restricted to protons alone. Similar advantages apply to other nuclei and, further, increased sensitivity can be attained through a more favourable Boltzmann distribution among spin states of the nuclei. In particular, ^{13}C studies at natural abundance are greatly facilitated (figs. 11-15 ref. 22). The application of ^{1}H and ^{13}C studies in biochemical studies has done much to establish the utility of n.m.r. in this field. The establishment of an 'Enzyme Group' in Oxford employing n.m.r. spectroscopy is indicative of the advances being made, as we shall see below.

Becconsall, Curnuck and McIvor[*23] have reviewed extensively further applications of high field n.m.r. spectroscopy and the number of nuclides studied is remarked upon[*24].

Techniques to increase the sensitivity of the n.m.r. method are of considerable importance, particularly for nuclei other than hydrogen. The older technique commonly employed to accomplish this was that of employing a computer of average transients (CAT) to sum together many sweeps of the spectrum under consideration. This approach demands not only a considerable time for spectral accumulation, but also requires high spectrometer stability to eliminate any drift over the long averaging times necessary. The development of the Fourier Transform technique[*25] has brought considerable advances in sensitivity. In essence, the sample whose spectrum is being measured is irradiated, not with continuous monochromatic but varying radiation, but with pulsed wide band polychromatic radiation. Rather than observe an absorption of radiation, the complex emission of the radiation is recorded. If this spectrum is then 'fourier transformed', then we can derive the normal absorption spectrum of the sample. The fact that the sample can be pulsed many times a minute means that the accumulation times for equivalent sensitivity are considerably reduced from those of 'continuous wave' spectroscopy. Coupled with the fact that the spectrometer on which such experiments are carried out will be a sophisticated instrument with good long term stabilisation, then we can achieve greatly enhanced sensitivity in equivalent time periods to those used earlier. Thus nuclides of low inherant sensitivity and/or low natural abundance can be examined within reasonable time periods. One particularly significant nucleus in this respect is C^{13}[26,27]. The natural abundance of C^{13} is about 1% and in consequence, we can only observe this magnetic nuclei (in the presence of non-magnetic C^{12}) with very sensitive instrumentation. The low abundance can, in certain respects, be advantageous. The likelihood of spin-spin coupling between such rare nuclides in a molecule is extremely low due to the remote chance of more than one C^{13} occuring sufficiently close together in a molecule to couple together.

In essence, therefore, C^{13} n.m.r. spectra at natural abundance are the superposition of the resonances of individual uncoupled C^{13} nuclei at each position in the molecule. (By way of corollary, should we want C^{13} coupling information, then C^{13} enrichment will be necessary.) At the same time it may be advantageous to eliminate the multitude of H^1 couplings to C^{13} in which case the technique of wide band decoupling is employed.[27]

Many other nuclei than C^{13} can benefit by this approach. The scope of fourier transform techniques, particularly at high fields, now provides us with a virtual arsenal of probes into molecular behaviour.

Recently a technique which might well be labelled 'the poor man's superconductor' has become extremely popular. In this technique[28] advantage is taken of the fact that a system complexed to a paramagnetic ion will experience strongly anisotropic 'secondary'[*29] magnetic fields. In practice, this is like the local superimposition of a high magnetic field on the normal applied field of the spectrometer. This technique, employing 'shift reagents', has the distinct adavantage of cost over the use of high 'superconductor' external magnetic fields and has all the advantages of increased chemical shift differences. There are, needless to say, disadvantages. The primary disadvantage lies in the fact that the shifts induced in the various nuclei need not leave the spectrum in the natural order of chemical shifts but may move resonances about in a somewhat confusing fashion. Since the amount and sense of the secondary shift experienced depends on the geometrical relation of the nucleus in question to the paramagnetic ion, these shifts are sometimes referred to as geometric shifts. Recent progress has been made, however, in mathematically overcoming the difficulties of tracing the movement of chemical shifts in the spectrum by applying observations at varying concentrations of shift reagent. Here, though, another problem can arise. Many shift reagents and the corresponding complexes are not very soluble and it may be difficult to obtain one good spectrum at one concentration without a requirement for ten or more differing concentrations. Some complexing reagents are better in this respect than others. It is also fair to remark that not all interesting molecules can be complexed in an attempt to unravel their shift and coupling patterns. Furthermore, the use of such reagents under conditions where we seek accurate parameters for the uncomplexed molecule is clearly not applicable.

One of the most significant advances in n.m.r. technique, and one which was initiated early in the development of n.m.r. generally, is that of nuclear magnetic multiple resonance. In this technique, transitions between energy levels of a nuclear spin system are measured in the presence of two or more irradiating fields. Depending upon the particular approach selected, such experiments can be used to unravel complex spectra by various techniques including 'spin decoupling', the use of the second irradiation at varying powers to achieve 'selective spin decoupling', 'spin tickling' and 'Overhauser effects'.[*30] A further variation of double resonance technique is provided by InterNuclear Double Resonance (INDOR) experiments[*31] which provide a means of detecting hidden resonances. With such techniques we can accurately map the nuclear transitions observed in an n.m.r. spectrum and provide detailed information on the molecule in question.

The most prominent fields of n.m.r. application currently in vogue make wide use of the advances in instrumental technique represented by fourier transform spectroscopy in high magnetic fields. A great deal of interest in 'biochemicals' has been stimulated recently[20h] particularly in the realm of macromolecules. Conformational studies on proteins[*32, *33] have been reported recently and such papers are indicative of the promising role n.m.r. spectroscopy will have to play in the near future in the advancement of biochemical studies. The existence of a group of workers under Richards in Oxford sponsored to study enzmyes by n.m.r. spectroscopy is clear indication of the importance of this field. The immediate application of fourier transform instruments to natural abun:

:dance C^{13} n.m.r. studies is also of great promise, for the whole realm of organic chemistry lies open to a fresh and hopefully enlightening investigation of carbon skeleton resonances. Conformational studies in particular may be expected to benefit from this new approach. Again application of this technique to biochemicals is of great significance. In passing, the rather succinct review of C^{13} fourier transform n.m.r. studies in 'Annual Reports, 1971'[34] should be mentioned. The versatility of C^{13} studies is well illustrated here.

Whilst progress in numerous other branches of n.m.r. studies has also been made in the last few years[20h], any discussion of them is well beyond the scope of this introduction and also this thesis. It is hoped that some idea of the scope of n.m.r. studies outlined in this thesis can be obtained from the specialist reviews which appear in later parts of this work.

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Theoretical Methods in Nuclear Magnetic Resonance Spectroscopy.

Introduction.

Spectroscopy can be defined as the study of the interactions between matter and electromagnetic radiation, a process in which energy is absorbed or emitted according to the Bohr frequency condition

$$E = \nu h.$$

where E is the energy difference, normally quantised, between the initial and final states of the matter.
where h is Planck's constant and
where ν is the frequency of the electromagnetic radiation.

The various branches of spectroscopy are delineated by the nature of the energy transitions involved, as differing techniques are required for the generation and detection of radiations of the widely differing frequencies encountered in the electromagnetic spectrum. With the wide scope of spectroscopic methods available, and they are too commonplace to require detailing here, spectroscopy can be considered, on balance, the most powerful tool the chemist possesses for the investigation of molecular structure and molecular processes.

No spectroscopic technique has been embraced so rapidly and enthusiastically as nuclear magnetic resonance (n.m.r.) spectroscopy. Its value as a means of monitoring chemical reactions, of characterising new compounds, and of elucidating the structure of molecules is unsurpassed. It is of very great importance in providing information about the detailed magnetic interactions that occur within and between molecules. Consequently, the information derivable from such studies about the detailed nature of molecules and molecular interactions is immense.

All forms of spectroscopy give spectra which may be described in terms of frequency, intensity and shape of spectral lines or bands. These observable parameters depend on the molecular parameters of the system and it is the relation between the observable parameters and the molecular parameters that is the occupation of the practising spectroscopist. In the n.m.r. experiment, the molecular parameters of interest are the shielding constants of various nuclei, the coupling constants between various nuclei and the lifetimes of the various energy states. The means of relating spectral observables to these parameters, and the relation of these molecular parameters to further details of molecular structure and interaction have demanded, in many spectroscopic techniques, the application of relatively sophisticated mathematics. This has been particularly true of n.m.r. spectroscopy if detailed understanding of the molecular parameters is required. However, n.m.r. spectroscopy benefits from the fact that it can be used qualitatively with a large degree of success, requiring no mathematical applications what so ever. This respect of the technique has no doubt endeared it to many chemists. But it is also true that a large amount of sophisticated and valuable information is only obtainable from n.m.r. spectra by those who are willing to apply the necessary mathematical techniques. It is fortunate that several scientists (physicists and chemists in as much as this distinction means anything in this field) have tackled the mathematical problems involved in the subject, and have provided the mathematically ignorant with the fruits of their labours in the form of readily available computer programs which provide a simple means of obtaining sophisticated results from n.m.r. observations.

From the earliest stages of the development of n.m.r. spectroscopy, this mathematical interest has grown. The calculation of n.m.r. spectra and spectral parameters by purely theoretical techniques is the goal of many theoretical chemists, though the greatest success has been achieved in the former case, that of calculating n.m.r. spectra from defined or assumed n.m.r. molecular parameters. The problem of ab initio calculation of n.m.r. molecular parameters, as such, presents a considerable challenge to the methods of theoretical chemistry and the opportunities available here are dramatic. These parameters are very sensitive to the exact nature of the molecules (for example, the electronic distribution) and the establishment of theoretical techniques for the correct prediction of these parameters would be a major achievement. In this sense, n.m.r. spectroscopy provides the theoretical chemist with a rigourous test of his methods.

It is, however, with the category of spectrum calculation from defined or assumed molecular n.m.r. parameters that we shall be primarily concerned. To the practising n.m.r. spectroscopist, the ability to calculate the spectra expected under the immense variety of conditions of n.m.r. experiments provides a powerful technique for exploring the nature of the molecules and their interactions with other molecules under study. From the observed data, theoretical methods can thus be used to establish n.m.r. parameters for the system with a high degree of accuracy. The molecular behaviour revealed in these parameters can be examined in detail and the purposes of chemistry to 'understand molecules' are advanced.

It is the purpose of the following pages to illustrate briefly some of the techniques applicable to a restricted field of n.m.r. studies. The field chosen is that of 'high resolution spectra' taken under 'steady state conditions' in the presence of only one irradiating field. The significance of these restrictions will become obvious as the methods are developed. The nature of these conditions will be remarked upon in passing, where appropriate, as they are common terms within the context of n.m.r. spectroscopy and do not merit a major digression at this point.

The history of the development of these techniques in n.m.r. spectroscopy is not yet complete, as publications appear steadily[*1] detailing methods, both new and refinements of the old, for calculation of n.m.r. spectra under a variety of conditions. Sophisticated computer programs are available to accomplish most of these calculations. It seems practical, at the present state of development, to almost automate the process of acquiring molecular n.m.r. parameters from any given spectrum under a limited number of specified conditions.

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Elementary Principles.

Quantum Mechanics of Angular Momentum.

Any attempt to understand the nature of n.m.r. spectra of any degree of complexity requires the use of quantum mechanics. Unfortunately, this subject has gained a reputation second to none for the levels of incomprehension generated in the minds of most normal chemists[*1]. The mathematical nature of the subject, which many chemists find forbidding, is no doubt partly responsible for this but further, the practicioners of this art are singularly uncommunicative of its mysteries. As a result, a great deal of misunderstanding arises early in a study of the subject due to a jargon barrier.

In this situation, many expositions of the subject have come to rely upon a postulatory approach. Although this approach does not lead immediately to great understanding, it is expedient in the current circumstances to adopt this approach to enable the necessary background of n.m.r. spectral calculations to be established with the minimum of delay.

The text by White[2] provides a useful introduction to the development of quantum mechanical methods from those of classical mechanics, whilst Hanna's "Quantum Mechanics in Chemistry" illustrates the postulatory approach to the subject[3].

quantisation of angular momentum.

One of the fundamental postulates of modern chemical physics is that the total angular momentum of any isolated particle cannot have any arbitrary magnitude, but may only take certain discrete values. This principle of *quantisation* is by now familiar to almost every chemistry undergraduate. Angular momentum is quantised and its magnitude P can be specified in terms of a *quantum number* R as shown in equation (1).

$$P = \hbar\,(R(R+1))^{\frac{1}{2}} \qquad (1).$$

where $\hbar$ is $h/2\pi$, h being Plank's constant. R is either integral or half integral.

As angular momentum is a vector property, then for a full description of the vector, direction as well as magnitude has to be specified. Direction can be defined indirectly by the use of another quantum number which we shall call m_R, such that the magnitude of the component of angular momentum, P_z, along the prescribed direction (z) is given by

$$P_z = \hbar m_R \qquad (2).$$

where it is readily shown that m_R can take values of R, R − 1, R − 2,......, − R.

<u>spin angular momentum and nuclear spin.</u>

The particular example of angular momentum of central interest in n.m.r. experiments is that of nuclear spin. There is no classical analogue of spin and, consequently, we cannot derive its properties directly from classical mechanics as is possible for 'orbital angular momentum'. The absence of an appropriate classical analogue implies that explicit expressions for spin properties cannot be obtained at all, so that they must be represented by abstract symbols whose properties are revealed by experiment. We will develop the theory of spin angular momentum upon the basis of a few plausible assumptions whose validity can be established by experiment. Transitions between spin angular momentum energy levels were first suggested by Pauli in 1924 in order to explain the hyperfine structure that had been observed in atomic spectra. The origins of this nuclear spin can be traced to the detailed nature of the internal construction of the nuclei, but for our present interests, we may safely disregard the origins of this phenomenon.

As we have assumed above, the spin angular momentum of a particle is represented by a vector operator. This means that the spin operators constitute a set of three linearly independent component operators dis:

:tinguished by subscripts referring to the three orthogonal axes of a right handed cartesian coordinate system. So

$$\underline{I} = (I_x, I_y, I_z) \qquad (3).$$

where $\underline{I}$ is the spin vector.

The physical interpretation of the component operators is that an observer O in the coordinate system K uses I_x, I_y and I_z to compute quantum mechanical averages that are interpreted as the expectation values for the components of the spin angular momentum along the Cartesian axes. Since the component operators are identified with observable quantities, it follows from the general principles of quantum mechanics that the component operators are linear and Hermitian.[2a,3a,4,*5] In addition to the component operators, a fourth spin operator is defined by the equation

$$\underline{I}^2 = \underline{I} \cdot \underline{I} = I_x^2 + I_y^2 + I_z^2 \qquad (4).$$

This operator is called the square of the spin vector and its expectation value is interpreted as the square of the spin angular momentum. These spin angular momentum operators can be treated by the appropriate methods of operator algebra to derive results of quantum mechanical interest.

We then assume that the components of the spin vector in the coordinate system K satisfy commutation relations identical to those satisfied by orbital angular momentum operators.

wave functions.

The functions upon which quantum mechanical operators operate are known as wave functions (or state functions) and are functions of the variables of the particular system considered. We will introduce here Dirac's notation for wave functions, as it is well suited to spin funct:

tions. In this notation $|n\rangle$ is a wave function or ket and $\langle n|$ is its complex conjugate or bra. Whenever a bracket is completed, integration over all variables is implied. So the normalisation condition is

$$\langle n|n\rangle = 1.$$

and the expressions $\langle m|H|n\rangle$ and $\int \psi_m^* \hat{H} \psi_n d\tau$ are equivalent.

The wave function itself cannot be observed, but the results of any operation can be predicted from it. If $|n\rangle$ is an eigenfunction of an operator A, then

$$\hat{A}|n\rangle = a|n\rangle \qquad (5).$$

and the result of the observation corresponding to $\hat{A}$ is always a. Though $|n\rangle$ might not be an eigenfunction of $\hat{A}$, it can always be written as a linear combination of eigenfunctions of $\hat{A}$. Suppose

$$|n\rangle = c_1|p\rangle + c_2|q\rangle \qquad (6).$$

where $|p\rangle$ and $|q\rangle$ are normalised eigenfunctions of $\hat{A}$ with eigenvalues p and q.

The hypothesis is that the probabilities of observing p and q are $c_1c_1^*$ and $c_2c_2^*$ respectively where c^* is the complex conjugate of c. The expectation value of A is given by

$$\langle A\rangle = c_1c_1^*p + c_2c_2^*q \qquad (7).$$

which can be written

$$\langle A\rangle = \langle n|\hat{A}|n\rangle \qquad (8).$$

because $|p\rangle$ and $|q\rangle$ which have different eigenvalues are always orthogonal. A wave function may in certain circumstances be a wave function of two or more different operators. If the two operators commute, then there are a complete set of functions which are simultaneously eigenfunctions of both operators. The concept of commuting operators is defined by equation (9) as

$$[\hat{A},\hat{B}] = \hat{A}\hat{B} - \hat{B}\hat{A} = 0 \quad (9).$$

By adaptations of the above theorems to spin operators, the necessary results required in applications to n.m.r. spectroscopy can be derived. However, rather than derive them at length, they will merely be stated here with comments where appropriate.

spin operators and spin functions.

There are three independent components of spin angular momentum with corresponding operators $\hbar I_x$, $\hbar I_y$ and $\hbar I_z$ and these act on the spin wave functions of the particles in question. The commutation relations between these operators are

$$\begin{aligned} [\hat{I}_x,\hat{I}_y] &= i\hat{I}_z \\ [\hat{I}_y,\hat{I}_z] &= i\hat{I}_x \\ [\hat{I}_z,\hat{I}_x] &= i\hat{I}_y \end{aligned}$$

where $i^2 = -1$.

From these relations we can deduce that there are no states which are simultaneous eigenstates of all three operators. This means that a spin function in an eigenstate of I_z with eigenvalue m will give an exact value for the observation of the z component of angular momentum only. Now the square of the magnitude of the angular momentum corresponds to the operator $\hbar^2 I^2$ where I is constructed from its components. This operator commutes with its components and so it is possible to define both the magnitude of the angular momentum and any one of its component magnitudes simultaneously. Thus we may choose a set of normalis:

:ed functions I,m which are eigenfunctions of both I^2 and I_z. These are the 2I + 1 states with total angular momentum $\hbar\,(I(I + 1))^{\frac{1}{2}}$ with a z component of angular momentum $\hbar.m$. To derive the allowed values of I and m from the commutation relations (10), it is necessary to introduce the raising and lowering operators $\hat{I}_+$ and $\hat{I}_-$ which convert the state $|I,m\rangle$ into $|I,m + 1\rangle$ and $|I,m - 1\rangle$ respectively. These operators are

$$\begin{aligned} \hat{I}_+ &= \hat{I}_x + i\hat{I}_y \\ \hat{I}_- &= \hat{I}_x - i\hat{I}_y \end{aligned} \qquad (11).$$

Nuclei in their ground states have definite values of I, and (2I + 1) different energies in a magnetic field (see below). As those nuclei with $I = \frac{1}{2}$ are the most important by far in n.m.r. experiments we shall, from here on, consider only such cases. This has the further advantage of simplifying the discussion of calculation techniques, though no <u>particular</u> principles are being employed. Nuclei with $I = \frac{1}{2}$ exist in two states $|\frac{1}{2},\frac{1}{2}\rangle$ and $|\frac{1}{2},-\frac{1}{2}\rangle$ which are often designated $|\alpha\rangle$ and $|\beta\rangle$. To summarise this then

$$\begin{array}{llllll} I^2|\alpha\rangle & = & \frac{3}{4}|\alpha\rangle. & I^2|\beta\rangle & = & \frac{3}{4}|\beta\rangle. \\ I_z|\alpha\rangle & = & \frac{1}{2}|\alpha\rangle. & I_z|\beta\rangle & = & -\frac{1}{2}|\beta\rangle. \\ I_+|\alpha\rangle & = & 0. & I_+|\beta\rangle & = & |\alpha\rangle. \\ I_-|\alpha\rangle & = & |\beta\rangle. & I_-|\beta\rangle & = & 0. \end{array} \qquad (12).$$

Many of the common isotopes, in particular ^{12}C and ^{16}O, have I = 0 and consequently, due to a lack of spin angular momentum components other than zero, they do not exhibit n.m.r. spectra. This is in itself fortuitous for many organic compounds would exhibit extremely complex ^1H spectra if the ever present carbon and oxygen gave coupling effects (see later) to the protons with $I = \frac{1}{2}$. The significance of the spin angular momentum quantum number of hydrogen being $\frac{1}{2}$ cannot be overstated. The whole field of organic chemistry is open to n.m.r. experimentation and this fact is undoubtedly responsible for the very rapid development of n.m.r. as a physical tool of great usefulness to chemists.

Nuclei with spin quantum number greater than $\frac{1}{2}$ can, for several reasons we will not consider here, be mainly neglected in terms of n.m.r. spectra.

Nuclei in a Magnetic Field.

For nuclei with spin quantum number greater than zero there is associated a magnetic moment μ given by

$$\underline{\mu} = g_N \mu_N \underline{P/\hbar} \qquad (13).$$

where where μ_N is the nuclear magneton and has a value of $5.0505 \cdot 10^{-27}$ Joules/Tesla, P is the spin angular momentum and g_N is the nuclear g-factor.

Usually nuclear magnetic moments are described in terms of magnetogyric ratios γ, rather than nuclear g-factors. The value of γ is defined as the ratio of the magnetic moment to the angular momentum (taking explicit account of the sign of the relationship).

$$\underline{\mu} = \gamma \underline{P} \qquad (14).$$

and so we see

$$\gamma\hbar = g_N \mu_N$$

and

$$\mu = \gamma\hbar\,(I(I + 1))^{\frac{1}{2}} \qquad (15).$$

In the absence of a magnetic field the energy of an isolated nucleus is independent of the quantum number m_I. This states that the energy of a nucleus is independent of its orientation. When a magnetic field of strength B is applied in a direction defined as z, then we can define, both classically and quantum mechanically the interaction energy U by

$$U = -\underline{\mu}\cdot\underline{B} = -\mu_z B$$

where μ_z is the component of $\underline{\mu}$ in the direction z.

This component, in the case of nuclear spin is defined by m_I, and so we can eventually deduce

$$U = -\gamma \hbar m_I B \qquad (16).$$

and we will observe 2I + 1 non-degenerate energy levels each separated by $\gamma \hbar B$. Restricting our attention to the two levels from nuclei with $I = \frac{1}{2}$, we will observe transitions between the levels induced by the appropriate energy of electromagnetic radiation. The overall selection rule operating here is $\Delta m_I = \pm 1$, though in this particular instance there is no option.

$$h\nu = \gamma \hbar B$$
$$\nu = \gamma/2\pi \; B \qquad (17).$$

Normally fields in the range 1 – 5 Tesla are used and this involves frequencies of the order of tens to hundreds of MHz. found in the radiofrequency range of the electromagnetic spectrum.

We can see from equation (17) that the resonance frequency is proportional to the strength of the magnetic field. Thus in an attempt to achieve resonance of any nucleus, either the field B or the frequency ν may be varied until the conditions of (17) are satisfied. If we consider two nuclei of differing magnetogyric ratios, then from (17) we can see, that the nucleus with the higher magnetogyric ratio will resonate at an increased frequency or a decreased field with respect to the nucleus with the lower ratio. For reasons which are detailed elsewhere in this thesis, it is preferable to use, if at all possible, a higher field.

It is an interesting feature of magnetic resonance experiments that the values of the frequency energies absorbed by the system are to a large part dependent upon conditions specified by the observer and are not intrinsic properties of the system itself.

electronic shielding and chemical shifts.

So far we have assumed that all the nuclei in a given molecule experience exactly the same (applied) magnetic field and that one resonance condition being satisfied, then all the nuclei of the same species will absorb energy simultaneously from the applied radiofrequency source. Fortunately, this is not the case. The presence of the sample itself perturbs the applied magnetic field. This it does in two ways giving rise to a bulk macroscopic effect and a local microscopic effect. The origin of these effects can be traced to the behaviour of the molecular electrons in the applied field. The motion of the electrons gives rise to diamagnetism, a magnetic field effect which opposes the main field. It is the variations in this local field which give n.m.r. its great potential as a spectroscopic tool. If we take account of the effective field at any point in the molecule (say B) we can define this in terms of the applied field B_0 and a screening constant σ as follows.

$$B = B_0(1 - \sigma) \qquad (18).$$

The dimensionless number σ is a small fraction, usually listed in parts per million of the main field, and is known as the shielding constant. Since this shielding is caused by the electronic environment of the studied nucleus, it will come as no suprise, that the shielding varies with the position of the nucleus within a given molecule, and nuclei of the same type in a molecule will be subject to slightly varying fields, due to variations in electronic shielding expressed by differing σ's. The resonance condition can be redefined as in equation (19).

$$\nu_j = \gamma/2\pi \, B_o(1 - \sigma_j) \qquad (19).$$

as applied to nucleus j.

The differences in σ_j give rise to the observation of different nuclei of the same type resonating separately in a spectrum – a phenomenon known as chemical shift. The chemical shift of one resonance relative to another is what is observed when two lines appear separately in a spectrum.

The question of a standard to which to refer all chemical shifts is an obvious corollary of the above discussion. The use of internal T.M.S. is by now well known and needs no comment here! Application of other standards for nuclei other than hydrogen is normally necessary. As the measured chemical shifts in the spectrum, if expressed in Hz., are proportional to the spectrometer operating frequency it is desirable to report chemical shifts in the dimensionless 'parts per million' (ppm) units. Proton resonances in ppm relative to TMS are said to be based on the δ scale. The δ values are positive if the sample absorbs to high frequency of the reference absorption at constant field. The relationship is expressed by equation (20).

$$\delta = 10^6(\nu_{sample} - \nu_{TMS})/\nu_{TMS} \qquad (20).$$

at constant B_o.

In terms of shielding constants this can be stated

$$\delta = 10^6(\sigma_{TMS} - \sigma_{sample}) \qquad (21).$$

It is clear that a high frequency shift implies a decrease in σ, i.e. deshielding.

spin-spin coupling.

The phenomenon of the chemical shift is not sufficient to describe the spectrum observed for most molecules in solution. Additional features in the spectrum arise due to the magnetic effects of the various nuclei upon each other. This phenomenon, known as spin-spin coupling, cannot be explained completely by any classical analogy, and it involves the interaction of the spin angular momentum components of the various nuclei with each other, by mechanisms which depend largely on electronic interactions between the nuclei in question. Though somewhat complex in nature, these couplings, termed J_{kl} for coupling between nuclei k and l, can be understood on a first order basis in terms of small additional magnetic fields at the nuclei, which vary in a quantised fashion depending on the spin orientation of the particular nucleus. This additional field is a property of the nucleus and the interaction pathway in question, and is thus not affected by the value of the external field. Thus coupling constants do not vary with the spectrometer operating frequency.

If a particular nucleus k has $2I_k + 1$ spin orientations, namely 2 orientations if we apply our restriction to spin $\frac{1}{2}$ nuclei only, then any nucleus l coupled to this nucleus k will cause the resonance line of k to be split into two equal intensity lines equally spaced about the original line position, and separated by a given frequency J_{kl} known as the spin-spin coupling constant between k and l. Where there are more than two interacting nuclei, and where we have cases of identical nuclei coupling to another nucleus, then the 'splitting' patterns become more complex, though still capable of being understood on the basis of this simple logic. The elements of this 'first-order or semi-classical' theory are, by now, well known and they are not of immediate interest here. We shall concern ourselves with establishing the ground work for an understanding of the more complex, but necessary, full quantum mechanical treatment.

spin functions and product functions.

As we have seen the wave functions for spin $\frac{1}{2}$ nuclei are often labelled α for $m_I = +\frac{1}{2}$ and β for $m_I = -\frac{1}{2}$. As is fairly obvious, in the above case of simple first-order spectra, all transitions in the spectrum can be labelled with the spin states (α or β) of the other nuclei in the system, excluding the one undergoing resonance transitions. The particular relation of α and β can be swopped without any material effect on the spectrum.

By normal quantum mechanical considerations, the overall spin 'state' of the assembly of nuclei in a molecule may be designated by the product of the spin functions of the individual nuclei. It is expedient to list the various spin states of a system with the spin functions of the various nuclei multiplied in the same order from case to case. This then allows us to write $\alpha_A\beta_M\beta_X$ as $\alpha\beta\beta$ where the order AMX is understood. These product functions are a suitable 'basis' for expressing the more complex situations which must be treated by quantum mechanics.[2b] These product functions may be classified according to the value of the total component of spin angular momentum $m_T = {}_j m_j$, where summation is over all the nuclei of the system. So, for example, a $\beta\beta\beta$ product function has $m_T = -3/2$ whilst $\beta\alpha\alpha$, $\alpha\beta\alpha$ and $\alpha\alpha\beta$ would all have $m_T = +1/2$.

Energies and Spectra.

Though the practical problem to be solved in n.m.r. spectroscopy is that of establishing the n.m.r. parameters - chemical shift and coupling constant - from an observed spectrum, the approach adopted is to work in reverse; given a set of chemical shifts and coupling constants, what is the appearance of the experimental spectrum under specified conditions? In this manner, a theoretical spectrum is matched to an experimental spectrum and the n.m.r. parameters of the theoretical spectrum are assumed to be applicable to the experimental spectrum. The problems of unambiguous definition of spectral parameters by this approach have been considered at length in specific cases,[*6] and whilst the problems cannot be totally circumvented, we can normally be quite sure that we have achieved a unique solution of the problem.

Following the normal methods of quantum mechanics, we must solve the operator equation for which the corresponding observable is the en:

:ergy of the system, namely the Schroedinger equation. The operator under consideration is the Hamiltonian of the system.

the Hamiltonian.

As is obvious, the energy of a system is an observable and the corresponding operator H is known as the Hamiltonian of the system. The operator equation is written as

$$H \psi = E \psi \qquad (22).$$

The complete Hamiltonian for a molecule is a complicated operator containing terms appropriate to energies deriving from many sources. The operator can be divided into terms corresponding, approximately, to these individual energies and the wave functions can then be written as products of functions describing the various interactions involved. So, for example, we can write a wave function as a product of electronic, vibrational, rotational and nuclear spin functions, each of which are eigenfunctions of an effective Hamiltonian. The nuclear spin Hamiltonian contains nuclear spin operators and constants, the coupling constants and chemical shifts, whose values depend on the electronic, vibrational and rotational states of the molecule. The nuclear spin states are eigenstates of this Hamiltonian.

The use of a Hamiltonian which excludes consideration of anything but the spin states of the nuclei of the system is justified, in as much as the energetic interactions of the magnetic field and the radiofrequencies, applied to the molecules under examination, do not affect the physical conditions of the molecule except by interaction with the nuclear spins. Even electronic spin levels, in which the degeneracy is lifted by application of the magnetic field, are not perturbed to any significant extent by the applied radiation in most high resolution experiments.

The form of the Hamiltonian operator for a collection of nuclei in a magnetic field can be developed from the preceding considerations. From equations (16) and (17), expressing the Hamiltonian in frequency units rather than energy units by dividing through by Planck's constant (equation (17)), we may express the interaction of the various nuclei with the applied field, allowing for the effect of shielding (equation (18)), as

$$H = -\textstyle\sum_j (2\pi)^{-1}\, \gamma_j\, B_o (1 - \sigma_j)\, I_{z)j} \qquad (23).$$

where $I_{z)j}$ is the operator whose observable is the z component of spin angular momentum for nucleus j.

The use of units of frequency and not energy is conventional and convenient. The eigenfunctions are unchanged from those of the true Hamiltonian operator whilst the eigenvalues give energy level frequencies directly, rather than transition energies. It should be remarked that this Hamiltonian is appropriate for molecules which make frequent random collisions, and is not appropriate to molecules in definite rotational and vibrational states and to those in solids, which have more complex Hamiltonians. The observed σ and J (coupling constant) values are mean values, taken over the rotational and vibrational states present in any system, and they will show temperature variations due to changes in the population of individual states. All terms, which depend upon the orientation of the molecule in the applied field, average to zero under the conditions of rapid tumbling in gas and liquid samples.

It can be shown[7] that the interaction between nuclear spins, represented phenomenologically by the coupling constant J_{kl}, is described in the Hamiltonian by the scalar product of the z spin components multiplied by the constant J_{kl}.

$$H \quad = \quad +\tfrac{1}{2}\sum_{k\neq l} J_{kl}\, I_k \cdot I_l \qquad (24).$$

The complete spin Hamiltonian is the sum of equations (23) and (24).

It is clear that considerable simplification of the Hamiltonian occurs in practice for all operators contained within it do not operate on all eigenfunctions of the spin system.

the state of the system.

To describe the state of a given spin system, it is possible to employ the simplest spin states of the isolated nucleus as a basis. For spin $\frac{1}{2}$ nuclei, to which we shall confine our attention, these basis states are labelled α and β. It is, in practice, more convenient though, to employ linear combinations of the simple product states (e.g. $\alpha\beta$). A system of N nuclei with N chemical shifts and $\frac{1}{2}N(N - 1)$ coupling constants will allow a set of 2^N simple product functions which can be used as a basis. We are now presented with the problem of finding a linear combination of these basis sets which are stationary states of the Hamiltonian, or in other words, are eigenfunctions of the Hamiltonian with corresponding eigenvalues that are (in this case) energy level frequencies. These states will also be eigenstates of any operator which commutes with the Hamiltonian and one such operator is that corresponding to the z component of total spin angular momentum, F_z. ($F = \sum_k \hat{I}_k$). The eigenvalues of F_z are m_T introduced earlier. Clearly a considerable amount of mixing of basis states will be involved, as many combinations of such basis states have the same m_T values. Such basis states are mixed by the coupling terms of the Hamiltonian operator.

If $|\phi_1\rangle \ldots\ldots |\phi_n\rangle$ are the set of product functions which have eigenvalue m_T for F_z, then the n stationary states $|\psi_1\rangle \ldots\ldots |\psi_n\rangle$ which correspond to the same m_T are linear combinations of these $|\phi_j\rangle$.

$$|\psi_k\rangle \quad = \quad \sum_j c_{kj}\, |\phi_j\rangle \qquad (25).$$

These stationary states (equation (25)) are eigenstates of H. Expansion of the Hamiltonian equation for product functions in terms of the basis functions gives rise to the familiar secular equations which are conveniently written in matrix form as

$$\begin{bmatrix} H_{11} - E & H_{12} & \cdots\cdots\cdots \\ H_{21} & H_{22} - E & \cdots\cdots\cdots \\ \cdot & & \\ \cdot & & \\ \cdot & & \end{bmatrix} \cdot \begin{bmatrix} c_1 \\ c_2 \\ \\ \\ \\ \end{bmatrix} = 0. \quad (26).$$

which is true for each k.

These are consistent only if the determinant of the left hand matrix (the secular determinant) is zero. Solving this n order equation for E gives n possible values for E and n spin eigenfunctions. This process is repeated for each value of m_T.

The process of solving this set of secular equations is equivalent to 'diagonalising the Hamiltonian matrix'[*5]. It is possible to change the basis of the Hamiltonian, that is change the basis functions, such that the form of the Hamiltonian matrix is considerably simplified. If eigenstates are chosen as the basis, then all off diagonal elements of the matrix go to zero and the diagonal elements provide the energies directly. The process of diagonalising the matrix is by no means simple and in all but the most simple cases it is performed by processes of iteration on electronic computers. Explicit solutions for matrices greater than 2 x 2 are not attainable.

Several methods have been developed to simplify the problem of matrix diagonalisation which, on the surface, may not appear to be directly related to the difficulties of matrix algebra. For instance, considerable simplification of the matrices involved can be achieved if we can take explicit account of any magnetic and even chemical equivalence of the nuclei in the molecule. Magnetically equivalent nuclei are those which experience identical (in every respect) interactions with all other nuclei. Chemically equivalent nuclei are isochronous (of the same chemical shift) but do not experience identical couplings to all other nuclei in the molecule. If a group of nuclei are magnetically equivalent, they can be replaced by a single composite particle[8] resulting in considerable simplification of the matrices to be diagonalised. As chemically equivalent nuclei are related by symmetry operations of the point group of the molecule, group theoretical methods can be used to construct a basis of symmetry functions[9], though generally the highest degree of symmetry accounted for in computer programs is that of a symmetry axis.

Having established the transition frequencies obtained for a given set of parameters, it only remains to establish the transition intensities. These are relatively trivially calculated from prescribed formulae which need not concern us here.

Spectral Lineshapes and Relaxation Processes.

Early experimenters in n.m.r. were mainly interested in dynamic processes and line shapes and they found that a classical macroscopic description of magnetic resonance phenomena satisfied their requirements. Bloch[10] pioneered a mathematical approach to this subject in the form of equations (which now bear his name) describing the state of macroscopic magnetisation in a system.

Any sample placed in a magnetic field develops a macroscopic magnetic moment dependent upon the value of the field; the temperature, which defines in part the spin distribution between available energy levels; the magnetogyric ratio of the nuclei involved, which defines the magnitude of the individual nuclear moments and the number of nuclei present. As it is a macroscopic theory, it is appropriate to consider the magnetisation per defined number of spins. If the z direction is taken along the applied field vector B_o, then the magnetisation M_o is in the same direction and takes the value

$$M_o = \frac{1}{4} N(\gamma\hbar)^2 B_o/kT \qquad (27).$$

where N is the total number of spins and the high temperature approximation $kT \gg |\gamma B_o|$ has been used.

If the spins in the system are perturbed from this equilibrium condition by the application of an external radiofrequency causing resonance, then on the cessation of irradiation, the components of M, the total magnetisation, parallel and perpendicular to M_o decay with different time constants T_1 and T_2. With the z axis defined along B_o

$$\frac{d}{dt} M_z = -(M_z - M_o)/T_1 \qquad (28).$$

$$\frac{d}{dt} M_x = -M_x/T_2$$

$$\frac{d}{dt} M_y = -M_y/T_2 \qquad (29).$$

This approach to thermal equilibrium in the field is known as relaxation with T_1 and T_2 as relaxation times. The decay of the longitudinal component M_z is accompanied by an energy flow between the nuclear spin system and the other degrees of freedom of the system known as the lattice. The relaxation time T_1 which describes this flow, is known as the spin-lattice relaxation time, or the longitudinal relaxation time. T_2 is known as the transverse relaxation time or the spin-spin relaxation time. The latter name arises because direct interaction between the spins of the different nuclei can cause relaxation of M_x and M_y without energy transfer to the lattice. In studies on fluids, however, such spin-spin processes have a negligable effect and the relaxation in the system can be considered purely in terms of spin-lattice effects in T_1 and T_2.

Relaxation of nuclear spins is much slower than the relaxation associated with rotational and vibrational levels and so relaxation times of seconds are common in n.m.r. spectroscopy. Transitions between nuclear spin levels can only be induced by magnetic fields and consequently, nuclei rely upon random magnetic fields brought about by the Brownian motion of other nuclei to effect relaxation. The longitudinal or spin-lattice relaxation depends upon fourier components of these fluctuating fields, perpendicular to the static applied field, oscillating at the resonance frequency. The excited population states relax until they reach the population distribution defined by the Boltzmann distribution for that temperature. Thus we can see that the relaxation time T_1 is concerned with the relative populations of states and hence the intensities of signal observed.

The effect of magnetic nuclei interacting among themselves, described by the spin-spin relaxation time T_2, is to cause uncertainty in the lifetime of any one nucleus in a given spin state. By Heisenberg's Uncertainty Principle, this results in an increased uncertainty as to the energy of the transition with a consequent spread in measured values of the transition energy. This results in an increase in line width of the observed spectrum. We can generally account for the line width of a signal by the variation of T_2.

The line shapes most commonly met in spectroscopy are those known as Gaussian and Lorentzian. We will not concern ourselves here with the particular mathematics of each line shape. It suffices to remark that the Lorentzian line is fairly well established as that most appropriate to describing high resolution n.m.r. signals. A particular feature of this line shape is that its width measured in Hz. at half maximum height is defined as

$$\delta\nu_{\frac{1}{2}} = (\pi T_2)^{-1} \qquad (30).$$

The aspect of uncertainty associated with line width of a signal is also exhibited by systems undergoing exchange of nuclei between distinct sites. As the exchange rate increases, the uncertainty with which the individual lines can be determined increases with a consequent broadening of the signals. Eventually the signals become so broad that the two signals coalesce, a well known phenomenon. As the rate increases even further, it is only possible to measure an average position for the line, though this can be measured with greater accuracy, the greater the rate of exchange.

The application of Bloch equations, with their built in relaxation concepts, to such exchanging systems was originally tackled by Gutowsky and coworkers[11,12] and later in a mathematically simpler version by McConnell and coworkers.[13,14] The results developed by these authors have been widely applied in the literature but, unfortunately, in the approximate forms that can be derived from the general equations. In consequence, many approximate solutions of rate studies abound employing such equations, with the concurrent difficulties this causes. More recent studies have employed a full mathematical description of the line shapes, and Reeves and Shaw have extended the Bloch description by employing matrix techniques.[15] In a further paper, the application of these methods to first order coupled spectra is described.[16]

The application of Bloch equations to exchange problems is now very much overshadowed by the use of exact quantum mechanical techniques to these systems. The use of such techniques (to be described below) is often advantageous, as the programs involved are applicable to all orders of coupling and do not depend upon first order approximations for their validity. Free from the requirement to establish first order or uncoupled systems for study, the spectroscopist can advance his studies into previously uncharted fields. The very complexity of spectra which was once so disadvantageous can now be seen as a positive advantage.[17]

References (Elementary Principles).

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Major Quantum Mechanical Techniques.

Two further approaches to quantum mechanical calculation of n.m.r. spectra have yet to be mentioned and we will discuss, briefly, the salient points of both of these techniques below. Both categories of technique have been applied to non-exchanging and exchanging system spectra, though in the present work, only one of these categories was employed in the calculation of spectra. Techniques described earlier were employed for the calculation of non-exchanging spectra whilst the direct methods to be described below were employed for the calculation of exchange spectra. This resulted from the availability of computer programs.

The first category to be discussed below is that of density matrix techniques, and the particular instance of the application of density matrix algebra can be classified as belonging to indirect techniques. The term 'indirect' is intended by exponents of the second 'direct' technique to point to the contrast in results obtained from these two methods. In the indirect methods, the final result of the necessary calculations is a listing of energy levels and allowed transitions between them. In direct or superoperator methods, the final calculation output is a listing of the transition energies (or frequencies) of the spectrum directly, without the need to calculate energy levels in the first place.

The relative merits of either method are difficult to assess and it seems at least, that no great computational advantages acrue to either method. Is is perhaps mathematically satisfying, if nothing else, that superoperator methods are capable of supplying directly the physical parameters of interest, namely the transition frequencies, though the chore of assembling transition frequencies from calculated energy levels is probably the least of the computational problems involved in these methods.

Density Matrix Methods.

The use of the density matrix to describe states in quantum mechanics is a well known mathematical technique. Any comprehensive dis:

:cussion of these techniques is far beyond the scope of not only this thesis but also the present author! Several authors have discussed density matrix techniques, in particular Fano/[1] who considered general density matrix methods and operator techniques, and Abragam/[2] whose discussion was orientated strictly towards n.m.r., but in a detailed theoretical fashion. Lynden-Bell/[3] has provided the most satisfactory description of these methods for our purposes, though the results quoted by her are not presented with proofs as such. For such proofs, the work of the other two authors above can be consulted.

The density matrix finds its most useful application in discussing line shapes of complicated systems but the principle of the density matrix is most easily discussed with a trivial example. In this context, it would appear that little is to be gained as against the more straight forward methods described earlier, but the link between the density matrix approach and the earlier work is best made in this fashion.

There are various ways of describing the state of a system, but of particular interest for our present purposes is the construction of wave functions from complete basis sets of orthogonal, normalised functions. So we can expand Ψ in terms of ϕ as follows.

$$\Psi = c_1\phi_1 + c_2\phi_2 + c_3\phi_3 + \dots \qquad (1).$$

This method is convenient particularly for spin systems where the basis set contains a relatively small number of functions.

Now the state of the system can be described by a matrix formed from the expansion coefficients c_i in equation (1) above/[*4, *5].

$$p_{ij} = c_i c_j^* \qquad (2).$$

If we now seek the expectation value for a given operator Q acting on a system described by the density matrix p, this can be deduced to be

$$\bar{Q} = \text{trace } pQ = \text{trace } Qp \quad (3).$$

where Q is the matrix with elements Q_{ij} and the trace of the matrix is the sum of the diagonal terms.

The trace of a matrix is independent of the choice of basis functions and consequently, calculations with density matrices may employ whatever basis is most convenient.

the density matrix approach to an ensemble of non-isolated systems.

In most n.m.r. experiments we are dealing not only with an ensemble of systems (namely a collection of nuclei in molecules), but at the same time we must account for the interaction of these systems with each other and with their surroundings (viewed perhaps as a lattice or a thermal bath). We can construct, for this ensemble, a mean density matrix $\bar{p}$ defined as

$$\bar{p} = \textstyle\sum_N p_{ij} / N \quad (4).$$

and the expectation value of the operator Q operating on the system is

$$Q = N \text{ tr. } \bar{p}Q \quad (5).$$

assuming that the same basis set applies to all N molecules.

Mathematically, wave functions are specific kinds of density matrices and are applicable to describing only 'closed' systems, that is, systems not depending upon any factors external to them for their properties. Density matrices on the other hand are perfectly applicable to describing 'open' systems for which no wave function could exist. So in particular, a density matrix may describe the nuclear part of a wave function for which no nuclear wave function is appropriate since the nuclei are not in a pure state. Another aspect of this flexibility arises in the case, for example, of two strongly coupled nuclei (the AB case). Whilst nucleus A alone cannot be described by a wave function it can be described by a density matrix.

the density matrix operator.

As the form of the density matrix will vary depending on the basis chosen to express it in, it is convenient to define a density matrix operator, p, from which the density matrix can be formed in any basis, by application of

$$p^{\phi}_{ij} = \int \phi_i \, p \, \phi_j \, dt \qquad (6).$$

or in Dirac notation

$$p^{\phi}_{ij} = \langle \phi_i | \, Q \, | \phi_j \rangle \qquad (7).$$

If we choose a basis X where p is diagonal, then

$$p = \sum_i | X_i \rangle \, P_i \, \langle X_i | \qquad (8).$$

where P_i are numbers

also only has diagonal elements. This is the density matrix operator and from it the density matrix can be written in any basis

$$p^{\phi}_{ij} = \sum_k \langle \phi_i | X_k \rangle \, P_k \, \langle X_k | \phi_j \rangle \qquad (9).$$

interpretation of the density matrix.

The particular interpretation of a density matrix depends in part upon the basis in which it is expressed. The basis in which p is diagonal is the natural basis for the system; the diagonal elements then represent the probabilities of finding the system in the given pure state corresponding to the diagonal element in question. If p is not diagonal, then, whilst the diagonal elements still represent probabilit:

:ies, the exact nature of the states in question is not so easy to define. The nature of the off diagonal elements is open to various interpretations which vary from instance to instance. In n.m.r. problems, we will often use a basis in which the spin Hamiltonian and the density matrix are diagonal in the absence of an applied radiofrequency field. When the radiofrequency field is applied, magnetisation is induced in the plane perpendicular to the static applied field B_0 and the off-diagonal elements, p_{ij}, in this basis, are proportional to the part of the magnetisation that can be attributed to the transition between states i and j.

The equation of motion of p can be expressed in a diagonalising basis set by

$$i \hbar \frac{d}{dt} \hat{p} = [\hat{H}, \hat{p}] \qquad (10).$$

where H is the Hamiltonian. This is identically expressed in matrix form by removal of the operator 'caps'. H is expressed in the same basis as p.

If p and H are both diagonal in some representation, then they commute and p does not vary with time. Since we are considering a relaxing system with local fluctuations in H, then the equation of motion employs mean values as follows

$$i \hbar \frac{d}{dt}\bar{p} = \overline{Hp} - \overline{pH} \qquad (11).$$

the density matrix description of the n.m.r. experiment.

In the n.m.r. experiment, the sample is placed in a strong magnetic field B_0 and an oscillating magnetic field $B_1 \cos \omega_1 t$ is applied at right angles to B_0. We then can record an induced absorption signal at right angles to both of these fields. The appropriate Hamiltonian for a nucleus of spin $\frac{1}{2}$ is given by

$$H = \gamma B_0(1-\sigma)I_z + \gamma B_1 \cos \omega_1 t \, I_x \qquad (12).$$

this can then be written in units of $\hbar$ with α and β as basis states as

$$H = \begin{vmatrix} \frac{1}{2}\omega_0 & \tilde{D} \\ \tilde{D} & -\frac{1}{2}\omega_0 \end{vmatrix}$$

where $\tilde{D} = D(\exp(i\omega_1 t) + \exp(-i\omega_1 t))$

and the equation following will be satisfied.

$$i\dot{p} = [H,p] \qquad (13).$$

We are interested in the spectral signal which is dependent on the ensemble average of the magnetisation and for this we can eventually derive the equations

$$\begin{aligned} i\dot{\bar{p}}_{12} &= -\tilde{D}\bar{m}_{12} + \omega_0\bar{p}_{12} \\ i\dot{\bar{m}}_{12} &= 2\tilde{D}(\bar{p}_{21} - \bar{p}_{12}) \\ \bar{p}_{12} &= \bar{p}_{21}^{*} \qquad (14). \end{aligned}$$

We must now introduce relaxation into these equations. We will assume that $\bar{m}_{12}$ and $\bar{p}_{12}$ decay to their equilibrium values m_0 and zero exponentially with time constants T_1 and T_2 which need not be the same. The equations then become

$$\begin{aligned} i\dot{\bar{m}} &= 2\tilde{D}(\bar{p}_{21} - \bar{p}_{12}) - iT_1^{-1}(\bar{m} - \bar{m}_0) \\ i\dot{\bar{p}}_{12} &= (\omega_0 - iT_2^{-1})\bar{p}_{12} - D\bar{m} \qquad (15). \end{aligned}$$

From these equations it is possible to proceed in various ways. If we split D into two rotating components, we can derive the Bloch equations. Alternatively, we can assume B_1 is small and solve the equations to successive orders in B_1. This procedure is the most generally applicable. The solution of this method to provide the absorption signal observed in most n.m.r. experiments, requires the use of fourier analysis. With the application of a line shape function, the resulting imaginary portion of the signal is abstracted and corresponds to the absorption mode signal. The approach can be modified in as much as fourier component analysis can be avoided by transforming the entire set of equations into one based upon a rotating coordinate frame. As we will encounter below, this approach has been used by Alexander/8 in a particular context.

density matrix application to chemical exchange.

Both Kaplan/7 and Alexander/8 have employed density matrix methods to calculate the spectra to be observed in cases of nuclear exchange between different environments. In mathematical terms, the effect of the presence of exchange in the system studied, is to introduce extra terms into the equations detailing the rate of change with time of the density matrices describing the conditions of the various nuclei. The terms evolved are complex and the detailed line shapes have to be calculated numerically, preferably with a computer. The latest extension of density matrix methods to spin exchange situations has been developed by Dahlqvist and Forsén/9. They employ a rotating frame for analysis of the system, and adopt a procedure for accomodating the variation of the density matrix with time that follows Kaplan/7. Very recently, Kaplan and Fraenkel/10 have published what is claimed to be a simplification of most density matrix methods employed heretofore. Their permutation of indices method allows a physical picture of the exchanging system to be developed in mathematical terms.

Superoperator Methods.

In all the methods described above, the transitions frequencies, observed in a spectrum, had to be derived from the energy differences between calculated levels in the spectrum of a system. An alternative approach, which was first published by Banwell and Primas[11] in 1963, does not depend on unobservable quantities, the eigenvalues and eigenfunctions of the system, but on directly observable resonance frequencies and transition intensities. Because of this close relationship to experimental observation, Banwell and Primas termed this method the 'direct' method in contrast to the indirect procedures normally employed, some of which have been outlined above. Though Banwell and Primas outlined their method in 1963, it was not until 1968 that Binsch published a practical approach to the method which he consequently programmed for electronic computers in FORTRAN IV.[12,13] The genus of programs deriving from this approach were employed by him for the calculation of exchange spectra, in some instances incorporating invariance properties of the molecules in question.[14] Further developments along these lines have seen the application of these methods to the calculation of spectra by an iterative fitting procedure, the method resulting in great simplification of the fitting problem.[15,16] Anderson[17] has further extended the techniques to the calculation of double resonance spectra.

characterisation of the direct method.

For N particles of spin $\frac{1}{2}$ the quantum mechanical state space is of dimension $2^N = n$. There are thus n eigenvalues of the Hamiltonian and n^2 differences between them, ignoring selection rules at this stage. The essence of the direct method is to discover an operator whose eigenvalues are the transition frequencies and this must be an operator over a vector space of dimension n^2. Such a space can be derived from the n-dimensional state space of the spin operators which gives rise to n^2 linearly independent matrices with only one non-zero element. Over this n^2-dimensional algebra, we may define superoperators, being normal operators except in their mode of derivation.

The analogy between operators and superoperators may be expressed as follows. Ordinary operators (say $\hat{A}$) relate any function ϕ of a state space to a new function ϕ' of the same space.

$$\phi' = \hat{A}\,\phi \qquad (16).$$

Similarly a superoperator a is a rule relating an operator $\hat{X}$ to a new operator $\hat{X}'$. It is possible to generate a superoperator matrix algebra along similar lines to ordinary operator matrix algebra.

One particular superoperator a^D defined by the equation

$$a^D(\hat{X}) = \hat{A}\hat{X} - \hat{X}\hat{A} \qquad (17).$$

for all $\hat{X}$

and we call a^D the derivation superoperator generated by $\hat{A}$; it has the property of forming the commutator between its generating operator $\hat{A}$ and the operator $\hat{X}$ upon which it operates.

For application to n.m.r. we consider the eigenvalue problem of the derivation superoperator h^D belonging to the spin Hamiltonian $\hat{H}$. We seek a set of operators $\hat{X}_a$ such that

$$h^D(\hat{X}_a) = \omega_a(\hat{X}_a) \qquad (18).$$

where ω_a are the eigenvalues of $\hat{X}_a$ and the eigenoperators of h^D.

The essence of the direct method derives from the following facts. The eigenvalues ω_a of the superoperator h^D are equal to the differences between the eigenvalues of $\hat{H}$ and are, therefore, transition intensities. Further, the relative intensities of the transitions at given frequencies, ω_a, are easily derived. In other words, by use of the superoperator h^D, we can define the n.m.r. spectrum.

Several approaches, varying to some extent in details rather than central principles, have been published to solve the mathematical problems presented by this approach. Banwell and Primas detail the reduction of this problem to a matrix eigenvalue problem and the necessary techni:

:ques for deriving an explicit expression for the spectrum.

The first practical application of these superoperator methods was published by Binsch[13] in 1969. Prior to this he developed the necessary theory[12] using the framework of the Liouville representation of quantum mechanics since the derivation superoperator of Banwell and Primas is identical with the Liouville operator defined by Fano[18]. Though familiarity with the work of both Banwell and Primas, and Fano requires a good deal of close study of these two papers, the results derived by Binsch are capable of being presented qualitatively in a very simple fashion. A spectral vector Q and a shape vector S can be defined as a result of mathematical manipulation. The line shape function is proportional to the scalar product of Q and S and the absorption spectrum can be abstracted as the negative real part.

$$Y = -C\,\mathrm{Real}(Q.S) \qquad (19).$$

The function Y contains the total information necessary for the description of the spectrum and need only be calculated once per spectrum rather than point by point throughout the spectrum as required by other approaches. The final step, of point by point computation of the absorption line, requires the components of Q to be calculated for each point in the spectrum, which are then multiplied by the shape function S. The negative real part of the product is abstracted as the absorption signal.

As long as we are interested only in the chemical shift and coupling parameters of an n.m.r. spectrum it seems that there is little to be gained in employing this direct method of calculation, rather than the indirect method more commonly employed. However, for the treatment of non-trivial relaxation phenomena the current approach is uniquely applicable.

exchange effects treated by direct methods.

The first major application of direct methods published was describ:

ed by Binsch in 1969.[13] In the following year Binsch and Klier[14] published details of the computer program DNMR3, based on the Liouville formalism, but incorporating the results of group-theoretical considerations to simplify the computational procedures. Certain permutation symmetry properties allow the use of smaller Liouville subspaces without loss of any of the spectral information. This results in a simplification of computing requirements (time and size of store required) which is ample justification for the necessary trouble needed to identify suitable cases for symmetry simplification. (It needs to be pointed out that without the use of symmetry properties, the size of the arrays required in the direct method very soon gets to utterly unmanagable proportions. So, for example, a six spin system exchanging between two nuclear configurations requires the diagonalisation of two complex matrices of dimension (600 x 600) - a problem of almost lunatic proportions.) The practical advantages to be gained from symmetry simplification are much greater in cases of exchange spectra than in the calculation of static n.m.r. spectra.

The development of direct methods for the calculation of static spectra has been somewhat delayed, due no doubt in part to the ready availability of satisfactory alternative methods. One feature of the direct method, which suggests that it might be advantageous to apply it to static spectra, is the fact that the transition frequencies are directly obtainable as a result of the calculations. So in instances of least squares fitting of experimental and theoretical spectra, a common requirement, there are clearly advantages in deriving the absorption frequencies directly from the operator calculations. The process of deriving the deviations between experimental and theoretical spectra and incorporating the necessary corrections into the next cycle of calculations is considerably simplified.

Cohen has derived rules for establishing the elements of the derivation superoperator h^D from those appearing in the corresponding energy matrix H.[15] With Emerson, she has presented a weighted least squares procedure based on iteration of the transition matrix h^D, where the opportunity to iterate directly on transition frequencies is utilised[16].

