AN ELECTRON SPIN RESONANCE STUDY OF THE CHLORPROMAZINE CATION

BY

ROBERT L TAPPING

B.Sc., The University of British Columbia, 1967

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

Master of Science

in the

Department of Chemistry

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

October, 1968

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and Study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of CHEMISTRY

The University of British Columbia
Vancouver 8, Canada

Date OCTOBER 31, 1968

ABSTRACT

The cation radical of chlorpromazine in solution was studied in detail by electron spin resonance. The 16 line spectrum was interpreted in terms of a nitrogen atom, two equivalent protons at the first side chain carbon atom, and three almost equivalent protons from the ring system. The relative magnitudes of the splitting constants require many of the spectral lines to be coincident, and the result is the 16 line spectrum observed. Analysis of the splitting constants was done using Hückel molecular orbital calculations, from which it was deduced that the chlorpromazine cation structure is folded about the N-S axis, with an included angle of 104°.

The spectral asymmetry observed in sulfuric acid solution was interpreted in terms of random molecular motions causing a fluctuating environment to arise at the nuclear positions. This leads to a modulation effect on the nuclear magnetic moment, and is responsible for linewidth variation. Further broadening due to exchange effects is discussed qualitatively. The asymmetry of the spectra enable the sign of the nitrogen splitting to be estimated -- it was found to be positive.

A brief discussion of the electrical properties of chlorpromazine, using HMO calculations, was included, and some discussion of the mechanism of chlorpromazine drug action was also considered for completeness.

TABLE OF CONTENTS

page

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENT

I wish to thank my research supervisor, Dr. J.B. Farmer for his encouragement and assistance in this work. I also wish to thank Dr. R. Srinivasan for some helpful remarks, and Mr. D. Kennedy for his assistance in using the HMO computer program. Mr. T. Markos of the electronics shop also deserves thanks for answering false alarms and assisting with the spectrometer, besides maintaining the upkeep of the spectrometers.

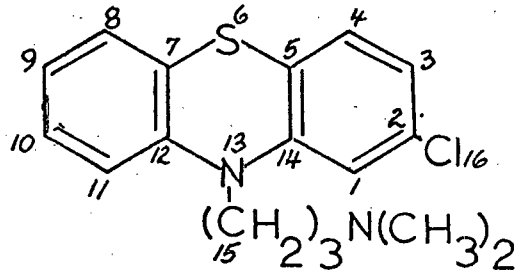
INTRODUCTION

The many and intricate problems involved in understanding such an apparently simple thing as a living cell have resulted in much attention being focussed on the biological sciences by students of the physical sciences. The chemical and physical questions are often within the realm of physical science, especially when separated from the biological structure, and so there is no barrier preventing overlap of the different disciplines. The separation of the sciences into various departments has often resulted in duplication of experiments and loss of potential applications to a subject requiring a fresh approach. Now, however, many fields described variously as biophysics, neurophysics, biochemical physics, quantum biology, etc. are offering a challenge to scientists who want to apply pure physics, for example, to the problems of cell membranes.

Electron spin resonance (esr) studies are especially adaptable to many biological problems, and the systems studied often involve very complicated molecules. Careful approximations are then needed to apply the theories of esr to such molecules, without losing too much information about the biomolecule. Simple biomolecules are, of course, being studied most, and in this work a relatively simple drug molecule was examined. Drugs are not usually species native to living (especially animal) systems, but do interact in interesting and generally unknown ways (unknown in the sense that the mech-

anisms of drug action are not precisely understood at the cellular and molecular levels, in many cases).

Chlorpromazine (CPZ):



where the numbers indicate the numbering convention to be used in this work, is easily available to esr study, and is an asymmetric structure. Most esr theory has been established for symmetrical species, for mathematical convenience, so an esr study of CPZ should enable a comparison to be made between the results generally obtained for symmetrical molecules and the interpretation of a molecule like chlorpromazine.

Chlorpromazine is usually used as a hydrochloride, and is a white polycrystalline solid that is readily oxidisable by biological, chemical, and electrochemical means, and also exhibits both impurity and intrinsic semi-conductor properties.

The simple theories to be applied to this esr study of CPZ are hoped to provide evidence that the techniques of chemical physics, for example, may be of use in explaining biological functions. Most of the work here will concentrate on explanation of the esr spectra and physical properties of CPZ, but some qualitative discussion will be given to the role of chlorpromazine as a drug.

EXPERIMENTAL METHODS

A: ESR SPECTROMETERS

Two spectrometers were used. The first, designated ESR-3, is similar to the Varian V-4500 100KHz unit operating at X-band frequency (~9200MHz), with microwave power supplied by a Varian V-153 klystron with Kepco transistorized DC power supply to stabilise the filament voltage. The magnet is a Varian V-4012 12" model with 2.5" pole gap, modulated at 100KHz. The magnetic measured with a proton resonance magnetometer, with the probe connected to an FM-modulated 20Hz oscillator. The oscillator supplies a variable frequency of about 14MHz to the probe, and the frequency is read off a Hewlett Packard 5425L electronic counter after being made to beat with a signal generator. Power was monitored with a Hewlett Packard 430C microwave power meter.

The other spectrometer was a Varian E-3 bench model. This instrument has a 4" magnet with 1.2" pole gap and is modulated at 100KHz. Microwave frequency and power are read off the microwave bridge, and field measurement is by means of a Fieldial. Accuracy is ±3% of the field reading. This, of course is considerably less accurate than the proton resonance magnetometer, which is accurate to about 0.1G. The E-3 has an X-Y recorder for signal output.

B: SOLVENTS USED

Nitromethane (CH_3NO_2) and acetonitrile (CH_3CN) were obtained from Eastman Organic Chemicals (Spectro Grade), and were used without further purification. When not in use, the

solvents were kept under vacuum. Sulfuric acid (H_2SO_4) was obtained from British Drug Houses (Analar, 95.5% min.) and was dried on a vacuum before use.

C: COMPOUNDS INVESTIGATED

Chlorpromazine-HCl was obtained from Poulenc, and was used without further treatment. Promazine-HCl was a gift of J. Wyeth Co., and was also used without further treatment.

For the electrolytic oxidation, the auxiliary compound used as supporting electrolyte was $LiClO_4$ (G.F. Smith Chemical company), and was dried over vacuum for several days before use. It was found that the electrolysis failed to give a stable radical if all compounds were not dried carefully before use.

Chemical oxidation in nitromethane/aluminum chloride used aluminum chloride obtained from British Drug Houses. The highly hygroscopic nature of $AlCl_3$ meant that it had to be stored over a vacuum all the time.

D: VARIABLE TEMPERATURE APPARATUS

Temperature variation was effected using a Varian V-4547 Variable Temperature Accessory. For low temperatures dry nitrogen gas was passed through a stainless steel coil which was immersed in a suitable coolant. The cooled gas then passed through a cylindrical dewar equipped with a stick heater, and into a special dewar situated in the cavity. To control the temperature either the flow rate could be adjusted or the heater could be used to warm the gas. For high temp-

erature work, the cooling device was omitted and the stick heater used to warm the gas to the desired temperature.

Temperature was measured with a copper/constantan thermocouple and a Rhodes potentiometer. During all runs differing from room temperature, the cavity was kept at a reasonably constant temperature by passing dry nitrogen gas through it. The temperature variation for all runs was never worse than $\pm 2^{\circ}C$, and was often constant to within 0.2 degrees for a particular run.

E: SAMPLE PREPARATION BY ELECTROLYTIC OXIDATION

An electrolysis cell designed by P.H.H. Fischer (105) was used, with best results obtained using acetonitrile as the solvent and $LiClO_4$ as the supporting electrolyte. The solution was prepared in the cell by dissolving CPZ and $LiClO_4$ in the acetonitrile and then degassing on a vacuum line. Passage of 20 amps at 5 to 10 volts for 30 to 60 minutes produced the characteristic red CPZ cation. The concentration of CPZ in the initial solution was about 10^{-3}M for most satisfactory results.

F: SAMPLE PREPARATION USING CHEMICAL OXIDATION

Sulfuric acid oxidation was used most frequently. This was most easily carried out by preparing a sample of CPZ in 95.5% H_2SO_4 beforehand, and transferring a portion to an esr sample tube equipped with a stopcock. The solution could then be degassed and esr spectra recorded. Optimum concentrations for this method were 10^{-3} to 10^{-2}M.

Oxidation in $AlCl_3/CH_3NO_2$ was considerably more precise.

A sidearm was attached to the esr sample tube below the stopcock, and in this sidearm were placed the requisite amounts of $AlCl_3$ and CPZ. Nitromethane was then distilled into the sidearm, and the reaction completed. The resultant red solution of CPZ^+ was then transferred to the bottom of the esr tube. In this manner, the reactants were kept degassed at all times and the concentration of the initial could be fairly accurately known. Optimum concentrations here were found to be 10^{-3} to 10^{-4}M.

Oxidations in phosphoric and hydrochloric (conc.) acids was effected in the same manner as for sulfuric acid, yielding similar red solutions. The spectra of these solutions were not examined in great detail.

Temperature studies were made only on the sulfuric acid solutions. Attempts to do the same for the acetonitrile and nitromethane solutions resulted in the solvents (which were under vacuum) being troublesome due to boiling and evaporation above 40°C.

THEORETICAL ASPECTS

I HYPERFINE SPLITTING AND SPIN DENSITIES

A: PROTON HYPERFINE SPLITTING IN AROMATIC RADICALS

When aromatic hyperfine splittings were first observed by Weissman et al (1-3) in 1953, the first explanation was that somehow there was interaction of the electronic magnetic moment with proton moments. Such an interaction was considered necessary to explain why naphthalene anions exhibited detailed hyperfine structure (1). Clearly the electronic wave function was not zero at some proton positions, a fact that contradicted the general ideas of aromaticity at that time. In the conventional planar aromatic molecule the pi-electron charge resides in the lobes of the carbon p_z orbitals -- either above or below the aromatic ring. There is then a node at the carbon nucleus through which the unpaired electron, in a radical, must become zero. Thus no interaction (in a conventional sense) between the electron and proton (through the C-H sigma orbital) seemed possible. Weissman (1) speculated that zero-point vibrations by the proton may be responsible, since only small admixtures of states are required to produce the observed magnitudes of hyperfine splittings (3). This is because a pure hydrogen 1s orbital has a splitting of about 510G. Subsequently the vibronic interaction approach was shown to be wrong (4), since the splitting constants were not proportional to the square roots of the nuclear masses, as a vibronic interaction theory would predict (5).

In eliminating bending vibrations of the C-H bond, Venkataraman and Fraenkel (4) suggested that the unpaired electron is not in a pure pi state in an aromatic radical (or any pi radical), and transfers some spin density to the protons by configuration interaction between the sigma and pi states. H.M.McConnell (6-9) and several others examined such a mechanism, and the most extensive work is McConnell's -- much of what immediately follows is based on McConnell's investigations.

The details of McConnell's theory are presented quite fully in Appendix 2, but a brief discussion of the use of "McConnell's relation" is given here. Essentially, the spin polarisation arising from the presence of an unpaired electron in a pi system can produce an appreciable spin polarisation in s-atomic orbitals of the aromatic protons by an atomic exchange coupling mechanism. Both Weissman (10) and McConnell have explained this, and the result is often written quantitatively as:

$$a^H = Q^H_{cc} \rho^\pi_c \qquad (3\text{-}1)$$

where a^H is the proton hyperfine coupling constant, ρ^π_c is the unpaired spin density at the carbon atom of the C-H bond, and Q^H_{cc} is the spin polarisation constant (or sigma-pi factor, etc.) for the case in question.

Usually the relationship described by eq (3-1) is assumed to be linear, and in such an assumption there is a potential hazard. McConnell's derivation, given in Appendix 2, describes the splitting generally as:

$$a_j \cong 1640 \rho_j f_j \qquad (3\text{-}2)$$

The spin attenuation factor f_j can then be associated with Q, but since f is, in general, expected to differ from proton to proton, Q must also be susceptible to the same behaviour. It is usually convenient to ignore such behaviour, however, in treating most free radicals.

B: NITROGEN HYPERFINE SPLITTINGS

The observation that spin polarisation was responsible for proton hyperfine splittings can clearly be applied to any other nucleus possessing a spin magnetic moment and attached to, or in, a ring system or pi system. Karplus and Fraenkel (13) examined C^{13} in great detail and showed that C^{13} splittings are dependent on the pi-electron spin densities at nearest-neighbour atoms as well as at the C^{13} nucleus itself. Experimental verification has shown this theory to be essentially correct (13,14). Other atoms considered in the same manner are F^{19} (15) and N^{14} (16-20). these treatments, however, require considerably more discussion. The fluorine case is not of interest here, except to mention that Hinchcliffe and Murrell (15) obtain only order of magnitude agreement and certainly more work is needed in this particular case.

As references 16-20 show, considerable disagreement as to an explanation for N^{14} hyperfine splittings was the situation for some time. A thorough and reasonable treatment of the problem, however, has been given by Henning (21), and application of the theory has been quite successful. Thus a brief description of the method is useful.

Clearly s relationship like eq (3-1) could be used

for N^{14} hyperfine interactions. In fact, Carrington and Santos Veiga (16) used such a relationship and claimed fair success. However, one important aspect may have been overlooked by some, and that is that results like those of Carrington were for a family of like compounds. Use of eq (3-1) for any atom should strictly be limited to such families in order to have meaningful use of the relationship. Henning actually performed a least-squares fit and an error test on:

$$a^N = Q^N \rho_N^{\pi} \qquad (3\text{-}3)$$

and applied it to γ,γ-dipyridyl, 1,4- and 1,5-diazonaphthalene, and pyrazine. His results indicated that a relationship of the form of eq (3-3) does not exist for the general case.

If the isotropic hyperfine interaction between an electronic moment ($g_e\beta_e\underline{S}(k)$) and a nuclear moment ($g_n\beta_n\underline{I}_n$), described by the Fermi contact Hamiltonian (see Appendix 1) is represented as:

$$a^N = 8/3\ g_n\beta_n \langle\psi|1/M_s \textstyle\sum_k \delta(r_{nk}) S_z(k)|\psi\rangle$$

ψ then can be considered to be the state in which the free radical system exists, and $\psi(0)$ is the ground state with eigenvalue M_s since it is an eigenstate of $S_z = S_z(k)$. $\psi(0) \equiv \psi_0$ can be represented as

$$\psi_0 = |\sigma_1\bar{\sigma}_1 \ldots \sigma_m\bar{\sigma}_m\, \pi_1\bar{\pi}_1 \ldots \pi_n\bar{\pi}_n\, \pi_{n+1}| \qquad (2\text{-}4)$$

where σ represents an α spin and $\bar{\sigma}$ a β spin. (The above is for an anion but the result can be applied equally well to cations).

The sigma and pi orbitals can be written more ex-

plicitly (21):

$$\pi_i = \sum_r a_{ir}(p_z)_r \qquad (3\text{-}5)$$

where the molecular orbitals π_i are linear combinations of carbon and nitrogen $2p_z$ atomic orbitals with z perpendicular to the molecular plane, and

$$\sigma_j = \sigma_{xy} = [2(1+\langle h_x|h_y\rangle)]^{-1/2}[h_x+h_y]$$
$$\sigma_j^* = \sigma_{xy}^* = [2(1-\langle h_x|h_y\rangle)]^{-1/2}[h_x-h_y] \qquad (3\text{-}6)$$

for the bonding and antibonding cases, respectively. The σ_j orbitals making up the j in-plane bonds are linear combinations of sp^2 hybrids, $(h_x|h_y)$, of atoms x and y constituting the x-y bond, where $\langle h_x|h_y\rangle$ is the overlap integral.

It should be noted that the sigma orbitals are necessarily symmetric in the molecular plane, and further that both the nitrogen 1s and lone-pair orbitals are similarly symmetric, so the sigma system just described can include the "odd" nitrogen orbitals. Now if excited states are designated ψ_i, interelectronic repulsions (represented as $\sum\sum_{\mu<\nu} e^2/r_{\mu\nu}$) can mix ψ_0 with ψ_i, giving:

$$\psi = \psi_0 + \sum_i [\langle\psi_0|\mathcal{H}|\psi_i\rangle/(E_0-E_v)]\psi_i \qquad (2\text{-}7)$$

to first order (see, for example, any text on simple first order perturbation theory, i.e. ref. 22 p245). Because the total electronic Hamiltonian is a sum of one-electron and two-electron operators, only singly and doubly excited configurations need be considered (21). Thus, considering only those configurations ψ_i which give a first order contribution to the spin density at the nuclear position $\underline{r}_n$, the spin density there can be written:

$$\rho(\underline{r}_n) = \langle\psi_0|M_s^{-1}\sum_k \delta(\underline{r}_{nk})S_z(k)|\psi_0\rangle + 2\sum_i\left[\langle\psi_0|\mathcal{H}|\psi_i\rangle(E_0-E_v)\right]\langle\psi_i|M_s^{-1}\sum_k \delta(\underline{r}_{nk})S_z(k)|\psi_0\rangle \quad (3\text{-}8)$$

since $\rho(\underline{r}_n)=\int\psi^*\sum_k 2S_{zk}\delta(r_{nk})\psi d\tau$ (22) and ψ as in eq (3-8). In other words, the unpaired spin density at the nucleus, which is controlled by the delta function of electron-nuclear position, is the difference between the average number of α spins and β spins (governed by $2S_{zk}$) -- thus if there are more α spins the spin density is positive, and vice-versa.

For the ground configuration ψ_0 the π orbital containing the odd electron has a node in the molecular plane, so that the first term in (3-8) must vanish. Thus, considering the non-vanishing contributions to the spin density it can be noted that the delta function requires the electron to "jump" between orbitals which are non-vanishing at the nucleus -- the spin density at the nucleus is therefore produced by one-electron "jumps" between excited states, resulting in the possibility of two spin doublet states and one spin quartet (6,21). The ground configuration ψ_0 is a doublet, so the quartet can be ignored and two doublets can be derived:

$$\text{pure singly excited: } \psi_s=\frac{1}{\sqrt{2}}\left\{|\sigma_1\bar{\sigma}_1\cdots\sigma_i\bar{\sigma}_p^*\cdots\bar{\pi}_{n+1}|-|\sigma_1\bar{\sigma}_1\cdots\bar{\sigma}_i\sigma_p^*\cdots\pi_{n+1}|\right\}$$
$$\text{or } \psi_s=\frac{1}{\sqrt{2}}(\alpha\beta\beta-\beta\alpha\alpha) \quad (3\text{-}9)$$
$$\text{pseudo singly excited: } \psi_{ps}=\sqrt{6}\left\{\alpha\alpha\beta-\beta\alpha\alpha-\alpha\beta\alpha\right\}$$

Equations (3-9) are well-known wave functions (6, 21,22), and it can be seen immediately that ψ_s cannot contribute to the spin density since it cancels internally (21), so ψ_{ps} is the only configuration needed to first order. Using the appropriate matrix elements (12):

$$\langle \Psi_0 | \mathcal{H} | \Psi_{\rho s} \rangle = -(\sqrt{3}/\sqrt{2}) \langle \sigma_i \pi_{n+1} | e^2/r_{12} | \pi_{n+1} \sigma_\rho^* \rangle$$
$$\langle \Psi_{\rho s} | \mathcal{H}' | \Psi_0 \rangle = (2/\sqrt{6}) \sigma_i(\underline{r}_N) \sigma_\rho^*(\underline{r}_N) \qquad (3\text{-}10)$$

where $\mathcal{H}' = M_s^{-1} \sum_k \delta(r_{nk}) S_z(k)$

Now $\pi_i = \sum_r a_{ir} (p_z)_r$, as before, so

$$\langle \Psi_0 | \mathcal{H} | \Psi_\rho \rangle = -(\sqrt{3}/\sqrt{2}) \sum_r \sum_s a_{n+1,r} a_{n+1,s} \langle \sigma_i (p_z)_r | e^2/r_{12} | (p_z)_s \rangle$$

and the atomic orbital spin density matrix for Ψ_0 is (21):

$$\rho_{rs}^\pi = a_{n+1,r} a_{n+1,s} \qquad (3\text{-}11)$$

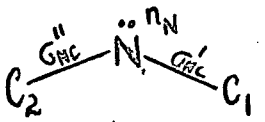
Therefore combining gives:

$$a^N = \mathrm{Tr}(Q^N \rho^\pi) \equiv \sum_r \sum_s Q_{rs}^N \rho_{sr}^\pi \qquad (3\text{-}12)$$

and thus the hyperfine coupling matrix Q^N can be written:

$$Q_{rs}^N = -16/3 \pi g_n \beta_n \sum_i \sum_\rho' \left\{ \langle \sigma_i (p_z)_r | e^2/r_{12} | (p_z)_s \sigma_\rho^* \rangle / [E(0) - E(i \to \rho)] \right\} \times$$
$$\times \sigma_i(\underline{r}_N) \sigma_\rho^*(\underline{r}_N) \qquad (3\text{-}13)$$

In eq (3-13) the summation over i and p should, in principle, be extended over the excitations of all the sigma bonds in the molecule, but it is convenient to restrict the summation to sigma orbitals adjacent to the atom in question, i.e. $(1s)_N$, σ'_{NC}, σ''_{NC}, and n_N for nitrogen:



Then $\sigma_i(\underline{r}_N) \sigma_\rho^*(\underline{r}_N)$ can be considered negligible for all other orbitals. Such a restriction is necessary for ease of computation, and is commonly used in simplified molecular orbital theory. McConnell's relationship (eq (3-1)) is based on this assumption. In other words, it is assumed that the exchange integral for non-nearest-neighbour atoms is vanishingly small.

So a matrix for Q^N can be set up:

$$Q^N = \begin{pmatrix} Q^N_{NN} & Q^N_{NC} & Q^N_{NC} \\ Q^N_{CN} & Q^N_{CC} & 0 \\ Q^N_{CN} & 0 & Q^N_{CC} \end{pmatrix}$$ where, by symmetry, $Q^N_{NC1}=Q^N_{NC2}$, $Q^N_{C1N}=Q^N_{C2N}$, $Q^N_{C1C1}=Q^N_{C2C2}$

so, from eq (3-12)

$$a^N = Q^N_{NN}\rho^\pi_{NN} + Q^N_{CC}(\rho^\pi_{C1C1}+\rho^\pi_{C2C2}) + (Q^N_{NC}+Q^N_{CN})(\rho^\pi_{C1N}+\rho^\pi_{C2N}) \qquad (3\text{-}14)$$

Henning shows in detail (21) that the bond excitation $\sigma_{NC'} \rightarrow \sigma^*_{NC'}$ is antisymmetric, which leads to the result that $Q^N_{NC}=-Q^N_{CN}$. Thus eq (3-14) becomes:

$$a^N = Q^N_{NN}\rho^\pi_{NN} + Q^N_{CC}(\rho^\pi_{C1C1} + \rho^\pi_{C2C2}) \qquad (3\text{-}15)$$

Henning also carried out a similar argument for a C-H fragment, considering the only relevant excitation to be $\sigma_{CH} \rightarrow \sigma^*_{CH}$, and arrived at a matrix representation for Q^H:

$$Q^H = \begin{pmatrix} Q^H_{HH} & Q^H_{HC} \\ Q^H_{CH} & Q^H_{CC} \end{pmatrix}$$, but since the proton does not bear a p-orbital, $Q^H_{HH}=0$, $Q^H_{HC}=Q^H_{CH}=0$, since no excitation can occur between them. Thus the only non-vanishing matrix element is Q^H_{CC}, as shown earlier by McConnell (6).

C: HYPERCONJUGATION AND SPIN POLARISATION CONTRIBUTIONS

How important is hyperconjugation in aromatic systems? The question has been debated by several authors (24-29) in in considerations and analyses of esr spectra, with the situation so far tending to favour hyperconjugation over spin polarisation for the interaction of methyl and methylene groups with an aromatic ring system. These groups are the ones of most interest here, and will be the only ones

considered.

McConnell's equation (3-1) for protons has often been applied to methyl protons (24,25), and methylene protons (27) with some success, but the obvious inconsistency in Q values (varying from 20 to 30 gauss, with no particular correlation within "families" of molecules) suggests that a more fundamental relationship holds. Indeed, in this experiment an apparent Q value in the neighbourhood of 11G is obtained if spin polarisation conditions are considered. The whole question of hyperconjugation versus spin polarisation, which was raised in some detail by Colpa and de Boer (26), seems better expressed as "how much does spin polarisation contribute to hyperconjugation (or vice-versa) when considering the methyl and methylene hyperfine structure in esr spectra". Levy (28) has considered this point in quantitative terms, and his discussion will be applied here. It should be noted, however, that some modification may be needed to completely explain experimental results, but this will be further elaborated later.

Levy's formulation is useful in the sense that its accuracy depends largely on the molecular orbital treatment used to obtain the coefficients of the appropriate wave function, and as such is very adaptable to simplified theories. Using Hückel theory Levy obtained reasonably good results -- certainly more consistent than many previous explanations (25,26). Two expressions are derived, one for methylene protons and one for methyl protons. The derivation is straightforward and is

based on calculations of the spin densities at the protons concerned, and using Slater atomic orbitals (see, for example, ref. 30) an expression for the total spin density at the proton can be calculated from:

$$\rho(p) = \sum_{l,m} C_{ol} C_{om} \psi_l(p) \psi_m(p) \qquad (3\text{-}16)$$

where $$\psi_o = \sum_i C_{oi} \psi_i \qquad (3\text{-}17)$$

The final results are:

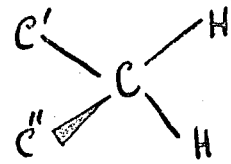
$$a_{CH_2} = 327 C_H^2 + 19.8 C_c^2 + 161 C_c C_H + (5.95 C_H + 1.46 C_c) \cdot (C_{c'} + C_{c''}) - 3.09 (C_{c'}^2 + C_{c''}^2) \qquad (3\text{-}18)$$

where the spin polarisation contribution is included in the last term and is derived from (27):

$$a_{sp} = Q\rho = Q(C_{c'}^2 + C_{c''}^2) = -3.09\rho \qquad (3\text{-}19)$$

where C' and C'' represent the adjacent carbon atoms.

i.e.



For the methyl case,

$$a_{CH_3} = 219.8 C_H^2 + 13.17 C_c^2 + 107.7 C_H C_c + 3.997 C_H C_{c'} + 0.973 C_c C_{c'} - 3.09 C_{c'}^2 \qquad (3\text{-}20)$$

where again the last term represents the spin polarisation contribution.

Care must be taken in applying these relationships to non-simple systems (either aliphatic or aromatic) since often many assumptions have been made in arriving at a situation in which the use of such relationships as eqs. (3-18) and (3-20) is plausible, and the results may not be entirely justifiable. However, if the necessary care is taken, the results should indicate the extent to which hyperconjugation

and/or spin polarisation contribute to the esr spectra.

D: CALCULATION OF SPIN DENSITIES

The close relationship between spin densities and the observed hyperfine splitting in esr spectra leads to the conclusion that a knowledge of the coefficients of the relevant molecular orbitals (and hence a knowledge of the unpaired electron density) leads to an estimation of the hyperfine coupling constants. In using any molecular orbital theory to estimate spin densities a very important point to consider is the ease of calculation of the desired values. Since this usually implies a simplified treatment, the parameters calculated from such coefficients should reflect the same degree of approximation. The two methods to be considered here for molecular orbital calculations are the Hückel molecular orbital method (HMO) and the McLachlan self-consistent field theory (SCF). A brief discussion of each might be useful:

(i) Hückel molecular orbital theory (32,34):

Basically, all wave functions ψ are solutions to the Schrödinger equation, $\mathcal{H}\psi = E\psi$, where $\mathcal{H}$ is the Hamiltonian operator which includes all interactions between m electrons and n nuclei. The lack of exact expressions for ψ has usually meant that considerable approximation must be made, however. Further, since the wave function contains far more information than can be obtained from it at any time, the approximations made must be suitable for the purpose. The first approximation here is that ψ can be considered the product of a set of σ-bonds, which are further divisible into relatively non-

interacting localised bonds, and π-bonds;

$$\psi = \phi_\sigma \phi_\pi \qquad (3\text{-}21)$$

Thus if it is assumed that ϕ_σ can be considered as a product of 2-center bonds only (i.e. the individual σ-bonds are considered to determine ϕ_σ), and ϕ_π is approximated in the LCAO method as a combination of $2p_z$ orbitals, each of which shares the same nodal plane (the carbon skeleton in planar aromatic rings):

$$\text{i.e.} \qquad \psi_j = \sum_{r=1}^{n} c_{jr} \varphi_r$$

for the LCAO molecular orbitals.

The π-system is considered alone, and the Hamiltonian can be initially considered a one-electron operator, and to solve for the set of coefficients giving the best energy for the molecular orbital the variation principle can be used (see, for example, ref. 35):

$$\epsilon = \frac{\int \psi \mathcal{H} \psi \, d\tau}{\int \psi^2 \, d\tau} \geq E_0 \qquad (3\text{-}22)$$

In other words, eq (3-22) is the expectation value of ψ over the Hamiltonian operator and represents an approximation to the energy of ψ. Any wave function $\psi' \neq \psi$ (i.e. the approximation to be used) will therefore give a higher energy than the ground-state energy E_0 -- where $\psi' = \psi$, $\epsilon = E_0$. Minimising eq (3-22) with respect to the coefficients

$$\frac{\partial \epsilon}{\partial c_r} = 0$$

leads to (32):

$$\sum_r C_r (H_{rt} - \epsilon S_{rt}) = 0 \qquad (3\text{-}23)$$

where $H_{rs} = \int \varphi_r H \varphi_s \, d\tau = H_{sr}$

$$S_{rs} = \int \varphi_r \varphi_s \, d\tau = S_{sr}$$

If there are n coefficients, clearly there will be n eq-

uations of the form (3-23) -- where t ranges from 1 to n.

Now, in the Hückel approximation the Coulomb integrals, $H_{rr}=\int \varphi_r H \varphi_r d\tau$, represent approximately the energy of an electron in a (carbon) $2p_z$ orbital; so for the π-lattice, consisting of carbons entirely, it can be assumed that all H_{rr} are equal and thus $H_{rr}=\alpha$. The resonance, or bond, integrals, H_{rs}, represent an atomic orbital interaction energy, and if r and s are not bonded $H_{rs}=0$, if r and s are adjacent and bonded, $H_{rs}=\beta$. The overlap integrals, S_{rs}, can be represented by the delta function, $S_{rs}=\delta_{rs}$, since $S_{rr}=1$ for normalised atomic orbitals, and S_{rs} is assumed to be 0 for $r\neq s$. Finally, it can be shown that (32):

$$\epsilon_j = \alpha + m_j\beta \qquad (3\text{-}24)$$

for the energy of the j'th molecular orbital.