Anderson[17] in 1969 extended the direct method to n.m.r. double resonance spectra, but was sceptical of the value of this approach. However, his objections to the method were answered in a paper by Gestbloom, Hartmann and Anderson[17] in which it was shown that a suitable choice of basis operators yields the complete double resonance spectrum, except for the signs of transition intensities, in closed form.

Postscript.

It only remains to mention the methods employed in the computer programs mentioned later in this thesis. These programs are QUABEX[19] which employs closed form equations appropriate to a coupled AB system as are described in 'Elementary Principles'; UEAITR[20] which employs an extension of the methods detailed in 'Elementary Principles' and follows Castellano and Bothner-By[21]; and DNMR3[14] which employs direct methods as outlined immediately above.

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Conformational Analysis

by Nuclear Magnetic Resonance Spectroscopy.

"Nuclear magnetic resonance is one of the most powerful tools to give direct insight into both the structure and the stereochemistry of organic compounds. It is therefore no wonder that the technique has been applied extensively in conformational problems - "...... /[1]

"It is now established that n.m.r. spectroscopy provides more information about the shape of molecules in solution than any other physical method,"...... /[2]

Introduction.

From its inception, nuclear magnetic resonance (n.m.r.) spectroscopy has provided a tool of impressive scope and subtlety in the investigation of molecular structure. Its earliest application to the determination of molecular identity is now commonplace. As the body of information from such studies has grown it has proved possible to establish empirical rules relating n.m.r. parameters to various features of molecular structure. As a consequence, the method has developed into a unique probe of the intricacies of molecular geometry. The ability to distinguish even conformational species in a system has been in large part responsible for the rapid advances made in conformational analysis in the last fifteen years[1].

The relationship between n.m.r. spectroscopy and conformational analysis has been a symbiotic one. Upon a basis of a knowledge of the conformations of necessarily rigid structures (derived mainly from x-ray spectroscopic studies), the development of n.m.r. empirical correlations of spectral parameters with molecular structure has proceeded to such an extent that considerable feedback in terms of the determination of the nature of unknown conformations has occured. These parallel and mutually interactive developments have been remarked upon[2]. In many respects this symbiosis is in the nature of the n.m.r. method. Reliable theoretical calculations of n.m.r. parameters (ab initio) are rarely achieved and so the development of n.m.r. empirical correlations is necessary. This state of affairs represents a serious challenge to theoretical methods and enormous advances in the power of such methods will need to be achieved before quantification of the factors determining n.m.r. parameters will be routine.

Despite such limitations, the future of n.m.r. conformational studies seems promising. Recent advances in instrumental techniques, such as the application of pulsed radio-frequencies in fields of ever increasing strengths have opened up large areas of chemistry to detailed investigation. Of particular significance is the current interest in, and development of, applications to biochemical systems where conformational studies are of the utmost importance.[3] Since n.m.r. methods are capable of studying the most subtle of molecular interactions under conditions which generally constitute a trivial perturbation of the observed system, then the great importance of n.m.r. techniques is now indisputable.

The Importance of Conformational Analysis.

Conformational Analysis is concerned with the nuances of the spatial geometry of molecules. Such considerations are of immediate significance in studies of the intimate behaviour of molecules. If the purposes of chemistry are to include a detailed comprehension of the behaviour of molecules, in isolation or with each other, so as to provide us with sophisticated control in the molecular world, then conformational analysis is of the greatest importance. With such sophistication will come many advantages in diverse fields of human endeavour.

It is not possible, however, to examine the conformations of reacting molecules at the moment of reaction. The excited state intermediates involved are far too short lived to allow any degree of precision in estimating their energy content.[*4] The differential energy contents of conformers can often be measured in calories rather than kilocalories and in consequence we are restricted to conformational studies of ground state species. This fact imposes serious though unavoidable limitations on any study of reacting systems. It is only legitimate to draw close analogies between ground state and reactive state species where the two are found not to differ greatly in energy. In less favourable circumstances we must recognise our speculations for what they are! It is not unrealsitic though to ob:

:serve that with the course of time such speculations will find confirmation and mature to respectable theories or they will be refuted by further facts.[*5]

Conformational Analysis : a Definition!

It is best at the outset to admit defeat in any attempt to rigorously define the subject matter of conformational analysis. Many definitions have been proposed including one from popular journalism, quoted by Eliel:-

> Conformational analysis is "the way molecules shape up to do business with other molecules."[6]

Most definitions are obviously based upon some definition of 'conformation', a term introduced into the chemical literature by Haworth in 1929.[7] These, by and large, have become historically outmoded. Eliel offers:-

> Conformation denotes "any one of the infinite number of momentary arrangements of the atoms in space that result from rotation about single bonds."[8a]

while Dauben and Pitzer offer:-

> "By 'conformation' is meant any arrangement in space of the atoms of a molecule that can arise by rotation about a single bond and that is capable of finite existence."[9]

The definition of 'conformation' has been restricted to rotation about single bonds, not for logical but for historical reasons. In essence there is no distinction between cis-trans isomerism about a double bond and any rotation about a single bond. In practice a distinction arises in that isomers about a double bond can have separate existences at room temperature whilst those about single bonds normally can not.

> "Conformational Analysis is an analysis of the physical and chemical properties of a compound in terms of the confor:

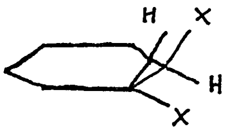
mation (or conformations) of the pertinent ground states, transition states, and in the case of spectra, excited states."[8b]

Despite the obvious scope of this definition, in practice the scope of conformational analysis has been restricted by and large to a consideration of the conformations of cyclic systems with some remarks on the existence of rotational barriers in simple hydrocarbon systems which act as models for more complex systems[10,11]. Any extension of the subject is largely based on the requirements of mechanistic studies[11a]. Such an extension is historically conditioned as is clearly illustrated by Barton[12] whose studies of the reactivities of cyclohexane systems (in steroids for example) led him to produce his now famous paper in 1950[6,13]. It is fair to comment that under the influence of spectroscopic techniques, the historical stress on mechanistic studies developed from 1930 to 1960 has now been largely superceded. In this respect, the ease of application of n.m.r. techniques to the study of molecules in solution, at least their normal if not their natural environments[14], must be held mainly responsible for this state of affairs.

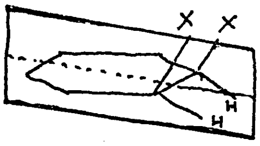
The History, Development and Current Scope of Conformational Analysis.[10,11]

The origins of conformational studies can be traced back to the earliest work on the structure of cyclic compounds and through that to the original studies of optical activity initiated by Pasteur's discovery of the phenomenon in tartaric acid in 1848. The molecular asymmetry implicit in such activity led van't Hoff (primarily) and Le Bel to develop the tetrahedral model of carbon bonding geometry (circa 1880) which was experimentally confirmed with the advent of x-ray and electron diffraction techniques. The requirement for centres of asymmetry, together with van't Hoff's postulate of unrestricted rotation about single bonds to carbon, initially demanded carbon substituted with four distinct groups before optical activity could be observed. Otherwise any asymmetry in a structure (such as in some 'fixed' conformations of 1,2-dichloroethane achieved by forbiding rotation about the C–C bond) was lost by the natural averaging rotations through 360° by such bond systems. If we could prevent this type of free rotation then it should be possible to introduce asymmetry into structures which do not possess asymmetric carbons.

An obvious restriction of such free rotation is observed in cyclic structures. Thus a structure such as (I) is asymmetric and will exhibit optical activity whilst its isomer (II) has a plane of symmetry and is optically inactive (fig. 1.1-2).



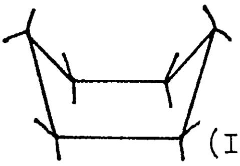
(I)



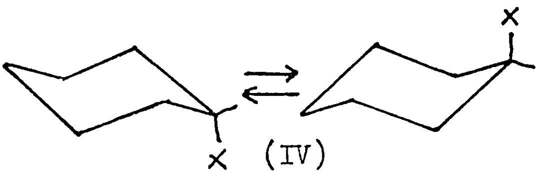
(II)

Fig. 1.1 - 1.2.

Perhaps influenced unduly by this concept of restricted rotation, Baeyer in 1885 proposed completely restricted rotation in planar rings (such as shown above) for <u>all</u> carbon ring systems. On the basis of tetrahedral carbon being the ground state (lowest energy) configuration for all carbons with saturated valencies, he observed that only cyclopentane would approximate to an unstrained system with nearly normal bond angles. From combustion data available at the time it was apparent that cyclohexane was considerably more stable, than a planar model with distorted ring angles would allow. In 1890, Sachse pointed out that nonstrained cyclohexane could be constructed from tetrahedral carbon. He observed that a flexible unsymmetrical form (III) and two rigid symmetrical forms (IV) could be constructed, the latter only being distinguishable if the rings are monosubstituted (fig. 2.1-2).



(III)

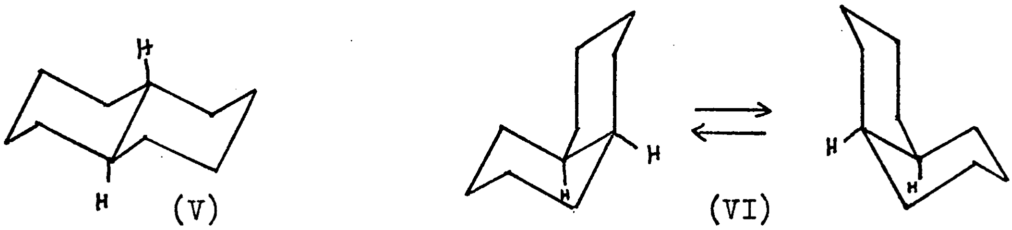


(IV)

Fig. 2.1 - 2.2.

For this insight, it may well be proper to consider Sachse as the founder of conformational analysis. Unfortunately, Sachse further proposed that the two forms (IVa,b) should not be interconvertable at ordinary temperatures. Failure to isolate any cyclohexane isomers resulted in a total rejection of the Sachse hypothesis for another thirty years.

In 1918 Mohr revived Sache's hypothesis when he proposed that the chair forms (IVa,b) should be fairly readily interconvertible by rotation about single bonds, this path involving, at the most, some hindrance to rotation and bond angle strain. He further predicted the existence of two stable isomers of decalin, the cis and the trans (V and VI) (fig. 3.1-2).



(V) (VI)

Fig. 3.1 - 3.2.

A planar form of trans decalin would have to be extremely unstable if it could exist at all and consequently we have here a good test of the Sachse-Mohr and contrary hypotheses. The isolation by Huckel in 1925 of cis- and trans-decalin (the trans in fact the more stable) was ample vindication of the Sachse-Mohr hypothesis. However, acceptance of such principles was sporadic in the next twenty-five years though significant early contributions to the field of conformational analysis were made by carbohydrate studies. Yet, during this time (at first tentative) indications of cyclohexane geometry were published, including a distinction between axial and equitorial bonds, and later direct evidence from Hassel's electron diffraction studies proved the nature of cyclohexane.

Although not unaware of such studies, it was left to Barton in 1950 to bring home to organic chemists the great significance of the distinction between axial and equitorial bonds in the realm of intimate reaction processes. He pointed to the thermodynamic stability of equatorial isomers over axial and extended these concepts to studies of the rigid cyclohexane rings in steroidal molecules.

Since 1950 work in conformational studies has mushroomed and concepts of conformation now pervade most areas of chemistry. In this context the catalytic effect of the publications of Barton and Hassel[*13] has been recognised[*15]. At the same time, the development of spectroscopic techniques into routine 'every-day' practices has contributed a great deal to these studies. Whilst in 1950 most studies (other than in the solid state) employed chemical arguments, by 1970 the incidence of such arguments in papers directed primarily to the analysis of conformation had dropped considerably to be replaced by spectroscopic techniques. By 1960 x-ray and electron diffraction techniques had been joined by greatly improved microwave, infra-red and ultra-violet spectroscopies, and the totally new methods of optical rotatory dispersion/circular dichroism and n.m.r. spectroscopy. Without perhaps too much bias, it can be remarked that this last has probably been the most important.

Though the technique of n.m.r. spectroscopy began to appear in the chemical literature in the early 1950's, it was not until the later years of that decade that significant results in terms of conformational analysis began to appear. In 1957 Lemieux and coworkers[16], in a preliminary communication, pointed out that equatorial protons in six-membered rings appear at lower field than the corresponding axial protons. Further, the coupling between protons which are diaxially trans to one another is two to three times greater than between protons in axial-equitorial or di-equitorial relationships. Such observations are the basis of conformational analysis, and as such it is appropriate to locate the origins of n.m.r. conformational analysis in such papers.

In 1959 Karplus published the first of his now famous (Karplus) relationships[17] approximating the value of the coupling constant expected between protons in an ethane type fragment ($-CH_2-CH_2-$) in terms of a dependence on the dihedral angle between the protons.

$$J_{HH'} = \left| \begin{array}{c} 8.5\cos^2\phi - 0.28 \quad (Hz) \\ 0^\circ \leq \phi \leq 90^\circ \\ \\ 9.5\cos^2\phi - 0.28 \quad (Hz) \\ 90^\circ \leq \phi \leq 180^\circ \end{array} \right| \qquad \phi = \text{dihedral angle.}$$

Four years later, Karplus clarified his arguments in a communication[18] in which he delineated the various factors which are likely to affect this coupling other than dihedral angle. In doing this he had been stimulated by the rapidly increasing use of the above relation and the confusion developed in some authors' minds, by which they supposed that the coupling depends <u>only</u> on the value of the dihedral angle.

Early in 1960, Jensen and coworkers[19] had established a free energy barrier, of 9.7 kcal./mole (at -66.5°C) for the chair/boat interconversion barrier in cyclohexane, from the temperature dependence of the signals arising from axial and equitorial protons. Reeves and Strømme[20] about the same time established a similar barrier of 10.8 kcal./mole at -55°C for bromocyclohexane.

By the early 1960's it was becoming apparent that n.m.r. was a potentially powerful tool for studying conformational processes. Gillespie and White[21] commented in 1962 that it was "to be expected that proton chemical shifts and coupling constants would be increasingly used for conformational analysis of cyclic systems". By 1965, Eliel could write[1]: "nuclear magnetic resonance is one of the most powerful tools to give direct insight into both the structure and the stereochemistry of organic compounds. It is therefore no wonder that the technique has been applied extensively in conformational problems - ".

Over half the conformational free energy differences for monosubstituted cyclohexanes quoted in this paper[1] had been established by n.m.r. methods. Franklin and Feltkamp[22] in reviewing the use of n.m.r. in the conformational analysis of cyclohexanes proposed that n.m.r. was one of the best methods available for these conformational studies.

As will be seen to some extent later, the impact of n.m.r. studies in the last ten years has been impressive. No longer are studies restricted to relatively simple carbocyclic systems. Organic and inorganic systems of increasing complexity have been studied. In conjunction with x-ray studies, n.m.r. studies are now probing the conformational nature of systems as complex as enzymes. The application of advanced techniques is ensuring a rich harvest of conformational and other data for those equipped to seek it.

"While conformational analysis in model systems for its own sake offers less of a challenge now than it did say twelve years ago, it continues to be an extremely useful tool in the investigation of more general chemical phenomena, such as non-bonded interactions between atoms, physical and chemical effects of unshared electron pairs, solvent effects and hydrogen bonding effects. Some hetero systems, notably those containing sulphur, provide a framework for potentially highly stereoselective reactions of possible biochemical import."[23]

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fig.	1.1 - 1.2.	from ref. 11.
fig.	2.1 - 2.2.	from ref. 11.
fig.	3.1 - 3.2.	from ref. 11.

The Physical Approach to Conformational Analysis.

Conformational arrangements in molecules are now almost invariably determined by physical means. With such information, we attempt to understand the reactions and other properties of the compounds under study. However, the predominance of physical methods in chemistry and their application to conformational analysis has only occurred in the last twenty years. Prior to this of course, many notable advances were made in x-ray and electron diffraction studies[*1] yet most conformational studies had to be largely chemical in nature, a fact amply illustrated by the material in Barton's epic paper[2]. Consequently, progress, though significant, was limited by the paucity of detailed information on the conformations of molecules. Since 1950, and particularly since 1960 with the advent of n.m.r. spectroscopy, a virtual flood of conformational analysis papers has built up. With the increase in quantitative as well as qualitative data, we are now in a situation where we must develop much more accurate theoretical methods to systematise our, now quite thorough, intuitive understanding[*3]. In some respects, some notable progress in the calculation conformer stabilities of carbocyclics has been achieved[*4]. It is not necessary for the present studies to examine at all closely such methods of thermodynamic calculation. Use will be made of such results later, but references will be mainly for supportive purposes and the results can be quoted without criticism.

Thermodynamic Considerations.

The course of any chemical system and the composition of the system as a function of time can be predicted if the values of the rate and equilibrium constants can be predicted. The concepts of rate and equilibrium are of universal significance with the concept of equilibrium holding central importance in thermodynamic theories. Since rate constants in reactions are generally most satisfactorily treated by the transition state (or activated complex) theory, which is in itself an extension of theories dealing with equilibrium then a brief discussion of equilibrium is an appropriate prelude to a consideration of conformational thermodynamics. Upon such foundations have been developed very simple realtions between rates and equilibrium constants on the one hand, and appropriate thermodynamic parameters on the other.

The discussions evolved here are intended to provide the necessary thermodynamic background to conformational considerations. From a study of conformational equilibria and the energy factors involved, we can develop a qualitative picture of the conformational processes in a system with the multifarious interactions involved and relate these to the measurable thermodynamic parameters. On such a basis we can begin to estimate quantitatively the extent and nature of the interactions in a given conformation. Such work can lead in turn to the a priori estimation of relative conformer stabilities and is particularly significant in systems which cannot be unambiguously defined by some means of direct observation. A combination of such approaches can lead to unambiguous conformational determinations in relatively complex systems.

the concept of equilibrium.

Matter in any system can be visualised as being distributed throughtout a myriad of different energy levels. Obviously, the number of possible arrangements of this system is well nigh infinite. Yet the problem of defining a system in macroscopic terms is not unduly great. This arises from the fact that the probabilities of most conceivable arrangements of the matter throughout the energy levels of the system are extremely low and can be discounted in any description of the system. Any system in equilibrium is in a state of 'maximum probability'. Two systems in such a condition may be mixed and then a new state of equilibrium may develop.

However, it is not sufficient that such a state of greater stability than the separate states should exist. There must be a physically feasible pathway from the current situation to the hypothetically predicted one. All stages of this pathway will require significant probabilities of existence.

The nature of the distribution of matter among energy levels is described by the Boltzmann Distribution Law:-

$$\frac{n''}{n'} = e^{-E^{o}/RT} = e^{-(\epsilon'' - \epsilon')/kT}$$

where n is the number of molecules in a given state.

E^{o} is the energy per mole of substance.

ϵ is the energy per molecule of substance.

R is the molar gas constant.

k is the Boltzmann constant.

T is the absolute temperature.

n''/n' becomes smaller as E grows larger and T smaller. So the higher the energy level and the lower the temperature, then the less the population of the state in question. Consequently an equilibrium will be established in a system where physically feasible pathways from low probabilty to high probability are themselves of high probability and consequently low energy. Alternatively, if the interconverting pathway is one of high energy, then we might be able to supply this energy in some form or other and hence establish an eqilibirium over a large barrier.

This situation can be expressed diagramatically (fig. 1.1). If we mix A and B which potentially yield the more probable condition C:-

$$A + B \longrightarrow C$$

then an energy/probability profile will be:-

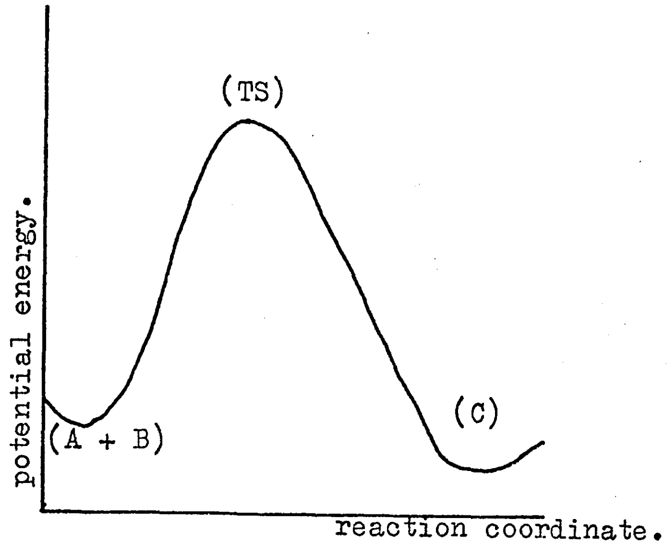


Fig. 1.1.

Obviously the probability of state (T.S.) will govern the number of species in this state and further will also govern the number of passages from state (A + B) to state (C) and vice versa. At the same time we can also appreciate that it is more likely for species deriving from the (A + B) state to acquire the energy of (T.S.) than species from (C). Therefore statistically we expect to see a loss of species (A + B) and a gain in species (C). Though this point has been somewhat laboured, it is relevant in the context of the n.m.r. experiment where under certain circumstances we can get a 'snapshot' of passages over this barrier.

Due to the macroscopic scale of our investigation, it is possible to regard the 'barrier' shown in the figure above as a continuum of probabilities or energy levels. We now wish to relate the barrier to conversion (ΔE) to some physically measurable phenomenon concerned with conversion rate, and further, the position of equilibrium (the relative amounts of (A + B) and (C)) to some measure of the average energy difference between them. The connection between microscopic and macroscopic thermodynamic theories is not logically deductable. It rests on a comparison of results taken from the two fields.

If we consider a system:-

$$P + Q \longrightarrow R + S$$

then the equilibrium constant is defined as:-

$$K = \frac{a_R \cdot a_S}{a_P \cdot a_Q}$$

where a_R is the activity of R in the assembly. Now we can define a free energy difference ΔG^o between the two systems in some standard condition by:-

$$\Delta G^o = -RT.\ln(K^o).$$

Further:-

$$\Delta G^o = \Delta H^o - T.\Delta S^o.$$

where ΔH^o is the standard enthalpy difference and ΔS^o the standard entropy difference. R is the universal gas constant and T is the absolute temperature. The microscopic concepts underlying these two terms cannot be rigorously defined. The following parallel may be drawn, but it must be noted that it is not rigorously correct.

If we consider again the energy diagram relating the two sides of the equilibrium and we imagine a sudden freezing of the system to 0^oK then we can postulate that all systems would occupy the lowest energy levels. As a consequence there is no activated species (T.S.). Then:-

$$\Delta G = \Delta H$$

and ΔH represents the energy difference between the ground states on each side of the frozen equilibrium. Then, by raising the temperature, we begin to populate higher energy levels in both systems. This not only represents an entropy increase but also, in a sense, an increase in the randomness of the systems with increasing population of higher energy levels. At the same time, the population of the activated species (T.S.) begins to build up and the rate of passage over the activation barrier rises. ΔS represents the difference in this degree of randomness on each side of the barrier. Factors affecting randomness are, however, multifarious and considerations such as these cannot lead to a full comprehension of entropy.

equilibrium and rates.

From such deliberations the Transition State Theory was developed[*5]. This theory is based on three fundamental assumption which we shall present before proceeding to state the results of the theory.

(1) In the process of reaction, the molecules must traverse certain states of potential energy higher than the potential energy of either the reactant or the product states.

(2) The populations of these higher potential energy levels that must be traversed by reacting molecules are in statistical equilibrium with the ground states from which the reacting molecules came.

(3) The rate of reaction is proportional to the concentration of molecules in these higher energy levels.

The correctness of assumption (2) is not at all obvious for reacting systems. However, it clearly applies in the case of conformational equilibria which represent true equilibrium situations. It is important to point out that there are two kinds of species in the transition state set, namely those whose direction of travel is in one direction and those whose direction is in the other direction. The Transition State Theory then considers that the rate of reaction of (A + B) to give (C) is proportional to the concentration of the transition species travelling from (A + B) to (C). In terms of quantum energetics, this states that the physical process accompanying the energetic boost to the transition state (say a bond stretching) continues on to become the reaction change (say a bond breaking) and does not stop in the transition state and fall back. From the statistical nature of the situation, this will be true for the vast majority of the species passing through the transition state. Only very few species will have exactly the energy of the basic transition state which might allow them to come to rest in such a situation with a permissable decay to their point of origin.

The rate constant derived from Transition State Theory can be stated as follows:-

$$k = \frac{\kappa.\mathrm{k}.T}{h} K^{\neq}$$

where k is the rate constant.

k is the Boltzmann constant.

κ is the transmission coefficient and is the fraction of the species which pass right through the transition state. As we have stated, this is certainly very close to unity.

h is Planck's constant.

T is the absolute temperature.

$K^{\neq}$ differs from an ordinary equilibrium constant in only one factor and hence it is appropriate to define quantities $\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$, the free energy, enthalpy and entropy of activation respectively, based upon the identity:-

$$\Delta G^{\neq} = - R.T. \ln(K^{\neq}).$$

In consequence:-

$$k = \frac{\kappa.\mathrm{k}.T}{h}.e^{-\Delta G^{\neq}/RT} = \frac{\kappa.\mathrm{k}.T}{h}.e^{-\Delta H^{\neq}/RT}.e^{-\Delta S^{\neq}/R}$$

the comparison of transition states.

It is appropriate to remark here on the diesis ($\neq$) quantities introduced above. These terms are not rigorously comparable with the equilibrium terms ΔG^{o}, ΔH^{o}, and ΔS^{o} due to a small difference in the definitions of $K^{\neq}$ and K^{o}. Further the assumption of κ being unity could hypothetically be incorrect. This would express itself in errors in $\Delta S^{\neq}$ and hence $\Delta G^{\neq}$ with consequent difficulties in applying these terms in meaningful comparisons, though such a situation might be redeemed by κ being constant in a series of related reactions. In such a case, the relative values of $\Delta S^{\neq}$ will have a simple meaning. In practice, however, not only do comparisons between transition states in terms of various $\Delta G^{\neq}$ etc. lead to harmonious results, but also parallels which can be drawn between ΔG^{o} and $\Delta G^{\neq}$ lead to simple rather than complex relations, a fact which tends to bear out the validity of the comparison.

It is appropriate at this stage to describe briefly the conformational situations to be met in later discussions.

conformers and conformational barriers.

"By 'conformer' is meant any arrangement in space of the atoms of a molecule that can arise by rotation about a single bond and is capable of finite existence"[6]. Whilst this definition by no means encompasses the entire concept of 'conformational isomerism', it serves as a useful introduction to 'rotational isomerism' about bonds, which is the basic physical phenomenon observed in all conformational systems.

The early theory of organic chemistry contained the postulate that rotation about the axis of a carbon to carbon single bond was completely unhindered. Thus no rotamer preference could be exhibited in a system such as 1,2-dichloroethane in which it was assumed that the chlorine atoms, one on each carbon, could assume an infinite number of positions, in relation to one another, of equal energy. It later became apparent though, that there could well be barriers to rotation about carbon-carbon single bonds[7a]. In 1936, Kemp and Pitzer[8] proposed a barrier to rotation in ethane of about 3kcal./mole. This value has been confirmed experimentally[7a] as a reasonable estimate of this rotation barrier.

Although the source of this barrier is still more a matter for speculation[9–11], we can regard conformations, in which hydrogens are opposed directly to hydrogens, as of higher energy than the alter:

:native staggered form.[12] In consequence, noting the threefold symmetry of ethane about the C–C axis, we can draw up a potential energy curve for rotation about this axis as shown in fig. 2.1.

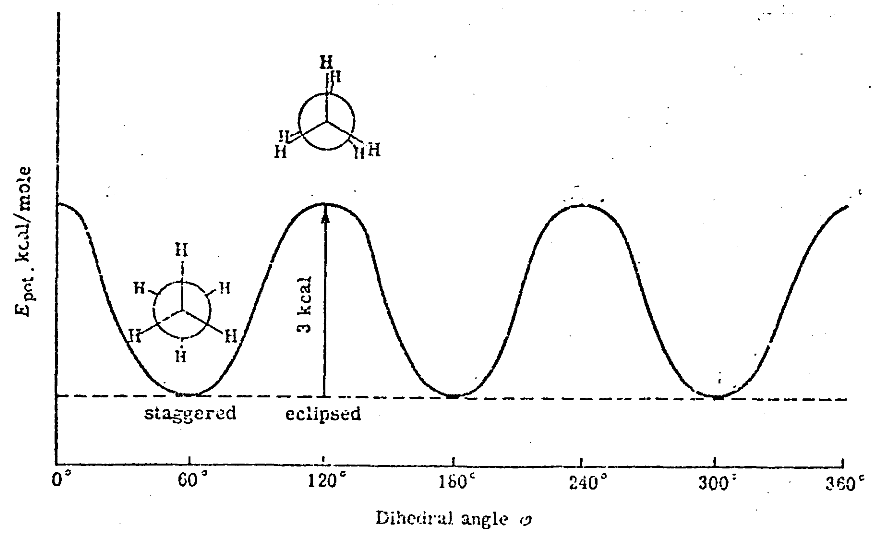


Fig. 2.1.

Obviously we can conveniently regard the potential barrier as arising from the near approach of hydrogens in the eclipsed form. Obvious extensions of this reasoning lead to a potential barrier, fig. 3.1, for butane (C_2–C_3) rotation.

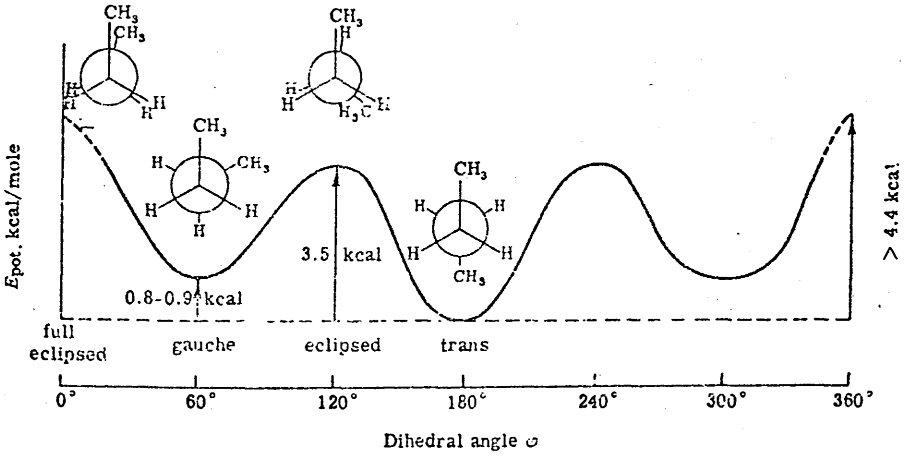


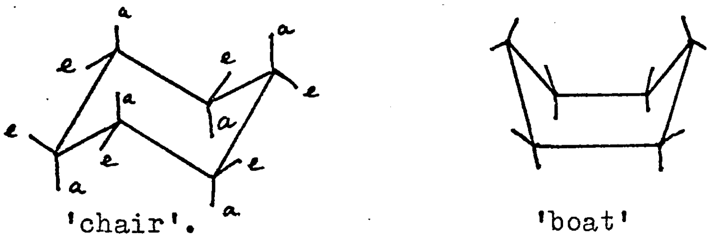
Fig. 3.1.

Although the exact magnitudes of these barriers are not known,[7a] the essential argument above leads to predictions of the right order. The extension of this reasoning to other acyclic systems is readily achieved.[7a, 13a]

The central importance of cyclohexane in conformational studies has already been remarked upon and in the following discussion we will extend energetic concepts to a discussion of this molecule.

Two basic sources of strain (increased potential energy) can be recognised in cyclic systems. The first recognised is angle strain (Baeyer strain) arising from deformations of the optimum valence angle. This is present particularly acutely in small rings (C_3 to C_4) which exhibit near planar structures. The second strain arises in the manner of the potential barriers mentioned above. This bond opposition strain (Pitzer strain) can be regarded as arising from the repulsion of neighbouring non-bonded atoms. It is also present in small rings where the planar structures force bond eclipsing of the carbon substituents.

Sachse's observation/[14] that cyclohexane can adopt two distinct types of non-planar structure in which all angle strain is obviated is one of the major insights in the history of conformational analysis (fig. 4.1).



'chair'. 'boat' Fig. 4.1.

The first is the rigid chair form in which we can note the existence of two distinct types of C-H bond:- those axial 'a' and those equatorial 'e'. The rigid chair form is also free of any bond eclipsing strain as all the C-H bonds are staggered round the ring. The second is the mobile boat form, a symmetrical example of which is shown. This form suffers from bond eclipsing strain and further severe interactions as arrowed between the hydrogens arising from Van der Waals repulsion. These strains can be alleviated somewhat by twist-distortion from the symmetrical species but considerable strains will still occur. A path for interconversion of chair form to flexible form can also result in conversion to <u>another</u> chair form in which bonds once axial are now equitorial. The barrier to such an interconversion has been measured experimentally/[15] at about 10 kcal./mole. Theoretical cal:

culations on various flexible forms[7a] allow estimates of their potential energy and in consequence we can draw a potential energy diagram relating the various forms as shown in fig. 5.1.

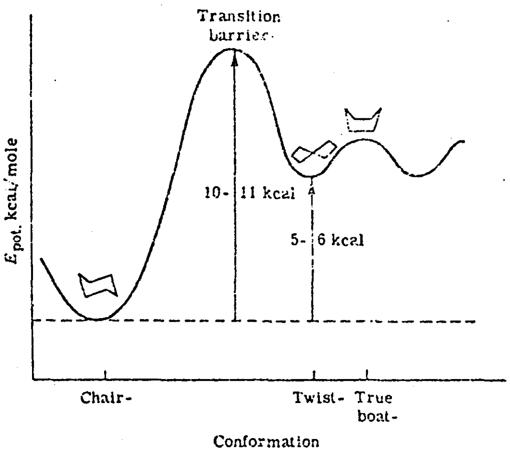


Fig. 5.1.

With an energy difference of 5 kcal./mole between chair and twist-boat form, then only about one molecule in a thousand will be in the latter form at room temperature. Consequently the twist boat form can be neglected in any consideration of the physical properties of cyclohexane.

If we extend our considerations to monosubstituted cyclohexanes we will immediately observe the possibility of isomerism which is of the conformational kind. The substituent will be able to occupy either an axial or an equitorial position in the chair form of cyclohexane. Consideration of the separate environments encountered in these two conformers suggests[7b,13b] that the equàtorial substituent will experience less interaction with the adjacent hydrogens than the axial substituent will experience. Though many other factors will influence the relative stability of the two conformers it is generally true that the equatorially substituted conformer will predominate. The table below provides an interesting correlation between the percentage of the most stable conformer and the energy difference between conformers. As can be seen it takes no more than 2.5 kcal./mole energy difference before the population of the less stable isomer is reduced to insignificance. This is the basis of the use of tertiary butyl substituents to force conformation in ring compounds.

Obviously, such reasoning can be extended to further substituted cyclohexanes and to other ring systems entirely.

Whilst the discussion above has been related primarily towards ring systems, much of what has been said applies directly to conformational studies of conjugated systems, an example of which is illustrated in fig. 6 below.

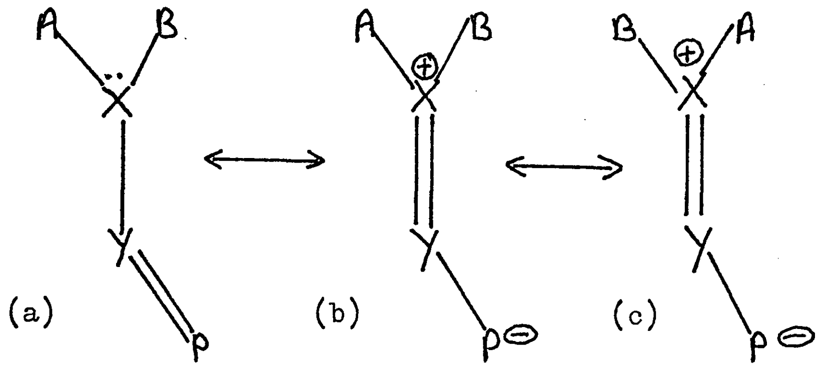


Fig. 6.1.

It is now well known that the barriers to rotation around formal single bonds in conjugated systems very often are greatly enhanced by the rigidity imparted to them by delocalisation of the π electrons between the double bond systems. In consequence, rotation about the X-Y bond can be described energetically in terms comparable to rotation about double bonds as in ethylene for example. The potential energy curve for such a rotation is illustrated in fig. 7. The assumption made in this figure is that species (b) and (c) are not of equal energy and as a result, species (b) will be more populated than species (c).

extrathermodynamic relationships: the Hammett equation.

Any simple relations found among thermodynamic parameters relating to various systems are not part of the formal structure of thermodynamics and are hence called extrathermodynamic relationships. The approach, however, is similar to that of thermodynamics in that no investigation of the detailed microscopic mechanisms of the reactions are

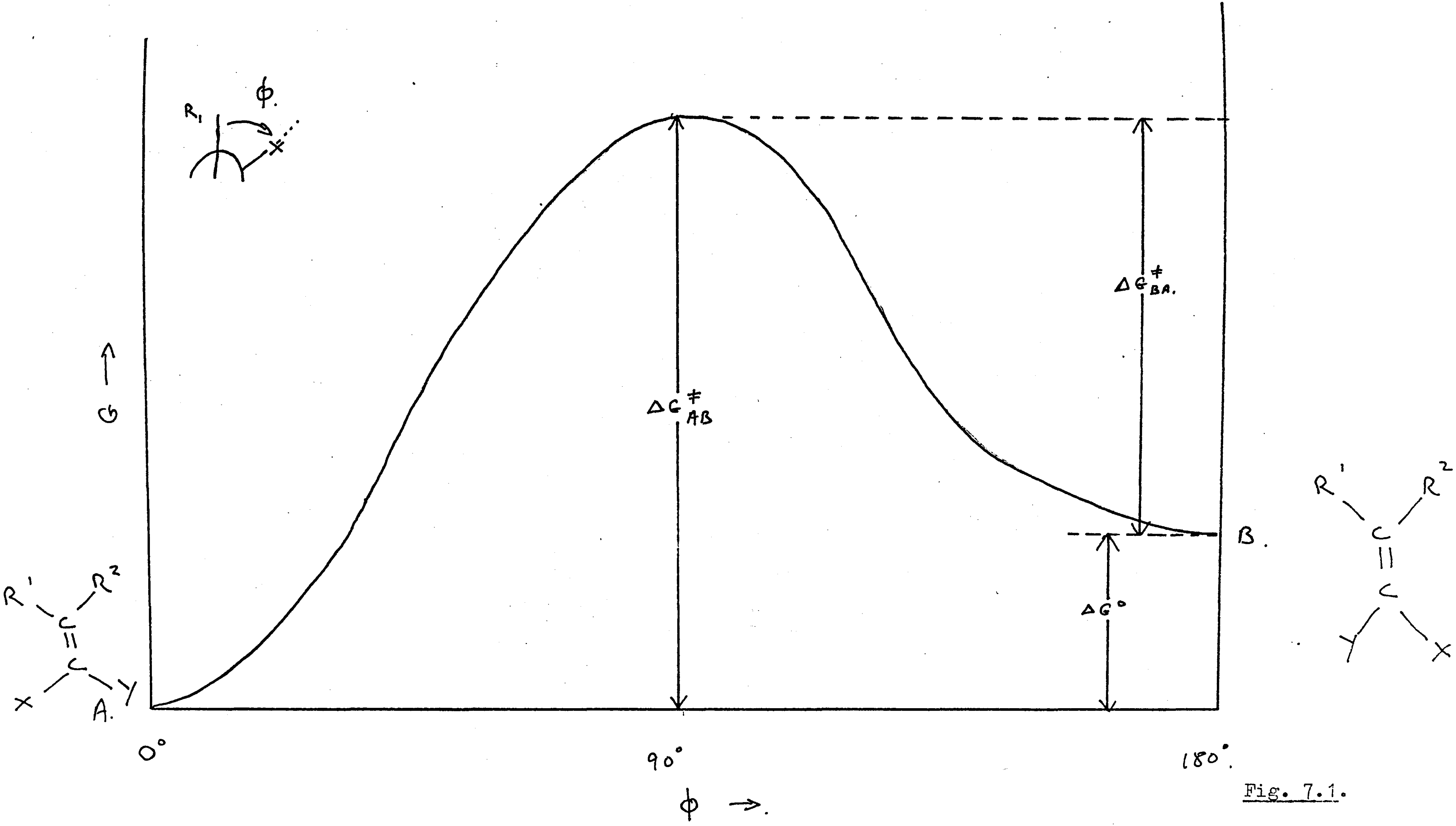

R₁
φ.
X
G
$\Delta G^{\neq}_{AB}$
$\Delta G^{\neq}_{BA}$
ΔG°
B.
A.
R¹
R²
C
C
X
Y
0°
90°
180°.
φ →.

Fig. 7.1.

required even though the results of such investigations can shed information on the microscopic mechanisms.

Useful extrathermodynamic relationships are usually simple in form. This is perhaps suprising when we consider the complexity of the solution systems to which the relations are normally applied. The mathematical simplicity of many of these relations results, in large part, from the tendency of such quantities as the standard free energy to be additive functions of molecular structure. This plausibly arises from the changes in molecular structure affecting only a relatively small proportion of the molecule whilst the remaining contributions to the thermodynamic parameters are nearly equal in any series. If reaction zones (or zones of interest in general) and the changes occuring within them are similar for a series of systems then we expect such quantities as ΔG^{o}, $\Delta G^{\neq}$ to be very similar in these related systems.

To the lowest approximation, we can assume that molar values of a property are precisely additive functions of independent contributions assignable to part structures of the molecule. So molar properties are additive-constitutive functions. To enable us to deal succinctly with molecules in solution, we shall adopt the additivity principle in a modified way. We divide a molecule into two zones, one of which contains a variable substituent, the other of which contains the zone of primary interest. Each of these zones will be considered to contribute an additive term to the free energy and also as interacting with the other zone. Then

$$\bar{G}^{o}_{RX} = G_{R} + G_{X} + I_{R,X}$$

where $I_{R,X}$ is the interaction term.

Now during the actions of interest, the R region remains intact and the X region is altered. The term G_R cancels out in the quantities $\Delta\bar{G}^{o}$ or $\Delta\bar{G}^{\neq}$. Or else the X region remains intact on introducing a substituent (changing R) with the consequence that the term G_X cancels out in the substituent effects $\delta_R\bar{G}^o$ etc. As an example consider the ionisation of a carboxylic acid R_oCOOH. Then

$$\Delta\bar{G}^o_{R_oCOOH} = \bar{G}^o_{R_oCOO^-} + \bar{G}^o_{H^+} - \bar{G}^o_{R_oCOOH}$$

$$= \bar{G}^o_{H^+} + G_{COO^-} - G_{COOH} + I_{R_o,COO^-} - I_{R_o,COOH}$$

The substituent effect in this reaction is defined as

$$\delta_R\Delta\bar{G}^o_{COOH} = \Delta\bar{G}^o_{RCOOH} - \Delta\bar{G}^o_{R_oCOOH}$$

$$= (I_{R,COO^-} - I_{R,COOH}) - (I_{R_o,COO^-} - I_{R_o,COOH})$$

A typical extrathermodynamic relationship will involve substituent effects on the standard free energy changes or equilibrium constants of two related reactions. This can be immediately extended to activation parameters, though such a step cannot, as we have shown, be logically justified.

the Hammett $\rho\sigma$ relationship.

This, the best known of the extrathermodynamic relations, relates the effect of meta and para substituents on the rate and equilibrium constants of aromatic side chain reactions. It is based on the fact that as the substituent is varied the logariths of the rate constants, or the equilibrium constants, for a large number of aromatic side chain reactions are linearly related to one another. Any one of these reactions could have been used to define a set of substituent constants (σ) in terms of which the free energy changes of the others might be described. These parameters are in fact based on the acid dissociation constants of benzoic acid in water. This relationship is therefore essentially a proportionality between $\delta_R\Delta\bar{G}^o$ for a particular benzene side chain reaction and $\delta_R\Delta\bar{G}^o$ for the ionisation of the corresponding benzoic acids.

Let R_o be phenyl and R the meta or para substituted phenyl group. Then substituent effects on the ionisation of benzoic acid are given by

$$\delta_R\Delta\bar{G}^o_{COOH} = (I_{R,COO^-} - I_{R,COOH}) - (I_{R_o,COO^-} - I_{R_o,COOH})$$

and correspondingly for the ionisation of phenol

$$\delta_R \Delta \bar{G}^o_{OH} = (I_{R,O^-} - I_{R,OH}) - (I_{R_o,O^-} - I_{R_o,OH})$$

However, from these two equations alone, we cannot generate a linear realationship between the substituent constants. We require the additional postulate that the interaction terms I are factorable. We can call this assumption the 'separability postulate'.

$$I_{R,X} = I_R . I_X$$

In consequence

$$\delta_R \Delta \bar{G}^o_{COOH} = (I_R - I_{R_o})(I_{COO^-} - I_{COOH})$$

$$\delta_R \Delta \bar{G}^o_{OH} = (I_R - I_{R_o})(I_{O^-} - I_{OH})$$

Therefore

$$\delta_R \Delta \bar{G}^o_{OH} = \frac{(I_{O^-} - I_{OH})}{(I_{COO^-} - I_{COOH})} . \delta_R \Delta \bar{G}^o_{COOH}$$

Several points arise from the above equation. Firstly notice the equal status for the interaction terms for the reaction zone and the rest of the molecule. This is of course logical in that the interaction zone is purely a matter of arbitrary choice. The operators δ_R and Δ, which are commutable are also formally equivalent by the same token.

Implicit in the derivation of this equation are two assumptions. The first of these is that we have assumed that structures R and X interact by a single physical mechanism. The interaction depends only on a single pair of independent variables, one characteristic of R and the other characteristic of X. Even when the interaction proceeds by a single mechanism, we can only hope to separate $I_{R,X}$ into separate factors if the variables involved are scalar quantities and their variations are small. In the case of vector or tensor variables then $I_{R,X}$ can only be factorised if certain physical constraints are applied. Thus we find a far greater precision in extrathermodynamic relationships applied to rigid, planar, aromatic systems than to highly flexible aliphatic systems.

It is often obvious, however, that more than one interaction mechanism is at work. These mechanisms have been divided by Taft[16,17] into polar (electrostatic), steric and resonance effects. Though considerable effort has been expended along these lines, further mention of this work here, is not merited.

Returning to the Hammett relation, we can derive the following definitions.

$$C_6H_5COOH \xrightleftharpoons{K_A^o} C_6H_5COO^- + H^+$$

$$XC_6H_4COOH \xrightleftharpoons{K_A^x} XC_6H_4COO^- + H^+$$

$$\sigma_X = \log\left(\frac{K_A^x}{K_A^o}\right) \text{ in water at } 25^\circ C.$$

The effect of substitution on the rate or equilibrium constants for other benzene side chain reactions can now be expressed as a function of σ. So

$$\log\left(\frac{k_X}{k_o}\right) = \log\left(\frac{K_X}{K_o}\right) = \rho\,\sigma_x$$

The constant ρ is a function of the reaction and will also vary with the reaction conditions. One of the most significant of these variables is the temperature. If such a linear free energy relationship is to maintain its linear form at more than one temperature, then constraints are applied to enthalpies and entropies. If a reaction correlates with σ and shows this correlation at more than one temperature then

$$\delta_R \Delta H^{\neq} = \beta\, \delta_R \Delta S^{\neq}$$

Such considerations must be borne in mind.

We have already mentioned the problems posed by having more than one interaction mechanism. The general applicability of this relationship in aromatic systems where at least two interaction mechanisms (inductive and mesomeric) are operational, does imply that such mechanisms are facets of an underlying more basic mechanism. This is clearly not so. It can be shown, however, that a linear relationship can still be obtained from several interaction mechanisms provided their relative importance in a series of reactions remains constant. For two interaction mechanisms, the following holds

$$\delta_R \log k = \rho'\sigma' + \rho''\sigma''$$

σ' and σ'' change independently since the interaction mechanisms are independent. The substituent effect will only be described by a single parameter as long as ρ'/ρ'' is constant.

$$\delta_R \log k = \rho'(\sigma' + (\rho''/\rho')\sigma'')$$

Here $\sigma' + (\rho''/\rho')\sigma''$ is characteristic of the substituent only.

In practice though, there seems to be no very good reason to suppose that the ratio ρ''/ρ' in benzoic acids is of any universal validity. As such it is suprising that the Hammett relation works so well. In consequence, the exceptions that there are are merely demonstrative of a change in this ratio and are no cause for suprise.

One such cause of variation which can be ascribed to varying ρ''/ρ' ratio arises with substituents which exhibit large resonance effects. In these cases the inductive effect has been unable to keep pace with the resonance effect and as a result, $\sigma_{\text{subst.}}$ seems to vary between reactions in which resonance is not involved and those in which it is involved. The relative significance of the interactions varies and a single σ can no longer cover the variation. We will find this effect in such reactions as those in which charge is developed and is capable of direct resonance interaction with the substituent. The breakdown here can be ascribed to the discrepancy between ρ''/ρ' in benzoic acids and in these interacting systems. The simplest solution to the problem is to redefine the reference reaction in an appropriate fashion and at the same time attempt to normalise the new scale with the old. In the case of electrophilic substituent constants, this was done as follows. Resonance effects for certain meta substituents are liable to be rather unimportant. Therefore, adopting the solvolysis of substituted 2-phenyl,2-propyl chlorides in 90% acetone at 25°C as reference, we plot log (k/k_o) versus Hammett σ for various meta substituted species and derive ρ_o. Then

$$\sigma_X^+ = \frac{\log(k_X/k_o)_{\text{standard reaction}}}{\rho_o}.$$

In consequence, most σ^+_{meta} are about equal to σ_{meta} substituent constants whilst σ^+_{para} will differ notably from σ_{para}. A similar procedure provides σ^-, the nucleophilic substituent constants.

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Physical Methods of Conformational Analysis.

The purpose of this section is to provide a very brief introduction to those physical methods of investigation which have been employed in the work described in this thesis. No attempt can be made to detail any of these physical methods and many suitable introductions to each are readily available. Further, we will delay consideration of n.m.r. methods to the next section.

non-spectroscopic methods.

dipole moments.

The existence of an electrostatic dipole due to the separation of charge inherent in bonding together two non-identical atoms is commonplace. The dipole moment created gives rise to a permanent polarisation when placed between the plates of a condenser. In this way, the dipole moment of a molecule, which is a vector, can be determined. Useful geometrical information is obtainable from the magnitude of the dipole moment. A knowledge of the individual dipole moments of functional groups in the molecule, taken from model compounds, permits vectorial calculation of the dipole moment expected for a given conformation of a molecule, and experimental verification of a given value of dipole moment is supportive evidence, in many instances, for a specific conformation.

Numerous other non-spectroscopic methods are available, but their use is limited, primarily because spectroscopic techniques are much more powerful tools in probing molecular structure.

spectroscopic techniques.

A large variety of spectroscopic techniques are available to the physical chemist in his examination of molecular structure. In practice, two broad categories of technique are employed. There are those techniques which can determine, in favourable circumstances, full details of the molecular geometry of any compound, the most obvious of these being X-ray crystallography. There is also the related subject of electron diffraction[1], which, in the hands of Odd Hassel, has made an important contribution to conformational analysis. But by far the majority of spectroscopic techniques provide partial information about the geometry of the molecule. However, it can be the case and often is with such techniques as microwave spectroscopy and n.m.r., that sufficient evidence of a general kind is available elsewhere to enable the additional evidence provided by these techniques to be definitive.

Several criteria must be met before we can observe separate spectra from the differing conformers of a compound. Considering Heisenberg's Uncertainty Principle, one form of which states that

$$\Delta t.\Delta E \quad = \quad h/2\pi$$

where Δt is the time of spectral observation.
where ΔE is the precision of energy measurement and h is Planck's constant.

If a conformer is isolated for a time Δt, then Heisenberg's Uncertainty Principle allows its energy to be measured with a precision ΔE. Then the larger the energy changes involved, then the shorter the time of observation necessary to distinguish a given energy state. If we do not allow sufficient time for the observation, by interposing a conformational change during the necessary period, then only an average measurement will be obtained[*2]. It therefore might appear desirable to employ a spectroscopic technique which relies on the observation of large energy changes. We would then expect to be able to observe even short lived species. But we must bear in mind that conformational changes often involve only very little energy - often little more than a few kilocalories perhaps. We would then require not only to be able to observe this small difference superimposed on large energy changes of the observations, but we would also require that the spectroscopic energy levels of the approproate excited state were disposed in a very similar manner to those of the ground state species. This is by no means guarunteed or even likely where the two states in question are well separated in energy.

The other extreme involves the use of much lower observational energies E, with the necessary longer observation times t. In many cases where this approach is applied, it may be necessary to operate at much reduced temperatures to extend conformer lifetimes. Whilst this in itself presents experimental difficulties, there are often considerable advantages in making observations of conformers over a range of lifetimes. N.m.r. spectroscopy is a technique which falls in this latter category. As will be shown shortly, this ability to make observations over a region of varying conformer lifetimes is of great importance in conformational analysis.

infra-red/raman spectroscopy.

By far the majority of information on the vibrational energy levels of a molecule is obtained by infra-red rather than raman spectroscopy. Though the calculation of the vibrational spectrum to be expected from any but the most simple molecules is a daunting task, the characteristics of various functional groupings and the effects of minor environmental influences can be detected by vibrational spectroscopy. Application to different physical states of a compound can be used to detect conformational changes with change of state. This can be of interest in as much as compounds are quite often conformationally pure in the solid state. On melting, the appearance of further bands in the i.r. spectrum can be taken as suggestive of conformational equilibria in the melt (or for that matter in solution). Unfortunately, not all compounds are conformationally pure in the solid state and the observation of no changes in the i.r. spectrum on melting or dissolving cannot be taken as conclusive evidence for conformational purity.

Use of i.r. techniques quantitatively is not straightforward. The strength of any absorption band in the system depends not only on the quantity of species giving rise to that band but also on the extinction coefficient of the absorption. One solution to this problem is to determine the extinction coefficients for conformationally pure model compounds, but the use of such a model is by no means free of the danger of serious error, as we can have no absolute confidence in the values of the extinction coefficients derived. A more refined approach to this problem is to examine the variation of the spectra of any one system with temperature and observe any changes in the intensities of the absorptions which may be correlated with changes in conformer populations. Extinction coefficients are normally considered to be free of major variations with temperature. The relative values of extinction coefficients are most likely to remain constant with temperature. In this manner, we can gain some estimate of conformational dynamics.

x-ray diffraction.

The major drawback in the use of x-ray diffraction methods is their restriction to crystalline material. The information obtained applies strictly only to the solid state and whilst the main details of molecular conformation will remain constant, the nuances of geometrical detail, which are the primary concern, will vary from situation to situation. As long as this restriction on x-ray methods is borne continually in mind, then their application to conformational problems is of immense worth. A considerable amount of conformational work is necessarily based on information derived by x-ray methods and in most cases, x-ray methods have been used to define model compound conformations from which many empirical correlations have been built up (particularly in n.m.r. spectroscopy).

The technique is based upon the observation of a diffraction pattern from a monochromatic beam of x-rays which is allowed to impinge on the molecules of interest held in a crystal lattice. From this diffraction pattern, it is possible to establish, often with considerable expenditure of computing time, the accurate geometry of the molecule. Problems are met in the application of this technique, but at the present time progress has been such that application of X-ray methods is now almost routine in many circumstances. The technical implementation of X-ray methods can be almost totally automated in many instances.

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Acknowledgements (Physical Methods).

figs. 2.1, 3.1, 4.1, 5.1 from Hanack, M., "Conformation Theory", Academic Press, 1965.

Nuclear Magnetic Resonance Studies in Conformational Analysis.

Since 1960, high resolution n.m.r. spectroscopy has revolutionised that branch of conformational analysis concerned with the determinations of conformations of molecules in solution. "It is now established that n.m.r. spectroscopy provides more information about the shape of molecules in solution than any other physical method".[1] Both chemical shifts and spin-spin coupling constants are profoundly sensitive to the spatial arrangement of atoms in molecules. However, owing to the largely empirical nature of chemical shift and coupling constant calculations, the application of n.m.r. spectroscopy to elucidate molecular conformations in solution is inexact and is based upon empirical correlations developed initially from the spectra of rigid molecules. Yet despite these limitations, n.m.r. spectroscopy is probably the most powerful technique available for conformational studies.

Considering the central importance of cyclohexane in early conformational studies[2,3] and its occurance in many natural products, often with fixed and known geometry as in the steroids, it is not suprising that cyclohexane systems have been extensively studied by n.m.r. spectroscopy.[*4,5] Such studies have given rise to a vast amount of data on the spectral parameters of conformationally interesting systems. In consequence, the methods of analysis applicable to cyclohexane systems are well established[6] and serve as a secure base for the examination of more complex systems. Particular trends can be recognised for chemical shifts[7a] and more significantly for coupling constants.[7b] From these trends have been established the necessary tools for conformational studies by n.m.r.

In view of this central importance of cyclohexane for conformational studies by n.m.r., it is appropriate to illustrate some basic principles of the application of n.m.r. spectroscopy in conformational studies by reference to work on cyclohexanes. Methods developed in this brief survey are, in part, employed in later ring conformational studies.

It is further desirable in many instances to establish the thermodynamic relationships between various conformers in a system. The first such system to be defined thermodynamically by n.m.r. spectroscopy was dimethylformamide[8] in which two discrete conformers arising from hindered rotation about the C-N bond are observed. Since this initial study in 1955, a large amount of data on many systems has accumulated. It has become apparent that many of the n.m.r. studies of thermodynamic parameters are thoroughly unreliable, a point we will return to and discuss in some detail in the practical sections of this thesis. With a reputation for unreliability developed in this area, there has been a justifiable reluctance on the part of many authors to attempt anything but approximate comparisons of thermodynamic parameters using n.m.r. data. This state of affairs need no longer exist and there is reason to be optimistic about future developments in this field.

Basic Principles.

For convenience in discussion, we can distinguish two broad categories of n.m.r. experimental approach, namely 'static' and 'dynamic'. The origins of this distinction lie in the requirements for spectral observation outlined in Heisenberg's Uncertainty Principle which was discussed earlier. It is the requirement, in n.m.r. spectroscopy, that observation times are typically measured in seconds rather than in milli- or nano-seconds which gives rise to the spectral behaviour which is often dependent on the lifetime of any finite species involved. In n.m.r. the observation times are often of comparable order to the lifetimes of the species involved. We will distinguish 'static' spectra as those which are temperature independent in the sense that a small change in temperature(say 5°) causes a negligable change in the observed spectrum, whilst 'dynamic' spectra are those where such a temperature change results in significant spectral changes. The underlying theory of such effects has been dealt with in the first part of this thesis.

Any system which is capable of some kind of conformational mobility can be expected to exhibit spectra of both the 'static' and the 'dynamic' kind depending on the temperature range of the observations. The distinction is further useful in as much as methods of analysis applied to systems of the 'static' kind are largely empirical in their origins and can sometimes be quite approximate, whilst those appropriate to the 'dynamic' kind require further application of quantum mechanical exact treatments, based on the derived empirical information, to obtain reliable data.

The distinction between *configuration* defined by Eliel[9a] as "the arrangement in space of the atoms or groups around the disymmetric or rigid part of the molecule" and *conformation*[9b] used to "denote any one of the infinite number of momentary arrangements of the atoms in space that results from rotation about single bonds" is somewhat vague when these phenomena are studied by n.m.r.[*10]

When studied by n.m.r. it is perhaps better to consider three merging categories of compound.[11]

1). An isomer can be long lived on the n.m.r. time scale and hence might be considered as a configuration. In this case we can characterise and distinguish between various isomers and measure such properties as relative populations, differences in coupling constants between species etc.

2). Isomers can be short lived on the time scale of n.m.r. observation and we can merely observe an average spectrum for several interconverting species. Should one isomer be more populated than others, a greater weighting of its exspected spectral parameters in the spectrum average may allow us to establish the nature of this isomer and the position of equilibrium in the system.

3). Isomers whose interconversion rates are comparable with the n.m.r. observation time scale will give rise to spectra whose detailed features may be highly sensitive to interconversion rates. By lowering the temperature of observation and consequently the rates of conversion of the isomers we will eventually be able to observe a superposition of the spectra of individual isomers (case 1). By raising the temperature of observation, an average spectrum of all isomers will be possible (case 3).

To establish the observation time scale of an n.m.r. experiment, consider a nucleus which is susceptible to n.m.r. observation present in two isomers 'A' and 'B' of a system. Then if the chemical shift of the nuclei in the two isomers are $_A$ Hz. and $_B$ Hz. respectively and the rate of exchange of the nucleus between isomer sites is t/sec., then the above three cases are characterised as follows.

1). $(\nu_A - \nu_B) << t.$

2). $(\nu_A - \nu_B) \approx t.$

3). $(\nu_A - \nu_B) >> t.$ (units of Hz. i.e. exchanges /sec.).

As mentioned in case 3 above, variation of the temperature at which the system is observed allows us to observe the entire spectrum of behaviour outlined for many systems. This can lead, with care in the application of experimental procedures, to reliable thermodynamic parameters for the conformational system. In fact in many cases, such a comprehensive approach is necessary for any degree of accuracy in the estimation of thermodynamic parameters.

We will now illustrate the application of n.m.r. spectroscopy to conformational analysis by considering its application to studies of cyclohexane systems.

cyclohexane systems.

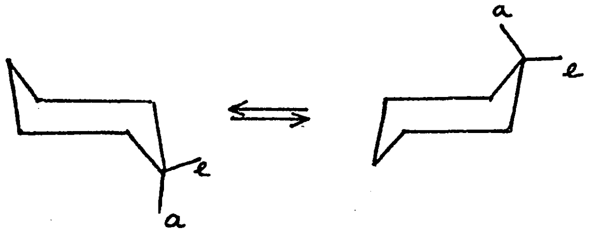
The application of n.m.r. spectroscopy to the conformational analysis of cyclohexane systems has recently been surveyed quite extensively in two recent reviews.[7b,12] Both reviews provide a comprehensive introduction to the subject.

As there are two empirical parameter sets which can be derived from the n.m.r. spectrum of any compound, namely the chemical shifts and spin-spin coupling constants, then conformational analysis of the

compound can be based on observation of either or both of these parameter
significant interest is still maintained in these studies for the recen
sets. Whilst n.m.r. applications to cyclohexane rings are now routine, significant interest is still maintained in these studies for the recent literature to provide examples of the methods illustrated below.

<u>chemical shifts.</u>

Whilst absolute values of chemical shifts are not likely to be too informative, the relative values observed in any given system have been noted to follow a simple basic rule[13]. Any equatorial proton on any substituted or unsubstituted cyclohexane carbon will resonate at lower field than an axial proton in the same situation. (The terms equatorial and axial are defined by fig. 1.1 below.) Several methods for determining quantitatively thermodynamic parameters from chemical shifts have been established[7c,12].



'a' = axial.

'e' = equatorial.

Fig. 1.1.

Measurement of the area of signals due to contributing conformations is a method which is applicable to any system in which signals due to individual conformers can be observed. If we can integrate separate signals from the same nuclei in individual conformers, then we have a direct measure of the relative proportions of the conformers present. Consequently, we can establish the position of equilibrium and the free energy difference between conformers. The application of this method will often require the use of low temperature studies, as barriers to ring inversion are generally too low to permit observation of separate signals at room temperature. We can extend our studies in such a situation by examining the change of conformer equilibria with change in temperature and hence derive enthalpy and entropy data for the equilibration(s). The use of varying solvents has also been employed to in:

:fluence equilibria.

Bushweller and coworkers/[14] have published a recent example of this approach in establishing the 'A' value of the deuterioamino group at $-93^{\circ}C$ by applying this peak area method/[*15]. They used a hexadeuterio system to eliminate ring methylene coupling to the 1-proton of interest. The areas of this proton signal in each conformation were measured either by weighing cut outs of the peaks or by area measurement with a hand planimeter/[*16]. Values of 1.2 - 1.4 kcal./mole (depending on solvent) were obtained, and are in remarkably good agreement with the results obtained by other more indirect methods (see references in this paper).

Though not strictly related to simple integration of signals, a further powerful extension of the n.m.r. approach depending primarily on a shift difference between exchanging nuclei in different conformers, is the application of rate studies to the barrier to conformational exchange. A relevant example of this is the study of cyclohexane-d_{11} published by Anet and Bourn in 1967/[17]. By the application of a full lineshape analysis (discussed theoretically earlier in this thesis) and by double resonance techniques (with which we will not be concerned here) they measured inversion rates for cyclohexane-d_{11} from -117° to -24° covering a range in rate of over 500,000 and concluded their study with a thorough discussion of the pertinent results. They established a set of thermodynamic parameters for cyclohexane in which a good deal of reliance can be placed.

Anet and coworkers have published recently an interesting extension of the use of differing chemical shifts in cyclohexane studies/[18]. Determination of the 'A' value of the methyl group proves to be an impossible task by ^{1}H n.m.r. spectroscopy due to the lack of chemical shift between conformers, even at the highest field strengths. Examination of the ^{13}C spectrum of methylcyclohexane at 63.1 MHz. and at $-110^{\circ}C$ indicates weak bands which could be unambiguously assigned to the conformer with methyl axial. The value of the equilibrium constant observed was about 100, corresponding to an A value of 1.6 kcal./mole.

If we can establish the chemical shifts of a given nucleus appropriate to the pure conformers in a system, then it is possible to calculate the conformer ratios of mixed systems from an observation of the average chemical shift of the nucleus in question. There are two general approaches to the problem of establishing the pure conformer shifts. We can derive this information from

(a). the low temperature spectrum where separate spectra of the conformers are observable. This method relies on there being no change in the chemical shift in the conformers over a range of temperature or at least on our being able to observe a trend in such changes sufficient for us to reliably extrapolate them into the region of averaging spectra. Such methods are ultimately open to error from any extrapolation which does not in fact hold up over the required temperature range. Such problems are familiar ones in variable temperature n.m.r. studies.

(b). the spectra of conformationally biased forms. The most common example of conformational biasing is the use of 4-t-butyl substituents in cyclohexane studies. In principle, the t-butyl group will always be disposed equitorially because of its size. The application of this method is obviously fraught with difficulties. We assume not only that the t-butyl group has no effect on the n.m.r. parameters of the system, and subtle effects are often observed in cyclohexane studies, but also the conformer with the substituent of interest axial will be conformationally pure. This is by no means assured if R (the substituent) interacts at all significantly in the axial position. Results achieved by such methods must be treated with caution. One particular example of the extreme effects t-butyl substituents can have is provided by the results of Barili and coworkers/19 who observed that substitution of a dibromocyclohexane with t-butyl caused a twist-boat conformer to become relatively stable when compared with the chair forms. This twist-boat contributed to a significant extent to the conformational situation.

A further application of chemical shift techniques arises in the substitution of the ring with another magnetic nucleus such as fluorine.

This technique has been very successful in many circumstances[*20] particularly in medium ring compounds but it is also fair comment that conformational results obtained in this manner are not directly applicable to the parent ring. Fluorine as a substituent can have a significant conformational effect of its own.

coupling constants.

A considerable amount of information on proton-proton coupling constants has been acquired in the last fifteen years. We should remark at this stage, though, that the state of affairs with regard to couplings involving other nuclei is not yet so favourable. Consequently, we will restrict our attention to proton-proton couplings entirely. From proton studies, many useful empirical correlations have been developed, the most significant of which is the Karplus relation.[21,22] This relates vicinial (1,2) proton-proton coupling to the dihedral angle between the protons. Many forms of Karplus relation have now been developed[*23] but we will postpone mention of these until we require them specifically later. Dependence of the vicinal coupling constants on factors other than the dihedral angle was implicit in the original treatments, yet the magnitudes of these influences is such that they can be regarded as perturbations of the original Karplus equation. These perturbations concern

(a) the electronegativities of substituents.
(b) the orientation of substituents.
(c) the hybridisation of carbon atoms.
(d) the bond angles.
(e) the bond lengths.

Many systems of conformational interest show a considerable amount of coupling structure in their spectra arising from many sources. With such complexity, it is often desirable and even necessary to eliminate some of these couplings by isotopic substitution techniques. So, for example, we can replace hydrogen by deuterium and employ wide band deut:

erium decoupling to eliminate some spectral complexity. Homonuclear (narrow band) decoupling (c.f. heteronuclear above) can also be employed in spectral analysis.

As with chemical shifts, we can employ a similar approach to the values of coupling constants observed in a system. If the spectrum we observe is an average of two or more conformer spectra, then by establishing suitable model compounds, it may be possible, from the coupling constants observed in the average spectrum, to establish possible conformer ratios in the mixture. Again the selection of model systems is fraught with difficulty and is possibly even more prone to error than the use of models in chemical shift studies. We may also, as previously, examine spectra at low temperature when the individual coupling constants for each conformer can be directly measured. Extrapolation of coupling constants into unobservable regions is a fairly reliable procedure as coupling constants generally vary little with temperature.

Most applications of coupling constants do rely on an implementation of the Karplus equation in one form or another. As the Karplus relationships relate the value of the vicinal coupling constant expected in a system to the value of the dihedral angle (ϕ in fig. 2.1) between the coupling nuclei, then all other things being equal, which they often are, then the particular value of the coupling constant observed in a system will give a very good indication of the dihedral angle between the two nuclei in question. Dihedral angles are a sensitive indication of molecular geometry, particularly in cyclic systems, and consequently we can use coupling constants as sensitive probes of (ring) geometry. If we are able to observe coupling constants for various pairs of nuclei around a ring, then the predicted dihedral angles around this ring will define, quite unambiguously in many cases, the conformation of the ring to within quite close limits.

A particular refinement of such logic is contained in the use of 'R' values.[24] These values are dimensionless quantities (the ratios of pairs of coupling constants) and are independent of factors such as substituent electronegativities, depending only (to a first approximation) on ring conformation. Certain changes in 'R' value from the ring norm are encountered as distortions of the ring are encountered. Multiple 'R' value determinations around the ring in question can be used to define ring geometry with a high degree of certainty. Other attempts to establish dimensionless constants which shed light on the conformation of a ring have been made including the most recent 'Dihedral Angle Estimation by the Ratio Method' of Slessor and Tracey[25].

The application of complete lineshape studies, with information derived from individual conformer spectra at low temperatures, is described later in this thesis, as is an application of geometry definition from coupling constant information. These two methods illustrate the power of n.m.r. spectroscopy in establishing both static and dynamic parameters for conformational systems.

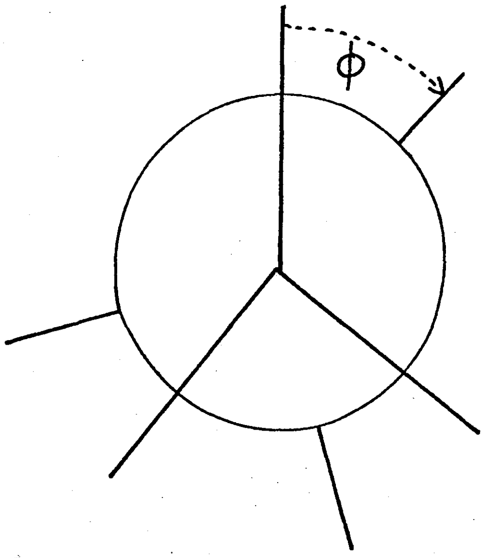


Fig. 2.1.

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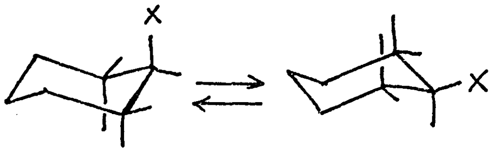

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A Theoretical Approach to Conformational Analysis.

"The idea that one might calculate in detail the energy of a given molecular conformation has long intrigued chemists, as it offers promise of the prediction of the most stable conformations or the intimate transition state geometry and energy in organic reactions. A number of such calculations has been made[*1] with varying success, and it is well ......to offer a brief summary of the problems involved in such calculations[*2]. The first and most formidable difficulty is that of selecting the particular functions which relate energy to geometrical parameters of the molecular conformations being examined; such functions ......are generally derived indirectly from various empirical sources as spectroscopic or thermodynamic data. Secondly, one must choose a particular conformation on which to apply these functions. In order to ascertain the most stable conformation of a given molecule, it is theoretically necessary to calculate the sum of energies related to the various geometrical parameters of a given conformation, and to minimise this sum with respect to independent variation of each of these parameters (i.e. by progressive distortion of the given conformation). This statement of approach to the problem serves to underscore the vast complexity of the calculations in any molecule of organic chemical interest, since the number of independent geometrical variables can be overwhelming while the calculation of the total energy of any single set of geometric parameters is itself extremely ponderous. In order to reduce the problem to workable dimensions, it is generally necessary to simplify it by certain assumptions of conformation or of parameter constancy, and frequently by simplifying or simply ignoring certain of the relevant energy functions themselves. These simplifications, however, too often so drastically alter the complexion of the problem as to render the answers either suspect or unreasonable."[3]

The basis of the work of Hendrickson, a founder figure in this field, was to break through the barrier of undue simplification by em:

ploying computers for the calculations, so allowing far greater mathematical effort, in a reasonable time, with untiring accuracy and a consequent capability of a more intimate probing into these problems than is possible by hand calculation. The application of such computer methods is now commonplace and, although the early intuitive understanding of the relative stabilities of conformers has not been overturned, the degree of subtlety and precision now possible in this work is remarkable.

Hendrickson, for the purposes of calculation, recognises four categories of interaction energy, namely bond angle strain (Baeyer strain), bond length strain, torsional or eclipsing strain (Pitzer strain), and the strain of non-bonded interactions. The problems of selecting functions to represent these strains have occupied considerable discussion in this field and several authors have selected differing sets. The unavoidable empirical parameters involved in all these functions require to be optimised with experimental data from one source or another. The nature and suitability of the source employed is open to discussion.

The vast majority of the applications of this technique have been in the field of medium ring conformational studies. This stems from the requirement for a challenge of managable proportions for these methods, to allow testing and optimisation of the techniques. In his first publication on this subject, Hendrickson,[13] after considering in detail the nature of the functions he was to employ in his calculations, considered the conformational situation in cyclopentane, cyclohexane and cycloheptane. His observations on the energy content of various conformations of the two normal rings were in good agreement with those energies aduced experimentally. His detailed discussion of the conformations possible in cycloheptanes, and the interconversion routes likely to be followed between conformations, has laid the basis for many spectroscopic studies of cycloheptane systems.

The conformational situation presented by rings above cyclohexane in size is greatly complicated by the general flexibility of all, including the most stable, conformations. There is a consequent lack of definition, not experienced in cyclohexane, in the nature of the position of substituents on these rings. It is possible, though, to define substituents as axial or equatorial in a loose sense, in as much as the latter are more in the plane of the carbon skeleton whilst the former are more perpendicular to it. However, in each conformation, each skeleton position differs from its neighbour in the quality of interactions experienced by the substituent group, be it only hydrogen. These characteristics will differ from conformation to conformation. It is then possible, bearing these observations in mind, to consider in detail conformer stabilities and the energetics of interconversion pathways between conformations. In this manner, many of the n.m.r. observations on such rings at low temperatures have been rationalised.

Once the stabilities of unsubstituted ring conformations have been established and the energetics of routes for conversion between them estimated, the next obvious task is to consider the stabilities of various conformations for substituted rings. In the second paper in his series on "Molecular Geometry"[4], Hendrickson considers the energetics of the situations pertaining in methylcyclohexane and methylcycloheptane. On the basis of such information, the conformational analysis of substituted rings can be discussed and this leads to interesting conclusions as to the relative stability of multi-substituted ring conformations.

In paper IV of this series[5], saturated carbocycles with eight, nine and ten members are discussed and a very necessary nomenclature to describe the topology of these and others rings is introduced. (We shall not concern ourselves with this nomenclature here.) Considering the computed energies of the carbocycles so far discussed, Hendrickson noted the following significant fact. The most important energy component for deciding the conformational nature of a ring system is the torsional energy. This is a major part of the total energies in all the prefered forms and is the least subject to alteration within a family of forms. Non-bonded repulsions can give rise to definitively large energy contributions but a small increase in bond angles normally serves to cancel these out. Hence each, invariably symmetrical, family of forms has a more or less characteristic torsional strain, not subject to much variation via bond angle opening and which usually, therefore, determines which family of forms will be the preferred one. The detailed form within that family, which is the most stable, is then determined by angle variation largely to eliminate non-bonded repulsions.

In paper V of this series[6], Hendrickson employed experimental data for cycloalkanes and n-butane to re-standardise the constants in the energy functions and then recalculated his previous work. In the following paper (VI[7]), he calculated the strain energies for methyeycloalkanes of six- to ten-membered rings for all possible substituent positions on each symmetrical conformation. Such results are a necessary basis for the conformational analysis of substituted cycloalkanes. Several generalisations result from these calculations. Equatorial and 'isoclinal' ring positions are virtually all strain free whilst axial positions are all strained, with one important exception.

Paper VII[8] deals with modes of interconversion in medium rings, considering both ring inversion and pseudorotation pathways. This is further extended to substituted systems. Pseudorotation pathways are characteristically found to have much lower barriers to interconversion than inversion pathways. The flexibility of many of the medium rings reflects this low pseudorotation barrier. However, such a barrier may rise considerably for substituted rings and pseudorotation may in many cases be blocked completely for all practical purposes.

Of course, other authors have contributed to this field, though, with few exceptions, their work has not exhibited the meticulous detail of Hendrickson's work. One such exception is to be found in a paper by Bixon and Lifson.[9] The original contribution of these authors was the adjustment of the functions employed for calculating the various energies mentioned above. In this, there is evidence in one case that they have achieved a closer estimate of physical reality. Srinivasan and Srikrishnan[10] in considering the results of X-ray studies of cyclooctane ring systems noted that deviations of theoretical from experimental results were least for Bixon and Lifson's work. On the other hand, we cannot overlook that this is only one ring system examined in the solid state, and this may not be typical of all cycloalkanes under all conditions.

An extension of Hendrickson's technique to unsaturated carbocycles has been reported by Favini and coworkers in a series of papers[11-14]. These authors present their results with little discussion and, as yet, application of these calculations has not been as extensive as in the saturated carbocycles.

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Conformational Analysis of Medium Ring Systems.

As we have noted, not only were the early studies of molecular conformation initiated by an interest in ring systems, but a great deal of the recent progress in conformational analysis has derived from n.m.r. studies of conformations in rings. The importance of rings in conformational analysis is a reflection of the obvious geometrical fact that a cyclic system is considerably more conformationally restricted than the corresponding open chain system. This does not merely restrict the number of possible isomers in a system but further, generally gives rise to considerably higher barriers to conformer interconversion and allows their 'separation' by a wider range of spectroscopic techniques.

Commonly, analyses have been restricted to rings with six members or less, a further reflection of a need for a restriction of conformational possibilities to make tractable the problems involved. We can note that the majority of conformationally defined rigid systems possess rings of five or six members and are to be found among the vast numbers of natural products for which many solid state X-ray structures have been determined.

During the last decade, considerable advances have been made in advancing conformational studies into the field of medium rings. The extension of n.m.r. analyses to rings with seven and more members is now so far advanced that, not only must analyses of six membered rings be considered routine, but the analysis of medium rings can be considered an accurate technique capable of yielding completely definitive results. Studies on these systems are now frequently published in which accurate thermodynamic parameters are quoted for conformational processes.

In progressing to rings with seven or more members, the conformational possibilities multiply rapidly and these rings still present a significant challenge to our techniques. Success in meeting this challenge results mainly from the application of n.m.r. spectroscopy on the one hand and techniques of theoretical 'stability' calculations on the other. Theoretical calculation of ring conformation stabilities satisfactorily defines the limits of many conformational processes and allows us to eliminate from consideration many otherwise plausible conformations which would possess too high an energy. Whilst intuitive recognition of some of these unlikely conformers has always been possible, the quantification of these ideas lends precision to such concepts. Within such restrictions, n.m.r. spectroscopy often unambiguously defines the character of the most stable conformations observed, whilst substance is often added to these conclusions by the observation of similar conformations in the solid state by X-ray spectroscopy. Of course, the existence of an alternative conformation defined by X-ray work does not deny the existence of other conformations in solution. The combined application of theoretical methods and practical n.m.r. spectroscopy is nicely illustrated by many of the papers of Roberts and coworkers[*1].

A Review of N.M.R. Studies of Medium Ring Compounds.

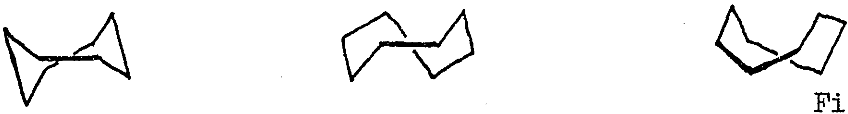
Two useful summaries of the fairly sparse early work in this field are available in the monographs of Hanack[2] and Eliel et al[3]. In the following review, we will consider the studies of eight membered carbocyclics in some detail and briefly survey the work on seven, nine and ten membered rings. Heterocyclics are very briefly considered where results in such systems are pertinent to carbocyclic studies.

eight membered rings.

cyclooctanes.

"Cyclooctane is unquestionably the conformationally most complex cycloalkane owing to the existence of so many forms of comparable energy and this fact has caused great difficulty in the interpretation of physical data."[4] The most stable conformer is calculated to be the 'boat-

1. boat-chair. 2. chair-chair. 3. boat-boat.



4. twist-chair-chair. 5. twist-boat-chair. 6. twist-tub.

Fig. 1.1 - 1.6.

chair' (fig. 1.1), but within 2 kcal./mole of this form exist five more symmetrical forms: 'chair-chair' (extended crown), 'boat-boat' (saddle), 'twist-chair-chair', 'twist-boat-chair' and the 'twist-tub' (fig. 1.2-6 respectively). These six conformations of nearly equal energy represent discrete energy minima on complex interconversion profiles[*5] and it would therefore be no suprise to find substitution of the parent ring giving rise to almost any of the above conformations as the most stable.

The earliest results bearing on cyclooctane conformations in solution generally involved the application of i.r. and dipole moment studies on substituted rings. Allinger in 1959[6,7] from studies on cyclooctanones concluded that these rings existed as a mixture of extended crown and boat-chair forms, but he later changed his mind in the light of further evidence and favoured the existence of only one conformer, the stretched crown form[8], in cyclooctanone. Generalisation of these results to cyclooctanes in general, though not warrented, was necessary by such an approach as cyclooctane itself was not sufficiently susceptible to examination by the techniques applied in these studies. This evidence was, however, accorded considerable weight at the time, even though some authors[*9] preferred other forms.

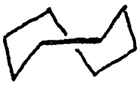
The first conclusive n.m.r. study of cyclooctane was published by Anet and Hartman[10] in 1963, though earlier papers by Harris and Sheppard[11] and by Meiboom[12] had postulated rather contradictory results from observation of non-deuterated cyclooctane. Anet, using perdeuteriocyclooctane measured a free energy of activation for the ring inversion process of 8.1 kcal./mole at $-111.5^{\circ}C$. At the same time they argued that the existence of only two lines in the low temperature spectrum of the mono-protio-cyclooctane indicated that only one conformation, or one group of easily interconverted conformations, exists and that, further, the evidence is in accord with the existence of the 'skewed crown' conformation in cyclooctane and its derivitives. An examination of cyclooctane substituted cis with hydrogens in the 1,2 and 5,6 positions showed a vicinal coupling in the low temperature spectrum of only 2.85 Hz. The absence of a large cis vicinal coupling supports a crown or stretched crown conformation.

In 1966, Anet and St. Jacques[13] published further n.m.r. observations on cyclooctane and several substituted cyclooctane systems. Using specifically deuterated cyclooctanes they established the following results. Firstly, the suggestion of Dale[9] that cyclooctane exists in a 'saddle' conformation is not consistent with the facts and neither is the existence of 'tub' conformations of any kind (fig. 2.1-2.). Results are consistent with the crown or with the stretched or 'twisted' crown (fig. 2.3) provided the latter two undergo rapid averaging. The boat-chair form also conforms with observations provided some process is available to average the ten different protons of this form into two equal sets. One such process is pseudorotation,[*14] a low energy process, which is likely to be still fast even at these low temperatures. A further process is wagging of a methylene group to give reversible formation of a crown. By such processes, a mixture of crown forms, boat-chair forms and twist boat-chair forms (fig. 2.4) can all be included in the conformational mixture.

1. saddle.

2. tub.

3. stretched crown.



4. twist-boat-chair.

Fig. 2.1 - 2.4.

In the sequential paper[15] Anet and St. Jacques published the results of their studies on three monosubstituted cyclooctane systems. The spectra of methyl- and t-butyl-cyclooctane are temperature dependent and exhibit the same kind of behaviour as does the acetonide of cyclooctane-trans-1,2-diol (fig. 3.1). Referring to these cyclooctanes as I, II and III respectively, we can note that I and II cannot exist at room temperature in one conformation as do the corresponding cyclohexane compounds. Temperature-dependent spectral changes for the methylene protons occur between -100 and -120° for these two compounds. At the same time, the concurrent existence of two t-butyl bands in the ratio 2:1 for II was not taken as indicative of restricted rotation of the t-butyl group but as evidence of the same process giving rise to the temperature dependent effects on the methylene protons.

A later study of the low temperature spectra of t-butylcycloalkanes published by these authors in 1968[16] indicated that restricted rotation of the t-butyl group is observed in these systems at varying temperatures and in particular that the spectral effects observed above for II are ascribable in part to hindered rotation of the t-butyl group and not solely to ring inversion processes. However, the concurrent changes in the ring methylene protons indicate that the ring inversion process proceeds at the same rate as t-butyl restricted rotation. In consequence, the conclusions of the earlier paper are still valid.

Anet and St. Jacques developed the following argument in favour of boat-chair conformations for cyclooctane systems. Firstly, since the spectral changes in I and II occur in the same temperature region as those in non-substituted systems, then this strongly suggests that essentially the same kind of process is being observed. Particularly with regard to II, it will be necessary for any stable conformation to have unhindered 'equitorial' sites available for placing the large substituent. Whilst crown species do have such 'equitorial' sites, interconversion between several crown forms, which from calculations[17] appears to be extremely facile even at -200°, averages all these 'equitorial' sites. Consequently only 'axial' sites then remain to provide for the second low temperature resonance. This seems highly unlikely in I and II and is impossible in III (fig. 3.1), which shows similar low temperature effects though at -70 to -80° C.

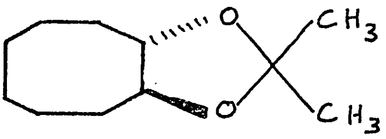
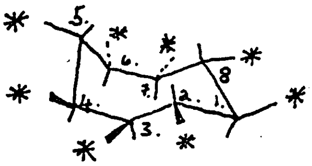


Fig. 3.1.

Directing attention to boat-chair conformations, the authors develop arguments to show that these conformations possess two distinct sets of bonds, only interconverted by ring inversion. The members of each set are interconverted by pseudorotation or 'methylene wagging' processes, both facile processes. The two sets (fig. 4.1) are: set A (1e,2e, 3e,4a,5a,6a,7e,8e), set B (1a,2a,3a,4e,5e,6e,7a,8a). A large group can be accomodated in five equatorial positions in set A and in three positions in set B. Also, it is possible to have two equatorial substituents on adjacent carbons in each set as required by III. Interconver:



* = equitorial.

Fig. 4.1.

:sion between A and B requires ring inversion as in cyclooctane itself. At high temperatures this leads to a relatively narrow line for the methylene protons rather than a single sharp line. On balance, therefore, it seems more likely that cyclooctane and its simple substituted derivitives possess mainly a boat-chair conformation at low temperatures. Contributions, to a lesser extent, from crown contributions cannot be completely ruled out.

It is interesting to note here, by way of an aside, how the application of n.m.r. kinetic techniques has advanced considerably over the few years represented by the publication of the above mentioned papers. For instance, the observation of restricted rotation in t-butyl groups would once have been considered as almost impossible. In a very recent public:

ation[18] the rate of t-butyl rotation in 2-t-butyl 1,3-diheteroatomic rings is considered in the light of the roles of bond angle and bond length, within the rings, in determining the size of the rotational barriers.

A different approach to the problem of conformational processes in rings is exemplified by the work of Roberts and coworkers, in particular their studies of the conformations and conformational equilibria in cyclooctane systems.[19] Conformational processes in systems can be examined by the application of several 'nuclear probes'. Often, the probe used is the hydrogen nucleus which is abundant in organic chemical systems. This nucleus can be attached directly to the carbon skeleton under consideration, or it can be placed in a substituent group on this skeleton. The results derivable from these two environments can differ somewhat, depending on the nature of the substituent. It is also possible to substitute other magnetic nuclei, either directly onto the skeleton or into substituents and employ them as probes of molecular conformation. Roberts, in particular, employs fluorine in this approach. The simplification achieved in the spectra observed can be considerable and is often as convenient as massive deuteration of the parent compound in question. A further advantage deriving from the use of fluorine is the considerably increased chemical shifts encountered compared with hydrogen 'probes'. This simplifies the spectral details to first order and allows us to resolve magnetic environments which in terms of hydrogen would be too similar to result in clearly resolved chemical shifts. Should we wish to examine in detail the conformational processes in a ring system, then by substitution at various positions on the ring, we can follow specifically the processes which each particular nucleus on the ring undergoes. The picture built up from a study of several differently substituted rings should provide definitive comment on the conformational processes observed.

Unfortunately, this approach is subject to limitations. The great:

:est difficulty encountered in this field is the effect of the fluorine substituent on the conformation of the molecule in question. In many cases, particularly cyclooctanes, the ring conformations accessible by the molecule do not differ greatly in energy. It is quite possible for the effects of the dipole moment of the C-F bond to so alter relative stabilities in the ring system that rather different conformations are found to be the most stable, depending on the position of substitution on the ring. The investigation of subtleties of this nature is, though, part of the challenge of this approach. In terms of the parent ring system, however, the use of selective deuteration to achieve the same end is free from such effects but it does normally involve more lengthy chemistry to arrive at a specifically 'hydrogenated' ring.

Until recently, the majority of nuclei, other than hydrogen and fluorine, were too insensitive to provide, readily, spectra for conformational purposes. The advent of commercial fourier transform n.m.r. spectrometers is beginning to make its impact in the field of n.m.r. conformational studies. The use of ^{13}C studies of ring systems has provided a powerful new probe into the conformations accessed by the carbon ring. The information derived from such a ring study differs from that available, for example, from a study of geminal proton signals, and it is by combination of studies from several nuclei that the most definitive results on ring conformational processes are available.

In their studies of 1,1-difluoro and 1,1,4,4-tetrafluorocyclooctane, Roberts and coworkers[19] found that boat-chair conformations were preferred at low temperature. At higher temperatures, pseudorotation within the boat-chair series of compounds became rapid and, at higher temperatures still, equilibrations leading to ring inversion become rapid on the n.m.r. time scale. In other words, the processes deduced by Anet above are again encountered in this ring system. A concurrent study of 1,1,2,2-tetrafluorocyclooctane indicates, however, that fluorine can influence the preferred conformation of this ring system, dep:

ending on the substitution pattern. At low temperature, the twist-boat conformation appears to be preferred, whilst at higher temperatures, pseudorotation among 'boat-boat' (saddle) conformations becomes rapid. At still higher temperatures, ring inversion becomes rapid. Perfluorocyclooctane seems to prefer either twist-boat or boat-boat conformations at low temperature.

This paper is an extremely good example of n.m.r. spectroscopy being applied to the definitive analysis of ring conformations. Roberts has taken great care to develop his arguments on sound lines and his discussion of cyclooctane conformations is particularly illuminating. From reading this paper, the scope and power of n.m.r. methods are clearly demonstrated.

A very recent paper by St.-Jacques and Prud'homme[20] describes investigations of the low temperature conformations of cis- and trans-1,5-diacetoxycyclooctane. Both molecules exist in boat-chair forms at low temperatures with the acetoxy groups quite possibly occupying positions on the ring consistent with those positions calculated[21] to be the most favourable for substituent groups. The spectral changes on raising the temperature require passage through a pseudorotation cycle for the cis isomer and passage through an inversion barrier for the trans compound.

Two useful surveys of the cyclooctane field have been published. In the first Anet[22] reviews the problems and some of the results in the conformational analysis of eight membered carbocycles. Much of this work has been considered elsewhere in this review and will not be mentioned here.

Several X-ray studies of cyclooctane systems have been reported and Dunitz reviewed this field in 1968.[23] Srinivasan and Srikrishnan have recently provided our second useful survey (of X-ray work to date). In this[24] they noted that two distinct types of solid state conformation are met in cyclooctane derivitives, namely the boat-chair, which is the most commonly met, and the crown which represents a third of the solid state conformations so far studied. An interesting comparison between solid state and theoretically predicted geometries of these most stable conformers is included in the summary of Srinivasan and Srikrishnan in which it is found that the theoretical predictions of Bixon and Lifson are the closest to these solid state results.[25] Whether or not this holds true for the solution state is another matter, but it is a satisfactory reflection on theoretical methods that the amount of agreement observed between the two structures - predicted and observed - is as high as it is.

More recent studies on eight membered rings have also considered oxygen heterocycles. In this field both Dale and coworkers[26] and Anet and coworkers[27] have published very similar results. "The primary reason why cyclooctane......prefer(s) the boat-chair to the diamond-lattice type boat-boat conformation is clearly the transannular repulsion that would exist between two pairs of 1,5-hydrogen atoms in the latter."[26] On the possibility that this repulsion might be reduced or eliminated by substituting oxygen for these CH_2 units, several oxygen heterocycles have been studied. Anet's studies[27] at 251 MHz. are the easier results to digest. Results from 1-oxocane and 1,3-dioxocane are nicely rationalised on the basis of boat-chair conformations. In the latter case, two possible boat-chairs exist which cannot be completely interconverted by pseudorotation. The remaining compounds, 1,3,6-trioxocane and 1,3,5,7-tetraoxocane, show rather similar behaviour, though the detailed nature of the spectra acquired suggest there may be differences in their low temperature behaviour. It is possible that here, twisted boat-chairs, twisted chair-chairs and symmetrical crown forms should be invoked to explain the spectral behaviour.

unsaturated cyclooctane derivitives.

Interest in eight-membered carbocycles has not merely been confined to saturated systems and unsaturated systems from cyclooctanones on the one hand to cyclooctatetraenes on the other have been studied by n.m.r. spectroscopy.

The theoretical work of Hendrickson has been extended by Favini and coworkers to calculations on unsaturated ring systems. Both cis[28] and trans[29] cyclooctene have been studied, though the detailed mode of presentation of results employed by Hendrickson is not followed. The calculated minimum energy form for cis-cyclooctene is a flattened structure somewhere between a true boat and a true chair. A further publication from these authors presents results for the three possible cis-cyclooctadienes[30]. For both cis-1,3 and 1,4-cyclooctadiene a boat-chair conformer is calculated to be the most stable. For cis-1,5-cyclooctadiene a twist-boat conformation is calculated to be the most stable.

In 1966, Anet and coworkers[31] published their observations on a number of unsaturated cyclooctane systems. Observation of the low temperature spectrum of 5-t-butylcyclooctanone showed behaviour strongly reminiscent of t-butylcyclooctane and in consequence, they postulated a conformational picture similar to that observed in t-butylcyclooctane. This logic leads to the postulate that 5-t-butylcyclooctanone exists as a mixture of two sets of conformers at low temperatures. Interconversion between members of the same set is rapid but conversion between sets is slow at these temperatures. These results are in agreement with the earliest suggestions of Allinger[*32] for cyclooctanones but contrary to his conclusions expressed in 1961[33] and 1962[8]. These later results are considered by Anet to be unreliable since they depend on the comparison of i.r. spectra in the solid and liquid phases. Conformational purity cannot be established beyond doubt, merely because the i.r. spectra of the solid and the liquid are identical. The possibility of solid solutions often invalidates the logic of this approach.

Cyclooctanone, cyclooctene, and 1,3-cyclooctadiene also show temperature dependent effects. From simple considerations, cyclooctanone should exist in a boat-chair form with the carbonyl group at the position labelled 3 (fig. 5.1). The n.m.r. spectra of variously proton-substituted cycloocatanones-d_{13} are consistent with this view. The barriers to pseudorotation and ring inversion are fairly close in this compound unlike 5-t-butylcyclooctanone where only pseudorotation can be observed at low temperature.[22] Studies on cic-cyclooctene-d_{13} and -d_{12} indicate that a form of boat-chair, perhaps twisted, is the preferred low temperature conformer.[22] The temperature spectra of deuterated 1,3-cyclooctadiene have yet to be reported and the fully protio spectra are too complex to allow detailed conclusions, merely that conformational processes similar to those occuring in the cyclooctanones were being observed.

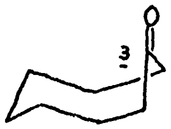


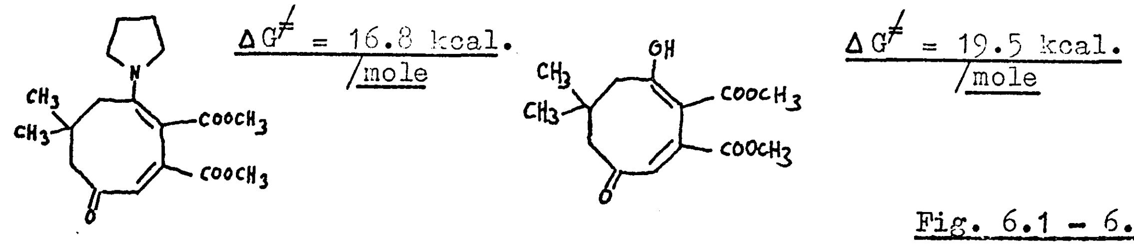
Fig. 5.1.

Interestingly, the n.m.r. spectrum of cis-cis-1,5-cyclooctadiene is temperature independent. It seems unlikely that the inversion barrier for this ring should be so much lower than for the other unsaturated rings met here, and it is more likely that we are observing accidental equivalence of the methylene protons in this compound.

The fluorine labelling technique has been applied to the study of 1-fluorocyclooctene at low temperatures.[34] Weigert and Strobach discerned evidence for both ring inversion and pseudorotation being slow. Anet and Degen[35] have recently published results of their studies of 5-oxocanone. Though not directly pertinent to any of the carbocyclic studies detailed here, this paper illustrates the application of high field n.m.r. studies using two nuclei (^{1}H and ^{13}C) and is extremely interesting in this respect. The information to be derived from the different nuclei is different and so these studies complement each other nicely in establishing the nature of the low temperature conformation of this mole:

cule. Whilst ^1H spectra are sensitive to ring inversion phenomena in this compound, ^{13}C spectra only exhibit temperature dependent effects with radical changes of ring geometry.

Cone and coworkers[36] have studied the ring inversion in the 2,4-cyclooctadienone systems shown in fig. 6.1-2 and have established the ring inversion barriers shown. They argue for a comparably large inversion barrier in the parent cyclooctadienone though the hypothesis is by no means firmly established. A similar barrier is observed in the dibenzocyclooctadienones[37] in which through conjugation is not present. However, increased rigidity will be imparted to the ring by the aromatic rings and consequently no rigorous conclusions can be drawn from comparison of these results (fig. 7.1,2).



$\Delta G^{\neq}$ = 16.8 kcal./mole

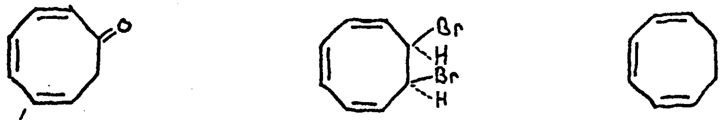
$\Delta G^{\neq}$ = 19.5 kcal./mole

Fig. 6.1 - 6.2.

(a) R = H
(b) R = Me, $E_{act} \simeq$ 17 kcal./mole

Fig. 7.1 - 7.2.

Further increases in the degree of unsaturation of cyclooctane ring systems have been studied by several authors. The inversion barriers observed are considerably less than those immediately above for cyclooctadienone systems. The barriers observed for several compounds are given in fig. 8.1-3. It is significant to note that the inversion barrier measured for 1,3,5-cyclooctatriene is considerably lower than the other two related compounds shown. The lowering of the inversion barrier on going from dienes to trienes can be explained quite satisfactorily by the increased conjugation in any transition state with



$\Delta G^{\neq}$ = 11.9 | 13.0 | 6.2 kcal./mole

Fig. 8.1 - 8.3.

coplanar double bonds. Such a transition state seems likely for the interconversion of stable boat conformers found in these systems. The marked decrease for the parent triene inversion barrier cannot be readily rationalised as yet.

Further unsaturation in the cyclooctane system leads us to cyclooctatetraene, a fascinating molecule in its own right. This molecule exhibits the phenomenon of valence bond isomerism defined by Vogel[41] as "a reorganisation of , or of and , electrons accompanied by changes in interatomic distances and bond angles but without migration of atoms or groups."[*42] It is "an intramolecular arrangement which obeys first order kinetics, is practically uncatalysable, is independent of solvent, and can be influenced only by temperature. It belongs to the class of 'no mechanism' reactions."[43] These fast reversible bond shifts can barely be detected by chemical means, but can be recognised by n.m.r. spectroscopy due to kinetic influences on the spectrum. If we consider cyclooctatetraene, then we can see that the molecule can undergo three different isomerisations as shown in fig. 9. Firstly,

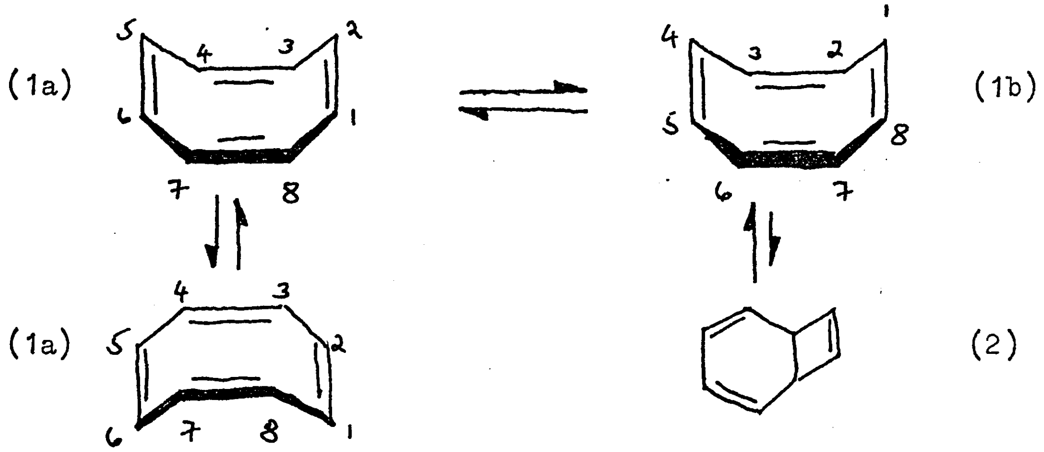


Fig. 9.

there is the ring inversion, (1a to 1a), due to rotation about C–C single bonds. This is of the same category as the conformational changes considered in the rest of this section. There is no reorganisation of bonding electrons, so no valence bond isomerism. Secondly, (1a to 1b) is a reversible bond migration involving all four double bonds. The molecular structure remains unchanged, but, if we number the carbons, or identify a carbon by a unique substituent, then these two structures differ. Thirdly, as far as this reaction type is concerned, there is no real difference between (1a to 1b) and the dynamic equilibrium of cyclooctatetraene with bicyclo(4,2,0)octa-2,4,7-triene (1a,1b and 2). This again is a reversible valence isomerisation.

The fluctuation of bonds in cyclooctatetraene has been recognised using n.m.r. by Anet and coworkers[44,45] and Roberts and coworkers[46] using fluorocyclooctatetraene. The postulated planar transition state for bond isomerisation is, furthermore, a likely transition state for ring inversion. This point has been taken up by Anet[45] using heavily deuterated and substituted cyclooctatetraenes. He went on to distinguish two planar transtion states. In the transition state for bond shift, the bond lengths in the planar ring are all equal, whilst in the transition state for ring inversion, the bond lengths alternate. Such an alternating system would, by the Jahn-Teller theorem applied to orbitally degenerate planar states, be more stable than the system with equal bond lengths.

seven membered rings.

Hendrickson, in 1961, initiated his studies of molecular geometry by theoretical methods by studies which included a consideration of the conformational minimum energy for cycloheptane.[47] In the succeeding papers in this series, he refined his cycloheptane calculations and considered substituted cycloheptanes and the interconversion paths between various conformers.[48,21,5] The most stable conformation of unsubstituted cycloheptane is calculated to be a twist-chair form (fig. 10.1), but the problem of calculating the stabilities of substituted cycloheptanes is far from simple. The increase of the complexity of the problem on going from cyclohexane to cycloheptane is significant, as there are no longer merely two distinct sites for the substituent in the most stable conformation of the unsubstituted ring, as in cyclohexane, but up to fifteen if the entire chair series of conformations is considered. The minimum energy form for methylcycloheptane is a twist-chair form with the methyl equatorial (as we would exspect).[48] Several interesting points arise about this substituted chair form of which the following two should be noted. The axis carbon of the twist-chair has two equivalent substituent positions, unlike any of the other carbons of cycloheptane. The calculated energy of these positions is virtually the same as that of the equitorial positions, so no energy penalty is paid by groups occupying these positions rather than equitorial positions in the twist-chair. This has the important consequence that any 1,1-disubstituted cycloheptane will probably take up the single conformation of a twist-chair with the substituents on the 'axis' carbon.

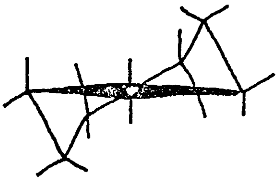


Fig. 10.1.

Secondly, the interactions experienced by axial groups increase considerably on passing from C_5 rings, on the one hand, to (C_8 - C_{12}) rings on the other and results from the very severe transannular interactions which build up, particularly with the medium rings.

The minimum energy conformation of cycloheptene has been calculated to be a chair form, with C_s symmetry,[28] whilst 1,3-cycloheptadiene is calculated to be most stable in a form with C_2 symmetry in which the planar ethene moities do not occupy the same plane. No conformational freedom is possible with 1,4-cycloheptadiene and only a C_s symmetrical form is possible.

As we have seen above, the study of conformational equilibria and equilibration, by n.m.r., in cyclic compounds is considerably facilitated by the use of ^{19}F spectra from gem-difluoro derivitives. Roberts has developed this theme[49] at some length. In his studies of 1,1-difluorocycloheptane[49] Roberts reported no chemical shift difference between these two fluorines down to -180°C. In consequence, inversion is either very fast, even at such low temperatures, or the low temperature favoured conformation possesses fluorines which are equivalent due to molecular symmetry. The former possibility seems unlikely whilst we have seen above that the twist-chair form of cycloheptene has just the required symmetry axis. A further possibility is for a facile pseudorotation to invert the configuration of the cycloheptane ring with similar results. Again this does not seem the most likely explanation. However, if we now consider 1,1,3,3-tetrafluorocycloheptane then, unless an inversion process is facile down to -180°, we would observe at least one pair of non-equivalent fluorines. As no non-equivalence is observed, then we must conclude that pseudorotation (rather than inversion) is a facile process. As Hendrickson calculated an energy difference between the twist-chair and pure chair forms of cycloheptane, which alternate around the pseudorotation cycle, of only 2 kcal./mole,[48] then we can conclude that the fluorines have had little effect in blocking the pseudorotation cycle (presumably size being the dominant factor in any such blocking). To decide between the two possibilities of inversion and pseudorotation, Roberts studied 1,1-difluoro-4,4-dimethylcycloheptane. In this molecule, we would exspect the methyl groups by virtue of their size to occupy the axis positions leaving the fluorines to take up non equivalent axial and equitorial positions which will not be averaged unless inversion or pseudorotation occurs. With gem methyls, pseudorotation should be far less favourable than for cycloheptane itself or the gem-difluoro compounds. In fact 1,1-difluoro-4,4-dimethylcycloheptane exhibits, at -163°C, two resonances for the fluorines which is consistent with the lack of both inversion and pseudorotation processes to average the fluorines at this temperature. The conformational process averaging the fluorines has an activation energy of about 6 kcal./mole at -160° and, since Hendrickson's calculation of the pseudorotation barrier in gem-dimethylcycloheptane yielded a barrier of 9.6 kcal./mole, we can conclude that interchange results from ring inversion in this system, whilst the exceedingly rapid exchange in 1,1,3,3-tetrafluorocycloheptane involves pseudorotation.

In a later publication[50] Roberts and coworkers published a comprehensive report on cycloheptane and cycloheptene derivitives. The results described above were corroborated and further studies indicated some of the preferred low temperature conformations of these compounds. 4,4-difluoro-1,1-dimethylcycloheptane exists predominantly in a twist-chair conformation with the methyl groups on the axis carbon. 1,1-difluoro-4,5-trans-dibromocycloheptane exists predominantly in two different twist-chair conformations with the fluorines in the axis positions. 5,5-difluorocycloheptene, at low temperatures, exists in a single conformation best represented as a chair.

St. Jacques and Vaziri[51] have studied ring inversion in cycloheptene and deduced a barrier to inversion of 5 kcal./mole. Interestingly, this barrier is lower than that observed for 5,5-difluorocycloheptene (7.4 kcal./mole) and much lower than that observed for 4,4,6,6-tetradeuteriobenzocycloheptene (10.9 kcal./mole). The factors affecting the conformational barriers in these rings are clearly complex and, whilst the authors indulge in speculation as to the origin of these differences, no satisfactory explanation in quantitative terms is yet forthcoming.

Studies on benzocycloheptenes are well represented in the literature. St. Jacques and Vaziri[52], using the Karplus relation, established the low temperature conformation of benzocycloheptene as a chair, whilst Grunwald and Price[53] studied 1,1,4,4-tetramethyl-6,7-benzocycloheptene in some detail. They concluded that at low temperatures two conformers are present, a boat and a chair. Quantitative studies were also performed on the position of the conformer equilibrium and the rates of interconversion of the two isomers.

A large number of results on heterocyclic benzocycloheptenes appears in the German literature[*54,*55].

Considerably less work has been done on cycloheptadiene systems.

Crews has published a communication[56] on the nature of the geometry of the preferred conformation in this system in which he refutes the electron diffraction results of Chiang and Bauer[57] who found that the 1,3-diene system was completely coplanar. This is in contrast to the observed structure of cyclohept-1,3,5-triene which has a skewed orientation across the trigonal single bonds. From an analysis of the 300 MHz. proton spectrum of the 1,3-diene Crews favoured a distorted tub model for the ring system. Bridged biphenyl systems which might be considered in the category of cycloheptadienes (dibenzocycloheptadienes) have gained some attention[58,59].

Studies on cycloheptatrienes are well advanced. Part of this interest lies, of course, in the possibility inherent in these compounds for valence tautomerism to yield norcaradiene. Anet has studied ring inversion in cycloheptatriene[60] and has discerned that the molecule is non-planar at -150° where the activation energy for inversion is 6.3 kcal./mole. This non-planarity is consistent with the findings of Conrow and coworkers[61] who found non-planarity in a series of heavily alkylated cycloheptatrienes. Jensen and Smith have published similar evidence for non-planarity[62] and they noted the absence of any evidence for the existence of norcaradiene (fig. 11.1) in equilibrium with cycloheptatriene conformers. Heyd and Cupas[63] studying 7-t-butyl-1-methylcycloheptatriene observed slow inversion of the ring at room temperature. The conformer with an 'axial' t-butyl group is more stable than the conformation with the 'equatorial' t-butyl group. Furthermore, restricted rotation of this t-butyl group is observed in the less stable conformer, the group giving rise to three singlets, one from each methyl of the group. This is the first observation of three distinct methyl signals from the t-butyl group. The factors influencing the stabilities

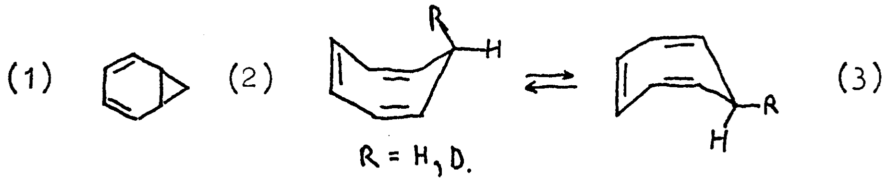


Fig. 11.1 - 11.3.

of these two conformers are discussed in some detail in this paper. The axial-equitorial equilibration of substituent groups on cycloheptatriene has been observed by Bushweller and coworkers for the case of 7-cyanocycloheptatriene[64]. No norcaradiene valence tautomer was observed in this system.

Studies of this system by fluorine labelling have been reported by Roberts and his coworkers[65]. They could not detect an inversion barrier in 7,7-bistrifluoromethylcycloheptatriene even at -185° and ascribed this to a reduced puckering of the ring with 7,7 substitution. This leads to a very low barrier to inversion.

nine membered rings.

Theoretical calculations on nine membered rings were initiated by Hendrickson in 1964[17]. The most stable form of cyclononane has been calculated to be a twist-boat-chair form defined in Hendrickson's papers of 1967[4]. Geometries of unsaturated cyclo-9 compounds have been calculated by Favini and coworkers. The most stable form of cis-cyclononene is a planar symmetrical boat-boat structure[28] whilst the cis,cis-cyclononadienes show an asymmetrical form for the 1,4 isomer and a boat-chair with a plane of symmetry for the 1,5 isomer[66].

N.m.r. studies in nine membered rings have been limited, by and large, by the increased complexity of the system compared with seven and eight membered rings. Dale has examined 1,1,4,4-tetramethylcyclononane and some of its derivitives at low temperature by n.m.r[67,68]. He observes that only the D_3 form of cyclononane - the twist-boat-chair form - can fit the spectral observations and energetic requirements. In the cases of 7-substitution also studied, the argument holds good. The high barriers observed to conformational exchange are probably a reflection of the blocking of pseudorotation cycles by substituents as the inside of the cyclononane ring is crowded with hydrogens. The barriers observed then, conform to true inversions. It is suggested that this high inversion barrier is present in many medium sized rings, but it is not normally measured due to the pseudorotation cycle achieving similar results to an inversion process. There are, however, cases on record (among the cycloheptanes for instance) where this has been demonstrated not to be the case. The above evidence refers to rings which are relatively heavily substituted and it can be argued that the influence of substituents is such that we cannot generalise these results to unsubstituted cyclononane. Further, X-ray diffraction studies present a varying picture for the conformational situation in cyclononane derivitives. Anet and Wagner[69] have published 251 MHz. ^{1}H continuous wave and ^{13}C fourier transform results for cyclononane itself. Both sets of spectra show temperature dependent behaviour and together with results from 1,1-dimethylcyclononane, lend support to the D_3 twist-boat-chair structure for cyclononane.

ten membered rings.