If heteroatoms are to be included, modification of the Coulomb and resonance integrals can be effected as follows:

$$H_{rr} = \alpha + h\beta$$
$$H_{rs} = \begin{cases} k\beta & s=r\pm 1 \\ 0 & s\neq r\pm 1 \end{cases} \qquad (3\text{-}25)$$

where h and k are determined somewhat semi-empirically for each heteroatom in question(32,36). The spin density can now be calculated at the r'th atom from the following relationship:

$$\rho_r = c_r'^2 \qquad (3\text{-}26)$$

where c_r' is the coefficient of the half-occupied molecular orbital at the atom in question. This relationship follows from (3-8) and the wave function just described.

(ii) McLachlan self-consistent field theory (33,39):

The McLachlan SCF method applies best to alternant

hydrocarbons (32,33,39) and some difficulty arises when applying this method to non-alternant systems, especially if heteroatoms are present. It does, however, explain negative spin densities and has been of some use in calculations on nitro- and cyano-aromatic radicals (36,37).

The SCF total π-electron Hamiltonian can be written:

$$\mathcal{H} = \left(-\tfrac{1}{2}\nabla^2 - \sum_r V_r\right) + \tfrac{1}{2}\sum_{r\neq s} e^2/r_{rs} \qquad (3\text{-}27)$$

where V_r is the potential due to the screened nucleus r. McLachlan (39) showed that electrons of α and β spin occupy different orbitals without affecting the electronic wave function. In other words, they occupy spatially different orbitals. Thus the total π-electron wave function becomes

$$\psi_\pi = n\left(\phi_1^{\alpha}(1)\alpha(1)\,\phi_1^{\beta}(2)\beta(2)\ldots\right) \qquad (3\text{-}28)$$

McLachlan used Hückel molecular orbitals as starting orbitals and calculated the effects of electronic interactions (electron-electron perturbations) on the HMO coefficients. To do this he defined the modified Coulomb integral

$$\alpha_r' = \alpha_r + 2\lambda C_{r,n+1}^2\beta \qquad (3\text{-}29)$$

where $c_{r,n+1}$ are the coefficients of the r'th atomic orbital of the half-filled HMO, and α_r the Coulomb integral in the Hückel approximation. If c'_{ri} is the HMO coefficient, then the electron-electron perturbation becomes (39):

$$\sum_{i=1}^{n}\left(C_{r,i}^2 - C_{r,i}'^2\right) \qquad (3\text{-}30)$$

Thus the spin density becomes, in McLachlan's method (33):

$$\rho_r = C_{r,n+1}^2 + \sum_{i=1}^{n}\left(C_{r,i}^2 - C_{r,i}'^2\right) \qquad (3\text{-}31)$$

and in calculations λ is usually taken to be $\sim$1.2. This theory works well with alternant hydrocarbons, as mentioned

earlier, and also with some non-alternant hydrocarbons (fluoranthene, acenaphthylene), using Q^{H}_{CC}=-24.2G. As will be shown later, this value of Q is most suitable for this work, although application of any of the theories just outlined to chlorpromazine results in deviations from experiment that suggest careful interpretation of any quantitative values.

II PARAMAGNETIC RELAXATION IN LIQUIDS

A: THE SPIN HAMILTONIAN

Very often the hyperfine structure of spin resonance spectra in liquids exhibits a definite asymmetry or a linewidth alternation effect. Such phenomena have been shown to be due to nuclear orientation, solvent viscosity, etc., and most have been well-discussed (40-57). The relaxation effects to be discussed here are those explaining spectral asymmetry and linewidth narrowing, since the more complicated linewidth variations are probably not applicable to this experiment. The quite complicated relaxation and density matrix treatments of such as Kivelson and Freed and Fraenkel (43,44,49-51,54) will not be considered in any detail, therefore.

Before approaching any theoretical derivations, some postulates on the nature of the system to be studied have to be made, in order to choose the appropriate Hamiltonian to describe the pertinent interactions. McConnell (40), in his original treatment assumed that in solution an ordered state exists. That is, the paramagnetic species being considered

behaves as if it were in a regular crystal field, but unlike solid-state crystal behaviour is able to undergo Brownian motion. Ideally, then, the paramagnetic ion acts as a tumbling microcrystal. Such motion causes a fluctuating force to act randomly on anisotropic g-tensor and hyperfine interactions. Thus the greater this anisotropy, the greater the relaxation effect. If the crystal field surrounding the ion is then assumed to have a certain symmetry, the appropriate spin Hamiltonian can be applied with respect to the random fluctuating forces. The treatment outlined by Pake (58) is sufficient for this treatment, especially since only an order of magnitude agreement is expected. Slichter (59) and Abragam (60) also give thorough discussions, as do the other references listed at the beginning of this section.

A major approximation to be made is that the microcrystal exerts an axially symmetric force on the paramagnetic ion (this is somewhat justifiable simply by noting that the majority of the unpaired spin density resides on the nitrogen atom, and primarily there in the p_z orbital. Thus in relation to the nitrogen part of the molecule axial symmetry is a fair approximation), and the appropriate spin Hamiltonian is (see Appendix 3):

$$\mathcal{H} = \beta[g_{\parallel} H_r S_r + g_{\perp}(H_p S_p + H_\zeta S_\zeta)] + D S_r^2 + A_{\parallel} I_r S_r + \dots \quad (3\text{-}32)$$

transforming to laboratory co-ordinates, and noting that for spin $\frac{1}{2}$ systems D=0, and defining:-

$$g = \tfrac{1}{3} g_{\parallel} + \tfrac{2}{3} g_{\perp}, \quad \Delta g = g_{\parallel} - g_{\perp}$$
$$a = \tfrac{1}{3} A_{\parallel} + \tfrac{2}{3} A_{\perp}, \quad b = A_{\parallel} - A_{\perp} \quad (3\text{-}33)$$

the Hamiltonian can be written (see ref. 58 for all terms):

$$\begin{aligned}\mathcal{H} = {} & g\beta H_0 S_z + a\,\underline{I}\cdot\underline{S} + \tfrac{1}{3}(\Delta g\beta H_0 + bI_z)(3\cos^2\theta - 1)S_z \\ & + \tfrac{b}{2}\sin\theta\cos\theta\,(I_+ e^{-i\phi} + I_- e^{i\phi})S_z \\ & + \tfrac{1}{2}(\Delta g\beta H_0 + bI_z)\sin\theta\cos\theta\,(S_+ e^{-i\phi} + S_- e^{i\phi}) \\ & + \tfrac{b}{4}\sin^2\theta\,(I_+ S_+ e^{-2i\phi} + I_- S_- e^{2i\phi}) \\ & - \tfrac{b}{12}(3\cos^2\theta - 1)(I_+ S_- + I_- S_+)\end{aligned} \qquad (3\text{-}34)$$

which was the way McConnell first wrote the Hamiltonian. In eq (3-34) the time-dependence of the terms in θ and ϕ has been left implied, rather than writing $\theta(t), \phi(t)$ etc.. Terms involving S_+ and S_- will give rise to electron spin-lattice relaxation, wheras terms in I_+ and I_- will give nuclear relaxation effects.

B: RANDOM CORRELATIONS

The next problem is to determine the behaviour of $\mathcal{H}$ in a randomly fluctuating environment (which will cause the spins to experience a modulated magnetic field), and to do this a knowledge of random functions is necessary. This is more fully discussed in Appendix 4. The most formidable, or perhaps uncertain, problem involves the definition of the correlation functions $G(\tau)$ and $g(\tau)$ (appendix 4) where:

$$G(\tau) = \overline{|f(x(t))|^2}\; g(\tau) = G(0)\,g(\tau) \qquad (3\text{-}35)$$

and f(x(t)) is a random function of time since x(t) is by definition. Any convenient definition of $g(\tau)$, then, will define $G(\tau)$, since $G(0)$ is usually available in the problem being considered -- it is certainly evaluable in this case. For mathematical ease, then, the most commonly used form of $g(\tau)$ is as follows:

$$g(0) = 1 \quad , \quad g(\tau \to \infty) = 0 \qquad (3\text{-}36)$$

and $\quad g(\tau_c) \sim g(0)/2$

where τ_c is the correlation time for the system being considered. There is clearly a lack of precision in the definition of τ_c, and the only real limit is that $G(\tau)$ be small for $|\tau| \gg \tau_c$. In other words, the correlation must be poor (a small value of the correlation function) when the interval being considered deviates considerably from the true one. Appendix 5 shows how the correlation function can be derived, and Appendix 6 gives the relaxation rate $1/T_1$ in terms of the correlation function already derived. Slichter (59) and Pake (58) give very complete derivations of the spin-lattice relaxation, and Abragam (ref. 60, p 283) also gives a good treatment. Following these references, and Appendix 6, the general result can be derived that:

$$\left(\tfrac{1}{2}T_1\right)_{km} = \overline{W}_{km} = \hbar^{-2}\int_{-\infty}^{\infty} G(\tau)\, e^{-i\omega_{km}\tau}\, d\tau \qquad (3\text{-}37)$$

Now the time-dependent perturbation can be written as the product of a spin operator, A_{op}, and a time-dependent part, F(t), that describes the variation of the lattice coordinates with time:-

$$\mathcal{H}_1(t) = A_{op}\, F(t) \qquad (3\text{-}38)$$

or, more completely,

$$\mathcal{H}_1(t) = \sum_i A^i_{op}\, F^i(t) \qquad (3\text{-}39)$$

for each nucleus.

Clearly, if the Hamiltonian considered applicable for the problem is separable into a spin and lattice product, the relaxation effects of the perturbation can be treated. Con-

sider, then, that:

$$G(\tau) = \overline{|f(\cos\theta(t))|^2}\, \exp(-|\tau|/\tau_c) \qquad (3\text{-}40)$$

where $f(\cos\theta(t)) = \langle m|\mathcal{H}_1(t)|k\rangle$

and $g(\tau) = \exp(-|\tau|/\tau_c)$

and $j(\omega) = 2\tau_c/(1+\omega^2\tau_c^2)$ -- see Appendix 4

so $\left(\frac{1}{2T_1}\right)_{km} = \hbar^{-2}|\langle k|A_{qp}|m\rangle|^2\, \overline{|F_{km}(t)|^2}\, 2\tau_c/(1+\omega^2\tau_c^2)$ (3-41)

For the case of an aromatic π-radical, $S=\frac{1}{2}$ and in the esr case the transitions occur between $m_S=+\frac{1}{2}$ and $m_S=-\frac{1}{2}$, with $\Delta m_I=0$. The spatial part of the operator will be a function of angle, as already described. Thus, selecting from eq (3-34) the term:

$$\mathcal{H}_1(t) = A_{qp}F(t) = \tfrac{1}{2}(S_+e^{-i\phi} + S_-e^{i\phi})(\Delta g\beta H_0 + bI_z)_{\sin\theta\cos\theta} \qquad (3\text{-}42)$$

since it is the most important spin-lattice term -- the others become negligible in comparison for this case. Then:

$$G(\tau) = \tfrac{1}{4}(\Delta g\beta H_0 + bm_I)^2\, |\langle -\tfrac{1}{2}|S_-|\tfrac{1}{2}\rangle|^2\, \overline{|\sin\theta\cos\theta e^{i\phi}|^2}\, e^{-|\tau|/\tau_c}$$

$$= \tfrac{1}{30}(\Delta g\beta H_0 + bm_I)^2\, e^{-|\tau|/\tau_c} \qquad (3\text{-}43)$$

therefore $\frac{1}{2T_1} = \hbar^{-2}\tfrac{1}{30}(\Delta g\beta H_0 + bm_I)^2\, 2\tau_c/(1+\omega^2\tau_c^2)$ (3-44)

Which is the equation to be used in this case.

C: LINEWIDTH AND THE NUCLEAR QUANTUM NUMBER

Asymmetric spectra in electron spin resonance have been studied and explained for many cases (40,41,43,45,46,65) and for the purposes of this work a brief description of one effect will be given. Again, the part of the Hamiltonian to be considered dominant will be the part that is diagonal in nuclear quantum number, as this term will be most affected by variations in the magnetic environment at the nucleus (for this simplified case). Complete details will be omitted princip-

ally because the results obtained are concerned primarily with an explanation of the observed results, and only secondarily with quantitative agreement.

If a simplified first-order perturbation is considered, and it is assumed that $b \ll g\beta H_0$ (this is not a strong assumption, since experimental work indicates that these two terms are nearly equal), and if the diagonal term in eq (3-34):

$$1/3\, b(3\cos^2\theta - 1) I_z S_z$$

is considered, then if the microcrystal is fixed in space, the diagonal element of this term for some state $|m_I m_S\rangle$ corresponds to a local hyperfine magnetic field displacing the electron resonance frequency by $\delta\nu = \delta\omega/2\pi$ Furthermore (since $h\nu = g\beta H_0$):

$$\hbar\,\delta\omega = b/3\,(3\cos^2\theta - 1)\, m_I \qquad (3\text{-}45)$$

and, as is well known, under rapid tumbling the angular term tends to an average value of zero and the resonance is undisplaced.

Therefore, knowledge of the effect of τ on eq (3-45) should indicate the manner in which the dipole-dipole coupling will affect the resonance (since $b/3\,(3\cos^2\theta - 1)$ occurs in the dipolar coupling Hamiltonian, $\mathcal{H}_d = -g\beta g_n \beta_n \left(\frac{\mathbf{I}\cdot\mathbf{S}}{r^3} - \frac{3(\mathbf{I}\cdot\mathbf{r})(\mathbf{S}\cdot\mathbf{r})}{r^5}\right)$. Narrowing arises here because of the fluctuating magnetic environment of the ion and if such an environment is considered to have two values, shifting the center of the resonance, ω_0, by either $+\delta$ or $-\delta$, then the lifetime of existence in either state can be defined to be τ. The spin can therefore precess at $\omega_0 \pm \delta$ with the magnetic field varying randomly at either locale.

If, however, no fluctuation between the environments occurred, then the decay time (T_2, the Bloch transverse relaxation time, see Appendix 7) will be $T_2^0 \cong 1/\delta$.

The fluctuation of each precessing spin is, in effect, a random walk about the spin's phase angle with respect to the rotating frame. Then a mean-square phase difference, $\Delta\phi^2$, can be defined (66):

$$\Delta\phi^2 \cong n(\tau_c\delta)^2 \qquad (3\text{-}46)$$

where n is the number of changes of environment, and $\tau_c\delta$ then measures the mean phase accumulation per second. Since T_2 is essentially the time in which in-phase precessing spins become 1/e out of phase (58), and $(\Delta\phi^2)^{1/2}$ must be of the order of one radian, and if the elapsed time is T_2;

$$n = T_2/\tau_c$$

$$\text{so} \quad 1 \approx (T_2/\tau_c)(\tau_c\delta)^2 \qquad (3\text{-}47)$$

and the linewidth is equal to $1/T_2 \sim \tau_c\delta^2$ for $\tau_c < 1/\delta$ or if $\tau_c > 1/\delta$, $1/T_2 = 1/T_2^0 \sim \delta$.

In other words, if $\tau_c < 1/\delta$ the environment has fluctuated before the transverse spin component has decayed in consequence of the $T_2^0 \sim 1/\delta$ decay. Therefore $\tau_c < 1/\delta$ is the criterion for averaging away broadening effects (δ is the frequency measure of dipolar coupling).

General theories by Kubo and Tomita (67) and other considerations of density matrix and relaxation treatments show that δ can be taken to be the amplitude of any randomly fluctuating perturbation diagonal in m_s (58), which averages to zero over long times and has a correlation time τ_c. This

cannot be applied to long τ_c (a rigid lattice) where the linewidth is $\delta (\tau_c > 1/\delta)$.

Off-diagonal random perturbations can contribute to spin-lattice relaxation, as was shown in the previous section, and under conditions of extreme narrowing $\tau_c \ll 1/\delta$, $1/T_1$ can contribute a term comparable to $1/T_2$ (58) to the total linewidth because the finite spin state lifetime, T_1, broadens energy levels in accordance with $T_1 \Delta E \sim \hbar$. Even including this effect, however, $1/T_2 \sim \tau \delta^2$ is still quite valid as an order of magnitude expression.

In organic radicals the averaging away of anisotropic effects is usually nearly complete in low-viscosity solutions. This is because τ is short and g- and A-tensor anisotropy is usually not large. Hence the isotropic Hamiltonian:

$$\mathcal{H}^0 = g\beta H_0 S_z + a \underline{I} \cdot \underline{S} \qquad (3\text{-}48)$$

is often approximately valid.

If it can be shown that the molecule obeys the axial Hamiltonian and if there are reasons for considerinf g- and A-tensor anisotropy, then the diagonal term of the axial Hamiltonian:

$$1/3 (\Delta g \beta H_0 + b I_z)(3\cos^2\theta - 1) S_z \qquad (3\text{-}49)$$

and for sufficiently rapid motion, using eq (3-45):

$$\delta = 1/3 (\Delta g \beta H_0 + b m_I)/\hbar \qquad (3\text{-}50)$$

so $$1/T_2 \approx \tau_c (\Delta g \beta H_0 + b m_I)^2/\hbar^2 \qquad (3\text{-}51)$$

represents the motional (residual) linewidth to be expected. Clearly, the nuclear quantum number, m_I, will determine the linewidth, and quite different linewidths are to

be expected for different values of m_I. In general, $1/T_2$ will be less for negative m_I than positive. Such an observation, or the opposite, should enable the manner of nuclear splitting to be determined for esr spectra.

Finally, a more general result (which is essentially the same as eq (3-51), but can include as many terms or effects as wanted) was developed by Kivelson (45):

$$1/T_2 = Km_I^2 + Lm_I + C \qquad (3\text{-}52)$$

where the linear term is the intramolecular dipole interaction just considered and is responsible for spectral asymmetry. For the nitrogen atom L is negative (68), and in general eq (3-52) enables the sign of the splitting constant to be determined.

Spectral narrowing or broadening due to exchange effects will not be considered here, but will be discussed very briefly in the next section when the spectral lineshapes are considered.

RESULTS AND DISCUSSION

A: A BRIEF INTRODUCTION

The spectra observed in sulfuric acid, shown in figs. 1a-i, were assigned to the cation of chlorpromazine (CPZ^+), and the spectra shown in figs. 2a-d were assigned to another oxidation product, to be discussed more fully later. The transition to the spectrum exhibited in figs. 2 was not expected, but adds useful information to the expected behaviour of chlorpromazine -- this will be more fully discussed when the electrical properties of chlorpromazine are considered. This will also be correlated with the biophysical and biomedical aspects of CPZ. For the majority of the discussion the properties of CPZ^+ will be the main point of interest. Spectra obtained under different circumstances are shown in figs. 3a-e and will also be discussed later -- no discussion of the spectra of promazine hydrochloride (for the structure of this, and other common phenothiazine drugs, see Appendix 9) is given since attempts to obtain resolved and useful spectra in various media were unsuccessful. It was hoped that some information on the esr spectrum of a symmetrical, but very similar, "relative" of CPZ would add to the knowledge of CPZ in particular, and all phenothiazine drugs in general.

B: THE HYPERFINE STRUCTURE OF CPZ^+

Analysis of the spectrum of CPZ^+ proved difficult. The sixteen line spectrum observed clearly consisted of many co-incident (accidentally) lines, so no easy separation of

components was possible. Assignments were effected by examination of a) the spectra of phenothiazine and some of its simpler derivatives (69-79), and b) by examination of the Hückel spin densities at various ring positions. Neither a) nor b) was particularly successful, but closer examination of the electrolysed CPZ samples (fig. 3a) combined with a computer-simulated spectrum finally resulted in an excellent agreement between observed and calculated spectra (all esr simulations were made using a program written by C.S.Johnson of Yale University and P.J.Black of this university). The splitting constants obtained were not entirely expected from considerations of either the other phenothiazines, or the limited work done on chlorpromazine already. However, the "fit" suggested the following basic splitting constants:

$$\begin{aligned} a^N &= 6.700 \text{ G} \\ a^1_2 &= 3.400 \text{ G} \\ a^2 &= 1.620 \text{ G} \\ a^3 &= 1.600 \text{ G} \end{aligned} \qquad (4\text{-}1)$$

where a^N is the nitrogen-14 splitting constant, a^1 the splitting due to the CH_2 group attached to the nitrogen atom (carbon number 15, or C-15), and a^2 and a^3 the splittings due to ring protons. Some confusion exists with these constants -- initially, from Hückel calculations, it was expected that there would be four almost equivalent ring protons (this equivalence is not equivalence in the symmetrical sense, but in the sense that the spin densities are almost equal -- this means that the splitting constants will be almost equal, if the proton spin polarisation, or Q, constants are the same at all these positions. In other words, "accidental" equiv-

alence is involved), but the results indicate that only three ring protons are contributing to the structure observed, and these are nearly equivalent. Further, the spectral fit requires two protons to be more equivalent than the other (although for a more realistic fit all protons should have slightly different splitting constants -- this is not warranted in view of the approximate nature of much of the calculation, and the term "equivalent" will continue to be used to describe protons with similar spin densities, even if there is no structural symmetry). If two protons have a=1.62G, and one has a=1.60G, then eq. (4-1) holds. However, if the opposite is true then a^1 should be ~3.37 G. The final assignment of this will be made in the next sections, after a discussion of the Hückel calculations has been made.

C: HÜCKEL CALCULATIONS

Hückel calculations (done using a computer program written by D.Kennedy, and modified slightly to do a McLachlan calculation also by F.Nakano, both of this university) were carried out on a planar structure initially, but it was later considered better to modify these calculations to include folding about the N-S axis. The exact angle of folding was determined by carrying out calculations for a series of angles and fitting the results to the splitting constants considered in the previous section. This method was restricted primarily to a^N, and somewhat less to a^1, since most of the effect of structural folding about the N-S axis should be evidenced at, or near, the nitrogen atom. Folding, or flapping, of the side-

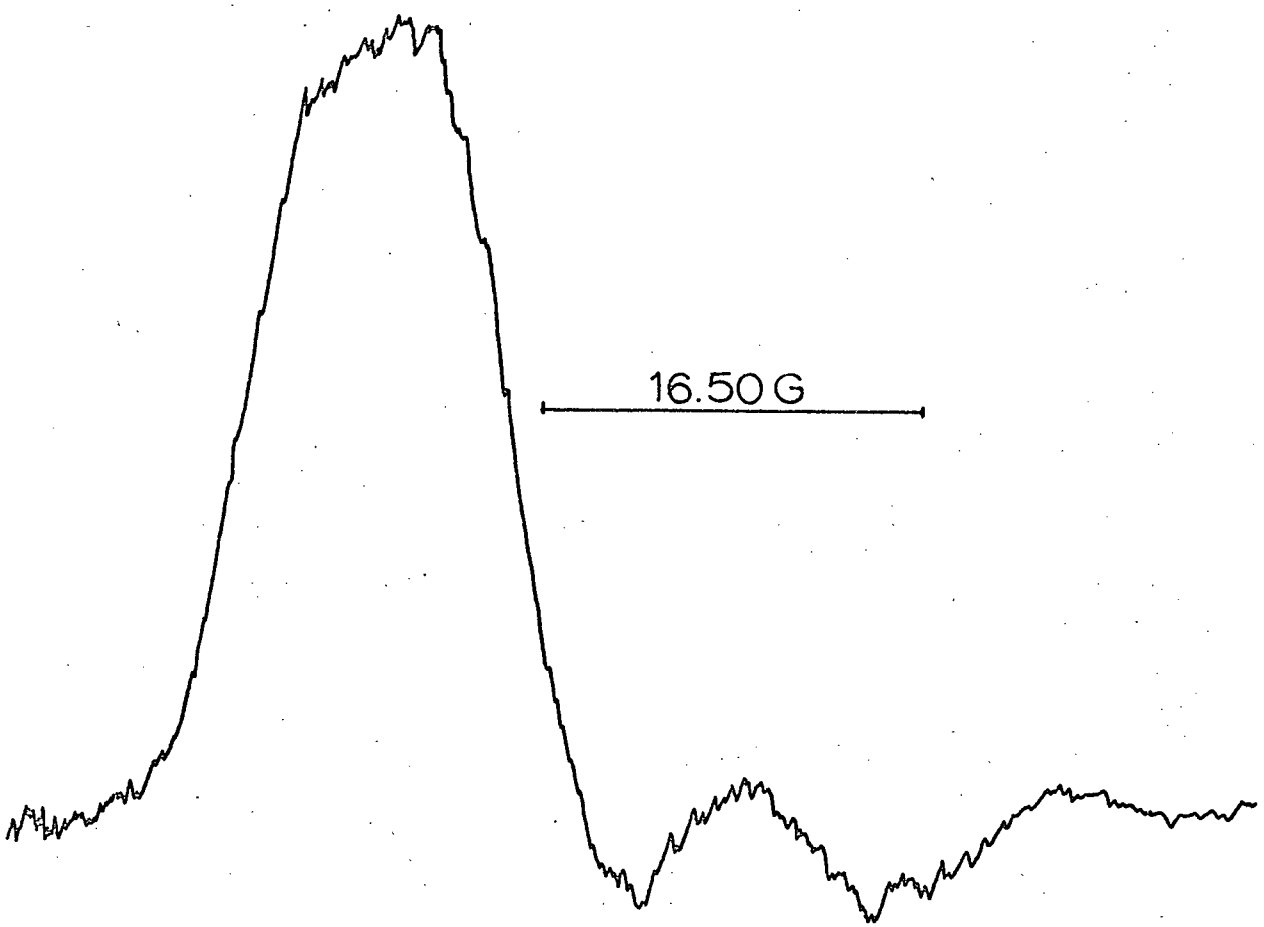


Fig 1a CPZ^+ in H_2SO_4 glass at --90°C

All spectra that follow are at room temperature, unless otherwise specified. Spectrometer conditions for all spectra were about: 3250G field with 0.1 to 0.75 G modulation; 9.10 GHz microwave frequency at a 5milliwatt power level.

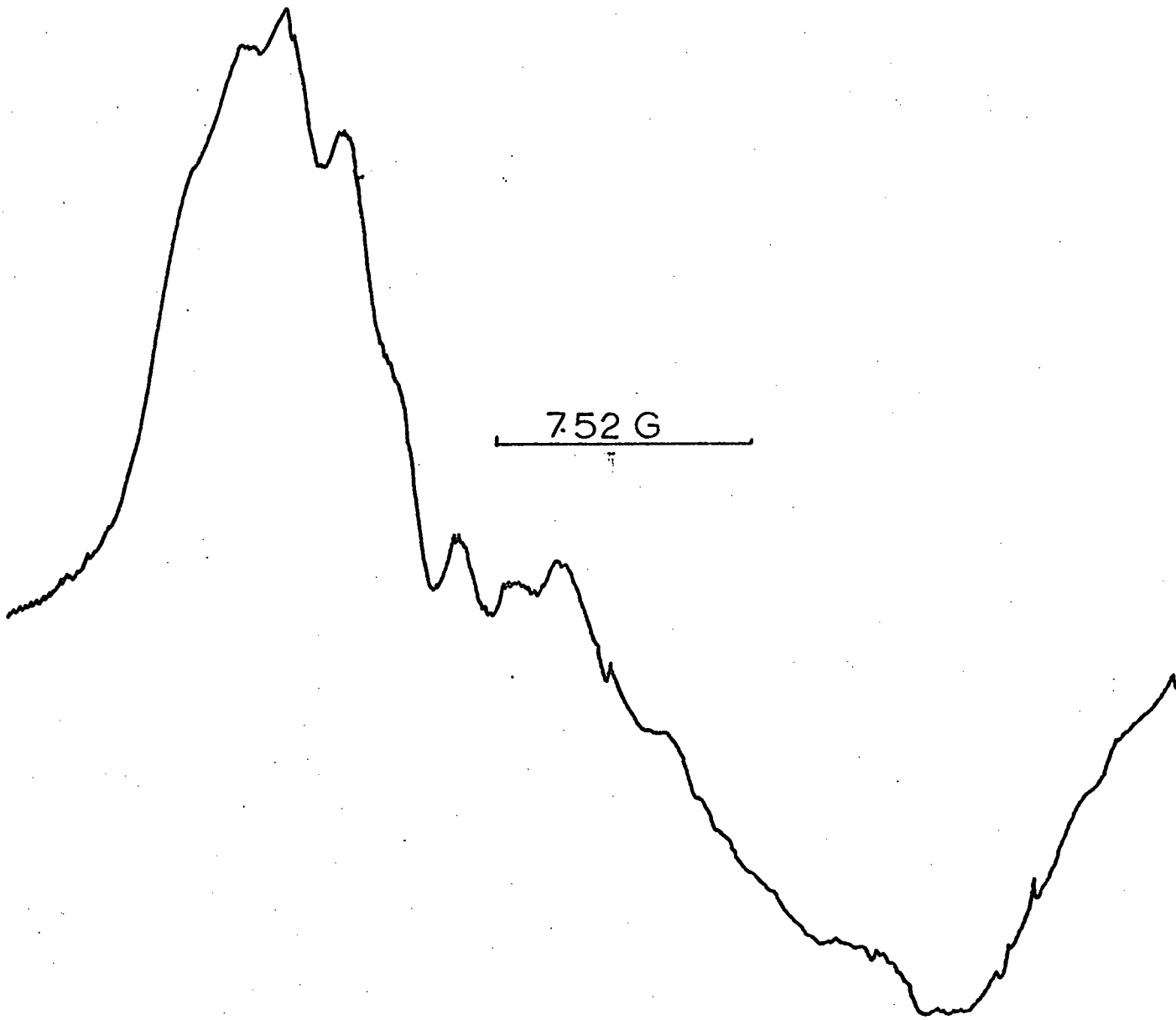


Fig 1b CPZ^+ at 9°C (all spectra shown in figs 1a-i are for H_2SO_4 solution)