Again, Hendrickson, in 1964, performed theoretical calculations on ten membered rings.[17] The most stable form of cyclodecane has been calculated to be a boat-chair-boat form defined in Hendrickson's papers of 1967.[4] Favini and coworkers[29] have calculated the stability of cis-cyclodecene conformations. The results are not clearly in favour of any one conformer and a series of conformers labelled as boat-chair with a plane of symmetry, chair-chair with a plane of symmetry, chair-chair with an axis of symmetry and chair-boat with an axis of symmetry are all of comparable energy.

N.m.r. studies on non-bridged ten membered rings have not been widely reported. Roberts and Noe[70] have studied ring inversion in 1,1-difluorocyclodecane and the results were interpreted in terms of a boat-chair-boat conformation. The discussion included with this paper is thorough and detailed. X-ray studies on cyclodecane species invariably show a boat-chair-boat (fig. 12.1) conformation and it seems likely that this represents a significant energy minimum for it to turn up as

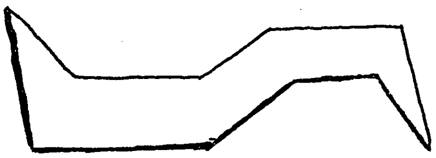


Fig. 12.1.

commonly as this. Roberts further discusses the possible pathways for effecting ring inversion in this system.

A further study published by Roberts and coworkers,[71] in which 3,3-difluoro-trans-cyclodecene was studied at various temperatures, led to the conclusion that at -152°, at least five out of a possible eight conformers were present.

Dale has studied the conformation of cis,cis-cyclodeca-1,6-diene and its derivitives.[72] The remarkable predominance of the cis,cis-1,6-isomer in the thermodynamic equilibrium between fifteen possible cyclodecadienes has been explained on a basis that this is the only isomer for which a strain free conformation can be found. The structure is one in which all bonds are correctly staggered and no transannular repulsions occur. The n.m.r. spectrum of this compound at high temperature and low is only consistent with this stable 'armchair' conformation (fig. 13.1).

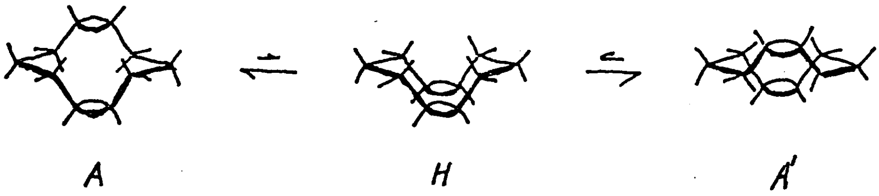
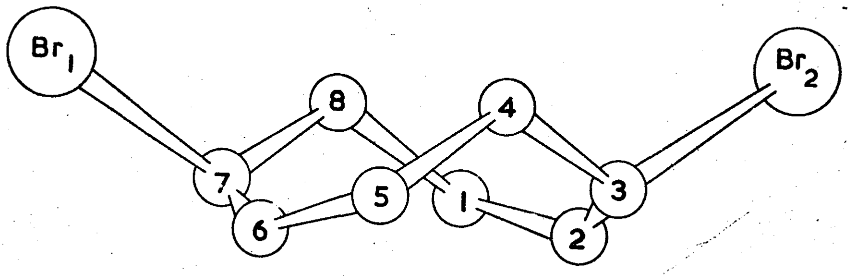
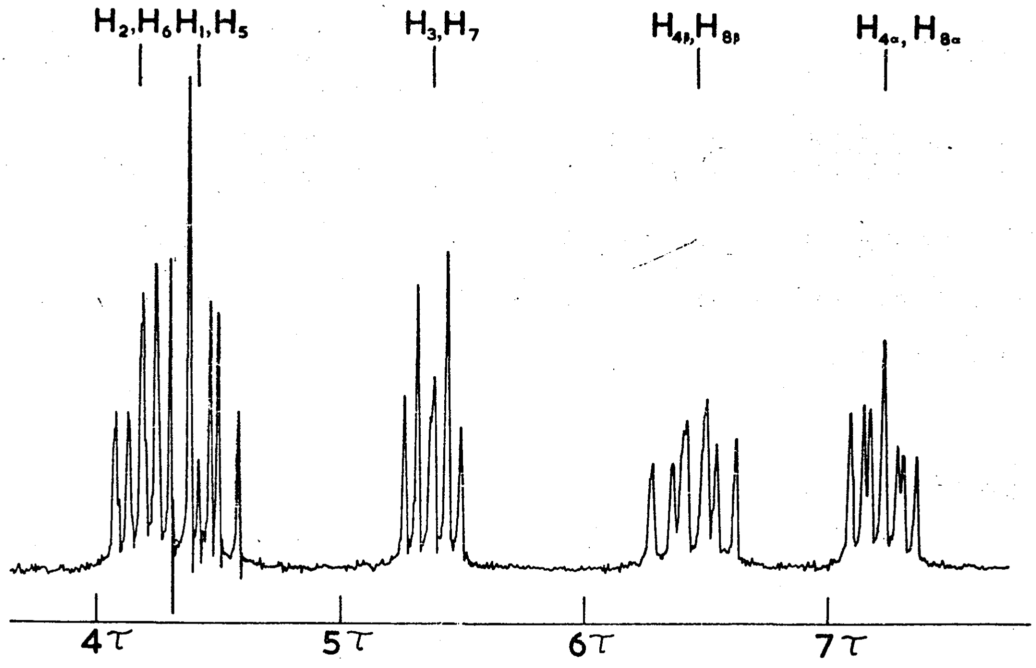


Fig. 13.1.

A and A' are the stable ground state 'armchair' conformations, whilst H is the postulated high energy 'hammock' transition state for interconversion of 'armchairs'.

A Conformational Analysis of a Medium Ring Compound:- syn-3,7-dibromo-cis,cis-cycloocta-1,5-diene.[73]

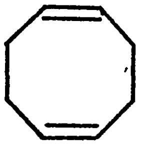




As we have seen above, considerable interest has centred around the conformations of eight membered carbocycles and the common incidence of boat-chair conformations in cyclooctanes is well known.

Related unsaturated systems present a less coherent picture and in particular, it is to be noted that cyclooctadienes have received little attention. Whilst Anet[31] has observed temperature dependent spectra for cycloocta-1,3-diene, though he did not attempt to derive quantitative information from the effects observed, the low temperature spectrum of cycloocta-1,5-diene does not show variations due to the observation of kinetic effects. As it seems unlikely that the barriers to inversion or pseudorotation in cycloocta-1,5-diene are dramatically lower than in the other unsaturated eight membered rings studied, it must be accepted that the low temperature forms of cycloocta-1,5-diene show a chemical shift equivalence of the methylene protons in each pair around the ring. An electron diffraction study of gaseous cycloocta-1,5-diene (IV) (fig. 14.1)[74] and a dipole moment study of 1,6-dichloro-octa-1,5-diene[75] both indicate the predominant presence of boat forms. A twist-boat conformation has been observed in (all-*ax*)-2,6-dimethylcycloocta-3,7-cis,cis-diene-1,5-dicarboxamide by X-ray methods[76]. On the other hand, dibenzocycloocta-1,5-diene has been found to exist as a chair in the crystalline state[77]. A number of crystal analyses of cycloocta-1,5-diene metal complexes have been undertaken[*78] though the results cannot be taken to have any direct bearing on the preferred conformation of uncomplexed diene. In all these cases, a boat form with approximately C_{2v} symmetry is observed.

The possibility arose to study exhaustively by a number of physical methods the conformational situation in both crystal and solution of a dibromocyclooctadiene derivitive (V). This compound, *syn*-3,7-dibromo-*cis,cis*-cycloocta-1,5-diene (fig. 14.2) had already been briefly reported by Cope[79] without an assignment of structure. Techniques of X-ray crystallography, n.m.r. spectroscopy, i.r. spectroscopy and dipole moment methods were applied in establishing the conformation of this ring system in solid and solution.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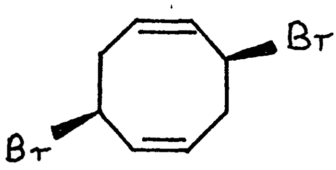
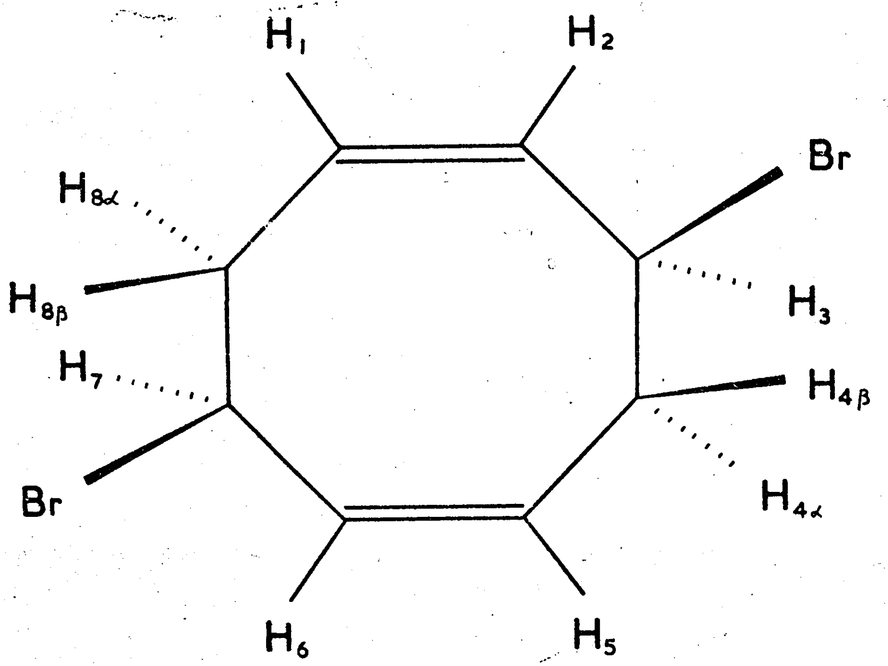
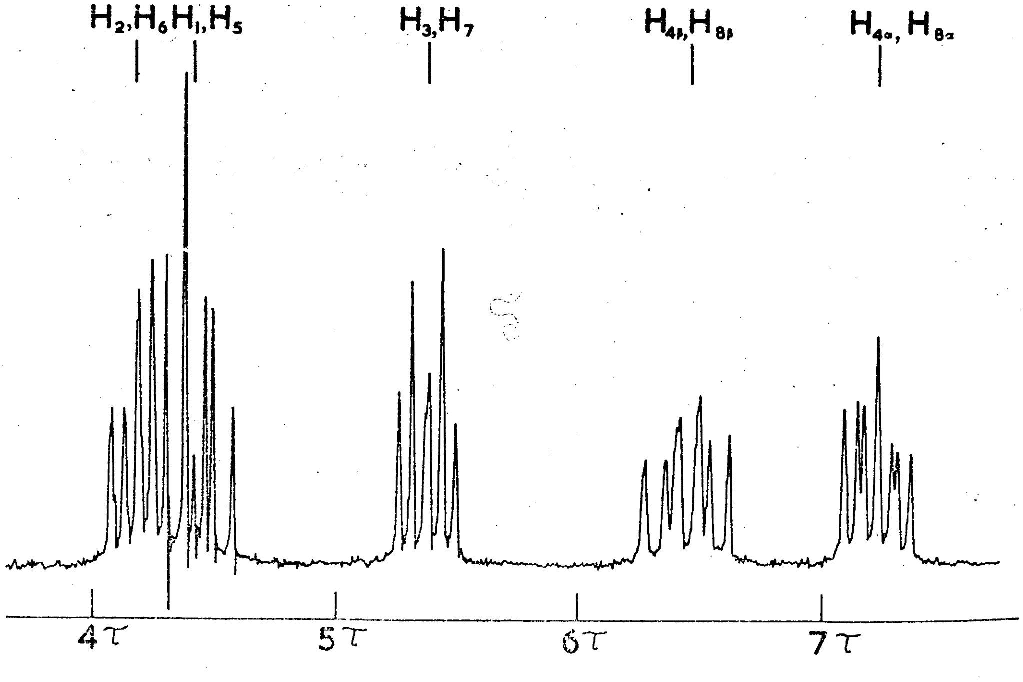


(2)

Fig. 14.1 - 14.2.

The preparation of this compound is described in the 'practical' section of this thesis.


H₁
H₂
Br
H₈α
H₈β
H₃
H₇
H₄β
H₄α
Br
H₆
H₅


H₂,H₆
H₁,H₅
H₃,H₇
H₄β,H₈β
H₄α,H₈α
4τ
5τ
6τ
7τ

<u>molecular structure in the crystal.</u> /*80

The conformation adopted by V in the crystal is that of a twist-boat with a dihedral angle of approximately 74° between the mean molecular planes containing the double bonds. A molecular drawing with the numbering of the atoms used for identification in the X-ray analysis is shown in fig. 15.1.

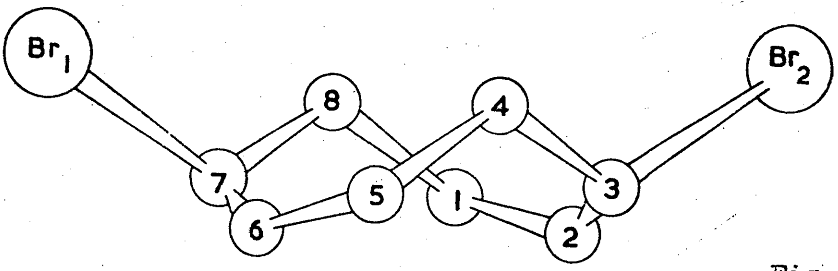


Fig. 15.1.

The dihedral angle between the planes defined by C(2), C(3) and C(4) and C(3), C(4) and C(5) (defined as δ_{2345}) is 65°. (The parameter δ_{2345} proves to be of importance in interrelating solution and crystal conformations.) The C(3)–Br(2) bond is inclined at an angle of 57° to the C_2 symmetry axis of the molecule.

<u>analysis of the proton magnetic resonance spectrum.</u>

The 100 MHz. ^{1}H n.m.r. spectrum of V (in $CDCl_3$) is shown in fig. 16.1 (fold-out). Although the ten protons of the molecule correspond to the general type of spin system AA'BB'CC'DD'EE', the appearance of the spectrum is simplified due to the absence of large transannular couplings J_{15}, J_{26}, J_{37}, $J_{4\alpha 8\alpha}$, $J_{4\beta 8\beta}$(numbering scheme in fig. 17.1 (fold-out)) and the presence of substantial chemical shifts, the spin system approximating to AA'BB'MM'XX'YY'.

Initial values of the chemical shifts and coupling constants were obtained in an essentially first order manner. These parameters were refined using the computer program UEANMR (the non-iterative mode of UEAITR/81) on a UNIVAC 1108 computer equipped with CALCOMP plotter/*82.

At the time of this work, a maximum of seven non-equivalent spins could

Table 1.

^{1}H n.m.r. parameters for syn-3, 7-dibromo-cis, cis-cyclo-octa-1, 5-diene

Solvent	Chemical Shifts	(τ p.p.m.)	Coupling Constants[a] (Hz)			
	ν_1, ν_5	4.41	$J_{1,2}$; $J_{5,6}$	11.2_0		
	ν_2, ν_6	4.17	$J_{2,3}$; $J_{6,7}$	5.6_5		
$CDCl_3$	ν_3, ν_7	5.37	$J_{3,4\alpha}$; $J_{7,8\alpha}$	5.2_8	$J_{3,4\beta}$; $J_{7,8\beta}$	12.2_0
	$\nu_{4\alpha,8\alpha}$	7.21	$J_{4\alpha 5}$; $J_{8\alpha,1}$	8.1_3	$J_{4\beta 5}$; $J_{8\beta,1}$	8.6_0
	$\nu_{4\beta,8\beta}$	6.44	$J_{4\alpha,4\beta}$; $J_{8\alpha,8\beta}$	-13.9_5		
	ν_1, ν_5	4.99				
	ν_2, ν_6	4.52				
C_6D_6	ν_3, ν_7	5.92	b			
	$\nu_{4\alpha}$, $\nu_{8\alpha}$	7.74				
	$\nu_{4\beta}$, $\nu_{8\beta}$	6.72				

Notes.

(a). Line width variations in the experimental spectrum (fig. 16.1) reflect in part non-zero values of allylic and homallylic couplings; while no attempt has been made to accurately evaluate these, approximate estimates are consistent with semiquantitative predictions of couplings for the conformation found. Computer matching of theoretical (with and without long range couplings) with observed spectra justify the value of the main couplings shown in the Table.

(b). The value of couplings found in benzene-d_6 solution are the same as those given above for $CDCl_3$ solution.

be treated at any one time by the computer program so a non-iterative refinement of the spectral parameters was performed for each proton in turn - for example, H_2 was considered in the context of the seven spin group (8α, 8β, 1, 2, 3, 4α, 4β). The final set of consistent chemical shifts and coupling constants is shown in the upper portion of Table 1. The results of a similar analysis for a C_6D_6 solution of V are included in Table 1 and showed markedly altered chemical shifts but unaltered values of coupling constants. Both sets of spectra were finally checked for complete consistency by the use of an overlay of theoretical and experimental spectrum. For this a plotting routine was provided with a suitable value for the lineshape observed in the spectrum and the theoretical spectrum output on the CALCOMP plotter.

An attempt was made to observe any kinetic effects in the spectrum by lowering the temperature of a methylene chloride sample to less than -60^{o}C. No effects were observed. Due to the insolubility of V in any solvent, lower temperatures were not observed. Though the possibility of kinetic effects being observed at lower temperatures yet must be born in mind, it does not seem likely from the general results to be described in the following pages. Furthermore, bromine substitution seems to cause considerable increases in inversion and (particularly) pseudorotation barriers in ring systems/39 and the non-observance of kinetic effects in the spectrum by -60^{o} would imply either a rather low barrier and/or a very small chemical shift difference between sites for a given proton in different conformations. An examination of possible stable conformations for this system in addition to that predicted (and found) to be the most stable/30 indicate that this is extremely unlikely. In consequence it is fair to conclude that the conformation observed in solution at room temperature accounts for the large majority of species present. Further evidence to this effect is presented in the i.r. section, and all the results presented here confirm this view, that only one main conformer accounts nicely for the results observed in solution.

molecular conformation in solution.

From the coupling constant information derived for V in solution it is possible to unambiguously define the predominant conformation present. The experimental vicinal coupling constants of the $-CH_2-CHBr-$ fragment have been interpreted using a Karplus equation in the form[83]

$$J_{vic} = a + b\cos\theta + c\cos2\theta \qquad (1)$$

where the constant b has been taken as −1.0 Hz. after Pachler et al.[*84] It can be shown[86] that a is numerically equal to J_{av}, the average vicinal coupling constant of an ethane-like -CH-CH- fragment, given by

$$J_{av} = 18.0 - 0.8\sum E \qquad (2)$$

where $\sum E$ is the sum of the electronegativities of the atoms bonded directly to the two central C atoms. In order to determine c, a second equation relating the vicinal couling constant to the dihedral angle is required. From a study of substituted ethanes it was found[87] that the trans proton-proton coupling J_{180} (dihedral angle 180°), is a function of the electronegativities of the substituents attached to the -CH-CH- fragment, and can be expressed as follows

$$J_{180} = 28.4 - 1.04\sum E \qquad (3).$$

Substituting the value of J_{180} so derived into the Karplus equation (1) yields c.

Huggins electronegativities have been employed in this work. A problem in the use of electronegativities arises here, in as much as the electronegativity of an olefinic carbon is not defined by Huggins. Hinze and Jaffé[88] have concluded that electronegativity is not a property of atoms in their ground states, "but of atoms in the same condit:

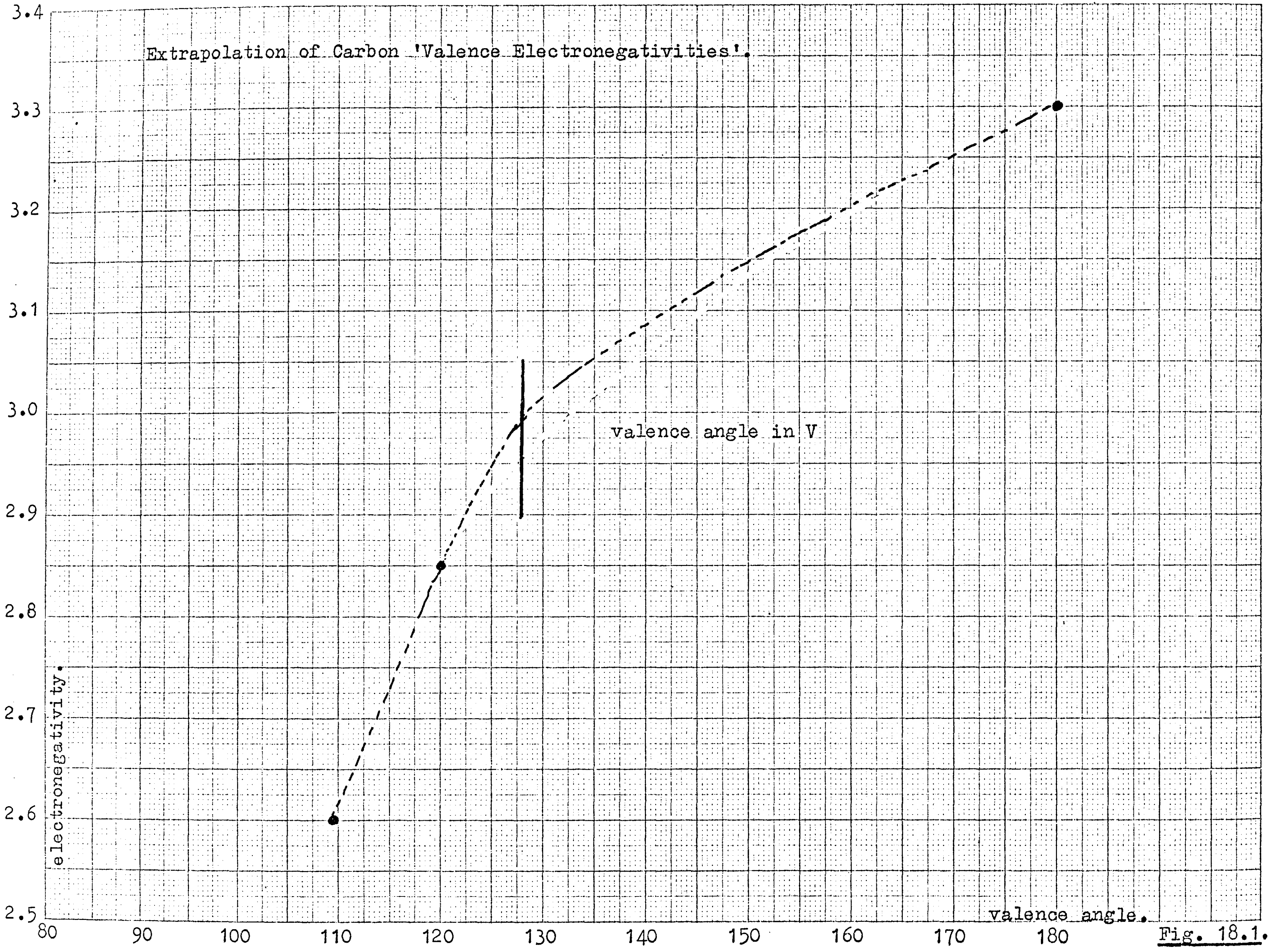
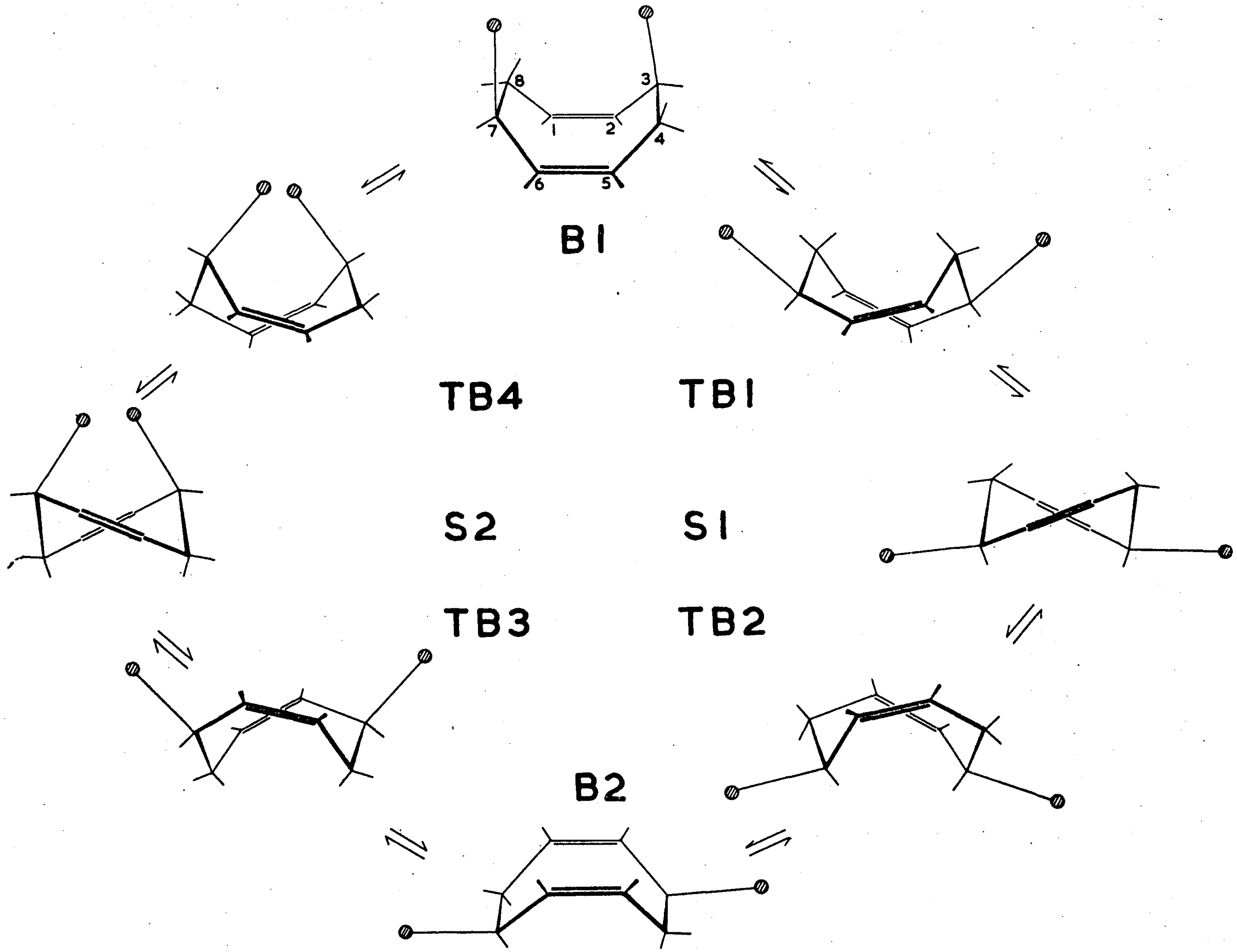

Extrapolation of Carbon 'Valence Electronegativities'.
valence angle in V
electronegativity.
valence angle.
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
80
90
100
110
120
130
140
150
160
170
180

Fig. 18.1.

ions in which they are found in molecules, the valence state". They found that electronegativity could only be defined meaningfully for bonding orbitals and adopted the term 'orbital electronegativity' for the values they obtained. We have accepted this approach here and have used an 'adjusted Huggins electronegativity' for the ring framework orbitals of the olefinic carbons. A reasonable value for the Huggins electronegativity of an olefinic carbon is 2.85 whilst values of 2.60 and 3.3 are accepted for sp_3 and sp hybridised carbons respectively. Given the opened ring angles C(8)-C(1)-C(2) and C(1)-C(2)-C(3) found in the crystal structure of this compound, it is reasonable to employ an extrapolated value (for extrapolation see fig. 18.1 (interleaved)), of 3.0. Correspondingly opened angles are also found in cycloocta-1,5-diene vapour[74].

Applying the arithmetic of the previous page (equations (1),(2), (3)), we calculate values for the constants a and c of 5.57 and 5.64 Hz. respectively. For the purposes of establishing the conformation of this ring system, tables of dihedral angle versus 'Karplus' coupling constant were computer calculated on a basis of the above equations. This facilitated variation of ring angles to achieve a best fit to the observed spectrum since there was no need to laboriously recalculate coupling constants every time the ring conformation was disturbed.

The trans-coupling constant $J_{3,4\beta}$ proves to be a key coupling in defining the conformational situation in solution. Its value of 12.2 Hz. (in both $CDCl_3$ and C_6D_6) implies by equation (1) a 3,4 -dihedral angle of 180°. Owing to the dependence of vicinal couplings on factors other than electronegativity[85,89] (for example, orientation of substituents, and changes in H-C-C angles) equation (1) is not expected to be a precise relationship and an uncertainty of ±10° maximum would be appropriate for this angle. This 12.2 Hz. coupling immediately precludes the possibility that the conformational situation corresponds to rapidly interconverting chair conformations for, as can be seen from mole:


B1
8
3
7
1
2
4
6
5
TB4
TB1
S2
S1
TB3
TB2
B2

Dihedral Angle Interrelation Table for Pseudorotation of the Boat Forms of (II) (for one enantiomer of Symmetry C_2 throughout).

Description of Conformation[a]

Dihedral Angle Type for values (in degrees) given in row of Table	B1			TB1			S1			TB2			B2			TB3			S2			TB4			B1
δ_{2345}[b]	0	+20	+40	+60	+80	+100	+120[c]	+100	+80	+60	+40	+20	0	-20	-40	-60	-80	-100	-120	-100	-80	-60	-40	-20	0
H2, H3	+15	0	-20	-40	-58	-75	-115	-162	-174	-170	-165	-156	-135	-120	-100	-80	-62	-45	-5	+42	+54	+50	+45	+36	+15
	(+12	0	-21	-35	-60	-95	-106	-120	-142	-150	-145	-138	-128	-116	-95	-81	-56	-21	-10	+4	+26	+34	+29	+22	+12)
H2, Br	+135	+120	+100	+80	+62	+45	+5	-42	-54	-50	-45	-36	-15	0	+20	+40	+58	+75	+115	+162	+174	+170	+165	+156	+135
	(+128	+116	+95	+81	+56	+21	+10	-4	-26	-34	-29	-22	-12	0	+21	+35	+60	+95	+106	+120	+142	+150	+145	+138	+128)
H3, H4α	0	+20	+40	+60	+80	+100	+120	+100	+80	+60	+40	+20	0	-20	-40	-60	-80	-100	-120	-100	-80	-60	-40	-20	0
	(0	+20	+40	+60	+80	+100	+105	+100	+80	+60	+40	+20	0	-20	-40	-60	-80	-100	-105	-100	-80	-60	-40	-20	0
H3, H4β	+120	+140	+160	±180	-160	-140	-120	-140	-160	∓180	+160	+140	+120	+100	+80	+60	+40	+20	0	+20	+40	+60	+80	+100	+120
	(+116	+136	+156	+176	-164	-144	-139	-144	-164	+176	+156	+136	+116	+96	+76	+56	+36	+16	+11	+16	+36	+56	+76	+96	+116
H4α, H5	-15	-36	-45	-50	-54	-42	+5	+45	+62	+80	+100	+120	+135	+156	+165	+170	+174	+162	+115	+75	+58	+40	+20	0	-15
	(-12	-22	-29	-34	-26	-4	+10	+21	+56	+81	+95	+116	+128	+138	+145	+150	+142	+120	+106	+95	+60	+35	+21	0	-12)
H4β, H5	-135	-156	-165	-170	-174	-162	-115	-75	-58	-40	-20	0	+15	+36	+45	+50	+54	+42	-5	-40	-62	-80	-100	-120	-135
	(-128	-138	-145	-150	-142	-120	-106	-95	-60	-35	-21	0	+12	+22	+29	+34	+26	+4	-10	-21	-56	-81	-95	-116	-128)

Notes.

(a). For the values in rows without parenthesis in the main body of the Table, B1 should be read as B1(u), TB1 as TB1(u) etc., the letter 'u' indicating undistorted angles; for the parenthesised values (which refer to the distorted angles described in the text) B1 should be read as B1(d) etc.

(b). The ring dihedral angle (illustrative values given) is the angle between the planes defined by C(2), C(3) and C(4) and C(3), C(4) and C(5). see Fig. 15.1 for numbering scheme.

(c). For S1(d) and S2(d) this value should be replaced by an appropriately signed angle with magnitude 105°. The probable error in angle measurement of models is *ca.* ±5°, though the estimation of angles from distorted Dreiding models may be subject to a somewhat greater uncertainty. Note the inherent symmetry aids in construction of the Table. e.g. a row for H2, Br when read in reverse order with all the signs changed gives the corresponding row for H4β, H5.

:cular models, the 180° dihedral angle is never realised in the chair. form. Indeed, rapid interconversion required to explain the observed spectrum (fig. 16.1) would imply a weighted mean from these chair forms for $J_{3,4\beta}$ of about 6.7 Hz. in harsh disagreement with the observed fact.

The conformational situation for the flexible non-chair forms of V is illustrated for pseudorotation of one enantiomer in fig. 19.1 (in: :terleaved). There are two distinct boat forms B1 and B2, two distinct skew forms S1 and S2, and an unlimited number of twist-boat forms of which four are shown, TB1, TB2, TB3 and TB4, these representatives being arbitrarily defined with the magnitude of the ring dihedral angle δ_{2345} equal to 60°. All the conformational possibilities in the pseudorotation cycle may be considered by reference to Table 2. The top of this table gives values of the ring dihedral angle δ_{2345}, and the main body of the table gives the corresponding values of the H-C-C-H dihedral angles (for example, 3,4β is denoted H3, H4β). Thus, for any value of the ring dihedral angle, a vertical correlation exists so that the corresponding H-C-C-H dihedral angles can be read off in the approp: :riate column. The signs have been retained with the dihedral angles[*90] to give a better indication of ring geometry during the pseudorotation cycle. The values currently appropriate are given outwith parentheses and are measured to ±5° for the enantiomer of fig. 19.1, using the sign convention employed by Dunitz[23].

One observes from table 2 that the indicated 180° dihedral angle H3, H4β occurs only twice in the pseudorotation cycle, once at TB1(u) and then again at TB2(u)[*91] Both TB1(u) and TB2(u) have the same value of ring dihedral angle, namely +60°. We may discriminate between these two by considering the coupling constant observed between protons H(2) and H(3). The dihedral angles observed here are -40° for TB1(u) and -170° for TB2(u). It is accepted that vicinal coupling of the type =CH-CH- is closely related in its dependence on dihedral angle to that in fully saturated systems[89] Employing equation (1) with values of <u>a</u>,

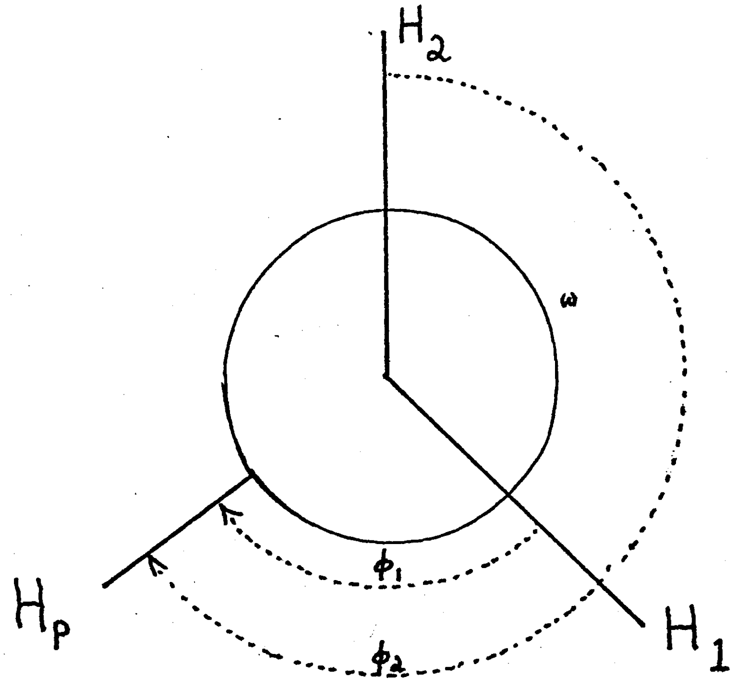


Fig. 20.1.

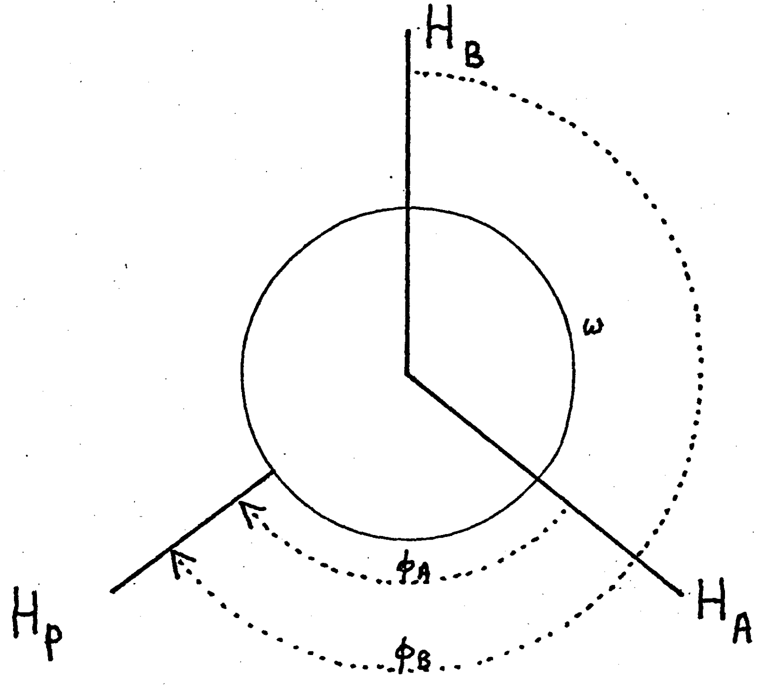


Fig. 20.2.

b and c of 5.88, -1.0 and 5.76 respectively calculated as shown above, we would predict a value of $J_{2,3}$ of 6.1 Hz. for TB1(u) and 12.3 Hz. for TB2(u). The observed value of 5.65 Hz. for $J_{2,3}$ is therefore in good agreement with the existence of TB1(u) and at variance with the presence of TB2(u) as a major contributor to the observed conformational spectrum as this would lead to a high predicted average coupling.

The original form of the Karplus equation is shown in equations (4) and these have been used by Slessor and Tracey[92] as the basis of a method they term "Dihedral Angle Estimation by the Ratio Method", in short DAERM.

$$J_1 = k_1.\cos^2\theta_1 - c \qquad 0 \leq \theta_1 \leq 90^\circ$$

$$J_2 = k_2.\cos^2\theta_2 - c \qquad 90 \leq \theta_2 \leq 180^\circ$$

where k_1 and k_2 are the Karplus constants,

and c is a constant. (4)

Their presentation can be generalised as follows. If we consider the Newman projection of the coupling path in an ethane-like fragment as shown in fig. 20.1 (interleaved) then we can show that the following holds.

$$\frac{J_1 + c}{J_2 + c} = \frac{k_1 \cos^2\theta_1}{k_2 \cos^2\theta_2} \qquad (5)$$

k_1 applies to angles in the range 270° - 90°.

k_2 applies to angles in the range 90° - 270°.

now if we define ω as $({}_2 - {}_1)$, thus is the tetrahedral angle, then eventually we can show that

$$\tan\theta_1 = \cot\omega \pm \frac{\dfrac{k_1}{k_2} \cdot \dfrac{J_2 + c}{J_1 + c}}{\sin\omega} \qquad (6)$$

From the theoretical parameters calculated by Karplus, the ratio k_1/k_2 is very nearly constant and equal to 0.9. The theoretical value of c is 0.28. To completely generalise equation (6), we may rewrite it as follows.

$$\tan \theta_A = \cot\omega \pm \frac{\dfrac{k_A}{k_B}\;\dfrac{J_B + c}{J_A + c}}{\sin\omega} \qquad (7)$$

So, depending on the magnitude of θ_A and θ_B the values of k_A and k_B will vary, where θ_A and θ_B are defined in fig. 20.2.

There are a total of twelve possible solutions to equation (7). The majority of these are redundant or of no interest in a given situation. We must select the appropriate solutions for the particular situation of interest. In many instances we achieve only two solutions. It is then possible to distinguish between these by two suitable processes. We may eliminate one possibility from the evidence obtained from another vicinal coupling in the same ethane-like fragment, or we may substitute the values found for the dihedral angles back into the equation and calculate values for the Karplus constants k_A and k_B. Only a certain range of constants is applicable and dihedral angle solutions giving rise to unreasonable k values can be rejected. This approach is clearly demonstrated by the publications[92,93] in which the DAERM method is employed.

In the current study of V, this method yields results as follows. With ω equal to 120°, dihedral angles of -29° and -149° are evaluated for the dihedral angles $H_{4\alpha,5}$ and $H_{4\beta,5}$ of TB1(u), these being in moderate agreement with the observed values (deduced above) of -50° and -170°. The value of the coupling $J_{3,4\alpha}$, 5.28 Hz., is greater than that predicted for TB1(u) where a dihedral angle of 60° yields a predicted coupling of 2.2 Hz. This discrepancy is, however, almost certainly a reflection of the non-Karplus dependence of coupling on substituent

Table 3.

Bond Lengths and E.S.D.S.

Br(2)-C(3)	1.963 ± 23 Å
C(1)-C(2)	1.371 ± 30 Å
C(2)-C(3)	1.491 ± 29 Å
C(3)-C(4)	1.507 ± 30 Å
C(4)-C(5)	1.467 ± 35 Å

Interbond Angles and E.S.D.S.

Br(2)-C(3)-C(2)	106.4 ± 13°
Br(2)-C(3)-C(4)	110.9 ± 17°
C(1)-C(2)-C(3)	128.3 ± 21°
C(2)-C(3)-C(4)	118.9 ± 17°
C(3)-C(4)-C(5)	113.3 ± 21°
C(4)-C(5)-C(6)	130.2 ± 20°

Intermolecular Contacts below 4 Å

Br....Br	iv	3.72 Å	Br....C(2)	v	3.98 Å
Br....C(1)	ii	3.92 Å	Br....C(1)	i	4.00 Å
Br....C(1)	iii	3.95 Å			

orientation. Directly analogous behaviour has been observed in other systems[94].

Whilst the above evidence is unequivocably in favour of TB1(u) as the preferred conformation, inspection of undistorted Dreiding models indicates an unacceptably short C(4)....C(8) transannular contact of about 2.3Å for this conformation. This compares with minimum transannular C....C distances in cyclodecane systems listed by Dunitz[23] which are all, to a greater or lesser extent, over 3Å.

There is little doubt that the solution to this apparent contradiction lies in the markedly opened ring angles which are commonly found in medium-sized carbocycles. Such opened ring angles are confirmed for the solid state structure of this compound. Table 3 provides the necessary structural data deduced in the X-ray analysis. In order to consider forms which are almost certainly more realistic in terms of ring angles, we have employed Dreiding models with ring angles at olefinic carbon of 128° and the remaining C-C-C angles at 117° (the mean angles found[74] for IV in the vapour phase): the H-C-H and H-C-Br angles were kept at 109°28', with the bisectors of these angles also bisecting the appropriate ring angle.

Dihedral angles for this distorted model as a function of δ_{2345} are given in parenthesised rows in Table 2. Again a dihedral angle of 180° for H3, H4β occurs only twice in the pseudorotation cycle, once close to TB1(d) and again close to TB2(d)[*91]. This occurs at forms both having the common value of δ_{2345} of +65°. For the position close to TB1(d) the respective magnitudes of the dihedral angles H2, H3; H3, H4α; H3, H4β; H4α, H5; H4β, H5 are 38°, 64°, 180°, 33°, 149° and the corresponding values for the form close to TB2(d) are 149°, 64°, 180°, 78°, 38°. Considering the coupling $J_{2,3}$ which is found to be 5.65 Hz. experimentally, the form with a value of $_{2345}$ of +65° close to TB1(d) which has a predicted value of 6.5 Hz. is indicated, and not the alternative form near TB2(d) which has a predicted coupling of 9.4 Hz. For the form near TB1(d) the method of Slessor and Tracey[92] (DAERM) with $\omega = 116^\circ$ gives calculated dihedral angles H4α, H5 and H4β, H5 of 31° and 147° as the only relevant solution in satisfactory agreement with the measured angles for this form. The magnitude of the ring dihedral angle for the form close to TB1(d) found above is 65° and the C-Br bonds make an angle of about 55° with the C_2 symmetry axis, common to all forms in the pseudorotation cycle. In this form, the transannular C(4)....C(8) separation now takes the value of about 3.0Å corresponding to an enormous reduction in transannular strain energy over the undistorted form TB1(u). This value of 3.0Å is consistent with the transannular distances in cyclodecane systems reviewed by Dunitz[23] and mentioned earlier.

However, the possibility that the spectral observations arise from rapidly interconverting distorted chair conformations must be considered, despite the quality of the results derived above. Examination of 'opened angle' chair forms leads to a predicted $J_{3,4\beta}$ coupling of 9.9 Hz., again in rather serious disagreement with the observed value of 12.2 Hz. That chair forms might contribute to the observed spectral parameters cannot be entirely eliminated on these grounds but the overall quality of the results obtained would be degraded by allowing more than an insignificant amount of chair forms to contribute to the overall conformational picture.

If we compare the deductions above concerning the solution conformation with the conformation in the solid in which δ_{2345} is 65° and the C-Br bonds make an angle of 57° with the symmetry axis, then there is little doubt that a common conformation exists in solid state and in solution. Whilst major amounts of other conformations in solution would be expected to cause a noticeable disagreement between at least one weighted coupling and the observed value, minor populations of other conformations cannot be excluded on this basis owing to the limited accuracy of relations of the Karplus type. In fact, evidence to be presented shortly, does suggest the existence of other conformations to a minor extent in solution. It should further be mentioned that the twist-boat conformation found as the major form above is inherently non-rigid (being subject to pseudorotation motions) and that the observed coupling constants found in solution would also be compatible with a limited degree of torsional oscillation about $\delta_{2345} = +65^{\circ}$ on the pseudorotation cycle.

dipole moment measurement.

In order to check the identity of the conformation in solution and crystal phases the molecular dipole moment expected for the crystal conformation has been calculated at 2.2 D, using a value of 2.0 D for the partial moment along the C-Br bond.[95] An experimental dipole moment in benzene solution (neglecting atomic polarisation) of 2.4 D is consistent with the view that the predominant conformation in solution corresponds to that found in the crystal.

comparison of crystal and solution infrared spectra.

A general comparison of crystal (KBr disc) and solution (CS_2) infrared spectra in the range 1200 $cm.^{-1}$ to 550 $cm.^{-1}$ was made using a Perkin Elmer 225 Grating Infrared Spectrophotometer with the following results. Infrared spectrum of V, $\nu_{max.}$ in $cm.^{-1}$ (CS_2): 1163 (m); 1148 (s); 1113 (w); 1025 (w); 980 (w); 965 (w); 935 (w); 925 (w); 910 (w); 838 (m); 785 (s); 749 (s); 720 (s); 714 (m); 708 (sh); 575 (m). Infrared spectrum of V, $\nu_{max.}$ in $cm.^{-1}$ (KBr disc): 1165 (m); 1150 (s); 1110 (m); 1040 (w); 1030 (w); 984 (w); 972 (w); 921 (w); 908 (w); 838 (s); 780 (s); 750 (s); 718 (m); 705 (s); 575 (m). This shows an extremely close correspondence. However, the most interesting feature of the infrared spectrum derives from the short transannular contact of 3.04 Å (see figs. 17.1 and 21.1 (interleaved)) between the symmetry related carbons of the methylene groups - C(4) and C(8). This value compares with that, 3.06 Å, observed in 1-p-bromobenzenesulphonyloxymethyl-5-

methylbicyclo(3,3,1)nonan-9-ol and similar distances in other carbocyclic bicyclo(3,3,1)nonane derivitives.[96,97] In all these compounds, abnormal methylene scissoring bands near 1490 cm.$^{-1}$ are observed and are credited to the transannular interaction of methylene protons in each of these compounds. Several authors[*98] concur in this assignment of the abnormality to hydrogen-hydrogen non-bonded repulsions across the rings in question. Interestingly, Eglinton and coworkers[97] observed these abnormal bands in both solid state and solution and thereby deduced molecular conformation as an extrapolation of the solid state conformation determined by X-ray studies. In the light of this we might expect a similar band for V whose methylene groups are also forced into close proximity across the ring. Such an absorption is in fact observed at 1487 cm.$^{-1}$ (m), $\Delta\nu_{\frac{1}{2}}^{a}$ about 4 cm.$^{-1}$ in the solid (KBr disc). A similar band is observed in solution at 1488 cm.$^{-1}$ (m), $\Delta\nu_{\frac{1}{2}}^{a}$ about 5 cm.$^{-1}$ (in CCl_4) and hence we are safe in concluding that the main conformer in solution is the same as that in the crystal. It should be mentioned though, that in the region 1400 to 1500 cm.$^{-1}$, on passing from the solid state to solution, two new bands appear at 1428 and 1473 cm.$^{-1}$. These bands are both weak, each having a value of apparent extinction coeficient no greater than a tenth of the 'abnormal' band. This would suggest that relatively minor amounts of other conformations could coexist with the main form in solution.

consistency of the n.m.r. data for V.

Whilst the major contribution to establishing the conformation of V in solution was derived from a study of the n.m.r. vicinal coupling constants observed from the spectrum, it is useful to cross check the results now achieved by a consideration of other coupling constants in the system. Firstly though, we can remark upon the value of that vicinal constant which was not treated by means of the Karplus equations above.

Whilst Cooper and Manaat[99] have suggested that it is possible to obtain accurate estimates of bond angles about vinyl systems by use of n.m.r. coupling constants, the value observed in the current system can only be used in a confirmatory sense. The cis-olefinic coupling constant of 11.2 Hz. is in keeping[*100] with a -C=C-C- angle in excess of 125°. The crystal value observed for the angle C(1)-C(2)-C(3) is 128.3°.

Furthermore, it is possible to consider the line broadening in the n.m.r. spectrum produced by unresolved long range couplings. Consideration of the spectrum of V reveals the following. The signals arising from protons 1 and 5 are the sharpest lines in the spectrum and hence must experience little long range coupling. Examination of Dreiding models (with expanded ring angles) indicates that (a) there are no planar 'W' paths for long range couplings over four bonds[*101a] to protons 7 and 3 respectively, (b) the 'allylic' paths to protons 3 and 7 respectively are associated with an angle ϕ[*101b] of about 35° consistent with a very small or zero coupling, and that (c) there are no other appropriate coupling paths. Thus the proposed conformation satisfactorily rationalises the appearance of the signals from protons 1 and 5. The signals from protons 2 and 6 are considerably broader than those above and examination of the model reveals (a) that an almost planar 'W' path to protons 4α and 8α respectively is available[*101a] and (b) at the same time a near planar 'W', which is an allylic path[*101b], is available to 8α and 4α respectively. No other significant coupling paths are available, but these two are sufficient to explain the almost triplet (or doublet of doublets) character of the 2 and 6 resonances. Signals from 3 and 7 show a moderate degree of broadening which can only arise (by examination of the model) from 'homoallylic' paths[*101c] 8α and 8β and 4α and 4β respectively. The 4α and 8α signals are similarly broadening due to the long range couplings detailed above, that is couplings from 4α to 2 and 6 and similarly from 8α to 6 and 2. The signals of the 4β and 8β protons are broader still. Homoallylic coupling to 7 and 3 is present but the full width only seems rationalisable on the basis of an enhanced relaxation of these nuclei by each other, due to their close proximity in the preferred conformational form.

stability of the main conformer.

While rationalisation of the predominance of the main conformer found in solution strictly requires the application of strain calculations, we may remark that such calculations on IV[30] favour a twist-boat over a boat or chair form. Examination of the infrared spectrum of IV (cis,cis-cycloocta-1,5-diene) shows a similar abnormal methylene scissoring band at 1487 cm.$^{-1}$ which can be taken as confirming the presence of a similar structure as in V. The electron diffraction results for the gaseous conformation of IV[74] shows a boat form but it seems likely, from the i.r. results on the neat liquid, that some twist is present in the ring causing the abnormal methylene scissoring by transannular hydrogen contacts.

The particular twist-boat conformation adopted by V suffers neither Johnson allylic $A^{(1,2)}$ strain[102] (arising from the eclipsing or partial eclipsing of C–Br bonds with the adjacent olefinic C–H bonds (see table 2)) of TB2(d) and TB3(d) or of B2(d), nor the severe transannular Br....Br strain of TB4(d) and S2(d), nor finally, the H....Br repulsions of B1(d) and the chair forms.

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fig. 2.1 - 2.4.	from ref. 19.
fig. 4.1.	after ref. 15.
fig. 6.1.	from ref. 36.
fig. 7.1 - 7.2.	from ref. 37.
fig. 8.1 - 8.3.	from ref. 40.
fig. 9.1.	after ref. 42.
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fig. 11.1 - 11.3.	from ref. 62.
fig. 13.1.	from ref. 72.

Conformational Analysis in Conjugated Systems.

Prelude: n.m.r. observation of rotational barriers.

N.m.r. spectroscopy provides the chemist with a means of studying intramolecular movements with activation energies from about 5 to about 25 kcal./mole. Below 5 kcal./mole, processes are too fast on the n.m.r. time scale to allow discrimination of the individual conformations contributing to the observed physical properties of the system; the average spectrum observed is generally insensitive to the molecular motions. Above 25 kcal./mole, species, differing by some intramolecular motion, are sufficiently long lived to provide completely independent spectra, again insensitive to the molecular motion in question. Though information of value can be derived from these spectra, thermodynamic considerations relating to the intramolecular motion cannot be probed and in many instances, these parameters are of primary interest.

We have already considered cyclic systems where activation barriers in this range are often met, and we have remarked upon the possible sources of the barriers in these molecules. Non-cyclic molecules also display barriers to internal motions, particularly significant being barriers of a rotational kind where one part of a molecule can be visualised as rotating about a bond or bond system linking it to the rest of the molecule. The simplest of all molecules to exhibit any barrier to internal motion is ethane where a 3 kcal./mole activation barrier to rotation about the C-C bond is estimated.[*1] The source of this barrier in ethane is still very poorly understood.[*2] The various factors which are capable of raising the rotation barrier in molecules are far better understood, at least in a qualitative sense. Before we can examine rotational barriers by n.m.r. spectroscopy, we require some additional hindrance to rotation from one or more of these sources.

Two major factors are observed to cause notable increases in the barriers to internal rotation of the constituent parts of molecules relative to one another. Firstly, the substitution of bulky groups at the ends of the bond system about which rotation occurs can cause steric obstruction of the rotation with a consequent increase in the measured activation barrier. Perhaps one of the most interesting fields of study, where such steric barriers are observed by n.m.r., is that concerning the hindered rotation of t-butyl substituents in various systems. Bushweller and coworkers have measured the thermodynamic parameters for t-butyl rotation in t-butyldimethylamine and found a barrier of 6.0 ± 0.1 kcal./mole at $-153^{\circ}C$ ($G^{\neq}$).[3] A slightly higher barrier of 6.4 ± 0.2 kcal./mole at $-148.2^{\circ}C$. was measured for t-butyl rotation in t-butyldichlorophosphine by the same school.[4] Robert and Roberts[5] had earlier measured an almost identical barrier for the same compound. The ability to observe such rotational effects is an indication of the power of n.m.r. methods to probe subtle molecular activity. Secondly, increase in the bond order about which rotation occurs imparts rigidity to the system, again resulting in an increase in rotational activation energy. It is with this latter group of systems that we have been primarily interested in the last few years.

However, we do not, by merely increasing the barrier to rotation about bonds so that they lie somewhere within the region specified above, guaruntee that the rotation will be susceptible to observation by n.m.r. spectroscopy. Means of probing the conformational condition of the molecules will be required. Two major requirements will need to be met.

Initially, the different rotamers arising from the rotational movement in question must be distinguishable by n.m.r. spectroscopy. For this to occur we require at least that the nuclei being observed resonate at different frequencies for the different rotamers under study. Such differential chemical shifts are often induced by other (magnetically anisotropic) substituents included in the molecule, often for this specific purpose. When a given nucleus resonates at different chemical shifts in different rotamers, then we can observe temperature dependent spectra, the basis for establishing thermodynamic parameters for the rotation. The nature of the individual rotamers may also be established from the observation of not only the chemical shifts induced by a given substituent, but also of the variation of coupling constants between nuclei which, as we have seen, depend on the angular relationship of the nuclei to each other. Whilst the previously reported study of the conformation of a medium ring system relied mainly upon variations in spin-spin coupling constants to define conformation, the present studies on conjugated systems (to be reported below) rely mainly upon differences in chemical shifts induced by magnetically anisotropic groups, often integral parts of the conjugated system under consideration.

Strictly speaking, any bond system is likely to be magnetically anistropic but generally, the overall symmetry of the molecule, whether time averaged or not, will eliminate any differential shielding effects from this source. However, in cases of restricted rotation, time averaged symmetry is not necessarily observed and in consequence the molecular asymmetry may be reflected in a differential shielding of given nuclei which, under averaging conditions would be at least isochronous.

Magnetic anistropy is particularly pronounced in systems with π electrons, of which the aromatic ring is a classic example. Though the exact nature of the areas of shielding and deshielding effect to be expected from various possible π-systems is in dispute[6], the existence of these effects is extremely fortuitous for many n.m.r. studies. In this way, geometrical asymmetry is translated into an observable shift asymmetry in the n.m.r. spectrum.

The calculation of thermodynamic parameters from n.m.r. spectra requires an accurate knowledge of the appropriate spectral parameters of the system. In calculating activation thermodynamics, we will require precise measurements of two additional parameters to those normally considered necessary to characterise the n.m.r. spectrum. These are the rates of exchange of the rotamers in the system between the various conformations populated at the particular temperature of measurement, and an accurate measure of this particular temperature. The need to derive rate parameters for a series of different temperatures also imposes a requirement for accurate temperature control, in the n.m.r. sample, at temperatures in the range -180°C to +200°C or higher. The particular difficulties this requirement creates are discussed fully later in this thesis. The practical derivation of thermodynamic data is also dealt with later.

Conjugated Systems.

The concept of 'resonance' is by now so well established in the structural theory of organic chemistry that it needs no explanation here. Any two π-bond systems, when linked together by a single bond as in the structure of N,N-dimethylformamide (fig. 1), cannot be precisely represented as non-interacting, as the valence bond formula I would suggest, but require to be represented as a hybrid of I and II (fig. 1.1,2); that is, as some structure which is neither I nor II but a compromise between them. In terms of molecular orbital theory, the electrons of the π-bond systems are delocalised to some extent over the intermediate single bond. So the π-electron system is to some degree extended over the entire length of the O=C-N chain in N,N-dimethylformamide (DMF). This may be restated in terms of the single bond (C-N) acquiring partial double bond character with a consequent increase in rigidity associated with double bonds. At the same time, the formal double bonds of a system lose some of their double bond character with a resulting decrease in the barrier to rotation about these bonds. This decrease is rarely sufficient to permit observation of rotational isomerism about these bonds by n.m.r. spectroscopy.

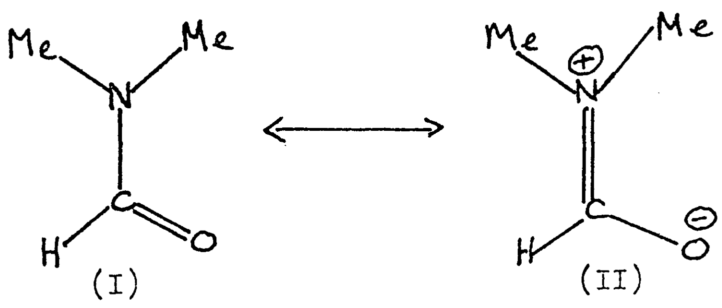
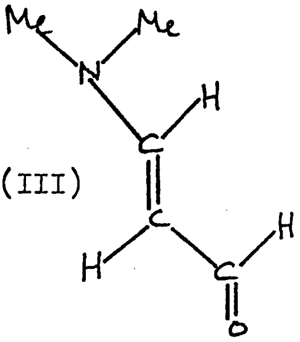


Fig. 1.1 - 1.2.

It should be noticed that we have considered in the present case interaction of n-π electrons on nitrogen with p-π electrons on carbon and oxygen It is further possible to extend resonance interaction beyond that shown in DMF by interposing further π-systems between carbon and nitrogen. These systems are nearly always p-π - p-π systems as found in carbon - carbon double bonds, triple bonds or the delocalised π-electrons found in aromatic structures. The vinylogous amide III (fig. 2.1) is an example of such a system as is the substituted pyrrole IV (fig. 2.2).

(III)



(IV)

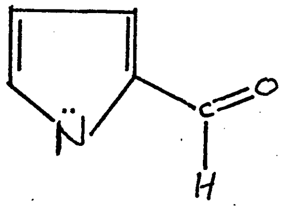
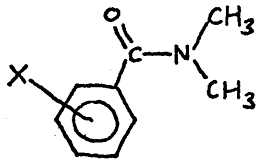


Fig. 2.1 - 2.2.

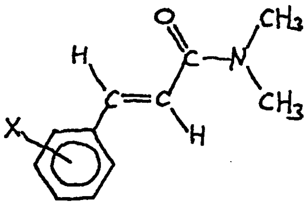
The dipolar nature of several common π-electron systems is well known. This is illustrated by the valence bond description of DMF in which the carbonyl function withdraws electrons from the rest of the molecule by an inductive effect, and, more significantly for our present interests, by a resonance effect as shown. The magnitude of this resonance effect will determine the degree of double bond character in the C(=O)-N bond and in consequence the activation barrier to rotation about this bond. This postulate has been amply confirmed in practice. At the same time, we also observe that the existence of the lone pair of electrons on nitrogen, a source of electron density, means that the electron withdrawing tendency of the carbonyl function is reinforced by the presence of this electron lone pair. Had the dimethylamino function been replaced by an electron withdrawing group such as another carbonyl, then no enhanced barrier to rotation would have been observed about the C(=O)-C(=O) bond of the diketone.

Attenuation of the effect of a group such as carbonyl is achieved by interposing a vinyl function between the carbonyl and the nitrogen lone pair. The efficiency of the vinyl group for transmission of the electronic effects of such substituents is observed to be notably less than 100%, and considerable interest focusses around the energetic details of these interactions. Perhaps the most interesting function to interpose in the basic DMF system is the aromatic benzene nucleus. The extent of interest in benzene chemistry and the many attempts, initiated by Hammett's $\rho\sigma$ relationship, to describe quantitatively aromatic reactivity lend a certain significance to the attempts to understand the energetics of the π-bond system in this structure. It is well recognised that the π-electrons in benzene are by and large responsible for its unique chemical behaviour.

Many other geometrical arrangements of π-electron systems are feasible, and one type which has attracted a good deal of study is that in which two electron withdrawing groups situated at extreme ends of a conjugated system compete for the electrons donated by some group placed somewhere in the system between them. Two examples of this are provided by the benzamides V and the cinnamamides VI (fig. 3.1,2), and in a different fashion by the formanilides VII (fig. 3.3). Consideration of the results from such systems will be treated very briefly in the following review sections.



(V)



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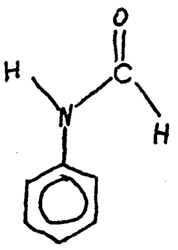


(VII)

Fig. 3.1 - 3.3.

It is clear from what was said earlier about the requirements for observation of rotational barriers by n.m.r. spectroscopy, that these conjugated systems are, by and large, well suited to study in this manner. The necessary barriers to rotation are provided by the electron delocalisation in the system. The geometrical asymmetry is assured almost as a matter of course by the asymmetrical nature of most π-electron systems. The translation into an observable n.m.r. shift asymmetry is achieved by the magnetic anistropy of the functional groups normally present in the molecule. However, despite the pronounced anistropy of many of the functional groups commonly included in conjugated systems, the attenuation of the anisotropic effects is such that more distant sites may experience little or even no chemical shift difference between the exchanging sites on the rotational isomers. In many cases, though a differential shift is still induced, it is so small that it is of little use to the spectroscopist as essential spectral detail is concealed within linewidth effects.

One obvious possible solution of this problem is to acquire the spectra at a higher spectrometer magnetic field, as the increase in field, whilst maintaining spectral resolution, will increase the separation of chemically shifted resonances in the spectrum. In many cases, however, this course of action is not appropriate, either due to the inability to achieve a sufficiently high field to separate extremely close resonances, or more mundanely due to the non-availability of the necessary instrumentation.

The solution of this problem can often be achieved by the use of Aromatic Solvent Induced Shifts (ASIS)[*7]. Hatton and Richards[8] in studying the effect of various aromatic solvents upon the methyl shifts observed in DMF and N,N-dimethylacetamide (DMA), noticed that the solvent induced shift differed between the methyls cis and trans to the carbonyl oxygen. The amount of shift which each methyl receives depends upon the concentration of aromatic solvent present. The overall effect varies with the aromatic solvent used, but generally the methyl signals converge upon one another and almost invariably cross over and diverge from one another again, now interchanged in the spectrum, as the concentration of aromatic solvent is increased. It seems likely that this effect arises from a stereospecific association of the aromatic solvent with the DMF or DMA molecule. The positive end of the solute molecular dipole, situated on the amide nitrogen, is likely to associate with the aromatic ring of the solvent , perhaps lying planar to the plane of the solute. The negative oxygen of the amide can then be visualised as being displaced as far as possible from the negative π-clouds of the aromatic ring. In this fashion, asymmetric solvation is achieved. This orientation of solute and solvent can be represented as in fig. 4 (from Hatton and Richards[8]). These authors[9] observed similar effects in other planar conjugated systems such as mesityl oxide, though the actual shifts observed were smaller than those observed with amides. In the course of the current studies to be reported below, similar ASIS have been employed to magnify differential chemical shifts in para substituted dimethylanilines[10].

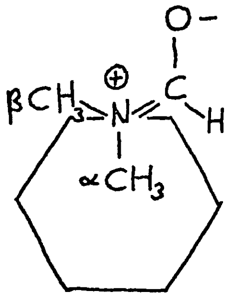


Fig. 4.[8]

There are, unfortunately, disadvantages in the use of ASIS effects. In the first place, we may wish to study a given system in a specific solvent (or solvent mixture) and the requirement to use aromatic solvents, perhaps even in varying concentrations which may be required to induce satisfactory shifts in a series of compounds, imposes serious limitations on the data to be derived from any set of measurements. The very nature of the effect induced by aromatic solvents suggests that the interaction of solute and solvent is by no means trivial. This will be reflected in the thermodynamic parameters derived for the rotational barriers and it is of interest to consider the possible nature of these complexes.

Several authors have attempted to show that the interaction between aromatic solvent and solute molecules can be described in terms of fixed stoichiometry where dipole-dipole interactions are the binding force holding the complex together. Ronayne and Williams[11] have suggested that benzene solvent molecules will solvate electron deficient sites of local dipoles in solute molecules, probably in transient 1:1 associations. The orientation of the benzene solvent molecules may well be non-planar in the associations with the benzene ring as far away from the negative end of the dipole (which may be local or molecular) as possible. Whilst the evidence for 1:1 complexing presented by these authors was not good, a point they recognised, they nevertheless considered the expediency of employing some simple model to describe the solute-solvent interaction as sufficient justification for its use meantime. Baker and Davis[12] in 1968, advanced the suggestion that planar aromatic solutes need not be solvated by aromatic solvents in parallel layers but that benzene solvent might spread itself between two electron deficient sites in two different molecules of a solute such as 2-isopropyl-5-methylbenzoquinone, where each solute molecule contains two electron deficient sites.

Matsuo, in 1968, was critical of the concept of dipole-induced-dipole interactions and proposed a contrary model where van der Waals forces are considered to be the critical factor in any associations[13]. Further, the concept of 1:1 association is considered unsatisfactory in this light and a more general concept of solvent clusters is devised to replace specific association models. The importance of dipole interactions, though not considered to be critical by Matsuo, is invoked to explain the orientation necessary for aromatic solvent molecules which induce differential shifts. Further, he attributes a greater significance to solvent molecules in the inner solvation shell of the solute though still suggesting that these molecules are in rapid equilibrium with the surrounding solvent medium. In many respects then, Matsuo's model is not a radical alternative to specific 1:1 solvation models, but a less quantitative and probably more realistic view of a complex situation.

Baker and Wilson[14] in 1970, observed a continuum of behaviour for various solutes in benzene between the extremes of stoicheiometric 1:1 association and non-association. In many instances, the stoicheiometry of association with benzene was far from simple and in many cases could barely be considered meaningful, though it was noteworthy that in cases where one particular approach of a benzene molecule to a solute molecule is greatly favoured energetically, then 1:1 stoicheiometry was observed.

Several other valuable contributions to this field have been made but as some of the results are pertinent to later studies, we will postpone consideration of them here.

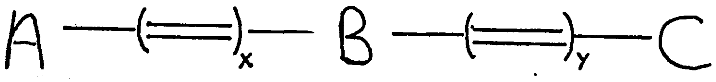
A Review of N.M.R. Studies in Conjugated Systems.

It is not the intention of this review to be thorough. Four very useful reviews of the subject matter of this section have been published in the last few years and, consequently, there is little point in duplicating them here. The review by Binsch[15] published in 1968 is a concise introduction to the topic and covers most of the early work in this field, though studies which employed approximate methods for n.m.r. calculations were not covered in any depth, as results derived from them were generally considered to be suspect to a greater or lesser extent. In 1970, Kessler reviewed the detection of hindered rotation by n.m.r. spectroscopy[16] and considered amide studies in some detail. Other rotations about bonds of partial double bond character he treated less completely. A subsequent review by Sutherland[17], published in 1971, though only complete up to the beginning of 1970, provides comprehensive coverage of this field under the general remit of n.m.r. investigation of the kinetics of conformational change. Finally, Stewart and Siddall[18] have reviewed the applications of n.m.r. spectroscopy to the studies of amides and thioamides, including the measurement of rotational barriers and the related subject of isomer ratios. Consideration of anilide studies is also included.

For our present purposes, it is useful to categorise studies of conjugated systems in terms of the nature of the conjugated paths involved rather than in terms of the particular chemical compound considered.

Admittedly, this is only a change of emphasis, but it is a useful one in that it allows us to systematise the results along lines more pertinent to our present studies.

Functional groups in organic chemistry can be characterised electronically as interacting by inductive and mesomeric mechanisms. In terms of rotational barriers in conjugating systems, clearly the mesomeric interaction is of major importance. Mesomerically, groups can be classified on a scale varying from strong electron donar to strong electron acceptor. Cooperative or competetive interactions will be established between such groups conjugatively connected. So, for example, in the generalised structure VIII (fig. 5), we can vary the nature of A, B and C with consequent results upon the rotational barriers in the system.



(VIII)

Fig. 5.

If, for example, B is an electron acceptor as is C, then A as an electron donar will interact strongly with B and cause considerable delocalisation of electrons into the conjugating system between A and B. The rotational barriers in this part of the system will be increased by this interaction. With increasing length of the conjugation chain, that is with increasing x, the interaction will be attenuated, with a corresponding decrease in the rotational barriers to be observed. As B and C are both electron acceptors, there will be little interaction between them (competitive interaction) and rotational barriers in the intermediate chain will be low. If, on the other hand, C were an electron donar, both A and C would compete to donate electrons to B and reduced barriers in the A - B chain would be accompanied by increased barriers in the B - C chain.

Much of the interest in rotational studies in these systems has focused on attempts to quantify the rotational barriers observed in terms of the variations of groups A, B and C in the systems. However, factors besides the electronic play a part in establishing the observed rotational barriers. The most important of these arises from steric interactions between substituents of various sizes on the conjugated system. Steric interactions, which often operate to oppose planarity in the conjugated system, may prohibit some or all of the electronic interactions between substituents A, B and C and affect the barriers accordingly. In some instances, however, the steric interaction is such as to destabilise the transition state for rotation by causing large groups to pass each other during the motion. In this instance, the rotational barrier will be raised.

systems involving only one interaction.

Such systems can be generalised as in fig. 6, where A and B are groups capable of conjugated interactions with an intervening π-bond system or with each other.

$$A - (=)_x - B.$$

but where x = 0.

Fig. 6.

The prototype of all such systems, and all rotational systems in general to be studied by n.m.r. spectroscopy, is N,N-dimethylformamide. The first observations of rotational isomerism by n.m.r. spectroscopy were made by Phillips in 1955[19] on DMF and DMA. The N-methyl resonances in these systems exhibit chemical and magnetic non-equivalence due to hindered rotation about the C(=O)-N bond, even at room temperature. Lack of ease of rotation about this bond can be ascribed to the cooperative interaction of the dimethylamino and carbonyl functions described as a valence bond hybrid of structures I and II (fig. 1.1,2). In

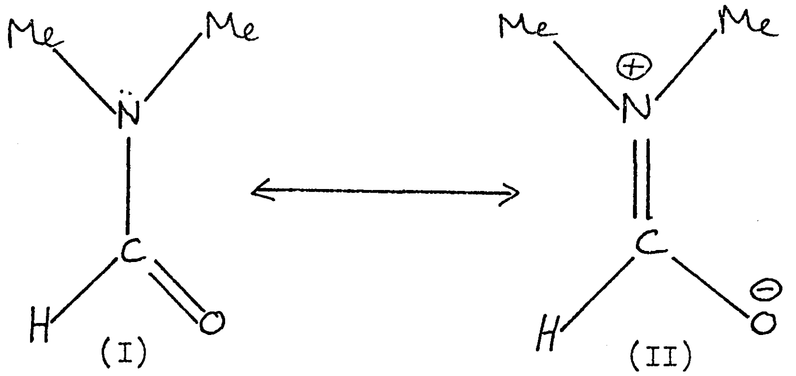


Fig. 1.1 - 1.2.

molecular orbital terms, there is electron delocalisation from the nitrogen lone pair (π-orbital) into the π-orbitals of the carbonyl group. The electron polarisation in this system will cause the major electron density to build up on the carbonyl oxygen atom, a point reinforced by the fact that protonation studies on DMF indicate that the protonation site is predominantly oxygen.[20,21] This cooperative conjugation causes the DMF (and DMA) molecules to be planar (in particular about nitrogen) with amino methyl groups placed cis and trans to the carbonyl oxygen. The resulting molecular asymmetry is reflected in a shift difference between these two methyls induced by the magnetic anisotropy of the carbonyl function.

In 1956, Gutowsky and Holm[22] described mathematically the rate dependence of the signal shapes from the exchanging methyls of DMF and DMA. Unfortunately, in this paper, several approximate relations were established between line shape and rate of exchange of the methyl groups and these were used in several subsequent papers on amide rotation barriers with a resulting large inaccuracy attendant upon each estimate of the rotational barrier. Only recently have reliable activation parameters been obtained for amide rotations by total line shape comparison methods. Whilst early results showed fairly wide variations in the parameters obtained, more recent results employing such methods are by and large in agreement.[*23]

The presence of the dimethylamino group in DMF and DMA is particularly suited to line shape studies in as much as the system approximates to an AB system if long range couplings to these methyls are neglected. Numerous studies on N,N-dimethylamides have been reported where the group R (in $RC(=O)NMe_2$) takes various forms from simple alkyl groups to groups with strong inductive and conjugative interactions with the carbonyl function. A table of such studies is provided by Stewart and Siddall[24]. The importance of steric effects of the group R have been remarked upon and Kessler[16]. He observes that large substituents upon the nitrogen and in the acyl residue of amides increase the energy content of the almost planar ground state because of their steric interaction with the result that the energy difference to the rotational transition state becomes smaller. This is generally true, an exception being the locking of the dialkylamino group by large substituents on the phenyl ring of benzamides. In this case, the transition state is raised in energy. Obviously though, competitive resonance effects, where R donates electrons mesomerically to the carbonyl, will cause reductions in the C(=O)-N rotational barrier as in, for example, the instance where R is phenyl ($\Delta G^{\neq}$ = 16 kcal./mole c.f. ca 21 kcal./mole for DMF). The accumulated data is presently too limited to allow any thorough breakdown of R group influences into steric and electronic components. Two more recent studies of amide barriers as affected by R group variations are given in refs. 25 and 26. Instances of competitive mesomeric interaction will be considered in some more detail later.

In the basic mesomeric system A - B (fig. 6) where A represents the dimethylamino function, various simple variations of B are possible and have been listed in the tables of refs. 23 and 24 above. Variations in group A are also possible and some of these are listed in the review of Stewart and Siddall[27] though at the moment we will not consider cases of competitive mesomerism arising from nitrogen substituents.

Major structural alterations can be affected in B by replacing the oxygen atom by for instance sulphur. Studies on thioamides have become relatively common in recent years. Generally, the barrier to rotation about the C(=S)-N bond is ca. 3 kcal./mole larger than the barrier about the C(=O)-N bond in the corresponding identically substituted compound. Again, Stewart and Siddall provide a table of such barriers[28] together with a comparison table for amides and thioamides[29]. Some controversy has arisen recently over the nature of the factors causing this increase in rotational barrier. Moriarty and coworkers[30] have expressed the opinion that these increases arise mainly from steric interactions with the sulphur atom. This view has been opposed by Walter and coworkers[31] who offer a rather full argument to establish their hypothesis that it is the electronic effect of sulphur which is dominant in the increased rotational barriers observed for thioamides.

Studies on amidinium salts, where sulphur is replaced by NH_2^+, again show enhanced rotational barriers as we would expect on the basis of mesomeric arguments[32].

Rotational barriers have been observed about N-N bonds in the case of dimethylnitrosoamine IX (fig. 7). Phillips and coworkers[33] originally studied this molecule in 1957 and it has been studied a number of times since[34]. Various investigations of the rotational barriers in alkyl nitrites X (fig. 7) have been performed with activation barriers in the region of 9 kcal./mole being found compared with ca. 22 kcal./mole for IX.

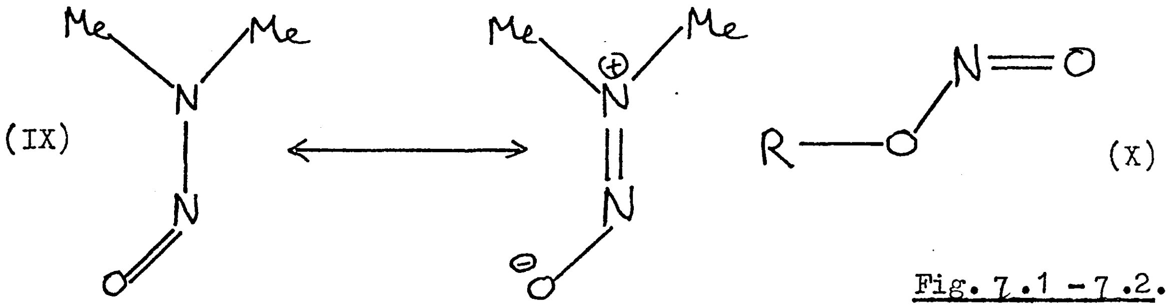


Fig. 7.1 - 7.2.

systems involving extended conjugation paths.

Systems of the type shown in figure 8 will be considered here. These are systems where conjugation with C=C systems is wholly or partly responsible for the observation of rotational barriers about the A-C or B-C bonds. We will consider first, that category where only one group interacts mesomerically with the carbon double bond system.

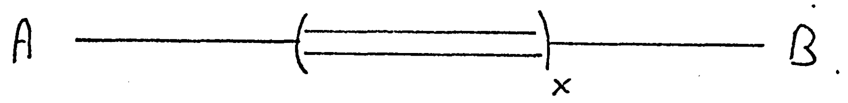


Fig. 8.

The major compound of note in the first category is benzaldehyde, XI, studied by Anet and Ahmad in 1964.[35] They detected a 7.9 kcal./mole rotational barrier for torsion about the C(=O)–C(phenyl) bond. This compares with a 1.15 kcal./mole barrier in acetaldehyde[36] and highlights the importance of mesomeric barriers in aromatic compounds.

The effect of substitution para to the aldehyde group in benzaldehyde was also studied by Anet and Ahmed. Such a system can be regarded as an amide with extended conjugation in the instance where the para substituent is dimethylamino for example. The rotational barrier observed for XII (p-dimethylaminobenzaldehyde) was 10.8 kcal./mole. The corresponding barrier in the p-methoxy compound is 9.2 kcal./mole (fig. 9). Related studies by Dahlqvist and Forsen and coworkers have established rotational barriers in 2-formylfuran,[37] 2-acetylfuran[38] and N-methylpyrrole-2-aldehyde,[39] as shown in figure 10.

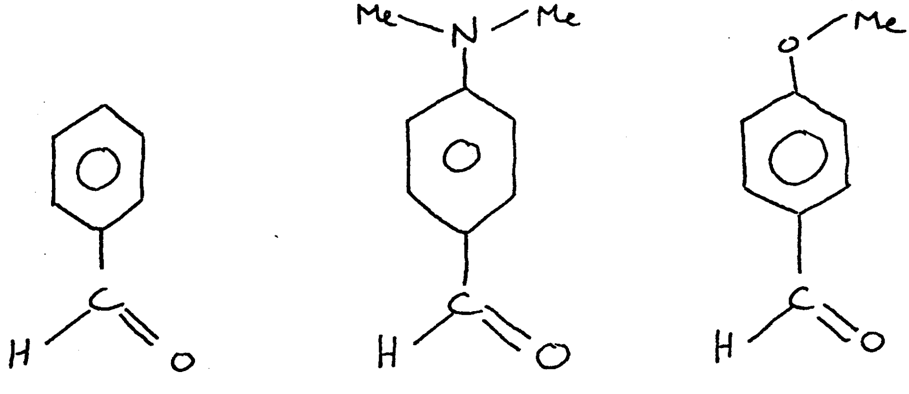


Fig. 9.1 - 9.3.

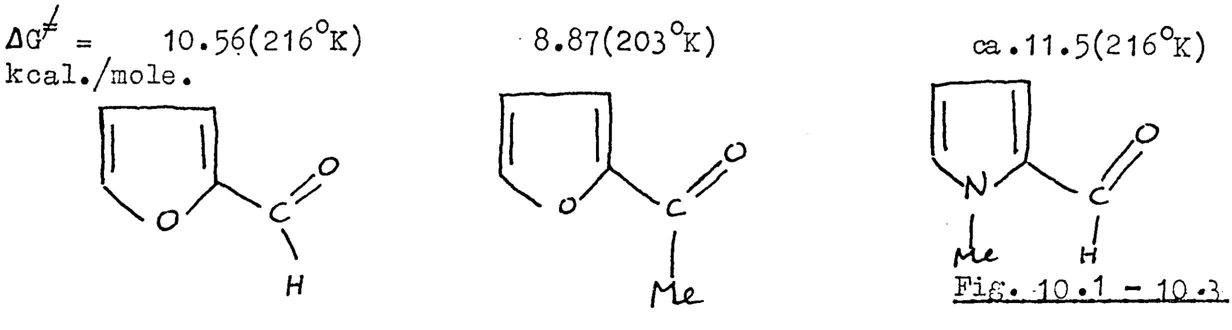
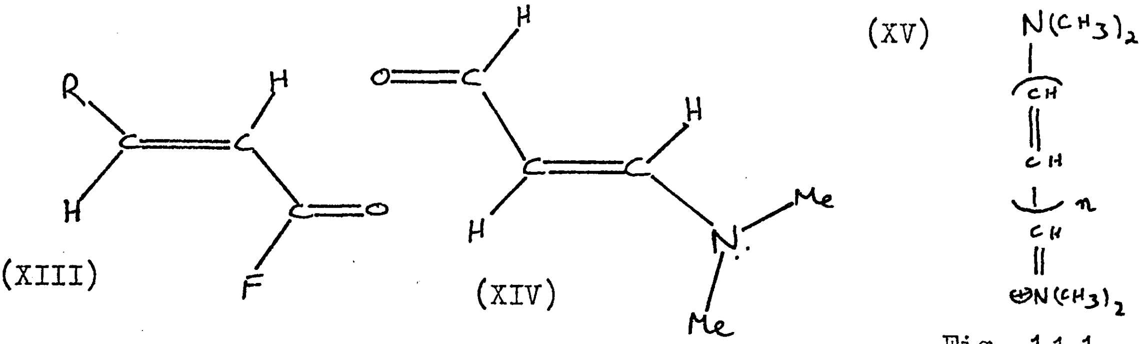


Fig. 10.1 - 10.3.

Similarly, related studies in non-aromatic systems have been published. Lin and Servis[40] have observed rotational isomerism in the acyl fluorides XIII (fig. 11.1) with activation energies between 5.5 and 7.5 kcal./mole. Kozerski and Dabrowski[*41] have studied hindered rotation in enamino aldehydes and ketones XIV (fig. 11.2), noting values for C_3-N and C_1-C_2 rotations in the systems. Values range between ca. 11 and ca. 15 kcal./mole. A wide variety of related compounds, some exhibiting competitive mesomeric effects are tabulated by Sutherland[42]. This author also tabulates the results of similar studies in fulvenes[43]. An interesting example of the attenuation effect of increasing conjugation between two mesomerically interacting substituents is provided by the cyanine dyes XV (fig. 11.3) where the activation energy for dimethylamino rotation decreases in the order 17 to 10 to 7 kcal./mole as n goes from 1 to 2 to 3.

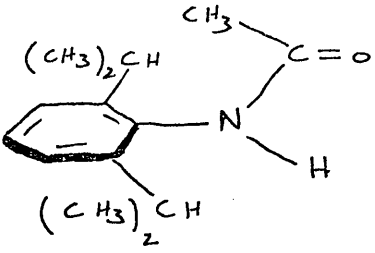


(XIII) (XIV) (XV)

Fig. 11.1 - 11.3.

systems exhibiting competitive mesomeric interactions.

Many groups of authors have been interested in systems, in the main aromatic, in which a mesomeric group of interest is flanked on either side by other mesomeric groups which may or may not interact with the central group in a cooperative sense. So, for example, in structures XVI[44] and XVII[45] (fig. 12.1,2) the central amino function interacts cooperatively with the carbonyl or nitroso group, whilst at the same time, the possibility of interaction with the aromatic system is present. The main interest in these systems lies more in the effect of steric interactions between the aromatic ring ortho substituents and the carbonyl or nitroso groups.



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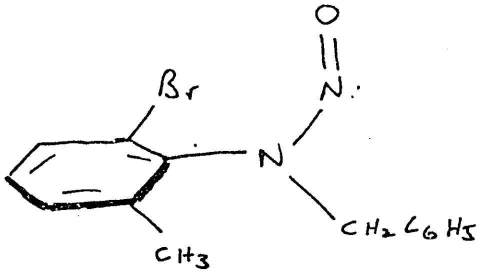


(XVII)

Fig. 12.1 - 12.2.

Perhaps one of the simplest systems in which to observe the effects of competitive interaction is in the carbamates. Machacek and Vecera[46] observed reduced barriers to rotation about the C-N bond in the carbamates XVIII (fig. 13.1) where R is phenyl or α-naphthyl. Incidently,

(XVIII)

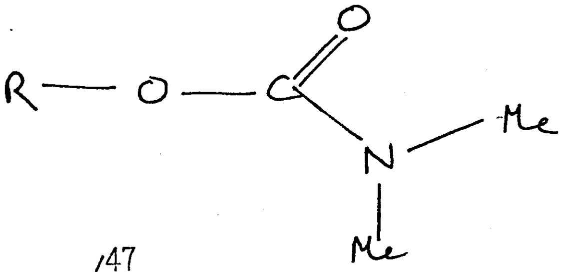


Fig. 13.1.

Inglefield and Kaplan[47] have observed large negative entropies for this rotational barrier in cases where R is methyl for both carbamate and thiocarbamate. These were not observed for XVIII. Numerous variations within the context of this basic structure have been reported.

One of the most prolific fields for such studies has been that where the substituent corresponding to O-phenyl in XVIII above has been a substituted aromatic ring directly bonded to the carbonyl carbon or bonded via a conjugated carbon chain. Thus Spassov and coworkers[48] have examined the N-C(=O) rotational barriers in a series of meta- and para- substituted dimethylcinnamamides XIX (fig. 14.1) where moderately good correlations with various substituent constants for the aromatic ring substituents have been observed. These correlations indicate the influence of electron withdrawal into the aromatic ring upon the rotational barrier. The sensitivity of the barrier is not high as we would expect with the interposed carbon double bond attenuating mesomeric effects. De Boer and coworkers, in a series of papers, have examined

(XIX)

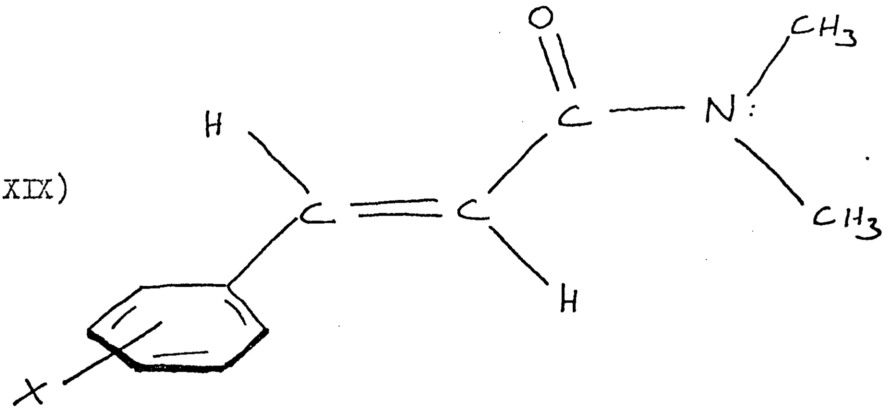


Fig. 14.1.

N,N-dimethylbenzamides and cinnamamides[49], and several correlations of parameters for these systems with Swain and Lupton's[50] substituent constants have been derived[51,52]. Jackman and coworkers[53] have correlated rotational barriers in N,N-dimethylbenzamides with Hammett σ and σ^+ substituent constants. Niwa[54] has examined Hammett correlations in meta- and para- substituted formanilides and has observed the need for the use of σ^+ and σ^- substituent parameters for strongly mesomerically interacting para- substituents.

Not all studies in this category of competitive mesomerism study molecular parameters with a view to establishing correlations with various substituent constants. Walter, Schaumann and Rose[54] have studied rotational barriers in urea, thiourea and selenourea. The rotational barrier in formamide has been shown to be 17.8 kcal./mole in diglyme[55] These authors argue that several factors will tend to reduce the rotational barrier in urea and its homologues. Firstly, "replacement of the formyl hydrogen in formamide by the amino group will raise the steric strain in the planar ground state and thus increase its energy". Secondly, "the lone electron pairs on both hydrogen atoms compete in the mesomeric interaction with the" functional group π "orbitals producing in each half of the molecule a weaker partial double bond than in formamide". Thirdly, "when one amino group is turned out of the plane of the molecule during the rotational process, undisturbed mesomerism in the other half of the molecule is possible and thus the energy of the transition state is lowered". We can therefore see that the factors involved in establishing the value of any rotational barrier are complex, and examination of these various factors free from interference from each other, though difficult, is essential for a complete understanding of the contributions to the energy of the systems under study.

Studies on Aromatic Systems.

"The determination of electronic interactions in aromatic molecules has long been the aim of many chemists. Sure knowledge of the mechanisms and magnitudes of such interactions would allow the prediction of many physical properties, reaction rates, and equilibrium constants, and also assist in the correlation of the mass of existing data." Furthermore, "aromatic and, in particular, benzene derivitives have provided the majority of the series of compounds used by physical organic chemists to examine correlations between structure and reactivity. The benzene nucleus contains both the usually distinguished types of bond; the σ bond has cylindrical electronic symmetry about the bond direction while the π bond has a node in the bond axis. The π electrons in benzene can also be regarded as delocalised and we thus have a relatively simple and symmetrical system of fixed geometry allowing investigation of features of the major bonding concepts."/[56]

Major interest in the bonding system of benzenes focusses on the π contribution, and whilst we cannot rigorously separate σ and π components in any particular bond, for all practical purposes we can regard bonds simply as composed of varying discrete contributions from both these sources. It is now generally recognised that the σ contribution to the interaction of a substituent with a benzene system is of limited significance. Far more important is the electrostatic field effect a substituent may exert at centres of interest within the molecule quite far removed from its point of attachment. Such an effect is often referred to under the general term 'inductive effect' though no implication that the effect is operative via a σ bonding transmission should be understood. Further, for simplicity, it is often assumed that the field effect of a substituent (the inductive effect) has no action upon π elec:

trons in the molecule. This clearly cannot be the case, but the task of unravelling the inter-related effects of one group of electrons upon another is complex. Extremely crude measures of these effect are often quite sufficient for the majority of purposes.

The exact nature of π interactions is not free from dispute either. It has been suggested by Clark[57], for example, that the major part of π electron disturbance caused by substituents having free electrons on the atom attached to the ring is caused by non-bonded repulsion between these electrons and the benzene π electrons rather than by mesomeric interaction. An electron diffraction study of aniline[58] which indicates substantial bending of the amino group relative to the ring, has been interpreted as providing supportive evidence of this electron repulsion. However, in p-substituted aniline derivitives, the evidence is entirely consistent with enhanced mesomeric interaction, there even being a suggestion of C_{Ar}-N bond shortening. This is consistent with a strong through resonance interaction with the p-substituent.

Hammett relationships.

We have already considered in some detail, the origins of Hammett $\sigma\rho$ relationships. The value of ρ varies with the electronic demands of the reaction or property measured. The nature of o is more complex. σ is a measure of the transmission of the substituent's electronic effect to the reaction site and as such, it is not dependent just on an interaction with the benzene ring. If the reaction site is especially capable of interacting with the substituent, by a through resonance effect for example, then an enhanced effect is observed for the substituent and an enhanced σ value must be employed. This is a somewhat unsatisfactory state of affairs and several attempts have been made to derive a more fundamental set of substituent constants. So, for instance, Taft and coworkers[59] pioneered attempts to split c values into inductive and 'resonance' contributions; inductive covered effects arising from σ bond mechanisms and through space field effects. Substituent parameters have since proliferated in the literature, but as pointed out in a recent communication by Brownlee and Topsom[60], this is generally unnecessary as most correlations can be expressed in terms of varying contributions of σ and π factors described by σ_I and σ_R^o. The precise mixture of these two constituents to decribe the observed effects will vary widely and in consequence, the use of relatively simple σ^+ and σ^- parameters for example, is sometimes favoured on the grounds of simplicity. Though in some instances, it may be necessary to use these simpler parameters due to lack of information, necessary to define properly the contributions of σ_I and σ_R^o, it is better to attempt to obtain sufficient data to allow definition of results in terms of the more general constants.

n.m.r. observation of Hammett relationships.

A significant number of n.m.r. studies of various kinds on aromatic systems have revealed correlations between various parameters of the system, such as chemical shifts and coupling constants, and Hammett substituent constants. In particular, studies of various substituted anilines have provided a number of significant correlations.

Several authors have sought correlations between substituent constants and rotational barriers in aromatic substituted amides. Jackman and coworkers[53] studied C–N rotation barriers in eighteen substituted N,N-dimethylbenzamides by complete lineshape analysis of the methyl signals. The barriers to rotation ($\Delta G^{\neq}$) are, to a first approximation, sensitive to effects which manifest themselves in the ground state rather than the transition state. Thus in fig. 15, substituents R_1 which are electron donating and R_2 and R_3 which are electron withdrawing are expected to reduce the rotational barrier. The existence of non-bonded interactions between R_1 and R_2 and R_3 will also lower the barrier since these interactions are reduced in the transition state. In the current instance, the study of a series of m- and p-substituted benzamides will allow us to examine the effects of electronic factors in isolation from variations in steric factors since all non-bonded interactions will remain essentially the same. The correlation between $\Delta G^{\neq}$ and Hammett σ constants is fair (correlation coefficient $r = 0.93$) whilst correlation with σ^{+} is better ($r = 0.97$) This better correlation with σ^{+} implies that the barrier is significantly influenced by mesomeric electron donation by suitable p-substituents with through conjugation from electron donars such as OMe or NMe_2 to the carbonyl group of the amide. The values of ρ and ρ^{+} of +1.56 and +1.13 respectively, indicate that the barrier is relatively sensitive to electronic effects, the (+) sign signifying that the barrier rises with increased electron withdrawal. Interestingly, correlations, though relatively poor ones, exist between the differences in chemical shifts of the methyl signals and σ, σ^{+} and $\Delta G^{\neq}$, this last showing the strongest correlation ($r = 0.976$).

Korver and coworkers[61] have also studied N,N-dimethylbenzamides but their treatment of substituent effects follows van Bekkum, Verkade and Wepster[62] and Swain and Lupton[63], both of which highlight the importance of through resonance conjugation to the carbonyl group where possible.

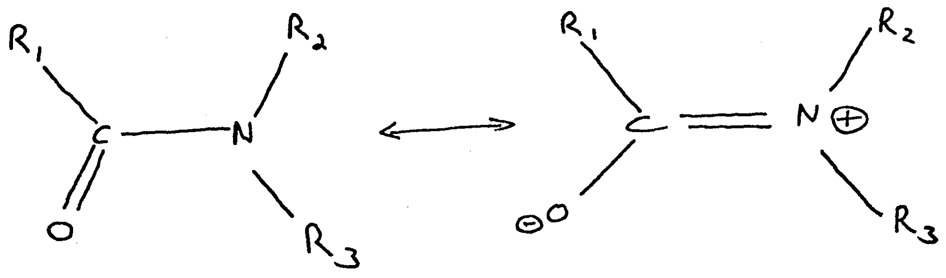


Fig. 15.1 - 15.2.

Spassov and coworkers[48] have studied rotational barriers in m- and p-substituted cinnamamides and have observed correlations between $\Delta G^{\neq}$ and substituent constants. The better correlation observed is with σ rather than σ^{+} constants ($r = 0.95$ and $r = 0.90$ respectively). This implies a decreased significance for through resonance effects and this reduced significance of electron withdrawal in enhancing the barrier is reflected in ρ and ρ^{+} values of 0.85 and 0.60 respectively. This is not unexpected in view of the increased conjugation path in the cinnamamides

comunexpected in view of the increased conjugation path in the cinnamamides

In many studies, correlation between Hammett σ constants and chemical shifts have been observed.[*64] Schaefer and coworkers[64] have observed a correlation between the amino proton shifts on m- and p-substituted anilines, measured in dilute cyclohexane solutions, and Hammett σ constants for the substituents. These authors also suggest that the shift observed is probably proportional to the π electron density on nitrogen. Rae and Dyall[65] have observed a correlation between the methyl shifts in p-substituted dimethylanilines and the enhanced substituent constants σ^-. A correlation coefficient of 0.965 is observed. Using this correlation, these authors estimate a value for the σ^- coefficient for the nitroso group of 1.57 ± 0.09, a value which is not attainable unambiguously from chemical reactivity measurements. Lynch and coworkers[67] have observed similar results to those above in their work on anilines.

Methyl ^{13}C-H coupling constants and chemical shifts have been observed to follow Hammett correlations in dimethylanilines amongst other substituted aromatic compounds. The use of σ^- and σ^+ values again improves the correlation in those cases of substituents capable of direct resonance interaction (from the p position) with the dimethylamino function.

Calder and Garratt[68] have examined p-substituted nitrosobenzenes with a view to establishing a Hammett correlation between σ for the para substituent and the barrier to rotation about the C_{Ar}-$N_{nitroso}$ bond. Barriers to this rotation were obtained by approximate methods. Unfortunately, no attempts were made to correct these barriers for a constant observation temperature (temperatures were varied over a range of 160° maximum) and no correlation coefficient of the $\sigma/\Delta G^{\neq}$ comparison was calculated. In the circumstances, it is difficult to draw any conclusions as to the existence of a correlation or not.

Mislow[69] and coworkers have examined the effect of substituents on the rate of pyramidal inversion in 1-aryl-2,2-dimethylaziridines (fig. 16). The inversion barriers show a linear correlation (judged, by the authors, visually) with Hammett σ^- substituent constants. ρ is found to be ca. -3 at -60°. The greater the mesomeric electron withdrawal, the lower the barrier to inversion. These results are ascribed to conjugation of the lone pair on the inverting centre with the attached arene π system, an effect which finds its maximum expression in the transition state for the inversion process.

n.m.r. studies of aromatic rotational barriers.

Despite the obvious interest in rotational barriers in general and aromatic rings in particular, not a great deal of attention has been devoted to rotational barriers about bonds to the benzene nucleus. In particular rotations analogous to those so thoroughly studied in amides have received scant attention. So, for example, it was not until recently that the N-C_{Ar} rotational barrier was examined in p-formyldimethylaniline (p-dimethylaminobenzaldehyde!). This molecule is the aromatic analogue of DMF. Interest in this particular molecule was first shown by Anet and Ahmad in 1964/[35] when they observed a rotational barrier of 10.8 kcal./mole at -71°C. for the rotation of the formyl group in p-dimethylaminobenzaldehyde. At the same time, barriers of 9.2 and 7.8 kcal./mole were measured for the same rotation in p-methoxybenzaldehyde and benzaldehyde respectively. These barriers were derived from a measure of the free energy to rotation at the coalescence point only/[*70].

Klinck, Marr and Stothers/[71] examined the correspondingly substituted acetophenones as well as the substituted benzaldehydes described above. Toluene solutions of these compounds were studied. Whilst free energy barriers to rotation in the benzaldehydes in agreement with the work of Anet were recorded, this was only true at or near the coalescence temperatures. At ambient temperatures, much larger barriers were measured corresponding to large negative entropies of activation! These effects are not to be observed in vinyl chloride as solvent and it seems unlikely that they are an artifact of the n.m.r. measurement process.

One other simple disubstituted aromatic compound has attracted considerable attention from n.m.r. spectroscopists. This is p-nitrosodimethylaniline. C_{Ar}-N=O rotation was first examined in this molecule by MacNicol, Wallace and Brand/[72] who observed a barrier of 11.8 kcal./mole at -58°C. In a related study, MacNicol, Porte and Wallace/[73] observed a rotational barrier for the same bond in the conjugate acid of p-nitroso-N,N-dimethylaniline. This barrier has a lower limit of 16.8 kcal./mole at 33.5°C. This is only consistent with protonation on the nitroso oxygen in this molecule and not the amino nitrogen. This is clear indication of the extent of the resonance interaction in this compound, where the electron density at the nitroso oxygen is sufficiently enhanced to permit protonation on this site in preference to the amino site.

Korver, van der Haak and de Boer/[74] report a value of 14.9 kcal./mole ($\Delta H^{\neq}$) compared with MacNicol's equivalent value of 11.2 kcal./mole. The origin of this difference may lie in the different solvents used, chloroform as against acetone, but it is also possible that as both groups use approximate methods in deriving their results, then there will be some errors, possibly gross in these values. Calder and Garratt /[68], as mentioned above, have studied p-substituted nitrosobenzenes and report a value of 12.4 kcal./mole at ca. 0°C. This is certainly more in keeping with MacNicol's estimate of this barrier, though once again approximate methods were used to establish this value.

MacNicol/[75] observed the barrier to rotation of the dimethylamino group about the C_{Ar}-NMe_2 and estimated the barrier to rotation to be 10.6 kcal./mole at -76°C., again clearly consistent with considerable delocalisation of the amino lone pair of electrons in cooperative conjugation with the nitroso group.

Other studies in aromatic systems have been made where rotation about a bond to the ring is examined, but these are concerned with barriers arising from steric factors and are not of immediate concern here; for example, the work of Jouanne and Heidberg/[76].

Current Studies of Rotational Barriers in Aromatic Systems.

As we have seen, the observation of rotational barriers in p-disubstituted benzenes is to be expected in cases where the two substituents are capable of cooperative mesomeric interaction with one another. Thus if one substituent exhibits a +M effect (donates electrons mesomerically to the benzene ring) and the other a -M effect, then extended conjugation is observed with a resulting increase in the bond orders of formal single bonds in the system. In the structures represented by I (fig. 16), the valence bond isomer Ib contributes significantly to a resonance hybrid representation of the true molecular structure.

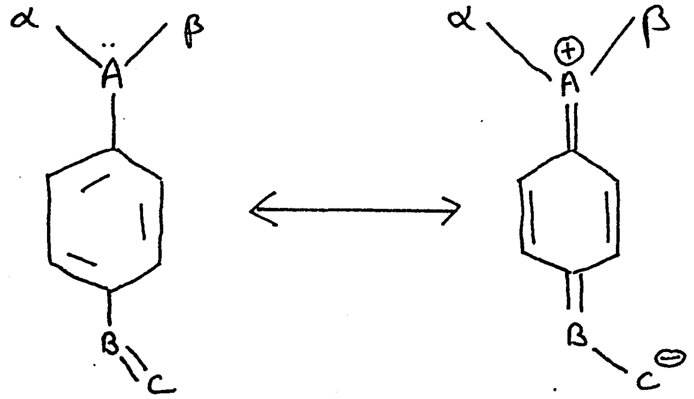


Fig. 16.1 - 16.2.

Further, we can see that the requirements for observation of rotational barriers will be met if the group -B=C is sufficiently magnetically anisotropic to induce significant differential in the chemical shifts at positions in the benzene ring and in the group A, if non-linear. That this is the case for substituents such as -CHO, -C(CH$_3$)O and -N=O, and protons on the benzene ring has long been recognised[35,71,72]. The possibility that these anisotropic groups could induce sufficient shift differential at the para position was not immediately realised. During preliminary studies of the low temperature spectrum of 9-nitrosojulolidine (fig. 17) a significant chemical shift difference was observed at the methylene protons in the saturated rings and this implied the possibility of observing a similar shift between methyl signals in p-nitroso-N,N-dimethylaniline, provided the dimethylamino rotation could be slowed sufficiently to prevent averaging of the methyl signals. MacNicol, in a preliminary communication[75], observed a shift difference of 4.1 Hz. between the methyls when rotation of the dimethylamino group

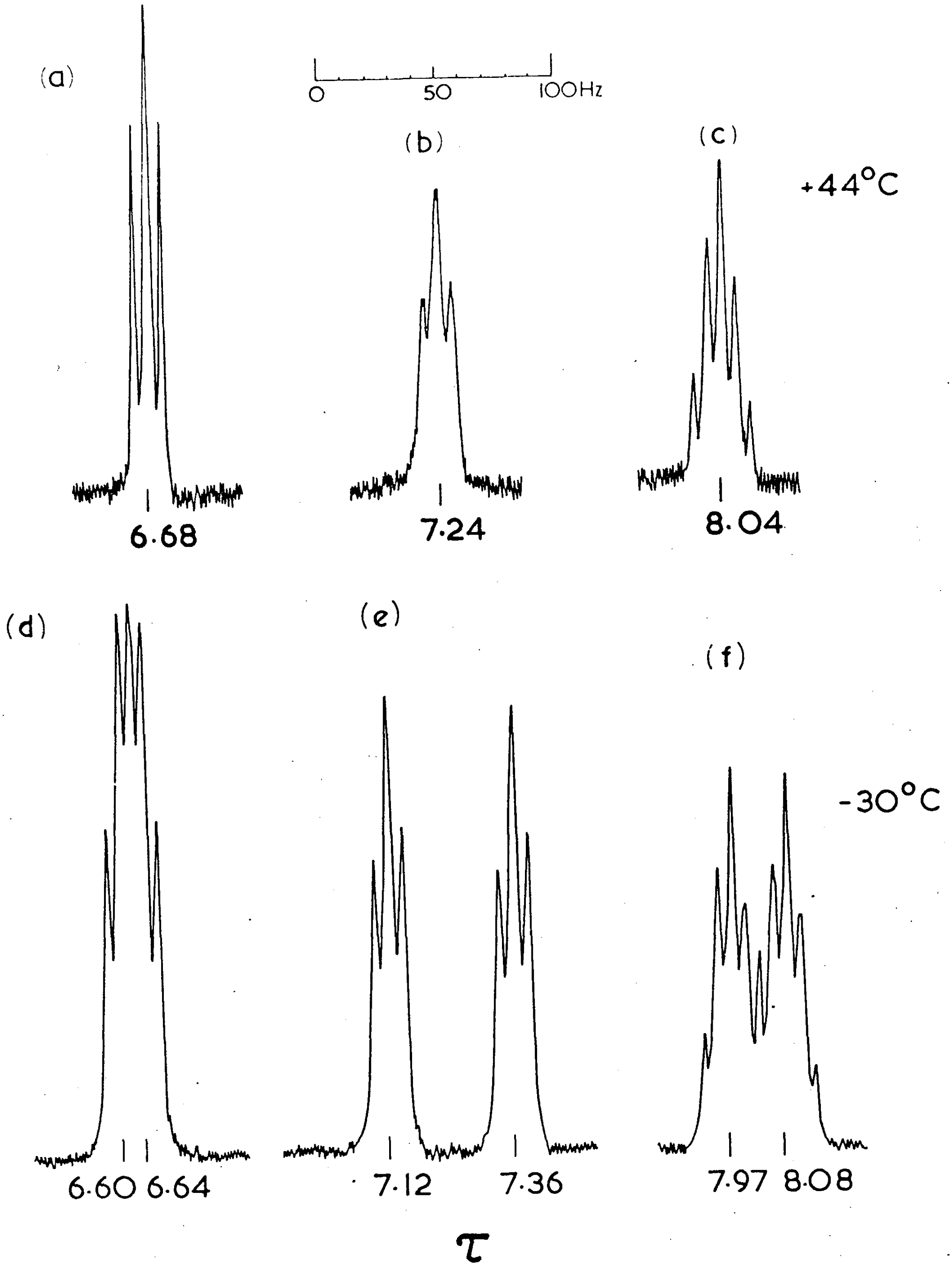
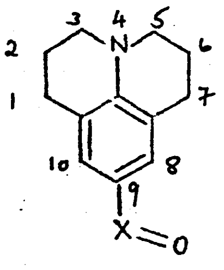
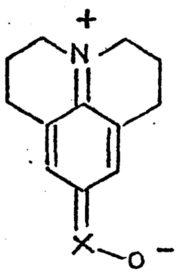


Fig. 17.1 - 17.2.



(I) ; X=N

(III); X=CH



(II) ; X=N

(IV) ; X=CH

Fig. 18.1 - 18.2.

had almost ceased at -90°C.

It was the initial intention of the current studies to extent these observations to as many series of aromatic compounds as possible, with a view to establishing accurate barriers to internal rotation in these systems. Due to the importance of the benzene system, these barriers would be of considerable theoretical interest. Unfortunately, our work was seriously curtailed by inadequacies in our temperature control equipment which remained uncorrected for several reasons.[*77] In consequence, the work detailed below constitutes merely the introduction to a series of studies which are only now being undertaken with radical improvements in our instrumentation (as detailed in the practical section of this thesis).

Studies on Julolidine Systems.

The structure and numbering of the julolidine systems studied are shown in figure 18 opposite.

The first attempts to prepare 9-nitrosojulolidine (II) were reported by Pinkus in 1892,[78] and Smith and Yu, in 1952,[79] confirmed his lack of success in this venture. The preparation of this compound by the action of nitrosyl chloride on julolidine is described in the practical section of this thesis.

Due to the tendency of nitroso compounds to form dimers, the monomeric nature of (II) in solution was established by osmometric determination of the molecular weight (200.5 in CCl_4; true molecular weight 202). A concentration insensitive $n - \pi^*$ band for the nitroso group is also observed in the ultraviolet spectrum at 652nm. ($\log\varepsilon$ 1.81) in EtOH. The $\pi - \pi^*$ absorption of the chromophore in this molecule occurs at 448nm. with $\log\varepsilon$ of 4.54, indicating a significant decrease in the energy of this transition to be associated with increased electron delocalisation and stabilisation of the excited state, when compared with p-nitroso-N,N-dimethylaniline (λ_{max} 420nm. $\log\varepsilon$ 4.48).[80]

At 44°C., the 220MHz. proton n.m.r. spectrum of II (ca. 0.1M in

$CDCl_3$) comprises a broadened aromatic resonance centred near δ 7.3 and methylene signals as shown in the upper protion of fig. 17. Lowering the temperature reduces the rate of rotation about the Ar-N=O bond and by -30°C, the aromatic protons show an AB quartet pattern with ν_{AB} 1.82 ppm. (401 Hz.) and J_{AB} 2.2 Hz. The methylene resonances exhibit further splittings as shown in the bottom half of fig. 17. The induced shifts are: 0.044 ppm. (9.68 Hz.) for $N-\underline{CH_2}$; 0.108 ppm. (23.76 Hz.) for $N-C-\underline{CH_2}$; and 0.241 ppm. (53.02 Hz.) for $Ar-\underline{CH_2}$. Observation of a chemical shift differential, even for methylenes furthest from the nitroso group, reflects the large magnetic anistropy of the nitroso function and suggests the likelihood of observing similar results in p-nitroso-N,N-dimethylaniline, provided the dimethylamino rotation is slow enough to permit observation of separate resonances. In II, spectral changes resulting from conformational changes in the trimethylene chains were not observed down to -60°C. In the symmetrical 9-nitrojulolidine, prepared by oxidation of II with m-chloroperbenzoic acid, no temperature dependent effects were observed, even in the trimethylene chains at similar temperatures.

A similar investigation of 9-formyljulolidine (III) at lower temperatures revealed hindered rotation of the formyl group. The chemical shift in the aromatic AB quartet was 25.8 Hz. with a coupling constant of 1.9 Hz. The chemical shifts imparted in the methylene chains were only sufficient to cause broadening of these signals with no 'frozen' shifts being resolved.

The activation parameters for these rotations were calculated by complete line shape matching of experimental and theoretical spectra calculated on the basis of the system being a simple coupled AB spectrum. This is a slight simplification, in as much as some residual coupling will exist to the methylene protons adjacent to the ring. This unresolvable coupling is accounted for by the use of an effective relaxation time T_2 slightly in excess of true requirements. Though this approach does introduce errors, noticeable in the limits of slow and fast exchange, it was adopted at the time as more sophisticated computer programs, cap:

:able of including the extra coupling in the calculations, were not available.

Several problems arise with fitting the spectra of II. It is noticeable that the chemical shift at low temperatures, the frozen shift, varies with temperature. In consequence, an extrapolation into the region of exchange broadening of this frozen shift is necessary and as this extrapolation is over a temperature range of greater than 60°C, there are obvious dangers inherent in the process. It may well be objected that the extrapolation need not hold over such a temperature range, but in the circumstances, there is little option but to accept it. Any attempt to fit, theoretically, rate constant and chemical shift are frustrated by the enormous size of the chemical shift in the first instance. This leads to a high level of indeterminancy if both these parameters are fitted. A second problem introduced by such a large shift is one of fitting the spectrum in the middle regions of the exchange process. These large shifts give rise to very broad signals of low intensity which cannot be accurately matched. These problems taken together, then mean that the regions of medium and high exchange rate are poorly defined. Consequently we must rely on the lower exchange rates to establish the thermodynamic parameters of the rotation. This is unfortunate in that a restricted temperature range is involved, with resulting uncertainty in the definition parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$, though the accuracy of the lower rate constants should be quite high.