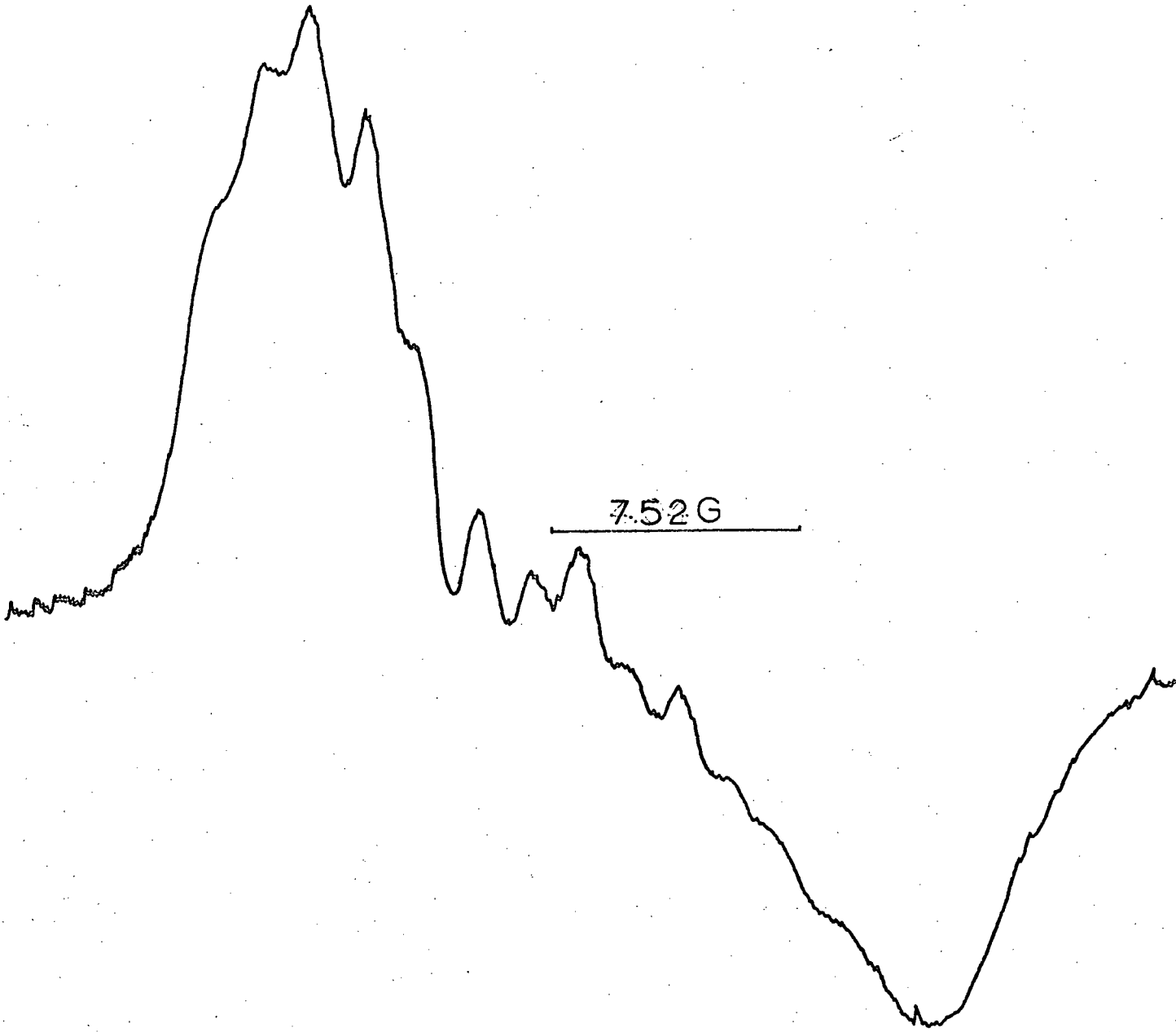


Fig 1c CPZ^{+} at 16°C

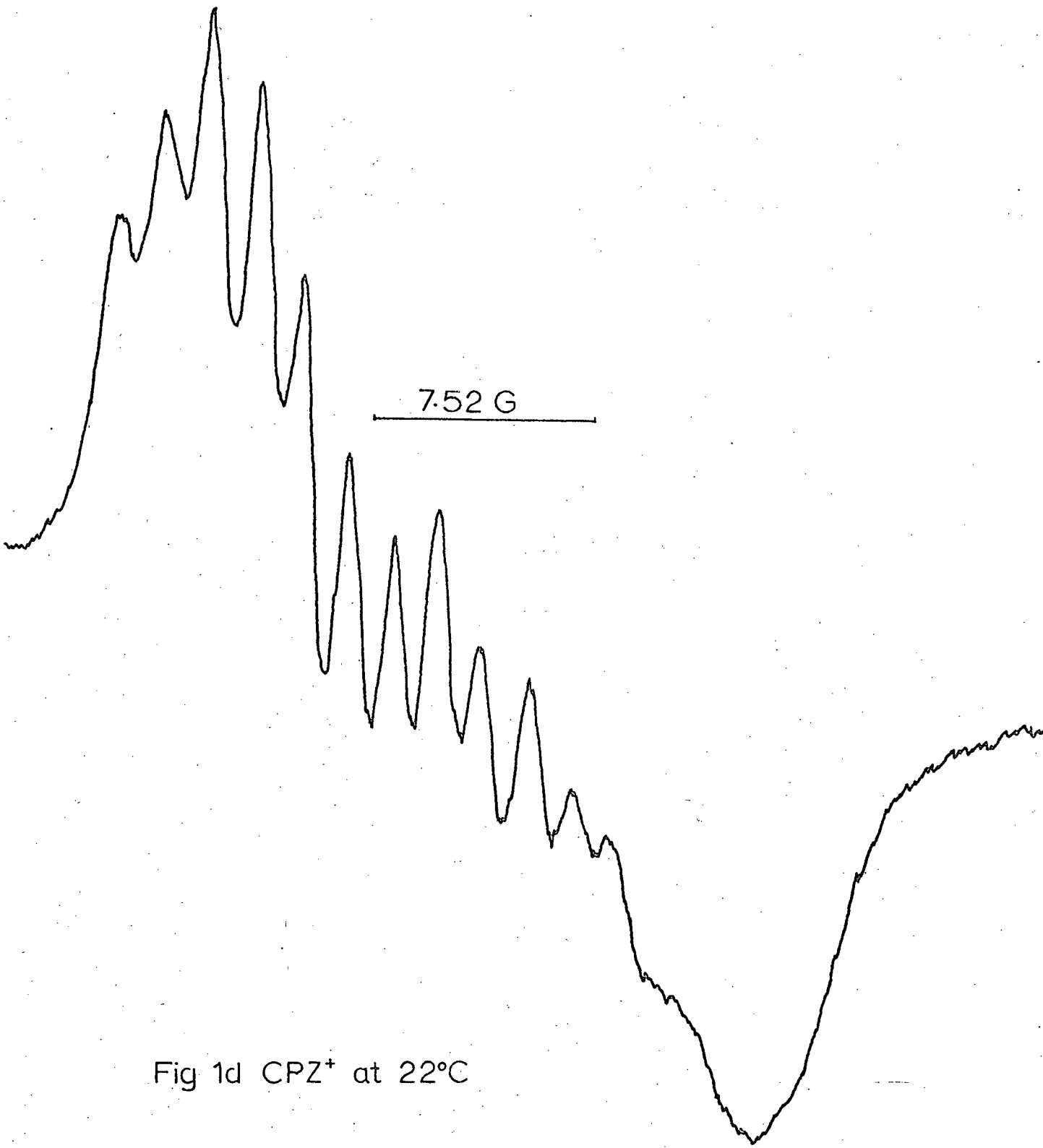


Fig 1d CPZ^{+} at 22°C

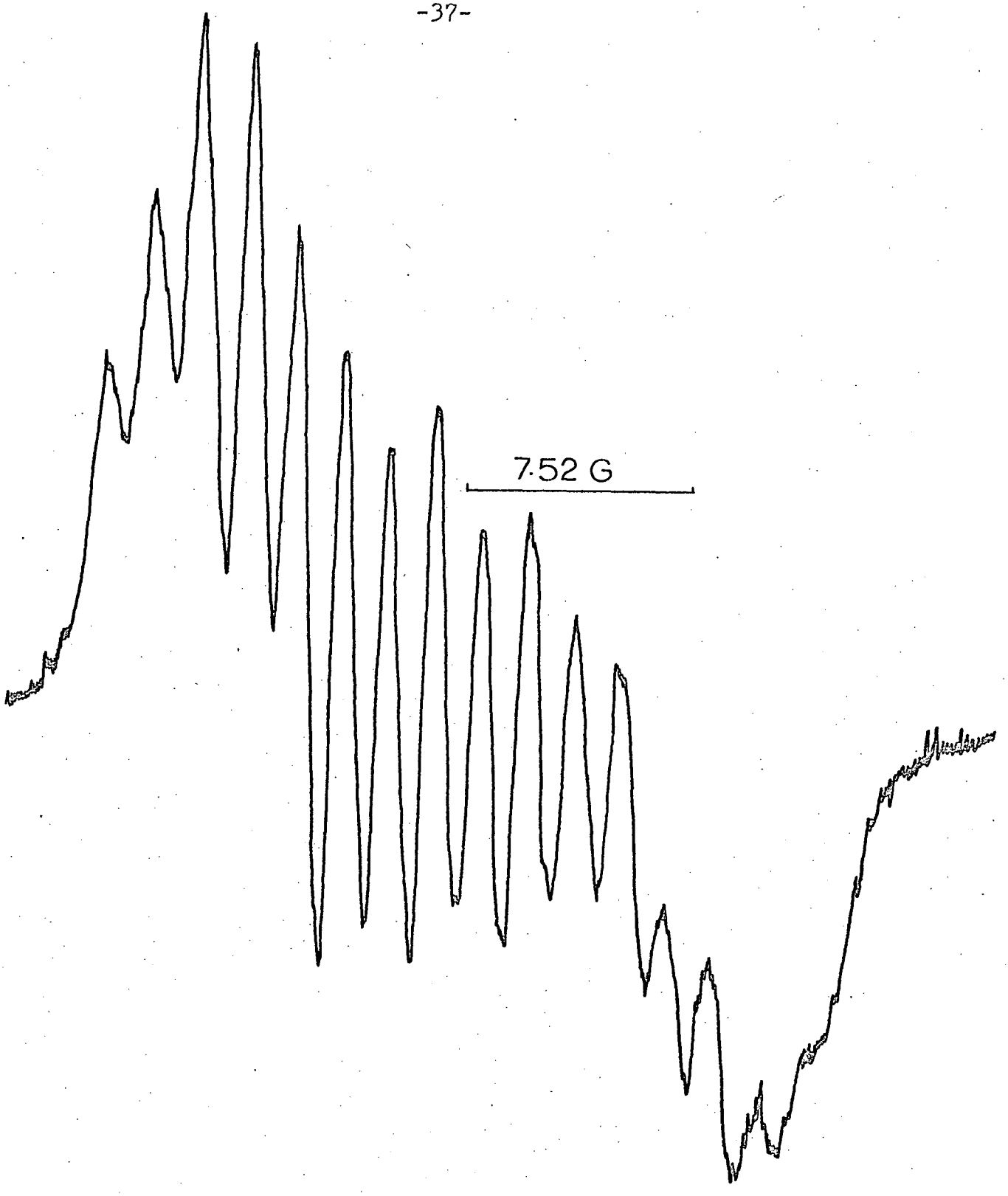


Fig 1e CPZ^+ at 50°C

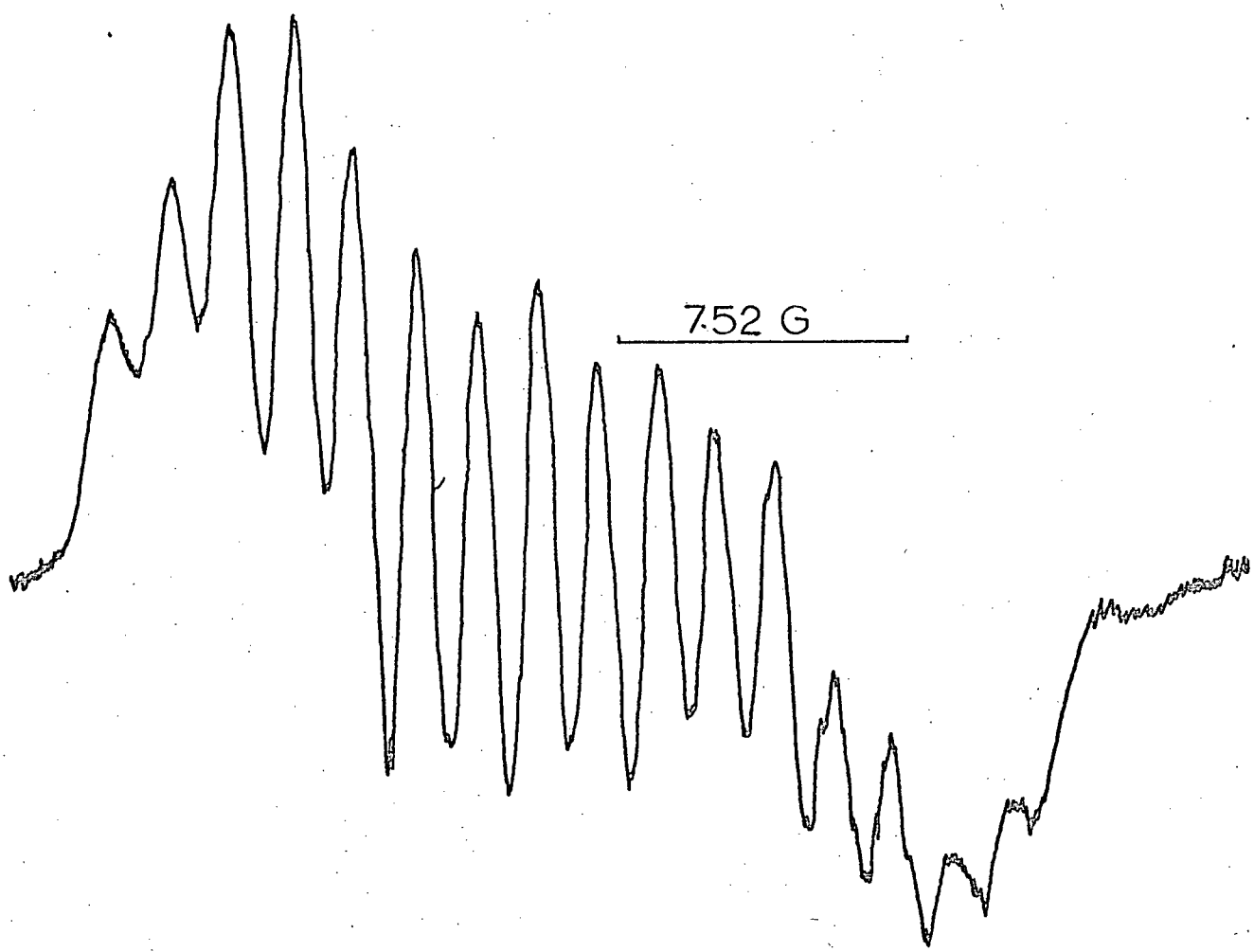


Fig 1f CPZ^{+} at 75°C

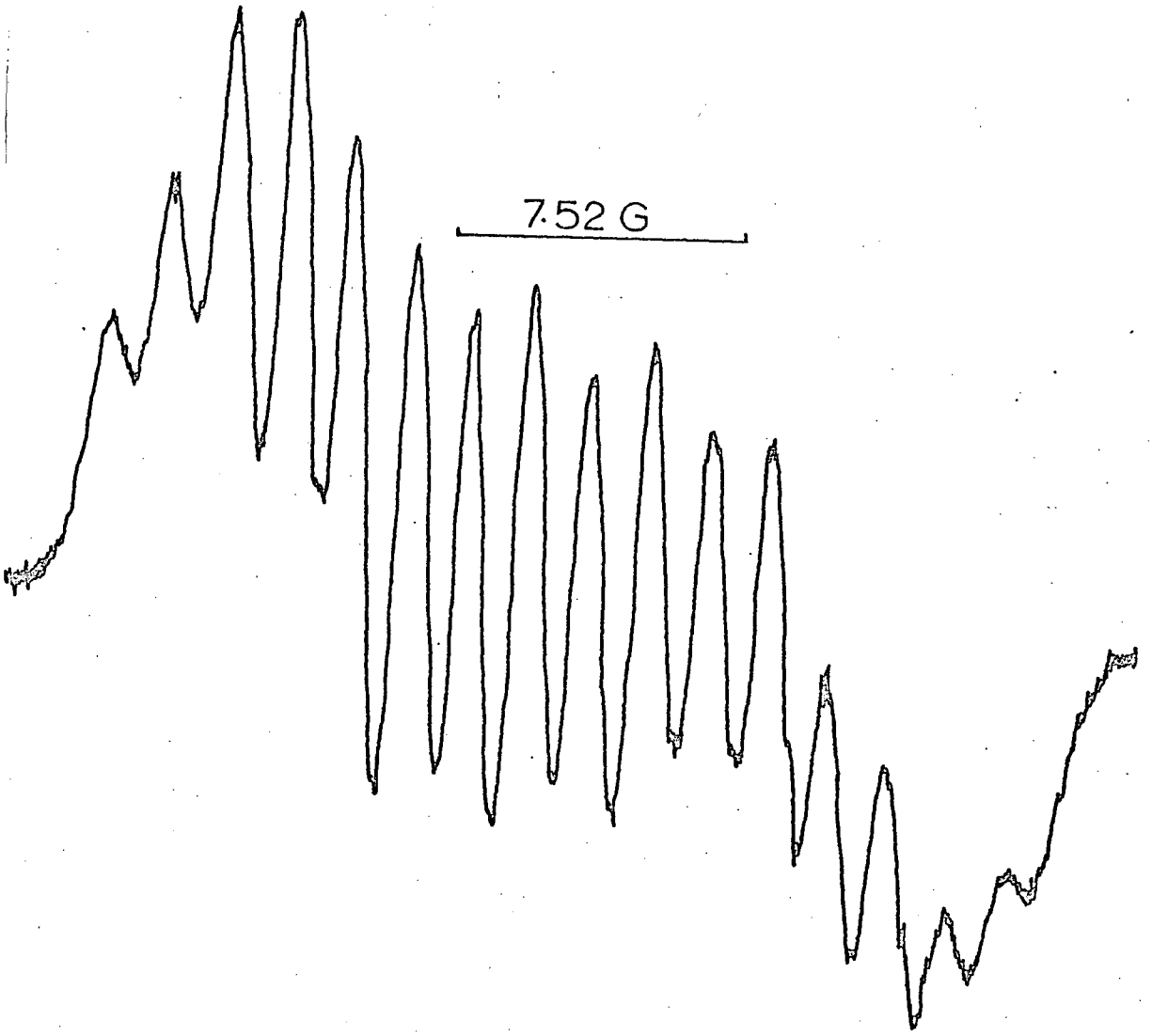


Fig 1g CPZ^{+} at 92°C

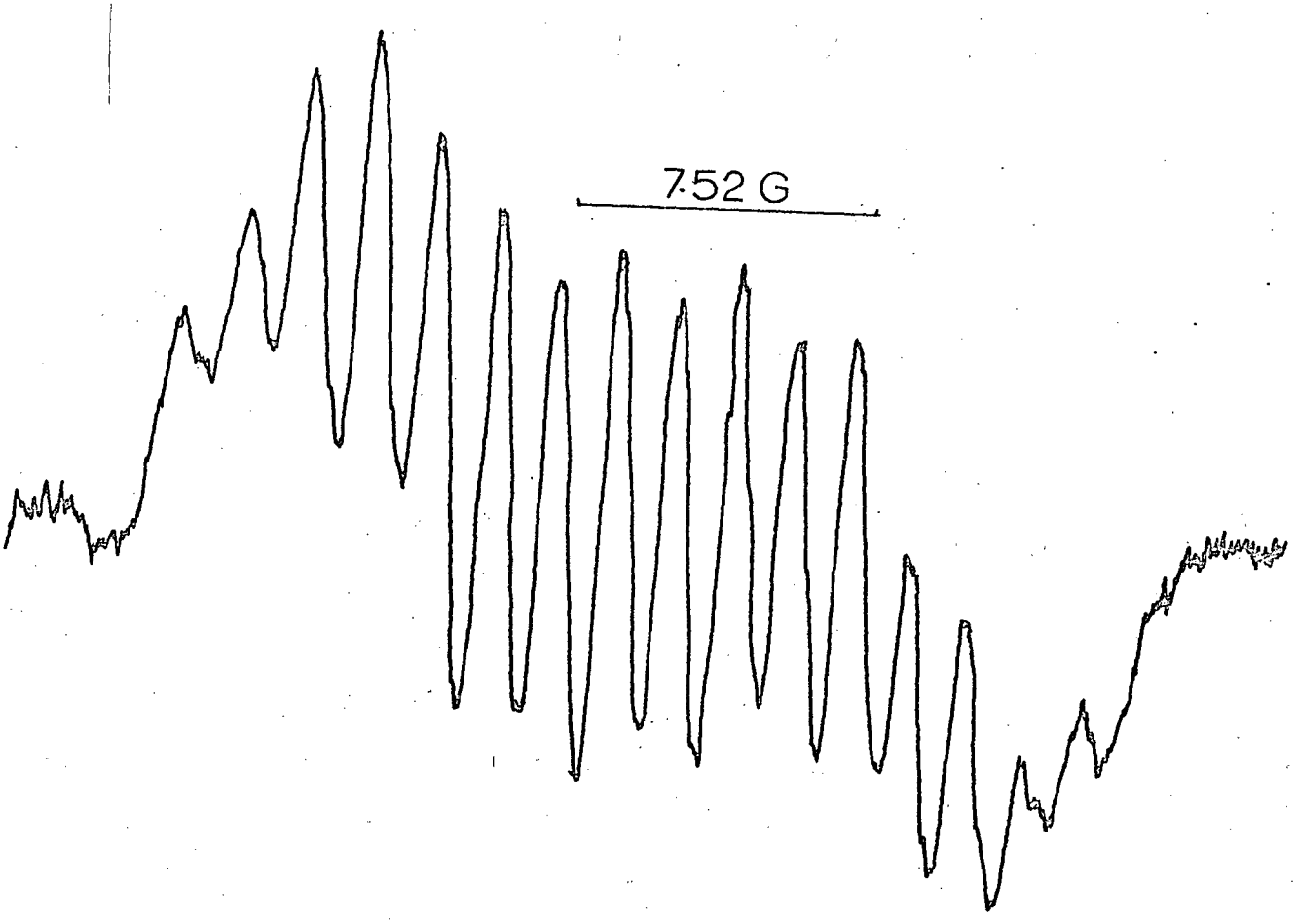


Fig 1h CPZ^{+} at 111°C

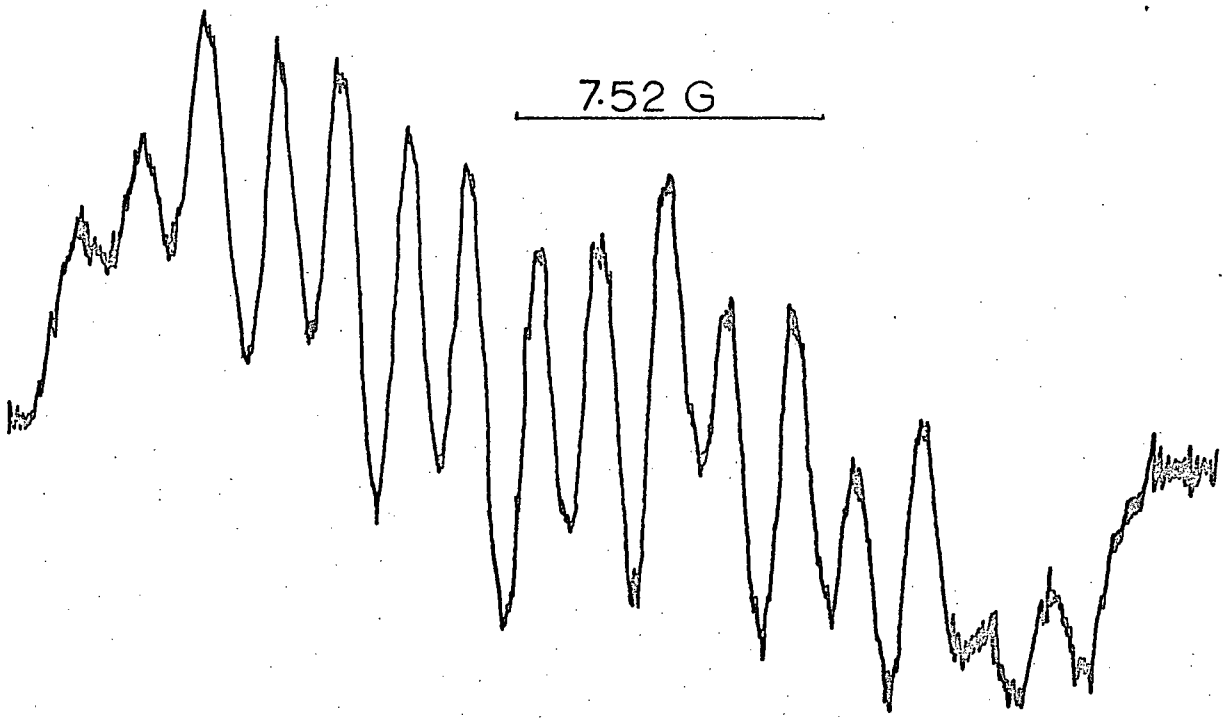


Fig 1i CPZ^{+} at 131°C – note the change becoming apparent on the right where the temperature was drifting up towards 136°C