As a consequence of these factors, the quality of results derived for the rotational barrier in II are probably not as good as they might be. In particular, the entropy of activation appears to be on the high side and so the enthalpy of activation takes on an unrealistic value. The results are listed in Table 1. As we can see from the free energy of activation at 250°K (14.2 kcal./mole), there is a considerable resistance to rotation about this bond. This must reflect a very high mesomeric donating power for the quinolizidine unit. This probably arises from

Activation Parameters for Internal Rotation.

Compound.	Solvent.	Tc^a(°C.)	$\Delta H^{\neq\ b}$(kcal./mole)	$\Delta S^{\neq\ b}$(kcal./mole)	$\Delta G^{\neq\ b}$(kcal./mole)
9-nitrosojulolidine (II)	$CDCl_3$.	29 (±4)	17.1 (±1.5)	11.6 (±6)	14.2 (±0.2) 250°K.
p-nitrosodimethylaniline[72]	acetone.		11.2 (±1.1)	-3.0 (±5)	12.1 (±0.5) 298°K.
" (IV)[68]	CD_2Cl_2.	-3 (±3)			12.4 270°K.
" [74]	$CDCl_3$.		14.9 (±0.1)	4.8 (±0.4)	
nitrosobenzene. [81]	vapour.		3.9 (±1)^c		
9-formyljulolidine (III)	$CDCl_3$.	-51 (±2)	11.9 (±1.0)	3.9 (±4)	10.9 (±0.2) 250°K.
p-dimethylaminobenzaldehyde.	CH_2Cl_2.	-71			10.8 202°K.
benzaldehyde. [35]	vinyl chloride	-123			7.9 150°K.
" [82]	vapour.		4.9 (±0.43)^c		

Notes.

(a). The coalescence temperature.

(b). All activation parameters derived in the present work correspond to a transmission coefficient of unity.

(c). This strictly corresponds to V_2 of the potential function $V = \frac{V_2}{2}(1 - \cos 2\ )$; however, the difference between V_2 and $H^{\neq}$, the zero point vibrational energy, is small and may be neglected for the present comparison.

Table 1.

an enhanced planarity about the nitrogen in the quinolizidine unit, when compared with the analagous p-nitroso-N,N-dimethylaniline (IV). Though several authors have studied (IV) and have come to different conclusions, there is general agreement that the barrier in the aniline is reduced from that in the julolidine. The ultraviolet spectra of (II) and (IV) demonstrate the same effect, with a bathochromic shift being observed between (II) and (IV) as mentioned above. The total effect of the quinolizidine unit can be estimated by comparing the barrier in (II) with that in nitrosobenzene. Bearing in mind that the comparison is liable to be inaccurate due to the factors previously mentioned, then we can note that an enthalpy difference of ca. 13 kcal./mole is observed. This will reflect a mesomeric contribution to the free energy barrier of greater than 10 kcal./mole.

Similar measurements for the rotation of the formyl group in 9-formyl julolidine (III) indicate a barrier of 10.9 kcal./mole at 250°K. Comparison with the corresponding p-dimethylaminobenzaldehyde (V) indicate that the two barriers are considerably closer than for (II) and (IV) above. A certain amount of through resonance contribution is certainly lost on substituting formyl for nitroso in the 9 position, but as greatest reliance can be placed in our current results for (III), this result may reflect some error in the results for (II). This comparison suggests that the enhanced planarity in the quinolizidine structure is not so marked as the above results suggest. Comparison of the results for (III) with the vapour enthalpy barrier in benzaldehyde suggests a mesomeric contribution of about 7 kcal./mole to the enthalpy, whilst the results from benzaldehyde in vinyl chloride solution suggest no more than 3kcal./mole for the resonance contribution from the quinolizidine unit to this barrier.

Studies on N,N-dimethylaniline Systems.

MacNicol first reported observation of hindered rotation of the dimethylamino group in p-nitroso-N,N-dimethylaniline[75] (IV). We have since undertaken a preliminary survey of other para substituted dimethylanilines in an attempt to observe dimethylamino rotational barriers.

Studies on p-dimethylaminobenzaldehyde (V) have indicated that, although hindered rotation of the dimethylamino group could be observed qualitatively, the chemical shift imparted by the magnetic anisotropy of the carbonyl function is no more than sufficient to broaden the dimethylamino resonances. No chemical shift which would allow resolution of the two signals arising from methyls cis and trans to the carbonyl π orbitals was observed. In a similar manner, p-dimethylaminoacetophenone (VI) did not yield an observable chemical shift.

As we have seen earlier, it is well known that aromatic solvent molecules can impart dramatic solvent induced shifts to , generally polar, solute molecules in the solution. In particular, Hatton and Richards[9] have demonstrated that ASIS in DMF result in different shifts being observed at each methyl of the dimethylamino function. This presumably relates to an asymmetric solvation of the molecule, reflecting the molecule's short term asymmetry in the rotational isomers. There has been considerable discussion as to the nature of any complex formed between solute and solvent in these cases, and in particular, several authors have proposed discrete geometries for hypothetical solute-solvent complexes. As Engler and Laszlo[83] have pointed out, there is very little justification in most cases for regarding the interaction between solute and solvent in terms of a discrete complex. All that can be argued, is that the time averaged effect of transient solvations is not completely random, but is influenced to a greater or lesser extent by the polarity of the solute molecule. In the particular case of asymmetric polar solutes, whether this asymmetry is also transient or not, the aromatic solvent cluster surrounding the solute molecule is also asymmetric, resulting in an asymmetric pattern of ASIS in the molecule.

It is interesting to reflect, however, whether the nature of the solvation by aromatic molecules alters as (a) rotational lifetimes in the solute molecule alter and (b) the temperature of the system changes. It seems not unreasonable to suggest that the nature of the solvation cluster around the molecule will alter as rotational rates in the molecule change. At the same time, it is well known that the effects, in terms of chemical shifts for example, of an aromatic solvent can be very temperature dependent.[84] Considering these factors in isolation for the moment, we can suggest that the effect of raising rotational rates within a molecule is to reduce the effective asymmetry of the solvation cluster around that molecule. As there is less time for asymmetry in the molecule to be reflected in asymmetric solvation, this presumably requiring a finite time for establishment, then as rates increase, the real chemical shift induced by solvent decreases. On the assumption that we do not allow for this effect, then we apply a frozen shift observed at low temperatures to regions of exchange where a smaller shift is appropriate. In consequence, we overestimate the rates of exchange at any given temperature and cause an increase in the estimate of both enthalpy and entropy of the activation process.

Temperature effects on the shifts observed between nuclei need not lead to a decrease in shift on raising the temperature.[84] It is quite possible for the real shift to increase with rising temperature and, as a result, the opposite effect to that described above can be observed. The enthalpy and entropy of the activation process are reduced, with the entropy becoming negative to compensate for the loss in enthalpy. During these changes, it is noted that free energy is relatively unaffected.

In the current instances, large negative entropies are observed and hence we might suspect some differential temperature effect to be confusing the estimate of appropriate 'frozen' shifts applicable to these systems. Observation of the trend of the frozen shifts at temperatures well below unity rate of exchange has failed to reveal any temperature trend for the 'frozen' shift in (IV). It does not seem possible then to

N.M.R. Parameters for Internal Rotation of Dimethylamino Groups in Dimethylanilines.

Compound.	$\lvert\delta\nu\rvert^{a}$ (Hz)	$T_c^{\,b}$ ($^{\circ}$C)	$\Delta G^{\neq}_{c}{}^{c}$ (kcal./mole)	$\Delta G^{\neq cd}$ (kcal./mole)	log k^{e} (133°K)	σ^{-}
p-nitrosodimethylaniline (IV)	7.1	-87.5	9.9 ($\pm$0.1)	8.6 ($\pm$0.2)	-1.66	1.57
p-formyldimethylaniline (V)	5.4	-125	7.8 ($\pm$0.1)	7.6 ($\pm$0.2)	0.01	1.126
p-acetyldimethylaniline (VI)	8.2	-134	7.2 ($\pm$0.1)	7.0 ($\pm$0.1)	0.93	0.874
dimethylaniline				5.1 ($\pm$1.0)	4.09	(0)
p-nitrodimethylaniline				7.9 ($\pm$0.4)	-0.50	1.27

Notes.

(a) The 100MHz. 'frozen' shift separation for syn and anti methyl groups measured at low temperature with a mixture of toluene-d_8 and vinyl chloride (ca. 1/1, v/v) as solvent. These shifts are sensitive to the proportion of solvent components.

(b) The coalescence temperature ($\pm$2°).

(c) Evaluated with a transmission coefficient of unity.

(d) At 133°K.

(e) Obtained from (IV) and (V) by extrapolation of high temperature kinetic data: rates of NMe_2 rotation (k in s^{-1}) were measured by matching experimental and computer calculated spectra, the former being recorded when the rate of X=O rotation is negligable.

Table 2.

account for these unusually large negative entropies in terms of errors of this nature. The fact that these effects are almost invariably observed with aromatic solvents does suggest though, that some factor arising from the use of solvent shifts is operational in causing these entropies, which in themselves are not chemically reasonable.

In the current studies, 50% toluene-d_8 has been employed together with 50% vinyl chloride as solvent mixture. This particular mixture has the advantages of a low freezing point, good solvation powers for polar solutes at low temperatures and ASIS of a differential kind, required to permit observation of resolved signals from the dimethylamino methyls at low temperatures.

The enhancement of magnetic anisotropy of the para group observed in each case is satisfactory (see Table 2). No attempts have been made to allow for variations of this solvent shift with temperature since extrapolation from low temperatures was prohibited by the limits of solubility and solvent viscosity. Full line shape analyses were undertaken, though the quality of fit achieved deteriorated at low temperatures. The free energies of activation obtained at the coalescence temperatures are least subject to error, and the extrapolations necessary for comparison of the free energies at the same temperature have been made to the lowest coalescence temperature since the results derived at higher temperatures are the more reliable. Thus the greatest extrapolation was performed on the results of (IV), which are the most reliable of the three sets, whilst the results of (V) where the fit is poorer are only extrapolated 10°K. The results of (VI) are not extrapolated.

It is to be noted that very large and negative entropies of activation are observed in the current series. Similar effects were observed by Klinck, Marr and Stothers/[71] for rotational barriers in (IV) and (VI) in pure toluene, though of course the rotations in question concerned the para group. It is notable that the activation barrier in (IV) is reduced from 10.6 to 9.9 kcal./mole on moving from CD_2Cl_2 to the present solvent mixture.

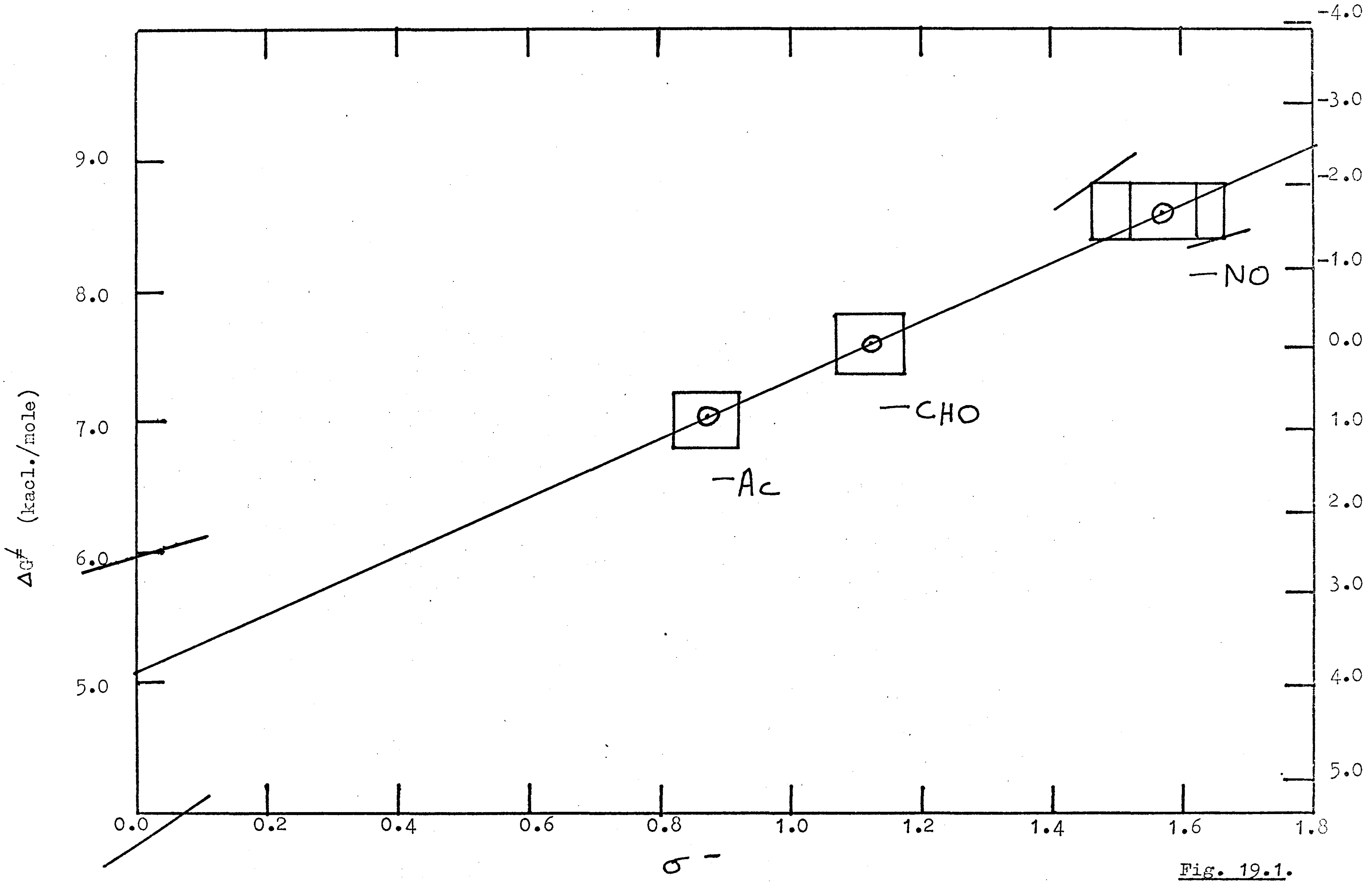

$\Delta G^{\neq}$ (kacl./mole)
9.0
8.0
7.0
6.0
5.0
LOG k
-4.0
-3.0
-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
σ^-
-Ac
-CHO
-NO

Fig. 19.1.

As can be seen, the free energies of activation for the dimethylamino rotation at 133°K. show a marked dependence on the para group. The decreasing resistence to internal rotation of the NMe_2 group indicates a decreasing tendency for delocalisation of the nitrogen lone pair of electrons into cooperative mesomerism with the para group. The trend parallels the known mesomeric accepting powers of these groups. It is interesting to plot these free energies against the Hammett σ^- constants for the para group. The σ^- value for the nitroso group has been taken from the n.m.r. data of Rae and Dyall/65 for benzene solutions. No chemical method provides a satisfactory value of this constant and it is felt that this source provides as good an estimate as any. It is based on the observation of a correlation between the N-Methyl proton chemical shifts in a series of para substituted N,N-dimethylanilines and the Hammett σ^- constants. Other σ^- values are taken from the major compilations of Jaffe/85 and Wells/86.

Though only three points can be plotted, it is interesting to assume the existence of a linear Hammett correlation, the current points at least, lying on a straight line! Fig. 19 shows the line obtained. The equation of the line shown is

$$\log(k/k_o) = \rho\sigma^- \qquad (1)$$

where $k_o = 4.09$ and

$\rho = -3.7$.

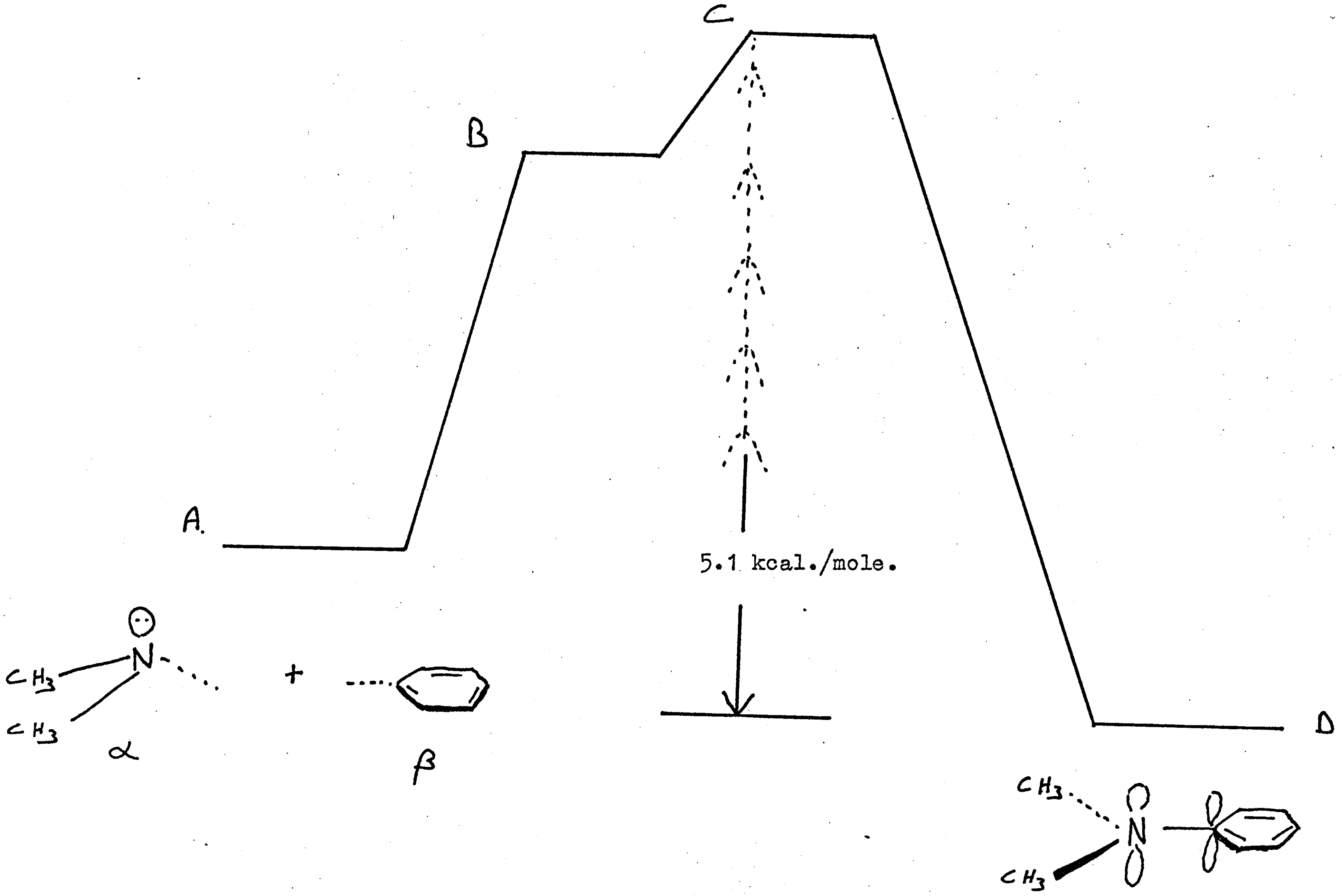
Log k_o describes the rate of internal rotation in dimethylaniline itself at 133°K, and is equivalent to a rotational barrier of 5.1 kcal./mole. The error estimates on this figure can be placed at ±1 kacl./mole on the basis that the Hammett correlation holds exactly, but that the errors in free energy barriers and σ^- constants are as shown in fig. 19.

The basis upon which this estimate of the rotational barrier in dimethylaniline has been made is open to many serious objections, but there is little doubt that the result obtained is intuitively of the right order. The use of the Hammett correlation, which in essence has been assumed, is open to dispute. As we have seen, several authors in studying various systems have obtained Hammett correlations of varying degrees of consistency. The σ^- parameter can be recognised as containing a term covering field effects of the para group and a term covering resonance effects. Whilst there is no disputing the significance of resonance effects in establishing rotational barriers, the field effects do not necessarily seem to lead to any contribution to barriers at all. In consequence, it may seem surprising that a Hammett correlation to rotational barriers is ever observed. However, this can be understood on the assumption that the field effect varies in proportion to the resonance effect. Whilst this then results in a decreased gradient of the Hammett plot to be observed if true resonance parameters are plotted against rotational barriers, it does not affect any of the conclusions reached here.

It is informative to consider the nature of the interaction represented by the measured energy barriers in dimethylanilines and related compounds. Factors which can affect the value of the rotational barriers in such compounds are numerous. The simplest possible assumption which can be made is that the observed rotational barriers represent the total resonance interaction of the dimethylamino group with the attached phenyl system. This requires that the mechanism of rotation of the dimethylamino function is purely one of rotation of the planar group from a state of maximum resonance interaction where it is coplanar with the phenyl ring to a state of zero resonance interaction which is one where the two planes (of dimethylamino group and phenyl ring) are orthogonal. No steric interactions between these two units is contemplated in this model for the rotational process.

Such a model is, of course, untenable. It is reasonable to assume at least a small steric interaction between the dimethylamino methyls and the phenyl ring ortho protons in the coplanar ground state of the system. This is releaved during rotation with the result that the ob:

Fig. 20.1.



:served rotational barrier underestimates the resonance energy to the extent of this steric interaction which will be zero in the transition state. If we allow ca 1.5 kcal./mole for this steric interaction, then the resonance energy is apparently worth ca. (5.1 + 1.5) kcal./mole : 6.6 kcal./mole.

Recently reported values for amine inversion barriers in trialkylated systems[87-90] imply that a similar barrier of 6.5 kcal./mole should exist in dimethylphenylamines, were such systems pyramidal. In other words, it seems appropriate to associate a strain of ca. 6.5 kcal./mole with flattening the nitrogen pyramid in anilines. If this pyramid collapses during rotation so that the transition state is not orthogonal but pyramidal about the nitrogen, then the resonance energy is apparently worth (5.1 + 1.5 + 6.5) kcal./mole, i.e. ca. 13.1 kcal./mole. The fact that the nitrogen may not collapse leads to problems in estimating the true worth of the resonance energy.

Consideration of fig. 20 may clarify the matter. If we consider the two partial structures α and β shown and define the process of bringing them together into a bonded unit as being energetically of no consequence, then we can define our datum energy level as the energy of the combined unit. This corresponds to level A. If we now force flattening of the amino function we exalt the total energy of the system to level B. Similarly introduction of steric strain raises the energy to level C. As level A is a perfect description of a strainless pyramidal transition state, then introduction of resonance stabilisation can be seen to reduce the energy to level D. But the true description of the transition state may lie at any point between A and C. As a result, the figure of 5.1 kcal./mole estimated for the rotational barrier in dimethylaniline may refer to any of the continuum of transitions between the limits D$\longrightarrow$A and D$\longrightarrow$C. In other words, the resonance energy lies somewhere between ca. 5.1 and ca. 13.1 kcal./mole.

It is also possible that the ground state of this system need not consist of a perfectly planar nitrogen with fully developed strain as assumed above. There is evidence in the case of dimethylaniline itself to suggest that the nitrogen is not completely planar. The Me-N-Me angle has been measured by electron diffraction techniques as 116° ± 2°[91]. Whilst this does not change the argument for a minimum resonance energy of 5.1 kcal./mole, it suggests that under any circumstances, the above estimate for an upper limit to the resonance energy is too optimistic. On the other hand X-ray evidence of the solid state geometries of p-nitroso-N,N-dimethylaniline[92] and p-nitro-N,N-dimethylaniline[93] indicates that the geometry around the nitrogen is completely planar. Whilst on the one hand, this does not preclude partial collapse in solution in these systems, it also suggests that a strictly common geometry about the dimethylamino function in this series of anilines in solution is not to be found. It seems likely, that if any aniline is to show partial collapse at nitrogen in the ground state then it will be the parent compound where the advantages accruing from resonance interaction, only fully developed in a planar ground state, are the least.

A related instance of such a barrier during which nitrogen passes from a pyramidal to a planar condition is observed in p-substituted 1-aryl-2,2-dimethylaziridines (fig. 21). Here the inversion barrier[69] shows a linear correlation with Hammett σ^- substituent constants with ρ equal to -2.8 to -3.3 at -60°C. The transition state for this inversion

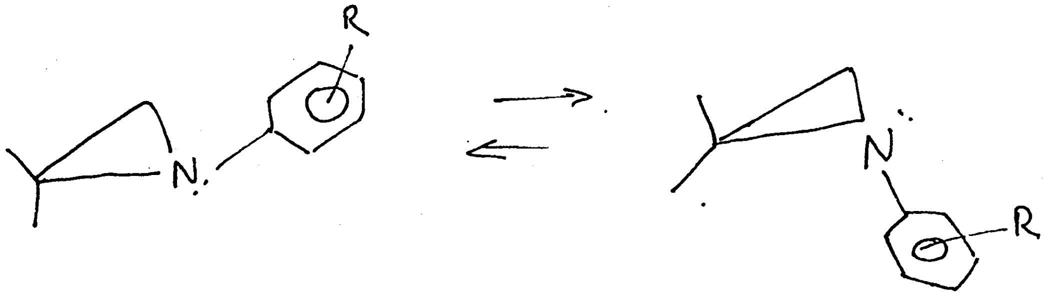
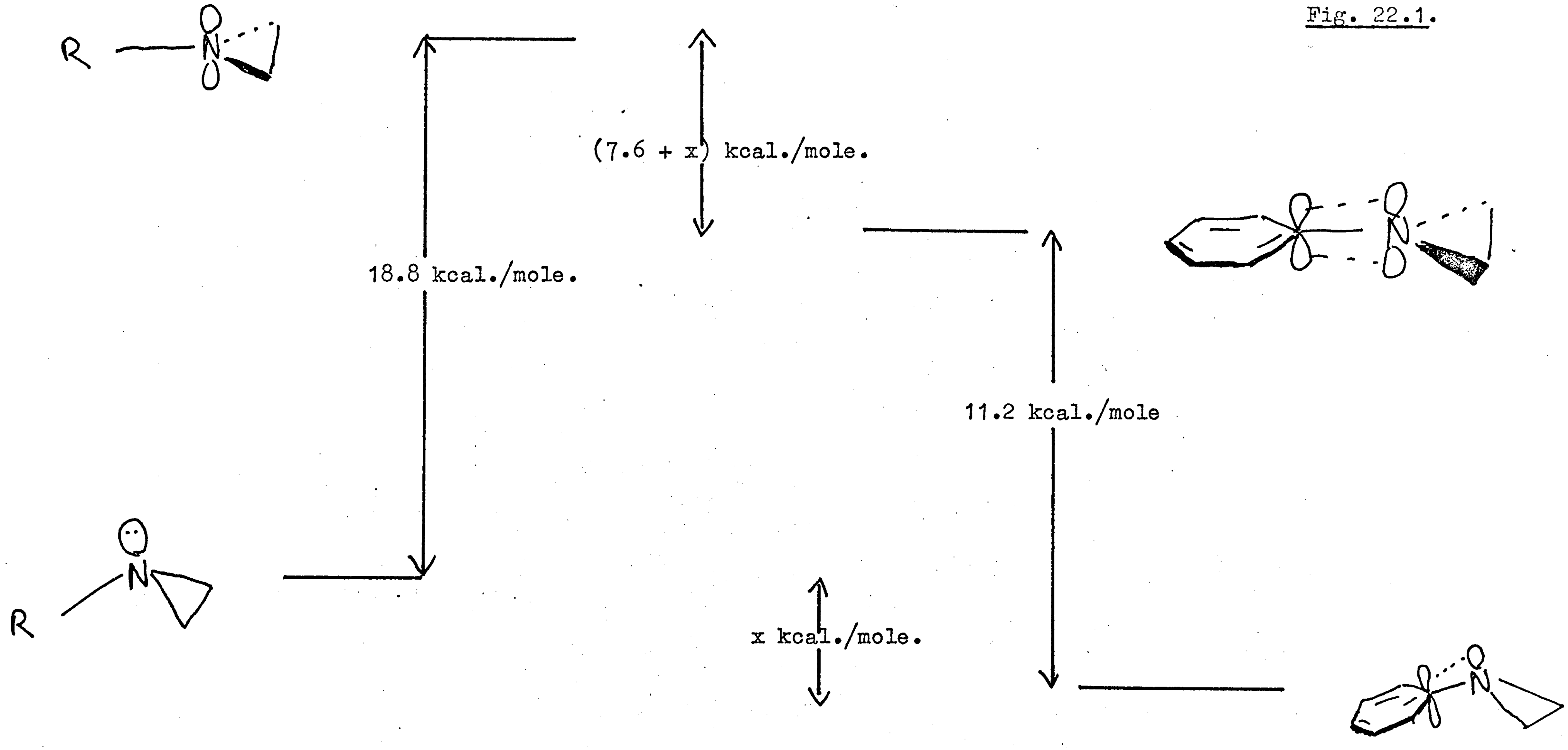


Fig. 21.1 - 22.2.

is a completely planar state probably bearing many analogies with the supposed planar ground state of the rotational isomers discussed above. In this transition state, the inversion barrier for the aziridine ring is reduced by resonance interaction between the nitrogen lone pair elec-

Fig. 22.1.



trons and the aromatic nucleus (bearing possibly a para group). It is interesting to note that whilst the energy barrier to inversion in the alkyl substituted aziridines is about 18.8 kcal./mole[94,95], that in the phenyl aziridine is 11.2 kcal./mole. Examination of fig. 22 indicates the possible resonance effects of the phenyl system. All steric factors, which will not vary significantly from alkyl to phenyl aziridines, have been assumed to be equal in both ground and transition states. The observed difference in inversion barriers of 7.6 kcal./mole can be seen to be the minimum value for the total resonance contribution to stabilising the transition state on the assumption that the ground state does not experience any resonance stabilisation also. There is reason to suspect some degree of resonance stabilisation of this ground state for an electron diffraction study of phenylaziridine itself[96] indicates that though the geometry about the nitrogen is pyramidal, there is a tendency for the amino lone pair to be aligned in a satisfactory orientation for some stabilising overlap with the phenyl π orbitals. The planes of the aziridine and phenyl rings show coplanarity of their normal planes. This overlap can not be of great significance, however, and the resulting estimate of the total resonance stabilisation cannot be much in excess of 9 kcal./mole. Allowing for the possibility of differing steric factors, it still seems unlikely that the high value of 13 kcal./mole could be accepted, by this argument, as a likely resonance energy.

Returning to the Hammett correlation assumed in the anilines, it is possible to derive an estimate for rotational barriers in molecules where various factors preclude their direct measurement. So in the case of p-nitro-N,N-dimethylaniline we can, by using the σ^- value of the nitro group at 1.27, estimate a rotational barrier in the aniline of 7.9 (±0.4) kcal./mole. Though a useful feature of the Hammett correlation in its own right, we may make further use of this value if we consider the related inversion barrier in the nitrophenylaziridine. Here the barrier is 8.2 kcal./mole, yielding a minimum resonance stabilisation of 10.6 kcal./mole. This is 2.7 kcal./mole in excess of the rotational barrier in the aniline. The difference observed in the unsubstituted cases was 2.5 kcal./mole, a satisfactory agreement. The additive effect of the nitro group in both cases is practically the same and consonant with a resonance stabilisation providing the vast majority of the stabilisation.

From these two sets of results, we can see that there is a minimum difference of 2.5 kcal./mole between the two cases of resonance interaction. These results thus tend to implicate some non-planarity in the aniline ground state to explain this difference for otherwise the aniline ground state and the aziridine transition state are exactly analogous as are the aniline transition state and the aziridine ground state in which we will propose insignificant resonance interaction. It should be stressed, though, that the steric factors have been assumed unable to account for this minimum difference and it is possible that, with all factors contributing in unexpected fashion, there is no case to answer as steric factors can account for the difference.

An interesting postscript to these preliminary studies in dimethylanilines has been published recently by Grindley, Katritzky and Topsom. /97 These authors have related σ_R^{o} constants to an energy scale. On the assumption that "the energy barrier to rotation of a substituent about the ring-substituent bond in a substituted benzene can be equated to the difference in energy of resonance interaction between the position of maximum energy (usually the orthogonal position of 90° twist) and the position of lowest energy (usually at or near coplanarity of substituent and ring) <u>less</u> the corresponding difference in strain energy." This strain energy can be neglected for positions of substituents orthogonal to the plane of the ring, i.e. for substituents twisted out of conjugation. Employing σ_R^{o} values derived from their infra-red work, these authors establish the following relationship between the resonance energy R and these substituent constants.

$$\underline{R} \quad = \quad \underline{a}.\sigma_R^{o} \qquad (2)$$

where, by simple arithmetic, a median value a can be established at 32.7 ± 1.3 kcal./mole.

In deriving this result, considerable use has been made of the rotational barriers in anilines measured and estimated above[98] and consistency among this set of results for the value of a is observed.

An interesting feature of the σ_R^{o} values employed is the fact that a value of −0.134 is assigned to a twist dimethylamino function[99] whilst −0.533 is assigned to the planar dimethylamino function. This results in a calculated resonance energy for the planar dimethylamino group of 17.43 kcal./mole whilst the twist dimethylamino group has a resonance interaction worth 4.38 kcal./mole. The difference of 13.05 kcal./mole is equivalent to our estimate of the resonance interaction in dimethylaniline. From the reasoning employed above, this value seems excessive. If we suspect this value then, plausibly we must look for possible sources of error in the reasoning employed in deriving it. Putting aside possibilities of incorrect results for rotational barriers being employed in the calculations as these all lead to inconsistency in the derived values of a, we can consider the assumptions employed in deriving the equations themselves. In the light of our discussion above, the possibility of a non-planar ground state in the case of the dimethylamino function seriously needs consideration. We can allow for this on the basis of a reduced σ_R^{o} for the ground state of the dimethylamino unit. Trial calculations with the difference $(\sigma_{R\,\mathrm{planar}}^{o} - \sigma_{R\,\mathrm{twist}}^{o})$ reduced from 0.399 to 0.35 and 0.30 lead to the following results:

for = 0.35, $\underline{S}_{NMe_2}$ = 6.35 kcal./mole, resonance$_{NMe_2}$ = 11.33/11.76 kcal./mole.
mean a value 33.50 ± 1.2

for = 0.30, $\underline{S}_{NMe_2}$ = 4.61 kcal./mole, resonance$_{NMe_2}$ = 9.71/10.30 kcal./mole.
mean a value 34.33 ± 2.1

Clearly, the calculations are relatively insensitive to the value of the resonance energy in dimethylaniline and its derivitives. The results derived above on the stated assumptions are quite consistent with the values of resonance energy indicated by the previous arguments. The figure of 10 ± 1 kcal./mole is suggested as a reasonable estimate of the total resonance energy of the dimethylamino function. Whilst in keeping with the results derived from various sources in the last few pages, this estimate is very much less than that derived from Katritzky's σ_R^o parameters which suggest the high value of 17.4 kcal./mole for the resonance energy in a planar ground state. Whilst the estimate of 10 k l./mole probably refers to a non-planar ground state resonance energy, it seems unlikely that the value could be as high as 17.4 kcal./mole. The suggested existence of resonance energy in the twist position for the dimethylamino function leads to the suspicion that the constituent parameters, in the case of dimethylamino at least, do not solely estimate the resonance energy. The difference value between these supposed resonance contributions given by Katritzky's calculations as ca. 13 kcal./mole must be considered the maximum possible resonance interaction in dimethylaniline.

Postscript: The Magnetic Anisotropy of the Nitroso Group.

During their studies of hindered rotation in nitrosobenzene systems (see above) several authors have assumed that the ring protons cis to the -N=O function are deshielded by the effect of the N=O magnetic anisotropy. Sundberg, in 1967,[100] published his observations on 2-alkyl substituted nitrosobenzenes in which a high field shift was observed for the ortho ring protons compared with the corresponding value in unsubstituted nitrosobenzene. U.v. evidence suggested that no serious nonplanarity about the nitroso-ring bond was present and in consequence it seemed necessary to postulate that the effects observed were due to steric hindrance in the ortho-alkylated case causing the nitroso oxygen to prefer the non-alkylated side of the ring. Though some slight non-planarity can be accomodated by the u.v. results, it seemed necessary to revise the commonly held opinion that the nitroso function was de:

shielding in this orientation. The concurrent observation that the ortho alkyl groups were considerably deshielded from their normal positions established the nature of the nitroso magnetic anisotropy as opposite to that which had heretofore been associated with it. Tanaka and coworkers[101] observed the same effect in 2-methyl-4-N,N-dimethylaminonitrosobenzene. Our own observations on this compound lead to the same conclusion.

Okazaki and Inamoto have also remarked upon this anomalous shift effect in nitrosobenzenes.[102] Calculations of the shifts due to the magnetic anistropy effects of the nitroso function proved satisfactory in predicting the shifts to be observed in a series of ortho substituted nitrosobenzenes. The possibility arises that it may be possible to employ such calculations to estimate the geometrical relationships of various groups within these molecules. This of course requires the establishing of accurate parameters to describe the nitroso magnetic anisotropy.

In the current case it is desirable to be able to define the geometry about the amino function in para-substituted anilines. Unfortunately, preliminary calculations indicate that the sensitivity of chemical shifts to be expected at distances equivalent to the amino-nitroso distance in anilines is low and as a result, the relatively subtle geommetrical effects sought are masked by the insensitivity of the method.

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fig. 3.1 - 3.2.	from Spaargaren, K., Korver, P.K., van der Haak, P.J., de Boer, Th. D., Org.Mag.Res., 1971,3,615.
fig. 4.1.	from ref. 8.

Practical Aspects of Nuclear Magnetic Resonance Spectroscopy in Conformational Analysis.

Spectroscopy Techniques.

The experimental methods of n.m.r. spectroscopy depend heavily on advanced electronic techniques. In addition to this, great care has to be taken with many of the factors which influence spectral quality and which are under the direct control of the experimentalist. In this area, significant improvements in the technique can often be made. N.m.r. spectroscopy has gained a poor reputation in quantitative studies particularly because of the inaccuracies which have plagued kinetic work. It is now almost cliche to remark/1 upon the wide range of free energies of activation 'measured' for C-N bond rotation in N,N-dimethylformamide. The large amount of inconsistency in these results may be traced to many sources, and is a clear indication of the problems to be surmounted in quantitative work by n.m.r. spectroscopy. However, effort expended to the end of improving n.m.r. measurements, particularly in kinetic work, is effort well spent, as n.m.r. spectroscopy is often the only technique available for acquiring a particular set of results. Kinetic processes with activation barriers of between approximately 5 and 25kcal./mole are generally only measurable by n.m.r. and reliable data on such molecules could open up a wide field to quantitative study.

The problems of spectral analysis in n.m.r. can be divided into two categories. Firstly we must ensure that the quality of the spectra obtained are of a high order, and secondly we must ensure that the processes of deriving quantitative information from these spectra, which often involve a considerable amount of numerical calculation, are as reliable as possible. Only if reliability and accuracy can be established in both these stages of the process of deriving quantitative results, can we exspect the results to be meaningful. The absence of such care in acquiring data has lead to the abundance of approximate and quite often erroneous results in the literature. Fortunately, with the increased awareness of the pitfalls awaiting the spectroscopist, such results have diminished considerably in recent years.

The Problems of Spectral Quality.

Problems of spectral quality are numerous and can perhaps conveniently be classified as arising from two sources. In the first place, it is obviously necessary that the n.m.r. equipment applied in our studies should provide the information we expect to obtain from it. In other words, the spectrum we observe (on paper for example) must be the true spectrum of the system in question and not depend, to a greater or lesser extent, on artifacts imposed by the spectrometer itself. This is, of course, easily said but in practice it is rarely, if ever, achieved. On the assumption that the electronic aspects of the instrument are optimally designed, constructed and maintained (and this is not likely to be the case), we can still find many sources of probable error in the manner the instrument is set up and operated on any particular occasion. Worse still, these sources of error will not be constant from one series of spectra to another, but will vary unpredictably with time, operator and other factors. The most obvious example of these difficulties are those encountered in obtaining a good and reliable homogeneity in the magnetic field. As judged by the width at half the height of a reference signal in the sample solution under examination, this is continually varying with time during the running of the spectrum. Almost all high resolution instruments operate at less than optimum homogeneity because of the difficulty of maintaining this optimum value under all conditions of spectral observation. As an instance, whilst the physically necessary inhomogeneity which is expressed as the line width of a signal can be readily accomodated theoretically, the occurance of a 'hump'[*2] under the lineshape of signals is never considered theoretically and almost always exists experimentally. This phenomenon can result in the variable enhancement of signal intensity across the resonance absorption signal with consequent errors in establishing theoretical/experimental spectral matches.

It is also very common to find non-linearity of the recorded spectrum with respect to frequency, and, if not accounted for, can lead to errors in the resonance position of peaks in the spectrum. Relative chemical shifts, and in bad cases even coupling constants, may be in error. In such cases one is attempting to consider non-existent spectra, and, if nothing else, this is a waste of time.

Perhaps though, the second source of errors is the more important for it is less predictable than the former kind. These are errors which do not arise from ultimate machine limitations but from experimental inaccuracy and operator oversight. Thus errors in the simple handling of the spectrometer are worth watching out for. Use of too high an irradiation power, for example, leading to 'saturation'[*3] of the nuclei giving rise to the absorption can cause spectral distortion.[*4] Incorrect setting of the spectrum phase on the signal detector gives rise to some dispersion[*5] signal being mixed in with the absorption signal to form the spectrum. This can be particularly difficult to eliminate where we are observing a small signal on the 'wings' of a larger signal. Too high a sweep rate also leads to trouble in as much as the spectra we normally try to match theoretically are 'steady state spectra'.[*6] The effect of tube spinning (which is used to achieve greater resolution) can be destructive of spectral quality if the tube is unbalanced. And so the list could continue.

One of the most significant sources of error in conformational studies by n.m.r. spectroscopy is the poor temperature control which is often established in variable temperature work. Not only does this represent directly an error in its own right, but temperature variation causes changes in spectral appearance due to phase changes or exchange rate changes or homogeneity changes and often any combination of these three.

The problem of temperature control in n.m.r. spectroscopy is a vexed one. Despite the obvious research interest in reliable temperature control, commercial suppliers do not, as yet, offer any major sophistications in this field.

There are two discernable requirements for satisfactory temperature control.

1/. The temperature should be very stable and uniform over the entire sample volume.

2/. This temperature should be known accurately.

The achievemnet of stable temperatures in a sample is in itself no mean feat.[*7] The common approach to this problem requires a heating or cooling gas stream to be passed over the sample held in the n.m.r. tube. Thus the problem of temperature control is one of controlling the temperature of a gas stream. In what follows, we will restrict our attention to the problems of operating at low temperatures, but all that is said applies also to temperature control above ambient temperatures.[*8]

The control unit employed in our present studies is the standard manufacturer's unit (Varian 4343) which, ironically[*9], is presently operating well within specifications. Temperature control is by means of a sensing unit held in the gas stream just below the spinning sample tube. This unit is a platinum resistence thermometer with very fine turns of platinum wire to allow a high degree of sensitivity to small temperature variations in the passing gas stream. This thermometer controls the input current to a heater inserted coaxially into the gas stream below the sensing unit. This arrangement satisfies stability requirements at all temperatures reached (-170° being the lowest). To achieve these very low temperatures it is essential that all the insulation (dewaring) in the probe (Varian 4333) and inlet channels is of a high efficiency. Otherwise, heat losses are such that low temperatures cannot be achieved without increasing the cooling of the nitrogen coolant gas to such an extent that condensation takes place. Wet nitrogen gas spraying onto the heater and sensor units causes severe temperature instabilities. In certain circumstances, very low temperatures with very high cooling rates for the coolant gas are necessary. In such instances, helium, though notably more expensive than nitrogen, should be used for cooling if instability from the above condensation is to be avoided. In one or two instances, not directly related to the work reported in this thesis, this approach has effectively cured temperature instabilities at very low temperatures.

Secondary procedures applied to temperature control are the careful stabilisation of input temperatures and flow rates of the gas stream to maintain constancy of operating conditions. Furthermore, spinner gas flow rates are kept as constant as possible under conditions which must vary due to different spinner rate requirements. The stability and reproducability of the temperature control were found to be affected by the temperature of the spinner gas, so this gas temperature was maintained constant by passing the gas through a long length of plastic tubing immersed in the stabilised water cooling supply to the spectrometer electromagnet.

Uniformity of temperature over the entire volume of the sample has not been achieved. This is a common and almost insurmountable failing in such experiments[*10] given the current design of variable temperature probes. The input cooling gas in such probes normally passes from bottom to top of the sample volume, gaining heat as it flows. At the same time, the temperature gradient which normally exists down the sample tube accentuates the temperature gradient within the sample itself. In practice, it is not possible to avoid this gradient. This can be minimised by employing quite high gas flow rates to ensure ample cooling capacity for the system. Further sophistication such as insulating and cooling the entire length of the n.m.r. tube requires major changes in probe design and is far outwith our resources. In the long run, a temperature gradient up the tube has to be tolerated. This is particularly bad at very low temperatures.

The second problem, that of establishing accurately the sample temperature, ultimately presents insurmountable difficulties. This has been tackled by several approaches described in the literature. For absolute security in measuring sample temperatures, it might seem essential to have the temperature sensing unit permanently inserted into the sample itself under running conditions. This is of course not possible with any common temperature sensing device, since the presence of the object in question constitutes a major disturbance to the magnetic field. The most common means of circumventing this objection lies in the use of a temperature sensitive chemical shift from a sample inserted into the sample tube inside a coaxial capillary. This device is then sensitive to the actual temperature within the sample under running conditions, but despite this apparent security in temperature measurement, there are major objections to this method.

The first objection arises in cases where the resonances from the 'n.m.r. thermometer', as it is commonly called, overlap with resonances in the sample spectrum. In such cases the technique whereby the thermometer system contained in another tube is substituted for the sample tube can be employed. The most obvious objections to this approach can be summed up in the comment that now we are no longer measuring the temperature under the same conditions as in the sample. No amount of precautions can guaruntee that these two temperatures will be the same. Of course, the likelihood that they will be as close as to be considered identical is high if sufficient precautions are taken to allow time to stabilise under identical conditions to those prevailing during running of the sample spectrum. It is also true that ultimately the coaxial insertion technique suffers from exactly the same objection. To calibrate the thermometer system in the first place, a tube substitution technique was very likely used. Calibration would be by means of reference to some temperature standard, probably a thermocouple, which would have to be inserted into an open spinning n.m.r. tube of suitable solvent. The thermometer system could not be employed within this tube as any risk of changing its constituents by having an open tube would have to be scrupulously avoided.[*11] So the initial calibration depends not only on a constant temperature being maintained between tubes but also in the situation where one sample has a heat conducting insert in it. Though considerable care is normally taken with such calibrations, it is clear that their final accuracy cannot be completely guarunteed.

A further objection to such an n.m.r. thermometer approach arises from the fact that it is difficult to establish a low temperature thermometer system. Even with any such system developed, its usefulness at higher temperatures is limited and such a thermometer would have to be exchanged for another calibrated to higher temperatures. This in itself then necessitates two identical samples being made up with different thermometer 'inserts'.

Ideally, one would like a temperature sensing system which was independent of the sample tube being run at any particular moment. This clearly allows that we will forego the illusory certainty of measurement associated with the capillary insertion technique. One such approach has been adopted in the current studies. In effect, the particular system in question is calibrated by means of a thermocouple as the main standard.

In the Varian probe system under consideration, the following modification has been affected. By means of pyrex glass reeds, two very fine thermocouple wires are lead past the heater and sensor unit of the Varian stabiliser and spot welded to form a couple at a point some 2cms. beneath the sample tube. From this couple (Chromel/Alumel) a potential is derived during running of temperature variable spectra. This potential cannot be directly related to temperature (even in the gas stream) because of the stray potentials generated in passing over the hot heater unit in the system. This potential is, however, almost exactly reproduc-

:ible between identical running conditions. This potential has been calibrated against the tube temperature for a given point in the tube - hopefully at the radiofrequency coil height - taken by means of a precalibrated thermocouple about which a sample tube, with a given height of appropriate solvent, spins. Clearly such a system is open to many objections on the basis of the number of possible variables in the system. In practice, a calibration has been established between the observed potential and the tube temperature and a smoothed mathematical relationship derived between them. There-after, this calibration is checked at frequent intervals and any drift from calibration is restored by minor variations in the input temperatue or gas flow rate. Under all circumstances this approach has proved satisfactory. A very high reproducability of temperature sensitive spectra for a given 'calibration' temperature has been observed.

Whilst short terms drifts in the calibration can be checked in this manner, long term drifts due to deterioration of the components of the system, particularly the probe dewar, must be accounted for by complete recalibration of the entire system. Such deterioration must be spotted in the first place and consequently it is extremely important to carry out frequent calibration checks. Eventually, the system deteriorates so far, generally due to the probe dewar, that a replacement unit is necessary. Unfortunately, as variable temperature n.m.r. studies are not every one's interest, this replacement often awaits major physical damage being inflicted on the probe by extremes of operating temperature before the necessary maintainance is carried out!

Such a system has been found in practice to be easiest and probably the most accurate means of establishing known and stable temperatures in the current equipment. Temperature measurement is by direct read off from a calibration table and providing operating conditions are maintained constant and sufficient time is allowed to reach equilibrium at the start of each run, then no deviations from calibration have been discov:

:ered.

Whilst many authors find spinning rate a significant factor in the calibration conditions, in our experience, the calibration is rather insensitive to this factor. This possibly reflects the very high cooling gas rates used. It is also fortunate since the Varian H.A.100 instrument has no provision for measuring the spinning rates employed, and whilst the spinner gas flow rate could be held constant, the tube spinning rate varies with several factors only one of which is the gas flow rate.

We now feel fairly confident that the problem of temperature control and measurement has been fairly satisfactorily overcome. With correctly established sample temperatures which are free from systematic error and contain very small random errors, we can confidently tackle the problem of measurement of rate processes in solution. With careful adjustment of all spectrometer variables (such as phase control), exact reproducability of spectra is observed. In these circumstances, the common practice of averaging the results of several runs in achieving the appropriate parameters for any given spectrum was abandonned. It was considered that if this procedure led to large uncertainties then the entire results could only be suspect and if, as was observed, uncertainties were small, then the averaging process was a needless waste of time. In any final estimate of the accuracy of the results uncertainties are normally quite liberally estimated but this practice also is quite dubious. Uncertainties are not intended as safety margins for a researcher's reputation but properly as reliable estimates of the possible error in acquiring the results in question. Whilst often, errors quoted may be in retrospect unrealistic, they should be treated as the best estimate available at the time. The only final test of such factors lies in the reasonableness of the results achieved and often it must be left to posterity to have the final word on this.

Several important points need to be made about the process of ob:

taining the spectra from which rate parameters are to be derived. Firstly it is of great convenience in fitting any set of spectra with their theoretical matching spectra if the homogeneity of the magnetic field is held constant throughout. As we have mentioned, it is not normally possible to achieve as good resolution at low temperatures as at high and so it is better to compromise the resolution obtained at high temperatures in the interest of facilitating spectral matching of a temperature series. In estimating the resolution achieved in any system it is better that the homogeneity standard chosen should be a molecule of similar size, shape, and polarity as the sample molecules. In this way we can assume that we are observing a similar homogeneity effect as the sample molecules. It is of course difficult to find such a homogeneity molecule which at the same time does not show any line broadenning due to unresolved small couplings or even exchange effects. The latter cannot possibly be tolerated in a homogeneity standard but the former are acceptable as long as they do not vary with temperature! In the absence of any such molecule, some standard line such as T.M.S. might be used on the assumption that variations in temperature do not subject the sample molecules to influences from the solvent which are specific and temperature variable.

Secondly we must be open to the likelihood that some or all of the 'static' parameters characterising the spectrum may in themselves be temperature variable. The most common instance of this occurs in establishing the value of the chemical shift difference between two sites of a given nucleus undergoing exchange. This difference is required in the fitting process and it is often the case that the difference observed at low temperatures where separate signals can be observed is not that appropriate to higher temperatures, where we cannot see separate signals. The only policy that can be adopted in this situation is that of observing the behaviour of these shifts over a range of temperatures where separate signals can be observed and extrapolating this behaviour into temperature regions where separate signals cannot be observed. This extrapolation assumption in itself leads to uncertainty, and it by no means need hold up over even short extrapolation ranges. In some cases spectral variations are sufficiently sensitive to changes in the shift difference here to exhibit anomalies if the extrapolation which has been assumed does not in practice hold up. In many other cases we can only hope that the coincidence of the final averaged resonance position with that predicted by extrapolation is sufficient justification for this approach. Though less common, it is also observed on occasions that coupling constant values are changing with temperature and this variation must also be taken into account[*12].

Clearly then, we require to observe the spectra of the samples in question over a greater range of temperature than merely that involved in the process of signal coalescence. This is not always easily achieved for in many cases we are working at the limits of temperature control or solubility of the sample. If we cannot achieve this exaggerated spread of temperature measurements then we have to rely on using non-extrapolated values of the static parameters. This can only be justified where the extrapolation region is short. Yet this in itself presents difficulties for the shorter this region, the less well defined any least squares line for rate and temperature observations will be. In the majority of cases we are limited to the physical situation presented by nature and consequently <u>again</u> the accuracy requirements on the temperature measurement are narrowed. It is possible in difficult cases to use spectrometers operating at higher field to exaggerate the chemical shift difference involved but this approach is limited and likely only to be of dramatic value in very precarious cases.

We can see then, that the acquisition of usable, let alone reliable, spectra for variable temperature work is fraught with difficulties. However, as experience is gained in this field problems such as these become routine and in consequence confidence in the technique is established. With care, extremely reliable measurements can be made and the results achieved can be regarded as accurate.

The Problems of Deriving Quantitative Parameters.

As we have shown earlier in this thesis, the necessary quantum mechanical techniques for calculating n.m.r. spectra under a variety of conditions are well established. The basic problem now presented is one of establishing theoretically the necessary spectral parameters (chemical shifts, coupling constants, homogeneities, rates of exchange between sites etc.) which accurately describe the experimental situation. Two distinct categories of spectral situation can be recognised. There is the problem of deriving an accurate set of chemical shifts and coupling constants appropriate to a given experimental situation in which no rate processes are being observed. There is also the problem of deriving rates of exchange of nuclei between sites in 'exchange' spectra. For this it is almost mandatory to have established accurate values of the chemical shifts and coupling constants for the static situation, though in certain situations the problem may be sufficiently overdefined to allow a measure of uncertainty in the chemical shift or the coupling constant between two sites or nuclei.

The Determination of Accurate Static Parameters.

The prerequisite of such a determination is a highly accurate spectrum taken under optimum conditions on the spectrometer. In particular, the resolution for such a spectrum should be maximised to allow precise determination of all but the smallest coupling constants and chemical shifts. As we are normally concerned with 'steady state' spectra,[*13] in the discussion that follows we will concern ourselves exclusively with this case. In consequence, it should be noted that all experimental sweep rates employed should be very low and and the observation radiofrequency should be well below saturation strength.

Many computer programs have been written to calculate the n.m.r.

steady state spectrum observed given an appropriate set of chemical shifts and coupling constants.[*14,*15] In the more sophisticated of these, the programs can be used to vary an initial set of chemical shifts and coupling constants to give a best fit to the observed spectrum.[14,15] There are several methods of performing this operation and these can be divided into two categories. In the first category come programs which iterate the input parameters to yield a best fit to the energy transitions observed in the spectrum.[*16] The necessary input to such a program will consist of an initial set of spectral parameters and a listing of the energies involved in the spectrum transitions. This in itself is a cumbersome procedure due to the necessity of determining all these energies from the transition frequencies of the spectrum. In the second category come programs which, rather than employ transition energies, employ transition frequencies and so eliminate the drudgery of the conversion procedure. Though on the face of it this does not seem a great saving, when we consider that we are no longer required to positively identify transitions but merely place them on a frequency spectrum, we can see that this approach is the more desirable for the uncertainties it eliminates. There are several programs which adopt this approach but we will concern ourselves here with the one which has been exclusively used in the work described in this thesis. This program is UEAITR.[17] Initially an approximate spectrum is calculated from an approximate set of spectrum parameters and at this stage the program outputs an ordered series of transition frequencies with identifying labels. The numeric labels are then matched with the true values of the transition frequencies derived experimentally. The program then iterates the approximate set of parameters by variation of specified shifts and coupling constants to obtain a best fit of the theoretical to the experimental transitions. No account is taken of transition intensities, but, if the correct solution has been obtained, these should also match, allowing for the possibility of spectrometer distortion in this respect.

Several points need to be made at this stage. Obviously the amount of detail in terms of the individual transitions observed in the spectrum depends somewhat on the homogeneity of the magnetic field. At the same time, however, many transition will be so close together that they constitute one resonance line in the spectrum. These transitions may differ slightly in reality and hence a limit will be placed on the accuracy of the iterated fit by the loss of information from the necessary procedure of assigning very close transitions to one very close mean transition frequency. With poorer magnetic field homogeneity, it may not be possible to derive accurately small coupling constants in the spectrum due to the mean assignment of truely distinct transitions. It is also possible to confuse the order of two transitions where their signals overlap and mis-assign these transitions by up to a Hz. or more. Errors of this kind must be watched for. Obviously the poorer the quality of the spectra, the poorer the final fit of the matched parameters due to errors of the above kinds.