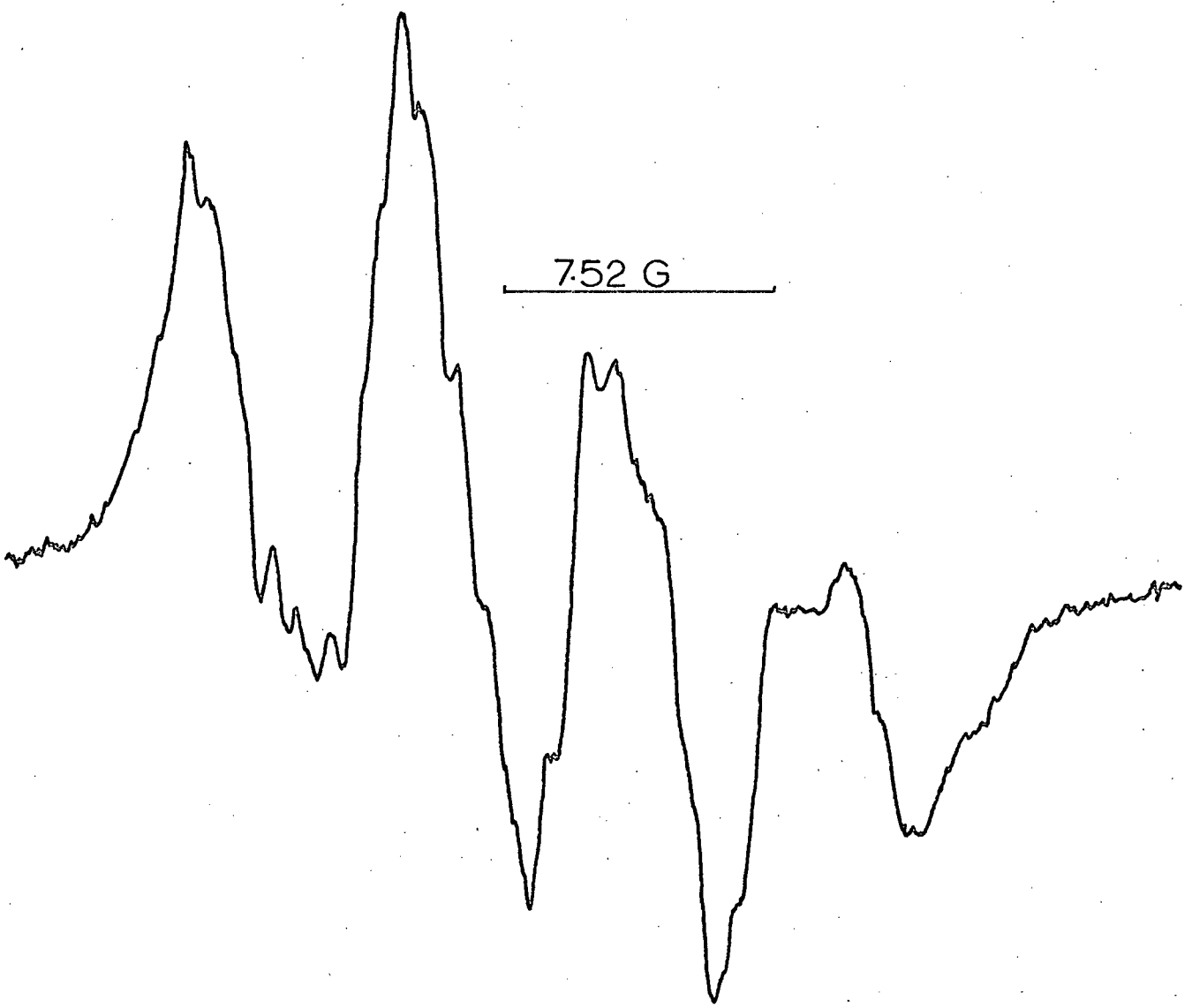


Fig 2a "changed species" (CS) at 21.8°C

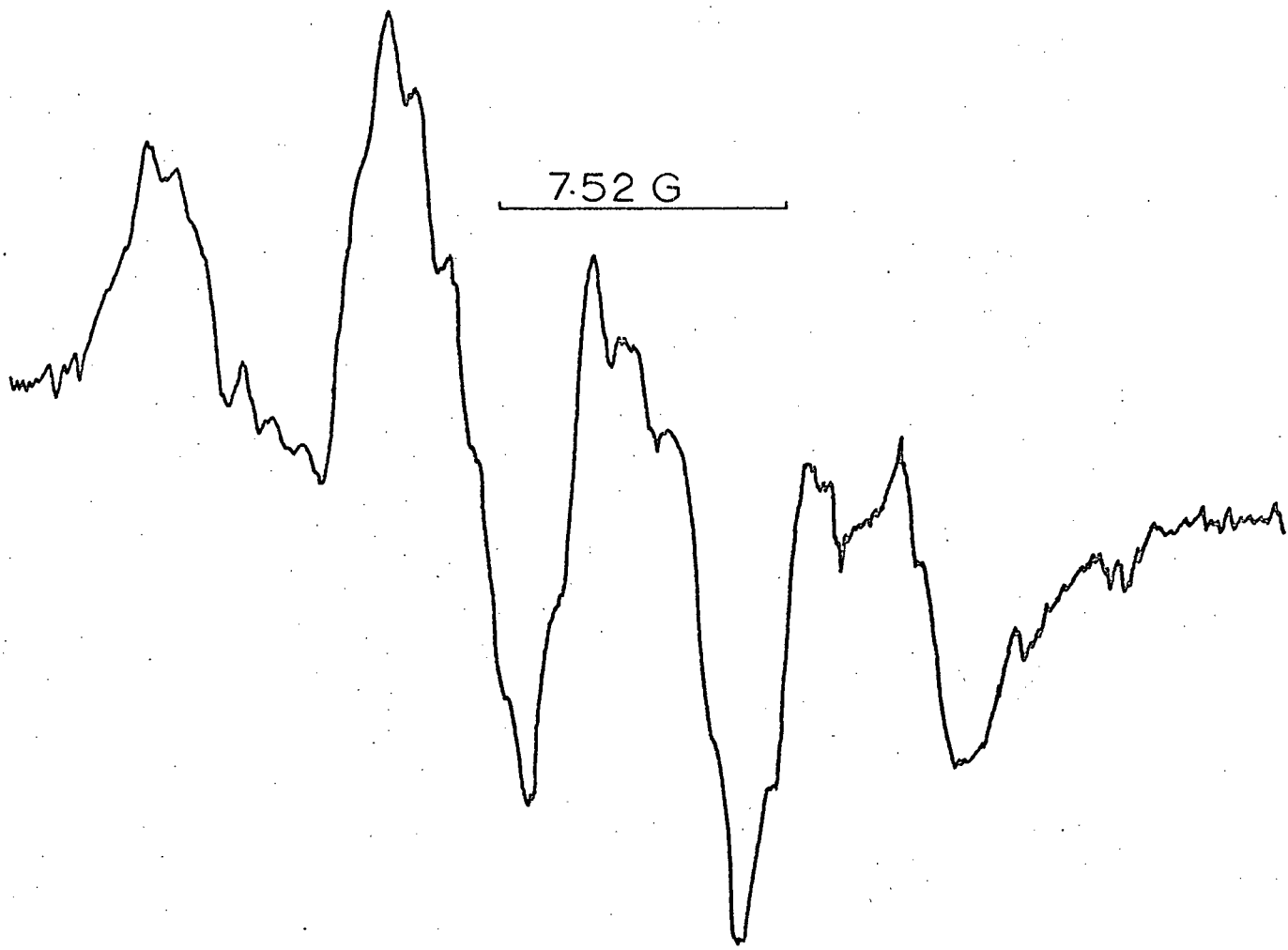


Fig 2b CS at 59°C

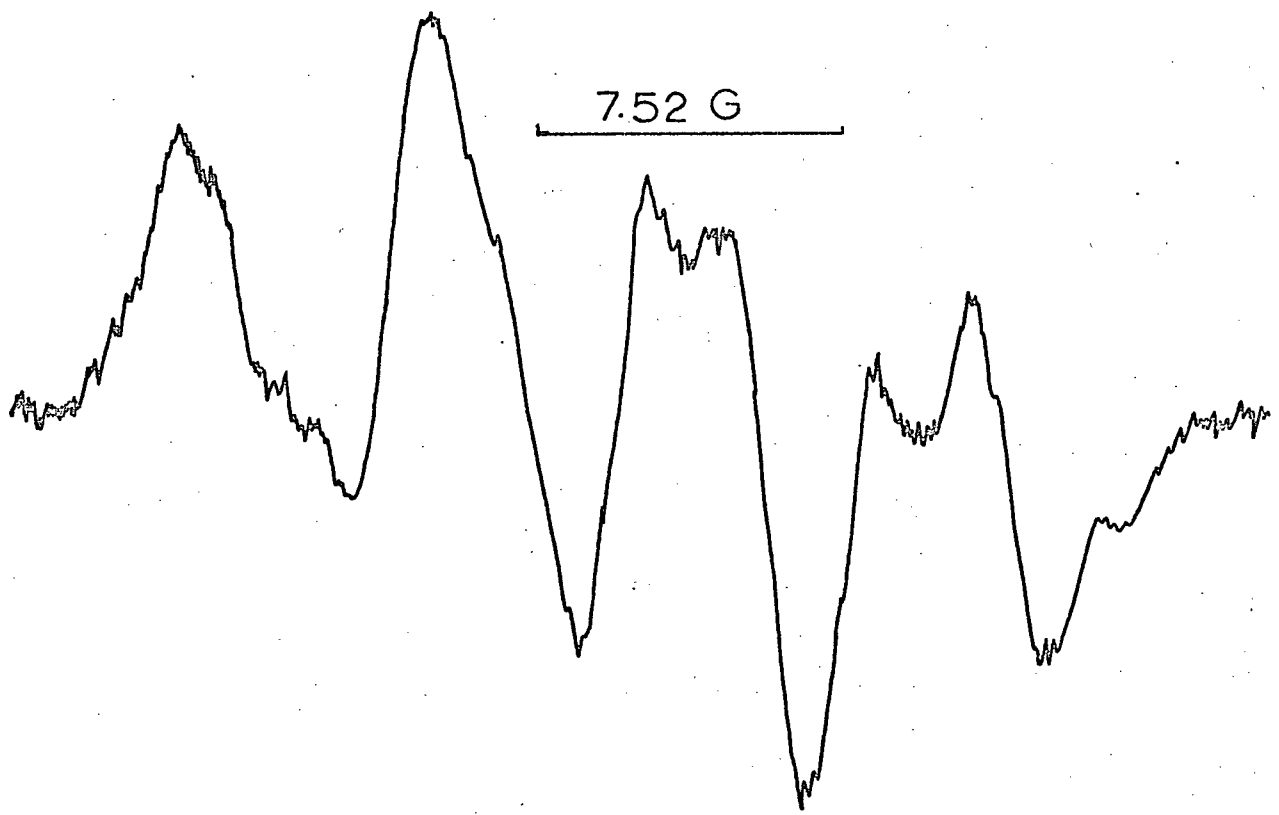


Fig 2c CS at 141°C

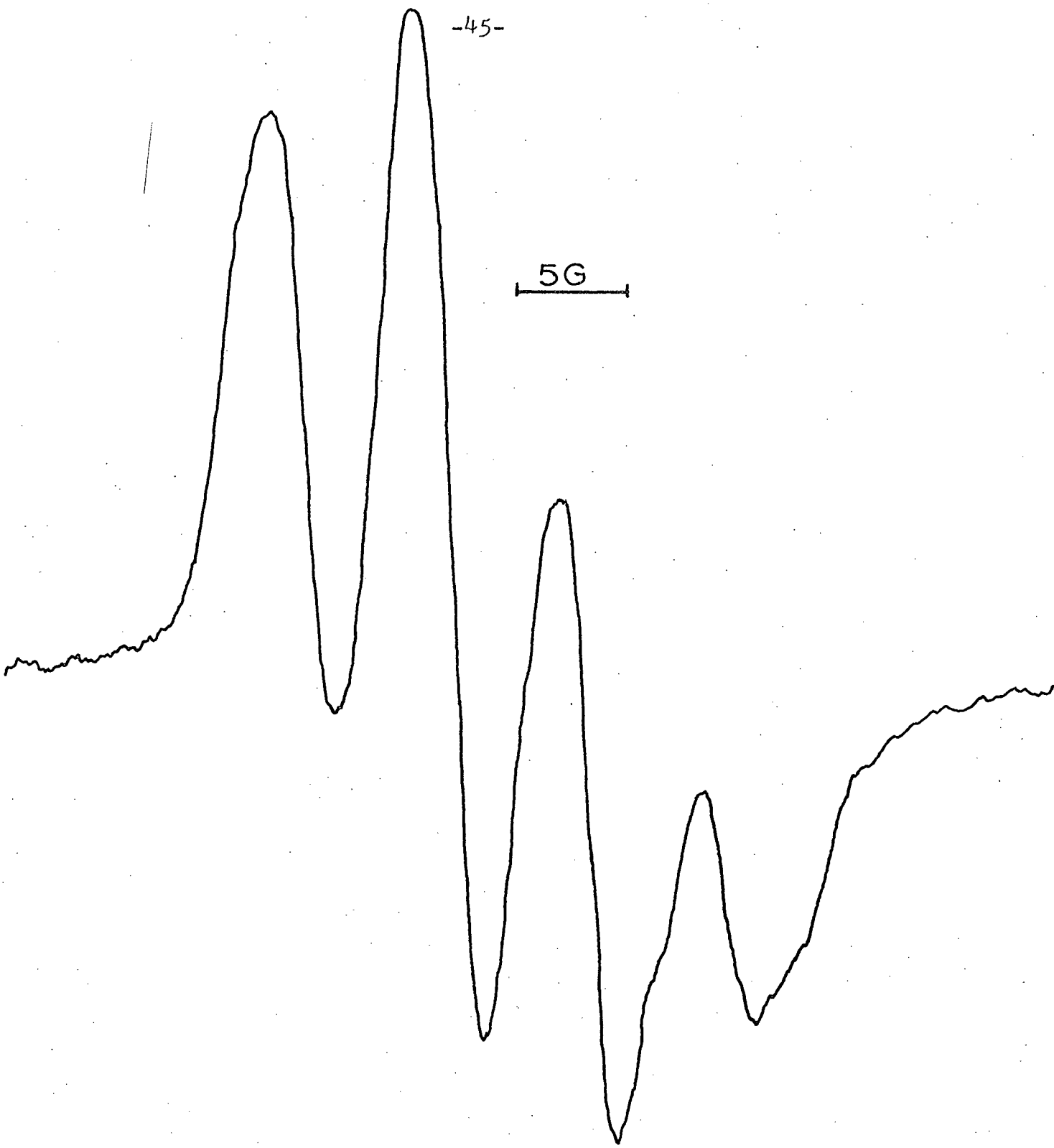


Fig 2d low resolution spectrum of "changed" CPZ species shown in figs 2a-c

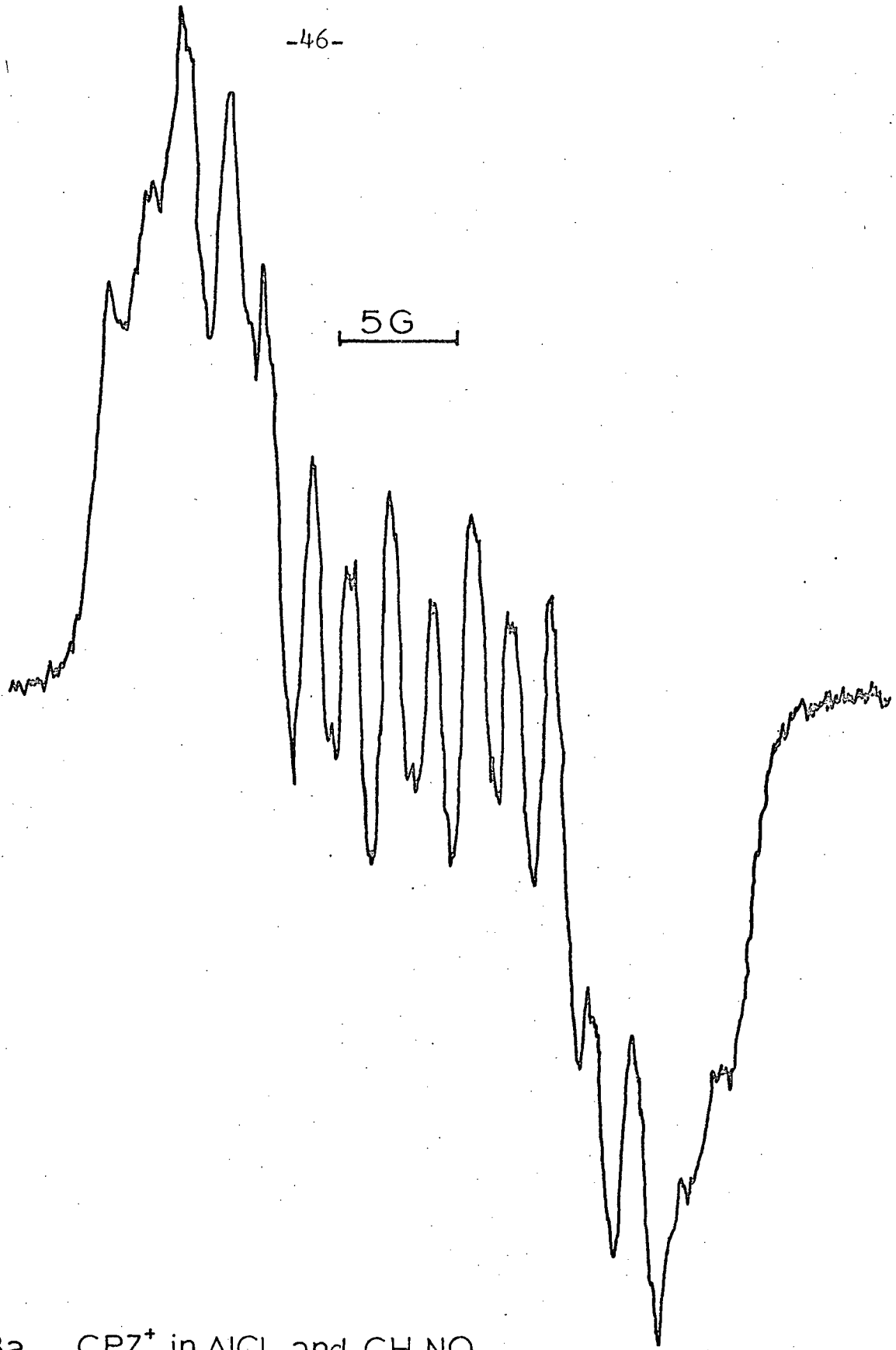


Fig 3a CPZ^{+} in $AlCl_3$ and CH_3NO_2

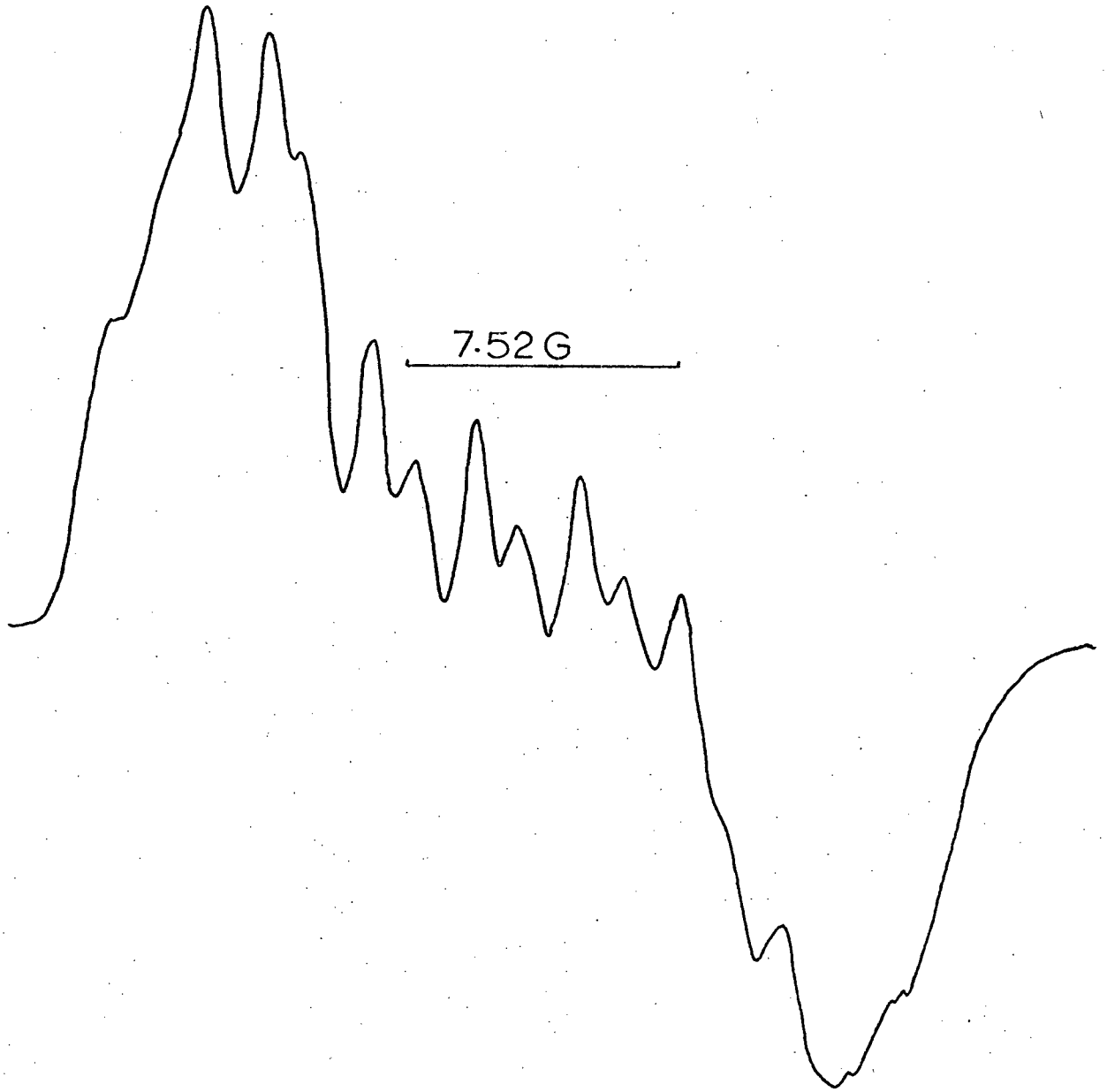


Fig 3b CPZ^{+} in conc HCl

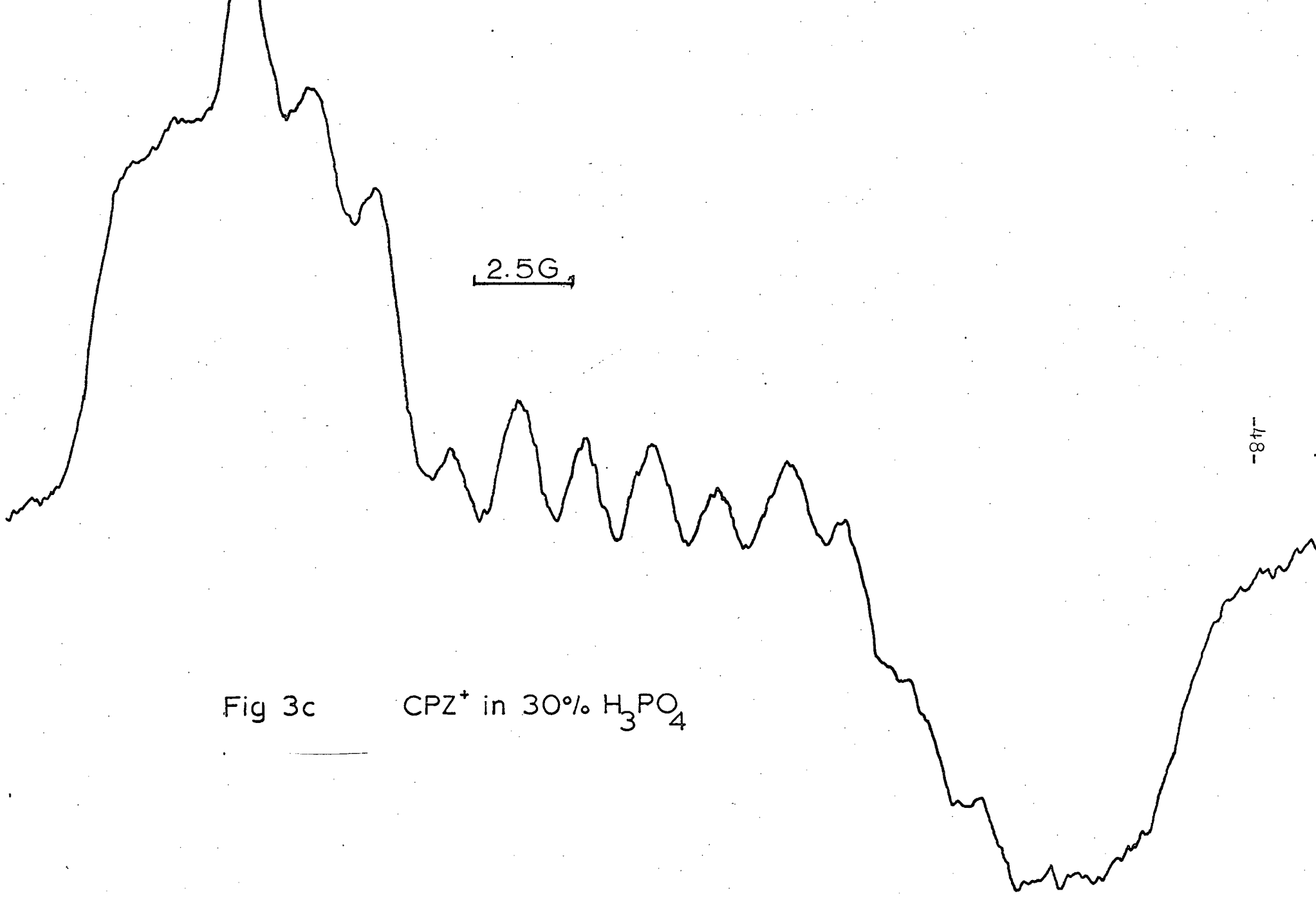


Fig 3c CPZ$^+$ in 30% H_3PO_4

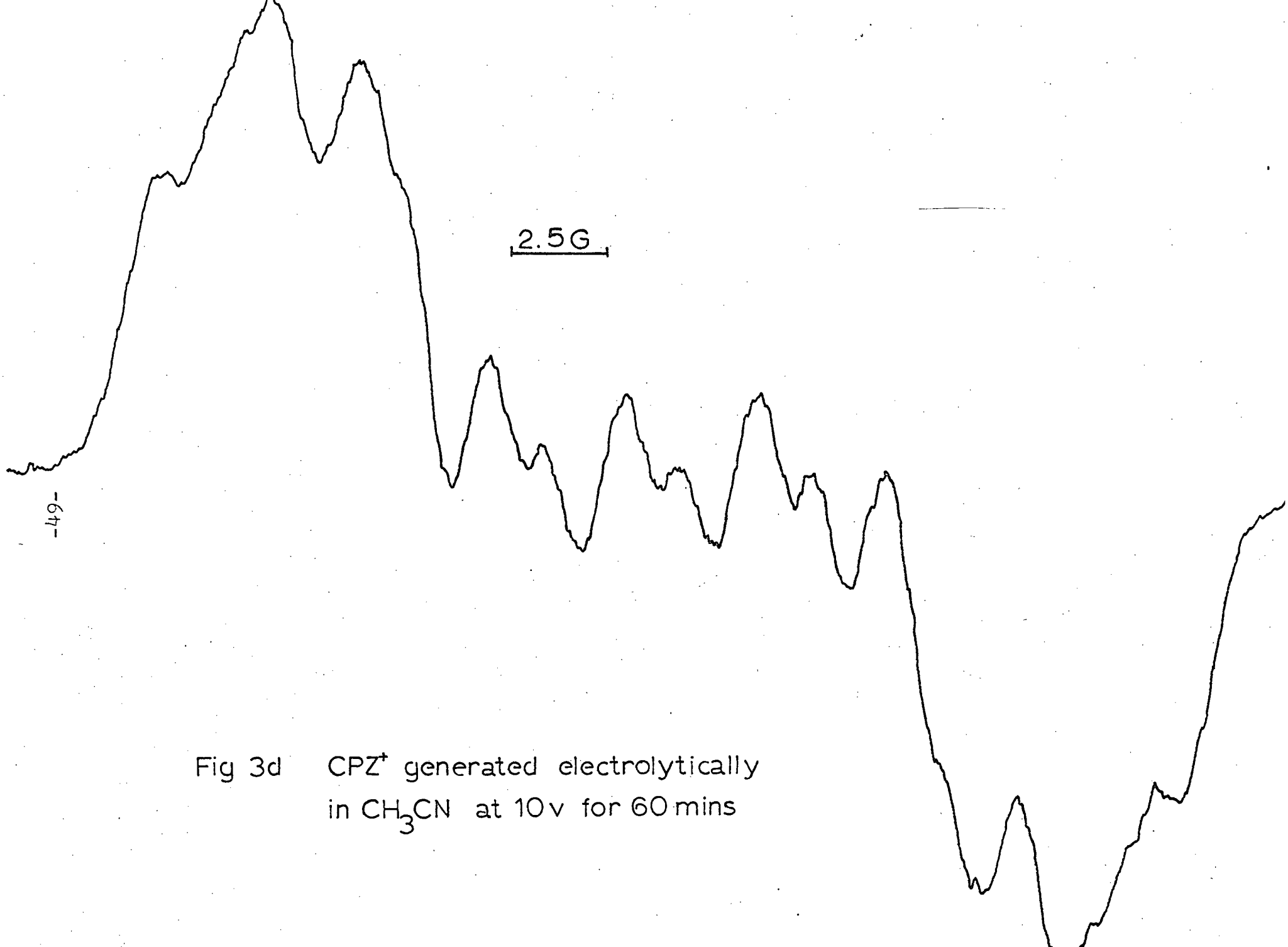


Fig 3d CPZ^{+} generated electrolytically in CH_3CN at 10v for 60 mins

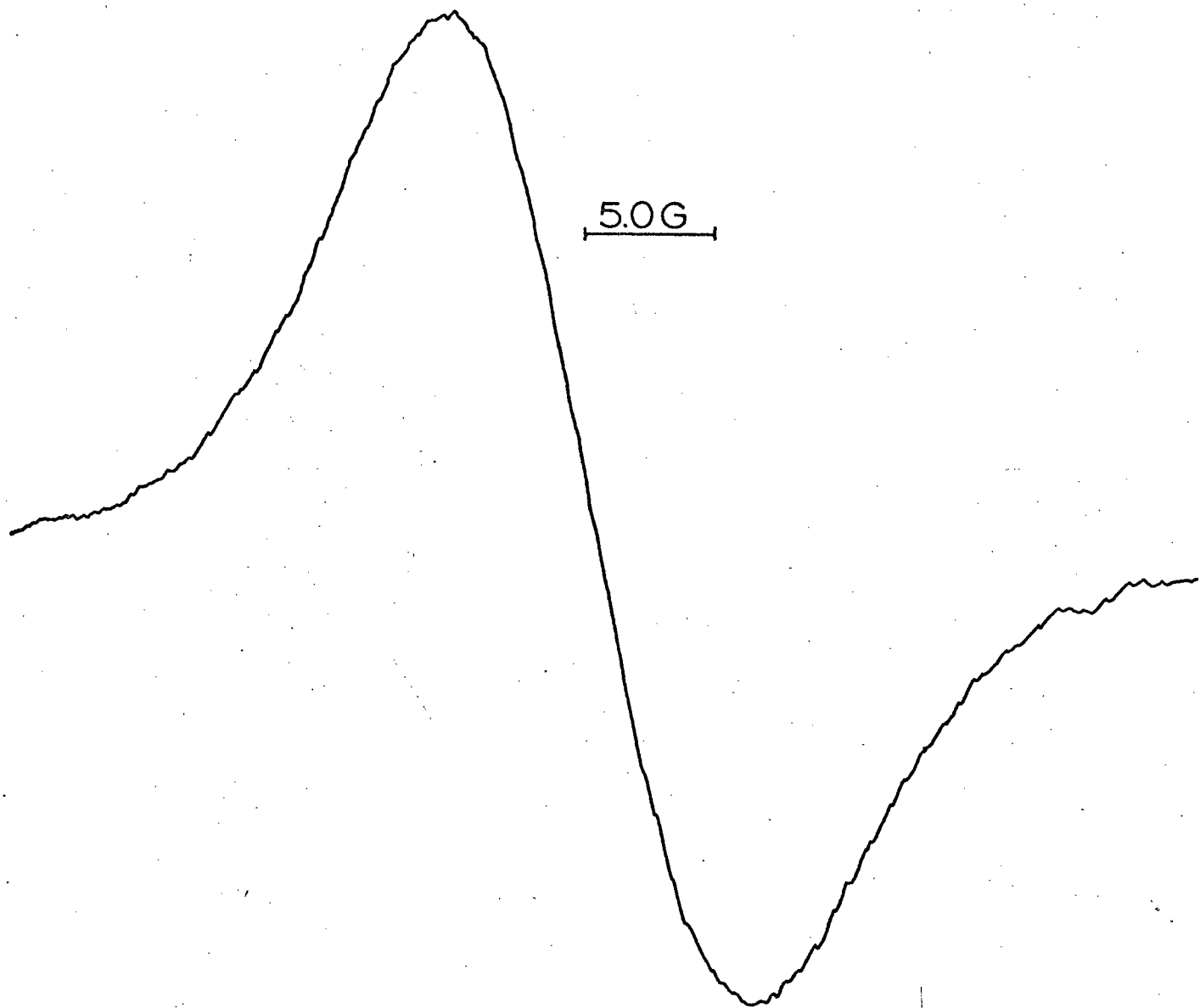


Fig 3e CPZ reacted with I_2, spectrum in 50:50 acetonitrile:dimethoxyethane

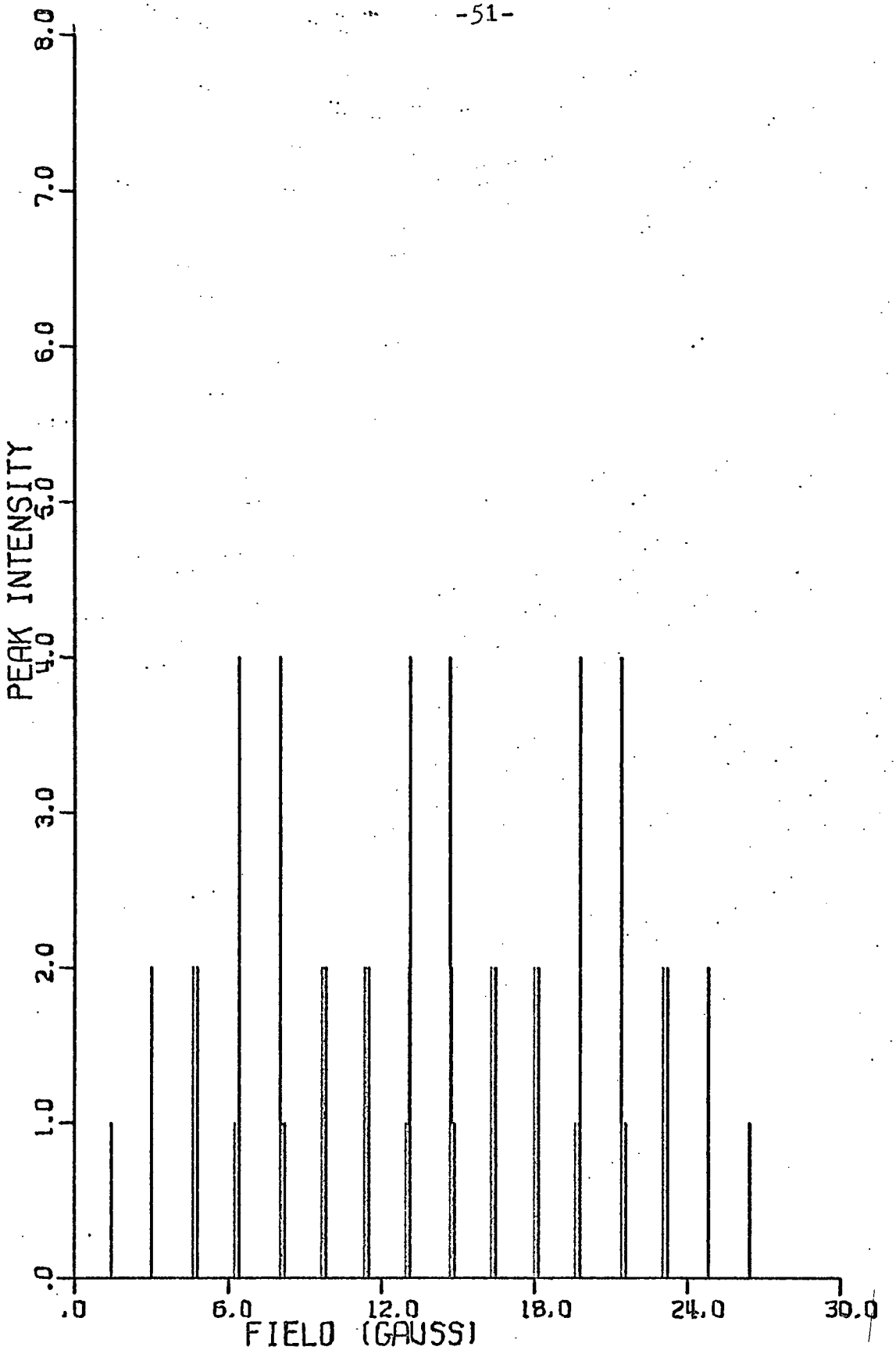


Fig 4a computed stick diagram for CPZ^+

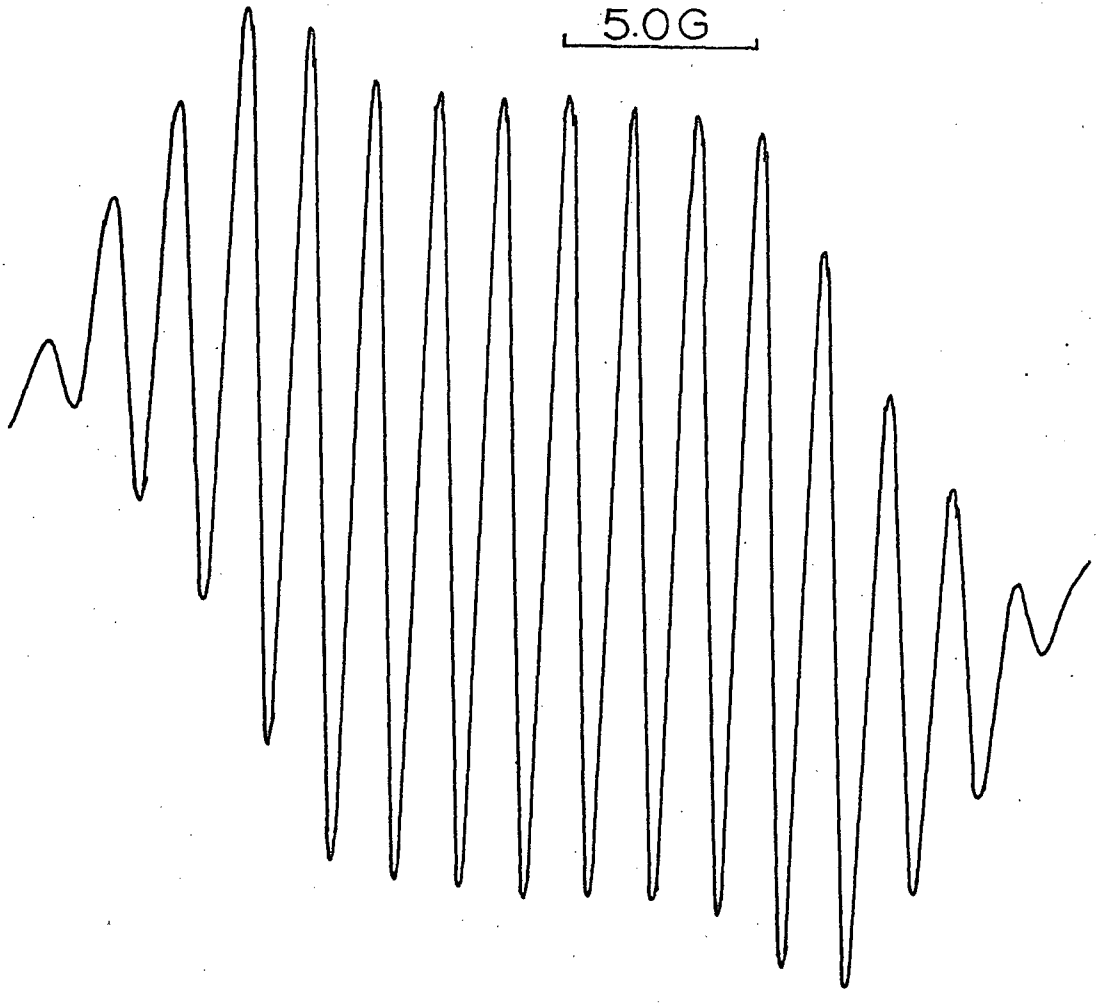


Fig 4b computed spectrum for CPZ^+ in H_2SO_4 with linewidth 1.0 G

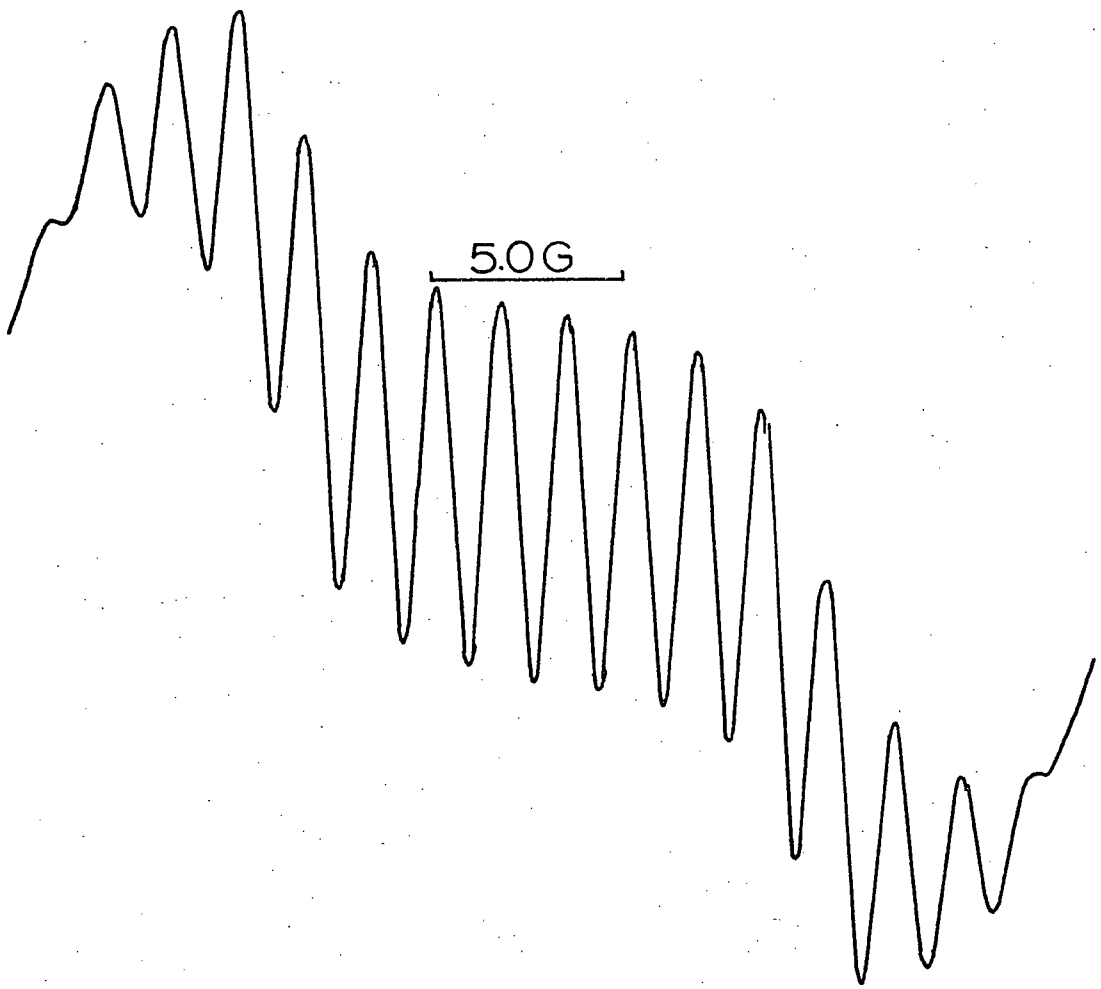


Fig 4c computed spectrum - linewidth 1.5 G

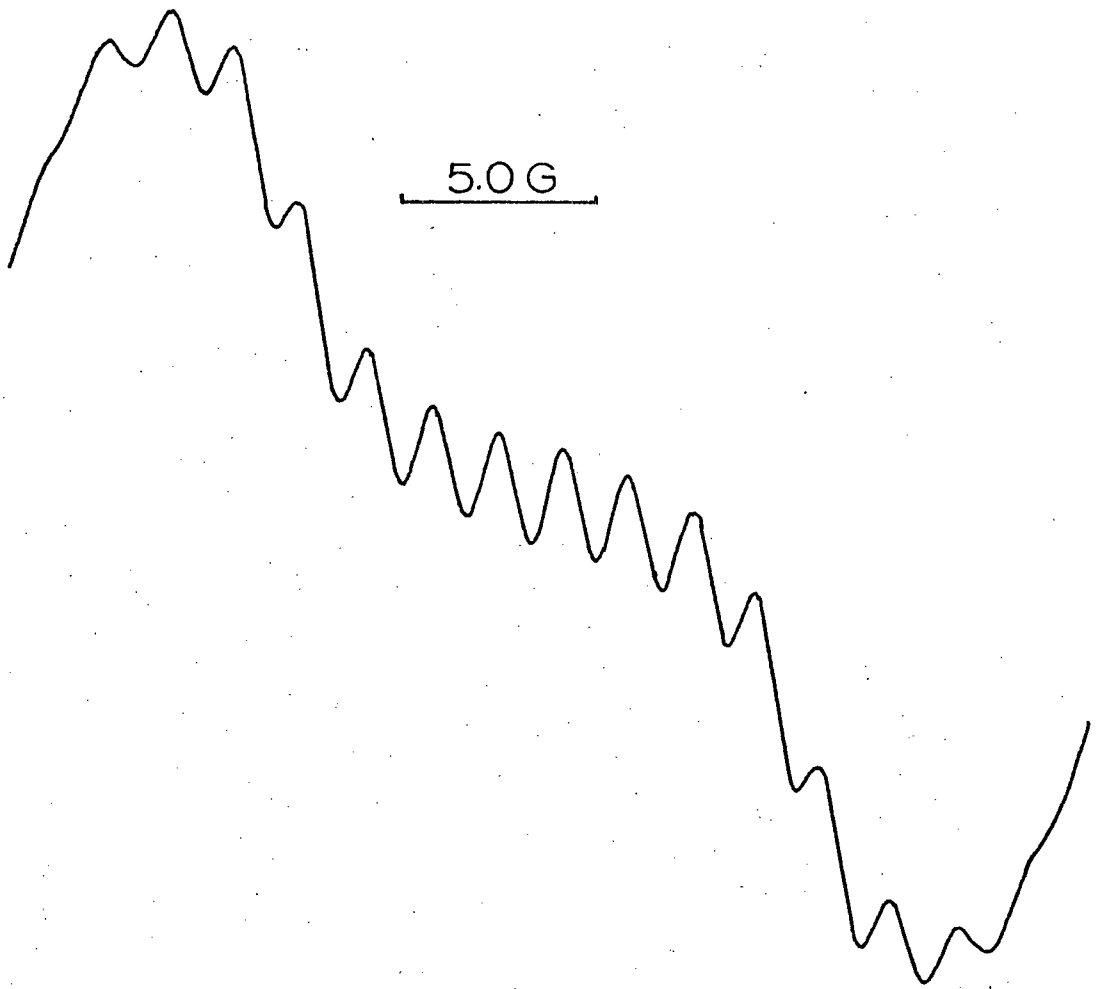


Fig 4d computed spectrum - linewidth 2·0G

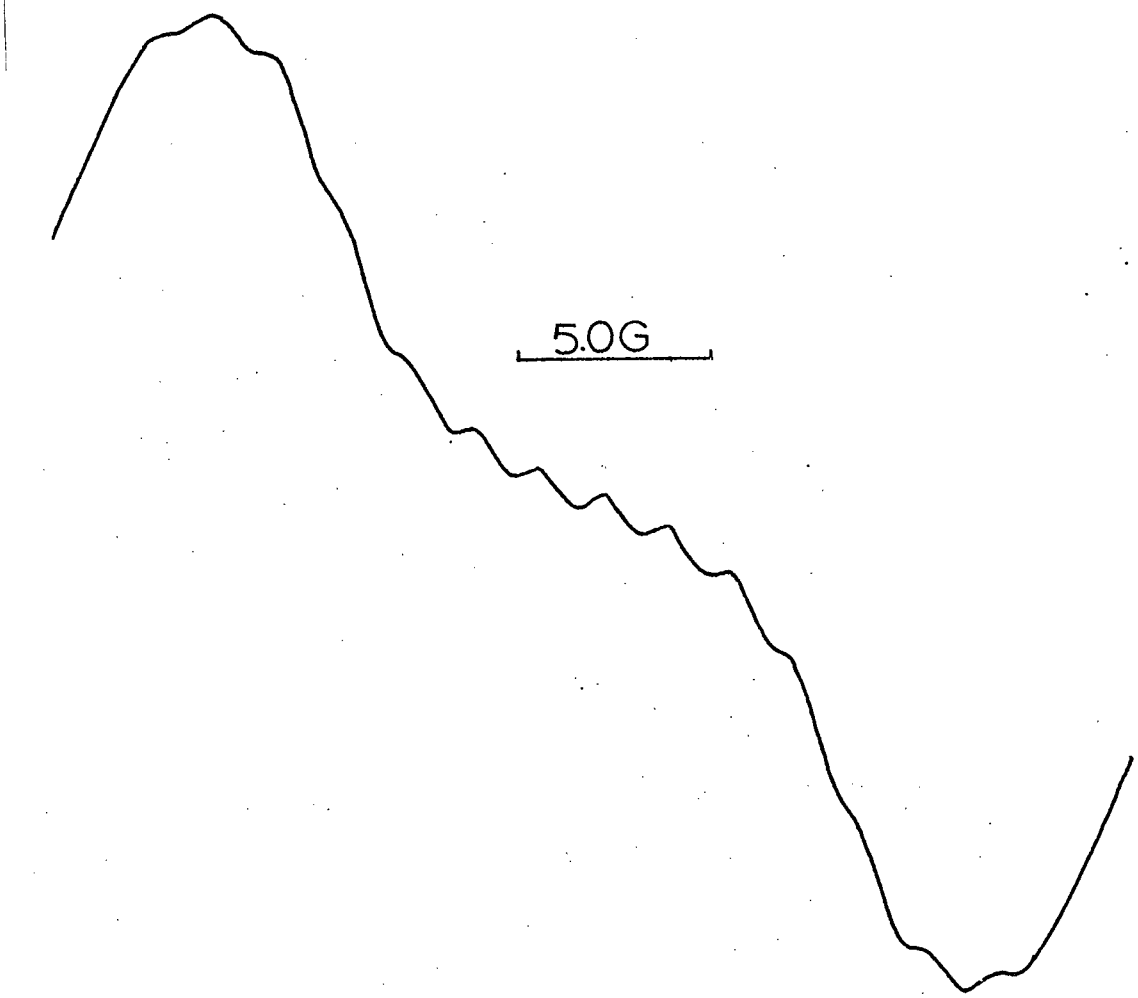


Fig 4e computed spectrum
linewidth 2·5G

chain was considered but should not be applicable here since the $-CH_2$ hyperfine coupling constant is known for whatever position the side-chain takes, even if the exact orientation of the sidechain remains unknown. This aspect of the structure will be considered in more detail subsequently. Thus, the final assignment of a^2 and a^3 could be made once the best set of splitting constants was known. As will be given later in more detail, the amount of folding was determined to be approximately 38 degrees from planar, for both aromatic rings. Table I summarises the Hückel calculation results. The spin densities at carbons 1, 3, 9, and 11 are the largest and are considered here to be those responsible for the ring proton hyperfine structure, and since the spin density at carbon 1 is consistently the lowest of these four for both Hückel and McLachlan calculations, the observed hyperfine splitting is assigned to carbons 3, 9, and 11. This is somewhat arbitrary but necessary in order to account for the observed spectrum properly. The spin density calculations could well be in error on the amount of influence the chlorine atom at position 2 has on either of the neighbouring protons, since no estimates of such an influence are available, and none were estimated because of the lack of literature on the subject. Thus the three protons were considered responsible for the final structure. It is possible that correct interpretation of the Cl role would give one of carbons 1 and 3 a larger spin density than has been calculated, and therefore diminish the other so that the interpretation given is essentially correct. In any

TABLE I SPIN DENSITIES

ATOM:		N	C-15	C-12	C-14	C-1	C-3	C-9	C-11	S
0°	HMO	.232	.000	.044	.044	.052	.066	.062	.056	.137
	McL.	.314	-.006	.017	.018	.066	.076	.071	.071	.141
10°	HMO	.239	.000	.046	.046	.046	.071	.062	.055	.144
	McL.	.330	-.000	.017	.018	.059	.083	.070	.070	.149
15°	HMO	.237	.000	.044	.044	.045	.069	.060	.053	.141
	McL.	.323	-.006	.016	.018	.057	.080	.068	.068	.146
30°	HMO	.272	.000	.045	.046	.040	.067	.058	.048	.154
	McL.	.395	-.000	.013	.014	.053	.077	.066	.064	.155
38°	HMO	.307	.000	.043	.043	.036	.056	.053	.043	.160
	McL.	.469	-.008	.005	.006	.051	.061	.058	.055	.152
40°	HMO	.310	.000	.043	.044	.035	.063	.054	.042	.162
	McL.	.481	-.000	.005	.006	.050	.071	.062	.060	.154
45°	HMO	.338	.000	.041	.041	.033	.060	.052	.039	.167
	McL.	.548	-.000	-.008	-.003	.049	.066	.060	.059	.148

HMO means Hückel calculated values, McL. means McLachlan self-consistent field calculations. Notice the occurrence of negative spin densities in the McLachlan calculations where the Hückel calculations indicate a zero spin density.

case, the Cl atom is expected to have considerable influence on the unpaired spin density at the neighbouring atoms. The spin 3/2 state necessary to obtain the final spectral agreement cannot be assigned to the Cl atom, since in most aromatic systems quadrupolar relaxation effects in solution are expected to be sufficient to remove any Cl hyperfine splitting. Further, the protons (or, rather, the carbons they are bonded to) must have a significant spin polarisation interaction to account for observable splittings.

Before any further comparisons with experimental values are attempted, a brief discussion on the Hückel calculations will be given.

The heteroatom technique (ref. 32, chaps. 4 and 5) was used throughout to account for all heteroatoms and the sidechain. If α_0 and β_0 are the Coulomb and resonance integrals for the benzene ring, then the relationships:

$$\alpha_X = \alpha_0 + h_X \beta_0$$
$$\beta_{CX} = k_{CX} \beta_0 \qquad (4\text{-}2)$$

can be used, where X represents the heteroatom in question. Most, if not all, of the values for h_X and k_{CX} are approximate, and few attempts have been made to establish whether unique values of these parameters exist. It is possible to use a technique (the auxiliary inductive parameter, or AIP) for heteroatoms, whereby the inductive effects of the heteroatoms is accounted for. In other words, the more electronegative heteroatom polarises the C-X bond, thus increasing the effective electronegativity at the carbon atom. For a given bond, C_α-X, it is possible to write:

$$h_{C\alpha} = \delta h_x \qquad (4\text{-}3)$$

where δ is the auxiliary inductive parameter, and values varying from 1/10 to 1/8 for δ are commonly used. Since experiment suggests that such an inductive effect is negligible after one σ-bond (32), and since much discussion on the actual effectiveness of δ exists, little weight will be assigned to it here since computations suggest that the same results are achieved by modifying h_x itself, and including any inductive effects in the original Hückel assumption empirically. The appropriate parameters used, therefore, were:

$$h_N = 0.95;\ h_S = 1.50;\ h_{Cl} = 3.00;\ h_{H_3} = 0$$

$$k_{C-N} = 1.0;\ k_{C-S} = 1.0;\ k_{C-Cl} = 0.6;\ k_{C-H_3} = 3.0$$

Initially these values were taken from the literature (32,79), but h_N and k_{C-Cl} were later modified to the above values.

D: COMPARISON OF CALCULATED SPIN DENSITIES WITH EXPERIMENT

The calculated spin densities are for a model that has an angle of 104 degrees between the aromatic rings. This will be further discussed in the next section. The actual experimental/computational comparison will not be directly made on the spin densities, but on the splitting constants. The final assignment of splitting constants is as follows:

$$\begin{aligned} a^N &= 6.70\ G \\ a^1 &= 3.40\ G \\ a^2 &= 1.62\ G \\ a^3 &= 1.60\ G \end{aligned} \qquad (4\text{-}4)$$

where a^1 describes the $-CH_2$ splitting at the C-15 position, a^2 the splitting due to the nearly equivalent protons at C-3

and C-9, and a^3 describes the splitting due to the proton at C-11. Splittings from other protons must be assumed to be too small to be observed, or completely hidden in the spectrum. Hyperfine coupling from the natural abundance of S^{33} (0.74%) is probably not observable here, even in the $AlCl_3/CH_3NO_2$ system, although it has been observed in the slightly similar cations of thianthrene and various substituted thianthrenes with a^S about 8 or 9 G (80). Hückel calculations made for the thianthrenes did not include the sulfur d-orbitals, as significant agreement was obtained using only the p-orbitals -- further discussion of this point will be given when the energy levels of CPZ^+ are considered.

The computation of the nitrogen hfs constant was made using eq (3-15). Consideration of the Q values to be used was determined mainly by Q^H_{CC}, the proton sigma-pi parameter. The many literature values of this parameter have all been assigned to give good experimental agreement with calculations. Consequently, values of Q ranging from -22.5 (for the benzene anion) to -30.0 have been used. Recently, Carter and Vincow (81), working on the benzene cation, have suggested that for cations Q^H_{CC} should be higher than for anions. Using the HMO and McLachlan spin densities showed that in this experiment Q^H_{CC} = -29.2 G. This is a good result for a typical aromatic cation, and is close to the calculated value of -28 G (for an anion), but slightly higher as predicted by Carter and Vincow. Using this value to find Q^N from the data presented by Henning (21) suggested that Q^N_{NN} = 20.0 G and Q^N_{CC} = 7.0 G (by