An obvious refinement of such procedures develops the complete theoretical spectrum from such transitions and together with a lineshape function and specified homogeneity outputs the complete spectral lineshape to a plotting device for comparison with the experimental spectrum. It is also possible to input the entire experimental spectrum to the program and by a line search identify many of the transition frequencies in the spectrum. From this information and an approximate set of parameters the process of deriving accurate parameters can be carried through to the extent of least squares fitting the lineshape spectrum. Such sophistication depends though on the ability to store and input spectral lineshapes to a computer. As we have not yet acquired such a facility, these later sophistications have not been implemented in our studies. However, the extent of overlap matching possible with a plotter system provides very satisfactory confirmation of results.

The Determination of Accurate Dynamic Parameters.

The basis of most accurate assessments of dynamic parameters must be a knowledge of the static parameters of the system in question. If we are observing exchange of nuclei between different sites in a system, then the average spectrum is calculated from the spectral parameters of the individual contributing species in the system. Whilst we may be able to observe the spectra of such contributing species at low temperature and fit theoretical spectra accurately to them we should remember that such low temperature spectral parameters need not apply at higher temperatures where only the average spectrum cah be observed. We have already remarked at length on the techniques and assumptions employed to circumvent this problem. The whole subject of variable temperature work is fraught with such difficulties. In many instances it can only be the reasonableness of the results achieved that are a satisfactory assurance of the correctness of our approach. In such cases, we cannot exspect to achieve refinement in measuring thermodynamic parameters. Ironically, in such cases, the more complex spectral patterns often give the more reliable results.

This arises from the fact that in complex systems the exchange processes have varying effects on the appearance of the resonances from the various nuclei. So at one region of exchange rates some resonances may be dramatically affected whilst some may be more or less unaffected. These unaffected resonances can act as built in standards for the homogeneity of the system. In some instances it may be possible to observe a particular resonance line which is totally unaffected throughout the course of the exchange region. Even if such a line does not exist, the interplay of effects on the various lineshapes of signals in the system often uniquely define the appropriate exchange parameters for the system at that temperature. By such means,[*18] it is possible to achieve a high degree of accuracy in rate studies by n.m.r. spectroscopy.

The most satisfactory method of fitting experimental spectra with their theoretical counterparts would be to input the entire experimental spectrum to a computer with the necessary static parameters for the system in question and allow the computer to find the best fit theoretical match to the experimental spectrum. It is hypothetically possible to design a computer program system that would take raw data in the form of experimental spectra and follow through the procedure of spectral fitting employed by the chemist in a reasonably short time. Interaction between such a program and the chemist would be desirable in order to direct intelligently the activities of the program. Whilst considerable effort would need to be expended in setting up such a system initially, such a package would save countless man-hours of fitting time. Of course, it would have to be employed intelligently and uninformed use of such a system could only lead to completely erroneous results.

The computer programs employed in the current dynamic n.m.r. studies are described fairly fully in the appendix to this section. They are of two kinds. The first two are simple programs employing closed formulae for the calculation of exchange spectra for A/B systems. They find immediate application in the work on p-substituted dimethylanilines described earlier where the exchange process brought about by rotation of the dimethylamino group was studied. The third program employs superoperator theory (as described earlier) and results in the calculation of complex exchange spectra in terms of two complex vectors. From these vectors the normal absorption spectrum can be built up. A recent application of this approach is detailed in the paper by Binsch et al.[19] and indicates clearly the potential for accuracy in kinetic n.m.r. results. Several other authors also deserve mention for their recent sophisticated work.[20]

A sophistication in our approach to calculating these exchange broadenned spectra allows the summation of several spectra deriving from any of the above programs to yield one complete spectrum. This is applicable in situations where non-exchanging signals may require adding into the total spectrum or where exchanges in more than one set of isomers are under way at once. An exact overlay spectrum can then be produced on a CALCOMP plotter.

The final stage of these calculations involves the fitting of derived rate and temperature data to an Eyring equation by a least squares method which is that of Wentworth.[21] A copy of the program employed is given in an appendix to this section. This routine allows individual weighting of the data points if required and permits the correct representation of these weighting factors in the non-linear form of the fitted equation. Output from the program yields the least squares values of $\Delta G^{\neq}$, $\Delta S^{\neq}$ and $\Delta H^{\neq}$ for the conformational process.

By such means, it is possible to achieve reliable, accurate thermodynamic parameters from dynamic n.m.r. measurements.

Chemical Preparations.

Of the chemicals studied during the course of the work described in this thesis the following are commercially available and may also be prepared by standard methods:

p-nitroso-N,N-dimethylaniline (purified by recrystallisation from benzene).

p-dimethylaminobenzaldehyde was used as provided commercially.

p-dimethylaminoacetophenone was locally available in a pure condition.

The following synthetic methods were employed to produce the remaining compounds required.

9-nitrosojulolidine.

Julolidine (ca. 0.01M in sodium dried ether) is cooled to $-15^{\circ}C$.

in an ice-salt bath with the exclusion of light by masking with aluminium foil and the exclusion of oxygen by operating under an atmosphere of nitrogen (dry). Nitrosyl chloride, dried by passage through calcium chloride, which also serves to remove any hydrogen chloride present, is condensed into the ether at -15°C. for approximately 20 mins. This results in a saturated solution of nitrosyl chloride in ether, or in an excess of the reagent. This system is stirred (magnetic unit) for about half an hour under nitrogen, and then the temperature is allowed to return to ambient during which time, nitrogen gas flushes excess nitrosyl chloride out of the system (fumecupboard!). The resulting red solid is dissolved in a minimum of water and the resulting acid solution is neutralised with sodium carbonate solution, extracted with ether and then the extracts dried over sodium sulphate. The dried ether solution is evaporated to dryness on a rotary evaporator and the green-brown residue is taken up in the minimum of hot ethanol and allowed to crystallise. This yields crude 9-nitrosojulolidine which is best recrystallised from concentrated acetone solution. The resulting solid is in the form of prisms with a steel blue lustre, m.pt. 163.5 - 164°C. C, 71.21%; H, 6.89%; N, 13.77%: $C_{12}H_{14}N_2O$ requires C, 71.26%; H, 6.98%; N, 13.85%.

This method is essentially that described by Williams.[22]

9-nitrojulolidine.

This compound is prepared by oxidation with metachloroperbenzoic acid of 9-nitrosojulolidine.

9-nitrosojulolidine is dissolved in ether and the oxidising agent is added gradually until the solution no longer gets any yellower in colour (about 1.3 times the stoichiometric amount of perbenzoic acid but this depends on the quality of the acid used). The solution is then extracted with acid several times and the combined extracts are neutralised and extracted thoroughly with ether. The ether extracts are dried, evaporated to dryness and the residue recrystallised twice from ethanol yielding bright orange needles of 9-nitrojulolidine, m.pt. 162-164°C.

C, 66.09%; H, 6.52%; N, 12.83%: $C_{12}H_{14}N_2O_2$ requires C, 66.03%; H, 12.84%; N, 6.47%.

syn-3,7-dibromo-cis,cis-cyclo-octa-1,5-diene.

Cycloocta-1,5-diene (47g., 0.44 mol.), N-bromosuccinimide(106g., 0.6mol.) and benzoyl peroxide (4g.) in 'Analar' carbon tetrachloride (300ml.) were heated under reflux for three hours. After removal of the precipitated succinimide and concentration of the solution, the mixture was set aside at -25°C for several days. During this time a precipitate deposited. This is filtered off and the mixture returned to the cold where further precipitate forms. The dried precipitate is dissolved in benzene and forced down a short column of grade III neutral alumina. This process effectively frees the required product of traces of impurity and allows the dibromodiene to crystallise from the benzene eluant as long white needles. m.pt. 122.5-123.5°C with sublimation. C, 36.3%; H, 3.8%; required for $C_8H_{10}Br_2$ C, 36.1%; H, 3.8%.

This method is an adaptation of that described by Zabkiewicz[23].

References (Practical Aspects).

1. Allerhand, A., Gutowsky, H.S., Jonas, J., Meinzer, R.A., J.A.C.S., 1966,88,3185.

2.* this hump is caused by inhomogeneity in the magnetic field.

3.* saturation occurs when the populations of the nuclear spin levels diverge seriously from their Boltzman distribution and tend to become equal.

4.* though programs do exist for the calculation of such spectra, for our present purposes we are not interested in such effects and hence classify them as distortion.

5.* the absorption and dispersion mode signals can be detected orthogonal to one another from the n.m.r. sample. the dispersion signal is the first derivitive of the absorption signal and constitutes a distortion of the pure absorption mode for which we do not make allowance.

6.* steady state spectra are achieved by using slow sweep rates and low irradiation power in as much as these conditions allow the entire spin system to attain an equilibrium condition which we observe, not a state of change.

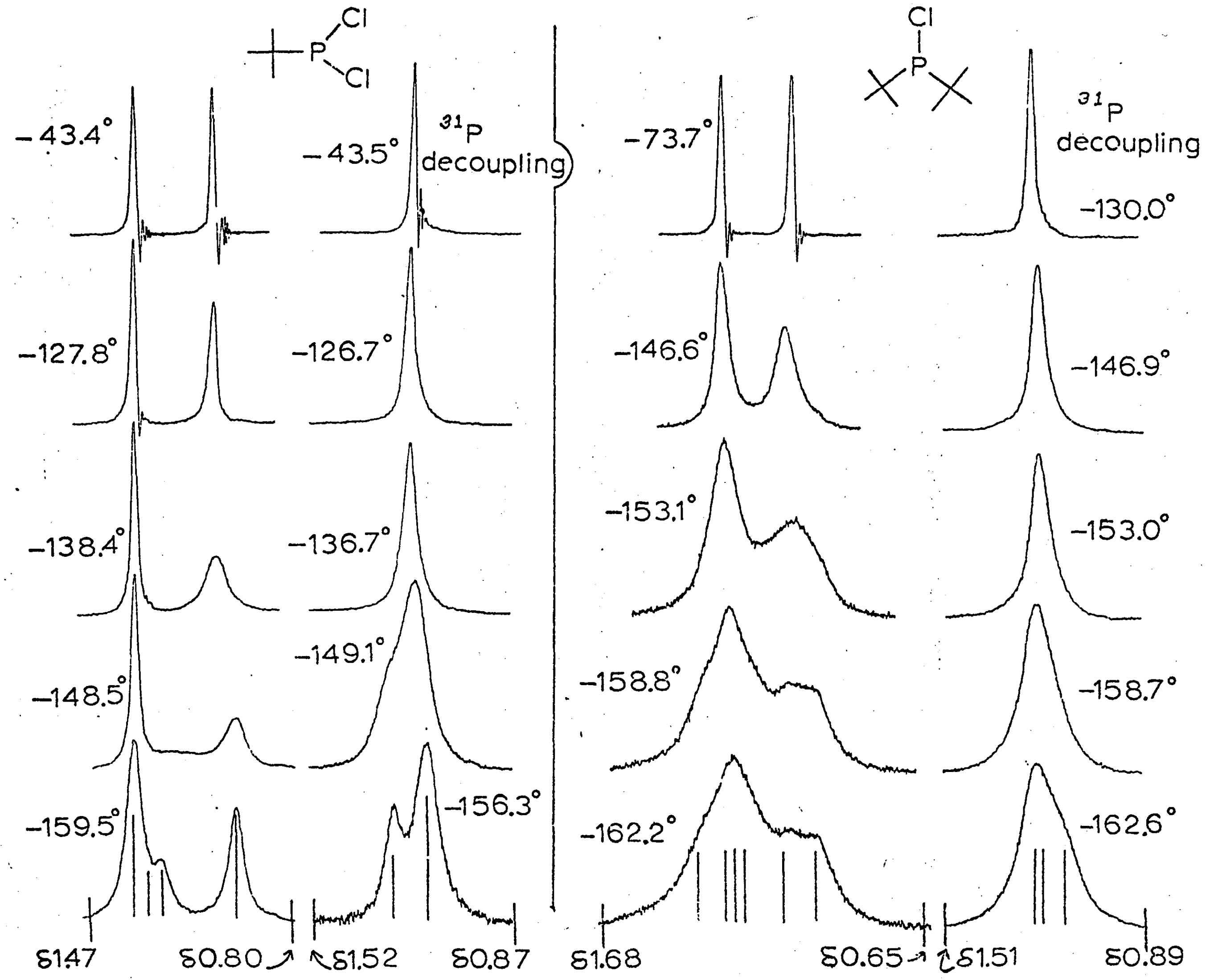
7.* as can be seen from the least squares plots given in the appendices, uncertainty in temperature is probably responsible for the majority of the uncertainty in many sets of results.

8.* most authors have discovered the greatest difficulty in achieving accurate temperature control at low temperatures.

9.* ironically, in that work was delayed for 18 months while a number of electronics technichians could not find a simple fault.

10.* it is unfortunate also in that it causes further artificial broadening of spectral lines.

11.* such chemical shift thermometers often rely on the observation of an exchanging proton to establish a temperature measuring device. the proton shift is particularly sensitive to impurities.


-43.4°
-127.8°
-138.4°
-148.5°
-159.5°
-43.5°
³¹P decoupling
-126.7°
-136.7°
-149.1°
-156.3°
δ1.47
δ0.80
δ1.52
δ0.87
-73.7°
-146.6°
-153.1°
-158.8°
-162.2°
³¹P decoupling
-130.0°
-146.9°
-153.0°
-158.7°
-162.6°
δ1.68
δ0.65
δ1.51
δ0.89
Cl
P
Cl
Cl
P

12.* the work of Binsch illustrates these points well. e.g. Steigel, A., Sauer, J., Klier, D.A., Binsch, G., J.A.C.S., 1972,94,2770.

13.* see 6*.

14.* e.g. LAOCOON2: Castellano, S., Bothner-By, A.A., J.Chem.Phys., 1964,41,3863.

15.* LAME, LACX: Haigh, C.W. in Mooney, E.F. (edit.), Ann.Reps.N.M.R. Spect., 1971,4,311.

16.* e.g. Swalen, J.D., Reilly, C.A., J.Chem.Phys., 1962,37,21.

17. Johannesen, R.B., Ferretti, J.A., Harris, R.K., J.Mag.Res., 1970, 3,84.

18.* as an example of this point that complex spectra are sometimes more informative than simple spectra, note the valuable fitting features introduced into the spectra of the phosphines shown in fig. 1 (from Bushweller, C.H., Brunelle, J.A., Anderson W.G., Bilofsky, H.S., Tet.Lets., 1972,3261.)

19. see ref. 12.

20.* for instance the work of J.D. Roberts and coworkers and the work of K.I. Dahlqvist and coworkers.

21. Wentworth, W.E., J.Chem.Educ., 1965,42,96.

22. Williams, D.A.R., B.Sc. Thesis, University of Glasgow, 1968.

23. Zabkiewicz, J.A., Ph.D. Thesis, University of Glasgow, 1965.

Appendix A : Computer Programs.

It was necessary for the current studies to acquire and develop a suite of programs for the calculation of continuous wave, steady state n.m.r. spectra. The operational programs fall into two categories. There are those which can be used for the non-iterative fitting of line-shapes for exchanging systems, and one which can be used for the calculation and iterative fitting of non-exchanging systems. Further incidental programs have been developed for least squares fitting of rate temperature data to Eyring's equation, and for the calculation of vicinal coupling constants at 1° intervals through 360° from a form of Karplus equation. As this last program is merely a time saving convenience and illustrates no significant principle, no further mention will be made of it.

The programming language used in all these programs is FORTRAN (UNIVAC level V). This is a sophisticated version of FORTRAN and permits many facilities of great convenience to a programmer which are not generally available in other versions of FORTRAN such as IBM level IV. It is not the purpose of this appendix to detail any of these sophistications and it is assumed that where mention is made of them, the reader will accept their existence as stated without further comment.

Details of the computer installation used in this work are given in Appendix B.

Programs for the Calculation of Exchanging Systems.

Programs developed in this category are of two types. The first type are restricted in the size of the system they can handle whilst the second type, consisting of one general program, can handle any size of system by the relatively simple procedure of redimensioning by parameter variables, though obvious restrictions are imposed by time required and the computer store available.

There are three programs in the first category. Whilst the last of these is general and capable of the calculations performed by the first two, it is more demanding in computer store and so advantage is taken of the first two where relatively simple systems are being calculated.

1/. QUABEX. This is used for the calculation of coupled A/B spectra with equal populations of A and B exchanging with each other.

2/. CLATUX. This is used for the calculation of non-coupled A/B spectra with variable populations of A and B exchanging with each other.

3/. DNMR3. This is a versatile program used for the calculation of fairly complex systems incorporating features such as the above together with the possibility of several exchange sites and several nuclei. Symmetry properties of the molecule can also be used to advantage.

All these programs share a common graphics routine which plots the output spectra onto a CALCOMP plotter, and at the same time allows output of the plot vectors onto the line printer in case we wish to manually plot spectra. In practice this facility is rarely used and is normally supressed. For the purposes of composing spectra deriving from more than one species in a system, several calculations can be summed together and output to the plotter at once. This sophistication is useful particularly in adding in the signals from solvent peaks in a spectrum. To further facilitate this, any number of the above calculating routines can be combined into a main program and called individually to calculate 'subspectra'.

A further refinement has been developed to circumvent the cumbersome amounts of output from the plotter involved in fitting spectra manually. For A/B systems with equal populations, a routine is available to measure up the spectrum in terms of 'maximum to minimum ratio' and 'width at half maximum intensity' without plotting these spectra at all. As the A/B case has been frequently dealt with in our work, this facility has saved a considerable amount of time in the tedious process of measuring theoretical spectra.

Had facilities for digitising spectra and inputting them to the main computer been available, the obvious extension of this approach would have been the computer measurement of experimental spectra and adjustment of the calculation parameters for a least squares fit. Such routines/[1] are becoming available and used with due care, they can eliminate much of the drudgery of the current approach to matching spectra from experimental and theoretical sources.

There is one program in the second category. This is an extended version of DNMR3 with 'parametrised' arrays to permit unlimited (hypothetically) extension of the size of the spin system calculated. As originally written, DNMR3 was suitable for immediate conversion by use of parameter variables in array dimensioning. Currently the use of this routine is restricted by the available storage on the computer. (For details of this see Appendix B.) In using this facility, the entire program needs to be recompiled with every array change. This in itself is not a burden on a powerful machine, requiring about 15 seconds.

Programs for the Calculation and Iterative Fitting of Spectra.

The program employed in this category is UEAITR. At present none of the other well known programs in this category (e.g. LAOCOON3, LAME, LACX) are operational. Again there are two versions of the program. The first is the restricted system provided by the authors which can accomodate a maximum of seven spins. The second is a generalised system employing 'parametrised' arrays as above. In this case, however, it is only necessary to recompile the main routine of this program whilst all subroutines are unaffected by the array changes, having these dimenions transmitted in labelled COMMON. Again local temporary restrictions limit us to a maximum of eight spins (no overlay has been attempted) but with the capacities available on many machines the limitation met would be one of time rather than storage requirements.

It is convenient at this point to remark that input in all of the programs mentioned in this appendix is FREE FORMAT. This is a unique

FORTRAN V facility and permits input data to be presented in a continuous string per READ statement with the fields separated by commas. The convenience of this is obvious, though unfortunately this facility is difficult or impossible to achieve with other versions of FORTRAN.

"Rigorous Least Squares Adjustment".

The basis of this program is described by Wentworth[2] in the 'Journal of Chemical Education'. The equation

$$= \quad kT/h.\exp(-\Delta H^{\neq}/RT).\exp(\Delta S^{\neq}/R),$$

due to Eyring is employed and a least squares fit of the temperature and rate of exchange data for a given system is obtained. From this we can derive the free energy of activation having calculated the least squares values of the enthalpy and entropy of activation. The input is in terms of the coordinates of the endpoints of an approximate plot line of $\log(k/T)$ versus $1/T$ to provide initial estimates of enthalpy and entropy parameters, and the rate constants with appropriate temperatures. The variances of both can be included here or set to unity. The program is self-explanatory and a copy is included in this appendix.

References (Appendix A).