a polynomial fit routine, MPOLY, available from the U.B.C. computing center). Thus:

$$a^N = Q^N_{NN}\,\rho^{\pi}_N + Q^N_{CC}(\rho^{\pi}_{C_1} + \rho^{\pi}_{C_2}) \qquad (4\text{-}5)$$

$$\text{or} \quad 6.70 = (20.0)(\rho^{\pi}_N) + (7.0)(0.086) \qquad (4\text{-}6)$$

$$\text{therefore} \quad \rho^{\pi}_N = 0.3048$$

This value is in excellent agreement with the HMO value of 0.3068, but in poor agreement with the McLachlan value of 0.469. Further, throughout the variation in θ, the values of $\rho^{\pi}_{C_1}$ and $\rho^{\pi}_{C_2}$ remain almost constant, ranging from 0.041 to 0.046 (see Table I). Thus a deviation from any molecular shape that amounts to only $\pm$ 0.0020 in the unpaired spin density indicates that the bridging carbons C-12 and C-14 are not particularly sensitive to folding about the N-S axis. For the sake of comparison the values of the ring proton splitting constants are:

HMO: $a^2 = 1.635$ G, $a^3 = 1.17$ G (4-7)

McLachlan: $a^2 = 1.752$ G, $a^3 = 1.606$ G (4-8)

Clearly a combination of the two theories gives almost perfect agreement with experiment -- no attempt to further examine these constants will be made, however. For consistency with the rest of the calculations the HMO spin densities will be used. A detailed study on a series of related cations would give better information on the nature of the various spin polarisation constants , and a least squares analysis similar to that made by Henning for a series of N-heterocyclic aromatic anions could then be used to give more reproducible

values. The values used here, Q^H_{CC} = -29.2 G, Q^N_{NN} = 20.0 G, and Q^N_{CC} = 7.0 G are very consistent for cations, if allowance is made for the fact that the nitrogen constants perhaps do not vary as much for a cation as for an anion, with respect to the proton spin polarisation constants. No precedent exists for this hypothesis, but the computer calculation mentioned earlier suggests that the value of Q^H = -24.2 G that gives the used values of Q^N for anions (21) would be between -28 and -30 G for the cation, assuming that the Q^N stay the same. This, then, was the assumption used and the amount of folding about the N-S axis was determined from the best fit of the experimental splitting constants to the appropriate set of spin densities. Using such a calculation a value of 104 degrees for the angle between the aromatic rings was established. Other values of θ cannot give agreement of calculated splitting constants, using the spin polarisation constants just described, with both a^N and the proton splitting constants.

Calculation of a^1, the splitting due to the protons at carbon 15, the carbon attached to the nitrogen atom, was based on some special assumptions. In calculating the HMO parameters the $-CH_2CH_2CH_2N(CH_3)_2$ sidechain attached to the nitrogen atom was assumed to be effectively a $-CH_3$ group, and the H_3 part was treated as a heteroatom with the appropriate parameters (as already given). Of course, when the spin density at this heteroatom is considered, it must be remembered that the real situation is a $-CH_2$ group. Using these approximations an HMO calculation can be used to investigate the importance

of hyperconjugation over spin polarisation, or vice-versa.

Use of a simple spin polarisation treatment is not warranted in this case, since attempts to find a reasonable Q for the methyl spin polarisation failed, and use of existing accepted values for methyl and methylene groups (Q=-3.09G, ref. 27) failed to give reasonable results. It is highly probable, therefore, that hyperconjugation is much more important in this case than is spin polarisation. In fact, it seems likely that there is no spin polarisation contribution. This will be discussed now.

The hyperconjugation in CPZ^+ should arise from interaction of the π-system about the nitrogen atom with the C-H sigma bonds -- for excited states and carbonium ions hyperconjugation has been shown to be quite important (32), although it may not be for neutral molecules. Thus, in considering CPZ^+, Levy's equation, (3-20), for the splitting constant due to hyperconjugation with a methyl group was used, and HMO values of the coefficients were employed. So:

$$a_{CH_3} = 219.8\,C_H^2 + 13.17\,C_C^2 + 101.7\,C_H C_C + 3.997\,C_H C_{C'} + 0.973\,C_C C_{C'} - 3.09\,C_{C'}^2 \qquad (4\text{-}9)$$

and

$$a_{CH_3} = 3.212 - 3.09\,C_{C'}^2 \qquad (4\text{-}10)$$

In eq (4-10) the spin polarisation contribution, $-3.09\,C_{C'}^2$, is deliberately left unincluded. This term, when evaluated, is -0.948G. Thus a_{CH_3} is reduced to 2.264 if spin polarisation is included. Since a_{CH_3} is to be equated with a^1 to obtain an approximate measure of the validity of eq (4-9) here, the value a_{CH_3} = 3.212 G gives very good agreement, con-

sidering the approximations used, wheras the value $a_{CH_3} = 2.264$ is unrealistically low. Thus, by neglecting the effects of spin polarisation interaction at the methyl and nitrogen positions much better agreement between experiment and calculation is obtained. Condidering that the molecule under consideration is a cation and not a neutral molecule, hyperconjugation may well be a dominant effect because of the tendency of aliphatic groups (especially the methyl group) to donate electrons -- the positive nature of the nitrogen atom should enhance this effect and thus increase the hyperconjugative interaction. This is most certainly the experimental result here, and for cations in general a similar mechanism and result may be expected. Levy's calculations and comparisons for a series of anions indicated that the effects of hyperconjugation had been over-emphasised consistently. This is in excellent agreement with the mechanism just postulated -- in the case of the anion the negative charge would tend to oppose the flow of electrons from the methyl group (or methylene group). Thus Levy's calculations might be expected to be modified slightly for application to esr spectra, with the treatment he gives (eqs 3-18 and 3-20) being more applicable to neutral species in the sense that the hyperconjugation/spin polarisation balance is not the same for the radical as for the neutral analogue. In any event, the experimental fact here is that CPZ^+ interacts with the aromatic ring almost exclusively by means of hyperconjugation mechanisms which are enhanced by the cationic nature of the aromatic system.

E: THE "ANOMALOUS" SPECTRUM

The spectra shown in figure 2 are termed "anomalous" because they were totally unexpected. When the temperature study was being made on CPZ^+, a linear relationship between linewidth and temperature was looked-for. However, at a temperature of 125°C the spectrum began to change, and by 136°C the change was complete. Subsequently it was found that at room pressure (the esr sample was evacuated to about 10^{-4}torr) prolonged heating at 100°C produced the same result. This heating had to be greater than 120 hours, since less heating resulted simply in a slightly broadened, but normal spectrum -- heating to around 130° in the esr samples produced a change in 10 minutes. The change observed was not reversible upon cooling, although dilution with water sometimes restored the red colour (from a characteristic tan of the changed specie) but destroyed the spectrum. The red colour generally disappeared quite quickly. Analysis of this spectrum proved difficult, but some approximate values of splitting constants were obtained that generated calculated spectra of similar shape. Lack of resolution prevented a more serious assignment. The constants obtained were a^2 and a^3 remaining essentially unchanged, a^N varying from 6.6 to 6.8G, which brackets the value obtained for CPZ^+ (assuming this "new" species is not CPZ^+). The change in a^1, the splitting due to the group attached to the nitrogen atom, is quite interesting, however. Analysis indicated that a^1=6.8G, and the splitting is described by a doublet of equal intensities. This, of course, is character-

istic of a spin $\frac{1}{2}$ system -- in this case undoubtedly a proton. To account for these results structurally is not straightforward, however.

It is immediately obvious that the splitting of the group attached to the nitrogen atom in CPZ^+ is one half that of the same, or comparable, splitting for the new species. This could be coincidence, or could reflect a situation in which a proton has been lost from the $-CH_2$ group in CPZ^+. If the spin density remains essentially unchanged at all other positions then a splitting constant for the remaining proton would be twice as large as for the previous two protons, but only two esr levels would result from the single proton, changing the spectrum radically. In this particular case, also, there is the large complication that the new splitting is numerically the same as for the nitrogen atom, so an interaction of an unpaired spin with these two centers would result in a quartet of intensity ratio 1:2:2:1, and separation of peaks of 6.8G. Further interaction with the spin density at the ring protons would add structure around and between these peaks, as observed. Further, taking into account the broadening of the high-field lines, and checking with a low-resolution spectrum (fig. 2d), the experimental intensity ratios are 1:2:2.3:0.9, which is in excellent agreement with the calculated values for the case of a lost proton. A calculation using the same equation as before, eq (4-9), was made (modifying the coefficients to account for the loss of one proton), yielding:

$$a_{CH} = 7.24 \text{ G}$$

And a spin polarisation treatment for a single proton attached to the nitrogen atom directly gives:

$$a_{NH} = 7.53 \text{ G}$$

The latter calculation was made to include the possibility that the temperature change was, in effect, loss of the side-chain and protonation of the nitrogen atom, presumably from the solvent. This consideration was made because of the resemblance of the spectrum to an unresolved phenothiazine spectrum, which also has a 1:2:2:1 intensity distribution. The two calculations offer no definitive answer to the structural change problem, although the hyperconjugation calculation is slightly better. Energetically, it might be expected that loss of a proton to the solvent at temperatures greater than 125°C (in concentrated sulfuric acid) is the more likely answer.

The report (93) that a second electron may be released from the side-chain nitrogen, giving an intense blue di-cation could not be substantiated either experimentally or theoretically (by simulating a spectrum to fit the observed and predicted results). Further, it was not possible to include the side-chain nitrogen atom in the spectral structure analysis for either mono- or di-cationic structures. No blue solution could be obtained in solution (although it is readily obtained in the solid (93)), and the excellent agreement of the given results with calculations suggests that the side-chain is not involved in the esr considerations beyond the first carbon atom -- this is the usual aromatic situation.

F: THE CORRELATION TIME

The asymmetry exhibited in the spectra can be readily interpreted in terms of anisotropy in the g- and A-tensors, which leads to a linear dependence of linewidth on the nuclear quantum number, m_I. Aromatic molecules generally do not exhibit large anisotropies (except for special cases like nitrenes, where there can be appreciable spin-orbit coupling in certain states; i.e. in the triplet state), and in chlorpromazine the principal anisotropy is expected to arise from the nitrogen atom. It was found impractical to try to estimate the anisotropy of the other contributing atoms and interactions, so only the parameters of the nitrogen atom are to be considered. First, however, a discussion of the correlation time is appropriate.

It can be seen from figs. 1 that, at higher temperatures, the spectra become more symmetrical and better resolved. This is due to the lowering of the correlation time, τ_c, as the viscosity of the solvent decreases. The determination of the correlation time is quite a difficult problem, and is not usually attempted exactly for magnetic resonance experiments. The more elaborate theories of relaxation in liquids require only an estimate of the correlation time, often using precedents calculated in self-diffusion work, and thus only order of magnitude agreement with whatever the true correlation time is required. An exact calculation would, of course, be preferable.

Most of those using correlation times approximate

them using the Stokes expression for the viscous force on a sphere, which, combined with the theory of Brownian motion in liquids (55,58,82) gives:

$$\tau_c = 4\pi\eta a^3/3kT \qquad (4\text{-}11)$$

where a is the Stokes' radius of the rotating particle, and η the solution viscosity. Edelstein et al (53) found that values of a calculated from eq (4-11) were considerably smaller than the molecular dimensions would suggest. Further, O'Reilly (82) found, using quadrupolar relaxation times obtained from the nmr spectra of a serise of Cl-containing molecules, that τ_c calculated from eq (4-11) were an order of magnitude too long. However, O'Reilly used the molecular volume for a^3 in eq (4-11) and Edelstein found that this was not always valid. Any comparison of correlation times that compare some experimentally-determined value of τ_c with that determined from eq (4-11) must specify what a is. This is not straightforward, and is the reason many authors use eq (4-11), and if unexpected deviations occur, modify their parameters (53,58). Considering the physical basis for eq (4-11), however, leads to the conclusion that the Debye relationship was derived for a spherical macroscopic object, and incorporated into the Stokes expression, and is not directly applicable to the question of how a molecule or microcrystal moves, subject to Brownian motion, through a solution of known viscosity. Attempts to calculate a more precise value of τ_c for the CPZ^+ case were made using an expression for the free volume of a rigid-sphere molecule rotating randomly in a solution. Buehler et al (85) give:

$$V_f = \{ 20/3\, c^3 - 4/3\, c^2\sigma - 4c^2(r^2-c^2)^{1/2} + 2\sqrt{2}\,(c^3 - 6cr^2)(\sin^{-1} c/\rho + \sin^{-1} m) + 8r^3(2\sin^{-1} u_1 + \pi/2 - \sin^{-1} w - \sin^{-1} t) \qquad (4\text{-}12)$$

where $c=a/\sqrt{2}$, $a=\sqrt{2}r_o$, r_o being the collision sphere radius, and:

$$m = (\rho - 2\sigma)/3\rho$$
$$r = r_o$$
$$t = (r^2 + cr - c^2)/r\rho$$
$$u_1 = [(2r+c)(r+x_2) - (c+r)^2]/(r+x_2)\rho$$
$$w = (r^2 - cr - c^2)/r\rho$$
$$x_2 = 1/3\,(2c-\sigma)$$
$$\sigma = (3r^2 - 2c^2)^{1/2}$$
$$\rho = (2r^2 - c^2)^{1/2}$$

Using appropriate values of r_o (assumed here to be about the same as the dimensions of chlorpromazine, or about 10Å), values of $v_f^{1/3}$ ranged from 5 to 7 angstroms. Such values were surprisingly close to those expected (4 to 6 Å), in consideration of the remarks of Edelstein et al (53). Thus, substitution of v_f for a^3 in eq (4-11) was considered appropriate, and values of τ_c obtained ranged from 2.65×10^{-9} to 1.42×10^{-8} seconds, at room temperatures (21-22°C). This seems to be a reasonable result, especially when compared to the value for H_2O of 3×10^{-11} secs. (ref. 58, p110), which has a smaller radius and viscosity than chlorpromazine -- small enough to account for the 1/1000 to 1/100 difference in correlation time. This raises the fact that it should be possible to determine values of τ_c quite reasonably if a standard, such as water, was accurately known. Comparisons of dimensions and viscosity then should enable consistent values of τ_c to be obtained.

A thermodynamically obtained value of the correl-

ation time is available, and Watts et al (86) have derived the useful relationship:

$$D\eta/kT = \text{constant} \qquad (4\text{-}13)$$

where D is the diffusion coefficient for the liquid. Then using (83):

$$D = \left(\frac{kT}{2\pi m}\right)^{1/2} d^2/V_f^{1/3} \exp(-w/kT)\exp(-\Delta E/kT) \qquad (4\text{-}14)$$

where ΔE is the barrier height for diffusion, w is the work of formation of a hole, and d^2 the mean-square distance between lattice sites (w arises from considering that a molecule participating in the random motion of a liquid can be considered trapped in a hole and subject to Brownian collisions with other holes and particles). The use of eq (4-14) is not warranted here, since an estimation for w is not available for chlorpromazine. However, if w is known, an expression for τ_c can be formulated:

$$\tau_c = \left(\frac{d^2}{2\pi D}\right) \exp(-w/kT) \qquad (4\text{-}15)$$

which shows that exact values of τ_c are by no means unavailable for the right systems. A detailed study on linewidth variations would then not be subject to discrepancies at the solute/solvent level where approximations are often made, and where, perhaps, fewest approximations are desirable.

G: LINEWIDTH VARIATION

To apply any knowledge of the correlation function and correlation time to a radical tumbling randomly in a viscous solvent, some knowledge of the anisotropy in the g- and A-tensors is necessary. Such information is available often from glass spectra or spectra of randomly-oriented solids (85).

The spectrum of CPZ^+ in a glassy matrix of H_2SO_4 at -90°C gave some indication of A by measurement of the splitting of the outermost peaks (fig 1a). Further analysis of this spectrum was accomplished by analysis of other nitrogen-containing aromatics, as outlined by McConnell (71).

McConnell studied the intercalation of CPZ^+ in DNA helices (71) where the helix axis is held parallel and perpendicular to the applied field. CPZ intercalates such that the aromatic plane (probably the expected axis if the molecule were planar) is perpendicular to the helical axis. Thus an esr study of the orientation is relatively simple. The spectra obtained (very similar to the one obtained here) were not considered good enough to measure the A and g tensor elements, but were used as a check of estimated parameters. The estimated parameters are obtained by considering a similar molecule whose A and g parameters are known. Then a relationship can be proposed:

$$A_i/a = \text{constant} \qquad (4\text{-}16)$$

for a particular nitrogen-containing similar molecule, and where a is the isotropic splitting observed in solution, and A_i is the A component in the required direction i (with respect to the symmetry axis). Using this leads to a value for the constant of 2.35 and 0.33 for the perpendicular and parallel directions, respectively, of di-t-butyl nitroxide. Thus, for chlorpromazine:

$$\begin{aligned} 2.35 &\cong A_\perp/6.70, \quad & A_\perp &= 15.8 \text{ G} \\ 0.33 &\cong A_\parallel/6.70, \quad & A_\parallel &= 2.2 \text{ G} \end{aligned} \qquad (4\text{-}17)$$

The measured isotropic g-value for several spectra was remarkably constant, and checking with a DPPH internal standard (contained in a capillary mounted inside the sample tube) gave the same result of g=2.00626. McConnell's $g_{\parallel}$=2.003, and the $g_{\parallel}$ estimated from the glass spectrum obtained here, $g_{\parallel}$=2.0028 agree well, so the relationship:

$$g = 1/3(g_{\parallel}+2g_{\perp})$$

can be solved for $g_{\perp}$. This yields $g_{\perp}$=2.0079, which is slightly higher than McConnell's estimate of 2.006. Thus it should be feasible, using correct values of $\Delta g=|g_{\perp}-g_{\parallel}|$, τ_c and temperature to apply eq (3-51) and obtain an estimate of the linewidth variation to be expected. The calculations made essentially ignored any anisotropy in the proton hyperfine and Zeeman interactions, and thus considered only the nitrogen atom as the contributing factor. Further, considering all the approximations made, only order of magnitude agreement was expected, and so the neglect of proton hyperfine anisotropy for this particular case is probably more than within the overall experimental uncertainty. Table II shows the results of the calculations, and as can be seen, the asymmetric spectra of CPZ^{+} in H_2SO_4 at temperatures where the viscosity is still high (see Appendix 8 for the viscosities of sulfuric acid) is well explained. As the viscosity decreases, the shorter correlation time shows that, under the experimental conditions used, the high-field broadening should vanish, leaving an essentially symmetrical spectrum (of course, under conditions such that the measurable linewidth is of the order of milli-

TABLE II LINEWIDTHS CALCULATED FOR a=6.5Å

temperature	nitrogen spin state		
	+1	0	-1
282 °K	.162 G	1.47 G	4.1 G
289	.123	1.12	3.1
295	.09	.80	2.23
304	.06	.64	1.50
323	.04	.32	.835
333	.022	.25	.58
350	.02	.175	.48
360	.016	.142	.39
385	.012	.10	.29
395	.010	.09	.255
396	.010	.088	.250
409	.008	.08	.22

These numbers are for only a diagonal contribution from the spin Hamiltonian, a T_1 term may contribute as much as the above T_2 values if the correlation time is of the right size. Also neglected are any exchange effects on hyperfine broadening, and any other terms in the Hamiltonian that might give rise to broadening.

gauss, broadening effects would be more pronounced, and slight differences more easily seen). Attainment of the 16 line spectrum shown in fig. 1 allowed better splitting constant measurements to be made, also, which further showed that using 100KHz modulation, where the modulation-broadening amounts to about 70 milligauss, even in the absense of any other broadening effect, very little further resolution is likely since the 16 lines are coincident to the extent that only 100 milligauss or so separarate the coincident lines.

Examination of the calculated linewidths shows that best results seem to occur for a, the Stokes' radius, of the order 6.5 angstroms. Thus it is tempting to see if the appropriate correlation time for this value of a, at some set temperature, would be useful in calculating a value for the spin-lattice relaxation time, T_1. Kivelson (45) derived an expression for T_1 which showed that T_1 is dependent on the same m_I and m_I^2 terms as was T_2. At the limits of high temperature and low concentration, where $T_1 \approx T_2$ (45,87), a perfectly symmetrical spectrum should arise. In this experiment it appears that this condition may have been approached. If the dipole-dipole interaction is dominant (for which an expression for T_1 was calculated in section III), then eq (3-44) is applicable. This results in the values of T_1^{-1} shown in Table III. Stephen and Fraenkel (88) determined $1/T_1$ for H_2O to be of the order of 2×10^{-4} sec^{-1}, where $\omega^2\tau_c^2 \ll 1$ is assumed. In this experiment $\tau_c \sim 10^{-8}$ and $\omega \sim 3\times10^9$, so $\omega\tau_c$ is certainly not applicable. At room temperature, where the viscosity of sul-

TABLE III SOME REPRESENTATIVE T_1 TIMES FOR VARIOUS VALUES OF a, AND NITROGEN SPIN STATE $M_I = 0$

	a 6.00 Å	6.50 Å	7.00 Å
temperature	T_1(secs)	T_1(secs)	T_1(secs)
282 °K	$.171 \times 10^{-2}$	$.217 \times 10^{-2}$	$.271 \times 10^{-2}$
289	.130 "	.165 "	.206 "
295	$.935 \times 10^{-3}$	.119 "	.148 "
304	.630 "	$.800 \times 10^{-3}$	$.999 \times 10^{-3}$
323	.125 "	.440 "	.549 "
333	.237 "	.301 "	.375 "
350	.196 "	.248 "	.308 "
360	.169 "	.213 "	.265 "
385	.117 "	.147 "	.182 "
395	.106 "	.133 "	.164 "
396	.103 "	.128 "	.159 "
409	.088 "	.109 "	.135 "

These values are calculated somewhat approximately from the spin lattice term of the axial spin Hamiltonian that is considered most important to modulation of the nuclear and spin moments by lattice fluctuations or random molecular motions.

furic acid is about 40cp., Hyde and Brown (87) find T_1 about 1.4×10^{-5}. It would appear, then, that tetracene (the compound studied by Hyde and Brown) and chlorpromazine, which have a similar structure, exhibit a similar spin-lattice relaxation process, since the experimental T_1's here are around 10^{-5} secs.. For tetracene, it was found experimentally that $T_1 \propto \tau_c \propto \eta$, and since $1/T_1 \propto \tau_c/(1+\omega^2\tau_c^2)$--see eq (3-44)-- $\omega\tau_c \gg 1$ for the experimental conditions used. This is the same experimental situation here, but experimental values of T_1 were not measured so no check on the dependence of the spin-lattice relaxation time on the correlation time was possible. The theory used to derive T_1, and thus eq (3-44), predict a linear dependence, and this is what is found by Hyde and Brown. The importance of spin-lattice relaxation processes in determining the observed linewidth cannot be quantitatively determined without an experimental measurement of T_1, but in this case the linewidth may be more nearly:

$$1/T_2' = 1/T_2 + 1/T_1$$

as suggested by McConnell (40). If this is the case, then the calculated linewidths, T_2^{-1}, may be as much as one-half times too small for the case $\omega^2\tau^2 \geq 1$. Such is the situation for tetracene in sulfuric acid (87). Thus the rather small values of $1/T_2$ shown in Table II are probably too small because of the neglect of the spin-lattice relaxation. The T_1 effects can be added in, but since the exact amount of T_1 contribution to the relaxation process is not known, and since exchange broadening is also likely present (this will be dis-

cussed shortly), only approximate values could be given, and these would therefore have diminishing significance with respect to the approximations made to estimate the T_2 values.

To examine the linewidths a bit further; it is possible to express the overall linewidth as:

$$1/T_2 = Km_I^2 + Lm_I + C \qquad (4\text{-}18)$$

Now, an asymmetric spectrum allows an estimation of the sign of the splitting constant to be made. In this case, assuming the nitrogen to be responsible for the asymmetric shape observed, the sign of the nitrogen hyperfine coupling constant, a^N, can be determined if L is known (since only the linear term in eq (4-18) will give an asymmetric contribution). The sign of the splitting constants for C^{13} and S^{33} (89,90) have been determined in this fashion. In this instance, and L can be written in Kivelson's notation (45,89):

$$L = 4/15 \frac{g_s\beta_s g_I\beta_I H_0 \tau_c}{\hbar^2} \left\{ (3/2)^{1/2} (g_x - g_y)(c_i + c_i^*) + [2g_z - (g_x + g_y)] a_i \right\} \qquad (4\text{-}19)$$

where $$a_i = 1/2 \langle 0 | (3\cos^2\theta_i - 1)/r^3 | 0 \rangle \qquad (4\text{-}20)$$

$$c_i = 1/4\sqrt{6} \langle 0 | \sin^2\theta_i \exp(2i\phi_i)/r^3 | 0 \rangle \qquad (4\text{-}21)$$

and where $\langle 0|\ldots|0\rangle$ is the expectation value for the operator in question for the molecular ground state. Since, for CPZ^+, $g_x = g_y$, simplification is possible, and since for nitrogen-14:

$$g_s\beta_s g_N\beta_N \hbar^{-1} a_i = 38.1 \text{ MHz}$$

from reference 89, a_i must be positive and thus L must be negative since g_z is greater than both g_x and g_y. Since experimentally the broadest lines appear on the high-field

side of the spectrum, it is expected that lines with positive m_I will be narrowest, lines with negative m_I broadest. The high-field lines therefore are for negative m_I and thus the splitting constant a^N is positive. This is the accepted result (20,21).

If it were possible to assign a linewidth and position to every line in the spectrum, it would be plausible to attempt an analysis of the relaxation effects of all the participating atoms, and thus determine if there is any anisotropy due to the proton hyperfine interaction. In other words, the resultant lines would have measurable linewidths and the contributions from various methylene protons' spin states and ring protons' spin states to the linewidth could be subtracted out of the resultant linewidth to give the linewidth due to the nitrogen interactions with the unpaired spin. The result should be comparable to the linewidths calculated for this spectrum (CPZ^+ being considered). This is a qualitative analysis, but such an analysis could be useful. A modification of this treatment to a set of coincident lines is possible, whereby the stick diagram for the spectrum (fig 4a here) could be used to determine the individual contributions to each observed line. This was done in this case, giving a set of 16 equations that could be solved for the expected linewidth contributions for the various nitrogen spin states. In other words, equations like the following can be obtained:

$$-\beta+\delta = +\langle 01| + \langle 11| = L_5 - L_7 \qquad (4\text{-}22)$$

$$\beta = \langle 11| + b, \quad \delta = \langle 01| + b$$

and L is the linewidth of the particular resultant line, b the contribution to the linewidth from the $\langle -\frac{1}{2}, +\frac{1}{2}|$ state of the methylene proton splitting, and $\langle 0|$ or $\langle 1|$ the appropriate contribution from the nitrogen splitting. The particular value measured in eq (4-22) gives an average result of 0.5G. The significance here is that the number is always positive for all the spectra that were accurately calibrated. The original assumption that the nitrogen nucleus contributes most to the anisotropy broadening is substantially correct. Attempts to find similar correlations for the proton splittings resulted in negative results -- there was no consistent value for any splitting contribution to the broadening for the spectra considered, and the numbers themselves were small. Thus the effective contributions are practically zero, as expected. Only the signs of these numbers can be considered useful, the magnitude calculated is not necessarily representative of true linewidth differences, as will be explained shortly. It is possible, then, using this relatively empirical method to examine certain lines, to assign the sign of the splitting constants if the parameters of eq (4-18) are known. Usually, however, only a verification of the sign can be made, since the particular state contributing to the splitting must be known before the differences expressed in equations like eq (4-22) can be interpreted properly.

The quantitative aspects of eq (4-22) cannot be emphasised because the resultant lines do not necessarily have Lorentzian shape. Theories used to derive the relaxation times

have assumed this shape for the spectra in solution, but the resultant of a series of nearly coincident lines, which may be individually Lorentzian in shape, is not necessarily Lorentzian. The Bloch formulation of relaxation times predicts a Lorentzian lineshape for unsaturated resonance conditions, but only for well-separated lines. Thus although the final lineshape may appear to be Lorentzian, the actual linewidth is not the sum of the individual Lorentzian components, or any series of simple fractions of them (91). Thus, in this case, it would be unwise to attach too much emphasis to the measured linewidths in the final spectrum -- in fact, as shown on p87, fig. 5, the resultant linewidths do not all exhibit the same behaviour with temperature. Simulated spectra also had different linewidths to the actual spectra, and in general it can be assumed that linewidth analysis of the more complicated esr spectra will not show the temperature dependence expected without some knowledge of the broadening due to each nucleus present -- this information is often not available and thus many of the more complicated esr spectra are left unanalysed. A detailed computation of the actual lineshapes for each line here was not attempted, so quantitative aspects of eq (4-21) must be left at the empirical level already described.

H: POSSIBLE EXCHANGE EFFECTS

Figure 3 shows some spectra of CPZ^+ obtained in media other than sulfuric acid. It can be seen that the spectra in phosphoric and hydrochloric acids are very sim-

ilar to those in sulfuric acid. This was expected since the viscosity of these solvents is high enough to cause motional broadening (viscosities greater than $\sim 10^{-2} - 10^{-1}$ poise are in the range necessary to broaden the spectrum of CPZ^{+}). The lower viscosities of acetonitrile and nitromethane (around .4 to .8 cp), however, were expected to show symmetrical spectra of approximately the same shape as those for sulfuric acid at higher temperatures. In nitromethane (fig 3a) a well-resolved but s-shaped spectrum was observed, and lowering the concentration failed to remove the s-shape and still give a resolved spectrum. Thus the expected resolution, but not the shape, was obtained. The acetonitrile spectra were all similar to that shown in fig 3d, and here the unusual feature is that not only is the s-shape retained, but the linewidth broadening has caused enough overlap to obscure four lines. Attempts to resolve these spectra failed, and lowering the concentration below about 10^{-3}M resulted in loss of resolution. Thus it seems that in these media there is an exchange broadening effect. The apparent removal of this effect as the temperature is increased for the sulphuric acid system could not be duplicated with the lower-viscosity solvents, since they began to boil before any change was observed. For the sulfuric acid examples, the "flattening" of the overall lineshape is probably due to a volume increase in the solvent at higher temperatures thus effectively increasing the distance between the microcrystals or paramagnetic centers. This would diminish the exchange interaction between these centers.

The exchange interaction was not considered quantitatively here, but a brief description will be given in mostly qualitative terms. Exchange interactions generally occur in non-dilute systems, and a many-particle model of a system containing paramagnetic centers shows that Coulomb interactions between the electrons of neighbouring ions can lead (considering also the Pauli principle) to an interaction of the form:

$$\mathcal{H}_e^{ij} = -2 J_{ij} \underline{S}_i \cdot \underline{S}_j \qquad (4\text{-}23)$$

where $J_{ij} = \int\int \psi_A(\underline{r}_i)\psi_B(\underline{r}_j)(e^2/r_{ij})\psi_A(\underline{r}_j)\psi_B(\underline{r}_i)\,d\tau_i\,d\tau_j \qquad (4\text{-}24)$

and $\psi_A(\underline{r}_i)\psi_B(\underline{r}_j)$ describes the result of electronic overlap. Because large overlap leads to the general result that ψ_A and ψ_B are not orthogonal if A and B relate to different centers, it is customary to consider J_{ij} as a small perturbation on the electronic energies within the ion, rather than attempt computations on a new 2-center system where each center is on a different molecule. Thus large overlap will be neglected. The exchange integral, J_{ij}, falls off rapidly for large inter-ionic distance, so the exchange interaction can be localised to neighbouring pairs:

$$\mathcal{H}_e = -\Sigma 2 J_{ij} \underline{S}_i \cdot \underline{S}_j \qquad (4\text{-}25)$$

where the sum is over all nearest-neighbour pairs, and usually all nearest-neighbour pairs are assumed to have identical location within the system, thus $J_{ij} = J$.

Calculations of the effect of exchange interaction will not be given, but results for solution study show (58) that the effect of exchange interaction is essentially a narrowing, since exchange tends to average out electronic dipolar

interactions which normally would give a very broad spectral line (ref 22, pp 205-208). Solids show this clearly, but solution spectra are narrowed overall, but individual hyperfine lines become broadened. This arises when the concentration of the sample is such that exchange of the electrons on neighbouring nuclei occurs, and the hyperfine lines broaden by an amount $1/\omega_e$, where ω_e is the exchange frequency (ref 60, p 502), resulting in $1/\omega_e$ being the effective lifetime of an electron at the neighbouring nucleus. As the exchange frequency becomes comparable with the energy of the hyperfine interaction, the hyperfine structure gradually broadens and coalesces into a single line. In other words, the hyperfine interaction is no longer centered at one nucleus, but becomes averaged over pairs of nearest-neighbours' nuclei.

Thus, for the case of CPZ^+, it appears that a concentration of cations sufficient to observe the spectrum by esr techniques is high enough to cause some exchange interaction. Removal of this interaction was expected through the use of the nitromethane/aluminum chloride oxidation technique, since it has been reported that this technique yields close to 100% of the radical species (80). Thus, since the same source quoted results that indicate that sulfuric acid oxidation yields only about 1% radical, it should be possible to obtain resolved esr spectra for around 10^{-5}- 10^{-4}M solutions of CPZ in $AlCl_3/CH_3NO_2$. Many attempts to do this failed, with the optimum concentration for good spectra in both cases being about 10^{-3}M. Thus, if it is indeed exchange effects that give the s-shaped spectra, and it probably is, then the radical-generating ability of both

systems must be about the same for chlorpromazine.

Some Biological Aspects of Chlorpromazine

A: ELECTRICAL PROPERTIES

The report (94) that chlorpromazine behaves as an impurity semi-conductor below 32°C, and as an intrinsic semi-conductor above that temperature indicates the extremely low ionization potential of CPZ. The 32°C transition point has been associated with a crystallographic change which affects the sidechain as well as the ring system (94) -- a very important feature of this is that this change occurs in the region just below body temperature. Interestingly, the change occurs only in the polycrystalline material, and not in single crystals (95). Careful study of the esr spectra from room temperature to 50 degrees revealed no unusual change in the molecular structure of the ring and first part of the sidechain. The change at 125°C might be the same change reported for the conductivity studies, or a different effect entirely, but no change at 32°C in solution occurs. However, the conductivity studies were made on compressed pellets of the polycrystalline state, and this would have the effect of lowering the ionisation energy, or, equivalently, reducing the size of the energy gap. This is essentially what happens when carbon condenses into the diamond lattice, which is an intrinsic semi-conductor at the appropriate temperature. Thus the situation at 32°C might be equivalent to that at 125°C, if it is assumed that the change to intrinsic semi-conductivity is equivalent

to an increase in the number of carriers available. This means that something like a di-cation is formed, as described earlier when considering the changed spectrum above 125°C. The change then was not described explicitly as a change from a mono- to a di-cation, but this could be the result of losing a proton from the first sidechain methylene group to, say, the solvent.

Much discussion on the ability of the phenothiazines (see fig 7 for some representative examples) to form a cationic state has been centered about the energy of the highest-filled molecular orbital. Most studies have been made using HMO, and Karreman et al (96) report m_i, in the expression:

$$\epsilon_i = \alpha + m_i \beta \qquad (4\text{-}26)$$

to be negative. This would indicate that the energy of the highest-filled molecular orbital is representative of an anti-bonding orbital, since and are negative; wheras Orloff and Fitts (97) feel that consideration of the sulfur d-orbitals should be taken into account, thus making m_i positive (for chlorpromazine, it is very small and positive). This is intuitively more reasonable, since most phenothiazines are stable in the absence of light, but are non-explosive. They are, in other words, easily ionized but not overly unstable in their ground state. This would indicate that the highest-filled HMO is close to the energy of an isolated carbon 2p orbital.