1. Drakenberg, T., Dahlqvist, K.I., Forsen, S., Acta.Che.Scand., 1970,24,694.
2. Wentworth, W.E., J.Chem.Educ., 1965,42,96.

```
000   C      RIGOROUS LEAST SQUARES ADJUSTMENT.
000   C          APPLICATION TO SOME NON-LINEAR EQUATIONS.
000   C
000   C
000   C           WENTWORTH, W.E., J.C.ED., 1965,42,96.
000   C
000   C
000   C
000   C
000   C   THE FUNCTION FITTED IS AS FOLLOWS -
000   C
000   C   F=KAPPA.KBLTZ.T./HPLANK.(EXP(DELTAH/R.T).EXP(DELTAS./R)) - K.
000   C
000   C
000   C   WHERE K IS THE RATE CONSTANT, AN EXPERIMENTAL FACTOR.
000   C
000   C   WHERE KAPPA IS THE TRANSMISSION COEFFICIENT, AND IS A SIMPLE
000   C   SUPPLIED FACTOR, NORMALLY UNITY.
000   C
000   C   WHERE KBLTZ IS THE BOLTZMANN CONSTANT.
000   C
000   C   WHERE HPLANK IS PLANKS CONSTANT.
000   C
000   C   WHERE R IS THE GAS CONSTANT.
000   C
000   C   WHERE DELTAH IS THE ENTHALPY OF ACTIVATION, A PARAMETER TO BE FITTED
000   C
000   C   WHERE DELTAS IS THE ENTROPY OF ACTIVATION, A PARAMETER TO BE FITTED.
000   C
000   C   WHERE T IS THE TEMPERATURE IS DEGREES ABSOLUTE, AN EXPERIMENTAL
000   C   FACTOR.
000   C
000   C
000   C
000   C
000   C
000
000
000
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000
000
000
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```
000           IMPLICIT DOUBLE PRECISION (C,D,F,K,S)
000           DOUBLE PRECISION VADSSQ,VADHSQ
000           DOUBLE PRECISION L,R,T,Z,HPLANK,VECTOR,WEIK,WEIT
000           DOUBLE PRECISION XONE,YONE,XTWO,YTWO,GRAD,VAREXT
000           DIMENSION K(30),T(30),SIGMAK(30),SIGMAT(30),TEXT(12)
000           DIMENSION WEIK(30),WEIT(30)
000           DIMENSION VECTOR(2),COEF(2,2),COEFIN(2,2)
000           DIMENSION SIGEXT(20),VAREXT(20)
000           DIMENSION FUNCTO(30),DFBYDH(30),DFBYDS(30)
000           DIMENSION L(30)
000           EQUIVALENCE (SIGEXT(1),VAREXT(1)),(SIGINT,Z)
000     C
000     C
000     C  NOW READ IN DATA.
000     C
000     C
000         1 READ(5,1001) NRUN,
000      1001 FORMAT( )
000           IF(NRUN) 2,2,3
000         2 STOP
000         3 READ(5,1002) TEXT
000      1002 FORMAT(12A6)
000           READ(5,1003) XONE,YONE,XTWO,YTWO
000      1003 FORMAT( )
000           READ(5,1003) KAPPA,SIGINT
000           I=1
000         4 READ(5,1003) K(I),SIGMAK(I),T(I),SIGMAT(I)
000           IF(K(I).LT.0.0) GO TO 5
000           I=I+1
000           GO TO 4
000     C
000     C
000     C  DATA HAS BEEN COLLECTED.
000     C
000     C  PRELIMINARY CALCULATIONS.
000     C
000     C
000
000
000
000
000
000
000
```

```
000        5 NUMOB=I-1
000          BOLTZ=1.381D-16
000          HPLANK=6.622D-27
000          R=00.1987D+01
000          GRAD=ABS((YONE-YTWO)/(XONE-XTWO))
000          DELTAH=2.303*R*GRAD
000          DELTAS=2.303*R*(YONE+XONE*GRAD-10.3191-DLOG(KAPPA))
000          Z=SIGINT*SIGINT
000          DO 11 I=1,NUMOB
000          WEIK(I)=Z/(SIGMAK(I)*SIGMAK(I))
000       11 WEIT(I)=Z/(SIGMAT(I)*SIGMAT(I))
000          KPKBYH=KAPPA*1.381D-16/6.622D-27
000          ICOUNT=0
000     C
000     C NOW MAIN CALCULATING LOOP.
000     C
000       21 ICOUNT=ICOUNT+1
000     C
000     C RETAIN PREVIOUS VALUES OF DELTAH AND DELTAS.
000     C RETAIN PREVIOUS VALUES OF KEEPDH AND KEEPDS.
000     C
000          K22PDH=KEEPDH
000          K22PDS=KEEPDS
000          KEEPDH=DELTAH
000          KEEPDS=DELTAS
000     C
000     C SET MATRIX OF COEFFICIENTS ''COEF'' AND NORMAL VECTOR ARRAY
000     C ''VECTOR'' TO ZERO.
000     C
000          DO 31 I=1,2
000          VECTOR(I)=0.0
000          DO 31 J=1,2
000       31 COEF(I,J)=0.0
000     C
000     C NOW DEVELOP THE '2X2' MATRIX OF COEFFICIENTS ''COEF''.
000     C
000
000
000
000
000
000
000
000
000
```

```
000    C
000    C  THE METHOD OF LEGRANGE MULTIPLIERS LEADS TO NORMAL EQUATIONS
000    C  INCORPORATING ''L(I)'' AND APPROPRIATE PARTIAL DERIVITIVES DERIVING
000    C  FROM THE FUNCTION ''F''.
000    C
000    C  THE METHOD OF CALCULATION GENERATES THE NECESSARY FACTORS FOR EACH
000    C  POINT AND AUGMENTS THE APPROPRIATE SUMS BEFORE MOVING ON TO THE
000    C  NEXT POINT.
000    C
000    C  ANY REQUIRED AGAIN LATER ARE STORED IN ARRAYS.
000    C
000          DO 32 I=1,NUMOB
000          EXPTAH=-DELTAH/(R*T(I))
000          EXPTAS=DELTAS/R
000          IF(EXPTAH.LT.-700.0.OR.EXPTAS.GT.+700.0) GO TO 4444
000          KEXPDG=KPKBYH*T(I)*DEXP(EXPTAH)*DEXP(EXPTAS)
000    C
000    C  ALSO CALCULATE THE FUNCTION VALUES FOR INPUT DATA VALUES.
000    C
000          FUNCTO(I)=KEXPDG-K(I)
000    C
000    C  NOW CALCULATE THE APPROPRIATE DIFFERENTIALS.
000    C
000          DFBYDT=KEXPDG/T(I)+KEXPDG*(DELTAH/(R*T(I)*T(I)))
000          DFBYDK=-1.0D+00
000          DFBYDH(I)=-KEXPDG/(R*T(I))
000          DFBYDS(I)=KEXPDG/R
000          L(I)=-DFBYDK/WEIK(I)+DFBYDT*DFBYDT/WEIT(I)
000    C
000    C  NOW ADD INTO ''COEF'' SUMS AND ''VECTOR'' SUMS.
000    C
000          COEF(1,1)=COEF(1,1)+DFBYDH(I)*DFBYDH(I)/L(I)
000          COEF(1,2)=COEF(1,2)+DFBYDH(I)*DFBYDS(I)/L(I)
000          COEF(2,2)=COEF(2,2)+DFBYDS(I)*DFBYDS(I)/L(I)
000          VECTOR(1)=VECTOR(1)+DFBYDH(I)*FUNCTO(I)/L(I)
000       32 VECTOR(2)=VECTOR(2)+DFBYDS(I)*FUNCTO(I)/L(I)
000
000
000
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000
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000
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000
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```
000         COEF(2,1)=COEF(1,2)
000   C
000   C WE HAVE NOW SET UP THE NORMAL EQUATIONS.
000   C
000   C
000   C NOW CHECK THE DETERMINANT OF COEFFICIENTS 'COEF' FOR NON-SINGULARITY.
000   C
000         DET=COEF(1,1)*COEF(2,2)-COEF(1,2)*COEF(2,1)
000         IF(DET.NE.0.0) GO TO 33
000         WRITE(6,2000)
000    2000 FORMAT(' FAILURE. THE MATRIX OF COEFFICIENTS ''COEF'' IS SINGULAR,
000        1)
000         WRITE(6,2100) NRUN
000    2100 FORMAT(//' THE RUN NUMBER HERE WAS'I5)
000         WRITE(6,1002) TEXT
000         GO TO 1
000   C
000   C NOW INVERT THE '2X2' MATRIX 'COEF'.
000   C
000      33 COEFIN(1,1)=COEF(2,2)/DET
000         COEFIN(1,2)=-COEF(1,2)/DET
000         COEFIN(2,1)=COEFIN(1,2)
000         COEFIN(2,2)=COEF(1,1)/DET
000   C
000   C NOW CALCULATE THE REQUIRED CHANGES IN THE COEFFICIENTS.
000   C
000         DELTDH=COEFIN(1,1)*VECTOR(1)+COEFIN(1,2)*VECTOR(2)
000         DELTDS=COEFIN(2,1)*VECTOR(1)+COEFIN(2,2)*VECTOR(2)
000         WRITE(6,2002) ICOUNT,KAPPA,DELTAS,DELTAH,DELTDS,DELTDH
000    2002 FORMAT(' ITERATION NUMBER IS'I2///' CURRENT VALUES OF EQUATION PAR
000        1AMETERS ARE AS FOLLOWS.'//20X'TRANSMISSION COEFFICIENT ''KAPPA'' '
000        25X'='D14.6/20X'ENTROPY OF ACTIVATION ''DELTAS'' '8X'='D14.6/20X'EN
000        3THALPY OF ACTIVATION ''DELTAH'' '7X'='D14.6///' CORRECTION TO EQUA
000        4TION PARAMETERS AFTER THIS ITERATION ARE AS FOLLOWS.'
000        5//20X'IN ENTROPY OF ACTIVATION ''DELTAS'' '5X'='D14.6/20X'IN ENTHA
000        6LPY OF ACTIVATION ''DELTAH'' '4X'='D14.6////)
000
000
000
000
000
000
000
000
000
```

```
      DELTAH=DELTAH-DELTDH
      DELTAS=DELTAS-DELTDS
      IF(ABS(KEEPDH-DELTAH).LE.ABS(DELTAH*0.0001).
     1AND
     2.ABS(KEEPDS-DELTAS).LE.ABS(DELTAS*0.0001))
     3GO TO 100
      IF(ICOUNT.LE.2) GO TO 36
      IF(ABS(K22PDH-KEEPDH).LT.ABS(KEEPDH-DELTAH).
     1OR
     2.ABS(K22PDS-KEEPDS).LT.ABS(KEEPDS-DELTAS))
     3GO TO 9070
      IF(ICOUNT.GE.20) GO TO 37
   36 CONTINUE
      GO TO 21
C
C AT THIS STAGE LOOPING OCCURS UNTIL SATISFACTORY CONVERGENCE HAS BEEN
C ATTAINED OR TWENTY ITERATIONS HAVE BEEN COMPLETED.
C
C THE FOLLOWING SEQUENCES ARE CONCERNED WITH INFORMATION OUTPUT.
C
   37 WRITE(6,2004)
 2004 FORMAT(' NO CONVERGENCE HAS BEEN ACHIEVED AFTER 20 ITERATIONS.')
      GO TO 110
  100 WRITE(6,2005) ICOUNT
 2005 FORMAT(//' CONVERGENCE IS SATISFACTORY AFTER 'I2,'ITERATIONS.')
      WRITE(6,2100) NRUN
      WRITE(6,1002) TEXT
  110 WRITE(6,2006) KAPPA,DELTAS,DELTAH
 2006 FORMAT(' THE LEAST SQUARES VALUES OF THE FUNCTION PARAMETERS ARE A
     1S FOLLOWS.'//20X'TRANSMISSION COEFFICIENT ''KAPPA'' '5X'='D14.6,'
     2THIS WAS NOT FITTED.'/20X'ENTROPY OF ACTIVATION ''DELTAS'' '8X'='D
     314.6/20X'ENTHALPY OF ACTIVATION ''DELTAH'' '7X'='D14.6/' THE FINAL
     4 CORRECTIONS ARE STATED ABOVE.')
      WRITE(6,1004) (I,K(I),SIGMAK(I),T(I),SIGMAT(I),I=1,NUMOB)
 1004 FORMAT(' DATA POINT.     RATE CONSTANT,       VARIANCE,       TEMP
```

```
000        1ERATURE,         VARIANCE.'//(T4,I2,T18,D14.6,T37,D14.6,T52,D14.6,T7
000        22,D14.6))
000         GO TO 1
000    9070 WRITE(6,4567) ICOUNT
000    4567 FORMAT(' THE ROUTINE IS DIVERGENT AFTER THE ',I3,' TH. ITERATION.'
000        1)
000         WRITE(6,2100) NRUN
000         WRITE(6,1002) TEXT
000         GO TO 1
000    4444 WRITE(6,2100) NRUN
000         WRITE(6,1002) TEXT
000         WRITE(6,4545) ICOUNT,EXPTAH,EXPTAS
000    4545 FORMAT(1H1,' ERROR TERMINATION IN DEXP ROUTINE AT THE ',I2,
000        1'ITERATION. THE CURRENT VALUES OF THE EXPONENTS ARE - '//
000        220X'(-DELTAH/(R*T(I)))    =    ',D14.6//20X'(DELTAS/R)           =
000        3 ',D14.6)
000         GO TO 1
000         END
000
000
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000
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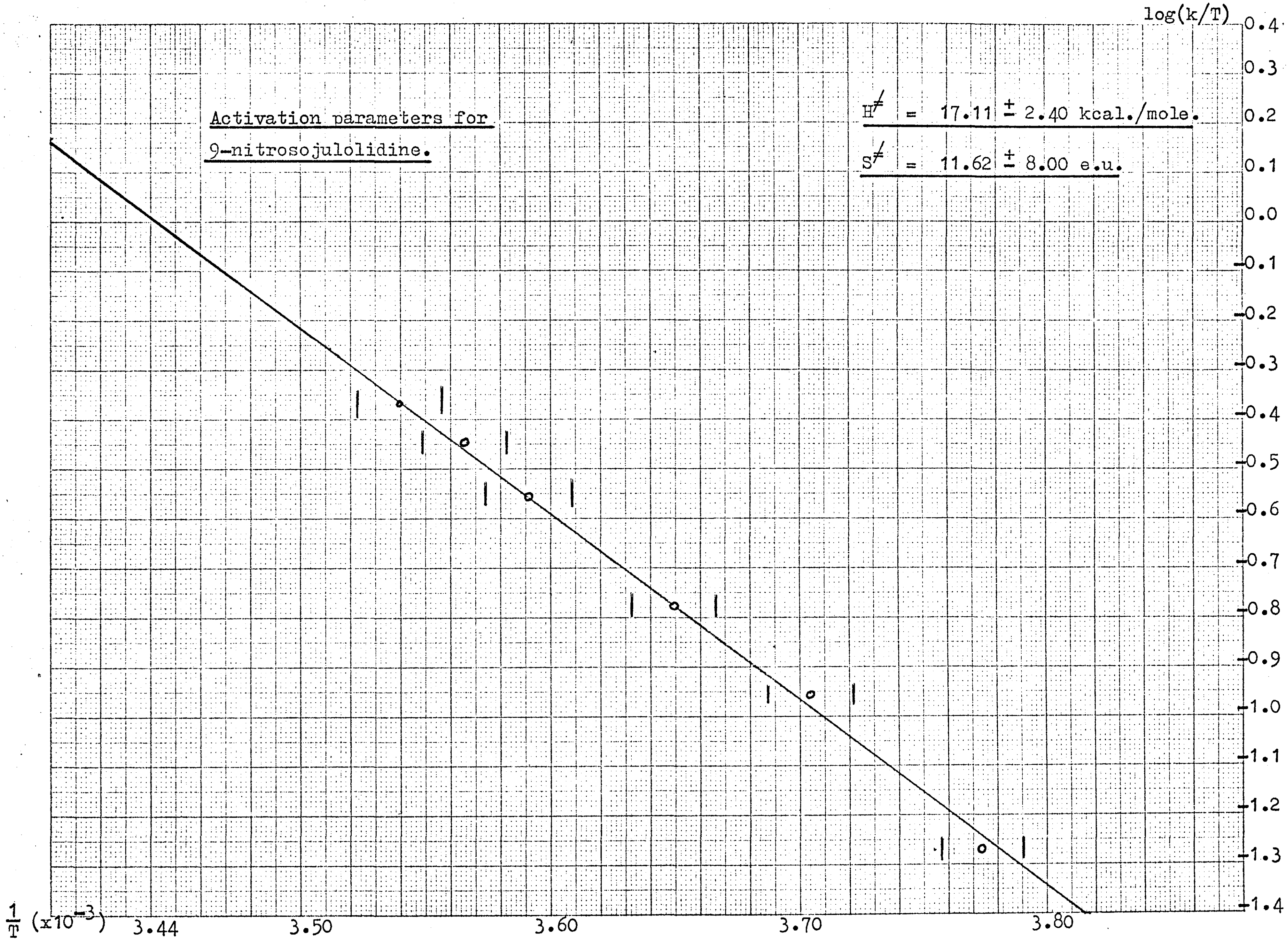
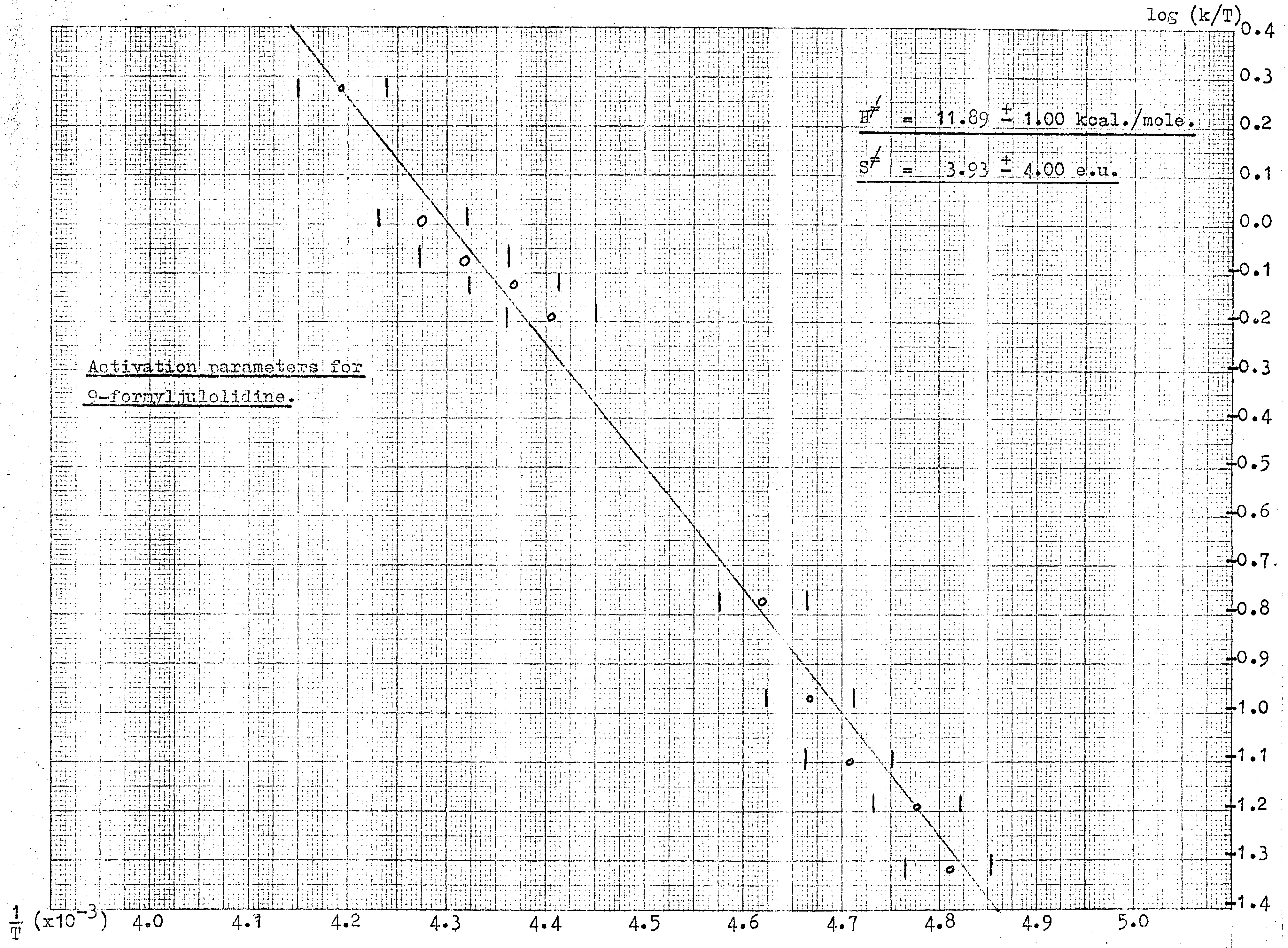
Appendix B: Quality of Results.

Notes.

The following graphs display the quality of results obtained for the Eyring plots for each of the compounds studied by variable temperature n.m.r. spectroscopy. The final graph in this series shows the extrapolation curves for the p-substituted dimethylanilines yielding free energy values at 133°K.

The four spectral overlays show the quality of fit achieved in the best set of results observed in these studies. Spectra A and B apply to 9-formyljulolidine, and spectra C and D apply to p-nitroso-N,N-dimethylaniline.

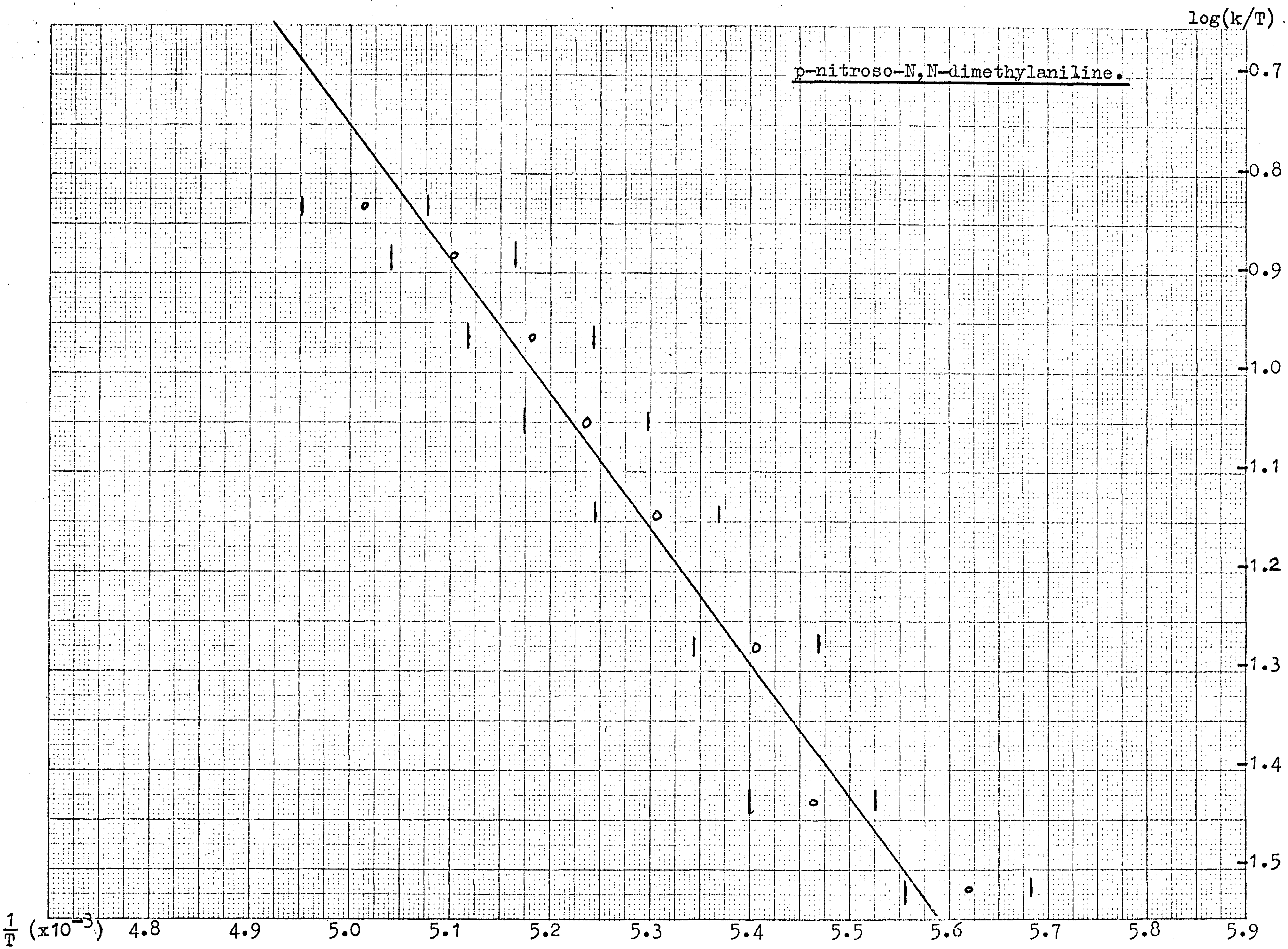

Activation parameters for 9-nitrosojulolidine.
H≠ = 17.11 ± 2.40 kcal./mole.
S≠ = 11.62 ± 8.00 e.u.
log(k/T)
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1.0
-1.1
-1.2
-1.3
-1.4
1/T (x10^-3)
3.44
3.50
3.60
3.70
3.80

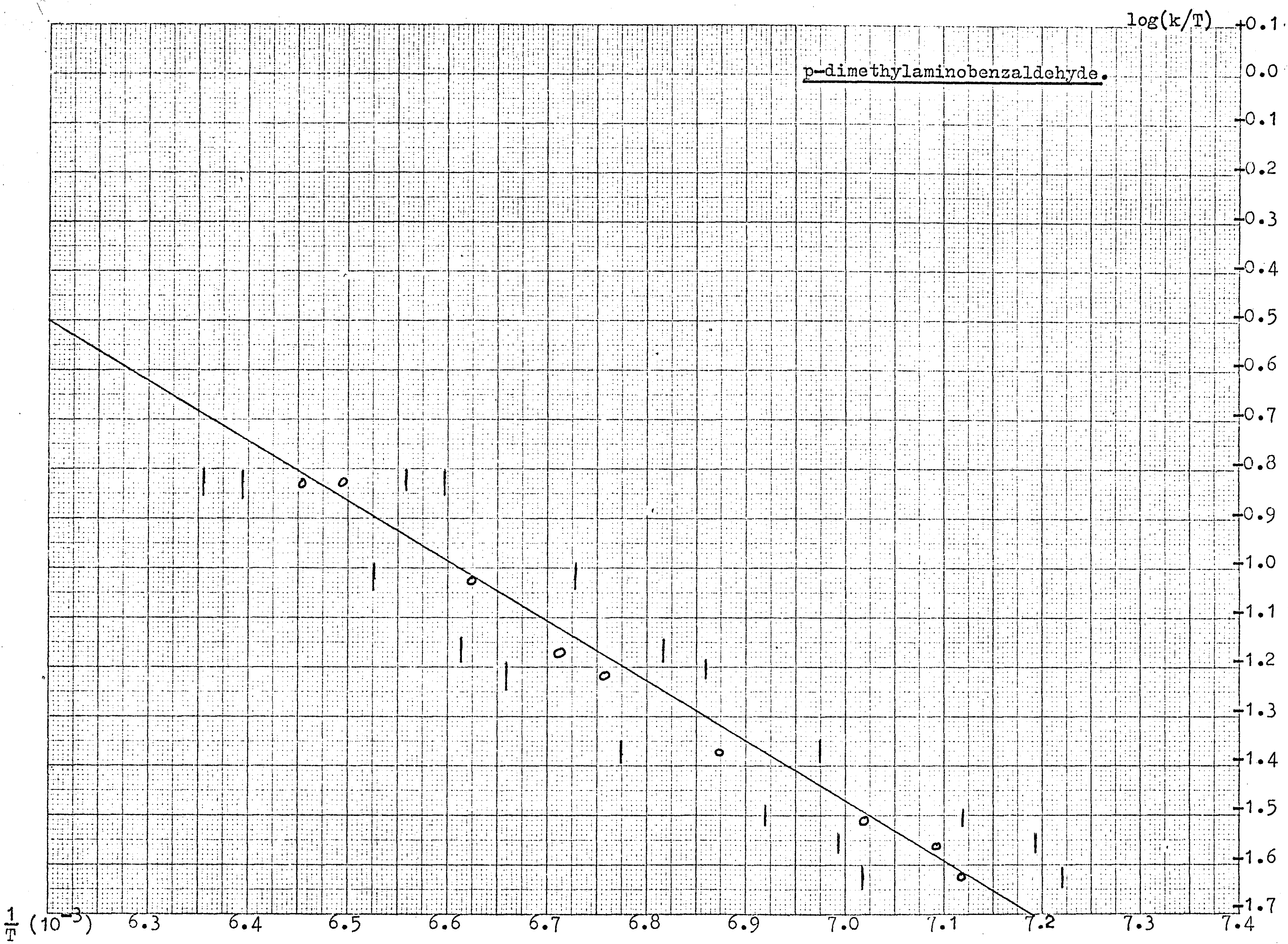


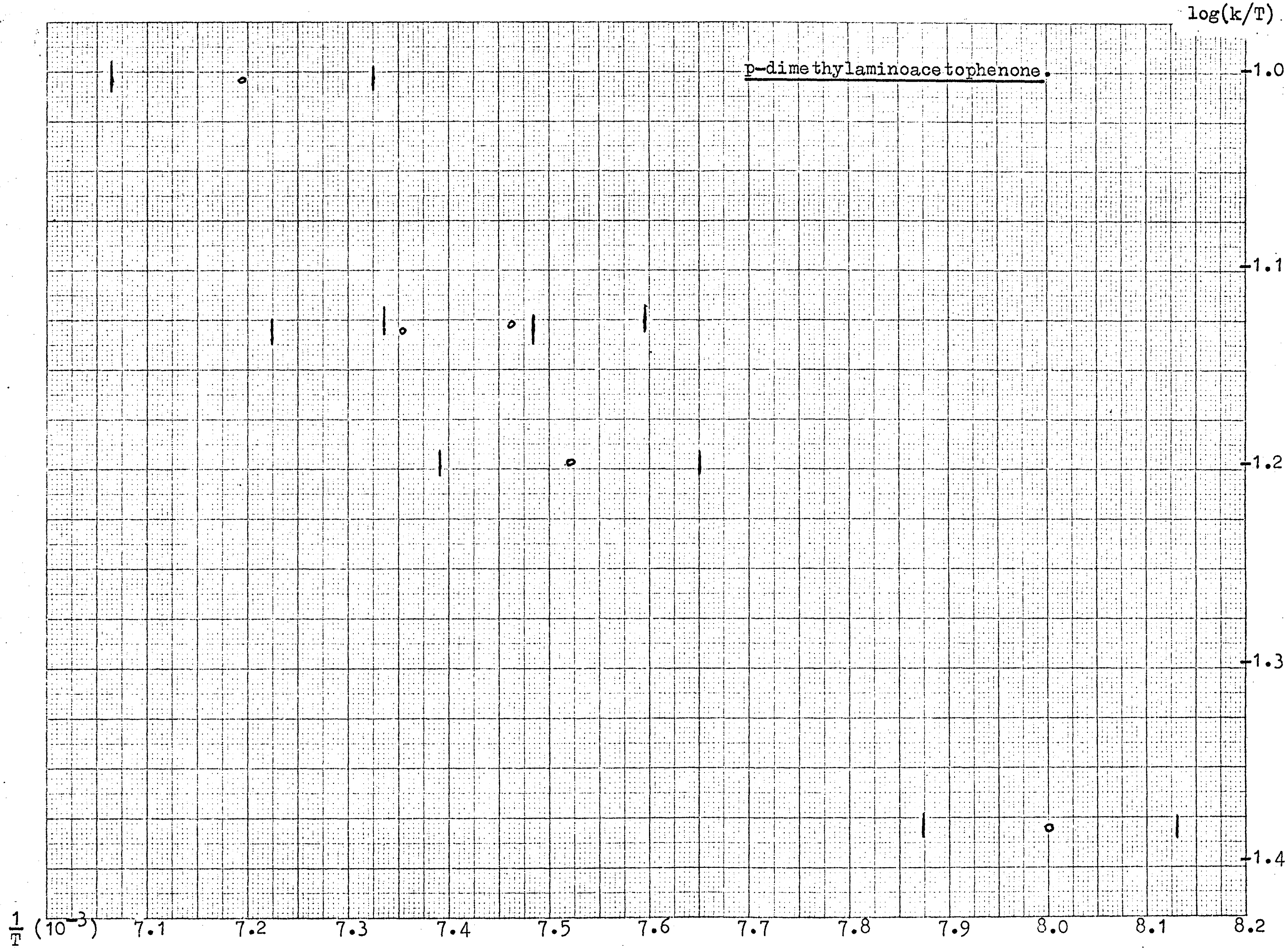
Activation parameters for 9-formyljulolidine.

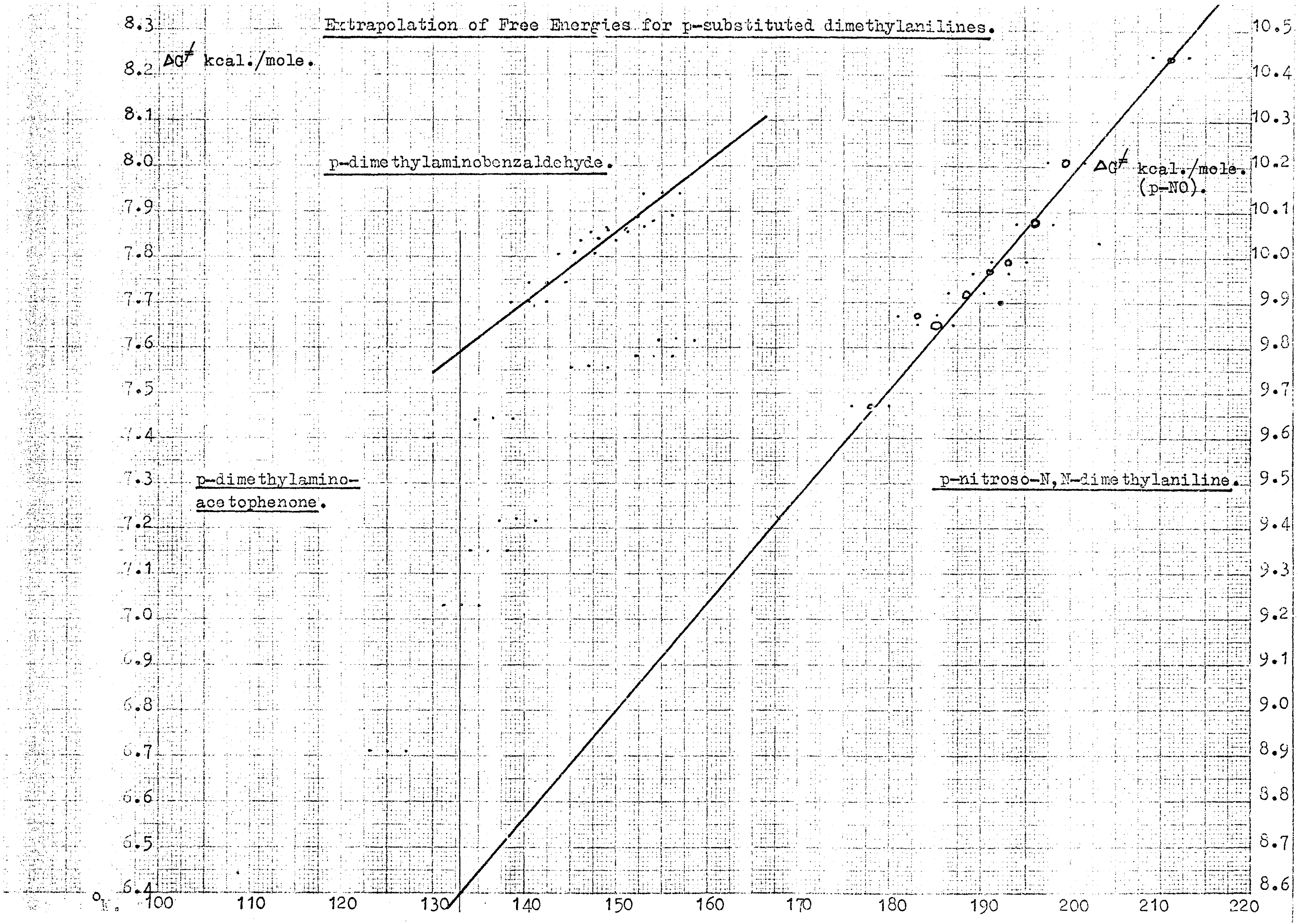
$H^{\neq}$ = 11.89 ± 1.00 kcal./mole.

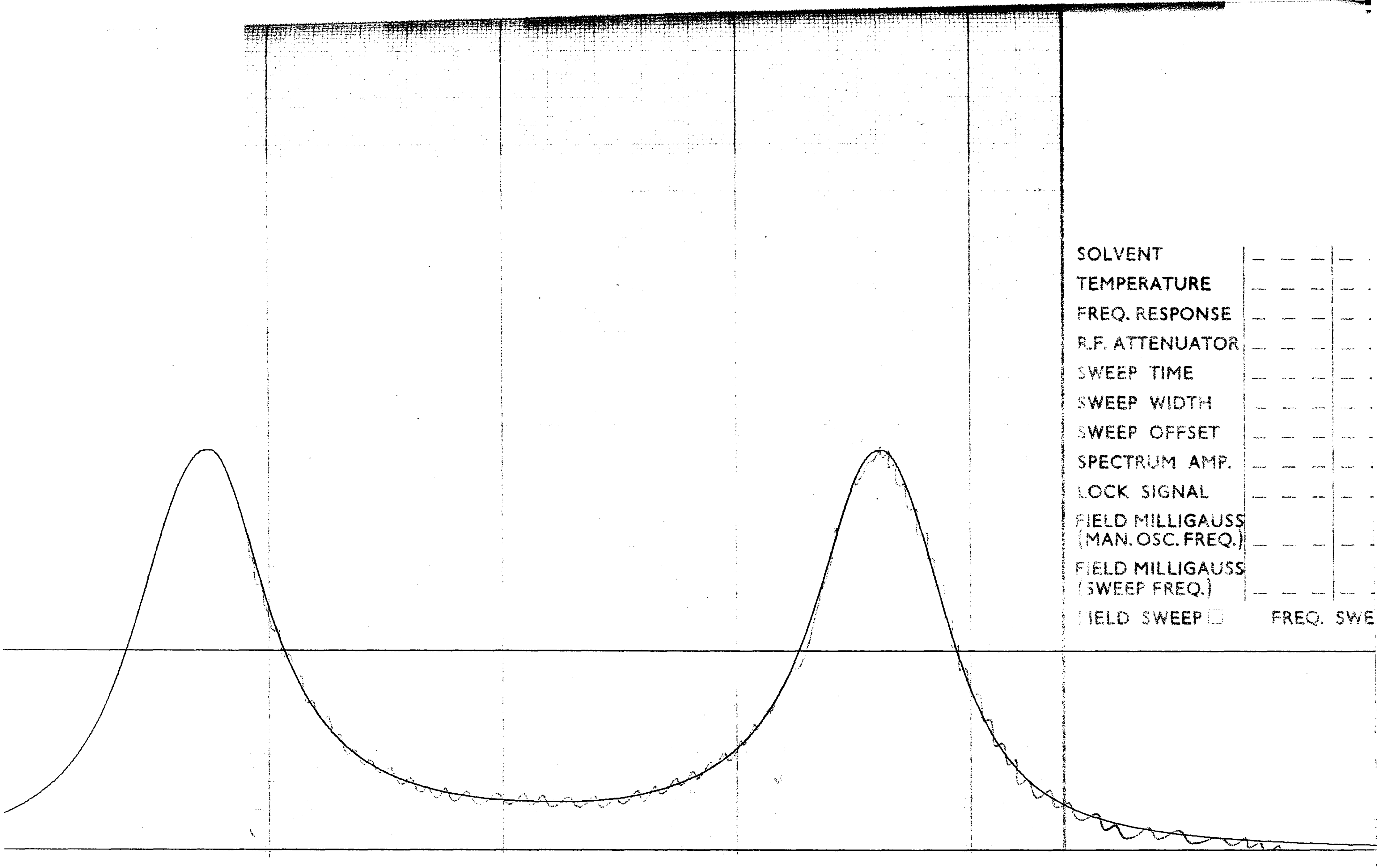
$S^{\neq}$ = 3.93 ± 4.00 e.u.


log(k/T)
p-nitroso-N,N-dimethylaniline.
-0.7
-0.8
-0.9
-1.0
-1.1
-1.2
-1.3
-1.4
-1.5
$\frac{1}{T}$ (x10^{-3})
4.8
4.9
5.0
5.1
5.2
5.3
5.4
5.5
5.6
5.7
5.8
5.9

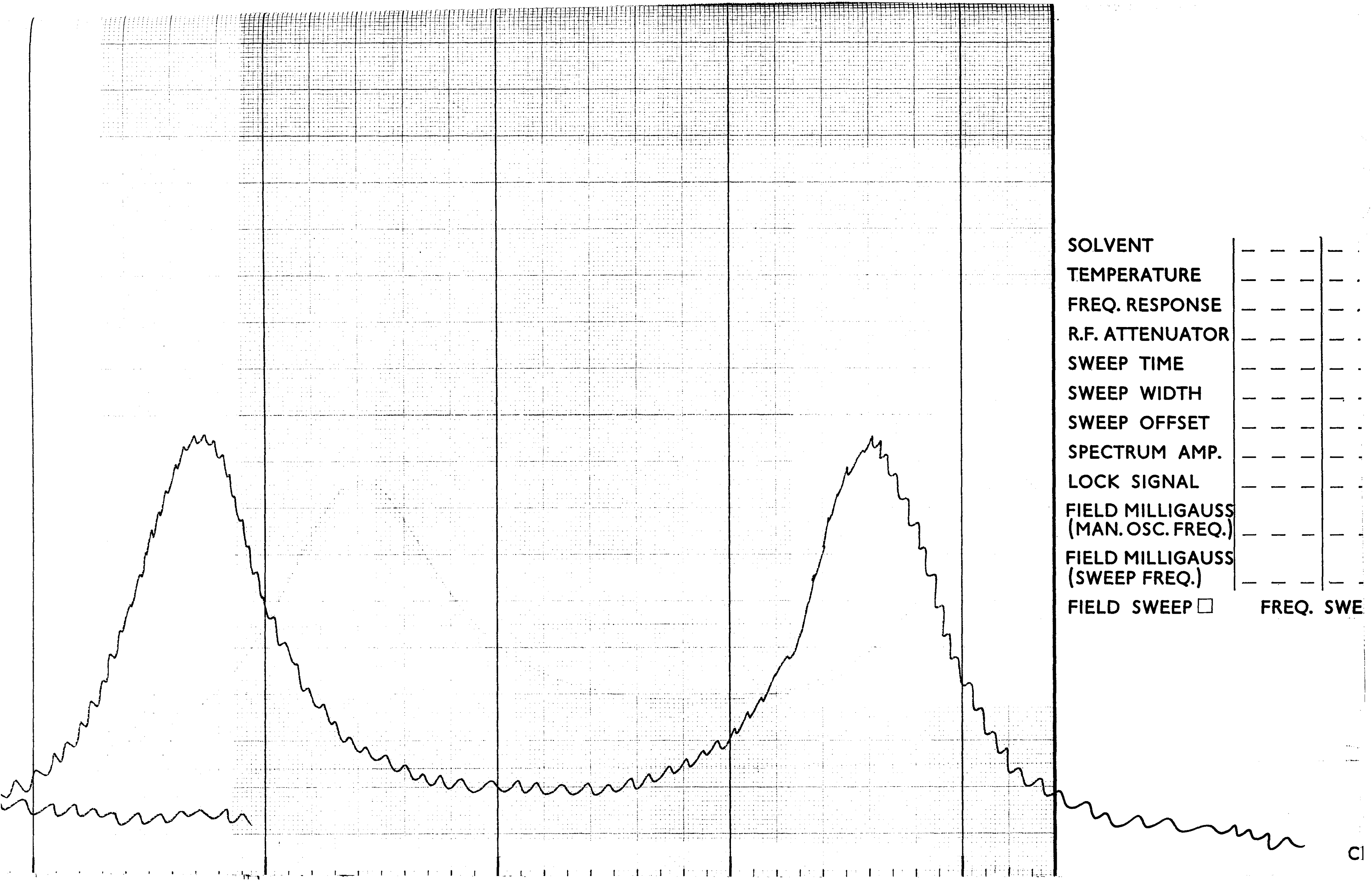

log(k/T)
p-dimethylaminobenzaldehyde.
+0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1.0
-1.1
-1.2
-1.3
-1.4
-1.5
-1.6
-1.7
$\frac{1}{T}$ (10^{-3})
6.3
6.4
6.5
6.6
6.7
6.8
6.9
7.0
7.1
7.2
7.3
7.4

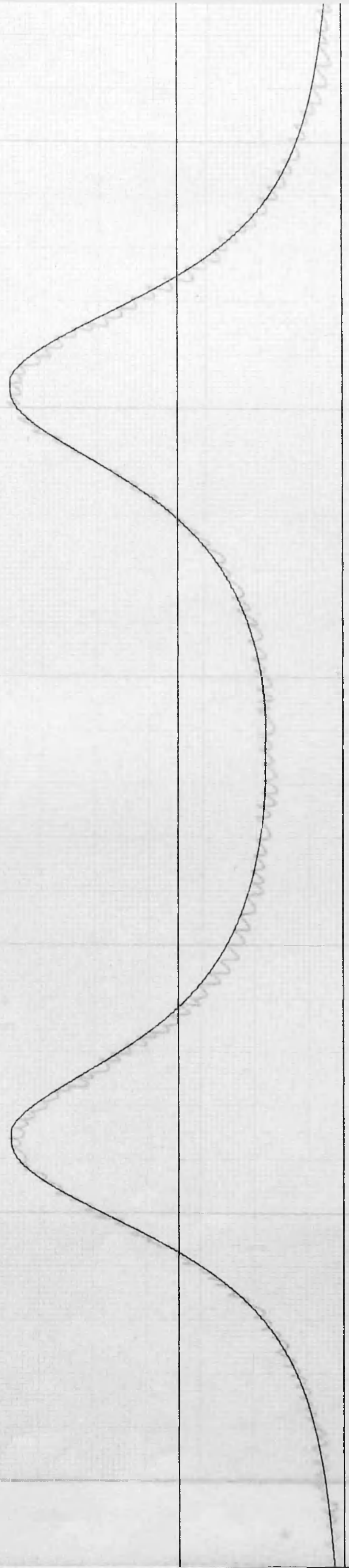

log(k/T)
p-dimethylaminoacetophenone.
-1.0
-1.1
-1.2
-1.3
-1.4
$\frac{1}{T}$ (10^{-3})
7.1
7.2
7.3
7.4
7.5
7.6
7.7
7.8
7.9
8.0
8.1
8.2

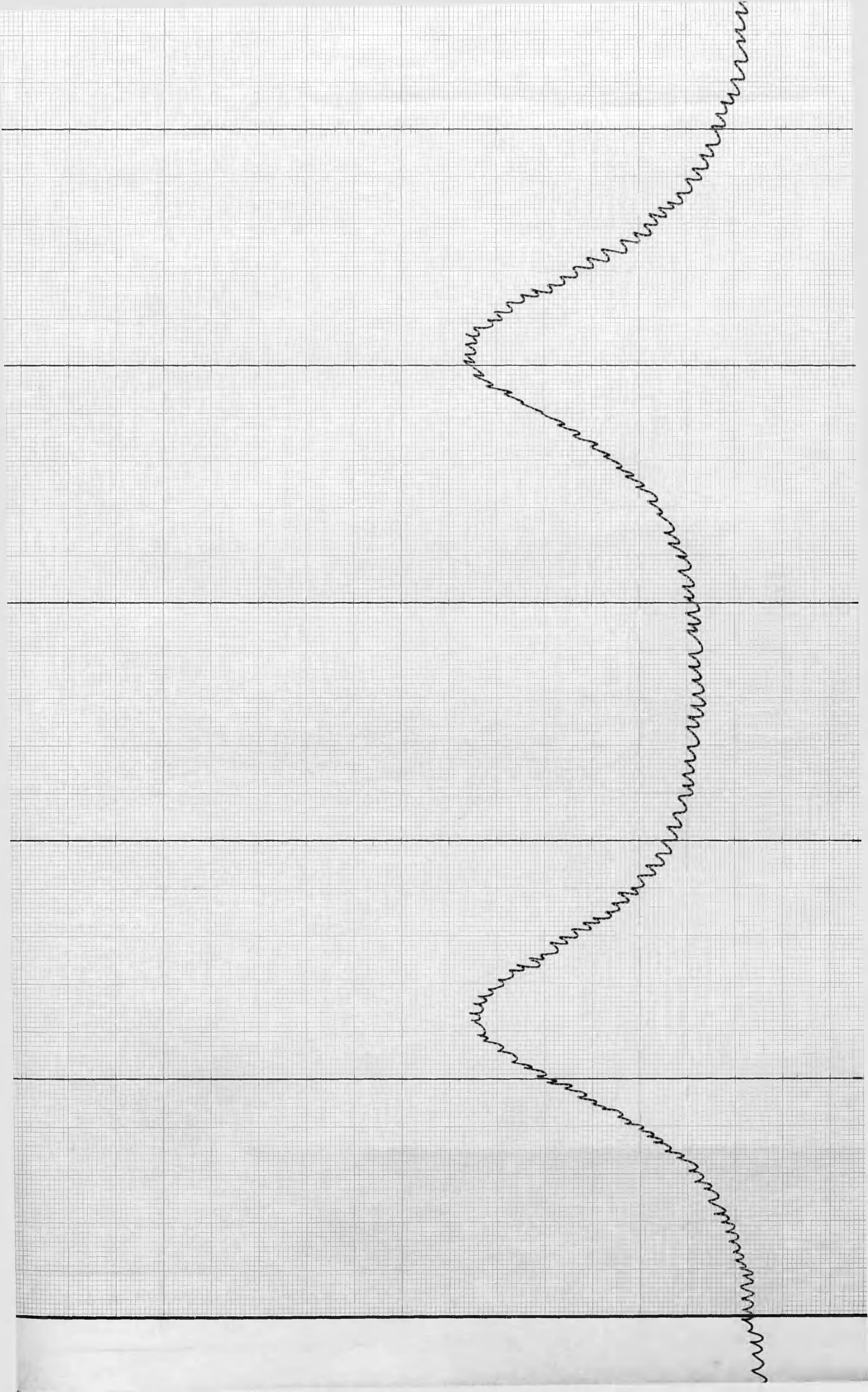

Extrapolation of Free Energies for p-substituted dimethylanilines.
ΔG≠ kcal./mole.
p-dimethylaminobenzaldehyde.
p-dimethylamino-acetophenone.
p-nitroso-N,N-dimethylaniline.
ΔG≠ kcal./mole. (p-NO).
σN.
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
10.5
10.4
10.3
10.2
10.1
10.0
9.9
9.8
9.7
9.6
9.5
9.4
9.3
9.2
9.1
9.0
8.9
8.8
8.7
8.6
100
110
120
130
140
150
160
170
180
190
200
210
220

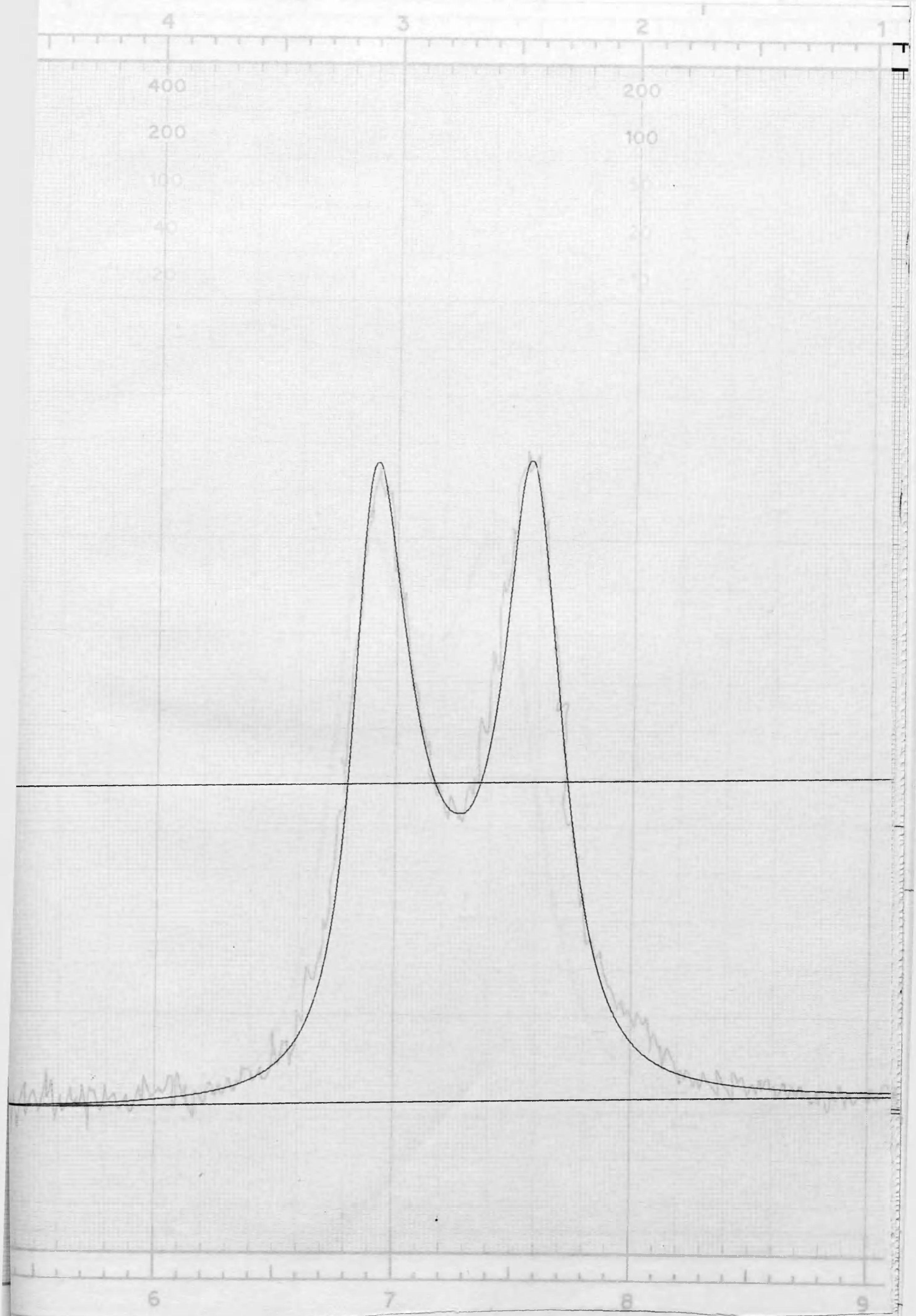


SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS (MAN. OSC. FREQ.)
FIELD MILLIGAUSS (SWEEP FREQ.)
FIELD SWEEP ☐ FREQ. SWE


SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS (MAN. OSC. FREQ.)
FIELD MILLIGAUSS (SWEEP FREQ.)
FIELD SWEEP ☐
FREQ. SWE
CI






4
3
2
1
400
200
100
40
20
200
100
50
20
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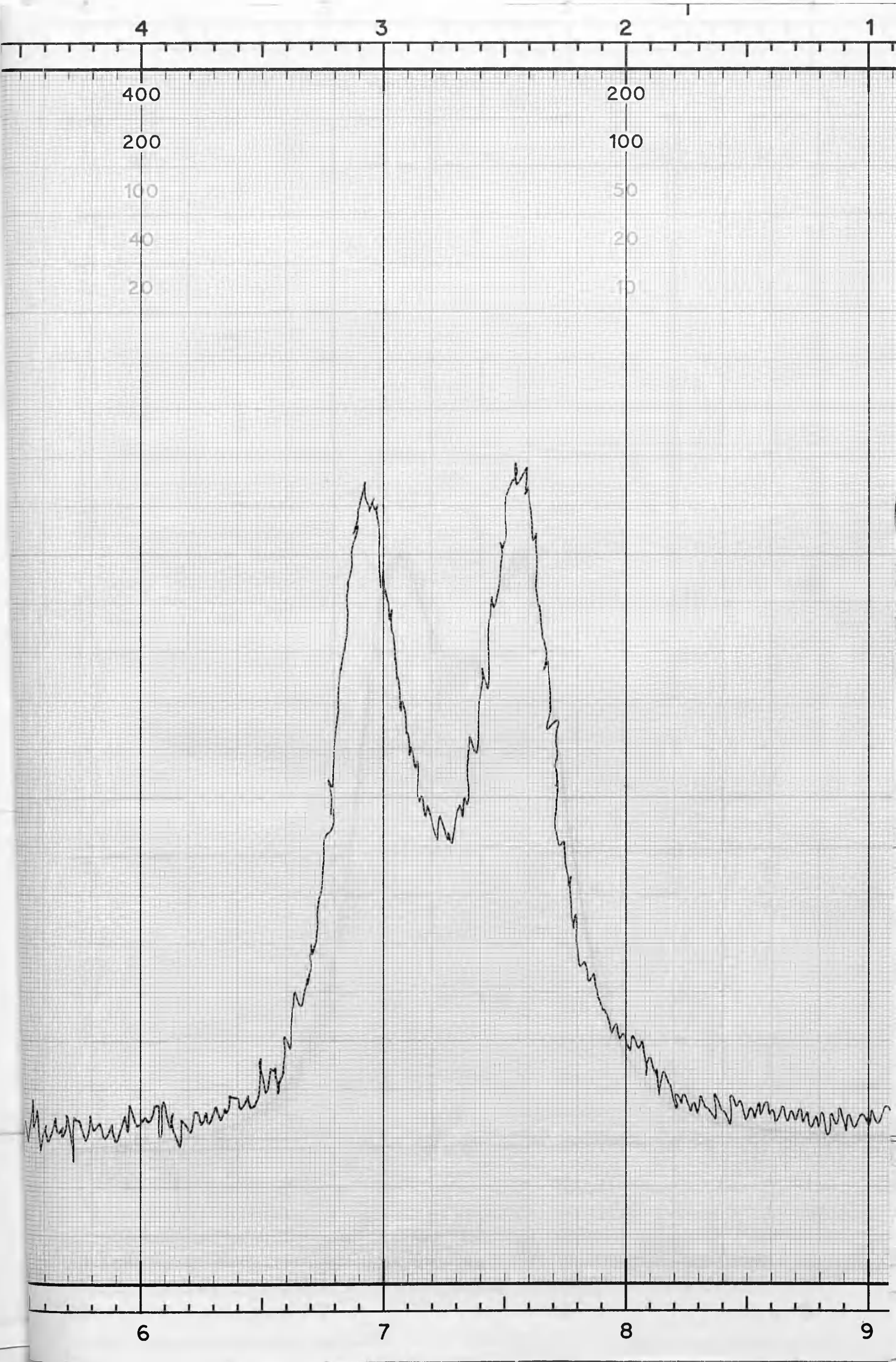
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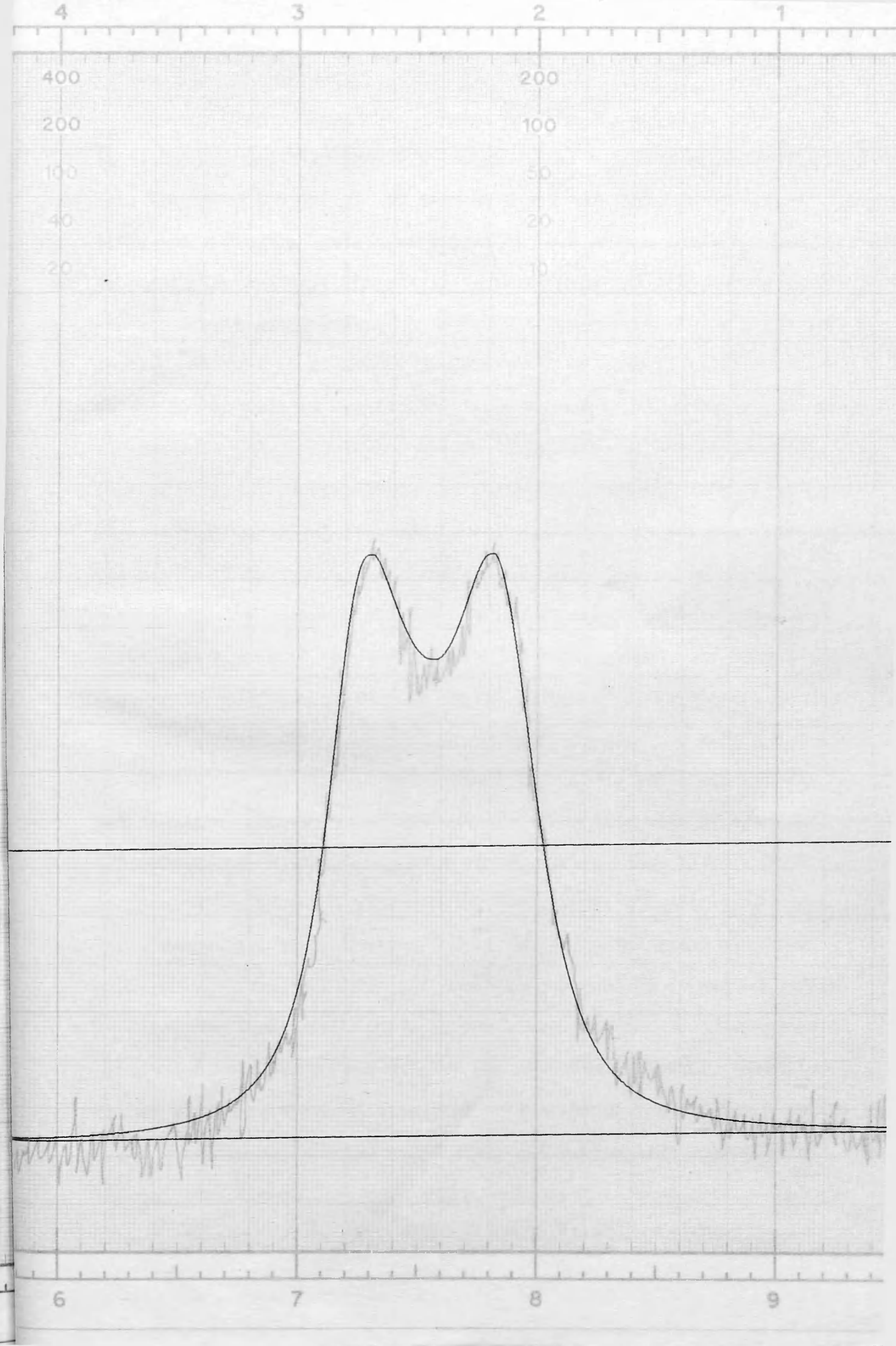
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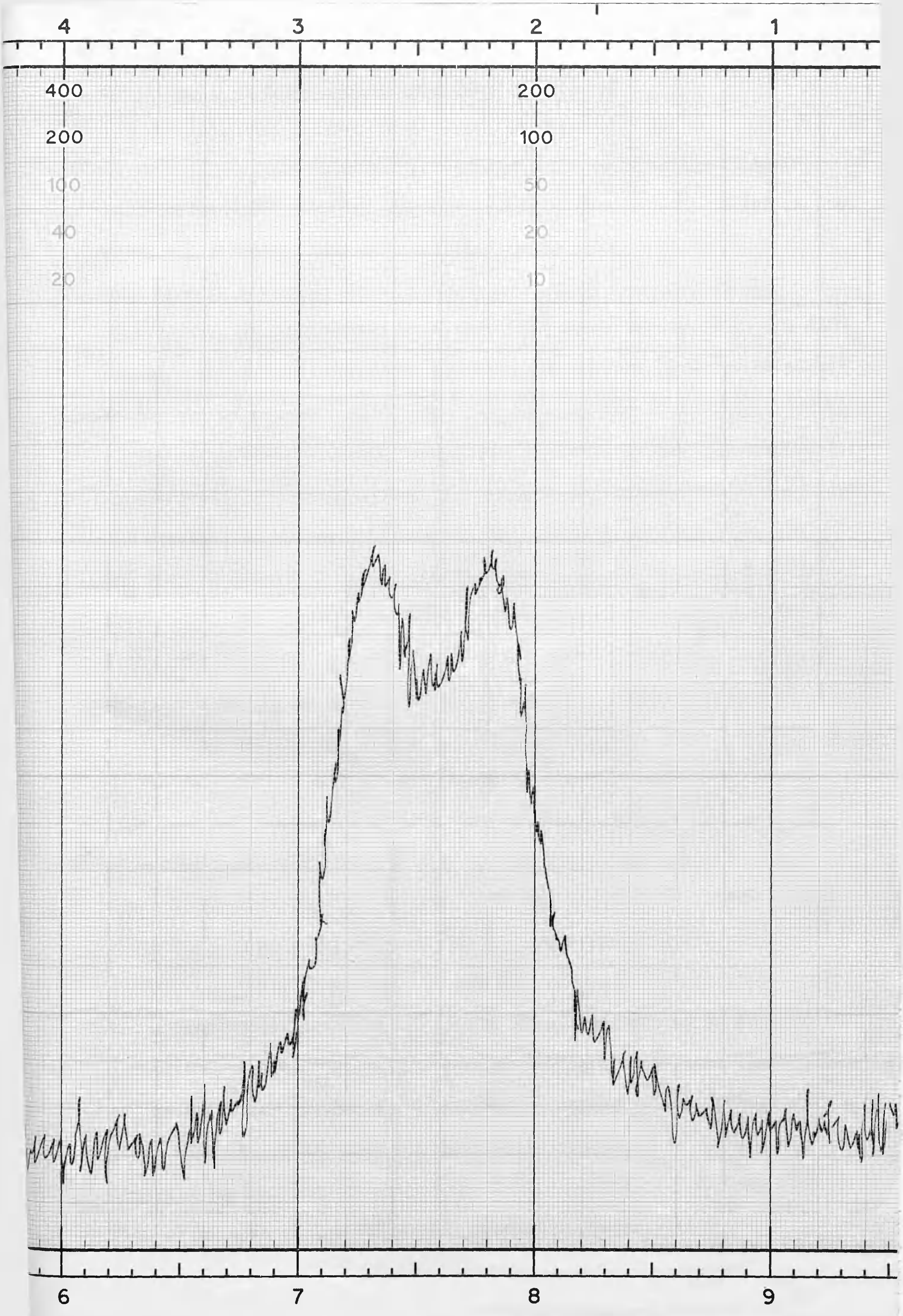
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Appendix C : Computer Configuration.

A very brief comment is in order here to describe the computing facilities employed during this research. The computer installation is a UNIVAC 1108 with 136K of fast access store. This in itself is limited and a further limitation arises in that only a maximum of half this area is available under extreme conditions for data storage. In consequence, large programs with vast data store requirements can only access a maximum of about 80K including 17K of code (i.e. instuctions). As far as the current use is concerned, access has been almost invariably in batch mode, although some remote teletype access is possible. However, without rewriting much of the program output, this is extremely wasteful in output time and is only suitable for emergancy use. The machine itself is quite powerful, so large iterations using UEAITR for example are ecomomic in time, taking about 1 minute to iterate an eight spin system to convergence. Whilst this is obviously only a very crude measure of its power, the system, given a larger memory, is capable of a great deal.

A CALCOMP 564 Digital Incremental Plotter is interfaced to the main machine, and as far as the user is concerned, this is accessed directly in the time-sharing mode of the system (Exec VIII). Plots are limited to 28.5ins. wide and 150.0ins. long. this provides ample scope for n.m.r. uses. Several fairly sophisticated graph plotting packages are available, but for spectral purposes it is normal merely to calculate data points sufficiently close together to allow stepwise connection of these points to give the simulated spectrum. Labelling of the resulting spectra is trivial to accomplish and reduction of the final spectrum to any size for display and publication purposes is also trivial. The example included after this appendix is a machine reduction to A4 size of the following calculated system.

Coupled AB System.

chemical shift of A = 220.0Hz.

chemical shift of B = 230.0Hz.

coupling constant J_{AB} = 1.5Hz.

relaxation time = 0.45 secs.

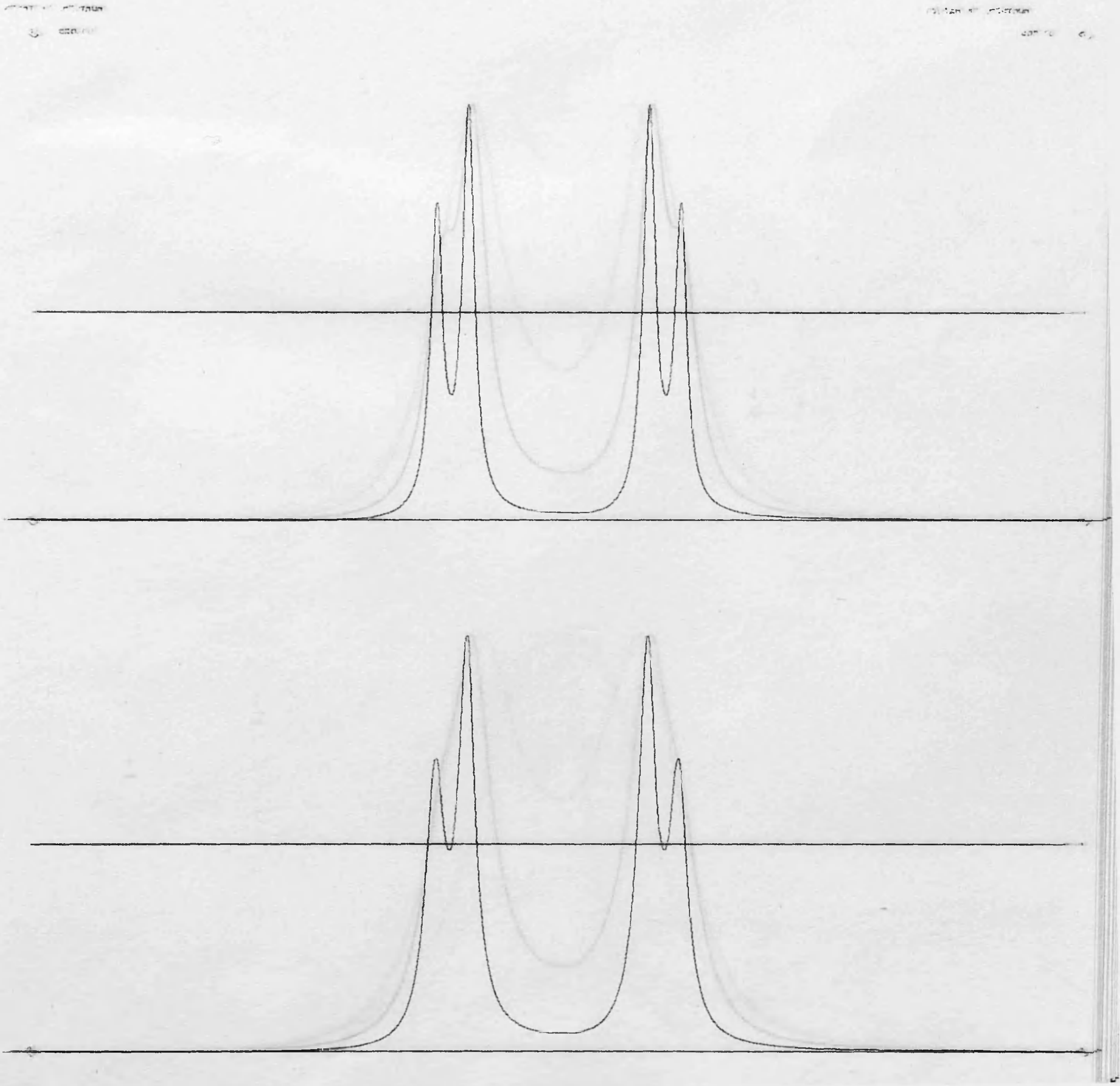
plotting scale is that of a 50 Hz scale expansion on a Varian H.A. 100.

The rates of exchange between the two sites are listed on the plotter output above the spectra, as is the peak height used for each spectrum. This latter is optionally an input variable to allow overlay matching of experimental and theoretical spectra.

RUN NUMBER = 30[illegible]

UPPER RATE CONSTANT = 0.0[illegible] PEAK HEIGHT USED = 240.00

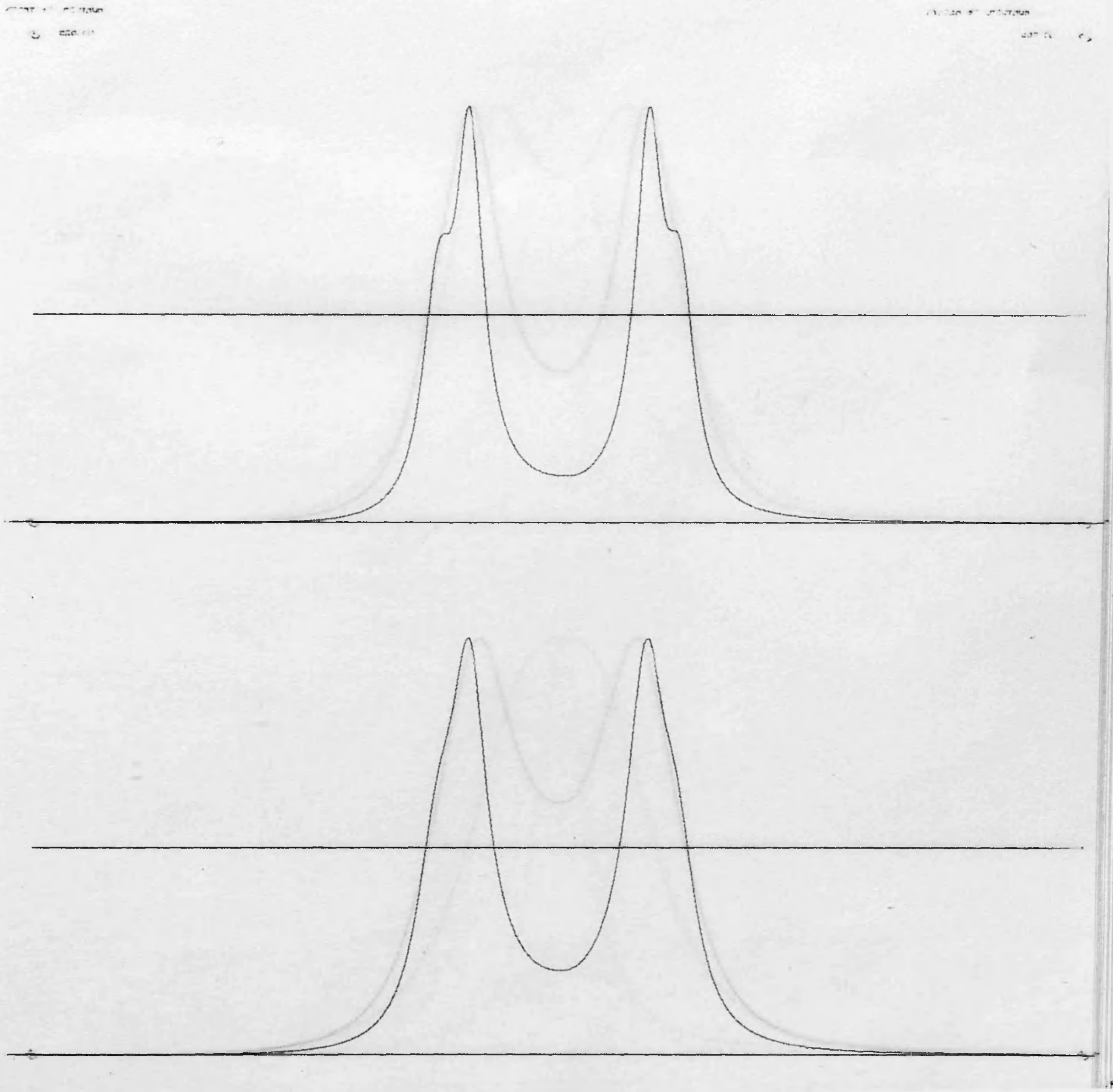
LOWER RATE CONSTANT = [illegible].00 PEAK HEIGHT USED = 240.00



RUN NUMBER = 30

UPPER RATE CONSTANT = 3.00 PEAK HEIGHT USED = 240.00

LOWER RATE CONSTANT = 5.00 PEAK HEIGHT USED = 240.00



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RUN NUMBER = 30[illegible]

     UPPER RATE CONSTANT = 0.020              PEAK HEIGHT USED =    240.00

     LOWER RATE CONSTANT = 15.00              PEAK HEIGHT USED =    240.00
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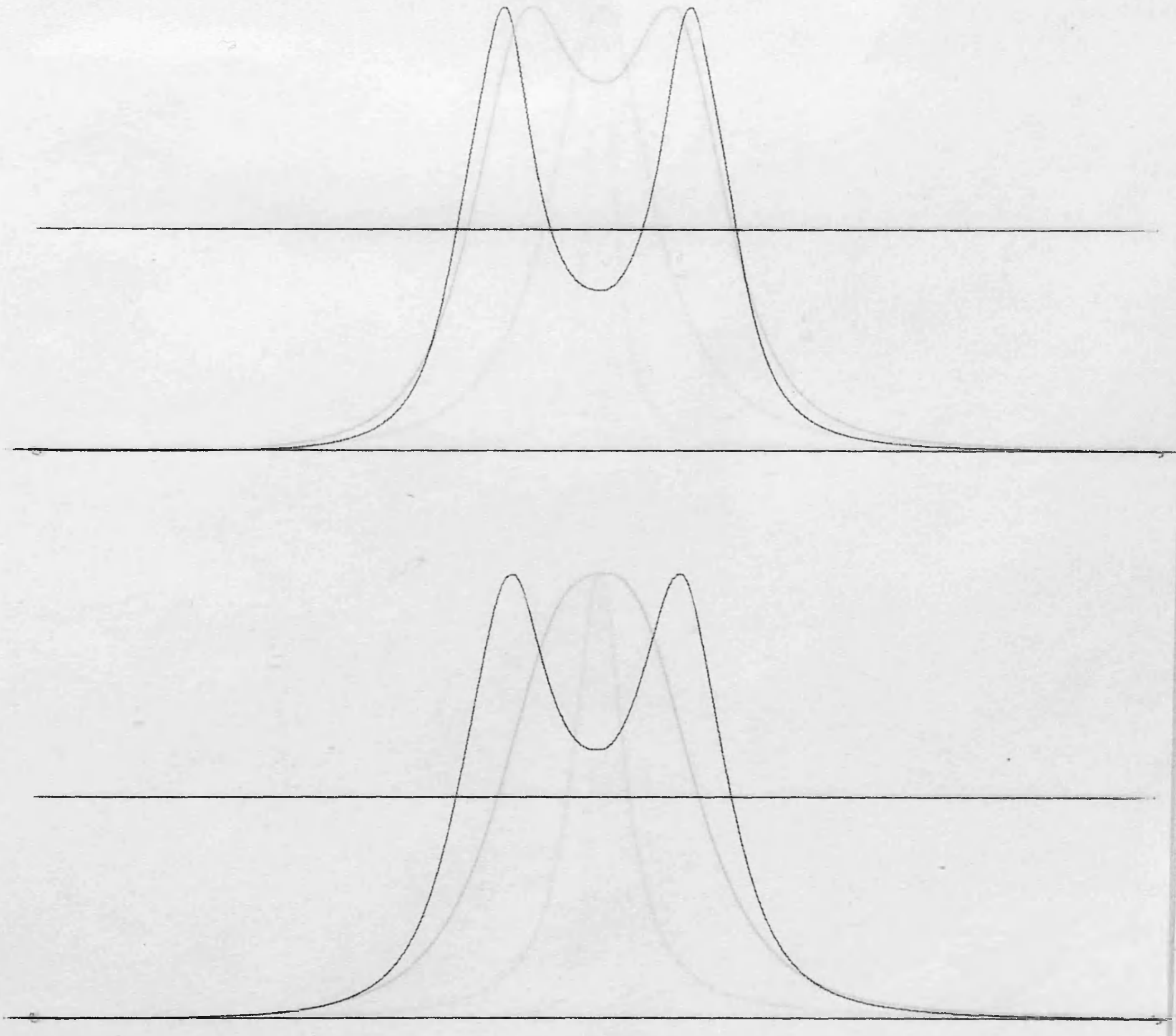

```
RUN NUMBER = 301

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    LOWER RATE CONSTANT = 25.00              PEAK HEIGHT USED =    240.00
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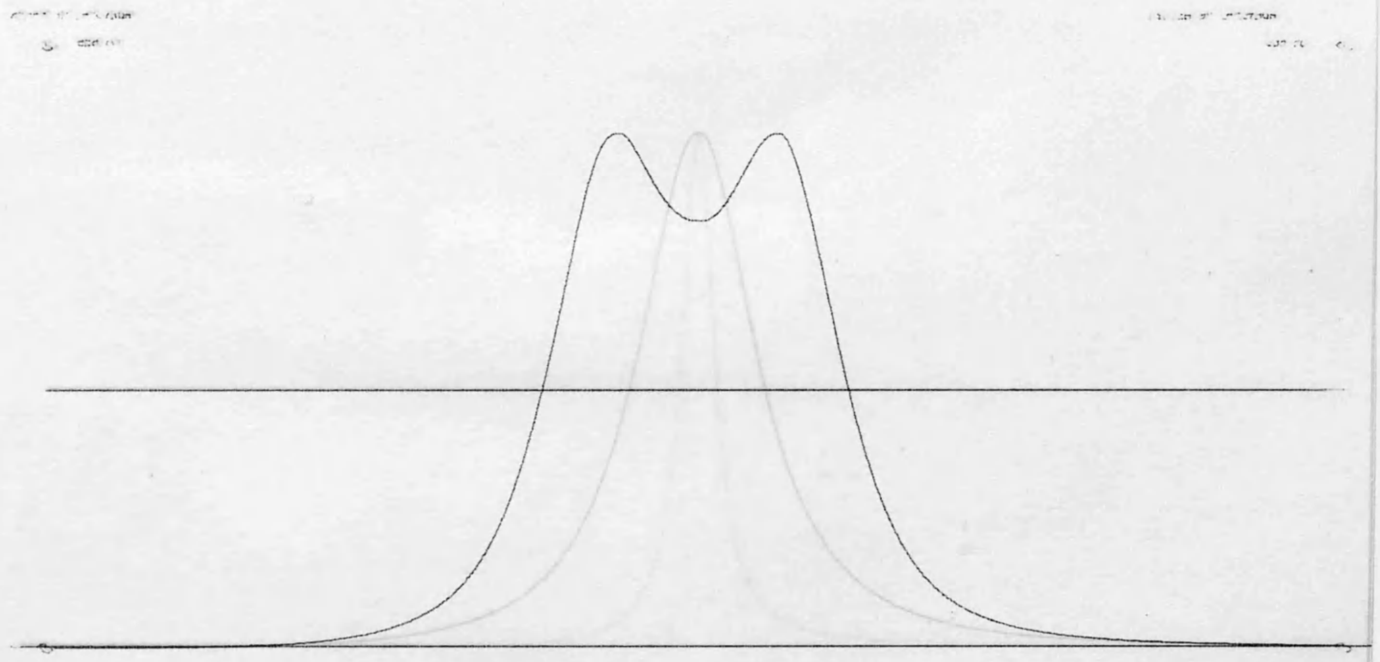
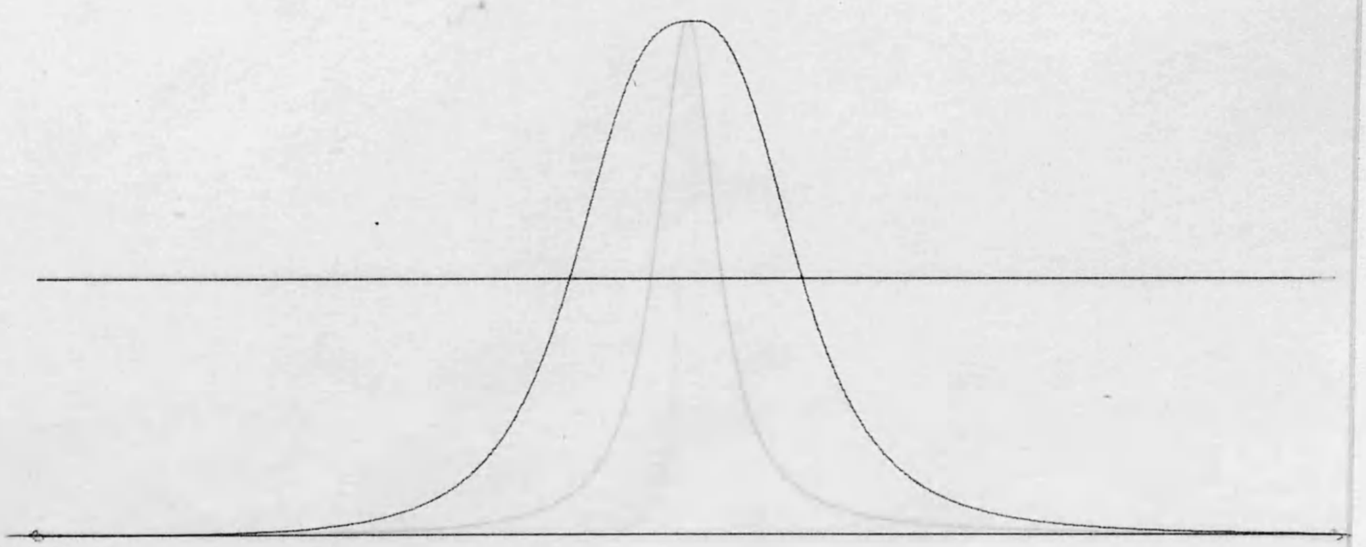
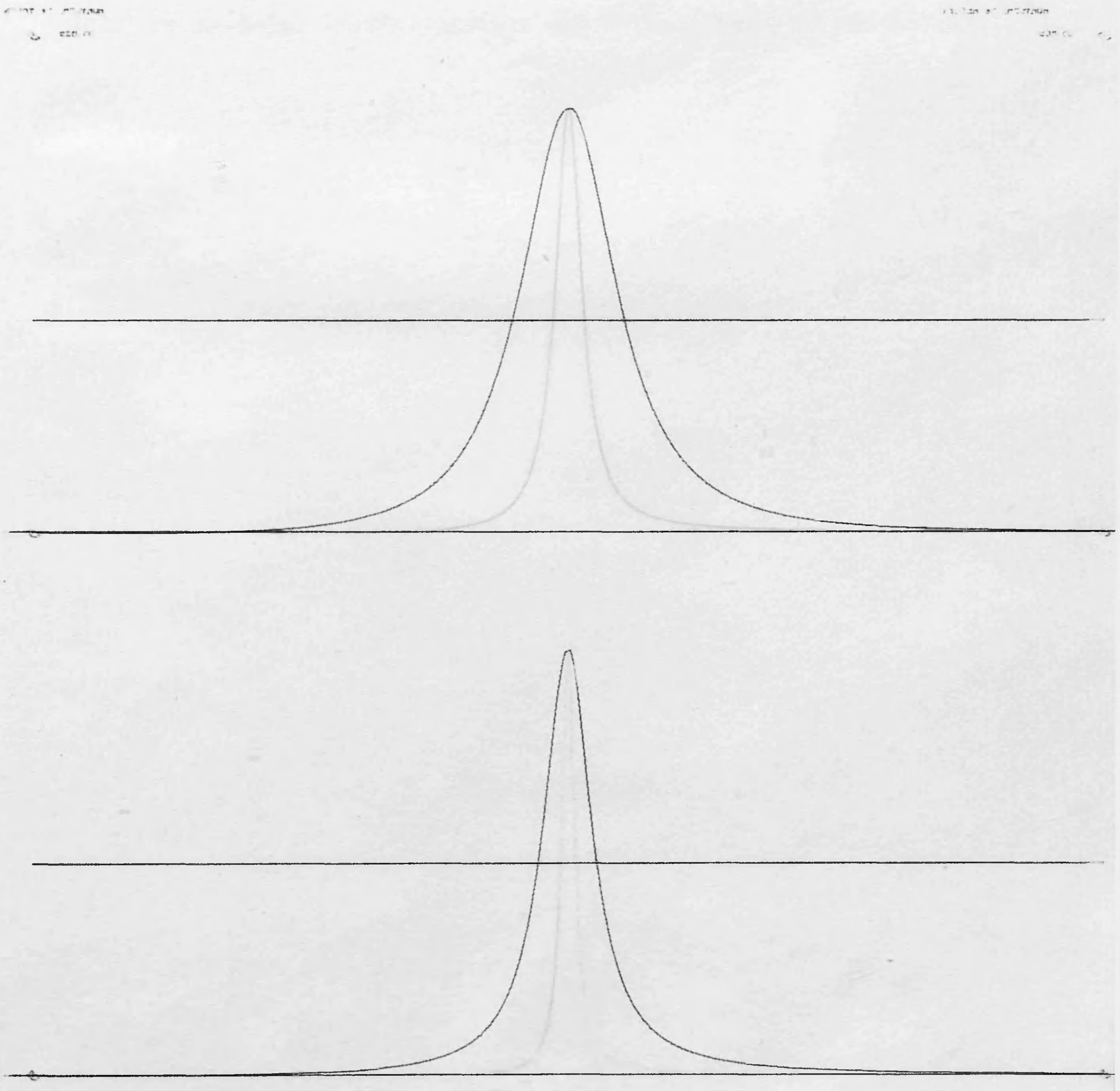




RUN NUMBER = 301

UPPER RATE CONSTANT = 40[illegible]   PEAK HEIGHT USED = 240.00

LOWER RATE CONSTANT = 80000.[illegible]   PEAK HEIGHT USED = 240.00



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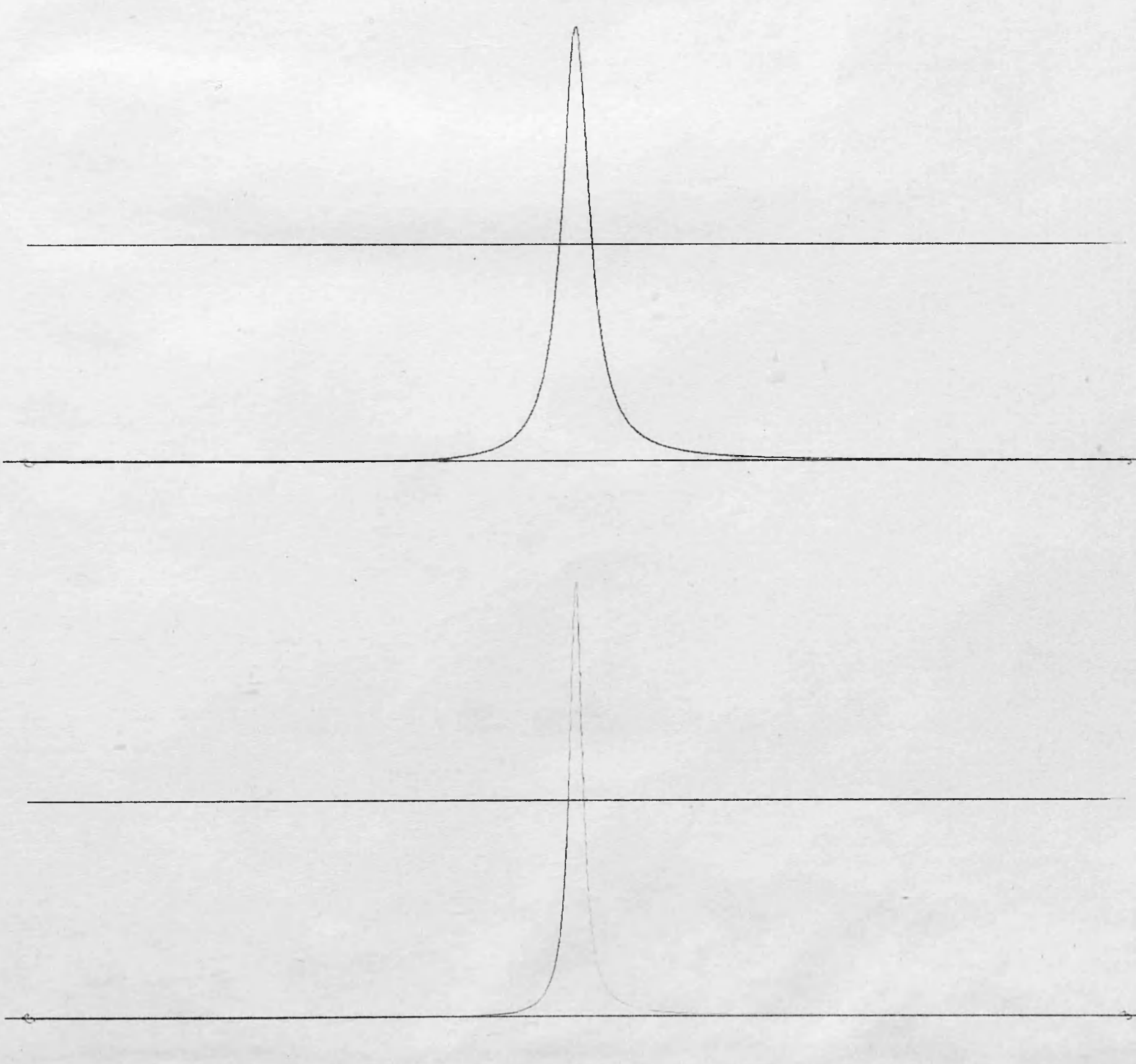
RUN NUMBER = 30[illegible]

    UPPER RATE CONSTANT = 200.00              PEAK HEIGHT USED :    240.00

    LOWER RATE CONSTANT = 10000.00            PEAK HEIGHT USED :    250.00
```



Relevant Publications.

Mackenzie, R.K., MacNicol, D.D., Chem.Comm., 1970,1299; "Internal Rotation in Dimethylaniline and para-Substituted Derivitives".

Dunlop, R., Mackenzie, R.K., MacNicol, D.D., Mills, H.H., Williams, D.A. R., Chem.Comm. 1971,919; "Synthesis and Structure of 9-Nitrosojulolidine".

Mackenzie, R.K., MacNicol, D.D., Mills, H.H., Raphael, R.A., Wilson, F.B., Zabkiewicz, J.A., J.C.S.Perk.II, 1972,1632; "A Study of the Conformation of syn-3,7-Dibromo-cis,cis-cyclo-octa-1,5-diene in the Crystal and in Solution by X-Ray Crystallography and Nuclear Magnetic Resonance".