Hückel calculations performed indicate that CPZ is bonding in its highest-filled HMO, and the variation of the energy of this orbital with the angle deviation from a planar structure is given in figure 6. It can be noted that the energy

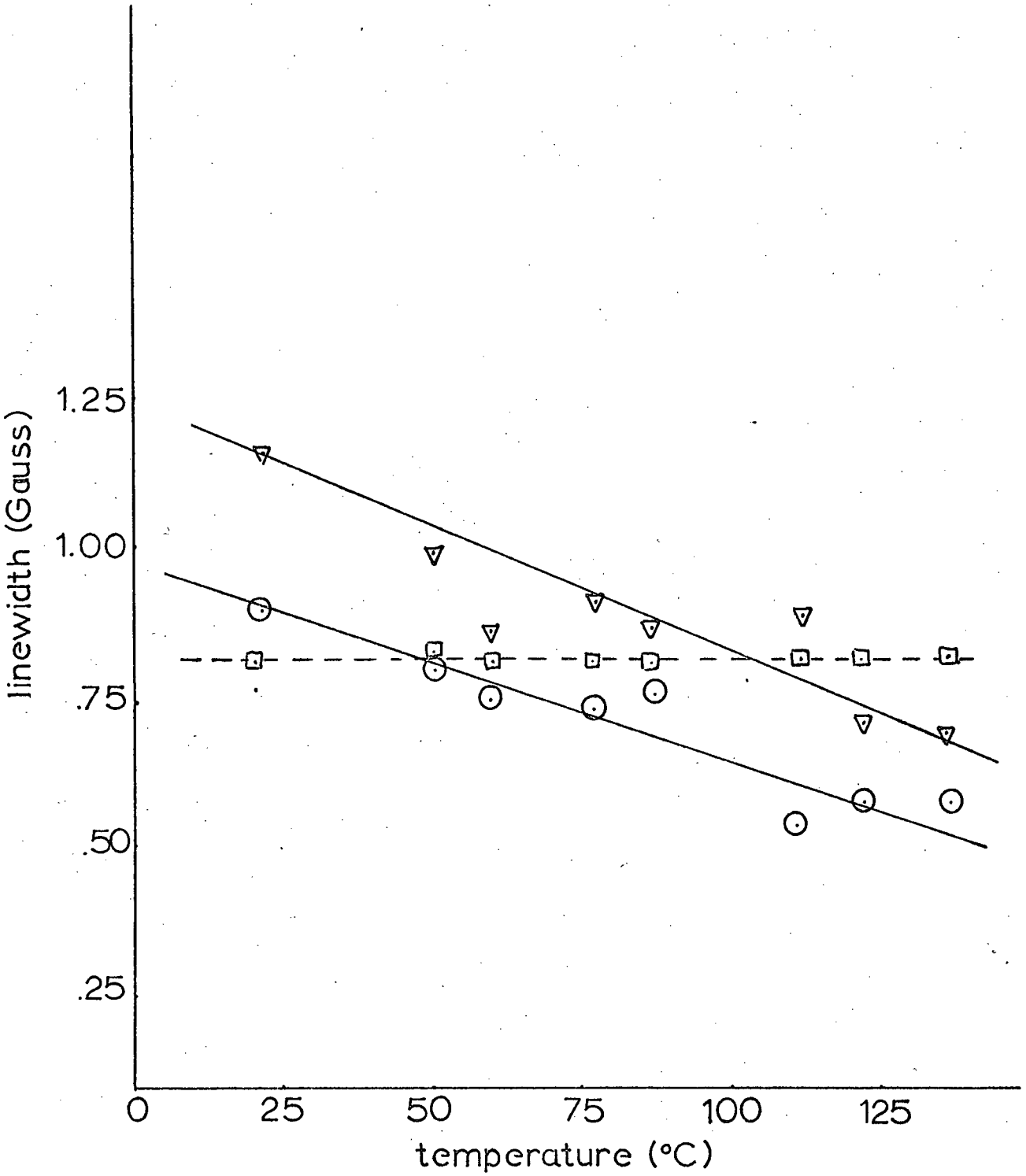


Fig 5 linewidth variation with temperature for CPZ^{+} in H_2SO_4

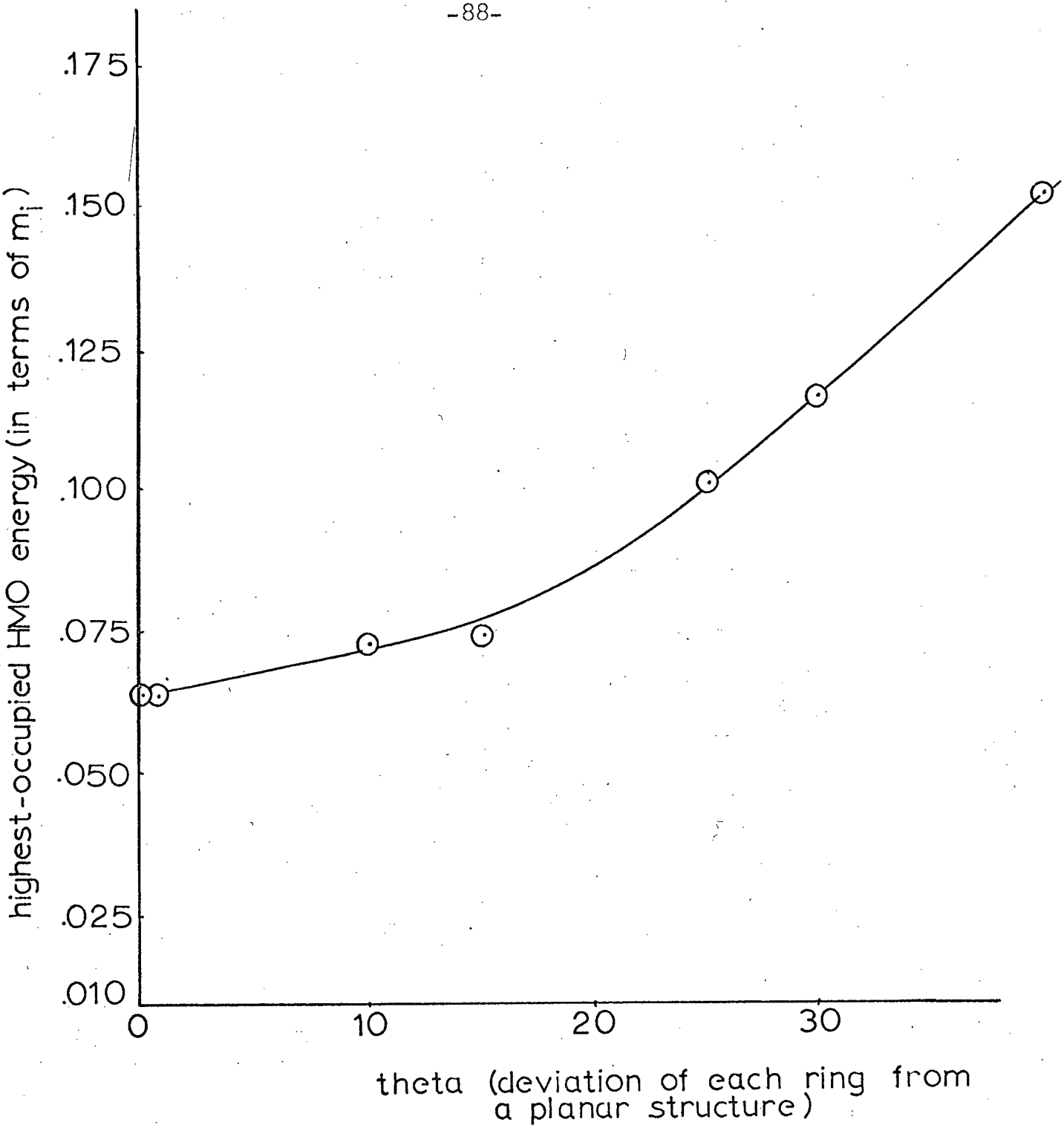
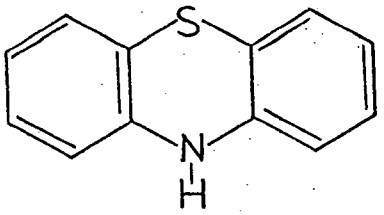
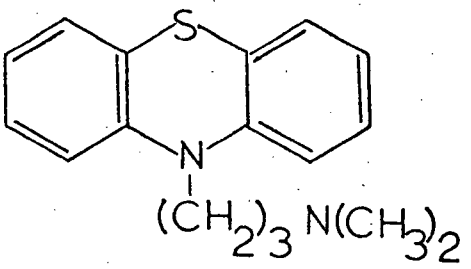


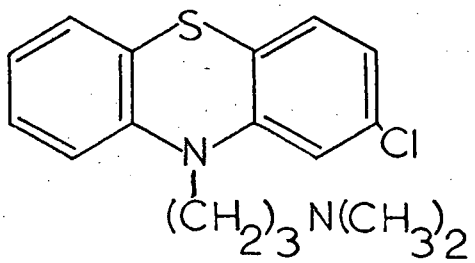
Fig 6 variation of energy (HMO) with theta



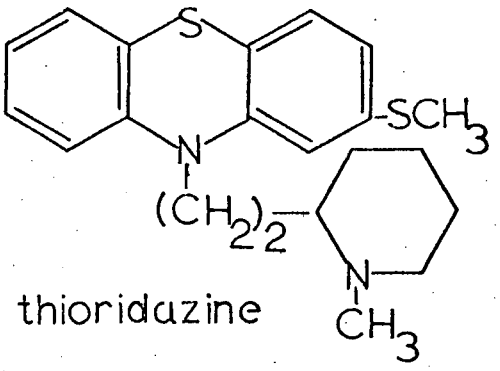
phenothiazine



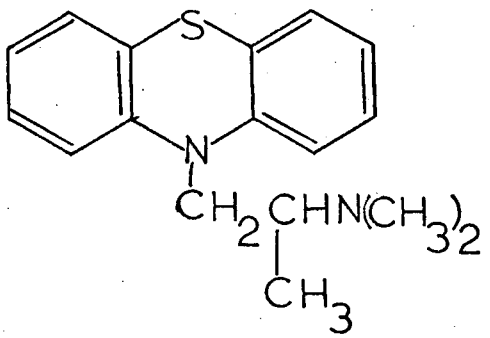
promazine



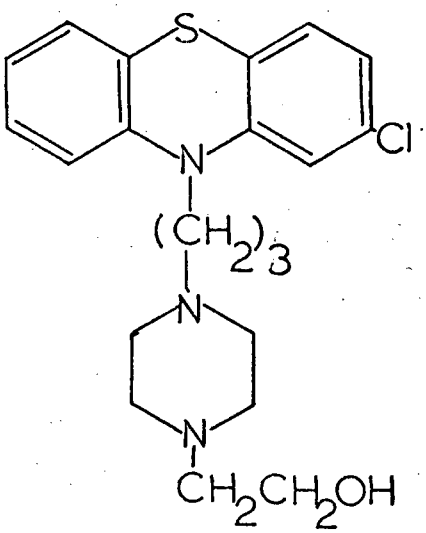
chlorpromazine



thioridazine



promethazine



perphenazine

Fig 7 some representative phenothiazine drugs

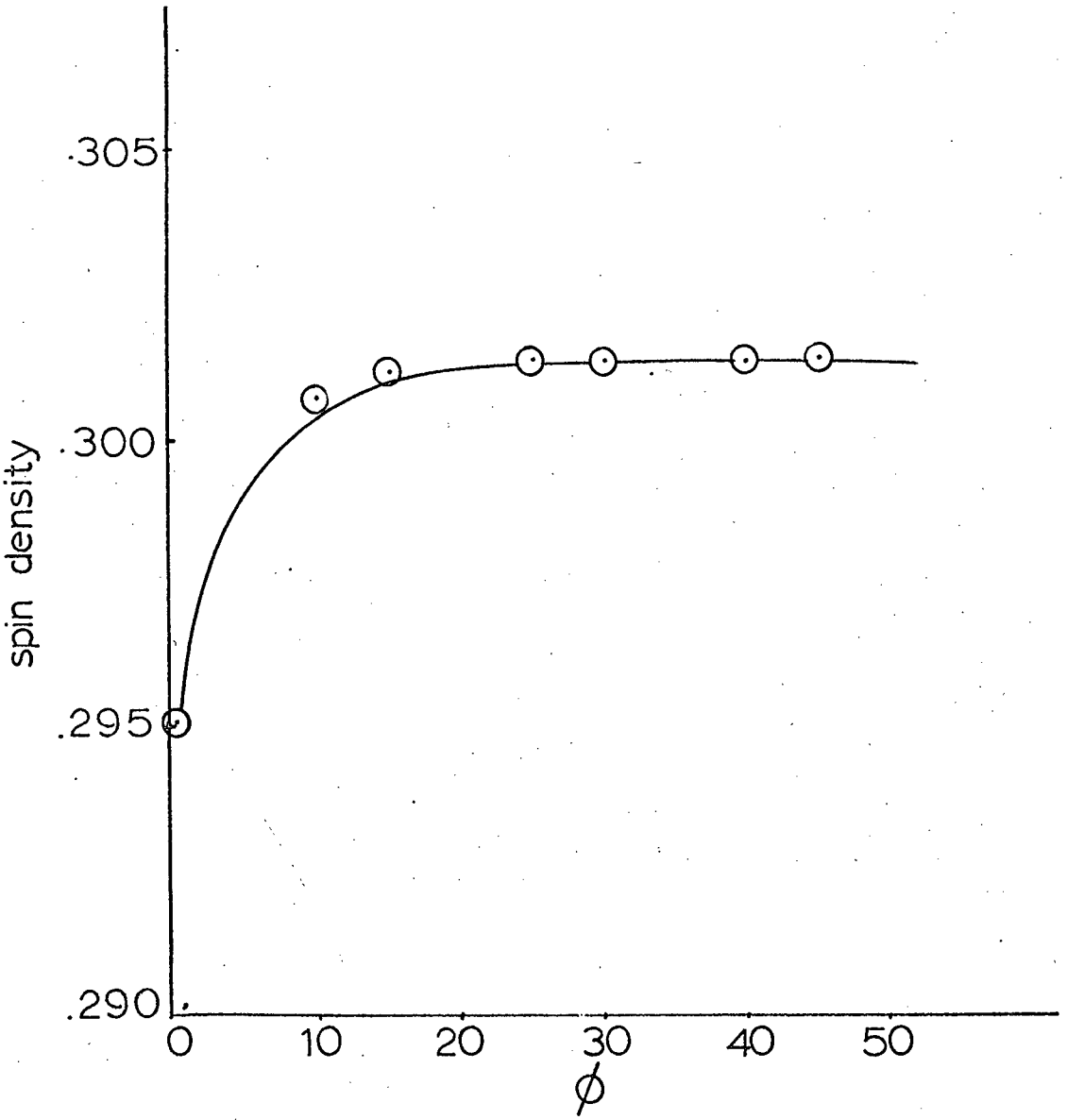


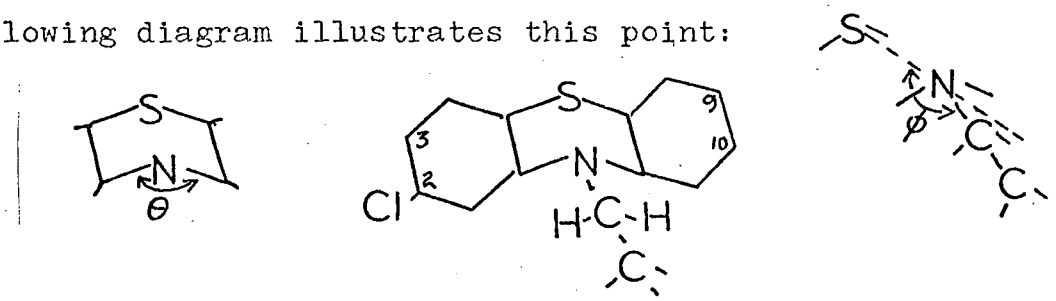
Fig 8 variation of ϕ (angle of sidechain bending) and nitrogen spin density

appears to become more bonding as theta increases towards 90 degrees (the plot is not of energy itself, versus theta, but of m_i in eq (4-26) versus theta). This, however, does not mean that this is the situation: all that it really indicates is that as $\cos\theta$ decreases to 0, the resonance integral for the C-N bond approaches the value for a C-C bond; this is because the angular variation was included into the Hückel calculations as follows:

$$\beta_{CN} = \beta^{o}_{CN} \cos\theta \qquad (4\text{-}27)$$

where θ is the folding angle. The same relationship was used to find the variation of nitrogen spin density with the position of the alkyl sidechain, as shown in figure 8. For the case of the folding angle, little can be deduced from the m_i values except that m_i is positive, and hence the Hückel approximation indicates that the energy of the highest-occupied orbital is lower than that of an isolated carbon 2p orbital and thus bonding with respect to this carbon orbital. Even for the planar structure, where m_i is small, but positive, a bonding situation is apparent, and it can be concluded that a more stable configuration than this (more bonding) will be most favourable, but this will not be the extreme approached at a folding angle of 90^{o} (when both rings are touching) as figure 6 would suggest. Thus a compromise is probable; and earlier spin density calculations showed that an angle of 104^{o} between the rings was consistent with the esr spectrum. This result would appear reasonable despite the indications of figure 6. The best position of the sidechain would appear to be

the logical one, that is, attached to the nitrogen atom parallel to the N-S "bond" and perpendicular to a plane bisecting the rings through the C-3, C-2, C-9, and C-10 bonds. The following diagram illustrates this point:



This point is included for completeness, since it has been postulated (96,97) that the sidechain is not in this position, but folded under the nitrogen in a position that can be best described as "tucked under" between the folded rings. Gutmann and Keyzer (95) support this sort of structure, but esr shows only that the nitrogen spin density, calculated by HMO methods, should be about .300 - .308. Figure 8 shows that this is the value over a wide range of angles (10° to 60°), and varying the position does not alter the m_i value of the highest-occupied orbital appreciably enough to attach any importance to this parameter.

The charge transfer mechanism has been investigated by Gutmann and Keyzer (95), with the result that chlorpromazine forms a complex with iodine of the form: $I_2^-:CPZ^+:I_2^o:CPZ^+:I_2^-$, where I_2^o is a neutral molecule. Above 50°C, in acetonitrile solution, this 2:3 ratio changes to a 1:2 complex. Since a 1:1 complex is also observed, but not discussed, it may be postulated that the 2:3 complex breaks at the neutral specie, leaving the 1:1 and 2:1 complexes. This would require weak bonds, which is typical for many biological charge-transfer

complexes. Since the chlorpromazine probably uses its π-system to stabilise the complex, the donation of charge to the acceptor species may involve the inclusion of the acceptor between the rings, where the negative charge on the acceptor may serve to stabilise the close proximity of the two partially positive aromatic rings. Interaction at either the nitrogen or sulfur atoms is possible, and both carry appreciable unpaired spin density in CPZ^+. The sulfur d-orbitals are natural candidates for partial bonding, as is the nitrogen lone-pair system. Sharing between the two centers could be possible for larger acceptors: no further discussion of this will be attempted, however, since a detailed study of charge transfer complexes of chlorpromazine was not made. A spectrum of the CPZ:I_2 complex in acetonitrile is given on page 50, and as can be seen, little information is available from this spectrum. A similar, but broader, spectral shape was obtained for the solid complex.

B: MECHANISM OF CHLORPROMAZINE ACTION

The tranquilising aspects of a relatively straightforward molecule like chlorpromazine implicate the complexities of the human nervous system. It has been suggested that the phenothiazines act as charge transfer donors in biological reactions, and it has further been suggested that most biological complexes have the majority of the electronic charge in the acceptor state (96). Chlorpromazine, like all the phenothiazines, donates electrons readily from a highest-

filled orbital that is close to the lowest-unoccupied orbital. A tranquilising reaction can occur by polarisation of the electric double layer of a cell membrane. The drug donates an electron to the accepting inside layer of the membrane, which then becomes negative with respect to the outer layer, and thus polarised. This tends to oppose the normal mode of nerve excitation, or any membrane crossing, by preventing the "sodium pump" action. A complete description of this, and the action of nerve cells is given in most texts on neurology, and a good, but brief, discussion may be obtained in reference 106. Briefly, the membrane becomes activated by a rapid influx of Na^+ ions and a corresponding loss of K^+ ions. Since the concentration of Na^+ over long times is constant outside the membrane, a "sodium pump" has been postulated to account for the subsequent removal of the Na^+ ions that enter during a nerve pulse, restoring the membrane potential and readying it for further activation. By blocking either the sodium pump, or the entrance of Na^+ into the membrane by polarisation of the membrane layers, nerve action is damped and tranquilisation occurs. This is probably the mode of tranquilisation of drugs like chlorpromazine. Chlorpromazine is certainly a strong enough donor to act unselectively, and this would explain its tendency to not only tranquilise, but also interfere with normal vision, induce anemic-like conditions, and cause extrapyramidal conditions. This will be treated briefly after a discussion of some biochemical aspects.

The binding mechanisms and metabolism of chlorprom-

azine are likely all based on the donating ability of the drug. Piette and Sandberg (99) used esr studies on spin-labelled erythrocyte ghosts (which are often considered to be good membrane models -- they are simply erythrocytes with all hemoglobin and cell function removed) to show that CPZ can bind at quite restricted (spatially) membrane positions, and in fact can do so strongly. If a spin label is weakly attached to such a position, CPZ tends to strengthen the binding and immobilise the spin label. Such a protective mechanism is probably present in the protection of cells against hemolysis; which chlorpromazine does at low concentration. At high concentration chlorpromazine itself will hemolyse cells. Such protective mechanisms require a stronger surface structure to arise when the protector interacts at the surface membrane. This is apparently common to all phenothiazine drugs, with protective ability decreasing in the order: perphenazine, chlorpromazine, promazine. This order is the same order for decreasing potency as a psychotropic agent. The actual binding mechanism is likely either by intercalation into a polymeric structure or by bonding at the sulfhydryl group of a protein. Piette's results indicate that CPZ can bond at the sulfhydryl group, and it has been shown that CPZ intercalates (probably in the cationic form) into the DNA helix structure (71). It is not generally known, for an indiscriminate reaction, whether chlorpromazine is oxidised first, or whether it becomes oxidised after binding by participating in a biological charge transfer reaction. Spirtes (100) suggests

that the latter is not the case, but his results seem somewhat inconclusive. It does appear, however, that the binding is easily reversible (95% of the CPZ can be removed by washing with a saline solution) and indiscriminate in binding site in a molecule containing only protein. In systems containing lipoproteins the binding is not easily reversible (100,99) and suggests therefore a more specific binding site.

Thus the occurrence of side effects with such drugs as the phenothiazine series is a logical result of the non-specificity of interaction at many membrane sites. The many metabolites of CPZ that are present in any human body that has been treated with chlorpromazine (these metabolites are all varying at the side chain positions, where the terminal nitrogen, in particular, loses either of the methyl groups, or both; also involved in the metabolism is the ring sulfur atom, which can be easily protonated) can all react at sites using the basic ring structure to effect a bond, but differences can occur in the side chain effects. The different phenothiazine drugs all differ most markedly in the side chain, so perhaps this part of the molecule is the most important in determining drug action differences. Thus indiscriminate action by one of these drugs at several sites could result in polarisation or hyperpolarisation of some membranes, depolarisation of others, binding with trace metals (72) that are needed for other metabolic processes, reduction of hemoglobin levels by hemolysis of the red blood cells when used in high doses, and etc.. Chlorpromazine is given in large doses to some of the more

severe cases of schizophrenia, in doses up to 2g per day. Such doses could easily result in the many side effects observed (anemia, oculatory trouble, extra-pyramidal symptoms) by interfering with cell function and nerve conduction. Of much interest is the occurrence of extra-pyramidal symptoms, which are well manifested in Parkinson's disease. If the area of interaction of chlorpromazine that causes this probable nerve interference could be isolated, much more information on the mechanism of nerve output would be available at the chemical level. Knowledge of the spectrum of chlorpromazine itself, then, might perhaps enable use of physical methods to be more relevant than they have been in the past. More work is being done in this area by physical scientists, and the function and structure of hemoglobin, for instance, has been well examined by esr and diffraction techniques, with the result that much of the behaviour of this molecule in the human body is now well understood. This is a relatively simple example, biologically, and of much more interest and complexity is the function of the nervous system and brain, and the manner of interaction of outside agents (e.g. drugs) at sites in the nervous system is enabling some information to be obtained at the molecular and cellular levels. Hopefully, physical techniques like electron spin resonance will be able to be used to solve some of these interesting problems. The function of the physical scientist in these applications will be to guide the biologist in his theories, and to open new fields to study by physical means and theoretical interpretation.

BIBLIOGRAPHY

1 S.I.Weissman, J.Townsend, D.E.Paul, and G.E.Pake, J.Chem Phys 21,2227 (1953)

2 S.I.Weissman, J.Chem Phys 22,1135 (1954)

3 T.L.Chu, G.E.Pake,D.E.Paul, J.Townsend and S.I.Weissman, J.Phys Chem 57,504 (1953)

4 B.Venkataraman and G.K.Fraenkel, J.Chem Phys 24,737 (1956)

5 C.J.Ballhausen, Introduction to Ligand Field Theory, (McGraw-Hill, New York, 1962) chapter 8

6 H.M.McConnell, J.Chem Phys 24,764 (1956)

7 H.M.McConnell and D.B.Chesnut, J.Chem Phys 28, 107 (1958)

8 H.M.McConnell, Proc Nat'l Acad Sci U.S. 43,721 (1957)

9 H.M.McConnell and D.E.Robertson, J.Chem Phys 28, 991 (1958)

10 S.I.Weissman, J.Chem Phys 25,890 (1956)

11 J.S.Griffith, The Theory of Transition-Metal Ions, (Cambridge University Press, 1964) p27 ff.

12 E.Condon and G.Shortley, Theory of Atomic Spectra, (Cambridge University Press, New York, 1935) pp 117,169

13 M.Karplus and G.K.Fraenkel, J.Chem Phys 35,1312 (1961)

14 H.Strauss and G.K.Fraenkel, J.Chem Phys 35,1738 (1961)

15 A.Hinchcliffe and J.Murrell, Mol Phys 14,147 (1968)

16 A.Carrington and J.Dos Santos Veiga, Mol Phys 5,21 (1962)

17 C.A.McDowell, K.F.Paulus, and J.Rowlands, Proc. Chem Soc 36, 60 (1962)

18 N.Atherton, F.Gerson and J.Murrell, Mol Phys 5,509 (1962)

19 E.Stone and A.Maki, J.Chem Phys 39,1635 (1963)

20 B.Barton and G.K.Fraenkel, J.Chem Phys 41,1455 (1964)

21 J.C.M.Henning, J.Chem Phys 44,2139 (1966)

22 A.Carrington and A.D.McLachlan, Introduction to Magnetic Resonance, (Harper and Row, New York,1967) p81 ff.

23 E.Fermi, Z.Physik 60,320 (1930)

24 A.D.McLachlan, Mol Phys 1,233 (1958)

25 J.R.Bolton, A.Carrington and A.D.McLachlan, Mol Phys 5, 31 (1962)

26 J.Colpa and E.de Boer, Mol Phys 7,333 (1963-4)

27 D.H.Levy and R.Myers, J.Chem Phys 43,3063 (1965)

28 D.H.Levy, Mol Phys 10,233 (1966)

29 N.K.Ray and P.Narasimahan, Chem Phys Letters 2,101 (1968)

30 R.Mulliken, C.Rieke, D.Orloff and H.Orloff, J.Chem Phys 17, 1248 (1949)

31 A.Streitwieser and P.Nair, Tetrahedron 5,149 (1959)

32 A.Streitwieser, Molecular Orbital Theory for Organic Chemists, (J.Wiley, New York, 1961) chapters 2 and 5

33 A.D.McLachlan, Mol Phys 2,271 (1959)

34 E.Hückel, Z.Physik 70,204 (1931)

35 S.Fraga and G.Malli, Many Electron Systems: Properties and Interactions, (W.B.Saunders, Philadelphia, 1968) p37

36 P.Rieger and G.K.Fraenkel, J.Chem Phys 39,609 (1963)

37 P.Rieger and G.K.Fraenkel, J.Chem Phys 37,2795 (1962)

38 F.Nakano, M.Sc. Thesis, U.B.C. (1966)

39 A.D.McLachlan, Mol Phys 3,233 (1960)

40 H.M.McConnell, J.Chem Phys 25,709 (1956)

41 R.Rogers and G.E.Pake, J.Chem Phys 33,1107 (1960)

42 D.J.O'Reilly, J.Chem Phys 29,1188 (1958)

43 D.Kivelson, J.Chem Phys27,1087 (1957)

44 N.Bloembergen, E.Purcell and R.Pound, Phys Rev 73,679 (1948)

45 D.Kivelson, J.Chem Phys 33,1094 (1961)

46 A.Carrington, Mol Phys 5,161 (1962)

47 J.Bolton and A.Carrington, Mol Phys 5,161 (1962)

48 B.R.McGarvey, J.Phys Chem 60,71 (1956)

49 J.Freed and G.Fraenkel, J.Chem Phys 39,326 (1963)

50 J.Freed and G.Fraenkel, J.Chem Phys 40,1815 (1964)

51 J.Freed and G.Fraenkel, J.Chem Phys 41,3623 (1964)

52 N.Edelstein, A.Kwok and A.Maki, J.Chem Phys 41,3473 (1964)

53 N.Edelstein, A.Kwok and A.Maki, J.Chem Phys 41,179 (1964)

54 G.Fraenkel, J.Phys Chem 71,139 (1967)

55 P.Ayscough, Electron Spin Resonance in Chemistry, (Methuen, London, 1967) pp129-136

56 H.Silescu, Mol Phys 14,381 (1968)

57 K.Rao and M.Sastry, Chem Phys Letters 2,20 (1968)

58 G.E.Pake, Paramagnetic Resonance, (Benjamin, New York, 1962) chapter 5

60 A.Abragam, Principles of Nuclear Magnetism, (Oxford Press, 1961)

59 C.P.Slichter, Principles of Magnetic Resonance, (Harper and Row, New York,1963)

61 A.Abragam and M.Pryce, Proc Roy Soc A205,135 (1954)

62 L.I.Schiff, Quantum Mechanics, (2nd. ed. McGraw-Hill, New York, 1955) p196 ff

63 R.Eisberg, Fundamentals of Modern Physics, (Wiley and Sons, New York, 1963) p226

64 A.Schalow and C.Townes, Microwave Spectroscopy, (McGraw-Hill,New York, 1955) chapters 14-17

65 A.Carrington and H.Longuet-Higgins, Mol Phys 5,447 (1962)

66 S.Chandrasekhar, Rev Mod Phys 15,1 (1943)

67 R.Kubo and K.Tomita, J.Phys Soc Japan 9,888 (1954)

68 E.de Boer and E.Mackor, J.Chem Phys 38,1450 (1963)

69 F.Heineken, M.Bruin and F.Bruin, J.Chem Phys 37,1479 (1962)

70 L.D.Tuck and D.W.Schieser, J.Phys Chem 66,937 (1962)

71 S.Ohnishi and H.M.McConnell, J.Amer Chem Soc 87,2293 (1965)

72 D.Borg and G.Cotzias, Proc Nat'l Acad Sci U.S. 48,623 (1962)

73 J-P.Billon, G.Cauquis and J.Combrisson, J.Chim Phys 61,374 (1964)

74 C.Lagercrantz and M.Yhland, Acta Chem Scand 15,1204 (1961)

75 L.Piette, P.Ludwig and R.Adams, Anal Chem 34,916 (1962)

76 L.Piette and I.Forrest, Biochim Biophys Acta 57,419 (1962)

77 C.lagercrantz, Acta Chem Scand 15,1545 (1961)

78 L.Piette, G,Bulow and I,Yamazaki, Biochim Biophys Acta 88, 120 (1964)

79 J.Lhoste and F.Tonnard, J.Chim Phys 63,678 (1966)

80 P.D.Sullivan, J.Amer Chem Soc 90,3618 (1968)

81 M.Carter and G.Vincow, J.Chem Phys 47,292 (1967)

82 D.E.O'Reilly and G.E.Schacher, J.Chem Phys 39,1768 (1963)

83 E.McLaughlin, Trans Faraday Soc 55,28 (1959)

84 F.Sears and M.Zemansky, University Physics, (3rd. ed., Addison-Wesley, Reading,Mass, 1963) pp116, 323

85 F.Adrian, J. of Colloid and Interface Science 26,317 (1968)

86 H.Watts, B.Adler and J.Hildebrand, J.Chem Phys 23,659 (1955)

87 J.S.Hyde and H.W.Brown, J.Chem Phys 37,367 (1962)

88 M.Stephen and G.Fraenkel, J.Chem Phys 32,1435 (1960)

89 E.de Boer and E.Mackor, J.Chem Phys 38,1450 (1963)

90 H.J.Shine and P.D.Sullivan, J.phys Chem 72,1390 (1968)

91 J.Gendell, J.Freed and G.Fraenkel, J.Chem Phys 41,949 (1964)

92 I.Gregory, Psychiatry:Biological and Social, (W.B.Saunders, Philadelphia, 1961) p119 ff

93 F.Gutmann and H.Keyzer, Nature 205,1102 (1965)

94 F.Gutmann and A.Netschey, Nature 191,1390 (1961)

95 F.Gutmann and H.Keyzer, J.Chem Phys 46, 1969 (1967)

96 G.Karreman, I.Isenberg and A.Szent-Györgi, Science 130,1191 (1959)

97 M.Orloff and D.Fitts, Biochim Biophys Acta 47,596 (1961)

98 B.Pullman and A.Pullman, Biochim Biophys Acta 35,535 (1959)

99 H.Sandberg and L.Piette, Agressologie 9,59 (1968)

100 M.A.Spirtes, Agressologie 9,189 (1968)

101 A.G.Bolt and I.Forrest, Agressologie 9,201 (1968)

102 A.Loewy and P.Siekevitz, Cell Structure and Function, (Holt, Rinehart and Winston, New York, 1963) chapter 15

103 J.Fernandez-Alonso, Advances in Chemical Physics, Vol VII (Interscience, London, 1964) p44ff

104 B.J.Gudzinowicz, Journal of Gas Chromatography 4,110 (1966)

105 P.H.H.Fischer, Ph.D. Thesis, U.B.C. (1963)

106 R.F.Thompson, Foundations of Physiological Psychology, (Harper and Row, New York, 1967) chapters 5-11

APPENDIX 1

THE FERMI CONTACT HAMILTONIAN

Probably the most important interaction in aromatic free radicals is the hyperfine interaction arising from interaction of electronic and nuclear moments and described by the so-called Fermi contact Hamiltonian. Different notations are often used, and different ones are to be found in this thesis, but all are equivalent.

We write, then, the Hamiltonian (22,23)

$$\mathcal{H} = 8\pi/3\, g_e\beta_e g_N\beta_N \Sigma_k S_z(k)\, I_{nz}\, \delta(r_{nk})$$

where $S_z = \Sigma_i S_{iz}$,

applying this to some polyelectronic wave function ψ,

$$\Psi = \psi\,\phi_{MS}\,\psi_{MI} = \Psi'\psi_{MI}$$

and writing $\mathcal{H} = g_e\beta_e a^N \underset{\sim}{S}\cdot\underset{\sim}{I} = g\beta a^N S_z I_z$

$$a^N = \langle\Psi|\mathcal{H}|\Psi\rangle / g\beta\langle S_z\rangle\langle I_z\rangle$$

$$= 8/3\,\pi\, g_N\beta_N \langle\Psi'|\,\mathcal{H}_S \Sigma_k\, \delta(r_{nk})\, S_z(k)|\Psi'\rangle$$

where $\Psi' = \psi\,\phi_{MS}$.

APPENDIX 2

PROTON HYPERFINE INTERACTION MECHANISM

Much of this appendix is based on reference 6, and is presented here in some detail in order to provide completion of the discussion on proton splittings. Basically, the problem is one of constructing suitable orbitals or wave functions, for the aromatic C-H fragment, which follow certain assumptions:

a) each normalised atomic orbital holds only one electron
b) the wave functions describing the electrons are to be eigenfunctions of S_z and S^2
c) one valence bond function must describe the ground state of the C-H fragment.

There are three normalised orbitals, the P_z, S and σ orbitals, with the free electron residing predominantly in the P_z orbital on the carbon. A three-electron system is thus the one under discussion, and the three spin-orbital configurations can be written:

$$\phi_1 = A\Theta(1,2,3)\alpha\alpha\beta$$
$$\phi_2 = A\Theta(1,2,3)\alpha\beta\alpha$$
$$\phi_3 = A\Theta(1,2,3)\beta\alpha\alpha$$

where A is an anti-symmetrization and renormalization operation (11), $\Theta(1,2,3) \equiv p_z(1)\sigma(2)s(3)$ is the spatial part of the wave function and $\alpha\alpha\beta$ etc. are spin product basis functions satisfying the first part of assumption (b). Now, to obtain eigenfunctions of S^2 it is necessary to take linear combinations of ϕ_1, ϕ_2 and ϕ_3 giving doublet ($S=\frac{1}{2}$) electronic state wave functions:

$$\varphi_1 = 1/\sqrt{2}\,(\phi_1 - \phi_2)$$
$$\varphi_2 = 1/\sqrt{6}\,(\phi_1 + \phi_2 - 2\phi_3)$$

and now all assumptions are satisfied.

φ_1 approximates a ground configuration, and φ_2 an excited configuration, so calculations of the energy difference between φ_1 and φ_2, ΔW, shows that the two levels differ by exchange integrals and the total one-electron nuclear attraction exchange energy of the C-H bond (6).

Since φ_1 cannot give hyperfine coupling with the proton by itself, a small admixture of excited state φ_2 is necessary, giving the mixed ground state wave function:

$$\varphi_1' = \varphi_1 + f\varphi_2 \qquad (1)$$

where f is a spin attenuation factor describing the amount of admixture, or configuration interaction, and hence the amount of coupling with the nucleus.

Thus if H is the complete 3-electron Hamiltonian, and $|f| \ll 1$, then $f=-(H_{21}/\Delta W)$, where $H_{21}=\langle\varphi_2|H|\varphi_1\rangle$. McConnell (6) expands H_{21} as follows:

$$H_{21} = -(\sqrt{3}/2)\left[\left(\int p_z(i)\sigma(j)(e^2/r_{ij})p_z(j)\sigma(i)\,d\tau_i\,d\tau_j\right) - \left(\int p_z(i)s(j)(e^2/r_{ij})p_z(j)s(i)\,d\tau_i\,d\tau_j\right)\right]$$

where $\int p_z(i)\sigma(j)(e^2/r_{ij})(p_z(j))\sigma(i)\,d\tau_{ij} = J_{p\sigma}$, the two-electron exchange integral, and similarly for J_{ps}. If the condition $J_{p\sigma} > J_{ps}$ holds, then

$$F = (\sqrt{3}/2)\, J_{p\sigma}/\Delta W$$

Using Slater's (12) method to evaluate the exchange integral, and if ΔW is in the range 5-15ev, then f~0.07-0.2. Thus the effective penetration of the odd electron into the σ system is given by f, which arises from consideration of an atomic exchange mechanism.

So far only an idealised, isolated C-H fragment has been considered. In the real case the total unpaired spin density is distributed over the whole π system--so for any proton position j

$$\psi_j = \varphi_1 + \rho_j f_j \varphi_2 \qquad (2)$$

where, in general, ψ will not be the same for all C-H bonds in most aromatic systems.

Now, to discuss the actual hyperfine splittings arising from the theorised spin polarisation, it can be usually assumed (especially in aromatic, organic free radicals) that Zeeman interactions are much stronger than the hyperfine interactions at the fields commonly used. Therefore the energy of the contact (or Fermi) hyperfine interaction given by the Hamiltonian (10):

$$\mathcal{H} = (16\pi\beta/3h)(\mu_I/I) \sum_{i=1}^{3} \delta(r_{iH})\, S_z(i)\, I_z$$

where $\delta(r_{iH})$ is the usual delta function for the distance r_{iH} between the electron and the proton.

The first order energy for $S=\frac{1}{2}$ can be calculated (6):

$$E_j(\pm\tfrac{1}{2}) = \langle \psi_j | \mathcal{H} | \psi_j \rangle = 2\rho_j f_j \langle \varphi_1 | \mathcal{H} | \varphi_2 \rangle$$
$$= (\rho_j f_j/\sqrt{3})(16\pi\beta/3h)(\mu_I/I)|s(0)|^2 I_z \qquad (3)$$

where $I_z=\pm\frac{1}{2}$, $I_z=0$ for allowed electronic transitions, s(0) is the value of the wave function at the nucleus and $E_j(-\frac{1}{2})=-E_j(+\frac{1}{2})$.

Thus for a splitting $\Delta\nu(H_j)$ in an electron spin resonance spectrum, equation (3) can be written:

$$\Delta\nu(H_j) = (2/\sqrt{3})(\rho_j f_j)(16\pi\beta/3h)(\mu_I/I)|s(0)|^2$$
$$= 2/\sqrt{3}\,(1420)\,\rho_j f_j$$
$$= 1640\,\rho_j f_j \text{ MHz}$$

APPENDIX 3

DERIVATION OF THE SPIN HAMILTONIAN

References 5 and 58 can be consulted for complete details. The spin-orbit Hamiltonian is:

$$\mathcal{H}^{(1)} = \lambda \underline{L}\cdot\underline{S} + \beta \underline{H}(\underline{L} + 2\underline{S}) \qquad (1)$$

which gives a second-order perturbation energy of:

$$E^{(2)} = 2\beta(\delta_{ij} - \lambda \Lambda_{ij}) S_i H_j - \lambda^2 \Lambda_{ij} S_i S_j - \beta^2 \Lambda_{ij} H_i H_j \qquad (2)$$

where $\Lambda_{ij} = \sum_{n\neq 0}' \dfrac{\langle\psi_0|\hat{L}_i|\psi_n\rangle\langle\psi_n|\hat{L}_j|\psi_0\rangle}{E_n - E_0}$

Λ_{ij} is an orbit interaction term between the ground and excited states, and if it is noted that $\beta^2\Lambda_{ij}H_iH_j$ will give rise to a uniform displacement of all levels (5) it can be ignored.

Writing: $$g_{ij} = 2(\delta_{ij} - \lambda\Lambda_{ij}) \qquad (3)$$

as the g-factor (describing, essentially, the amount of spin-orbit interaction), and letting $E_n - E_0 \gg \lambda$, attention must focus on the second term. This term will be responsible for zero-field splitting of the spin multiplet, and in an axially symmetric crystal field ($\Lambda_{xx} = \Lambda_{yy}$, $\Lambda_{zz} = \Lambda_{\parallel}$) $\underline{\underline{\Lambda}}$ is diagonal (61), so that:

$$-\lambda^2\Lambda_{ij}\hat{S}_i\hat{S}_j = -\lambda^2[\Lambda_\perp(\hat{S}_x^2 + \hat{S}_y^2) + \Lambda_\parallel S_z^2 \qquad (4)$$

but $$\hat{S}_x^2 + \hat{S}_y^2 = S(S+1) - \hat{S}_z^2 \qquad (5)$$

$$\therefore -\lambda^2\Lambda_{ij}\hat{S}_i\hat{S}_j = -\lambda^2[\Lambda_\perp S(S+1) - (\Lambda_\perp - \Lambda_\parallel)S_z^2] \qquad (6)$$

Now defining $D = (\Lambda_\perp - \Lambda_\parallel)\lambda^2$, and substituting into (2)

$$\mathcal{H} = g_\parallel \beta H_z \hat{S}_z + g_\perp \beta(H_x\hat{S}_x + H_y\hat{S}_y) + D\hat{S}_z^2 \qquad (7)$$

Or, completely generally,

$$\mathcal{H} = \beta(g_x H_x\hat{S}_x + g_y H_y\hat{S}_y + g_z H_z\hat{S}_z) + D\hat{S}_z^2 + E(\hat{S}_x^2 - \hat{S}_y^2) \qquad (8)$$

where D and E are zero-field splitting parameters and g the "spin-orbit" factor.

Now, for $S=\frac{1}{2}$, $D=0$, so eqn. (7) can be transformed into laboratory co-ordinates as follows (including the hyperfine interaction):

$$\text{Take } \mathcal{H} = \beta\left[g_{\parallel} H_r S_r + g_{\perp}(H_p S_p + H_q S_q)\right] + A_{\parallel} I_r S_r + A_{\perp}(I_p S_p + I_q S_q) + \cdots \quad (9)$$

as the Zeeman and hyperfine Hamiltonian. Then if H_0 is the field in the z-direction,

$$H_r = H_0 \cos\theta$$

where θ is the angle between the symmetry axis of the molecule, r, and the laboratory z-axis.

Then $\underline{H}\cdot\underline{S} = H_0 S_z$, and further:

$$S_r = S_z\cos\theta + S_x\sin\theta\cos\phi + S_y\sin\theta\sin\phi \quad (10)$$
$$= S_z\cos\theta + \tfrac{1}{2}(S_+ e^{-i\phi} + S_- e^{i\phi})\sin\theta$$

where $S_{\pm} = (S_x \pm iS_y)$ and ϕ is the angle between the xy plane and the pq molecular plane, perpendicular to z and r, respectively. A further point is that can be formulated as the sum of an isotropic (and therefore time-independent) and anisotropic (time dependent) term:

$$\mathcal{H} = \mathcal{H}_0 + \mathcal{H}_1 \quad (11)$$

where $\mathcal{H}_0 = g\beta H_0 S_z + a\,\underline{S}\cdot\underline{I}$

and $\mathcal{H}_1 = [\Delta g\beta H_0 + bI_z][\cos^2\theta - \tfrac{1}{3}]S_z + \tfrac{1}{2}[\Delta g\beta H_0 + bI_z] \quad (12)$
$\times(\sin\theta\cos\theta)[S_+ e^{-i\phi} + S_- e^{i\phi}] - \tfrac{1}{4}b[\cos^2\theta - \tfrac{1}{3}][S_+ I_- + S_- I_+]$
$+\tfrac{1}{4}b(\sin^2\theta)[I_+ S_+ e^{-2i\phi} + I_- S_- e^{2i\phi}]$
$+\tfrac{1}{2}b[\sin\theta\cos\theta][I_+ e^{-i\phi} + I_- e^{i\phi}]S_z$

where $g = 1/3(g_{\parallel} + 2g_{\perp})$, $a = \frac{1}{2}(A_{\parallel} + 2A_{\perp})$

$b = A_{\parallel} - A_{\perp}$

APPENDIX 4

THE CORRELATION FUNCTION AND ITS PROPERTIES (22, 58-60)

In the Hamiltonian given in Appendix 3 and Section III, the polar angle θ can be considered to determine the correlation of the molecule. The molecular symmetry axis will then determine the correlation, or lack of it, for a certain time period, and if the microcrystal is considered to be a unit sphere in shape, then

$$\langle 3\cos^2\theta - 1\rangle_{av} = \frac{\int_0^{\pi}(3\cos^2\theta - 1)2\pi \sin\theta \, d\theta}{\int_0^{\pi} 2\pi \sin\theta \, d\theta} = 0 \qquad (1)$$

when considering one of the terms in (2-34).

If the time average is not considered over a long period, but a suitably shorter one, then clearly $\langle 3\cos^2\theta - 1\rangle$ need not be 0 at any time t if $\theta(t)$ is a random function of time. There is thus always some time interval available at the end of which the function will not be zero, and in fact there is also an interval ending at τ where the sign of the random function, and the magnitude, is approximately the same as at the start. When this is true for any starting point then the process is termed a "stationary random process" and the time interval is the correlation time. Such a process is to be considered here.

Consider a random function $f(x(t))$ and a correlation function defined as:

$$G(t_1, t_2) = \overline{f(x(t_1))f^*(x(t_2))} \qquad (2)$$

where the bar denotes an average.

Since a stationary random process is being considered, $|t_2 - t_1| = \tau$. Then:

$$G(\tau) = \overline{f(x(t))f^*(x(t+\tau))} \tag{3}$$

and if $G(\tau) = G(0)g(\tau) = \overline{|f(x(t))|^2}g(\tau)$ and $g(0) = 1$. (4)

Equations (3) and (4) can be shown more explicitly by considering the appropriate probability distributions. If the definition $p(x_1,t_1;x_2,t_2)$ means that $x=x_1$ at t_1 and x_2 at t_2, and if $P(x_1,t_1;x_2,t_2)$ means $x=x_2$ at t_2 when it is known that $x=x_1$ at t_1, then:

$$p(x_1,t_1;x_2,t_2) = P(x_1,t_1;x_2,t_2)p(x_1,t_1) \tag{5}$$

or p is simply the product of P and the probability that $x=x_1$ at t_1. Thus the correlation function can be written:

$$\begin{aligned} G(t_1,t_2) &= \overline{f(x(t_1))f^*(x(t_2))} \\ &= \iint p(x_1t_1;x_2t_2)f(x_1)f^*(x_2)dx_1dx_2 \\ &= \iint p(x_1t_1)P(x_1,t_1;x_2,t_2)f(x_1)f^*(x_2)dx_1dx_2 \end{aligned} \tag{6}$$

and since the definition of the average value of a random function x(t) at some time t, subject to the probability distribution p(x,t) is defined by (60,p270):

$$\overline{x(t)} = \int xp(x,t)dx \tag{7}$$

and for f(x), a function of x and hence a random function of t if x is,

$$\overline{f(x(t))} = \int p(x,t)\ f(x)\ dx \tag{8}$$

For the stationary random process

$$\begin{aligned} G(\tau) &= \iint p(x_1,x_2,\tau)f(x_1)f^*(x_2)dx_1dx_2 \\ &= \iint p(x_1)P(x_1,x_2,\tau)f(x_1)f^*(x_2)dx_1dx_2 \end{aligned} \tag{9}$$

and if $G(\tau)$ is defined (somewhat loosely) to be small when $|\tau| >> \tau_c$, where τ_c is the correlation time, the correlation

time achieves a mathematical definition. Further, since

$$p(x_1,x_2,\tau) = p(x_2,x_1,\tau)$$

so $G(-\tau) = G^*(\tau) = G(\tau)$ since $p(x_1,x_2,-\tau) = p(x_1,x_2,\tau)$ and the last statement implies that past probability is the same as future probability. It is assumed here that there is always a time τ such that this holds.

It is now possible to define a series of spectral densities, which are Fourier transforms of G,(60):

$$j(\omega) = \int_0^\infty G(\tau)e^{-i\omega\tau}d\tau \qquad (10)$$

$$J(\omega) = 2\int_0^\infty G(\tau)\cos(\omega\tau)d\tau = \int_0^\infty G(\tau)e^{-i\omega\tau}d\tau \qquad (11)$$

$$k(\omega) = \int_0^\infty G(\tau)\sin\omega\tau d\tau \qquad (12)$$

and therefore $j(\omega) = \frac{1}{2}J(\omega) - ik(\omega)$ (13)

The reduced correlation function has already been defined in equation (4), so if it is represented as (60):

$$g(\tau) = \exp(-|\tau|/\tau_c) \qquad (14)$$

then $j(\omega) = 2\tau_c/(1+\omega^2\tau_c^2)$ (15)

This is often referred to as the spectral density, and clearly $j(\omega)$ at a given frequency ω is a maximum for $\tau_c = 1/\omega$, decreasing to 0 for either very short or very long τ_c. This shows the usual relaxation effect that can be found when working with liquid solutions in nuclear magnetic or electron spin resonance.

APPENDIX 5

THE CORRELATION FUNCTION FOR A SIMPLE CASE (59)

If a random function is limited in its randomness to an interval about some field value H_0, and if the deviation from H_0 is $\pm\delta$, and defining:

$$\begin{aligned} H_2 &= H_0 - \delta \\ H_1 &= H_0 + \delta \end{aligned} \qquad (1)$$

then for the correlation function $G(\tau) = \overline{f(t)f(t+\tau)}$ (2) it is possible to write $f(0) = H_1$ as a starting assumption (it could also have been $f(0) = H_2$, leading to the same result).

Now, if a probability is defined as follows:

$$P_1(\tau) = \begin{matrix} 0) \\ 1) \end{matrix} \text{ for } f(t) = \begin{matrix} (H_1 \\ (H_2 \end{matrix} \qquad (3)$$

and similarly for $P_2(\tau)$, then:

$$f(0)f(\tau) = H_1\left[P_1(\tau)H_1 + P_2(\tau)H_2\right] \qquad (4)$$

by simple substitution.

The average of (4) leads to the averages of $p_1(\tau)$ and $p_2(\tau)$ which predict that if at $\tau=0$ the field is H_1, it will be either H_1 or H_2 at time $\tau(\neq 0)$.

$$\therefore \quad \overline{f(0)f(\tau)} = H_1\left[H_1p_1(\tau) + H_2p_2(\tau)\right] \qquad (5)$$

and as $\tau \to 0$, $p_1(\tau) \to 1$ and $p_2(\tau) \to 0$ if $f(\tau)=H_1$ at $\tau=0$.

Therefore the probability that the field will jump from H_1 to H_2, W, obeys the rate equations:

$$\begin{aligned} \frac{dp_1}{d\tau} &= W(p_2-p_1) \\ \frac{dp_2}{d\tau} &= W(p_1-p_2) \end{aligned} \qquad (6)$$

must hold. Solving gives (ref,59, p231):

$$p_1(\tau) + p_2(\tau) = 1$$
$$p_1(\tau) - p_2(\tau) = C\exp(-2W\tau) \qquad (7)$$

but $C = p_1(0) - p_2(0) = p_1(0)$ since $p_2(0)=0$,

therefore it follows that since $p_1(0)=1$, $C=1$.

So
$$\begin{aligned}\overline{f(0)f(\tau)} &= H_1\left[H_1 p_1(\tau) + H_2 p_2(\tau)\right] \\ &= \delta\left[\delta(e^{-2W\tau} + p_2(\tau)) - \delta p_2(\tau)\right] \\ &= \delta\left[\delta e^{-2W\tau} + \delta p_2(\tau) - \delta p_2(\tau)\right] \\ &= \delta^2 e^{-2W\tau} \qquad (8)\end{aligned}$$

therefore $\overline{\overline{f(0)f(\tau)}} = \delta^2 e^{-2W\tau} = G(\tau)$

where $\overline{\overline{f(0)f(\tau)}}$ represents the complete ensemble average (i.e. taking into account both possible starting points for the field value, and noting that the field is equally likely to be either value initially, so the result for one starting point is the same for the other).

Finally, since $1/\tau_c = 2W$ (9)

$$\overline{f(t)f(t+\tau)} = \delta^2 e^{-|\tau|/\tau_c} \qquad (10)$$

where (9) follows from considerations of saturation and rate equations for a spin $\frac{1}{2}$ particle (see ref. 58, pp34-38), and τ_c is substituted for T_1, the Bloch longitudinal relaxation time.

APPENDIX 6

A RANDOM FUNCTION TREATMENT OF $\mathcal{H}_1(t)$

To apply the correlation function treatment to the Hamiltonian already described (3-34), it is convenient to write:

$$\mathcal{H} = \mathcal{H}_0 + \mathcal{H}_1(t) \tag{1}$$

where $\mathcal{H}_0$ is the isotropic part and $\mathcal{H}_1(t)$ the perturbing spin interactions which depend on lattice co-ordinates. The spins can then be considered a subsystem of the lattice (microcrystal) which contains atomic and molecular degrees of freedom--thus a difficult quantum-mechanical calculation for the entire spin and lattice system can be avoided by treating $\mathcal{H}_1(t)$ as a random function of time.

To solve the time-dependent Schrödinger equation (the eigenfunctions and eigenvalues of $\mathcal{H}_0$ are solutions of the time-independent Schrödingerequation, but $\mathcal{H}_1$ introduces a small time-dependent perturbation and thus stationary solutions of the time-independent equation do not exist):

$$i\hbar \frac{\partial \psi}{\partial t} = \mathcal{H}\psi \tag{2}$$

and if zero-order eigenfunctions are u_n such that:

$$\mathcal{H}_0 u_n = E_n u_n \tag{3}$$

then (62):

$$\psi = \sum_n a_n(t) u_n \exp(-iE_n t/\hbar) \tag{4}$$

Substituting eq (4) into into eq (2) yields:

$$\sum i\hbar \frac{da_n}{dt} u_n e^{-iE_n t/\hbar} + \sum_n a_n E_n u_n e^{-iE_n t/\hbar} = \sum_n a_n (\mathcal{H}_0 + \mathcal{H}_1) u_n e^{-iE_n t/\hbar} \tag{5}$$

Now, multiplying through by u_k^* and replacing $\mathcal{H}_0 u_n$

by $E_n u_n$, and integrating over all space, remembering that (62):

$$\int u_k^* u_n d\tau = \delta_{kn} \tag{6}$$

gives: $$\sum i\hbar \frac{da_n}{dt} u_n e^{-iE_n t/\hbar} + \sum a_n E_n u_n e^{-iE_n t/\hbar}$$

$$= \sum a_n (E_n u_n e^{-iE_n t/\hbar} + \mathcal{H}_1 u_n e^{-iE_n t/\hbar}) \tag{7}$$

$$\therefore \sum i\hbar \frac{da_n}{dt} u_n e^{-iE_n t/\hbar} = \sum a_n \mathcal{H}_1 u_n e^{-iE_n t/\hbar} \tag{8}$$

$$\text{so} \quad \sum i\hbar \frac{da_k}{dt} \int u_n u_k^* e^{-iE_n t/\hbar} d\tau = \sum a_n \int u_k^* \mathcal{H}_1 u_n d\tau \, e^{-iE_n t/\hbar} \tag{9}$$

$$\sum i\hbar \frac{da_k}{dt} e^{-iE_n t/\hbar} = \sum a_n e^{-iE_n t/\hbar} \langle u_k^* | \mathcal{H}_1 | u_n \rangle \tag{10}$$

Now, if $a_n = \delta_{nm}$ at t=0, then for $k \neq m$, and the system in state m at t=0,

$$a_k(t) = -i/\hbar \int_0^t \langle k | \mathcal{H}_1(t') | m \rangle e^{i\omega_{km} t'} dt' \tag{11}$$

where $$\frac{da_k}{dt} = -i/\hbar \sum a_n \langle u_k^* | \mathcal{H}_1 | u_n \rangle e^{-iE_n t/\hbar} \tag{12}$$

follows from eq (10), and $\omega_{kn} = E_k - E_n/\hbar$ defines the angular frequency (58).

So the behaviour of the coefficient a_k with time is defined. Now, if the probability that a system in a state m will be in a state k after some time interval t is (63):

$$P_{km} = a_k a_k^* \tag{13}$$

then the transition rate between these two states is:

$$\frac{dP_{km}}{dt} = W_{km} = a_k \frac{da_k^*}{dt} + \text{c.c.} \tag{14}$$

Therefore, substituting eq (11) into eq (14):

$$W_{km} = \hbar^{-2} \langle m | \mathcal{H}_1(t) | k \rangle e^{-i\omega_{km} t} \int_0^t \langle k | \mathcal{H}_1(t') | m \rangle e^{i\omega_{km} t'} dt' + \text{c.c.}$$

$$= \hbar^{-2} \int_0^t \langle k | \mathcal{H}_1(t') | m \rangle \langle m | \mathcal{H}_1(t) | k \rangle e^{-i\omega_{km}(t-t')} dt'' + \text{c.c.} \tag{15}$$

Now if $\mathcal{H}_1(t)$ is a random function, this randomness will be evidenced in the matrix elements. Therefore a transition rate average for the microcrystal is a measureable quantity defined by:

$$\bar{W}_{km} = h^{-2} \overline{f^*(t-\tau) f(t)} \, e^{-i\omega_{km} t} d\tau + \text{C.C.} \tag{16}$$

where $\tau = t - t'$ and $f(t) = \langle m | \mathcal{H}_1(t) | k \rangle$

Therefore, $$\bar{W}_{km} = \hbar^{-2} \int_{-t}^{t} G(\tau)\ e^{-i\omega_{km}\tau} d\tau \qquad (17)$$

Now since $G(\tau)$ becomes very small if τ_c is short, or long, compared to t (loss of correlation), the integrand must disappear before t deviates far from τ_c, so the limits in eq (17) can be replaced by $\pm\infty$. Further, in the high-temperature approximation, defined by (58-60):

$$\gamma\hbar H_0 = g\beta H_0 \ll kT \qquad (18)$$

(in this work $g\beta H_0 \sim 6\times10^{-20}$, $kT \sim 4\times10^{-14}$), and thus

$$1/T_1 = W(1+\exp(-\epsilon/kT)) \qquad (20)$$

from considerations of the Einstein coefficients of absorbtion and emission (see, in particular, ref. 64). Thus if $\epsilon \ll kT$

$$1/T_1 = 2W \qquad (21)$$

$$\text{so} \quad (1/2T_1)_{km} = \bar{W}_{km} = \hbar^{-2} \int_{-\infty}^{\infty} G(\tau)\ e^{-i\omega_{km}\tau} d\tau \qquad (22)$$

And from Appendix 4 eq (22) is simply the Fourier transform of the correlation function, defined to be the spectral density $j(\omega)$.

APPENDIX 7

THE BLOCH EQUATIONS--A BRIEF DEFINITION

The Bloch equations provided a correct description (for liquids) of the magnetic properties of ensembles of nuclei in external magnetic fields.

In an arbitrary magnetic field (homogeneous) the equation of motion of the nuclear magnetization for an ensemble of free spins is:

$$d\underline{M}/dt = \gamma \underline{M} \times \underline{H} \qquad (1)$$

In a static field, $H_z=H_0$ say, the trend of the magnetization to an equilibrium value $M_z=M_0=\chi_0 H_0$ can be fairly accurately described by:

$$dM_z/dt = -\left\{(M_z-M_0)/T_1\right\} \qquad (2)$$

Now, if the nuclear magnetization is given a component perpendicular to H_0 (by, for example, an rf pulse), the various local fields cause the transverse magnetization to decay (because the spins are not actually free, but interact with each other and their surroundings):

$$dM_x/dt = -M_x/T_2, \qquad dM_y/dt = -M_y/T_2 \qquad (3)$$

In the presence of an applied field (the sum of a DC field and a much smaller rf field) the motion due to relaxation can be superimposed on the free spin motion, yielding:

$$d\underline{M}/dt = \gamma \underline{M} \times \underline{H} - \frac{M_x i' + M_y j'}{T_2} - \frac{Mz - M_0}{T_1} k' \qquad (4)$$

i', j', and k' being unit vectors of the laboratory frame of reference, and T_1 the longitudinal relaxation time, T_2 the transverse relaxation time.

APPENDIX 8

Following are some values of viscosity for sulfuric acid as a function of temperature. As can be seen, no simple correlation seems to exist.

temperature	viscosity
0 °C	48.4 cp
15	32.8
20	25.4
30	15.7
40	11.5
50	8.82
60	7.22
70	6.09
80	5.19

Acetonitrile has a viscosity of .46 cp at 0°C

Nitromethane has a viscosity of .85 cp at 0°C, and .62 cp at 25°C